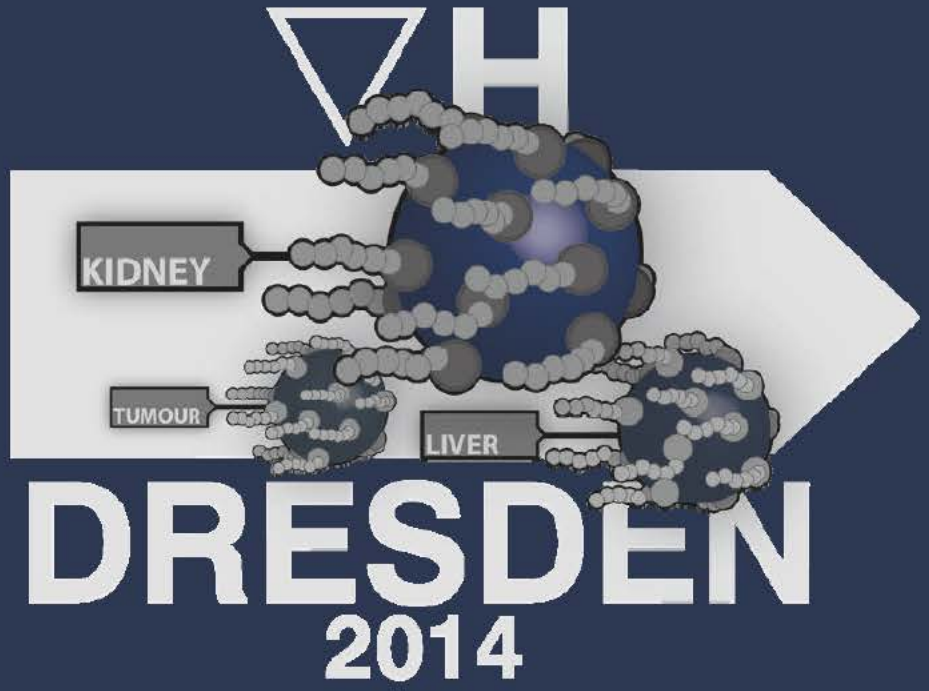
TECHNISCHE UNIVERSITÄT DRESDEN

10th International Conference on the

Scientific and Clinical Applications of Magnetic Carriers



Book of Abstracts

UBC

MEASURING AND AUTOMATION TECHNOLOGY

MAGNETOFLUIDDYNAMICS

10th Meeting - Dresden 2014

International Conference on the Scientific and Clinical Applications of Magnetic Carriers

Materials with properties controllable by external fields become more and more important not only for technical but for applications in the biomedical area.

The development over the past decades has shown that a growing knowledge concerning basics in physics, chemistry and biology is a crucial precondition for a successful and safe development of new biomedical applications. Therefore, an intense cooperation between basic and application oriented research, synthesis, characterization, theory and application design can finally lead to particles and fluids suitable for the envisaged use.

The International Conferences on the Scientific and Clinical Applications of Magnetic Carriers have provided for nearly two decades a platform for interdisciplinary discussions strengthening the scientific progress in the field. Besides being a forum for scientific exchange about recent developments in the field of scientific and clinical applications of magnetic carriers, the conference will highlight – as in the past – one of the important aspects of the research field in early morning tutorials. While magnetism and magnetic materials have been in the focus of these tutorials during the last conferences, Joachim Clement will try this year to explain “Biology for Physicists, Chemists and Engineers”!

However a conference is not only characterized by the scientific sessions – the location where scientists meet to discuss their results can be a sign for such a meeting too. In this respect, the 800 years old city of Dresden, having a long and productive history as scientific center, is obviously an inspiring venue.

The Technische Universität Dresden, founded in 1828, belongs to the oldest technical universities in Germany and became one the eleven “Excellence Universities” in Germany in 2012. The faculty of mechanical engineering is one of the strongest engineering research centers in the country and includes a large research area in biomaterials.

Aside biomaterials the development and characterization of smart materials in general – from light weight composites to materials controlled by external stimuli – are one of the major profile lines of the research activities of TU Dresden. Within this context the establishment of the Chair of Magnetofluiddynamics, Measuring and Automation Technology anchored the field of magnetically controlled smart materials firmly within TU Dresden and gave us the possibility to invite you to 10th International Conference on the Scientific and Clinical Applications of Magnetic Carriers in Dresden.

We hope that the city as well as the scientific program will give you highly interesting and inspiring days full of discussions, new ideas and deepened contacts.

Dresden, June 2014

Stefan Odenbach

Urs Hafeli

10th Meeting - Dresden 2014

International Conference on the Scientific and Clinical Applications of Magnetic Carriers

TU DRESDEN, CHAIR OF MAGNETOFLUIDDYNAMICS; MEASURING AND AUTOMATION TECHNOLOGY

11:00	**Registration desk opens**			
	Opening Session			
13:00	Stefan Odenbach	Opening of the conference / Welcome		
13:20	Urs Hafeli	Short review of the last 2 years of magnetic carriers research	Vancouver, Canada	Talk 0
	Session 1	**Magnetic Separation**		
14:00	Viola Vogel	Nanomechanics By Which Immune Cells Pick Up Their Prey	Zurich, Switzerland	Invited Talk 1
14:40	Mathias Reisbeck	Volumetric Measurements Of Cells In Whole Blood For Point-Of-Care Applications	Erlangen, Germany	Talk 1
15:00	Kazunori Hoshino	Single-Cell PCR Analysis Of Circulating Tumor Cells Captured By Immunomagnetic Microchip	Connecticut, USA	Talk 2
15:20	JitKang Lim	Rapid Magnetophoretic Separation Of Microalgae	Nibong Tebal, Malaysia	Talk 3
15:40	**Coffee break**			
	Session 2	**Nanotechnology**		
16:20	Longfei Ye	Monitoring Nanoparticle Self-Assembly Dynamics In Extreme Magnetic Field Gradients: A New Metrology For Colloidal Magı	Columbia, USA	Talk 4
16:40	Clara Marquina	Antibody Distribution On Bio-Functionalized Magnetic Nanoparticles Analyzed By Spatially-Resolved EELS	Zaragoza, Spain	Talk 5
17:00	Lamar Mair	Single Particle Tracking Reveals Biphasic Transport During Nanorod Magnetophoresis Through Extracellular Matrix	Baltimore, USA	Talk 6
17:20	Binh Pham	High Iron Content Magnetic Nanoparticles As Effective Delivery Vehicles Of Anti-Cancer Drugs Into A Solid Tumour Model	Sydney, Australia	Talk 7
17:40	Sudeshna Chandra	Dendrimer-Magnetic Nanoparticles As Multiple Stimuli Responsive And Enzymatic Drug Delivery Vehicle	Mumbai, India	Talk 8
18:00	**Informal reception and welcome cocktail (Apero)** - *generously sponsored by* ***TurboBeads*** *and* ***Chemicell***			

Wednesday, June 11, 2014				
08:00	**Registration desk opens**			
08:30	Joachim Clement	Daily tutorial "Biology for the Physicist, Chemist and Engineer"	Jena, Germany	Tutorial 1
	Session 3	**Biological Applications**		
09:00	Ludwig Schulz	Interaction of ferromagnetic and superconducting permanent magnets - superconducting levitation	Dresden, Germany	Invited Talk 2
09:40	Randall Erb	Manufacturing Ordered Biocomposites With Weak Magnetic Fields	Boston, MA, USA	Talk 9
10:00	Katrin Zimmermann	Magnetic Nanoparticles Assisted Modulation Of The Vascular cGMP Pathway	Bonn, Germany	Talk 10
10:20	Kathy Saatchi	Magnetic Nanoparticles As A Delivery System For Adipose Tissue-Specific Rosiglitazone Targeting In Type 2 Diabetes	Vancouver, BC, Canada	Talk 11
10:40	**Coffee break**			
	Session 4	**Biological Applications**		
11:20	Ryan Middleton	Magnetic Antibody-Linked Nanomatchmakers For Therapeutic Cell Targeting	West Hollywood, CA, USA	Talk 12
11:40	Maxim Nikitin	Denaturation-Resistant Magnetic-Fluorescent Colloidal Superstructures Assembled Via The Proteinaceous Barnase Barstar	Moscow, Russia	Talk 13
12:00	Joost Pouw	Performance Of Three Different Clinical Magnetic Nanoparticle Tracers For Sentinel Lymph Node Detection	Enschede, Netherlands	Talk 14
12:20	Yijie Chen	Highly Effective Inhibition Of Lung Cancer Growth And Metastasis By Systemic Delivery Of siRNA Via Magnetic Mesoporous	Shanghai, China	Talk 15
12:40	Adam Monsalve	Manipulating Signaling Proteins Via Magnetic Particles For Remote Cell Control	Gainesville, FL, USA	Talk 16
13:00	**Lunch**			

	Session 5	**Biological Applications**		
14:00	Annette Schmidt	Responsive Core-Shell Nanoparticles For Medical Applications	Köln, Germany	Invited Talk 3
14:40	Stephan Karl	A Novel Rotating-Crystal Magneto-Optic Technique For Malaria Diagnosis	Melbourne, Australia	Talk 17
15:00	Raoul Kopelman	Evaluating Metastatic Potential By The Cell Magneto-Rotation Method	Ann Arbor, MI, USA	Talk 18
15:20	Martin Koch	Interaction Of Dynamic Magnetic Fields With Magnetic Particles Immobilized At Lysosomes	Seeheim, Denmark	Talk 19
15:40	**Coffee break**			
	Session 6	**Biosensors**		
16:20	Amy Buck	Magnetic Separation Of Algae Expressing Enhanced Intracellular Ferritin Concentration	Cleveland, OH, USA	Talk 20
16:40	Caio Quini	Renal Function Evaluation By Alternating Current Biosusceptometry Of Magnetic Nanoparticles	Botucatu, Brazil	Talk 21
17:00	Marco Donolato	Molecular Diagnostics Based On Magnetic Nanobead Clustering Dynamics Monitored Using A Blu-Ray Optomagnetic Read	Kgs. Lyngby, Denmark	Talk 22
17:20	Petr Nikitin	New Method Of Investigation Of Affinity Properties Of Magnetic Nanoparticles With Recognition Receptors	Moscow, Russia	Talk 23
17:40	Giovanni Rizzi	On-Chip Magnetic Bead-Based DNA Melting Curve Analysis Using A Magnetoresistive Sensor	Kgs. Lyngby, Denmark	Talk 24
18:00	**Poster session I with Bier and Bretzeln** - generously sponsored by ***Diagnostic Biosensors***			

Thursday, June 12, 2014				
08:00	**Registration desk opens**			
08:30	Joachim Clement	Daily tutorial "Biology for the Physicist, Chemist and Engineer"	Jena, Germany	Tutorial 2
	Session 7	**Magnetic Imaging/MPI**		
09:00	Christoph Alexiou	Application Of Magnetic Nanoparticles (Spion) In Medicine – The Seon-Concept	Erlangen, Germany	Invited Talk 4
09:40	Yanglong Hou	Multifunctional Magnetic Nanoparticles For Targeted Cancer Diagnosis And Therapy	Beijing, China	Talk 25
10:00	Frank Wiekhorst	Magnetic Particle Spectroscopy To Quantify Blood Half-Life Of Superparamagnetic Iron Oxide Nanoparticles In A Mouse Str	PTB, Berlin, Germany	Talk 26
10:20	Sylvie Begin	Dendronized Magnetic Core-Shell And Cubic Shaped Nanoparticles Designed For Targeting, Mri And Hyperthermia	Strasbourg, France	Talk 27
10:40	**Coffee break**			
	Session 8	**Magnetic Imaging/MPI**		
11:20	Martijn Visscher	Depth Limitations For In Vivo Magnetic Nanoparticle Detection With A Compact Handheld Device	Enschede, Netherlands	Talk 28
11:40	Daniel Baumgarten	Magnetorelaxometry Imaging Of Magnetic Nanoparticles With Inhomogeneous Fields Based On Plane-Wise Sensitivity	Ilmenau, Germany	Talk 29
12:00	Annika Kasten	Tracking Of Adipose Tissue-Derived Progenitor Cells Using Two Magnetic Nanoparticle Types	Rostock, Germany	Talk 30
12:20	Olivier Sandre	Nano-Thermometer With Thermo-Sensitive Polymer Grafted USPIOs Behaving As Positive Contrast Agents In Low-Field Mr	Bordeaux, France	Talk 31
12:40	Katharina Bayer	Magnetic Nanoparticles In Mural Tumors Detected And Quantificated By Micro-Computertomography	Dresden, Germany	Talk 32
13:00	**Lunch**			
	Session 9			
14:00	Dieter Scharnweber	Engineering Cellular Microenvironments – Chemistry Meets Physics	Dresden, Germany	Invited Talk 5
14:40	**Poster session II**			
16:00	**Boat trip on the Elbe** - generously sponsored by **micromod; dinner in the castle "Schloss Pillnitz"**			

Friday, June 13, 2014				
08:00	**Registration desk opens**			
08:30	Joachim Clement	Daily Tutorial "Biology For The Physicist, Chemist And Engineer"	Jena, Germany	Tutorial 3
	Session 10	**Grant Panel Discussion**		
09:00	Alexander Pfeifer	DFG-Forschergruppe 917: Nanoparticle-Based Targeting Of Gene- And Cell-Based Therapies	Bonn, Germany	Talk 33
09:20	Stefan Odenbach	SPP1681: Field Controlled Particle Matrix Interactions	Dresden, Germany	Talk 34

09:40	Heinrich Hofmann	NFP64: Chancen Und Risiken Von Nanomaterialien, Nationales Forschungsprogramm	Lausanne, Switzerland	Talk 35
10:00	Christer Johansson	EU-FP7: Nanomag	Göteborg, Sweden	Talk 36
10:20	Urs Hafeli	Panel Discussion About The Current Climate For Getting Grants In Our Field	Vancouver, Canada	
10:40	**Coffee break**			
	Session 11	**Analytical Methods**		
11:20	Adriele Prina-Mello	Quantification Of Superparamagnetic Nanoparticle Concentration Using Particle Electron Paramagnetic Resonance: An In V	Dublin, Ireland	Talk 37
11:40	Robin Ras	Magnetic Droplets For Exploring Dynamics And Dissipation On Superhydrophobic Surfaces	Espoo, Finland	Talk 38
12:00	Tim St Pierre	The Interaction Between Schistosome Eggs And Magnetic Microspheres	Crawley, Australia	Talk 39
12:20	Johannes Nowak	The Magnetoviscous Effect Of A Biocompatible Ferrofluid Diluted With Sheep Blood	Dresden, Germany	Talk 40
12:40	Stephen Sherman	The Relationship Between Mason Number And Bingham Number In Magnetorheological Fluids	College Park, USA	Talk 41
13:00	Robert Müller	Detection Of Magnetic Nanoparticles After Perfusion Of A Placenta	Jena, Germany	Talk 42
13:20	**Lunch**			
	Session 12	**Magnetic Drug Delivery**		
14:20	Jeffrey Anker	Detecting Mechanical and Chemical Changes Through Tissue Using Magnetically Modulated Optical Sensors	Clemson, USA	Talk 43
14:40	Kirsten Pondman	In Vivo Magnetic Drug Delivery Using FePd Nanowires	Enschede, Netherlands	Talk 44
15:00	Anjali Seth	Magnetic Beads To Enhance Drug Penetration Across Intestinal Membrane	Paris, France	Talk 45
15:20	Shimon Lecht	Non-Invasive In Vivo Magnetic Targeting Of Mouse Embryonic Stem Cells To The Lung	Philadelphia, USA	Talk 46
15:40	**Coffee break**			
	Session 13	**Magnetic Drug Delivery**		
16:20	Alessandro Russo	Treatment Of A Critical Long Bone Defect Using Magnetic Scaffolds Reloaded By Magnetic Nanoparticles-VEGF	Bologna, Italy	Talk 47
16:40	Jan Dieckhoff	Single-core magnetic markers in rotating magnetic field based homogeneous bioassays and the law of mass action	Vancouver, Canada	Talk 48
17:00	Christophe Monnier	Janus Magnetic Liposomes For Drug Delivery	Marly, Switzerland	Talk 49
17:45	**City tour, reception at the Dresden transport museum** - generously sponsored by **Zepto Life Technology**			

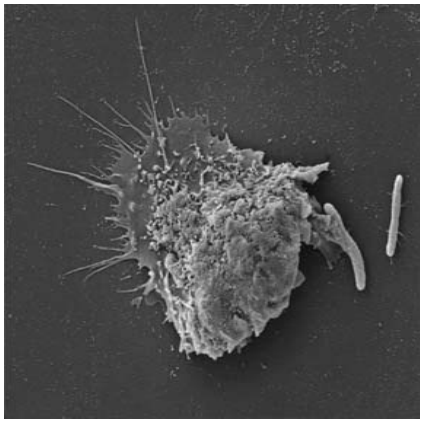
Saturday, June 14, 2014				
08:30	**Registration desk opens**			
	Session 14	**Hyperthermia**		
09:00	Julian Carrey	Magnetic Hyperthermia From The Physics Side: State Of The Art And Open Questions	Toulouse, France	Invited Talk 6
09:40	Cristina Blanco-Andujar	Reproducible Microwave Synthesis Of Multi-Core Iron Oxide Nanoparticles For Magnetic Hyperthermia And In Situ Tracking	London, UK	Talk 50
10:00	Robert Ludwig	Analysis Of Molecular Effects After Treatment Of Pancreatic Cancer Cells With (Magnetic Fluid) Hyperthermia	Jena, Germany	Talk 51
10:20	Sara Majetich	Terahertz Absorption In Iron Oxide Nanoparticles	Pittsburgh, USA	Talk 52
10:40	Satoshi Ota	Measurement Of Magnetic Rotation Of Magnetic Nanoparticles In Cultured Cells Under Alternating Field	Yokohama, Japan	Talk 53
11:00	**Coffee break**			
	Session 15	**Nanoparticle Synthesis**		
11:40	Ying Jing	Smart And Biocompatible Fe-Si Nanoparticles	Minneapolis, USA	Talk 54
12:00	Ben Erné	Diverging Magnetic And Physical Size Distributions Of Superparamagnetic Nanoparticles	Utrecht, Netherlands	Talk 55
12:20	Jian-Chao Si	Solvothermal Synthesis Of Tunable Magnetite Nanorods And Its Transfer From Organic Phase To Water Phase	Xi'an, China	Talk 56
12:40	Fernando Herranz	Microwave-Assisted Chemoselective Functionalisation Of Iron Oxide Nanoparticles For Cardiovascular Imaging	Madrid, Spain	Talk 57
13:00	**Closing Comments and Announcement of the NEXT MEETING: Urs Hafeli / Stefan Odenbach**			
13:15	**Meeting ends**			

Nanomechanics by which cells explore their environments and pick up their prey

Viola Vogel

Laboratory of Applied Mechanobiology, Department of Health Sciences and Technology, ETH Zurich, Switzerland. E-mail: viola.vogel@hest.ethz.ch

Cells exploit mechanical forces to sense the physical aspects of their microenvironments. They pull on the surrounding extracellular matrix and the anchorage of cells to their environment is essential for their survival. If they encounter microbes or (magnetic) particles, cells exploit similar mechanisms to pull on the objects, move towards them and if possible initiate phagocytosis. Various examples will be presented illustrating sophisticated nanomechanical concepts by which cells can feel nanoscale topographical features, and how our immune cells exploit mechanical forces to fight bacterial infections.



Electron microscopy image showing how a macrophage approaches surface-bound E. Coli bacteria. Image taken by Jens Möller - for more information see [2].

1 J Albuschies, V Vogel**, The role of filopodia in the recognition of nanotopographies**, Scientific Reports, 3 (2013) 1658

2 J Möller, T Lühmann, M Chabria, H Hall, V Vogel, **Macrophages lift off surface-bound bacteria using a filopodium-lamellipodium hook-and-shovel mechanism,** Scientific Reports**, 3** (2013) 2884

3 S Schürle, M Selman Sakar, A Meo, J Möller, B E Kratochvil, C S Chen, V Vogel and B J Nelson, **Three-dimensional, automated magnetic biomanipulation with subcellular resolution**, Robotics and Automation (ICRA), IEEE International Conference (2013) 1452-1457

Volumetric Measurements of Cells in Whole Blood for Point-of-Care Applications

M. Reisbeck[1,2*], M. Helou[1,3], L. Richter[1], B. Krafft[1], O. Hayden[1]

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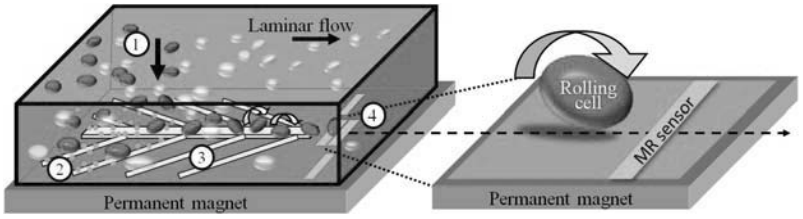
For routine and point-of-care (POC) applications the workflow of flow cytometry requires (1) an integration of pre-analytical steps, (2) fast turn-around-time, and (3) effortless data analysis for non-expert usage. To achieve such an ambitious goal the methodology of fluorescence flow cytometry is challenged by the fact that blood samples require dilution, often lysis of red blood cells, and some centrifugation step to remove excess fluorescence background after immunophenotyping.

Here, we discuss a time-of-flight (TOF) magnetic flow cytometry approach[1] for POC applications which potentially enables a fully integrated workflow on a cartridge. The envisioned system does not require any sheath flow buffer but operates with whole undiluted blood. Amongst other the TOF measurement is an enabler to derive cell volumes in whole blood with a resolution and precision only known from Coulter methods. With an external magnet field immunomagnetically labeled cells are enriched on the substrate surface where integrated magnetoresistive sensors detect the rolling specimen at a highly controlled sensor-to-analyte distance. To achieve high recovery rates magnetophoresis with a chevron pattern of nickel stripes is applied to align immunomagnetically labeled cells on the substrate surface. Furtherrmore, the chevron pattern is useful for in-situ filtration of non-bound 200 nm superparamagnetic labels which is due to magnetic forces exceeding the lift force generated by the laminar flow profile. Case examples of cell detection in whole blood are discussed and results are benchmarked against established methods.

The project “MRCyte” is supported by the German Federal Ministry of Education and Research under the program ‘Werkstoffinnovationen für Industrie und Gesellschaft – WING’.



Schematic of an integrated workflow with in-situ magnetic enrichment (1), magnetophoretic focusing of immunomagnetically labeled cells (3), in-situ filtration of excess labels (2) and magnetoresistive TOF measurement (4).

[1] Helou et al, Lab Chip, 2013, 13, 1035

Single-cell PCR analysis of circulating tumor cells captured by immunomagnetic microchip

K. Hoshino[1*], H.W. Chung[2], C.H. Wu[2], K. Rajendran[2], Y.Y. Huang[2], P. Chen[2], K.V. Sokolov[2], J. Kim[2], and X.J. Zhang[2]**

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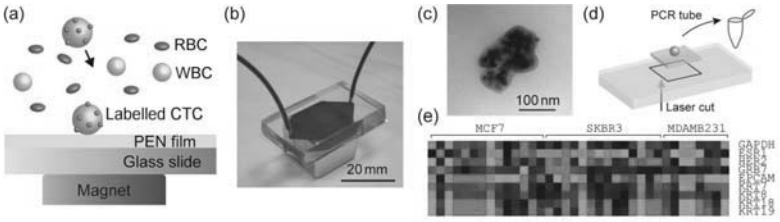
[2]The University of Texas at Austin, 1 University Station C0800, Austin, TX 78712-0238, USA
*hoshino@engr uconn edu, **john zhang@engr utexas edu

We have demonstrated a microfluidic immunomagnetic assay with the downstream single-cell polymerase chain reaction (PCR) analysis of circulating tumor cells (CTCs) CTCs are cells that have detached from a primary tumor and circulate in the blood stream Detection of CTCs may provide important information for possible early cancer detection and decisions on individualized treatment. CTCs are challenging to study for two reasons: a low cancer-blood cell ratio (between 1 and 10^7) and the number of cancer cells often less than 5 in 5-10 mL of the patient's blood PCR is among the most widely utilized techniques for genomic analysis of tumors PCR has a strong potential for the analysis of CTCs because the techniques and methodology studied for tumor tissues can be applied to obtain equivalent information from CTCs Developing a single-cell PCR technique that can extract useful information from a very small number of cells is crucial A critical component for "rare cell" PCR analysis is the purity of the sample An advantage of our method is that collected cancer cells are fixed on a standard microscope glass slides and several existing microscopic observation techniques can be used before single cell PCR analysis

Figure (a) shows a diagram of the experimental setup Cancer cells are labeled with Fe_3O_4 magnetic nanoparticles (size: 100-200 nm) which are functionalized with anti-epithelial cell adhesion molecules (anti-EpCAM) As the blood sample flows through the microchip, labelled cells are captured onto a polyethylene naphthalate (PEN)-film coated glass slide Figure (b) is a photograph of the microfluidic chip Figure (c) is a TEM photograph of the magnetic nanoparticles Details of our microchip-based separation method has been reported elsewhere The capture rates for spiked experiments were demonstrated to be more than 80-90%[1] We have successfully separated cancer cells from blood samples of breast, colon, lung and prostate cancer patients at the UT Southwestern Medical Center at Dallas[2] Once a cancer cell is located by fluorescence observation, an area of about 500 μm x 500 μm of the film around the cell is cut by the laser microdissection technique (see figure (d)) A combination of detailed immunofluorescence observation and laser cutting enables selection of important cancer cells and elimination of contaminants Reverse transcription single cell qPCR analysis was performed using a commercially available high throughput system (BioMark HD System) Three different breast cancer cell lines of MCF7, SKBR7, and MDA-MB231 were tested with eight different gene sequences of GAPDH, ESR1, HER2, GRB7, EPCAM, KRT7, KRT8, KRT18, and KRT19 The result showed in figure (e) demonstrated a good match with that from a few thousand control cells, showing promise for our method of single cell separation and analysis



1 Hoshino K, Huang YY, Lane N, et al Microchip-based immunomagnetic detection of circulating tumor cells *Lab on a Chip* 2011;11(20):3449-3457
2 Huang Y, Hoshino K, Chen P, et al Immunomagnetic nanoscreening of circulating tumor cells with a motion controlled microfluidic system *Biomed Microdevices* 2013;15(4):673-681

Rapid Magnetophoretic Separation of Microalgae

Pey Yi Toh,[1] Bee Wah Ng,[1,2] Chi Han Chong,[3] Abdul Latif Ahmad,[1] Ji-Won Yang,[4] Derek Juinn Chieh Chan,[1] JitKang Lim[1,5*]

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The rising cost and dwindling reserves of fossil fuels have stimulated interest and various research efforts over the past few decades in the development of alternative energies One of the promising technologies in biofuel production is through transesterification of microalgal lipid to biodiesel Even though biodiesel from microalgae looks promising, the dewatering of microalgae culture is a major bottleneck towards the realization of any large-scale industrial processing

Here we propose the use of magnetic iron oxide nanoparticles (IONPs) for microalgae separation Magnetic collection of biofuel producing strain of microalgae *Chlorella sp.* from culture media facilitated by low magnetic field gradient was achieved in real time [1] By using a cationic polyelectrolyte poly(diallyldimethylammonium chloride) (PDDA) as a binding agent, we have successfully promoted the attachment of IONPs onto the microalgal cells Transmission and scanning electron microscopy (TEM & SEM) together with Fourier transforms infrared (FTIR) spectra analysis are employed to confirm the full attachment of PDDA functionalized IONPs onto microalgal cells and how the particles distributed on the cell's surfaces From the cross section TEM images of cells, IONPs shown the tendency to be internalized into *Chlorella sp.* cells but not affect the biofuel quality [2]

These encouraging outcomes prove the reliability of magnetophoretic separation, with 99% of separation efficiency, for microalgal biomass collection and can be implemented as an effective downstream process for biofuel production

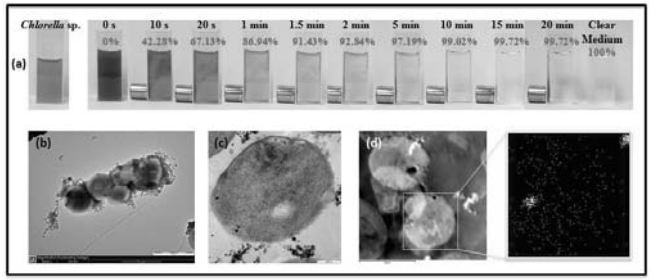

Figure 1 (a) Time lapse images showing the rapid magnetophoretic separation of microalgae, (b) microalgal cells-IONPs clusters after subjected to magnetic separation, (c) Particle attachment onto the microalgal cell, and, (d) internalization of IONPs into microalgal cells confirmed by FE elemental mapping

References:

[1] J K Lim, C J C Derek, S A Jalak, P Y Toh, N H Yasin, B W Ng, A L Ahmad, *Small* 8 (2012) 1683—1692
[2] P Y Toh, B W Ng, C H Chong, A L Ahmad, J W Yang, C J C Derek, J K Lim, *RSC Advances* 4 (2014) 4114—4121

Monitoring nanoparticle self-assembly dynamics in extreme magnetic field gradients: A new metrology for colloidal magnetic nanomaterials

L. Ye, B. Fellows, T. Pearson, Y. Cordeau*, O. T. Mefford*, and T. M. Crawford†
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***Materials Science and Engineering, Clemson University, Clemson, SC**

For clinical and biomedical applications of magnetic nanoparticles, colloidal stability of the particles is an absolute requirement for high biodistribution and bioavailability. Traditional techniques to measure this stability include light scattering and optical imaging. We have developed a new technique that provides enhanced levels of stability detection compared to these techniques. This sensitivity is obtained by utilizing optical diffraction to monitor magnetic-field directed self-assembly (MFDSA) of magnetic nanoparticles into patterned arrays. Using extreme magnetic field gradients (– 10^7 T/m) at the surface of disk drive media, our team has demonstrated a low cost technology for nanomanufacturing user-designed custom polymer nanocomposites with – 25 nm resolution [1]. Magnetic nanoparticles are attracted from a dilute colloidal suspension to assemble on the field gradient pattern. By recording a series of parallel lines, we have manufactured an all-nanoparticle diffraction grating and tested it in a calibrated spectrograph [2]. To understand the dynamics of the self-assembly process, we monitor diffracted intensity in real-time as the nanoparticles self-assemble into the grating (Figure 1 – inset) [3]. This approach works because diffraction is extremely sensitive to the underlying pattern, which was created with – 10 nm resolution by commercial magnetic recording. Solution pH, ferrofluid concentration, and nanoparticle stability are all observed to impact the dynamics of grating formation [3]. Further, Figure 1 shows that the rate of diffracted intensity increase can be strongly enhanced by adding phosphate buffered saline (PBS) to the assembly suspension. Importantly, these changes in assembly dynamics occur at PBS concentrations too low to cause measureable aggregation in the bulk colloidal fluid, as no change in scattered intensity is observed by either in-situ scattering measurement or via Dynamic Light Scattering (DLS) studies on identical colloid/PBS fluids. We hypothesize that the extreme field gradients cause local aggregation of nanoparticles at salt concentrations too weak to affect bulk colloidal stability. We have simulated intensity vs. time by solving the nanoparticle trajectories with Newtonian mechanics, and using generalized multiparticle Mie theory to predict diffracted intensity. While the simulations are similar to the assembly curves [3], more complicated dynamics are also observed that are not yet predicted by the model. In addition to identifying novel self-assembly mechanism in extreme field gradients, monitoring nanoparticle self-assembly with diffraction could provide a *new, highly sensitive probe of colloidal magnetic fluids*. Because subtle changes in particle surface coating and colloidal stability can affect long timescale aggregation, this measurement could enable a better understanding of interparticle interactions and impact commercial applications of magnetic carriers for MRI contrast, hyperthermia, and drug delivery. Finally, this real time measurement technique can provide feedback to help create unique structures for both diagnostic and therapeutic applications using the MFDSA process.

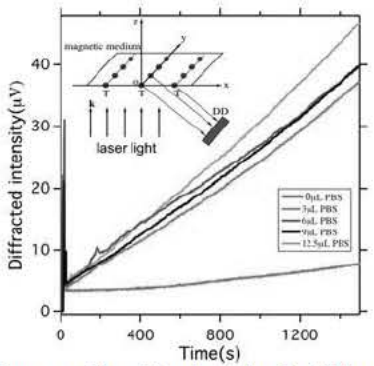

Figure 1 – Diffracted intensity vs time for differing amounts of PBS added to a dilute Fe3O4 nanoparticle solution. Note the large jump in rate of intensity increase caused by the smallest amount of PBS. Inset: Geometry for diffraction monitoring of magnetic-field directed self-assembly.

[1] J. Henderson, S. Shi, S. Cakmaktepe, and T. M. Crawford. Nanotechnology 23 185304 (2012).
[2] L. Ye, B. Terry, O. T. Mefford, C. Rinaldi, and T. M. Crawford. Optics Express, 21,1066 (2013).
[3] L. Ye, B. Qi, T. Pearson, Y. Cordeau, O. T. Mefford, and T. M. Crawford. J. Appl. Phys., 115 17B513 (2014).

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Antibody Distribution on bio-functionalized Magnetic Nanoparticles analyzed by Spatially-Resolved EELS

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Abstract

In biomedical applica ions, core-shell magnetic nanoparticles are commonly used as supports for macromolecules of biological interest. The shell, either organic or inorganic, allows in principle the use of different functionalization protocols to link a large variety of biological moieties, depending on the final purpose.
The functionalization of nanoparticles wi h antibodies makes possible the use of the nanoparticles in applications based on immuno-recognition processes, in which he particles act, for example, as carriers for targeted drug delivery, as labels for immuno-assays [1] etc. An adequate immobilization strategy is critical in order to guarantee not only the stability of the antibody binding on the nanoparticle surface, but also its correct orientation. Therefore, detailed knowledge of the functionalized nanoparticle surface is crucial when working with nanopar icle-antibody conjugates. Some information can be obtained by means of biochemical techniques but there is still a need for characterization at microscopic level.
We have made use of Spa ially Resolved Electron Energy Loss Spectroscopy (SR-EELS) using Scanning Transmission Electron Microscope (STEM) for the identification and determina ion of the spatial distribution of the components/elements of immuno-functionalized core-shell superparamagnetic magne ite nanoparticles [2] at subnanometer scale [3]. SR-EELS measurements have allowed the study and direct identifica ion of he biological moieties (protein G and anti-Horseradish peroxidase antibody, which was used as a model system) on the nanoparticle. Our findings provide information on the spatial localization/distribu ion on the nanopar icle surface. We conclude that the data obtained in this study, together with those gathered by conventional biochemistry techniques, provide insight into the efficiency and potential applications of these nanoparticles in biomedicine and related fields.

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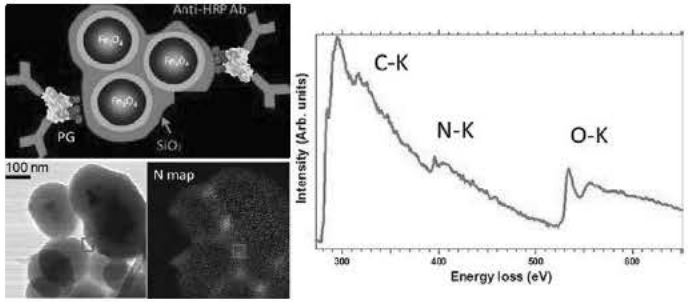

Single Particle Tracking Reveals Biphasic Transport During Nanorod Magnetophoresis Through Extracellular Matrix

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Magnetic drug targeting has been proposed as a means of efficiently targeting drugs to tumors However, the extracellular matrix (ECM) remains a significant barrier to long-range magnetophoretic transport through the tumor volume The ECM is a complex meshwork of collagen, laminin, and other proteins It is a viscoelastic, biphasic biopolymer which frequently ensnares particles as they move through the volume of a tumor While ensemble measurements of nanoparticle magnetophoresis have been reported, a single particle level understanding of magnetophoretic transport remains at large Do particles move through the ECM with constant velocities? Do they exhibit substantial motion in the direction normal to the axis of field gradient directed pulling? We perform in vitro quantification nanorod magnetophoresis through ECM based on single particle observations, and these single particle observations allow us to answer these and other questions

We investigate the transport properties of nanorods with diameters of 18, 55, and 200 nm Nanorods are grown via template guided electrodeposition, and their surfaces are modified with PEG so as to minimize adhesion to ECM proteins We find that smaller diameter particles achieve larger velocities through ECM despite experiencing smaller magnetic forces Additionally, two interesting dynamics are elucidated First, 18 nm diameter nanorods experience bimodal stick-slip motion through ECM during static field magnetophoresis, while similar bimodal transport is not observed for 55 nm nor 200 nm diameter nanorods Second, smaller particles experience larger deviations in their orientation angle with respect to the magnetic field This work elucidates important dynamics of nanoparticle transport through complex, porous biomaterials that may go unnoticed during ensemble measurements We feel our observations of individual particles move through the complex structure of ECM in vitro provides several interesting talking points fundamental to the study of magnetophoresis in biology and medicine

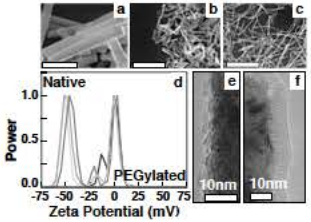

Figure 1: Scanning electron micrographs of nickel nanorods with nominal diameters of (a) 200 nm, (b) 55 nm, and (c) 18 nm Scale bars in (a) – (c) are 1 μm Zeta potential measurements of rods reveal drastic differences before and after PEGylation (d) TEM images reveal the rough native oxide surface (e) and the smooth, functionalized PEG surface (f)

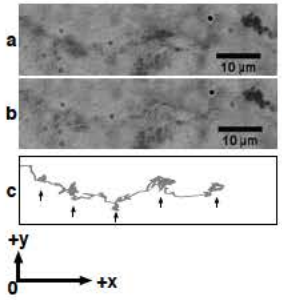

Figure 2: Acceleration-deceleration motion observed for 18 nm diameter nanorods during magnetophoresis (a) Minimum intensity projections of nanorods moving through ECM (1 frame per second) can be tracked (b) and demonstrates locations of significant steric hindrance (c, arrows) Particle motion, and direction of increasing magnetic gradient, is in the +x direction Significant motion in the +/-y directions, as well as motion in the –x direction, elucidates the complexity of magnetophoretic transport for small diameter nanorods in dense polymer networks

High Iron Content Magnetic Nanoparticles as Effective Delivery Vehicles of Anti-cancer Drugs into a Solid Tumour Model

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Diffusion of active cytotoxic agents throughout an entire solid tumour is a particular challenge to successful drug delivery. Anti-cancer chemotherapeutic drugs such as doxorubicin and mitoxantrone only penetrate to about 70 microns from a blood supply while the rapid growth of solid tumours leads to poor development of vasculature with much tumour tissue being considerably more distant from a blood vessel. Considerable effort has been expended to design effective and efficient targeting and controlled release systems for cancer treatment using nanomaterials to incorporate drugs by conjugation or encapsulation. However, poor nanoparticle stability and ineffective or uncontrolled drug release has impacted adversely on their effectiveness. Moreover, release of conjugated active compounds from particles is often problematic, resulting in cellular accumulation of the active compound in lysosomes or failure of the active compound to reach the site of effective action.[1-4] However, notwithstanding these efforts, without drug penetration of the entire tumour mass chemptherapy will ultimately be ineffective.

We present a novel approach using custom designed superparamagnetic iron oxide (γ-Fe_2O_3) nanoparticles (SPIONs) to co-administer with chemotherapy drugs. Our SPIONs were stabilized either with only one type of the steric stabilizer (homogenous coating) or with a heterogeneous mix of the steric stabilizers with different end functionality. The SPIONs has iron content of as high as 55 weight % and are stable under physiological conditions. Figure 1 shows that optimised SPIONs facilitate and enhance penetration of doxorubicin though out a solid tumour, but do not alter the cellular interaction mechanism of the cytotoxin. The effectiveness of the nanoparticle/drug co-administration is strongly governed by both the functionalized end group and the composition of the polymeric stabilizers and is unique for each drug.

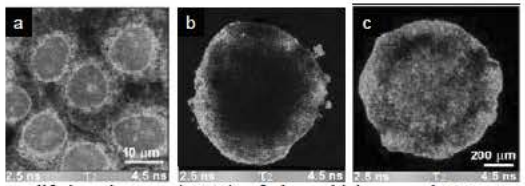

Figure 1: Fluorescence lifetime images (FLIM) of doxorubicin treated DLD-1 colon cancer cells in monolayers (a); in spheroids without SPIONs (b) or with SPIONs co-administration (c) The false colour FLIM image of the cell monolayer treated with Dox allows for the cellular localizations of different lifetimes to be easily observed: the orange colour indicates nuclear Dox, green indicates cytoplasmic localized Dox

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Dendrimer-Magnetic Nanoparticles as Multiple Stimuli Responsive and Enzymatic Drug Delivery Vehicle

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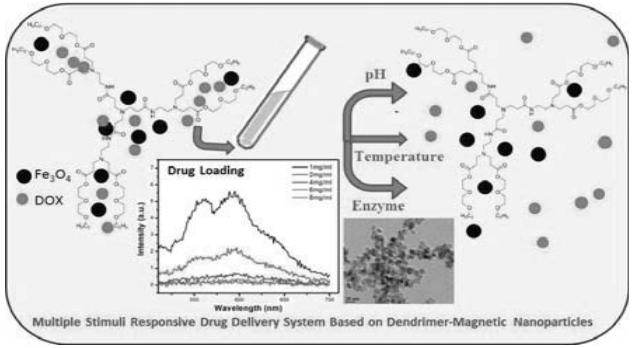
The unique ability of iron oxide magnetic nanoparticles (MNPs) to be guided by an external magnetic field has been utilized for magnetic resonance imaging (MRI), and targeted drug and gene delivery The motivation for this study is to combine the functions of longevity (PEGylation in dendrimer), targetability (use of MNP to assist in magnetic guidance to tumor site) and stimuli sensitivity (pH, temperature) in addition to leveraging the tumor microenvironment (acidic pH, over-expression of enzymes promoting degradation)

Iron oxide nanoparticles were synthesized by co-precipitation method and were stabilized by (poly)ethylene glycol-functionalized PAMAM dendrimers having six end-grafted ethylene glycol ether-tentacles of type $CH_2CH_2C(O)O-(CH_2CH_2O)_2C_2H_5$, (designated as PEG-PAMAM-MNPs) The XRD pattern of PEG-PAMAM-MNPs indicates formation of a single-phase Fe_3O_4 inverse spinel structure TEM shows particles are spherical though irregular shaped with mean size of ~7 nm and the nanoparticles exhibited typical superparamagnetic behavior without hysteresis or remanence The BET surface area, total pore volume and average pore diameter are 138 6 m^2/g, 0 4 cm^3/g and 109 4 Å, respectively

The interaction of doxorubicin (DOX) with PEG-PAMAM-MNPs is evident from the predominant quenching of DOX fluorescence The loading efficiency is strongly dependent on the ratio of particles to DOX which is attributed to the electrostatic interactions between positively charged DOX and negatively charged carboxyl and ethylene glycol moieties of the dendrimers A maximum of ~ 98 7% drug loading efficiency (w/w) was achieved A sustained release of ~25% of loaded drug in acetate buffer (pH 4 3) against PBS (pH 7 3) were observed after 70 h *In-vitro* drug release goes up to 30% at 43°C, a possible hyperthermic temperature Enzyme cathepsin B has also been used as effective biomolecule to trigger drug delivery from the system with a sustained release of ~45% for 72 h Thus, in conditions simulating the extra-cellular matrix or lysosomes of target cells, it is inferred that the enzyme cleaves the dendrimer, promoting a faster release rate The concept of applying a stimulus (*via* pH or temperature change) followed by enzymatic breakdown of the dendritic system is a new approach to develop a controlled drug release system, where both sustained and burst release of drug is achieved



Schematic representation of multi responsive PEG-PAMAM-MNPs

Interaction of ferromagnetic and superconducting permanent magnets - superconducting levitation

Prof. Dr. Ludwig Schultz
Professor, Director of the Institute for Metallic Materials, IFW Dresden Department of Materials

Abstract

New means of urban transportation and logistics will become realistic with superconducting magnetic bearings using nanostructured bulk high temperature superconductors. The advantage of superconducting magnetic levitation is that it works passively stable without any electronic control but with attracting and repelling forces to suspend a vehicle pendant or standing upright from zero to high speed - perfect conditions for the idea of rail-bound individual transport with cabins for 4 - 5 passengers requested call by call.

In Dresden the world largest research and test facility for transport systems using HTS bulk material in the levitation and guidance system in combination with a permanent magnet track was put into operation using a vehicle for 2 passengers running on an 80 m long oval driveway. In the presentation the superconducting materials as well as the principle of superconducting levitation by flux pinning in high temperature superconductors will be described. Future directions of superconductivity-based magnetic levitation and bearing for automation technology, transportation and medical treatment under enhanced gravity will be given.

Manufacturing Ordered BioComposites with Weak Magnetic Fields

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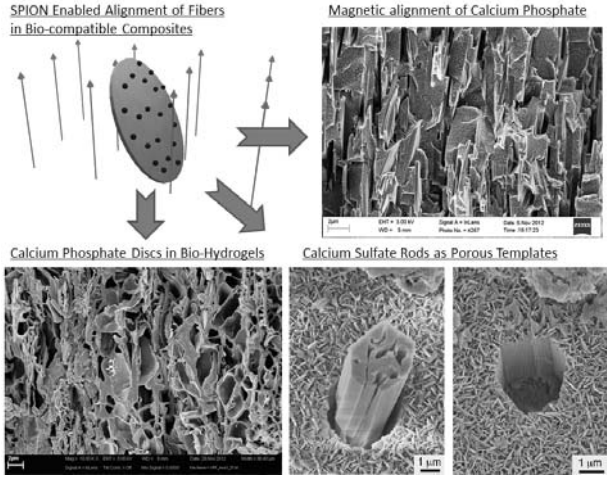
Recently, we have found an ultra-high magnetic response in stiff anisotropic particles by adsorbing nominal amounts of magnetite nanoparticles onto the surface of the particle [1] This modification allows for the remote control of particle orientation and spatial positioning under magnetic fields only an order of magnitude larger than the Earth's magnetic field This level of control, among numerous exciting possibilities, can lead to the positioning of particle reinforcement in manmade materials that mimics the structures found in natural systems such as seashells or mammalian bone [2]

Here, we apply this technique to produce a new family of biocomposites Our overarching aim in this work is to develop biocompatible composite materials that exhibit both high strength for bearing load and high water content for cellular viability and bioactivity We target a range of strong biocompatible particles from calcium phosphate rods and platelets to calcium sulfate fibers that could serve to reinforce biopolymers in vivo We demonstrate the creation of aligned particle architectures in a variety of matrices including calcium cements and alginate and chitosan hydrogels

We have developed an energy model for these particle suspensions that explain this ultra-high response and suggest the key parameters essential in these systems We take on the case of magnetic alignment under shear, which dominates discontinuous fiber production We determine that magnetic alignment can be made significant enough to overcome particle alignment during typical extrusion processes that are best described with Jeffrey orbitals and average orientation tensors This work offers a way forward in recreating these defined reinforcement architectures within manufactured polymers



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Magnetic nanoparticles assisted modulation of the vascular cGMP pathway

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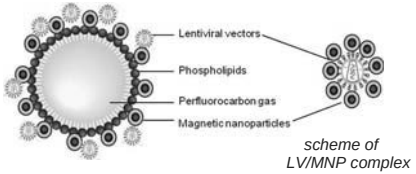
Abstract

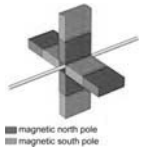
Cyclic GMP (cGMP) is a major mediator of relaxation in the vascular system. It is produced by the enzyme soluble Guanylyl Cyclase (sGC) in response to nitric oxide (NO) from neighbouring endothelial cells, and activates Protein Kinase G (PKG), which in turn mediates relaxation through phosophorylation of various targets. One of the major substrates of PKG is the VAsodilator-Stimulated Phosphoprotein (VASP). VASP is a member of the Ena/VASP protein family together with Ena/VASP-like protein (Evl) and Mammalian enabled protein (Mena). Recent studies show that VASP-deficient brown adipocytes have an increased activity of the small GTPase and Ena/VASP binding partner Rac1 and elevated levels of sGC. These data suggest a regulatory role for VASP in cGMP-mediated processes. Preliminary data acquired from the analysis of VASP-deficient ($VASP^{-/-}$) mice provide also evidence for the importance of VASP in the cGMP mediated relaxation pathway. However, the role of VASP in vascular smooth muscle relaxation is currently unknown. Furthermore, we are interested in the regulation of NO production in the vascular endothelium. For both approaches, functional measurements are required. Therefore, we use an *ex vivo* perfusion system that enables homogenous transduction of a perfused murine aorta. This is possible due to a special magnetic configuration that results in a homogeneous and radially symmetric gradient of the magnetic flux density in the aorta. The aorta is perfused with complexes of lentiviral vectors (LVs) and magnetic nanoparticles (MNPs) or MNP loaded microbubbles that are attracted in the magnetic field, enabling an efficient and homogenous transduction of the vessel. Besides using the intact aorta to target the endothelium, the vessel can also be denuded by removing the endothelium for targeting the smooth muscle cells. The genetically modified intact or denuded aorta can subsequently be subjected to contractility and relaxation measurements using a wire myograph.

The MNPs of the core-shell type have a ferrimagnetic core (Fe_3O_4) surrounded by different coatings. We combine these MNPs with LVs that are versatile tools for genetic modification and stable long term expression as they are able to integrate into the host genome. The applied microbubbles consist of a lipid layer that contain a high molecular weight hydrophobic gas (octafluorpropane) in the interior and can be decorated with MNPs and LVs, making them efficient gene transfer vehicles that can be attracted by a magnetic field. Through subsequent destruction of the bubbles using ultrasound application they release their cargo. By applying LVs encoding e.g. for constitutively active Rac, VASP or PKG or different shRNAs in the *ex vivo* loop system, the functional readout will give deeper insights into the cGMP pathway in vessels which in turn is of great importance in the development of new therapies for vascular homeostasis.



scheme of LV / MNP decorated microbubble

scheme of LV/MNP complex



magnet configuration surrounding the vessel as used in ex vivo loop system

Magnetic Nanoparticles as a Delivery System for Adipose Tissue-Specific Rosiglitazone Targeting in Type 2 Diabetes

Kathy Saatchi[2], Sarah Tod[1], Donna Leung[2], Kenton Nicholson[1], Christian Buchwalder[2], Veronika Schmitt[2], Urs O. Häfeli[2], Sarah L. Gray[1*]

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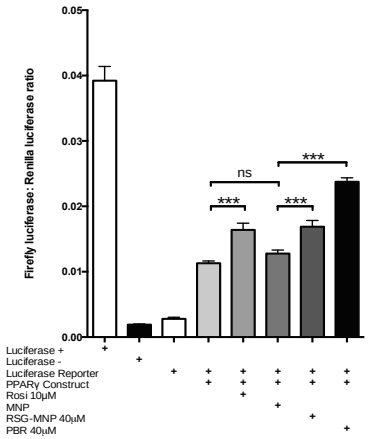
Thiazolidinediones (TZDs), such as rosiglitazone (RSG) are high affinity ligands for the nuclear receptor, peroxisome proliferator activated receptor gamma (PPARγ). TZDs induce potent anti-diabetic effects in Type 2 diabetics by enhancing insulin action. Much of the anti-diabetic effects of TZDs are mediated by PPARγ activation in adipose tissue, improving lipid and glucose clearance by activating adipocyte differentiation and lipogenesis and promoting an insulin sensitizing adipokine profile (Ahmadian et al., 2013). However since 2007, TZD use has been significantly limited due to a potential increase in cardiovascular side effects when administered systemically (Lago et al., 2007). To reduce or even eliminate these side effects, it is hypothesized that targeted TZD delivery to adipose tissue is desirable.

To accomplish this, magnetic nanoparticles (MNPs) coated with alendronic acid (Al) or undecylenic acid (Un) were assessed for their suitability as therapeutic delivery agents for adipose tissue-targeted RSG therapy. Al-MNPs and Un-MNPs were incubated in concentrated solutions of RSG (350 µg/ml in water) to allow successful adhesion of drug molecules to surface coatings by lipophilic interactions. Thereafter, MNPs were magnetically separated from binding solutions, washed, and subjected to a timed release study under sink conditions in PBS. High performance liquid chromatography was employed to measure the amount of drug bound and released. Results show that RSG adsorbed to and was then released from both MNP types. We observed a rapid burst release (within the first 6hrs) and by 24hrs 21.2±4.9% and 8.36±0.98% of bound RSG was released from Al- and Un-MNPs respectively. MTT assays revealed that neither Al- nor Un-MNPs were cytotoxic to two beta-cell lines (INS-1 and Min6 cells). However, a dose independent effect on cell viability was found in 3T3L1 pre-adipocytes. RSG-UnMNPs were shown to bind and activate PPARγ in HEPA1-6 murine liver cells using a PPARγ response element (PPRE)-luciferase reporter assay. Additionally, we have assessed the ability of RSG-MNPs to target adipose tissue in a rodent model of obesity using *in vivo* imaging (SPEC/CT) of radiolabelled RSG-MNPs. Our results suggest that MNPs are a viable delivery agent to target RSG to adipose tissue. Future studies aim at assessing the effect of adipose-targeted RSG-MNP therapy in a rodent model of obesity induced Type 2 diabetes.



Magnetic antibody-linked nanomatchmakers for therapeutic cell targeting

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A central challenge in therapeutics is how to achieve selective, targeted cell-cell interactions. Conventional cell therapy is limited by inefficient interaction between potentially beneficial cells and the injured tissue. In the case of ischemic injury (e.g., heart attack or peripheral vascular disease), we seek to bring healing cells together with injured cells more effectively. Novel methods are required to attract the right cells to their targets, and to engage them with the target tissue. Here we put forward the concept of *magnetic antibody-linked nanomatchmakers for therapeutic cell targeting*. Iron nanoparticles, which can be detected by magnetic resonance imaging (MRI) and enriched by magnetic focusing, are coated with antibodies directed against the therapeutic cell and the disease target. The resultant nanocomplex enables molecular matchmaking, physical targeting, and noninvasive imaging. By varying the antibodies and/or adding a drug payload onto the iron core, the strategy is broadly generalizable. Moreover, translatability to patients should be possible, given that both the iron nanocore and recombinant human antibodies are widely utilized clinically.

The underlying logic is as follows: 1) Disease occurs when an insult outpaces the organism's ability to resist that insult. 2) Whether the inciting event is a pathogen, tumor growth, or ischemia, natural defenses do exist, but they may not suffice to repel or offset the threat. 3) At least part of the deficit is due to ineffective co-localization of healing cells and injured cells. 4) Nanoparticles engineered specifically to co-localize healing cells and injured cells ("nanomatchmakers") have the potential to accelerate the healing process. 5) Utilizing multiple distinct principles (molecular targeting plus physical enrichment) to achieve co-localization will be superior to reliance on a single principle of action. If the logic holds, then the development of novel nanomatchmakers has the potential to create an important treatment paradigm of general applicability.

Desirable features of a nanomatchmaker include: 1) Ability to tailor particles for precise cellular matchmaking at a molecular level; 2) Capacity for enrichment in diseased tissue by simple physical principles, above and beyond molecular targeting; 3) Detectability by noninvasive imaging; 4) Ease of delivery; 5) Ease of manufacturing; 6) Ready translatability to the clinic. At the proof-of-concept level, we have developed a prototype nanomatchmaker which fulfills all the criteria listed above. The prototype achieves *in vivo* cell-mediated tissue repair, imaging and targeted enrichment without transplantation into the target organ. Iron nanoparticles are conjugated with two types of antibodies (one against antigens on healing cells, the other directed at injured cells) to produce a magnetic bi-functional cell engager (MagBICE). MagBICE serves as a matchmaker to bring the two cells together for therapeutic intent, and the iron core enables imaging as well as physical enrichment. We treated acute myocardial infarction (MI) by targeting bone marrow-derived stem cells (expressing CD45) to injured cardiomyocytes (expressing myosin light chain [MLC]). *In vitro*, MagBICE exhibited minimal cytotoxicity and specifically bound bone marrow-derived stem cells and injured cardiomyocytes, conjoining the two. In rats with MI, intravenously-infused MagBICE concentrated in injured heart muscle, as visualized by MRI. Furthermore, MagBICE captured circulating bone marrow-derived stem cells and targeted these cells to the injured heart tissue, reducing scar formation and improving pump function. Targeting was further enhanced by magnetic attraction, with a magnet placed over the injured heart. Thus, we have achieved significant therapeutic efficacy, rivaling that of conventional cell therapy, with a novel intravenously-infused nanoparticle.

Denaturation-Resistant Magnetic-Fluorescent Colloidal Superstructures Assembled via the Proteinaceous Barnase Barstar Interface

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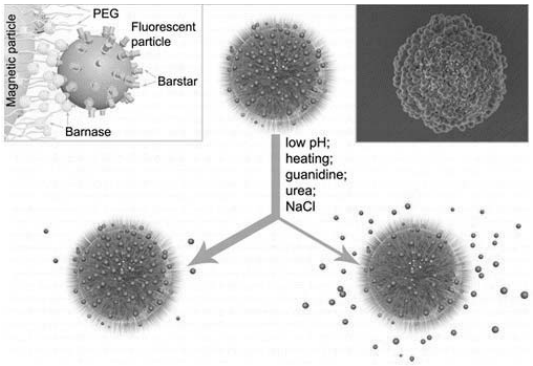
To date, a number of biomolecule-mediated nanoparticle self-assembly systems have been developed that are amenable to controllable disassembly under relatively gentle conditions. However, for some applications such as design of self-assembled multifunctional theragnostic agents, high stability of the assembled structures can be of primary importance. Here, we report extraordinarily high durability of protein-assisted nanoparticle self-assembly systems yielding bifunctional (magnetic & fluorescent) colloidal superstructures resistant to extreme denaturing conditions intolerable for most proteins (e.g., high concentrations of chaotropic agents, high temperature) [1].

Use of proteinaceous "molecular glues" for nanoparticle self-assembly purposes is of interest due to the advantages of introducing new functionalities to the self-assembled structures via additional protein modules fused to initial molecules mediating assembly. Among them, we find the barnase-barstar system (BBS) particularly noteworthy due to benefits offered by genetic engineering of this entirely protein-based system and ease of heterologous prokaryotic expression of the proteins in ample amounts [2].

In this work, we address the question of stability of the BBS-"glued" assemblies subject to destruction. To this end, we test their behavior under severe protein denaturing conditions such as high temperature and low pH as well as high salt and chaotropic agent (urea and guanidinium hydrochloride) concentrations.

Experiments show that the obtained constructs possess unusual stability and tolerate conditions far beyond physiological ones. The BBS was also compared to other widely used self-assembly systems, in terms of resistance of the preassembled structures to the extreme conditions as well as with respect to their ability to mediate assembly of the initial conjugates involving the components of these systems.



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Performance of three different clinical magnetic nanoparticle tracers for sentinel lymph node detection

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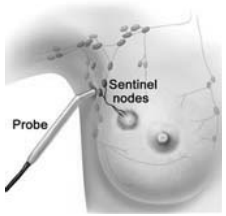
As most solid cancers, breast cancer predominantly metastasizes via the lymphatic system. The presence of metastases is diagnosed by resection of the sentinel lymph nodes (SLNs), which are the first draining lymph nodes from the primary tumour, followed by histological analysis. SLNs can be localized and resected with a hand-held gamma probe after injection of a radioisotope interstitially into the breast. However, the use of radioisotopes exposes patient and health care workers to radiation, is heavily controlled by legislation.

A novel magnetic technique without these drawbacks, using a magnetic nanoparticle tracer and a handheld magnetometer (SentiMAG, Endomagnetics LTD.), has recently been developed [1, 2]. In these trials a magnetic tracer with a hydrodynamic particle size of 60nm was used. The ideal magnetic is rapidly distributed to the SLNs, retained in the first nodes reached and accumulates in high concentration in these nodes and not in higher echelon nodes. We evaluated the performance of three different magnetic tracers, approved for use in humans, on these aspects. Rienso, Sienna+ and Endorem, with hydrodynamic particle sizes of 20, 60 and 80-150 nm respectively, were diluted to 11.2 mg Fe/mL. In 18 mini-pigs (6 per tracer), 0.5 mL of magnetic tracer was injected into the third inguinal mammary gland, bilaterally. Transcutaneous magnetometer measurements of the draining lymph node basins were performed to assess the speed of uptake of the different tracers. After 4 h the SLNs were identified with the magnetometer and excised. Quantification of tracer uptake in each node was undertaken using VSM measurements.

SLNs were successfully identified in all 36 procedures. The smaller Rienso tracer identified a mean of 2.9 nodes (1-5) per procedure, the intermediate sized Sienna+ 1.8 nodes (1-4) and the larger Endorem 1.7 nodes (1-4). The mean iron content of the SLNs identified by Rienso was lower compared to Sienna+ and Endorem. Transcutaneous magnetometer measurements indicated that the intermediate sized Sienna+ tracer is distributed most rapidly from the injection site to the SLNs, uptake was noticed within 10 minutes in all Sienna+ procedures.

In conclusion, the 60 nm hydrodynamical diameter Sienna+ is currently the most suitable tracer for magnetic SLN detection with the SentiMAG handheld magnetometer. It distributes rapidly from the injection site to the SLNs, is retained in the first nodes reached, and accumulates in high concentrations.



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Highly Effective Inhibition of Lung Cancer Growth and Metastasis by Systemic Delivery of siRNA via Magnetic Mesoporous Silica-based Nanocarrier

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Lung cancer has been the leading type of cancers with regard to mortality and mobility New versions of RNAi-based therapy are greatly required to tackle the challenges of lung cancer In this study, we developed a novel siRNA delivery vector based on our magnetic mesoporous silica nanoparticles (M-MSNs) platform This nanocarrier was constructed by loading siRNAs into the mesopores of M-MSNs, followed by polyethylenimine (PEI) capping, PEGylation and fusogenic peptide KALA modification The resultant delivery system exhibited prolonged half-life in bloodstream, enhanced cell membrane translocation and endosomal escapablity, and favorable tissue biocompatibility and biosafety Systemic application of vascular endothelial growth factor (VEGF) siRNA via this nanocarrier resulted in remarkable tumor suppression, both in subdermal and orthotopic lung cancer models, while tumor metastasis was also significantly reduced, overall leading to improved survival In addition, the magnetic core of the particles and the functionalized fluorescence markers conveniently enabled *in vivo* imaging of target tissues Taken together, this M-MSNs-based siRNA delivery vehicle has shown very favorable applicability for cancer therapy

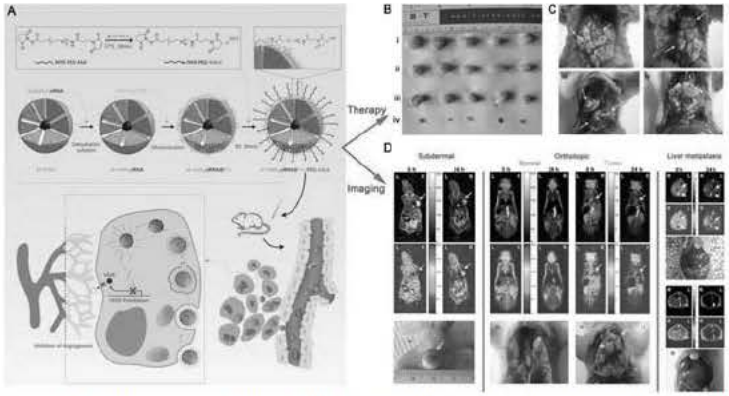

Figure. (A) Schematic representation of the design of this work: synthesis and application of this nanocarrier Photographs of tumor tissues were collected at the end of experiments from (B) subdermal model and (C) orthtopic model (D) Monitoring nanocarrier delivery into tumors in subdermal and orthotopic (both tumor *in situ* and metastasis) models by T_2-weighted MR imaging (MRI) The four groups are: i) saline; ii) M-MSN_NC siRNA@PEI-PEG-KALA; iii) M-MSN@PEI-PEG-KALA and iv) M-MSN_VEGF siRNA@PEI-PEG-KALA

Manipulating Signaling Proteins via Magnetic Particles for Remote Cell Control

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Magnetic nanoparticles (MNP's), in particular iron oxides, represent an attractive option for biomedical research and clinical applications as they can be remotely manipulated via external applied magnetic fields. MNP's are currently used as MRI contrast agents and are in use in clinical trials of magnetic fluid hyperthermia (MFH) in Europe. Recent MFH studies have shown experimentally that surface heating (Magnetically-Mediated Energy Delivery - MAGMED) occurs under alternating fields where bulk solution heating was not observed. [1][2] This highly localized heating phenomena offers a unique opportunity to deliver energy to surface bound ligands as a mechanism of remote control over biological molecules. This offers the possibility of manipulating the activity of molecules remotely *in vivo* using externally applied magnetic fields.

In addition, magneto-mechanical forces can be applied to magnetic particles targeted to cell membrane receptors via the application of external, high gradient magnetic fields. To study the downstream effects, signaling molecules are monitored during the experiment. Ca^{2}, one of the more prevalent secondary messengers, proves useful for demonstrating magneto-mechanical actuation via release of intracellular calcium stores or activation of mechanosensitive ion channels. Intracellular concentrations of Ca^{2} are tightly regulated, and small changes in cellular environment, physical or chemical, can result in phenotypic cellular changes. [3] Previous studies have shown that mechanical stimuli can induce calcium changes within cells using magnetic microparticles subjected to magnetic field gradients. [4] We have utilized novel, laser-machined, high gradient NdFeB needles with a 100 µm tip diameter to actuate magnetic particles tagged to surface receptors. Fluo-4-AM, an intracellular Ca^{2} dye, increases its fluorescence 100-fold upon binding Ca^{2}, allowing for real time monitoring of the signaling pathway via fluorescence microscopy and time lapse image capture. We have shown successful activation of membrane receptors via magneto-mechanical actuation *in vitro* utilizing micromanipulator controlled NdFeB magnetic needles and are currently developing strategies for activation and deactivation of additional cell signaling molecules.

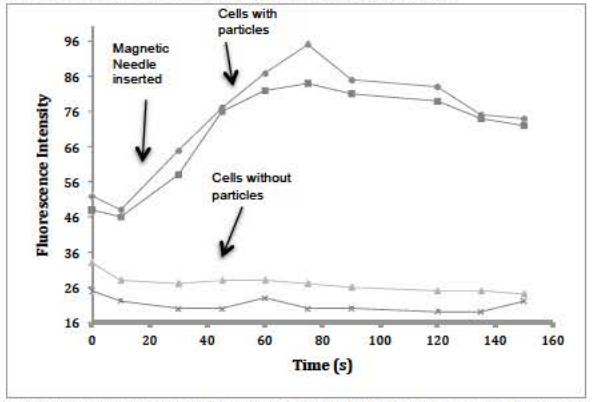

Figure 1: Ca^{2} fluorescence intensity as a function of time following micro-magnetic needle actuation

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Responsive Core-Shell Nanoparticles for Medical Applications

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Abstract

The convergence of responsive organic moieties with magnetic nanosized objects offers various application perceptions in the biomedical area as therapeutic or diagnostic agents. The talk will summarize recent developments with respect to site-specific or on-demand activity of nanoscopic magnetic carriers with a focus on biocatalytic systems and the delivery of bioactive small molecules. Combining concepts from polymer and colloid chemistry and material science, we are engaged in the development of novel perspectives to get organic-inorganic hybrid nanostructures into biological interaction.

A Novel Rotating-Crystal Magneto-Optic Technique for Malaria Diagnosis

Stephan Karl[1*], Agnes Orban[2], Adam Butykai[2], Wasan Forsyth[1], Danika Hill[1], Louis Schofield[1], Ivo Mueller[1], Thomas Haenscheid[3], Istvan Kezsmarki[2]

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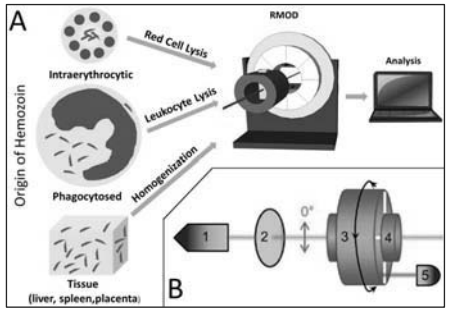
Malaria killed approximately 600,000 people in 2012. Efficient diagnostic tools are a cornerstone of malaria control. Currently used diagnostic tests either lack sensitivity or are too expensive to afford for resource limited countries, which bear most of the malaria burden.

We have developed a novel rotating-crystal, magneto-optic diagnostic (RMOD) device for malaria diagnosis and tested it under laboratory conditions and on blood samples collected from returned travellers with malaria infections. The RMOD technique is based on detecting *hemozoin*, a by-product of malaria parasite metabolism inside infected red blood cells. Hemozoin is a crystalline heme compound that can be found not only inside red blood cells but also in leukocytes and tissues of infected individuals (Figure). It exhibits nearly ideal paramagnetic properties. Due to their elongated shape, hemozoin crystals align when exposed to a strong, homogenous magnetic field. When this field is rotated, the hemozoin crystals follow the rotation in a manner that is dependent on crystal-size and the viscosity of the sample suspension. This rotation is detected optically using a laser diode and a detector. The RMOD technique is easy to perform and does not require additional expensive reagents.

We have shown that the RMOD technique has a detection threshold for malaria parasites exceeding that of light microscopy (~10-50 parasites per microliter of blood), the technique most widely used for malaria diagnosis. Furthermore, we have shown that parasite maturation could be measured using RMOD methodology at unprecedentedly low parasite levels and in a clinically relevant time-frame (<6h). Therefore, RMOD represents a promising technology not only to diagnose malaria but also to develop novel, convenient and very sensitive ways to measure parasite maturation in antimalarial drug susceptibility assays. In the future, this may make it possible to customize antimalarial treatment based on the resistance profile of the infecting parasite strain.



Panel A: Origins of Hemozoin. Hemozoin can be found in red blood cells infected with malaria parasites (*Plasmodium sp.),* in leukocytes and in certain tissues. **Panel B: RMOD technique.** Polarized light from a laser diode (1,2) passes through the sample placed inside a rotating magnetic field (3,4). Synchronous rotation of hemozoin crystals result in a hemozoin concentration-dependent signal (5).

Evaluating Metastatic Potential by the Cell Magneto-Rotation Method

Remy Elbez, Hernan Roca, Ken Pienta and Raoul Kopelman
The University of Michigan, Ann Arbor, MI

The Problem: Over the past decades, it has become accepted that cancer turns lethal mostly because of metastatic spreads toward other tissues. While the body, with treatment, can fight one localized tumor, the battle becomes more unbalanced as soon as other organs are also colonized and cease to function optimally. Therefore, controlling metastasis, by stopping malignant cell migration, would significantly improve the chances of survival of patients, as well as their quality of life, due to a restricted domain of tissues bearing tumors. However, most therapies focus on a reduction of the tumor volume as a criterion for treatment success, but, in many cases, unfortunately, **current therapy fails to detect/neutralize the cells that are likely to regenerate a tumor, such as the Cancer Stem Cells (CSCs).** In addition, targeted therapies usually stress one particular kind of markers, but, then again, they may become powerless against rapid mutations of the cancer. Instead of looking for particular markers, we believe that monitoring what cancer cells do, rather than what they exhibit (i.e. their surface markers), could help identify the most aggressive cells, among the general cancer cell population. By providing the opportunity to extract common patterns of metastatic cells, one could potentially bypass the effects of inevitable mutations and prevent both metastatic spread and a relapse of the patient, sometimes years later. **Therefore, a quantitative method for evaluating the metastatic potential of individual cells is badly needed.**

The technology: Towards achieving the above scheme, we designed the **Cell Magneto-rotation (CM)** method, by which one can monitor the shapes of suspended single cancer cells, without the cells being attached. Cells are magnetized using superparamagnetic nanoparticles, and can be actuated by an external rotating magnetic field. Combining the changes in rotation speed with image analysis for each of the single cells we image (between 100 and 200 at a time), we can monitor changes in morphology (e.g. turning amoeboid or protrusive) that we relate to their metastatic potential. More specifically, our goal is to detect how the Epithelial to Mesenchymal Transition (EMT), one of the critical transforming steps that a cell undergoes to become metastatic, affects the patterns of morphology changes in cells. Most of the detection methods available today either rely solely on biomarkers, which, as mentioned, may evolve and change during the course of a therapy, and/or on cells attached to a surface. Contrary to the latter option, with CM, we can identify specific behavior in real time and detect minute changes in the shape of the suspended cell. This could as well provide a very precious insight into **what makes a Circulating Cancer Cell (CTC) metastatic, its metastatic potential, and what agent could stop or neutralize it,** either before entering the bloodstream, or by preventing its attachment to the endothelial wall.

Highlights of progress: So far, we have successfully shown that **CM is harmless to the cells, is able to detect, in real time, morphology changes in single cancer cells, especially changes that characterize their metastatic potential, and is able to monitor cells' response to a chemical stressor in their environment (a drug or a toxic agent).** Using a multiplexed trapping device, we measured the repartition of different morphological types of suspended cells among an epithelial PC-3 cell line and a (stable through passages) mesenchymal PC-3 cell line (that was obtained through EMT of the previous PC-3 cell line). Our results showed that mesenchymal cells rely on protrusions to probe their environment and move, while epithelial cells are mostly round or use small surface blebs. However, when we disturbed the cytoskeletal structure using different inhibitors, mesenchymal either turned toward a fast shape-changing amoeboid-type, or to a round shape cell. These cells, epithelial and mesenchymal, were shown to share the same genotype, but have a very different phenotype. In order to increase the volume of data that we can treat, and to increase the accuracy of our pattern recognition, we are currently running cell identifications on a computer cluster. We are also investigating potential correlations between cell phenotypes and their motility characteristics.

We acknowledgeNIH/NCI/ IMAT grant R21 CA160157 (RK & KP).

Interaction of Dynamic Magnetic Fields with Magnetic Particles Immobilized at Lysosomes

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Abstract

In this study superparamagnetic iron oxide particles (Spions) were employed. The Spions were loaded with antibodies for the lysosomal membrane and moved by a dynamic magnet field above an adherent cell layer (Figure 1). A virus trying to invade a cell is emulated by the particle's rolling motion above the cell's surface. An invasion of the beads into the cells was finally accomplished endocytotically (First step). Then, inside the cells, close to the lysosomal membrane, the Spions were immobilized due to a covalent antigen/ant body binding. A following wiggle action (Second step) could permeabilize the lysosomal membrane, setting free aggressive enzymes inside the cytosol, which provoked apoptosis.

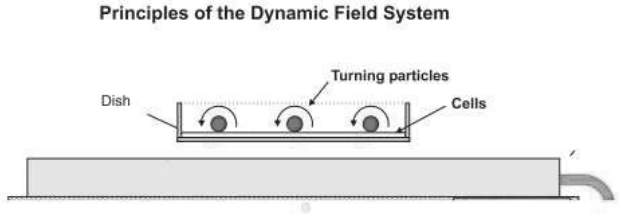

Fig.1 Principle of he first step, where he particles are moved above the cell layer by a magnetic dynamic field, herewith copying a virus which is infecting a cell.

Magnetic separation of algae expressing enhanced intracellular ferritin concentration

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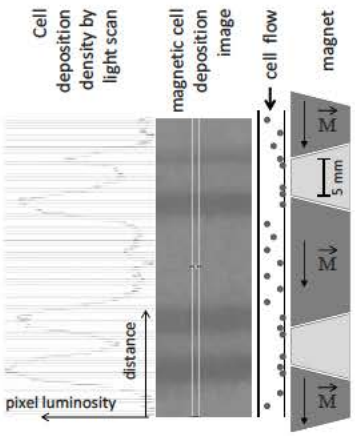
Algae were investigated in the past as a potential source of biofuel and other useful chemical derivatives. An important step in algae processing is dewatering of cellular mass prior to lipid extraction. Magnetic separation of algae has been proposed by others based on iron oxide nanoparticle binding to cells. We have investigated feasibility of magnetic separation based on the presence of natural iron store in the cell, the ferritin, based on development of *Auxenochlorella protothecoides* (*A. p.*) strains with enhanced assimilation, storage and tolerance to paramagnetic elements. A number of *A. p.* constructs were developed and tested for inserted genes and for increased cell magnetophoretic mobility (by cell tracking velocimetry, CTV). The cells were cultured in increasing concentration of soluble iron compound ($FeCl_3$ EDTA, from 1x to 8x compared to baseline) in culture media (Sueoka's high salt media with a modified trace metals solution and added vitamin B1) in order to increase their intracellular iron concentration. The cell magnetic separation conditions were tested using a thin rectangular channel pressed against interpolar gaps of a permanent magnet forming a separation system of a well-defined fluid flow and magnetic fringing field geometry (dubbed magnetic deposition microscopy, or MDM, Figure).



Following culture, the cell suspension was pumped through the MDM system (Figure) to test for the presence of the magnetically susceptible cells. The presence of magnetic cells in suspension was detected by formation of characteristic deposition bands at the edges of the magnet interpolar gaps (Figure) amenable to optical scanning and microscopic examination. The results were corroborated by inductively coupled plasma mass spectroscopy (ICP-MS) and by cell tracking velocimetry (CTV) confirming increasing cellular Fe uptake with increasing Fe concentration in the culture media in wild type strain (shown in Figure) and in selected genetically modified constructs. The well controlled field and flow parameters of the MDM analysis allowed theoretical modeling of the magnetic cell separation process and extrapolation of key magnetic separation parameters to industrial scale algae dewatering.

Renal Function Evaluation by Alternating Current Biosusceptometry of Magnetic Nanoparticles

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The collection and clearance of magnetic tracers in the kidney of rats were assessed trough the time evolution of magnetic signals obtained with an AC biosusceptometer This device consists of a pair of air core transformers, one working as a reference and the other as measuring transformer and has been extensively used to study gastrointestinal motility (1) and pharmaceutical sciences (2,3) in our group

Eight male Wistar rats weighing from 200 to 250 g were employed in this experiment A magnetic nanoparticle (MNp) tracer based on manganese and iron oxide with an average diameter of 13 nm was used (4) After anesthesia the animal was positioned as shown in figure 1 (left) with the sensor fixed at the lumbar projection The magnetic tracer was administered through and infusion in the right femoral vein

Figure 1 (right) shows a typical plot of the signal versus time In all data obtained, it is possible to observe the arrival of the MNps at the kidney, the increase in signal intensity indicating the collection of MNps in the organ and its clearance The clearance appears to have two stages with different decay times The time it takes for the signal to decay at half of its maximum intensity ($T_{½}$) was measured in all animals giving $T_{½}$= (1 7 s ± 1 4)

The AC biosusceptomter has sensitivity to detect the presence of the MNps in the kidney and dynamical studies of the kidney activity can be performed This instrument will be used to explore the presence of MNps in other organs

Acknowledgements: Partial financial support: FAPESP, CNPq and CAPES

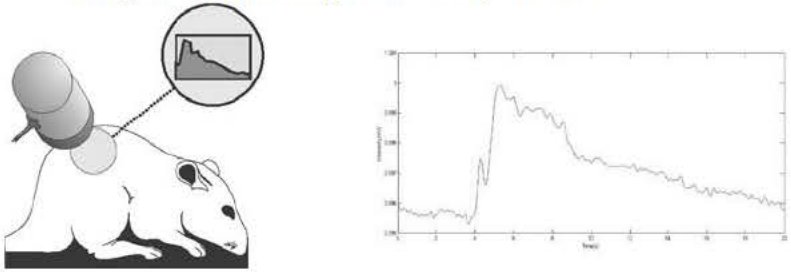

Figure 1: Positioning of the sensor to acquire the magnetic signal from the kidney (left) and typical signal versus time After the injection, there is a rapid increase of the signal that decays to base line after a few seconds

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Molecular diagnostics based on magnetic nanobead clustering dynamics monitored using a Blu-ray optomagnetic readout system

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The detection of specific DNA sequences has facilitated the diagnosis and targeted treatment of several human diseases Although great advances have been made, pathogenic bacteria are mainly identified using bacterial culture, colony counts or using polymerase chain reaction In this work we demonstrate detection of DNA coils formed from *Vibrio cholera*, via padlock probe recognition and isothermal rolling circle amplification at pM concentrations [1] The readout is based on a novel opto-magnetic approach exploiting the change of the clustering dynamics of magnetic nanobeads (MNBs) when these are bound to biomolecules

The technique relies on measurements of the light transmission modulation caused by the AC magnetic field-stimulated reversible formation and disruption of elongated MNB supra-structures during a cycle of the uniaxial applied magnetic field MNBs that bind to the μm-sized DNA coil cannot rotate under the field action to form MNB chains This results in a strongly modified opto-magnetic signal The non-contact readout system uses a commercial Sony Blu-ray pickup head (the same as in a PlayStation 3) as a single and unique optomagnetic component and it is combined with a centrifugal microfluidic platform for easy multiplexed analysis (Fig 1a)

We show that the method can detect DNA coils down to a concentration of 10 pM with a linear range up to a few hundreds of pM (Fig 1b) Compared to a readout using magnetic susceptometry[1,2], the presented system shows a similar or enhanced sensitivity and the approach is easily integrated with upstream sample processing in a low-cost disposable system In conclusion, dynamic properties of magnetic nanoparticles are for the first time combined with existing technologies (Blu-ray reader) to achieve bacterial DNA detection in a miniaturized and truly low-cost platform

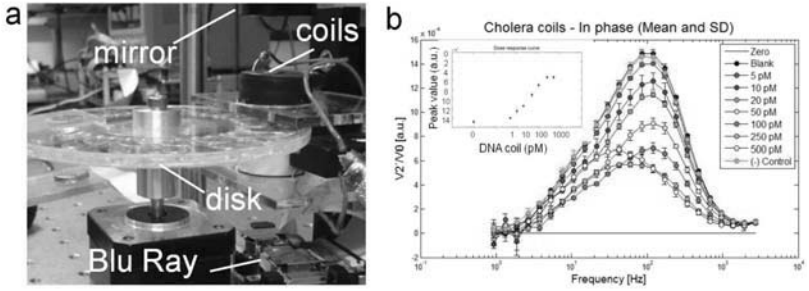

Figure 1 (a) Picture of the set-up used for the measurements, where a Sony Blu-ray pickup-head is used as a readout element The light, modulated by MNBs (Micromod 100 nm BNF starch, 0 1 mg/mL), reflected by the mirror is analyzed using a data acquisition card **(b)** Data obtained (2nd harmonic, in phase component) for different concentrations of DNA coils formed from cholera by rolling circle amplification The inset shows the dose response curve with a detection limit of 10 pM

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New method of investigation of affinity properties of magnetic nanoparticles with recognition receptors

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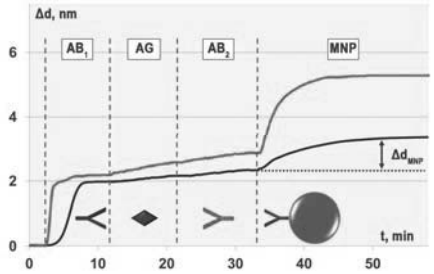
Magnetic nanoparticles (MNP) are very promising labels for biosensing [1]. This application field requires quantitative estimation of the recognition properties of receptors on the MNP surface depending on the method of their coupling to MNP. In this work, a novel method for quantitative study of the affinity constants of the receptors on MNP has been developed based on the spectral correlation interferometry (SCI) [2]. The SCI allows recording of thickness changes Δd averaged over the sensing area of a layer of molecules or nanoparticles on a surface of a cover slip with a picometer resolution.

The kinetic constants of interacting agents are measured by processing of the SCI sensograms, which are $\Delta d(t)$ dependences of binding reactions, using the equilibrium association model. The representative sensograms for all stages of a sandwich immunoassay with using MNP as the labels for detection of cardiac troponin I (cTnI) are shown in Fig. 1. The obtained kinetic association constants for each stage of the assay are given in Table. The values of kinetic association constants observed at the MP stage are 2–3 orders of magnitude higher than those of molecular antibody (AB) association with antigen (AG). Such good kinetic characteristics of AB coupled with MNP are due to polyvalence of MNP having several AB simultaneously on the surface of nanoparticles.

The developed method, being of special interest for investigation and kinetic characterization of interaction of nanoparticles with molecules, offer practical prospects. In particular, the developed optomagnetic biosensor based on the SCI with MNP employment demonstrates high sensitivity and wide dynamic range for detection of the antigens. The 50-nm MNP employed as labels yield 100-fold amplification of the SCI signals, and the achieved detection limit for cTnI is 0.1 ng/ml, which is relevant to earlier diagnostics of myocardial infarction. This biosensing approach with disposable sensor chips of inexpensive cover slips and MNP is an economically sound alternative for immunoassays for disease diagnostics, detection of pathogens in food and environmental monitoring.



Surface type	Observed kinetic association constant, $M^{-1}s^{-1}$		
	AG stage	AB_2 stage	MNP stage
Epoxylated	6.4×10^5	1.2×10^5	1.6×10^8
Biotinylated	8.2×10^5	1.7×10^5	6.4×10^7

Table. Dependence of the kinetic association constant observed at each stage of the assay for different surface types

Fig.1. Sensograms of the assay on the biotinylated (bottom) and epoxylated (top) surfaces of the cover slip: AB_1 – capture antibody; AG – cTnI; AB_2 – tracer antibody; MNP – association with receptors coupled with magnetic nanoparticles

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On-chip magnetic bead-based DNA melting curve analysis using a magnetoresistive sensor

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We present real-time measurements of DNA melting curves in a chip-based system that detect the amount of surface-bound magnetic beads using so-called planar Hall effect bridge (PHEB) magnetic field sensors. The sensors use a new differential sensor geometry (Fig. 1) that detects the difference between the amount of beads between the top and bottom sensor branches.[1] The sensor surfaces are functionalized with wild type (WT) and mutant type (MT) capture probes, respectively, differing by a single base insertion (a single nucleotide polymorphism, SNP). Matching biotinylated targets in suspension couple streptavidin magnetic beads to the sensor surface. The beads are magnetized by the field arising from the bias current passed through the sensor and thus no external magnetic fields are needed. Here, we expand on our previous work[1] by demonstrating the first on-chip measurements of the melting of DNA hybrids upon a ramping of the temperature. This overcomes the limitation of using a single washing condition at constant temperature.[2] Moreover, we demonstrate that a single sensor bridge can be used to genotype a SNP.

The sensors (Fig. 1) are based on the anisotropic magnetoresistance of permalloy, exchange-biased to have a magnetization along the *x*-direction in zero external magnetic field. An alternating bias current of amplitude I_x = 25 mA and frequency f = 167 Hz is passed through each sensor. The magnetic bead signal is found in the out-of-phase 2nd signal V_2'' obtained by lock-in technique from the bridge voltage V_y.[1] As the bottom and top halves of the sensor bridges are identical, the bridge output is proportional to the *difference* between the amount of beads experienced by them. This efficiently eliminates a background from magnetic beads in suspension as well as due to unspecifically bound beads. Three sensors on a sensor chip were functionalized with WT and MT capture probes as illustrated in Fig. 1. A reference sensor functionalized directly with biotinylated DNA was used to correct for the temperature dependence of the sensitivity. In the experiments, equal volumes of the stock solution of 50 nm Streptavidin Microbeads (Miltenyi Biotec) and 10 nM WT DNA target were mixed and injected on the sensor. After hybridization for 60 min, the unbound target and magnetic beads were washed away with 0.05×saline-sodiumcitrate. Then, the sensor signals were measured while increasing the temperature at a rate of 0.1°C/s. Fig. 2 shows the sensor signals relative to the positive reference vs. temperature. The mismatched DNA duplexes formed between the WT target and MT probes melt at a lower temperature than the matching ones between the WT target and WT probes. The signals tend to zero when the temperature increases above 60°C. The signal from the WT-MT sensor is identical to the difference between the signals from the WT and MT sensors and it displays a clear maximum at the temperature with the highest difference between matched and mismatched DNA hybrids and thus allows for single sensor detection of the SNP.

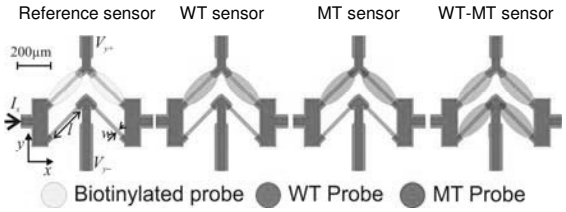

Fig. 1. Sensor geometry and illustration of the functionalization of the sensors with biotinylated WT, MT and reference capture probes. Each sensor arm (shown in light green) has a length l = 250 µm and width w = 25 µm.

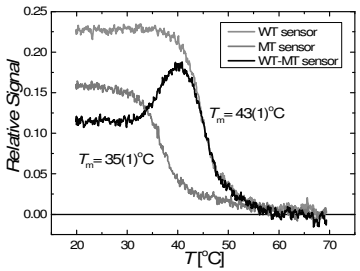

Fig. 2. Sensor signals vs. temperature for the indicated sensors. Signals are reported relative to that obtained from the reference sensor. The obtained melting temperatures are indicated.

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Application of Magnetic Nanoparticles (SPION) in Medicine – The SEON-Concept

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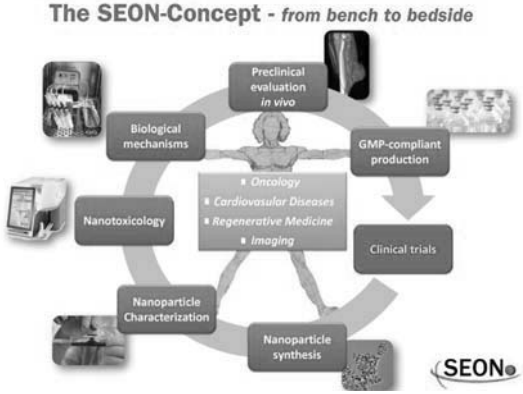
Magnetic Nanoparticles are used for a variety of applications in medicine This ranges from *in vitro* diagnostic tests, *in vivo* imaging, targeted drug delivery and tissue regeneration To translate basic findings into clinical trials several requirements such as detailed synthesis and characterization of the nanoparticles, nanotoxicological testings, *ex v*ivo models to simulate *in vivo* conditions for appropriate adjustment of the necessary parameters and pre-clinical animal studies have to be addressed These results are of pivotal importance to start with respective GMP production and approval, which is essential for translating these products into clinical trials (scheme) SEON (Section of Experimental Oncology and Nanomedicine) addresses these issues with a special focus on drug delivery in oncology[1] and their promising potential applications in cardiovascular[2], regenerative medicine[3] and imaging[4] The aim is the translation of the preclinical results into clinical trials and the respective steps necessary to gain this ambitious object



Scheme of the SEON-Concept, addressing the respective steps to translate basic/pre-clinical results into clinical trials

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Acknowledgement:
The authors are grateful to the Else Kröner-Fresenius-Stiftung, Bad Homburg v d H , Germany, the German Research Foundation (grant reference AL 552/5-1), the German Federal Ministry for Education and Research (grant reference FKZ:01EX1012B), the Bavarian State Ministry of Environment and Consumer Protection reference number U8793-2012), the Emerging Fields Initiative of the University Erlangen-Nürnberg and the EU (project FP7-NMP-2012-LARGE-6-309820, NanoAthero) for financial support

Multifunctional Magnetic Nanoparticles for Targeted Cancer Diagnosis and Therapy

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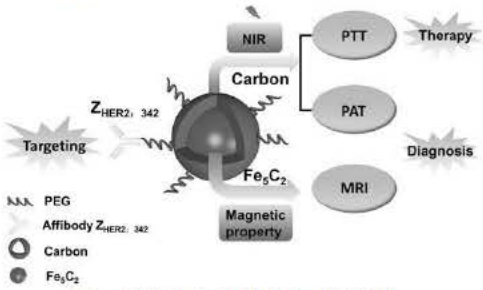
Magnetic nanoparticles (NPs), which possess controlled size, shape and magnetic moments, have been applied as multifunctional probes in biomedical field, including MRI, drug delivery and magnetic hyperthermia, by enhancement of contrast in magnetic resonance imaging (MRI) and emote manipulation.[1]

In this talk, we will first present general protol of monodisperse magnetic NPs, and then give an example of hollow manganese phosphate (HMP) NPs with particle size of 18 nm and a 10 nm hollow structure, for pH-modulated cancer cell targeted MRI and drug delivery.[2] Folic acid (FA) was selected as a target molecular for specific binding with cancer cells, and doxorubicin was loaded into the hollow structure for cancer therapy. This multifucntional probe can specifically target cancer cells overexpressing FA receptors, and be engulfed by lysosomes. The HMP NPs were dissolved at low pH environment in lysosomes, which can release Mn^{2+} for sensitive MRI, and DOX loaded for effective killing of cancer cells.[3]

We then talk about Hagg iron carbide (Fe_5C_2) magnetic NPs for bimodal tumor imaging and therapy (Scheme).[4-6] Interestingly, due to the presence of carbon layers of NPs, with high absorption in near-infrared (NIR) optical region, Fe_5C_2 NPs can be used for photoacoustic tomography (PAT) and photothermal therapy (PTT). The probe exhibits high saturation magnetization, r_2 relaxivity and temperature increasing after exposure to NIR. The conjugation of Herceptin enabled the targeting to Her2-overexpressed cells (SK-OV-3 cells). After incubation with NPs in vitro, SK-OV-3 cells showed much lower MRI T_2 signal, and no noticeable in vitro toxicity has been observed. Determined by using a fluorescent viability stain, cells incubated with NPs and exposed to NIR light were found to have undergone photothermally induced morbidity. The in vivo experiments were carried out on nude mice with ovarian cancer modal. After injection of NPs through the tail vein, it showed long-lasting negative-contrast enhancement MRI as well as high PAT signal at the tumor site. High tumore ablation was achieved after NIR irritation. From the loss of body weight, morphological and pathological examinations, almost no systematic toxicity has been observed. Our results highlight the great potential of Fe_5C_2 NPs as a multifunctional probe for cancer theranostic applications.



Schematic illustration for the design of Fe_5C_2 NPs as a targeted theranostic platform.

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Magnetic Particle Spectroscopy to quantify blood half-life of superparamagnetic iron oxide nanoparticles in a mouse stroke model

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The application of magnetic resonance imaging (MRI) employing superparamagnetic iron oxide nanoparticles (SPIOs) as a contrast agent is presently investigated as a modality to monitor signal intensity changes by SPIOs in the ischemic region during the acute stage of (experimental) stroke [1] In a preclinical stroke study of middle cerebral artery occlusion (MCAO) in mice we employed Magnetic Particle Spectroscopy (MPS) to determine the blood half-life of three different types of SPIOs and their uptake in organs [2]

At different time intervals after iv-injection of a SPIO dosage (300 or 1000 µmol/kg body weight), consisting of either VSOP (citrate coated SPIOS, Charité Berlin) or Feraheme® (carbohydrate coated, Amag Pharmaceuticals), about 50 µl blood samples stabilized in EDTA were taken from the mouse and measured by MPS MPS detects the nonlinear magnetic response of SPIO exposed to an oscillating magnetic field (25 mT at 25 kHz) The amplitude of the MPS signal is proportional to the SPIO amount while biological tissue and paramagnetic blood iron do not contribute

Before injection, no magnetic signals could be detected in blood, while the SPIO concentration increased dramatically within the first two minutes after the infusion reaching concentrations larger than 100 (400) ng Fe/mg blood for the 300 (1000) µmol/kg dosage With increasing time after injection the SPIO concentration monotonically decreased as shown for the 300 µmol/kg dosage in Fig 1 (left) for both SPIO types By fitting a single exponential $c(t)=c_0 \exp(-t/\tau)$ the blood half-life τ was extracted As depicted in Fig 1 (right) Feraheme SPIO circulate longer than VSOPs Furthermore the half-lives are dosage dependent

Note that the MPS signal reflects only the iron of magnetic nanoparticles and is not compromised by natural body iron Due to its high sensitivity only small sample volumes of 10 to 100 nanograms of SPIO iron per sample are required for a reliable SPIO quantification The short measurement time and easy sample handling make MPS the ideal high-throughput magnetic nanoparticle quantification tool

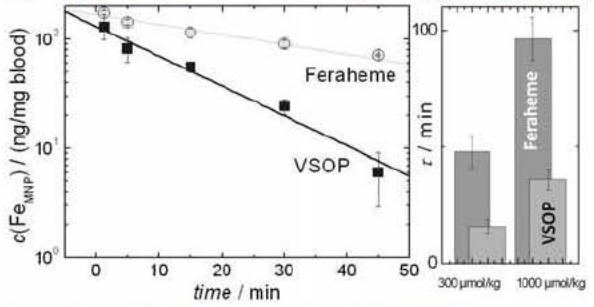

Fig 1. Blood kinetics for Feraheme and VSOP at 300 µmol/kg dosage (left) and corresponding blood half-lifes τ (right) for both dosages

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Dendronized magnetic core-shell and cubic shaped nanoparticles designed for targeting, MRI and hyperthermia

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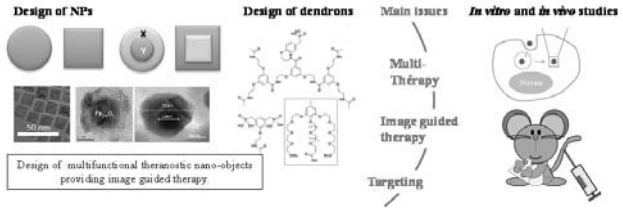
Some of the significant and most promising applications for inorganic nanoparticles (NPs) lie in the fields of biology and biomedicine Due to their magnetic properties tuned by their shape and/or composition, superparamagnetic iron oxide NPs (SPIO) with appropriate surface chemistry can be used in numerous in vivo applications such as MRI contrast enhancement, hyperthermia treatment, cell sorting, drug delivery
In that context, we propose a concept combining a dendritic coating of magnetic oxide nanoparticles with phosphonate anchors Indeed, phosphonates ensure a strong anchoring at the NPs surface while preserving their magnetic properties, and dendritic shells, in addition to their small and easily controllable size (as a function of their generation), are promising building blocks simultaneously solving the problems of biocompatibility, large in vivo stability and specificity Dendronized iron oxide nanoparticles were demonstrated to induce any cytotoxicity I*n vivo* and *in vitro* MRI measurements showed that the contrast enhancement properties of the dendronized NPs were higher than those obtained with commercial polymer-coated NPs Moreover, both types of dendronized NPs were eliminated by urinary and hepatobiliary pathways without unspecific uptake especially in the RES organs and in the lungs The design of dendronized NPs was further improved to obtain theranostic nano-objects (which can both identify disease states and simultaneously deliver therapy) by adjusting the morphology and the composition of the inorganic magnetic core and by designing multifonctionalized dendrons These NPs were found suitable to combine imaging and therapy by hyperthermia Finally these dendronized NPs bearing melanin vectors were demonstrated very suitable to specifically target *in vivo* tumoral cells



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Oral abstract

Depth limitations for in vivo magnetic nanoparticle detection with a compact handheld device

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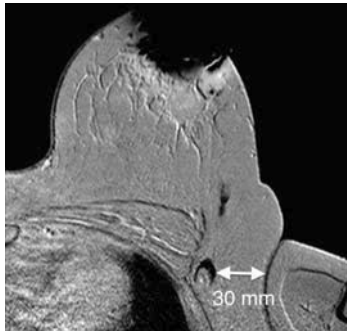
In vivo magnetic particle detection with a compact handheld device was recently demonstrated in clinical trials for the Sentinel Lymph Node Biopsy (SLNB) procedure in breast cancer patients [1,2]. An important outcome from this research is that the clinical requirements for sensing depth and sensor size are more demanding than can be realized reliably with the existing detection technology. We will give a short review of the existing detection technology and its limitations in terms of the diamagnetic properties and the irregular geometry of the human body surrounding the magnetic nanoparticle target.

Given the large ratio between the magnetic susceptibility of the particles and the tissue (>10^6), the uncertainties in the human skin thickness(~1 mm) and the limited sensor area (~10 mm), the particle sensitivity is limited to 1 – 10 µg in a 1 – 10 mm sensing window. In our patients we observe varying particle quantities 1 – 350 µg in the excised Sentinel Lymph Nodes. The depth estimation, obtained from preoperative MRI images, shows that a significant number of these nodes is located much deeper than 25 mm in the body. Due to the irregularly shaped, water-like diamagnetic body, the clinically required detection depth cannot be realized with a linear magnetic susceptibility based sensing method.

The main conclusion is that the clinical case needs a different detection technology, instead of a further improvement of the susceptibility measurement. An available method is MRI which is costly and presently not usable in the operating theatre. A more attractive alternative that is usable in the operating theatre was recently introduced as DiffMag [3]. By utilizing the highly non-linear superparamagnetic magnetization relation, this technology can realize the clinical demands for SLNB detection. By carefully compensating the diamagnetic signal from the human body, a DiffMag system can detect superparamagnetic nanoparticles system, up to a depth which is significantly larger than the sensor diameter.



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Magnetorelaxometry imaging of magnetic nanoparticles with inhomogeneous fields based on plane-wise sensitivity

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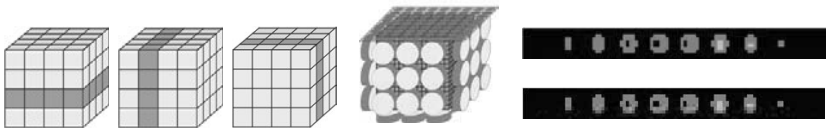
Promising biomedical applications of magnetic nanoparticles share the need for a quantitative knowledge of their in-vivo distribution. Magnetorelaxometry (MRX) non-invasively obtains the characteristic relaxation behavior of the particles after being exposed to sudden changes of an external excitation field. From multichannel MRX measurements employing homogeneous excitation fields, the distribution of the particles can be quantitatively determined by minimum norm estimation techniques [1]. The sequential activation of inhomogeneous excitation fields leads to a considerably enhanced imaging quality [2]. In first studies, single coils were consecutively activated. We aim at further advancing this imaging technology by finding suitable activation patterns involving multiple excitation coils.

In this work, these patterns are defined based on the spatial sensitivity [3] in the source space that describes the influence of a voxel on the sensor system. It is determined by the geometric relation between the voxel and sensor positions as well as the excitation field in the voxel. While the first are fixed within a given setup, the latter can be controlled by the currents in the excitation coils. Defining a target sensitivity, the required excitation currents can be estimated by solving an inverse problem.

In our work, the target sensitivities are maximized in single planes of the source space while preserving a low sensitivity elsewhere (see fig. a). These planes are moved through the source space in all three orientations, defining one excitation pattern per plane position. In an inverse paradigm, all voxels except for one plane are sensitive. Both approaches are investigated in simulation studies using a surrogate setup (fig. b) and their imaging quality is evaluated for varying number and dimension of the planes.

Our results (fig. c) demonstrate the principal applicability of spatial sensitivity based approaches of defining inhomogeneous activation patterns for magnetorelaxometry imaging of magnetic nanoparticles. The obtained activation patterns targeting plane-wise sensitivity and non-sensitivity, respectively, allow for a similar imaging quality using a lower number of activation sequences compared to the conventional single coil activation.



a) target sensitivity patterns **b) surrogate sensor and excitation setup** **c) simulated particle distribution (top) and example reconstruction (bottom)**

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Tracking of adipose tissue-derived progenitor cells using two magnetic nanoparticle types

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Magnetic resonance imaging (MRI) is to be considered as an emerging detection technique for cell tracking experiments to evaluate the fate of transplanted progenitor cells and develop successful cell therapies for Tissue Engineering. Adipose tissue engineering using adipose tissue-derived progenitor cells has been advocated for the cure of soft tissue defects or for persistent soft tissue augmentation.

For cell labeling, bionized nanoferrite particles (BNF) and superparamagnetic iron oxide dextran particles (nanomag®-D-spio(SPIO)), both coated with poly-D-lysine and 100 nm in diameter, were used. For initial *in vitro* studies, adipose tissue-derived mesenchymal stem cells (ASC) were labeled with BNF (10/25/50 µg Fe/ml) and SPIO (25/50/100 µg Fe/ml). Regarding the influence of nanoparticle labeling on cellular functions, both nanoparticle types altered the proliferation as well as differentiation potential of ASC in a dose-dependent manner. Compared to unlabeled cells, proliferation of ASC was enhanced three times (BNF) as well as twice (SPIO) at the lowest labeling concentrations but increased as labeling concentrations were likewise increased. For testing the adipogenic differentiation potential, the accumulation of lipid droplets was analyzed. The treatment with BNF resulted in a concentration-dependent reduction of adipogenic differentiation, whereas only SPIO-labeling at 100 µg Fe/ml decreased lipid droplet accumulation. To test the MRI detection *in vitro*, nanoparticle labeled ASC were embedded in 1.5 % agarose and scanned using a high-field 7.1 Tesla animal MR system (ClinScan, Bruker). Both BNF-labeled as well as SPIO-labeled cells were successfully detected at all labeling concentrations (Figure 1).

According to findings of the *in vitro* study, ASC were labeled with both BNF and SPIO at the lowest labeling concentration. Labeled cells were seeded onto collagen scaffolds and subcutaneously implanted into severe combined immunodeficiency (SCID) mice. MRI scans were performed at several time points (24 h up to 4 months) resulting in a successful visualization of the cell seeded scaffolds. Moreover, volumetric analyses were performed revealing a significant volume loss over time.

In conclusion, first insights are provided showing the successful transfer of an *in vitro* cell tracking model using MRI in an *in vivo* SCID mice model.

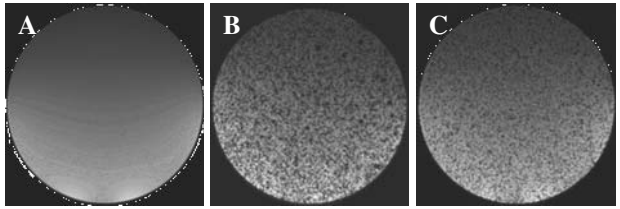

Figure 1: Visualization of (A) unlabeled cells, (B) BNF and (C) SPIO labeled cells (labeling concentration: 50 µg Fe/ml) embedded in agarose using a 7.1 Tesla animal MR system (ClinScan, Bruker).

Nano-thermometer with Thermo-sensitive Polymer Grafted USPIOs behaving as Positive Contrast Agents in low-field MRI

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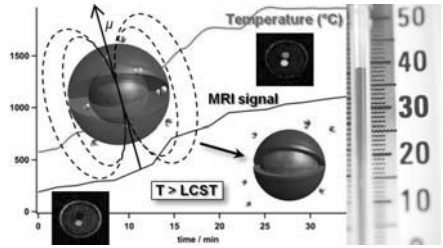
We designed ultra-small superparamagnetic iron oxide (USPIO) nanoparticles of constant core diameter ~10 nm with a poly(ether) shell "breathing" reversibly between a highly hydrated state at low temperature and a de-hydrated state above the LCST of the chains, two statistical copolymers of ethylene and propylene oxide, Jeffamine® M-2005 (PEO_5-*st*-PPO_{37}) and M-2070 (PEO_{46}-*st*-PPO_{13}) Their LCSTs were measured by DLS and NMR at 22±1°C for M-2005 and 52±1°C for M-2070 Several attempts were made in the literature to compare the efficiency as MRI contrast agents of magnetic nanoparticles (MNPs) with the so-called "outer sphere" model developed in the nineties [1] On the one hand this model contains very few parameters, namely the size and the magnetization of the sphere limiting the volume accessible to water protons On the other hand, these parameters can hide more subtle differences between the samples, like the permeability to water protons or more generally the "hydrophilicity" of the particles In the case of particles made of an assembly of several USPIOs arranged as a cluster, there were experimental evidences that a hydrophilic polymer coating significantly raised up the efficiency as negative (T_2) contrast agents, as shown for magnetic minigels [2]

In the present work, we examined the case (to our knowledge not reported yet) of the effect of the hydration degree in the USPIO-case, *i.e.* for un-clustered MNPs Researchers in this area realized that small USPIOs maintained in a perfect individually dispersed state thank to a repulsive polymer coating (PEG, polysaccharides…) behave not only as negative MRI contrast agents, but also as positive (T_1) contrast agents [3] This seems to be a particularly interesting challenge for the chemists to develop coatings based on (bio)-polymers to prevent the clustering of USPIOs in physiological conditions The positive contrast (hyper-signal compared to pure water) is indeed a property that can be obtained with contrast agents truly at the nano-scale, and that disappears as soon as the MNPs are slightly aggregated (the effect of USPIOs clustering being more sensitive on the T_2 relaxation of the neighboring protons than on their T_1 relaxation) This is thus an example of true "nano effect" in the biomedical area! With this fundamental view in mind, we built a simple system of USPIO cores that can be compared in two hydration states: either hydrated or dehydrated The longitudinal and transverse relaxivities can be understood within the frame of the outer sphere model, with a relaxometric radius and an overall magnetization that vary in perfect agreement with the picture of a polymer shell hydrated below the LCST and collapsed above it, thus impermeable to protons (see above sketch)



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Magnetic Nanoparticles in Mural Tumors detected and quantificated by Micro-Computertomography

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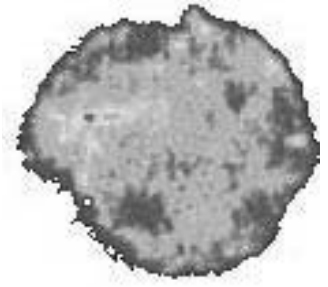
Magnetic nanoparticles enable a new field of promising opportunities for medical applications. Particularly magnetic drug targeting for cancer research is an interesting approach. For further research regarding this application the knowledge of the biodistribution and quantity of the nanoparticles in biological tissue during and after therapy is essential. For this purpose we used micro-CT imaging to analyze the distribution.

Our investigations focus on determining the amount of nanoparticles incorporated in a mural tumor (FaDu cell line). Due to the fact that mural tumors have a small volume, there are only minor masses of 30-300 µg nanoparticels to detect. To achieve exact results we developed a new method for calibrating the micro-CT. In contrast to earlier CT-calibrations, especially considering the procedure used by Rahn (Rahn et al. 2012), we used Magnetorelaxometrie (MRX) to quantify mural tumors and therefore to define the calibration function. Via MRX the mass of magnetic particles was measured for each mural tumor. After scanning those mural tumors under equal measurement conditions the average gray values within the tumor has been extracted. The last step of the calibration procedure is attaching the average gray value obtained by micro-CT to the respective MRX measured concentration of nanoparticles, allowing the quantification of the concentration of magnetic nanoparticles in the tumor.

This study used eleven mural tumors to define the calibration function of the micro-CT scanner. Therefore the estimation of the amount of nanoparticles with different characteristics in mural tumor tissue is enabled. This method offers a compatitive edge, since smaller particles in such low concentration cannot be measured via MRX.

As the result of our research, micro-CT enables to quantify and investigate tumor tissue with minor masses of small magnetic nanoparticles for deeper knowledge of the distribution of magnetic particles in tissue achieved with magnetic drug targeting.



Mural tumor extracted from a micro-CT-scan The red and yellow areas mark the presence of magnetic nanoparticles

Engineering Cellular Microenvironments – Chemistry Meets Physics

Prof. Dr. Dieter Scharnweber

Professor, Max Bergmann Center of Biomaterials, Institute of Materials Science, TU Dresden, Germany

Abstract

Prof. Scharnweber takes an engineering approach in developing strategies to mimic both the biochemical and physical properties of native cellular microenvironment. His talk will focus on aspects of matrix engineering with glycosaminoglycan derivatives: on how their structure determines their interaction with proteins, on how they can direct stem cells fate in combinations of biochemical and physical signals, and on the potential applications of magnetic nanoparticles in such signal combinations.

Interdisciplinary Research Unit **Nanoguide / FOR 917**

Magnetic Nanoparticle based targeting of gene- and cell-based therapies

Speaker: Univ.-Prof. Dr. med. Alexander Pfeifer *(Institute of Pharmacology and Toxicology, University of Bonn)*
Vice-Speakers: Univ.-Prof. Dr. med. (I) Bernd Fleischmann *(Institute of Physiology I, University of Bonn)*; Prof. Dr. rer. nat. Christian Plank *(Institute of Experimental Oncology and Therapy, Technische Universität München)*

The Research Unit FOR 917 focuses on the use of magnetic nanoparticles (MNPs) as tools for studying physiological and pathophysiological processes in the cardiovascular system. MNPs can be manipulated by magnetic gradient fields, which can be used not only to enhance gene transfer, but also to target the genetic material (nucleic acids including DNA, RNA as well as viral vectors) to a defined region.

At the cellular level, we use MNP-guiding with tailored magnet gradient fields e.g. to generate gene gradients. Thereby, dosage effects of single genes as well as interplay between genes is investigated in the setting of cardiac pacemaking and cellular reprogramming.

On a tissue and organ level, we study MNP-assisted delivery of genetic material to vessels and the heart under physiological conditions. Because cells that have taken up nanoparticles become “magnetic”, these particles can also be used for the targeted positioning of cells with magnetic gradient fields.

The position and local concentration of MNPs and magnetic cells *in vivo* is measured using magnetic resonance imaging (MRI) as well as by magnetorelaxometry (MRX). Overall, these characteristics make MNPs an important tool to address biological questions as well as for the development of novel therapeutic approaches for gene- and cell-based therapies in the cardiovascular system.

Magnetic targeting is a complex endeavor that requires close collaboration of different scientific fields. A major characteristic of FOR917 is that its members cover a broad scientific spectrum ranging from pharmacology and physiology to physics and engineering.

Initially, the focus of the Research Unit FOR917 was mainly focusing on technical issues of efficient magnetic targeting of genes and cells including the optimization of physical and chemical properties of MNPs, the design and measurement of magnetic fields as well as the design of biological models to test MNP targeting. Presently, the Research Unit is applying magnetic targeting to address biological questions - ranging from cardiac pacemaking, to vessel tone and angiogenesis - as well as to develop novel therapies in the cardiovascular system.

The biological research focus of FOR917 lies on the cardiovascular system. Cardiovascular disease remains the leading cause of death in developed countries. Since cardiovascular lesions are characteristically localized, site specific targeting is required for successful gene and cell therapies. Herein, we combine MNP-based gene- and cell targeting to address biological as well as clinically relevant questions.

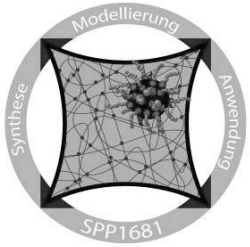
⇨ FOR917: Research Unit/Forschergruppe funded since 2009 by the DFG

DFG Deutsche Forschungsgemeinschaft

DFG-Priority Programme 1681

„Field controlled particle matrix interactions: synthesis multiscale modelling and application of magnetic hybrid materials“

(SPP 1681)



The use of magnetic fields is an external stimulus for the control of material properties, which is of considerable technical interest, since magnetic fields can easily be generated and controlled Magnetically controlled materials such as suspensions of magnetic nano - and microparticles - ferrofluids and magneto - rheological fluids - have the ability to exhibit strong changes of material behavior at reasonable technical effort In the aforementioned fluids, the matrix in which the particles are embedded, ie the carrier liquid, constitutes only a thermal bath which, although changing the typical time constants of the material, does not provide any specific interaction between the particles and the matrix In contrast, magnetorheological elastomers in which magnetic particles are embedded in an elastic matrix are a first step in the direction of magnetic hybrid materials with controllable particle-matrix interaction

In the center the priority program focuses on five key issues: First, it must be clarified, how (1) the material behavior of a magnetically controllable hybrid material is influenced by the particle-matrix interaction and how appropriate materials can be synthesized A multi-scale modelling of the material properties (2) is the fundament for the understanding of the behavior of the materials necessary to explain their magnetic controllability at a microscopic level The odelling is also needed for the establishment of constitutive material laws, which are needed for the design of applications Closely connected to this modeling of the material properties is (3) the experimental evaluation of the material properties and its connection to changes in the microstructure Based on this understanding of the magnetic hybrid materials one can answer the question (4) what kind of possibilities they offer in novel actoric and sensory applications, as well as the question (5) how the effectiveness of the biomedical use of magnetic nanoparticles can be improved by a control of the interaction between the functionalized particles and tissue

For more information: http://www mfd mw tu-dresden de/spp1681/index php/willkommen

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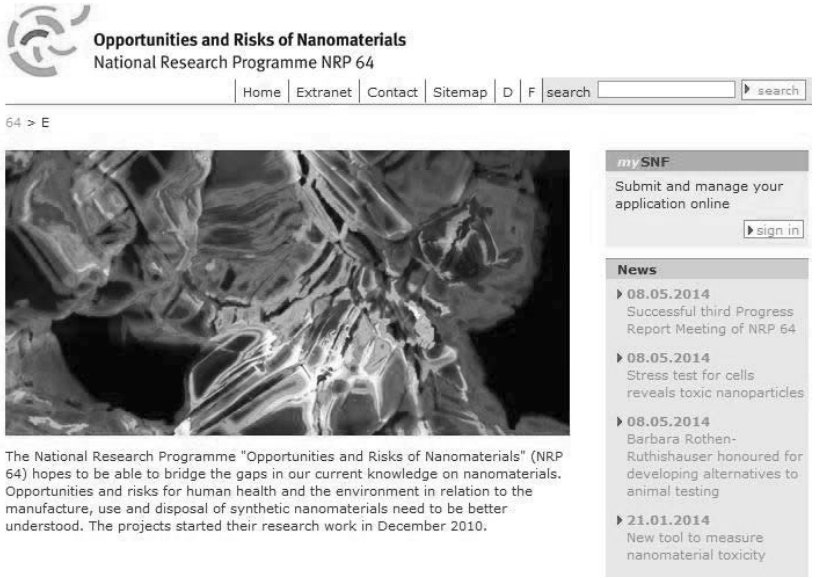

NRP 64 aims to identify opportunities arising from the use of nanomaterials for health care, the environment and natural resources. At the same time, it intends to reveal the potential risks that nanomaterials pose in these areas.

NRP 64 specifically aims to:

- gain insights into engineered nanomaterials, their development, use, behaviour and risks;
- develop methods and tools to monitor the behaviour of nanomaterials and their potential effects on humans and the environment;
- develop tools that maximise the advantages of nanomaterials and minimise the risks for humans and the environment;
- support the development and application of safe and effective technologies based on nanomaterials;
- make information available for decision-makers, including manufacturers, distributors and consumers;
- enhance and strengthen specialist knowledge and competencies for developing innovative nanomaterials and assessing risk in Switzerland.

For more information, please contact Heinrich Hoffmann, Heinrich.Hofmann@epfl.ch

NanoMag

SEVENTH FRAMEWORK PROGRAMME

NanoMag - Nanometrology Standardization Methods for Magnetic Nanoparticles

The objectives of the EU financed NanoMag project are to standardize, improve and redefine analyzing methods of magnetic nanoparticles. Using improved manufacturing technologies, synthesized magnetic nanoparticles with specific properties will be analyzed with a multitude of characterization techniques (focusing on both structural as well as magnetic properties). Bringing the results together will give a self-consistent picture which describes how structural and magnetic properties are interrelated. All of the NanoMag results will be used to define standard measurements and techniques which are necessary for defining a magnetic nanoparticle system and for quality control. The application areas of magnetic nanoparticles in the NanoMag project is focused on biomedical applications, for instance biosensing (detection of different biomarkers), contrast substance in tomography methods (Magnetic Resonance Imaging and Magnetic Particle Imaging) and magnetic hyperthermia (for cancer therapy).

NanoMag brings together leading experts in; manufacturing of magnetic single- and multi-core nanoparticles, analyzing and characterization of magnetic nanostructures, and national metrology institutes. In the NanoMag consortium we have gathered partners within research institutes, universities and metrology institutes, all carrying out front end research and developing applications in the field of magnetic nanoparticles.

The NanoMag project started in November 2013 and will continue until November 2017. The NanoMag consortium is; Acreo Swedish ICT AB, Swedish ICT Research AB, University College London, Uppsala University, The Spanish National Research Council (CSIC), Micromod Partikeltechnologie GmbH, Technical University of Denmark, University of Cantabria, Chalmers University of Technology, Federal Institute of Materials Research and Testing (BAM), Technical University of Braunschweig, nanoPET Pharma GmbH, Solve Research & Consultancy AB, University of Lübeck, Eindhoven University of Technology, The Physikalisch Technische Bundesanstalt (PTB), SP Technical Research Institute of Sweden, National Physical Laboratory (NPL).

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Quantification of superparamagnetic nanoparticle concentration using particle Electron Paramagnetic Resonance: an in vitro and in vivo validation study

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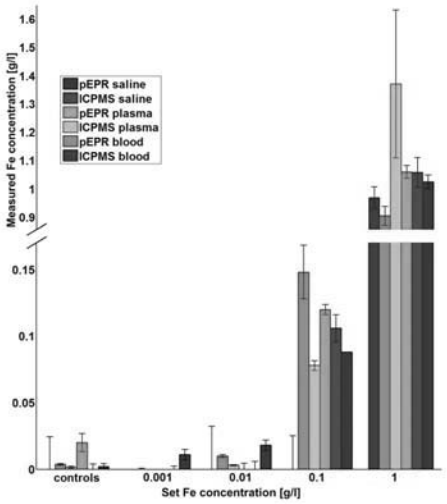
Abstract

Superparamagnetic iron oxide nanoparticles (SPION) have increasignly showing an important role as drug carriers and imaging agents It is therefore essential to detect these therapeutic agents in pre- and clinical research environments

In this work we present the biodistribution results of SPIONs in mice and rats using a new technique, particle Electron Paramagnetic Resonance (pEPR) This technique is based on electron paramagnetic resonance which selectively measures the magnetization of magnetic nanostructures such as SPION The pEPR technique was initially compared to Inductively Coupled Plasma Mass Spectrometry in vitro by testing different SPION concentrations suspended in blood, plasma, and saline, as shown in figure The pEPR technique was then adopted for measuring the *in vivo* samples The biodistribution (by pEPR and MRI) of SPION were evaluated following a single intravenous dose We believe pEPR is novel, and has great potential to become an easy "single step" process to distinguish between SPION and naturally present iron Therefore pEPR is a good alternative and has benefits such as sample preparation and selectivity compared with the ICP-MS technique



Acknowledgements

This work was supported in part by the European Commission under MULTIFUN project (FP7 NMP-Large ref 262943)

MAGNETIC DROPLETS
FOR EXPLORING DYNAMICS AND DISSIPATION
ON SUPERHYDROPHOBIC SURFACES

Jaakko V I Timonen[1,2], Mika Latikka[1], Olli Ikkala[1], and Robin H A Ras[1]

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Aqueous droplets show a number of fascinating dynamical effects on superhydrophobic (= water repellent) surfaces, including giant hydrodynamic slip and nearly frictionless motion and small roll-off angles [1] Quantification of the small but non-zero "friction" experienced by individual moving drops has proven to be challenging under well-controlled tangential and normal forces

In this work we describe a new way for investigating dynamics and energy dissipation on superhydrophobic surfaces by using magnetic drops as probes (Figure 1) [2] These drops consist of ca 0 2% of 4 6±1 4 nm superparamagnetic iron oxide nanoparticles well-dispersed by surface-bound citrate anions in water Density, surface tension and viscosity are within a couple of percent from those of pure water The magnetic nanoparticles allow any vectorial force to be induced on the drop by applying an appropriate external magnetic field We focus on trapping the magnetic probe drop in a harmonic potential well (resulting in a Hookean restoring force) and demonstrate both freely decaying and externally driven horizontal oscillations of the drop on the test surface We calculate two dissipative forces (due to contact angle hysteresis and viscosity) by analyzing the damping rate and/or frequency-dependent oscillation amplitude, and quantify these two as a function of normal force [2]

On the other hand, strongly magnetic droplets with nanoparticle loading up to 25% can be split on a superhydrophobic surface into multiple droplets by applying a perpendicular magnetic field The resulting daughter droplets self-assemble into various static arrangements in a similar harmonic potential well as in the dissipation measurements (Figure 1 right) These static arrangements can be switched reversibly into dynamic dissipative ones by applying a time-varying oscillating magnetic field [3]

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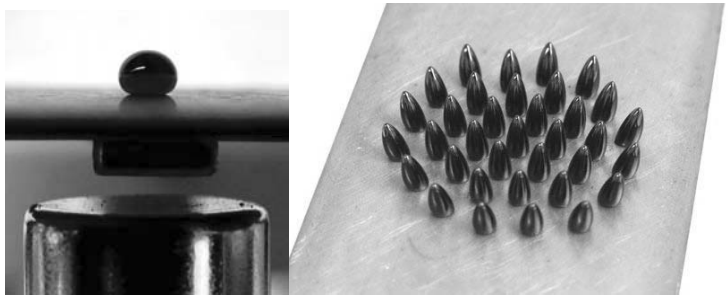

Figure 1: Magnetic droplets on a superhydrophobic surface (left) Droplet oscillator for probing friction experienced by a moving droplet [2] (right) Self-assembly of magnetic droplets [3]

The Interaction Between Schistosome Eggs and Magnetic Microspheres

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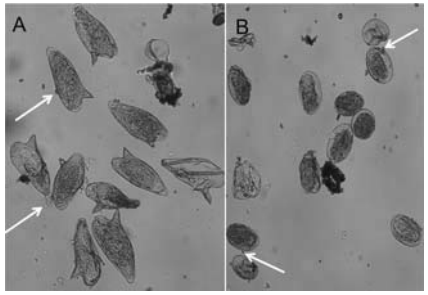
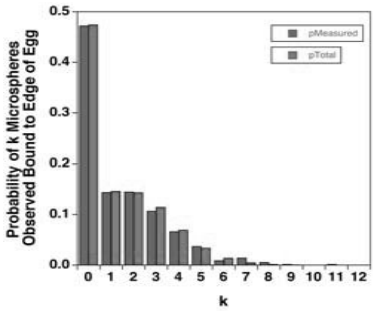
Schistosomiasis is a public health problem affecting more than 200 million people in Asia, Africa and America. Two main species may cause the intestinal infection in humans: *Schistosoma mansoni* and *Schistosoma japonicum*. Helmintex® is a new very sensitive method for detection of *Schistosoma* eggs in human faeces based on the interaction of eggs and paramagnetic microspheres, with 100 % sensitivity at limit of 1.3 eggs per gram. The objective of this study was to investigate the magnetic properties of *Schistosoma* eggs and the interaction of microspheres with the eggs to enable optimization of the Helmintex® method. Eggs from both species were isolated from livers of infected mice and separately incubated with four types of microspheres at pH7 and pH 8 at an egg/microsphere ratio of 1:500 for 30 minutes with no applied magnetic field. The polystyrene microspheres were a) magnetic iron oxide coated; b) magnetic iron oxide and streptavidin coated; c) uncoated, d) streptavidin coated. The conjugates were sieved to remove unbound microspheres. An optical microscope was used to determine the distribution of the numbers of microspheres bound per egg. The observed distributions were well modeled with double Poisson distributions. At pH 7, both the *S. japonicum* and *S. mansoni* eggs appeared to fall into two types, one type having a greater affinity for magnetic iron oxide coated spheres than the other. *S. japonicum* eggs had a higher affinity for magnetic iron oxide coated microspheres than *S. mansoni*. Strepdavidin coating reduced the affinity for both species. At pH 8, the affinities of both species of eggs for the magnetic microspheres was reduced. In the absence of magnetic iron oxide coating, there was very little affinity of the eggs for microspheres. These observations suggest that the interaction between the microspheres and eggs is more likely to be related to electrostatic interactions between eggs and magnetic iron oxide rather than through magnetic interactions.



A *S. mansoni* and **B** *S. japonicum* eggs incubated with magnetic microspheres Arrows indicate bound microspheres



Example double Poisson distribution of number *k* of microspheres bound to edge of eggs (Blue data: red fit) Data indicate two categories of eggs

The Magnetoviscous Effect of a Biocompatible Ferrofluid diluted with Sheep Blood

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Chair of Magnetofluiddynamics, Measuring and Automation Technology, Institute of Fluid Mechanics
Technische Universität Dresden, Germany

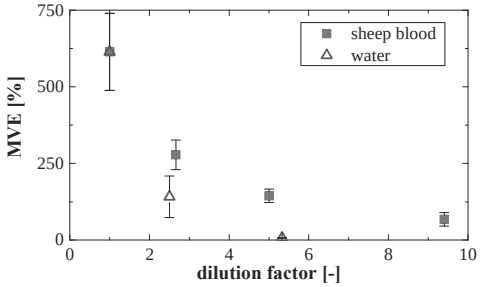
Biocompatible ferrofluids are receiving a great interest regarding the use in the biomedical context. Those potential application include e.g. possible treatments of cancer like magnetic drug targeting or magnetic fluid hyperthermia besides several other approaches.

For a possible use of those suspended magnetic nanoparticles in the biomedical area the detailed knowledge of the flow characteristics is essential. For ferrofluids used in the engineering context the magnetoviscous effect is well known and investigated in some detail, resulting in an increasing viscosity if an external magnetic field is applied. This effect was measured to be present for biocompatible ferrofluids as well, leading to an increasing viscosity above one order of magnitude if an external magnetic field is applied.

During a potential clinical use of ferrofluids a dilution with blood occurs. A detailed knowledge regarding the possible interactions of the structures formed by the fluids' nanoparticles and the blood cells has to be available to guarantee a safe and effective application.

This experimental study focuses on the investigation of the relative change in viscosity if a ferrofluid is diluted with sheep blood and a magnetic field is applied. The figure attached depicts the effect depending on the dilution if water respectively sheep blood is used. Therefore a difference can be determined, resulting in a stronger effect if the animals' blood is used. As a result the above mentioned interaction of blood cells and structures of the fluids' nanoparticles can be assumed. Furthermore a rather strong change of viscosity of the mixture despite the comparatively weak magnetic field can be measured.

The results found in this experimental study prove an influence of the formations formed by the ferrofluids' nanoparticles on the viscosity if those fluids are mixed with sheep blood, having the potential to influence safety and effectiveness regarding potential biomedical applications.



The magnetoviscous effect of a biocompatible ferrofluid depending on the dilution factor for two diluting agents The magnetic field strength is H=35 kA/m and a shear rate of $\dot{\gamma} = 6\ s^{-1}$ is applied

10th Inter. Conf. on the Scientific and Clinical Applications of Magnetic Carriers, Dresden, Germany. June 10-14, 2014. Oral or Poster Presentation.

The Relationship Between Mason Number and Bingham Number in Magnetorheological Fluids

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Magnetorheological (MR) fluids under shear are typically described through two non-dimensional numbers, the Mason number and Bingham number The Mason number, *Mn*, which is the ratio of particle viscous forces to magnetic forces, is typically used for predicting the particle microstructure, as well as modeling behavior at the micro-scale The Bingham number, *Bi*, which is the ratio of bulk magnetic forces to bulk viscous forces, governs macroscopic scale fluid behavior, and can be used to predict the force output of a MR damper For example, it is well know that the dynamic range, *D*, defined as the ratio of the on-state to the off-state torque of an MR clutch, is given by $D=1+Bi$ In this paper, we show that Bingham and Mason number are inversely related First, we make this claim through analysis If we observe that both non-dimensional numbers represent ratios of magnetic and viscous forces, and assume that such forces are linearly related across scales, then we can justify the hypothesis that the Mason number is inversely proportional to the Bingham number If we apply the well known experimental result that normalized apparent viscosity has the form of $1 + K/Mn$, and show that the normalized apparent viscosity of a Bingham plastic is, by definition, $1 + Bi$, then it can be proven that the Bingham number is inversely proportional to the Mason number Second, we can also experimentally validate this hypothesis using magnetorheometer testing, in this case, of a 40 vol% MR fluid (Lord Corp MRF140) Measurements of apparent viscosity taken on a custom-built high shear rate Searle cell rheometer (shear rates up to 10,000 s^{-1}) are shown in Fig 1 The data are shown as symbols, for a wide range of applied field values (shown in the legend) The analytical curve is shown is shown as the solid black curve The data and analysis match quite well, which demonstrates that this relation holds at high shear rates This demonstrates that the Mason number allows microscale-based analyses to be extended to device scales, where Bingham number based analysis is most useful As such, a microstructural investigation of novel particle and fluid formulations can now be placed in the device context through a simple algebraic relation

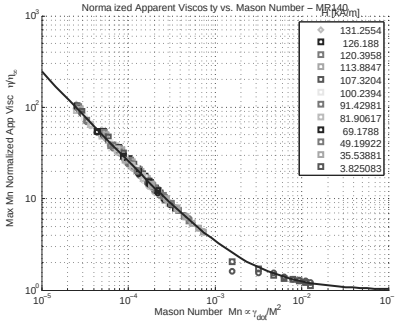

Figure 1 Normalized apparent viscosity vs Mason number for a MR fluid (Lord MRF140), on a high shear rate rheometer operating at shear rates of up to 10,000 s^{-1} This demonstrates that the relationship between Bi and Mn holds at high shear rates

Detection of magnetic nanoparticles after perfusion of a placenta

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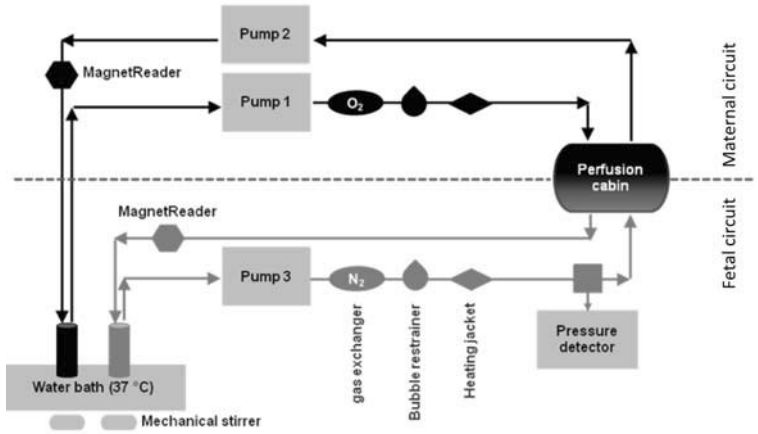
Nanoparticles (NP) are potential tools for medical applications. Nevertheless, the current lack of knowledge about their potential toxicity connected with a possible spatial distribution in the human body requires of new methods to determine the latter one. Placentae can play a central role as human tissue models as they do not constitute an ethical problem. Furthermore, magnetic NPs are used as MRI contrast agent but their behaviour at the placenta barrier is not known. To date, no standardised methods are available for quantification of NP in human tissue.

Aim of our work are long term measurements of NP in a floating suspension in tube shaped sample volume in order to conclude their (time dependent) whereabouts after perfusion of a placenta for up to 6 hours. We used a modified Magnetreader what detects magnetic moments of a few μAm^2 via analysis of the higher harmonics caused by a frequency mix of ac-magnetic fields. Since the signal depends as well on the magnetisation curve of NPs the method is only semiquantitative.

The influence of the particle coating on as well the interaction (adhesion) in the measuring system as the binding in the placenta was investigated. The results suggest a transfer of a small amount of particles from the maternal to the fetal blood circuit.



Setup of the perfusion experiment

Detecting Mechanical and Chemical Changes Through Tissue Using Magnetically Modulated Optical Sensors

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Although optical measurements are widely used in chemical and mechanical sensors, they are challenging to employ for non-invasive imaging through tissue because absorption and scattering attenuates the optical signals, while tissue autofluorescence backgrounds can obscure the sensor signal We describe methods to overcome these limitations using sensors with magnetically modulated red fluorescence Although the senor fluorescence is attenuated, it is able to penetrate through thick tissue, while the magnetic modulation distinguishes the probe signal from the background autofluorescence

To demonstrate the approach, we fabricated magnetically modulated fluorescent particles comprising fluorescent magnetic microspheres coated with a thin hemispherical aluminum shell (~70 nm thick) coating half of the microsphere surface The opaque metal layer prevents excitation and emission light from passing through one side of the "magnetically modulated optical nanoprobes" (MagMOONs), which creates an orientation-dependent fluorescence intensity The magnetic particles also align in an external magnetic field and give blinking signals when they rotate to follow modulated external magnetic fields The blinking signals from these MagMOONs are distinguished from background autofluorescence and can be tracked on a single particle level in the absence of tissue, or for an ensemble average of particles blinking through tissue When these MagMOONs are dispersed in alginate gel, they become sensors for gelation when calcium ions are added, and de-gelation upon addition of alginate lyase Our results show MagMOONs start to blink after approximately 10 minutes following 2 mg/mL alginate lyase addition and the blinking is clearly detected through at least 4 mm of chicken breast tissue, superimposed on a rapidly bleaching autofluorescence background (see Figure 1) This is an important proof-of-principle for biosensors and drug delivery systems based on enzyme-catalyzed breakdown of gel components We also show that similar magnetic modulation can also be applied to spectrochemical sensors based on fluorescent indicator dyes Finally, we explain the effect of particle concentration, tissue thickness, and optical attenuation on the modulated signal using Monte Carlos simulations

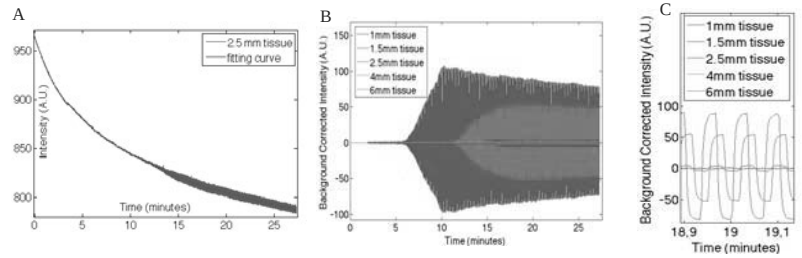

Figure 1. A) Plot of fluorescence signal through 2 5 mm chicken breast and the moving average fit **B)** Background-corrected magnetically modulated fluorescence signal through 1 mm, 1 5 mm, 2 5 mm, 4 mm and 6 mm chicken breast Modulation can be clearly seen after 6, 12, 15 min with 1 mm, 1 5 mm and 2 5 mm respectively **C)** Zoom-in to visualize modulation

In vivo magnetic drug delivery using FePd nanowires

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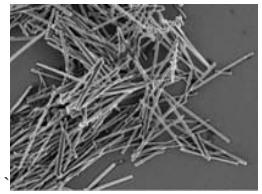
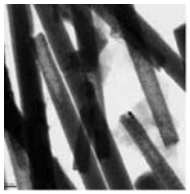
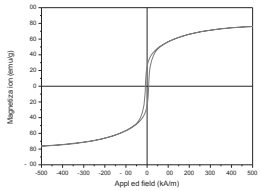
Magnetic drug delivery is a promising technique to target a drug to the region of the decease Unfortunately the commonly used spherical superparamagnetic nanoparticles need a very high magnetic field and gradient to be captured from the flow of blood Elongated nanoparticles have more advantageous magnetic and flow properties The magnetic moment in these particles is aligned along their long axes and the achievable magnetic moment for a single particle is much higher than for a spherical particle

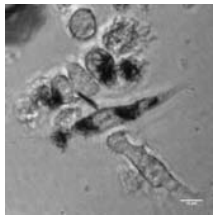
Recently we developed a biocompatible FePd magnetic nanowire prepared by electrodeposition inside the pores of a polycarbonate membrane similar to (Haehnel, Fahler, Schultz, & Schlorb, 2010) The nanowires have a very small size distribution length 1 9 ± 0 3 µm and diameter 88 ± 15 nm The Pd protects the Fe from oxidising, therefore the magnetic properties are maintained in solution over months The saturation magnetisation of the particles is very high, while in suspension the coercive field is reduced to nearly zero, providing superparamagnetic-like properties, which are advantageous to avoid clustering of the suspensions Coating with Pluronic-F108 increased the dispersability further and provides a layer in which drugs or as used in our experiments fluorescent Nile Red can be adsorped The nanowires were shown non toxic to cells and phagocytosed without signs of frustrated phagocytosis







The FePd nanowires were used in an in-vivo experiment with Wistar rats An electro magnet was developed providing the optimal magnetic field and gradient to capture the nanowires The magnet was designed in such way that it can be easily scaled up to use in human applications, making this in-vivo experiment a suitable scale model of a clinical experiment The nanowires were injected systemically into the tail vain and captured in the hind leg of the rat The targeting was proven very efficient by both magnetic measurements and microscopy



Haehnel, V., Fahler, S., Schultz, L., & Schlorb, H. (2010). Electrodeposition of Fe70Pd30 nanowires from a complexed ammonium-sulfosalicylic electrolyte with high stability. *Electrochemistry Communications, 12*(8), 1116-1119. doi: DOI 10.1016/j.elecom.2010.05.043

Magnetic Beads to Enhance Drug Penetration Across Intestinal Membrane

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Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation Low permeable drug class exhibits poor absorption *in vivo*, which leads to a poor bioavailability Some recent studies describe gastro retentive delivery systems maintained in the upper part of the Gastrointestinal Tract (GIT) to enhance the bioavailability of low permeable drugs After oral administration, such dosage forms release the drug slowly into the gastrointestinal tract (GIT) close to its absorption windows and maintain an effective drug concentration in the systemic circulation for a long time

In this study we decided to use magnetic retention in order to increase the bioavailability of a low permeable drug (BCS Class III, high solubility and poor permeability) across the intestinal membrane by inducing an over-concentration of the drug near its absorption window

Indeed the magnetic formulation is able to be retained at a specific location along the GI tract using an external magnet For this purpose we designed magnetic carriers containing magnetic nanoparticles (MNPs) suitable for oral delivery that exhibit a superparamagnetic behavior as well as a very high drug loading efficiency [1]

Ex vivo, *in vivo* and imaging experiments were carried to assess proof of concept *Ex vivo* experiments were performed using Ussing Chambers and shown a threefold increase of drug permeation across rat intestinal membrane Fluorescence and MRI imaging techniques were used to prove the accumulation of the magnetic beads in the upper part of the intestine with a magnet placed on the abdomen (Figure 1) Finally *in vivo* pharmacokinetic preliminary study proved that when using magnetic retention the bioavailability of the drug is increased by 40%

Using magnetic carriers to load and localize a drug near its absorption window by using an external magnet, enables to enhance significantly its permeation and its bioavailability This approach opens new perspectives in the field of low permeable drugs oral administration

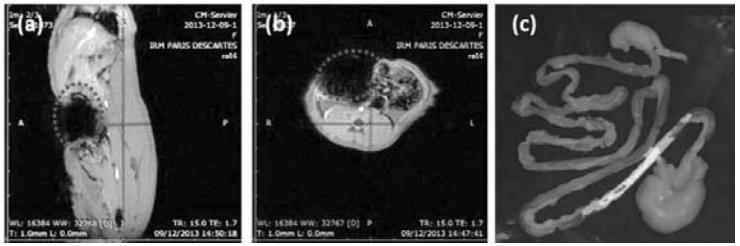

Figure 1: MRI sagittal section, (b) MRI axial section with magnet initial position
(c) Near-IR fluorescence image of a rat intestine

[1] A Seth, D Lafargue, C Poirier, J -M Péan and C Ménager, Performance of magnetic chitosan-alginate core-shell beads for increasing the bioavailability of a low permeable drug, Eur J Pharm Biopharm , submitted

Non-Invasive In Vivo Magnetic Targeting of Mouse Embryonic Stem Cells to the Lung

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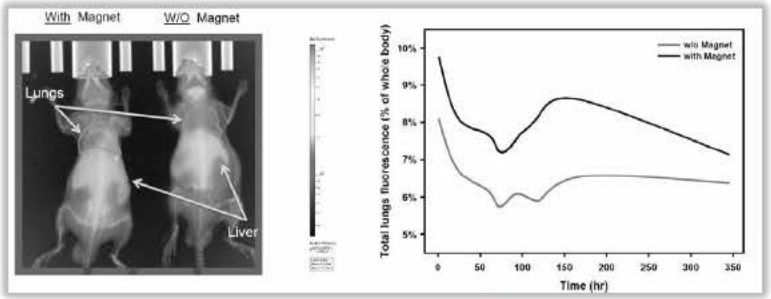
Cell therapy is one of the leading strategies in regenerative medicine offering a truly curative solution for repair of failing organs or diseased tissues. Current cell delivery techniques mainly rely on the cell's intrinsic ability to home to the region of interest due to pathophysiological cues. However, this process has low efficiency, may require administration of large number of cells and may involve clinically cumbersome routes of administration. To overcome these drawbacks, there is a need to develop efficient cell targeting strategies.

In this study we utilized polylactide (PLA)-based magnetite-loaded nanoparticles (MNPs) to load mouse embryonic stem cells (mESCs) which were chosen as model for cells with low intrinsic endo/pinocytotic activity. The uptake of fluorescently labeled MNPs by mESCs was quantitated using flow cytometry. The fluorescent intensity, indicative of MNP quantity, obtained from flow cytometry analysis linearly correlated with analytically determined intracellular magnetite content. Avoiding the use of commercially available transfection agents, we optimized the generation of MNP-loaded mESCs (Mag-mESCs) by systematic evaluation of conditions such as MNPs dose, duration of incubation, cell density, application of external magnetic field gradient and magnetite content within MNPs. At optimized conditions, 99±3% of the mESCs population was loaded with MNPs containing 2.8±0.2 pg/cell magnetite (*e.g.,* 8.4±0.6 pg iron/cell). The Mag-mESCs demonstrated magnetic responsiveness assessed by a vibrating sample magnetometer, magnetic cell patterning, magnetically levitated cell adhesion assay, and *in vitro* cell capture under flow. Intracellular presence of MNPs did not adversely affect cell viability, proliferation kinetics and pluripotent potential. Intravenously-injected Mag-mESCs were efficiently localized in the mouse lungs by applying a magnetic field gradient on dorsal side of the chest. Near-infra red whole-body imaging was performed over two weeks and revealed differences in kinetic behavior and distribution profile of the Mag-mESCs compared to unloaded cells. The application of the external field gradient resulted in distinct patterning of the Mag-mESCs in the lungs.

This study provides for the first time insight into the *in vivo* kinetics of MNP-labeled cells and demonstrates the ability to non-invasively influence *in vivo* cell distribution. The therapeutic implications of these findings are the scope of future studies in our laboratories.



Whole body NIR imaging of MNP-loaded mESCs targeted to the lung using externally applied magnetic field gradient.

Treatment of a critical long bone defect using magnetic scaffolds reloaded by magnetic nanoparticles-VEGF

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Critical long bone defect represents a significant problem for orthopaedic surgeons. In our study, we describe a novel approach to fill critical long bone defects with a biodegradable magnetized scaffolds as a template for cells attachment, proliferation, differentiation and extracellular matrix deposition and subsequent magnetic guided VEGF delivery of functionalized magnetic nanoparticles, in order to provide a controlled three dimensional architecture able to reproduce native biological and mechanical characteristics of bone.

A critical bone defect of 20.0mm in lengh, 6.00mm of inner diameter and 17.00 of outer diameter was created in 6 sheep metatarsus diaphysis. A porous ceramic composite scaffold made of Hydroxyapatite that incorporates magnetite (HA/Mgn 90/10) was implanted in the defect and proximally fixated by two small cylindrical permanent parylene coated NdFeB magnets (one 6.00 mm diameter magnetic rod firmly incorporated into the scaffold and one 8.00 mm diameter magnetic rods fitted into proximal medullary canal, both 10.00 mm long); stability of bone-scaffold-bone complex was improved using screws and plate as a bridge. Biocompatibility of scaffolds was previously assessed *in vitro* using human osteoblast-like cells. A finite element software (COMSOL Multiphysics, AC/DC Model) was used to calculate magnetic forces through scaffold.

Injection of magnetic nanoparticles functionalized with VEGF at the mid portion of the scaffold were performed one week after surgery using a cutaneous marker positioned during surgery as reference point. After sixteen weeks, sheep were sacrificed to analyze metatarsi. Macroscopical, radiological, microCT and histomorphological examinations were performed.
From macroscopical point of view, bone tissue formation was present inside scaffold pores and with complete coverage of scaffolds, in particular at magnetized bone-scaffold interface. X-rays show a good integration of the scaffold with a good healing process of critical bone defect, and without any sign of scaffolds mobilization. MicroCT confirmed this datas of new bone formation inside the scaffolds, in particular at magnetized bone-scaffold interface. Also histomorphological evaluation confirmed greater bone regeneration at magnetized interface, in both groups. Comparing groups bone regeneration was greater when VEGF-MNP were injected.

These results lead our research to exploiting magnetic forces to stimulate bone formation, as attested in both in vitro and in vivo models and to improve fixation at bone scaffold interface, as calculated by finite element software, and moreover to guide targeted drug delivery without functionalized magnetic nanoparticles dissemination in all body.

Single-core magnetic markers in rotating magnetic field based homogeneous bioassays and the law of mass action

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The application of functionalized magnetic nanoparticles (MNPs) as a test system in homogenous bioassays enables a quick and quantitative detection of proteins, e.g., biomarkers in medical diagnosis and therapy, directly in solution. Here, no wash-out steps to remove unbound markers are necessary. The required magnetic manipulation of the MNPs is realized with a rotating magnetic field (RMF). The RMF offers the possibility to perform a narrow-band measurement of the MNP response compared to switched magnetic fields and to gain a higher measurement effect compared to alternating magnetic fields [1,2].

In this work, we report on the effect of the absolute single-core MNP concentration on the quantitative detection of proteins with MNPs in a RMF. Therefore, the phase lag change $\Delta\varphi$ of commercial 30 nm iron oxide nanoparticles (Ocean Nanotech, Springdale, AR, USA) caused by bound proteins is measured with a fluxgate-based RMF system. As a model system the detection of anti-human IgG via protein G which is covalently linked to the MNP polymer shell is investigated. The measured phase lag changes for a fixed MNP and a varying IgG concentration are modeled with logistic functions (Fig. 1). The effect of the MNP concentration change is explained with the law of mass action and used to determine the parameters of the binding reaction. Further binding scenarios, e.g., for the detection of the medical relevant HER2 biomarker, are presented and investigated regarding the dependence on the MNP concentration.

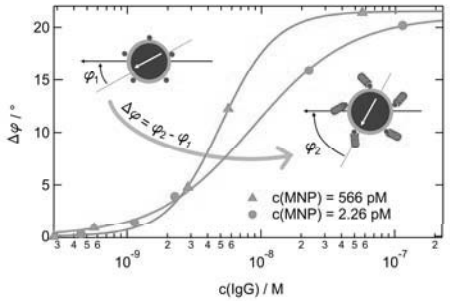

Fig 1: Measured phase lag change $\Delta\varphi$ in RMF due to bound IgG as function of the IgG concentration The MNP concentration variation affects the slope of the logistic functions (lines) which are fitted to the measurements The graphic illustrates the effect of the protein binding on the phase lag between the RMF and MNP magnetic moment

Acknowledgment

This work was supported by the European Commission Framework Programme 7 under the NAMDIATREAM project (NMP-2010-246479).

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Janus magnetic liposomes for drug delivery

C. A. Monnier[†], C. Bonnaud[†‡], D. Demurtas[§], D. Vanhecke[†], X. Montet[¶], M. Lattuada[†], B. Rothen-Rutishauser[†‖], A. Petri-Fink[†‡]

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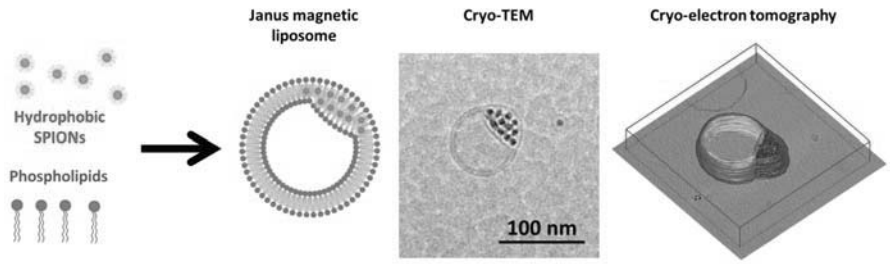
Delivering and releasing drugs at their target in a controlled fashion remains a key determinant of successful treatment and might contribute to reducing side effects.

By using liposomes as basic drug carriers and combining them with superparamagnetic iron oxide nanoparticles (SPIONs), we have developed nanoparticle-liposome hybrids with SPIONs directly embedded within the membrane bilayer. Unlike previous reports, the nanoparticles are clustered and diverged at one pole, giving these hybrids a Janus-like appearance. High-resolution cryo-electron microscopy techniques were used to characterize these vesicles under unadulterated conditions, and showed at unprecedented detail the lipid bilayer unzipping around the nanoparticles. The spatial organization and architecture of the embedded clusters could be rendered by cryo-electron tomography, which further revealed that these structures consist of hundreds of densely packed SPIONs – a quantity which has not been reached up to date.

SPIONs heat up when exposed to an alternating magnetic field, thus offering a potent release trigger as soon as the target is reached. Moreover, the present location of the injected medicine can be tracked by MRI. By implementing clusters, the resolution and quality of the MRI signal and release efficiency can be improved. This consequently opens a notable area of applications in both biological and medical sciences alike.



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Bonnaud *et al.* "Spatial SPION Localization in Liposome Membranes " *Magnetics, IEEE Transactions on* (2013)
Bonnaud, Monnier *et al.* " Insertion of Nanoparticle Clusters into Vesicle Bilayers " *ACS nano* (2014)

Theories and experiments on the way to optimize magnetic nanoparticles for magnetic hyperthermia

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Abstract

The main part of the speech will be devoted to a pedagogical presentation of theoretical aspects in magnetic hyperthermia using our results or some of the literature. The different approaches suitable for the calculation of the heating power as well as the underlying mechanisms will be presented. Emphasis will be put on common misconceptions or mistakes on this topic. We will start from simple systems where the nanoparticles are fixed and magnetically independent and then discuss the influence of mechanical rotation and magnetic interactions. Experimental results obtained on metallic nanoparticles synthesized in our laboratory and illustrating the theoretical aspects will be shown. The portrait of the ideal nanoparticle will tentatively be drawn. Also, a few useful setups developed in our group will be presented. The end part of the speech will be devoted to a discussion around puzzling experiments reported in the recent literature where cell death occurs without temperature increase of the cells. The various hypotheses permitting to explain them will be presented. We will conclude this part by showing that these experiments bring new hopes to the field of magnetic hyperthermia but also bring new difficulties to the optimization of nanoparticles to maximize cell death.

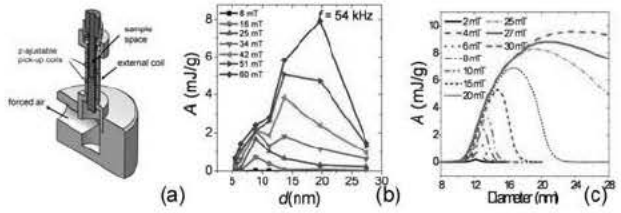

Figure : (a) Setup for high-frequency hysteresis loop measurements (b) Size dependence of the heating power measured on metallic Fe(0) nanoparticles (c) Size dependence of heating power calculated by numerical simulations of hysteresis loops

Reproducible microwave synthesis of multi-core iron oxide nanoparticles for magnetic hyperthermia and *in situ* tracking of induced cell death in a human melanoma cell model

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Previous studies have shown that magnetic heating properties of multi-core iron oxide nanoparticles prepared by conventional chemical routes are very sensitive to subtle changes in the reaction conditions, leading to issues of poor reproducibility and scalability.[1] This threatens to limit their application in pre-clinical and clinical settings. Firstly we developed a controlled synthesis for the preparation of iron oxide with sodium carbonate.[2] Here, we report on the use of a microwave reactor for a simple, reproducible and scalable synthesis of biocompatible nanoparticles by coprecipitation. Physicochemical characterization data are presented that show that the materials form multi-core structures, and that interparticle interactions are decisive in determining the heating properties of the nanoparticle suspensions.

The synthesized nanoparticles were then tested *in vitro* in a human melanoma DX3 cell model. A range of field amplitude and frequency values were evaluated to tailor the treatment to induce killing of the cells. The delayed cell response was analyzed by flow cytometry after 48 h following 1 and 2 h treatments. Furthermore, a novel magnetic hyperthermia device was constructed to allow live cell observations during and after the application of a time-varying magnetic field. The cell death mechanism was monitored by fluorescence microscopy and found to be via an apoptotic pathway.

To summarize, these results indicate: (1) microwave-synthesized multi-core particles retained their heating capability upon cell loading; (2) DX3 cells, loaded with iron oxide nanoparticles, can be effectively killed by a time-varying magnetic field to induce apoptosis; and (3) this further opens the possibility of the tailored treatments of near-surface or accessible tumors, on which further work has commenced.

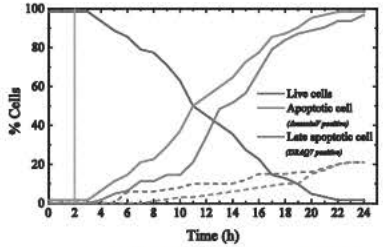

Figure 1. Magnetic hyperthermia treatment effect over 24 h on CA-io loaded DX3. Dashed lines indicate cell response during control experiment.

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2 Blanco-Andujar, C , et al , *J. Mater. Chem.* **2012**, *22*, 12498-12506

Analysis of molecular effects after treatment of pancreatic cancer cells with (magnetic fluid) hyperthermia

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Hyperthermia, the heating of cells to temperatures up to 43°C for 60 to 90 min, can effectively be used to inactivate and destroy tumor cells. One way of applying these temperatures is using superparamagnetic iron oxide nanoparticles (MNP) in combination with an alternating magnetic field. These particles are biocompatible, degradable and have the advantage to generate heat only in regions of their location. To better understand the cellular reactions, we analyzed the impact of different temperature dosages on cell viability, the expression of proliferation- and stem cell markers *in vitro*.

Pancreatic cancer cells (BxPC-3) were treated with increasing temperature dosages (37 - 47 °C for 60 min). The used temperatures were either generated by exogenous heat sources (e g. humidified air) or by the internalized MNPs within the cells after exposure to an alternating magnetic field (H = 15.4 kA/m, f = 435 kHz) (internal heating source).The expression of the proliferation markers K 67, TOP2A and TPX2 was analyzed using qRT-PCR. Cell viability and expression of the pancreatic stem cell markers CD24, CD44 and CD326 was investigated using flow cytometry.

Treatment of cells at 41 - 43 °C for 60 min using the exogenous heat source resulted in an increased mRNA expression of the proliferation markers KI67, TOP2A and TPX2 up to 30% 24h after hyperthermia compared to non-treated controls (37 °C). In contrast, magnetic fluid hyperthermia (MFH) of 41 - 43 °C / 60 min reduced the expression of proliferation markers up to 70 % compared to untreated controls at 24 hours after treatment. In contrast to the utilization of exogenous heating sources, MFH of 43 °C / 60 min distinctly reduced the amount of viable cells and increased the extent of apoptotic, late apoptotic/necrotic, and necrotic cells within the cell population. Higher temperatures (47 °C / 60 min) of both treatment setups dramatically increased the amount of late apoptotic/necrotic and necrotic cells. Application of exogenous heat using the same temperature dosage (47 °C / 60 min) significantly ($p < 0.05$) reduced the expression of the stem cell markers CD24, CD44 and CD326 by around 9 % (24 h post treatment).

In conclusion, hyperthermic temperatures exhibited distinct effects on cell viability, proliferation- and stem cell markers *in vitro*. Treatment of cells with MFH and temperatures between 43 - 47 °C for 60 min exhibited a greater impact on proliferation and viability of tumor cells compared to external hyperthermia. Therefore, MFH is a suitable and effective tool to inactivate tumor cells and inhibit tumor progression.

Terahertz Absorption in Iron Oxide Nanoparticles

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In hyperthermia cancer treatment, magnetic nanoparticles are excited by AC magnetic fields with frequencies ranging from 100 kHz – 1 2 MHz. Controversy remains concerning the details of the heating mechanism: whether Brownian or Néel rotation dominates, if there is an optimal particle size, and whether a macroscopic temperature increase is needed for cell death. It is feasible that local heat generation by phonons couples to nearby protein molecules and causes them to denature. Complex motion of large molecules is often excited with terahertz frequencies. To address these questions, we have used terahertz absorption spectroscopy to identify the fundamental excitations of iron oxide nanoparticles, and see how they change in an AC magnetic field. Monodisperse Fe_3O_4 nanoparticles were synthesized by high temperature decomposition in non-polar solvents and stabilized by oleic acid surfactant. Terahertz absorption spectra were measured as a function of temperature. A custom electromagnet was constructed to deliver a 155 kHz AC field with an amplitude ranging from 0-200 G, or a DC field of up to 1 kG. DC magnetometry measurements showed that a 200 G field was sufficient to reach 90% of saturation at room temperature. The finite size of nanoparticles leads to predicted quantization of acoustic phononmodes, with the lowest energy excitations are on the order of tens of wavenumbers. The energies do not shift in a magnetic field, confirming that they are due to phonons rather than magnons. However, the intensity of the phonon excitations changes with field. We describe the effect of the AC magnetic field amplitude, temperature, and particle size on the excitation spectra.

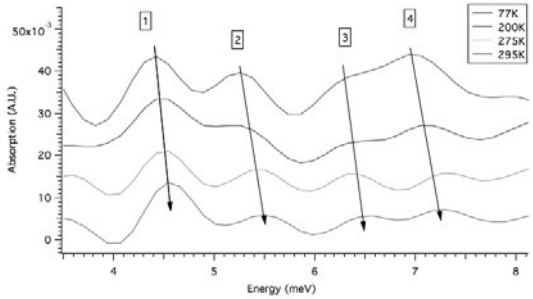

Figure 1. Normalized spectra as a function of temperature between 3 and 8 meV (~25-60 cm^{-1}) showing the periodicity of the excitation features in zero magnetic field, and their small temperature-dependent energy shift.

Measurement of magnetic rotation of magnetic nanoparticles in cultured cells under alternating field

Satoshi Ota[1*], Asahi Tomitaka[2], Tsutomu Yamada[1] and Yasushi Takemura[1]

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Magnetization rotation of intracellular and extracellular magnetic nanoparticles (MNPs) under AC magnetic field was evaluated We have succeeded in measuring AC hysteresis loops of dried, dispersed and fixed MNPs under ac magnetic field at 10–500 kHz [1] Heat dissipation of MNPs has quantitatively indicated without measuring temperature rise, which may be affected by sample or measurement conditions In this present study, AC hysteresis loops of MNPs added to cells were measured by inserting cultivated cells into the pick-up coil

Polyethylenimine (PEI)-coated Fe_3O_4 nanoparticles were prepared PEI and Fe_3O_4 nanoparticles were purchased from Polysciences, Inc and Nanostructured & Amorphous Materials, Inc respectively HeLa cells (human cervical carcinoma line) were cultured and PEI-coated MNPs (400 μg/well) were added into cells After 24 h from adding MNPs, cells were detached with trypsin and hysteresis loops were measured Magnetic field of 50 Oe was applied at 50 kHz of frequency The primary and hydrodynamic diameters of MNPs were 20–30 nm and 157 ± 42 nm in water, respectively Phase contrast and fluorescent microscopic observation confirmed that MNPs were internalized into cells MNPs bound on cell surface were also observed

Figure 1 (a) shows the magnified view of DC major loop of PEI-coated MNPs dispersed in water, fixed with agar and added to HeLa cells, respectively With respect to applying DC magnetic field, coercivity of the samples fixed with agar and added to cells were significant comparing to that of the sample dispersed in water This probably attributed to cluster formation due to aggregation during immobilization in the samples fixed with agar and added to cells [2] AC hysteresis loop of the sample added to cells was similar to the fixed sample because PEI-coated MNPs were aggregated in cells and on cell surface In contrast to DC major loops, coercivity of the samples fixed with agar and added to cells were negligible comparing to the sample dispersed in water in terms of AC minor loops Brownian relaxation was occurred in PEI-coated MNPs dispersed in water However, it was indicated that Brownian relaxation was not occurred in MNPs added to cells because aggregation inhibits the rotation of MNPs AC hysteresis loops measured at higher frequency are also discussed

[1] Nakamura et al , *IEEE Trans. Magn.*, 49, 240, 2013
[2] Dutz et al , *Nanotechnol.*, 22, 265102, 2011

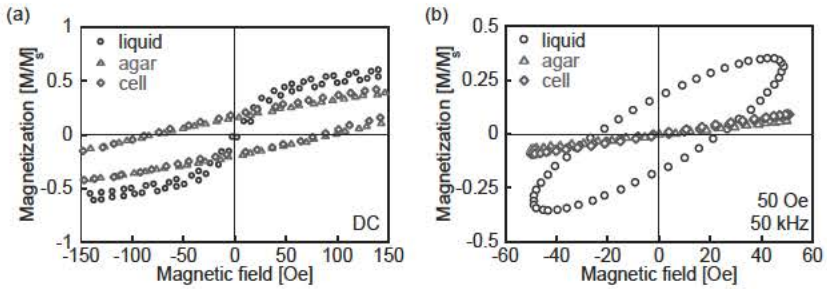

Fig 1 (a) Magnified view of DC major loop and (b) AC minor loops of PEI coated MNPs dispersed in water, fixed with agar or added into HeLa cells

Smart and Biocompatible Fe-Si Nanoparticles

*Ying Jing[1], Wei-Hang Ji[2], Wei Wang[1], Jinming Liu[1], Shihai He[1], Xiao-Ze Jiang[2], Timothy Wiedmann[3], Chun Wang[2] and Jian-Ping Wang[1] **

1.Department of Electrical and Computer Engineering;2.Department of Biomedical Engineering; 3. Department of Pharmaceutics, University of Minnesota, USA; *jpwang@umn.edu

Thermal energy has been realized as an important tool for medical applications. Due to its non-invasive, locally selective potential, considerable effort has been focused on the use of an external, alternating magnetic field for conversion of magnetic work to heat with iron oxide nanoparticles. Proper regulation of thermal energy remains a challenge due to the lack of feedback from the local temperature change to the external power supply. We report the development of biocompatible magnetic nanoparticles that have self-regulated heat generation.

To produce a functional material with intrinsic temperature regulation, we incorporated Si into Fe to produce the desired particles. It is recognized that the T_c is determined by the strength of quantum mechanical exchange-coupling between Fe atoms. As such, the underlying physics justify the use of Si to reduce T_c of Fe by tuning the interaction through a control of the exchange process. Importantly, Fe and Si are relatively nontoxic and therefore can be expected to be processed to produce a biocompatible material.

Fe-Si nanoparticles were fabricated by a sputtering-based gas-phase condensation process and engineered with an adjustable magnetic transition temperature through tuning the Si content. The magnetic moment of these particles is relatively high, and their biocompatibility was established in several cell lines. The nanoparticles were also combined with a thermo-sensitive polymer, which had the capability to release molecules with a magnetic stimulus, thereby providing a platform for locally controlled drug release.

Following the characterization of the magnetic properties of the NPs, the cytotoxicity and the rate of magnetic field heating was evaluated. To examine the biocompatibility of the Fe-Si NPs, the cytotoxicity was tested in cultured mouse embryonic fibroblasts (NIH 3T3) and human umbilical vein endothelial cells (HUVECs) using the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and Fe-Si nanoparticles were proved biocompatible. To test the possibility of using these particles for thermally stimulated drug delivery, a heating experiment was also performed in which the NPs were incorporated into a thermosensitive block copolymer. A poly(ortho ester amides) (POEA) block copolymer was synthesized according to a published method so that a gel-sol transition temperature at about 45 C was obtained.

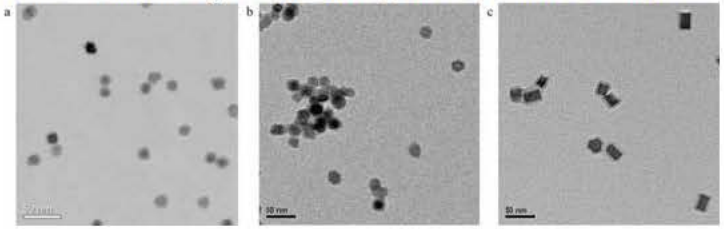

Figure 1. Bright field TEM images of Fe-Si NPs with **a,** 17at% Si. **b,** 25at% Si. **c,** 42at% Si

Diverging Magnetic and Physical Size Distributions of Superparamagnetic Nanoparticles

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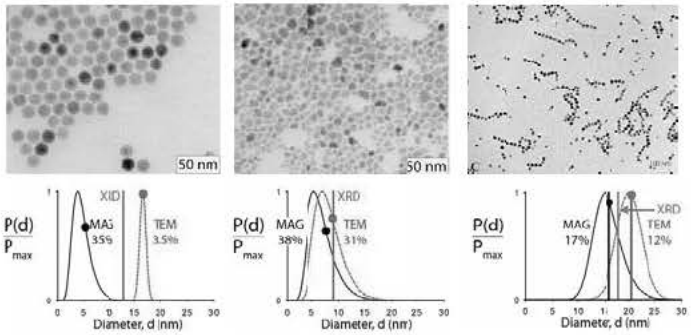
Much effort is devoted to the chemical synthesis of monodisperse iron oxide nanoparticles, the assumption being that monodisperse size equals monodisperse magnetic properties. Sharply defined magnetic properties are crucial for certain applications such as ac-field induced hyperthermia or magnetic particle imaging.[1] We discovered that 3.5% polydispersity in physical size may nevertheless correspond to 35% polydispersity in the effective magnetic diameter, see the figures below.[2] Such magnetic polydispersity implies that the magnetic relaxation dynamics span several orders of magnitude. The divergence between physical and magnetic size distributions is due to poor crystallization and depends on the synthesis method.

These important observations stimulated us to improve our ability to extract magnetic size distributions from magnetization curves. We developed software that does not make any *a priori* assumption about the shape of the magnetic size distribution, assuming neither a lognormal function nor a single population. We took a numerical inversion method well known from the light scattering analysis of colloidal dispersions, and we applied it to the model-independent analysis of the magnetization curves of superparamagnetic materials. We approximate the dipole moment distribution by a series of discrete bins and we fit these to the magnetization curve using a non-negative least squares method. Our mathematical approach was published at the beginning of this year, including validity tests performed on simulations and experimental data.[3] The software is available for free via the website of our university library.[4] The program runs on different platforms (Windows, Mac), works with different data formats (AGM, VSM, SQUID), and we call it MINORIM: Model-Independent NOn-Regularized Inversion Method.



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4. http://hdl.handle.net/10411/10164

Solvothermal synthesis of tunable magnetite nanorods and its transfer from organic phase to water phase

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[a]*Key Laboratory of Synthetic and Natural Functional Molecular Chemistry of Ministry of Education, College of Chemistry and Material Science, Northwest University,* [b]*National Engineering Research Center For Miniaturized Detection Systems,* [c]*College of Life Sciences, Northwest University, Xi'an, P. R. China*

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Compared with spherical nanoparticles, 1D magnetite nanorods offer longer blood circulation times, stronger interaction with tumors, enhanced retention at tumor sites and improved targeting efficiency, making them excellent candidate as targeting pharmaceutical carrier or MRI contrast agents. [1]

Herein, we present a facile solvothermal method to prepare single crystal Fe_3O_4 nanorods with tunable aspect ratio (length from 58 to 250 nm, width from 8 to 64 nm). Then the as-prepared oleic acid-capped hydrophobic nanorods were transferred into water phase by oxidation and decomposition of oleic acid with sodium periodate. The nanorods were characterized by FTIR, TGA, XRD, XPS, and HRTEM. The results indicate that the nanorods are successfully synthesized and transferred into water phase without change in morphs and crystallinity. Significantly, the Ms of nanorods increased from 62.5 to 71.3 emu/g after modification.[2] These water soluble nanorods would have great potential for various biomedical applications such as MRI, magnetic hyperthermia and targeting drug delivery.

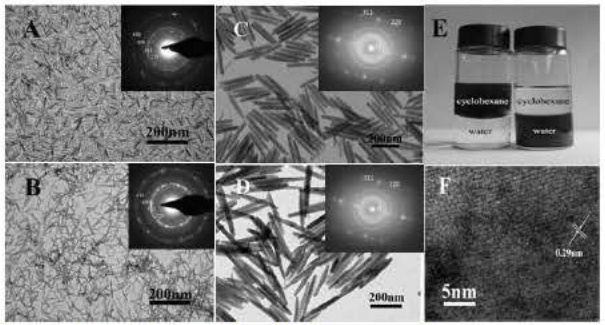

Fig. 1 TEM images (A and C) of nanorods in cyclohexane prepared solvothermally, and transfer of them into the water carrier (B and D) and the corresponding SAED (insets in A, B, C and D) and HR-TEM images (F) of iron oxide nanorods There is no significant change in size and morphology (length in A, B=58nm, in C, D=250nm) The nanorods dispersions before and after transfer are also showed (E)

Reference:

[1] Y. Geng, P. Dalhaimer, S. Cai, *et. al*, *Nat. Nanotechnol.*, **2007**, 2, 249–255.

[2] J.-C. Si, Y. Xing, M.-L. Peng, *et. al*, *CrystEngComm*, **2014**, 16, 512–516.

Microwave-assisted Chemoselective Functionalisation of Iron Oxide Nanoparticles for Cardiovascular Imaging

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The chemoselective and reproducible synthesis of iron oxide nanoparticles for biomedical applications is one of the most important challenges in the field of nanomedicine. This is particularly true if a final clinical application is intended. To achieve this aim we have combined two innovative approaches; the microwave-assisted synthesis of superparamagnetic iron oxide nanoparticles and their chemoselective functionalisation with several biomolecules, also performed in a microwave. We have synthesised six types of multifunctional nanoparticles with good magnetic properties, excellent reproducibility and different biomedical applications.

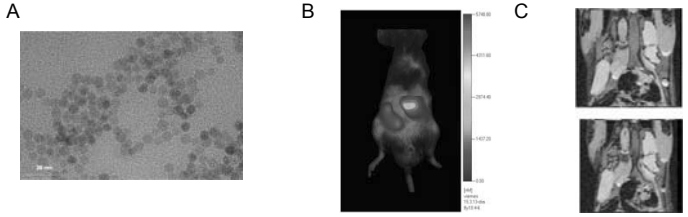

Figure 1. Selected examples of functionalised nanoparticles (A), in vivo optical imaging (B) and Magnetic Resonance Imaging (C)

Among the different applications we will demonstrate the *in vivo* detection of angiogenesis process (Figure 1) and the selective accumulation in atherosclerosis plaque. These nanoparticles have particularly interesting properties for biomedical imaging like a hydrodynamic size of 30 nm, a r_2 value of 173 $mM^{-1}s^{-1}$ and about 5 molecules of the active surfactant per nm^2. The selective accumulation of these particles in atherosclerosis models will be demonstrated by MRI, fluorescence imaging and histology.

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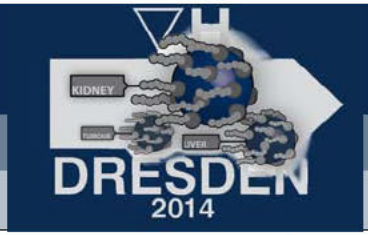
10th Meeting - Dresden 2014

International Conference on the Scientific and Clinical Applications of Magnetic Carriers

TU DRESDEN, CHAIR OF MAGNETOFLUIDDYNAMICS; MEASURING AND AUTOMATION TECHNOLOGY



10th International Conference on the Scientific and Clinical Applications of Magnetic Carriers - Dresden, Germany

Poster Presentations (in alphabetical order by first author)

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2	Ahrentorp	Fredrik	Effective particle magnetic moment of multi-core particles	Johansson	Christer
3	Al Akras	M Ali	Continuous and delayed photohemolysis sensitized with methylene blue and iron oxide particles	Al Akras	M Ali
4	Al-Kaidy	Huschyar	Use of superhydrophobic magnetite particles to build reaction capsules for lab-on-a-chip systems in microliter scale	Al-Kaidy	Huschyar
5	Andreu	Irene	Heating ability of cobalt ferrite nanoparticles showing dynamic and interaction effects	Andreu	Irene
6	Antal	Iryna	Aliskiren-loaded magnetic labelled PLA nanospheres for hypertension treatment	Antal	Iryna
7	Aurich	Konstanze	Evaluation of in vivo imaging of magnetically labelled blood cells	Aurich	Konstanze
8	Bahadur	Dhirendra	Bio-polymer stabilized Fe3O4-graphene as an amphiphilic drug carrier for thermo-chemotherapy of cancer	Bahadur	Dhirendra
9	Baker	Ian	Dartmouth center for cancer nanotechnology excellence: Magnetic hyperthermia	Baker	Ian
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11	Baldikova	Eva	Magnetically modified straw for dyes removal	Baldikova	Eva
12	Becnel	Andrew	Nondimensional scaling of magnetorheological rotary shear mode devices using the mason number	Becnel	Andrew
13	Bednarikova	Zuzana	Poly(lactide) nanoparticles loaded with albumin modified magnetite depolymerize insulin amyloid fibrils	Bednarikova	Zuzana
14	Belousov	Andrey	Preparation of nanotechnology as magnetically-resonant contrasting means during visualization of malignant tumour	Belousov	Andrey
15	Belousov	Andrey	Reduced of erythrocyte destruction by means of magnetite nanoparticles (MCS-B)	Belousov	Andrey
16	Benelmekki	Maria	Stable colloidal suspension of Fe-Ag nanoparticles encapsulated by an amorphous Si shell prepared by inert-gas-condensation meth	Benelmekki	Maria
17	Berenguel-Alonso	Miguel	Magnetic actuator for the control and mixing of magnetic bead-based reactions on-chip	Berenguel-Alonso	Miguel
18	Berrin	Saracoglu	3D formation of cancer stem cells within MCF-7 derived mammospheres and hyperthermia treatment	Berrin	Saracoglu
19	Beyk Beyk	Tina	Effect of precipitation agent on morphology of Fe3O4 nanoparticles in hydrothermal process	Ghasemi	Ebrahim
20	Blanco-Andujar	Cristina	Highly controllable microwave synthesis of biocompatible iron oxide nanoparticles with tailored magnetic relaxation properties	Blanco-Andujar	Cristina
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23	Bokharaei	Mehrdad	Encapsulation of Hydrophilic and Lipophilic Magnetic Nanoparticles in PLA Microspheres using a Microfluidics Chip	Bokharaei	Mehrdad
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53	Dvorakova	Veronika	Innovative approach for quantum dots antibody labeling based on antigen-modified magnetic particles	Dvorakova	Veronika
54	Dynes	Jake	A novel code for simulation of magnetic carrier laden fluids with structure dependent rheology in blood vessels	Yecko	Philip
55	Eamegdool	Steven	Iron oxide nanoparticles as multi-functional probes for tracking human foetal neural stem cells	Pham	Binh
56	Eberbeck	Dietmar	Magnetic behaviour of DDM128 in agarose gel, gelatine and sugar matrix	Eberbeck	Dietmar
57	El Hajj Diab	Darine	High-frequency magnetic field induced cell death in endocrine tumors cells targeted by magnetic nanoparticles	El Hajj Diab	Darine
58	Esposito	Tullio	CpG ODN coated magnetic nanoparticles have augmented activity via toll-like receptor 9 (TLR9) and potential vaccine applications	Esposito	Tullio
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85	Henriksen	Anders	Optimization of magnetoresistive sensor current for on-chip magnetic bead detection using the sensor self-field	Henriksen	Anders
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92	Hunt	Haley	Measurement of the size effects on the biodistribution of polymer sterically stabilized magnetic nanoparticles	Hunt	Haley
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97	Kačenka	Michal	Transverse relaxivity of silica coated manganite nanoparticles: The effects of composition and size	Kačenka	Michal
98	Kashevsky	Bronislav	Magnetic hyperthermia with high-coercivity nanoparticles	Kashevsky	Bronislav
99	Kim	Jongsik	Development of an intravascular magnetomotive optical coherence tomography system	Kim	Jongsik
100	Kistrup	Kasper	Liquid carry-over in an all-polymer chip system for magnetic bead-based solid phase extraction	Kistrup	Kasper
101	Kitenbergs	Guntars	Magnetic particle mixing with magnetic micro-convection for microfluidics	Kitenbergs	Guntars
102	Klein	Todd	Domain nucleation array and its interaction with magnetic nanoparticles	Klein	Todd
103	Klein	Stefanie	Iron oxide nanoparticles for radiation therapy	Klein	Stefanie
104	Knopke	Christian	Numerical simulation of different dipole-dipole-interaction models and their influence on temperature dependent magnetorelaxom	Knopke	Christian
105	Koktan	Jakub	Hybrid silica coated magnetic nanoparticles decorated with gold	Koktan	Jakub
106	Kolesnichenko	Vladimir	NMR relaxivity studies on surfactant-free superparamagnetic iron oxide nanoparticles: The effect of particle size, magnetization and	Kolesnichenko	Vladimir
107	Kolokithas-Ntoukas	Argiris	Condensed colloidal magnetite nanocrystal clusters for theranostic applications	Bakandritsos	Aristides
108	Kolokithas-Ntoukas	Argiris	Design and evaluation of epitaxially condensed colloidal nanocrystal clusters with superior magnetic properties for biomedical appli	Kolokithas-Ntoukas	Argiris
109	Komissarova	Lubov	Anti-tumor activity of hemin immobilized on magnetic microparticles	Komissarova	Lubov
110	Komissarova	Lubov	Possibility of using a new magnetic carbon sorbent as doxorubicin carrier	Gorbunova	Nellya
111	Koneracka	Martina	Magnetic fluids optimization for contrast enhancement in magnetic resonance imaging	Koneracka	Martina
112	Kopcansky	Peter	Destroying activity of magnetoferritin on lysozyme amyloid fibrils	Kopcansky	Peter
113	Koralewski	Marceli	Magnetooptical investigation of ferritin iron uptake and release	Koralewski	Marceli
114	Krafcik	Andrej	Computational analysis of magnetic field induced deposition of magnetic particles in lung alveolus in comparison to deposition prod	Krafcik	Andrej
115	Kralj	Slavko	Magnetic assembly of superparamagnetic nanoparticle clusters into peapod-like structures	Kralj	Slavko
116	Krämer	Florian	Colloidal stability of silica-encapsulated ni nanorods in moderate electrolytes and their biocompatibility to human brain microvascu	Krämer	Florian
117	Kubovcikova	Martina	Preparation, stability and biocompatibility of magnetic fluid modified by poly(ethylene glycol)	Kubovcikova	Martina
118	Kucerova	Jana	Magnetic beads-based DNA extraction: Different techniques compatible with PCR and microfluidic systems	Kucerova	Jana
119	Kulkarni	Sandip	Quantifying the motion of magnetic nanoparticles through liver, kidney and brain tissues	Lamar	Mair
120	Kumari	Monika	Assessing superparamagnetic iron oxide nanoparticles with first order reversal curves	Kumari	Monika
121	Kuznetsov	Oleg	Carbon-encapsulated iron nanoparticles for hyperthermia and other biomedical applications	Kuznetsov	Oleg
122	Lak	Aidin	Resolving particle size modality in iron oxide based magnetic ferrofluids using dynamic and static magnetic measurements	Lak	Aidin
123	Lamrani	Sabrina	X-ray diffraction and magnetic studies of permalloy thin films grown by evaporation	Lamrani	Sabrina
124	Landgraf	Lisa	High biocompatibility of asymmetric gold at iron oxide nanoparticles with excellent properties as drug carriers and for multimodal ir	Landgraf	Lisa
125	Leitgeb	Maja	Toxicity of magnetic chitosan micro and nanoparticles as carriers for biologically active substances	Leitgeb	Maja
126	Li	Wensong	Rapid and large-scale separation of magnetic nanoparticles by low-field permanent magnet with gas assistance	Yang	Liangrong
127	Liebl	Maik	A rabbit sized phantom for validation of magnetic nanoparticle imaging	Liebl	Maik

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128	Liu	Peng	Preparation and characterization of monodisperse magnetic microspheres using a T-shaped microchannel reactor	Liu	Peng
129	Löwa	Norbert	Detecting changes during cellular uptake of magnetic nanoparticles using magnetic particle spectroscopy	Löwa	Norbert
130	Löwa	Norbert	Hydrodynamic and magnetic fractionation of magnetic nanoparticles for MPI	Löwa	Norbert
131	Lüdtke-Buzug	Kerstin	Development of SPION-coatings for visualization of surgical instruments in magnetic particle imaging	Lüdtke-Buzug	Kerstin
132	Lunov	Oleg	Novel insight into mechanism of magnetic field action on cells with internalized nanoparticles	Lunov	Oleg
133	Lupu	Nicoleta	Novel Fe-ETM-Nb-B (ETM = TI, Ta, Mn) glassy alloys for use in magnetic hyperthermia	Lupu	Nicoleta
134	Macková	Hana	Investigation of oxidative stress of colloidally stable polymer-modified iron oxide nanoparticles and their anti-tumor activity	Macková	Hana
135	Maderova	Zdenka	The use of complex magnetic biomaterial for decreasing pseudomonas aeruginosa biofilm formation	Maderova	Zdenka
136	Mair	Lamar	Single-aperture microshell neuroparticlesTM for controlled CNS drug delivery	Mair	Lamar
137	Mandal	Swapan	Enhanced magnetic and size dependent properties of oleic acid stabilized BiFeO3 nanocrystals at room temperature	Mandal	Swapan
138	Mardinoglu	Adil	Modelling the size of SPIONs in stent assisted magnetic drug targeting applications	Mardinoglu	Adil
139	Martins	Murillo	Characterization with X ray and neutron scattering techniques of a magnetic bio-nanocomposite to be used in the treatment of brea	Martins	Murillo
140	Matuszak	Jasmin	Accumulation of circulating superparamagnetic iron oxide nanoparticles (SPIONs) in endothelial cells: Effects on endothelial viability	Matuszak	Jasmin
141	Meffre	Anca	Novel route of water soluble iron based nanoparticles for magnetic hyperthermia	Meffre	Anca
142	Melnikova	Lucia	Structural properties of magnetoferritin by small angle X-rays and neutrons scattering methods	Melnikova	Lucia
143	Mertz	Damien	Protein micro/nanoparticles assembled via isobutyramide groups	Mertz	Damien
144	Mihesan	Claudia	Formation by LAL and characterization of citric acid-coated iron oxide nanoparticles	Mihesan	Claudia
145	Mischenko	Ilya	Mössbauer evaluation of the interparticle magnetic interactions within the magnetic hyperthermia beads	Mischenko	Ilya
146	Mitamura	Yoshinori	Effects of a high gradient magnetic field on flowing erythrocytes in a hollow fiber membrane oxygenator	Mitamura	Yoshinori
147	Moise	Sandhya	A study of the cellular-nanoparticle interactions and assessment of the magnetic response of novel bacterially synthesized substitut	Moise	Sandhya
148	Mojica-Pisciotti	Mary	In vitro and in vivo experiments with functionalized SPIONs for medical applications	Mojica-Pisciotti	Mary
149	Mojica-Pisciotti	Mary	Iron oxide nanoparticles: An experimental study on the magnetic heating effect	Mojica-Pisciotti	Mary
150	Molcan	Matus	Energy losses in bacterial magnetosomes as potential hyperthermia material	Molcan	Matus
151	Moore	Lee	Design of a continuous biomagnetic algae harvester	Moore	Lee
152	Muela	Alicia	Hyperthermia response of magnetosomes extracted from magnetospirillum gryphiswaldense strain MSR-1	Fdez-Gubieda	M. Luisa
153	Müller	Robert	Optical detection of nanoparticles in a living system under the influence of a magnetic	Müller	Robert
154	Murakami	Makoto	Magnetic iron oxide nanoparticles having high AC-susceptibility	Murakami	Makoto
155	Mykhaylyk	Olga	Colloidal stability and magnetophoretic mobility of the silica iron oxide magnetic nanoparticles and their assemblies for gene delive	Mykhaylyk	Olga
156	Nantz	Michael	Amf-induced release of iron oxide-bound substrates via cyclization of thermally responsive amino-carbonates and -carbamates	Nantz	Michael
157	Narayanasamy	Kaarjel	Improving transfection efficacy using nanoparticles inmagnet-assisted gene delivery	Dobson	Jon
158	Naserimohajad	M. Mehdi	Design of High Frequency Magnetic Hyperthermia System for Human Cancer Treatment using Superparamagnetic Nano Particles	Naserimohajad	M. Mehdi
159	Natividad	Eva	Why measuring SAR in function of temperature may result useful and/or interesting	Natividad	Eva
160	Nehilla	Barrett	Rapid and controlled transition of magnetic nano- to micro-particles: A useful feature for bioseparations	Nehilla	Barrett
161	Nemala	H.	Investigation of magnetic properties of Fe_3O_4 nanoparticles using temperature dependent magnetic hyperthermia in ferrofluids	Vaishnava	Prem

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162	Nesztor	Dániel	Controlled clustering of PAM-coated superparamagnetic iron oxide nanoparticles through PEI	Nesztor	Dániel
163	Neubert	Jenni	Effects of different superparamagnetic iron oxide nanoparticles on murine primary brain cells	Neubert	Jenni
164	Niehaus	Jan	Controlled clustering and functionalization of SPIOs	Niehaus	Jan
165	Nikolaev	Boris	Instrumental approach for analysis of protein function in magnetic nanocarriers: 31P NMR study of atpase cycle of heat shock prote	Nikolaev	Boris
166	Nikolaev	Boris	Modelling of NMR relaxation immunoanalysis using superparamagnetic complement system: interferon-immunonanomarker	Nikolaev	Boris
167	Ooi	Chin Chun	Design for highly parallel and uniform magnetic cell separation	Ooi	Chin Chun
168	Orlov	Alexey	Express dry-reagent bioassay based on detection of magnetic nanoparticles from the entire volume of 3D structures	Orlov	Alexey
169	Ota	Satoshi	Differences between Brownian and Néel relaxation properties evaluated by AC susceptibility measurements	Ota	Satoshi
170	Pacakova	Barbara	Balanced nanoparticle spin disorder for enhancement of cancer treatment	Pacakova	Barbara
171	Palma	Susana	A new fucose rich bacterial exopolysaccharide for SPION stabilization	Palma	Susana
172	Pardowitz	Johannes	Field induced cluster formation detected by nuclear magnetic resonance	Pardowitz	Johannes
173	Parr	Marina	Electro-optical and DLS study of interaction between magnetic nanoparticles conjugated to Hsp70 and its antibodies	Parr	Marina
174	Payer	Petra	Mild magnetic separation of circulating tumour cells	Payer	Petra
175	Pivetal	Jeremy	Selective micro-patterning of microbial cells onto micro-magnet arrays for single cell analysis	Pivetal	Jeremy
176	Polikarpov	Mikhail	Mössbauer study of biodegradation of polymer coated magnetic beads	Polikarpov	Mikhail
177	Polikarpov	Dmitry	Mössbauer study of exogenous iron redistribution between the brain and the liver after administration of ferrofluid in the ventricle	Polikarpov	Dmitry
178	Pombo Garcia	Karina	Zwitterionic-coated ultrasmall iron oxide nanoparticles for magnetic resonance imaging	Pombo Garcia	Karina
179	Pömpner	Nadine	Uptake and cytotoxic effects of methotrexate coupled magnetic nanoparticles in different breast cancer cell lines for multimodal tre	Pömpner	Nadine
180	Pospiskova	Kristyna	Low-temperature postmagnetization of sensitive biological materials	Pospiskova	Kristyna
181	Prabu	Chakrapani	Encapsulation of methotrexate magnetic microcapsules for targeted rheumatoid arthritis therapy	Latha	Subbiah
182	Prabu	Chakrapani	Formulation optimisation and evaluation of prednisolone loaded magnetic shells	Selvamani	Palanisamy
183	Puddu	Michela	Stable and inert DNA/silica encapsulates with magnetic cores as tracing/tagging tools	Puddu	Michela
184	Pyanzina	Elena	Influence of magnetic interparticles interaction on the macroscopic behavior of magnetic fluids	Pyanzina	Elena
185	Pyshnyi	Michael	Multi-beam ultrasonic doppler imaging technique improves sensitivity and spatial resolution of visualization of magnetic micro- and	Pyshnyi	Michael
186	Qiuyu	Zhang	Fabrication and characterization of 1 D polymer magnetic nanochains with thermal and ph response for controlled drug release	Qiuyu	Zhang
187	Radon	Patricia	Magnetic particle spectroscopy for real-time quantification of magnetic nanoparticles in a flow phantom	Radon	Patricia
188	Radović	Magdalena	Multifunctional 90Y-labelled Fe3O4-PEG600 nanoparticles for possible application in combined radionuclide-magnetic hyperthermia	Radović	Magdalena
189	Raikher	Yuriy	Modelling of magnetic nanoparticle hyperthermia with allowance for the néel and brown relaxation mechanisms	Raikher	Yuriy
190	Ramachandra Kurup	Arathyram	Mussel inspired electrospun smart magnetic nanofibers for hyperthermic chemotherapy	Ramachandra K. S.	Arathyram
191	Ramaswamy	Bharath	Chaining and movement of magnetic nanoparticles in brain tissue	Lamar	Mair
192	Remmer	Hilke	Suitability of magnetic single- and multi-core nanoparticles to detect protein binding with dynamic magnetic measurement techniq	Remmer	Hilke
193	Ruiz	Amalia	Biotransformation of magnetic nanoparticles as a function of the coating in a rat model	Ruiz	Amalia
194	Rümenapp	Christine	Detection of molecules and cells using magnetic resonance with magnetic nanoparticles	Rümenapp	Christine

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195	Rümenapp	Christine	Monitoring of the aging of magnetic nanoparticles using moessbauer spectroscopy	Rümenapp	Christine
196	Sader	Maha	Use of magnetic nanoparticles functionalized with an antagonist of nucleolin named NUCANT 6L for therapy and diagnosis of breast	Sader	Maha
197	Sakellari	Despoina	Exploring multifunctional potential of commercial ferrofluids by magnetic particle hyperthermia	Sakellari	Despoina
198	Sanchez-Antequera	Yolanda	Magnetofection technology for efficient mRNA delivery to somatic cells	Sanchez-Antequera	Yolanda
199	Schamber	Stefania	Iron oxide polyelectrolyte multilayer particles: Transport of sirna into cells	Schamber	Stefania
200	Scharfenberg	Dorothee	Directing nanoparticle-loaded brain cancer cells by a magnetic field	Scharfenberg	Dorothee
201	Schlenk	Florian	Biocompatibility testing of intravenously applied iron oxide contrast agents in vitro and ex ovo	Fischer	Dagmar
202	Schmidt	Daniel	Parameterization of the harmonic content of the complex MPI signal of magnetic tracers using a set of polynomial coefficients	Schmidt	Daniel
203	Schneider	Thomas	Facile microwave synthesis of uniform magnetic nanoparticles for magnetic drug targeting	Schneider	Thomas
204	Schrittwieser	Stefan	Protein biomarker detection by a homogeneous label-free method based on rotational dynamics of hybrid magnetic nanorods	Schrittwieser	Stefan
205	Schumacher	Christoph	Quantitative recovery of magnetic nanoparticles from flowing blood: Trace analysis and the role of magnetization	Schumacher	Christoph
206	Seidel	Maria	Preparation and characterization of phantoms for imaging applications	Seidel	Maria
207	Senn	Nico	Assessing biodistribution of magnetic nanoparticles in mouse tissue using remanent saturation magnetization	Senn	Nico
208	Sergiu	Ruta	Theoretical study of magnetic hyperthermia: Investigation of superparamagnetic and hysteresis energy loss	Sergiu	Ruta
209	Shaw	Martin	Application of a novel magnetic immunoassay system to point of care diagnostics: Development and validation of a high sensitivity	Shaw	Martin
210	Shevtsov	Maxim	Functionalized superparamagnetic iron oxide nanoparticles (SPIONs) for diagnostics and therapy of malignant brain tumours	Shevtsov	Maxim
211	Shipunova	Victoria	Magnetic nanoparticles for imaging and quantitative analysis of the oncomarker HER2/neu expression on the cell surface	Shipunova	Victoria
212	Shubitidze	Fridon	Study of the heating mechanism of new type of magnetic nanoparticles with high specific absorption rate at low field strength	Shubitidze	Fridon
213	Siposova	Katarina	The molecular mass of dextran modifying magnetite nanoparticles affects destruction of insulin amyloid fibrils	Gazova	Zuzana
214	Skumiel	Andrzej	Advantages and disadvantages of different methods of temperature measurement in the magnetic fluid hyperthermia studies	Skumiel	Andrzej
215	Slabu	Ioana	Detection sensitivity of MRI and MPI for mesh implants with incorporated magnetic nanoparticles	Slabu	Ioana
216	Slabu	Ioana	Simulation of magnetic nanoparticle interactions in magnetic drug targeting models	Slabu	Ioana
217	Słomiński	Konrad	Influence of bsa concentration on acoustic properties of albumin-modified magnetic fluid	Jozefczak	Arkadiusz
218	Sobisch	Titus	Novel method for fast characterization of magnetic properties of particles and magnetic beads in centrifugal/magnetic field	Sobisch	Titus
219	Sodipo	Bashiru	Non-seeded synthesis and characterization of highly magnetic and ultra thin silica coated superparamagnetic iron oxide nanopartic	Sodipo	Bashiru
220	Soukup	Dalibor	The use of AC-susceptometry for in vitro magnetic nanoparticle investigations	Soukup	Dalibor
221	Sousa	Marcelo	Magnetic hyperthermia of Mn1-xCoxFe2O4 nanoparticles prepared via hydrothermal high-pressure synthesis method	Sousa	Marcelo
222	Sprenger	Lisa	Continuous size-dependent separation of microspheres in human whole blood in microfluidic cascading spirals	Sprenger	Lisa
223	Sreekumari	Aparna	Anisotropy of magnetoviscous effect in strongly interacting ferrofluids	Sreekumari	Aparna
224	Stange	Robert	Electromagnetic sample-mixer - Biomagnetic separation with variable magnetic fields	Stange	Robert
225	Stapf	Marcus	Intravenously applied PEG nanoparticles for magnetic hyperthermia enrich mostly in liver and lungs	Stapf	Marcus

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226	Steiner	Mark-Steven	High-purity enrichment of human hematopoietic stem cells utilizing MACS technology	Steiner	Mark-Steven
227	Stepanov	Victor	Theoretical aspects of AC susceptometry of magnetic nanoparticles in a suspension	Stepanov	Victor
228	Stone	Roland	Synthesis of a heterobifunctional polymer platform for tailored multimodal theranostic magnetic particles	Mefford	Thompson
229	Strbak	Oliver	A novel method for non-invasive iron oxide nanoparticles quantification using magnetic resonance imaging	Strbak	Oliver
230	Strbak	Oliver	Influence of saline and glucose molecules to contrast properties of clinically used MRI contrast agents	Strbak	Oliver
231	Sumari	Deborah	Magnetic cytosmear for specialized cytological analyses in global health and diseases	Sumari	Deborah
232	Syrovets	Tatiana	Swelling and apoptosis of monocytic leukemia cells in high gradient magnetic fields	Syrovets	Tatiana
233	Szczerba	Wojciech	Characterization of multicore superparamagnetic iron oxide nanoparticles using XAFS and SAXS	Thünemann	Andreas
234	Theumer	Anja	Functionalized superparamagnetic iron oxide nanoparticles exert diverse effects on multicellular spheroids	Theumer	Anja
235	Thomas	Guillaume	Dota-functionalized magnetite nanoparticles as contrast agents for MRI/PET double imaging	Thomas	Guillaume
236	Tokarev	Alexander	Reconfigurable anisotropic coatings via magnetic field directed assembly and translocation of locking magnetic chains	Tokarev	Alexander
237	Tomasovicova	Natalia	Elimination of magnetic nanoparticles with various surface modifications in the blood stream in vivo	Tomasovicova	Natalia
238	Tombácz	Etelka	Physicochemical and colloidal criteria of magnetic nanoparticle systems eligible for biological testing	Tombácz	Etelka
239	Torres	Teobaldo	Experimental observation of brownian contribution to the relaxation mechanisms of CoXFe3-XO4 nanoparticles and theoretical ana	Torres	Teobaldo
240	Tóth	Ildikó	Magnetic hyaluronate hydrogels: preparation and characterization	Tóth	Ildikó
241	Tóth	Ildikó	Preparation and characterization of chondroitin-sulfate-A-coated magnetite nanoparticles for biomedical applications	Tóth	Ildikó
242	Trachtova	Stepanka	Study on the encapsulation of magnetic cores using real time polymerase reaction	Trachtova	Stepanka
243	Turcu	Rodica	Magnetic microgels for drug targeting applications: Physical-chemical properties and cytotoxicity evaluation	Turcu	Rodica
244	Unterweger	Harald	Magnetic iron oxide nanoparticles with cisplatin-bearing polymer coating for targeted drug delivery	Unterweger	Harald
245	van Reenen	Alexander	Accurate quantification of magnetic particle properties by intra-pair magnetophoresis for nanobiotechnology	van Reenen	Alexander
246	van Reenen	Alexander	Dynamic magnetic particle actuation for integrated lab-on-chip biosensing	van Reenen	Alexander
247	van Reenen	Alexander	Magnetic field-induced rotaphoresis for controlled redistribution of magnetic particles over a surface	van Reenen	Alexander
248	van Vliembergen	Roland	A rotating molecular ruler: Determining nanometer-scale particle-particle distances in an optomagnetic cluster assay	van Vliembergen	Roland
249	Varchulová Novákov	Zuzana	Cytotoxicity tests of bacterial magnetosomes on cell lines HT-29 and A549	Varchulová N.	Zuzana
250	Veverka	Miroslav	Magnetic and relaxometric studies of silica-coated Co-Zn ferrite	Veverka	Miroslav
251	Vieira	José	Assisted formation of alkoxysilanes on the surface of ferrite nanoparticles and their magnetic properties	Chaker	Juliano
252	Volmer	Marius	Using permalloy based planar hall effect sensors to capture and detect superparamagnetic beads for lab on a chip applications	Volmer	Marius
253	von der Lühe	Moritz	Fe3O4@polydehydroalanine hybrid particles	von der Lühe	Moritz
254	Voronina	Natalia	Novel approach to magnetically guided delivery of microrna to endothelial cells	Voronina	Natalia
255	Wang	Yi	Experimental and statistical investigation of signal to noise ratio for GMR nanosensors for molecules detection	Wang	Yi
256	Wang	Jian-Ping	Recent Progress of Magnetic Biosensing Technology and Detection of Mercuric Ion for Environmental Monitoring	Wang	Jian-Ping

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257	Wereley	Norman	Remixability of magnetorheological fluid after exposure to centripetal acceleration	Wereley	Norman
258	Wu	Kai	Colorize magnetic nanoparticles using a new search coil based testing method	Wu	Kai
259	Xie	Lei	Measuring stratification in a magnetorheological fluid column using a vertical axis inductance monitoring system	Xie	Lei
260	Xue	Wei	Magnetic property analysis of cells with single-cell magnetophoresis	Xue	Wei
261	Yadavalli	Tejabhiram	Dual responsive fluorescent magnetic nanopolymers for targeted drug delivery	Yadavalli	Tejabhiram
262	Yagci acar	Havva	Development of magnetic and luminescent hybrid nanoparticles as theranostic materials	Yagci acar	Havva
263	Yoshida	Takashi	Effect of viscosity on harmonic signals from magnetic fluid	Yoshida	Takashi
264	Yu	Siming	Can SPIONs aggregation be controlled in biological media? (yes) …but … can SPIONs aggregation be advantageous for some applicat	Roig	Anna
265	Yu	Lina	DNA-conjugated magnetic nanoparticles for remotely controlled drug release	Yu	Lina
266	Yu	Lina	Enhanced stability of high moment FeCo nanoparticles with SiO2 protection layer for bio-application	Yu	Lina
267	Zablotskii	Vitalii	Magnetically driven differentiation of mesenchymal stem cells	Zablotskii	Vitalii
268	Zabow	Gary	In vivo MRI single-cell tracking using microfabricated magnetic microparticles	Zabow	Gary
269	Zaloga	Jan	Lauric acid - protein coated hybrid SPIONS with enhanced biocompatibility for magnetic drug targeting	Zaloga	Jan
270	Zavisova	Vlasta	Cytotoxicity of several kinds of magnetic fluids	Zavisova	Vlasta
271	Zborowski	Maciej	Magnetic field visualization in applications to magnetic cell separation and drug targeting	Zborowski	Maciej
272	Zelepukin	Ivan	Synthesis of SiO2-coated magnetic nanolabels with controlled surface properties	Zelepukin	Ivan
273	Zhong	Yi	Electrospun magnetic nanofibre mats - a new bondable biomaterial using remotely activated magnetic heating	Zhong	Yi
274	Zlateski	Vladimir	Efficient magnetic recycling of covalently attached enzymes on carbon-coated metallic nanomagnets	Zlateski	Vladimir
275	Zubarev	Andrey	Hyperthermia effect of non-spherical magnetic nanoparticles under alternating magnetic field	Abu-Bakr	Ali

Bioconjugation of multimodal nanoprobes for molecular imaging of vulnerable atherosclerosis plaques

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Atherosclerosis is an inflammatory disease associated with the formation of atheroma plaques liable to rupture. As the risk of plaque rupture is more related to the plaque contents than to the plaque size, a consequence is that the molecular imaging of these plaques has risen as a new imperative. Current studies tend towards the development of non-invasive targeted methods particularly by Magnetic Resonance Imaging to assess the cellular components that underlie the risk of rupture. Recently, human antibody fragments able to recognize molecules over-expressed during the course of atherogenesis have been selected either *in vitro* on activated platelets or *in vivo* in animal models of atherosclerosis, using phage display biotechnology and further processed as scFv (single chain Fragment variable) fragments in Pichia Pastoris[1].

In this communication, we report on the development of multimodal probes called VUSPIO[2] for Versatile UltraSmall SuperParamagnetic Iron Oxide (scheme thereafter)[2-6] based on covalent dextran/iron oxide nanoparticles-bearing heterobifunctional polyethylene oxide (PEO) spacers. Here, near-infrared fluorescent dyes as well as scFv have been grafted through a site-specific conjugation approach via thiol-alkylation of maleimido groups present at the end of PEO chains (Figure 1). In particular the number of scFv grafted per VUSPIO have been controlled by a set of biochemical approaches.

First results of the use of these nanoparticles will be also presented in the frame of two non-invasive imaging modalities: near-infrared fluorescence imaging and Magnetic Resonance Imaging (MRI) for molecular imaging of vulnerable atherosclerosis plaques in ApoE-/- mice.

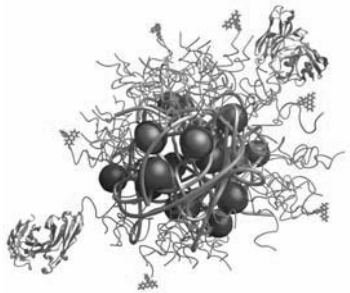

Figure 1 : Schematic representation of the multimodale nanoprobe VUSPIO

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Effective Particle Magnetic Moment of Multi-Core Particles

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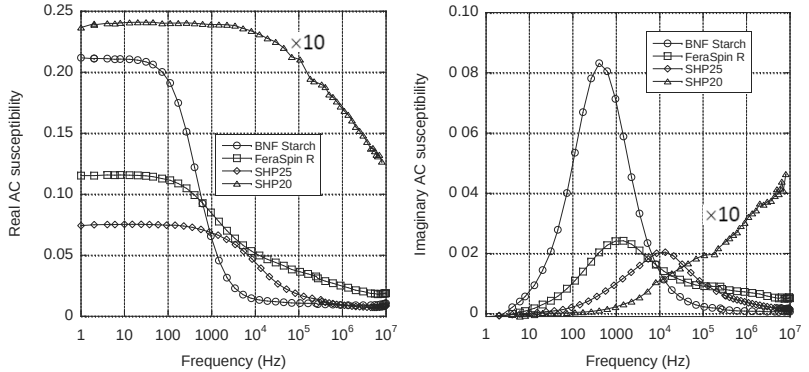
Magnetic multi-core particles consist of several magnetic single-domains geometrically positioned in different types of configurations Dependent on the size distribution and configuration of the single-domains inside the particle and the hydrodynamic particle size distribution, different types of magnetic behavior can be obtained The magnetization process of the magnetic multi-core ensemble will depend on both the individual magnetic moments of the single-domains as well as on the total effective magnetic moment of the particle (that depends on both the magnetic moment values and moment orientations of the individual single-domains)

In this study, we will investigate and present how the effective particle moment is coupled to the individual moments of the single-domains by using different measurement techniques: Static Magnetization, AC Susceptometry, Particle Rotation, DLS and TEM We will study two magnetic multi-core particle systems – BNF Starch from Micromod with a mean particle diameter of 80 nm and FeraSpin R from nanoPET with a mean particle diameter of 60 nm – and two single-core particle systems – SHP25 and SHP20 with mean particle core diameters of 25 nm and 20 nm from Ocean NanoTech AC susceptometry analysis of the four particle systems can be seen in the figure below



Real part (left) and imaginary part (right) of the AC susceptibility versus frequency of the four different particle systems. The susceptibilities are given as volume susceptibilities. The BNF Starch, FeraSpin R and SHP25 systems show Brownian relaxation peaks at frequencies between 460 Hz and 11 kHz while the SHP20 particle shows a Néel relaxation peak above 10 MHz. The susceptibility values for SHP20 have been magnified by 10 times. The particle concentrations are: 24 mg/ml for BNF, 10 mg/ml for FeraSpin R, 5 mg/ml for SHP25 and 5 mg/ml for SHP20. From dilutions of the samples we found no evidence of particle-particle interactions in the dynamic magnetic response.

The work in this study is from the EU FP7 NMP project NanoMag (www nanomag-project eu) started in November 2013, a new and innovative project on Nanometrology of Magnetic Nanoparticles with a consortium involving 18 research institutes, universities, companies and metrology institutes

CONTINUOUS AND DELAYED PHOTOHEMOLYSIS SENSITIZED WITH METHYLENE BLUE AND IRON OXIDE NANOPARTICLES (Fe_3O_4)

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Abstract

This research present the sensitization of methylene blue (MB), a photodynamic therapy photosensitizer which showed phototoxicity for many tumor cells *in vitro* incorporated with iron oxide nanoparticles (Fe_2O_3), which offer magnificent interaction both inside and outside the surface of biomolecules to bring about a radical change in cancer treatment and diagnosis, together with red blood cells (RBC's). The study investigated the sensitization of continuous photohemolysis (CPH) for MB with and without iron oxide, delayed photohemolysis (DPH) at room temperature, DPH at different irradiation temperature (T_{irr}) and at different incubation temperature (T_{inc}) for the same irradiation time (T_{irr}). Gompertz function is apply as an appropriate model to fit the collected experimental data for CPH and DPH with minimum errors. Fractional photohemolysis ratio (***a***) and fractional photohemolysis rate (***b***) of this model and relative steepness of the curves for the photohemolysis were measured for a series of sensitizer concentrations and DPH irradiation times. The power dependence found to be greater than one for DPH and less than one for CPH. Our results indicate the relative steepness for CPH and DPH are almost independent on MB and MB with iron oxide concentrations and at different T_{irr} and T_{inc}. In addition, the parameter ***b*** is independent of iron oxide concentration while the parameter ***a*** decreases with increasing iron oxide concentration. In conclusion, CPH and DFH process are much lower in the presences of methylene blue.

Keywords: Iron Oxide Nanoparticle, Photohemolysis, Methylene Blue

Use of superhydrophobic magnetite particles to build reaction capsules for lab-on-a-chip systems in microliter scale

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Magnetic nanoparticles and microparticles are used for the production of microreactors to subsequently be applied for lab-on-a-chip reactions. Lab-on-a-chip reactors are widely used in the field of microfluidics and are used in (bio) chemical analysis such as PCR and electrophoresis. In these conventional lab-on-a-chip systems, solvents and samples are passed through defined microfluidic channels and controlled by complex installations. The channels are for example realized by injection molding and hot embossing.

A significant simplification of lab-on-a-chip platforms is offered by the approach to move the liquid phase without these fittings on the surface of a reaction platform (lab-in-a-drop). The microreactors can be simultaneously positioned on a hydrophobic platform by means of electromagnetic field gradients [1]. This is possible as the outer shells of the microreactors are made of a thin layer of superhydrophobic magnetic particles. The superhydrophobic particles are synthesized by precipitation of Iron(II) and Iron(III) ions followed by a functionalization with fluorinated silanes.

The microreactors inherit an aqueous reaction solution of 3 – 20 µL. Due to the different surface tension of the particles and of the aqueous solution the hydrophobic particles envelop the solution by self-assembly. The prototype of a reaction platform for a random movement of the microreactors in two dimensions currently consists of a 3x3 matrix of electric coils that accommodate neodymium magnets. By the coils, the magnets can be moved perpendicular to the plane of the platform, so that the microreactors can follow the respective field gradients. The microfluidic platform could be used e.g. to detect the highly pathogenic avian influenza virus H5N1 in a throat swab sample by using magnetic forces to manipulate a free droplet consists of hydrophobic superparamagnetic particles In initial tests, the laccase A and ß-Glucosidase were used as a model system for the surface immobilization to perform subsequent color reaction tests with the immobilized systems and microreactors. An enzymatic fluorescence reaction is used as proof-of-principle to examine the functionality and analytical reproduc bility of the platform.

[1] N. Tippkötter, H. Al-Kaidy, R. Ulber; Europäisches Patent 13 003 400.2

Heating ability of cobalt ferrite nanoparticles showing dynamic and interaction effects

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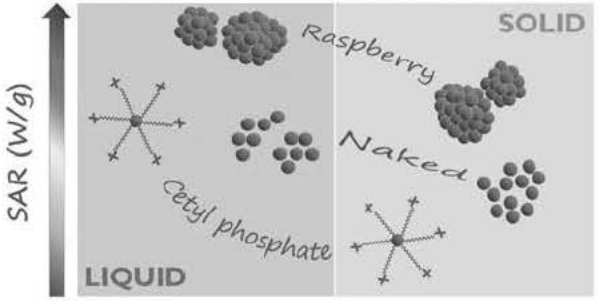
The heating ability of magnetic nanoparticles (MNPs) for magnetic hyperthermia is commonly quantified by means of the specific absorption rate (SAR), also referred to as specific loss power (SLP). This quantification is usually performed on colloids, even though the SAR values so obtained are often not representative of the nanoparticle performance after injection into the treatment site.

In this study, we present a combined thermal, magnetic and magnetothermal analysis that has given insight into the heating abilities of cobalt ferrite nanoparticles with different sizes and arrangements, dispersed either in liquid or solid media.

Higher SAR values were systematically obtained for samples in liquid media. However, the determination of SAR as a function of temperature has discarded an explanation based on the occurrence of different relaxation mechanisms in solid and liquid samples. On the one hand, heat capacity data together with zero-field-cooled and field-cooled magnetization curves have allowed correlating heating ability with ferrofluid dynamics originated by viscosity changes in samples dispersed in diethylene glycol. On the other hand, the higher degree of agglomeration attained by cetyl phosphate-coated MNPs after immobilization in paraffin wax seemed responsible for the decrease in SAR values and the shift in blocking temperature.

In sum, MNPs spatial arrangements acquired after ferrofluid injection in magnetic hyperthermia should be taken into account to predict SAR values during therapy.



Qualitative heating ability of $CoFe_2O_4$ nanoparticles with different sizes and arrangements

Aliskiren-Loaded Magnetic Labelled PLA Nanospheres for Hypertension Treatment

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In the early 21st century, hypertension (high blood pressure) is a global public health issue and contributes to the burden of heart disease, stroke and kidney failure and premature death and disability Aliskiren (ALIS) is a renin inhibitor used to treat hypertension by lowering blood pressure However, the limiting factor in clinical praxis is the relatively low bioavailability of ALIS One of the various possibilities how to decrease ALIS degradation, increase its bioavailability and consequently to maximize the effect of ALIS on kidney function is nanoencapsulation of ALIS Polymer nanospheres (PLANPs) created by Poly(D,L-lactide) (PLA) were used for drug encapsulation

In our study, we prepared and characterized ALIS-loaded magnetite labelled biodegradable PLA nanospheres Magnetic polymer nanospheres (PLAMNPs) with various Fe_3O_4/PLA (w/w) ratios were prepared by modified nanoprecipitation method Size and morphology of prepared PLAMNPs were studied by several techniques By scanning electron microscopy (SEM) approximately spherical shape of nanospheres was confirmed (fig 1) Dynamic light scattering (DLS) was used to determine hydrodynamic particle size distributions of magnetite as well as ALIS loaded PLANPs Moreover, the zeta potential measurement was carried out by the Laser Doppler Electrophoretic measurement technique to follow the behaviour of surface-adsorbed magnetite and drug, respectively As can be seen in fig 2, the optimal magnetite loading at ratio Fe_3O_4/PLA = 0 7 w/w was found (fig 2) Consequently, ALIS was encapsulated in PLAMNPS at theoretical loading 5 mg ALIS/100 mg PLANPs Differential scanning calorimetry (DSC) suggested that ALIS was molecularly dispersed in the polymer matrices Using infrared spectroscopy, ALIS was successfully identified in the magnetic labelled polymer nanospheres

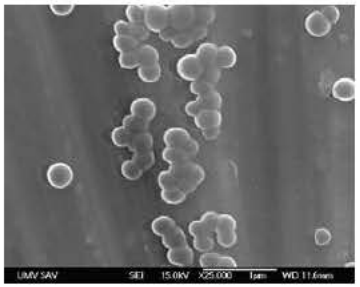

Figure 1: SEM image of ALIS loaded PLAMNPs

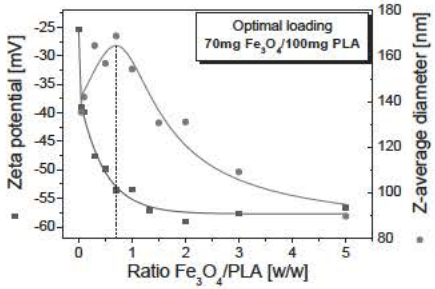

Figure 2: Zeta potential and Z-average of magnetite loaded PLANPs as a function of Fe_3O_4/PLA ratio

For the study of the ALIS encapsulated effect on systolic blood pressure male spontaneously hypertensive rats aged 12 weeks were assigned to untreated group and groups treated with non-encapsulated and encapsulated ALIS (25 mg/kg per day) for 3 weeks by gavage Encapsulated ALIS decreased blood pressure of the studied male spontaneously hypertensive rats even more significantly then common administered drug

Acknowledgments
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Evaluation of *in vivo* imaging of magnetically labelled blood cells

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Novel blood products require characterization of blood cell integrity and function. Cellular labelling by magnetic nanoparticles may be a promising approach to study kinetics of transfused blood cells *in vivo*. We labelled platelets and granulocytes with Resovist® iron oxide nanoparticles, an authorised medicinal product. Here we report on the monitoring of transfused nanoparticle labelled cells *in vivo* and *ex vivo*.

Cells were labelled with different Resovist® concentrations (5-20 mM). The intake of nanoparticles into the intracellular compartments was analyzed using electron and fluorescence microscopy and atomic absorption spectroscopy. The impact of magnetic labelling on platelet and granulocyte function was tested by determining activation markers using flow cytometry, platelet aggregation assay (aggregometry) and granulocyte agglutination test. MRI based detection using a 7-Tesla Small animal MRI scanner were employed to detect signals from *in vitro* phantoms of different cell suspensions as well as from intravenously injected cells (NOD/SCID mouse model). In addition, the NOD/SCID mouse model was used for survival studies of circulating labelled human cells administered intravenously. Finally, labelled blood cells were re-isolated from mouse blood by magnetic separation and recovery rate was determined by flow cytometry.

Labelling of platelets and granulocytes with 5 mM iron concentration of Resovist® resulted in an iron content of 0.2 pg/platelet and 1.3 pg/granulocyte, respectively. Neither platelet nor granulocyte function was affected significantly by magnetic labelling with Resovist®. After i.v. application into NOD/SCID mice labelled cells were visible preferential in the liver in the 7-Tesla Small animal MRI, and labelled cells were detectable in mouse blood after five hrs. In addition, we were able to re-isolate magnetically labelled human blood cells from mouse blood enabling us to perform subsequent investigations in regards of the impact of circulation-exposure on cells.

Magnetic nanoparticle labelling does not impair function and survival of blood cells significantly, thus allows for assessing the impact of different methods for blood product preparation *in vivo*.

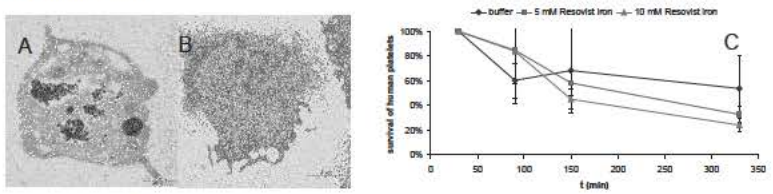

Figure Resovist® nanoparticles in A) platelets and B) granulocytes (TEM), C) survival of human platelets labelled with buffer, 5 mM, or 10 mM iron Resovist® in NOD/SCID mice

Bio-polymer Stabilized Fe_3O_4-graphene as an Amphiphilic Drug Carrier for Thermo-chemotherapy of Cancer

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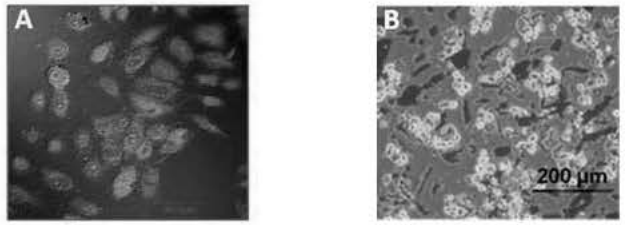
Graphene, a 2-dimensional material with promising characteristics is believed to be a potential material for several bio applications. But, its ability to react to an external magnetic field for hyperthermia applications is impaired. Thus, we report here a novel method to produce a nanocomposite of Fe_3O_4-graphene, stabilized with bio polymers that proves to be an effective dual drug carrier and also responsive to hyperthermia for effective cancer treatment.

The nanocomposite is stabilized due to covalent functionalization of the two polymers (PVP and PVA) with Fe_3O_4-graphene (PIG). Hydrophilic (Doxorubicin) and hydrophobic (Paclitaxel) drugs are used to examine the loading/releasing efficiency of the nanocomposite. The morphology of PIG is observed by TEM and SEM. PIG is found to be superparamagnetic with a magnetic moment of ~ 45 emu/g measured at a field of 1 T. The hyperthermia temperature (~42 C) is achieved in 15 min with 2.5 mg/ml (PIG in PBS). The entrapment efficiency of both Doxorubicin (DOX) and Paclitaxel (PTXL) is measured to be ~ 87±3 and 91±2 % of DOX and PTXL respectively. DOX and PTXL conjugated PIG exhibit a sustain release profile at acidic pH 4.3 compared to physiological pH 7.4 and controlled drug release under AC magnetic field is observed. The cellular toxicity assay suggests that PIG has good cytocompatibilty up to a concentration of 2.5 mg/ml on L929 and HeLa cell lines. But higher cytotoxicity effect is observed with DOX-PIG and PTXL-PIG with a concentration of 2.5 mg/ml (PIG in PBS) on HeLa cell line. Confocal microscopy confirms the cellular internalization of DOX conjugated PIG (Fig. A). Furthermore, *in vitro* thermo-chemotherapy studies suggest that both the heat and drug enhanced cancer cell destruction by inducing cell apoptosis (Fig. B).



(A) Cellular uptake of DOX-PIG and (B) *in vitro* thermo-chemotherapy on HeLa cell line.

Dartmouth Center for Cancer Nanotechnology Excellence: Magnetic Hyperthermia

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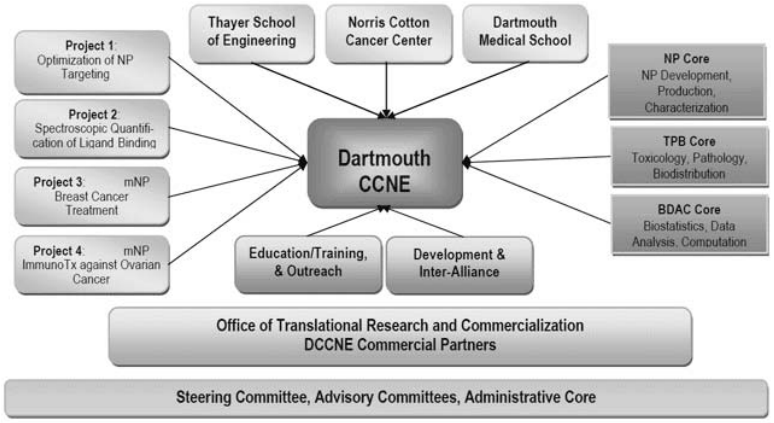
This presentation outlines the NIH-funded Dartmouth Center of Cancer Nanotechnology Excellence (DCCNE), see http://engineering.dartmouth.edu/dccne/), which focuses on the use of novel antibody-targeted magnetic particles (mNPs) subjected to an alternating magnetic field (AMF) for the treatment of tumors. The nanoparticles studied are either iron/iron oxide core/shell nanocomposite mNPs or iron oxide mNPs both with various organic coatings. There are four projects within the DCCNE, see Figure. The first focuses on producing novel antibodies, determining their effect on tumor accumulation for a range of mNP sizes in mouse models and comparing the results to untargeted mNPs. The second project focuses on developing new imaging technologies to determine the binding, location, and concentration of the mNPs based on combining optical ratiometric fluorescence spectroscopy with magnetic spectroscopy of particle Brownian motion. The other two projects are therapy-focused on breast cancer, ovarian tumors and melanoma in mouse models. The breast cancer work involves direct injection of mNPs into a tumor. The synergistic effects of chemotherapy and radiation therapy with magnetic hyperthermia treatments have been examined. The ovarian cancer work involves development of strategies to determine the therapeutic effectiveness of introducing antibody-conjugated mNPs into the peritoneal cavity of ovarian cancer models. Both the ovarian cancer work and the melanoma effort are focused on developing an immune response. Preliminary work on various oral tumors in dogs will also be outlined. The work has led not only to the development of treatment methodologies, but also to new nanoparticles, new nanoparticle measuring devices and new types of heating coils.

Structure of the Dartmouth Center for Cancer Nanotechnology Excellence



Biogenic nanoparticles produced by bacteria Klebsiella Oxytoca: structural investigations

M. Balasoiu[1,2], L.A. Ishchenko[3], S.V. Stolyar[3,4], A.I. Kuklin[1], Yu.L. Raikher[5]

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The development of techniques for the synthesis of nanoparticles of well-defined size, shape and composition is a challenge and an important area of research. Current chemical methods for the synthesis of nanoparticles are energy intensive, employ toxic chemicals, and often yield particles in nonpolar organic solutions, thereby precluding biomedical application. A promising new dimension in this field is the use of microorganisms for the production of inorganic nanoscale particles, due to the clean, nontoxic, economic and environmentally friendly ability of eukaryotic and prokaryotic microorganisms to form nanoparticles either intra- or extra-cellularly.

Biogenic minerals are composite materials containing an organic matrix and nano or micro-scale amorphous or crystalline materials. Also, they often show complex hierarchical structure from nanometer to the macroscopic scale. The mechanisms of biomineral formation are not fully understood and while they are of interest in their own right, they may also provide models for new materials concept inspire design solutions and give new insights into the genetic control of biological structure.

Results on structural properties determination of biogenic ferrihydrite nanoparticles, produced by bacteria *Klebsiella Oxytoca*, obtained by means of scanning electron microscopy, atomic force microscopy, small angle x-ray scattering, Mossbauer spectroscopy, magnetic measurements, FTIR and Raman spectroscopy are presented.

It was also revealed that the magnetic nanoparticles do not affect the activity of neutrophils, indicating, that the particles have not cytotoxity. The absence of toxic effects provides the basis for studying the effectiveness of ferrihydrite nanoparticles in combination with antibacterial drugs for their controlled delivery to the affected tissues.

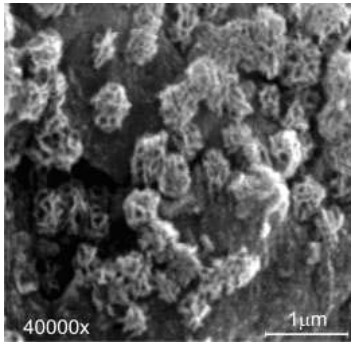

Fig.1 SEM image of a sample containing ferrihydrite nanoparticles separated from the bacterial biomass grown during 8 days.

Magnetically modified straw for dyes removal

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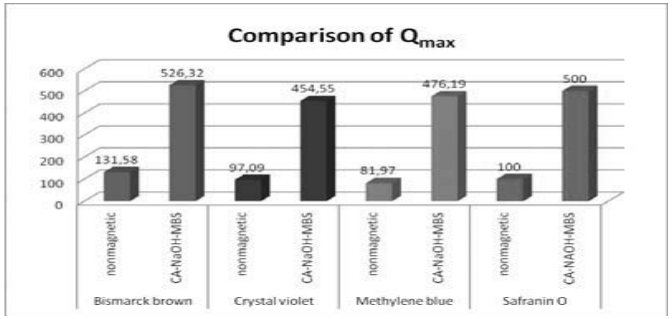
Department of Nanobiotechnology, Institute of Nanobiology and Structural Biology of GCRC, Ceske Budejovice, Czech Republic

Many scientific studies describe straw, a waste obtained after crop harvesting, as an interesting and very cheap material with various potential applications. It can serve not only as a relatively efficient adsorbent for wide range of xenobiotics, such as organic dyes, heavy metals, radionuclides or endocrine-disrupting compounds (e.g. bisphenol A), but also as a pseudoaffinity adsorbent for isolation of proteolytic enzymes.

This research is focused on utilization of barley straw as an efficient and cheap adsorbent for organic water-soluble dyes representing different classes, namely Bismarck brown Y (azodyes group), safranin O (safranin group), crystal violet (triphenylmethane group) and methylene blue (quinone-imine group). The sorption properties were tested for native nonmagnetic straw and for magnetic citric acid – NaOH modified straw (CA-NaOH-MBS).

Magnetic modification of barley straw was carried out using microwave-synthesized iron oxides microparticles, as described in detail by Safarik & Safarikova (2014), while the preparation of CA-NaOH-MBS was performed according to Gong et al. (2008).

The dyes adsorption was described using the Langmuir isotherm. The maximum adsorption capacities reached 82 – 132 mg of dye per g of native nonmagnetic straw and 455 – 526 mg of dye per g of magnetic chemically modified straw. It is apparent that a suitably chosen method of straw modification can significantly (more than four times in this case) increase the maximum adsorption capacities.



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10th Inter. Conf. on the Scientific and Clinical Applications of Magnetic Carriers, Dresden, Germany. June 10-14, 2014. Oral or Poster Presentation.

Nondimensional Scaling of Magnetorheological Rotary Shear Mode Devices Using the Mason Number

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Magnetorheological fluids (MRFs) exhibit rapidly adjustable viscosity in the presence of a magnetic field, and are increasingly used in adaptive energy absorbers for high speed impacts, corresponding to high fluid shear rates However, the MRF properties are typically measured at very low (<1,000 s^{-1}) shear rates A high shear rate (>10,000 s^{-1}) Searle cell magneto-rheometer along with a rotary-vane magnetorheological energy absorber (MREA) are employed to analyze MRF property scaling across shear rates using the nondimensional Mason number to generate a master curve of non-dimensional apparent viscosity vs Mason number A 40 vol% carbonyl iron - hydrocarbon oil MRF was characterized using the Searle cell magnetorheometer, and these experimental results are discussed, analyzed, and compared with the results from a full-scale rotary vane MREA using apparent viscosity and Mason number The Searle cell magneto-rheometer has a radius of 9-mm, height of 12-mm, and a shearing surface area of 678-mm^2 In contrast, the rotary vane MREA has a radius of 49 5-mm, a height of 85 5-mm, and a shearing surface area of 53,184-mm^2 Thus, the rotary vane MREA has 78 times the sheared surface area of the magneto-rheometer By incorporating a Reynolds temperature correction factor, data from both experiments are shown to collapse to a single master curve (Fig 1), supporting the use of Mason number to connect low- and high-shear rate characterization data This non-dimensional analysis shows that the typical low shear rate data can be scaled to a practical device having over 78 times the active surface area, across a wide range of temperatures (9°C - 55°C) and operating speeds (up to $\dot{\gamma}$=25,000s^{-1}), such that performance can be predicted from only knowledge of the MR fluid properties Connecting laboratory experiments with practical applications using Mason number can expand the design space of MREAs to high velocity impacts

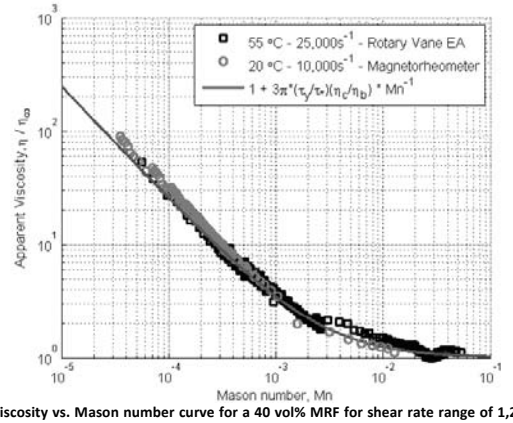

Figure 1 – Apparent viscosity vs. Mason number curve for a 40 vol% MRF for shear rate range of 1,250-25,000 s^{-1}. Data are from two devices: (1) a small-scale Searle cell magneto-rheometer, and (2) a rotary vane MREA, which has 78 times the sheared surface area of the magneto-rheometer.

Poly(lactide) Nanoparticles loaded with Albumin Modified Magnetite depolymerize Insulin Amyloid Fibrils

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Amyloid aggregation of proteins is associated with amyloid diseases, such as Alzheimer's and Parkinson's diseases or type II diabetes [1]. The frequent injections of the insulin into patients with diabetes may result in formation of amyloid deposits consisting of insulin fibrils. Insulin amyloid aggregation causes also problems in the production and storage of this drug and application of insulin pumps.

We have investigated interaction of insulin amyloid fibrils (IF) with nanoparticles formed from poly(D, L-lactide) (Pla) loaded with magnetite component modified with different amount of bovine serum albumin (Pla_{FeBSA}-NPs) (w/w BSA/Fe_3O_4 ratios 0.01, 0.05, 0.1 and 0.5). Hydrodynamic diameters of nanoparticles determined by dynamic light scattering were from 92 nm to about 121 nm. Analysis of scanning electron microscopy images showed almost spherical shape of studied nanoparticles. The composition of nanoparticles was chosen due to their biocompatible and biodegradable properties.

The interference of studied nanoparticles with insulin amyloid fibrils examined by Thioflavin T fluorescence assay leads to depolymerization of insulin fibrils in concentration-dependent manner with DC_{50} values determined in µM range. The extent of depolymerization was affected by different physico-chemical properties of nanoparticles. It must be noted that nanoparticles formed by poly(D, L-lactide) alone and this nanoparticles modified with BSA showed negligible potential to affect insulin fibrils.

The depolymerizing ability of Pla_{FeBSA}-NPs observed by ThT assay was confirmed by transmission electron microscopy (Figure 1). In presence of Pla_{FeBSA}-NPs the amount of insulin fibrils (Fig. 1A) was significantly reduced and their morphology was changed; the fibrils were truncated to shorter and thinner structures (Fig. 1B). Obtained results suggest that high depolymerizing activity of Pla_{FeBSA}-NPs is associated with presence of magnetite component in studied nanoparticles.

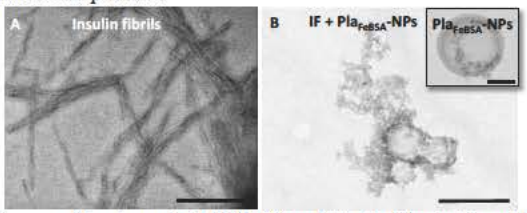

Figure 1 TEM images of insulin amyloid fibrils (A) and after their incubation with Pla_{FeBSA}-NPs (B), insert is TEM image of Pla_{FeBSA}-NPs alone (bar ~ 100 nm). Bars in TEM images represent 500 nm.

Acknowledgement: This work was supported by the research grants from Slovak Grant Agency VEGA 0181, 0041, UPJS grant VVGS-2013-98, the project ESF 26110230097 and APVV 0171-10

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Preparation of nanotechnology as magnetically-resonant contrasting means during visualization of malignant tumour

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The task was set in an experiment on animals to check possibility of the use of the before worked out and studied methodology of intravenous insert of the standardized form water solution magnetite of nanoparticles (preparation of ICNB) for contrasting of malignant tumour at MRI research. The main purpose – to change the indexes of relaxation of T1 and T2 in area of malignant tumour during realization MRI by means nanoparticles of ICNB. In investigation on animals (Vistar rats) was proof that magnetite of nanoparticles (ICNB) are contrast means for malignant tumour visualization. Was been shown that magnetite of nanoparticles have contrast effect when performing magnetic resonance imaging (MRI) (Fig. 1, 2). Was established, that after intravenous inject preparation of nanotechnology (ICNB) the magnetite of nanoparticles have selective accumulate in tumour and alter brightness of picture in 24-hours (Fig. 2, 3). On 4-th day investigation was established significant decries of dynamic brightness of the picture of tumour and muscles (Fig. 4). This fact is connected with elimination the ICNB out of rat's organism.

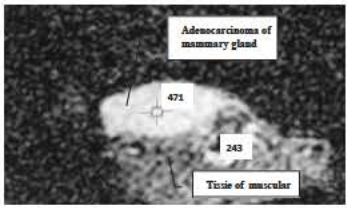

Fig 1 Initial MRI study the brightness of image the rat's adenocarcinoma of mammary gland and tissue of muscular (471 conventional sign – tumour; 243 conventional sign – tissue of muscular)

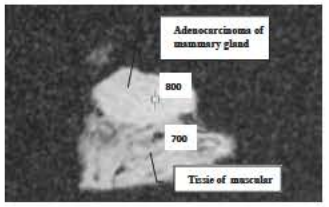

Fig 2 MRI study the brightness of image rat with the adenocarcinoma of mammary gland and tissue of muscular on the first minutes after intravenous insert of ICNB (800 conventional sign - tumour; 700 conventional sign - tissue of muscular)

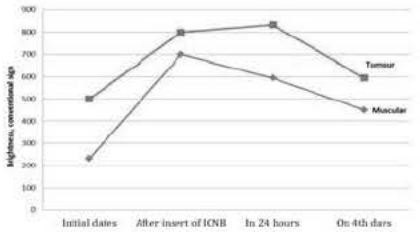

Fig 3 Dynamic of change magnetite of nanoparticles concentration in rat's tumour and muscular after intravenous insert ICNB preparation on various stages for MRI studies

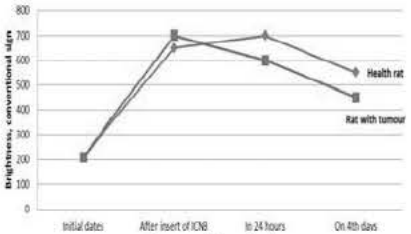

Fig 4 Dynamic of change brightness of image rats muscles in both groups on various stages for MRI studies after intravenous insert ICNB preparation

Reduced of erythrocyte destruction by means of magnetite nanoparticles (MCS-B)

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Metabolic restoration, prolongation of normal function of cells both inside and outside the organism is the main purpose of medical and biological trend in the 21st century Having solved this task the mankind will closely approach the mystery of longevity, treatment of previously incurable diseases, make a significant advance in the sphere of microbiology, transplantology, growing and storage of cells Will the nearest future allow to purposefully managing metabolism of cells, treating earlier incurable diseases etc? What should tools and methods be to meet this purpose? All these questions can be answer by the modern trend of science, i e nanotechnology

The main purpose of this work is decline of erythrocytes hemolysis by means of magnetite nanoparticles (magnet-controlled sorbent MCS-B) Conventional erythrocytes of person's venous blood were objects of the research The time of appearing the signs of erythrocytes hemolysis was registered by help of visual method In result of investigation it was established:

1 For inhibiting of hemolysis the optimum frequency rate (1-2 times) of processing the blood by nanoparticles (NPs) of MCS-B was determined

2 It was established that extracorporally processing the blood by MCS-B reliably reduces activity of Ca, Mg - ATPHese of erythrocytes and increases level of cytosolic calcium (Tables 1, 2)

Adenosine-triphosphateses	Control	Frequency rate processing of MCS-B		
		Single	Double	Triple
Na, K – ATPHese, protein mmol/mg in mines	6 34±0 5	6 11±0 6*	5 89±0 7*	5 93±0 4*
Ca, Mg – ATPHese, protein mmol/mg in mines	23 64±0 6	21 17±0 7**	18 45±0 5***	17 63±0 3***

Table 1 Results of research activity adenosinetriphosphateses before and after processing of erythrocytes by NPs of MCS-B (M±m; n=20)

Note: * - p>0 05; ** - p<0 01; *** - p<0 001

Ion	Control $x10^{-8}$	Frequency rate processing by MCS-B		
		Single $x\ 10^{-7}$	Double $x\ 10^{-7}$	Triple $x\ 10^{-7}$
Ca^{2} , m/ml cell	1±0 1	4 9 ±0 1*	5 6±0 2 *	6 5 ±0 1*

Table 2 Results research the level of ion Ca^{2} in erythrocytes before and after processing by NPs of MCS-B (M±m; n=20)

Note: * - p<0 001 in comparative with control

3 After processing of blood by means NPs of MCS-B the activity of Na, K - ATPHese of erythrocytes does not change (p>0 05) (Table 1)

4 Manifestation of hemolysis has not linear dependence on rise level of cytosolic calcium and frequency rate processing of blood by MCS-B

5 Likely that NPs of MCS-B are changing the state polarization of water molecules of micro-cellular space of erythrocytes It is influences on activity of hemolysis, activity of ATPHeses, opening of ion channels that in whole explains the decline of eryptosis mechanism

Stable Colloidal suspension of Fe-Ag Nanoparticles Encapsulated by an Amorphous Si Shell Prepared by Inert-Gas-Condensation method

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Stable colloidal magneto-plasmonic hybrid nanoparticles (HNPs) are promising for a large number of dual magnetic-optical bioapplications. Vapor-phase techniques offer a good alternative to chemical routes for the generation of tailored HNPs. However these techniques still face obstacles in regard to harvesting and transferring the nanoparticles (NPs) to a stable colloidal suspension. Herein, we prepare multifunctional HNPs composed of multiple iron (Fe) - silver (Ag) magneto-plasmonic cores encapsulated by silicon (Si) shells (FeAg@Si) using a co-sputtering gas aggregation technique. The effects of the pressure and power on the sputtered materials (Fe, Si, Ag) are correlated with the morphology and the magnetic behavior of the obtained HNPs. In contrast to previously reported magneto-plasmonic NPs, the amorphous Si shell provides an efficient tool to maintain both metallic components well bounded over time (> 6 months). FeAg@Si NPs exhibit ferromagnetic behavior at room temperature attributed to anisotropy at the Fe-Ag interface. On the other hand, these HNPs show an enhanced, red-shifted, light absorption band, due to the strong near-field coupling between the plasmonic cores and the dielectric shell. Furthermore, a facile and environmentally friendly method for harvesting FeAg@Si NPs has been developed using polyvinylpyrrolidone (PVP) as a stabilizer. Harvested HNPs show stable and homogeneous colloidal behavior when transferred to aqueous suspensions.

Keywords: Magneto-plasmonics, Core/shell materials, Sputter-Gas-Aggregation, Nanoparticles, colloids

Magnetic Actuator for the Control and Mixing of Magnetic Bead-Based Reactions *On-Chip*

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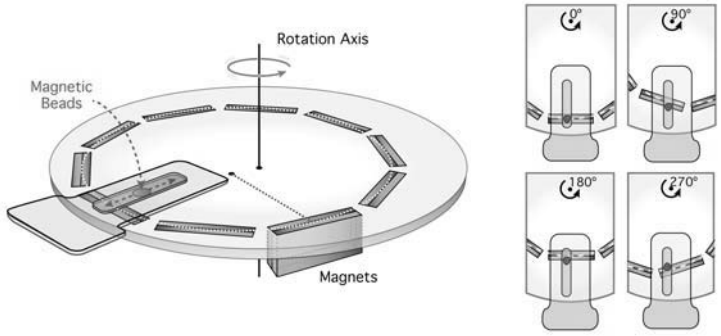
While magnetic bead (MB) based bioassays have been implemented in integrated devices, their handling *on-chip* is, in most of the cases, either not optimal –i.e. only trapping is achieved, with aggregation of the beads- or requires complex actuator systems. Herein, we describe a simple and low-cost magnetic actuator to trap and move MBs within a microfluidic chamber in order to enhance the mixing of a MB-based reaction. Thus, MBs are used both as a solid support, bearing an immobilized reagent, and as a stirring vehicle to achieve the mixing. The magnetic actuator consists of a rotating CD-shaped plastic unit, placed immediately under the microfluidic device, with a set of magnets circularly arranged and eccentric to the rotation axis. When rotating, the magnets move the MBs back and forth, thus generating the mixing with the reagents within the microfluidic device and increasing the effective surface area of the surface-activated MBs. The magnetic actuator has been used to enhance the amplification reaction of an enzyme-linked fluorescence immunoassay to detect *E. Coli* O157:H7 whole cells, an enterohemorrhagic strain, which have caused several outbreaks in food and water samples. A 2.7-fold sensitivity enhancement was attained with a detection limit of 603 CFU/mL, when employing the magnetic actuator. The MBs used in this study are commercially available, and can be purchased with a great variety of antibody surface functionalizations, making the magnetic actuator useful for a wide range of assays with off-the-shelf reagents.



Schematic representation of the magnetic actuator and its working principle.

3D FORMATION OF CANCER STEM CELLS WITHIN MCF-7 DERIVED MAMMOSPHERES and HYPERTHERMIA TREATMENT

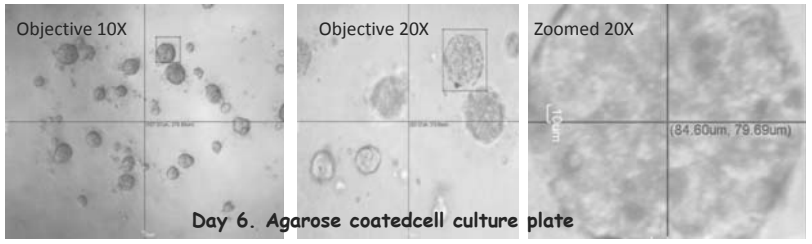
Cancer stem cells (CSCs) are cells within a cancerous tumour which have the same characteristics as normal stem cells such as the capacity to self-renew Hence they are able to give hole tumour from a single cell as they are totipotent Even after chemo/radiotheraphy treatment CSCs can give rise to new tumours We set in-vitro 3D assay to mimic tumours and their milieu and studied nanoparticle formulations

To this aim MCF-7 which is a breast cancer cell line is used to obtain CSCs These CSCs were grown in different conditions (different types of plates and medias) to optimize formation of stable mammospheres; which is a clump of mammary gland cells like tumours that forms under certain conditions Following this MCF-7 derived mammospheres are being cultured in 3D hydrogel constructs to imitate the extracellular matrix 3D hydrogels were prepared and casted in our lab

To effectively remove the cancerous tumour it is necessary to kill these CSCs and in this study our next step will be applying hyperthermia on preminary results within 3D hydrogel for promoting cancer stem cell death and see the effect of the heating and the distance of magnetic nano particles on mammospheres and the cancer stem cells

This study would help develop a way to target and kill cancer stem cells to increase the efficiency of tumour treatment

I am really into Cancer Stem Cells and I see the future in nanomagnetic particle treatments for cancer However I am quite new in nanomagnetic particles This conference will be a very good opportunity for me to follow up nanomagnegtic particle world and their usage I can learn more about them and improve myself



Day 6. Agarose coatedcell culture plate

Effect of precipitation agent on morphology of Fe_3O_4 nanoparticles in hydrothermal process

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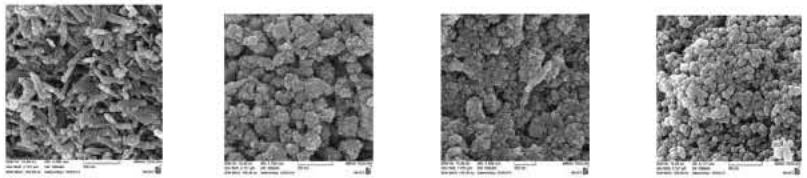
Abstract

Fe_3O_4 nanoparticles have been synthesized by hydrothermal technique using urea and sodium hydroxide as precipitation agents, $FeCl_2$ and $FeCl_3$ with a molar ratio 1:2 as precursor with assistance of CTAB surfactant were used The effect of different concentration of precipitation agents on the morphology and particle size was investigated The precipitated nanoparticles were characterized by x-ray powder diffraction (XRD), Alternative gradient force magnetometry and transmission electron microscopy XRD results indicated that magnetite can be detected as major phase Different morphologies of nanoparticles were seen with changing the kind of precipitation agent and their concentration The magnetic behavior of synthesized nanoparticles varies with their morphology The saturation magnetization was in range of 13-35emu/g

Keywords: Hydrothermal, Oxide iron, nanopigment, Magnetite



Effect of precipitation agent type and its concentration on morphology of Fe_3O_4 nanoparticles

Highly controllable microwave synthesis of biocompatible iron oxide nanoparticles with tailored magnetic relaxation properties

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The US nanomedicine industry totals around $34 2 billion and the demand for biomedical nanosized products is expected to grow a 17 1% in 2014 [1] Due to the growing market needs, the introduction of a cost-efficient, high-yield and reproducible method for the synthesis of magnetic nanoparticles would revolutionize the by improving the properties of the generated materials Microwave reactors have the potential to offer this possibility thanks to the introduction of new high performance bench-systems (e g MARS 6, CEM Corporation) that could generate around 500 g of particles per week in a high controlled and reproducible manner

Techniques such as magnetic resonance imaging (MRI), magnetic hyperthermia and magnetic particle imaging (MPI) heavily rely on the magnetic relaxation properties of magnetic nanoparticles Understanding the mechanism of relaxation in working conditions is crucial for their routine use Nonetheless, small changes to the synthetic conditions can lead to drastic variations on the frequency range of maximum imaginary component (χ'') of the complex susceptibility leading to products with unpredictable behavior or non-reproducible properties, as seen in the case of magnetic hyperthermia [2] To this aim we have investigated the effect of the synthetic conditions with a microwave reactor in the final magnetic relaxation properties by AC susceptibility measurements on iron oxide nanoparticles Citric acid and dextran ligands were used in the system to exemplify the drastic changes on the frequency of maximum susceptibility loss with the concentration of ligand in solution

The frequency of maximum χ'' was found to increase along with the concentration of ligand in solution The results reveal that it is possible to match a targeted frequency of maximum χ'' for a specific application through a carefully programmed microwave-based synthesis

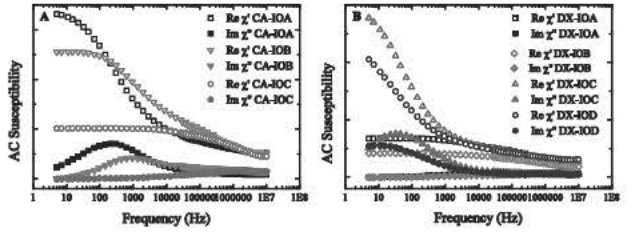

Figure 1. AC susceptibility (Re: real part, Im: imaginary part) measurements of A) citric acid-iron oxide NP series and B) dextran-iron oxide NP series.

1 The Freedonia Group 2010
2 Kallumadil, M , et al , *J. Magn. Magn. Mater.* **2009**, *321*, 3650-3651

Continuously Manufactured Magnetic Polymersomes – A Further Step Towards Theranostics

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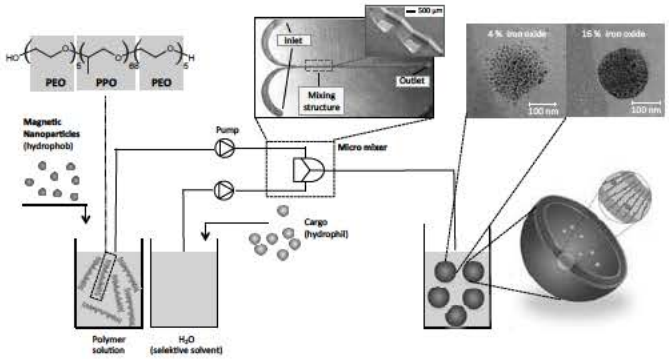
The overall aim of drug delivery devices is to maximize the therapeutic response while minimizing adverse side effects Thus, the requirements for nanotransporters are very high and include (i) protection and transport of the therapeutic agent, (ii) stability in blood stream, (iii) specific binding to diseased cells and internalization as well as (iv) a controlled drug release Recently, systems for combined diagnostic and therapeutic approaches, so called theranostics, have gained interest of many researches because of their immense potential for therapeutic monitoring The additional imaging capability of the nanocarriers will enable a non-invasive *in vivo* tracking of the nanotransporter and help to evaluate the therapeutic effects

Polymersomes are the synthetic variant of liposomes They are characterized by an improved stability and adjustable material properties compared to their lipid predecessors A critical step towards the clinical use of nanomedical devices is the ability to scale up the manufacturing process; therefore a microfluidic device was developed to continuously manufacture drug-loaded magnetic polymersomes

Hybrid polymersomes prepared from a FDA-approved Pluronic® polymer showed a relatively narrow size distribution Drug-loaded polymersomes that carry the anticancer drug camptothecin in their membrane reduced the cell viability of prostate cancer cells (PC-3) significantly, while drug-free polymersomes showed no cytotoxic effects Functionalized polymersomes with a covalently attached cancer targeting peptide (bombesin) as well as a fluorescence label (Alexa Fluor® 647) showed a specific cell binding and internalization and confirmed the successful approach towards active targeting Relaxometry measurements clearly demonstrated the capacity of magnetic polymersomes to generate significant T2-weighted MRI contrast The magnetic polymersomes were also shown to be suitable tracers for magnetic particle imaging (MPI)

Magnetic polymersomes have great potential for both diagnostic and therapeutic applications Diagnostically, tracking drug carriers inside the body, for example by MRI or MPI to ensure therapeutic monitoring, would be a huge benefit in nanomedical development Therapeutically, hybrid polymersomes filled with magnetic nanoparticles can also be valuable tools for hyperthermia treatment, magnetic drug release triggering and magnetic targeting



Schematic representation: Continuous manufacturing of drug-loaded magnetic polymersomes

Thermal Properties of Magnetic Microspheres

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Magnetic hyperthermia is an efficient method for cancer therapy since the magnetic nanoparticles have the capability to penetrate tumors or accumulate in close proximity of the cancer tissue, either by passive targeting (via the blood supply) or active targeting (remote magnetic targeting from outside the body). Treatment effects can be potentiated if anti-cancer drugs are combined with hyperthermia. Our aim, therefore, is to design a system where magnetic nanoparticles are co-encapsulated with anti-cancer agents into polymeric microspheres.

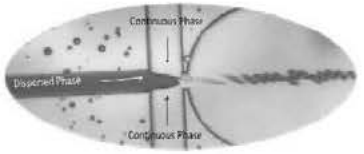

Figure 1: Droplet generation in microfluidic flow focusing system

Our magnetic and drug-loaded microspheres are prepared using microfluidic flow focusing (**Fig. 1**). In this method, two immiscible fluids are pushed together through an orifice and form droplets at the outlet (due to pressure differences). From each droplet, a microsphere forms after removing the polymer solvent. In our lab, we use the technique for the production of monosized PLA microspheres sized between 2-35 µm with standard deviations of less than 5%.

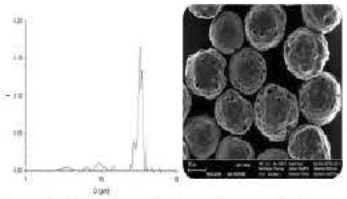

Figure 2: Scanning electron microscopic image of magnetic microspheres

The microspheres can be radiolabeled with ^{99m}Tc, ^{188}Re, ^{67}Ga or ^{68}Ga and used for imaging or radiation therapy. With slight modification in operational parameters, the microfluidic system was used to produce monosized magnetic microspheres (**Fig. 2**). In this paper, we show the method of production of monosized PLA microspheres loaded with lipophilic magnetic nanoparticles. The particles' thermal properties will be discussed. We plan to use them for magnetic targeting followed by magnetic heating for hyperthermia and thermal inducing drug release system.

Acknowledgments

This research was supported by a Canadian Institutes of Health Research (CIHR) and Natural Sciences and Engineering Research Council (NSERC) grant.

Encapsulation of Hydrophilic and Lipophilic Magnetic Nanoparticles in PLA Microspheres using a Microfluidics Chip

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Targeted delivery of the therapeutic agents in the body is one of the main challenges in medicine and drug formulation. Magnetic particles as a tool for targeted drug delivery were introduced more than three decades ago and have received extensive attention to this day [1-3]. One of the new approaches is fabrication of magnetically targetable microspheres (MMS) for sustained and controlled drug delivery. In this system, therapeutic agents and magnetic nanoparticles can be co-encapsulated in biodegradable polymeric microspheres. The MMS is directed toward the designated organ and accumulated there and drug can be released over an extended period of time.

We have shown before that highly uniform biodegradable microspheres can be made in microfluidic flow focusing system. In this method, two immiscible fluids are pushed together through an orifice and form droplets at the outlet (due to pressure differences).

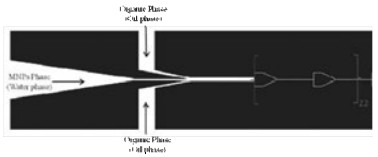

Figure 1: Schematic structure of the designed micromixer for generation of water in oil emulsion

In the current work, we will show how microfluidic systems can be used for encapsulation of magnetic nanoparticles with hydrophilic and lipophilic coating into biodegradable poly(lactic acid) microspheres using our microfluidic flow focusing system and our recently designed microfluidic mixer (**Fig. 1**). The optimum conditions for encapsulation of each kind of magnetic nanoparticles is shown and loading efficiency and morphology of the MMS produced are compared.

Acknowledgements

This research was supported by a Canadian Institutes of Health Research (CIHR) and Natural Sciences and Engineering Research Council (NSERC) grant.

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Magnetic human serum albumin microspheres as a possible radionuclide delivery platform in cancer therapy

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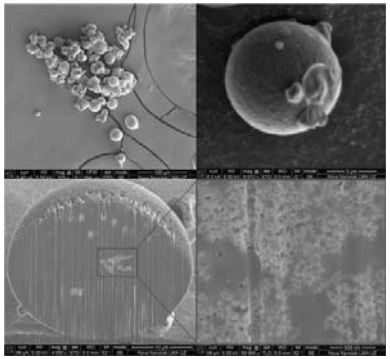
The promising applications of magnetic nanoparticles (MNP) in the future could be focused on their use as drug delivery nanovectors and in magnetic hyperthermia. Magnetite based MNPs are the commonly used in biomedicine due to their suitable magnetic properties, low toxicity and chemical stability. Here we present synthesis and characterization of magnetic microsphere (MM) intended for use as vectors in radionuclide therapy and as medium in magnetic hyperthermia.

Prepared naked Fe_3O_4 (A) and $Fe_{2.80}Gd_{0.20}O_4$/citric acid (B) nanoparticles were encapsulated in human serum albumin (HSA) using modified emulsification-heat stabilization technique. Scanning electron microscopy (SEM) was used in order to determine the morphology, size and size distribution of the magnetic microspheres. The internal structure of the MM was analyzed by SEM/FIB dual-beam device (Nova TM 200 NanoLab, FEI Company). The microspheres were relatively uniform in size, with average diameter of 10 μm. The EDX analysis confirmed that magnetic nanoparticles formed clusters inside microspheres.

All MM showed superparamagnetic behavior at room temperature with small values of saturation magnetization. Test for their applicability in hyperthermia treatment were performed. Low values of specific absorption rate (SAR) suggested the need for further optimization of microspheres' synthesis in order to improve their magnetic properties. TGA analysis indicated that 8 wt% and 11 wt% of samples A and B, respectively, were encapsulated in HSA.



SEM pictures of the naked Fe_3O_4/HSA microspheres and their Dual-beam analysis

In our earlier paper [1] synthesis of *in vivo* stable ^{90}Y-labeled citric acid-coated magnetite nanoparticles encapsulated into HSA microspheres was reported. Following the intravenous administration of the ^{90}Y-MM in rats, 88.81% of the activity was localized in the lungs after 1 h, with 82.67% remaining after 72 h. Consequently, designed magnetic human serum albumin microspheres are promising as vectors in radionuclide therapy.

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Multimodal imaging platforms based on SPIONs

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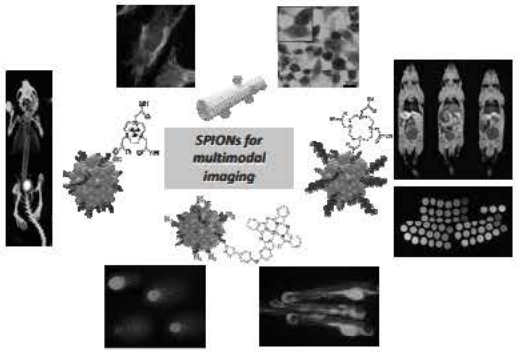
Nowadays, nanotechnology offers a large field of applications in medicine and biology, in particular regarding imaging In this study, we present the development of bimodal contrast agents based on functionalized SPIONs (SuperParamagnetic Iron Oxide Nanoparticles) for dual imaging MRI (Magnetic Resonance Imaging)/OI (Optical Imaging, here in the so-called imaging window from 650 to 1450 nm), MRI/PET (Positron Emission Tomography) or MRI/SPECT (Single Photon Emission Computed Tomography)

Since several years, our group has developed continuous hydrothermal syntheses of SPIONs, in subcritical and supercritical water conditions More recently, the therefore designed apparatus has been modified to allow the synthesis and the surface modification of SPIONs in one step For example, citric acid (CA) controls the crystallite size and the oxidation degree of metallic ions despite the very short reaction time (4s); superparamagnetic magnetite particles, with an average size of four nanometers and a good monodispersity were obtained [1] Other organic molecules are currently evaluated, such as L-DOPA and DHCA These organic molecules have an anti-oxidizing effect but increase the crystallite size (from 8 to 15 nm) whereas CA decreases the crystallite size of SPIONs (from 8 to 4 nm) [2]

In another approach the organic coating was covalently linked step-by-step onto SPIONs At first, SPIONs are modified by the grafting of organic functions (NH_2, COOH or SH) to allow the implementation of more specific organic molecules, among them: macrocyclic chelating agents for nuclear imaging (DOTA or NOTA), phthalocyanine derivatives for fluorescence detection and photodynamic therapy Second, a covalent coupling of functionalized PEG is necessary to ensure the biocompatibility and the stability of these nanoparticles Each coated-SPION was thoroughly characterized: UV-vis, XPS, TGA, ICP-OES, elemental analysis, TEM, DLS, IR [3] The grafting of zinc-phtalocyanine resulted in novel bimodal contrast agents detectable by both MRI and near infrared optical imaging [3] Otherwise the grafting of NOTA and ^{64}Cu labeling resulted in bimodal contrast agents detectable by both MRI and PET



Several biological assays have been performed on these multimodal SPIONs such as:

- cytotoxicity studies (MTT, kinetics of RNA, methylene blue),
- genotoxicity studies (comet assay),
- internalization studies on different cell lines (TEM, optical microscopy),
- evaluation on a zebrafish model, which proves that these iron oxide suspensions have no apparent perturbation on hatching, survival rate and malformations,
- and *in vivo* biodistribution evaluation thanks to MRI, PET and SPECT The first results show a reduced capture of PEGylated SPIONs by mice liver and suggest that our contrast agents freely circulate longer in mice compared to a commercial product tested [4]

These SPIONs have also been associated to titanate nanotubes, leading to a new nanovector detectable by MRI [5] This nanovector has already been evaluated for radiotherapy of glioblastoma [6] and DNA transfection [7]

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Synthesis of Nickel urchin-like chain: structural, microstructural and magnetic studies

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Urchin-like Ni chains were prepared by hydrothermal method at low temperature for 2.5 mol/L of NaOH. The as-prepared Ni nanoparticles, for different amount of NaOH, were characterized by X-ray diffraction, Scanning Electron Microscopy coupled to EDX and Vibrating sample Magnetometry. The phase purity, the lattice parameter and the grain size values were obtained from the fit of X-ray diffraction spectra with the Reitveld method. The fit of XRD patterns confirm the presence of the face-centred cubic (fcc) structure of Ni with a lattice parameter of 3.524 Å. Moreover, the grains size increase with the amount of NaOH. The SEM micrographs show that Ni chains were formed by an assembly of urchins having approximately 4-5 µm of size. The hysteresis loops were typical of a ferromagnetic system. The saturation magnetization, Ms, values were close to that of the bulk Ni. The coercive field, Hc, values depend on the morphology and are higher than the bulk Ni one.

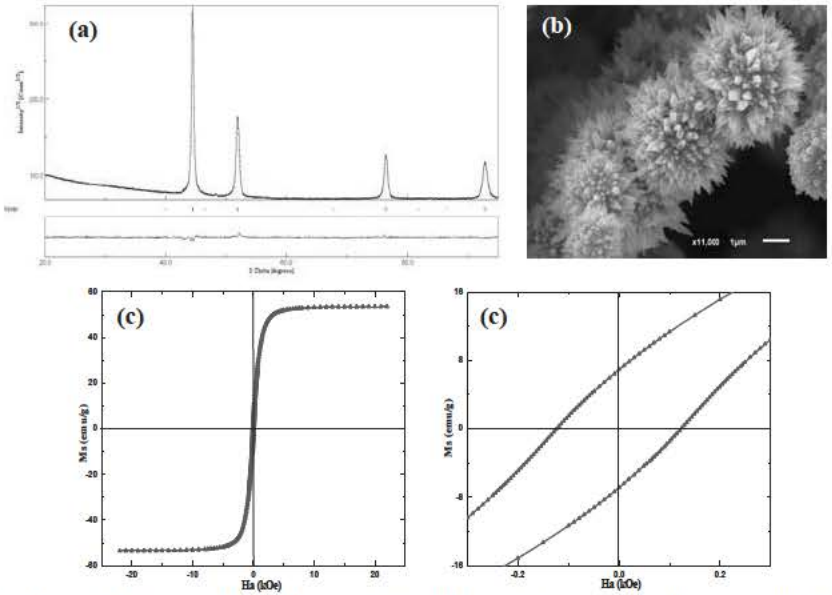

Fig1. (a) Rietveld refinement of the XRD pattern, (b). SEM image showing urchin-like chain and (c) Room temperature hysteresis loop.

Different ways to transfer iron nanoparticles into water: towards MRI T2 contrast agents of increased efficiency

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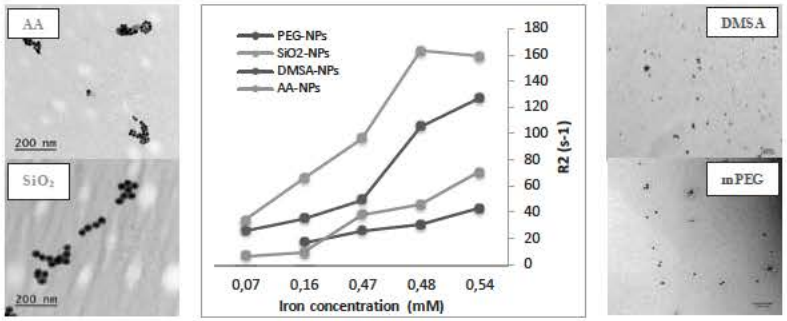
Magnetic nanoparticles can be efficient contrast agent for T2 weighted magnetic resonance imaging (MRI).[1] MRI contrast agents based on colloidal iron oxide nanoparticles (IO-NPs) are already available but they have still a poor efficiency due to some polydispersity or aggregation problems. Indeed, the size, surface state, colloidal stability and magnetization play important roles in the resonance relaxation properties. However, there is still great potential for improvement of MRI contrast agent due to the development of new synthetic pathways allowing the tuning of these key parameters.

We have investigated the effects of the surface coating on the efficiency of two different types of iron based NPs for targeted applications. Starting from the syntheses of iron oxide nanoparticles[2] (IO-NPS) and iron nanocubes[3] (I-NPs) of 13 nm size-diameter, we have used several methods to coat these NPs using different surfactants like modified polyethylene glycol (mPEG), azelaic acid (AA), dimercaptosuccinic acid (DMSA), or silica (SiO_2). The method of coating has been carefully chosen in order to provide the transfer of these NPs into water and to ensure their colloidal stability.

The single-core NPs were characterized by Diffusion Light Scattering (DLS), Transmission Electron Microscopy (TEM) and Thermogravimetry analysis (TGA). We have obtained stable and monodisperse colloidal solutions for the two types of NPs with every surfactant. In our case, I-NPs coated with silica shell gave us the highest r2 value for the I-NPs (628 $s^{-1}.mM^{-1}$). This result can be explained first by the still higher magnetization of I-NPs compared to the IO-NPs, even if partial oxidation occurs during water transfer, and by the ability of water to enter the porous silica shell.



Influence of the surface coating on the R2 value of I-NPs

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ELSEVIER SCIENCE

Preliminary study regarding the solar protector factor of magnetic nanocompounds

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Abstract

It was experimented the protector effect against UVR exposure of magnetic nanocompounds by establishing the solar protector factor values The experiments were done on white mice of which auricles were treated with a magnetic nanocompound ointment The animals were exposed to UV irradiations At the moment that the primary minimal erythemal signs occur the exposure to ultraviolet radiation has been finished and the animals have returned to the normal conditions of life The nanoparticles formed a protecting sunscreen with a SPF values average between 9 and 12, which can protect the skin for 3 to 4 hours

Keywords: magnetic nanocompounds; protection sun radiations
PACS Type your PACS codes here, separeted by semicolons;

1. Introduction

In these days is imperative to use sunscreens in order to protect the skin against UV radiations of the sun, which can induce morphological alteration from small erythema and premature photo aging to melanoma [1, 2] Pharmaceutical and cosmetical industries manufacture sunscreen agents with chemical, physical or biological (natural) composition, which are included in various types of products, with different values of the SFP, but their safety and efficiency are still in discussion [3, 4]

2. Materials and methods

The experiments for establishing the solar protection factor (SPF) were done on white mice of whose one auricle have been treated with a magnetic ointment, which present in composition magnetic fluid with Fe_3O_4 stabilized with oleic acid and beeswax, in lanolin The magnetic nanocompound was used in concentration of 6G, which from our previously experiments proved to be an efficient protector against UV radiations Also, this concentration is good as aesthetic aspect, too The mice were clustered in two groups of six animals One auricle of each mouse was treated with magnetic ointment based lanolin and the other serving as control, to determine the minimal erythemal dose (MED) One drop (0,016 ml) of the magnetic ointment was applied on both sides of auricle area (who summed up about 2 cm^2), which contained 0,111 mg magnetite nanoparticles

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Multitasking Iron Oxide Magnetic Nanoclusters for Diagnosis and Medical Treatment

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Today's patient treatment may necessitate designing advanced material platforms that could be utilized simultaneously for diagnosis and therapy Such a kind of "theranostic" agent should be simple and cost-efficient to synthesize On the other hand detailed characterisation of its physical and chemical properties, as well as its biocompatibility is essential

Working along this challenge, we have succeeded in developing a size-controllable and water-dispersible assembly of maghemite nanocrystals (NCs) that exhibits good colloidal stability without further surface functionalization These variable size Colloidal Nanoclusters (CNCs) (Fig 1a) have been characterized by SQUID magnetometry, Mössbauer spectroscopy and Transmission Electron Microscopy (Fig 1b) The experiments and Monte Carlo simulations point to the CNCs' weak ferrimagnetic response Our analysis reveals a behaviour that is the outcome of intra-cluster features that include dipolar interactions among the composing particles, as well as intra-particle exchange interactions [1] The comprehensive knowledge of the microscopic mechanisms involved warrants further exploitation of this system

In this respect, the potentiality of the CNCs is demonstrated by our relaxometric studies which show that these nano-platforms have a clear advantage against superparamagnetic (SPM) contrast agents, like Endorem®, as there is a significant enhancement of 4-times of their transverse ^{1}H-NMR relaxivity (r_2; Fig 1c) [2] Additionally, the CNCs' thermal response (Specific Loss Power; Fig 1b inset) in hyperthermia is compared against that of individual SPM NCs Our findings point how the CNCs ferrimagnetic nature and the corresponding intra-cluster interactions provide good ingredients for a high heating response Importantly, preliminary incubation experiments of the nanoclusters with mice spleen cells point to their low cytotoxicity and biocompatibility (Fig 1d) The tailored physical properties and the one-step synthesis render the CNCs a multifunctional material, which is likely to serve as a theranostic agent in biomedicine

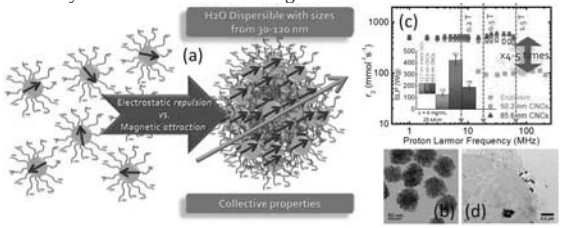

FIG 1 (a) Schematic of the CNCs formation (b)TEM image (c) r_2 and SLP (inset) values for CNCs (d) TEM from incubation of CNCs with mice spleen cells

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Dextran-ferrite Magnetic Nanoparticles Contrast-enhanced MRI and Combined Magneto-thermochemotherapy Cancer Treatment

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The early detection of proliferation, infiltration and metastases by MRI monitoring (MRM) is an important problem of oncology. We synthesized and tested dextran-ferrite sol (DFS) for contrast-enhanced MRI for the early detection of proliferation, infiltration and metastases. Dacarbazine (DC), Melphalan (MP) and and Docetaxsel (DT) containing Dextran-ferrite DFS was tested - for combined magneto-thermochemotherapy (CMTC) with slime aspiration to improve cancer treatment. Investigation of melanoma B 16 proliferation by BIOSPEC BC 70/30 (Bruker) was showed: weak signals of protons from small sites of pathogenic cells are neutralized by intensive signals from normal tissues. Ferrite nanoparticles can be used as MR-negative contrast agents[1]. Contrast enhanced MRI proliferation is represented in Fig. 1. Hypodermic and skin tumors were treated with the magnetically convenient drugs. Increase of drug concentration in tumor tissues due to the magnetic field was achieved by use of NdFeB bandages (induction 0.2-0.3 Tl)[2]. Quantification of magnetic nanoparticles in mice bodies was carried out by electron-sensor monitoring device based on non-linear magnetization of nanoparticles[3]. At first 60 female mice with melanoma B16 underwent non-enhanced MR imaging with T_2-weighted sequences. Then 0.2 ml 2.5% DFS (hydrodynamic of particles diameter from 30 to 130 nm, dose to 5.0 mg Fe/kg) was injected in mice caudal vein, and after 2-24 hours second MRM and DFS-enhanced T_2-weighted GRE sequences were performed. The DFS (70 mg/kg), DC 0.05 mg; MP 0.02 mg, DT 0.05 mg were injected into multiple tumor sites and concentrated in the tumor tissue with magnetic bandages. Treatment of tumor (~25 mm^3) by AC magnetic field at +48 C for 30 min led to its regression up to 45% and increase of survival up to 275%. The treatment of infiltration and metastases by caudal vein injection Cyclophosphamide and MP led to increase of survival up to160%.

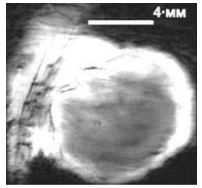

Fig 1 The primary tumor, black stain was formed by the B 16 cells containing DF particles.

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The surface-modified magnetite nanoparticles induce ERK1/2, SAPK/JNK and p53 phosphorylation in A549 cells

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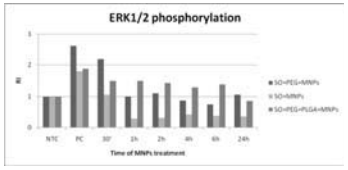
Magnetite is one of the most frequently used forms of iron oxide in nanoparticles Magnetite nanoparticles (MNPs) are easily manufactured and are considered to be biocompatible and nontoxic as iron metabolism is well controlled and excess iron is efficiently removed from the body MNPs are increasingly being investigated for variety of biomedical applications, both diagnostic and therapeutic
The unique physical and chemical properties along with their superparamagnetism make MNPs excellent contrast agents, prospective nanocarriers and heating mediators The nanoparticle uptake is dramatically affected by the physicochemical properties of nanoparticles such as the particle size, shape, surface charge and surface chemistry The nanoparticles are taken up by different routes of endocytosis (e g clathrin- and caveolin-dependent endocytosis) The mechanism of nanoparticles uptake is important for development of nanomedicines designated for specific cell type Because of the potential benefits of MNP use, human exposure to MNPs will increase, primarily in the context of nanomedicine-based diagnostics and therapy so the bio-safety of MNPs is a great concern

The goals of this study were as follows: i) the molecular and genetic characterization of the human alveolar adenocarcinoma cell line A549 in respect of their proficiency/deficiency in clathrin- and caveolin-dependent endocytosis using RT-PCR and Western Blot; ii) to investigate the impact of magnetite nanoparticles (Fe_3O_4) on cell signaling pathways (Western Blot) and iii) to evaluate the effect of surface coating on MNPs uptake and biological activity The spherical magnetic iron oxide nanoparticles with a 7 6 nm magnetite inner core and different hydrophilic shells were characterized in depth using different physicochemical assays The MNPs used in this study were coated with the following: i) sodium oleate (SO prevents aggregation and makes MNPs stable; SO-MNPs,), ii) SO-polyethylene glycol (PEG reduces interactions with plasma proteins and thus minimizes MNP internalization and clearance by macrophages; SO-PEG-MNPs), and iii) SO-PEG-poly[lactide-co-glycolic acid] (PLGA prevents degradation and aids in the regulation of drug release from nanoparticles; SO-PEG-PLGA-MNPs) Particle size distribution and zeta potential of surface modified MNPs in particular culture media were determined by dynamic laser light scattering (DLS) (Polymer Institute SAS) The MNPs uptake was observed by transmission electron microscopy (TEM) and the amount of internalized MNPs was quantified by atomic absorption spectroscopy (AAS) The mitogen-activated protein kinase cascades (ERK1/2 and SAPK) which are involved in the regulation of cell proliferation and differentiation, and reaction to cell stress, respectively and the p53 tumor suppressor protein (native p53 protein and phosphorylation of p53 at Ser-15) which plays a crucial role in the cellular responses to DNA damage were analyzed in this study

The A549 cells were proficient in both clathrin- and caveolin-dependent endocytosis The internalized MNPs localized in vesicle-bound aggregates were exclusively found in the cytoplasm The amount of internalized MNPs (pg Fe/cell) was relatively low and differed in dependence on surface modifications The SO-MNPs and SO-PEG-MNPs were internalized less efficiently than SO-PEG-PLGA-MNPs (0 151 pg Fe/cell and 0 118 pg Fe/cell, respectively *vs.* 0 504 pg Fe/cell) A significant up-regulation of ERK1/2 and SAPK was detected in cells treated with MNPs coated with organic moieties shortly after exposure Our results indicated that the surface coating of magnetite nanoparticles can affect the basic cellular processes such as cell cycle, proliferation and differentiation To better understand the potential nano:bio interactions at cellular and molecular levels, further studies are necessary



The ERK1/2 activation in A549 cells treated with surface-modified MNPs for different time intervals (30 min, 1 h, 2 h, 4 h, 6 h and 24 h). RI- (the relative band intensity) is the ratio of induced to control level of band intensity).

This study was supported by the VEGA grants 2/0051/09 2/0143/13 2/0163/12 and APVV-0658-11.

Theranostic Potential of Ferrofluids Containing Modified Ultra Small Magnetic Particles (USPIO-FF)

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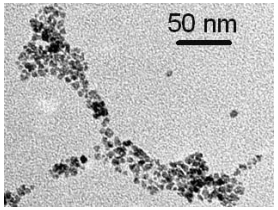
Multifunctional Ferrofluids (FF) show great potential for being simultaneously used in diagnostics and therapy, a relatively new field also known as theranostics. As a typical example one can combine Magnetic Resonance Imaging (MRI) for detecting cancer cells with therapeutic methods like drug targeting. For both applications the local particle and drug concentration at the target cells should be as high as possible to obtain significant MRI signal and high therapeutic effects. In our study two different strategies were applied to improve the local particle concentration:

I) Exploiting the high half life time of USPIO particles in the blood circulation (up to 10h), enabling a long contact time of the particles towards the target cells
II) Creating an antigen-antibody interaction to the target cells by modifying the USPIO particle's CMD surface with specific antibodies.

USPIO carboxymethylated dextran (CMD) magnetite particle FF were prepared in an one step process by aqueous co-precipitation in the presence of excess CMD and further dialysis and filtering processes. Additionally, a combined centrifugation-dialysis process was used for FF purification and enrichment of the particle concentration up to 10 mg Fe/ml. The as prepared aggregation stable USPIO-FFs were coated first with streptavidin and after that with biotinylated specific antibodies to establish an antigen-antibody-fixing.



TEM image of USPIO-CMD particles

The hydrodynamic size, polydispersity index (PI) and Zeta-potential of the USPIO-CMD-FF were measured by dynamic light scattering (DLS). The core size was determined by transmission electron microscopy (TEM), from vibrating sample magnetometry (VSM) magnetization curves, and X-ray diffraction (XRD). The amount of coupled and active streptavidine was determined by quantitative analysis of fluorescein-biotine coupling to the FF particles. MRI relaxation times were determined at 1.5 T for different USPIO concentrations.
Superparamagnetic behavior was confirmed by negligible coercivity and a relative remanence of 0.02. The hydrodynamic diameter from DLS was on the order of 20 to 30 nm. Core size was determined to be 5 to 7 nm, see Figure. The particles are suitable as contrast agents for MRI and show relaxation times similar to formerly commercially available products. The here presented multifunctional, in vivo applicable USPIO-CMD-FFs modified with antibodies are potential candidates for application in theranostics by combining MRI with drug targeting..

Acknowledgements
This work was supported wi hin the framework of the NIMINI-project No.: 01EZ0815. USPIO-FFs were prepared at Capsulution AG, Berlin and the antibody coating was performed at Surflay Nanotec, Berlin.

Experimental determination of dynamical hysteretic processes in superparamagnetic iron oxide nanoparticles

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Magnetic nanoparticles (MNP) are finding a rapidly increasing number and variety of biomedical applications due to their size-driven colloidal and magnetic properties at the nanoscale. Thus, MNP act as a suitable platform for contrast agents for magnetic resonance imaging, drug-delivery nanocarriers, and/or intracellular hyperthermia mediators. For the latter application, the conversion of electromagnetic energy into heat occurring in iron oxide nanocrystals has been proven to successfully remove tumors. In principle, heat dissipation mediated by MNP would originate from a hysteretic non-reversible magnetic behaviour appearing under alternating magnetic fields (H_{AC}) at high frequencies (~ 100 kHz). The thermal fluctuations of particle magnetic moment across anisotropy barrier or Brownian motion would lead to MNP magnetization reorientation and therefore to heating losses. Such magnetic moment relaxation processes are tightly dependent on size across the anisotropic energy barrier (ΔE_K) which is tuned by effective magnetic anisotropy and particle volume and ($\Delta E_K = K_{eff} V$). The complete understanding of the magnetization cycles is hence subjected to probe experimentally the onset of hysteretic processes (i.e., non-zero coercivity) under dynamical conditions.

Here, we report on magneto-optical measurements based on Faraday effect performed on a set of iron oxide nanoparticles whose size range from 12 to 22 nm. The MNP were synthesized by thermal decomposition of an iron precursor in organic media by a modified method previously reported. This modified route yields highly uniform IONP in size and morphology, showing superparamagnetic-like behaviour at room temperatures. The magneto-optical measurements were performed on water dispersions of MNP over a range of H_{AC} frequencies varying a six orders of magnitude in a wide (from 0.2Hz to 0.2MHz) and field amplitudes up to 50 mT. We observe the opening of the magnetization cycles when increasing H_{AC} frequency, amplitude and particle size (Fig.1). In addition, the onset of hysteretic processes for smaller sizes is found at larger frequencies (Fig.2). Our experimental technique allows to enter into the basis of the magnetic hyperthermia for exploring the dynamical conditions favouring the largest heat power from MNP.

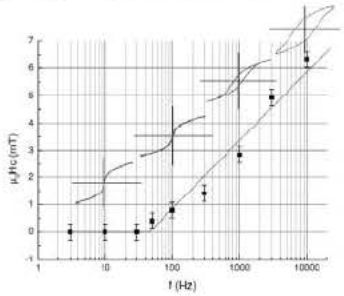

Fig 1: Evolution of magnetization cycles and coercive field ($\mu_0 H_C$) with frequency at constant field amplitude ($\mu_0 H_{max}$=50mT) for 14 nm size iron oxide MNP

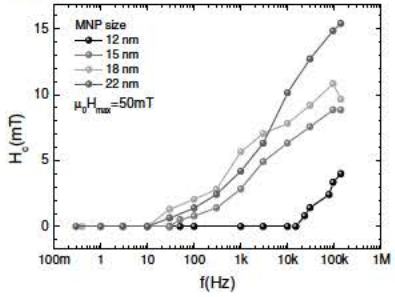

Fig 2: Evolution of $\mu_0 H_C$ with frequency at constant field amplitude ($\mu_0 H_{max}$=50mT) for iron oxide MNP with different sizes

Strategies in the design of colloidal low and high porosity silica-based magnetic nanoarchitectures

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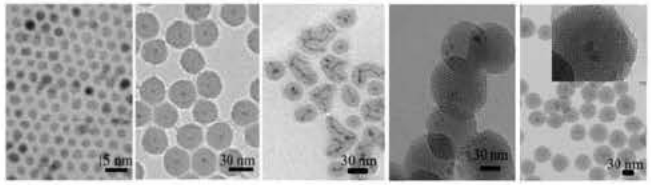
Abstract

Magnetic nanoparticles (MNPs) have been recently intensively studied for biomedical applications such as contrast enhancement agents in MRI, magnetic carriers for drug delivery systems and heating mediators in hyperthermia. [1] Biomedical use of nanoparticles imposes their uniform dispersion and stability in the biological fluids; moreover their size range should easily permit cell internalization through pinocytosis or endocytosis. Recent advances in synthesis have allowed to easily prepare a wide range of magnetic nanoparticles through aqueous or non-aqueous approaches. It has been shown that the non-aqueous routes are more efficient in producing stable colloidal nanoparticles with narrow size distribution, high crystallinity, tunable size and shape. However, this approach typically produces hydrophobic nanoparticles limiting their applications in biological and medical fields. Thus, their conversion into hydrophilic systems is a crucial step toward their widespread use. Therefore, a suitable surface modification, via exchange ligand and intercalation processes with organic molecules, or via inorganic coating/encapsulation, is needed. Among the several coating materials, silica promises an unparalleled opportunity for enhancement of colloidal properties and functions by using core-shell rational designs and profiting from its synthetic versatility

Hydrophobic nanoparticles made up of an inorganic core bound at the surface to the polar head of a long chain molecule (capping agent) represents an ideal building block to create composite systems with improved properties. This work shows how, starting from oleic acid-oleylamine capped magnetic nanoparticles, it is possible to design different silica-based colloidal nanoarchitectures. The capping agent bound at the surface of the nanoparticles and its affinity for the reactants chosen for their coating, more than the nanoparticle composition itself, are the key in order to orient the synthetic strategy versus the desired material. Following this general idea, monodisperse core-shell nanostructures with a single core with different shapes and compositions and a low-porous silica shell have been achieved. This has been possible thanks to the high affinity of the capping agent for the inner core of the micelles inside which the coating process with TEOS takes place. Magnetic multicore nanosystems with low and high surface area and an ordered (hexagonal or cubic) porous silica structure can be also created due to the high tendency of oleic acid or oleylamine to be intercalated with cationic surfactants and triblock copolymers. These colloidal magnetic nanocarriers can be considered promising versatile multifunctional systems for applications in theranostic as well as in bimodal (magnetic and optic) imaging applications.



Magnetic Hydrophobic Nanoparticles as a versatile platform for the development of low porosity core-shell (single and multicore) and high and ordered porosity (hexagonal and cubic) silica-based nanoarchitectures

AN INTEGRATED MAGNETIC PLANAR ACTUATOR REDEFINING MULTILEVEL (3D) MICROFLUIDIC STRATEGIES

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Super-paramagnetic micro particles (SMPs) are broadly used in medical and biological applications (from cellular to genomic scales), but the handling tools for those particles remain mostly non-integrated. Since a decade, a few solutions for integrated actuation have been proposed and paved the way to the micro-scale control of SMPs. So far, spiral planar coils showed the best compromises between the available magnetic force and the actuator footprint. Albeit the technology to integrate this type of coils with microfluidic structures exists, it is hard to find examples of dual architectures using those two aspects for concrete applications.

As a matter of fact, the fluidic structures of such an actuator should be designed so as to take advantage of the high impact of the magnetic force component developed on the orthogonal axis of a spiral planar micro-coil, which is impossible given the lack of simple fabrication techniques for 3D microdluidics.

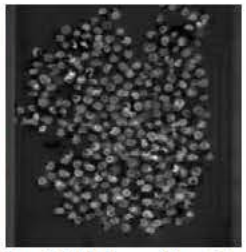

Figure1: THP1 Monocytes (about 15µm diameter) trapped on a planar microcoil.

We therefore developed a SU-8 dry film lamination technique, which can be used with standard micro technology processes. It allows us to combine a good resolution (the height and width of the coil turns are 5µm) and 3D structures, can be carried out on silicon, glass or flexible substrates, and is compatible with other commercially available low cost dry films for the microfluidic architecture. Our approach was then to place planar coils under two superposed channels, the top one containing a sample with magnetically targeted cells, and the bottom one a buffer to recover the magnetic beads an attached cells.

The devices were then tested with a setup including a current source (100mA injected in each coil, the coils being wired in three series of three), a Fluigent pressure controller, and a bright field microscope. In a first step (A), the magnetic particles (5µm diameter from Invitrogen) are vertically focused using the first six coils. Once the beads have reached the separation level, they are attracted towards the bottom channel with the last three actuators.

Using that system, we achieved to separate a solution of SMPs with an 80% efficiency at a 2.5 µL/min flow rate (4.6 mm/s). It is also possible to perform trapping (all the beads stay on the coils) at lower flow rate: trapping is observed simultaneously with separation (with a 100% yield) at 1µL/min (1.8 mm/s). We showed also that trapping of monocytes was possible on this coil design.

Currently we are working on the system characterization with a biological application. This type of systems is particularly suited to integrated detection techniques, and a next important step would be the conception of a fully coupled magnetic actuation and electrical detection microfluidic chip.

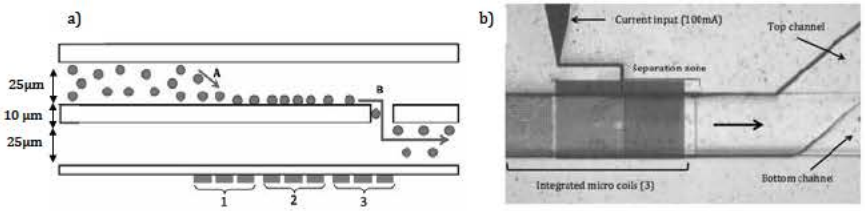

Figure 2: a) Scheme of the integrated magneto-fluidic actuator. SMPs are separated from the top channel to be released in the bottom channel, due to the magnetic attraction of nine microcoils. b) Top view photography of the microfluidic chip.

Labelling of Dendritic Cells with Polyelectrolyte-coated Ferumoxytol Nanoparticles for Tracking by Magnetic Resonance Imaging

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Engineered magnetic nanoparticles (MNPs) are emerging to be used as cell tracers, drug delivery vehicles, and contrast agents for magnetic resonance imaging (MRI) for enhanced theragnostic applications in biomedicine. In vitro labelling of target cell populations with MNPs and their implantation in animal models and patients show promising outcomes in monitoring successful cell engraftment, differentiation and migration using MRI.

Dendritic cells (DCs) are professional antigen-presenting cells that initiate adaptive immune responses. Thus, DCs have been the focus of cellular immunotherapy and are increasingly applied in clinical trials.

Here, we investigated the impact of different polyelectrolyte (PE) coatings around ferumoxytol particles for the labelling efficiency on different subpopulations of DCs. Ferumoxytol particles were coated with low (MW: 100-200 kDa) and high (MW: 400-500 kDa) molecular weight poly(diallyldimethylammonium-chloride) (PDADMAC) and low (MW: 25 kDa) and high (MW: 750 kDa) molecular weight poly(ethyleneimine) (PEI) using the Layer-by-Layer technique. The PE-coated particles were then used to label DC progenitors and differentiated DC subsets in vitro.

Particle size and zeta potentials measurements and thermogravimetric analysis (TGA) confirmed PE coatings of MNPs. Up-take in and labelling of DCs were visualized by transmission electron microscopy (TEM) and Prussian blue staining. Quantification of the iron uptake into the cells was measured with ferrozine assay.

The results from our studies revealed that PE-coated ferumoxytol particles show an outstanding potential for labelling of DC and DC progenitors (Figure 1).

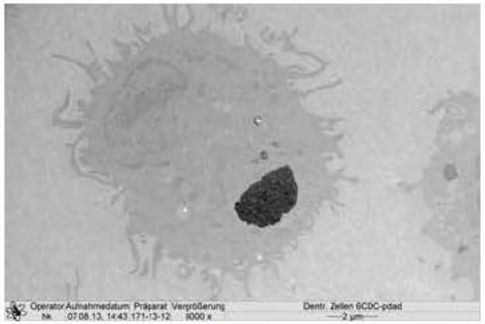

Figure 1. TEM image of labelled DC with the PDADMAC-coated ferumoyxtol particles.

Synthesis of Magnetic Polystyrene Nanoparticles using Amphiphilic Ionic Liquid stabilized RAFT mediated Miniemulsion Polymerization

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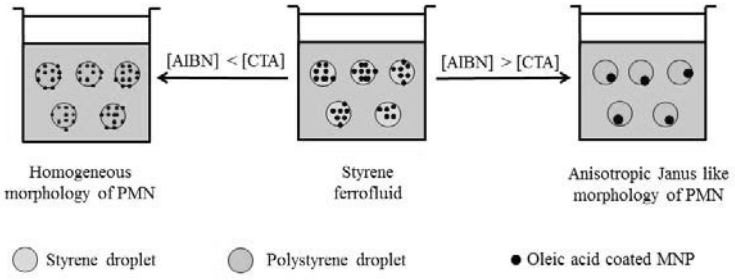
In this study, we have synthesized polymer magnetic nanoparticles (PMN) by miniemulsion polymerization (MEP). An imidazole based amphiphilic ionic liquid has been used as surfactant in miniemulsion polymerization of styrene to synthesize the PMN. The magnetic nanoparticles (MNP) used in this work were synthesized using well known co-precipitation method in presence of oleic acid for hydrophobization of MNP surface. Following the demand for producing magnetic colloidal nanoparticles with good stability as well as with high content of magnetic nanoparticles (MNP), we have reported an efficient pathway to increase the MNP content in the composite through RAFT mediated MEP. A carboxyl-terminated chain transfer agent (CTA) has been found to be useful to increase the MNP content in PMN. The content of MNP was possible to adjust by controlling the initiator to CTA mole ratio. The influence of MNP on the molar mass distribution of polystyrene in PMN both in absence and presence of CTA has been investigated. The characterization of the materials has been performed using several well-known techniques such as TEM, SEC, DLS, NMR and TGA. Finally the magnetic properties of the materials were determined by means of a vibrating sample magnetometer (VSM).



Schematic representation of the influence of initiator to CTA mole ratio on the morphology of PMN

Magnetite-Silica-Titania Nanocomposites and Their Photocatalytic Activities

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Colloidal nanocomposites of magnetite-silica-titania (Figure 1a) were prepared in order to obtain magnetic nanoparticles with high photocatalytic activities. Superparamagnetic magnetite nanoparticles were coated with photocatalyst anatase titania, while silica was employed as an interlayer in order to prevent the loss of photocatalytic activity of titania. The large band gap of silica can prevent an increase in electron-hole recombination occurring when titania is in direct contact with the narrow bad gap magnetite. Magnetite nanoparticles were synthesized using thermal decomposition of iron-oleate complexes in presence of oleic acid. Magnetite nanoparticles were then coated with porous silica using reverse microemulsion process. The silica-coated magnetite nanoparticles were then deposited with anatase titania using sol-gel process under low temperature to avoid the agglomeration of the nanocomposites. The resulted magnetite-silica-titania nanostructures were characterized by transmission electron microscope (as shown in Figure 1b), x-ray diffractometer, x-ray fluorescent spectroscope, transforms infrared spectroscopy, dynamic light scattering analyzer and surface area analyzer. The resulted magnetite-silica-titania nanoparticles showed high photocatalytic activity in the photodegradation of methylene blue under UV irradiation, while they were easily removable using an external magnetic field. The nanocomposites with high colloidal stability, biocompatibility, and photocatalytic activity could be useful in biological applications.

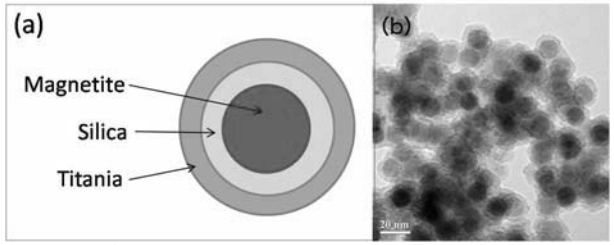

Figure 1: (a) Structure of magnetite-silica-titania nanocomposites and (b) TEM images of the nanocomposites.

Nanoparticles of Conjugated Methotrexate-Cationic Human Serum Albumin-Superparamagnetic Iron Oxide: Synthesis, Characterization and Drug Loading Behavior

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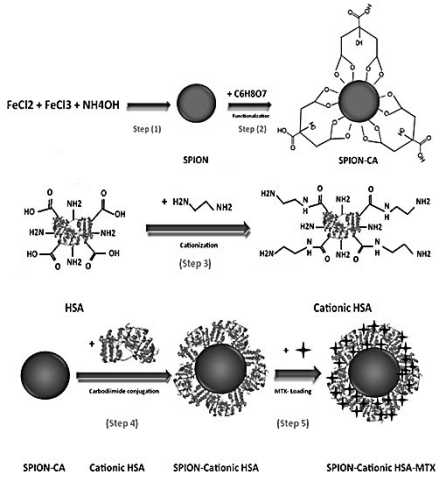
ABSTRACT

The primary insufficiency of chemotherapeutic drug is their potential side effects to the healthy tissues and their relative non-specificity To overcome this limitation, drug delivery system is used Magnetic-based delivery systems are based on binding drugs with magnetic fluids that concentrate the drug in the site of interest by using an external magnetic field

In the current study, we aimed to develop a novel drug carrier, cationic human serum albumin (HAS) conjugated superparamagnetic iron oxide nanoparticle (SPION), which can be loaded easily high doses of methotrexate (MTX) as a model cancer chemotherapy drug to evaluate its potential as a magnetic drug carrier system SPIONs were synthesized by co-precipitation and citric acid was selected to provide stability of SPION Carboxylic acid terminal group provides a site for further surface modification Afterwards, the SPIONs were covalently modified by cationic HAS using carbodiimide chemistry HSA was cationized by substituting anionic side chain carboxyl groups with amine groups Because of negative charge of cell surface membrane, this surface provides sites of interaction for cationic nanoparticles Finally MTX attached into cationic HAS conjugated SPIONs by entrapping negatively charged drug onto positively charged nanoparticles through electrostatic interactions, to target MTX onto tumor environment

The obtained nanoparticles were characterized by XRD, TEM, SEM, FTIR, Bradford assay, VSM, zeta potential and HPLC analysis, proved stepwise modification of SPIONs with citric acid, cationic HAS and MTX

The present finding shows that cationic HAS conjugated SPIONs could be loaded high amount of chemotherapeutic agents (e g methotrexate) and encouraging carrier for magnetically targeted drug delivery



Scheme for the functionalization procedure of superparamagnetic iron oxide nanoparticles described in this work.

Study of aggregation of magnetic microcarrier based on SiO_2 by NMR relaxometry and conductometry

Yu.S. Chernenco[1], K.G. Gareev[1], S.A. Ionin[1], B.D. Klimenkov[1], I.E. Kononova[1], Ya.Yu. Marchenko[2]

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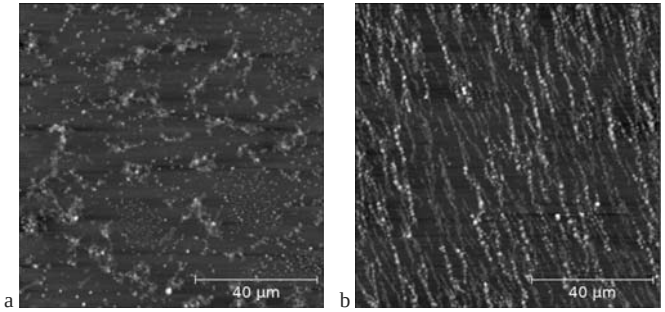
One of the problems with the medical use of magnetic nanoparticles as MRI contrast agents and targeted drug delivery is keeping the risk of thrombosis as a result of the aggregation of magnetic nanoparticles in a strong magnetic field tomography [1]. Magnetite coated silica cores' obtained by sol-gel technique intensive aggregation under the influence of external magnetic field is convenient to simulate after-analysis conditions in MRI diagnostics.

Fe_3O_4/SiO_2 colloid particles have high aggregative stability [2] which is broken at imposing a uniform magnetic field of 0.33 T. As it was stated the effect is due to the formation of linear aggregates which is clearly seen in the images obtained by AFM microscopy. According to NMR relaxometry data formation of linear structures in colloids provokes an increase of the spin-spin relaxation time of water protons which should lead to the artifact distortion in T_2-weighted MRI imaging in the area of aggregating magnetic nanoparticles. Change in electric conductivity of Fe_3O_4/SiO_2 colloid influenced by static magnetic field is the second factor of possible settings' violations of MR imager receiving-transmitting system.

Resistance of solutions was measured using RLC- meter E7-20 (JSC "MNIPI"). Magnetic field was produced by cylindrical coil and has been set on for a period of 180 s. Using magnetic field of 500 A/m the Ohmic resistance of the colloid decreased by 2-4 % depending on the content of initial tetraetoxisilane (TEOS) soles. Aggregates of magnetic nanoparticles formation in a colloidal solution magnetic field also is affected by silica xerogels' surface morphology so specific surface area (SSA) on TEOS concentration dependence was analyzed. For thermal desorption measurements SORBI analytical device (JSC "META") was used. A correlation between NMR relaxivity r_2, relative resistivity change and SSA was stated in this work.



AFM images of Fe_3O_4/SiO_2 layers dried with magnetic field 50 mT (a) and without magnetic field (b)

The study was partially supported by RFBR, research project No. HK 14-03-31534\14.

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In vitro Cytotoxicity of Biocompatible Fe-Cr-Nb-B Magnetic Nanoparticles against Human Osteosarcoma Cancer Cells under High Frequency Electromagnetic Field

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In the last years, more and more studies are dealing with the magnetic hyperthermia as a possible cure for cancer treatment In a simplistic approximation, the cancer cells will be destroyed by the heat generated by the magnetic particles (eddy currents) under a high frequency electromagnetic field, while the normal ones should remain intact However, one of the most important parameters to be monitored during the magnetic hyperthermia is the local temperature generated by the eddy currents Ideally, this temperature should be in the interval of 41-46^{0}C, the process being also called moderate hyperthermia by some authors In this temperature range, the intra- or extra-cellular degradation mechanisms will be activated / initiated and the cancerous tissue will be destroyed by either necrosis or apoptosis

Many of the present studies are using superparamagnetic iron oxide nanoparticles (SPIONs) for magnetic hyperthermia However, the heating of Fe-oxides (mainly Fe_3O_4) up to moderate temperatures (below 50^{0}C), but most importantly the preserving in the temperature range of 40-45^{0}C requires a very rigorous control of the power of the high frequency generator To overcome such disadvantages, we have developed a new type of ferromagnetic nanoparticles (the saturation magnetization is higher compared with Fe-oxides and the hysteresis losses are reduced as well) based on glassy Fe-Cr-Nb-B alloys [1], with low Curie temperatures compared with SPIONs, which can be tailored easily and precisely in the 30-50^{0}C by modifying the Cr content, with an accuracy of less than 1^{0}C

The purpose of the present study was to evaluate in vitro the cytotoxicity of $Fe_{68.2}Cr_{11.5}Nb_{0.3}B_{20}$ alloy nanoparticles, coated or not by a biocompatible layer and marked as samples A to E (A – nanoparticles of 60-80 nm coated by chitosan 3 5%; B - nanoparticles of 60-80 nm coated by chitosan 10%; C – nanoparticles of 20-30 nm coated by chitosan 5%; D – nude nanoparticles of 60-80 nm; E – nude nanoparticles of 20-30 nm) The effect of Fe-Cr-Nb-B magnetic nanoparticles on tumor cells (human osteosarcoma cancer cells) was investigated prior and following particle activation by an a c electromagnetic field of 350 mT (f = 153 kHz) created by a home-made magnetic-induction hyperthermia unit Cell behavior was evaluated by phase contrast microscopy and MTT viability assay Cell viability by MTT assay is a colorimetric method that uses a tetrazolium salt (MTT) which is transformed by mitochondrial dehydrogenases in purple formazan granules that can be subsequently dissolved by DMSO; this method was used to evaluate the cell survival following incubation with the proposed samples Microscopic evaluation confirmed that samples C and D and partially the sample B showed cytotoxic activity on human osteosarcoma cells following induced hyperthermia induced by magnetic field activation Microscopic evaluation was confirmed by MTT assay results for samples C, D and E while for sample B the microscopic observation was not sustained Sample A was demonstrated to be toxic even without magnetic activation Our results are encouraging to further explore the effect of magnetic activated nude/coated nanoparticles on normal/tumor cell lines, using higher cell amounts or three dimensional cell cultures

This work was supported by a CNDI–UEFISCDI grant, Project #148/2012 (HYPERTHERMIA).

[1] H Chiriac et *al.*, J Appl Phys 115 (2014) 17B520

Uniaxial vs. Cubic Magnetocrystalline Anisotropy on the Dosage-Dependence Hyperthermia Properties of Ferromagnetic Nanoparticles

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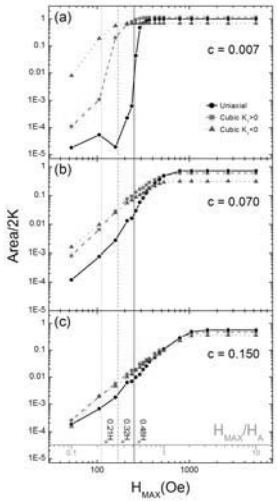
Success of magnetic hyperthermia cancer treatment relies on a good control of the heat dissipated by magnetic nanoparticles under the application of an external AC magnetic field The heating performance of the particles is strongly dependent on their magnetic anisotropy, which plays a double key-role: it is the heating-mechanism source (determines the maximum achievable dissipation power); and establishes a first threshold in the range of field amplitudes (H_{max}) required to achieve relevant heating through the ratio H_{max}/H_A [1, 2]

In principle, cubic anisotropy would be more suitable for hyperthermia applications based on its higher heating efficiency for limited H_{max} values [3] However, it is usually assumed in the literature that the anisotropy of magnetic nanoparticles can be described as an effective anisotropy of uniaxial type [2] Such strong assumption, favored by the small size of the particles usually considered for hyperthermia with a large contribution of surface/shape effects of uniaxial type [4], is borne out by the good agreement between simulation and experiment [5]

Nevertheless, most hyperthermia-agent magnetic nanoparticles are iron-based, with cubic magnetocrystalline anisotropy, and there is a growing tendency to use larger particle sizes –for which the magnetocrystalline anisotropy becomes more important- due to their superior heating performance [5, 6] At the same time, it is well known in the literature the important role that interparticle dipolar interactions play in the hyperthermia output [1, 6, 7], and interaction effects will also be more relevant for larger sizes Therefore, it points out the importance of understanding the role of uniaxial *vs.* cubic magnetocrystalline anisotropy in the concentration-dependent hyperthermia performance of nanoparticle systems

We used a Monte Carlo technique to investigate the heating properties of the particles as a function of field amplitude, concentration (c), and type of anisotropy At low concentration, particles with cubic anisotropy perform larger hysteresis losses at lower H_{max} values than those with uniaxial anisotropy This result confirms the better adequacy of cubic anisotropy for hyperthermia purposes, due to its lower coercivity in comparison with the uniaxial ones However, those differences tend to disappear for higher interaction conditions where the curves converge to a common trend This similarity between the cubic and uniaxial cases for high interaction conditions may explain the good success of the usual uniaxial-anisotropy assumption made in the literature (in real experiments some interaction is always present and often even leads to aggregation) It is important to keep in mind that such approximation does not hold for low concentrations, where the beneficial aspects of the cubic anisotropy could provide advantages for magnetic hyperthermia We believe these finding provide further understanding of the basic hyperthermia mechanisms and thus may help to the design of better hyperthermia protocols



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Optimized treatment planning of tumors under consideration of magnetic nanoparticle distribution using microCT

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A promising minimal invasive method for the effective treatment of tumors is magnetic fluid hyperthermia (MFH). But due to the inhomogeneous distribution of the magnetic nanoparticles (MNP) within the tumor, regions with temperature underdosing may arise. This temperature gradient leads to a reduction in the therapeutic efficiency.
In this study, we used microCT imaging to characterize the intratumoral MNP distribution to further improve the therapeutic success by individual therapeutic planning.

Mice were subcutaneously implanted with human breast adenocarcinoma (2 x 10^6 MDA-MB-231 cells). MNP distribution was checked via microCT after intratumoral injection (iron oxide, DMSA coated, core diameter 11.7 nm; dose 0.24 mg/100mm3 tumor volume).
Within an interval of seven days, the mice were exposed twice to an alternating magnetic field (AMF; H = 19 mT, f = 435 kHz, for 60 min).The tumor surface temperature was monitored using an infrared thermography camera.

The intratumoral MNP distribution pattern was clearly shown via microCT images. The exact location of the MNP in the tumor and its position to non-tumor structures could be determined. By an individually adapted MFH therapy (e.g. magnetic field parameters according to the position of the nanoparticle deposits), the tumor volume could be distinctly reduced over time. The observed tumor regression correlated well with the MNP distribution and the generated hyperthermic temperatures (≥ 43°C).

In conclusion, by knowing the MNP distribution pattern and identification of regions with MNP underdosing an individual planning of MFH treatment could be performed. The intratumoral MNP distribution pattern mainly governed the generated temperature spots within the tumor.

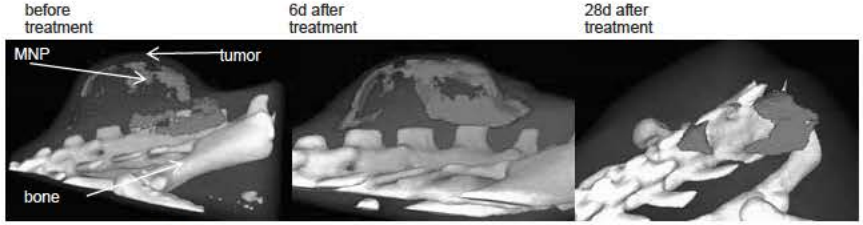

Figure 1 Location and distribution of MNP over the time

Nanostructural characterization of bio-magnetic cobalt ferrite-alginate nanospheres

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Magnetic nanocomposites are of great interest both to physical and biomedical technologies.[1, 2] Hydrogels can be a suitable solution for providing he nanoparticles with the required hydrophilicity and biocompatibility.[3] By means of gelation techniques it is possible to syn hesize composites with nanoparticles entrapped and confined in a well defined volume. Moreover, nanoparticles would ideally be separated one from each other by the polymer network barriers. In he case of magnetic nanoparticles this aspect is particularly interesting: during he embedding process the formation of the polymer network will prevent an increase of the nanoparticles aggrega ion state by keeping the inter-particle distances, so hat the intensity of the magnetic interactions does not increase. To our knowledge, only a few works describe he structure of nanosized alginate beads obtained from ionotropic method. In addition, very lit le is known about what happen to such porous structure when lowering the bead size, especially concerning its ability to entrap nanoparticles.

We have obtained alginate magnetic nanospheres by **combining an aerosol technique with the ionotropic gelation method**.[4] A very good dispersion of the nanoparticles in the polymeric matrix has been obtained, leading to the forma ion of **highly stable water-dispersed magnetic nanobeads**. Our syn hetic approach, which stands out for its **simplicity**, leads to a **significant reduction of the bead sizes**, much lower han hat of other nanocomposites based on alginate gels obtained by more complex techniques. The capability of the alginate porous structure to entrap nanosized objects can be easily exploited to entrap any other magnetic and non-magnetic nanopar icles, as well as to other nano-sized objects, as a first step for he design of new smart materials for biotechnological and biomedical applications. The nanobeads have been characterized in environmental-like conditions by means of advanced electron microscopy techniques as Environmental SEM (ESEM), High Angle Annular Dark Field-Scanning Transmission Electron Microscopy (HAADF-STEM) and cryoTEM. The proposed syn hetic method and the combination of the different electron microscopy techniques can be extended to design and characterize a variety of nanosized soft-materials.

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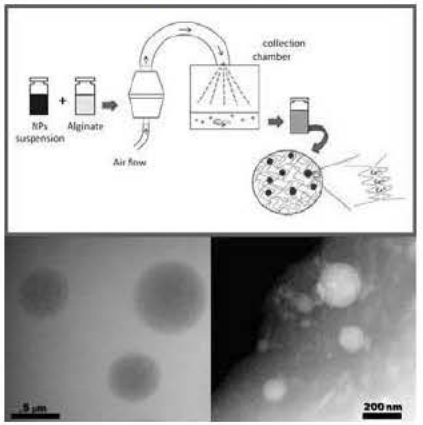

Combination of the Hyperthermia and Photodynamic Therapy on Cancer Treatment Using Target Delivery Chloroaluminum Phthalocyanine Magnetic-Nanoemulsion

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During cancer treatment, therapeutic compounds often need to be delivered into individual tumour cells to exert anticancer effects. Targeted delivery of drug molecules using nanodevices can improve biodistribution and increasing efficacy and reducing side effects. In addition, the Photodynamic therapy (PDT) is a light-based procedure with a long history of successful clinical track for treatment of oncological and non-oncological diseases. The visible light energy activated the photosensitizer (PS) molecule, which in the presence of oxygen leads to the production of reactive oxygen species inducing a toxic biological reaction by a called photodynamic process. The photodynamic pathways generate a cascade of events including initiation of apoptotic and necrotic process both in tumour and in the neovasculature, leading to a permanent lesion and destruction of the tumour. Magnetic nanoparticles (MN) have richan extensive research interest with respect to hyperthermia (HPT) process induced by magnetic field acting on magnetic nanocarriers. The MN targeting has been widely used in a wide spectrum of *in vitro* and *in vivo* application worldwide, including cell separation, gene transfection, and cancer treatment. Combination of *in vivo* magnetic targeting could be used as a valuable approach for controlled delivery of therapeutic agents. PDT and HPT are well-established tumour therapy with minimal side effects while acting synergistically. Current nanotechnology incorporates controlled release of PDT-PS and biocompatible MN based on the development of advance drug delivery systems (DDS).

In this study we developed an innovative magnetic-nanoemulsion (MNE) citrate functionalized loaded with PS chloroaluminum phthalocyanine. The MN was incorporated into nanoemulsion using a highly stable ionic magnetic fluid in a spontaneous emulsification method as described by Primo et al 2008. Our findings demonstrate excellent physical and chemical stability of MNE with a size less than 200 nm, exhibiting a narrow size distribution (PI index less than 0.2) and the zeta potential higher around |40| mV. The *in vitro* studies using the human mesenchymal stem cells derived from bone marrow, glioblastoma and fibroblast cell line indicate biocompatibility of MNE establishing a safe DDS with drugs concentration for the specific cells types. Confocal studies clear indicate the intracellular localization and active site of the drug combination. As a result, combined HPT and PDT showed a more pronounced synergistic effect than the additional of the individual therapies. This combination has therefore become a promising paradigm for cancer intervention. Traditionally, the combined therapy relies on two separate treatments, which have to be carefully arranged in order to achieve synchronized effects. Such observations can be useful for developing further protocols to advance *in vivo* assays available for clinical oncology.

Micro CT-based Determination of Ferrofluid Iron Concentration

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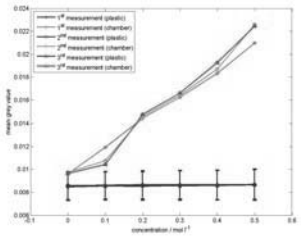
Magnetic nanoparticles are used in a wide range of applications. This includes various fields in particular in medical applications as hyperthermia and diagnostic imaging. For the latter an imaging technique named Magnetic Particle Imaging (MPI) has emerged in 2005. Actually MPI has accelerated the development of tailored magnetic nanoparticles as tracers. The administration of an appropriate ferrofluid to the human body makes a thorough characterization of the nanoparticle suspension regarding parameters as core diameter hydrodynamic diameter or iron concentration necessary. Methods to do so are for example transmission electron microscopy X-ray diffraction Mössbauer spectroscopy magnetic particle spectroscopy (MPS) photon cross-correlation spectroscopy (PCCS) or atomic absorption spectroscopy (AAS). A pragmatic and promising approach for the determination of the SPION iron concentration is micro computed tomography (μCT).

The micro-CT based iron-content determination is carried out using a Skyscan 1172 high-resolution micro-CT and the software NRecon (both Bruker microCT Belgium). The latter is based on the Feldkamp Davis and Kress cone-beam algorithm. A phantom meeting the requirements of a quantitative X-ray measurement has been designed. The evaluation has been done using the mean grey value images in an isotropic voxel gridding of 9.5 μm edge length. Appropriate technical measurement parameters had been found in a preceding study [1] (tube voltage: 37 kV X-ray beam filtration: 0 5 mm aluminium filter). In the study presented here measurements were performed with aqueous SPION suspensions with increasing iron concentration. To calibrate and/or eliminate effects of temperature dependence and going along with this density and viscosity variations of the suspension these parameters have been considered as well. All μCT results are compared with the results of photometry as reference.

The mean grey values of the μCT voxels show a linear dependence on the iron concentration of the sample. As expected the sample temperature which has been varied in the interval of 0 °C to 40 °C does not show any influence on the measured mean grey values.

The results of the study presented here indicate that the determination of the iron concentration in ferrofluids using μCT is possible. Thus this approach is a promising alternative to time-consuming methods as photometry AAS or invasive techniques as histological staining. The influence of the temperature of the liquid matrix on the results of the μCT measurements has been thoroughly investigated. However further studies on this topic need to be carried out using alternative methods for ferrofluid characterization as MPS or PCCS.



Correlation of iron concentration of the SPIONs in liquid solution with the mean grey values of the voxels in the corresponding μCT measurements.

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Preparation of Manganese Perovskite Magnetic Nanoparticles and Their Mechanical Treatment

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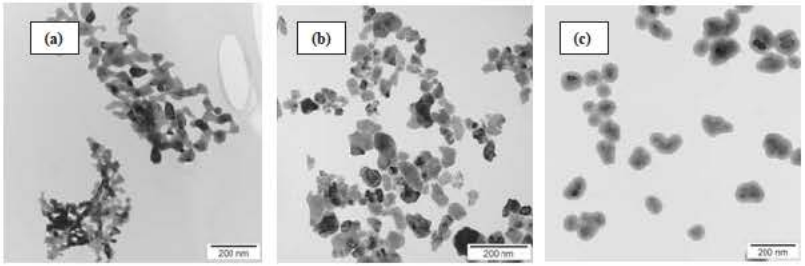
Magnetic nanoparticles of lanthanum manganese perovskite $La_{1-x}Sr_xMnO_3$ could find applications as a contrast agent for magnetic resonance imaging or colloidal mediator for magnetic fluid hyperthermia. These nanoparticles have several times higher relaxivity and higher heating efficiency than the commercial product based on iron oxide. In addition, heating the particles can be managed very well by appropriate setting Curie temperature which reduces the risk of overheating and damage of surrounding healthy tissue.

Nanoparticles of manganese perovskite were prepared by sol - gel method [1]. Raw nanoparticles show high toxicity which is why they are usually covered by silica shell. This coating provides good protection against toxic effect of cores while separating it entirely from the biological system and stability of the suspension as well. Encapsulation was performed using modified Stöber sol - gel method [2]. Yield of encapsulated nanoparticles with suitable size is pretty small. A way how to eliminate this disadvantage is to find much more suitable mechanical treatment of raw magnetic cores. Magnetic cores after annealing are connected with bridges which have to be removed. Appropriate results were achieved by combination of rolling and milling rather than by milling only. For this purpose rolling broke down bridges successfully. Furthermore, the best way of milling was searched.



Transmission electron micrographs of magnetic cores after (a) annealing, (b) mechanical treatment, (c) encapsulation by silica shell.

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Determination of Magnetic Property Distributions through First Order Reversal Curves (FORC)

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In an ideal magnetic nanoparticle system, all magnetic nanoparticles are identical in both their physical and magnetic properties. In reality, no matter what method is chosen for the synthesis, there are distributions in physical (size, composition, crystallinity, etc.) and magnetic (moment, coercivity, anisotropy, etc.) properties. Herein, we will introduce the method of First Order Reversal Curves (FORC) as an analysis technique for identifying distributions in the coercivity, interactions, and anisotropy of magnetic systems. Assumptions underlying the intrinsic theory will be discussed, and how they are interpreted in the context of actual data. An example system of $Fe–(Ni_{0.5}Zn_{0.5})Fe_2O_4$ nanoparticles will be used to highlight the information that can be obtained from FORC and its impact on application development. In particular, we found an (expected) difference in the interaction field distribution due to changes in the amount of iron nanoclusters present in the sample, as evidenced by a broad transition to saturation for the higher iron content sample, and a much sharper transition for the lower iron content sample. FORC measurements quantified these differences as an average interaction field of (0.9±0.3) mT and (2 3±0.2) mT for the higher and lower iron content samples, respectively. More importantly, the width of the H_B distribution is (64±1) mT and (41 2±0.6) mT for the higher and lower iron content samples, respectively. In addition, the formation of another, secondary, interaction field occurs with sample annealing, and is much larger in both average interaction field - ranging between (-46±3) mT and (-104 ± 3) mT - and the width of the interaction field - two-three times that of the primary interaction field width. This increase in the interaction field with increasing iron content and appearance of a secondary interaction field with annealing is expected to have an impact on the high frequency behavior, perhaps by requiring larger fields to reverse the magnetization.

Single-core magnetic markers in rotating magnetic field based homogeneous bioassays and the law of mass action

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The application of functionalized magnetic nanoparticles (MNPs) as a test system in homogenous bioassays enables a quick and quantitative detection of proteins, e.g., biomarkers in medical diagnosis and therapy, directly in solution. Here, no wash-out steps to remove unbound markers are necessary. The required magnetic manipulation of the MNPs is realized with a rotating magnetic field (RMF). The RMF offers the possibility to perform a narrow-band measurement of the MNP response compared to switched magnetic fields and to gain a higher measurement effect compared to alternating magnetic fields [1,2].

In this work, we report on the effect of the absolute single-core MNP concentration on the quantitative detection of proteins with MNPs in a RMF. Therefore, the phase lag change $\Delta\varphi$ of commercial 30 nm iron oxide nanoparticles (Ocean Nanotech, Springdale, AR, USA) caused by bound proteins is measured with a fluxgate-based RMF system. As a model system the detection of anti-human IgG via protein G which is covalently linked to the MNP polymer shell is investigated. The measured phase lag changes for a fixed MNP and a varying IgG concentration are modeled with logistic functions (Fig. 1). The effect of the MNP concentration change is explained with the law of mass action and used to determine the parameters of the binding reaction. Further binding scenarios, e.g., for the detection of the medical relevant HER2 biomarker, are presented and investigated regarding the dependence on the MNP concentration.

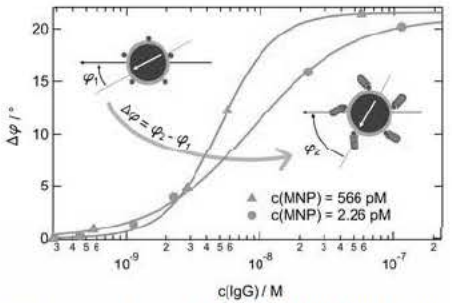

Fig 1: Measured phase lag change $\Delta\varphi$ in RMF due to bound IgG as function of the IgG concentration The MNP concentration variation affects the slope of the logistic functions (lines) which are fitted to the measurements The graphic illustrates the effect of the protein binding on the phase lag between the RMF and MNP magnetic moment

Acknowledgment

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One pot synthesis of magnetic chitosan loaded with tryptophan

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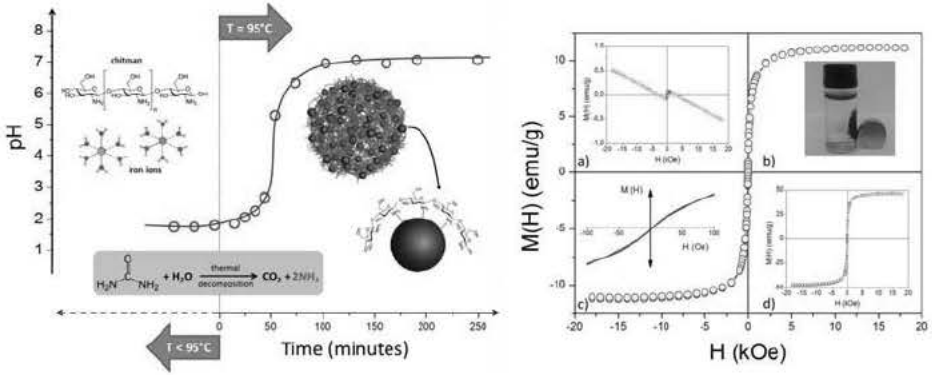
The biocompatibility and toxicity of magnetic nanosystems (MNS) are essential criteria for biomedical applications In this way, chitosan (CS), a natural polysaccharide with free amine groups, is a useful coating, mainly for pharmaceutical applications, since it presents low toxicity and improved mucoadhesive features Moreover, the physical-chemical behavior of CS allows incorporation of pharmaceuticals in its structure and opens the possibility for applications in drug delivery Here, the nanomagnets act as probes to magnetically drive the MNS to a specific region and/or, through their magneto-thermal properties, can control a drug release with an external magnetic field

In this way, one proposes in this work the elaboration of a (50-100 nm) MNS that is composed by magnetite nanoparticles dispersed in CS and loaded with tryptophan, synthesized by homogeneous precipitation with urea, in one only step The characterization of the materials was performed utilizing XRD, TEM, FTIR, TGA, magnetization and DLS (zeta potential) measurements Tryptophan was utilized to evaluate the ability of synthesized MNS acting as a nanocarrier for controlled drug release The degree of incorporation of tryptophan and its liberation profile were investigated by UV-VIS dosage of aqueous solutions containing the MNS at different pH and temperature conditions



Left – Schema of synthesis: during urea decomposition, pH raises and iron ions co-precipitates and CS coacervates together Right – Magnetization of MNS (blue circles); (a) magnetic contribution of CS; (b) the magnetic chitosan; (c) and (d) magnetization of magnetic nanoparticles inside the MNS

Fe_xO_y Nanopowders prepared by CO_2 Laser Vaporization – Control of Crystal Phase Composition

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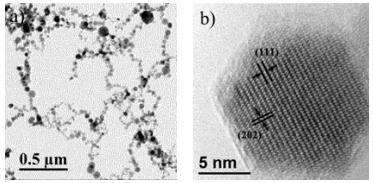
Iron oxide (Fe_xO_y) nanoparticles are typically synthesized by wet chemical reactions using additives to control size, shape, and properties. Here, CO_2 laser vaporization (LAVA) with subsequent gas phase condensation at normal pressure was used for the preparation of Fe_xO_y nanopowders. Samples were prepared from a coarse hematite (α-Fe_2O_3) powder. A high power CO_2 laser beam was focused into the powder. Absorbing the laser radiation the powder heated up and vaporized. Quenched in the flowing process gas clusters were formed by homogeneous nucleation. Supersaturation led to the condensation of melt droplets. The O_2 content of the condensation atmosphere was varied applying different combinations of argon, air, and oxygen as the process gas. Basic investigations [*Kurland, H.D., et al., JMMM 2007, 311(1), 73-77*] revealed a close connection between the oxygen content of the condensation atmosphere in the LAVA process and the phase composition of the Fe_xO_y nanopowders. In our present work [*Stötzel, C., et al., Cryst. Growth Des. 2013, 13(11), 4868-4876*] this impact of the O_2 partial pressure on the LAVA prepared nanopowders and thus on their physical properties is studied systematically.

Prepared samples were characterized using X-ray diffraction combined with Rietveld refinement and transmission electron microscopy (TEM). The contents of Fe^{2+} ions was determined by quantitative cerimetric redox titration. Vibrating sample magnetometry was used to determine the magnetic properties of the FexOy nanopowders. Furthermore, the presence of ozone (O_3) in the zone of condensation was checked using an ultraviolet absorption ozone analyzer.



TEM micrographs of LAVA prepared iron oxide NPs: a) typical chain-like agglomerate and b) high resolution micrograph of a γ-Fe2O3 NP.

In O_2 depleted condensation atmospheres maghemite (γ-Fe_2O_3) forms the dominant crystal phase. Increasing the O_2 partial pressure leads to an increasing formation of ε-Fe_2O_3. This also results in a change of the magnetic properties of the Fe_xO_y nanopowders since ε-Fe_2O_3 has a small saturation magnetization in combination with a high coercivity. The O_2 partial pressure and thus the O_3 content in the condensation atmosphere of the LAVA process strongly impacts structural and accordingly magnetic characteristics of the prepared FexOy NPs. Hence, their saturation magnetization and coercive field can be adjusted within certain limits by controlling the O_2 partial pressure during the gas phase condensation of the NPs. Based on the results and on density functional theory (DFT) calculations a model which describes the formation of the initial nucleation stages of iron and oxygen in the vapor phase is proposed.

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Formation of a Protein Corona around Magnetic Nanoparticles after Administration into a Biological System

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A common route to transfer pharmaceutical substances to their destination is the administration of nanoparticles (serving as drug carriers) loaded with suitable drugs to the peripheral blood. When exposing these nanomaterials, e.g. superparamagnetic iron oxide nanoparticles (SPIONs), to the peripheral blood a protein corona consisting of various components is formed immediately. The composition of the corona as well as their amount bound to the particle surface is dependent on different factors, e.g. particle size and surface charge. The actual composition of the formed protein corona might be of major importance for cellular uptake of magnetic nanoparticles. The aim of these initial experiments is to analyze the importance of temperature on the formation of the protein corona during in vitro serum incubation.

SPIONs were prepared following the alkaline precipitation route and coated with different shells (amino-dextran, dextran, and carboxymethyl-dextran). The obtained core/shell nanoparticles were incubated in fetal calf serum (FCS) at 50°C, 37°C, and 15°C. 50°C and 37°C were realized by magnetic heating (hyperthermia) of the SPIONs within the serum. 37°C and 15°C were achieved by adding the SPIONs to FCS with the desired temperature. The SPIONs were incubated for 15 minutes and then cooled down to room temperature. Before and after incubation the zeta potential and the magnetic concentration of the incubated particles were determined. One part of the nanoparticle solution was applied to a TBS polyacrylamide gradient gel (4-12%) under denaturing conditions and protein bands were visualized by Coomassie blue staining.

Zeta potential of carboxymethyl-dextran coated SPION before and after FCS incubation.

sample	heating	zeta (mV)
no incubation	-	-19 5
15 °C	bath	+0.1
37 °C	bath	-35.4
37 °C	magnetic	-34 9
50 °C	magnetic	-12.7

The table shows the zeta potential as a function of incubation temperature for CM-Dextran coated samples. It is clearly demonstrated that incubation temperature has an explicit influence on the composition of the corona. The electrophoretic analysis of the components of the protein corona shows that the predominant protein is serum albumin with its derivatives. SPIONs which were treated with hyperthermia contain more protein than nanoparticles exposed to external heating. In these first investigations we found very promising results regarding the influence of temperature as well as the type of heating on corona formation. Due to the possibility of heating by magnetic losses (additionally to the external heating) magnetic nanoparticles are very interesting model particles for ongoing investigations.

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Innovative approach for quantum dots antibody labeling based on antigen-modified magnetic particles

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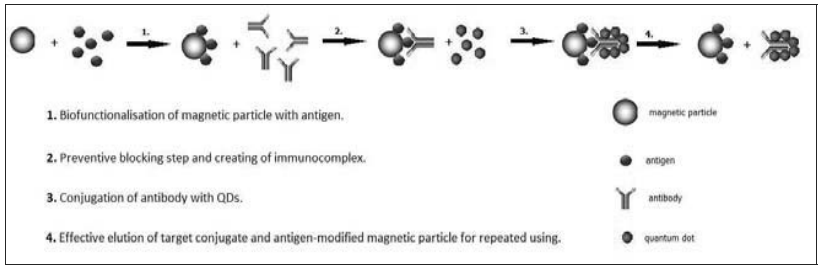
This work is aimed at preparation of specific conjugate of IgG antibody molecule and quantum dots (QDs) which serves as highly sensitive label in ELISA based immunosensor for routine screening of clinically important substances such as tumor markers. The crucial advantage of our approach is based on the use of antigen-modified magnetic particles enabling easy handling and controllable antibody multilabeling.

Our protocol is comprised of several basic but essential steps (see the scheme) that needed to be optimized. Firstly the problem of difficult separation of whole created conjugate from free fraction of antibodies and QDs in solution had to be solved. For this purpose we used magnetic particles which represent unique anchor for easy fixing, separation and successive elution of antibodies labelled by QDs. We carried out biofunctionalisation of magnetic particles by antigen creating biospecific pair with target antibody which is subsequently labelled by QDs. During our optimization procedure we have already tested one or two-step protocol of conjugation of antibodies with QDs including well-known carbodiimide technique in or without presence of sulfo-NHS. Thanks to the use of antigen-modified magnetic particles the binding sites of labelled antibody are prevent and maintain accessible after effective elution. Additionally antigen-modified particles can be used and thus saves expensive reagents and time.



Acknowledgement:
This work was supported by project of Grant Agency of Czech Republic GA P206/12/0381 and project CZ.1.07/2.3.00/30.0021 „Enhancement of R&D Pools of Excellence at the University of Pardubice“.

A Novel Code for Simulation of Magnetic Carrier Laden Fluids with Structure Dependent Rheology in Blood Vessels

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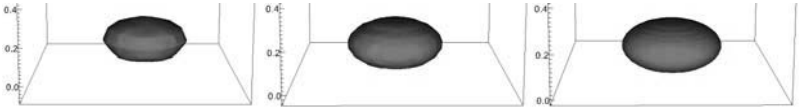
Biomedical applications of Magnetic Nano-particles (MNPs) *in-vivo*, such as MRI contrast enhancement, hyperthermia, and *magnetic drug targeting* (MDT) at tumor sites, show great promise in animal and clinical trials but their optimization and broader use demands more trials. Computer simulation is a critical design tool, reducing the reliance on costly trials. Simulation of *in-vivo* MDT presents serious obstacles, mainly the difficulty of predicting the complex interactions among MNPs, applied magnetic fields, and the heterogeneous environment of blood, vessels and tissue

The MONTCLAIR code was developed to examine multi-phase flows of magnetic fluids under applied magnetic fields and includes Maxwell stresses, nonlinear magnetic material (Langevin model) and multi-color capability to simulate multiple fluid or fluid-like objects (e.g., red blood cells). But the code is limited to 2D and is not parallel. Our new VOF multi-phase fluid code, MAGPARIS is fully parallel and models three-dimensional flows; the new code is designed *ab initio* to avoid cumbersome structure that can impede the extension of multi-phase codes for complex multi-physics applications. MAGPARIS is also built on a 3D fixed mesh and parallelism is handled by message passing interface (OpenMPI) using ghost layers; the code shows good scalability on several architectures. The incompressible Navier-Stokes system in MAGPARIS is differenced using a finite-volume formulation and the solution is computed using a projection method on a staggered MAC grid. Convection terms are integrated explicitly using a QUICK or 2nd order centered scheme, while viscous terms may be solved explicitly or implicitly and VOF advection is based on the momentum-conserving scheme of Weymouth and Yue. Solution of the elliptic pressure equation in a manner that enforces divergence-free solutions may be done by SOR or GMRES multi-grid solver via the HYPRE library; the elliptic Maxwell equation for the magnetic potential is similarly solved. These algorithms give a fast, efficient, robust and highly scalable and flexible multi-phase code; output adopts VTK and is conveniently visualized with VISIT or PARAVIEW.

We present here initial results on the accuracy, efficiency and scalability of MAGPARIS for the simulation of flows relevant to MDT. In particular, we examine a concentrated region of MNP laden fluid translating near a blood vessel wall, and present the convergence and scaling of the code as the size and resolution of the blood vessel and MNP fluid region are independently varied. The basic framework of MAGPARIS is based on well-estabblished and easily extended algorithms, facilitating the inclusion of rheology models, as for blood or for MNP regions. Our x-ray rheometry of magnetic fluids has produced a model for field dependent viscosity in cases where thread-like agglomerations of MNPs occur; the form of this model is a simple drag proportional to $p(\mathbf{u_S}\cdot\mathbf{u_S})-(1-p)(\mathbf{u_S}\cdot\hat{\mathbf{t}})^2$ (where $\hat{\mathbf{t}}$ is the unit field direction and p is the relative drag for transverse vs longitudinal flow, approximately equal to 2). Finally, we project the near term capabilities of the code in terms of efficiency and variety of MDT scenarios that are capable of being modeled.



Advection test: oblate region of magnetic fluid near vessel wall at bottom and propagating downstream (left to right); shown are 16^3 (left, 5 CPU sec), 32^3 (center, 24 CPU sec) and 64^3 (right, 159 CPU sec) grid resolutions; vessel is 1×1 unit cross-section; only part of the domain is shown.

Iron Oxide Nanoparticles as Multi-functional Probes for Tracking Human Foetal Neural Stem Cells

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Stem cells with self-renewal and the capacity to differentiate into multiple cell types are attractive candidates in a rapidly evolving area of stem cell therapy in regenerative medicine. However due to the lack of consistent and unbiased data about the differentiation and the fate of stem cells *in vitro* and *in vivo*, interpretation of therapeutic effects remains challenging in this field.[1,2] Suitable imaging techniques that can monitor the function, survival, migration, and host tissue integration of transplanted stem cells would greatly enhance their clinical application. Stem cells prelabelled with iron oxide nanoparticles as negative contrast agents have been investigated using non-invasive magnetic resonance imaging (MRI).[2,3] This technique allows long-term monitoring of migration, integration and stem cell fate following transplantation into living animals.

This study investigates the full biological impact of introducing our customized superparamagnetic iron oxide nanoparticles (SPIONs) into primary human foetal neural stem cells (hNSCs) *in vitro*. SPIONs with a core diameter of 10-15 nm maghemite iron oxide core were sterically stabilised by 95% methoxy-poly(ethylene glycol) (MPEG) and either 5% NH_2 end-functionalised, or 5% Rhodamine B end-functionalised, polyacrylamide. Our results showed that SPIONs were observed throughout the cytoplasm, but dynamically relocating toward the nucleus within 24 hrs treatment (see Figure 1-A). Upon loading, cellular viability, total iron capacity, differentiation and average distance of migration were measured to determine optimal loading conditions. We demonstrate that prelabelling of hNPCs with our in-house customised SPIONs has no significant detrimental effect on cell biology and that SPIONs, when utilised at an optimised dosage, are an effective means of noninvasively tracking prelabelled hNPCs (Figure 1-B).

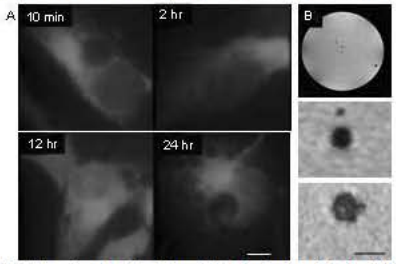

Figure 1: Confocal images of hNSCs incubated with 10 µg/mL Rhodamine labelled SPIONs (A): SPIONs were observed relocating inside stem cells from the cytoplasm to the nucleus within 24 hr treatment, scale bar 5 µm *In vitro* MRI of hNPCs neurospheres (B): hNPCs were incubated with 10 µg/mL SPIONs for 24 hr, TE = 3 5 ms, 20 mm thickness slice over the full field of view, scale bar 500 µm

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Magnetic behaviour of DDM128 in agarose gel, gelatine and sugar matrix

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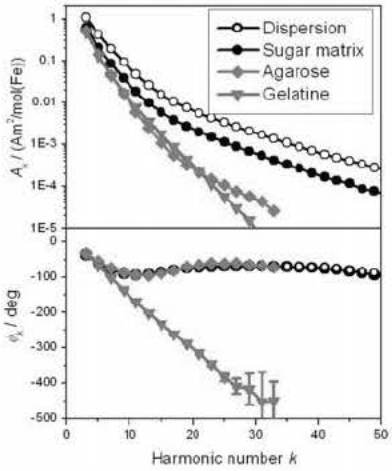
The quantification of magnetic nanoparticles (MNP) within the different organs of the body is important for a proper adjustment of medical applications like e g hyperthermia, and for clinical registration studies Magnetic Particle Imaging (MPI) is a very promising technology for the quantitative imaging of MNP The MPI signal of a reference MNP-sample yields the base for the quantification However, which state of the MNP is correct? Here, the influence of the immobilisation of the MNP and the type of the matrix on the MPI signal, here approximated by Magnetic Particle Spectroscopy (MPS) which can be regarded as an one voxel MPI-system, was investigated

In order to check the influence of *local* dipole-dipole-interaction (DDI) highly diluted (c(Fe)=0 7 mmol/L) different size fractions of DDM128 (precursor of Resovist®, the present gold standard in MPI) were embedded in a sugar matrix, agarose gel and gelatine The samples were measured by MPS, M(H), and Magnetorelaxometry (MRX) From M(H) and MRX the (bimodal) distributions of magnetic sizes and anisotropy energies were extracted Surprisingly, it was found that the magnetic size distributions of the single fractions of larger MNP are still bimodal



MPS data (amplitude and phase) of the fraction of largest DDM128-MNP embedded in indicated matrices.

As already reported by e g Weaver et al, immobilisation leads to an attenuation of the MPS amplitudes, here A_3 drops down to about 60%, 50%, 48% due to freeze drying, immobilisation in agarose, gelatine, respectively, for the different fractions of larger MNP Despite these relatively weak variation in A_3, the whole spectra differ much stronger (Figure) These strong differences were observed *only* for the fraction of largest MNP (mean magnetic diameter of about 25 nm) and also occur in M(H) (initial susceptibility drops by 60%) as well as MRX data Hence, this effect might be attributed to DDI caused by a locally limited MNP aggregation The aggregate structures in gelatine and agarose (perhaps also in sugar matrix) obviously differ deduced from different patterns of changes in MPS (Figure), M(H) and MRX signals

In conclusion, sensitive magnetic measurement techniques, in particular the combination of them, allows for the detection and quantitative analysis of alterations in magnetic super structures of embedded MNP which may significantly change specific signal amplitudes of these MNP, e g in MPI and MRI, and magnetic parameters like SAR (specific absorption rate), the key parameter in magnetic hyperthermia

High-frequency magnetic field induced cell death in endocrine tumors cells targeted by magnetic nanoparticles.

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Nanotherapy using hyperthermia by targeting magnetic nanoparticles (MNPs) grafted with peptidic ligands is a promising therapeutic strategy. However, nanoconjugation of peptides can dramatically affect their properties with respect to receptor recognition parameters, mechanism of internalization, intracellular trafficking and fate. These issues are essential for setting-up anti-cancer therapies. Here, we designed a MNP composed of i) an iron oxide nanocrystal ii) a ligand of a G-protein coupled receptor, the cholecystokinin-2 receptor (CCK2R) that is over-expressed in several malignant cancers iii) a fluorophore. Accumulation of MNPs inside the lysosome is specific and increases with the ligand density at the MNP surface. Magnetic measurements show that 2.2±0.2 pg of iron are accumulated inside the cells. For magnetic hyperthermia experiments, a magnetic field of 275 kHz and 40 mT was applied during two hours on four compartments Cell-view dishes containing MNP loaded cells and adequate controls. The temperature was maintained at 37 C with Heat-Gun during experiments. Given the small heating power of the nanoparticles (13 W/g), the low amount of internalized nanoparticles, and the 2D geometry, the presence of nanoparticle did not increase the temperature of the cells. In spite of this, application of the alternating magnetic field caused the death of cells containing MNPs (17.1 ± 1.6 % of cell death).

These promising results call further investigations aiming at better understanding precise mechanisms by which MNPs initiate lysosomal membrane permeabilization and induce cell death.

Reference : C. Sanchez *et al.*, ACS Nano **8**, 1350 (2014)

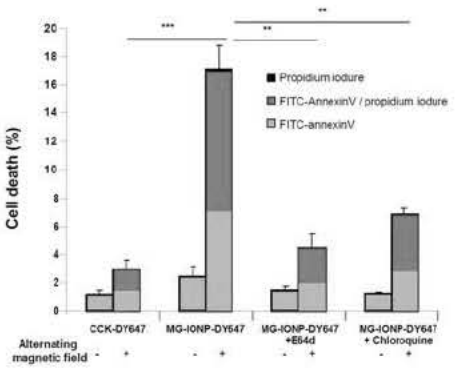

Figure: Tumor cells with overexpressed CCK2R were incubated with the functionalized MNPs (labeled MG-IPO-DY647) or the free ligand (labeled CCK-DY647) for 24h at 37°C When indicated, E64d or chloroquine (lysosomial activity inhibitors) was added in the medium Cell death was determined 4h later by confocal microscopy by counting positive cells for FITC-AnnexinV and/or propidium iodure labelings

CpG ODN Coated Magnetic Nanoparticles have Augmented Activity via Toll-Like Receptor 9 (TLR9) and Potential Vaccine Applications

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The ultimate aim of vaccination is to induce antigen-specific immunological memory against a pathogen in order to prevent the associated disease in the future. However, many modern day vaccines consist of recombinant protein antigens that tend to be poorly immunogenic on their own; this has created a significant need for new and more powerful adjuvants. Many adjuvants mimic evolutionally conserved pathogen structures that are recognized by pattern recognition receptors, such as the Toll-Like Receptors (TLRs), in the host; signalling through these receptors can activate and or modulate the immune system to create a more protective response against an antigen.

Unmethylated single-stranded cytosine-phosphate-guanosine (CpG) oligodeoxynucleotides (ODNs), which mimic bacterial DNA, are recognized by TLR9 found in antigen-presenting cells (i e., plasmacytoid dendritic cells) and B cells. Since TLR9 is located within the endosomal compartment, CpG ODN must be internalized to have an effect. With no specific transporter, CpG ODN is taken up through non-specific and inefficient means; as a result, CpG ODN in solution can move away from the site of vaccine administration and interact with distant immune cells producing unwanted side effects. Attaching CpG ODN to nanoparticles can improve the safety of efficacy of this adjuvant by limiting its distribution and augmenting its uptake into antigen-presenting cells, respectively.

We have recently adsorbed negatively charged CpG ODN 1826 to 50nm positively charged uncoated magnetic nanoparticles (MNPs) (Chemicell GmbH 4130-1). These coated MNPs were incubated overnight in HEK293 cells co-transfected with the murine TLR9 gene and an inducible SEAP (Secreted Embryonic Alkaline Phosphatase) reporter gene (Invivogen hkb-mtlr9). Activation of the intracellular TLR9 receptor was determined by quantifying the amount of SEAP secreted using a QUANTI-Blue assay (Invivogen rep-qb1). We found that by simply adsorbing CpG ODN 1826 to MNPs, 1/10th of the amount of CpG ODN was required to produce a comparable response to CpG ODN in solution. These functionalized MNPs are currently being investigated for use in intradermal vaccines with or without the presence of an external magnetic field.

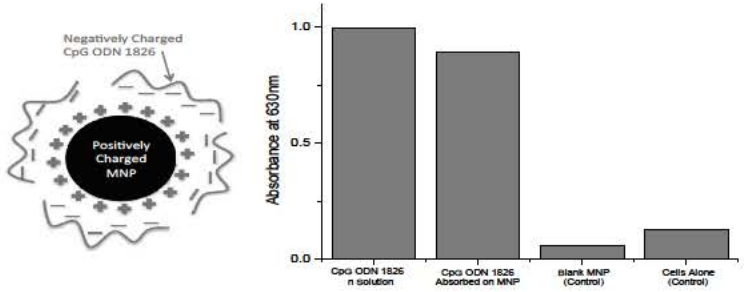

Figure: schematic of negatively charged CpG ODN 1826 adsorbed to positively charged MNPs (Left). 100uL of 8ug/mL CpG ODN adsorbed to MNPs produced a comparable response to 100uL of 80ug/mL CpG ODN in solution in HEK293 cells containing the murine TLR9 receptor; minimal stimulation of TLR9 with MNPs alone (Right).

This work is made possible with a Collaborative Health Research Projects (CHRP) Grant (#446570-13) from the Canadian Institutes for Health Research (CIHR) and the Natural Sciences and Engineering Research Council of Canada (NSERC)

Chain formation rates for magnetic nanoparticles

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The self-assembly, chaining, and clumping of bio-magnetic nanoparticles is a concern in some applications (drug delivery, hyperthermia) and a desired effect in others (self-assembled filters in microfluidic devices)[1] Here we present finite-temperature simulations of colloidal magnetic nanoparticles as a function of time to examine what parameters affect their assembly[2] Our simulation treats the particles as hard spheres defined by a hydrodynamic radius and with a point magnetic dipole moment defined at the center In addition to the hard shell interaction, the particles experience torques and forces due to the dipole-dipole interactions which are minimized when the particles chain together The equations of motion include viscous damping and random thermal fluctuations[3] Results for a system of magnetite nanoparticles in blood with volume fraction of 5 2%, hydrodynamic radius of 10 nm, and particle saturation magnetization of $M_s = 3\ 16 \times 10^5$ A/m show that the rate at which chains are formed decreases with temperature and are on the order of microseconds Fig 1 shows that the number of unchained particles decreases over time This data is the average from 20 simulations Fig 2 shows that chains of length 2 initially increase and then decrease as they form chains of lengths 3 and higher Fitting the plots in Fig 1 with a decay function $n = A\exp(-t/\tau)$, gave decay times of $\tau = 4\ 3$ μs for the T = 300 K case and $\tau = 3\ 1$ μs for the T = 0 case We will discuss the effect of volume fraction and applied fields on the chain formation rates

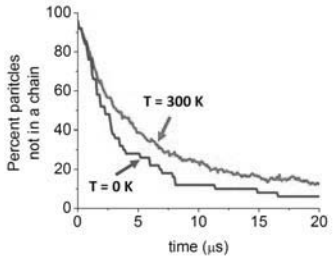

Figure 1

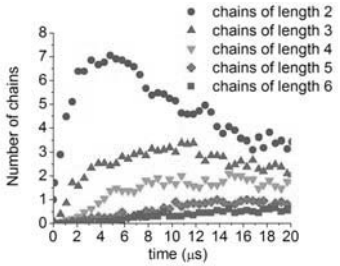

Figure 2

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Smart Platform for Theranostic Applications Based on Cobalt-Doped Ferrite Nanoparticles Mineralized in Ferritin Cages

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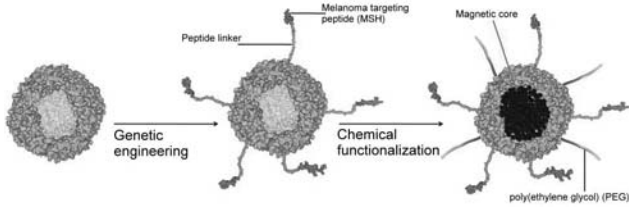
The application of magnetic nanoparticles (MNP) in the biomedical filed has attracted considerable attention in the last decade, particularly as heat mediators for magnetic fluid hyperthermia The most important requirement that a system based on MNP must satisfy for its clinical application is biocompatibility In this contribution, we present some recent results obtained on Co-doped iron oxide NPs mineralized within the internal cavity of a human H chain ferritin (HFt) protein This system represents a viable theranostic platform, since HFt is biocompatible, has the appropriate size to freely circulate in the body and it is naturally tailored for iron sequestration and NP incorporation The principal drawback of HFt for their use in hyperthermia is that the largest attainable size is limited by the proteic shell to 8 nm, which, with standard iron oxide, is not sufficient to provide a sizable temperature increase in the target tissue In order to increase the heating efficiency, we investigated the possibility of doping the NPs with a small amount of the more anisotropic Co^{2+} ion

Well dispersed, highly monodisperse Co-doped iron oxides NPs (HFt-NPs) with average size of 6-7 nanometers and varying Co content between 5 and 15% were obtained through biomineralization inside HFt cavity [1] The HFt-NPs were modified by genetic engineering so as to carry the α-melanocyte-stimulating hormone peptide (α-MSH), which has been already demonstrated to have excellent targeting properties towards melanoma cells with high selectivity [2] Moreover, PEG moieties were linked to the proteic shell in order to ensure stability against opsonisation The hyperthermic properties of Co doped magnetite HFt-MSH-NPs were investigated through calorimetric technique, and correlated with structural features (crystallinity, composition) and magnetic properties (magneto-crystalline anisotropy) We found that a Co doping of 5% strongly enhances the hyperthermic efficiency, while a larger doping is detrimental, since it affects the crystal quality of the NPs

The *in vitro* hyperthermic efficiency of sample doped with 5% of Co was tested on B16 melanoma cell lines Cells incubated with Co doped HFt-MSH-NPs and exposed to an alternate magnetic field shows a significant reduction on cell viability Clear indications of an advanced stage of apoptotic process were also observed by immunocytochemistry analysis On the other hand, the same treatment performed with the undoped sample had no effect on cell viability, proving that the Co doping is necessary in order to increase the hyperthermic efficiency The Co doped HFt-MSH-NPs alone showed a low cytotoxicity, due to the small amount of Co doping



Schematic representation of the HFt-MSH-NPs preparation α-MSH peptide is linked to the N-terminus of each of the 24 subunits by a peptide linker Only 5 of the 24 derivatized N-termini are shown, for clarity (from Ref [1])

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Simulation and Experimental Investigation of the Effects of High Moment Magnetic Nanoparticles on the Generation of Local Reversal Nucleation

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In theory, the intensity of the magnetic signal obtained by giant magneto-resistive (GMR) sensors is calculated by averaged the magnetic nanoparticles' dipole field across the sensing area This makes sensing magnetic nanoparticle impossible by using a large surface area GMR sensors since the magnetic signal will cancel out In this paper, localized sensing scheme has been purposed and discussed

Domain nucleation has been observed and studied in antiferromagnetic (AFM) materials coupled to soft magnetic thin films The widespread localized nucleation over the entire film is observed after applied field reaches a critical value (for Permalloy, the critical field is about several tens Oe) It is believed the strength of the exchange bias varies at the microscopic scale across the film As a result, those regions could nucleate at smaller field compared to bulk value Similar effect could happen with the help of high moment magnetic nanoparticles such as FeCo It have been proved extreme powerful in bio-sensing because of its high moment under small field Fig 1 shows the simulated dipole field of a FeCO particle A maximum local field of 16 Oe is generated at a distance of 50nm, which is the typical distance for immunoassay application Such field is strong enough to have some local impact on the free layer of GMR sensor Simulation results are shown in Fig 2, localized reverse nucleation site is generated because of presence of the MNP Detection of high moment MNPs using large surface area GMR sensors have been demonstrated

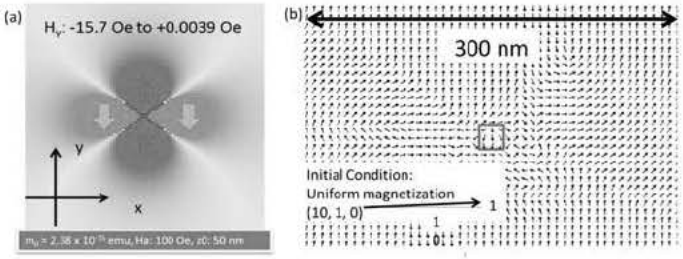

Figure 1. (a). Local magnetic dipole field of a FeCo at 50nm particle height, (b) OOMMF simulation result of the impact of the FeCo MNPs on the magnetic free layer of the GMR sensor. No external field is applied to the film and the initial film configuration is set as shown in the inset.

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A MICROFLUIDIC MAGNETIC HYBRID ACTUATOR FOR ADVANCED HANDLING FUNCTIONS AT CELL RESOLUTION

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In microfluidics, the use of super-paramagnetic microparticles (SMPs) has experienced a dramatic increase over the last decade, but control of the magnetic field at micro scale is still a topical issue. Permanent magnets don't offer a programmable approach, external coils require a certain power, and neither are usually integrated. Coils were thus integrated to microfluidic chips, but obviously a limitation has been reached when it comes to the size of planar coils with five, ten or more turns: their use is generally in bulk mode rather than aiming for cellular resolution. Hybrid systems, which include external magnets to generate a high and homogeneous magnetic field, and integrated coils that produce a high gradient, are seemingly a promising way to reach a higher precision in magnetic actuation, not mentioning the forces they create on SMPs can be attractive or repulsive.

The goal of our work, for one part, is to develop a simple solution for the micro-fabrication of this kind of devices, but also to delve into the design possibilities, for instance to create a separation stage or investigate more exotic functions like focusing (without leading to a dilution or an increase in the flow rate, unlike most hydrodynamic focusing techniques).

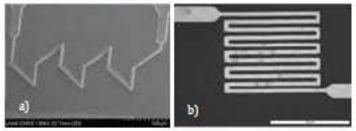

Figure 1: a) SEM image of a micro-coil designed to perform focusing. **b)** Optical microscope picture of a micro fabricated shift register.

Common micro-technology processes (metallization and electro-chemical growth) have been used to create the micro-coils (they are 5 µm wide and high wires). As for the microfluidic channels, two layers of low cost dry film photoresist (DF-1020) were laminated then structured with photolithography. It is also important to stress that this technique (if piling more layers) can plainly lead to 3D microfluidic structures.

The experimental setup comprises a pressure controller for fluid handling, a bright field fluorescence microscope, an EMCCD camera, two rectangular NdFeB magnets (with a 1.3 T remanence) and a chip holder (see Fig. 2). We developed an electronic board that is able to deliver positive and negative currents to the coils (to change the sign of the magnetic force). For the magnetic carriers, we used 5 µm diameter Spherotech (fluorescent) beads, and THP1 monocytes labeled with Invitrogen anti-CD14 Dynabeads.

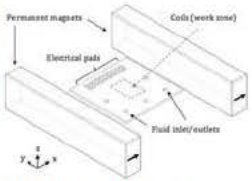

Figure 2: Scheme of the hybrid magneto-fluidic chip set up.

Two different designs were tested for the focusing function, and led to promising results. On Fig. 3, we can see two 5µm Invitrogen particles (their velocity is about 560 µm/s) experiencing a deviation of 22 µm in 140 ms. In other series of tests, we obtained the same range of deviation at much higher velocities (about 2 mm/s), and we also made sure we can achieve focusing on the whole width of the micro-channel.

Currently we are working on the characterization of other types of micro-coils we built (for separation and a shift register to control the SMPs flow). Introducing tridimensional microfluidic structures would open new avenues for the realization of complex lab on chips. A very intriguing lead lies in achieving the integration of the homogeneous magnetic field source, which is quite weak so far but work is still in progress, especially in the field of NMR on chip analysis.

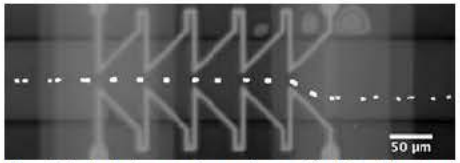

Figure 3: Stacked microscope images of two particles being deflected and aligned by the micro coils.

Characterization of Iron Oxide SHP-type Nanoparticles from Ocean NanoTech by Mössbauer, Magnetization and X-ray Diffraction Methods

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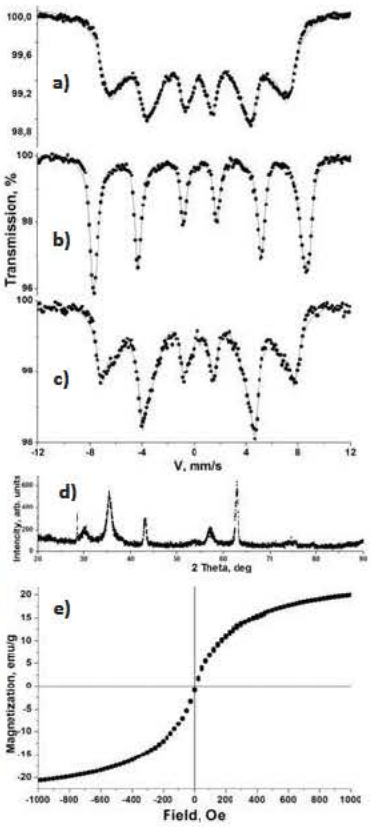
Joint analysis of the Mössbauer and magnetization data in the framework of the single model of magnetic dynamic is known as a powerful tool for precise characterization of iron oxide nanoparticles Simultaneous fitting of the magnetization curve and the group of three Mössbauer spectra taken at two different temperatures and in a weak external magnetic field made it possible to describe quantitatively the biodegradation process in the mouse liver [1] and to define the evolutions of nanoparticle's size and concentration of exogenous and endogenous iron with time after intravenous injection of ferrofluid It should be mentioned, that the size of the nanoparticle determined by the method depends on its quantum mechanical magnetic properties and can be different from the size, determined by other methods Therefore, in the present study we compared the results on investigation of the same set of nanoparticles by this magnetic and by nonmagnetic X-ray diffraction method for nanoparticle characterization

We explored the set of water soluble SHP-type iron oxide nanoparticles with amphiphilic polymer coating produced by «Ocean NanoTech» company [2] with average diameters in the range of 5-25 nm, previously determined by transmission electron microscopy The Mössbauer, magnetization and X-ray diffraction measurements of each sample were carried out The comparative analysis of the results showed that the Mössbauer data are absolutely necessary for the correct interpretation of the results of the magnetization or the X-ray diffraction measurements



Experimental data for 20 nm SHP-type water soluble iron oxide nanoparticles:
a) ^{57}Fe Mössbauer spectra, measured at 300 K,
b) ^{57}Fe Mössbauer spectra, measured at 78 K,
c) ^{57}Fe Mössbauer spectra, measured in the magnetic field 3 4 kOe at 300 K,
d) X-ray diffraction picture
e) magnetization curve at 300 K

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2 http://www oceannanotech com

Specific Absorption Rate Dependence on Temperature in Magnetic Field Hyperthermia Measured by Dynamic Hysteresis Losses (AC Magnetometry)

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Magnetic nanoparticles are intensively studied for their potential use for magnetic field hyperthermia (MFH), a treatment that has passed a phase II clinical trial against several brain cancers (glioblastoma) at the end of 2011 Their heating power, characterized by the "specific absorption rate", can be temperature dependent, especially when the objective is to obtain a self-regulated heating by an adjustable Curie temperature *e.g.* with lanthanum strontium manganese oxide (LMSO) nanoparticles However, SAR is often considered temperature independent in the literature, mainly because of the difficulties that arise from the measurement methodology Using a dynamic magnetometer presented in a recent paper,[1] we measure here the thermal dependence of SAR for superparamagnetic iron oxide nanoparticles (NPs) of three different size-ranges, respectively around 8 5 nm, 11 nm, and 18 nm These maghemite NPs were dispersed either in water trough a polymer coating or in a fluorinated oil with *e.g.* 10 times lower heat conductivity,[2] a factor that is determinant to minimize thermal losses and reach higher plateau temperature in MFH.[3] We studied also LMSO nanoparticles dispersed in water that are designed to limit the upper heating temperature We present here a parametrical study extending from 10 to 60°C in temperature, from 75 to 1031 kHz in frequency, and from 2 to 24 kA·m^{-1} in magnetic field strength It was observed that SAR values of maghemite NPs of the two lower size-ranges decrease with temperature up to 40% and that this decrease depends on the applied magnetic field frequency On the contrary, the 18 nm diameter NPs exhibit an increase of SAR when temperature is raised This thermal behavior can be fully explained within the scope of linear response theory based on Néel and Brown relaxation processes, using independent magnetic measurements of the specific magnetization and magnetic anisotropy constant of the samples On the other hand, LSMO nanoparticles show a much stronger decrease with temperature, up to 80%, in the same range In this case, the SAR decrease ascribed to the reaching of the Curie temperature of the material that is estimated near 60°C by this AC magnetometry method The precise knowledge of the SAR values and of the environmental parameters (like the local heat conductivity) was of great help to design the conditions of preliminary *in vivo* experiments of MFH on either tumor models made of a magnetically-doped hydrogel introduced subcutaneously or on true tumors An iron oxide concentration of 17 mg/mL in 100 µL volume tumors (Fig a) was sufficient to induce a thermal dose (CEM43) and to detect bioluminescence produced by luciferase enzyme through thermo-sensitive gene activation[4] (Fig b)

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Magnetic beads as an immunosupport for component-resolved diagnostic of cow's milk allergy

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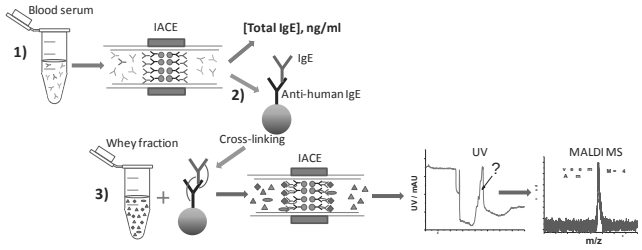
Application of magnetic beads (MBs) as an immunosupport for various immunoassays in clinical practice is very attractive due to easy beads manipulation, variety of surface chemistry to immobilize target molecules and increased surface area-to-volume ratio.[1]

Herein, tosyl-activated MBs (Estapor, Merck Millipore) were successfully used for the performance of component-resolved diagnostic (CRD) of cow's milk allergy (CMA) using immunoaffinity capillary electrophoresis (IACE) coupled with matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS).[2] These pre-activated MBs, ready and easy to use, were modified with anti-human IgE antibodies without additional chemical activation. Once the hydroxy groups are activated, the resulting sulphonyl ester can subsequently react covalently with our anti-human IgE containing amino or sulfhydryl groups.

As presented in the scheme below, first coated MBs were used as in immunosupport for the total IgE quantification in a blood serum of the CMA patient by IACE-UV analysis. The same protocol was used at the second step to extract the IgE antibodies from the serum of the patient and to further cross-link the obtained immunocomplex anti-human IgE-human IgE antibodies formed on the MBs surface. During the third step, prepared immunosupport was utilized for the performance of CRD by IACE analysis with UV and MALDI MS detection to identify the proteins triggering the allergy directly in the milk extract. Bovine serum albumin, lactoferrin and α-casein (S1 and S2 forms, as was revealed by MALDI MS) displayed the binding with extracted IgE antibodies indicating, that this particular patient is allergic to these proteins.

The developed method requires only 2 µl of blood serum for all the experiments. Application of MS detection opens the possibility for direct identification of allergens molecular mass and structure, while the use of MBs greatly simplifies and improves the experimental workflow.



Scheme. CRD of cow's milk allergy using IACE-MALDI MS analysis

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Agglomeration Effect on the Rheological Properties of Fe_3O_4 Kerosene-Based Ferrofluid

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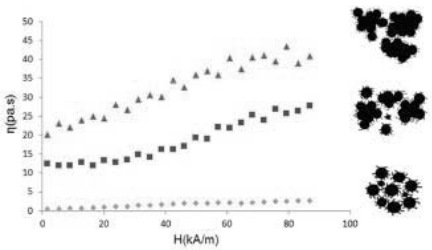
Abstract

In this research the effect of Fe_3O_4 nanoparticles agglomeration on the rheological properties of a Fe_3O_4 kerosene-based ferrofluid (FF) were investigated. Fe_3O_4 nanoparticles were synthesized using chemical co-precipitation method. The different sizes of agglomerates were prepared via controlled addition of different concentrations of oleic acid.

Dynamic laser scattering was used for agglomerated size detection. Fe_3O_4 particles were characterized using x-Ray powder diffraction, Transmission electron microscopy and Fourier transform infrared spectroscopy and magnetic properties were studied using alternative gradient force measurement. The rheological properties of FFs were studied using a standard rotating rheometer,

DLS results showed that the size of agglomerates can be controlled by surfactant concentration. XRD results revealed the presence of magnetite as major phase. No other minor phase was detected. The saturation magnetization of nanoparticles decreased when agglomerate size is increased. Rheological results showed, yield stress increased with more agglomeration with/without magnetic field. It was revealed that the thixotropic behavior increased when the agglomeration increased. Finally it was shown that the agglomeration effectively enhance the magnetoviscous effect.



NGF Releasing Magnetic Nanospheres – Moveable Chemotactic Gradients to Direct Neurite Extension

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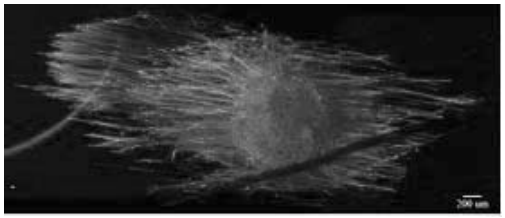
Following neural injury, regenerating axons must traverse through large gaps (within the peripheral nervous system) or through a glial scar environment (in the case of spinal cord injury). Many different modalities exist for directing axonal regeneration experimentally including aligned topography, electrical stimulation, or gradients of axon-extending ligands. Specifically, gradient systems direct extending neurites in culture. However, one limitation in using gradient designs is that axons within such constructs may remain inside the construct and fail to migrate to distal targets. By designing moveable gradient systems, it may be possible to direct axonal extension into and through the injury site. We present our development of a moveable chemotactic system facilitated by the combination of magnetic materials with chemokine-releasing polymers that preferentially direct neurite extension within proof-of-concept experiments.

Poly-L-lactic acid (PLLA) and oleic acid coated iron oxide nanoparticles (10 nm) were dissolved in a dichloromethane/ SPAN-80 solution. Nerve growth factor (NGF) in an aqueous solution was added to the PLLA solution and sonicated. An aqueous solution was added consisting of glycerine and Tween-80. After a final sonication step, the organic solvent was evaporated, the resulting magnetic nanospheres (MNS) washed, and then lyophilized. Scanning electron microscopy (SEM) was used for MNS imaging. NGF release from the MNS was characterized using a NGF ELISA. To assess the ability of the MNS to direct neurite extension, E9-stage chick dorsal root ganglia (DRG) were plated on aligned PLLA electrospun fibers. MNS were placed into the culture system and moved to one side of the DRG using magnets. Cultures persisted for two days, and explants were imaged using a beta-tubulin stain. Neurite extension was measured on both sides of the DRG and compared between groups.



DRG cultured on aligned, electrospun fibers in which NGF nanospheres were placed to the left of the DRG.

MNS were around 500 nm in diameter, and iron oxide nanoparticle pockets existed within the spheres. Using a NGF ELISA, NGF release from the MNS persisted up to 21 days. Interestingly, a specific concentration of MNS (100 NGF) was able to promote longer extension of neurites in the direction of the MNS.

NGF-releasing spheres containing iron oxide nanoparticles were moveable within a culture situation, and longer neurites were measured extending towards the particles. Current work is examining the ability of the spheres to direct neurite outgrowth while slowly moving the spheres away from the DRG.

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How Temperature determines Structure of Maghemite Nanoparticles: A Small-Angle X-ray Scattering Study

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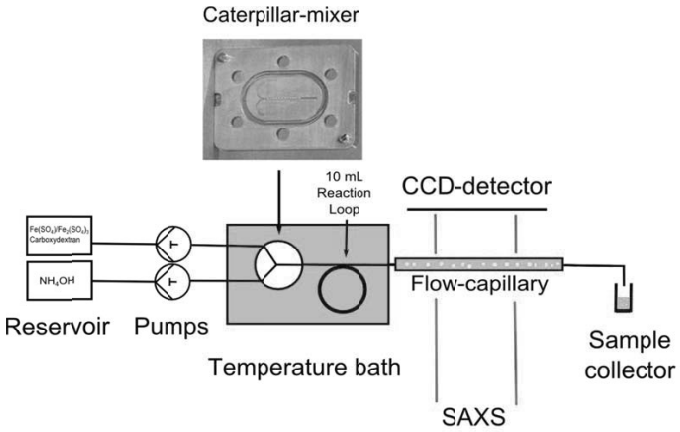
We report on the continuous synthesis and online analysis of superparamagnetic iron oxide nanoparticles The figure below shows a sketch of the experimental setup used in our study Therein the mixture of ferric and ferrous sulfate was performed in a micro mixer device (caterpillar mixer) at different temperatures and different flow rates Nanoparticle formation was triggered by ammonium hydroxide Carboxydextran provides colloidal stability Online small-angle X-ray scattering (SAXS) produces data for determination of the particle's structure Here, synchrotron radiation at the BAMline of the Berlin Electron Synchrotron (BESSY) was used as photon source for SAXS Application of the Guinier-Porod model provides quantitative structure information on the result of the particle synthesis at temperatures of 30°C and 80°C It was found that fractal aggregates of very small primary particles with radii of 1 1 nm are formed at 30 °C In contrast, the size of the primary particles is 3 4 nm to 3 6 nm at 80°C Furthermore, no aggregation was observed for the synthesis at 80°C While the temperature has as striking influence on the synthesized particles no significant influence was found for different flow rates A mechanism for the differences in formation of the particles will be discussed



Experimental setup for a continuous synthesis of carboxy-dextran stabilized iron oxide nanoparticles The microreactor (caterpillar-mixer) is directly connected to the small-angle X-ray instrument via PEEK tubing The SAXS instrument is equipped with a flow-capillary for online analysis

Investigations on a branched tube model in magnetic drug targeting – measurements and simulations with water and blood

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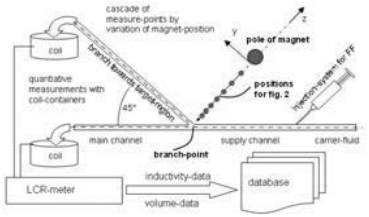
Magnetic drug targeting has been established as a promising technique for tumour treatment. Due to its high targeting efficiency unwanted side effects are considerably reduced, since drug-loaded nanoparticles are concentrated within a target region due to the influence of a magnetic field.

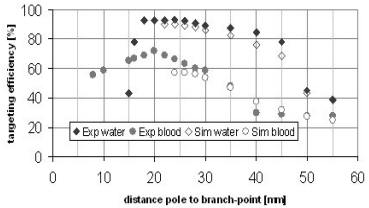
In order to contribute to the understanding of basic phenomena experiments and simulations on a glass tube model as a model-system for a blood vessel supplying a tumour were performed in [1-3]. The artery-model, see Fig. 1, is a half-Y-branched glass tube (inner diameter d_i=1.6mm), where the branching tube is thought to supply the target area. To obtain results for one magnet-position an injection-procedure is performed following a real medical application recommended in [4]. Therefore, 1ml of ferrofluid is injected during 10 minutes into the tube. Quantitative data is obtained by measurements of inductivity of calibrated coil-like containers capturing the outflow of each branch.

In previous works the ferrofluid was injected into water. The current work are measurements and simulations, where the ferrofluid is injected into both water and blood of sheep. The blood is stabilized with EDTA, which is a commonly used anticoagulant.

In the simulation model the fluid flow is described by the Navier-Stokes equation, the magnetic field is derived from Maxwell's equations and mass flux is given by the advection-diffusion equation. The magnetic volume force acting on a volume of magnetic fluid combines the magnet and the ferrofluid data and is proportional to the field dependent magnetisation and the gradient of the field strength. The diffusion equation additionally allows the implementation of a concentration-dependent magnetic volume force. A Carreau-Yasuda-model is implemented to model the shear thinning flow behaviour of blood.

Fig. 1 indicates the positions of the magnet for fig. 2, which shows as the targeting efficiency the percentage of ferrofluid that can be targeted into the branch leading to the tumour. It can be seen, that the targeting efficiency for blood (circles) is lower than that of water (diamonds), which is due to influences of the shear thinning flow behaviour of blood. Compared to the initial efficiency without field for both fluids the efficiency can be increased considerably.





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Simulation and Experimental Study of Magnetic Fields Generated By the Magnetic Nanoparticles using Magnetic Resonance Imaging

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Introduction:

In biomedicine, the magnetic nanoparticles are widely used as a contrast agent for MRI [1,2], as a therapeutic agent for magnetic hyperthermia [3] or as a transport agent for delivery of different drugs to the site of interest in the human body [4, 5] Nowadays, they found also application in many other research areas [6, 7, 8, 9] The aim of this study was to investigate the influence of magnetic nanoparticles composition on MR image, and such to understand the artifacts formation, which is typical for liver and kidney MRI In our study, we analyzed the magnetic field of the near surroundings of the group of magnetic nanoparticles Fe_3O_4 which are regarded as small magnetic dipoles

Methods and Materials:

Magnetic properties of the one nanoparticle Fe_3O_4, with a size of 10 nm, were simulated and discussed in [10] The magnetic field distribution of the group of magnetic nanoparticles was simulated in Matlab environment (version R2011b, Mathworks Inc , USA) The magnetic field distribution of the group of nanoparticles was simulated using the equations published in [10] To calculate the magnetic field of each particle in the near surroundings, the cube model with the size of $20\times a$ was selected, where a is the particle size (in our case 10 nm) Simulated magnetic particle is situated in the center of each cube In our study we used four nanoparticles, which were evenly spaced between each other In each simulation, the distance between the particles was evenly incremented (Fig 1)

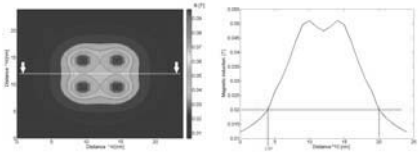

Fig. 1. Left Contour plot of the magnetic field of the four nanoparticles. Distance between centers of nanoparticles was 50 nm. Right Profile of magnetic field in selected layer - white arrows in contour plot at the left side. Diameter of contour with value of magnetic field 0.02 T is 160.3 nm.

Fig. 2. MRI of two capillaries at top of figure is capillary without ferrofluid with diameter 1.2 mm at the bottom of figure is an identical capillary as the first but with ferrofluid EM. Diameter of inhomogeneity was 20.8 mm.

On the basis of simulation we carried out the experiments on MR scanner ESAOTE Opera The simulation determines the shape of the magnetic field generated by the magnetic nanoparticles in their close surroundings, for two (10 and 50) distances of magnetic nanoparticles For the purpose of this experiments, we identified isolines with the magnetic field intensity equal to 20mT The results of the simulations show that the change of area delineated by isolines was lower than 10 nm This change corresponds with the size of a single magnetic nanoparticle Our MRI experiments have shown that the same volume of magnetic nanoparticles both in aggregate state and in planar shape can cause, in the studied plane, an artifact of the same diameter Artifact diameter in both experiments, shown on a Fig 2, had a difference of 0 2 mm at a nominal resolution of 0 547 mm/pixel The experimental results confirm the results of the simulations In the studied layer of the artifact (or in the area with decrease of signal in T2 weight images), diameter of the artifact was the same for both states of magnetic nanoparticles

Conclusion:

We have presented a theoretical simulation of the magnetic field variation due to thin layer of magnetite nanoparticles Result of this simulation was compared with an experiment which was carried out on a MRI scanner with vertical orientation of the basic magnetic field The simulation and experiment showed that by using the nanoparticles contrast media it is possible to evaluate the concentration or susceptibility of the particles in thin layer but not their distribution in this layer

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Development of Non-Polymeric Amphiphilic Coating for Metal Oxide Nanoparticles to be Used as Delivery and Imaging Agents

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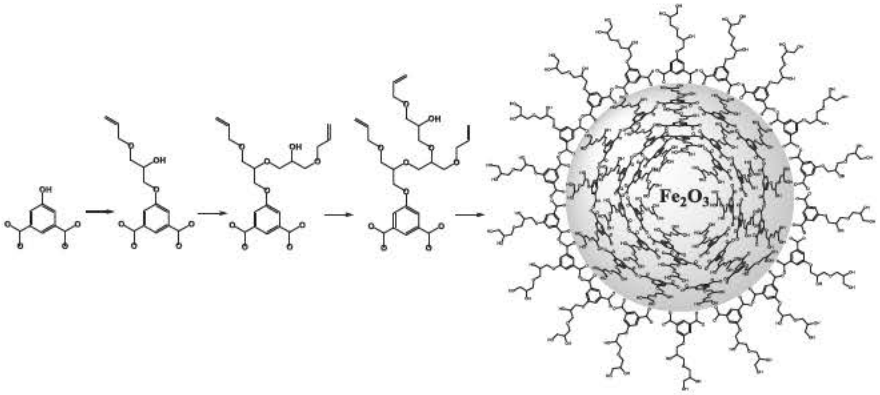
Development and study of the magnetic nanoparticles for biological and clinical applications remains one of the most challenging research areas in chemistry and materials science The performance of these particles as, for example, drug delivery, MRI, hyperthermia or cell tracking agents, depends on their magnetic susceptibility, however, their ability to form stable aqueous colloids, the mobility, and diffusion properties in biological media, largely rely on organic coating Functional nanoparticles used in clinical research these days are usually coated with hydrophilic biocompatible polymers such as dextrans or poly(ethylene glycol)s Excessively large macromolecules of these polymers make the nanocomposite unwieldy, and thus limit its mobility and penetration properties Due to large diamagnetic component, polymers suppress the desired response to an external magnetic field In addition, they restrict water exchange between superparamagnetic core and biological fluids, which is highly desired for the MRI contrast agent applications

To address some downfalls associated with polymers, in this work we attempted to develop a non-polymeric organic coating of an adjustable size, based on isophthalic acid Due to two carboxyl groups of the acid being adequately spaced from one another, it is likely that they would bind to different metal centers on the nanoparticle's surface, which should assure the corresponding complex's stability in aqueous colloids against hydrolysis The precursor 5-hydroxyisophthalic acid was functionalized via the phenolic hydroxyl group by a nucleophilic oxirane ring opening addition reaction with allyl glycidyl ether The length of the hydrophilic chain can be adjusted, depending on demand, by changing the stoichiometric ratio of the nucleophile to oxirane monomer, namely 1-1, 1-2 and 1-3 adducts were obtained in pure form Dihydroxylated derivative of the 1-1 adduct, 5-diglyceroxy isophthalic acid, was synthesized and shown to bind to the surface of 5 nm γ-Fe_2O_3 nanoparticles in reaction with their surfactant-free diethylene glycol colloids The reported method can be extended to the synthesis of O-substituted derivatives of other hydroxyacids of potential applications in biology and medicine This method is facile and optimized for minimizing waste, and it is therefore consistent with principles of green chemistry



Automatic Microsystem for Multi-Step Magnetic Bead-Based Biochemical Assays

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Hybridization analysis is widely used as well in biochemical, clinical and forensic diagnosis as in identifying pathogens by detecting a specific nucleotide sequence in a sample. The most common methods to perform these analyses are through the PCR (polymerase chain reaction) method or by using microarray-based DNA chips, which usually require skilled personnel or are limited by the analysis time [1-2]. Microfluidic systems can overcome these limitations and also allow automation of the entire bioassay. Since channel distances are of few micrometers, the use of such devices can shorten diffusion distances, and therefore, considerably reduce hybridization time [3].
We have developed an automatic microfluidic system for the specific detection and quantification of *Escherichia coli* (*E. coli*) in a short analysis time by the use of a magnetic bead-based enzyme-linked oligonucleotide sandwich assay. The proposal takes advantage of the use of modified magnetic beads (MBs) with the capture probe chemically attached as bioassay supports, which allow enhancing the reagents mixture inside the microfluidic system by implementing a magnetic actuator. In this way, incubation times are minimized. Furthermore, the MBs are easily retained, thus simplifying the required cleaning steps. The *E. coli* is optically determined through the enzymatic reaction of β-galactosidase (attached to the oligonucleaotide probe) with ortho-nitrophenyl-β-galactoside, which generates a colored product that absorbs at 420 nm. The proposed microsystem appears to be a useful alternative to perform automatic hybridization analyses in a rapid, simple and reproducible way.

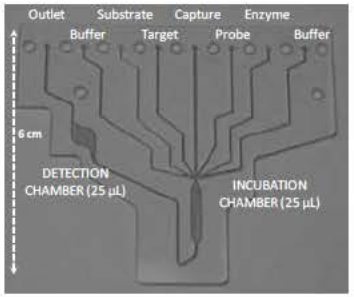

Figure. Photograph of the polymeric microfluidic platform to perform he multi-step magneto-biochemical assay.

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Initial evaluation of the interaction between iron oxide nanoparticles and *Caenorhabditis elegans*

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The properties and behavior of nanoparticles in biological systems can be assessed using cells or complete organisms. Studies based on simple organisms offer more physiological relevance than cells, and represent a valuable step before experimentation with vertebrate models. *Caenorhabditis elegans* (*C. elegans*) is a 1-mm long free-living soil nematode widely used in biomedicine as a model organism. Its simplicity, transparency, short life cycle, highly conserved genome and small body size together with the ease of cultivation in the lab make *C. elegans* a promising animal model to evaluate nanoparticles *in vivo*.

Superparamagnetic iron oxide nanoparticles (SPIONs) are a successful example for medical applications of inorganic nanoparticles. They are used in magnetic resonance imaging (MRI) as contrast agents, in drug delivery, and in hyperthermia therapy, among other biomedical uses.

The fate of in-house fabricated SPIONs has been investigated using *C. elegans.* Particles were identified in the alimentary and reproductory systems (see Figure 1). Iron intake has been assessed around 120 pg/worm The superparamagnetic character of SPIONs was maintained inside the worms. High concentrations of nanoparticles affected the survival rate of the treated worms. Finally, worms were induced to excrete the NP retained in their intestine, which showed a slightly decrease in size.

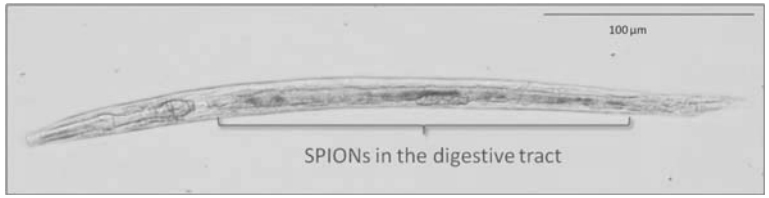

Figure 1

Biomineralization magnetic nanoparticles by human's bacterial symbionts

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In the past decade, biologists are trying to adapt the bacteria to diagnose and treat cancer, such as for delivery to cancer cells specific molecules that trigger the process of self-destruction. Bifidobacteria, E. coli and other bacteria-symbionts can be modified in such a way that they will produce in the tumor substances that destroy cancer cells.

It is known that tumor cells containing biogenic magnetite nanoparticles. Also increased level of magnetite nanoparticles observed in carcinogenesis - melanoma, breast, ovary, testicle, meningioma, glioblastoma, astrocytoma, glioma, glioma, Ehrlich carcinoma and in metastasis of tumors [1].

In paper [2] it is shown that a number of human symbionts such as *Salmonella, Clostridium*, *Listeria monocytogenes, Bifidobacterium breve,* and *E.coli* accumulate in malignant tumors, which can be explained by the presence of magnetite nanoparticles. To confirm the possibility of biosynthesis of magnetite nanoparticles by human's symbionts - anaerobic bacteria and identification of proteins that are responsible for the formation of magnetic nanoparticles made a comparative analysis of amino acid sequences the proteins of magnetosome island of magnetotactic bacteria *M. Gryphiswaldense* and beneficial bacterial symbionts: *Bifidobacterium, Propionibacterium, L. Acidophilus, E.coli, L. Plantarum, L. Fermentum* by method for assessing the statistical significance of adjustment protein sequences using the program BLAST. The degree of homology between proteins indicates the possibility of the formation of magnetic nanoparticles in these organisms, as evidenced by the value of E-numbers (<10-5). Ability biosynthesis of magnetic nanoparticles by symbionts confirmed by experimental work [3], which shows that these symbionts of human as *L. plantarum* and *E.coli* was found magnetosensitive structure.

Since the tumor cells contain about 10 times more of magnetite nanoparticles that of healthy cell, the force of magnetic dipole-dipole interaction between magnetically dosage form with tumor cells is much greater than with healthy and can actually be regarded as an additional strength of specific binding [4]. In paper [3] calculated strength of the interaction of magnetic nanoparticles in tumor cells with exogenous magnetic nanoparticles within magnetoliposomes what equal to approximately 9^{-10} N, which is close to the order of magnitude of the forces specific antigen-antibody binding, so it is important to consider when designing systems for drug delivery forms.

In the future, the use of bacteria to treat tumors allow physicians to choose the most appropriate methods for removal of malignant tumors and reduce damage to the body that cause aggressive methods of cancer treatment.

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Cationic superparamagnetic iron oxide nanoparticles affect the survival-associated AKT-FOXO3 axis

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Introduction: Nanomaterials attract widespread interest in both research and industry because of their fascinating features While several iron oxide-based superparamagnetic nanoparticles (NP) are already clinically approved for applications in humans as contrast agents their precise biological effects on the distinct tissues or individual cell is still unclear As the human blood-brain barrier is a critical and sensitive interface necessarily exposed to systemically applied NP we investigated the NP-induced effect on the central Akt signalling pathway in human blood-brain barrier-forming cells
Methods: Human brain microvascular endothelial cells (HBMEC) representing an important component of the blood-brain barrier, were cultured in RPMI1640 + 10% fetal calf serum ELISA-based vitality assays were performed as described [1] Long-term cell viability was analysed with the xCELLigence system (Roche Applied Bioscience) Subconfluent cell layers were exposed to 25µg/cm2 NPs comprising coatings of different polymers, i e carboxymethyldextran (anionic), starch (neutral), and polyethylen-imine (PEI-750kDa, cationic) The Akt signalling cascade was studied via western blotting using phospho-Akt(Ser473) and pan-Akt antibodies, as well as beta-Actin for control Transcription levels of Akt target genes FOXO3 and Survivin were analysed by quantitative PCR Immunofluorescent staining using AF647-labeled anti-Foxo3 antibodies revealed subcellular distribution of the Akt-target protein
Results: Real-time cell analysis over 72 hours reveals that HBMEC tolerate both neutral and anionic NP at concentrations up to 100µg/cm^2 In contrast, cationic PEI-coated NP attenuate cellular viability at concentrations exceeding 25µg/cm^2 for up to 24 hours Signaling cascade analyses reveal a two-fold increase of phospho-AKT after incubation with cationic particles potentially triggering survival cascades PEI polymers alone show similar but less pronounced effects Anionic NP formulations slightly but persistently increase Akt phosphorylation by 40% On the expression level all NP and free polymer formulations increase the levels of Akt-activated Survivin The cationic NP show the most pronounced effects The Akt target protein Foxo3 appears to be regulated in treated HBMEC, too In consequence, Foxo3 protein exhibits a sustained nuclear translocation upon exposure to cationic NP
Conclusion: We show that superparamagnetic iron oxide nanoparticles affect blood-brain barrier forming HBMECs in central cellular signalling despite of their charge Especially cationic PEI-coated but also anionic CMX-coated NP increase essential survival-associated pathways The consequences of these observations for the integrity of the tissue remain to be investigated

This work was supported in part by DFG high priority program 1681, CL202/3-1 and by the BMBF joint research project NanoMed, FKZ 03X0104D

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High pressure synthesis of FePt nanoparticles with controlled morphology and Fe content

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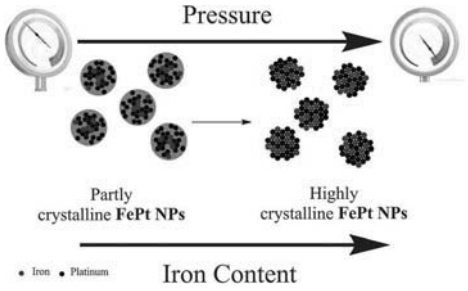
Magnetic nanoparticles (MNPs) are intensively researched due to their large potential in biomedicine, catalysis, and high density information storage. FePt NPs could be an alternative for commonly used magnetite NPs and the synthesis of FePt NPs is an active area of research. The challenge is to increase the Fe content and saturation magnetisation of FePt NPs so that they can be used in many practical applications. Fine tuning of synthetic methods is required in order to achieve the enhanced magnetic properties of FePt nanoparticles and novel methods are being sought. Here, use of an autoclave is shown to increase the Fe content, crystallinity and the subsequent magnetic properties of FePt pseudo cube nanoparticles compared to those synthesised under atmospheric pressure. Decreasing amount of oleic acid is also shown to increase the iron content and can lead to elongated FePt nanoparticles under normal pressure. Further application of nanoparticles synthesised in organic media often requires functionalisation or exchange of stabiliser chemicals. Greater demand for control over such functionalisation requires more information about nanoparticle-stabiliser chemical interactions. Infra-red studies indicate mono and bi dentate coordination with oleic acid, however shifts of spectra show that the strength of the bi-dentate interactions weaken with increasing oleic acid amount



Ref: L. A. W. Green and **N. T. K. Thanh*** (2014) High pressure synthesis of FePt nanoparticles with controlled morphology and Fe content. RSC Advances. 4: 1168-1173

Multicore magnetic FePt nanoparticles: controlled formation and properties

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Research in magnetic nanoparticles (NPs) has become one of the most active and exciting fields in materials science. The challenge is to produce magnetic NPs with high magnetic saturation without exceeding the super-paramagnetic limit so that they may be used as non-permanent magnets in biomedicine and catalysis. FePt offers enhanced saturation magnetisation properties compared to iron oxide, however synthetic methods require fine-tuning to achieve these superior properties. Multicore FePt NPs up to 44 nm in diameter and composed of Pt rich FePt nanocrystals within an iron rich FePt matrix not previously seen in the literature are presented here. The results indicate that coordination of Fe and Pt intermediates with oleic acid and oleylamine respectively hinders deposition of each respective metal in the growth of discrete and multicore NPs.

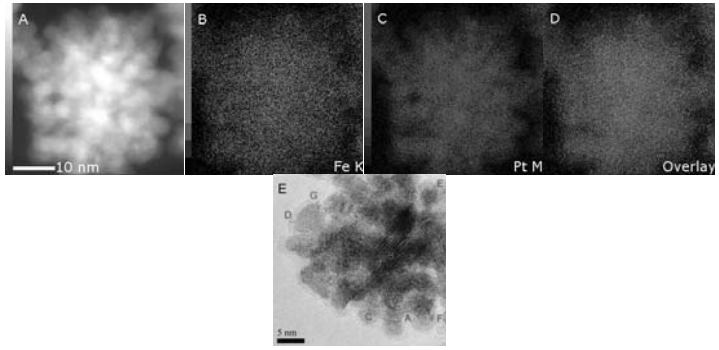

Fig 1, STEM-HAADF images and elemental mapping of sample mcNPs prepared in dioctyl ether with 4 5 mmol (17 %) OA and tSf equal to 31 5

Ref: Green, L.A.W., Thuy, T.T., Mott D., Maenosono, S., **Thanh, N.T.K.***, (2014). Multicore magnetic FePt nanoparticles: controlled formation and properties. RSC Advances. 4: 1039 - 1044

Nanomagnetic Activation as a Way to Control the Efficacy of Nucleic Acid Delivery

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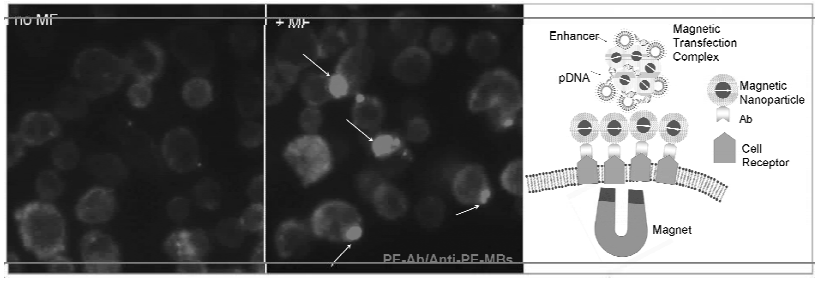
Magnetic transfection complexes formed by the self-assembly of magnetic iron oxide nanoparticles, which were modified to perform gene delivery with plasmid DNA and an enhancer under an inhomogeneous magnetic field, allowed for efficient plasmid DNA delivery into primary mouse embryonic fibroblasts and porcine fetal fibroblasts, as measured by vector internalization and transgene expression Sixty percent of cells were transfected at low pDNA doses of 4-16 pg pDNA/cell Efficient transfection of these cells is important for the generation of induced pluripotent cells or cell transdifferentiation and the generation of transgenic animals Specific labeling of the cell surface receptors of the mouse fibroblasts with magnetic nanoparticles, both in the adherent state and in suspension, yielded an average cell magnetic moment of 60-95 picoemu/cell and resulted in a 3-fold and 2-fold increased dose of internalized pDNA upon magnetofection and lipofection, respectively Increased vector internalization yielded a 2-4-fold enhancement of transgene-expressing cells Non-specific cell labeling had no effect on the efficacy of the reporter expression, despite the acquisition of similar magnetic moments per cell We suggest that magnetic labeling of cell-surface receptors combined with the application of a magnetic field (nanomagnetic activation) can affect the receptor-mediated internalization of delivery vectors and be used to control nucleic acid delivery to cells



Acknowledgements We gratefully acknowledge the support from the German Research Foundation through the DFG Research Unit FOR917 (Project PL 281/3-1, Project PL 281/3-1, TR 408/6-1), from the German Federal Ministry of Education and Research through the grant ZIM-KOOP 'STEP-MAG' KF2257005 NT2, and from the Excellence Cluster 'Nanosystems Initiative Munich'

Magnetic particle dynamics in turbulent flow

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In the field of biomedicine the applications of magnetic beads have increased immensely in the last decade Drugs are delivered exactly to desired targets Contrast agents for magnetic resonance imaging (MRI) are helping health professionals to more easily locate disturbance sources Bioseparation of DNA, blood cells, various macro-molecules, antigens etc is now possible Even the destruction of tumor tissue with high-frequency magnetic fields has been demonstrated

To improve current applications we are working on the manipulation of magnetic beads in a controlled and reproducible manner using newly developed simulation methods Magnetic particle dynamics have been implemented into the soft matter simulation package ESPResSo [1] The extended simulation environment incorporates magnetic particles in lattice-Boltzmann fluid dynamics with applied external magnetic fields Magnetostatics, hydrodynamics, as well as complex behaviour in microfluidic systems including particle-particle or particle-surface interactions can be investigated Possible applications include blood cell flow with interacting magnetic beads (Fig 1)

Figure 1: Circulating tumor cell (pink) interacts with chained magnetic particles in the blood flow

The magnetic gradient force on a softmagnetic bead is given by the negative gradient of the energy E in the field B ($\vec{F}=\vec{\nabla}(\vec{m}\cdot\vec{B})$) In case of a second bead in the system, the force on the first bead is given by $\vec{F}_1=\mu_0\int(\vec{M}_1+d\vec{M}_1)\cdot\vec{\nabla})(\vec{H}_{ext}+d\vec{H}_2)dV_1$ The magnetization $\vec{M}_1$ is created by the external field $\vec{H}_{ext}$ Here the field is the sum of the field from field sources like permanent magnets or coils and the dipolar field from neighbouring magnetic beads The induced magnetic field $d\vec{H}_i$ (from magnetized bead 2) changes the magnetization in bead 1 ($d\vec{M}_1$) The equation is valid for multiple particles and need to be solved for every particle pair in the system

For the description of the fluid dynamics we use the lattice Boltzmann method (LBM) Consider a uniform lattice consisting of square cells (Fig 2), placed over the rectangular three- dimensional domain The LBM models the fluid consisting of fictive particles which perform consecutive propagation and collision processes over this discrete lattice mesh In preliminary work we implemented elastic objects into ESPResSo using an Immersed Boundary Method (IBM) [2] The boundary of each suspended object is represented by a set of discrete Lagrangian immersed boundary (IB) points that do not need to lie on the fluid grid (Fig 2) Stiff bonding forces between the IB points provide the fixed shape of a magnetic bead

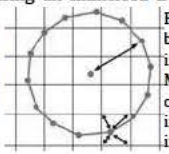

Figure 2: Magnetic bead represented by immersed boundaries (red dotts) in lattice-Boltzmann grid (2D) Magnetostatics are calculated in the center of the bead whereas fluid interactions are handled at the immersed boundary points

The simulation consists of several steps Magnetic forces are calculated at a center point of the bead and transferred to IB points Fluidic drag forces at each IB point are obtained by the difference between interpolated lattice velocity v_f and the particle velocity v_p ($F_j=\xi(v_p-v_f)$) ξ is a friction coefficient, which is calibrated for spheres in fluids The system gets propagated with solving the fluid dynamics equations on the grid as well as the motion equations for the magnetic beads

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Characterization of individual superparamagnetic particles using a torsional molecular spring

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Superparamagnetic particles are used in biophysical studies to apply forces and torques on biomolecules such as DNA and proteins [1,2]. The particles contain a distribution of magnetite grains in a matrix of polystyrene and show significant particle-to-particle variations in their magnetic properties. In this work, we describe a method to extract detailed magnetic properties of individual particles, bound to a surface by a protein complex that acts as a torsional molecular spring.

In a previous work [2] we showed that particles bound to a surface by a protein G-IgG complex (Figure 1a) exhibit a sawtooth like behaviour when exposed to an in-plane rotating field. Here, we demonstrate that the pattern of rotation sensitively depends on the magnitude of the applied field (see Figure 1b,c). For a magnetic field **B** below the coercive field of the particle **Bc (B<Bc)**, the particle shows an oscillating motion with a frequency equal to that of the applied field. When the coercive field of the particle is strongly exceeded **(B>Bc)**, the oscillation frequency of the particle is doubled (Figure 1c). In the intermediate regime **(B≈Bc)**, secondary peaks appear in the data (Figure 1b) which are a reflection of the magnetic microstructure of the particle. To interpret the data, we have developed a model that takes into account the remagnetization of magnetic grains angularly distributed within the particle. Using the model, the secondary peaks can be interpreted in terms of the angular distribution of the magnetic grains inside the particle. Furthermore, we are able to quantify the effective remanent magnetic moment of the particle by combining data of the maximum angle of deformation with data of rotational Brownian motion.

In this presentation, we will explain the torsional measurement techniques and the magnetic model, which give an unprecedented view into the magnetic properties of the grain ensemble inside single magnetic particles.

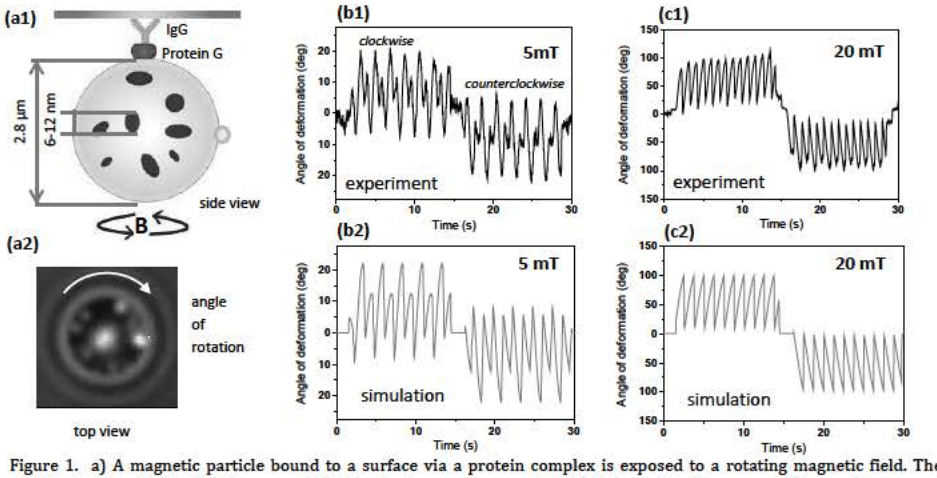

Figure 1. a) A magnetic particle bound to a surface via a protein complex is exposed to a rotating magnetic field. The rotation is visualized using fluorescent labels, a2 shows an image of a labelled particle, the arrow indicates the sense of rotation. b) Particle oscillations in a rotating field of 5mT and 0.4Hz, where B≈Bc. Panel b1 shows experimental results, panel b2 shows simulations based on a magnetic model of the particle. c) Particle oscillations for a field of 20 mT and 0.4Hz, where B>Bc.

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Tunning magnetic and relaxometric properties of ferrihydrite

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Several diseases are characterized by an excess of iron in the brain, liver, spleen or heart and magnetic resonance imaging (MRI) is a non-invasive novel alternative for the diagnosis and follow-up of these diseases It is generally accepted that ferrihydrite constitutes the crystal core of ferritin, the storage protein essential to cellular iron metabolism, however, the crystalline structure or the magnetic properties of ferrihydrite, crucial for the knowledge of its relaxometric properties, are still a controversial issue Generally, ferrihydrite has been described to be antiferromagnetic with superparamagnetic behaviour at room temperature Interestingly, recent studies on the magnetic properties of ferrihydrite during the aging process to hematite in the presence of citrates have revealed an intermediate phase with pronounced ferrimagnetism relative to the initial disordered ferrihydrite [Michel et al , PNAS, 2010, 107, 2787]

We have prepared a series of samples obtained during the aging process of ferrihydrite to hematite to gain better understanding on the relaxometric properties of biomineralized ferrihydrites, as well as to explore the possibility of optimizing the ferrihydrite aging process to improve the relaxivity of the material for its use as a MRI contrast agent A detailed characterization of ferrihydrite during the aging process in the presence of citrates has been performed by X-ray diffraction, Transmission Electron Microscopy (TEM), AC and DC magnetic measurements and Nuclear Magnetic Resonance measurements

An increase on the ferrihydrite nanoparticle average size and saturation magnetization has been found during the aging process The high ratios between the transverse and longitudinal relaxivities (r2/r1) indicate the possible use of ferrihydrite as a negative contrast agent The detailed magnetic characterization of the intermediate phases also shows some sort of spin-glass-like behaviour at low temperatures

Our results provide new insights into the magnetic and relaxometric properties of intermediate phases of ferrihydrite during the aging process to hematite, although the unravelling the relationship with the crystalline structure of the nanoparticles is still a challenging goal

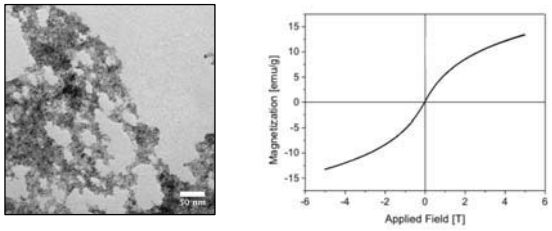

Figure. TEM micrograph and field dependent magnetization of two samples obtained during the aging process of ferrihydrite to hematite in the presence of citrates.

Development of novel functional magnetite nanoparticles for evaluation of human mesenchymal stem cell (hMSC) labelling in a tissue-engineered airway

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With the successful transplantation of a tissue-engineered larynx into a patient[1], the clinical use of stem cell therapy is promising The cellular distribution, function and viability of human mesenchymal stem cells (hMSCs) must first be evaluated in a safe and non-invasive manner [2]
Several studies using commercially available (Feridex® and Resovist®) or synthesised iron oxide nanoparticles have allowed labelling and tracking of hMSCs *in vitro* by magnetic resonance imaging (MRI) [3-5] However, most of these materials are not suitable for biomedical applications as they are made in organic solvents and require complex post-synthesis phase transfer by ligand exchange To overcome this, we present the use of a microwave-assisted simple one-pot synthesis of iron oxide nanoparticles by the polyol method for their use as contrast agents in MRI This novel method is reliable and leads to mono-disperse, water-soluble and stable nanoparticles further functionalised for biomedical applications with different coatings such as citrate or fluorescent silica coating Their enhanced cellular uptake and magnetic properties allow their use in cellular tracking by MRI

In this study, experiments are carried out to optimize the synthetic method, properties (size, coating), and dose of the nanoparticles for their uptake by hMSCs MRI of hMSCs labelled with nanoparticles as contrast agents is a useful tool towards further understanding their role in tissue-engineered organs While active targeting of magnetic nanoparticles with specific antibodies has been thoroughly studied to control their biodistribution, a novel strategy to obtain information on the differentiation stages of transplanted hMSCs *in vitro* was studied The use of a superparamagnetic iron oxide nanoparticle based imaging modality could be therefore applied to assess the success of stem cell therapy

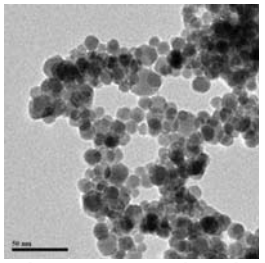

Figure 1 TEM image of novel magnetite nanoparticles synthesised by the polyol method

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Measurement of Magnetic Moment via Optical Transmission

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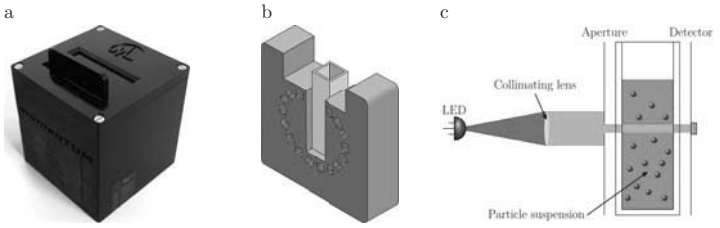
Magnetic nanoparticles are characterized by several different properties, e.g. size distribution, particle composition and magnetic moment. The magnetic moment is a very important property for drug targeting and related applications as well as for the simulation thereof. However, the measurement of the magnetic moment of nanoparticles, nanoparticle-virus-complexes or microspheres in realistic solutions can be difficult and often yields unsatisfying or incomparable results.

To measure the magnetic moment, we designed a custom measurement device (figure a) including a magnetic set-up (figure b) to observe nanoparticles indirectly via light transmission (figure c). We present a simple device of a manageable size which can be used in any laboratory as well as a novel evaluation method to determine the magnetic moment of nanoparticles via the change of the optical density of the particle suspension in a well-defined magnetic field.

In contrast to many of the established measurement methods, we are able to observe and measure the individual nanoparticles or complexes in their natural state in the respective medium. The nanoparticles move towards the magnetic field source and thereby away from the observation point. Due to this movement, the optical density of the fluid decreases and the transmission increases over time at the measurement location. This behavior, also called magnetophoretic mobility, describes the particle movement. By comparing the measurement with parametric simulations, we can the observed behavior to the magnetic moment.



Photograph of the device (a), schematic of the light path (b) and of the magnetic set-up (c)

Biogenic Magnetite Nanoparticles as New Tracers for MPI and MRI

David Heinke[1*], Alexander Kraupner[1], Nicole Gehrke[1], Dietmar Eberbeck[2], Rene Uebe[3], Dirk Schüler[3], Andreas Briel[1]

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The process of formation of solid inorganic material within biological systems is termed biomineralization and occurs in various organisms such as humans, sponges and some molluscs. These biominerals often exhibit extraordinary properties such as mechanical robustness and extreme lightweight as in the case of bones. Further biomineral examples are calcium carbonates, pyrites and various oxides. In the case of iron oxides, the formation process can be distinguished into biologically-induced and biologically-controlled biomineralization, wherein the latter results in highly defined magnetic nanoparticles. One remarkable example are the so-called magnetosomes, which are membrane-enclosed iron oxide nanoparticles formed by magnetotactic bacteria, which serve as magnetic sensors for magnetotaxis, the orientation along the earth's magnetic field. Such magnetosomes consist of pure, almost defect-free magnetite crystals stabilized by biomembranes forming monocrystalline nanoparticles of distinctive monodispersity in size and shape.[1] Such features seem to be ideal requirements for the application of such particles in Magnetic Particle Imaging (MPI) as well as Magnetic Resonance Imaging (MRI).

Both MPI and MRI are diagnostic imaging modalities, which require the use of a magnetic tracer material. While in the latter the tracer exhibits a contrast enhancement, MPI, as a new and promising imaging technology, enables the three-dimensional direct detection of magnetic nanoparticles with high temporal and spatial resolution.

In this work we test the potential of several magnetosomes extracted from magnetotactic bacteria of the strain *Magnetospirillum gryphiswaldense* and various mutants thereof as new tracer materials for MPI and MRI in comparison to the current gold-standard Resovist®. Magnetosomes with different particle sizes are investigated, which offer the possibility of size-dependent studies. In addition, we investigate the physicochemical and morphological properties in order to understand the relation between particle structure and MPS efficacy.

The results show that such magnetosomes depict MPS amplitudes that exceed that of Resovist® by a factor of up to 6.8 at the third harmonic while simultaneously exhibit highly improved relaxation rates in MRI experiments. Furthermore, a size-dependence of both the MPS signal and the R_2-relaxation is observed, where the highest amplitudes and lowest R_2-relaxations are obtained for the smallest particles.

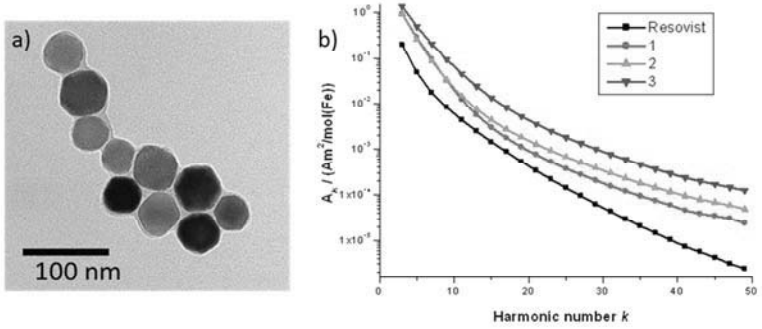

Fig. 1: a) TEM image of magnetosomes with stabilizing biomembranes and b) MPS spectra of various magnetosomes (1-3) as well as Resovist measured at 25 mT/μ_0 and 25.25 kHz.

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Heat transition during magnetic heating treatment: Study with tissue models and simulation

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Magnetic heating treatment (MHT) is known as a promising therapy for cancer diseases Depending on concentration and specific heating power of the magnetic material, as well as on parameters of the magnetic field temperatures between 43-55°C can be reached This paper deals with the evaluation of heat distribution around such a heat source in a tissue model, thereby focusing on the heat transfer from tissue enriched with magnetic nanoparticles to regions of no or little enrichment of magnetic nanoparticles

We examined the temperature distribution with several tissue phantoms made of polyurethane (PUR) with similar thermal conductivity coefficient as biological tissue Phantoms A, B, and C are composed of a cylinders with one sphere inside Thereby the spheres have different diameters in order to study the influence of the surface-to-volume ratio Phantom D consists of a cylinder with two included spheres as shown in Figure 1a) The inner parts of the phantoms consist of a defined mixture of PUR gel and magnetic fluid These parts represent tumor tissue enriched with magnetic nanoparticles The outer parts, which stand for non enriched surrounded tissue, consist of PUR only

The phantoms were placed into a water bath with an adjusted temperature of 37 °C Then, they have been exposed to an alternating magnetic field The magnetic strength was varied between 4 39 and 8 71 kA/m, while the frequency was 284 kHz The temperature measurements were performed by thermocouples which are placed on defined positions (Figure 1a)) These positions have been validated with X-ray microcomputed tomography (µCT), thus providing 3-dimensionally exact data for the latter simulation In Figure 1b) the simulated temperature profile for phantom D is shown

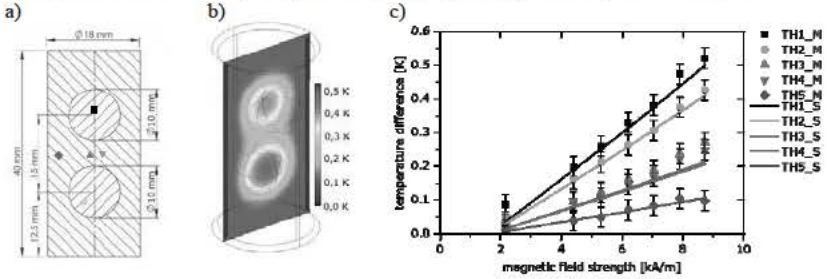

Figure 1a) Technical drawing of phantom D. The included symbols represent the measuring points. b) Simulation results of phantom D. c) Comparison of measured (symbols) and simulated (lines) data of phantom D.

We achieved an agreement between the measured and simulated temperatures for all phantoms produced in this experimental study Figure 1c) shows representatively results for phantom D The established experiment allows a theoretical predication of temperature profiles in tumors and surrounding tissue for the potential cancer treatment and therefore an optimization of e g the respective magnetic nanoparticles concentrations for the desirable temperature increase

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Optimization of magnetoresistive sensor current for on-chip magnetic bead detection using the sensor self-field

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We present a systematic study of the bias current of so-called planar Hall effect bridge (PHEB) magnetoresistive sensors (Fig 1a) integrated in a lab-on-a-chip system in order to maximize the signal from magnetic beads with minimal sensor self-heating We have previously demonstrated the use of PHEB sensors as the magnetic bead based readout for on-chip DNA detection using both volume and surface based detection schemes [1,2] In these studies, the magnetic beads were magnetized by the field arising from the sensor bias current I_x, thus eliminating the need for external electromagnets The contributing to the sensor signal V_y due to magnetic beads is proportional to I_x^2 and therefore it is desirable to maximize I_x However, the maximum bias current is limited by the maximum acceptable Joule heating of the sensor Here, we study the self-heating of sensors as function of the sensor current for a fixed sensor length l=250µm and for a range of sensor widths w (Fig 1b) We identify the currents giving rise to a maximum allowed self-heating of 5 C and show that the self-heating is determined by the dissipated power per sensor area These results are relevant for the application of the sensors for characterization of magnetic beads as well as for biodetection applications of the sensors

The sensor geometry and stack are given in Fig 1a The sheet resistance of the sensor stack was 10 Ω First, the temperature dependence of the bridge resistance $R(T) = V_x(T)/I_x$ was calibrated via measurements of $R(T)$ for all sensor bridges for T = 20, 25, 30, 40, 50 and 60 C using an external Peltier based temperature controller [2] Then, with the temperature controller set to 25 C, measurements of R were carried out as function of I_x and converted to a temperature increase ΔT Fig 1b shows ΔT vs I_x for the indicated sensor widths w The values of ΔT are found to be proportional to I_x^2 (the Joule heating) The currents corresponding to a self-heating of 5 C are given in the figure Fig 1c shows the dissipated power $P = R(T)I_x^2$ to obtain a 5 C sensor self-heating vs the sensor area $A = 4lw$ We find that the two are proportional The observations are consistent with a model where the power dissipated per sensor area is constant and dominated by the thermal resistance of the 1 µm thick oxide separating the sensor stack and the underlying silicon wafer

We have determined a suitable current in our PHEB sensors for having maximum bead signal and magnetization, while ensuring the joule heating will not degrade any biology and thus release the magnetic beads when doing surface based bead diagnostics

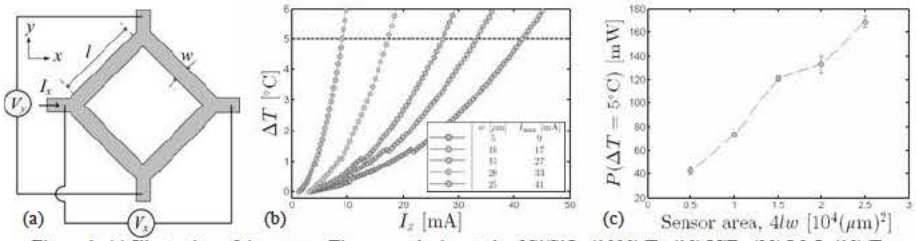

Figure 1: (a) Illustration of the sensor The sensor had a stack of Si/SiO_2 (1000)/Ta (10)/NiFe (30)/MnIr (10)/Ta (5)/Ormocomp resist (1000), thicknesses in nm (b) Increase of sensor temperature ΔT vs current for five different sensors (c) Joule heating power resulting in ΔT = 5 C vs sensor area $A = 4lw$

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Separation of the mixture of particles into individual component with the aid of magneto-Archimedes separation

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Using a high magnetic field such as more than 10 T, relatively large magnetic force can be exerted even on diamagnetic and paramagnetic materials It is well known that water and some diamagnetic materials can be levitated by using high magnetic force Based on the magneto-Archimedes principle, this levitation of diamagnetic materials can be attained using ordinal superconducting magnet with the aid of the magnetically induced buoyancy force that comes from its surroundings Furthermore, not only diamagnetic materials, but also paramagnetic materials can be levitated by the magneto-Archimedes levitation When feeble magnetic materials levitated in the field, the stable levitation position depends on the materials because it is determined by the difference in volume magnetic susceptibilities and densities between objects and their surroundings Based on this feature, mixture of materials can be separated into each individual component

We have successfully demonstrated the separation of the mixture of particles whose size is less than 100 μm into each component In the experiment, several glass particles different in size or colors (that means different in their ingredients) were used The superconducting magnet that can generate up to 13 T magnetic field was used Even though their densities and susceptibilities were similar with each other, they were separated by the magneto-Archimedes separation due to their slight difference in their physical properties This technique is expected to be applied for *in-situ* analysis of content in some sample fluid Details of this separation will be reported in this presentation

X-ray diffraction, Mössbauer and magnetic studies of $(Fe_{70}Co_{30})_{100-x}Si_x$ nanostructured powders elaborated by mechanical alloying

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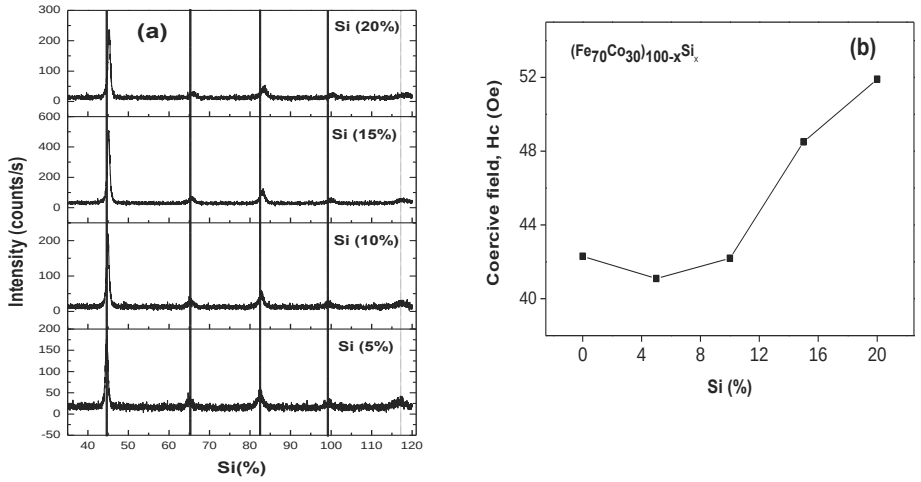
Abstract

This work focuses on the elaboration of nanostructured $(Fe_{70}Co_{30})_{100-x}Si_x$ (x = 0, 5, 10, 15, 20. at%) powders by mechanical alloying process. The powders were milled for same milling times of 72 h. The structural, hyperfine and magnetic properties of as-prepared alloys were characterized by X-ray diffraction, ^{57}Fe Mössbauer spectrometry, and vibrating sample magnetometry (VSM). From X-ray diffraction spectra, we have shown that, for all $(Fe_{70}Co_{30})_{100-x}Si_x$ powders, the Fe(Co, Si) solid solution was completely formed. Moreover, we have found that the lattice parameter decreases with increasing Si content. The adjustment of $(Fe_{70}Co_{30})_{100-x}Si_x$ Mössbauer spectra evidenced the formation of ferromagnetic disordered Fe(Co, Si) phase. The hysteresis loops confirmed the ferromagnetic character of $(Fe_{70}Co_{30})_{100-x}Si_x$ nanostructured powders. We have found that the saturation magnetization, Ms, decreases with increasing Si content. For the corecivity, Hc, we have shown that Hc exhibits a minimum value of 41 Oe for x= 5%. All these results will be correlated and discussed.



(a) X-ray diffraction spectra of $(Fe_{70}Co_{30})_{100-x}Si_x$ **(b)** Coercive field, Hc, versus Si content

Magnetic Macroporous Particles as an Essential Tool of Multiparametric Degradation Approach for Production of Size-Defined Hyaluronan Fragments

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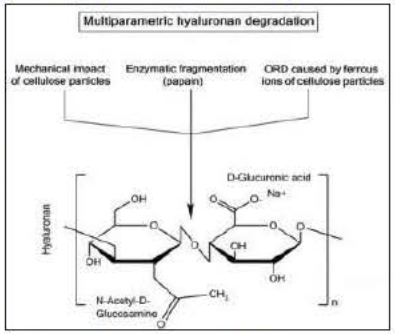
[a]Department of Biological and Biochemical Sciences; [b]Department of Analytical Chemistry, [c] Synthetic polymers, Fibres and Textiles Chemistry Unit, University of Pardubice, Studentska 573, 53210 Pardubice, CZ; [d]Contipro Pharma a s , Dolni Dobrouc 401, 561 02 Dolni Dobrouc, CZ

Currently, the interest of hyaluronan (HA) and its fragments has been already increasing due to their beneficial physicochemical and biological characteristics. The impacts of this versatile biomolecule influenced by molecular weight of polymer chains are utilized in the large spectrum of biomedical and biotechnological areas[1]. The common degradation methods of HA fragments production have some limitations, particularly high size polydispersity of final fragments and/or present of reaction contaminants. And therefore, the aim of this study was to develop the new approach to efficiently and safely produce pure size-defined HA fragments.



Novelty of our multiparametric approach is based on the mutual cooperation of three factors: the mechanical effect of magnetic macroporous beads made from nontoxic and biocompatible cellulose, oxidative-reductive depolymerization caused by accessible iron ions incorporated in the structure of carriers and the ability of plant-derived enzyme to cleave the glycosidic bonds. The complementary impact of such magnetic macroporous carriers with covalently bound enzyme papain generates easily and safely size-defined HA fragments. Native polyacrylamide gel electrophoresis was used to evaluate the efficiency of HA fragmentation process and size exclusion chromatography/multi-angle light scattering was applied to precisely estimate and monitor the kinetics of degradation process.

Additionally, we assume that a magnetically stabilized fluidized bed with the continuous and dynamic contact of the carrier and viscous HA molecules could also contribute the fragmentation efficiency. In this case, such arrangement can be used even for large-scale production in the pharmaceutical or cosmetic industry.

References:

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Acknowledgement: *This work was financially supported by European Union's LOVE FOOD project under Contract No. 317742.*

Novel Monodisperse Carboxyl Functionalized Poly(Ethylene Glycol)-Coated Magnetic Poly(Glycidyl Methacrylate) Microspheres: Application to the Immunocapture of ß-Amyloid Peptides

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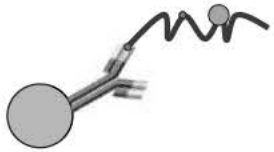
Identification and evaluation of small changes in amyloid β-peptide (Aβ) levels in cerebrospinal fluid (CSF) is of crucial importance for early detection of Alzheimer's disease. Microfluidic detection methods are very convenient as they enable effective preconcentration of Aβ from the CSF using magnetic microparticles coated with Aβ antibodies.

We have developed novel monodisperse poly(ethylene glycol) (PEG)-coated magnetic poly(glycidyl methacrylate) (PGMA) microspheres containing controlled amount of carboxyl groups. The 5 μm particles were synthetized by multiple swelling polymerization of glycidyl methacrylate (GMA), 2-[(methoxycarbonyl)methoxy]ethyl methacrylate and ethylene dimethacrylate in the presence of cyclohexyl acetate porogen. Subsequently, iron oxide was precipitated in the pores. The microspheres were then coated with β-methoxy-ω-amino-PEG/β-amino-ω-*t*-Boc-amino PEG mixture (M_w = 5,000). After the *t*-Boc removal, controlled concentration of carboxyl groups, e.g , 1.8 and 18 μmol/g, was introduced on the particle surface by succinylation.

Properties of the microspheres were determined by scanning and transmission electron microscopy, atomic absorption and FT-IR spectroscopy. Low nonspecific adsorption of bovine serum albumin, γ-globulin, fibrinogen, pepsin and chymotrypsin were confirmed on the PGMA-PEG-COOH particles compared with the original PGMA microspheres.

The magnetic PGMA-PEG-COOH microspheres were bio-functionalized with monoclonal anti-Aβ 6E10 antibody to pre-concentrate Aβ 1-40 by immunoprecipitation. The captured Aβ 1-40 peptides were derivatized with FluoProbe 488 NHS dye, eluted from immunocomplex and analyzed by capillary electrophoresis with laser-induced fluorescence detection. The microspheres containing 18 μmol COOH/g efficiently captured Aβ 1-40 peptides from model Tris-HCl/SDS solutions with 50-500 nM of Aβ 1-40. The magnetic PGMA-PEG-COOH seem to be thus promising support in imunoassays and other affinity applications.

Acknowledgement. Support of European Commission (grant No. 246513 NaDiNe) and Ministry of Education, Youth and Sports CR (project No. EE2.3.30.0029) is acknowledged.



Schematic representation of the Aβ-peptide (≧_) derivatized with the FluoProbe (●) captured on a magnetic PGMA-PEG-COOH microsphere coated with monoclonal anti-Aβ 6E10 antibody.

Simple, Water Base Protein Conjugation and/or Assembly of Complex Magnetic Nanoparticles.

C.Y. Huang, E. Chung, S.J. Cooper, R. de las Heras, B.T. Ohse, Y. Gao, D. Jennins, T. Ling, C. Munian, L. Yang, P. Vukovic, A. Wong, N.J. Maeji*.

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Recently, a simple one-pot recipe for coatings using Fe(III) and tannic acid was published (Science 2013, DOI:10.1126/ science.1237265). The method is versatile, forming coatings of about 10 nm in thickness and suitable for all manner of nano- and microscopic objects. A major limitation of this method, which can also be considered a key benefit, is pH sensitivity. The coating degrades under acidic conditions, which maybe useful for drug delivery, but not for applications where greater stability is required.

Affinity - and hence stability - for some chelating ligands can be greatly improved by selection of alternative metal ions and polymerisation of these metal ions to form oligomers. Multiple chelation enables strong avidity or multi-component binding to almost any surface even though each interaction by itself is relatively weak. Surfaces can be nano- or micro-scale particles with some electron donating potential, as well as any synthetic or biological polymers such as proteins. We have developed a panel of such metal polymers, called Mix&Go, which represent a "one-size-fits-all" surface chemistry approach to create coatings and/or "glues" as thin as <1 nm in thickness (Anal. Biochem., 363 (2007) 97-107).

Apart from simplicity, there are a number of additional benefits to using these aqueous metal oligomers. Once bound to any surface, such as a nanoparticle, they form an activated surface for protein binding, which, in theory, is indefinitely stable. Binding kinetics of Mix&Go to particles, and proteins to Mix&Go activated particles is in the order of seconds to minutes. We have shown that the cationic character of Mix&Go activated particles prevents aggregation/clumping of colloids as small as <20 nm. In addition, the combination of weak binding forces that come together to form a strong interaction results in minimal functional damage of proteins on binding.

Using the advantages of magnetic separations, Mix&Go activation allows the assembly of complex, multi-functional nanoparticles in a simple, reproducible manner.

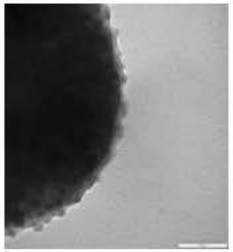

Figure 1. Transmission electron microscopy (TEM) of 200 nm magnetic particles coated with QDot via Mix&Go activation. The QDots are seen as 6 to 8 nm dimples from the background contour of the magnetic particle.

Measurement of the size effects on the biodistribution of polymer sterically stabilized magnetic nanoparticles.

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Iron oxide magnetic nanoparticles have a rapidly growing potential for use in biomedical applications. One of which is in an experimental cancer treatment called magnetic hyperthermia.[1] The safety and efficacy of this new biomaterial is largely affected by biodistribution.[2] Factors affecting biodistribution have been studied in the past and include size, surface charge, and route of administration.[3] However, the magnitude of impact each factor adds is not fully understood.

In order to evaluate the effect nanoparticle size has on in vivo aggregation, a series of magnetic iron oxide nanoparticles was synthesized, ranging in size from 10 – 25 nm. These particles were functionalized with multi-dentate heterobifunctional polymers; and novel surface coating developed in our laboratory. The coating is composed of a poly(acrylic acid) (PAA) that has been modified with polyethylene oxide (PEO) for stability in biological environments. To enhance anchoring of the polymer scaffolding to the magnetic nanoparticle, the PAA-PEO is modified with nitroDOPA. The coated nanoparticles can be tailored for various applications by "click" chemistry of the alkyne end groups on the PEO-PAA scaffold.

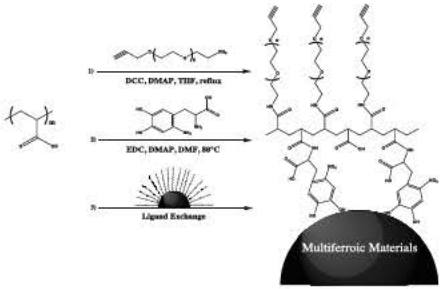

Figure 1: Model of Nitro-DOPA-PAA-PEO-Alkyne synthesis and particle modification

The particles were characterized with dynamic light scattering (DLS) and transmission electron microscopy (TEM). Preliminary toxicity studies were conducted to determine safety for testing in animals. Particles were proven nontoxic by MTT Assays in both fibroblasts and HepG2 human liver cells. An animal biodistribution study is currently underway.

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Novel carboxylated PEG-coating on magnetite nanoparticles designed for biomedical applications

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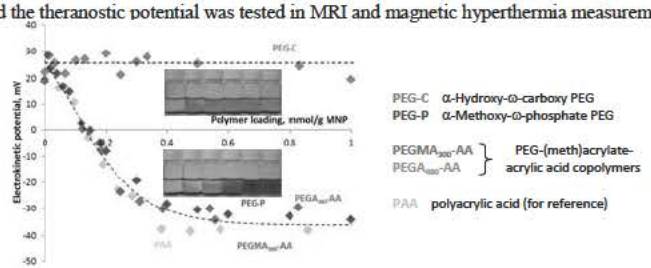
Hydrophilic magnetic nanoparticles (MNPs) designed for diagnostic or therapeutic applications (e g MRI, hypertermia, drug-delivery) are in the focus of scientific interest last decades A protective layer is needed to prevent the aggregation, to stabilize the dispersion and to hinder the chemical and biological degradation of nanomagnets Recently the PEGylation, i e the covering nanoparticles by polyethylene glycol (PEG) (called also as polyethylene oxide (PEO)), is the most favoured way to ensure their biocompatibility [1]

Based on our former results [2], functional (e g carboxyl, phosphate) groups of organic molecules are necessary to attach properly the protective layer to the surface of nanomagnets In this work, we combine the high hydrophilicity of coating provided by PEG chains with the strong linkage through carboxylic groups New type of functionalized PEG-polymers was synthesized (PEGMA-AA and PEGA-AA), where the number of anchoring groups and the length of PEO blocks are optionally variable parameters according to the needs The main goal of this paper is to characterize this new PEG-coating and to study its effect on the colloidal stability of MNPs Two commercially available carboxyl and phosphate functionalized PEG products were chosen for comparison The PEGylated nanomagnets were characterized by spectroscopy and by dynamic light scattering (DLS) and electrophoresis measurements as well at different pHs (3-10) and various PEG-polymer loadings (0-1 mmol/g MNP); the correct characterization of colloidal stability, i e , the quantification of salt tolerance was performed at neutral pHs by DLS

Infrared spectroscopy (ATR FT-IR) data revealed that these new PEG-polymers bind through carboxylic groups on the nanomagnets surface Electrophoresis experiments showed that the chemically attached PEG-polymers influence the aggregation of nanomagnets depending on the amount of added molecules At low polymer concentrations, only the partial charge neutralization of MNP's positive surface charge at pH~6 5 takes place, while the complete recharging can be reached, if the amount of the carboxylates is large enough at higher polymer loadings (see Figure below) An increase in hydrodynamic diameters was measured for coated nanoparticles by DLS, which suggests a steric contribution to the stabilization besides the electrostatic one The hemocompatibility was checked and the theranostic potential was tested in MRI and magnetic hyperthermia measurements



The surface modification effect of the carboxylated PEG polymers at various loadings (pH ~6 5, 10 mM NaCl)

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A Hajdú, M Szekeres, IY Tóth, RA Bauer, J Mihály, I Zupkó, E Tombácz, Coll Surf B 94:242– 249 (2012)
Acknowledgement: This research was supported by the OTKA (NK 84014) grant as well as by European Union and the State of Hungary, co-financed in the framework of TÁMOP-4 2 4 A/ 2-11/1-2012-0001 'National Excellence Program'

Synthesis of magnetite-silica-PPEGMA nanocomposite size series for drug delivery applications

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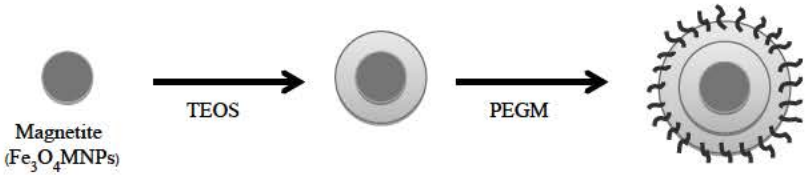
Magnetically-assisted drug delivery are of interests and potentially useful in medical applications.The effectiveness of the delivery systems is dependent on the size and the magnetization of the drug carriers. To investigate the effect from size and magnetization of the carriers, different sizes of magnetic nanoparticles (MNPs) with narrow nanoparticles size distribution including Fe_3O_4 (magnetite) MNPs and core-shell (Fe_3O_4@SiO_2) MNPs coated with Poly(Poly(ethylene glycol) methyl ether acrylate) (PPEGMA) were synthesized. Poly(ethylene glycol) or PEG entities were modified onto the surface of the MNPs to reduce the non-specific binding and increase biocompatibity. Fe_3O_4MNPs were synthesized using thermal decomposition technique, while core-shell (Fe_3O_4@SiO_2) MNPs were done by reverse microemulsion method. The core-shell Fe_3O_4@SiO_2MNPs were then functionalized to possess PPEGMA via atom-transfer radical polymerization.

The size of core-shell Fe_3O_4@SiO_2MNPs can be easily controlled by adjusting the ratio of Fe_3O_4 to the silica source, tetraethyl orthosilicate (TEOS). The monodispersity and morphology of all MNPs (Fe_3O_4MNPs,core-shell (Fe_3O_4@SiO_2) MPs and PPEGMA-coated MNPs) were characterized by transmission electron microscopy (TEM). X-ray diffraction (XRD) confirmed that the crystalline structure of Fe_3O_4 MNPs remained unchanged after coating with silica to obtain the core-shell Fe_3O_4@SiO_2 nanostructures. Successful coating of PPEGMA onto the core-shell Fe_3O_4-SiO_2 was observed using infrared spectroscopy (IR). These magnetite-silica-PPEGMA nanocomposites were used to investigate the effect of sizes and magnetization of the drug carriers in drug delivery applications.



Schematic representation of coated-PPEGMA MNPs

The Steric Stabilization of Magnetic Nanoparticles is Crucial for Hyperthermia Applications

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Magnetic nanoparticles are receiving considerable research input for biomedical applications such as hyperthermia, MRI and drug delivery. For these applications the design of the magnetic nanoparticles and their stabilization is of fundamental importance. For many applications large superparamagnetic particles have a distinct advantage. For example, large particles can generate more heat at clinically acceptable field strengths and frequencies and have higher relaxivities. Superparamagnetic particles are obtained when particles of a normally ferromagnetic material are reduced in size to the point where they are small enough to undergo spontaneous changes in magnetisation due to thermal energy[1, 2]. In iron oxide type magnetic materials this size is typically smaller than about 40 nm in diameter. However, as the size of superparamagnetic particles is increased beyond 11 nm[3] the generation of stable dispersions becomes more problematic due to very strong attractive magnetic interactions overcoming the thermal energy at room temperature. Sirtex Medical has perfected the art of making large single domain maghemite particles and our group has developed the polymer technology that enables reasonably large particles to be stabilized against these attractive forces with a minimal amount of polymer[4-6], although size limitations do still exist.

In this work, we describe an approach for the steric stabilization of these nanoparticles using short chain block copolymers prepared by reversible addition fragmentation chain transfer (RAFT). The block copolymers form the thinnest possible steric stabilizing layer while remaining strongly attached to the nanoparticle surface over a wide range of nanoparticle concentrations. The anchored stabilizers can be readily modified to carry targeting groups, anticancer agents, fluorescent visualization aids, and groups that confer stealth properties. We have demonstrated that these sterically stabilized magnetic nanoparticles are very efficient negative contrast agents having a transverse relaxivity value of 950 $mM^{-1}s^{-1}$ which is approximately 10 times higher than the best commercially available Sample.

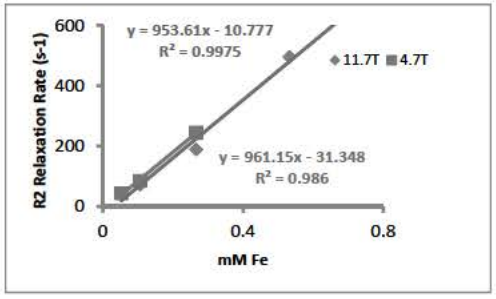

Figure 1 Transverse relaxivity as a function of iron concentration

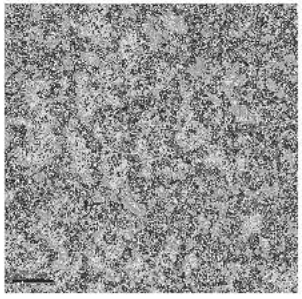

Figure 2 TEM image of magnetic nanoparticles

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Detection of Dendronized Superparamagnetic Nanoparticle Using Gradiometer Induction Sensors for Intraoperative Localization of The Sentinel Lymph Node in Cancer Treatment.

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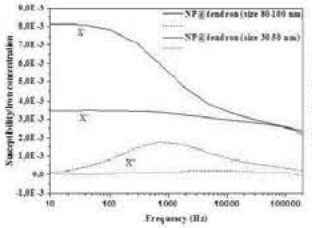
The dynamic magnetic behavior of iron oxide suspensions has been studied in view of many medical applications such as hyperthermia or magnetic particle imaging. They are now considered as a potential alternative to radioactive colloids used to detect the sentinel node in cancer surgery. Our study concerns on the one side suspensions of dendronized iron oxides and their dynamic magnetic properties in the 10 Hz-100 kHz frequency range, and on the other side their detection using a hand-held probe working at 25-75 kHz.
Iron oxide nanoparticles of 10 nm in diameter have been produced in large quantities. Dendrons of first or second generation with (or not) a Patent Blue dye and/or a fluorescent dye at the periphery have been grafted on the nanoparticles. The hydrodynamic size, the structure and composition of the iron oxide core and the amount of dendrons have been characterized and related to the dynamic magnetic susceptibility. We show that the structure and the composition of the aggregates strongly impact the magnetic properties of the suspensions and therefore are critical for optimizing the detection sensitivity.
A magnetic probe based on an AC magnetic field excitation of the nano-object coupled to an inductive gradiometer sensor has been designed to achieve this measurement. A conductive layer surrounding the probe is used to provide a shielding, thanks to the eddy current which will limit the leakage magnetic field outside of the probe. The principle of the probe and its ability to measure the magnetic signature of the magnetic nano-objects will be discussed.

Acknowledgments
This work was supported by the European Union in the framework of the program «Nano@matrix» INTERREG IV Upper Rhine Valley.



Typical dynamic susceptibilities of dendronized iron oxide suspensions for a magnetic detection in the 25-75 kHz frequency range

Transverse relaxivity of silica coated manganite nanoparticles: the effects of composition and size

M. Kačenka,[1,2*] P. Veverka,[1] O. Kaman,[1,2] V. Herynek,[3] M. Veverka,[1] E. Šantavá,[4] I. Lukeš[2] and Z. Jirák[1]

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Among other applications, nanoparticles of $La_{1-x}Sr_xMnO_3$ (LSMO) manganites are intensively investigated for the possible use in biomedicine, particularly as potential agents for magnetic resonance imaging and magnetically induced hyperthermia. High transverse relaxivities of the cell labelling agents based on the LSMO cores have been recently published by our group.[1] Although magnetic and structural properties of the LSMO nanoparticles have been thoroughly described,[2] no systematic study dealing with the influences of the composition and the size of the particles on the transverse relaxivity r_2 has been published so far.

The magnetic nanoparticles of the $La_{1-x}Sr_xMnO_3$ perovskite phase in the range of composition x = 0.20–0.45 were synthesized by the Péchini method followed by a mechanical treatment. Subsequently, the particles were coated with a uniform silica layer using tetraethoxysilane and subjected to a size fractionation leading to a highly stable suspension (see Fig. 1).

The effects of the manganite composition (x) and the nanoparticle size (the size of the magnetic core and the thickness of the silica shell) on the r_2 relaxivity were analysed on the basis of detailed static magnetic and relaxometric measurements. The observed r_2 relaxivities were ranging 200–450 $s^{-1}mmol^{-1}l$ at body temperature (see Fig. 2) and their temperature dependences were in good agreement with the temperature dependences of the magnetization.

In conclusion, the silica encapsulated manganite nanoparticles are very promising negative contrast agent for magnetic resonance imaging.

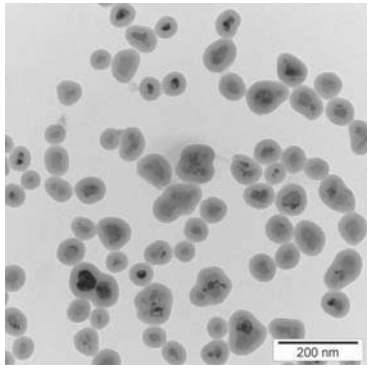

Fig 1.: Representative TEM micrograph of LSMO@SiO_2 with d_{XRD} ~ 20 nm and thickness of silica shell of ~ 20 nm.

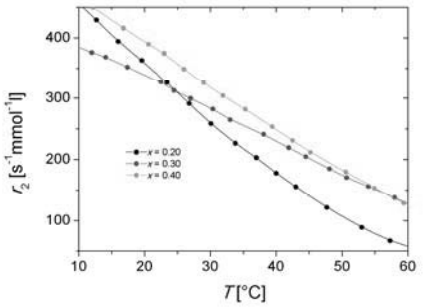

Fig 2.: Dependence of r_2 relaxivity on temperature for LSMO@SiO_2 with different composi ion but the same size (d_{XRD} ~ 20 nm, silica shell thickness ~ 20 nm).

The work was supported by the Czech Science Foundation project P108/11/0807 and Ministry of Industry and Trade of the Czech Republic project FR-TI3/521.

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Magnetic Hyperthermia with High-Coercivity Nanoparticles

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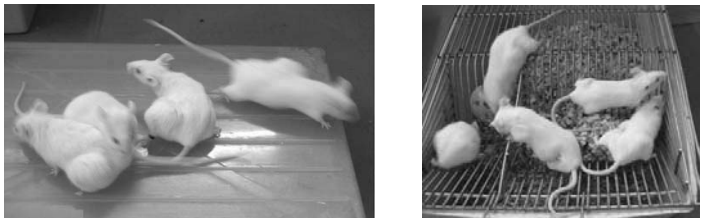
Last decades witness growing interest in magnetic hyperthermia. The idea is simple – to destroy tumor thermally by its local heating above the physiological temperature with the use of small magnetic particles delivered inside malignant area and absorbing there the externally applied alternating magnetic field. However, intensive studies, related mostly with superparamagnetic nanoparticles, have not promoted practical implementation of this idea in any proportion with exponentially increasing number of scientific publications. It may appear that superparamagnetic nanoparticles are more exiting subject for physical and chemical studies than the tool of practical hyperthermia.

Here, we present the results of our systematic studies of local magnetic hyperthermia with hard-magnetic nanoparticles, obtained since our report on the 8th MC conference (B.E. Kashevsky et al. Low-frequency ferromagnetic hyperthermia is feasible. AIP CP. 1311, 2010, P.280), where we established that such particles are theoretically manifold better energy absorbers as against superparamagnetic particles subject to the physiological limitation $H_0 f < 4.85 \cdot 10^8$ A/(m·c), imposed on the field amplitude H_0 and frequency f by the nonspecific body heating by eddy currents, described producing of nanoparticles with desirable coercivity, as well as our theoretical and experimental studies of the dynamic magnetic hysteresis and energy absorption in both solid and liquid systems of high-coercivity particles, and the effective regime of tumor thermal distraction evaluated in experiments with rats. Now we developed criterion of the particle-field system optimization, studied the influence of the interparticle magnetic interaction on the energy absorption, and in experiments with mice evaluated antitumor effectiveness of the developed thermal regime of hyperthermia alone and in combination with chemotherapy. On average, 25 p.c. of animals were healed in the first case, and 80 p.c. in the second.



Mice with tumors (left), and mice with tumors thermally healed (right)

Also, we developed the optimized system for controlled local magnetic hyperthermia of large animals (dog, cat, rabbit). The inner diameter of the field generating coil is 20 cm, the field frequency of 9.52 kHz, the field amplitude of up to 650 Oe [$H_0 f = 5 \cdot 10^8$ A/(m·c)], the maximum SAR with the developed particles is equal to 62 W/g (twofold bigger than SAR in the above experiments with mice).

Development of an Intravascular Magnetomotive Optical Coherence Tomography System

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Molecularly sensitive exogenous/endogenous contrast agents for optical coherence tomography (OCT) have been investigated to identify diseased sites, enhance diagnostic capabilities, and improve clinical outcomes [1,2] Contrast agents have been engineered for OCT to take full advantage of their optical properties such as absorption and scattering Our group has been investigating the use of magnetically responsive particles as dynamic contrast agents, such as magnetic nanoparticles (MNPs) and microspheres (MSs) for molecular-specific OCT imaging [3,4] Magnetomotive–OCT (MM-OCT) is a functional extension of OCT which utilizes magnetically responsive materials (e g , MNPs and MSs) that are modulated by an alternating external magnetic field for dynamic contrast enhancement

Atherosclerosis is a vascular disease in which plaque builds up inside the arteries Plaque is made up of many different substances found in the blood such as cholesterol, fat, calcium, etc Advanced lesions can limit the blood flow and eventually cause vascular occlusion due to blood coagulation triggered by their rupture Plaque rupture often occurs in vulnerable plaques Currently, standard intravascular OCT (IV-OCT) systems are commercially available and have been used in clinical applications, with a performance that is superior in resolution and scanning speed to intravascular ultrasound imaging systems The addition of contrast agents (e g , MSs and MNPs) for IV-OCT imaging can potentially enable molecularly sensitive and site-specific cardiovascular imaging In this study, we developed a catheter-based intravascular magnetomotive optical coherence tomography (IV-MM-OCT) system, and demonstrated its performance by using functionalized magnetic MSs to target the $\alpha_v\beta_3$ integrin that is overexpressed in diseased rabbit aortas

Figure 1A shows the schematic diagram of the IV-MM-OCT system for *ex vivo* imaging of rabbit aortas Healthy or diseased rabbits were intravenously injected with one of the following three solutions *in vivo*: 1) phosphate buffered saline (PBS), 2) non-targeted MSs (~10^9 MSs/mL), and 3) RGD-targeted MSs (~10^9 MSs/mL) After 30 min of *in vivo* circulation, rabbits were euthanized and their aortas were imaged with a custom-built IV-MM-OCT system Structural OCT (1300 nm spectral domain-OCT system, $\Delta\lambda$=105 nm, axial resolution of 7 4 μm) data was taken at regular intervals during a pullback rate of 0 018 mm/sec and a pullback distance of 32 mm with a custom-built metal-free OCT catheter At each step, M-mode images consisting of 512 A-lines were acquired at a A-scan rate of 2,795 Hz Longitudinal B-mode images (2,048 A-lines) were then reconstructed by taking discrete Fourier transforms of the resampled M-mode images The targeted or non-targeted MSs were modulated by an external magnetic field at 250 Hz generated by two electromagnetic coils (primary and secondary) Results (Fig 1B) showed that there were statistically significant differences in mean MM signal between groups: diseased-targeted MSs vs diseased-non-targeted MSs ($p<0$ 01) and diseased-targeted MSs vs healthy-PBS ($p<0$ 01)

In conclusion, we have developed a prototype catheter-based IV-MM-OCT system using an external dual-coil configuration and have successfully detected early stage fatty streaks and advanced atherosclerotic lesions using $\alpha_v\beta_3$ integrin-targeted magnetic MSs The molecularly sensitive and dynamic contrast generated by the functionalized magnetic MSs can potentially improve the diagnostic capabilities of intravascular OCT In this developmental study, we employed *in vivo* injection of MSs and *ex vivo* IV-MM-OCT imaging Our future work includes *in vivo* IV-MM-OCT imaging with a modified electromagnetic coil that can be placed externally on the chest and will be suitable for human/large animal investigations

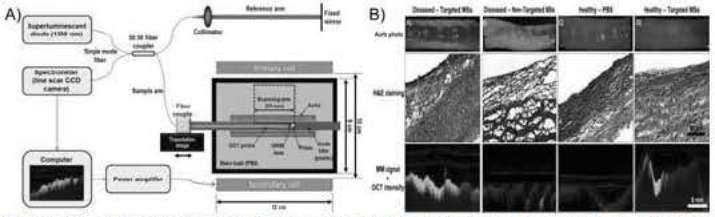

Fig 1 Schematic diagram of the MM-OCT setup (A) and IV-MM-OCT images (B) MM signal in green channel and OCT intensity in red channel

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Liquid carry-over in an all-polymer chip system for magnetic bead-based solid phase extraction

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Miniaturisation of sample preparation is a key challenge in point-of-care diagnostics due to the complex nature of raw biological samples Paramagnetic particles (PMPs) have shown great promise to assist in this regard[1, 2]: (1) targets can be specifically captured on the PMPs; (2) PMPs can be manipulated using external magnetic fields independent of the sample chemistry, (3) the use of PMPs enables stationary microfluidics, which greatly simplifies the external system needed to operate the lab-on-a-chip system A central requirement for such a sample extraction system is to have a minimal carry-over of the input volume that often contains components interfering with downstream processing, since this will reduce the need for washing steps

We present an injection moulded, ultrasonic welded cyclic olefin copolymer (COC) chip system capable of extracting PMPs from a 200 μL input volume to a 100 μL outlet with minimal carry-over The extraction process is facilitated by two passive capillary microvalves and an immiscible phase (FC-40 oil) Fig 1a shows an overview of the chip layout The volume carry-over was investigated by adding a dye solution and 5-140 μg PMPs (MyOne DynaBeads, Life Technologies) to the inlet and Milli-Q water to the outlet The PMPs were then transferred from inlet to outlet using an external permanent magnet fitted in a motorised stage operated at 1 mm/s See Fig 1b for a photograph of an experiment The PMPs were removed and the carry-over volume was estimated by correlating the fluorescence of the outlet to the inlet via a standard curve

The average carry-over volume was found to be 0 0035(6) μL/(μg PMPs) (Fig 1c), corresponding to a PMP volume fraction of 14 % Below 10 μg of PMPs, the bead cluster could not penetrate the interphase (green region), above 100 μg of PMPs the system was not able to consistently transport all beads resulting in a larger SD (light blue region) and above 120 μg of PMPs liquid bridging occurred (dark blue region), effectively setting the lower and upper compatibility limit of the system

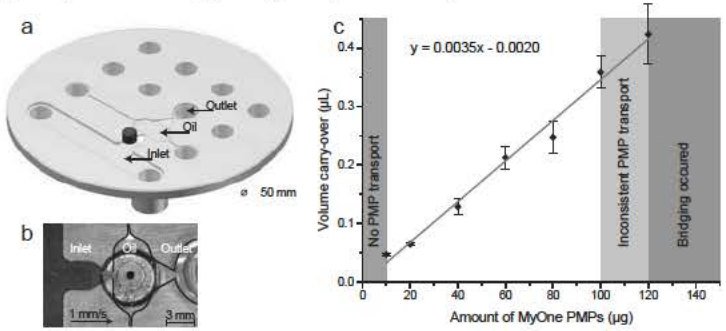

Figure 1 (a) 3D illustration of the chip system consisting of an injection moulded base with a thin COC sheet bonded on top The red cylinder represents the magnet used to actuate the PMPs The channel cross-section at the capillary valve is width×height = 500×150 mm^2 **(b)** Photograph of the carry-over process, where the PMPs have been left in the middle of the oil channel with the permanent magnet situated below **(c)** Average carry-over volume (n=3) vs amount of MyOne PMPs The red line is a linear fit (R^2 = 0 99)

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Magnetic particle mixing with magnetic micro-convection for microfluidics

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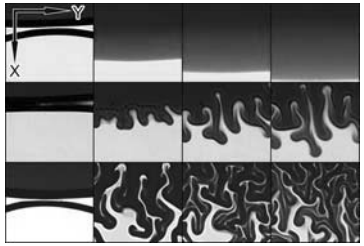

Figure 1: Mixing of ferrofluid and water. Rows from top: no field, $B = 6.9$ mT and $B = 13.8$ mT. Columns from left: times $t = 0.0$ s, 0.5 s, 1.0 s and 1.5 s. Field of view for images is 0.55x0.50 mm.

Mixing continuously remains a vital problem in microfluidics due to the small Reynolds number for the flows in microchannels. Researchers try to enhance the diffusion dominated mixing by various methods that include advanced design of channel systems, creation of complex structures or moving parts in the channels, acoustic waves, etc. Here we propose to use magnetic micro-convection phenomenon [1,2] for mixing enhancement in cases when one of the mixable fluids is a magnetic particle suspension.

Applying an external magnetic field that is perpendicular to the observation plane, a finger like instability is formed (see Fig.1) on the interface of water and magnetic particle suspension (water based ferrofluid) in a Hele-Shaw cell of thickness $h = 120$ μm. We show that the development of fingers increases mixing speed, as visible from average concentration development for X-axis (see Fig.2), that is calculated from concentration fields, averaging over Y-axis. For a magnetic field of $B = 13.8$ mT we find that our system is 50% mixed (as defined in [3]) over $L = 0.5$ mm in less than $t = 1.5$ s.

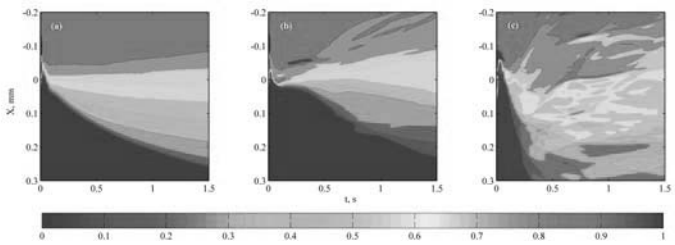

Figure 2: Evolution of the normalized average ferrofluid concentration ($c_{max} = 1$) over time t in the mixing direction X for (a) no field, (b) B=6.9mT, (c) B=13.8mT.

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Iron Oxide Nanoparticles for Radiation Therapy

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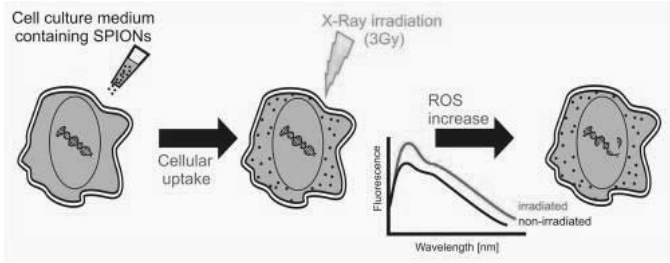
Radia ion herapy often combined with surgery and/or chemo herapy is applied to more than 50 % of pa ients at some point of their treatment. The cytotoxic effects of ionizing radiation occur from their ability to produce DNA double-strand breaks hrough formation of free radicals within cells. However, the curative potential of radiotherapy is often limited by intrinsic radioresistance of cancer cells and normal tissue toxicity. To overcome this resistance and enhance the effectiveness of ionizing radiation, radiosensitizers are used in combination with radio herapy. In our studies we used carboxylic acid terminated and uncoated superparamagnetic iron oxide nanoparticles (SPION) to increase the formation of reactive oxygen species (ROS) in cells. [1]

SPION with a mixed phase composition (γ-$Fe_2O_3)_{1-x}(Fe_3O_4)_x$ and sizes between 9 and 20 nm were syn hesized via co-precipitation and either left uncoated or were subsequently surface-stabilized with citrate or malate anions. The sizes, morphology, surface chemistry, and magnetic properties of the nanoparticles were characterized using TEM, FTIR spectroscopy, and superconduc ing quantum interference device (SQUID) measurements, respectively. While the cellular uptake of the nanoparticles was verified by TEM, their biocompa ibility was examined by MTT assay and trypan blue staining. The cells were irradiated with a single dose of 1-3 Gy using a 120 kV X-Ray tube. X-ray induced changes of the oxidation state and site geometries of surface iron ions of uncoated and citrate-coated SPION were explored by collecting Fe K-edge XANES and EXAFS data. After X-ray irradiation, the intracellular ROS formation was investigated by measuring the fluorescence increase of the DCF dye, the ratio of gluta hione to glutathione disulfide, and the concentration of malondialdehyde being a product of the lipid peroxidation.

SPIONs enter the cells via endocytosis, whereas the main part of the uncoated SPIONs remain in the vesicles. The organic coatings of the citrate and malate SPIONs facilitate their release in he cytoplasm. Iron ions can participate in the Fenton and Haber-Weiss chemistry and thus, may catalyze the ROS formation in he cytoplasm. Cells loaded with citrate coated SPIONs show no higher ROS concentration than in media-cultured cells. However, after irradiation the ROS formation is observed to increase drastically. This enhancing effect is explained wi h the impact of X-rays onto the SPION surface, which is due to the destruction of surface structures. The freed SPION surface, now containing easier accessible iron ions, should act as a more efficient catalyst for ROS production than he completely coated surface. [2-3]



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Domain Nucleation Array and its Interaction with Magnetic Nanoparticles

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We propose, implement and investigate a Domain Nucleation Array (DNA) for biomedical sensing to meet several criteria with regard to interaction with Magnetic Nanoparticles (MNPs). First of all, the MNPs sensor should cover a large surface area to match the capability of fluid dispensing systems for chemical activation of the sensor surface in order to immobilize the MNPs. The challenge with meeting this criterion is that calculations clearly show that sensitivity to MNPs is reduced to zero for an infinite plane of single-domain magnetic thin film. One way to overcome this challenge is to break the magnetic structure into domains. Another important criterion for MNPs interaction is for a small change to influence a large result. With domain nucleation and depinning processes, we do have a system that starts small and grows large.

Fabrication steps are illustrated in Figure 1. The geometry of the array cell is based on previous work regarding domain wall depinning in the presence of MNPs, and so we hypothesize that the depinning field of the array will depend on the presence of MNPs. Initial data shown in Figure 2 supports this hypothesis. Further experimentation and analysis will allow optimization of the system in terms of array cell features and spacing.

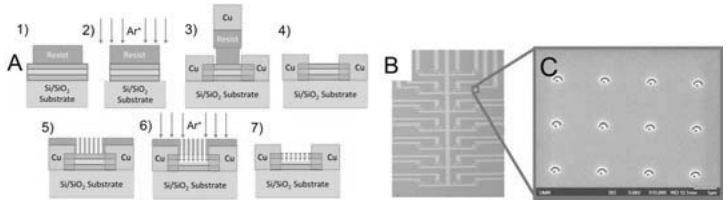

Figure 1 A) Fabrication Steps 1 - Photolithography, positive resist; 2 - Ion milling, resist removal; 3 - Photo-lithography, positive bi-layer resist; 4 - Lift off deposited Cu to create electrodes; 5 - E-beam lithography, positive resist; 6 - Ion milling, resist removal 7 - Result B) Optical image of sensors after fabrication step 4. C) Scanning Electron Microscopy image of small portion of GMR element after fabrication step 5.

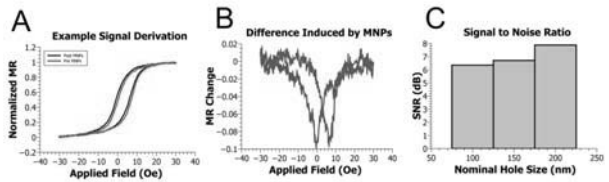

Figure 2 A) Comparison of GMR curves before and after the application of MNPs. MNPs Ocean Nanotech, 35 nm Fe3O4 + Protein-G in DI water, diluted to 100 ng/mL Fe ion concentration. B) Difference between Post-MNPs curve and Pre-MNPs curve. C) Average signal to noise ratio versus feature size

Numerical simulation of different dipole-dipole-interaction models and their influence on Temperature Dependent Magnetorelaxometry

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Magnetic nanoparticles (MNP) are employed in a broad variety of biomedical applications like imaging, drug targeting or hyperthermia. These in-vivo applications crucially depend on information about the magnetic characteristics of the MNP. We used temperature dependent Magnetorelaxometry (TMRX) to investigate the magnetic relaxation behavior of small iron oxide MNP. To this end, MRX measurements at various fixed temperatures (10 K to 300 K) were performed with a conventional SQUID magnetometer (MPMS-XL, Quantum Design). In TMRX the variation of the relaxation amplitude (magnetic moment of the sample) within a defined time interval is displayed over temperature. TMRX measurements turned out to be very sensitive to particle size distribution, quantity and particle aggregation. In order to investigate the influence of the particle interaction on the relaxation behavior we simulated MRX signals of Feraheme® at low temperatures and compared the simulations with measured TMRX data. The sample was immobilized by freeze drying prior to TMRX measurement. Modeling the TMRX spectra taking into account size parameters (d_V = 7.2 nm, σ_d = 0.3) obtained from M(H)-measurements was not sufficient to describe the measurement results adequately. It became apparent, that the Néel relaxation formula for single non-interacting particles alone was not sufficient to describe the measured data, as the calculated blocking temperatures were too low. We therefore included the dipole-dipole-interaction, because the competing component of which slows down the magnetic dynamics like in spin glasses. For the anisotropy we used a value of K = 10000 J/m³ typical for magnetite. With these we modeled TMRX curves implementing different approaches of dipole-dipole-interaction.

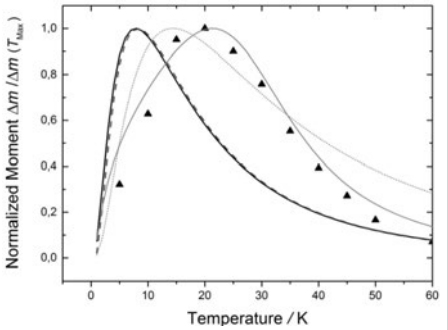

Figure 1 shows the measured TMRX curve of Feraheme® (symbols) together with the simulated curves for non-interacting particles (black line) and the different interaction approaches. The best description of the measured curve was obtained by the simulation, in which only same sized particles interact with each other (grey line). However, the small fitted average distance with 1.07 nm is not realistic. Another approach in which the a distribution of different magnetic moments interact with one another lead to a more realistic distance of 6.93 nm (dotted line). However, this also leads to a broadened curve shape, which would need a smaller variance σ_d to fit the measured curve. Other simulations, in which the interaction energy is calculated from the mean magnetic moment of the particle distribution turned out to be too weak to influence the blocking temperature significantly even for small particle distances < 0.1 nm (dashed line).

With its extension to lower temperatures TMRX allows for a detailed investigation of the magnetic behavior of MNP with which it is possible to simulate and compare different approaches of dipole-dipole-interaction.

Hybrid silica coated magnetic nanoparticles decorated with gold

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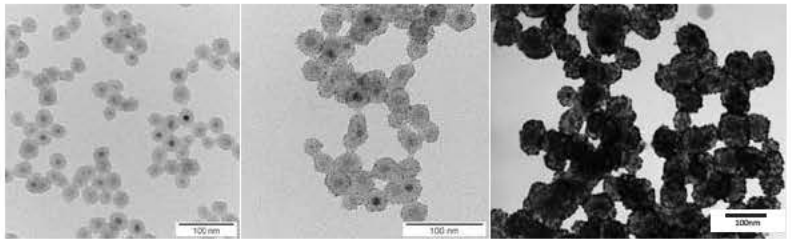
Development of complex magnetic nanoparticles with well defined properties is an important issue of the current theranostics. In these particles the core provides magnetic properties relevant for a particular application while the shell forms a stable barrier and enables further functionalization of the particles modifying their optical and surface properties. The present contribution describes several new types of magnetic nanoparticles decorated with gold and suggests their possible applications.

The ferrite nanoparticles of a general composition $Co_yZn_xFe_{3-y-x}O_4$ and manganite cores based on $La_{1-x}Sr_xMnO_3$ phases were prepared. The former were synthesised either by the thermal decomposition or by coprecipitation while the latter were obtained by the citrate method. The resulting particles were encapsulated into hybrid silica shell containing amino groups and the shell was further decorated with gold nanostructures using two step *seed and growth* procedure.

The chemical composition of the magnetic cores was determined by XRF and the mean size of crystallites $d_{XRD} \approx 15$ - 30 nm was evaluated by XRD. TEM studies revealed that the manganite particles and the coprecipitated ferrites are rather clusters of several crystallites than single-crystal particles in contrast to the products of the thermal decomposition. The processes of seeding and gold reduction were investigated by both UV/Vis absorption spectroscopy and TEM. The final products were characterised by DLS measurements and their static magnetic properties were probed by SQUID magnetometry. Finally, relaxometric studies focusing the transverse T_2 relaxivity were performed in the magnetic field of 0.5 T.

The support by the Ministry of Industry and Trade through the grant FR-TI3/521 and by the Grant Agency of the Czech Republic through the project P108/11/0807 is gratefully acknowledged.



Examples of silica coated magnetic nanoparticles TEM images before and after gold deposition. The scale bars are 100 nm.

NMR Relaxivity Studies on Surfactant-free Superparamagnetic Iron Oxide Nanoparticles: the Effect of Particle Size, Magnetization and an Iron Oxidation State

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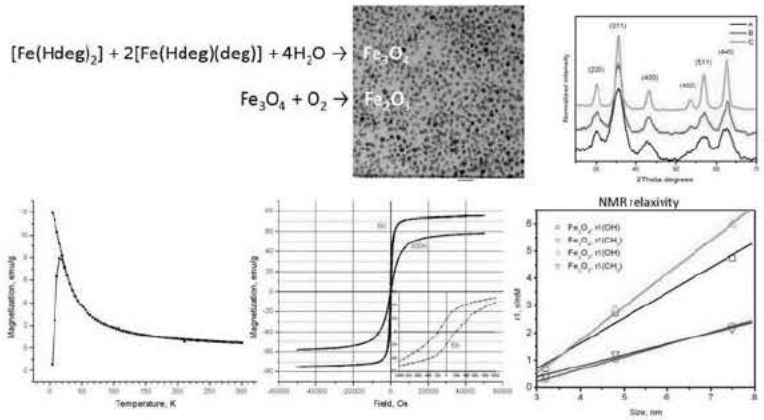
Searching for a novel material to be used as positive-image MRI contrast agent, alternative to gadolinium chelates, was a primary motivation of this work. Magnetite nanoparticles in the size range of 3.2-7 5 nm were synthesized with high yields under variable reaction conditions using high temperature hydrolysis of the precursor iron(II) and iron(III) alkoxides in surfactant-free diethylene glycol solutions. The average sizes of the particles were adjusted by changing the reaction temperature and time, and by using sequential growth technique. In order to obtain γ-iron(III) oxide particles in the same range of sizes, diethylene glycol colloids of magnetite were oxygenated at room temperature. As-obtained colloids were characterized by DLS and NMR; powdery products obtained by coagulating the same colloids with oleic acid, were characterized by TEM, XRD, TGA, FTIR and magnetic measurements. NMR r_1 and r_2 relaxivity measurements in diethylene glycol (for OH and CH_2-protons) and in water, have shown the decrease in r_2/r_1 ratio with the particle size reduction, which correlate with the results of magnetic measurements on magnetite nanoparticles. Saturation magnetization of the oxidized particles was found to be 20% lower than that for Fe_3O_4 with the same particle size, but their r_1 relaxivities are similar. Since oxidation of magnetite is spontaneous under ambient conditions, it was important to learn that the oxidation product has no disadvantages as compared to its precursor, and therefore it may be a better imaging agent due to its chemical stability.



Condensed Colloidal Magnetite Nanocrystal Clusters for Theranostic Applications

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Among the contemporary strategies for targeted therapy and diagnosis is the development of colloidal magnetic nanoassemblies [1] Herein, we report the synthesis and characterization of a unique magnetic colloidal superstructure based on condensed magnetite nanocrystal clusters (co-MNCs), as shown in Figure 1a,c, as well as their efficient in vivo imaging using nuclear medicine techniques Clustering of magnetic nanoparticles has received particular interest due to the enhancement in various properties that can induce,[2] including the r_2 relaxation in magnetic resonance imaging (MRI), in comparison to other types of magnetite colloids, such as clusters of bridging configuration (Figure 1b,d) [3] The development of co-MNCs requires solvothermal conditions and/or high temperatures [2] In this report, such systems were synthesized through one-step soft chemical route at 50 ^{o}C and ambient pressure in presence of alginate The product displays excellent attributes with regard to **i)** magnetic manipulation, **ii)** saturation magnetization, **iii)** negative contrast enhancement in MRI (250 $mM^{-1}_{Fe}\ s^{-1}$) and **iv)** loading of the anticancer drug doxorubicin as well as of radioactive tracers (Figure 1e,f) [4] Particularly, regarding the magnetic manipulation, it was found, via magnetophoretic studies, that condensed clustering imparts enhanced response, as compared to other magnetic colloids, even though saturation magnetization and hydrodynamic radii are identical Results will be also presented manifesting the effective PEGylation of the system through two alternative pathways: covalent conjugation and self-assembly (Figure 1g)

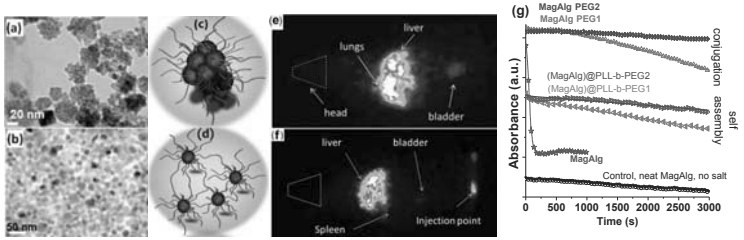

Figure 1. TEM images of (a) condensed and (b) bridging motif of magnetite colloids (c,d) schematic representation of the respective super-structures (e,f) Biodistribution results after radiolabeling of the colloids, using in vivo SPECT imaging (g) Salt-stability assays of PEGylated products and control samples performed with turbidimetry

1 O Veiseh, J W Gunn and M Zhang, *Adv. Drug Deliv. Rev* , 2010, **62**, 284
2 Z Lu and Y Yin, *Chem. Soc. Rev.*, 2012, **41**, 687
3 A Bakandritsos, A Papagiannopoulos, E N Anagnostou, K Avgoustakis, R Zboril, S Pispas, J Tucek, V Ryukhtin, N Bouropoulos, A Kolokithas, T A Steriotis, U Keiderling and F Winnefeld, *Small*, 2012, **8**, 2381
4 G Zoppellaro, A Kolokithas-Ntoukas, K Polakova, J Tucek, R Zboril, G Loudos, E Fragogeorgi, C Diwoky, K Tomankova, C Avgoustakis, D Kouzoudis, A Bakandritsos, *Chem. Mater*. 10 1021/cm404053v, (2014)

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Design and Evaluation of Epitaxially Condensed Colloidal Nanocrystal Clusters with Superior Magnetic Properties for Biomedical Applications

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Condensed clustering of magnetic nanoparticles is becoming an increasingly hot topic in the field of theranostics and biomedical applications [1] Their unique architecture, with densely packed magnetic iron oxides, can lead to enhanced magnetic properties and therefore favour their use for a plethora of biomedical applications, such as MR Imaging and manipulation by magnetic fields Their superior magnetic properties, gives them a significant advantage compared to similar soft clustered (loosely packed) systems Herein, we report the synthesis of condensed-clustered magnetic nanoassemblies through a one-step soft biomineralization route at 50 ^{0}C and ambient pressure in the presence of alginate as the polymeric corona The magnetic NCs were evaluated for their ability to generate heat through Alternating Magnetic Fields (AMF) for hyperthermia and as bimodal contrast agents for MRI and SPECT applications Furthermore MagAlg was evaluated for its potential use as a drug delivery system Its interactions with the anticancer agent doxorubicin were studied, as well as its ability for remote triggered release under AMF However, the system lacks of stability upon drug loading and dispersion in blood isotonic media In order to overcome this drawback the installation of a second polymeric canopy of poly(ethylene glycol) (PEG) was attempted through a layer-by-layer self assembly process with the use of two different PEGylated copolymers, a poly(quaternary ammonium)-block-PEG copolymer [2] and PEGylated polylysine block copolymer The characterization and evaluation of the PEGylated product was performed with static and dynamic light scattering and by salt stability assays through turbidimetry [3]

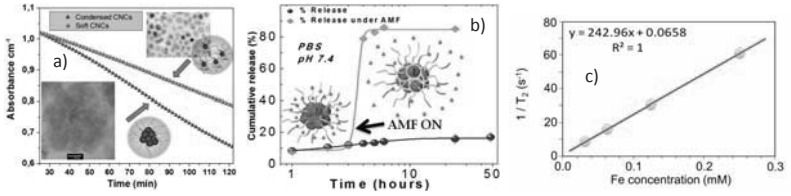

Figure 1. a) Magnetophoretic response of magnetic nanoassemblies based on condensed and soft clustered MIONs under low gradient magnetic field **b)** Drug release profiles of MagAlg with and without the presence of AC magnetic field (400kHz, 50 kA/m) **c)** Transverse relaxation rate of MagAlg NCs, along with the linear regression fit

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Anti-tumor Activity of Hemin Immobilized on Magnetic Microparticles

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In literary data hemin has been found to show a cytotoxic action on tumour cells which is probably due to its oxidation properties. Earlier we showed a dose-dependent oxidant action of hemin on the speed of limonene oxidation. Hence it is worthwhile to study anti-tumor activity of hemin immobilized on magnetic microparticles in Lyiss carcinoma in mice.

We have carried out hemin immobilization on nano-structured microparticles of FeC composite of content: 44%Fe, 56%C, metallic iron of content: 90% restored iron and 10% Fe_3O_4 synthesized by plasmochemical method. Hemin immobilization was carried out by physical adsorption as well as by conjugation with gelatin or dextran after modification of the particles surface. The powders of ferromagnetics were treated (suspension in distillate water) by ultrasonic waves in order to eliminate aggregation and to attain a homogenous distribution of the particles in suspension. The particles' surface was covered by gelatin, or dextran. Carboxilate-magnetic particles were obtained by gelatin coating with the following aldehydes modification, aldehyde-magnetic particles - dextran coating with $NaJO_4$ activation. The sorption capacity of FeC composite, FeC modified by gelatin, Fe modified by dextran to hemin was: 127.0 mg/g, 117.5 mg/g and 63.0` mg/g, respectively.

We have taken 20-22-g mice of F1(C57xDBl). A 10^9 cells/mouse Lyiss carcinoma suspension was injected into a hip muscle. The mammals were divided into 6 groups. Hemin (0.2 ml) was injected to mice intratumorally: 1 and 2 groups – a solution of hemin in the 50 mkM and 100 mkM concentrations, respectively, 3 and 4 groups – a suspension of hemin immobilized on FeC microparticles in the same concentrations. After the injection of the particles suspension we put Sm-Co magnet (induction of 0.15 Tl) to the tumor for 3 min. Groups 5 and 6 were control. We have discovered reduction of tumor size in experimental groups of mice in comparison with the control groups and an increase in the survival of mice of groups 3 and 4.

The results suggest prospects for further research of anti-tumor activity of hemin immobilized on magnetic microparticles.

Possibility of Using a New Magnetic Carbon Sorbent as Doxorubicin Carrier

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A new magnetic carbon sorbent (FeCnew) was obtained by a technology based on pulse (fast) pyrolysis of sawdust treated by a ferrooxalate solution in the laboratory plant of I. B. Samoilov[1]. Possibility of using it for ecological purposes has been shown[2].

The work gives data on the sorbent's microstructure obtained with the help of optical microscope and scanner electron microscope, which allow to conclude that FeCnew sorbent is a ferromagnetic carbon nanocomposite.

Investigations of the laboratory sample FeCnew absorptive capacity to doxorubicin (DR) and dynamics of its desorption and the same for FeC composite of content: 44%Fe, 56%C, metallic iron of content: 90% restored iron and 10% Fe_3O_4, obtained by a plasmochemical method[3] were carried out. The powders of ferromagnetics were treated (suspension in distillate water) by ultrasonic waves (frequency 22 kHz) in order to eliminate aggregation and to attain a homogenous distribution of the particles in suspension. The surface microparticles of FeC composite was modified by gelatin. The absorptive capacity of magnetic microparticles to DR in was studied a physiological solution by evaluating optical density of a supernatant at 480 nm after incubation with DR. The absorptive capacity of magnetic particles to DR was: 60 mg/g, 43 mg/g, 41 mg/g and 34 mg/g for FeC, FeCnew, FeC modified by gelatin, and metallic Fe, respectively. The dynamics of the immobilized DR desorption was carried out by incubation of magnetic preparations with fresh aliquots of 0.6% albumin in physiological solution at 37^0C (pH 7.4) following registration of the supernatant absorption visible spectra and evaluation of DR concentration on the calibri curve. A total meaning of DR desorption from FeCnew after the four-hour incubation was 67% and after that a release of DR markedly decreased and the curve of desorption reached the plato. It was established that the modification of FeC composite surface by gelatin led to reduction of DR release in 3.5 times.

Thus, FeCnew as well as FeC composite obtained by plasmochemical method[3] are perspective as carriers for a magnetically-guided targeted delivery of DR.

References

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2. Application for invention No 2013119975 from 30.04.2013

3. Russian patent No 210952. 1996

Magnetic Fluids Optimization for Contrast Enhancement in Magnetic Resonance Imaging

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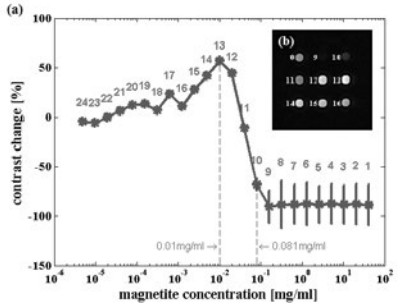
To meet biomedical requirements magnetic fluids (MF) have to fulfil the following criteria: (i) superparamagnetic properties, (ii) invisibility to RES, (iii) ability to load drugs, and (iv) ability to conjugate to a targeting ligand or antibody

With the above intention, we have been developing a magnetic fluid that contains a magnetite core coated by sodium oleate (SO) to prevent aggregation of magnetite nanoparticles (MNPs) We have optimized the various formulation parameters and the complex physicochemical characterization of the prepared MF has been accomplished by the routine methods Magnetic measurements proved that the MNPs are superparamagnetic in nature Magnetic core diameter 10 nm was calculated from the magnetization curve, and hydrodynamic diameter 61 nm was obtained from dynamic light scattering (DLS) measurement The FTIR spectra showed that SO molecules were linked to MNPs through chemical bonds Magnetite concentration in prepared MF was 76 mg per ml MF was diluted several times with the aim to prepare concentration gradient of magnetite nanoparticles and to find out the most suitable concentration range for the most optimal contrast enhancement in MRI A number of MRI protocols were tested with the help of clinical MRI system ESAOTE E-Scan Opera XQ 0 178 T



Relative change of contrast (intensity) of MF with different magnetite concentration relative to intensity of reference sample (0)

We have found that the T_2-weighted Spin Echo (SE), with repetition time TR = 1500 ms, and echo time TE = 50 ms, is the most appropriate MRI sequence for tested MF The most visible contrast change was observed for concentration range 10-81μg/ml, which determines the usefulness of MF in practical applications (see figure) In addition, through the incorporation of specific targeting ligand, the efficiency of the MF as MR imaging contrast agent and as carriers for drug delivery will greatly increase

Acknowledgments
This work was supported within the projects No 26110230097 in frame of Structural Funds of European Union, VEGA 0041, 0045 and APVV-0742-10 and APVV-0431-12

Destroying activity of magnetoferritin on lysozyme amyloid fibrils

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In the human body the protein amyloid aggregates, due to their deposition in specific tissues or organs, cause many serious diseases (diabetes mellitus, Alzheimer's disease, etc.). Recently, we have found that magnetite nanoparticles have ability to affect amyloid aggregates of lysozyme and insulin [1, 2]. In our study we examine effect of magnetoferritin (MFer), biocompatible magnetite nanoparticles, on lysozyme amyloid aggregates (LAA) associated with lysozyme systemic amyloidosis. The interference of LAA and MFer was investigated at ratios of LAA:MFer = 1:1 and 1:5 using small angle X-rays scattering technique (SAXS) and Tioflavin T fluorescence measurements (ThT assay). By controlled chemical synthesis magnetoferritin complexes with two loading factors (LF - number of iron atoms per one complex) of 168 (MFer(168)) and 532 (MFer(532)) were prepared. SAXS experiments indicate that presence of MFer caused structural changes of LAAs. Analysis of data obtained for solution containing LAA with MFer(532) (LAA:MFer = 1:5) clearly indicate decreasing of the lower limit of radius of gyration from 30 nm to 20 nm compare to lysozyme fibrils alone and almost non-effected structure of MFer complexes (Fig. 1). These results suggest reduction of LAA, probably due to the truncation of the LAA by MFer. The decreasing of the amount of LAA was observed also by ThT assay. The fluorescence intensities of LAA in presence of MFer(532) and MFer(168) was significantly decreased - 40% and 55% decay (ratio 1:1) and 50% and 62% decay (ratio 1:5). These data strongly support SAXS data assuming reduction of the LAA as results of their interaction with MFer.

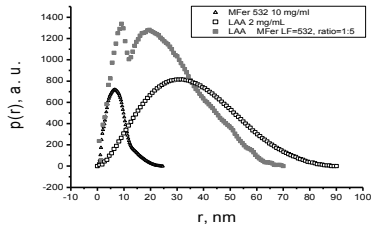

Fig. 1 Pair distance distribution functions of MFer, LAAs and mix LAA+MFer in ratio 1:5

[1] Andrea Bellova, et al. Nanotechnology 21 (2010) 065103 (6pp)
[2] Katarina Siposova, et al. Nanotechnology 23 (2012) 055101 (10pp)

Acknowledgements

This work was supported within the project PHYSNET, VEGA 0041, 045, 0181 and APVV 0171-10.

Magnetooptical Investigation of Ferritin Iron Uptake and Release

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Ferritin, iron storage protein of living organisms, consisting of apoferritin hollow cage and ferrihydrite-like mineral core, is capable accommodating up to 4500 iron atoms. Understanding the management of iron *in vivo*, especially incorporation and release mechanisms, is of great importance in the study of many diseases especially neurodegenerative disorder. Ferritin iron core composition significantly differs between physiological and pathological ferritins. Magnetooptical investigation of ferritins *in vitro* is suitable method for qualitatively and quantitatively to distinguish various magnetic core structures [1].

Our work presents experimental studies of magnetooptical properties of reconstructed and reduced horse spleen ferritin (HSF) core treated by chemical process. Iron release from ferritin was done by partial core reduction of HSF followed by iron(II) chelation. The iron uptake was realized using the apoferritin shell, oxidant and iron(II) source in anaerobic conditions. Magnetically induced optical birefringence (Δn) was measured at room temperature for ferritin aqueous suspensions and their mimetics. Light beam from a He-Ne laser (632.8 nm) was used.

It was shown that magnetic birefringence and Cotton-Mouton constant of studied compounds provides evidence that the ferritin core behaves as a non-Euclidian solids and uptake and release process is not symmetrical (Fig. 1). Our observation corroborate very recent model [2] of geometrical core structure proposed for ferritin when iron release.

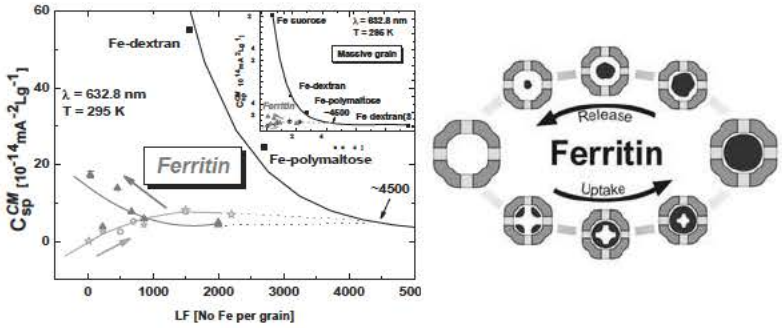

Fig. 1 Specific Cotton-Mouton constant versus the number of Fe atoms per grain and the model of geometrical structure of ferritin core during iron uptake and release.

[1] M. Koralewski et al. Nanotechnology **23**, 355704 (2012)
[2] G. Ciasca et al. Appl. Phys. Lett. **100**, 073703(2012)

The work was supported by the project in the frame of SF EU No. 26110230097, APVV 0171 10, Vega 0045

Computational analysis of Magnetic Field Induced Deposition of Magnetic Particles in Lung Alveolus in Comparison to Deposition Produced with Viscous Drag and Gravitational Force

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Lung diseases are some of the most common medical conditions worldwide. Relatively large diameters of airways in each generation of pulmonary acinus together with mucociliary clearance permit using relatively large carriers for lung treating. Recently, it was pointed on using magnetic particles and gradient magnetic fields to targeting in mice's lungs [1]. We have therefore aimed on investigation of it's dynamics on alveolar level.

We have modeled alveolus in single alveolus configuration represented as hemispherical cavity attached at rim to a flat plane and in rhythmical self-similar expansion and contraction. Spherical particles with non-zero magnetic moment have been exerted to Stokesian viscous drag flow field due to expansion flow and shear flow (their superposition), with added influence of gravitational and gradient magnetic field. Expansion flow induced by the self-similar expansion and contraction of the alveolus with zero downstream flow inside the adjacent airway was obtained analytically [2]. Shear flow over a hemispherical rigid cavity with vanishing velocity at the boundaries was evaluated numerically [3]. As a source of gradient magnetic field we have used cylindrical Halbach array (octapolar magnet) [4] modeled numerically by finite element method. Trajectories of particles have been calculated numerically for each particle as single particle problem solving Newton dynamical equation as a system of ordinary differential equations in MATLAB.

We have simulated in 3D motion of spherical particles of magnetite with 1 μm in diameter, as well as water aerosol droplets (3.5 μm in diameter) with content of superparamagnetic iron-oxide nanoparticles (SPIONs; with same properties as in [1]). We have concluded that the magnetic force can overcome both, aerodynamic viscous drag force in alveolus and gravitational force, even in the case of aerosol droplets with SPIONs (see Figure 1) when the whole magnetic moment of droplet is reduced in comparison with magnetite spheres.

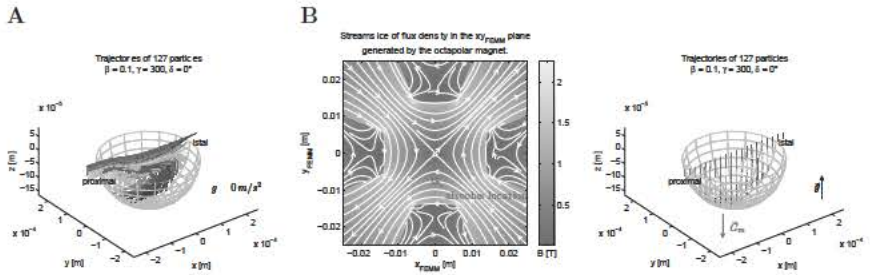

Figure 1: Trajectories of the aerosol droplets with SPIONs during 20 breathing periods (beginning with expiration) in alveolus in the 21st airway generation under the influence of (**A**) the viscous drag force (only), and (**B**) the viscous drag, gravitational and magnetic (gradient $G_M \approx 100$ T/m; octapolar magnet as magnetic field source) forces (all particles have been captured with alveolus wall in the first breathing period). Particles are distinguished with different colors.

Acknowledgement: To Grant Agency of the Slovak Academy of Sciences (VEGA 2/0013/14 and 1/0871/14), and CVTI MATLAB cluster Slovakia.

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[3] C. Pozrikidis. *Physics of Fluids*, 6:68–79, 1994.
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Magnetic Assembly of Superparamagnetic Nanoparticle Clusters into Peapod-like Structures

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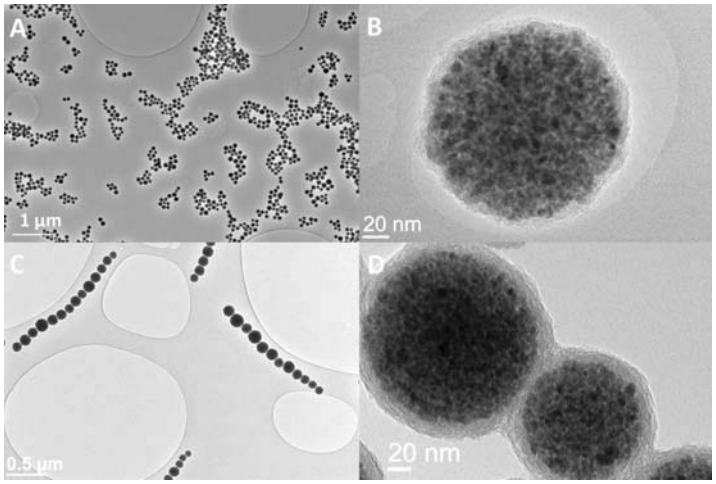
Being cost-effective, colloidal assembly has been widely studied for the preparation of one-dimensional nanostructures such as nanorods, nanotubes, and nanowires which have attracted special attention owing to their unique properties and potential applications in the fabrication of functional devices.

We have developed a flexible approach for the preparation of individually fixed peapod-like nanoparticle cluster structures by combining magnetic assembly with sol-gel processes. The superparamagnetic maghemite clusters were first coated with a thin silica shell (Figs. A and B), then assembled into peapod-like structures by applying a magnetic field, and these structures were then additionally coated with a thin layer of silica to fix the peapod-like structure (Figs. C and D). Varying the exposure to magnetic field and the initial silica coating thickness we could fine-tune the interparticle spacing and the length of the peapod-like structures.



Colloidal Stability of Silica-Encapsulated Ni Nanorods in Moderate Electrolytes and their Biocompatibility to Human Brain Microvascular Endothelial Cells

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Ni nanorods with $\langle L \rangle = 250\,\text{nm}$ and $\langle D \rangle = 22\,\text{nm}$ were synthesized by the AAO-template method. These nanorods are ferromagnetic single domain particles and exhibit distinct optical anisotropy. Alignment of the rods in external magnetic fields can be detected by magnetization and optical transmission measurements. Analysis of the rotation dynamics allows to extract information regarding viscoelastic properties of the surrounding matrix and hydrodynamic parameters of the nanorods [1]. Colloidal stability of the nanorods is achieved by steric stabilization using a 4 nm polyvinylpyrrolidone (PVP) layer but relies mainly on electrostatic repulsion at pH $\leq$ 6 in water of low ionic strength to counteract long range dipolar attractive forces. At physiological ionic strength, the electrostatic repulsion is lost and the steric repulsion of the PVP layer is insufficient to obtain stable dispersions. In order to increase the range of steric repulsion, the rods were coated with a 50 nm inorganic silica shell (Fig. 1). We determined the fraction of non-agglomerated particles at pH $\approx$ 6-7 for different NaCl concentrations (up to 0.1M) as a function of time by static magneto-optical transmission measurements (Fig. 2). 2h after salt addition, 50 % of the initally present individual nanorods were still not agglomerated. This stability in nearly physiological salt concentrations provides a time frame to perform experiments in biological systems.
For characterization of the rods' biocompatibility towards the highly-sensitive human blood-brain barrier, different cell viability tests were performed. As an appropriate *in vitro* cell model human brain microvascular endothelial cells (HBMEC) were incubated with the Ni nanorods. Corresponding to recent studies [2], cell viability was investigated using both luminescence-based CellTiter-Glo (Promega) and fluorescence-based PrestoBlue (Invitrogen) assays. The assay readouts reveal that silica-coated rods do not diminish cell viability even after 24h of incubation (Fig. 3). Taken together, these experiments highlight the enormous potential of such stable silica-coated nanorods for their application in biological systems.

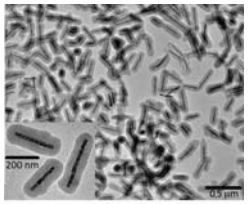

Figure 1: Transmission electron micrograph of silica coated nanorods.

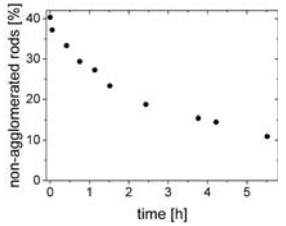

Figure 2: Time dependence of the fraction of non-agglomerated rods in a 0.1M NaCl solution.

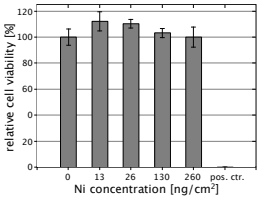

Figure 3: CellTiter Glo assay of HBMEC after 24h incubation with silica-coated nickel nanorods.

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Preparation, stability and biocompatibility of magnetic fluid modified by poly(ethylene glycol)

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Water-based magnetic fluids (MFs) have found application in a variety of fields in biotechnology and medicine The coating of the nanoparticles is one of the most important factors responsible for their compatibility in the organism For our purpose poly(ethylene glycol) (PEG) was chosen because it is non-immunogenic, non-toxic, non-antigenic, biocompatible and soluble in water and organic solvents

We have studied the magnetic fluid consisting of magnetite nanoparticles (Fe_3O_4) stabilized by sodium oleate and modified by PEG with the molecular weight 2 kDa (MFPEG) We have found that hydrodynamic diameter (measured by dynamic light scattering, DLS), zeta potential and isoelectric point depended on the amount of PEG used for MF functionalization These properties were studied in the range PEG/Fe_3O_4 from 0 05 to 20 (w/w) The ratio PEG/Fe_3O_4 up to 10 had no significant influence neither on the hydrodynamic diameter of magnetic particles nor their zeta potential Increase of PEG content above value 10 caused increasing of the hydrodynamic diameter and decreasing of the zeta potential absolute value Adsorbed amount of PEG on magnetic particle surface was determined by spectroscopic method SQUID measurements confirmed the superparamagnetic behaviour of the magnetic particles at room temperature Saturation magnetization of the MFPEGs was 0 9 Am^2/kg and prepared MFPEGs contained 15 mg Fe_3O_4 per 1 ml of MF Morphology of the coated magnetic particles in MFPEGs was studied by scanning electron microscopy (SEM) The surface was primarily smooth with a mean diameter ca 58 nm (Fig 1) Differential scanning calorimetry (DSC) for pure PEG, lyophilised MF (magnetic particles coated with sodium oleate), MFPEGs with different PEG to Fe_3O_4 ratios x and a physical mixture of PEG and MF was carried out (Fig 2) in order to verify the coating formation on the surface of magnetic particles

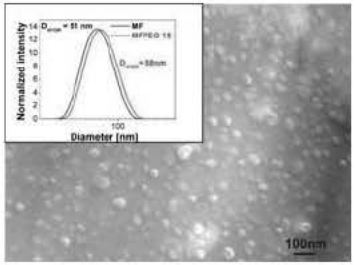

Figure 1: SEM image of MFPEG (Inset: DLS size distribution of MF and MFPEG15)

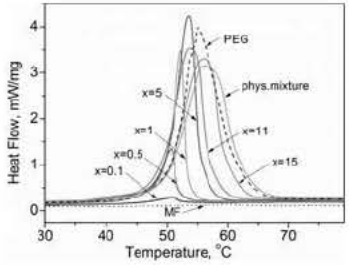

Figure 2: DSC thermograms of pure PEG, MF, MFPEGs with different PEG/Fe_3O_4 weight ratios x and a physical mixture of PEG and MF

Prepared modified magnetic particles with PEG have high absolute values of the zeta potential (ca -50 mV), suitable diameter and good colloidal stability Biocompatibility of the prepared samples was proven by measuring of fluorescence intensity using Texas red–labelled bovine serum albumin (BSA) and is critical for future in vivo applications

Acknowledgments: This work was supported by the projects No 26220120021, 26220220005 and 26110230097 in the frame of Structural Funds of European Union, by Slovak Academy of Sciences - VEGA 0041, 0045 and by Slovak Research and Development Agency – contracts No APVV-0742-10 and APVV-0171-10

Magnetic beads-based DNA extraction: different techniques compatible with PCR and microfluidic systems

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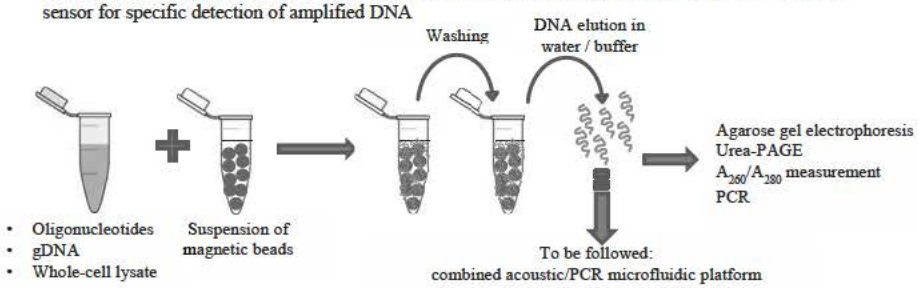
Different approaches for DNA extraction with the use of magnetic beads were investigated Due to the subsequent application, the main effort was made on the methodologies which are easily transferred to the microscale format and which are compatible with the PCR reaction Fast DNA adsorption and elution together with efficient extraction was also demanded Such approaches typically rely on solid-phase extraction (SPE) methods based on the "bind-wash-elute protocols" The most widely applied solid supports for SPE of DNA are silica based[1] Then, DNA adsorption on positively charged surfaces [(2)] or solid-phase reverse immobilization under the presence of PEG [(3)] is often used as well

In this study, magnetic particles with different terminal functional groups (silanol, carboxyl and amine) and with size between 1 and 3 μm served as a solid phase for the aforementioned SPE methods The DNA extraction efficiency from three types of materials differing in the complexity – 19 bases long oligonucleotide with Cy3 dye or gDNA of *Salmonella enterica* serotype Typhimurium pre-isolated or from whole-cell lysate – was monitored and compared Moreover, specific isolation through the hybridization between the oligonucleotides immobilized on the beads and complementary sequences of the isolated DNA was performed as well UV/VIS measurement, agarose electrophoresis, urea-PAGE and PCR were utilized for quantitative and qualitative evaluation of eluted DNA Extraction efficiency and elution volume were another important evaluation criteria It was confirmed that the suitability of the chosen method and particular protocol depends on the length of DNA to be isolated The advantages and disadvantages of all methods were discussed In future, the on-chip extraction is going to be transferred into microscale format with integrated micro-PCR module and sensor for specific detection of amplified DNA



General scheme of methods based on the principle of solid-phase extraction used in this study for bacterial DNA extraction and purification

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Quantifying the Motion of Magnetic Nanoparticles through Liver, Kidney and Brain Tissues

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We have developed a technique (Fig 1) for quantifying the motion of magnetic carriers through various tissue types under the influence of a magnetic field, in order to understand how carrier properties (size, coating, and agglomeration) affect passage through tissue types (e g liver, brain, and kidney)

We place fluorescent magnetic nano-particles above freshly excised tissue and then apply a known calibrated magnetic field gradient After a chosen time, the 3-dimensional distribution of the particles in the tissue is measured by automated 3-dimensional cryostat imaging [1] The degree of particle penetration into the tissue is then quantified by a standardized metric

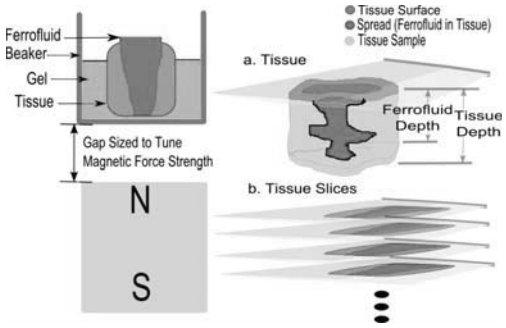

Fig. 1. (Left) Experimental setup: magnetic particles are pulled through tissue. (Right) Representative distribution of ferrofluid in tissue, with quantitation metrics labeled.

Experiments performed by pulling a known volume of ferrofluid with Chemicell particles of various sizes (100 nm, 300 nm, 500 nm and 1 μm) and with different coatings (chitosan [+34 mV zeta potential], lipid [-19 mV] and starch [-8 mV]) through rat liver, kidney and brain tissue, allowed us to measure which particles moved most or least effectively through which tissue types (Fig 2 table) We found that chitosan particles, with +34 mV zeta potential, moved better through the brain, liver and kidney than starch particles of all sizes (100 nm – 1 μm) Also, smaller chitosan particles moved more effectively than larger ones in brain and liver, most likely because tissue resistance increased faster with particle size than did magnetic forces However, once particle size exceeded 300 nm, the resulting larger magnetic forces did overcome tissue resistance for chitosan particles in kidney tissue In contrast, larger starch particles moved better than smaller ones in brain and kidney tissue; however, in the case of the liver, there seemed to be an increase in tissue resistance (as shown by a slight dip in penetration) above a 300 nm particle size Overall, the transport of particles in tissue is nuanced, and depends both on particles properties (size, coating) and tissue types

Particle Movement In Tissue (in mm after 45 minutes)									
BRAIN				LIVER			KIDNEY		
Zeta (mV)	34	-19	-8	34	-19	-8	34	-19	-8
Coating / Size	Chitosan	Lipid	Starch	Chitosan	Lipid	Starch	Chitosan	Lipid	Starch
100 nm	5.62***	3.7***	2.4***	5.28***	3.99***	2.86***	4.06***	3.54***	1.78***
300 nm	4.7**	5.08***	3.08**	4.28***	2.8***	3.97***	3.14***	5.1***	2.9***
500 nm	4.38***		3.36***	4.82***		3.4***	5.63**		4.86***
1 micron	4.68**			3.43***			6.06***		
	Relatively low	<2.5			High		4.5-5.25	*** mean from N 3	
	Moderate	2.5--3.5			Very High		>5.25	** mean from N 2	
	Relatively high	3.5--4.5			Unavailable				

Fig. 2. Tissue penetration after 45 minutes of pulling by a 0.4 Tesla magnet for various particle sizes (100 nm – 1 μm diameter), coating (chitosan, lipid and starch), and tissue types (rat brain, liver and kidney). Colors denote degree of penetration into the tissue, from red (low penetration) to green (high), as noted in the legend at the bottom.

In summary, we have validated an experimental method to measure the effectiveness of particle motion through different tissue types Based on preliminary data (table above), we found that particle size and coating parameters significantly influence particle motion, and that how they do so depends on the type of tissue they are traveling in We hope to collaborate with other magnetic targeting groups, to help quantify the motion of their carriers, so that optimal magnetic carriers (sizes, coatings, shapes) can be selected for future animal and human clinical trials

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Assessing Superparamagnetic Iron Oxide Nanoparticles with First Order Reversal Curves

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Superparamagnetic iron oxide nanoparticles (SPION) have attracted immense interest due to various technological applications that exploit their unique magnetic properties. Their monodispersibility with controlled size, stability, composition, magnetic properties and functionality are critical for any application. Often studies present the hysteresis properties that assess only the bulk magnetic behavior of the SPION. First order reversal curves (FORC), however, provide an efficient way to obtain a detailed magnetic characterization of SPION in terms of composition, domain state and particle interaction. Establishing FORC diagrams for a wide range of well-characterized SPION is essential in interpreting magnetic behavior; therefore, we present FORC diagrams for different SPION. The sample set comprises: a) magnetite formed by biomineralization processes, which includes whole-cell bacteria and isolated magnetosomes; b) chemically synthetized uncoated and multi-core coated magnetite nanoparticles; and c) mixtures of superparamagnetic (SP) and single domain (SD) magnetite particles, which in this case is SD magnetite represented by the bacteria containing magnetite in chains.

The study demonstrates that magnetite nanoparticles prepared by biomineralization process show lower degree of magnetic interaction. This can be attributed to the presence of lipid membrane that separates individual particles, which also helps to prevent oxidation. The multi-core magnetic nanoparticles have the narrowest size distribution as indicated by a smaller spread in coercivity spectra. Uncoated synthetic particles show an increase spread in coercivity and the magnetic interaction, which reflects the variations in the size distribution, agglomeration and the amount of oxidation. Mixtures that are predominantly SP with a small percentage of SD bacterial particles show a bimodal distribution. In addition the study demonstrates the effectiveness of evaluating the derivative of the magnetic moment of the reversible and irreversible part of the induced magnetization with respect to the reversal field. Masking the dominant part on the FORC diagram aids to reveal the existence of secondary/minor magnetic contributions and thus helps in a more accurate interpretation of the magnetic properties.

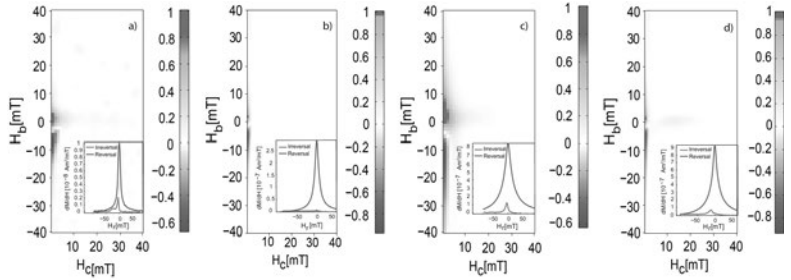

Figure: *FORCs for SPION of predominately magnetite: a) a magnetotactic bacterial sample; b) multi-core synthetic sample: c) uncoated synthetic sample; and d) mixture of superparamagnetic and SD sample. Inset shows the derivative of the magnetic moment of the reversible (blue curve) and irreversible (red curve) part of the induced magnetization with respect to the reversal field.*

Carbon-encapsulated iron nanoparticles for hyperthermia and other biomedical applications.

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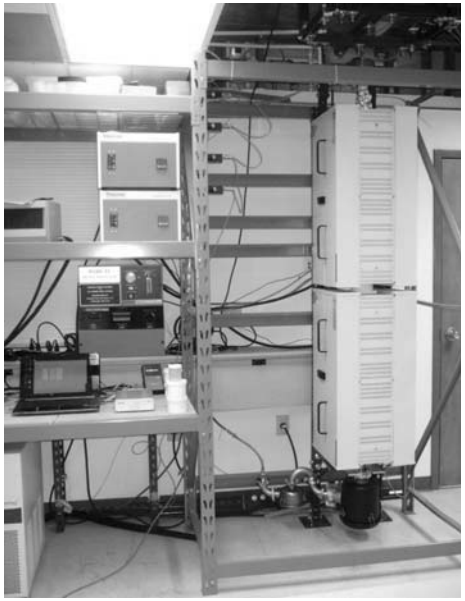
Metal magnetic nanoparticles have superior magnetic properties compared to metal oxide nanoparticles, and are highly desired for various biomedical applications, including hyperthermia. But in aqueous solutions, including biological tissues, unprotected metal magnetic nanoparticles quickly oxidize and lose their advantages.

We developed a method of producing carbon-encapsulated iron nanoparticles using the CVD technique [1].

By varying the synthesis parameters it is possible to produce particles with the desired average diameter. The average diameter can be from 1 nm to 100 nm. The particles maintain their magnetic properties even weeks after mixing with water.

We can produce large amounts of the particles in our USA facility using our setup (see Figure).



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Resolving Particle Size Modality in Iron Oxide Based Magnetic Ferrofluids Using Dynamic and Static Magnetic Measurements

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Particle size distribution plays a crucial role in classifying and targeting appropriate applications for magnetic nanoparticle suspensions (ferrofluids). Up to now, several research studies have been dedicated to identification of the analysis techniques which can reliably be used to probe particle size distribution. However, no considerable attention has yet been given to investigate more complex samples with bi- or tri-modal size distribution. In one of the few studies, Thünemann et al. combined A4F with SAXS to fractionize and resolve the size modality of Resovist® nanoparticles [1]. It is necessary to study complex magnetic ferrofluids more deeply to elucidate the challenges one has to deal with for modeling their behavior.

This study aims to present and discuss a set of characterization techniques required to resolve particle size distribution in iron oxide based magnetic ferrofluids. To design the experiments, two nanoparticle non-aqueous suspensions with mean core and hydrodynamic diameters of 12 and 25 nm (acquired from TEM) and 16 and 35 nm (measured by DLS), designated as f_1 and f_2 respectively, are mixed. The samples are analyzed using complex ac susceptibility, dynamic light scattering and magnetization versus field *M-H* measurements. To describe the experimental results using the relaxational behavior of magnetic nanoparticles, we expanded and modified the existing magnetic models. Fig. 1 reveals the normalized imaginary part of the complex ac susceptibility measured on suspensions at different f_1 and f_2 volume fractions. The solid lines are the best fit, obtained using the expanded Debye model. We realized that it is possible to reconstruct the ac susceptibility results of both mono- and bi-modal suspensions using a single set of core and hydrodynamic parameters.

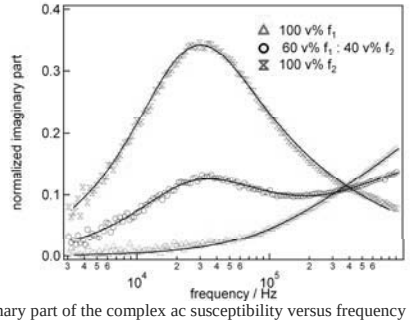

Fig 1: Normalized imaginary part of the complex ac susceptibility versus frequency measured on suspensions with different f_1 and f_2 volume fractions at a field amplitude of 95 μT The solid lines are the best fit obtained using the modified Debye model

Acknowledgment

EU funding via the European Commission Framework Programme 7 under NANOMAG Project (NMP-LA-2013-604448) is appreciated.

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X-ray diffraction and magnetic studies of permalloy thin films grown by evaporation

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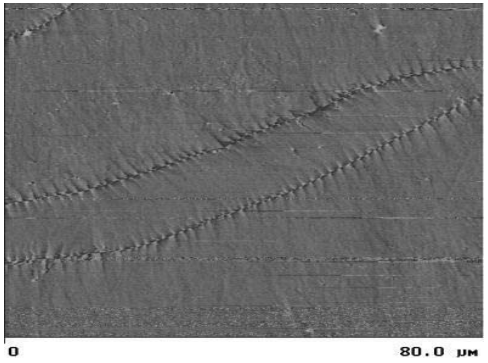
We have studied the effect of thickness on the structural and magnetic properties of permalloy thin films evaporated on glass substrate. The films thicknesses range from 16 nm to 90 nm. From X-ray diffraction spectra, we have shown that the thinner films present a <111> preferred orientation. However, the thicker films exhibit a polycrystalline structure. The grains size increases and the lattice parameter decreases with increasing thickness. The coercive field, Hc, decreases from 6.5 Oe for 16 nm to 1.75 Oe for 90 nm. From Magnetic Force Microscopy MFM observations, the cross-tie walls have been only observed for the two thicker films. Moreover, the domains structures have been also observed with magneto-optical Kerr microscopy. All these results will be correlated and discussed.



Example of MFM image of Permalloy film with a thickness of 60 nm.

landgraf.lisa87@gmail.com Jena, 28.02.2014

High biocompatibility of asymmetric gold at iron oxide nanoparticles with excellent properties as drug carriers and for multimodal imaging purposes

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Introduction

Due to the asymmetric structure of Janus particles (JPs) with two different surfaces they offer high versatility as drug delivery systems Furthermore, JPs exhibit excellent magnetic and optical properties which make them useful in many applications Information about their biocompatibility on the human blood system is missing This study focused on newly developed Au@Fe_3O_4 JPs with varying position of amino groups

Methods

The cytotoxicity profile of the nanoparticles was studied on monocytes and endothelial cells JPs are composed of gold at a silica-PEG-FITC coated iron oxide domain with thiole-groups attached to the gold part Biocompatibility was conducted via ATPLite, ROS, H2A X and comet assay Microscopy was used to analyze directed uptake

Results

Investigations with the ATPLite assay revealed a similar biocompatibility of Au@Fe_3O_4 JPs compared to spherical Fe_3O_4 up to 50 µg/ml Fe(II)/(III) (85 35% viability after 72 h) The comparison of bare Au@Fe_3O_4 and Au@MnO JPs showed no cytotoxicity of the iron oxide containing ones Coupling of NH_2-groups to the JPs lead to cell viability of only 10 6% caused by destruction of endosomal and lysosomal membranes A high release of ROS was measured after exposure to Fe_3O_4 nanoparticles compared to Au@Fe_3O_4 (189 23 % vs 18 67%) Despite uptake intensities of 60%-70% of administered dose, a directed uptake depending on the position of amino groups on the JPs was not observed

Interestingly, JP associated DNA damage (comet assay: 10% higher tail intensity vs untreated cells) was independent from corresponding effects on cellular ATP levels (96% vs control)

Toxicity of magnetic chitosan micro and nanoparticles as carriers for biologically active substances

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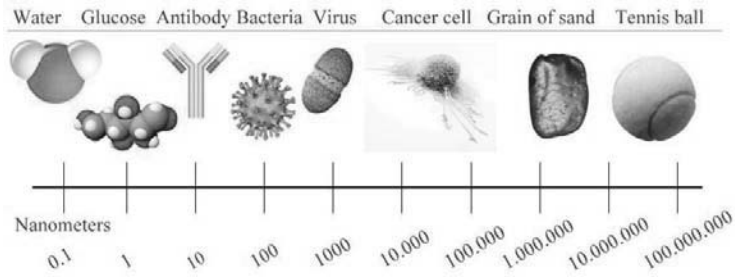
Nanoparticles of inorganic magnetic core surrounded by layers of functional coatings are potential representatives of nanostructures for immobilization of bio-substances. Magnetic nanoparticles (MNPs) are often bound together in aggregates due to a strong magnetic dipole, which has a lot of advantages, such as large surface area for binding biologically active substances.

Chitosan is a polysaccharide polymer, which is produced commercially by deacetylation of chitin. It is non-toxic, hydrophilic, biocompatible, biologically degradable, anti-bacterial and has hydroxy and amino groups in its structure. Because of all these chemical and biological properties it is a desirable bio-product for immobilization of enzymes and for binding of other biologically active substances. It also has the ability to provide optimal micro environment and sustains biological activity and stability.

Magnetic micro and nanoparticles were synthesized with chitosan by three different methods; microemulsion process, suspension cross-linking technique and covalent binding of chitosan. Toxic effect of the prepared magnetic particles was determined as well and was examined on five different bacterial cultures; *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis* and *Klebsiella pneumoniae*. At concentrations of 10-30 mg of magnetic particles per 0.5 McFarland Standard solution of *E. coli* and per 400 CFU of *S. aureus*, *P. aeruginosa*, *E. faecalis* in *K. pneumonia*, no inhibition on the chosen bacterial cultures was detected.



Nanoparticle scale

Rapid and Large-Scale Separation of Magnetic Nanoparticles by Low-Field Permanent Magnet with Gas Assistance

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Abstract

A new approach of gas-assisted low-field magnetic separation and device are developed for rapid and large-scale separation of magnetic nanoparticles. The greatly improved speed of low-field magnetic separation can be further increased by increasing gas flow rate. The limitation of magnetic force on the capture distance hindering the scale-up of magnetic separation process can be overcome. These effects of bubbles are feasible for magnetic nanoparticles with different flotability. A medium-free continuous gas-assisted magnetic separator on small pilot scale using low-field permanent magnet is developed. This separator has continuous scale of 18 l h^{-1} and batch scale of 2.5 l in 1.8 min for separation of proteins-loaded magnetic nanoparticles from dilute solution of 0.5 mg ml^{-1}, as an example of biotechnology application.

Key words: bubbles; gas-assisted magnetic separation; low field; nanoparticles; permanent magnet

A rabbit sized phantom for validation of magnetic nanoparticle imaging

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For novel biomedical applications of magnetic nanoparticles (MNP) like magnetic drug targeting or magnetic hyperthermia the quantitative knowledge of the MNP distribution inside a body is essential. Several MNP specific imaging modalities (e.g. Magnetic Particle Imaging (MPI) and magnetorelaxometry (MRX)) are potentially able to accomplish this task. However, these imaging techniques have to be validated in terms of quantitative reproducibility and the feasibility under pre-clinical conditions has to be demonstrated.

A necessary prerequisite of a validation study is a suitable phantom with well known properties. We developed a rabbit sized phantom (figure 1) that was designed according to the experience gained in a previous *in-vivo* MNP imaging study where the therapeutic efficiency of magnetic drug targeting was investigated in rabbit tumor models by MRX. The diamagnetic phantom body made of Plexiglas® has a length of 50 cm from tail to ear, 40 cm from ear to front leg and a height of 8 cm thus reflecting a typical rabbit.

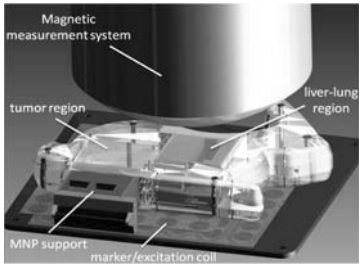

Figure 1: Draft of the rabbit sized phantom with two MNP supports modeling liver and tumor region of the rabbit. Below the phantom are excitation coils and on top a multi-channel superconducting interference device (SQUID) system.

Gypsum cubes (1cm^3) homogeneously loaded with MNP serve as basic component to model complex MNP distributions. Two supports inside the phantom (each of dimension 9 cm × 9 cm × 6 cm capable to house 320 ($8N_x \times 8N_y \times 5N_z$) MNP loaded cubes) offer the possibility to generate MNP distributions at spatially distinct body regions (tumor region at hind leg and liver-lung region) of a rabbit. Additionally, vessels can be used as well to model MNP injection during drug targeting therapy. Defined drills located at the top and bottom of the phantom guarantee an accurate positioning of marker and/or excitation coils with a fixed position relative to the MNP distribution that shall be investigated in the magnetic measurements.

In figure 1 a validation setup for an MNP imaging procedure is shown. It was used to investigate the quantitative reconstruction of an MNP distribution by spatially resolved MRX. Our results demonstrate that the phantom is a suitable tool for providing complex and reproducible MNP distributions with defined conditions in terms of geometry and MNP content for validation of MNP imaging techniques preparing the application in pre-clinical environments.

Preparation and characterization of monodisperse magnetic microspheres using a T-shaped microchannel reactor

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In recent years, researchers show great interest in polymer composite microspheres, especially in magnetic microspheres, which were widely used for targeted drug release as well as adsorption and immobilization of enzymes[1–3]. The existing methods to prepare magnetic microspheres, such as spray-drying, evaporation and complex coacervation have limitations to control the mean size of microspheres at micrometer scale[4].

Due to the easy control of microsphere size, a T-shaped microchannel reactor (See **Fig. 1**) was employed to prepare monodisperse magnetic microspheres instead of the traditional three-necked flask equipped with the mechanical stirrer. Solvothermal was adopted to produce hydrophilic ferriferrous oxide (Fe3O4) nanoparticles with high magnetic responsiveness, which was subsequently emulsified with a dichloromethane solution of polylactic acid (PLA) in the presence of a gelatin stabilizer. This water-in-oil (W/O) emulsion and an additional aqueous phase, namely an aqueous polyvinyl alcohol (PVA) solution, were injected into the T-shaped microchannel reactor and converged at the joint to yield a W/O/W composite emulsion. Evaporation of the solvent in the microchannel gave rise to the target magnetic microspheres (See **Fig. 2**). The results show that the magnetic microspheres have a uniform particle size and good magnetic responsiveness, indicating their potential use in targeted drug delivery for cancer treatment and thermotherapy.

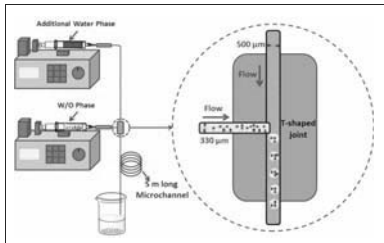

Fig. 1. Schematic diagram of the microchannel system and a photo of T-shaped microchannel reactor

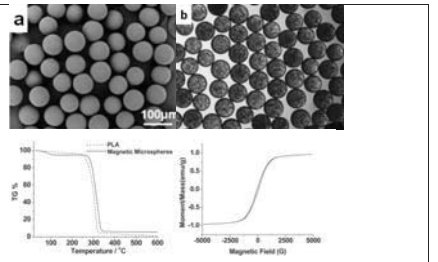

Fig. 2. (a) SEM; (b) Optical microscope image; (c) TGA curves of PLA and magnetic microspheres; (d) Magnetization curve of magnetic microspheres.

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Detecting changes during cellular uptake of magnetic nanoparticles using Magnetic Particle Spectroscopy

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Introduction

Outstanding biocompatibility and superparamagnetic properties make magnetic nanoparticles (MNP) ideally suitable for a brought spectrum of diagnostic and therapeutic applications Due to their potential to label immune cells in vivo, nanoparticles are intensely investigated to study various infective-, inflammatory- and autoimmune diseases [1] Electrostatically stabilized citrate-coated very small superparamagnetic iron oxide particles (VSOPs) are a promising class of nanoparticles suitable for cell labeling VSOPs are supposed to bind to negatively charged glycosaminoglycans on the cell surface before being internalized by the cells [2]

Materials & Methods

Magnetic Particle Spectroscopy (MPS) has been proven a powerful tool for the sensitive and specific detection of MNP in biological environment, especially in cells [3] MPS is based on the nonlinear magnetic susceptibility response of MNP induced by an oscillating magnetic field The signal generated by the changing magnetization of the MNP then contains higher harmonics of the excitation frequency and thus permits the quantification of the magnetic nanoparticle iron content without being affected by tissue or non-particular body iron Furthermore, the MPS spectra provide information about the magnetic state of the analyzed nanoparticles, especially changes due to the environment can be visualized

We employed MPS to quantify the cellular VSOP uptake in THP-1 monocytes (THP-Mo) and macrophages (THP-MΦ) cell lines The VSOP quantification is obtained by the third harmonic μ_3 divided with the specific third harmonic μ_3*=1 0(1) 10^{-3} Am^2/(gFe) (μ_3 normalized to iron amount) of a corresponding reference sample with known VSOP amount As a second parameter we used the ratio of fifth and third harmonics μ_5/μ_3 to assess changes in the dynamic magnetic behavior of the VSOP due to their environment Additionally we employed the photometric phenanthroline method (Phen) as an independent analytic gold standard to independently quantify the VSOP uptake in reference and cell samples

Results

Quantifying the VSOP uptake in cells led to systematic overestimation of the iron amount as determined from the third harmonic μ_3 of the MPS signal compared to the corresponding Phen value (up to 50%) However, for both cell types the ratio $m(Fe)_{MPS}/m(Fe)_{Phen}$ compensating for the overestimation was linearly related to the μ_5/μ_3 ratio of the MPS spectra as shown in Fig 1 Interestingly, this behavior was dependent on the incubation time (inset Fig 1), it was found to be strongest for the shortest time of VSOP incubation (30 min) We attribute this behavior to the interaction of the VSOP with the cells during their uptake

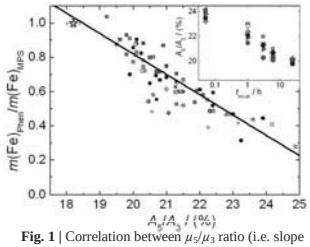

Fig. 1 | Correlation between μ_5/μ_3 ratio (i.e. slope of MPS spectrum) and MPS overestimation of cellular VSOP uptake. The star in the upper left marks the μ_5/μ_3 ratio of fluid stock VSOP. Inset Incubation dependent μ_5/μ_3 ratio found for VSOP uptake in THP-Mo cells

Conclusion

MPS in combination with Phen is a powerful tool to analyze cellular uptake of VSOP and enables to detect changes in magnetic behavior due to interactions of nanoparticles with their biological environment The concentration independent μ_5/μ_3 ratio is used to ensure an accurate quantification of cellular VSOP uptake

Acknowledgments

This work was financially supported by the DFG research units FOR917 and KFO213

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Hydrodynamic and Magnetic Fractionation of Magnetic Nanoparticles for MPI

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Introduction

The properties of magnetic nanoparticles (MNP) vary dramatically with size and often exhibit a broad distribution To this end, in many applications only a small proportion of particles contribute to the desired magnetic effect This applies in particular to the novel modality of imaging called Magnetic Particle Imaging (MPI) which is based on the nonlinear magnetization properties of MNP [1] Both, sensitivity and spatial resolution depend on the size of the nanoparticle core and other physical properties Up to now Resovist® has been the mostly used imaging tracer because of its favorable MPI performance The reason for that is not yet fully clear due to the very complex structure of Resovist® Studies revealed that Resovist® exhibits a bimodal size distribution, consisting of small primary particles, some of which form stable aggregates Thus, particle size fractionation is expected to result in significant MPI signal enhancement

Materials & Methods

In this work we separated Resovist® by two different methods: Asymmetric flow field-flow fractionation (A4F) and static magnetic fractionation (SMF) A4F is based on an elution method where hydrodynamic extension of MNP influences their retention time, whereas SMF separates particles according to their magnetic moment [2][3] The resulting separated fractions were magnetically analyzed by magnetorelaxometry (MRX) measurements of samples in liquid state to estimate the distribution of hydrodynamic sizes and to evaluate the separation process In addition, MRX measurements on immobilized samples of each fraction were used to gain information on the distribution of anisotropy energies E_A and on the responsiveness of MNP to the MPI excitation field [4] From quasistatic $M(H)$ measurements of the initial susceptibility we determined the mean effective magnetic core size of each immobilized fraction The MPI performance for each of the fractions was assessed by measurements with a magnetic particle spectrometer (MPS) which can be considered as a zero-dimensional MPI scanner

Results

The combination of fractionation methods, generating well defined size classes, with basic magnetic characterization techniques ($M(H)$, MRX) shows that in Resovist® hydrodynamic size and effective magnetic core size are not correlated linearly Furthermore, it turns out that the separated fractions of Resovist® exhibit a broad spectrum of anisotropy energies E_A which have a significant influence on the MPS signal [4] Both fractionation methods result in a maximum MPI signal gain (third harmonic amplitude) of about 100% after normalization to iron amount compared to standard Resovist® However, the slope of the harmonic decay for the best performing A4F fraction is shallower and thus promises higher spatial resolution in MPI (see Fig 1)

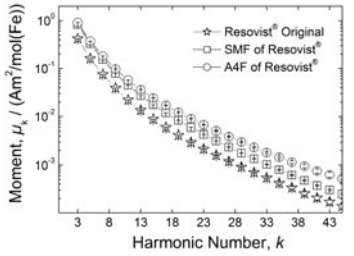

Fig. 1 | MPS measurement of Resovist® and its fractions from A4F and SMF (drive field of B_{exc}=25 mT and f_0=25 25 kHz) All spectra were normalized to the samples iron content

Conclusion

We demonstrated the potential of improving MPI performance by fractionation of MNP present in Resovist® by A4F and SMF These results are a major step forward towards understanding MPI performance of Resovist® which is important to design novel MPI tracer and will help for further developments of separation techniques

Acknowledgments

This work was financially supported by the DFG research unit FOR917 (Nanoguide)

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Development of SPION-Coatings for Visualization of Surgical Instruments in Magnetic Particle Imaging

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Magnetic Particle Imaging (MPI) is a new imaging modality, which measures the spatial distribution of superparamagnetic iron oxide nanoparticles (SPIONs) [1] MPI is also a quantitative imaging modality, which provides high sensitivity and high spatial resolution [2] However, it is necessary to develop SPIONs, which meet the requirements of MPI in the best possible way and are superior to the current gold standard Resovist® [3]

Image 1 MPS setup (Fork Labs project)

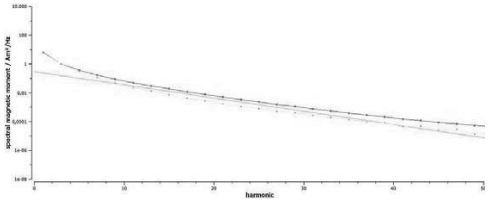

Image 2 MPS measurement comparison of self-synthesized SPIONs (green) and Resovist ® (yellow)

In order to analyze the magnetic properties of SPIONs for MPI, we use MPS, i e magnetic particle spectroscopy, which consists of a coil set-up that produces a static and sinusoidal varying magnetic field The SPIONs under investigation are subjected to this fields and their re-magnetization dynamics characterizes the particle quality with respect to MPI Hence, MPS is MPI without spatial coding

In this contribution, it is focused on the development of SPIONs that are dispersed in polymers, which opens a wide field of new potential medical applications

It is a common practice to use coatings to protect materials, for example, against corrosion, or aging [4] Here, surgical instruments are prepared for visualization in MPI by transferring novel SPION coatings onto their surfaces For instance, catheters are introduced via the saphenous vein into the patient Today, this is done under radiological monitoring, which means radiation exposure not only for the patient but also for the medical staff Therefore, implants, catheters or endoscopes [5] may be coated with the SPION suspensions and would allow MPI-guided minimally invasive surgical interventions

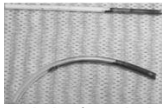

Image 3 Coated tubes for medical applications

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Novel Insight into Mechanism of Magnetic Field Action on Cells with Internalized Nanoparticles

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Magnetic fields may have many influences on physical and chemical processes determining machinery of living cells. Among them the effects related to the magnetic gradient forces exerted on the diamagnetic cell cytosol and paramagnetic ions seem to be most important [1,2]. Inside a living cell internalized magnetic nanoparticles (NPs) may serve as short-range sources of high-gradient magnetic field (HGMF). We show that in the surrounding of a NP exposed to alternating magnetic field (e.g. in the case of magnetic hyperthermia treatment) the gradient of magnetic field can reach a huge value, up to 10^7 T/m. The spatial distribution of such spots with a high-gradient magnetic field is determined by an intracellular distribution of NPs which concentrated mostly in lysosomes (Fig. 1A). It has been showed that positively charged nanoparticles may induce lysosomal destabilization with subsequent induction of apoptosis due to the so-called 'proton sponge' effect [3,4]. Therefore, we hypothesized that due to spatially and temporally modulated magnetic fields the lysosomes loaded with NPs attract the intracellular paramagnetic ions (Ca^{++}, Na^+, K^+ and etc). Such a magnetic gradient force induced redistribution of the paramagnetic ion concentration may affect ion channel function leading to lysosomal destabilization (see Fig.1B). Subsequent lysosomal swelling and rupture leads to the lysosomal content leakage resulting into apoptosis activation [3,4].

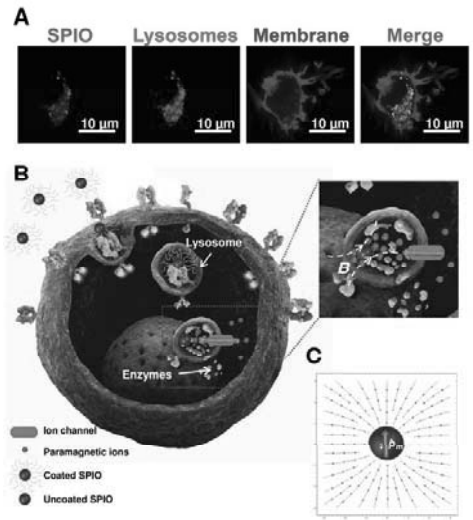

Fig. 1. (A) Colocalization of fluorescently labeled SPIO nanoparticles with lysosomes. (B) Suggested mechanism of HMGF-induced lysosomal destabilization and subsequent apoptosis. (C) Calculated vector field of the magnetic gradient in the vicinity of a nanoparticle.

The suggested intracellular mechanisms might be responsible for the cell death caused by alternating magnetic fields without noticeable temperature increase [5]. Furthermore, the controlled redistribution of intracellular ions and application of focused stress induced by high-gradient magnetic fields to NP-loaded cells opens new perspectives for modulation of cellular functions.

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Novel Fe-ETM-Nb-B (ETM = Ti, Ta, Mn) Glassy Alloys for Use in Magnetic Hyperthermia

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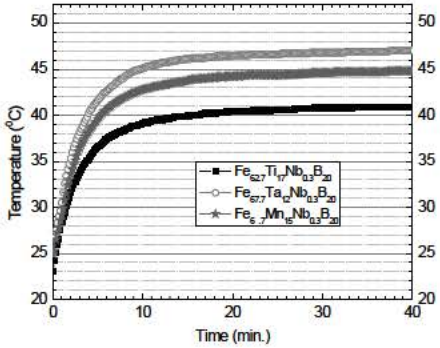
Our previous studies indicated that $Fe_{79.7-x}Cr_xNb_{0.3}B_{20}$ (x = 11.5÷13 at.%) rapidly quenched alloys show glassy structures and Curie temperatures (T_C) of 17÷57^{0}C, depending on Cr content [1]. The magnetic hyperthermia specific tests required minimum amounts of magnetic particles of at least 10 mg [1], whilst for safety therapeutic purposes it would be better to use less than 10 mg. This can be achieved by increasing the saturation magnetization of the metallic particles [2] and keeping T_C low.

For this purposes, in this work, we studied the effect Ti, Ta or Mn additions on the microstructure, magnetic properties and temperature transition of melt-spun ribbons (MSRs) and submicron powders (20 to 400 nm, depending on the milling time) prepared by high-energy ball milling from MSRs precursors, in oleic acid. Mn, Ti, and Ta additions double the saturation magnetization (80 emu/g) of $Fe_{79.7-x}ETM_xNb_{0.3}B_{20}$ glassy alloys compared with Cr glassy alloys (40 emu/g) [2]. Mn is antiferromagnetic and favors the formation of Fe-Mn antiferromagnetic clusters surrounded by ferromagnetic Fe-B-based amorphous matrix. Thus, the larger the Mn content the more numerous the antiferromagnetic interactions are, suggesting a transition temperature evolving more towards a Néel temperature for Mn contents over 16 at.%. Ti and Ta are big non-ferromagnetic atoms and contribute strongly to the stability of the glassy structure, but in the same time will favor the Fe-Fe antiferromagnetic interactions by increasing the distance between Fe atoms. T_C will decrease by increasing Ta or Ti content, passing through zero for Ti or Ta contents of 18-19 at.%. Such a specific behavior with T_C around room temperature was observed only for powders with glassy structures, i.e. containing small clusters of less than 10 nm embedded in an amorphous residual matrix.

The heating efficiency curves of the $Fe_{79.7-x}ETM_xNb_{0.3}B_{20}$ nanopowders of 20-100 nm in the presence of an a.c. HF field of 350 mT (f = 153 kHz), as a function of ETM content are presented in the figure. The temperature increases rapidly in the first 8 min., then reaches an equilibrium constant value, independent of the heating time. This specific behavior is a clear evidence for the suitability of using Fe-ETM-Nb-B submicron powders for hyperthermia applications, since it allows keeping unchanged the temperature in a desired area for a given period of time. The equilibrium temperature can be tuned in a narrow range either by modifying the ETM content or by controlling very strictly the milling conditions.



This work was supported by a CNDI–UEFISCDI grant, Project #148/2012 (HYPERTHERMIA).

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Investigation of Oxidative Stress of Colloidally Stable Polymer-Modified Iron Oxide Nanoparticles and Their Anti-Tumor Activity

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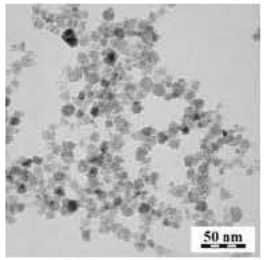
Colloidally stable maghemite (γ-Fe_2O_3) nanoparticles were obtained by the coprecipitation of ferrous and ferric chlorides followed by oxidation with sodium hypochlorite. Poly(*N,N*-dimethylacrylamide-*co*-acrylic acid) [P(DMAAm-AA)], which was prepared separately by radical polymerization in toluene and tetrahydrofuran solution, was then used as a coating. The nanoparticles and the polymer chains were thoroughly characterized by transmission electron microscopy (TEM), elemental analysis, FT-IR spectroscopy, dynamic light scattering and zeta-potential measurements. Oxidation of blood lipids, gluthathion and proteins in blood serum by superparamagnetic P(DMAAm-AA)-γ-Fe_2O_3 nanoparticles was investigated using 2-thiobarbituric acid and ThioGlo fluorophore.

Finally, magnetic nanoparticles were administered *per os* and antitumor activity was tested on lung Lewis carcinoma in male mice line C57BL/6 as an experimental *in vivo* metastatic tumor model. Size of the tumor was measured, as well as the number of metastases in lungs was determined. Antitumor and antimetastatic activity of nanoparticles was compared with effect of commercial $CuFe_2O_4$ ferrite particles and conventional antitumor agent cisplatin. Newly developed surface-modified γ-Fe_2O_3 nanoparticles proved to possess comparable antitumor and antimetastatic activity.



TEM micrograph of neat γ-Fe_2O_3 nanoparticles.

Acknowledgment: This work was supported by EC (project DiaTools No. 259796) and Ministry of Education Youth and Sports (project BIOPOL No. CZ.1.07/2.3.00/30.0029).

The use of complex magnetic biomaterial for decreasing *Pseudomonas aeruginosa* biofilm formation

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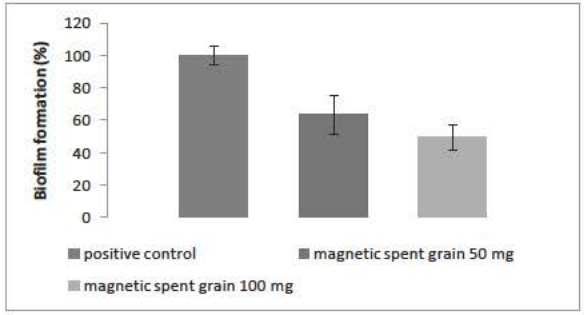
The formation of bacterial biofilms has significant negative effect on the function of filtration devices and related negative economic effects. *Pseudomonas aeruginosa*, an opportunistic human pathogen, is often chosen as a model microorganism for biofilm formation. Biofilm formation is regulated through quorum sensing systems which produce and release small signalling molecules that increase their concentration as a function of cell density. In the case of *P. aeruginosa, N*-(3-oxododecanoyl)-L-homoserine lactone and *N*-butanoyl-L-homoserine lactone are utilized as signalling molecules.

The aim of this study was to find a simple procedure to decrease a biofilm formation in water environments. We prepared several magnetically modified biomaterials (tea leaves, coffee grain, saw dust and other) by one-pot microwave assisted synthesis. The diameter of the deposited magnetic particles and their aggregates was less than 1µm. Using a microplate-based screening assay based on crystal violet staining, the effects of magnetic biocomposites on *Pseudomonas aeruginosa* GB29 biofilm formation were evaluated.

The most promising biocomposit (magnetically modified spent grain) was applied on a larger scale. The magnetic biocomposit did not reduce planktonic cell growth and only affected biofilm formation. It was observed a significant reduction of the biofilm formation by *P. aeruginosa* by ca 50%. The ability of efficient signal molecules adsorption by magnetic spent grain was confirmed by model adsorption experiments.

The results demonstrate that waste biomaterials with magnetic modification can be used for a range of new and beneficial applications.



Effect of magnetic biocomposite on *P. aeruginosa* GB29 biofilm formation.

Single-Aperture Microshell Neuroparticles™ for Controlled CNS Drug Delivery

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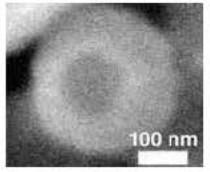
Nanoparticle delivery of therapeutics to brain holds significant promise for increasing local drug concentration while decreasing systemic dose. Brain tumor treatment requires precise targeting, which could potentially be achieved using magnetically manipulated particles. We previously demonstrated the ability to direct particles from a nostril injection site, across the cribiform plate, and into the brain of a living rat, as well as magnetically move particles across the brain midline in an extracted rat brain. To date, in vivo nanoparticle manipulations in brain have implemented particles consisting primarily of spherical superparamagnetic iron oxide particles modified with various chemical coatings. The pharmacokinetics of drug release from such particles can be a complex function of local pH and other environmental factors. An alternative approach to drug delivery that is widely used for sustained release is to encapsulate the drug and then puncture the capsule (e.g., with a laser) so that the drug's diffusion rate is determined primarily by the resulting aperture. We report development of an experimental single-aperture magnetic particle using biocompatible poly (lactic-co-glycolic) acid (PLGA) particles as support materials.

Experimentally, 200 nm diameter PLGA particles were used as biocompatible templates. These particles were first dispersed in deionized water and sonicated for 10 minutes. The particles were deposited onto chromium-coated (100 nm thick adhesion layer) glass cover slips. The cover slips with deposited particles were sputtered with an initial 35 nm layer of iron and a 15 nm capping layer of gold. The particles were then released from the substrate via sonication and re-suspended in deionized water. The particles were loaded with temozolamide (TMZ), a drug that has been approved for the treatment of brain cancer. Binding assays revealed a loading of approximately 1,000 TMZ molecules per neuroparticle. The particles were shown to have strong magnetic properties, and to have highly uniform size distributions (as would be expected from a template-based fabrication method). Brain transport and dissolution studies are underway with different template materials, and with hollow particles (i.e., with the templates dissolved). Initial data suggests that bare iron coatings can be made to dissolve in days (in oxygenated saline).

We conclude that it is possible to fabricate magnetic particles with non-magnetic cores and single-aperture outer magnetic shells in order to achieve controlled release of drugs loaded into the particles. We anticipate that this strategy will allow designers to decouple the magnetic and pharmacokinetic properties of the particles.



Enhanced Magnetic and Size Dependent Properties of Oleic Acid Stabilized $BiFeO_3$ Nanocrystals at Room Temperature

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$BiFeO_3$ (BFO) has generated great interest over the years as a key multiferroic material which simultaneously display ferroelectricity and ferromagnetism, and can be potentially used for memory storage devices. However, the material suffers a number of shortcomings, namely, high calcination temperature, presence of impurities, nonstoichiometry, large crystal size. A finer control over the kinetics of formation of BFO is very much necessary to exhibit pronounced coupling between the electrical polarization and magnetization for practical device applications.

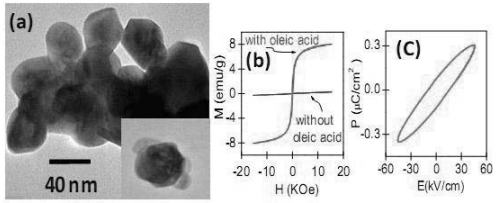

FIG.1. (a) TEM image of $BiFeO_3$ nanocrystals of size 40 nm. (b) Room temperature M–H hysteresis loop of $BiFeO_3$ nanocrystals synthesized with (red curve) and without (blue curve) oleic acid. (c) Room temperature P–E loop of the nanocrystals.

We successfully carried out a low temperature chemical synthesis route using oxalic acid as a chelating agent and oleic acid as a stabilizing agent to synthesis BFO nanocrystals with various sizes in the range 10-120 nm. Use of oleic acid (*cis*–9–octadecenoic acid) has been found to be very effective to get finer control over the size of BFO nanocrystals (Fig. 1a) and its distribution. We find that large scale phase–pure single crystalline BFO can be synthesized at an optimum calcination temperature 420^0C which is significantly lower compared to all previous reports so far. We also show that the BFO nanoscrystals exhibit distinct size dependent multiferroic properties. The smallest BFO nanocrystal synthesized of size ~ 12 nm shows remarkably high (6.23 emu/g) magnetization values. Such BFO nanocrystals with enhanced magnetic and ferroelectric properties can be potentially used for magnetoelectric devices.

Modelling the size of SPIONs in stent assisted magnetic drug targeting applications

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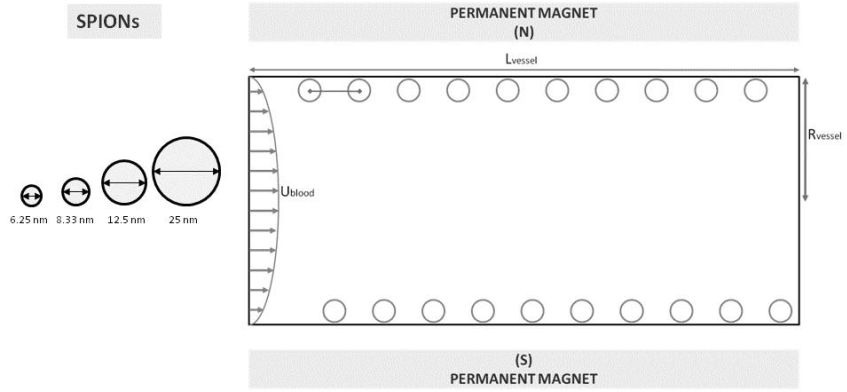
Superparamagnetic iron oxide nanoparticles (SPIONs) continue to offer promise for clinical applications since they are employed as magnetic resonance imaging (MRI) contrast agents and their features could be easily tailored by including targeting moieties, fluorescence dyes, or therapeutic agents. Here, we studied the magnetizable stent assisted magnetic drug targeting (SA-MDT) system, which uses high gradient magnetic separation in a physiologically stretched vessel by the employment of a 2D mathematical model. A ferromagnetic, coiled wire stent was implanted to aid collection of magnetic drug carrier particles in an elastic tube that has similar mechanical properties to the blood vessel and the changes in the mechanical behaviors were analyzed under the influence of mechanical forces generated. Here, we focus on the theoretical modeling of the interaction between the drug carrier particles enriched with 4 different size of diameters (6.25, 8.33, 12.5, 25 nm) of SPIONs derived from polyol methods coated with oleic acid in a magnetizable stent assisted magnetic targeted drug delivery system. The amounts of the SPIONs included in the drug carrier particles are inversely proportional with the diameter changes in SPIONs in the equal exposed area in each simulation. The amount of the carrier particles at the desired site under the influence of different magnetic field strength and blood velocity are optimized. The unique combination between physico-chemical properties and multiparametric theoretical model and its analysis is therefore allowing for the optimal identification of the functional nanoparticle requirements prior to moieties, fluorescence dyes, or therapeutic agents' fictionalization for targeted pharmaceutical applications.



Schematic of the control volume (CV) used for studying the behavior of different size of superparamagnetic iron oxide nanoparticles (SPIONs) enriched magnetic drug carrier particles in stent assisted magnetic drug targeting applications.

Characterization with X ray and Neutron scattering techniques of a magnetic bio-nanocomposite to be used in the treatment of breast cancer

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Breast cancer is a public health problem throughout the world. Moreover, breast cancer cells have a great affinity for hydroxyapatite, the main component of bones, which has also shown to reduce the metastatic activity of such cancer. In this work we developed a bio-nanocomposite (bio-NCP) in order to use such affinity in the treatment of the disease[1]. The bio-NCP consists of magnetic nanoparticles of Mn and Zn ferrite synthesized by the co-precipitation method, coated with the polymer chitosan by a reverse micelle procedure. The surface of such polymer was then modified with nanocrystals of apatite trough a mimetization method. Additionally, to enhance the antitumor activity of our material, the drug paclitaxel was also included to it, as an encapsulated molecule. However, despite of the remarkable effectiveness of paclitaxel against breast cancer, it is also well known that its molecular conformation, which is closely related to its mechanism of action, can be easily changed depending on the enviroomental conditions[2]. So, our research group is now performing a study on the molecular conformation of the encapsulated paclitaxel by using a combination of X ray and neutron scattering techniques together with theoretical calculations.

Scanning transmission X ray microscopy (STXM) has been used to determine the distribution of paclitaxel´s molecule inside the bio-NCP (Figure 1). To do so, images on the benzene ring absorption border were collected and a contrast between the drug, which contains 3 of those groups, and the polymer could be observed. Then, Inelastic Neutron Scattering combined with theoretical DFT calculations could provide information regarding the serious constrainement on the molecule after the encapsulation procedure, specially in the bioactive side chain. Meanwhile, our research group is also performing in vitro tests, which, so far, have shown that the modification with hydroxyapatite allows the bio-NCP to be inert to macrophage cells.

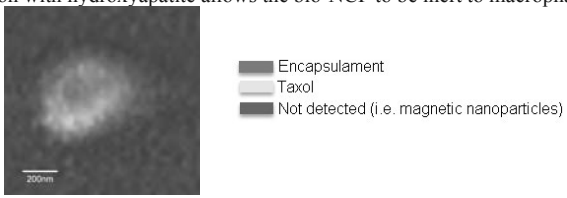

Figure 1 STXM image of the bio-NCP and the distribution of Taxol

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Accumulation of circulating superparamagnetic iron oxide nanoparticles (SPIONs) in endothelial cells: Effects on endothelial viability and monocytic cell adhesion.

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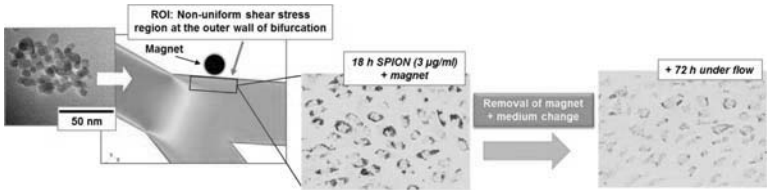
In cardiovascular medicine, magnetic targeting is considered a promising method to accumulate the nanoparticles at the sites of atherosclerotic lesions However, little is known about the biological effects of magnetic nanoparticles on the vascular wall The aim of this study was to analyse the endothelial accumulation of circulating SPIONs (superparamagnetic iron oxide nanoparticles), without or with external magnetic force Moreover, the effects of SPION uptake on endothelial morphology, resistance to physiologic levels of shear stress, and TNF-α-induced monocytic cell adhesion were investigated

Human umbilical vein endothelial cells (ECs) were grown in the bifurcating flow-through slides (Ibidi, Munich) until 90% confluence Subsequently, the cells were perfused at 10 dyne/cm^2 for 18 h with medium containing SPIONs at a concentration of 30 µg/mL (without magnet), or 3 µg/mL (with magnet) The iron content of ECs was estimated using Prussian blue stain In some experiments, the effects of SPION uptake on monocytic cell recruitment in response to TNF-α were analysed EC morphology and resistance to physiologic levels of shear stress were investigated by extending the exposure to shear stress in the absence of SPIONs for up to 96 h, following the initial 18 h perfusion with SPION-containing media

In the absence of magnetic force, a uniform distribution of endothelial SPION uptake independent of channel geometry or hemodynamic conditions was observed, indicating that no increased accumulation of SPIONs occurs at non-uniform shear stress region at the outer walls of bifurcation Application of external magnet allowed enhanced accumulation of SPIONs at the regions of non-uniform shear stress even at 10-fold decreased nanoparticle concentrations, accompanied by a reduced endothelial uptake in laminar shear stress regions Increased uptake of SPIONs at non-uniform shear stress region was well tolerated by ECs and did not affect endothelial cell viability or resistance to prolonged shear stress exposure At the tested concentrations, SPIONs were largely metabolized within 3 days post-application (see Figure) Importantly, no significant increase in TNF-α-induced monocytic cell recruitment was detected upon SPION treatment

Magnetic targeting allows localized accumulation of increased amounts of SPION at the region of interest under physiologic-like flow conditions, thus enabling a substantial reduction of the applied dose These findings indicate that magnetic targeting can constitute a suitable technique for the delivery of imaging and therapeutic nanoparticles to atherosclerotic lesions



Novel Route of Water Soluble Iron based Nanoparticles for Magnetic Hyperthermia

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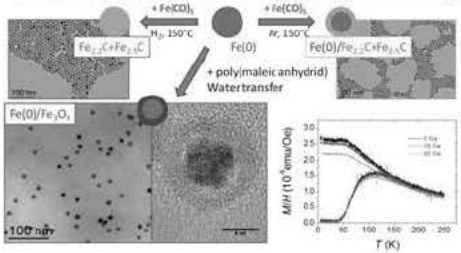
Monodisperse and air stable magnetic nanoparticles displaying high magnetization and tunable anisotropy are highly desirable for several biomedical applications as magnetic hyperthermia Metallic We showed recently that Iron(0) nanoparticles with high magnetization could be good candidates for hyperthermia but lack the air-stability and water solubility criteria [1] In contrast, iron oxide nanoparticles display a good air-stability, water solubility and they are one of the few nanomaterials than can be injected into the body being benign and non toxic However, they present a low magnetization An improvement of these behaviors requires tuning the oxidation of the particles [2] In this respect, core shell nanoparticles composed from a metallic core (iron(0) or iron carbide) and a biocompatible shell are particularly attractive since combining high magnetization, air stability and may be biologically compatible

Here, we will show a novel route for the preparation of one of these core shell materials, water soluble, which present remarquably magnetic properties and very promising hyperthermia behavior Recently, we reported the first organometallic synthesis for the preparation of monodisperse iron(0), iron carbides and iron/iron carbides nanocrystals with controlled sizes and compositions [3], [4] Iron carbides nanoparticles are obtained by the decomposition of $Fe(CO)_5$ on preformed iron(0) seeds The amount of carbon diffused can be controlled by adjusting the experimental conditions such as temperature and reducing agent Their size is well controlled by adjusting the seeds one These nanoparticles display excellent magnetic properties and air-stability Interestingly, adjusting the carbon distribution within the nanoparticles offers the possibility to tune finely their magnetic anisotropy Hence, some of these nanoparticles display the highest efficiency so far reported for magnetic hyperthermia in the current operating treatment conditions Very recently, we have developed a coating route of some of these iron based nanoparticles with an amphiphilic polymer This polymer is based on a poly(maleic anhydride) backbone and enables (i) the phase transfer of these magnetic nanoparticles from organic solvents to aqueous solution, and (ii) the covalent linkage of different biological molecules on its surface A combined study with Dynamic light Scattering (DLS), Superconducting Quantum Interference Device measurements (SQUID) and High Resolution Transmission Electron Microscopy (HRTEM) showed that the polymer coated nanoparticles still present a homogeneous size and composition and are stable For example, the coating of iron(0) nanoparticles of about 11 nm, leads to homogeneous core/shell $Fe(0)/Fe_3O_4$ nanoparticles of about 12nm with remarquably magnetic properties Some toxicity study will be also presented here



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Structural properties of magnetoferritin by small angle X-rays and neutrons scattering methods

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The protein cage of ferritin, iron storage protein, has been shown to be a suitable environment for magnetite or maghemite synthesis, enabling formation of magnetoferritin macromolecule. The structure of such biological complex containing an iron oxide and a protein shell (apoferritin) in aqueous solution was investigated by powerful small-angle X-rays (SAXS) and neutrons (SANS) scattering for different loading factors (average number of iron atoms per complex). The protein shell of magnetoferritin complex with iron loadings higher than 158 has exhibited partial destruction as compared to the native hollow state of apoferritin (Fig. 1). These changes were followed by the increase of polydispersity and the change of match points in the SANS contrast variation with the loading factor growth. It could be expected that the structure of the magnetoferritin package was changed due to the magnetic core presence. From the SAXS, SANS, transmission electron microscopy, dynamic light scattering data and the determined peroxidase-like activity of magnetoferritin nanoparticles it could by supposed that the part of magnetic component amount is bound by electrostatic adhesion to the outer part of the protein shell. The obtained results are important for future applications of magnetoferritin or in the new development of synthesis nanotechnology.

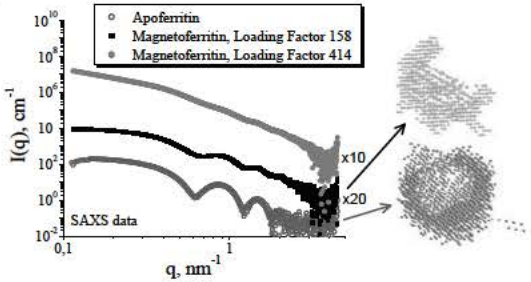

Fig. 1 The SAXS data of apoferritin and magnetoferritin with corresponding *ab initio* models

Acknowledgements

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Protein micro/nanoparticles assembled via isobutyramide groups

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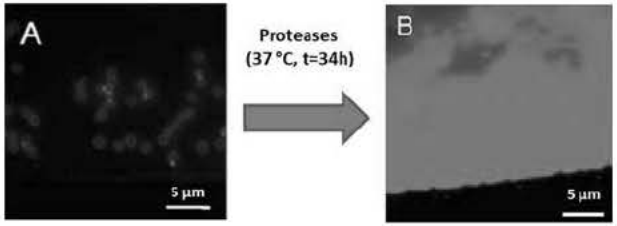
The development of polymer nanoparticles has become central to many applica ions in Nanomedecine. However a key challenge is to develop simplified approaches to design novel polymer particles with improved properties compared with exis ing methods in terms of biodegradability, toxicity and processing. Aside, there are very few methods allowing the efficient fabrication of particles made of biological macromolecules especially proteins. Human proteins such as human serum albumin are emerging as relevant building blocks to design safe and efficient polymer nanocarriers.

In coll. wi h the Univ. of Melbourne (Prof. F. Caruso), we pioneered an inedited approach based on the property of isobutyramide (IBAM) grafts to assemble non-covalently, protein-based hollow capsules and particles without the need of an addi ional cross-linking or other adjuvant. The process consists in a single adsorption step of proteins onto silica templates prealably grafted with IBAM groups or derivatives (e.g., bromoisobutyramide, BrIBAM) followed by template removal.[1] The driving force for the adsorption is attributed to strong H-bonds between the IBAM interface and the polypeptide chains of the proteins. We applied this method towards the design of bioresponsive hollow capsules and particles made of a range of proteins, including enzymes, insulin and human serum albumin.[2,3] Fur hermore, such carriers were shown to release chemotherapeutic drugs upon biological stimuli (e g. through protease degrada ion or reductive cytosolic mimetic condi ions).



Fluorescence microscopy images of : (A) HSA capsules (1 µm size) functionalized with doxorubicin, a naturally red fluorescent chemotherapeutic agent, and (B) doxorubicin release through enzymatic protease degradation of the capsules.

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Formation by LAL and characterization of citric acid-coated iron oxide nanoparticles

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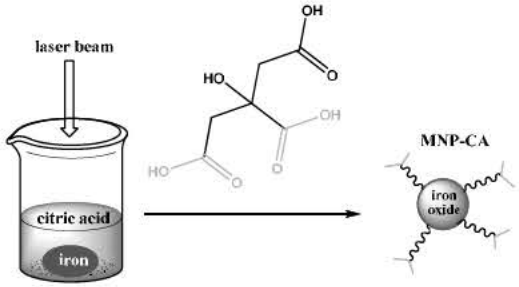
Abstract

This work presents the synthesis of magnetic nanoparticles coated with a hydrophilic shell of citric acid, by a one-step technique based on laser ablation in liquid. The obtained nanoparticles were characterized in terms of size distribution and stability by DLS and microscopic techniques; the morphology was investigated using HRTEM and the surface chemistry was studied by XPS technique and FTIR spectroscopy. The results show the formation of stable spherical nanoparticles, having a single size distribution centered around 60 nm. The nanoparticles are composed of an iron oxides core, stabilized by a citric acid coating. *This work was supported by Reaserch Projects for Young Research Teams - PN-II-RU-TE-2011-3-0174, Contract No. 91/2011-10-05.*



Citric acid stabilized iron oxide nanoparticles formed by laser ablation in liquid

Keywords pulsed laser ablation, iron oxides, magnetic nanoparticles, liquid media

Mössbauer Evaluation of the Interparticle Magnetic Interactions within the Magnetic Hyperthermia Beads

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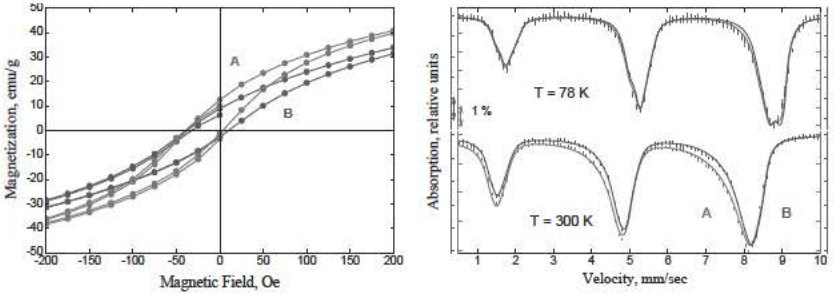
Asymmetrical shape of the Mössbauer spectra lines of an ensemble of superparamagnetic nanoparticles is a sign of interparticle interaction [1] The phenomenon was used for evaluation of the magnetic interactions inside two hyperthermia beads The beads were about 30 microns in diameter and contained around 10^9 of the same of iron oxide nanoparticles per bead It was found that they can generate very different amounts of heat when exposed to the same oscillating magnetic field Sample A produced heating at 9 13 W/g; 20 W/cc Sample B produced heating at 0 85 W/g; 1 7 W/cc

The measurements of the magnetization curves were carried out on the vibrating sample magnetometer at room temperature The areas of the hysteresis loops for two samples are 3373 emu/g Oe for B and 2568 emu/g Oe for A Thus, it turns out that the sample B has about 25% larger hysteresis loop than A, despite the less heat production This unexpected result was verified by Mössbauer method The asymmetrical shapes of the lines on the Mössbauer spectra of the samples confirmed the presence of the interparticle interactions in the beads The *KV* parameter in A and B samples was determined from the numerical fitting of the experimental spectra The *KV* is connected with Neel formula for relaxation of magnetization vector of superparamagnetic particle It is proportional to the barrier height, which magnetization vector have to overcame in order to change its orientation to opposite one For A the barrier height *KV* = 1210(30) K and for B *KV* =1770(60) K Thus, the sample B demonstrated about 30% larger barrier height than A The results are discussed in the framework of the Neel and Brownian mechanisms of the heating



Magnetic and Mössbauer measurements of samples A and B

Reference

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Effects of a High Gradient Magnetic Field on Flowing Erythrocytes in a Hollow Fiber Membrane Oxygenator

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INTRODUCTION

Effects of a high gradient magnetic field on flowing erythrocytes in a hollow fiber membrane oxygenator were analyzed Deoxygenated erythrocytes are paramagnetic and oxygenated erythrocytes are diamagnetic Flow of blood in an oxygenator is affected by a gradient magnetic field because deoxygenated blood with $\chi = -4.04 \times 10^{-6}$ (χ: magnetic susceptibility) becomes oxygenated blood with $\chi = -5.52 \times 10^{-6}$ and magnetic force is given by $F = \mu_0 M \nabla H$ (F: force, μ_0: permeability of a free space, M: magnetization of blood, H: magnetic field) Magnetic force applied to deoxygenated blood is in an inlet direction and that applied to oxygenated blood is in an outlet direction The magnitude of the outlet-ward force is greater than that of the inlet-ward force

METHODS

The model used for analysis is shown in Fig 1 A hollow fiber membrane oxygenator is placed inside a superconductive solenoid coil (ID: 0 0165 m, L: 0 1 m) Blood in the membrane oxygenator is exposed to an axially non-uniform magnetic field Deoxygenated blood enters the hollow fibers (number: 2269, OD: 300 μm, ID: 200 μm, L: 0 2 m) in a Poiseuille flow and is oxygenated at the center of the coil

Motion of the blood is governed by the continuous equation and the Navier-Stokes equation The equations were solved on the basis of the following assumptions: (1) Blood flow in the hollow fibers is laminar and axially symmetric and (2) the magnetic field inside the coil is axially symmetric and radially uniform

RESULTS

Magnetic pressure was increased by the magnetic force Magnetic pressure of 23 Pa was induced by blood under the conditions of B = 6 2 T (B: magnetic flux density) and grad B = 381 T/m and that of 58 Pa was induced under the conditions of B = 9 9 T and grad B = 609 T/m

Blood pressure increased at the outlet of the oxygenator The relationship between pressure increase in the oxygenator and maximum magnetic field is shown in Fig 2 for various blood flow rates (Reynolds numbers of 0 001 to 0 003)

CONCLUSION

The results suggest that a membrane oxygenator works as an actuator and there is a possibility of circulation of blood through an oxygenator by a high gradient magnetic field

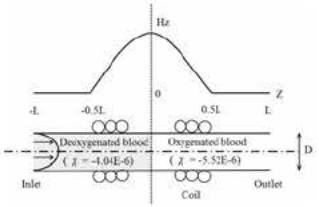

Fig 1 Proposed model for analysis

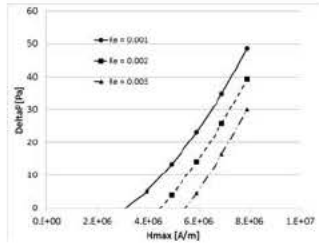

Fig 2 Relationship between pressure increase in a hollow fiber membrane oxygenator and maximum magnetic field

A study of the cellular-nanoparticle interactions and assessment of the magnetic response of novel bacterially synthesized substituted ferrites

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Magnetic nanoparticles with tuned properties are important for developing biomedical applications. In this study we assess nanoparticles, produced by the iron reducing bacteria *Geobacter sulforeducens,* containing varying amounts of cobalt or zinc within a magnetite core in order to modify their physical and magnetic properties such as size and magnetic anisotropy. Both the bacterial origin (biogenic), which allows large scale production in an environmentally safe way, and doping with zinc and cobalt, could alter the cytotoxicity of the nanoparticles compared to chemically synthesized magnetite nanoparticles. Here this was assessed by simultaneous fluorescent staining for live and dead cells (Fig. 1), and quantified by measuring the percentage of viable cells using the flow cytometry technique. Cytotoxicity was studied in the osteosarcoma cancer cell line (MG-63), and in primary cells of human mesenchymal stem cells. Following this, the cell-nanoparticle interaction and cellular uptake were quantified. In particular, the alteration of the magnetic response of the nanoparticles in an aqueous environment compared to their behaviour when associated with cells was studied using AC susceptibility measurements. The results show that the biogenic origin did not confer cytotoxicity to the nanoparticles and the doping of zinc and cobalt did not increase the particles' toxic effects unless present in excessively high doses. Also, the zinc ferrites were found to have improved magnetic response compared to chemically synthesized magnetite nanoparticles in a cellular milieu. The study sheds light on the biocompatibility and improved magnetic response of these promising new nanoparticles, and helps optimize the dosage and field conditions that improve efficiency of cell-based nanoparticle applications.

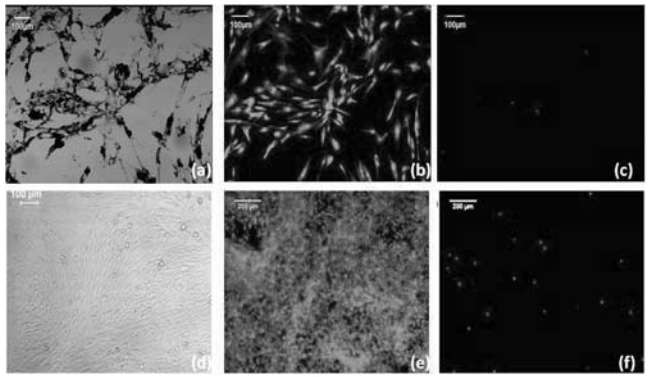

Figure1: Human mesenchymal stem cells exposed to 500µM of $Co_{0.4}Fe_{2.6}O_4$ (a: Bright field) for 72 hours, were stained with the live cell stain, Calcein AM (green)(b) and dead cell stain, Ethidium homodimer (red) (C) to assess cytotoxic effects of the cobalt doping. Corresponding images for osteosarcoma MG-63 cells treated with 500µM of $CoFe_2O_4$ for 72 hours is shown below (d,e,f).

In vitro and *in vivo* experiments with functionalized SPIONs for medical applications

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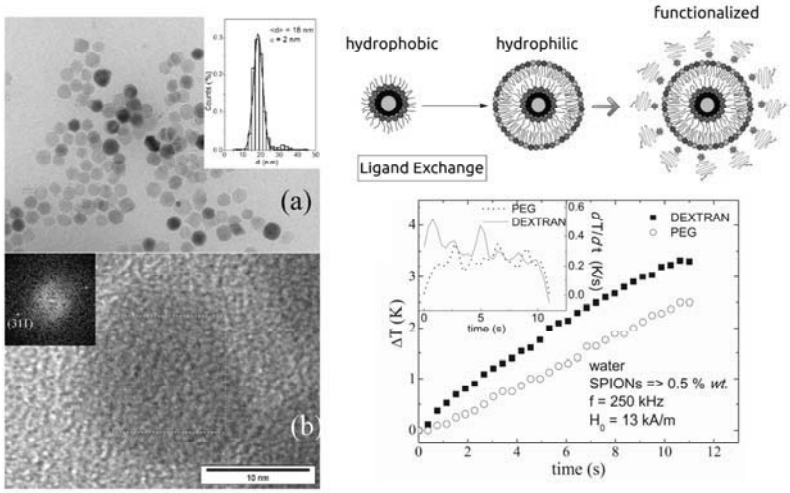
The potential of magnetic nanoparticles as medical tools is one of the most promising up-and-coming alternatives for cancer treatments. Their use in applications such as drug delivery, gene therapy and hyperthermia among others is a topic of great interest. In this research work, Fe_3O_4 superparamagnetic iron-oxide nanoparticles (SPIONs) with narrow size distribution were synthetized by a thermal decomposition process. As a result, well-crystalline SPIONs were formed with d=18 nm and σ=2 nm. Then, the SPIONs surface was modified to make them hydrophilic ones by a post-synthesis procedure and they were functionalized with DEXTRAN and polyethylene glycol (PEG). The nanoparticles presented high saturation magnetization and superparamagnetic behavior at room temperature, and the hydrodynamic diameters of DEXTRAN- and PEG-coated SPIONs were measured as 170 and 120 nm, respectively. To quantify the DEXTRAN- and PEG-coated SPIONs response to the heating process, the specific power absorption (SPA) were measured in an AC magnetic field with amplitude of 13 kA/m and frequency of 256 kHz, giving 400 and 320 W/g respectively.

With these nanoparticles, the biodistribution was assessed and *in vitro* studies using VERO and MDCK cell lineages were performed to study the cytotoxicity and cell uptake of the SPIONs. For both cell lineages, PEG- and DEXTRAN-coated nanoparticles presented high cell viability for concentrations as high as 200 µg/mL. *In vivo* studies were conducted using BALB/c mice inoculating the SPIONs intravenously and exposing them to the presence of an external magnet located over the tumor. It was observed that the amount of PEG-coated SPIONs in the tumor increased up to 160% when using the external permanent magnet as opposed to those animals that were not exposed to the external magnetic field. So, the enhancing of the uptake of these functionalized SPIONs is achieved for the conditions described.



Left (a) TEM Image and (b) HR-TEM Image of SPIONs Right Schematic representation of the surface modification process and time dependence of temperature of SPIONs

Iron oxide nanoparticles: An experimental study on the magnetic heating effect

M. L. Mojica Pisciotti[1], E. Lima Jr.[1], R. D. Zysler[1], M. Vásquez Mansilla[1], H. E. Troiani[2], G. F. Goya[3]

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The hyperthermia technique consists in inducing cell death by generating an increase of the local temperature of a tumor. This heating is mediated by superparamagnetic iron oxide nanoparticles (SPIONs) that are absorbed by cancer cells and when they interact with an AC magnetic field, transform the energy received from the field in thermal energy. So, the aggressive change of temperature cause the death of the cancer cells.[a] Then it is desirable to design SPIONs with controlled diameter and narrow size distribution. Moreover, the effectiveness of hyperthermia is focused on using SPIONs with a high biocompatibility and optimized magnetic properties.

In this work we have synthetized Fe_3O_4 SPIONs through the method of high temperature decomposition of iron acetylacetonate $Fe(acac_3)$, which offers an optimal control over size and dispersion. We obtained well-crystalline nanoparticles of different sizes and studied their morphological and magnetic properties. SPIONs exhibited high saturation magnetization and superparamagnetic behavior at room temperature.[b,c] Once hydrophobic SPIONs were obtained, they were suspended in aqueous media by the method of ligand exchange. Specific absorption rate (SAR) measurements were performed on a commercial device (200 Oe with different frequencies). These measurements showed high SAR values, which suggest that SPIONs treated with the method described above are appropriate for hyperthermia experiments. Also, there was found an expected dependence with concentration in all the cases, as well as with the media where they were suspended.

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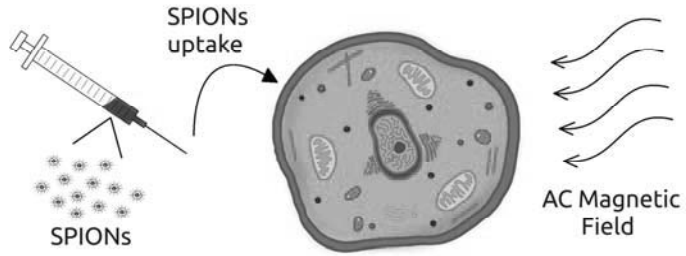
[c] Sun S. and Zeng H. *J. Am. Chem. Soc.* **124** (28), 8204-8205 (2002)



Schematic representation of the hyperthermia technique: SPIONs uptake process followed by the application of an AC magnetic field.

Energy losses in bacterial magnetosomes as potential hyperthermia material

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Magnetic hyperthermia is a promising technique for cancer treatment. It is based on the fact that magnetic nanoparticles (MNPs) exposed to an alternating magnetic field release a heat. Magnetic losses in liquid suspension of magnetosomes can be investigated by analysis of minor hysteresis loops and specific absorption loss power determined calorimetrically. Hysteresis losses may be determined in a well-known manner by integrating the area of hysteresis loops, a measure of energy dissipated per cycle of magnetization reversal. It depends strongly on the field amplitude as well as the magnetic prehistory.

In this contribution we present the calculation of the energy contribution from hysteresis losses as a function of applied magnetic field. Losses were calculated from the minor hysteresis loops of magnetosomes extracted from *Magnetotacticum Spirillum*-AMB1. Samples of magnetosomes were divergent in length i.e. chains of magnetosomes have been modified due to mechanical effects during sonication. Figure 1 shows the energy losses of magnetosomes is reduced (even) twice as a consequence of sonication treatment. This result is compatible with hyperthermia measurements (Specific Absorption Rate) that show the magnetosomes are auspicious materials for applications in hyperthermia, and therefore in cancer treatment.

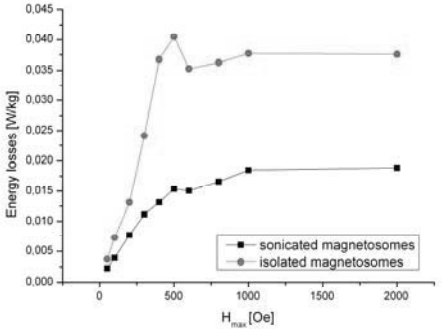

Fig. 1. Hysteresis loss of magnetsomes as function of magnetic field amplitude of minor hysteresis loops.

Acknowledgements
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Design of a continuous biomagnetic algae harvester

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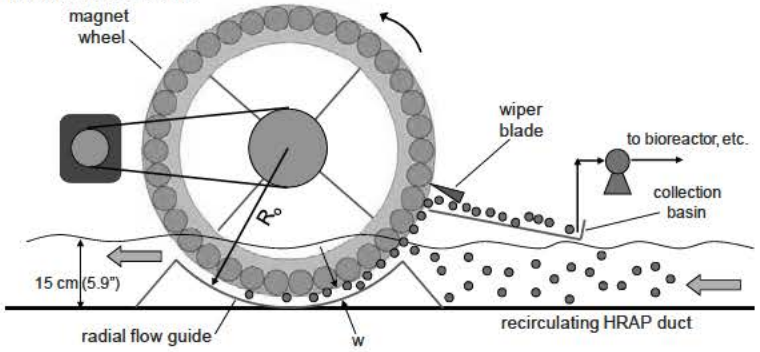
Algae can be grown to provide food for humans and animals, specialized nutritional and commercial products, and for biofuels, such as biodiesel and bioethanol. Algae growth yields among the highest biomass per land area of any plant type. Moreover, it can be easily fed, often with agricultural or industrial wastewater, sunlight and atmospheric CO_2. A key challenge in algae production is the high cost of harvesting from growth environments, typically called High Rate Algae Ponds (HRAP). The classical means of harvesting - filtration, centrifugation, flocculation-assisted sedimentation or flotation – all have serious drawbacks in the form of high equipment and energy costs. Our group has developed genetically-engineered strains of *Chlorella* that uptake iron from the medium and sequester it in the form of ferritin. Ferritin is superparamagnetic and contains up to 8000 Fe atoms per unit. Thus, magnetic separation is proposed as a lower cost alternative for algae harvesting. Inspired by the wet drum magnetic separator, a continuous magnetic separator has been modeled and designed with features specific to the requirements of algae harvesting. It contains diametrically polarized neodymium cylinders attached to a high-permeability flux return path resulting in a wheel-like assembly. The wheel is to be rotated at low angular velocity as biomagnetic algae is pumped in a narrow angular duct defined by the magnetic wheel and a flow guide. The algal cells deposit on the wheel and are swept off by a stationary brush into a catch basin, as the wheel emerges from the suspension. The geometry allows the separation to be modeled as flow between parallel plates with one wall in motion, while an external pressure gradient is applied to the fluid, and with an external body force applied to the discontinuous phase. The theoretical development, sorting predictions and design features are presented.



Hyperthermia response of magnetosomes extracted from *Magnetospirillum gryphiswaldense* strain MSR-1

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A relatively unexplored method for the production of magnetite nanoparticles is the biological synthesis by the magnetotactic bacteria. Magnetotactic bacteria [1] are microorganisms that have the ability to align and navigate along the geomagnetic field lines due to the presence of a chain of magnetic nanoparticles called magnetosomes. In this work, we have obtained magnetosomes from *Magnetospirillum gryphiswaldense* that produces magnetite, Fe_3O_4, cubo-octahedral shaped nanoparticles with an average size diameter of ~45 nm, Fig. 1a. Bacteria were broken with a cell disruptor and the magnetosomes were magnetically separated by placing the cell extract in a magnetic rack. Afterwards, the isolated magnetosomes were subjected to three different purification treatments: i) rinsing with 10mM HEPES/200mM NaCl under low power ultrasonication; ii) removing DNA with 5U/ml of DNase for 1h before treatment described in i); iii) passing through a MACS magnetic separation column after treatment described in ii). In order to check the level of purification infrared absorption measurements were carried out on the magnetosomes suspensions. The experiments were performed with magnetosomes suspended either in PBS or in 2% agarose gel at a magnetite concentration of 200 μg/ml. The suspensions were magnetically characterised and the specific absorption rate (SAR) was measured using AC magnetometry and calorimetric methods. All samples assayed presented high SAR values as shown in Fig. 1b for preparation i) and the results were similar in both hyperthermia methods employed. At present, we are evaluating the cytotoxicity of magnetosomes on macrophage cell line ANA-1 (Fig. 1c).

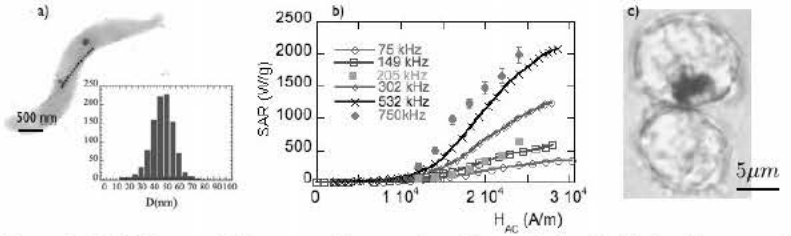

Figure 1 a) TEM image of *Magnetospirillum gryphiswaldense* and size distribution histogram of isolated magnetosomes; b) Specific absorption rate (SAR) measured with AC magnetometry (75, 149, 302, 532 kHz) and calorimetric methods (205, 750 kHz); c) Optical microscopy image of macrophages incubated with magnetosomes Prussian blue staining reveals the presence of iron inside one of the cells

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Optical detection of nanoparticles in a living system under the influence of a magnetic field

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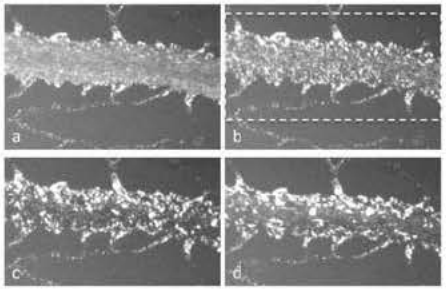
Particles are important in diagnosis and therapy. However most of the *in vitro* experiments do not mimic the dynamic conditions of the *in vivo* situation. Hence several chicken-based test systems using eggs were employed for research. Blood flow has exceptional rheological properties. Existing velocimetry studies on chick embryo were performed on candled eggs by means of µPIV (micro particle imaging velocimetry). The in-vivo transport of magnetic particles in rats was observed and transport modes considered assuming a constant size (no agglomerates) [A. Nacev, et al., Nanomedicine 2010 5(9) 1459-1466].
Aim of our work was a first in-vivo observation of MP transport in chicken egg vessels in presence of a magnetic field by single particle tracking. For that we demonstrate the spatial resolution of our observations on a cross section of a vein and a temporal resolution by observation of the cardiac cycle in an artery. Microscopical images were recorded with a AxioImager Z1.m (Carl Zeiss, Jena, Germany) and a PCO Sensicam camera in dark field reflection and fluorescence mode, respectively. Single particle tracking and track analysis is realized with a plugin for the image processing package Fiji [http://fiji.sc/TrackMate].



Formation of agglomerates in a vein under a magnetic field: before applying a field (a), after ≈ 4s (b) and 10s (c) applying a field, respectively, and ≈ 8s after removing the field (d).

Magnetic Iron Oxide Nanoparticles Having High AC-Susceptibility

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Magnetic field detection sensors such as magneto resistive sensors have recently been spotlighted in the area of biomedical in-vitro diagnostics, particularly in the format of immunoassay where magnetic particles are used as labels. Among such sensors, AC field-based detection is more advantageous than DC field-based detection because of its ability to measure magnetic label capture curves in real time and bring in additional kinetic information. Superparamagnetic nanoparticles are required for such application not only to avoid aggregation of the magnetic nanoparticle labels in aqueous solution but also to utilize frequency domain signal detection. Therefore, magnetic nanoparticles (MNPs) with high AC-susceptibility are critical to successful development of such AC field-based sensors with high sensitivity and fast reaction speed.

In this paper, we present the development of superparamagnetic nanoparticles possessing high AC-susceptibility. The magnetic iron oxide nanoparticles are synthesized using a modified version of the thermal decomposition method. We find that thus-prepared MNPs show significantly higher AC-susceptibility than commercially available MNPs of same material and size by a factor of up to 7 times. After extensive high resolution transmission electron microscopy (HRTEM) and X-ray diffraction (XRD) characterizations, we attribute such high AC susceptibility of our MNPs to the predominance of a single domain, superior crystallinity, and minimum content of undesired phase (particularly FeO).

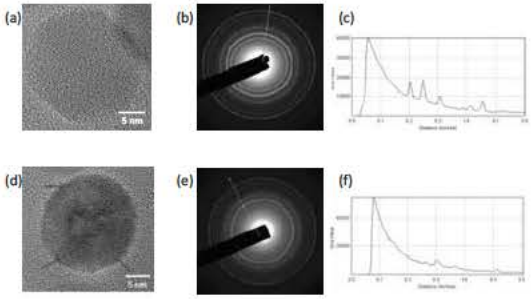

Figure 1 Comparison of high-resolution TEM images [(a) and (d)], selective area diffraction (SAD) patterns [(b) and (e)], and profiles of SAD cross section [(c) and (f)] between the magnetic nanoparticles synthesized in this study [(a), (b), and (c)] and commercially available magnetic nanoparticles of same material and size [(d), (e), and (f)].

Colloidal Stability and Magnetophoretic Mobility of the Silica Iron Oxide Magnetic Nanoparticles and Their Assemblies for Gene Delivery

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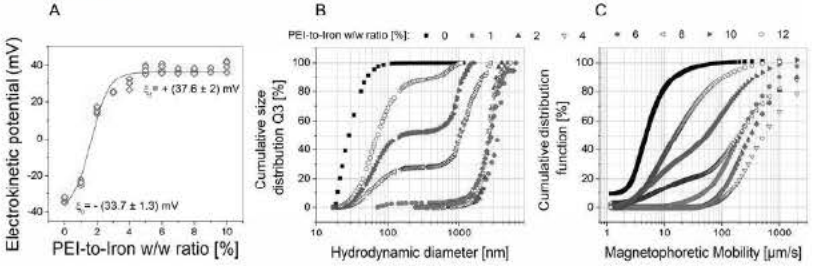
Application of magnetic nanoparticles for nucleic acid delivery requires carefully designed colloidal and magnetic properties of the particles and their assemblies with gene delivery vectors [1] To this end we focused on the nanoparticles having a magnetic iron oxide core of about 10 nm that are stabilized by a silica oxide with surface phosphonate groups (negative surface charge at physiological pH) and decorated with the cationic polyelectrolyte polyethylene imine (PEI) [2] In this paper the relationships between degree of nanoparticle loading with PEI, electrokinetic potential, particle size distribution, dispersion stability and sedimentation, and magnetophoretic behavior were investigated by detecting *s*pace and *t*ime resolved *e*xtinction (concentration) *p*rofiles (STEP) over the entire sample from bottom up to top in-situ during centrifugation or/and upon magnetophoresis in the applied gradient magnetic fields The particle decoration by PEI renders the sedimentation behavior from polydisperse sedimentation of primary particles (zero PEI loading) via a completely flocculated dispersion (zone sedimentation at 1-2% PEI loading) to again a polydisperse sedimentation at high PEI loading (PEI–to iron w/w ratio of 12%) As a transient state it was found that for PEI loadings by more than 4 % a sub fraction of individual particles appears, which ratio increases gradually until at 10-12 % PEI concentration the particles are completely dispersed In contrast the measurement of zeta-potential shown in *Figure A* only slightly changed between 4 and 12 % PEI However, high resolution measurements of size distribution show gradual approach towards insulated particles size (no or 0% PEI) between 8 and 12% loading with PEI Size distribution patterns deduced from the STEP measurements (shown in *Figure B*) resemble the magnetophoretic mobility cumulative distribution functions (*Figure C*) Assembling of the primary or decorated nanoparticles into gene delivery viral, non-viral nucleic acid complexes, and vesicles (microbubbles) drastically modify colloidal stability and magnetophoretic mobility of the delivery vehicles affecting nucleic acid delivery efficacy in vitro, ex vivo and in vivo



Acknowledgements We gratefully acknowledge the support from the German Research Foundation through the DFG Research Unit FOR917 (Project PL 281/3-1), from the German Federal Ministry of Education and Research through the grant ZIM-KOOP 'STEP-MAG', and from the Excellence Cluster 'Nanosystems Initiative Munich'

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AMF-Induced Release of Iron Oxide-Bound Substrates via Cyclization of Thermally Responsive Amino–Carbonates and –Carbamates

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We studied a panel of thermally sensitive amino-carbonates and amino-carbamates to evaluate their cyclization rates on heating. After analyzing the influence of chain length, steric factors, *gem*-dimethylation and additional functionalities, we have determined which carbonate and carbamate configurations are well-suited to undergo intramolecular nucleophilic attack by pendant amines. In this event (Figure), the formation of an oxazolidinone (Y = O) or cyclic urea product (Y = NH) releases an alcohol substrate, and this step is of interest as a potential drug delivery mechanism. Since Fe_3O_4 nanoparticles (NPs) readily heat when placed in an alternating magnetic field (AMF), we examined whether this magnetic field-induced heat could be used to trigger the aforementioned ring-closures. We present here our efforts to covalently attach the amino-substrates to both unmodified and silica-coated NPs, and the results of AMF exposure on the loaded NPs.

Figure. Thermally induced intramolecular ring closure

n = 1 - 3
Y = CH_2, O, NH
X = O

Improving transfection efficacy using nanoparticles in magnet-assisted gene delivery

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Nanomagnetic transfection is a method for delivering genes into a cell using an external magnetic force to increase the interaction between cells and magnetic nanoparticle-DNA complexes. This method has been as an alternative to other non-viral transfection techniques because it has potential to increase transfection efficiency, reduce transfection time, improve cell viability, and deliver genes to cells that are difficult to transfect [1, 2]. Recently, we have developed an oscillating magnet array system that enhances partice/DNA uptake through promotion of endocytosis [3, 4]. Here, using commercially available magnetic nanoparticles (MNPs) and green fluorescent protein (GFP) plasmid reporters, we evaluate the effect of varying frequency and amplitude of the oscillating magnet arrays on the transfection efficacy of mammalian cells.

MNPs used for nanomagnetic gene transfection generally consist of superparamagnetic iron oxide cores, which respond to external magnetic fields, with cationic polyethylenimine (PEI) polyplexes for DNA adsorption. The physical and chemical properties of these particles, particularly PEI, have the potential to be toxic to mammalian cells [5, 6]. Therefore, the biocompatibility of MNPs is evaluated to ensure transfected cells maintain good viability, and proliferation and differentiation abilities.

We also focus on optimizing transfection parameters (particle:DNA ratios, seeding cell density, complex concentration) for immortalized, model cell lines such as HeLa cells frequently used in *in vitro* studies to achieve the highest transfection using MNPs.

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Design of High Frequency Magnetic Hyperthermia System for Human Cancer Treatment using Superparamagnetic Nano Particles

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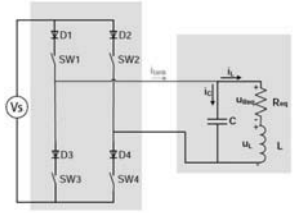
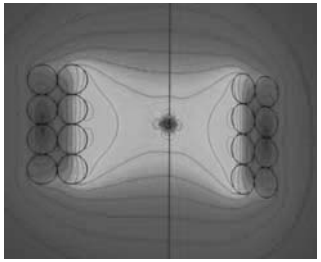
Using superparamagnetic nano particles (SNP) has been considered to be an effective method in targeted drug delivery and magnetic induction hyperthermia for cancer treatment This method has been investigated widely using in-vivo and in-vitro methods and so many successful results have been reported in the literature The systems which are being used for magnetic induction hyperthermia are basically systems used for induction heating in industrial applications These systems in order to be used for human treatment applications need some modifications to optimize magnetic circuit efficacy and also minimize probable destructive effects on non-cancerous organs

In this research magnetic hyperthermia systems have been investigated in different aspects including power electronics, Magnetics and thermal efficiency First magnetic circuit and Electro Magnetic Coil (EMC), with proper dimensions for human use, have been modeled and studied using Finite Element Analysis in COMSOL-Multiphysics In this stage magnetic efficacy has been studied by modeling a cancerous tumor while SNPs have been injected in it In the second part the power electronic circuit is modeled based on analytic calculations and experimental data obtained from MIRobin 200, provided by Pars Robin Smart Devices In the next step the parameters of the magnetic circuit and EMC obtained from first stage are used to model the whole system and find optimal values for resonance circuit in high frequencies After that thermal issues in EMC have been studied to prevent overheating and injury because of high temperature coils in contact with patient's body Finally the designed system was built in smaller scale as a proof of concept and was tested on a sample of magnetite nano-particles

This research discusses different aspects and challenges in using magnetic hyperthermia systems for human cancer treatment and proposes an analytic and experimental approach for effective design of these systems





Why measuring SAR in function of temperature may result useful and/or interesting

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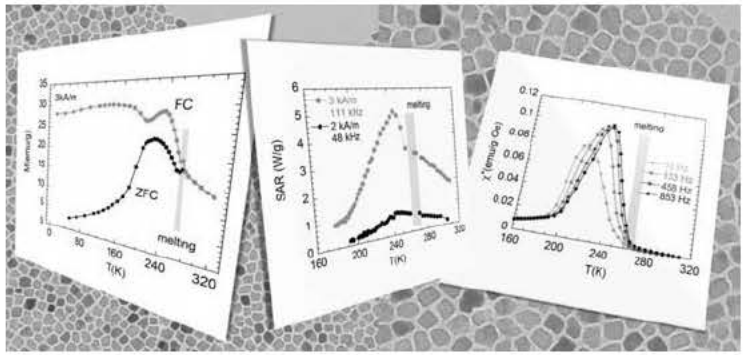
The heating ability of magnetic nanoparticles (MNPs) for magnetic hyperthermia is commonly quantified by means of the specific absorption rate (SAR), also referred to as specific loss power (SLP). This heating ability is related to the magnetization reversal processes that occur when MNPs are subjected to an alternating magnetic field. Accordingly, SAR values depend, like magnetic properties, on temperature.

Magnetic hyperthermia therapy involves temperatures from 36 up to about 50 C. It is then essential to evaluate SAR in this narrow temperature range, in function of the amplitude, H_0, and frequency, f, of the applied magnetic field. Some materials may show a weak SAR variation in this range, making reasonable the use of average values for therapy planning. But in other cases, SAR values may change appreciably as temperature increases. An extreme case is found in self-regulating MNPs, in which the SAR drop at the temperature range of interest is the basis of their functionality.

Also, the determination of SAR in a wider temperature range may provide further information about the MNPs, necessary for the feedback synthesis-characterization-application. For example, it is well-known that the thermal dependence of the out-of-phase ac magnetic susceptibility, χ'', provides useful information of certain magnetic transitions. At low H_0 values, where the linear response theory is fulfilled, SAR is linearly proportional to χ'', thus providing similar information, but obtained with f and H_0 values more adequate for magnetic hyperthermia.

In this contribution, we describe a measuring technique suitable for obtaining SAR(T) data, as well as give several measuring examples that point out why measuring SAR in function of temperature may result useful and/or interesting.



Thermal dependence of static magnetization, specific absorption rate and ac susceptibility of a ferrofluid

Rapid and Controlled Transition of Magnetic Nano- to Micro-particles: A Useful Feature for Bioseparations

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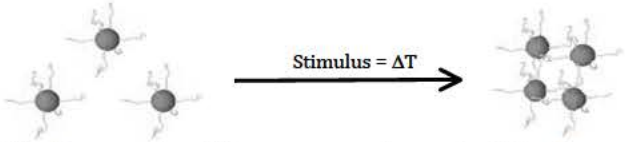
Magnetic microparticles are used extensively both by life science companies and academic researchers to perform bioseparations and molecular assays. They are also integrated in numerous FDA-approved clinical immunoassay kits (e.g., Abbott ARCHITECT HIV® Ag/Ab Combo test) for rapid separation and quantification of disease biomarkers from patient serum samples. Magnetic nanoparticles (mNPs) offer many advantages over microparticles for these applications. First, they have favorable diffusion coefficients, which enables efficient interrogation of the sample. Second, they have a higher surface area:volume ratio, which enables more binding of target molecules. However, the potential advantages of mNPs have not been realized because mNP preparations often exhibit poor colloidal stability, and the mNPs are too small to separate with simple magnets.

Nexgenia is commercializing a reagent system that combines stimuli-responsive polymers with mNPs and biomolecules. The physicochemical properties of stimuli-responsive polymers change (i.e., from hydrophilic to hydrophobic) in response to environmental triggers such as temperature, solution ionic strength or pH. Biomolecules and mNPs modified with these polymers exhibit similar stimuli-responsiveness. With this reagent system, the advantages of mNPs are maintained (e.g., high diffusion rates and high surface area:volume ratio) during binding reactions. Then, an environmental trigger causes the stimuli-responsive biomolecules and mNPs to form large, micron-sized aggregates that are easily isolated with a simple magnet (Figure 1).

The polymer poly(*N*-isopropylacrylamide), or pNIPAM, is used to make the mNPs temperature-responsive. pNIPAM is synthesized using Reversible Addition Fragmentation Chain Transfer (RAFT), which results in nearly monodisperse polymers with sharp temperature transitions. Resultant polymers are then further modified to enhance chemical and thermal stability. Stimuli-responsive mNPs are synthesized in a one-pot reaction and are immediately water-soluble. The mNPs comprise a γ-Fe_2O_3 core and a corona of stimuli-responsive polymers with a polymer:Fe ratio of 1.4 ± 0.28 (measured by thermogravimetric analysis). The hydrodynamic diameter of the mNPs is 25 ± 4.0 nm, and the particle distribution is fairly monodisperse (PDI = 0.112 ± 0.040). The mNPs are soluble at room temperature (< 28 C), but they are hydrophobic and aggregated at slightly higher temperatures (~ 32 C). This hydrophilic/hydrophobic transition is quantified via the lower critical solution temperature (LCST), and the mNP LCST is 29 ± 0.56 C. Therefore, mNPs in a solution cannot be isolated with a magnet at 25 C (separation efficiency = $1.8 \pm 4.0\%$). The mNP separation efficiency is $99 \pm 0.58\%$ after 2 minutes at 37 C, so the temperature transition is both discrete and rapid. Additionally, the hydrophilic/hydrophobic transition can be repeated more than ten times by cycling the solution temperature with no deleterious effect on mNP performance or size. These stimuli-responsive mNPs show useful and consistent properties, and Nexgenia's unique reagent system has applications in clinical immunoassays, biomarker discovery, and cellular and other laboratory bioseparations.



Stimuli-responsive mNP
Iron core and polymer corona
Hydrophilic and soluble
Cannot be isolated with magnet

Aggregate of stimuli-responsive mNPs
Hydrophobic
Large enough for magnetic separation
Used to isolate polymer-conjugated biomolecules

Investigation of magnetic properties of Fe_3O_4 nanoparticles using temperature dependent magnetic hyperthermia in ferrofluids

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Rate of heat generated by magnetic nanoparticles suspended in a liquid is affected by their magnetic properties, temperature and the viscosity of the carrier liquid. We have investigated temperature dependent magnetic hyperthermia in ferrofluids, consisting of dextran coated superparamagnetic Fe_3O_4 nanoparticles, subjected to external magnetic fields of various frequencies (188-375 kHz) and amplitudes (140-235 Oe). Transmission electron microscopy measurements show the nanoparticles are polydispersed with a mean diameter of 13.8 ± 3.1 nm. The fitting of experimental dc magnetization data to a standard Langevin function incorporating particle size distribution yields a mean diameter of 10.6 ± 1.2 nm, and a reduced saturation magnetization (~ 65 emu/g) compared to the bulk value of Fe_3O_4 (~ 95 emu/g). This is due to the presence of a finite surface layer of non-aligned spins surrounding the ferromagnetically aligned Fe_3O_4 core. We found the specific absorption rate, measured as power absorbed per gram of iron oxide nanoparticles, decreases monotonically with increasing temperature for all values of magnetic fields and frequencies. Using the size distribution of magnetic nanoparticles estimated from the magnetization measurements, we fitted the specific absorption rate versus temperature data using a linear response theory and relaxation dissipation mechanisms to determine the value of magnetic anisotropy constant (27.6 ± 1.9 J/m^3) of Fe_3O_4 nanoparticles

Controlled clustering of PAM-coated superparamagnetic iron oxide nanoparticles through PEI

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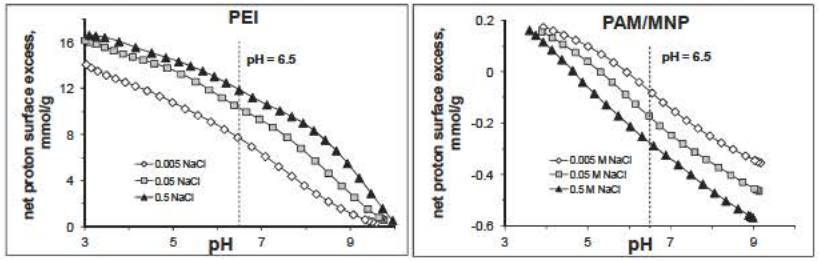
The growing interest in the use of superparamagnetic iron oxide nanoparticles (SPIONs) for biomedical purposes indicates the need for products with enhanced properties such as SPION clusters, which show greater potential in theranostic application. Recently clustered PEG/OA coated magnetite nanoparticles were synthesized which showed superior MRI contrast capability when compared them to the non-clustered product[1]. Our goal was to produce nanoclusters controlling the size and properties of the materials. Poly(acrylic acid-co-maleic acid) coated magnetite nanoparticles[2] (PAM@MNP) were electrostatically adhered with the help of polyethylenimine (PEI). To synthesize the cluster, naked MNPs were coated with PAM and the product was compacted and then washed to remove the excess of PAM. The precursors of nanoclusters, i.e., PAM@MNP and PEI were characterized with potentiometric acid-base titration. Particle size and ζ-potential for the individual precursors were also measured using dynamic light scattering (DLS) and electrophoretic mobility measurements, respectively, at different pH and varying PAM@MNP or PEI concentrations. The clustering of the coated MNPs was achieved by mixing identical portions of PEI solutions and PAM@MNP magnetic fluid at pH=6.5 and constant salt concentrations in a controlled manner using ultrasonic bath. The concentration of PEI and salt was varied and the obtained products were characterized using DLS and electrophoretic measurements. A clustered SPION products were achieved using well-controlled mixing of PAM@MNP magnetic fluid and PEI solutions. Based on the results the clustered products are expected to have enhanced MRI contrast and hyperthermia properties.



Surface protolytic reactions of PEI and PAM@MNP measured by potentiometric acid-base titration.

Literature:

1. E. Illés, M. Szekeres, E. Kupcsik, I.Y. Tóth, K. Farkas, A. Jedlovszky-Hajdú, E. Tombácz, PEGylation of surfacted magnetite core-shell nanoparticles for biomedical application. Colloids and Surfaces A , 2014. http://dx.doi.org/10.1016/j.colsurfa.2014.01.043
2. I.Y. Tóth, E. Illés, R.A. Bauer, D. Nesztor, M. Szekeres, I. Zupkó, E. Tombácz, 2012. Designed Polyelectrolyte Shell on Magnetite Nanocore for Dilution-Resistant Biocompatible Magnetic Fluids. Langmuir 28: 16638–16646.

Acknowledgements: This work was supported by OTKA (NK 84014).

EFFECTS OF DIFFERENT SUPERPARAMAGNETIC IRON OXIDE NANOPARTICLES ON MURINE PRIMARY BRAIN CELLS

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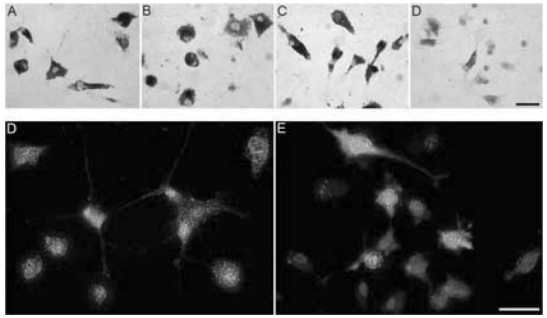
Superparamagnetic iron oxide nanoparticles (IONPs) are promising tools for non-invasive imaging of pathological processes within the central nervous system (CNS). Since crucial information regarding adverse effects of local particle interactions or even accumulations is still lacking, we focused on answering the question if clinically approved IONPs may influence the vitality and morphology of brain cells.

In our approach, we investigated the effect of IONPs *in vitro* using cell cultures two main cell types of the CNS, namely the information transmitting neurons and one type of glial cells. We selected the numerous microglial cells that play the pivotal role in the innate immune response of the CNS and can be activated to a phagocytic state upon various kinds of brain pathology. We prepared primary cell cultures of microglia and neurons as well as neuron-glia co-cultures from mice and exposed these cultures to either one of the two monomer coated Very Small Iron Oxide Particles, differing in size (VSOP-R1/-R2) or polymer coated ferucarbotran (Resovist®; Bayer Schering Pharma AG) or ferumoxytol (Feraheme®; AMAG Pharmaceuticals, Inc.), respectively. IONPs were applied in concentrations of 0.5mM, 1.5mM and 3.0mM for 6h and/or 24h.
We observed severely compromised microglial viability as determined by Propidium iodide (PI) with increasing IONP concentrations, except when exposed to ferumoxytol. Furthermore, iron contents of microglia visualized using Prussian blue staining, revealed saturation with increasing incubation time, whereas numbers of dead cells were still increasing. Primary neurons showed morphological alterations, i.e. neuronal degeneration after IONP exposure as compared to untreated controls. Probably due to the protective effect of phagocytic active microglia, the vitality of neurons in neuron-glia co-cultures was not substantially affected following IONP exposure.

Our results elucidate potential cytotoxic effects of IONP exposure on essential CNS cells and contribute to assess the prospects and limitations for IONP applications *in vivo*.



Prussian blue staining of primary microglial cells, previously exposed to 3.0 mM of VSOP-R1 (A), VSOP-R2 (B), ferucarbotran (C) and ferumoxytol (D) for 24 h (scale 40µm). Immunofluorescent staining of microglia is shown for cells exposed to 1.5 mM of VSOP-R1 (D) and ferumoxytol € for 24h (scale 20µm).

Controlled clustering and functionalization of SPIOs

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On the last meeting in 2012 we have presented our first results in producing stable and defined clusters of iron oxide nanoparticles using our continuous phase transfer process. For these results we had used oleic acid coated iron oxide nanoparticles with a diameter of 10 nm and the amphiphilic diblock polymer PI-PEO. Through variation of the mixing characteristics of our setup we were able to influence the number of iron oxide particles per micelle, spanning the range from 30 nm to 170 nm. This led to an increase of r_2 from 50 to 200 m/M*sec.

Today we present the enhancements of this approach. We have varied the particle diameter, the ligands of the particle surfaces, the polymer length and the encapsulation conditions to increase the reproducibility and the desired increase in r_2. We will show that all mentioned influence factors have to be taken into account for the best performance, but especially the ligands on the particle surfaces which determine the particle-particle distance inside the cluster have to be adjusted. We will show ligand exchange procedures prior the encapsulation, their characterization with thermogravimetry and their influence on the relaxivity.

These Pi-PEO micelles exhibit very long in vivo circulation times of 10 hours and above. To create specificity of this contrast agent we have worked on the attachment of affinity molecules to the outer shell of the micelles. We will show different approaches to reach this target: direct coupling of these molecules to amino groups at the PEO end or indirect coupling to the micelle using avidin/neutravidin.

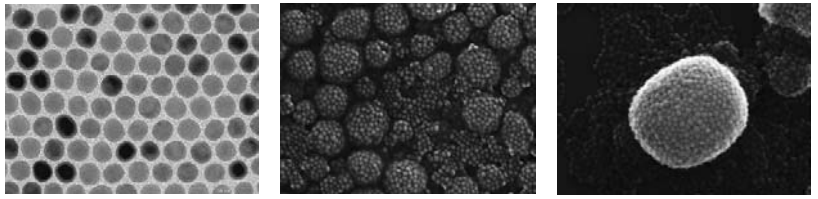

Fig 1 – TEM image of iron oxide nanoparticles prior to encapsulation (left) and SEM images of 150 nm clusters containing these particles in different magnifications (middle and right)

Instrumental approach for analysis of protein function in magnetic nanocarriers: 31P NMR study of ATPase cycle of heat shock protein Hsp70 conjugated with SPION

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Magnetic nanoparticles (MNPs) conjugated with 70-kDa heat shock protein Hsp70 were shown to provide efficient tumour contrast enhancement on magnetic resonance images in the model of intracranial glioma in rodents (Shevtsov et al. Neuro-Oncol. 2014;16(1):38-49). The diagnostic potency of functionilized MNPs depends on the biological activity of Hsp70. This protein consists of an N-terminal ATPase domain (nucleotide binding domain, NBD) and a C-terminal substrate binding domain (SBD). The ATPase cycle determines the binding of the Hsp70 to proteins and peptides. The mechanism by which ATP interacts (through adenosine nucleotide or three phosphate groups) with NBD is still unclear.

Interaction of ATP with Hsp70 conjugated to MNPs was investigated by 31P, 1H-NMR methods. The spectrum and magnetic relaxation times of 31P were measured at CXP-300 spectrometer in suspensions supplemented with ATP, ADP, buffer components, Mg^{2+} and hydrophobic peptide KKFYQLALTKK. The 31P NMR spectra of ATP consisted from three well-resolved lines of P_α, P_β, P_γ phosphate groups (**Fig. 1A**). Introduction of magnetic conjugates with Hsp70 to ATP solution stimulated the ATP hydrolysis. The generation of P_i, AMP and ADP spectrums followed the decrease of intensity of triplet ATP lines. The entrance of ATP into NBD was demonstrated by measurement of spin-relaxation time T1 of each 31P nuclei in ATP (**Fig. 1B**). The relaxation times were estimated with help of pulse sequence 180^0-90^0 without saturation at long repetition time 35s. The gradual increase of relaxation times from P_α to P_γ group is considered as evidence of preferred ion-ion interaction of ATP with various phosphate-binding loops of Hsp70 such as Thr14 and Thr204. The analysis of experimental data obtained by 31P NMR method suggests that ATP interacts through its terminal phosphate groups (i.e., P_β and P_γ) with Hsp70 (**Fig. 1C**). Subsequent ATP hydrolysis stimulated the binding of KKFYQLALTKK peptide by Hsp70. The proposed approach of 31P NMR analysis of ATP interaction with Hsp70 conjugated to MNPs provides a novel method for assessment of Hsp70 molecular activity.

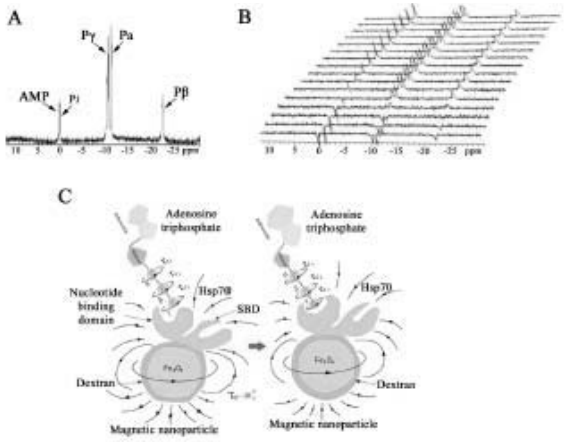

Figure 1. **(A)** Spectrum of phosphates in the presence of Hsp70. **(B)** The spin-lattice relaxation of nuclei 31P ATP/ADP in systems of magnetic conjugate with Hsp70. **(C)** Schematic representation of ATP interaction with NBD of the Hsp70 conjugated to nanoparticles.

Modelling of NMR relaxation immunoanalysis using superparamagnetic complement system: interferon-immunonanomarker

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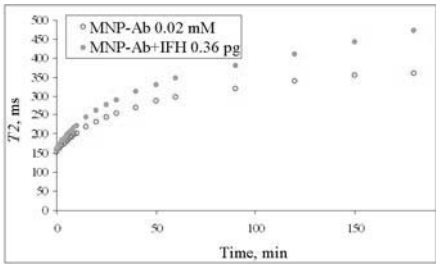
Relaxation immunoanalysis of interferon α -2*b* using superparamagnetic nanomarkers is based on measurement of water protons relaxation time in suspension vs. degree of aggregation of magnetic nanoparticles in the presence of antibodies (Ab). Immunochemical activity is measured in terms of magnetic relaxation times T_2 of water protons in conjugates during a considerable incubation times in homogeneous magnetic field of high strength. High sensitivity of the method is provided by specificity of immune reaction and by selection of high frequency fill-in by short radiofrequency impulses of generator.

The aim of this study is to evaluate (using interferon model) possibilities of testing antigen-antibody reactions mediated by magnetic nanoparticles by sensitive measurement of disturbances in homogeneous magnetic field by magnetic conjugates, and also by study of conjugates influence on the rate of magnetic relaxation of water protons.

In antigen-antibody reaction, nanoparticles, conjugated with interferon α-2b, connected to antibody, create an associate. Formation of magnetic conjugate of α-2b interferon and antibody complex leads to appearance of clusters of nanoparticles. This process is additionally accelerated by influence of strong magnetic field. Presence of stable visually undetectable clusters of iron oxide magnetic nanoparticles induces additional magnetic interactions, which lead to further growth of clusters, which are not destructed by Brownian motion. These clusters are of flocular nature in which magnetic nuclei of particles are included into the associates with effective hydrodynamic size of 10 to 0.1 μ.

The experiments were carried out using impulse NMR spectrometer CXP-300 (Bruker), supplied with cryomagnet with vertical void, in which magnetic field of 7.1 Tl of high homogeneity is generated. Investigations were carried out in standard cylindrical NMR ampoules of 5 mm diameter. Suspensions of magnetic nanoparticles and of magnetic conjugates of 500 μl volume were used as a control. In order to carry on the specific reaction suspension of conjugates was added to monoclonal antibodies solution to receive the concentration of suspension 4 $\mu g.ml^{-1}$. The frequency of proton resonance was 300.13 MHz. Times of spin-spin relaxation T_2 were measured using modified impulse sequence CPMG 90 -$[\tau\text{-}180_x\text{ -}2\tau\text{-}180_{-x}\text{ -}2\tau\text{-}180_x\text{ -}2\tau\text{-}180_{-x}\text{ -}\tau]_n$. Duration of 90 impulse was 5.5 μs, 180 – 11 μs, τ is varied within the interval of 800 μs to 2000 μs, number echo signals n = 512. Human recombinant interferon α-2b and magnetic conjugates are prepared in the State Institute of Highly Pure Biopreparations, St. Petersburg. Magnetic nanoparticles were synthesized using Massart method. Sample of FluidMAG-DX, Chemicell used as a control. Amount of conjugated protein was controlled by immunofluorescent analysis and by DLS. Content of protein in magnetic conjugates was not less than 0,06 ng per 1 mg of iron. Modeling of immune reaction of the pair: interferon-antibody in the medium of magnetic particles revealed the acceleration of *T2* of water protons up to 400 ms. The sensitivity of method is 36 pg of protein. The relationships of spin-spin relaxation *T2* of water protons in 500 μl of suspension of magnetic antibodies (0.02 mM) with 0.36 pg of interferon vs. time is presented in the graph.



Design for Highly Parallel and Uniform Magnetic Cell Separation

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Magnetic separation of cells has become increasingly common as purification and isolation of these cells can facilitate further biological analysis such as genetic analysis via Polymerase Chain Reaction (PCR) Current magnetic separation techniques typically fall into 2 dichotomies, fast tube-based bulk separations which rely on a non-proximal permanent magnet and the weaker, less uniform field gradients, and sophisticated microfluidic designs which achieve fine control and separation, but at lower throughputs A potential problem with adapting a microfluidic device's design principle to a higher throughput, microfluidic device is the non-uniform fluidic forces that will develop due to the scale

Here, we present COMSOL simulation results illustrating how a magnetic separation design utilizing a dense array of pores, while being consistent with maintaining a device's high volumetric flow-rate, can also homogenize fluidic flow through the device, eliminating non-linear laminar flow effects from the tube walls Each individual pore is effectively de-coupled from its' neighbors, thus ensuring identical fluidic and magnetic forces are felt by each cell as it passes through any pore within the device, eliminating issues where cells have variable probabilities of capture depending on their position In addition to the simulation, we also present experimental results showing the capture distribution of cells within the device to be uniform, thus further illustrating the flow homogenization process

The phenomenon illustrated here suggests a simplistic solution to scaling various microfluidic devices might be to parallelize the device while maximizing the fluidic resistance in order to attain **flow homogenization** We conclude by presenting results for a scaled up version of our magnetic separation device, capitalizing on this flow property to attain capture efficiencies of **>90%** at flow rates of **40 mL/hr** for NCI-H1650 lung cancer cells labeled with 150nm-sized magnetic nanoparticles

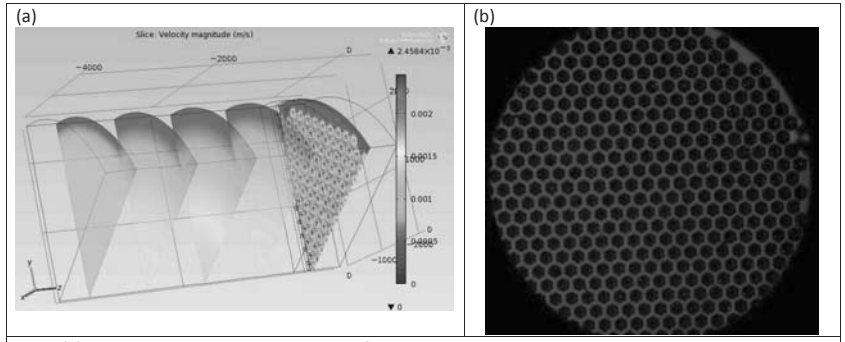

Fig 1. (a) COMSOL simulation illustrating the flow homogenization that develops across the device due to high fluidic resistances of each pore. (b) Uniform distribution of cells (green dots) on the device illustrates the flow homogenization of the device.

Express dry-reagent bioassay based on detection of magnetic nanoparticles from the entire volume of 3D structures

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Rapid quantitative bioassay has been developed on the basis of dried immunoreagents and magnetic nanoparticles (MNPs) used as nanolabels. All these components are reactivated by tested human serum sample. MNPs specifically caught on fibers of 3D membrane structures (Fig.1a) are detected from the entire volume of the structures rather than from its surface only as it is typically done while using of flat biochips (including GMR) or traditional optical labels. MNPs are counted by exposing of sample to an *ac* magnetic field at two frequencies f_0 and f_1 with recording the signal, which is proportional to the MNP quantity, at the combinatorial frequency $f_1 \pm 2f_0$ [1]. This highly sensitive detection method is robust, features high signal-to-noise ratio and extraordinary large linear range [2].

The advantages of the developed bioassay have been demonstrated by quantification of oncology markers in human serum. The detection limit of prostate-specific antigen was as low as 25 pg/mL in a wide dynamic range of concentrations that exceeded 3 orders of magnitude (Fig. 1b). These results are better than those obtained by standard much more labor- and time-consuming approaches such as ELISA. As the developed bioassay is based on dry chemistry, it is stable during long-term storage, easy to use and does not require skilled personnel. Besides, the developed detectors allow unique opportunity for effective optimization of the immunoassay protocols by recording of spatial MNP redistribution along the length of the test strip due to a bioreaction (Fig. 1c).

The proposed method can be considered as a promising diagnostic platform for highly sensitive quantitative detection of protein markers of various disease as well as bioactive agents in complex biological fluids.

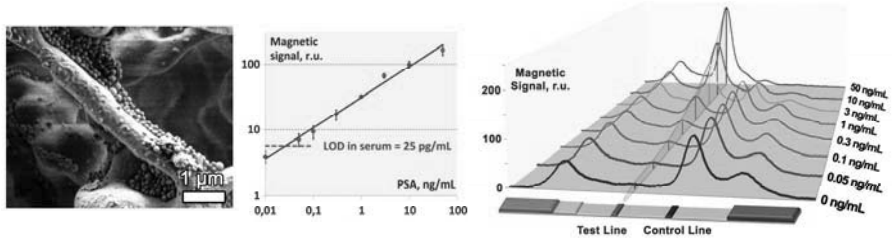

Fig. 1. A) SEM image of MNPs specifically caught on fibers of 3D membrane structure.
B) Calibration curve for PSA in human serum.
C) Redistribution of MNPs along the strip due to the reactions for various concentrations of antigen.

[1]. P.I. Nikitin, P.M. Vetoshko. Patents RU 2166751 & 2177611 (2000), EP 1262766 (2001).
[2]. A.V. Orlov et al. Analytical Chemistry, 2013, 85(2), 1154-1163.

Differences between Brownian and Néel relaxation properties evaluated by AC susceptibility measurements

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Magnetic relaxation time and heat dissipation of magnetic nanoparticles (MNPs) have been evaluated by measuring AC hysteresis loop at high frequency instead of measuring temperature rise [1] Magnetic properties of MNPs are measured by this measurement without influence on the state, the weight nor density of MNPs In this study, susceptibility of dispersed and fixed superparamagnetic iron oxide nanoparticles, and magnetic loss of dispersed samples depending on the concentration of the sample were measured

A commercial magnetic fluid, M-300, purchased from Sigma Hi-Chemical Inc is a water-based magnetite nanoparticle The primary and hydrodynamic diameters of M-300 were 11 ± 3 nm and 52 ± 15 nm, respectively The samples were dispersed in water or fixed with an epoxy bond To prepare the fixed sample, a magnetic fluid of the same volume as the dispersed sample was dried and mixed with epoxy bond The frequency range was 2–1000 kHz, and applying magnetic field was 10–30 Oe

Figure 1 shows the susceptibility of the dispersed and fixed samples in a magnetic field of 30 Oe χ' decreased with an increase in frequency because a decrease in magnetization occurs with an increase in frequency Only Néel relaxation occurred in the fixed sample, whereas both Brownian and Néel relaxation occurred in the dispersed sample It was assumed that the loss peak of Néel relaxation was confirmed at >1 MHz The peak at f = 5–6 kHz assumed a Brownian loss peak because this peak was not observed in the fixed sample The peak frequency calculated with the conventional theory was 3 3 kHz The measured Brownian peak agreed with the calculation The conventional theory has shown that Brownian and Néel relaxation occur in parallel, and the rotation that occurs with the shorter relaxation time is dominant However, coexistence of Brownian and Néel relaxation is observed Brownian relaxation occurred despite faster rotation of magnetic moments than that of agglomerated particles because the rotation of particles was probably interrupted by dipole–dipole interaction [2]

The dependency of susceptibility on magnetic fields indicated that Néel loss increased with the increase in magnetic field because the magnetic moments followed the magnetic field when the field was higher In contrast, Brownian loss decreased with the increase in magnetic field due to aggregation of particles by the high magnetic field Moreover, the dependency of susceptibility and AC hysteresis loop on the concentration of MNPs indicated that Brownian loss was inhibited in the higher concentration because of dipole–dipole interaction

[1] Nakamura et al , *IEEE Trans. Magn.*, 49, 240, 2013
[2] Zhang et al , *Phys. Rev. Lett.*, 77, 390, 1996

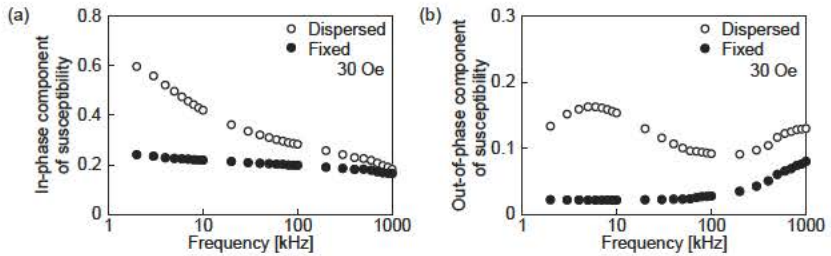

Fig 1 (a) In-phase and (b) out-of-phase components of susceptibility

Balanced nanoparticle spin disorder for enhancement of cancer treatment

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Superparamagnetic iron oxide nanoparticles (SPIONs) are widely used in modern biomedical applications such as magnetic resonance imaging, vector drug delivery and heating agents in magnetic fluid hyperthermia The magnetic fluid hyperthermia is based on the increase of the specific absorption rate (SAR) of the affected tissues which increases the efficiency of their heat damage Our work introduces an innovative insight into the predictions of the heating efficiency (SAR) of the SPIONs, which disproves the generally accepted stereotypes in classification of the SPIONs by means of particle size and spin order The common approach is to consider the bulk-like properties of the SPIONs omitting the internal particle order, of both the structure and spins, which is the governing factor for the SPION heating efficiency

We have experimentally observed that some level of the internal particle structure and spin disorder is necessary to optimize the SAR value In order to quantify SAR dependence on SPION properties correctly, we have introduced two universal parameters that quantify this disorder (Figure 1a) and cover multiple effects that affect SPION response to high-frequency and low-amplitude magnetic field used in hyperthermia treatment We have observed that SAR is maximized under specific disorder value with respect to the particle size (Figure 1b) The advisability of introduction of such parameters is demonstrated on 10 samples (Figure 1c) of SPIONs prepared either by or aqueous routes and one sample which contains the highly crystalline, but multi-domain SPIONs; with different particle size, possessing different magnetic and structural properties

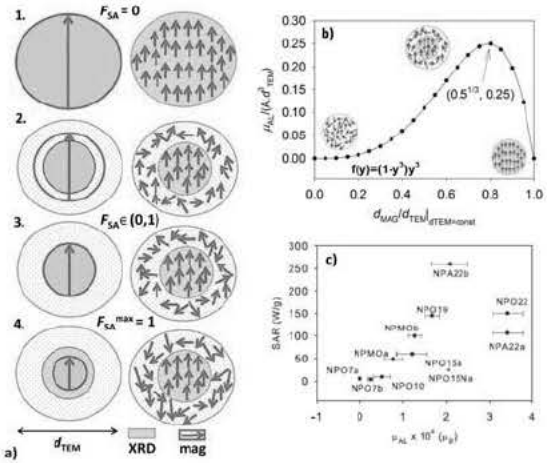

Fig. 1: a) Illustration of the limiting cases of the internal structure of SPIONs (consistent with the text), considering real, coherently diffracting and magnetic sizes, described by diameters d_{TEM}, d_{XRD} and d_{MAG}, respectively The relative ratio of these diameters in single NP for each case is depicted on the left, one of the simplest representations of SPION structure, which considers magnetically ordered crystalline core and misaligned spins in the shell is on the right b) The dependence of the SAR value for the single-domain NPs on the parameter, μ_{AL}.
c) The dependence of the SAR value on the particle alignment parameter, μ_{AL} which is defined as: $\mu_{AL} = F_{sa} \cdot \mu_m$, where μ_m is the particle magnetic moment and F_{sa} is the relative alignment of spins within the particles

A new fucose rich bacterial exopolysaccharide for SPION stabilization

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An *in-house* isolated bacterial strain *(Enterobacter* strain A47 (DSM 23139)) was found to produce a hydrophilic fucose rich exopolysaccharide (EPS).[1] Fucose is a very interesting sugar due to the high added value associated with its rarity and applicability in fields like cosmetics and pharmaceutics. Indeed, fucose-containing oligomers or polymers were shown to have biological proprieties such as anti-carcinogenic, anti-inflamatory and induction of neuronal growth.[1,2]

Given the importance of fucose and the excellent stabilizing and emulsifying proprieties of EPS, it was evaluated in this work, for the first time, as stabilizing agent for iron oxide magnetic nanoparticles (MNP). The physico-chemical proprieties of the resulting system were systematically characterized and its interactions with cells were evaluated through *in-vitro* assays.

Several polysaccharides are usually employed to stabilize MNP[3], but due to the similarity in composition, we have used Gum Arabic (GA) as a model to establish the MNP-polymer coupling procedure. In order to provide a stable bond between the polymer and the MNP, we tested a covalent binding procedure using carbodiimide chemistry, according to the research strategy depicted in Fig. 1A. MNP were produced by thermal decomposition[4] followed by phase transfer through ligand-exchange. Citric acid (CA)[5] and meso-2,3-dimercaptosuccinic acid (DMSA)[6] were tested as ligands. We found out that the best route to covalently bind GA to the DMSA-coated MNPs consisted in the establishment of an amide bond between the amine groups of the polymer and the carboxylate groups of DMSA. This procedure was also used to couple EPS to MNP-DMSA.

The two composite magnetic nanosystems (MNP-DMSA-GA and MNP-DMSA-EPS) are very stable in aqueous media and consist of several 8 nm magnetic cores entrapped in a network of biopolymer which totalizes a hydrodynamic diameter of 185 nm for MNP-DMSA-GA and 140 nm for MNP-DMSA-EPS. These particles are efficient T_2 MRI contrast agents (Fig. 1B) and possess a high r_2/r_1 value (350 for MNP-DMSA-GA and 132 for MNP-DMSA-EPS). *In vitro* experiments with HCT116 cell line were performed to study the effect of the particles in cell viability (MTT metabolic activity assay) (Fig. 1C). Prussian Blue staining was used to microscopically identify iron location in cell culture samples. Labeling efficiency analysis was complemented with the determination of iron content in cells by Inductively Coupled Plasma (ICP) spectroscopy and with *in vitro* MRI.

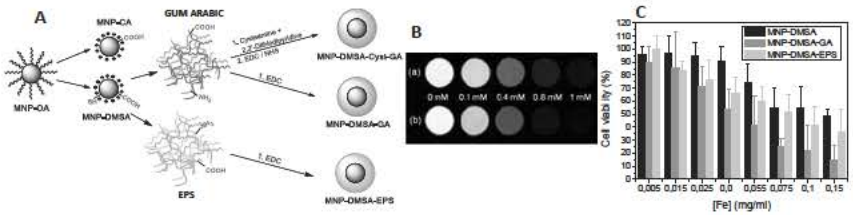

Fig. 1. (A) MNP production routes; (B) MRI phantom images of water dispersions of MNP-DMSA-GA (a) and MNP-DMSA-EPS (b) at increasing iron concentrations; (C) Evaluation of MNPs biocompatibility.

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Field induced Cluster Formation Detected by Nuclear Magnetic Resonance

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Introduction

Magnetic nanoparticles (MNP) made of iron oxide are prevalent in magnetic resonance imaging (MRI) as they serve as contrast agents which shorten the spin-spin proton relaxation times (T_2) To estimate the effects on water relaxation in terms of transverse relaxivity r_2 (increment brought to the dispersant water protons' transverse relaxation rate by 1 mmol L^{-1} of Fe ions) NMR relaxometer are typically used When MNPs are placed in the homogeneous magnetic field of the relaxometer aggregation might occur Experimentally, r_2 of protons in water containing MNP was found to change with time after the sample was inserted in the relaxometer [1] To ensure the reproducibility of r_2 estimation in NMR relaxometry and to understand the aggregation process several MNP systems were characterized

Materials & Methods

We investigated a set of commercial available magnetite based single core MNP suspensions SHP-10, SHP-15, SHP-20 (Ocean NanoTech, USA) having mean cores sizes of about 10 nm, 15 nm, and 20 nm, respectively (documented in the corresponding data sheets) Furthermore, we used multicore MNP systems of different cluster sizes provided by MagneticFluids (GER) In addition to available TEM data we used Magnetorelaxometry (MRX) and quasistatic *M(H)* measurements to estimate the distribution of clusters sizes and effective magnetic core sizes according to [2][3] The obtained parameters were used to gain a specific coupling parameter λ that depends on the effective magnetic moment μ, the hydrodynamic diameter d_{hyd} and the temperature T The transverse relaxivity r_2 was measured on a 1 5 T NMR relaxometer (minispec mq60, Bruker, GER) using a CPMG spin-echo sequence measuring every 30 s for 30 min

Results

All particles showed an exponential decay of r_2 with different time constants that correlate to the calculated coupling parameter λ of the single core MNP system As r_2 of the largest MNP with a core size of d_c=20 nm decreased by 17% within the 30 min observation time the smaller particles with d_c=15 nm and d_c=10 nm decreased by 8% and 4%, respectively For the multicore MNP a coupling constant λ smaller than for SHP-15 was calculated, nevertheless, a strong time dependence of the measured transverse relaxivity r_2 was observed (14% decrease in 30 min) Interestingly, for SHP-20 a process with a second time constant was found which may indicate the presence of superstructures (Fig 1)

Conclusion

The results of this work are important for the reliable determination of the transverse relaxivity r_2 of contrast agents for MRI It has to be taken into account that even for MNP of sizes below d=20 nm a significant decrease of the transverse relaxivity r_2 can occur which is expected to be related to field-induced aggregation of clusters into linear chains [4] Further work is necessary to be able to reliably predict the kinetics of transverse relaxivity r_2 during NMR measurements

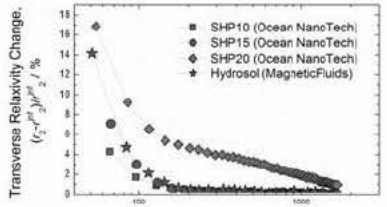

Fig. 1 | Change of transverse relaxivity r_2 in relation to the r_2^{inf} value at infinite time point (determined by fitting an exponential decay function to the measured data).

Acknowledgments

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Electro-optical and DLS study of interaction between magnetic nanoparticles conjugated to Hsp70 and its antibodies.

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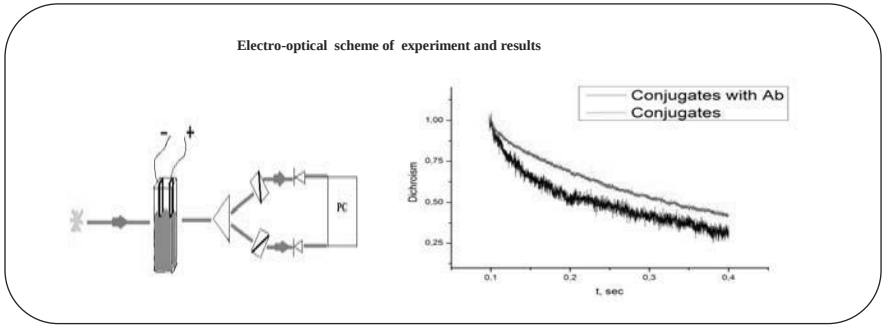
Magnetic nanoparticles (MNPs) conjugated with the heat shock protein (Hsp70) have been used for MR contrast enhancement and targeting drug delivery (Shevtsov et al Neuro-Oncology 2014:16(1):38-49). Biological efficiency of conjugates depends on the interaction of Hsp70 with receptor on cell membranes. The immune recognition events of magnetic conjugates can be modeled and succussefully studied by electro-optical methods and dynamic light scattering (DLS).

Recombinant human heat shock protein Hsp70 was prepared from E. coli transformed with a pMSHsp70 plasmid. Magnetic conjugates were formed from dextrane-coated MNPs and Hsp70 by coupling COO protein groups to carbodiimide activated surface dextran. The biological activity of Hsp70 in the conjugate was assessed by the chaperone ELISA-assay. Magnetic characteristics of conjugate were estimated by proton relaxometry. The particle size and size distribution of MNPs were studied by transmission electron microscopy (TEM) (Jeol, Japan). DLS measurements were carried out in NPs dispersion at home-made correlation spectrophotometer and Zetasizer Nano (Malvern Instruments, UK). The photon autocorrelation function in quasielastic laser light scattering, the static light scattering at various angles, the refraction increment in dependence of MNPs concentration were studied in buffer dispersions.

The reaction of immune recognition Hsp70 by its antibody in the suspension of magnetic conjugates with monoclonal antibody was analyzed with help of special electro-optical setup. The light was transmitted through suspension exposed to a sinusoidal electric field as shown in Figure. The difference (dichroism) between the intensity of the light that went through the suspension with the polarization parallel to the direction of the electric field and the light transverse polarized was measured. When the field is switched off the system relaxes with characteristic time connected with size conjugate. The formed immune complexes decrease the intensity of light scattering in 3,5 times. The MNPs conjugate with antibody arise constant of rotational diffusion in 3,25 times compared nonbinding case. The interaction between antibodies and Hsp70 conjugates seem to make the MNPs scatteres less transparent in electric field. The autocorrelation function of DLS is due to contributions of small MNPs with dimension 6-10 nm and fraction of clusters with average diameter 100 nm. The study suggests that MNPs conjugates with Hsp70 have notable electric moments for induction anisotropic transmission effects in external electric field.



Mild magnetic separation of circulating tumour cells

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Breast cancer is the most frequently occurring cancer of women in the developed world[1] Most of the patients did not die as a result of the primary tumour but later due to metastases Circulating tumour cells (CTC's) thus play an important role It is the current belief of the scientific world that a reduction of circulating tumour cells correlates with a reduction of the risk of metastasis and the spread of cancer

Our research focussed on the depletion of breast cancer cells from peripheral blood with the method of non-specific separation (without antibodies) The interaction of Carboxymethyl Dextrane (CMD) coated magnetic nano-particles with living cells is cell-type specific Under specifically defined conditions (incubation time, plama addition etc) tumour cells show a more intense interaction with the magnetic nanoparticles With the use of magnetic separation it is possible to achieve a depletion of tumour cells This method is based on a method developed by Clement et al [2] who utilized super-paramagnetic nanoparticles and magnetic separation in a high magnetic field gradient (MACS) We developed, a new mild flow separation method that makes use of magnetite nanoparticles (mean size 25 nm) along with a low field gradient and an external separation column

Magnetite based nanoparticles with a mean size of 25 nm were prepared by a wet chemical precipitation method We utilized a partial oxidation of Fe(II) salt under a constant pH of 11 at 80°C We then characterized the prepared nanoparticles with SEM, X-ray and VSM The biocompatible coating of the prepared nanoparticles with CMD was carried out using ultrasound before and after the coating process to get a stabilized magnetofluid

During development of our separation method we optimized incubation and separation conditions by using breast cancer cell line MCF-7 and leukocytes separately, followed by cell mixtures We verified our method by using 25 blood samples from breast cancer patients, which we distinguished between fresh and 24h stored blood samples The circulating tumour cells were quantified before and after separation by the maintrac[3] method i e leukocytes containing tumour cells were prepared by erythrocyte lysis, labelled with fluorescence markers (EpCAM and CD45) and analysed by a laser scanning cytometer (LSC)

For magnetic labelling the leukocytes of breast cancer patients were incubated with CMD magnetofluid for 10 min at 37°C The labelled cell suspension was gently pumped through a blood bag ($3cm^3$) inside a permanent magnet The negative fraction passed through the separator (effluent) and was the useful product of our separation As a result we achieved a very high depletion of tumour cells < 3% remaining in all investigated 24h stored blood samples This result is coupled with maintaining 56 ± 8% of vital leukocytes in all fresh blood samples We tested the recovery of this method We are now scaling up our method to a blood bag volume of $100cm^3$

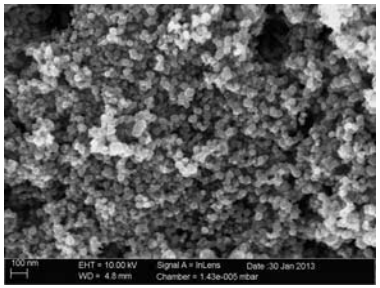

Fig. 1 SEM of nanoparticles 20-40nm (∅ 25nm)

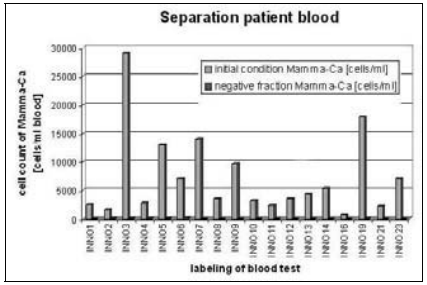

Fig. 2 Mamma-Ca blood (24h stored) before and after using magnetic separation method

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Selective micro-patterning of microbial cells onto micro-magnet arrays for single cell analysis

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In various contexts such as pathogen detection or analysis of microbial diversity where cellular heterogeneity must be taken into account, there is a growing need for tools and methods that enable microbiologists to analyze bacterial cells individually Advances in micro and nano-fabrication technology are leading to the development of platforms for single cell studies In micro-systems, cells may be individually micro-patterned on well-defined areas of a substrate where a core set of micro-system technologies can be combined for the simultaneous chemical or physical analyze of each cell [1] As an essential step in developing such devices, the ability to micro-pattern cells on a surface has received a lot of attention these last years Numerous methods including micro-well arrays, dielectrophoretic, acoustic, or optical micro-patterning have been widely investigated [2] However, such techniques do not provide specificity for cell patterning Specificity could be obtained using a chemical patterning strategy but this approach requires highly complex surface chemistry steps, which are often difficult to implement [3]

In this work, we report on the development of new strategies to selectively micro-pattern large arrays of single bacterial cells, based on the use of micro-magnet arrays [4] *E. coli* bacterial cells (2 µm in size), were used as models to demonstrate the capacity of such micro-magnet arrays for single bacterial cell micro-patterning So as to be adaptable to several applications in the field of microbiology, cells were magnetically and specifically labeled using two different strategies, 1) immunomagnetic labeling and 2) magnetic *in situ* hybridization (Figure 1)

Results show that specifically targeted bacteria can be successfully micro-patterned onto the micro-magnet array (figure 2), demonstrating the potential of this approach for the development of micro-systems dedic ated to individual bacteria analysis Efforts are now being directed at the integration of a detection tool to provide a complete micro-system device for a variety of microbiological applications

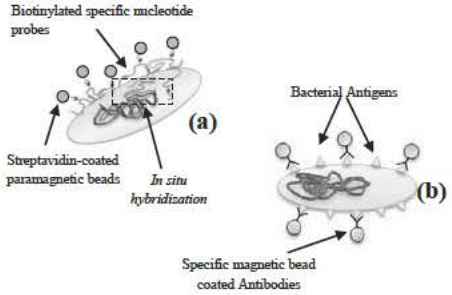

Figure 1. Principle of bacterial cell labeling using (a) an immunomagnetic labeling and (b) a magnetic *in situ* hybridization

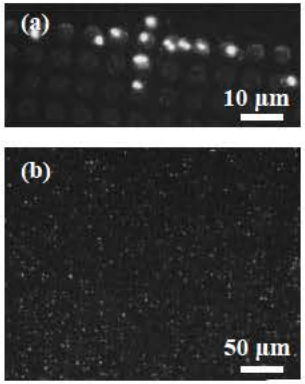

Figure 2. Optical microscopy images of magnetically labeled *E.coli* bacterial cells micro-patterned onto the micro-magnet surface (a) Zommed view of single cell micro-patterning of *E.coli* magnetically labeled by magnetic *in situ* hybridization ; (b) Enlarged view of single cell micro-patterning of *E.coli* magnetically labeled by immunomagnetic labeling

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Mössbauer Study of Exogenous Iron Redistribution Between the Brain and the Liver After Administration of Ferrofluid in the Ventricle of the Rat Brain

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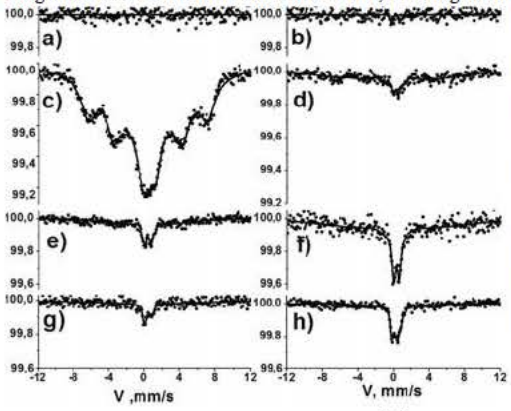
Of late, a vigorous growth of investigations of iron-containing magnetic nanoparticles for biomedical applications *in vivo* has been observable owing to assumption of their prompt biodegradability in a live organism Really the biodegradability of the ferrofluids based on iron oxide nanoparticles and their complete excretion from a live organism depend crucially on a method of their synthesis In ref [1], a magnetic iron oxide based ferrofluid was administered into a cerebral cavity of a rat by a direct transcranial injection Three months later the brain was extracted and analyzed with the histological and Mossbauer spectroscopy methods It was found that Fe_3O_4 nanoparticles, which comprised 92% of all the iron content of the ferrofluid, had completely biodegraded or had been excreted from the brain, while the iron chemical compound attending the process of ferrofluid synthesis remained intact in the brain In the present study we tried to elucidate the mechanism, by which 92 % of the particles released the brain Fe_3O_4 based ferrofluid was synthesized and proved to be free from the concomitant chemical compound [2] It was injected transcranially in the ventricle of the brain of 16 Adult Wistar male rats Mössbauer spectra of the liver and brain measured in different time intervals after the injection are shown in Figure It was found that in the brain (left column) the dextran coated intrinsic nanobeads first of all break up into separate superparamagnetic nanoparticles Then the concentration of the particles monotonically falls with time In a few hours after injection, the liver spectrum (right column) demonstrates an appearance of a weak six-line component corresponding to the initial nanobeads and central superparamagnetic doublet corresponding to the separated nanoparticles Then the concentration of exogenous iron in the liver continues to rise, reaching its maximum in 1 day spectra With further increase in time after injection the concentration of nanoparticles in the liver begins to fall Joint analysis of the Mössbauer spectra within the previously developed method [3] allowed us to determine the quantitative characteristics of the biodegradation process



^{57}Fe Mössbauer spectra measured at 300 K of:
brain (a) and liver b) before injection;
brain in 2 hours (c) and liver in 2 hours (d) after injection;
brain in 1 week (e) and liver 1 day (f) after injection;
brain in 1 month (g) and liver in 2 weeks (f) after injection

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Mössbauer Study of Biodegradation of Polymer Coated Magnetic Beads

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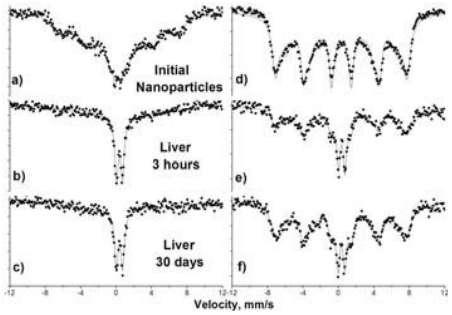
Mössbauer spectroscopy is a powerful tool for studying of the dissolution of magnetic beads *in vivo* This method provides a means of segregation of spectral contributions from exogenous iron contained in beads and endogenous iron contained in ferritin or hemoglobin [1] Furthermore, Mössbauer spectroscopy gives information about magnetic interactions between superparamagnetic iron oxide nanoparticles inside the beads It was shown by the method that the polymer coated iron oxide nanoparticles after injection into the tail vein of mice accumulate mainly in it's liver and spleen with subsequent biodegradation [2] The first fast stage in biodegradation is destruction of the outer polymer shell, which leads to the decrease of the magneto-dipole interaction between the neighboring superparamagnetic nanoparticles within several hours after intravenous injection of the ferrofluid As a result, the Mössbauer spectra of the studying liver and spleen samples change from the magnetically split sextet, usually observed in the spectra of the initial ferrofluid, to the doublet with intensity increasing over time after injection [3] In the present work, a comparative analysis by Mössbauer spectroscopy of the biodegradation process of two types of ferrofluids based on the citrate and silica coated iron oxide nanoparticles was carried out We measured the Mössbauer spectra of intrinsic ferrofluids and samples of mice liver tissues at different time intervals after its injection The study showed a significant diversity in the behavior of the nanoparticles in the liver In the Mössbauer spectrum of liver tissues containing the citrate stabilized nanoparticles, a sextet component inherent to the intrinsic ferrofluid spectra **(a)** completely disappears in a 3 hours after injection **(b)** It means that within this time almost all injected magnetic beads were dissolved by biochemical environment The 2nd type of ferrofluid shows different behavior The corresponding Mössbauer spectrum of the liver tissues demonstrates a presence of an intense sextet component, identical to the spectrum of initial particles **(d),** even in 30 days after injection **(f)**, i e a significant number of magnetic nanobeads is still retain its integrity



^{57}Fe Mössbauer spectra measured at 300 K of:
a) intrinsic citrate magnetic beads,
b) mice liver in 3 hours after injection of the citrate magnetic beads,
c) mice liver in 30 days hours after injection of the citrate magnetic beads,
d) intrinsic silica magnetic beads,
e) mice liver in 3 hours after injection of the silica magnetic beads,
f) mice liver in 30 days after injection of the silica magnetic beads '

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Zwitterionic-coated ultrasmall iron oxide nanoparticles for magnetic resonance imaging

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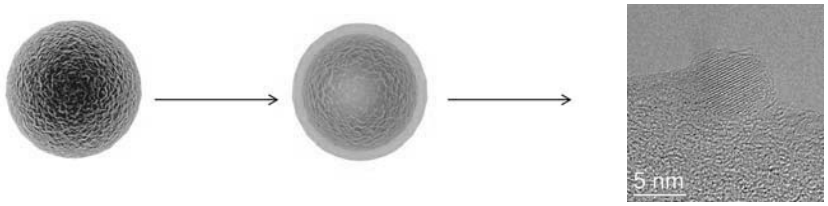
Ultrasmall superparamagnetic iron oxide nanopar icles (USPIONS) have been applied *in vitro* and *in vivo* as contrast agents to improve the sensitivity of magne ic resonance imaging (MRI). Most of the clinically approved iron-containing particles are used as MRI contrast agents for the liver. This kind of particles is accumulated in the liver as a result of opsonization and scavenging by the mononuclear phagocyte system. Currently, novel coating strategies are applied to evade phagocytosis and to pave the way to evolve contrast agents wi h fewer off-target effects.

We have developed a novel nanoparticle platform by introducing a zwitterionic polymer layer onto the magnetite particle surface (ZW-USPIONS). Firstly, magnetite (Fe_3O_4) crystals of about 5 nm were synthesized *via* thermal decomposition of iron oleate in presence of oleyl alcohol. Subsequently, the hydrophobic magnetite nanoparticles were stabilized using a zwitterionic polymeric layer to render them water-soluble and to provide an extraordinary stability over a broad pH range and different ionic strength. Purification of the polymer-coated nanoparticles *via* ultracentrifugation becomes a critical step for getting rid of the unbound polymer and to produce monodisperse samples with a defined hydrodynamic diameter by intensity of *ca.*15 nm measured by dynamic light scattering and to give a nearly neutral zeta potential in a pH range of 6.8 to 9.

Thorough characterization of the ZW-USPIONS has been performed. X-ray diffraction studies show the presence of magnetite (Fe_3O_4). The dependence of magnetisation on temperature and magnetic field in sta ic fields up to 7 Tesla was determined by using a commercial SQUID magnetometer. High-resolution transmission electron microscopy (HR-TEM) confirms well-defined narrow-sized particles. The presence of a tiny polymer layer around the crystals was also studied by elemental analysis, Raman spectroscopy, Fourier transform infrared spectroscopy (FT-IR) and thermogravimetric analysis (TGA).

The *in vitro* cytotoxicity of the ZW-USPIONS was evaluated by 3-[4,5-dimethylthialzol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay. Toxic response was not observed with nanoparticle concentrations up to 100 µg/mL in a range of human cell lines. SDS-PAGE and Gel electrophoresis studies were performed to analyse the composition of the nanoparticles-protein complex formed upon incubation wi h human serum. The zwitterionic-coated nanoparticles have shown anti-fouling properties and a significant decrease of non-specific bounded proteins compared to negatively and positively charged coatings. These properties render the functionalized ZW-USPIONS suitable for being used as MRI-agents.



USPIONS ZW- USPIONS HR-TEM of ZW-USPIONS

Schematic representation of the coating of ZW-USPIONS

Uptake and cytotoxic effects of methotrexate coupled magnetic nanoparticles in different breast cancer cell lines for multimodal treatments

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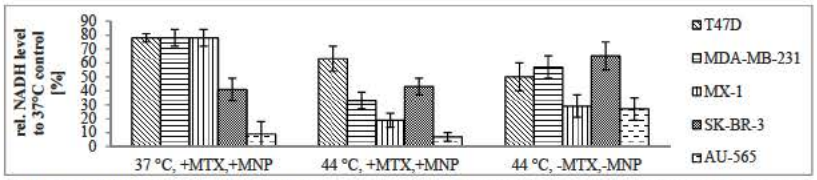
Introduction: Magnetic nanoparticles can be used as a multimodal tool for anti-tumor therapy in controlled release of chemotherapeutic agents like methotrexate (MTX) after magnetic targeting and subsequent induction of localized magnetic hyperthermia in an alternating magnetic field The cytotoxic extend of the anti folate MTX is known to differ among different cell lines To date it is unclear if the uptake level of MTX via transport through the reduced folate carrier (RFC) or the folate receptor alpha (FRα) correlates with cytotoxicity For this reason we investigated the expression level of FRα and the RFC concerning MTX cytotoxicity

Material/Methods: Carboxylate groups of MTX were covalently coupled to the amine-groups of the superparamagnetic, polyethylene glycol (PEG) iron oxide nanoparticles (MTX-MNP) by the carbodiimide method Various breast cancer cell lines (T47D, BT-474, MDA-MB-231, MCF-7, MX1, AU-565, and SK-BR-3) were treated with MTX-MNP at concentrations ranging from 25 to 100 µg MTX-MNP/ml medium Afterwards cells were heated to 44 °C for 1-2 h Cell viability was determined (cellular NADH levels) at 48 h and 72 h after MTX-MNP addition and correlated to non-treated controls
From whole cell lysates, the protein expressions of FRα as well as the RFC mRNA levels were determined by Western blot and qRT-PCR, respectively

Results: There was a medium to strong decrease of cell viability after hyperthermia in all tested cell lines, independently from incubation duration and MTX-MNP dosage In T47D, BT-474, MCF-7 and MX1 cells, there was only a slight decrease of cell viability at 48h and 72h of MTX-MNP treatment A reduction of cell viability to 46 % of controls was determined in MDA-MB-231 cells after MTX-MNP addition with a recovery thereafter With increasing incubation duration (e g 46 % and 73 % at 48 h to 9 % and 45 % after 72 h) cell viability decreased in AU-565 and SK-BR-3 cells Interestingly, there was a comparatively high and nearly equal mRNA level of RFC transcripts in all tested cell lines (4 1-5 2 C_P) except for MDA-MB-231(14 6 C_P) Contrariwise, the expression of FRα protein was strongly variable in all tested cell lines and independent from cytotoxicity during the MTX-MNP treatment

Conclusion: A multimodal treatment of (magnetic) hyperthermia and MTX can effectively inactivate certain breast cancer cells In our investigations, we found no correlation of cytotoxic effects from MTX-MNP to the expression level of FRα and the RFC in all tested cell lines Accordingly, cytotoxicity of MTX not depends on MTX uptake levels Consequently other mechanisms seem to be, at least in part, responsible for MTX cytotoxicity



Cellular viability (relative NADH level) 72 h after MTX-MNP exposure (normalized to untreated 37 °C control) Different breast cancer cell lines were treated with 100 µg/ml of MTX-MNP and afterwards heated to 44 °C for 1 h

Low-temperature postmagnetization of sensitive biological materials

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Simple, gentle and low-cost procedure for magnetic modification of sensitive non-magnetic materials has been developed. Magnetic iron oxides nano- and microparticles prepared by microwave-assisted synthesis have been successfully applied for direct postmagnetization of labile non-magnetic materials under low temperature in a freezer. These conditions have enabled magnetic modification of enzymes immobilized on non-magnetic carriers while keeping substantial part of their activity. Magnetized materials have rapid response to a permanent magnet.

Previously published methods based on the treatment by perchloric acid stabilized magnetic fluid, on the microwave irradiation of the treated material in the presence of ferrous sulfate at high pH or on the direct treatment of non-magnetic material by microwave-synthesized magnetic iron oxides nano- and microparticles at elevated temperature are mainly suitable for magnetic modification of stable non-magnetic inorganic or organic materials. In this study, subzero temperatures used for the fixation of magnetic particles on the surface or within the porous structure of magnetized material can overcome the steps incompatible with sensitive materials and biologically active compounds (e.g., high temperature, extreme pH-levels, presence of organic solvents, etc.).

Various types of potential enzyme carriers and other natural materials (e.g. cellulose powder, spruce sawdust, spent coffee grounds, spent black tea leaves, powdered peanut husks, *Posidonia oceanica*, montmorillonite K10, biochar, starch and biogenic iron oxides), cross-linked protein (enzyme trypsin) and two types of immobilized enzymes (*Candida rugosa* lipase on cellulose powder and commercial glucose isomerase from *Streptomyces murinus* – Sweetzyme® IT Extra granules) were magnetized. All prepared magnetized materials were stable and magnetic particles did not release from material during storage in water for two months. Activity of magnetically modified originally non-magnetic immobilized enzymes can differ. Both magnetized immobilized enzymes were stable during eight repeated reaction cycles and during one month storage in buffer nearly without the loss of enzyme activity. This smart method can be an inspiration as a possibility for magnetization of other types of sensitive biomaterials.

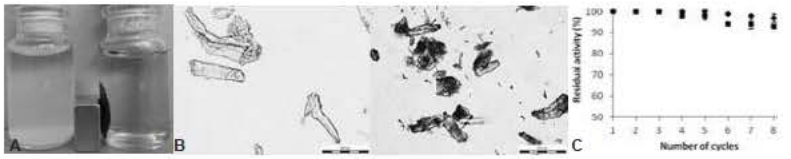

Fig. A/ magnetic separation of non-magnetic and magnetically modified cellulose particles; B/ optical microscopy of non-magnetic (left) and magnetic (right) cellulose; C/ operational stability of magnetically modified immobilized glucose isomerase (◆) and lipase (■).

ENCAPSULATION OF METHOTREXATE MAGNETIC MICROCAPSULES FOR TARGETED RHEUMATOID ARTHRITIS THERAPY

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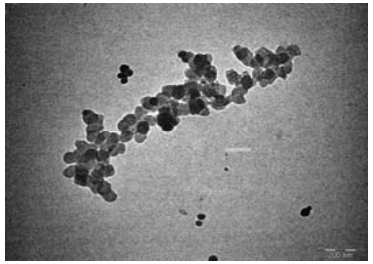
The present work reports the development of a sustained-release dosage form for methotrexate that could be used for the magnetic targeted drug therapy of rheumatoid arthritis. $CaCO_3$ microparticles were prepared by biomimetic mineralization method i.e. by addition of 50 ml of 0 2M calcium chloride solution to 50 ml of 0.2M sodium carbonate solution mixed earlier with 200 mg of polystyrene sulphonate. Size of $CaCO_3$ / PSS were characterized by SEM was found to be ~5 microns and exhibited spherical and porous morphology with a zeta potential of -11 mV. Methotrexate was loaded to $CaCO_3$ microparticles using solvent evaporation technique 200 mg of methotrexate was dissolved in 10 ml of absolute ethanol. Drug solution was added to prepared microparticles of $CaCO_3$ (400 mg) that was previously dispersed in water under stirring (400 r.p.m.) at room temperature for 12 hours and further evaporated to dryness. The drug loaded microspheres were coated with anionic and cationic polyelectrolytes by layer-by-layer technique alternatively for three times using polyallylamine hydrochloride and polystyrene sulphonate respectively. The electrolyte coating over the surface of microparticles was confirmed by zeta potential measurements.

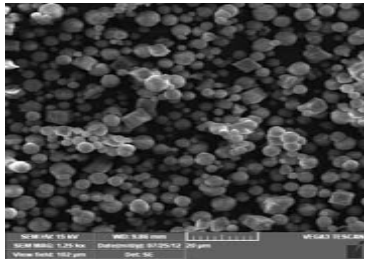
Ferro fluid was prepared by addition of ferric and ferrous salts in the molar ratio of 3:2 maintained at alkaline pH using NaOH stabilised by addition of Polyethyleneglycol 4000. The prepared ferro fluid (1 5 µl) was added to the drug loaded and polyelectrolyte coated $CaCO_3$ microparticles (20 mg) and incubated for 15 minutes with occasional shaking. The drug and ferrofluid incorporated $CaCO_3$ microparticles were further coated with cationic and anionic polyelectrolytes alternatively twice. The particles were further incubated along with 20 ml of 0 2 M EDTA solution to dissolve the core $CaCO_3$ to yield spherical capsules left intact with drug in the core and ferrofluid between the layers of polyelectrolytes as shells.

The drug loaded magnetic microcapsules were evaluated for various pharmaceutical parameters. Drug excipient interaction analysis was verified through FT-IR spectroscopy revealed that no chemical interaction exists between the methotrexate and used excipients. Crystallinity of $CaCO_3$ was determined through XRD analysis and found to be in amorphous state. Incorporation of drug and ferrofluid into microcapsules and the thermal stability of drug loaded microcapsules were observed through thermograms of $CaCO_3$, $CaCO_3$ loaded with methotrexate and $CaCO_3$ loaded with methotrexate further coated with polyelectrolytes. Polarity reversal of zeta potential analysed after every layer of polyelectrolyte coating confirms existence of polyelectrolyte layers. The zeta potential observed for the methotrexate loaded magnetic microcapsules was found to be +3 mV and exhibits a spherical surface morphology evidenced through TEM analysis.

Drug encapsulation efficiency and loading capacity was found to be 56% and 14.6% respectively. Drug release pattern was determined for 36 hours in phosphate buffer maintained at pH 7 and the drug release kinetics obeyed zero order. Stability studies indicate the prepared microcapsules were stable for a period of 30 months under a relative humidity of 65% at temperature of 25°C. The formulated microcapsules exhibited a magnetic susceptibility of 4 5 x 10^{-5}. The developed methotrexate loaded magnetic microcapsules offers a promising mode of targeted and sustained release drug delivery.



TEM image of prepared Iron Nanoparticles



SEM Image of $CaCO_3$ microparticles

FORMULATION OPTIMISATION AND EVALUATION OF PREDNISOLONE LOADED MAGNETIC SHELLS

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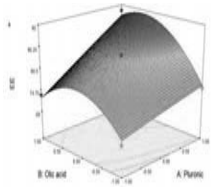
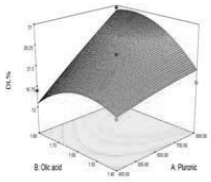
Prednisolone is a synthetic corticosteroid drug used for the therapy of rheumatoid arthritis. Prednisolone has a half-life of 1 hour and has many associated toxic effects with increased dose and dosing frequency. Hence, it is proposed to develop a sustained-release dosage form for prednisolone that could be used for the therapy of arthritis. $CaCO_3$ microparticles of even size were prepared by precipitation technique i.e., by addition of 50 ml of 0.2M calcium chloride solution to 50 ml of 0.2M sodium carbonate solution mixed earlier with 200 mg of polystyrene sulphonate. Magnetic ferrofluid was prepared by using co-precipitation technique by addition of ferric and ferrous salts in the molar ratio of 2:1 maintained at alkaline pH using NaOH. Upon neutralization, Box – Behnken design optimized quantity of pluronic (400 mg), oleic acid (1.6 mg) and prednisolone (450 mg) was added. Factors pluronic X_1 oleic acid X_2 and prednisolone X_3 were used to maximize the responses Y_1 Encapsulation Efficiency, Y_2 drug loading and to minimize Y_3 burst release. Layer by layer technique was employed to coat the $CaCO_3$ core alternatively with polyallyl amine hydrochloride (PAH) and Polystyrene sulfonate (PSS) five times. These coated particles were further incubated along with EDTA solution to dissolve the core $CaCO_3$ to yield hollow spheres. Polarity reversal of zeta potential analysed after every layer of polyelectrolyte coating confirms existence of polyelectrolyte layers corresponding to the polyelectrolyte coated. The zeta potential observed for the methotrexate loaded magnetic microcapsules was found to be -6.5 mV. The ferrrofluid-prednisolone loaded hollow spheres were evaluated for various pharmaceutical parameters viz., drug excipient interaction and functional integrity through FT-IR spectroscopy revealed no chemical interaction exists between the API and excipients, particle size was found to be 5 µm, $CaCO_3$ present in amorphous state along with polyelectrolyte layers evidenced through XRD analysis, spherical and porous nature was evidenced through SEM image. Drug release studies were carried out in pH 7.4 and drug release pattern was determined for 36 hours in phosphate buffer maintained at pH 7 that followed first order kinetics. Drug encapsulation efficiency and loading capacity was found to be 90.3% and 31.5% respectively. Stability studies indicate the prepared microcapsules were stable for a period of 3 months under a relative humidity of 65% at temperature of 25°C. The formulated microcapsules exhibited a magnetic susceptibility of 26 x 10^{-5}. The developed prednisolone loaded hollow spheres offers a promising mode of targeted and sustained release drug delivery which improves the patient compliance.

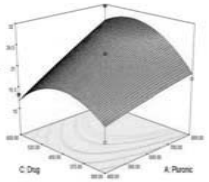
Response Surface Methodology graphs for the effects of Pluronic, Oleic acid and Prednisolone on enhancement of encapsulation efficiency, drug loading and minimizing burst release



Encapsulation Efficiency



Drug Loading



Burst Release

Stable and inert DNA/silica encapsulates with magnetic cores as tracing/tagging tools

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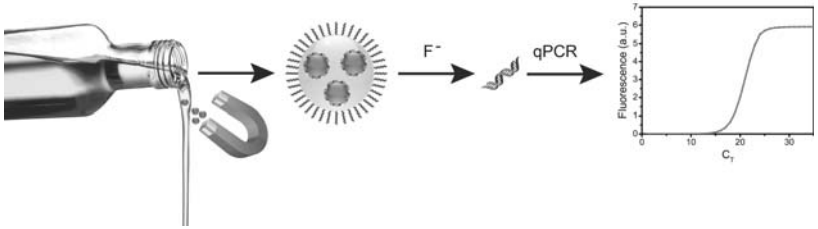
We developed a method to synthetize magnetic DNA/silica encapsulates [1] The nanoengineered particles consist of iron oxide cores, a silica protective shell,[2] and artificial dsDNA sequences layered in between The iron oxide accounts for the magnetic properties, while the silica matrix provides heat stability and surface functionality DNA can be recovered unharmed from the particles upon dissolution in fluoride comprising buffers and analyzed by qPCR and Sanger sequencing

The newly produced magnetic DNA/silica encapsulates are optimal tracing/tagging agents They are inert, resistant and harmless for humans, since iron oxide and amorphous silica are routinely used as food additives They are invisible, not affecting visible absorption properties of a transparent dispersant at concentrations lower than 10^3 µg/L Additionally they are cheap and easily detected The magnetic core of the particles facilitates handling and allows for sample up-concentration prior to analysis Therefore we developed a low-cost platform for tracing/tagging of liquid items The DNA/encapsulates are dispersed in the liquid media of interest and further retrieved by magnetic separation, followed by particles dissolution and DNA analysis by qPCR

We decided to utilize the magnetic spheres to tag oils and oil derived products which are routinely counterfeited to produce illegitimate profit To this aim, the DNA/silica encapsulates were functionalized with hydrocarbon chains to achieve dispersibility in hydrophobic dispersants The procedure was tested with a fuel (gasoline), a cosmetic oil (bergamot oil), and a food grade oil (extra virgin olive oil) We could successfully retrieve and detect the tags by qPCR in organic solvents (toluene, decalin) and in the oils We statistically discriminated 10 fold dilution steps of the oil suspensions, down to a concentration of 1 µg taggant per liter of oil (*i.e.* ppb levels) In this way we could authenticate tagged oil products and discriminate them from adulterated items

This methodology is applicable to any tracing/tagging scenario (*e.g.* particles used as hydrological tracers, as biological living species tracers, as anti-counterfeiting liquid item tags, as oil tags to verify/control stealing, adulteration and identify environmental pollution sources)



DNA recovery from oil particle suspensions and subsequent quantification by qPCR

1 Puddu, M ; Paunescu, D ; Stark, W J ; Grass, R N Magnetically Recoverable, Thermostable, Hydrophobic DNA/Silica Encapsulates and their Application as Invisible Oil Tags *ACSNano* **2014** (doi: 10 1021/nn4063853)

2 Paunescu, D ; Puddu, M ; Soellner, J O B ; Stoessel, P R ; Grass, R N Reversible DNA Encapsulation in Silica to Produce Ros-Resistant and Heat-Resistant Synthetic DNA 'Fossils' *Nat. Protoc.* **2013,** *8*, 2440-2448

The influence of magnetic interparticle interaction on the macroscopic behavior of magnetic fluids

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Ferrofluid is one of the examples of soft magnetic materials with controllable macro-properties used in various technological and medical applications. The main key to use these systems is to exploit magnetic interparticle and particle-filed interactions. Those interactions are known to have a very complex and long range nature and very often lead to desired or unsatisfactory self-assembly of particles in clusters of different size and topology. It is also well known that such factors as polydispersity, confinement and external magnetic field can drastically change the effective interparticle interactions.

Theoretical analysis of such complex systems is only possible if some assumptions are made, and the system is presented by a simple model, e.g. by dipolar hard or soft spheres' gas or liquid. In order to take the polydispersity into account, we choose a bidisperse system.

We focus on finding the correct bidisperse distribution in order to describe experimental data obtained for polydisperse magnetic fluids, such as magnetisation, and scattering patterns.

In the case of magnetic measurements we show that the bidisperse distribution could be easily found both for a strongly clustered or moderately interacting magnetic fluid. It is sufficient that the third and the sixth moments of the experimental and model distribution coincide.

However, to interpret experimental data obtained via one of the mostly used and widely spread techniques to study the microstructure, i.e. that from small angle neutron scattering (SANS), which allows obtaining the so-called structure factor, turns out to be a challenge. Here, using molecular dynamics simulations, we calculated polydisperse structure factor and compared it to a model bidisperse structure factor. It turned out that even though the position of the first peak is the same, if the bidisperse and polydisperse distribution have the same third and sixth moments, the peak height of a bidisperse structure factor is larger than the one of a truly polydisperse system for about 10%. So, we put forward an alternative way to chose the distribution.

We also present the results on diffusion, osmotic pressure and compressibilities for magnetic fluids, and show in which cases the bidisperse model is insufficient, and the computer simulations of many-component hard- or soft-spheres are to be used instead of analytic theory to elucidate the microstructural origins of the phenomena. As such we point out the key features of macroscopic response of ferrofluids.

Multi-beam ultrasonic Doppler imaging technique improves sensitivity and spatial resolution of visualization of magnetic micro- and nano-particles locations in biological soft tissues.

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Our group continues to improve our new method of ultrasonic tissue Doppler imaging with magnetic modulation for *in vitro* and *in vivo* detection and visualization of magnetic ultradisperse particles in biological soft tissues [1-3]. The method is based on inducing periodic movement of the particles and surrounding tissues using low frequency (1-100 Hz) periodic (e.g., rotating) magnetic field, and reading acoustic Doppler signal from the soft tissue [1]. Using proprietary signal processing it is possible to separate the signals from moving structures and determine their location in tissue. However, oscillating magnetic particles transfer their vibrations to the surrounding tissues, resulting in spatially enlarged but intensity diminished signals from the area with the particles, resulting in reduced sensitivity (for concentration of the particles in the tissue) and spatially distorted images. To increase sensitivity of the method and to improve spatial resolution we have created multibeam scanning technique with high pulse repetition frequency, which can scan some two-dimensional area at a frequency which is much greater than a frequency of the modulating magnetic field.

Experimental setup is based on new ultrasound scanner hardware (UDS–14) which was created by the Medical Acoustical Imaging Center, Ltd in February 2014. Linear probe operating at 7.5 MHz and a convex probe operating at 4 MHz are used. The testing of the system is underway, and preliminary results are encouraging.

1 M Ph Pyshnyi, O A Kuznetsov, S V Pyshnaya, G S Nechitailo, A A Kuznetsov, Synchronous ultrasonic Doppler imaging of magnetic microparticles in biological tissues *Journal of Magnetism and Magnetic Materials* 321 (2009) 1552-1556

2 M Ph Pyshnyi, A A Kuznetsov O A Kuznetsov, S V Pyshnaya Specialized technique of tissue Doppler imaging for locating magnetic nanoparticles Abstract to the 9th Int Conference on Scientific & Clinical Applications of Magnetic Carriers, Minneapolis, MN, P112

3 M Ph Pyshnyi, A A Kuznetsov O A Kuznetsov, S V Pyshnaya Specialized method of ultrasonic Doppler imaging for locating magnetic microparticles in soft tissues *Medical Physics* 3 (2013) 81-86

Fabrication and characterization of 1 D polymer magnetic nanochains with thermal and pH response for controlled drug release

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Abstract

One-dimensional (1D) Fe_3O_4/poly(N-isopropylacrylamide-methacrylic acid-N,N′-methylene-bisacrylamide)(Fe_3O_4/P(NIPAM-MAA-MBA)) peapod-like nanochains have been successfully synthesized by magnetic-field-induced precipitation polymerization using Fe_3O_4 as building blocks and P(NIPAM-MAA-MBA) as linker. Fe_3O_4 microspheres modified with vinyl groups can be arranged with the direction of the external magnetic field in a line via the dipolar interaction between Fe_3O_4 microspheres and linked permanently via P(NIPAM-MAA-MBA) coating during precipitation polymerization. Magnetic measurement revealed that these 1D peapod-like nanochains showed highly magnetic sensitivity. The temperature/pH sensitivity of 1D magnetic Fe_3O_4/P(NIPAM-MAA-MBA) nanochains was investigated by the temperature/pH dependence of hydrodynamic radius of Fe_3O_4/P(NIPAM-MAA-MBA) microspheres. The release behavior of phenolphthalein from 1D magnetic Fe_3O_4/P(NIPAM-MAA-MBA) nanochains indicated that drug release could be effectively controlled by altering the temperature/pH values of the environment.

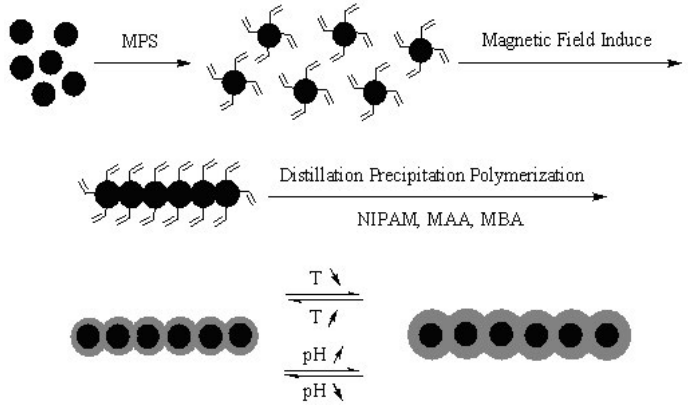

Fig 1 Schematic illustration for preparation of 1 D Fe_3O_4/P(NIPAM-MAA-MBA) nanochains

Magnetic Particle Spectroscopy for real-time quantification of magnetic nanoparticles in a flow phantom

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We established a simple flow phantom to assist the choice of suitable magnetic nanoparticles (MNP) for a preclinical combined magnetic drug targeting (MDT) and hyperthermia study in a tumor mouse model With this phantom physical parameters like magnetic field gradient strength/distance and physiological parameters like flow rate can be adjusted in a controlled way
We combined the flow phantom with a commercial Magnetic Particle Spectroscocopy (MPS) device for real-time detection of MNP during the magnetic targeting (MT) process MPS uses the non-linear magnetic susceptibility of the MNP for their sensitive and specific quantification Additionally, the MPS signal shape is used as an indicator for changes in the magnetic behavior of MNP

The MT flow phantom incorporate a reservoir filled with 1 5 ml MNP suspension and a peristaltic pump propelling the suspension at a flow rate of 350 µl/min through a plastic tube of 1 4 mm diameter A strong neodymium targeting magnet (remnant magnetization 1 2 T) is placed at a fixed distance of 1 mm to the tube at the beginning of MT Some 25 cm beside the tube is wound on a spool and positioned into the coil system of the MPS to quantify the MNP concentration in the tube far away from the magnet We used hydroxyethyl starch coated MNP (chemicell, Berlin, mean hydrodynamic diameter d_{hydr} = 200 nm) diluted in 0 1 % bovine serum albumin at a concentration c(Fe)=7 5 mmol/L Additionally, we performed MT of MNP diluted in EDTA stabilized human blood

Already after 1 min of MT a decrease of MPS signal was detectable indicating the accumulation of MNP by the magnet The retention behavior of MNP in BSA and in blood as a function of targeting time is shown in Fig 1 After about 10 min the retention of MNP in water was higher (35 %) than for MNP suspended in blood (10 %) most probably due to the higher viscosity of blood After about 500 min the retention shows saturation behavior with MNP accumulation of about 90 % for water and 85 % for blood for the chosen flow and tube parameter With increasing retention, a change in the MPS spectra shape was observed

Our flow phantom combined with MPS enables the quantitative assessment of MT efficiency

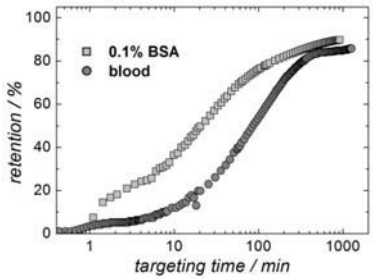

Fig 1: MNP retention as a function of magnetic targeting time for MNP suspended in 0 1 % BSA (squares) and in blood (circles)

Multifunctional ^{90}Y-labelled Fe_3O_4-PEG600 nanoparticles for possible application in combined radionuclide-magnetic hyperthermia therapy

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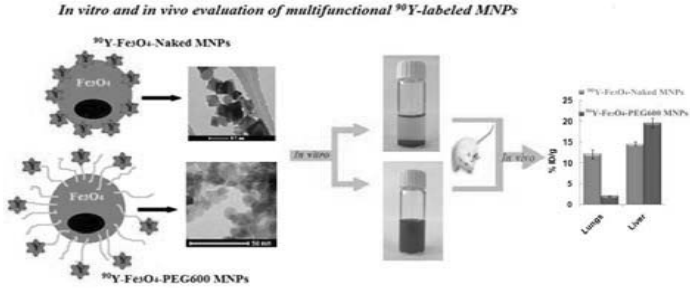
The idea of this work was to prepare ^{90}Y-labelled magnetic nanoparticles functionalized with polyethylene glycol 600 diacid (Fe_3O_4-PEG600 MNPs) for possible application in combined radionuclide-magnetic hyperthermia tumor treatment. Localized hyperthermia treatments would lead to increased perfusion in the tumor region, so, higher radionuclide delivery and oxygenation will enhance killing of cancer cells.

Fe_3O_4-PEG600 MNPs were synthesized by precipitation from ferrous/ferric chloride solutions with the addition of PEG 600 diacid during the nanoparticles synthesis in order to functionalize them. The hydrodynamic diameter of Fe_3O_4-PEG600 MNPs obtained from DLS data was d_{hyd} 46±0.6nm, reflecting the effect of the coating polymer layer on the 10 nm magnetic cores obtained from TEM images. Binding of PEG600 diacid generate highly negative surface charge of Fe_3O_4-PEG600 MNPs (-28 mV at pH 7) providing electrostatic repulsion between MNPs, therefore stable suspension was achieved. The obtained specific power absorption value for Fe_3O_4-PEG 600 MNPs was 200 W/g, indicated their potential in hyperthermia based cancer treatments. The biodistribution profile and *in vivo* stability of MNPs was evaluated in healthy male Wistar rats. Following the intravenous administration of the ^{90}Y-Fe_3O_4-PEG600 in rats, 19.61%ID/g of the activity was localized in the liver after 30 min, with 17.56%ID/g remaining after 72 h. Surface coverage of Naked MNPs by PEG600 enhances surface hydrophilicity preventing agglomeration and their accumulation in lungs as the target organ for micrometer sized particles. These results show importance of PEGylation of Fe_3O_4 in terms of increasing *in vivo* stability and their long-term retention in one organ.

Due to significant uptake of ^{90}Y-Fe_3O_4-PEG600 MNPs in liver and their low uptake by other tissues, MNPs labelled with beta-emitters could be suitable for use in combined endoradiotherapy-hyperthermia treatment especially for liver tumors.



Modelling of Magnetic Nanoparticle Hyperthermia with Allowance for the Néel and Brown Relaxation Mechanisms

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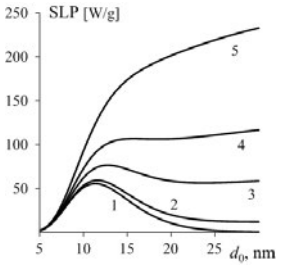
Nowadays magnetic hyperthermia is a point of strong interest. The topical research is growing inspired by the premonition that the method is close of being set into practice. In this context, the challenge for magnetic science is to provide the fundamental basis for predicting the amount of heat produced by the embedded single-domain nanoparticles. Such a particle, whose magnetic moment $\boldsymbol{\mu}$ has a constant length, dissipates the energy of the imposed AC field via two channels. First, the field makes $\boldsymbol{\mu}$ to rotate inside the particle, and the heat generated by internal friction is ejected outside by way of thermal conductivity. On the other hand, owing to the orientation-dependent anisotropy (bulk, surface and shape), the magnetic moment is coupled to the particle body. In result, the internal motions of $\boldsymbol{\mu}$ make the particle to rotate with respect to the matrix. This motion induces a flow around the particle, so that viscous dissipation heats the matrix directly.

Hereby we analyze the joint dissipation process under an AC field in a magnetic suspension. This is done in linear response limit of the consistent kinetic theory and is specified for low-frequency range. These conditions comply with the majority of practical hyperthermia cases, where the frequency and amplitude of the field are subjected to a number of physiological restrictions.

The results are given in terms of specific loss power (SLP) and applied to a model maghemite colloid with the reference particle diameter ~10 nm and a lognormal size histogram. Both the cases of bulk and surface magnetic anisotropy of the particles are accounted for. The developed description of SLP couples the main control parameters of the sample: the particle magnetization, anisotropy and the magnetic and fluid viscosities. It is well fit for optimization and readily admits replacing of a Newtonian carrier fluid by a viscoelastic one. Also it corrects a substantial underestimate of the viscous contribution inherent to the well-known phenomenological SLP models [1,2]. In the figure, as an example, we show how SLP of a model dispersion depends on the "center" of the log-normal histogram with a fixed width $s = 0.3$. The carrier fluid viscosity (in Poise) is $\eta = 10$ (1), 0.1 (2), $2\cdot10^{-2}$ (3), 10^{-2} (4), $5\cdot10^{-3}$ (5).



Authors acknowledge support of RFBR grants 12-02-00897, 14-01-96013, and MIG project S26/617 from the Ministry Education and Science of Perm region.

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Mussel Inspired Electrospun Smart Magnetic Nanofibers for Hyperthermic Chemotherapy

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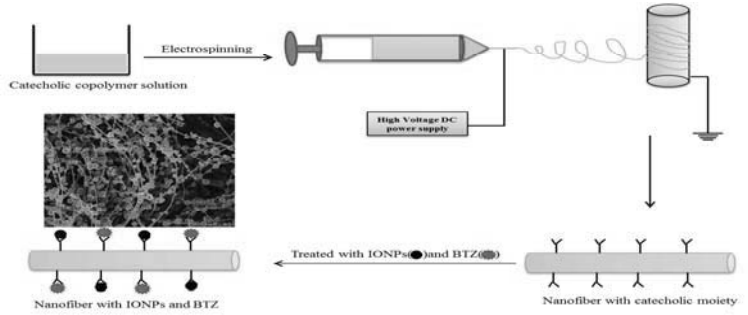
Iron oxide nanoparticles (IONPs) for magnetic hyperthermia cancer treatment have recently gained substantial interest The underwater adhesion of marine mussels relies on mussel foot proteins (mfps) rich in the catecholic amino acid 3, 4-dihydroxyphenylalanine (Dopa) As a side chain, Dopa is capable of strong bidentate interactions with a variety of surfaces, including many minerals and metal oxides The catechol moiety of DOPA is known to form strong, reversible interactions with $Fe3^{+}$ ions The catechol moiety was exploited for its ability to bind and release borate-containing therapeutics such as bortezomib (BTZ) and IONPs in a pH-dependent manner In acidic environments, such as in cancer tissue or the subcellular endosome, BTZ dissociates from the polymer-bound catechol groups to liberate the free drug, which inhibits proteasome function and the IONPs will cause the hyperthermia at alternating magnetic field So in this study, we developed an electrospun nanofiber containing catechol groups as a smart hyperthermia nanofibers with both heat-generating and drug releasing abilities for improved hyperthermic chemotherapy The nanofibers with an anticancer drug (BTZ) and magnetic nanoparticles (IONPs), which serve as a trigger of drug release and a source of heat, respectively were developed



Chaining and Movement of Magnetic Nanoparticles in Brain Tissue

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We experimentally investigated the motion of magnetic nanoparticles (MNPs) through live brain tissue Since we had previously analyzed MNP transport in blood flow [1], our interest now was to examine MNP motion through brain tissue (between vessels) We investigated if MNPs could agglomerate during such motion, if that aided or retarded their transport, and if motion of agglomerates could cause harm to brain tissue

In our experiments, we injected 5 µL of 300 nm starch coated MNPs (Chemicell) within a concentration range of 0 05 - 0 5 mg/ml in the pre-frontal cortex of rat brains and extracted tissue slices immediately (< 30 minutes) from the same region The brain slices were immersed in 1X phosphate buffer solution for all the experiments to maintain structural health The slices with MNPs were placed in between magnets as shown in Fig 1 and exposed to a uniform magnetic field produced by the magnets MNP chains formed in the slice as a result, and were observed using video microscopy To investigate transport, we removed one of the magnets and that created a magnetic gradient that moved particles towards the remaining magnet

We observed MNP chaining, and investigated the mechanism of chain formation There are two mechanisms widely reported for agglomeration of MNPs [2] In diffusion dominated agglomeration, diffusion of MNPs brings them close to each other until magnetic forces can bring them together In the drift dominated case, magnetic forces drive the motion of MNPs from the start

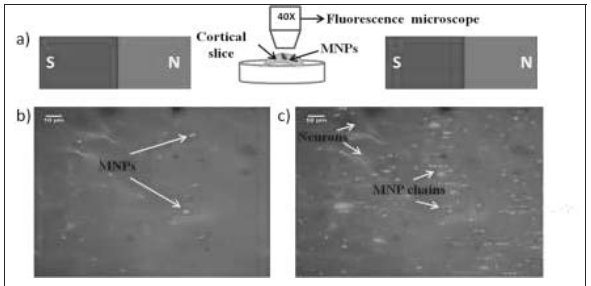

Figure 1: a) The two magnet setup to measure the chain length in brain tissue with MNPs . b) The brain tissue slice with MNPs (red) and neuronal cells (green) before applying the uniform magnetic field, and c) The MNP chains formed in the slice after applying the field.

Magnetic Field \ MNP Concentration	High Concentration (0.5 mg/mL)	Low Concentration (0.05 mg/mL)
High field (0.1 T)	12 51 ± 3 5 µm	5 84 ± 1 1 µm
Low field (0.02 T)	2 76 ± 0 8 µm	No Chaining

Table 1: Chain length after 600 seconds for different magnetic field intensity and MNP concentration in freshly excised brain tissue.

We varied both the MNP concentration and the magnetic field strength and observed the resulting chain lengths (Table 1) The chain length with high magnetic field strength and low concentration (5 84 ± 1 1 µm) was higher than with low magnetic field strength and high concentration (2 76 ± 0 8 µm) suggesting that magnetic drift dominated agglomerate formation We are currently investigating whether the agglomerated particles move faster than the singletons

Preliminary neuronal-cell patch-clamp measurements [3] suggest that agglomerate motion does not negatively affect the activity of primary neurons, but this data is only a first indication and more experiments are underway to better assess safety of MNP motion

In summary, we studied the motion of MNPs in brain tissue We found that 300 nm starch-coated MNPs undergo agglomeration due to magnetic drift, and preliminary data shows this motion does not influence neuronal activity

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Suitability of Magnetic Single- and Multi-Core Nanoparticles to Detect Protein Binding with Dynamic Magnetic Measurement Techniques

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Functionalized magnetic nanoparticles (MNPs) are well suited as markers for the quantitative detection of proteins in homogeneous bioassays. Here, the output signal is the response of the MNP dynamics to proteins that bind to the functionalized nanoparticle surface. The influence of the bound proteins on the output signal is strongly affected by the MNP hydrodynamic size and the magnetic core properties.

In this work different magnetic nanoparticles are investigated regarding the change of the MNP dynamics due to antibodies which bind via the biotin-streptavidin complex to the nanoparticle surface. Especially, MNPs with single- and multi-cores as well as different hydrodynamic sizes are compared. The nanoparticle response is measured and analyzed utilizing different dynamic magnetic measurement techniques: complex ac susceptibility (ACS) [1], fluxgate magnetorelaxometry (MRX) [2] and the rotating magnetic field (RMF) technique [3]. As a non-magnetic reference technique dynamic light scattering (DLS) is applied. Fig. 1 depicts the measured phase lags in a RMF as a function of the RMF frequency for a 30 nm single-core (SHS 30) and two multi-core MNPs: FeraSpin R and BNF Starch with hydrodynamic diameters of around 70 nm and 100 nm, respectively. Here one can see that the growth of the phase lag with frequency is determined not solely by the hydrodynamic diameter but also by the core properties, i.e., the ratio between Brownian and Neel time constants of particles. Thus, sample SHS 30 possesses a higher phase lag rise than FeraSpin R despite the smaller hydrodynamic size since the relative fraction of particles relaxing via the Brownian mechanism is larger.

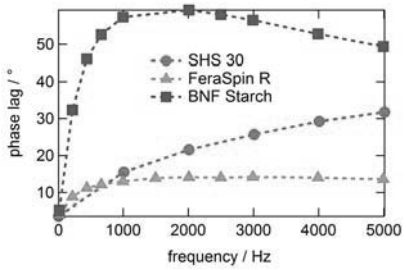

Fig 1: Phase lag measurement in a 1mT RMF for 30 nm single core (SHS30, Ocean Nanotech), 70 nm multi-core (FeraSpin R) and 100 nm multi-core (BNF Starch, Micromod) MNPs All MNPs are functionalized with streptavidin

Acknowledgment:

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Biotransformation of magnetic nanoparticles as a function of the coating in a rat model

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Long-term studies of *in vivo* in murine models have shown that DMSA-coated nanoparticles accumulate in spleen, liver and lungs tissues during extended periods of time (at least up to 3 months) without any significant signs of toxicity detected. During that time, nanoparticles undergo a process of biotransformation either reducing their size, particle aggregation or both.

Using a rat model, we have evaluated the transformations of magnetic nanoparticles injected at lower doses. We have found that low doses of magnetic nanoparticles are quickly metabolized by the animals. In fact, using a nanoparticle dose 4 times lower than in previous experiments, particles were not observed 24 h after the administration of DMSA-coated magnetic nanoparticles either in the liver or the lungs. Interestingly, an increased amount of ferritin, the iron storage protein, was observed in liver tissues from rats that were treated with the low dose of DMSA-coated magnetic nanoparticles in comparison with the control ones, suggesting a rapid metabolization of the particles into ferritin iron.

Two particle coatings, DMSA and PEG, have been administered to the animals, to evaluate the role of the coating in the degradation of the particles. We have found that, in comparison with the DMSA coated nanoparticles, PEG-coated magnetic nanoparticles are still detectable in several organs 24 h after their administration at low doses (see liver tissue samples in the figure).

Knowledge on the biodistribution, circulation time and degradation processes is required to gain a better understanding on the safety evaluation of this kind of nanomaterials for biomedical applications.

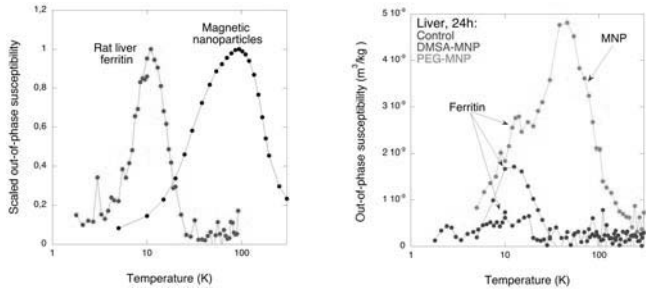

Figure. Left. Temperature dependence of the out-of-phase susceptibility of commercial rat liver ferritin and PEG-coated magnetic nanoparticles showing a maximum located at different temperatures. Right. Liver tissues from a control rat and animals 24h after the administration of low doses of DMSA and PEG coated magnetic nanoparticles.

Detection of Molecules and Cells using Magnetic Resonance with Magnetic Nanoparticles

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For the detection of small molecules, proteins or even cells, functionalised magnetic nanoparticles and magnetic resonance measurements can be applied [1, 2]. In this work, magnetic nanoparticles were functionalised with antibodies to detect two model systems. First, avidin was used as the model protein and second, *S. cerevisiae* as the model cell.

The manufactured magnetic nanoparticles were colloidal and showed a narrow size distribution. They were characterised according to their size, their core material, their magnetization and their surface chemistry. The size distribution was obtained using transmission electron microscopy and dynamic light scattering. The core material was characterised by Moessbauer spectroscopy, the magnetization was determined by M(H) measurements and the particle surface by infrared spectroscopy.

For the detection of molecules or cells, the magnetic nanoparticles were functionalised with antibodies, which bind specifically to the desired target. The binding of their antigen to the magnetic nanoparticles was detected through the change in the NMR T_2 relaxation time at 0.5 T (≈ 21.7 MHz).

With this method, avidin molecules and *S. cerevisiae* cells were detected. For visualisation the avidin molecules were labeled with FITC (Figure 1 a) and the magnetic nanoparticles for the detection of *S. cerevisiae* were additionally functionalised with rhodamine (Figure 1 b). The binding of the particles to *S. cerevisiae* and the resulting clustering was also seen in transmission microscopic images (Figure 1 c). The detection limit for FITC-avidin was determined to be 1.35 nM and 10^7 cells/ml for *S. cerevisiae*.

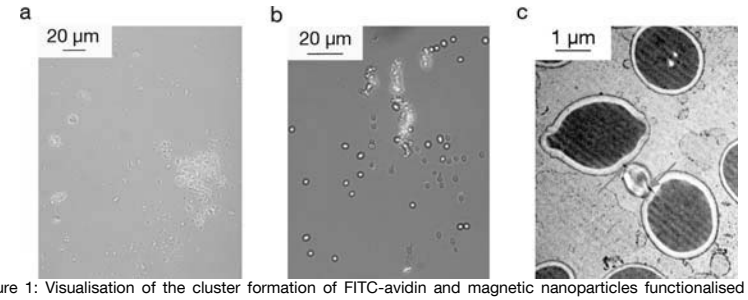

Figure 1: Visualisation of the cluster formation of FITC-avidin and magnetic nanoparticles functionalised with anti-avidin antibodies (a); Visualisation of the binding of rhodamine labelled anti-*S.cerevisiae* magnetic nanoparticles to *S.cerevisiae* cells (b); transmission electron microscopic image of the binding of antibody-labelled magnetic nanoparticles to *S.cerevisiae* cells (orange arrows indicate anti-*S. cerevisiae* magnetic nanoparticles) (c).

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Monitoring of the Aging of Magnetic Nanoparticles Using Moessbauer Spectroscopy

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Magnetic nanoparticles made of magnetite have good magnetic characteristics, due to their high saturation magnetisation and can be prepared by the co-precipitation of iron salts. In this work we show that magnetite nanoparticles change their magnetic and chemical characteristics over time depending on their storage conditions. To determine the oxidation state of the iron in the core of the nanoparticles Moessbauer spectroscopy was used. This method has the advantage to be very accurate, especially in distinguishing maghemite and magnetite.

The manufactured magnetic nanoparticles were prepared by a co-precipitation method and peptized using acidic media [1]. The size of the particles was characterised using transmission electron microscopy and dynamic light scattering. The core diameter of 5-7 nm was very small and a narrow size distribution was observed. The aging process of the magnetic nanoparticles was monitored until the core of the magnetic nanoparticles was completely oxidised to maghemite and no further change occurred (Figure 1). This process can be visualised rapidly, easily and accurately by Moessbauer spectroscopy. The aging process was already completed after two months if the particles were kept without coating in aqueous medium. The greatest change in the magnetite content of the particles was seen during the first 12 hours after they have been prepared. The signal of iron(II) ions in Moessbauer spectra observed at 4.2 K diminishes to only one fourth of the original signal of freshly prepared magnetic nanoparticles. If one wants to preserve the good magnetic characteristics of magnetite nanoparticles a coating that prevents oxidation is essential. The decrease of the saturation magnetisation value determined by M(H) measurements can be correlated to the decrease of magnetite content of the magnetic nanoparticles and therefore confirms the results obtained by Moessbauer spectroscopy.

Our results show that the point in time of the characterisation of small magnetic nanoparticles is crucial for the results. Even though magnetite nanoparticles may have been formed initially, depending on their coating and storage conditions their characteristics are changing over time.

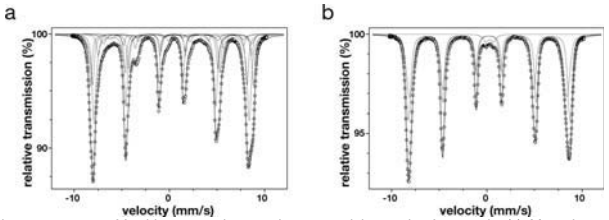

Figure 1: Moessbauer spectrum of freshly prepared magnetic nanoparticles made of magnetite (a); Moessbauer spectrum of the same sample as in a) after two months of storage in aqueous medium; the partilces have completely converted to maghemite.

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Use of magnetic nanoparticles functionalized with an antagonist of nucleolin named NUCANT 6L for therapy and diagnosis of breast cancer.

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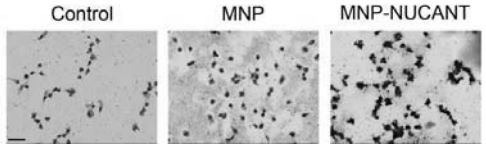
The present work is a part of the european project MultiFun (http://www multifun-project eu/), which focuses on the development and validation of a novel minimally-invasive nanotechnology system to improve breast and pancreatic cancer diagnosis and treatment The development of nanotechnology in medicine represents a new field of multidisciplinary investigations In this context, the MultiFun consortium assembles biologists, chemists and physicians working in 15 laboratories from 7 Europeans countries, all together aiming to develop a multimodal approach combining therapeutic and diagnostic features using magnetic iron oxide nanoparticles (MNP)
One of the major challenges in cancer treatment over the past decade has been the development of therapies with targeted systems Among these targeted system, nucleolin constitutes a molecule of interest as its expression is enhanced at the surface of tumour cell lines and activated endothelial cells Our laboratory has demonstrated that NUCANT 6L (N6L), a multivalent pseudopeptide, binds nucleolin with an affinity of a nanomolar range and exhibits anti-tumor activity *in vitro* as well as *in vivo* in various human tumor cell lines derived from mammary and colorectal carcinoma, melanoma, glioblastoma and lymphoma (Destouches et al , Cancer Research, 2011) In this context, N6L is currently in clinical phase II assay with ImmuPharma as promotor

In the present study, N6L is used to functionalize DMSA coated MNP (MNP-N6L) through controlled covalent linkage These nanostructures are used as carriers loaded with cytotoxic reagents to target and kill cancer cells It is important to control that functionalized MNP with N6L keep their functionality of targeting cancer cells through binding to nucleolin In order to answer this question, biological properties (tumor targeting and anti-tumoral effect) of these MNP-N6L are being evaluated *in vitro* and *in vivo*
Experiments performed *in vitro* on human breast carcinoma cell line MDA-MB 231 showed that MNP-N6L have the ability to recognize nucleolin and to target the cells In *vivo* studies are currently performed on tumor bearing nude mice to evaluate biodistribution, tumor targeting and anti-tumoral effect of MNP-N6L after repeated intravenous and peri-tumoral injection



As compared to MNP, MNP-NUCANT targets MDA-MB231 cells and after 1 hour of treatment, accumulates at the level of the cells. Cells appear in red and iron deposits in blue (x25). Bar = 50 µm

Exploring multifunctional potential of commercial ferrofluids by magnetic particle hyperthermia

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Biomedical exploration of novel magnetic nanocarriers with enhanced individual and collective features covering a multifunctional range of applications is still a pursuit for many research groups worldwide. Most of these studies utilize magnetic nanoparticles synthesized in-house, aiming in the material-side properties (sample control and property tuning), while issues concerning applicability (formulation, reproducibility, toxicity and quality assurance) are usually postponed for the later stages when MNPs will actually be introduced to biomedical practice.[1] Contrary to home-made magnetic nanoparticles, commercially produced materials may be rapidly pushed through the medical approval processes since commercial drive and company resources are focusing in the delivery of the new therapy to the patient as fast as possible.

In this work we examine a series of commercially available magnetic iron oxide nanoparticles (Nanomag®-D-spio[2], FeraSpin R[3] and FluidMag-DX[4]) as possible candidates for magnetic particle hyperthermia applications and their exploitation as multifunctional biomedical carriers combining their initial modality (i.e. MRI contract agents or drug carriers) with heat triggered actions.

To start with, the detailed structural and magnetic profile was recorded and found in good agreement with product datasheets. For hyperthermia measurements we applied two different setups of AC magnetic fields (210 and 765 kHz, 15-25 kA/m) and varying solution concentration (0.5-25 mg/mL). Thermal efficiency of these ferrofluids is quantified by estimating the Specific Loss Power factor (SLP), which refers to the amount of energy converted into heat per time and mass of the magnetic material. First results show an enhanced heating efficiency (Figure 1) that can be tuned by field and material parameters and these systems may be further exploited as multifunctional carriers beyond their current commercial use. The major advantage of such a study is that an optimum system directly addresses the multifunctional role in modern theranostics and may be further implemented in therapies with faster steps since major tasks have already been undertaken.

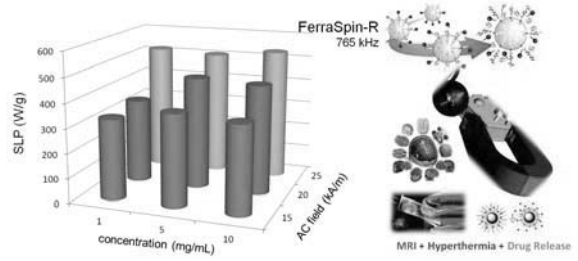

Figure 1: Left Figure: Heating response as quantified by Specific Loss Power factor: Concentration and Field effect. Right Figure: Multifunctional application scheme based on commercial MRI contrast agent combining additional heat-triggered actions such as hyperthermia and drug-release.

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[4] *http //www.chemicell.com/home/index.html*

Magnetofection technology for efficient mRNA delivery to somatic cells

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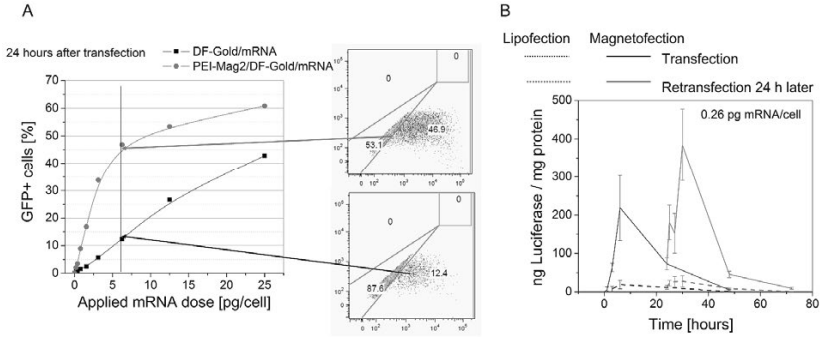
Messenger RNA (mRNA) transfection is a useful approach for cell reprogramming with minimal risk of transgene-mediated mutagenesis In the last decade it was shown that synthetic mRNA can be modified to increase its stability and decrease immunogenicity Based on Magnetofection approach we have established an efficient and robust protocol for modified mRNA delivery to the cultured Primary Mouse Embryonic Fibroblasts (PMEF) and other cell types such as human corneal endothelial and retinal pigmented epithelium cells We formulated optimized and well-characterized magnetic mRNA complexes Selected magnetic nanoparticles and the enhancers self-assembled with the mRNA into magnetic delivery vectors allow for the early onset, high level and favorable time course of the target protein synthesis compared to the non-magnetic complexes Transfection of PMEF using mRNA magnetofection resulted in 2 5-20 folds higher target protein expression compared to mRNA lipofection 50% PMEF cells were transfected using magnetofection compared to 10% transgene positive cells after lipofection at a dose of only 8 pg mRNA/cell Retransfection under magnetofection conditions after 24 h yielded a second “wave” of the protein expression at low applied mRNA dose whereas the lipofection failed The mRNA magnetofection protocol is a promising tool to achieve transient transgene expression in various cell types and could be used for rapid and safe generation of induced pluripotent stem cells



Iron Oxide Polyelectrolyte Multilayer Particles: Transport of siRNA into cells

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Due to new applications in nanotechnology and medicine nanoparticles have become a topic of great interest in colloid and materials science. By combining the tailored properties of magnetic iron oxide nanoparticles with biological components new products for medical applications are currently emerging. Here we present the development of a novel RNA delivery system.

The main properties an efficient delivery system requires shielding of the genetic material against nucleases and low toxicity of the carrier. By synthesizing monodisperse water soluble magnetic iron oxide nanoparticles (MNPs) in the size regime of 20 nm (confirmed by dynamic light scattering and TEM) we have generated magnetite (Fe_3O_4) core particles, which can be detected by magnetic resonance tomography.
The magnetite nanoparticles are charged on the surface, thus being able to interact with oppositely charged polyelectrolytes by electrostatic attraction. The coating of the iron oxide cores is conducted by a layer-by-layer assembly, which allows for the synthesis of multilayer particles with hydrodynamic radii below 50 nm, as monitored by dynamic light scattering. In a model system poly(*L*)lysine is used as the polycation and heparin as the polyanion. The successful formation of each layer is verified by zeta potential and DLS measurements.
In order to prevent interaction between charged MNPs and blood serum components partly PEGylated poly(*L*)lysine is used as the last layer of the multilayer complexes and provides the required stability of the multilayer particles upon addition of salt and proteins. The chain ends of the PEG-side chains may be functionalized for example with azide groups for copper-free click reactions for labeling with fluorescent dyes and conjugation of antibodies for targeted delivery into cells.

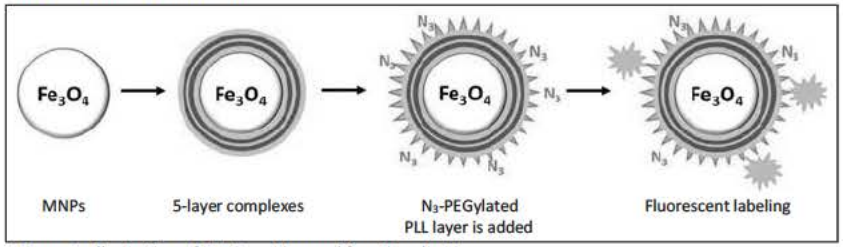

Figure 1: Illustration of MNP-coating and functionalization

In order to convert the model system described above into an RNA delivery system, negatively charged siRNA is introduced in one or more of the inner polyanionic layers instead of heparin. "In vitro" cell experiments with such nanoparticles are currently performed.

Directing nanoparticle-loaded brain cancer cells by a magnetic field

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Patients suffering from glioblastoma have a very poor chance to survive this kind of brain cancer (Stupp et al., 2005). The fast growth and high invasion potential of these cancer cells lead to a challenging problem for medical treatment of patients.

In our project, we aim to support the traditional medical therapy by guiding the migrating cells towards a predefined place within the brain tissue. Therefore, we want to load glioblastoma cells with magnetic nanoparticles (MNP) to create a susceptibility to an applied magnetic field (see Figure 1).

We analyzed the reaction of different glioblastoma cell lines (cells kindly provided by Prof. Dr. Katrin Lamszus from University Medical Center Hamburg-Eppendorf, Hamburg, Germany) of human and murine origin loaded with iron oxide nanoparticles coated with myristic acid (MA, kindly provided by Dr. Vékás from Laboratory of Magnetic Fluids, Timisoara/Romania) or feraspin XS (Miltenyi Biotech GmbH, Bergisch Gladbach, Germany). Cells were incubated with MNPs of 25 µg/ml iron concentration in cell culture medium (Dulbecco's modified medium containing 10 % fetal bovine serum) for 24 h. Afterwards, the cells were detached from the surface and seeded in a 12-well plate. A Polytetrafluoroethylene (PTFE) disc coated with fibronectin was placed on the surface of the cell culture medium and a neodym-magnet was fixed on top of the well-plate-cover. After 24 h of incubation, potentially adhered cells on the PTFE discs were fixed, stained and visualized by microscopy.

The results of the experiment show the differences of susceptibility of MNP-loaded cells towards a magnetic field. Pure cells with and without, and MNP-loaded cells without magnetic field were not detected on swimming PTFE discs.

Figure 1: Schematic presentation of the project aim

Literature:
Stupp, R et al (2005) N Engl J Med *352*, 987-996

Biocompatibility Testing of Intravenously Applied Iron Oxide Contrast Agents In vitro and Ex ovo

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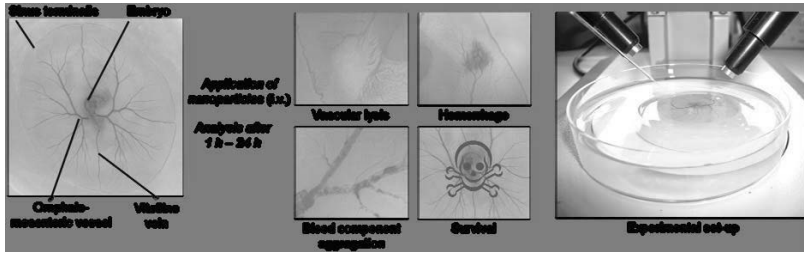
Superparamagnetic iron oxide nanoparticles (SPIONs) are used as contrast agents for diagnostic purposes in magnetic resonance tomography (MRT). Since they are commonly intended for systemic administration, intensive investigation of their biocompatibility is required. Several non-charged, anionic and cationic polymer coated superparamagnetic iron oxide nanoparticles were characterized regarding size and surface charge and analyzed in vitro and in vivo regarding their interaction with plasma proteins, particulate blood components, vessel forming endothelial cells and the blood brain barrier.

Zyto- and hemocompatibility (metabolic activity, hemolysis, erythrocyte and thrombocyte aggregation) of the about 150 nm sized SPIONs were found to be dependent on the molar mass of the coated polymer, charge, charge density, molecular flexibility and its three-dimensional architecture. With an increase of zeta potential, the binding of plasma proteins increased with the ranking neutral < anionic < cationic surface. As a trend, cationic particles were preferentially coated by human serum albumin whereas anionic particles showed highest affinity to γ-globulin. Fibrinogen binding was found to be independent of particle surface charge. Ex ovo in a shell-less hen's egg model all particles caused time dependent toxic effects over up to 24 h. Thrombotic events could be observed for all types of particles with a higher lethality for the cationic particles with high surface charge density. All particles did only negligible influence vascular lysis and hemorrhage. In a in vitro primary blood-brain barrier model only cationic SPIONs caused a decrease of the barrier integrity and changes of the cytoskeleton. In an adhesion model none of the SPIONs caused any adherence of monocytes on endothelial cells indicating the absence of proinflammatory effects. For data handling and establishment a data base concept was established.



Acknowledgements: Financial support from Federal Ministry of Education and Research (funding code 03X0104D) is gratefully acknowledged

Parameterization of the harmonic content of the complex MPI signal of magnetic tracers using a set of polynomial coefficients

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Magnetic Particle Imaging (MPI) is an imaging method to visualize magnetic nanoparticles, so-called MPI tracers, in the body It is based on the detection of higher harmonics induced by the nonlinear magnetization curve and the time lag of the magnetic moment of an ensemble of MPI tracers in an oscillating magnetic field

The number of observable harmonics and thus the spatial resolution of MPI are limited in real MPI data In order to investigate the dynamic magnetization in MPI it has been proposed to use an oscillating argument in the Langevin function that was modelled by a Taylor expansion However, real $m(H)$ curves deviate from ideal Langevin behaviour Furthermore, a Taylor expansion cannot reproduce the phase lag observed between excitation field and tracer response In addition, the argument of the Langevin function is limited by a radius of convergence of the Taylor series Thus, this approach is only suitable for very small fields and small magnetic moments with an idealized magnetization curve

We describe here the relation between an arbitrary magnetization curve and the MPI signal using polynomial base functions An analytical formulation of the $m(H)$ function is not required Instead, we use only a limited pair of values $[m,H]$ as input for the polynomial approximation For a given magnetic moment $m(H)=m(H_g)=m(H_0 \ldots H_G)$ and assuming $H=H(x)$ and $x=\omega t$ we describe the general function $m(x_g)=m(H_g(x_g))$ via:

$$\vec{m}(x_g)^T = \begin{pmatrix} a_n \\ b_n \end{pmatrix}^T \begin{bmatrix} \sin(x_g)^n \\ \cos(x_g)^n \end{bmatrix}, g = 1 \quad G; n = 1 \quad N \tag{1}$$

The terms $\sin(x)^n$ and $\cos(x)^n$ form an orthogonal basis linking the $m(H)$ curve to the harmonic content of the MPI signal The terms $a_1 \ldots a_N$ and $b_1 \ldots b_N$ in equation (1) can be calculated by a linear estimation technique This results in the description of the magnetic moment as a series of sine and cosine terms The above mentioned limitations regarding the field strength or the time lag are avoided With the notation

$$m(x) = \sum_{i=1}^{N} a_n \sin(x)^n + b_n \cos(x)^n \tag{2}$$

we can describe realistic $m(H)$ curves and MPI signals using polynomials which allows us to directly control the number of created harmonics via the polynomial order used and therefore study the impact of a limited number of harmonics on the resulting signal as well as on the magnitude of the harmonics

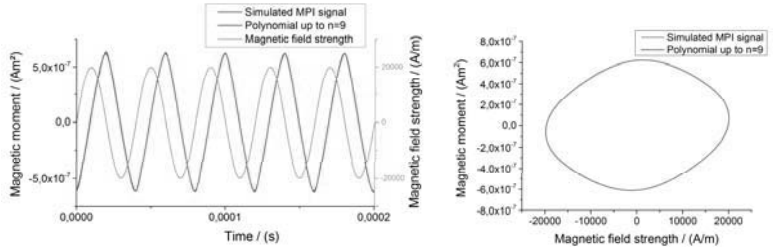

Fig. 1 Comparison of a numerically simulated MPI signal with its polynomial expression as a function of the time (left) and magnetic field (right)

To compare the result to those of a Fourier Transform, we may use the relation

$$\sin(x)^n = \sum_{n=0}^{N} K_n \sin(nx) \tag{3}$$

and its cosine counterpart The MPI signals derived from a Fourier Transform and the harmonics derived from polynomials coincide nearly perfectly in magnitude and phase Therefore we conclude that we can use this method to explore the connection between imaging performance and available harmonics via a variation of the number of polynomial coefficients We applied this method to describe simulated MPI signals (see Fig 1) as well as measured $m(H)$ data and explored the impact of a limited number of available harmonics on the signal

Facile Microwave Synthesis of Uniform Magnetic Nanoparticles for Magnetic Drug Targeting

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Drug delivery is an important method in the fight against cancer and other diseases as it increases specificity between the target site and the drug, thereby lowering side effects due to whole body drug exposure. Drug delivery can be facilitated by vectors that interact with a target site in the body (*e.g.*, an inflamed tissue). Magnetic nanoparticles (MNPs) can be used as such vectors and can be guided and enriched at the target site by directed magnetic fields. Magnetic drug targeting is a recent drug delivery method where the drug is bound to the MNPs and, after delivery to the target, is released to induce a therapeutic effect. Different factors can impact the quality of the magnetic drug carrier (MDC), which include the size distribution and composition of the magnetic carrier, the protective coating and release characteristics of the bound drug, as well as the cell permeability of the MDC. A major challenge in the development of MDCs for clinical therapy has been the poor size distribution of MNP methods producing large amounts of particles per batch, and the poor mass throughput of methods producing MNPs with excellent size distributions. In addition, the protective coating of the MNPs needs to be multifunctional; that is it needs to be a thin biocompatible coating and allow peptide and antibody conjugation, as well as encapsulate/bind and controllably release a drug.

Here we present a fast method to produce large quantities of MDCs with excellent size distributions by a combination of facile microwave synthesis and a bisphosphonate coating strategy (Fig. 1). The coatings are custom designed to provide the foundation for functional bioconjugation to cell permeable proteins, antibodies, and drugs. We present our initial results of the synthesis, conjugation, and biocompatibility studies, which are part of a larger effort to develop novel cell permeable MDCs or antibody-targeted MNPs.

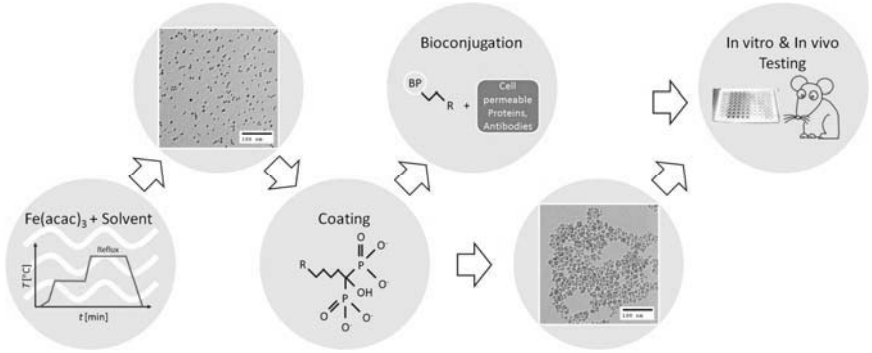

Figure 1. Flow chart of magnetic drug carrier development. The first step involves microwave synthesis.

Protein biomarker detection by a homogeneous label-free method based on rotational dynamics of hybrid magnetic nanorods

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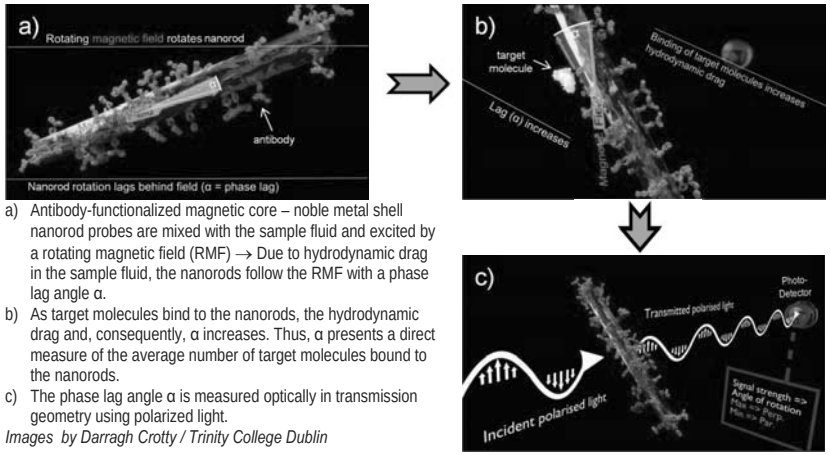
We recently introduced a homogeneous and label-free method for the detection of biomarkers directly in the sample solution.[1] The measurement method, sketched in the figure below, is based on optically detecting changes of the dynamics of magnetic nanorods[2] in an external rotating magnetic field on analyte molecule binding. The concept is ideally suited for point-of-care applications since it is highly robust, fast and easy to use. Basically, it only requires mixing of the nanoprobes with the sample solution ('mix & measure').

We report on the detection of the soluble domain of the breast cancer biomarker (sHER2) by our method. For this purpose, magnetic nanorods encapsulated by a noble metal shell are coated by an amphiphilic polymer to ensure stabilization in aqueous buffer solutions.[3] Functionalization is achieved via linker chemistry by monoclonal Herceptin antibodies as recognition agents for the sHER2 protein. All measurements are conducted in aqueous buffer solutions at physiological salt conditions under addition of large amounts (15µM) of bovine serum albumin as unspecific binding control.

The measured rotational dynamics correspond well to a previously developed empirical model,[4] and a limit of detection of sHER2 in the lower nanomolar range could be achieved. Along with the measured and simulated data, we present approaches to further improve the detection limit and support these by our latest experimental results.

Acknowledgments: This research has received funding from the European Community's 7th Framework Programme under grant agreement n NMP4-LA-2010-246479.



a) Antibody-functionalized magnetic core – noble metal shell nanorod probes are mixed with the sample fluid and excited by a rotating magnetic field (RMF) → Due to hydrodynamic drag in the sample fluid, the nanorods follow the RMF with a phase lag angle α.

b) As target molecules bind to the nanorods, the hydrodynamic drag and, consequently, α increases. Thus, α presents a direct measure of the average number of target molecules bound to the nanorods.

c) The phase lag angle α is measured optically in transmission geometry using polarized light.

Images by Darragh Crotty / Trinity College Dublin

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Quantitative Recovery of Magnetic Nanoparticles from Flowing Blood: Trace Analysis and the Role of Magnetization

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Magnetic nanomaterials find increasing application as separation agents to rapidly isolate target compounds from complex biological media (i e blood purification) [1] The responsiveness of the used materials to external magnetic fields (i e their saturation magnetization) is one of the most critical parameters for a fast and thorough separation [2,3] In the present study magnetite (Fe_3O_4) and non-oxidic cementite (Fe_3C) based carbon-coated nanomagnets are characterized in detail and compared regarding their separation behavior from human whole blood [4] A quantification approach for iron-based nanomaterials in biological samples with strong matrix effects (here, salts in blood) based on platinum spiking is shown Both materials were functionalized with polyethyleneglycol (PEG) to improve cytocompatibility (confirmed by cell toxicity tests) and dispersability The separation performance was tested in two setups, namely under stationary and different flow-conditions using fresh human blood The results reveal a superior separation behavior of the cementite based nanomagnets and strongly suggest the use of nanomaterials with high saturation magnetizations for magnetic retention under common blood flow conditions such as in veins

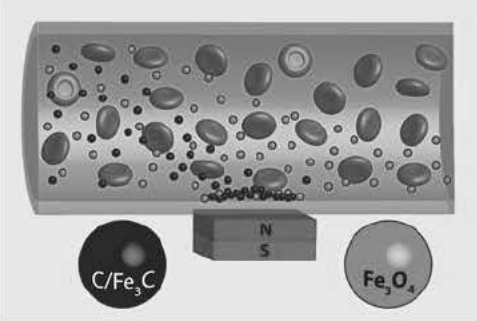

Figure 1 Magnetically highly responsive carbon-coated metal nanomagnets (C/Fe_3C) are thoroughly separated from flowing human whole blood, whereas iron-oxide nanomagnets (Fe_3O_4) are only partly retained under common flow conditions such as in larger veins

Preparation and Characterization of Phantoms for Imaging Applications

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Introduction

Magnetic nanoparticles (MNP) made of iron oxide are of great interest in bio- and nanomedicine Their superparamagnetic properties make them ideally suitable for a brought spectrum of diagnostic and therapeutic applications, e g cancer-targeted delivery, Magnetic Resonance Imaging (MRI) and Magnetic Particle Imaging (MPI) MPI recently emerged as a new imaging modality allowing for the direct measurement of MNP [1] Unlike MNP tracer used in MPI, MRI contrast agents are not directly visualized since they merely affect surrounding protons and consequently the MR signal Nevertheless, MPI strongly depends on the structure of the MNP such as magnetic moment and magnetic anisotropy Furthermore the embedding of MNP into matrices (e g tissue or gel) may attenuate the responsiveness to the fast alternating field due to complete or partial elimination of Brownian relaxation or (in case of larger MNP) strong magnetic dipole-dipole interaction [2]

Materials & Methods

In this study we investigated how the matrix and the MNP type define the magnetic properties of the studied systems Commercially available single core MNPs (Ocean Nanotech, USA) coated by oleic acid combined with an amphiphilic polymer, carboxy-dextran coated Resovist® (Bayer Health Care, GER) and silica coated SoMag5 were embedded into various phantoms typically used for evaluation of MRI systems We prepared water-based agarose gels which were also doped with 1 mmol/L copper sulfate, hydrogels as well as gelatine gels In addition the two novel MRI phantom materials Carbomer-980 and Carbopol-974P were used Subsequently the water dispersed MNP were mixed (homogenization by vortex mixing) with the gels to a final iron concentration of 1 mmol/L Additionally one MNP sample was freeze dried after adding mannitol solution

From quasistatic $M(H)$ measurements (i e DC magnetometry) we determined the mean effective magnetic core size of each sample according to [3] The spectral response to an oscillating magnetic field of the samples (embedded MNP, freeze dried MNP, MNP suspension) was measured using a magnetic particle spectrometer (MPS; B_{excit}=25 mT, f_0=25 kHz, T=37°C) which can be considered as a zero-dimensional MPI scanner The proton relaxation time T_1 and T_2 of each sample (native gel, embedded MNP, MNP suspension) were determined at 60 MHz (1 5 T) and 37°C with a Bruker mq60 minispec using a saturation recovery pulse sequence and a CPMG sequence, respectively.

Results

The measured transversal relaxation times T_2 of the native gels were in the range of human tissue whereas a T_1 modifier (copper sulfate) was necessary to reach longitudinal relaxation times of biological tissue We observed that MPS signal intensity (third harmonic amplitude μ_3) of MNP in those matrices varied by about 20% for small sized particles (SoMag5, SHP-10) whereas for Resovist® and SHP-25 μ_3 varied by 30% and 60%, respectively In contrast, the determined transversal relaxivities r_2 showed stronger variation compared to MPS signal intensities for smaller MNP In particular, r_2 of MNP of smaller size (SHP-10, SoMag5) the variation was significantly higher (60%) For larger sized MNPs (Resovist®, SHP-25) μ_3 varied by about 40%

Conclusion

Investigations of several MNP-matrix combinations demonstrate the range of MRI and MPI signal variations and show that MPI signal is sensitive to both MNP properties and environment as it is for contrast agent based MRI These results give an indication of expected MPI and MRI signal variations in tissue- or cell-targeted applications

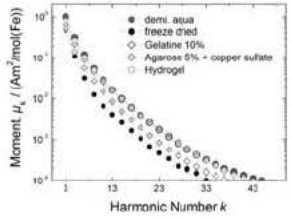

Fig. 1 | MPS measurement on SHP-25 (Ocean NanoTech, USA) in various matrices.

Acknowledgments

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Assessing Biodistribution of Magnetic Nanoparticles in Mouse Tissue using Remanent Saturation Magnetization

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Magnetic nanoparticles (MNP) enable interesting applications in drug targeting or magnetic hyperthermia The use of magnetic metal (cobalt, iron, iron carbide) nanoparticles holds particularly great promise as the high saturation magnetization increases targeting efficiency and heating properties of the particles However, assessing targeting efficiency, biodistribution and biodegradation of carbon-encapsulated metal nanoparticles is technically demanding The ability to trace the concentration of particles in tissue or blood usually relies on fluorescent or radioactive markers, requiring modification of the particle surface thus potentially alternating cellular uptake This work assesses the biodistribution of carbon-encapsulated cementite (Fe_3C) nanoparticles with PEG- or IgG-coating in C57BL/6JOlaHsd mice who have been treated via injection into the portal vein, with particular focus on brain tissue We measure remanent saturation magnetization, M_{RS}, in tissue and calculate concentration of Fe_3C nanoparticles based on a calibration curve Preliminary tests have shown that the method is capable of detecting MNP concentrations of < 100ppb using a SQUID magnetometer while providing a method for easy handling and reducing risk of tissue contamination during sample preparation Nanoparticle dosage (10mg/ml per injection) was administered either one or three times and afterwards the brain and other organs (e g lung, liver) were harvested after one week or one year A similar series of voluven (vehicle) treated mice were used as a control M_{RS} in the voluven-treated mice remained comparatively low with M_{RS} remaining in the sensitivity range of the instrument Therefore we can assume that the magnetic signal of the untreated brain and liver tissue is negligible M_{RS} of brain tissue of mice treated with the PEG and IgG particles shows high variation, but some samples display a significant concentration of MNP No statistically significant difference could be detected in the brain tissue for the mice that received MNP treatment once or three times If all brain tissue samples of the mice treated with PEG or IgG MNP are averaged for their respective groups, the PEG-treated mice show a mean concentration of 1 26 µg/g and the IgG-treated mice have a mean concentration of 3 02 µg/g If we consider the mice tissue that was harvested after one week compared to one year, we find that the concentration in the PEG-treated mice is statistically significantly lower after one year, whereas the IgG-treated mice have a statistically significantly higher concentration in their brain tissue after one year (Figure 1) For comparison purposes we also evaluated tissue from the liver (Figure 2) and the lung No statistical difference was found between one week and one year samples; however, both organs showed a significantly higher concentration of MNP compared to the brain, regardless of whether coated with PEG or IgG The average concentration is approximately 197 µg/g This result is compatible with histology results and similar studies that have shown that the liver and lungs have a high phagocytic activity

Although preliminary, our results indicate that once MNP are in the blood circulation they may be capable of settling in the brain These results also indicate that because the magnetic coercivity of the MNP does not change significantly as a function of time that the particles do not undergo alteration or reduction in size

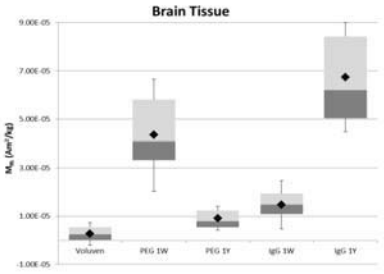

Figure 1: Whisker plots of Brain tissue with respect to treatment properties.

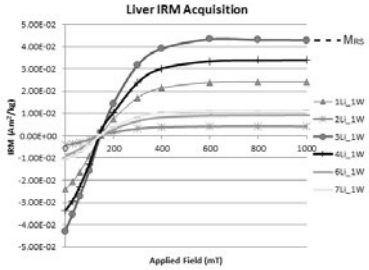

Figure 2: Isothermal remanent magnetization (IRM) acquisition curves of liver tissue.

Theoretical study of magnetic hyperthermia: Investigation of superparamagnetic and hysteresis energy loss

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A promising methodology for cancer treatment is magnetic hyperthermia Understanding the mechanisms of magnetic heating is crucial for synthesizing the optimal particles and to control the heating inside the human body Two of the candidate magnetic heating mechanisms are hysteresis loss and superparamagnetic loss The former is a result of 'thermal blocking' and the latter results from the inability of the moment to instantaneously follow the AC field leading to a phase lag To describe the superparamagnetic loss Rosensweig developed a theory based on a small field approximation and involving two relaxation times resulting from the Néel relaxation (τ_N) and Brownian relaxation mechanisms, which are considered field independent For typical magnetite systems used in hyperthermia, with relatively low anisotropy, the Néel relaxation time can vary by orders of magnitude during the field cycle

In this work we generalise the existing theory by including the field dependence of the Néel relaxation time and the orientation of easy axes We include the fact that the form of the superparamagnetic magnetisation curve depends on the anisotropy constant and particle orientation We also have developed a computational model of dissipated energy using a kinetic Monte Carlo model taking full account of the superparamagnetic and hysteresis contributions and also capable of introducing the interparticle magnetostatic interaction The model introduces dispersions of the main parameters, including the dispersions of grain size and anisotropy constants In addition it allows for a 3D random dispersion of the magnetic easy axes: an important factor if one is to make realistic comparison with experiment

The new model leads to an important change in the predicted heat dissipation In particular we demonstrate that the variation of heat output with particle diameter does not simply separate into superparamagnetic and hysteretic contributions, which overlap significantly, implying that any realistic model must take into account both contributions Including the field dependence of the Néel relaxation time, the superparamagnetic loss is shifted toward larger particle size, thus increasing the overlap with the hysteresis loss

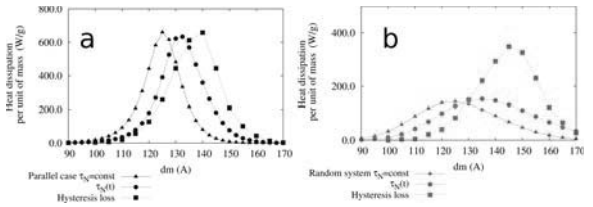

Figure 1: Heat dissipation per unit of mass as function of particle size for H_0=300 Oe and f=10^5 Hz The results are presented for a system of identical particles with easy axis parallel to the field direction (a, with black) and for a system with log-normal distribution of size, of anisotropy value and random spherical distribution of easy axis (b, with red) The results for τ_N being time dependent (with dots) are shifted from the results considering a constant value of τ_N (with triangles) There is a overlap with the hysteresis loss (with squares) Both types of energy loss have the same order of magnitude

Application of a Novel Magnetic Immunoassay System to Point of Care Diagnostics: Development and Validation of a High Sensitivity C-Reactive Protein (hsCRP) Assay.

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There is a significant trend for the diagnosis and monitoring of patients to be moved from central medical centres to closer to primary care (Point of Care (PoC) testing). The reasons for this are financial, in that time and money are saved for both the patient and the health care system and, more importantly, that it can improve therapeutic outcomes by enabling diagnoses and the implementation of therapy to be made earlier.

Lateral flow immunoassay is a widespread technology for PoC testing. This is a very user-friendly technique, however, it is limited by the accuracy and sensitivity of the detection and measurement of the antibody-bound material. Antibodies can be labelled with gold or nanoparticles where the result can be read visually or using fluorophores, but visual interpretation of results may lack sensitivity and precision, while utilizing fluorescent labels requires readers with potentially expensive and fragile optical systems.

Utilising antibodies labelled with paramagnetic nanoparticles (Magnetic ImmunoAssay, MIA) is a novel means of increasing the sensitivity and precision of lateral flow immunoassays while enabling the development of an inexpensive robust reader. The magnetic particles can be detected and quantified with great accuracy and precision, while the direct interaction between the magnetically labelled antibodies and the reader's electronics creates a system unique in its sensitivity and robustness. Furthermore, magnetometers have a wider dynamic ranges than optical systems, reducing the need for sample dilution while retaining sensitivity. This presentation will describe the application of this technology to a clinically important analyte; C-reactive protein.

The measurement of serum C-reactive protein (CRP) is an important test for inflammation and infection. There are two main areas for its application, the diagnosis and monitoring of bacterial infections, where strongly elevated serum levels (> 10 mg/L) occur, and the monitoring of cardiovascular risk where even slightly elevated levels (1 - 3 mg/L) are clinically significant.

The therapy of both cardiac disease and bacterial infection would be improved by rapid diagnosis with associated early onset of therapy. However, it is difficult to combine the sensitivity required for studying CRP in cardiac disease (high sensitivity CRP – hsCRP) with the broad dynamic range required for monitoring bacterial infections in the same assay.

By utilising a novel immunoassay technique utilising antibodies labelled with paramagnetic particles, Magnasense Technologies has developed a sensitive, precise CRP assay which can measure hsCRP and elevated CRP levels utilising the same assay procedure and sample dilutions.

Data from its development and validation will be presented.

Further assays are under development.

Functionalized superparamagnetic iron oxide nanoparticles (SPIONs) for diagnostics and therapy of malignant brain tumours

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Superparamagnetic iron oxide nanoparticles (SPIONs), due to their unique magnetic properties, have the ability to function both as magnetic resonance (MR) contrast agents, and can be used for thermotherapy [1,2]. SPIONs functionalized with recombinant human epidermal growth factor (SPION-EGF) or recombinant heat shock protein Hsp70 (SPION-Hsp70) [3,4] were studied as a potential agents for targeting malignant brain tumours. Synthesized nanoparticles were characterized by transmission electron microscopy (TEM), dynamic light scattering (DLS) and NMR relaxometry. The interaction of SPION conjugates with cells was analyzed in C6 glioma cell culture. The distribution of the nanoparticles and their accumulation in tumours was assessed by MR imaging in the orthotopic model of C6 glioma. SPIONs nanosuspensions had the properties of a negative contrast agent with high coefficients of relaxation efficiency. *In vitro* studies of SPION-EGF or SPION-Hsp70 nanoparticles showed high intracellular incorporation (**Fig. 1A**). Intravenous administration of conjugates in animals provided receptor-mediated targeted delivery across the blood-brain barrier and tumour retention of the nanoparticles. The accumulation of conjugates in the glioma was revealed as hypotensive zones on T2-weighted images with a two-fold reduction in T2 relaxation time in comparison to unconjugated SPION (**Fig. 1B**). Functionalized SPION conjugates provide targeted delivery and efficient MR contrast enhancement of experimental malignant brain tumour and thus could be applied for localized therapy.

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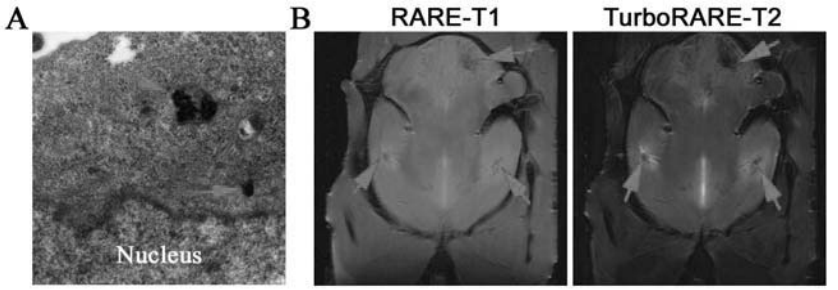

Figure 1. (A) Electron microscopy of the C6 glioma cells incubated with SPION-Hsp70 conjugates. Nanoparticles are pointed by red arrow. **(B)** MR scans of the C6 glioma treated with SPION-Hsp70 conjugates. Incorporation of nanoparticles is pointed by red arrows.

Magnetic nanoparticles for imaging and quantitative analysis of the oncomarker HER2/neu expression on the cell surface

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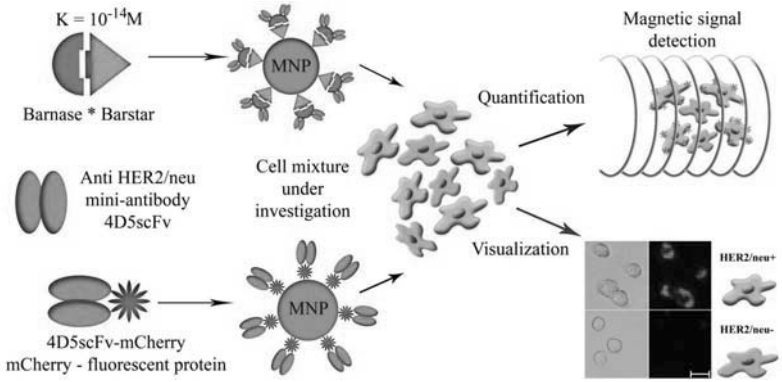
One of the important properties of magnetic nanoparticles (MNPs) as agents for theranostics is their ability to be surface-functionalized by various biomolecules, such as toxic and/or visualizing modules, as well as targeting agents for selective delivery of MNPs only to a specific cell type MNPs are promising objects for carrying out different types of immunoassays both *in vitro* and *in vivo* Selectively delivered MNPs within the body make it possible to carry out non-invasive immunoassay by means of MNPs localization detection by an external induction probe Similarly, such targeted particles could be used for quantitative detection of specific molecules in biological samples which can serve as an alternative method to some of the existing methods of disease diagnostics

For targeted delivery of MNPs to specific cells, full-sized antibodies, aptamers, different peptides and other molecules immobilized on the MNP surface by various means are successfully used In some cases, however, a more perspective approach for this purpose is to use molecular constructions based on the antigen-binding sites of the antibody, such as, for example, mini-antibodies of the scFv format (single-chain variable fragments) A small size (25–30 kDa) and the absence of the constant domain reduce the immunogenicity of such molecules (associated with the opsonization processes and activation of the complement system)

It should be also mentioned that biotechnological production of such constructions in prokaryotic expression systems is relatively easy; besides, different fully genetically encoded constructions could be developed on the basis on these mini-antibodies, containing, for example, toxic or visualizing modules

In this work, MNP-based constructions containing genetically engineered recombinant mini-antibodies that selectively recognize oncomarker HER2/neu on the cell surface of human breast adenocarcinoma SKBR-3 were obtained These structures were obtained through the use of the barnase*barstar module as a “molecular glue” between MNPs and mini-antibodies [S M Deyev et al , *Nat. Biotechnol.*, 2003] Ribonuclease barnase and its natural inhibitor barstar are small proteins of bacterial origin (12 and 10 kDa, respectively), which exhibit extremely fast kinetics and high affinity of binding ($K_D \sim 10^{-14}$ M^{-1}), which is comparable only to well-known streptavidin*biotin pair

Binding of the obtained constructs with target cells was quantitatively estimated by an our original magnetic material detection method based on the non-linear magnetization properties of magnetic nanoparticles [M P Nikitin et al , *J. Appl. Phys.*, 2008; M P Nikitin et al , *J. Magn. Magn. Mater.*, 2009] This method allows real-time measurement of a very small relative variation of magnetic susceptibility up to 10^{-8} at room temperature, thus providing sensitivity of several nanograms of MNP in 0 1 ml volume High selectivity of the MNP–HER2/neu binding was also demonstrated visually by means of fluorescent microscopy with use of fusion protein of anti-HER2/neu mini-antibody 4D5scFv and fluorescent protein mCherry Application of such targeted MNP opens up new possibilities for designing new effective quantitative methods of cancer diagnostics



Study of the heating mechanism of new type of magnetic nanoparticles with high Specific absorption rate at low field strength.

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Magnetic hyperthermia for cancer operates on the principle that magnetic nanoparticles introduced into a tumor produce heat when subjected to an alternating magnetic field (AMF) of suitable frequency and amplitude. A key issue with magnetic nanoparticles is that they must have a high specific absorption rate (SAR) so that not only is the dose of nanoparticles required for hyperthermia treatment minimized, but also so that low values of the product of magnetic field strength and frequency are used, thereby minimizing eddy current heating of tissue. Recently, we developed a new type of magnetic nanoparticle (MNP) with high SAR. The MNPs are made of gamma-Fe_2O_3 with saccharide chains implanted in their crystalline structure. The saccharides that we have used are mono- (glucose), bi- (sucrose) or poly (starch, dextran and others) as well as their derivatives (hydroxyethyl, carboxymethyl and others). Unlike MNPs commonly used for magnetic hyperthermia that have relatively large single crystals (12-30 nm) and/or irregular shape, our MNPs are built out of small (2-4 nm) single crystals, gathered in 20-40 nm aggregates with a hydrodynamic diameter of 110-120 nm. The MNPs form stable (>12 months) colloidal solutions in water, show very low saturation magnetization (2-7 emu/g) and no hysteresis, but produce significantly more heat than commercially-available MNPs at 300-400 Oe and 135 kHz. Even more valuable is the fact that they produce enough heat for therapeutic treatment at magnetic field strengths as low as 100-200 Oe while commercially-available NPs do not.

In addition to discussing the production and properties of novel MNPs, this presentation will discuss the physics of MNP heating mechanisms under an AMF and analyze the heating using a three dimensional numerical model, called the method of auxiliary sources. An external AMF induces a magnetic dipole moment inside a MNP, which produces a secondary magnetic field, that, in turn, induces an additional magnetic dipole moment. The strength and orientation of the induced magnetic dipoles depends on the external field, the MNP geometry and the magnetic susceptibility of the MNP. In this work, the induced dipole moments are calculated for different sizes and shapes of MNP, and MNP anisotropy effects are illustrated. Then magnetic forces, that depend on the MNP dipole moment and the total magnetic field around the MNP, are simulated. Finally, the induced dipole moment and forces are related to different heating mechanisms, such as Brownian motion and magnetic hysteresis. Contributions from each mechanism are estimated over different frequency ranges and examined for MNP hyperthermia. In addition, the frequency responses and hysteresis curves of MNP are measured and compared to numerical result to further understand the heating mechanisms.

The molecular mass of dextran modifying magnetite nanoparticles affects destruction of insulin amyloid fibrils

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The amyloid aggregation of poly/peptides is closely linked to the pathology of incurable amyloid-related disorders. Amyloid deposits consisting of insulin have been found in the sites of subcutaneous insulin application in patients with prolonged diabetes. There is no cure or treatment for amyloid-related diseases, however it is generally accepted that inhibition of protein fibrillization and/or reverse of aggregation represent promising approaches to cope with them. Recently, we have observed that Fe_3O_4-based magnetic nanoparticles are able to reduce amyloid aggregation of lysozyme or insulin [1, 2].

Using ThT assay and atomic force microscopy we have investigated the ability of Fe_3O_4-based nanoparticles modified by dextran (NP-Fe_{DEX}) to interfere with insulin amyloid fibrils (IF). Dextran, which differs in molecular weight (M.w. = 70 kDa (NP-Fe_{DEX}_1), 40 kDa (NP-Fe_{DEX}_2) and 15-20 kDa (NP-Fe_{DEX}_3)) was applied for increasing biocompatibility of magnetite nanoparticles.

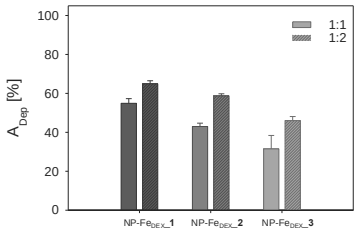

Fig 1 Depolymerizing activities A_{dep} of Fe_3O_4/based nanoparticles modified by dextran at two IF:NP ratiosFe_{DEX} 1:1 and 1:2

The depolymerizing activities (A_{dep}) of all three types of NP-Fe_{DEX} were determined after 24 h incubation of the insulin amyloid fibrils (58μg/ml IF) with NP-Fe_{DEX} for two ratios of IF:NP-Fe_{DEX} 1:2 and 1:1. The A_{dep} values were calculated as the difference of fluorescence intensity obtained for amyloid fibrils (taken as 100%) and normalized fluorescence detected after treatment with the NP-Fe_{DEX} (Fig. 1). For IF:NP-Fe_{DEX} ratio 1:2 the A_{dep} values varying from 65 % to 54% and for ratio 1:1 from 55% to 31%, respectively.

The obtain data clearly indicate that values of depolymerizing activities are determined by the different molecular mass of dextran molecules used for modification of magnetite nanoparticles. The most effective were nanoparticles NP-Fe_{DEX}_1 characterized by the highest molecular mass (M.w. =70 kDa). We assume that higher molecular mass of dextran provides more opportunities to interact with β-sheets in fibrils leading to disruption of these structures. We suppose that present findings represent a starting point for the application of the most active NP-Fe_{DEX}_1 as therapeutic agent targeting insulin-associating amyloidosis.

Acknowledgement: *This work was supported by the research grant projects 26110230097 in frame of SF EU, VEGA 0181, 0041, APVV 0171-10 and LD13021 (Ministry of Education, Czech Republic).*

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Advantages and Disadvantages of Different Methods of Temperature Measurement in the Magnetic Fluid Hyperthermia Studies

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Keywords *magnetic fluid, magnetic hyperthermia, thermocouple, pyrometer, fiber optic sensor, specific absorption rate*

We present the results of experimental studies *in vitro* of magnetic hyperthermia with magnetic fluids based on transformer oil ITO-100 Temperature measurements were carried out using different types of thermometers: the pyrometer, the thermocouples and the optical fiber sensor The hyperthermia experiments were carried out at frequency f = 440 kHz for various magnetic field amplitudes in the range up to 3 kA m^{-1} The volume concentration (ϕ_V = 2 76%) was determined from magnetic experiments and the mean diameter $\langle d \rangle$ = 12 7 nm and the standard deviation σ = 5 0 nm of the magnetic particles core were obtained from TEM technique The specific heat absorption rate and measuring errors were calculated and discussed The influence of eddy current induced in thermocouples on the accuracy in hyperthermia effect were described The usefulness of different methods of temperature measurements in the magnetic fluid hyperthermia studies was assessed

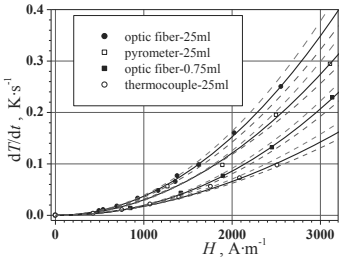

Fig.1. Dependences of $(dT/dt)_{t\ 0}$ on the alternating magnetic field amplitude H at frequency f = 444 kHz for MF samples measured by the different thermometers

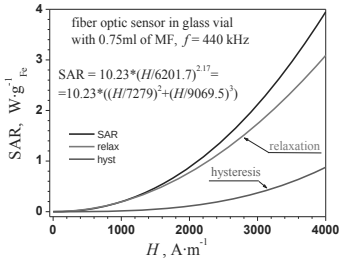

Fig.2 SAR functions as measured by the optic fibre sensor immersed in glass vial (0 75ml MF) with their components derived from relaxation and hysteresis contributions

Taking into account the principle of conservation energy, we may write that the power of heat losses, which is proportional to $(dT/dt)_t$=0, consists of two components arising from relaxation and hysteresis losses:

$$\left(\frac{dT}{dt}\right)_{t=0} = \left(\frac{H}{a}\right)^n = \left(\frac{H}{r}\right)^2 + \left(\frac{H}{h}\right)^3,$$

where a, n, r and h are the parameters obtained from the fit of the exponential function to the experimental data Presented dependences of $(dT/dt)_{t\ 0}$ on the alternating magnetic field strength amplitude H for magnetic fluid sample measured by the different thermometers indicate the different values obtained from the experiment (Fig 1) Despite these differences the parameter n is close to 2 for each of the thermometer used in this study It can therefore be concluded that different thermometers lead to the correct value of the parameter n, which means that all of the methods allows one to determine the dominant effect in dissipation of heat energy (magnetic relaxation or hysteresis)

This work was supported by a Polish National Science Centre grant, no DEC-2011/03/B/ST7/00194, VEGA 0043 and 0045, APVV 171-10 and the project 26110230097 in frame of Structural Funds of European Union.

Detection sensitivity of MRI and MPI for mesh implants with incorporated magnetic nanoparticles

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The concept of mesh implants visible in magnetic resonance imaging (MRI) and magnetic particle imaging (MPI) was realized by compounding superparamagnetic iron oxides (SPIO) into the base mesh implant material PVDF In order to determine the detection sensitivity in MRI of the mesh implants with incorporated SPIO, the relation between the SPIO concentration in the mesh implants and the R2* relaxivity values of the resulting meshes was investigated by means of MRI relaxometry Furthermore, by means of magnetic particle spectroscopy (MPS) the lowest detectable SPIO concentration in the mesh implants was determined which approximates the detection limit in MPI

To this end, both self-synthesized and commercially available SPIO were integrated at different concentrations into the base material of threads which were used to knit the mesh implants For each thread type and SPIO concentration, the R2* relaxivities and the MPS signals were investigated The induced susceptibility difference of the SPIO loaded threads was determined from the hyperintense areas in the MR image as a function of SPIO concentration and thread thickness

Significant SPIO concentration dependent changes in the R2* relaxivity values were observed emphasizing the effect of the magnetic static field inhomogeneities generated by the presence of SPIO (cf Figure 1) R2* relaxivity values between 30 s^{-1} and 40 s^{-1} were obtained The induced susceptibility differences values ranged from 2 3 ppm/(mg/g) to 4 ppm/(mg/g) The commercial SPIO caused stronger relaxivity changes and susceptibility differences which can be explained by their bigger SPIO crystal size and higher magnetization values The lowest investigated SPIO concentration in threads which lead to a significant signal in MRI was 1 mg/g
The MPS measurements revealed a linear dependency of the MPS signal amplitude with the SPIO content, and an MPS detection limit of 0 01 mg/g SPIO concentration was estimated

In conclusion, the applied methods are a feasible approach to estimate the detection limit of mesh implants in MRI and MPI and to support the optimization process in the development of various mesh implant types

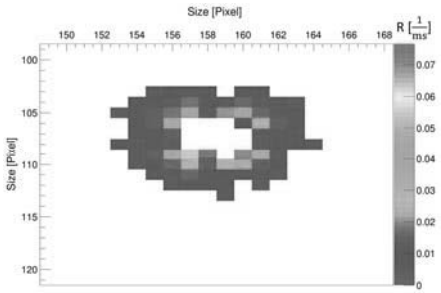

Figure 1: Relaxivity map of a SPIO loaded thread

Simulation of magnetic nanoparticle interactions in magnetic drug targeting models

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The interaction of magnetic fields with single suspended superparamagnetic iron oxides (SPIO) nanoparticles in blood flow is described in a magnetic targeting simulation model: Based on FEM simulations, this model traces the SPIO in a vessel and counts the number of SPIO that are adsorbed at the vessel wall facilitating a quantification of the efficiency of the targeting system It has been constructed for endoluminal tumours (e g prostate carcinoma, oesophagus adenocarcinoma or bile duct Klatskin tumours) which permit a minimally invasive endoscopic insertion of permanent magnets and coils very close to the tumour site to achieve a strong magnetic field and a high magnetic field gradient at this place Figure 1 displays a capillary simulation model A short part of a capillary (270 µm in length) is shown Beneath the capillary, a permanent magnet is placed in a distance of 350 µm to the capillary's wall (not shown in this picture) The simulation model was applied with the respective physical and chemical properties of SPIO, the blood flow properties and different magnetic field configurations generated by coils and permanent magnets Furthermore, SPIO interactions, such as steric repulsion, van der Waals attraction, dipole-dipole interactions, were implemented into the simulation models, and the adsorption rate of SPIO at the vessel wall was investigated

For the simulated SPIO, the highest total iron adsorption of 5 5 × 10^{-4} mg to the vessel wall within one hour was calculated for a SPIO mass fraction of 3 125 × 10^{-4} In this way, 10 7 % of the total amount of SPIO could be accumulated at the vessel wall

The simulations show a way for prediction of the delivery rate of drug targeting systems which can help to tremendously improve the efficacy of current treatment

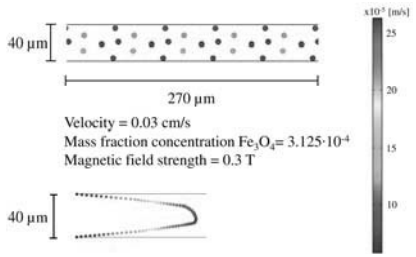

Figure 1: Simulation of a capillary model with single suspended SPIO The colours of the SPIO indicate their velocity value according to the velocity profile shown in the bottom of the picture

INFLUENCE OF BSA CONCENTRATION ON ACOUSTIC PROPERTIES OF ALBUMIN-MODIFIED MAGNETIC FLUID

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Recently, here is an interest in the potential applications of magnetic liquids in medicine. It was shown that magnetic nanoparticles have an impact on the process of amyloid aggrega ion which is responsible for several human pathologies called amyloid diseases. Specifically, the presence of biologically active second layer on the magnetite particles enhances depolymerization properties of magnetic liquid. We have studied the ultrasonic properties, density and viscosity of the albumin magnetic fluids (MFBSAs), which consisted of magnetite nanoparticles modified by different amounts of bovine serum albumin (w/w BSA/Fe_3O_4 ranging from 0.005 up to 15). A change in the ultrasonic properties with the variation of he amount of BSA/magnetite ratio was observed: both the speed and the attenuation of the ultrasonic wave rise with the amount of BSA present in MFBSAs. The viscosity also follows similar dependence on the BSA amount. The flow curves are linear and the shear stress raises with the BSA amount up to 2 Pa. The density for he low BSA/magnetite ratios is close to the values in pure water and changes significantly wi h the BSA amount. We expect the further investigation of the properties of the MFBSAs will get us closer toward the applica ion of the active MFBSAs as the therapeutic agent targeting amyloidosis.

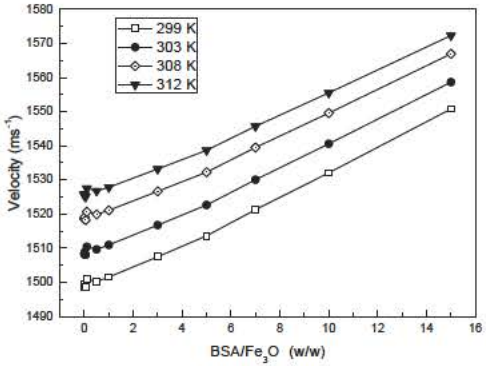

Fig.Ultrasonic wave velocity as a function of BSA/Fe_3O_4 (ratio).

This work was supported by a Polish National Science Centre grant, no DEC-2011/03/B/ST7/00194 and the projects 26220220005, 26220120033 and 26110230097 in frame of Structural Funds of European Union.

Novel method for fast characterization of magnetic properties of particles and magnetic beads in centrifugal/magnetic field

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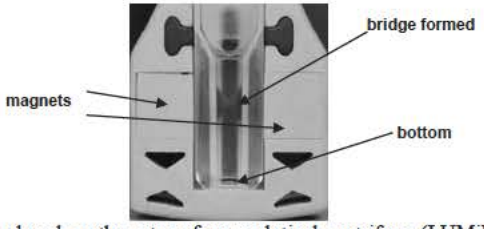
The paper introduces a new method for characterization of magnetic properties of particles and magnetic particle laden beads by a superposition of a stationary magnetic and a centrifugal force field.
Special cell holders were constructed containing two magnets on both sides of the holder (see figure below). A transparent cell with sample is placed into the holder and due to magnetic field magnetic particles or beads laden with magnetic particles form a bridge between magnets. The strength of interaction between the poles and particles or particle laden beads ("bridge stability") is proportional to the concentration of magnetic material and its magnetization.



Up to 4 holders are placed on the rotor of an analytical centrifuge (LUMiFuge/LUMiSizer; LUM Germany) and position/behaviour of bridges are investigated during centrifugation.
The instruments work based on the STEP-Technology, which allows measuring the intensity of the transmitted light as function of time and position over entire sample length simultaneously. This way the position of both, for- and back front of the bridge as well as its width can be traced directly in dependence on applied centrifugal force.
Preliminary investigations on magnetic flux density (B) distribution revealed that B is largest in the centre of the bridge, except for the x-direction (horizontal direction between the magnets), where it is at minimum. This is in line with results of a COMSOL simulation, and obviously can be directly observed from the figure.
A range of magnetic fluids and magnetic beads were characterized using this technique with cell holders with magnetic field strength of 0, 0.1, 0.2 and 0.3 Tesla. In a standard operating procedure rotor speed was increased stepwise (50 rpm) from 200 rpm to 1000 rpm and then reduced to 200 rpm in one step. For quantitative characterization of the magnetic properties the variation of bridge position and the critical break-up acceleration are determined.
Beside characterization of various products mentioned method found also application in determination of magnetite concentration in manipulated red blood cells [1].

Acknowledgement
We gratefully acknowledge the support from BMWi Federal Ministry for Economic Affairs FKZ 0327414C.

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Non-Seeded Synthesis and Characterization of Highly Magnetic and Ultra Thin Silica Coated Superparamagnetic Iron oxide Nanoparticles

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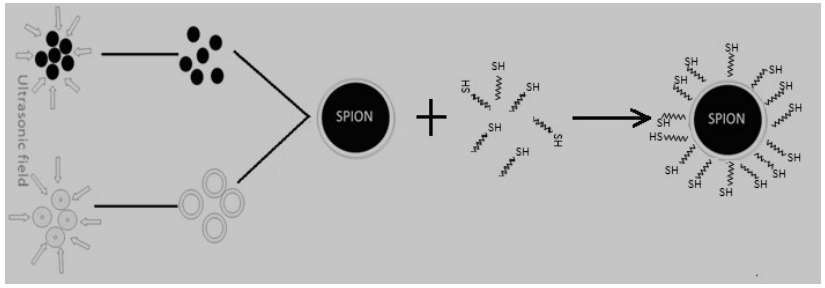
Surface modification of superparamagnetic iron oxide nanoparticles (SPION) with material such as silica nanoparticles (SiNP) is of intense interest to biomedical research and related applications. However, this material causes surface disorder of the magnetic nanoparticles. Therefore, the silica shell needs to be as thin as possible in order to preserve or retain the high inherent saturation magnetization of the SPION. Herein, for the first time we present a non seeded process of synthesising highly magnetic and ultra thin SiNP coated SPION. Both colloidal suspension of SPION and SiNP were synthesized separately by co-precipitation and sol-gel method respectively. The huge temperature and pressure plus the energy generated by acoustic cavitation process were employed to tune the pore size of SiNP. Consequently, SPION was incorporated into the frame wall of the porous silica shell. Elemental mapping using electronic spectroscopic imaging (ESI) technique was used to demonstrate the presence of Si, Fe and O in the composite nanoparticles. Physicochemical analysis using HRTEM, FTIR and XPS were used to confirm the binding and the presence of ultra thin silica shell on the SPION. The composite nanoparticles have average pore diameter and total pore volume of 7.2 nm and 0.0407 cm^3/g respectively. Our report clearly shows that nearly 70% of the initial Ms Value of the composite nanoparticles was retained. The reactivity of the prepared composite nanoparticles was exhibited by assembling decanethiol monolayer on the silica coated SPION. The silanol group of the silica shell provides the binding site for the alkyl group. Therefore, the thiol moiety became the terminal and functionalized group on the magnetic composite nanoparticles.



The use of AC-susceptometry for *in vitro* magnetic nanoparticle investigations

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Magnetic nanoparticles (MNP) for biomedical use undergo several preparatory processes. In order for them to be successfully used in cell-based applications, their properties must be retained as far as possible and it is thus important to be aware of any change in MNP properties which may occur at each step in the processing. Individual MNP in primary stable suspensionmay be single particles, or form clusters of variable particle number. Once transferred to cell culture media from primary suspension, MNP tend to develop a so-called protein corona. An increase in hydrodynamic size is observed which is due to this protein coating, further clustering or a combination of both. This clustering, which can occur following the change of microenvironment from water to media, is due to changes in ionic strength or the development of the protein corona. Sub-micron MNP clusters are readily internalized by cells, however, the clustering phenomenon can present problems; larger clusters are regarded as undesirable for *in vivo* applications due to the potential for such clusters to be phagocytosed by cells other than the target. Therefore, it is important that stability is preservedunder the various conditions MNP are exposed to during their lifespan.

In this study AC-susceptometry was used as a non-invasive method to investigate the stability of iron oxide nanoparticle suspensions in various biologically relevant solutions, and to assess methods to minimise the clustering of MNP for *in vitro* applications. MNP lifetime was mapped by measuring their magnetic relaxation response following internalization by live cells *in vitro* (Fig. 1), and their subsequent release from lysed cells. Our results provide evidence that both magnetic relaxation and stability of MNPs is micro-environment dependant. A full understanding of MNP magnetic behaviour following each step - from stable suspension to cellular internalization and subsequent release - is essential so that they reach their therapeutic target and function in the manner for which they were designed. The use of AC-susceptometry demonstrated here, yields results which provide useful insights vital for optimised use of MNP in biomedical applications.

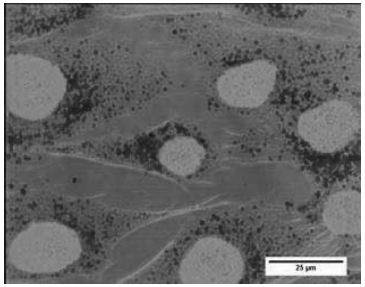

Figure 1
Composite Confocal micrograph of vertical sections using fluorescence and Bright Field microscopy through cultured osteosarcoma cancer (MG-63) cells following internalisation of iron oxide nanoparticles Cells were stained with Hoescht to demonstrate nuclei (pink staining) and with ActinRed to illustrate actin filaments (red staining); iron oxide nanoparticles are visible throughout the cytoplasm as dark granules Scale bar = 25µm

Magnetic hyperthermia of $Mn_{1-x}Co_xFe_2O_4$ nanoparticles prepared via hydrothermal high-pressure synthesis method

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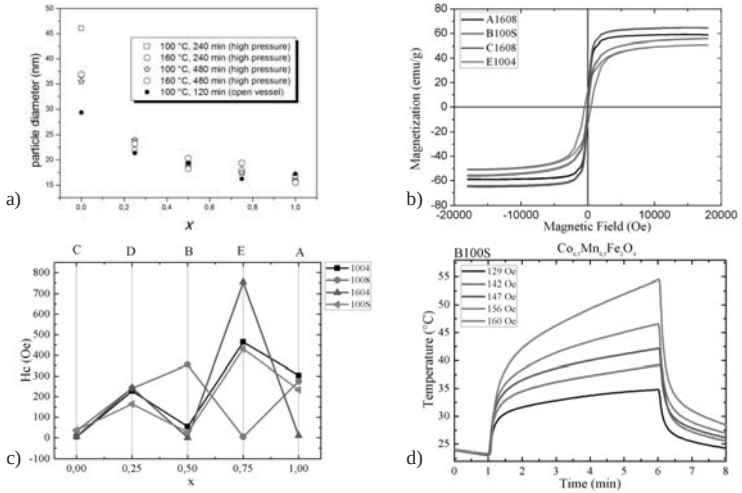
Magnetic nanoparticle hyperthermia is a promising technique for cancer treatment. So far, many studies had focused on magnetite/maghemite-based nanoparticles, but other ferrites (if adequately surface-coated) also have potential for such applications. In this work we report magnetic hyperthermia data of cobalt and/or manganese substituted ferrite ($Mn_{1-x}Co_xFe_2O_4$, where $0 \leq x \leq 1$) nanoparticles prepared via hydrothermal high-pressure coprecipitation, at distinct experimental conditions (pressure, temperature and time). The crystalline structure and particle diameter were determined from the analysis of the XRD data, revealing spinel structure for all samples with crystalline sizes ranging from 14 up to 45 nm and dependent on the experimental parameters. Room temperature magnetization measurements were also performed to evaluate the quasi-static magnetic properties showing magnetization (from 30 up to 45 emu/g) and coercivity values (from zero to 755 Oe) depending on the cation distribution profile. Both regimes were observed for the nanoparticles depending on the experimental conditions, *i.e.* from quasi-static superparamagnets (no coercivity) to blocked nanoparticles. Magnetic hyperthermia measurements were performed at 300 kHz at different magnetic field amplitudes. We found that the magnetothermal efficiency is strongly dependent upon diameter, saturation magnetization and magnetic anisotropy. The magnetic parameters are influenced by the cation distribution of the Co^{2+}, Mn^{2+} and Fe^{3+} ions from octahedral to tetrahedral sites and vice versa in the spinel structure during the nanoparticle synthesis. In particular, we found that the soft-like ferrites are more efficient for the hyperthermia application at low field amplitudes, while the hard-like ferrites have greater potential at higher field amplitudes. Finally, we conclude that the high-pressure synthesis method has great potential for the synthesis of mixed-ferrite based nanoparticles, whose properties can be finely tuned for hyperthermia applications.



(a) Particle diameter as a function of the substitution degree *x* (b) Magnetization curves of some samples (c) Coercivity field as function of the substitution degree *x* for all samples (d) Magneto thermal response for distinct field amplitudes for the B100S powder sample

Continuous Size-Dependent Separation of Microspheres in Human Whole Blood in Microfluidic Cascading Spirals

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Fluid flow in a curved duct consists of a primary flow along the duct's central line and a secondary one within the duct's cross section. The latter consists of the two counter-rotating Dean vortices [1, 2]. The flow of a colloidal suspension through such a duct, will size-dependently align the initially homogeneously suspended particles along an equilibrium position close to the inner wall, shown in **Figure 1**. Microfluidic spirals make use of this effect for separating distinct size fractions from a binary fluid in a continuous process at sample volumes of approximately 1 mL [3]. The separation itself is independent of the particles being neutrally or non-neutrally buoyant, which raises the opportunity to use magnetic particles and additionally influence the particles' transport by a magnetic field applied to the spiral [3].

A microfluidic device is investigated to separate and thereby concentrate rare components in human whole blood, such as parasites, to facilitate their detection. The device is a polymer cast made of polydimethylsiloxane (PDMS) and due to its low fabrication costs it is especially advantageous for applications in Africa. Microspheres, suspended in the blood samples in the present investigations substitute the parasites, and vary in their size distribution. A variation of the spirals geometry and the volume rate in the channel influences the separation dynamics and is investigated experimentally as well as numerically by computational fluid dynamics. The separation process by Dean forces described above can lead to an even higher concentration of the rare component by using a continuous system of two or more spirals in a row.

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Acknowledgments: Financial support by a fellowship within the Postdoc-Program of the German Academic Exchange Service (DAAD) and by a discovery grant from the Natural Sciences and Engineering Research Council (NSERC) in Canada is gratefully acknowledged.

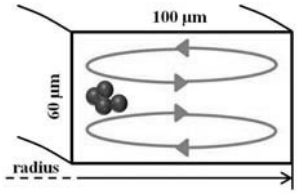

Figure 1: Particles' equilibrium position [3].

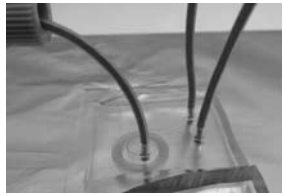

Figure 2: Blood flow in PDMS-microchip.

Anisotropy of magnetoviscous effect in strongly interacting ferrofluids

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Strongly interacting ferrofluids show various interesting flow properties in the absence and presence of an external magnetic field [1,2,3,4]. Hence there is an immense interest in understanding the influence of dipolar interactions and magnetic fields on the structure and dynamics of ferrofluids. In our work we study ferrofluids modeled as magnetically hard point dipolar particles of different dipolar interaction strength using extensive Langevin dynamics simulations. Our investigations under zero field conditions have shown an intricate correlation between structural and dynamical properties [3]. Above a certain critical interaction strength, we find dramatic changes in micro-structures from separate to inter-connected chains which affect the dynamics of the system. We have extended our studies to include the effect of applied field and applied shear on rheological properties of ferrofluids. The magnetoviscous effect and its anisotropy is one of the important properties which appears in ferrofluids in the presence of an external magnetic field. According to the relative orientation of the magnetic field to the flow geometry, different viscosity coefficients can be defined which are known as Miesowicz viscosities [4]. We compare the Miesowicz viscosities obtained from our simulations with experimental results of Ref. [2] and the predictions of the chain model [5]. This anisotropy in viscosity is essential in order to properly describe the behaviour of ferrofluids in general flow geometries that typically occur in magnetic drug targeting [6] and other biomedical applications.

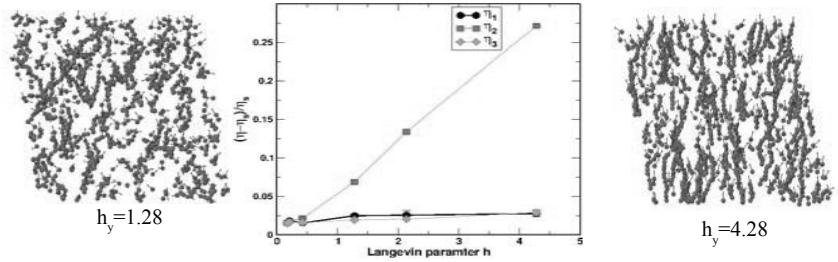

FIG.1: The relative change in Miesowicz viscosities η_1, η_2, η_3 as a function of Langevin parameter h (mH/kT), for dipolar interaction strength λ = 4.62 and reduced shear rate 0.004. The snapshots given show the system at different magnetic field strengths oriented in the gradient direction of flow.

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Electromagnetic Sample-Mixer – Biomagnetic Separation with variable magnetic fields

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The detection, identification and analysis of bacterial pathogens are highly important for identifying potential health risks. The first essential step is often enrichment of the pathogens to densities exceeding detection limits of analytical instruments. Conventional enrichment protocols may take up to several days, thus there is a clear need to shorten and improve them. A promising approach for this is Biomagnetic Separation (BMS). Here we present an innovative BMS device in which superparamagnetic beads are mixed with target structures (in this context bacteria), and accelerated with alternating magnetic fields to increase attachment rates [1], thereby reducing separation times, the numbers of beads required for batch treatment and costs.

The magnetic fields are generated by several electro-magnets exerting controlled forces on the superparamagnetic beads. The field geometry and its modulation result in the swarm of beads moving along specific trajectories through the sample container and collecting all target structures. With increases in the magnetic force the velocity of the beads, relative to the bacteria, can be dramatically increased thus greatly raising collision and attachment probabilities.

The recently developed and patented device has three key advantages: the capacity to accelerate the paramagnetic particles in a well-defined manner by simply modulating the voltage, the absence of mechanically moving elements, and the reductions in mixing time and numbers of beads needed. After optimizing settings of the device we confirmed its advantages by comparing its separation efficiency with those obtained both using a conventional Dynal Rotator and with no mixing.

Literature:

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Intravenously applied PEG nanoparticles for magnetic hyperthermia enrich mostly in liver and lungs

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Background: Hyperthermia is used as cancer treatment for effectively destroying cancer cells and tumors by locally heating tissues to temperatures above 43 °C. Particularly magnetic hyperthermia, generated by magnetic particles in an alternating magnetic field (AMF), is suitable for cancer treatment since the heat can be applied to the tumor region locally by sparing healthy tissues. At the moment, the intratumoral application of the magnetic material is considered to be the state of the art, limiting the therapy to well-defined tumors. This problem could be solved by applying nanoparticles to the vascular system, allowing their enrichment via the tumor vascularization and the treatment of very small tumors and even metastases. Until now, the intravenous application of nanoparticles is hindered by the fast clearance of the applied material from the bloodstream. Therefore, a human tumor xenograft mouse model was used to investigate the biodistribution of different PEG coated nanoparticles and their preferential sites of accumulation after intravenous application to the tail vein. Additionally, a special targeting magnet for the enrichment of magnetic nanoparticles in the tumor, allowing a more effective magnetic hyperthermia in later AMF treatment, was used.

Methods: In this study, 50 to 100 µl (approx. 240 - 480 µg iron) of differently functionalized (e.g. amino-, carboxy-end groups) 130 nm nanomag-D PEG (MW: 300 Da) nanoparticles (micromod, Germany) were intravenously injected in the tail vein of female SCID balb/c mice. Used particles showed hydrodynamic diameters (z-average) of about 180 nm with a polydispersidy index (PDI) < 0.2. The zeta-potential, characterizing the particle s surface charge, was determined to be approx. -25 mV. Particle size and charge was measured in water using a Zetasizer Nano ZS (Malvern Instruments GmbH, Germany). Enrichment of the tumor s particle load was investigated via magnetic targeting by placing a special magnet (640 mT, 10 T/m) over the tumor region. The retention capability of this magnet for the individual nanoparticles used was analyzed in a flow phantom under physiological conditions. Between injection of particles and the sacrifice of the animal different time points, particularly 1.5 and 24 h, were used. To investigate the fate of the nanoparticles in the body, biodistribution analyzes by magnetic particle spectroscopy were performed after homogenization of the sacrificed animal s organs.

Results: Approximately 1.5 h after intravenous injection, most nanoparticles were found in liver (≈ 45 %) and lungs (≈ 14 %). Interestingly at 24 h after i.v. injection, nanoparticles were primarily found in the liver (≈ 45 %) indicating a relocation of nanoparticles from the lungs (< 1 %) to other tissues since particle degradation is unlikely to occur with a short time period of only 24 h. Although flow phantom studies showed the magnetic attractivity of the used 130 nm PEG coated nanoparticles with the used magnet, magnetic targeting did not noticeably enrich nanoparticles in the tumor region, confirming their fast clearance of the bloodstream by the liver.

Conclusion: Since after i.v. application nanoparticles were cleared from the bloodstream primarily by liver and lungs possibly through the mononuclear phagocyte system, the development of longer circulating nanoparticles with the ability of their enrichment in the tumor region by sparing their accumulation in healthy tissues is of uttermost importance.

High-Purity Enrichment of Human Hematopoietic Stem Cells utilizing MACS technology

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Magnetic cell separation (MACS) has become a prominent method for the enrichment of hematopoietic stem cells from complex cell suspensions. For example, the magnetic cell separation system for the isolation of $CD34^+$ cells was recently approved by the U.S. Food and Drug Administration (FDA) to prevent graft-versus-host disease in the treatment of acute myeloid leukemia.

The isolation of hematopoietic stem and progenitor cells usually focuses on the immunological binding characteristics of antibodies to specific cell surface markers, such as CD34 or CD133. However, low abundance of these cells, especially in peripheral blood, renders the effective magnetic enrichment in high purity and viability (low content of cell debris) very challenging. The standard MACS system, characterized by super-paramagnetic iron oxide nanoparticles (SPIONs) in combination with unique ferromagnetic cell separation columns and separators is a powerful approach to enrich human $CD34^+$ and $CD133^+$ cells from peripheral blood, hematopoietic tissue, like bone marrow, non-hematopoietic tissue, like tumors, or cell culture. Based on this method, we present here, a new sort of SPIONs and respective MACS protocols that allow for an immunomagnetic isolation of CD34+ and CD133+ hematopoietic stem cells from various starting materials in highest purities and viabilities. Parameters of interest were cell purity, cell viability, and cell recovery of target cells. The developed MACS protocols result in stem cell populations containing significantly diminished amounts of dead cells and cell debris. For example, in a standard enrichment of $CD34^+$ cells from PBMC, purities of ≥96% among white blood cells and of ≥60% among all cells were analyzed by flow analysis (Figure 1). Comparison studies revealed a 50%-reduction of cell debris in relation to other commercial available cell separation methods. Further investigations on human hematopoietic tissue, like frozen and fresh cord blood as well as bone marrow also revealed highest $CD34^+$ and $CD133^+$ cell purities for the new particles and protocols. These findings may pave the way for the development of further magnetic cell separations to support scientists in research and clinical applications.

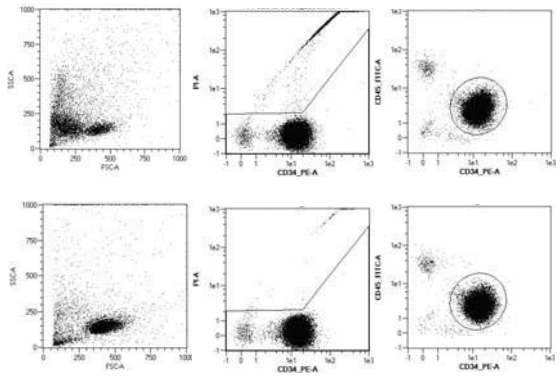

Figure 1 Flow cytometric analysis of $CD34^+$ cells enriched from PBMC. Upper row: Positively enriched cells using classic CD34 MicroBeads. Lower row: Positively enriched cells using CD34 MicroBeads UltraPure

Theoretical Aspects of AC Susceptometry of Magnetic Nanoparticles in a Suspension

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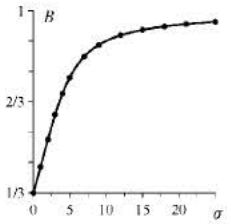
Magnetic nanoparticles with functionalized surface, if incubated in a solution with a target substance, e.g. biomolecules of a specific type, selectively bind to it forming magnetically labelled complexes. Therefore, the presence of such complexes can be characterized both in their number and relaxation rate, upon subjecting the sample to a probing AC field and measuring the response magnetic signal. Among various methods of this type, the most well-known one is magnetic AC susceptometry [1,2]. According to the standard scheme, the experimental output is interpreted in terms of the geometrical (so-called hydrodynamic) diameters of the particle-containing entities driven by the AC field. The increase in the hydrodynamic diameter leads to a decrease in the peak frequency of the imaginary part of the AC magnetic susceptibility.

Hereby we re-build this model on the basis of the kinetic (rotary diffusion) equation, which consistently allows for the motion of both a single-domain particle as itself in the surrounding fluid and the intrinsic orientational dynamics of the particle magnetic moment [3]. Although the derivation is rather long, the result obtained comes out quite compact. The AC susceptibility of an assembly of non-interacting particles exposed to a weak probing field takes the form

$$\chi = \chi_0\left(\frac{B}{1+i\omega\tau}+1-B\right); \qquad \tau=\frac{\tau_B\tau_N}{\tau_B+\tau_N},$$

where τ_B and τ_N are the relaxation times of the Brownian and Néel modes. Coefficient B in this formula characterizes the coupling between those modes and depends solely on the parameter $\sigma = E_A / kT$ that is the ratio of the particle anisotropy energy to the thermal one. The value of B varies from ⅓ for magnetically isotropic particles to 1 for the particles, which are completely magnetically rigid, i.e., possess infinitely high magnetic anisotropy, see the figure. In this aspect our theory corrects the commonly used AC susceptibility expression, where the assumption of the particle magnetic rigidity, although implicitly, but is ever present. In the talk the proposed approach is compared to the other conventional models, the essential differences between them are remarked and commented on; some numerical examples are also given.



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Synthesis of a heterobifunctional polymer platform for "tailored" multimodal theranostic magnetic particles

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Magne ic nanopar icles have been s udied for many years for use in biomedicine no only for heir high surface area bu also because of i s unique magne ic proper ies They can magne ically in erac wi h heir environmen be guided o a specific loca ion and manipula ed o release energy in he form of hea To ensure ha hese magne ic nanopar icles survive in he circula ory sys em hey mus be modified wi h ma erials o make hem colloidally s able in wa er and shield hem from he body s immune response o foreign objec s [1]

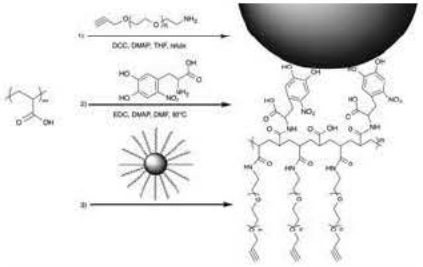

Figure 1 Reaction schematic to produce colloidal stable platform for multimodal theranostic mangetic nanoparticle

This presen a ion will describe he syn hesis of a mul i anchored universal ligand for iron oxide nanopar icles wi h improved s abili y in biological environmen s while also providing a pla form for addi ional func ionali y The par icles repor ed in his alk are coa ed wi h a poly(acrylic acid) oligomer ha has been modified wi h a he erobifunc ioal polye hylene oxide (PEO) wi h an erminal end capable of 'click chemis ry n addi ion he oligomer was modified wi h ni roDOPA o provide s rong binding o he surface and used in a muli den a e approach provides biocompa ibili y and enhanced s abili y in fe al bovine serum and phospha e buffer saline [2] These colloidally s able biocompa ible polymer par icles complexes were hen be modified wi h a near infrared dyes (e g Cy5) and u ilized in charac erizing he in egra ion of magne ic nanopar icles in biofilms (*Legionella pneumophila)* The par icles were hen added o he biofilm and heir posi ion was hen observed using a super resolu ion ground s a e deple ion microscope n addi ion o imaging we have also u ilized he same pla form for he arge ing of differen s rains of bac eria hrough 'clicking on species specific moie ies The modified par icles adhere o he arge ed bac eria s rains and agglomera e Through he applica ion of an al erna ing field magne ic energy can be ransformed o promo e cellular dea h resul ing in a mul i log reduc ion in bac eria popula ion

Wha will be presen ed represen s he ini ial indings of he research oppor uni ies available wi h his new pla form for diagnos ic and herapeu ic applica ions These universal magne ic nanopar icles can be modified wi h differen fluorescen dyes imaging biofilms carbohydra es for arge ing bac eria and o her moie ies for mul ifunc ional diagnos ic probes o show he versa ili y of his design

1 S one R Willi T Rosen Y Mefford O T & Alexis F Targe ed magne ic hyper hermia *Therapeutic Delivery* **2,** 815 838 (2011)
2 Saville S L S one R C Qi B & Mefford O T nves iga ion of he s abili y of magne i e nanopar icles func ionalized wi h ca echol based ligands in biological media *J Mater Chem* **22,** 24909 (2012)

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A Novel Method for Non-Invasive Iron Oxide Nanoparticles Quantification Using Magnetic Resonance Imaging

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Non-invasive quantification of the iron oxide nanoparticles with Magnetic Resonance Imaging (MRI) is one of the most demanded clinical applications nowadays First, it is because of their use as MRI contrast agent (CA) and delivery system in molecular imaging Second, because the biogenic iron oxide nanoparticles (ferritin, hemosiderin, and magnetite) have a big potential to become a biomarker of the pathological processes associated with the disrupted iron homeostasis in the human body (neuroinflammation, cirrhosis, etc) However, at present time there is no general method available Therefore, our intention is to develop a novel complex method, which allows non-invasive quantification of iron oxide nanoparticles, as well as particle's visualisation limits calculation The proposed method is still in progress, and currently enables quantification of the in-vitro samples

The method is based on calculation of so called "Effective protons" (EP), which are the protons, affected by the magnetic field of the iron oxide particles and produce such a contrast change in MRI To calculate the EP number, we need to determine the magnetic field parameters of the nanoparticles, and to prepare calibration samples with a concentration gradient of iron oxide nanoparticles

Resovist CA was chosen as a model system for MRI quantification in-vitro Resovist consists of magnetite nanoparticles coated with carboxydextran (purchased form Bayer Schering Pharma AG) The MRI experiments were performed with ESAOTE Opera (E-SCAN^{TM} XQ) 0 178 T system

Figure 1b demonstrates calculation of fitting parameters from the concentration gradient map (Figure 1a) It serves as a starting point in concentration determination of the "unknown" samples (Figure 2a) The results on the Figure 2b characterise the rate of quantification error in comparison with the real concentration value for individual "unknown" samples (Nr 1-9) with same concentration The error range in concentration determination is between 0 3 – 8 %, relative to true concentration value

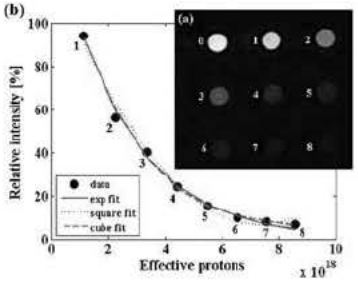

Figure 1: (a) Concentration gradient map, (b) EP fitting.

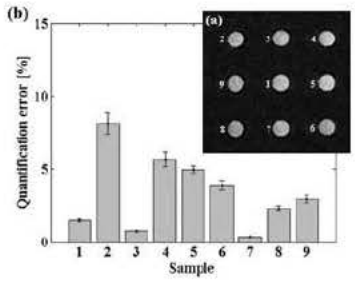

Figure 2: (a) "unknown" samples, (b) quantification error relative to true sample concentration.

Introduced in-vitro quantification result represents an ideal situation with one type and one size of particles, therefore the accuracy is quite high Samples with mixture of particles, and in-vivo quantification bring surely the bigger error, but the method is still in developing phase The main advantage of the proposed method is that enables incorporation of different particles sizes and coatings into calculation models and provides information about particles concentration in just viewed regions

Influence of Saline and Glucose Molecules to Contrast Properties of Clinically Used MRI Contrast Agents

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Currently, the Magnetic Resonance Imaging (MRI) is a technique routinely used in clinical practice, where the contrast agents (CA) are often used for contrast enhancement Generally, the contrast agents can be either iron oxide or gadolinium based nanoparticles in a carrier fluid Iron oxide based CA mainly affect T_2 relaxation time whereas gadolinium based CA affect T_1 relaxation time

In this study we have focused on MRI contrast properties of both types of contrast agents – iron oxide and gadolinium based, in the presence of altered concentration of saline and glucose molecules The reason is that saline and glucose molecules are the essential components of human body and their modified concentration levels are accompanied with several pathological processes, which can be examined with MRI We were interested if these altered concentration levels can have influence to the MRI contrast properties of clinically used CA, with emphasis on the post-processing data analysis

As an example of iron oxide based CA we have chosen the Resovist (Bayer Schering Pharma AG) and as gadolinium based the MultiHance (ALTANA Pharma AG) Several MRI protocols were tested with the help of clinical MRI system ESAOTE Opera (E-SCAN^{TM} XQ) 0 178 T

We have found that physiological concentration of saline and glucose molecules influences the CA contrast properties selectively on the basis of CA concentration (up to 30% for Resovist, and 15% for MultiHance relative to reference, see Figure 1) Moreover, the altered concentration levels of saline and glucose molecules change the signal intensity (contrast), for one selected pulse sequence and CA concentration, in range of 2 – 17 % (see Figure 2) Although, such contrast changes are on the visibility limit to the naked eye (≈ 15 %) with low-field MRI system, they will be clearly visible with high-field system (above 1 5 T) Furthermore, these findings can have crucial influence to the next data analysis, e g relaxation times comparison, distort such a final conclusions

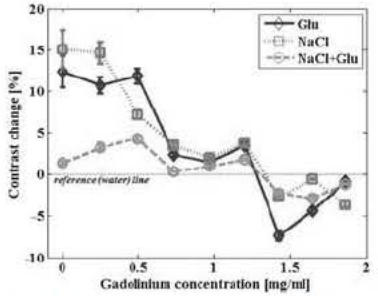

Figure 2: Contrast change in samples with saline and glucose molecules relative to water for different concentration of Gadolinium particles. (Measured with T_1 weighted Spin Echo sequence, repetition time TR = 600 ms, and Echo Time TE = 26 ms.)

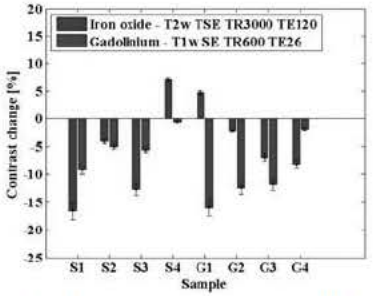

Figure 1: Contrast change for selected pulse sequence and CA concentration relative to different saline and glucose concentration. Samples: S1 - 4.5 g/l NaCl, S2 - 9 g/l NaCl, S3 - 13.5 g/l NaCl, S4 - 18 g/l NaCl, G1 - 0.5 g/l glucose, G2 - 1 g/l glucose, G3 - 1.5 g/l glucose, G4 - 2 g/l glucose. Iron oxide concentration: 103 µg/ml, gadolinium concentration: 1.3 mg/ml.

Magnetic cytosmear for specialized cytological analyses in global health and diseases

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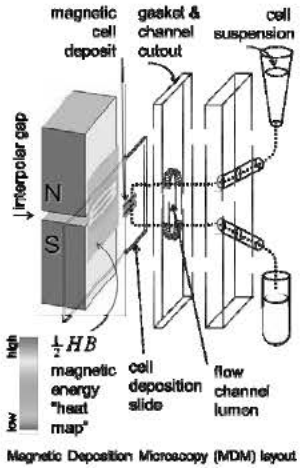
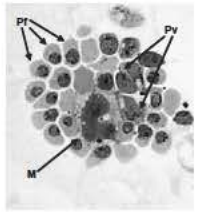
Disease diagnosis relies heavily on blood smear microscopy, especially in resource poor settings. Cytosmears are relatively easy to prepare and provide a flexible platform for subsequent cytological analysis, from a simple, direct microscopic inspection (in search of infectious parasites in malaria diagnosis) to cytochemical staining for nucleated cells (in hematologic diseases) to immunofluorescence staining for cancer biomarkers. We have developed a device that employs magnetic forces to directly deposit cells on the slide, referred to as the Magnetic Deposition Microscopy (MDM, **Figures**). It combines the simplicity of the cytosmear preparation with the added functionality of selectively capturing cells that are magnetized by extrinsic agents (such immunomagnetic nanoparticels) or by changes in the cell's own, intrinsic magnetization (such as due to low-spin to high-spin hemoglobin conversion or increased paramagnetic metal concentration, including iron and manganese). The MDM technique is highly sensitive to hemoglobin conversion to methemoglobin present in aging erythrocytes, to oxidation state of a paramagnetic manganese in bacterial spores, to the presence of hemozoin in erythrocytes infected by malaria parasites[1], to malaria gametocytes[2] and the elevated ferritin oncentration in cancer cell lines[3]. The system is currently undergoing modifications for field testing in malaria endemic regions and for label-free cancer cell separation.

[1]Am J Trop Med Hyg 2006, 74:568; [2]Malar J 2008, 7:66; [3]Anal Chem 2012, 84:4520



Magnetic Deposition Microscopy (MDM) layout



Paramagnetic capture on MDM slide of intraerythrocytic *P. falciparum* (Pf) and *P. vivax* (Pv) due to high-spin malaria pigment, hemozoin, also present inside a macrophage (M).

Paramagnetic capture on MDM slide of HeLa cells incubated in with 100 µM $Fe(NO_3)_3$ chelate (visible by unaided eye).

Swelling and Apoptosis of Monocytic Leukemia Cells in High Gradient Magnetic Fields

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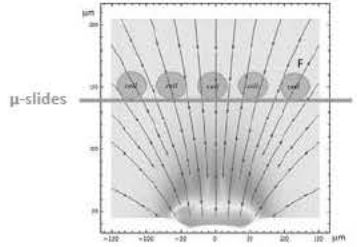
The influence of spatially modulated high gradient magnetic fields on cellular functions of human monocytic leukemia cells was studied THP-1 cells (30,000) seeded onto thin-bottomed ibidi µ-slides in 150 µl full growth medium were exposed to a non-uniform magnetic field with periodical spatial distributions of magnetic flux (see figure) Over the cells grown on ibidi µ-slides, the magnetic micro-array created a pattern with regular magnetic field domains exhibiting different strength and directions

The high-gradient magnetic field created by the patterned magnetic micro-array induced (i) swelling, (ii) prolonged increased oxidative burst, (iii) inhibited cell proliferation, and (iv) elicited apoptosis in THP-1 monocytic leukemia cells in the absence of any toxic chemical or biological agent Upon exposure, the cell volume was increased by up to 90 % and could be controlled by the adjustment of the strength of the magnetic field gradient, the size of the high-gradient domain, and, thus, the magnetic field distribution The observed effects were rather dependent on the strength of the gradient of the magnetic field than on the strength of the magnetic field itself Mathematical modeling indicated that mechanical stress exerted on the cells by high magnetic gradient forces is responsible for triggering cell swelling and formation of reactive oxygen species followed by apoptosis Increase in the membrane tension due to the exposure to high-gradient magnetic field and cell swelling will be discussed in relation to the possible activation of mechanosensitive channels

Thus, we show a new possibility to control cell functions by focused magnetic gradient forces, which might open new opportunities for disease treatment



Schematic representation of THP-1 cells seeded onto the bottom of an ibidi µ-slide Magnetic gradient forces are shown by arrows

Characterization of Multicore Superparamagnetic Iron Oxide Nanoparticles using XAFS and SAXS

W. Szczerba, and A.F. Thünemann*, E-Mail: andreas.thuenemann@bam.de

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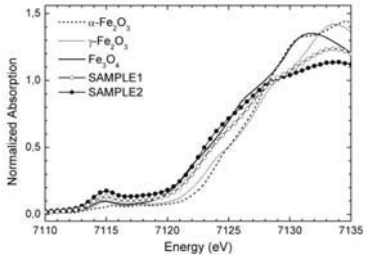
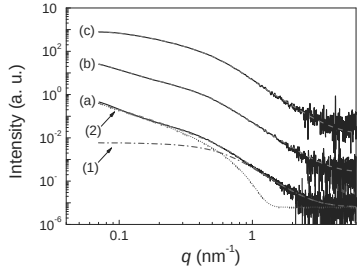
Size and chemical composition are, besides the magnetic properties, two parameters of iron oxide nanoparticles that are of great interest Especially, the unambiguous identification of the iron oxide phase, i e the differentiation between magnetite (Fe_3O_4) and maghemite (γ-Fe_3O_2), is of crucial importance in many fields of application In the study presented, two samples of superparamagnetic particles precipitated from iron salt solutions were investigated, with one of them being subsequently treated with nitric acid to get a dispersed solution The identification of the oxides species in the two samples was done using x-ray absorption fine structure (XAFS) spectroscopy XAFS can distinguish between magnetite and hematite in both, the hard x-ray range at the *K*-edge of iron and the soft x-ray range at the *K*-edge of oxygen and the *L*-edges of iron, by a simple 'fingerprint' comparison of the XAFS spectra In this case the hard x-ray spectra were investigated Surprisingly, both samples contain only magnetite Even the nitric acid treated particles do not show an oxidation to maghemite

Small angle x-ray scattering (SAXS) was employed to measure the particle characteristics of the two iron oxide samples The unified exponential/power-law approached was applied for quantitative SAXS data analysis It was found that the total size of the particles' aggregate decreases due to nitric acid treatment from 37 nm via 23 nm to 11 nm In contrast, the size of the primary particles stays constant at a diameter of 10 nm Aggregation numbers decrease from 148 via 23 to 12 as a result of nitric acid treatment followed by a subsequent storage for two month Combining the results of the SAXS analysis and the structural part of the XAFS spectra (EXAFS) reveals that the nitric acid treatment increases significantly the surface roughness of the iron oxide nanoparticles Both x-ray methods give accurate results on properties that are not easily accessible by other methods in such systems



XAFS near-edge spectra (XANES) of the samples measured and iron oxide standards normalized to the absorption energy step The absorption edge shift being an estimate for the formal valence of the as-precipitated nanoparticles (SAMPLE1) as well as for the nitric acid treated nanoparticles (SAMPLE2) falls together with that of Fe_3O_4



SAXS intensity and curve fits (solid and dashed lines, respectively) for as-precipitated (a), nitric acid treated (b) and stored for 2 months after treatment (c) Exemplarily for (a), the arrows (1) and (2) point at the scattering contributions of primary particles (dash-dotted line) and mass fractal structure (dotted line)

Literature: K Mandel et al J Nanopart Res 2012, 14, 1066

Functionalized superparamagnetic iron oxide nanoparticles exert diverse effects on multicellular spheroids

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Introduction: Superparamagentic iron oxide nanoparticles are used in many medical applications, e g drug delivery systems, contrast agents in magnetic resonance imaging (MRT) or in hyperthermal anti-cancer therapy successfully The mode of interaction of such nanoparticles with biological systems is affected by various parameters including particle size, shape, surface coating and interactions with biological borders The blood-brain barrier is a critical and sensitive interface in the body and is an important model system for the elucidation of the complex chemical, physical and biological interactions Three-dimensional cell culture systems consisting of barrier-forming cells are a further step to simulate the features of real tissues and should represent a suitable model to reflect the particles´ actions in the body, e g toxic effects
Methods: Human brain microvascular endothelial cells (HBMEC), a representative of the human blood brain barrier, were cultured in RPMI1640 + 10% fetal calf serum Viability assays were performed on HBMECs with the CellTiter-Glo® Luminescent Cell Viability Assay (Promega, Mannheim) after incubation with various concentrations of nanoparticles or the corresponding shell-building substances for three hours [1] Nanoparticles with different types of shells (starch, anionic carboxymethyldextran (CMD) and cationic polyethylenimine (PEI)) were provided by chemicell GmbH HBMEC spheroids were created by the hanging-drop method Formation and growth properties of spheroids were analysed with light microscopy repeatedly for several days after initiation Spheroids were incubated with nanoparticles to evaluate their viability with the LIVE/DEAD® Viability/Cytotoxicity Kit (life technologies, Karlsruhe) and confocal laser scanning microscopy The activity of intracellular signalling cascades was monitored by Western blot analysis
Results: Viability assays demonstrated that PEI-coated nanoparticles or PEI alone exhibit concentration-dependant cytotoxic effects on HBMECs starting at a concentration of 25 µg/ cm² Staining of multicellular spheroids confirmed these results by indicating an increased amount of dead cells when incubating spheroids with PEI-particles or PEI alone Starch and CMD-covered particles did not affect the viability of cells at any concentration tested By analysing the growth properties differences in spheroidal shape could be observed over time Immunoblotting focussing on the phosphorylation status of several proteins could show that especially PEI-particles influence intracellular signalling pathways, e g by strengthening pro-proliferative signalling via MAPK p44/42 The inhibition of the WNT-signalling cascade illustrated by an increase in GSK3beta phosphorylation supports this observation
Conclusion: HBMECs are capable to form multicellular spheroids Neutral, anionic and cationic superparamagnetic iron oxide nanoparticles interact with these spheroids Three-dimensional cell cultures offer more highly predictive data for designing nanoparticle-based therapeutics for *in vivo* applications as they provide a better insight into the situation of real tissues compared to two-dimensional systems

This work was supported in part by DFG high priority program 1681, CL202/3-1 and by the BMBF joint research project NanoMed, FKZ 03X0104D

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DOTA-functionalized magnetite nanoparticles as contrast agents for MRI/PET double imaging

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Superparamagnetic iron oxide nanoparticles (SPIONs) have shown a large interest in biomedical imaging (such as T_2 contrast agents for Magnetic Resonance Imaging (MRI)) thanks to their chemical and biological properties over the last several years [1,2] Nowadays, many studies highlight the multimodal imaging and the last advances in theranostic which combines diagnosis and therapy

In this work, a nanoparticle-based bimodal MRI/PET (Positron Emission Tomography) imaging contrast agent has been developed The first step consists of surface-modified Fe_3O_4 NPs by hydrophilic organic molecules namely citric acid (CA), 3,4-dihydroxy-L-phenylalanine (L-DOPA) and 3,4-dihydroxyhydrocinnamic acid (DHCA) Surface-modified NPs are synthetized with a very narrow size distribution thanks to a one-step continuous hydrothermal process [3] The second step is the conjugation of the surface-modified NPs with a chelating agent so as to form stable complexes with radionuclides The agents used in our study are polyazamacrocycles – 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) derivatives – in order to assure the chelation of copper (^{64}Cu) for PET imaging Demonstrated by both TEM and X-Ray Diffraction (XRD) analyses, DHCA-, L-DOPA- and CA-modified NPs lead to a modification of the crystallite size of the magnetite NPs and to an anti-oxidizing effect [3,4] Raman, Infra-Red and X-Ray Photoelectron (XPS) spectroscopies, combined with zetametry measurements highlight the grafting of DHCA, L-DOPA and CA on NPs Modified magnetite NPs lead to stable suspensions in water at physiological pH After the second grafting step, IR, XPS, ThermoGravimetric Analyses (TGA) and elemental analysis measurements have been performed in order to confirm the grafting of DOTA at the surface of the modified Fe_3O_4 NPs PET imaging showed that the radioactive tracer is chelated by DOTA and magnetic NPs are visible on MRI images [5]

This double grafting improves the stability and the biocompatibility of modified Fe_3O_4 NPs for MRI and appears as a relevant strategy to conjugate DOTA molecules for PET The as-prepared NPs have great interest and potential for use in bimodal imaging (MRI/PET): in fact, the combination of the high sensitivity of PET and the high spatial resolution of MRI are gathered in the single nanohybrid presented herein

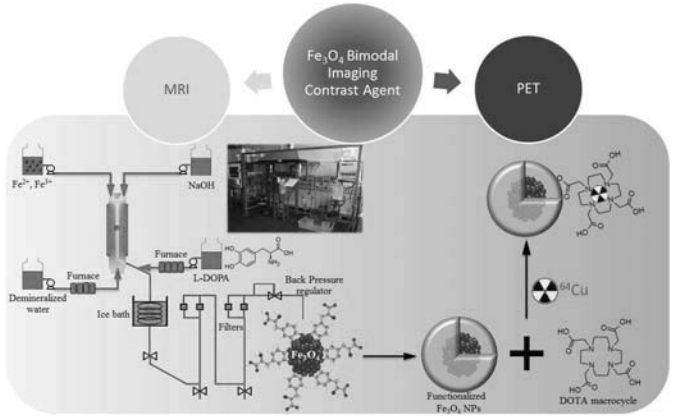

Fig: A two-step synthesis of DOTA-functionalized Fe_3O_4 NPs bimodal imaging contrast agent

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[5] L Maurizi, A L Papa, L Dumont, F Bouyer, D Vandroux, P Walker, N Millot, J Biomed Nanotechnol , in press

Reconfigurable anisotropic coatings via magnetic field directed assembly and translocation of locking magnetic chains

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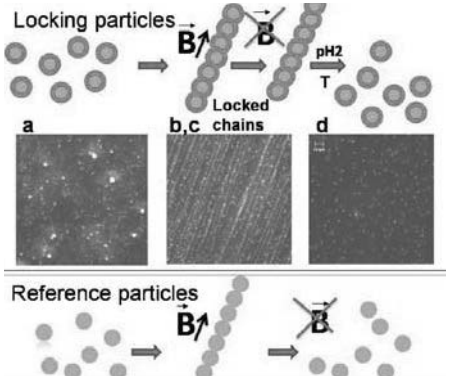
A method for generation of the remotely reconfigurable anisotropic coatings is developed in this work. To form these coatings, the locking magnetic nanoparticles (LMNPs) made of a superparamagnetic core and a two-component polymer shell were employed. Two different polymers form phase separated coaxial shells. The outer shell provides repulsive interactions between the LMNPs while the inner shell exerts attractive forces between the particles. Applying a non-uniform magnetic field, one gathers the particles together pushing them to come in contact when the internal shells could effectively hold the particles together. When the magnetic field is turned off the particles remain locked due to these strong interactions between internal shells.[1] The shells are made stimuli responsive hence, this locking can be made reversible and the chains can be disintegrated on demand. In a non-uniform magnetic field, the assembled chains translocate, bind to the solid substrate and form anisotropic coatings with the "locked" anisotropic structure. The coatings can be constructed, aligned, realigned, degraded, and generated again on demand by changing the magnetic field and particle environment. The mechanism of the coating formation is explained using experimental observations and a theoretical model.[2]



1 Motornov, M. , Tokarev, A. *et al.* Field-Directed Self-Assembly with Locking Nanoparticles. *Nano Letters* **12**, 3814-3820.
2 Tokarev, A. *et al.* Field-Directed Self-Assembly with Locking Nanoparticles. *Nano Letters* **12**, 3814-3820. Reconfigurable anisotropic coatings via magnetic field directed assembly and translocation of locking magnetic chains, *Advanced Functional Materials*, accepted, in press.

Elimination of magnetic nanoparticles with various surface modifications in the blood stream in vivo

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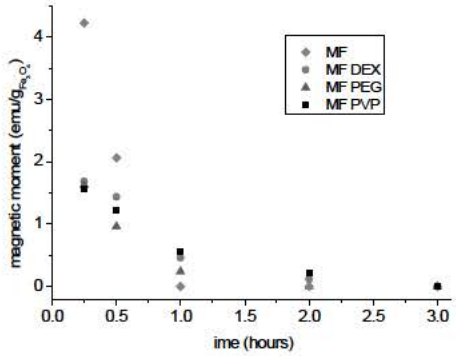
Magnetic nanoparticles offer opportunities toward developing effective drug delivery systems. The size and surface of the particles are crucial factors in their application in biomedicine. Application of an external localized magnetic field gradient to chosen site can be effective to attract drug-loaded magnetic nanoparticles from blood circulation. For this purpose the nanoparticles with surface modification for long-term circulation in blood are desirable.

In this work magnetic nanoparticles (MNPs) with different surface modification were prepared. The mean core diameter of magnetic particles was 10 nm. Nanoparticles were stabilized by sodium oleate and bovine serum albumin (BSA) in phosphate buffer to obtain stable magnetic fluid (MF). In the next step the sample was modified by different biocompatible substance such as poly(ethylene glycol) (PEG), dextrane (DEX), and polyvinylpyrrolidone (PVP). The prepared biocompatible samples were diluted in water for injection (1:1) and applied intravenously to the mice. The blood was collected after 15 min, 30 min, 1, 2, 3, 4, 5 and 24 hours, respectively. The blood was then lyophilized and magnetic moment of the samples was measured by SQUID magnetometer (Quantum Design MPMS 5XL). The obtained results showed that 15 minutes after MF administration the concentration of MNPs in the blood was was more than twice higher than in the case of MNPs modified by DEX, PEG or PVP. However, all MNPs of MF were trapped by reticuloendothelial system within 1 hour. On the other hand, in the case of MNPs modified by DEX, PEG of PVP magnetic nanoparticles circulated in blood up to 3 hours.



Time dependence of magnetic moment of different modified magnetic particles in blood stream.

Supported by Ministry of Education Agency for Structural Funds of EU in frame of projects 26220120021 and 26220220005 and 26110230097, APVV-99-026505, 0742-10

Physicochemical and colloidal criteria of magnetic nanoparticle systems eligible for biological testing

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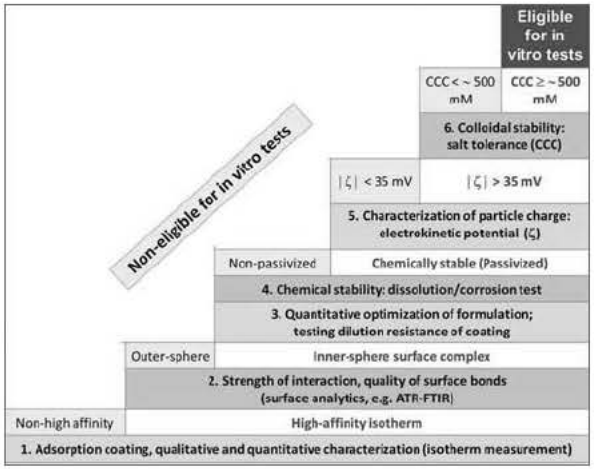
Despite the large efforts to prepare super paramagnetic iron oxide nanoparticles (MNPs) for biomedical applications, the number of FDA or EMA approved formulations is few. It is not known commonly that the approved formulations in many instances have already been withdrawn or discontinued by the producers; at present, hardly any approved formulations are produced and marketed. Literature survey reveals that there is a lack for a commonly accepted physicochemical practice in designing and qualifying formulations before they enter in vitro and in vivo biological testing. Such a standard procedure would exclude inadequate formulations from clinical trials thus improving their outcome.

We have developed a straightforward route to assess eligibility of carboxylated MNPs for biomedical tests applied for a series of our core-shell products, i.e., citric acid, gallic acid, poly(acrylic acid) and poly(acrylic acid-co-maleic acid) coated MNPs. The presentation is based on physicochemical studies (carboxylate adsorption/desorption, FTIR-ATR, iron dissolution, zeta potential, particle size, coagulation kinetics and magnetization measurements) and involves some in vitro and in vivo tests. Our procedure can serve as an example to construct adequate physic-chemical selection strategies for preparation of other types of core-shell nanoparticles as well.



Schematic presentation of the suggested optimization procedure of carboxylate@MNP core-shell nanoparticles developed for biomedical applications; the route of preparation is the adsorption of the carboxylates to the naked MNPs.

Reference:
M. Szekeres, I.Y. Tóth, E. Illés, A. Hajdú, I. Zupkó, K. Farkas, G. Oszlánczi, L. Tiszlavicz, E. Tombácz: Chemical and Colloidal Stability of Carboxylated Core-Shell Magnetite Nanoparticles Designed for Biomedical Applications, Int. J. Mol. Sci. 2013, 14, 14550-14574.

Acknowledgement: The financial support of OTKA (NK84014) is gratefully appreciated.

Experimental observation of Brownian contribution to the relaxation mechanisms of $Co_XFe_{3-X}O_4$ nanoparticles and theoretical analysis within the linear response theory.

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The use of magnetic nanoparticles (MNPs) for biomedical applications has experienced a steady growth during last years The need of applications imposes the optimization of different routes for synthesis and functionalization methods of colloidal MNPs systems in order to obtain a narrow size distribution and a high stability In the field of Magnetic Hyperthermia several ferrite systems have been studied from theoretical and experimental point of view using different models for explaining the results With this aim, we have produced a series of cobalt ferrite nanoparticles with a systematic size range shift between 5 and 25 nm, by thermal decomposition of Fe $(acac)_3$ and $Co(acac)_2$ Detailed structural and magnetic characterization of these samples revealed high crystallinity and narrow size distributions The resulting samples $Co_XFe_{3-X}O_4$ showed a deviation from the ideal x =1 stoichiometry to values down to x = 0 53 In order to know their efficiency as heating agents for Magnetic Hyperthermia, characterized by their Specific Power Absorption (SPA), all samples were analyzed in an applied magnetic field (H_0) up to 23 8 kA/m, and frequencies 229 < f < 828 kHz The obtained SPA values (H_0= 23 8 kA/m, f = 580 kHz) for MNPs with average diameter <d > = 13 3 nm were 1360 W/g and 282 8 W/g in hexane and water, respectively, in precise agreement with numerical simulations using the Neel-Brown relaxation model within the linear response theory (LRT) This demonstrated that for highly anisotropic systems like $CoFe_2O_4$, the dominant mechanism for magnetic relaxation is Brownian rotation within the carrier liquid

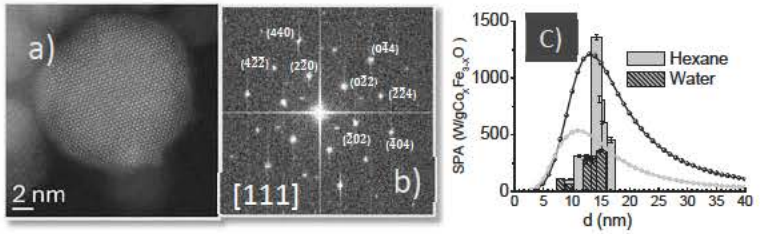

Figure1: a-HRTEM image of one MNP corresponding to a sample with <d>= 13,3 nm b- The Fast Fourier Transform (FFT) showed the lattice planes indexed according to the Fd3m space group c- Experimental values (bars) of SPA for samples dispersed in hexane and water showed the good agreement with the theoretical simulations (dots)

Magnetic hyaluronate hydrogels: Preparation and characterization

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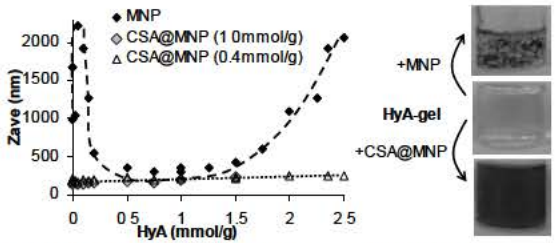
Magnetic hydrogels are in the focus of scientific interest (e.g. superparamagnetic magnetite nanoparticles (MNPs) in kappa-carrageenan nanospheres, *in situ* mineralization of MNPs in chitosan hydrogel, magnetic hydrogel formulated with chitosan, β-glycerophosphate and MNPs for a potential cancer treatment), but there is no publication about magnetic hydrogels prepared from hyaluronate (HyA) to the best of our knowledge. The bridging flocculation of MNPs due to the adsorption of giant HyA molecules can be hindered only by the pre-modification of the MNP's surface.

The aim of our research is the preparation of a HyA-based magnetic hydrogel, which can be potentially used as intra-articular injections for example in knee joints. Firstly purified magnetite sol was prepared by co-precipitation then surface-modification of MNPs was performed by the routines used in the lab of Aqueous Colloids Research Group[1]. The following surface-modifying agents were being tested: citric acid (CA), poly(acrylic acid) (PAA) and chondroitin-sulfate-A (CSA). The colloidal stability of the naked and the surface-modificated MNPs (i.e. CA@MNP, PAA@MNP and CSA@MNP) was characterized at various HyA loadings (pH~6.0, 0.01 M NaCl) by dynamic light scattering (DLS) and electrophoresis measurements. A few selected hydrogels were tested by rheology measurements, too.

The average values of the hydrodynamic diameter (Z_{ave}) determined by DLS measurements show that the naked magnetite is not suitable at all for magnetic hydrogels. However, for example the CSA@MNP with enough high CSA content (as seen the Figure below) is a potentially good material to prepare HyA-gels. Based on the rheology measurements (flow curves, creep-tests, oscillation measurements) it appears that the presence of CSA@MNP does not significantly affect the flow properties of the hydrogel. The results suggest that the HyA-based magnetic hydrogels should be able to be used as intra-articular injections.



Stability of MNP and CSA@MNP with different CSA contents at various HyA loadings (left) and photos of different HyA-gels immediately after the preparation (right) (pH~6.0, 0.01 M NaCl).

Literature:

1. Tombácz, E., I.Y. Tóth, D. Nesztor, E. Illés, A. Hajdú, M. Szekeres, L.Vékás; Adsorption of organic acids on magnetite nanoparticles, pH-dependent colloidal stability and salt tolerance. Colloids and Surfaces A: Physicochemical and Engineering Aspects 2013:435 91-96.

Acknowledgements:
This research was supported by the OTKA (NK 84014) grant as well as by European Union and the State of Hungary, co-financed in the framework of TÁMOP 4.2.4. A/2-11-1-2012-0001 'National Excellence Program'.

Preparation and characterization of chondroitin-sulfate-A-coated magnetite nanoparticles for biomedical applications

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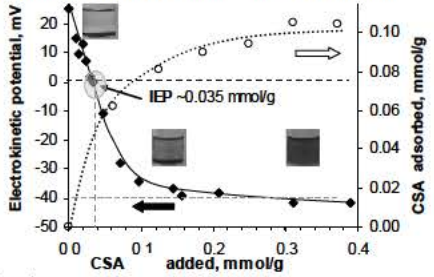
Superparamagnetic iron oxide nanoparticles (SPIONs) are in the focus of scientific interest because of their potential biomedical applications (MRI contrast agents, drug delivery, magnetic hyperthermia). The SPIONs have to be non-toxic, uniform in size, chemically stable and well-dispersed in aqueous media. Polysaccharide-coated magnetite nanoparticles (MNPs) are well known biocompatible magnetic products. Chondroitin-sulfate (CS) is a natural polysaccharide with different types (e.g. A and C) and the synthesis of magnetite nanoparticles in the presence of CS has already been patented.

The aim of our research was the characterization of the surface modified MNP with CSA, and the preparation of a magnetic fluid suitable for biomedical applications. Firstly purified naked MNPs were prepared by co-precipitation. The adsorption isotherm was determined by batch method (pH~6.5, 0.01 M NaCl) and the surface bonding was studied by infrared spectroscopy (ATR-FTIR). The CSA-coated MNPs (CSA@MNP) were characterized at different pH and at various CSA loadings by dynamic light scattering (DLS) and electrophoresis measurements. The colloidal stability of CSA@MNPs was tested in coagulation kinetic experiments (pH~6.5) and their biocompatibility by blood sedimentation and cell proliferation experiments[1].

The CSA adsorption on MNPs had a high-affinity isotherm (plateau at ~0.11 mmol/g), the different roles of $-COO^-$ and $-OSO_3^-$ groups in adsorption were determined by ATR-FTIR. The CSA can bind to the MNP's surface with high affinity because of the formation of inner sphere metal-carboxylate complexes. Electrokinetic potentials and hydrodynamic diameters were measured at increasing CSA loadings. The isoelectric point was at ~0.035 mmol/g CSA and the MNPs are totally covered at ≥0.2 mmol/g added amounts of CSA, so the particles are overcharged and colloidally stable (pH~6.5, 0.01 M NaCl) as seen in the Figure below. Small amounts of CSA induce the aggregation of MNPs, while its larger amounts can stabilize dispersions over a wide pH-range. The salt tolerance of CSA@MNPs rises up to ~0.5 M NaCl with increasing CSA loading. Well-stabilized magnetic fluid using CSA@MNP can only be prepared under special conditions, but the results of blood sedimentation and cell proliferation experiments suggest that it is a promising candidate for biomedical applications.



Effect of CSA addition on the charge state of MNPs and the colloidal stability of the dispersions (pH~6.5, 0.01 M NaCl)

Literature:

1. I.Y. Tóth, E. Illés, R.A. Bauer, D. Nesztor, M. Szekeres, I. Zupkó, E. Tombácz (2012) Langmuir 28: 16638–16646.

Acknowledgements:

This work was supported by OTKA (NK 84014) and TÁMOP-4.2 2.A-11/1/KONV-2012-0047.

Study on the encapsulation of magnetic cores using real time polymerase reaction

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Magnetic particles have found increasing applications in medical diagnostics, human and veterinary medicine and as therapeutics due to their unique properties and their ability to interact with various biomolecules of interest, including nucleic acids (DNA, RNA), protein or cells Solid phase magnetic driven separation techniques in combination with molecular diagnostic methods (polymerase chain reaction, PCR) have become popular to speed up and facilitate the nucleic acids separation and purification procedures

Magnetic particles are mostly based on magnetic iron oxide (magnetic core) covered by polymer surfaces suitable for modification by different functional groups (e g –COOH, $-NH_2$) Free or incomplete encapsulated cores and some components applied in the preparation of magnetic particles can interfere with polymerase chain reaction [1, 2] Therefore perfectly encapsulation of magnetic cores and removing all potential PCR inhibiting components are key factors for the application of magnetic particles in molecular diagnostics

For this reasons, polymerase chain reaction in quantitative real time (qPCR) and the software supplied with the qPCR, were used for the estimation of the inhibitory effect of different types of magnetic microparticles The set of magnetic non-porous poly(2-hydroxyethyl methacrylate-co-glycidyl methacrylate) - P(HEMA-*co*-GMA) microspheres (8 types, (Figure 1)) and poly(glycidylmethacrylate) - P(GMA) (6 types, (Figure 1)) covered by different content of carboxyl groups and 3 types of compounds used for magnetic core encapsulation were studied Linear regression analyses were used for the evaluation of the influence of the particles or compounds on the qPCR course From results, it follows that the tested particles can be split up to 3 groups according to the effect on the DNA amplification The results presented in this report show that polymerase chain reaction in real time is suitable method for the evaluation of the quality of magnetic particles

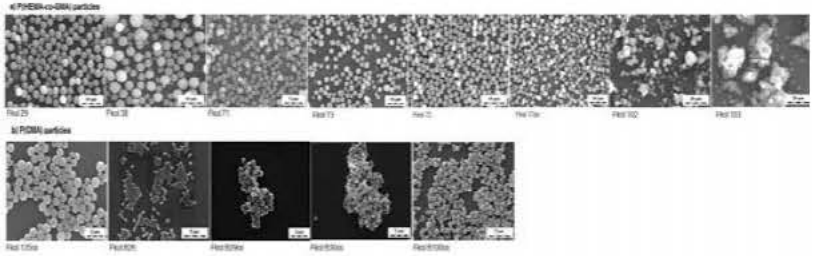

Figure 1: Electronmicroscopy (SEM) of magnetic micro- and nanoparticles, a) P(HEMA-co-GMA) particles, b) P(GMA) particles

Acknowledgements

The financial support of the Grant Agency of the Czech Republic, project No 13-32840P is gratefully acknowledged

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[2]Spanova A., Horak d., Soudkova E., Rittich B. Magnetic hydrophilic methacrylate-based polymer microspheres designed for polymerase chain reactions applications. Journal of Chromatography B. 800, 2004, pp. 27 – 32.

Magnetic microgels for drug targeting applications: physical-chemical properties and cytotoxicity evaluation

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The encapsulation of magnetic nanoparticles into polymeric microgel systems gives rise to biocompatible hybrid magnetic carriers with superparamagnetic behaviour, high saturation magnetization/large magnetic moment of particles, richness in surface functional groups, which are suitable for magnetically targeted drug delivery, hyperthermia treatments, magnetic resonance imaging contrast enhancement, magnetic separation. Magnetoresponsive microgels with high saturation magnetization values 45-56 emu/g have been obtained by a strategy based on the miniemulsion method using high colloidal stability organic carrier magnetic nanofluid as primary magnetic material. Hydrophobic nanoparticles Fe_3O_4/OA are densely packed into well-defined spherical nanoparticle clusters (NPCs) coated with polymers with sizes in the range 50-350 nm. Physical-chemical characteristics of magnetic microgels were investigated by TEM (Fig. 1(a)), SAXS (Fig. 1(b)), XPS and VSM measurements with the focus on the structure-properties relationship. The impact of magnetic microgels loaded with anticancer drug mitoxantrone (MTO) on the non-adherent human T cell leukemia line Jurkat was investigated in multiparameter flow cytometry. Parallel stainings with DiIC1(5), Annexin-A5-Fitc, and propidium iodide were performed to comprehensively monitor cellular viability as reflected by mitochondrial membrane potential, phosphatidylserine exposure and plasma membrane integrity. We showed that both fluid MTO and microgel-loaded MTO penetrate into cells, whereas the penetration of microgel-loaded MTO is slightly delayed. Fluid MTO and microgel-loaded MTO both induce apoptosis and later secondary necrosis in a time- and dose dependent manner. In contrast, microgels without MTO are not cytotoxic in the corresponding concentrations. Based on these results we conclude that MTO-loaded microgels might be promising structures being worth to further improve their features for application in magnetic drug targeting.

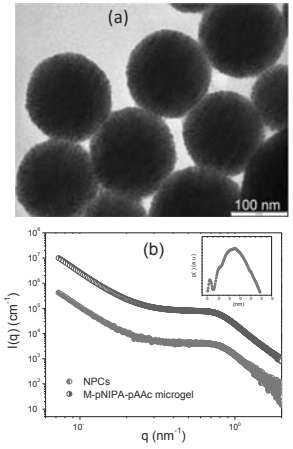

Figure 1 (a) TEM image of magnetic microgel M-pNIPA-pAAc; (b) SAXS data of NPCs and microgel Inset: pair distance distribution function of NPCs

Magnetic iron oxide nanoparticles with cisplatin-bearing polymer coating for targeted drug delivery

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Cancer is the second most common death in the US, with 580,350 expected cancer victims for 2013 [1]. A highly selec ive and efficient cancer herapy can be achieved using magnetically directed superparamagnetic iron oxide nanoparticles (SPIONs) bearing a sufficient amount of therapeutic agents [2]. In this project, SPIONs with a dextran and a cisplatin-bearing hyaluronic acid coating were successfully synthesized, as a novel cisplatin drug delivery system. In he first step, steric stabilized dextran coated SPIONs (DESPIONs) were fabricated with a cold gelation process (see figure). Their agglomeration sizes decreased with increasing dextran content during coprecipitation and were in the range of 20 and 40 nm, as it was shown with dynamic light scattering measurements. Transmission electron microscopy images as well as X-ray diffraction (XRD) analysis proved that the individual magnetite particles within those agglomerates were around 4.5 nm and monocrystalline. The small crystallite sizes led to the superparamagnetic behavior of the particles, which was exemplified in their magnetization curves, acquired with SQUID measurements. Those results also showed that an increase in dextran content during coprecipitation led to a decrease in saturation magnetization. After amination of DESPIONs, the esterification of hyaluronic acid (HA) to dextran was performed (HA-DESPION). Evidence for the resulting amid bond linkage was shown with fourier transform infrared spectroscopy (FTIR). The additional polymer layer increased the vehicle size from 22 to 56 nm, with a HA : dextran : magne ite weight ratio of 51 : 29 : 20. After incorporation of he drug, the particle size was further increased to around 77 nm wi h a ζ poten ial of -45 mV (in water at pH 7.4). Due to electrosteric stabiliza ion, no sign of precipitation for the particles occurred wi hin more than 8 weeks. The analysis of the drug release kinetic with the dialysis tube method revealed that it was driven by inverse ligand subs itution and diffusion through the polymer shell as well as enzymatic HA degradation. The biological activity of the par icles was investigated with the non-adherent Jurkat cell line in a flow cytometer. Furthermore, it was examined wi h the adherent PC-3 cell line through xCELLigence analysis. Both tests proved that particles without drug were not harmful to these cells, whereas par icles with cisplatin induced apoptosis in a dose dependent manner, with secondary necrosis after prolonged incuba ion. In conclusion, the combination of dextran coated SPIONs with hyaluronic acid and cisplatin represents a promising approach to be used in magnetic drug targeting for cancer therapy.

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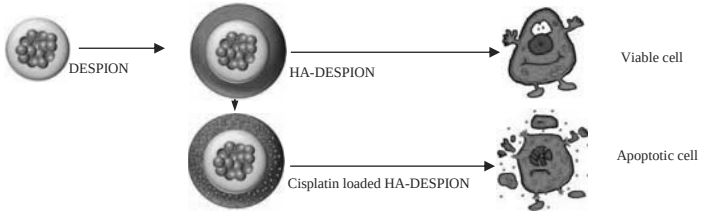

Figure Schematic representation of the biological activity of HA-DESPIONs with and without drug.

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Accurate Quantification of Magnetic Particle Properties by Intra-Pair Magnetophoresis for Nanobiotechnology

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The ability to analyze biological material at the single-molecule and single-cell level in a highly parallelized fashion will significantly enhance biomedical research and in-vitro diagnostics in the future. Magnetic particles play an important role in this development because such particles can be manipulated by magnetic fields without perturbing the biological matter under study. An important requirement is that the magnetic properties of the particles are accurately known, with single-particle resolution as well as with good statistics. However, a combined accurate and high-throughput method for the characterization of the field-dependent magnetization of magnetic particles does not yet exist.

Here, we present intra-pair magnetophoresis as a novel method to accurately quantify the field-dependent magnetic moments of magnetic particles and to rapidly generate histograms of the magnetic moments with high statistics [Reenen et al, Appl. Phys. Lett. 103, 043704, **2013**]. The high accuracy is achieved by recording particle movement in the high and local field gradients generated by the particles themselves (Figure 1). In this intra-pair magnetophoresis method (i) the field gradients and therefore the magnetophoretic velocities are high, (ii) the applied field strength is uniform and well-controlled, and (iii) many particles are simultaneously and repetitively measured. We demonstrate our method with particles of different sizes and from different sources, with a measurement precision of a few percent.

We expect that the intra-pair magnetophoresis methodology will be a powerful tool for the characterization and improvement of particles for the upcoming field of particle-based nanobiotechnology.

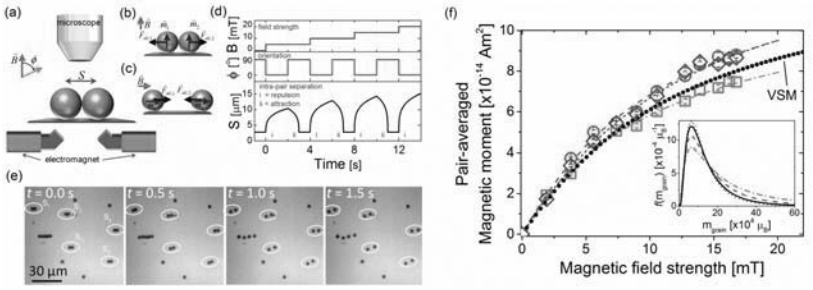

Figure 1. The intra-pair magnetophoresis methodology. (a) The separation S of superparamagnetic particle pairs due to magnetic dipole-dipole interactions is measured in (b) out-of-plane and (c) in-plane magnetic fields. (d) Repeated separation and rejoining of magnetic particles S (black line) at different field strengths (blue line) with alternating in-plane and out-of-plane orientation (red line). (e) Microscopy images of M-270 superparamagnetic particles at different times, upon application of an out-of-plane magnetic field at t = 0. The image is a zoom-in of the total field of view. (f) Magnetization curves determined for three particle pairs (open symbols) and compared to VSM measurements (Vibrating Sample Magnetometry; black circles) performed on an ensemble of the same batch of particles. Magnetization curves are fitted with a log-normal distribution-weighted sum of Langevin curves, representing the grain size distribution within the particles (see inset).

Dynamic Magnetic Particle Actuation for Lab-on-Chip Biosensing

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The demand for easy to use and cost effective medical technologies inspires scientists to develop innovative lab-on-chip technologies for in-vitro diagnostic testing. We study the use of magnetic particles actuated by magnetic fields to perform and optimize different microfluidic handling steps in an integrated biosensing assay (Figure 1). We have developed numerical models to simulate the collective particle behavior and the different binding processes in the assay. The model results are compared to experimental data and are used to develop novel magnetic actuation technologies.

We have investigated the affinity capture process of molecular targets by magnetic particles (see Figure 2). We quantified association rate constants of the capture process for different types of magnetic particle actuation within a fluid. It is found that without magnetic actuation, depletion zones in the target concentration are formed near the particles. Using magnetic field gradients and rotating fields to respectively move and rotate chains of particles within the fluid (Figure 2a), particle-fluid interactions are significantly enhanced and effectively reduce the depletion zones (Figure 2b). Using numerical Brownian dynamics simulations of the capture process (Figure 2c), we have confirmed these effects and computed similar rate constants (Figure 2d). Lastly, we have characterized association rate constants for various types of actuation, for varying magnetic actuation parameters and as a function of the magnetic particle concentration. We find that magnetic actuation can increase the capture rates by almost two orders of magnitude.

With these results we provide a fundamental basis for the use of magnetic particle actuation to effectuate target capture in stationary microfluidic sample volumes. We expect that the reported particle actuation methods will be very useful for future lab-on-chip biosensing applications.

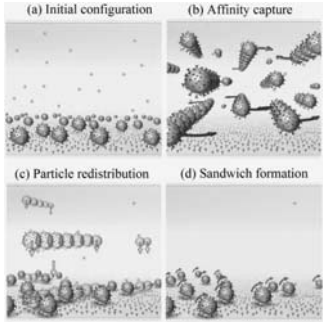

Figure 1 Processes in a microfluidic biosensing assay. (a) After initialization, magnetic particles are actuated (b) to capture molecular targets (green), (c) to concentrate and distribute them at the surface, and (d) to rapidly bind captured targets to the sensor surface.

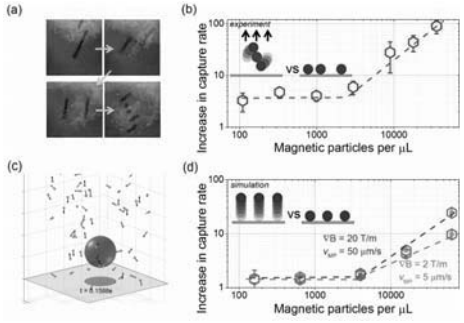

Figure 2 Results from experiments and simulations. (a) Chaotic fluid mixing induced by rotating particle chains. (b) Increase in target capture rate by particle actuation wrt no actuation. (c) Numerical model of the capture process based on Brownian dynamics. (d) The increase in capture rate computed in case of magnetic particles translating through the fluid.

Magnetic Field-Induced Rotaphoresis for Controlled Redistribution of Magnetic Particles over a Surface

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Magnetic particle-based assays in lab-on-chip devices require a high level of control over the behavior of the particles. By the application of magnetic fields, both the individual and the collective behavior of the particles can be manipulated. However, magnetic actuation is often accompanied by the aggregation of particles as well as the drift of particles toward magnet poles.

Here, we report a new method to manipulate large ensembles of magnetic particles in a highly controlled fashion, by so-called magnetic field-induced rotaphoresis: the conversion of rotational motion of particles near a surface into effective translational motion. Using experiments and numerical simulations, we show that particles can be moved along the surface at high velocities (several mm/s) by using an out-of-plane rotating magnetic field (Fig. 1). In addition, the particle clusters within the ensemble are completely disaggregated within a few seconds (Fig. 2) by controlling the field frequency and amplitude. Our experiments and simulatios show that rotaphoresis is an effective manipulation methodology for particles of various sizes and surface properties. As only externally generated magnetic fields are used, magnetic field-induced rotaphoresis is highly suited for stationary-fluidic lab-on-chip assays.

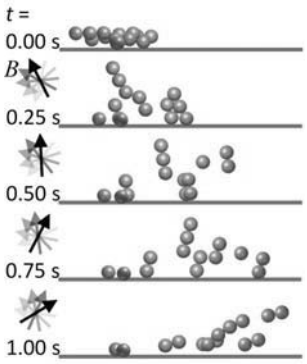

Figure 1 Concept of rotaphoresis. The figures correspond to a numerical Brownian dynamics simulation of the particle behavior.

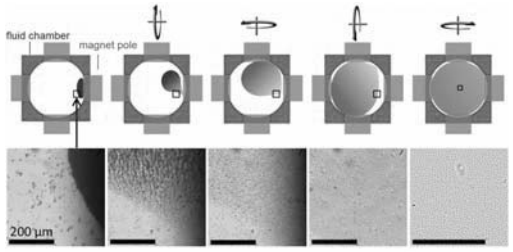

Figure 2 Experimental results showing that rotaphoresis, applied successively in different directions, can be used to evenly redistribute particles over a surface, within a time of 80 seconds.

A rotating molecular ruler: Determining nanometer-scale particle-particle distances in an optomagnetic cluster assay

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We investigate a fast and sensitive optomagnetic biomarker detection technology based on magnetic particles. Antibody-coated superparamagnetic particles capture biomarker molecules and form clusters with a biomarker molecule sandwiched between two particles. The particle clusters are actuated using a rotating magnetic field, which induces an oscillating light scattering cross-section (see Figs. 1a and 1b). Sub-picomolar biomarker concentrations can be resolved by the light scattering signals [Ranzoni et al, Nanoletters 2011; ACS Nano 2012].

In this paper we report a method to quantify inter-particle distances with nanometer resolution. The light scattering data show high-frequency signal components (see Fig. 1b). Simulations show that these high-frequency components hold detailed information about the geometry of the particle clusters, including a strong dependence on the inter-particle distance (see Fig. 1c). We will report the simulation results and experimental data of corresponding model cluster assays.

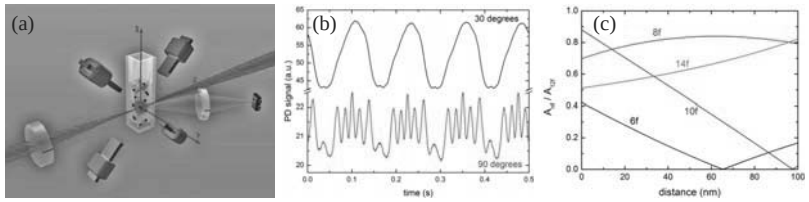

Figure 1 The particle-particle distance measurement technique. (a) Schematic representation of the light scattering setup. A quadrupole electromagnet creates a rotating magnetic field inside a cuvette. A laser beam is focused into the cuvette, the light scatters from the clusters and is collected at a photodiode. (b) Typical scattering signals at two different scattering angles. 30 degrees corresponds to the photodiode position displayed in figure 1a, 90 degrees corresponds to light scattering in the Y-direction. (c) Simulation of the Fourier amplitudes of the 90 degree scattering signal, normalised by the 12f amplitude, as a function of particle-particle distance.

Cytotoxicity tests of bacterial magnetosomes on cell lines HT-29 and A549

Zuzana Varchulová Nováková[1], Milan Timko[2], Anežka Hashim[2], Matúš Molčan[2], Peter Kopcansky[2], Iveta Gašparová[1], Daniel Böhmer[1], Ľuboš Danišovič[1]

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The aim of this work was the verification of functionality and biocompatibility of bacterial magnetic nanoparticles (magnetosomes) using different cytotoxic tests. Magnetosomes are bacterial magnetic nanoparticles that are formed in the process of biomineralization inside the magnetotactic bacteria. Magnetosomes are coated with organic membrane, which has a similar composition as the eukaryotic cell membrane, so they appear to be a suitable carrier for the targeted transport of drugs. Advantage of this targeted transport of drugs is the minimizing of harm to the organism, specific focusing on certain types of tissues, increased effect of the drug, reduced dose and hence side effects.

Magnetosomes were tested by basic cytoxicity tests – MTT and WST1 assays. The analyses were performed on cancer cell lines HT-29 (colon cancer) and A549 (lung cancer) using spectrophotometer Biotek ELx800. The absorbance in case of MTT assay was measured at wavelength 490 nm and in case of WST1 at wavelength 450 and 630 nm. The viability was calculated by formula: exposed sample / negative control. 100%.

Our results show that bacterial magnetosomes have a great potential as carriers of bioactive macromolecules and anticancer drugs because they had a minimal effect on viability of our chosen cell lines, which can be seen in the graph.

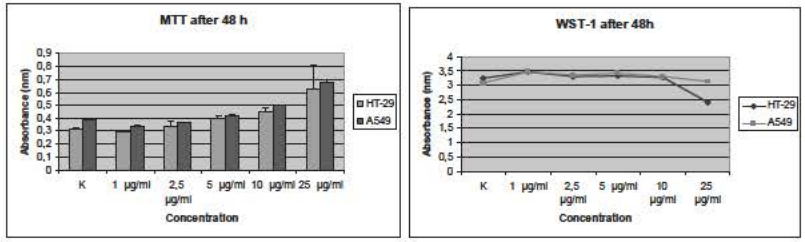

Figure 1: Cell viability (MTT assay, WST-1 assay) of cell line A 549 and HT-29 bacterial magnetic nanoparticles for 48h. Data presented are mean +- SD of triplicate values.

On the other hand they represent a risk because they are isolated from bacteria and that is why their biocompatibility requires more detailed studies. The further studies will be focused on analyses of selected genes involved in control of cell cycle (e g Bcl-2, TP53) and induction of apoptosis. In the future, magnetosomes could be used for biomedical purposes, especially for the purpose of hyperthermia, which may be combined with other methods such as chemotherapy and surgery.

Acknowledgements: *This work was supported within the project UK/341/2013, APVV 171-10 and the project 26110230097 in frame of Structural Funds of European Union.*

Magnetic and relaxometric studies of silica-coated Co-Zn ferrite

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The magnetic and relaxometric studies of water suspensions of silica-coated cobalt-zinc ferrite ($Co_{0.4}Zn_{0.6}Fe_2O_{4+\gamma}$) nanoparticles were carried out in order to evaluate their potential use as a negative contrast agent for MRI At the same time, preliminary cell viability tests employing the ferrite particles were performed

The ferrite cores were prepared by the coprecipitation method from a solution of respective nitrates at pH ~ 10 and temperature of 90 °C The annealing in air at 500 °C and 650 °C for 3 hours was leading to particles with the mean sizes of crystallites d_{XRD} = 11 nm and 51 nm, denoted as A and B samples, respectively, providing particles with d_{XRD} = 9 nm (A) and 22 nm (B) after mechanical treatment The particles were encapsulated by amorphous silica to ensure their colloidal stability in water and to enable their study in biological systems TEM showed uniform silica shell with the mean thickness of 14 nm (A) and 22 nm (B) The colloidal stability of suspensions was confirmed by DLS measurement and the mean value of the hydrodynamic size of 170 nm for both the samples was determined

The relaxometric studies included the field dependence of T_2 relaxivity (measurements at 0 5, 1 0, 1 5, 3 0 and 4 7 T) as well as its temperature dependence at 0 5 T The aqueous suspension of the silica-coated sample A, possessing the specific magnetization $\sigma_{0.5T}$(300K) = 30 $Am^2kg^{-1}_{CoZn\text{-}ferrite}$, exhibited transverse relaxivity r_2 = 440 $s^{-1}mM^{-1}_{CoZn\text{-}ferrite}$ at 300 K The silica-coated sample B with $\sigma_{0.5T}$(300K) = 41 $Am^2kg^{-1}_{CoZn\text{-}ferrite}$, showed even higher value of r_2 = 920 $s^{-1}mM^{-1}_{CoZn\text{-}ferrite}$ at 300 K The transverse relaxivity decreases considerably with the temperature since the Curie temperature is 330 K and 357 K for A and B, respectively The relaxometric behaviour of the particles indicates the static dephasing regime

The support by the projects GACR P204/10/0035 and GACR P108/11/0807 is gratefully acknowledged

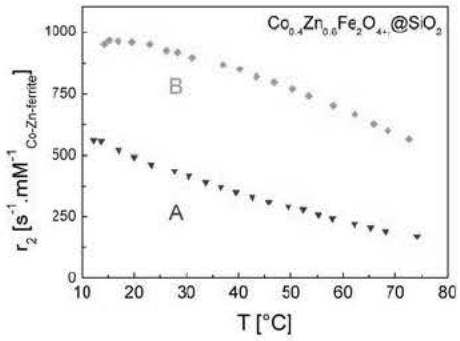

Figure: The temperature dependence of T_2 relaxivity for the silica-coated samples A and B dispersed in water

Assisted formation of alkoxysilanes on the surface of ferrite nanoparticles and their magnetic properties

J.V.A. Vieira[1]; Mac-K. M.S. Santos[1]; R.B. Cunha[2]; S. Quezado[3]; J.A. Coaquira[4]; J.A. Chaker[1,2*]

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The surface science of interfaces, such as metal oxide/biological environmental interfaces, requires both advances in experimental and theoretical methods in order for conceptual insights to emerge In this prospective, several aspects of the ferrites nanoparticles must be facet in terms of surface chemistry and its correlations in ability to attach organic bioactive molecules

This work aims to obtain magnetic iron oxide nanoparticles surface functionalized with alkoxysilanes containing different organic groups and evaluate the ability to attach the bioactive antineoplastic Chlorambucil, even improving the drug content Nanosized maghemite iron oxide particles (MNPs) were was synthesized using a conventional precipitation synthesis method in aqueous medium and the surface modification were conducted in ethanol throughout hydrolysis and condensation reactions mediated by ultrasonication The structure of the nanoparticles were characterized by X-ray diffractometry (XRD), infrared spectroscopy and small angle X ray scattering (SAXS), magnetic properties were studied by magnetization measurements using the vibrating sample magnetometer (VSM) To estimate the crystallite particle size, XRD patterns have been refined using the Rietveld method and modeling the peaks profile with a Pseudo-Voigt function SAXS scattering data was adjusted to analyze the nanometric surface profile and radius of gyration of particles using a unified power law according to Beaucage that consider particles coexisting between small sub-particles and describe a mass fractal regime with multiple-size-scale features parameterized

Figure 01 show the different alkoxysilanes precursors used in the modifications of maghemite surface: Tetraethyl orthosilicate (TEOS); 3-(Methylaminopropyl) trimethoxysilane (MAPTES); (3-Mercaptopropyl) triethoxysilane (MPTES); (Chloromethyl) trimethoxysilane (CMTMS); (3-Aminopropyl) triethoxysilane (APTES); 3-(Trimethoxysilyl) propyl methacrylate (META) Infrared spectroscopy from coated samples shows absorptions in 600 cm^{-1} and in 1080 cm^{-1} frequently attributed to Fe-O and Si-O-Si vibrations respectively This confirms the occurrence of oxide maghemite phase and the achievement of surface covering process For covered ferrite nanoparticles the radius of gyration depend on the type of alkoxysilanes used in preparation For META, APTES and CMTMS covered samples, the radius of gyration is equal 18 4, 15 9 and 11,9 nm, respectively This phenomenon can be resulted from steric contributions and/or formation of H-bond interactions The temperature dependence of the magnetic susceptibility was recorded on heating after field-cooled (FC) and zero-field cooled (ZFC) procedures The irreversible behavior of ZFC and FC curves reveals a typical thermal blocking process of MNPs proportional on the size of coated samples For MAPTES coated sample the blocking temperature is 275 ± 3K and the radius of gyration is 13 4 nm At the same time the blocking temperature for TEOS and APTES coated samples are 285 ± 3K and the radius of gyration is also equal to 16 0 nm, reveling good agreement between magnetization properties and nanometric structure

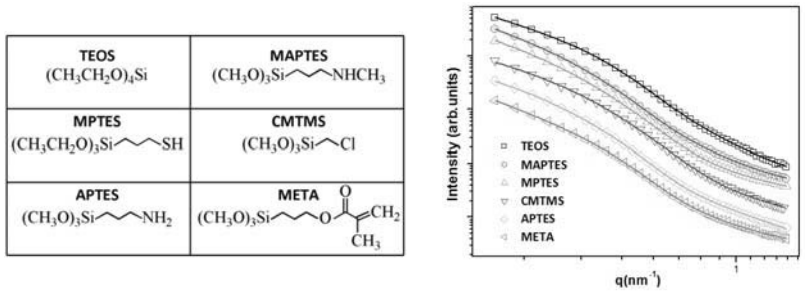

Figure 01 – Structural formula for different alkoxysilanes precursors used in the maghemite surface modifications; and Small angle X ray scattering curves for iron oxide nanoparticles surface functionalized with different alkoxysilanes

Using Permalloy Based Planar Hall Effect Sensors to Capture and Detect Superparamagnetic Beads for Lab on a Chip Applications

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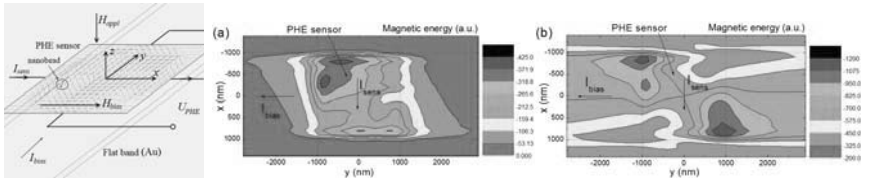
Detection of the fields generated by superparamagnetic (SPM) beads, which are used to label biological species of interest in Lab-On-a-Chip applications (LOC), can be made by using giant magnetoresistive (GMR), magnetic tunnel junctions (MTJ) or planar Hall effect (PHE) spin-valve sensors.

We have observed a strong reciprocal magnetostatic interaction between the SPM nanobeads and the surface of the PHE sensor. Large magnetic field gradients and field amplification in the sensor's vicinity have been observed, both by micromagnetic simulations and through experiments. They can be used to capture and manipulate the beads in some positions above the sensor surface, useful for detection. Controlling the field distribution by controlling the currents through the sensor and through the biasing system, particular magnetization states can be obtained. The nanobeads can be trapped in regions of minimum magnetic energy. In addition, an external magnetic field, H_{appl}, can be used. This can be useful to polarise the SPM beads. We observed that some particular magnetization states, like vortices, can be obtained on the sensor surface. They can be characterized by a fragile equilibrium which can be easily altered by the presence of a single SPM nanobead, 200 nm in diameter. This change in the magnetic state generates a change in the PHE signal. Disk-shaped and cross-shaped structures, made from Permalloy and Co/Cu/Permalloy, have been used for this study. The disk-shaped structures, 1 mm diameter and 20 nm thick Permalloy layer, were deposited without an induced anisotropy axis whereas the cross-shaped Co/Cu/Permalloy structures, 20 µm each side of the active region, were deposited in the presence of a 100 Oe magnetic field in order to have an induced anisotropy axis. To have a fine control of the sensor's magnetisation state, sensitivity and linearity, a biasing field generated by a current, I_{bias}, has been applied parallel to the driving current. The magnetic nanoparticles were placed above the sensor surface using small water droplets and captured in desired places by applying well defined magnetic field gradients due to the external fields and sensor's magnetization state. The setup allows us to make both DC and AC measurements to detect the nanoparticles located on the sensor's surface or in the fluid volume by magnetorelaxometry measurements. We obtained that optimum spatial position exists for the signal strength and quantification. Magnetic moments lower than $5 \cdot 10^{-6}$ emu can be detected which translates to a total mass of maghemite nanobeads lower than $2 \cdot 10^{-7}$ g by using the disk-shaped PHE sensor made from Permalloy. Aspects regarding the field scanning method and the response of this system, according to proposed physical and electronic setup, are discussed in this paper.



The structure used for micromagnetic simulations and the position dependences of the magnetic energy of a SPM bead of maghemite, 200 nm in diameter, placed at 200 nm above the PHE sensor surface when (a) H_{bias}=-12 5 Oe and (b) H_{bias}=-100 Oe; H_{appl}=0 The spatial distribution of the magnetic energy described in (a) is reached starting from a saturated state obtained for H_{bias}=500 Oe The biasing field is further increased to -100 Oe to have the state described in (b) The SPM beads can be trapped in regions of minimum magnetic energy

Fe_3O_4@Polydehydroalanine Hybrid Particles

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[2] *Institute of Biomedical Engineering and Informatics (BMTI), Technische Universität Ilmenau, Ilmenau, Germany; silvio.dutz@tu-ilmenau.de*

Typically, the application of nanoparticles into biological systems leads to the formation of a protein corona around these particles. This protein corona is supposed to have drastic influence on the biocompatibility and the interactions of such nanoparticular systems with the surrounding environment.[1] To investigate the influence of particle surface chemistry and surface charge on formation and composition of formed protein corona, our work focuses on the synthesis of a polymer shell with tunable charge and/or charge distribution around superparamagnetic iron oxide nanoparticles (SPIONs). Starting from 2-*tert*-butoxy-carbonylaminomethylacrylate (*t*BAMA), polymers with molar masses of approximately 20.000 g/mol have been synthesized and characterized.[2] By deprotection of either one or both of the protected functionalities (-COOH and $–NH_2$), these materials were transformed into polycationic (poly(amino methylacrylate), PAAMe), polyanionic (poly(*tert*-butoxycarbonylaminoacrylic acid), P*t*BAA) or even polyzwitterionic materials (polydehydroalanine, PDha). These materials were then used for coating Fe_3O_4 nanoparticles under different conditions and the resulting Fe_3O_4@polymer hybrid particles have been characterized by dynamic light scattering (DLS), transmission electron microscopy (TEM), and zeta potential measurements.

We show that coating with P*t*BAA and PDha was successful, as we found significant differences concerning dispersion behavior, size, surface charge and thermal decomposition. As found in magnetic measurements (VSM), the magnetic properties of the core particles remain unchanged, suggesting that agglomeration did not occur during the coating process. In ongoing studies the influence of different coating materials on protein corona formation during serum incubation of here prepared Fe_3O_4@polymer hybrid particles will be investigated.

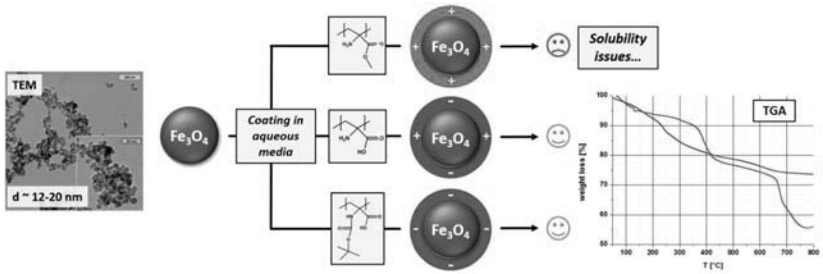

Figure 1: Schematic representation of nanoparticle coating with PAMA (red), PDha (purple), and PtBAA (blue); TEM micrograph of pristine Fe_3O_4 nanoparticles (left) and TGA curves of Fe_3O_4@polymer hybrid particles.

[1] S Tenzer, D Docter, S Rosfa, A Wlodarski, J Kuharev, A Rekik, S K Knauer, C Bantz, T Nawroth, C Bier, J Sirirattanapan, W Mann, L Treuel, R Zellner, M Maskos, H Schild, R H Stauber, *ACS Nano* **2011**, *5*, 7155-7167
[2] U Günther, L V Sigolaeva, D V Pergushov, F H Schacher, *Macromol. Chem. Phys.* **2013**, *214*, 2202-2212

Acknowledgements This work was supported by Deutsche Forschungsgemeinschaft (DFG) in the framework of priority programme 1681 (FKZ: SCHA 1640/7-1, DU 1293/4-1)

Novel approach to magnetically guided delivery of microRNA to endothelial cells

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The production of highly efficient and safe vectors for gene delivery has been a question of crucial importance. Nanoparticle based non-viral carriers designed recently show the potential to meet these 2 main requirements. Moreover, nanoparticles which can be targeted and therefore delivered specifically have considerable advantages like reduced off-target effects and declined toxicity.

Non-viral carriers based on cationic polymer polyethylenimine (PEI) and iron oxide magnetic nanoparticles (MNP) have been produced in our group in 2008. Since then an enhanced delivery of DNA, microRNA *in vitro* and targeted delivery of DNA *in vivo* have been demonstrated for these. Here, we show optimized transfection conditions for the localized delivery of microRNA with PEI-MNP complexes into endothelial cells *in vitro*.

Human umbilical vein endothelial cells (HUVECs) were transfected with Cy-3 labeled microRNA in different complex formation conditions (microRNA amount, NP ratio, amount of MNP). General tests for the evaluation of microRNA uptake efficiency (flow cytometry) and cytotoxicity (MTT assay) were carried out (HUVECs from different patients were tested independently). In addition, the intracellular localization of microRNA was confirmed using the results of confocal laser scanning microscopy (LSM) z stacks. Further, the optimal conditions for efficient vector targeting were defined. Thereby, conclusions about magnetically guided microRNA uptake and cytotoxicity were based on the results of LSM (Fig.1).

The application of a magnetic field under optimal conditions allowed us to guide and to localize the uptake of transfection complexes by HUVECs. Furthermore, we demonstrated that, when the delivered molecule is magnetically guided, the amount of transfection complexes can be reduced to ~30%, resulting in the efficient microRNA uptake in the area of interest and in significantly increased cell viability.

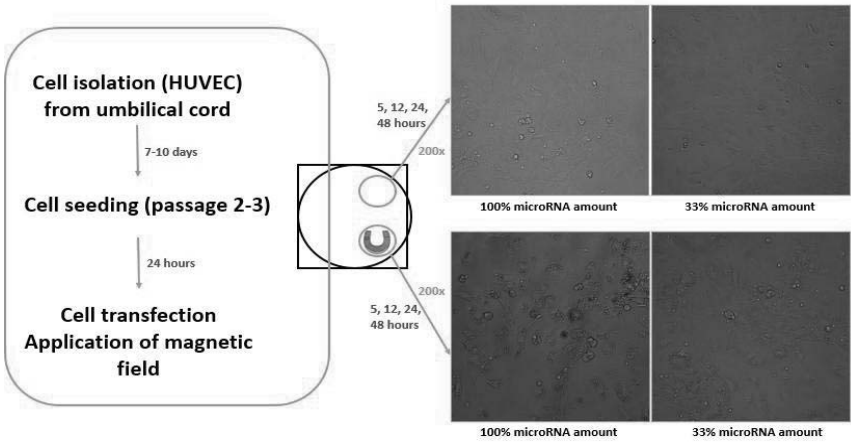

Figure1. Schematic representation of main experimental setup

Recent Progress of Magnetic Biosensing Technology and Detection of Mercuric Ion for Environmental Monitoring

Jian-Ping Wang*,†Wei Wang,† Yi Wang,† Liang Tu,† Todd Klein,† Lina Yu†, Yinglong Feng†

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Giant magnetoresistive (GMR) biosensors have emerged as powerful tools for ultrasensitive, multiplexed, real-time electrical readout, and rapidly biological/chemical detection while combining with high-moment magnetic nanoparticles. However, finding appropriate magnetic nanoparticles (MNPs) and its influences on the detection signal is a vital aspect to the GMR bio-sensing technology. Here, we report our recent developed bench-top and handheld GMR sensor–based detection systems capable of stable and convenient connection, and real-time measurement. Five different types of magnetic nanoparticles with sizes ranging from 10 to 100 nm were investigated for GMR biosensing. The experiments were accomplished with the aid of DNA hybridization and detection architecture on GMR sensor surface. We found that different MNPs markedly affected the final detection signal, depending on their characteristics of magnetic moment, size, and surface-based binding ability, etc.

Detecting pathogens in water and heavy metals in waste and fuels has been challenging. Samples are often too small or diluted. And the presence of particulate and organic matter can make it difficult to separate out the targeted element. We have demonstrated a novel sensing strategy employing giant magnetoresistive (GMR) biosensor and DNA chemistry for the detection of mercuric ion (Hg^{2+}) for the first time. This assay takes advantages of high sensitivity and real-time signal readout of GMR biosensor and high selectivity of thymine–thymine (T–T) pair for Hg^{2+}. The assay has a detection limit of 10 nM in both buffer and natural water, which is the maximum mercury level in drinking water regulated by U.S. Environmental Protection Agency (EPA). The magnitude of the dynamic range for Hg^{2+} detection is up to three orders (10 nM to 10 µM). GMR sensing technology was successfully demonstrated by testing the water from Lake Minnetonka at Minnesota. It can be foreseen that the GMR biosensor would become a robust contender in the areas of environmental monitoring and food safety testing.

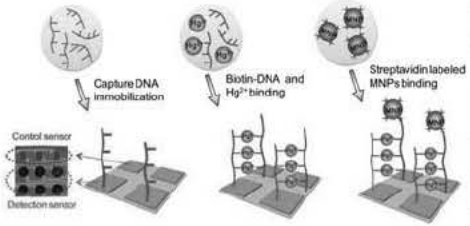

Fig. 1 Schematic illustration of proposed and demonstrated Hg^{2} detection using GMR biosensor

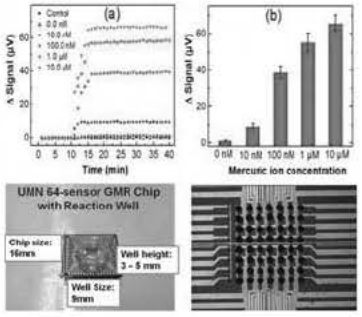

Fig. 2 (a) Real-time testing curves and (b) average signals (with standard deviation (SD)) for mercuric ions (Hg^{2}) in buffer (c) Fabricated GMR biochip (16 mm x 16 mm) with 64 sensors (d) DNA printed 64 (8×8 array, inserted image) sensors located in the central area of the chip, and each sensor was accordingly connected to peripheral contact pads on the periphery of the chip via contact lines

Experimental and Statistical Investigation of Signal to Noise Ratio for GMR Nanosensors for Molecules Detection

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Theoretically the relationship between the intensity of magnetic signals obtained and the distance of the magnetic nanoparticles from the giant magneto-resistive (GMR) sensors was calculated as the mean dipole field across the sensing area, A_s: $(1/A_s)\iint dA\, H_d \sim \iint dA\, r^{-3}$ and yet not has been verified by rigorous experimental and statistical methods The experimental analysis of this relationship has been developed in this work

A multi-layer GMR film structure was designed and deposited on 4-inch wafers in the six-target Shamrock sputter After fabricating the GMR films into the chips with nano-scale devices, a protection bi-layer of Al_2O_3 and SiO_2 has been coated on the chip surface Fig 1 (a) shows the GMR bio-sensing scheme in which the sandwich assay format is used Magnetic labels (streptavidin coated 50 nm MNPs) were bound to sensor surface via the biotin–streptavidin interaction The distance between magnetic particles and the free layer is determined by this scheme In terms of experimental control, we modified the thickness of Al_2O_3 which was controlled by Atomic Layer Deposition (ALD) The theoretical simulation shows the significant signal differences in Fig 1 (b) through the comparison of three cases 60 nm is the default distance including the radius of MNP and 30 nm thickness of the protection bi-layer in the system The distance of 120 nm presents the detection of sandwich structure and the case of 180 nm shows the result of the large protein detection The result also implies DC offset field would be helpful to improve the signals Afterwards we used the simulation result to infer the magnetic signals on different cases and measured the AC signals from the GMR sensors in Wheatstone bridge in the real-time detection of biotin-streptavidin bonding scheme with the same concentration Although the dipole field theory shows larger signals by using closer distance, some noise appeared due to leakage current in the solution during the test and temperature changes of the sensor since the thinner isolation bi-layer Also diffused particles brought more background signals when they could stay closer to the surface of the sensor An optimized thickness has been found through comparing the signal-to-noise ratio in this complete set of experiments

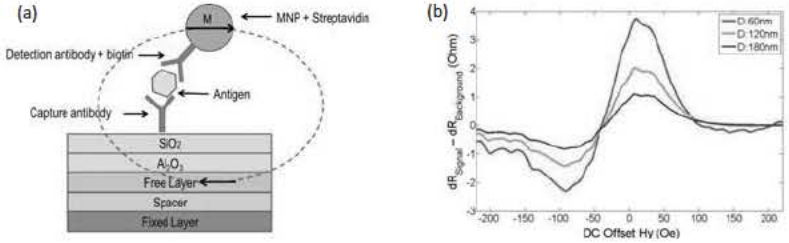

Figure 1. (a) GMR bio-sensing scheme with the sandwich assay, (b) ($\Delta R_{Signal} - \Delta R_{Background}$) calculated versus DC offset field based on three different distances: 60 nm, 120 nm and 180 nm.

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10th Inter. Conf. on the Scientific and Clinical Applications of Magnetic Carriers, Dresden, Germany. June 10-14, 2014. Poster Presentation.

Remixability of Magnetorheological Fluid after Exposure to Centripetal Acceleration

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The objective of this study was to clarify how a centrifugal force field might affect the performance of a helicopter lag damper with a magnetorheological fluid (MRF), which consists of iron particles suspended in a carrier fluid Iron particles in MR fluids have a tendency to settle under the force of a gravitational field Placing MRFs in the rotating system of a helicopter rotor will tend to increase this effect as centripetal acceleration increases as a function of rotor RPM Therefore, an MRF in a lag damper, devoid of any mixing action, will tend to settle in its container towards the most outboard volume of the container However, there are mitigating factors that can prevent such sedimentation or fluid stratification from becoming a problem First, current MR fluids are formulated such that the fluid can be easily remixed after sedimentation has occurred This is done using coatings on the particles to maintain stearic separation of particles, so that remnant magnetization does not cause closely packed particles to magnetically lock together and prevents the formation of a hard cake that is nearly impossible to remix Second, lag damper action will tend to remix the particles on a regular basis In-plane rotor blade vibrations will cause the lag damper to cycle, and this will remix the particles and maintain the suspension Third, tests performed in the University of Maryland Vacuum Whirl Chamber support the contention that the MR fluid remixes in a short time after being subjected to high centrifugal force fields The focus of this study is on item 3 above For rotor blade applications, MR fluid dampers were subjected to centrifugal force (CF) field during normal operation, which will accelerates particle sedimentation To investigate CF effects on MR lag dampers, two linear stroke MR dampers (LORD model RD-1005-3) were attached to a C-channel spin bar, and a series of experiments was conducted On the spin bar, the dampers were centered approximately 20 inches from the axis of rotation, one at each end, and spun at 350 rpm Off-field and on-field tests were performed on the damper before and after spinning No damper stroking took place during the hour long spin stage Fig 1 shows a picture of the test rig mounted in a vacuum whirl chamber After spinning, the MR damper was cycled on an MTS machine Fig 2 shows that after a short time, the force amplitude was rapidly recovered Extensive testing and characterization of the MRF performance will be covered in the full paper

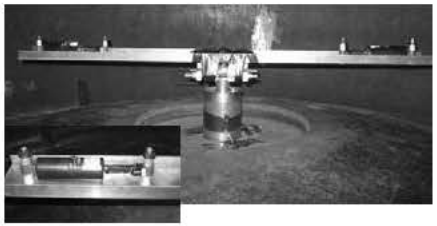

Figure 1: Whirl testing of two linear stroke, MR dampers

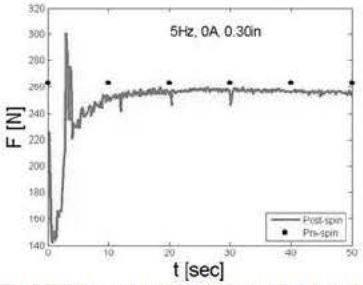

Fig 2 Hilbert envelope of force (no applied current)

Colorize Magnetic Nanoparticles using a New Search Coil based Testing Method

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Different magnetic nanoparticles (MNPs) have different spectral responses to AC magnetic field This specific feature of MNPs could be used as "colors" in the biomedical detection Our previous work demonstrated the feasibility of using the amplitude and phase of the 3rd harmonic of this response In this paper, we present a new approach to use the amplitude and phase information of both 3rd and 5th harmonics to increase the magnetic colorization accuracy In our experiment, a 50Hz low frequency sinusoidal magnetic field drives superparamagnetic nanoparticles into nonlinear region, and a high frequency sinusoidal magnetic field is applied A pair of balanced built-in search coils collects the mixing frequency signals The amplitudes and phases of the collected signal change due to the frequency dependence of Néel and Brownian relaxation Here the phases and amplitudes at different frequencies are used to estimate the hydrodynamic size of MNPs by a Least Mean Square method This method can effectively increase the testing speed and enable the search coil based biosensor for the use in point of care medical devices Digital acquisition card (DAQ, NI USB-6289, 18-Bit, 625 kS/s), LabVIEW and Matlab are used for instrument control and signal processing, respectively We have collected amplitudes and phases of the 3rd and 5th harmonics for 5 samples with different concentrations of small and large particles (see Table 1) Both 25nm and 10nm Fe_3O_4 nanoparticles are purchased from Ocean Nano Tech Inc

Table 1: Experiment Samples

Sample	1	2	3	4	5
25nm particles (1ug/uL)	20uL	40uL	60uL	80uL	100uL
10nm particles (1ug/uL)	80uL	60uL	40uL	20uL	0uL

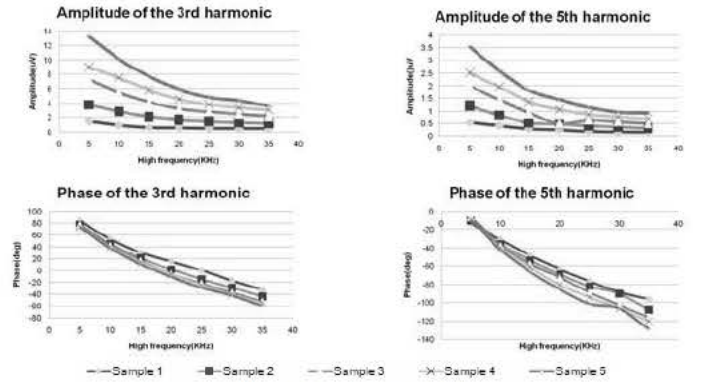

Figure 1: amplitude and phase of the 3rd and 5th harmonics

As shown in Fig 1, with the same concentration, larger size particles have higher amplitude and its amplitude changes more than small size particles as the frequency increases At lower sweeping frequency, the 5 samples have almost the same phase As the sweeping frequency goes higher, the phase of large particles drops faster We also notice that the data of 5th harmonic is more susceptible to noise, so in the next step we will add filters into this system to get a higher signal-to-noise ratio (SNR) More importantly, because the amplitudes of the 3rd and 5th harmonics are largely depended on the saturation magnetization M_s, we will report the testing results on different FeCo and $Fe_{16}N_2$ nanoparticles that have giant saturation magnetization

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10th Inter. Conf. on the Scientific and Clinical Applications of Magnetic Carriers, Dresden, Germany. June 10-14, 2014. Oral or Poster Presentation.

Measuring Stratification in a Magnetorheological Fluid Column Using a Vertical Axis Inductance Monitoring System

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A critical requirement in practical applications, especially in occupant protection systems using magnetorheological (MR) shock absorbers, is that magnetorheological fluids (MRFs) remain in suspension Our objective is to demonstrate a method to characterize stratification in an MRF column using a vertical axis inductance monitoring system (VAIMS) To quantify sedimentation velocity in am MRF column, an inductance-based solenoid sensor was constructed to track volume fraction of Fe particles (typically 7-10 micron carbonyl Fe) as a function of sensor location The mudline is the boundary between the settled MR fluid below and the clarified fluid above (Fig 1) As the MR fluid stratifies, the mudline travels downwards, until all the Fe particles in the suspension are fully deposited at the bottom of the container The magnetic permeability of the MR fluid, thus the inductance of the sensor, is highly dependent on the volume fraction of Fe particles For MR fluid placed in the sensor, sedimentation of the fluid, which reduces the iron concentration of the fluid enclosed by the sensor, reduces fluid permeability and, hence, sensor inductance Thus, by measuring the rate of the monotonically decreasing magnetic inductance resulting from the settling MRF at various heights, we can track and estimate the rate of change of the mudline location as the sensor traverses the MRF column The VAIMS includes an inductance meter (with data acquisition system), a sensor assembly (coil, cylinder for coil winding, and flux return), a vertically translating height gage and a base for holding/positioning the MRF column We measure the inductance as a function of sensor location on the z-axis Typical inductance data for MRF126 is shown in Fig 2, for up to 28 days of monitoring once a day The leftwards vertical dashed line shows the mudline on the first day, and the rightwards vertical dashed line shows the mudline after 22 days This displacement leads to an accurate measurement of sedimentation rate, and the continuous measurement of inductance leads to a characterization of volume faction, which is proportional to inductance Also, the measurement method provides substantial details about the density or volume fraction gradient down the column height (from left to right in Fig 2) Overall, the VAIMS provides essential insights into stratification behavior or MRFs

Fig. 1: MRF 126 after 41 days shows clear mudline in both 1-in and 0.25-in column

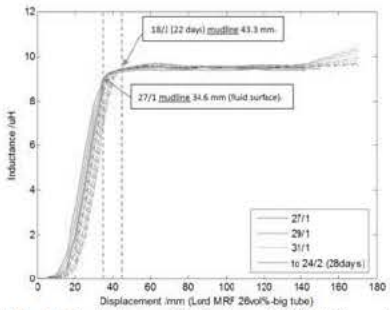

Fig. 2: Typical inductance distribution of MRF126 from top (left or 0 mm) to bottom (right or 180 mm).

Magnetic property analysis of cells with single-cell magnetophoresis

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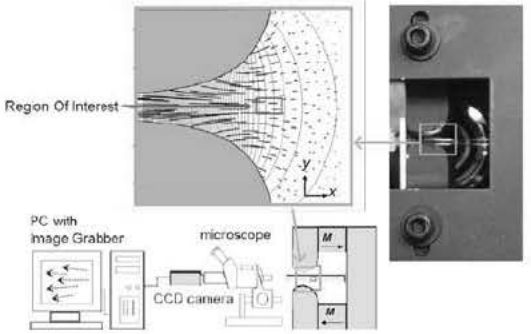
The magnetic properties of magnetic particles, cell-particle complex, or cells to be separated are of great interest since they are vital for the design and characterization of magnetic separation systems. To acquire such information, Chalmers Lab and Zborowski lab have designed and upgraded the single-cell magnetophoresis system, or cell tracking velocimetry (CTV, shown in figure), and its derivatives over the past 15 years. CTV combines techniques of magnetic field construction/characterization, microscopy, and image analysis. The carefully designed neodymium magnets and hyperbolic shape steel pole pieces together create a well-characterized, strong, uniform and horizontal magnetic field gradient within the region of interest (ROI), where a glass channel holding the cell or particle suspension goes through. When the motions of the cells or particle are in balance, their motion in horizontal direction is solely driven by the magnetic force. With the microscope and charge-coupled device (CCD) camera, such motions are captured and sent to our our image analyzer to acquire the horizontal velocity. With the knowledge of well-characterized magnetic field, the magnetic properties or a few hundred cells or particles can be calculated on a single cell/particle-basis simultaneously. Our current version of CTV provides a magnetic energy gradient up to 298 T-A/mm^2. The derivatives of CTV include the electromagnet cell tracking velocimetry (eCTV), in which the magnetic field is generated by an electromagnet and hence it is tunable for measuring various magnetic particles, and fluorescent CTV, which provide significant clarity for imaging fluorescent cells and particles. Using CTV we have analyzed a variety of cells including various forms of red blood cells, several cancer cell lines cultured in high-iron media, genetic-engineered *Auxenochlorella protothecoides* (algae), *Bacillus atrophaeus* spores, and a varities of magnetic particles. In summary, single-cell magnetophoresis system can provide a sensitive, accurate analysis of cell/particle magnetic properties on a single cell/particle basis, but over a large population of cells (a few thousands).



Dual responsive fluorescent magnetic nanopolymers for targeted drug delivery

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Abstract

A dual stimuli sensitive magnetic hyperthemria based drug delivery system has been developed for targeted cancer treatment. Thermosensitive amine terminated poly-n-isopropylacryalamide was tagged to pH sensitive chitosan nanoparticles. Folic acid and fluorescein were tagged to the nanopolymer complex via N-Hydroxysuccinimide and Ethyl-3-(3-dimethylaminopropyl)carbodiimide reaction to form a fluorescent and cancer targeting polymer complex. The preparation of the polymer complex was studied using an infrared spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. Gadolinium doped nickel ferrite nanoparticles were developed to improve T1 NMR image contrasting agents. Their proton relaxometric studies revealed a 200% increase in the proton relaxation rate. Thus nanopolymers were loaded with gadolinium doped nickel ferrite nanoparticles and curcumin using solvent evaporation method. Drug loading efficiency was calculated using visible spectroscopy at 425nm and found to be 86%. Thus loaded nanoparticles were tested for their targeting and anticancer properties on IMR32 nueroblast cell lines. The results indicated selective apoptosis of cancer cell lines within 3 hours of their incubation.

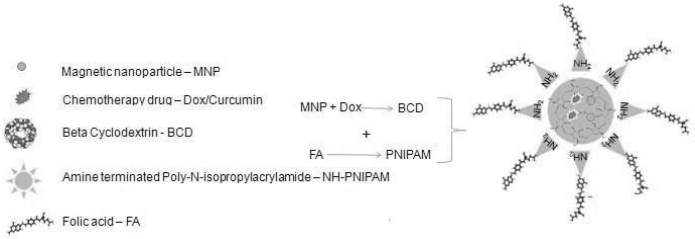

Figure: The formation of the drug loaded magnetic nanopolymer complex

Development of Magnetic and Luminescent Hybrid Nanoparticles as Theranostic Materials

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Superparamagnetic iron oxide nanoparticles (SPION) are one of the most studied nanopartides for in vitro and in vivo uses[1]. They are synthesized in various sizes (nm to micron sized beads) and utilized as contrast agents in MRI, sensors, in drug delivery and hyperthermia and cell separation. Luminescent semiconductor quantum dots (QD) may find even more application: electronics, energy, labeling, sensing, diagnosis and therapy [2]. Size tunable emission wavelength, photostability, broad absorption-narrow emission profile are some of the most attractive properties. Combination of these two entities in a single small size particle would bring together such unique properties allowing potentially dual sensing, multiplexing, diagnosis and magnetic targeting, diagnosis and therapy. Such hybrid structures may be formed in many different ways but usually requires labor intensive methods and/or produce large size particles. We have demonstrated a very simple method of developing such partides in small size regime and with high quantum yield using Cd-chalcogenides emitting in the visible range [3]. Yet, absorbance of SPIONs in the visible range, auto-fluoresence of biological constituents, penetration depth in the visible range and Cd-based cytotoxicity are the problems to be solved. Recently we have developed highly cytocompatable Ag_2S QDs emitting in the NIR range where absorption of the SPIONs is minimal. Here, we will demonstrate such hybrid nanoparticles both luminescent in the visible (Cd-chalcogenides) and in the NIR region (Silver-chalcogenides). Issues related to the absorbance/emission range of QDs and contribution to cytotoxicity will be discussed.

Fig. 1: $CdTe/Fe_3O_4$ hybrid nanopartides in water

[1]. N.A. Frey, S. Peng, K. Cheng, S. Sun, *Chem. Soc. Rev.* **2009**, 38, 2532–2542.
[2]. T. Jamieson, R. Bakhshi, D. Petrova, R. Pocock, M. Imani, A. M. Seifalian, *Biomaterials* **2007**, 28, 4717–4732.
[3]. R. Kas, E. Sevinc, U. Topal, H. Yagci Acar, *J. Phys. Chem. C* **2010**, 114, 7758–7766.

Effect of Viscosity on Harmonic Signals from Magnetic Fluid

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Magnetic nanoparticles (MNPs) in solution, i e , magnetic fluids, have been widely studied for magnetic particle imaging (MPI) In MPI, harmonic signals that are generated from nonlinear magnetization of MNPs are detected to image the spatial distribution of MNPs It is well recognized that magnetization of MNPs occurs via Néel and Brown mechanisms Since the Brownian relaxation time τ_B is proportional to the viscosity of the surrounding medium and the viscosity may change in practical applications, it is important to investigate the effect of viscosity on the harmonic signals from the magnetic fluid

We studied the third harmonic signal from the magnetic fluid when the viscosity of solution was changed We prepared two samples, i e , 60 µl of original Resovist (FUJIFILM RI Pharma) magnetic fluid was diluted with 230 µl of pure water (sample 1) or 230 µl of glycerol (sample 2) In Fig 1, experimental results on the third harmonic signal vs dc field are shown As shown, the dc field dependencies of the third harmonic were different each other, which indicated that the viscosity affected the third harmonic signal Since the dc field dependence of the harmonic signal is directly related to the spatial resolution in MPI, this result means that the spatial resolution is also affected by the viscosity of the magnetic fluid

Next, we performed numerical simulations on the dynamics of the magnetic fluid by taking into account the Néel and Brownian relaxation The magnetic moment and Néel relaxation time of the MNP was set to be m = 4 14×10^{-18} Am^2 and τ_N = 6 6×10^{-5} s, respectively Considering the difference in viscosity, we set τ_B = 2 8×10^{-5} s and 2 8×10^{-3} s for sample 1 and 2, respectively Circles and squares in Fig 2 show the simulation results, while the solid line was calculated with a conventional *Langevin function* by using m = 4 14×10^{-18} Am^2 As shown, simulation result for sample 1 agreed well with the Langevin function On the other hand, simulation result for sample 2 was very different from that expected from the Langevin function The third harmonic signal decreased with the increasing in the dc field more rapidly than the Langevin function We note that this strong field dependence was observed in the experiment, as shown in Fig 1 The mechanism that caused this difference will be discussed

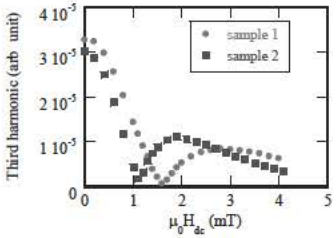

Fig 1 Experimental results of the third harmonics vs dc field when an excitation field with $\mu_0 H_{ac}$ = 1 41 mT and f = 1 kHz was applied Sample 1 and 2 were diluted with pure water and glycerol, respectively

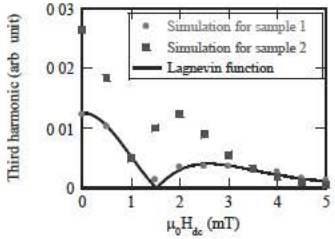

Fig 2 Numerical simulation results on the third harmonics vs dc field Circles and squares show the simulation results for sample 1 and 2, respectively Solid line is calculated with the Langevin function

DNA-conjugated magnetic nanoparticles for remotely controlled drug release

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Magnetic nanoparticles (MNPs) go through Néél and Brownie relaxation under an alternating (AC) filed and generate thermal energy to treat diseases [1] It is a great platform for the drug release if MNPs are modified with double-standard DNA (ds-DNA) In this paper, iron oxide nanoparticles (IO NPs) with ds-DNA on the surface were prepared Under the AC field (Hz=337 kHz, H_0=22 kA m^{-1}), IO NPs act as heat sources to dehydrate the ds-DNA attached when the temperature exceeds the melting temperature (Tm) of the ds-DNA and release the drug conjugated into solution The scheme is show in Fig 1(a) After centrifugation, the IO NPs on the bottom are redispersed in the PBS buffer, and the concentration variation of ds-DNA on IO NPs with field-applied time is measured by Microplate Spectrophotometer (BioTek Epoch) The concentration of ds-DNA on IO NPs is 213 ng/µl before the AC field applied, and lows down to 197, 183, 175 ng/ µl after the AC field applied for 60, 180, 300 seconds, respectively Because the drug release rate highly depends on Tm of ds-DNA used and the magnetic field can penetrate deeply into human bodies, this drug release process can be specially designed and remotely controlled

[1] Ying Jing, Shi-Hai He, Jian-Ping Wang, Fe3Si nanoparticles for alternating magnetic field heating, Journal of Nanoparticle Research 2013;15(4)

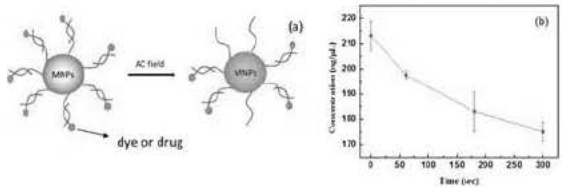

Figure1 (a) scheme of drug release process under the AC filed, (b) the concentration variation of ds-DNA left on IO NPs with field-applied time

Enhanced stability of high moment FeCo nanoparticles with SiO_2 protection layer for bio-application

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High moment FeCo nanoparticles (NPs) have promising application regarding to enhance efficiency of magnetic separation and sensitivity of bio-detection With the same size (13 nm), Ms of FeCo NPs is 3 87 $\times 10^{-15}$ emu per particle, almost 5 times higher than that of iron oxide, and 18 times higher moment can be obtained if a smaller field (10 Oe) is applied, as shown in Fig 1(b) However some issues such as the chemical stability, dispersity, biocompatibility, should be given special considerations to realize their practical application And wrapping SiO_2 is one of the easiest and cheapest ways to solve these problems The SiO_2 protection layer can protect FeCo NPs from oxidation, enhance dispersity, and apply a good medium for functionalization

In this paper, 13 nm cubic FeCo NPS were fabricated and wrapped by the SiO_2 layer using a reverse microemulsion method [1] The SiO_2 protection layer is about 10 nm, and well cover the FeCo NPs confirmed by the TEM and fourier transform infrared spectroscopy To facilitate further bio-application, FeCo NPS with SiO_2 layer were incubated by (3-Aminopropyl) triethoxysilane (APTES) to attach amino with which carboxy group on biomolecules can be bounded The amount of biomolecules attached on were determined, and the enhanced stability of the system were valued by comparing the magnetic properties decay of MNPs with and without SiO_2 protection layer

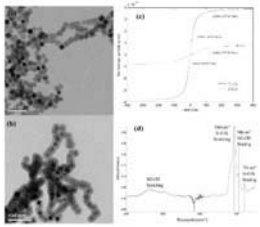

Figure 1 the TEM image of FeCo MNPs before (a) and after (b) modified with SiO2 protection layer confirmed by FTIR (d) Magnetic loops of 13 nm FeCo and Fe_3O_4 MNPs shown in (c)

[1]Cannas, C , et al , *CoFe2O4 and CoFe2O4/SiO2 Core/Shell Nanoparticles: Magnetic and Spectroscopic Study.* Chemistry of Materials, 2010 **22**(11): p 3353-3361

Can SPIONs aggregation be controlled in biological media? (YES) …but … Can SPIONs aggregation be advantageous for some applications? (YES)

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Superparamagnetic iron oxide nanoparticles (SPIONs) are widely used for biological and nanomedicine applications due to their biocompatibility and unique properties compared to their bulk counterparts. Still, simplified synthesis methods with the potentiality to be easily scaled up and straightforward protocols to stabilize magnetic colloids in a wide spectrum of biological media remain a challenge.

We will report on the synthesis of highly crystalline citrate coated iron oxide nanoparticles readily dispersible in water by an extremely fast and cost-effective microwave-assisted route. It will be followed by presenting a stabilization approach that may offer a general methodology to obtain dispersed SPIONs stable in different biological media. It consists of a protocol of pH adjusted-bovine serum albumin (BSA) adsorption on the SPIONs surface. BSA adsorption shows great efficiency in improving the dispersing SPIONs in PBS and several cell media. The formed BSA layer was imaged by negative staining TEM, and revealed by Cryo-TEM, FTIR, DLS and the zeta potential. Results indicated that BSA forms a monolayer with a thickness around 3 nm on the particle surface (see Figure 1).

In contrast, nanoparticles in the form of large aggregates can be advantageous for some applications. We have investigated the uptake of SPIONs by endothelial cells. Nanoparticles formed large aggregates when added to complete endothelial cell media and in this case the size of aggregates was controlled by adjusting the ionic strength of the media. The internalization of nanoparticles into endothelial cells was then investigated by transmission electron microscopy, magnetometry and chemical analysis together with cell viability assays. Interestingly, a seven-fold more efficient uptake was found for systems with larger nanoparticle aggregates which also showed significantly higher MRI effectiveness without compromising cell viability and functionality. Larger cellular uptake will be beneficial in applications concerning magnetic cell guiding or in vivo cell-tracking (see Figure 2).

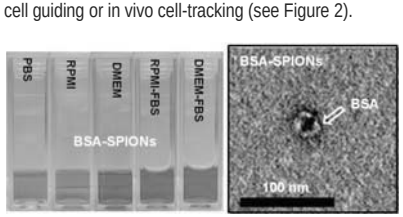

Figure1

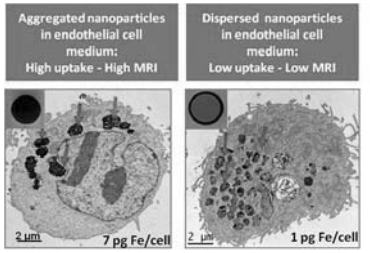

Figure 2

Magnetically Driven Differentiation of Mesenchymal Stem Cells

Vitalii Zablotskii[1*], Šárka Kubinová[1,2], Oleg Lunov[1], Alexandr Dejneka[1], Olexander Churpita[1], Peter Trosan[2], Vladimir Holan[2] and Eva Syková[2]

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Notwithstanding the fact that biological effects of magnetic fields have been explored for decades, the mechanisms of observed responses are still not known. Moreover, cellular responses to mechanical forces are known to play a substantial role in the majority of important biological processes. Understanding the molecular and biophysical foundations of the effects of magnetic fields on living cells will be instrumental for the development of new experimental and therapeutic strategies. Here we investigated a possibility of magnetically induced differentiation of cultured stem cells. In order to manipulate the functionality of mesenchymal stem cells (MSCs), an especial magneto-mechanical installation allowing changeable magnetic and mechanical vibrations was engineered. We found that the static and oscillating high-gradient magnetic fields (HGMFs) can trigger stem cell differentiation in the way different from a control group not subjected to the HGMF. Indeed, when adipogenic differentiation was induced, a significant decrease in the expression of the adipogenic genes *adipoq*, *adipsin*, *PPARγ* and *AP2* was found in cultures exposed to oscillating but not to static HGMFs. The adipogenesis was significantly down-regulated after 2 days (Fig.1) and completely blocked after 7 days of HGMF as well as mechanical vibrations. Interestingly, comet assay did not detect any DNA damage after exposure to static as well as oscillating HGMF or mechanical vibrations.

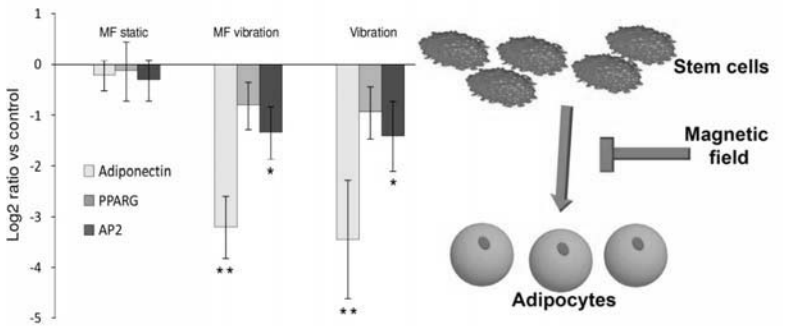

Fig 1 Expression of adipogenic genes in the MSC culture exposed to HGMF for 2 days and scheme of the cellular effect of HGMF

The results showed that vibrating, but not static, HGMFs blocked the adipogenic differentiation of MSCs, suggesting that oscillating HGMF may affect differentiation pathways by the mechanical stress applied to cell membranes, organelles and/or the cytoskeleton. Thus, understanding of interactions between living cells and external high-gradient magnetic fields may represent new approaches to control stem cell machinery.

In Vivo MRI Single-Cell Tracking using Microfabricated Magnetic Microparticles

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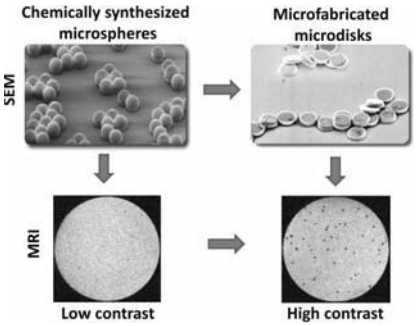
Magnetic nanoparticles are often used as T_2^* contrast agents for magnetic resonance imaging (MRI) Being magnetic, such particles dephase the surrounding MR water signal, in the process locally darkening the image in their immediate vicinity For cells loaded with such magnetic particles, this localized image darkening can also double as an effective cell labeling technique enabling MRI based cell-tracking studies that may offer value across many current medical research fields including stem cell regeneration treatments, immune cell therapies, and cell transplantations

Unfortunately, overcoming the relatively weak contrast signals generated by commercially available chemically synthesized magnetic micro- or nanoparticles requires either very high field (very expensive) research grade MRI scanners, or cells that are loaded with very large magnetic microparticles, which questionably impact natural cell viability and function With MRI signal contrast being proportional to particle magnetic moment, packing as much magnetic material into as small a particle volume as possible is therefore advantageous for advancing the field of MRI cell tracking generally, and more specifically for enabling quantitative single cell tracking on more accessible clinical field strength scanners

Over the past few years we have been investigating the possibility of microfabricating pure iron based microparticles for such cell tracking applications Compared to similarly sized, chemically synthesized alternatives, which are all based on iron-oxide, these microfabricated particles offer at least 10-fold increased MRI T_2^* contrast Here we consider the relative advantages and disadvantages of such contrast agent particles, discuss ways in which they might be microfabricated, and report their first successful in-vivo application for MRI tracking of cell migration through a rat brain from one day to up to six weeks post-injection



Microfabricated magnetic microparticles offer greater T_2^* magnetic resonance image contrast than traditional chemically synthesized alternatives

Lauric acid - protein coated hybrid SPIONs with enhanced biocompatibility for magnetic drug targeting

Jan Zaloga[1], Christina Janko[1], Johannes Nowak[2], , Rainer Tietze[1], Harald Unterweger[1], Ralf P Friedrich[1], Stefan Odenbach[2], Stefan Lyer[1], Geoffrey Lee[4], Christoph Alexiou[1]

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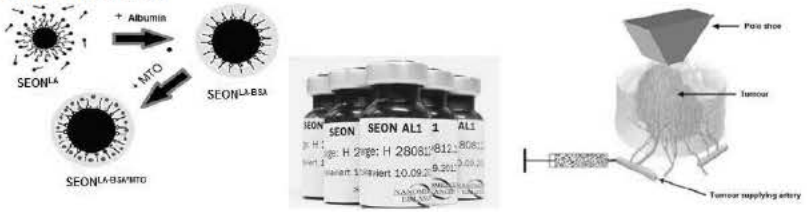
Core-shell superparamagnetic iron oxide nanoparticle (SPION) systems have demonstrated very promising properties for biomedical applications. Our group has previously shown their outstanding potential for drug delivery in animal models[1]. To make the final step into clinical trials, the synthesis has to be translated into a good manufacturing practice (GMP) environment and the particle properties have to be adjusted according to the guidelines for parenterals. To fulfill all the requirements for clinical use, such as biocompatibility, biostability, therapeutic efficacy and reproducibility of he synthesis, we developed a hybrid lauric acid - albumin coated SPION system based on our previous lauric acid particles. The structural investigations with fourier-transformed infrared spectroscopy (FTIR) and transmission electron microscopy (TEM) proved the core-shell structure.
The system demonstrated outstanding colloidal stability in biorelevant media like cell culture media or even whole blood. At he same time, it was still well controllable with a magnet. With VSM investigations we proved that the magnetic proper ies of the SPION system are retained. Even after complete magnetic aggregation, the par icles were redispersible again.
The *in vitro* toxicity was investigated thoroughly with flow cytometry on T-lymphoma (Jurkat) cells, as well as time-dependent viability investigations using the XCELLigence system on endothelia (HUVEC) cells, and we found that the system is very well tolerated by cells. Upon addi ion of the protein corona, the toxicity was significantly reduced.
We coupled the cytotoxic drug Mitoxantrone (MTO) to the particles, which exhibited high binding efficacy of up to 800 µg/ml ferrofluid. The so-prepared system is still colloidally stable, and the hydrodynamic size does not change. We investigated the release kinetics in relevant media like PBS and serum, and showed that the drug is released slowly from the SPION system. We investigated the *in vitro* therapeutic efficiency on prostate cancer (PC-3) and T-lymphoma cells. The MTO-loaded particles show excellent dose-dependent toxicity. The efficiency of the prepared $SEON^{LA\text{-}BSA\text{-}MTO}$ particles was even higher than that of the pure drug. In conclusion, we have prepared and developed a system that fulfils all the requirements for clinical use and are confident going forward to the translation to a GMP environment in the near future.

Acknowledegment: The authors would like to thank he DFG (AL 552/5-1 and AL 552/3-3), the Else Kröner-Fresenius S iftung (Bad Homburg v. d. H.), the EU project FP7-NMP-2012-LARGE-6-309820 "NanoAthero", he Bavarian Ministry for Environment and Consumer Protection (74-U8793-2012/7-35) and the Margarete Ammon S iftung, Munich, Germany for their financial support

Figure: Schematic representation of the GMP-production of the particles as a stepstone towards clinical trials



Reference: [1] Tietze R. et al. *Nanomedicine: NBM.* **2013**, 9: 961-71.

Cytotoxicity of Several Kinds of Magnetic Fluids

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Magnetic particles (MPs) with core diameter cca 10 nm were synthetized by precipitation technique and consequently stabilized by sodium oleate to obtain stable magnetic fluid (MF) The sample was modified by bovine serum albumin (BSA) in phosphate buffer (MFBSA) and in the next step by dextrane (DEX), polyvinylpyrrolidone (PVP) and poly(ethylene glycol) (PEG, with different molecular weight 400, 1000, 10 000 and 20 000 g/mol) to obtain magnetic fluids MFDEX, MFPVP and MFPEG

Cytotoxicity of prepared samples was tested *in vitro* on two cell lines B16 melanoma mouse cells and V79 fibroblastoid Chinese hamster cells by MTT test (colorimetric assay for assessing cell viability) MTT_{50} parameter calculated for every tested sample was expressed as Fe_3O_4 concentration in the sample (µg/ml) and means the concentration that reduces absorbance of MTT salt in tested cells by 50% compared to control untreated cells Influence on the growth of mouse B16 melanoma cells and V79 fibroblastoid Chinese hamster cells after 24-hour exposition period was observed at 4-6 dilutions of the tested samples As it can be seen on the fig 1 the smallest toxic effect on both tested cell lines was observed after treatment by the samples of MFBSA and MFPEG 10 000 The biggest difference of toxic effects on cell lines was achieved after application of MFPEG 400 and MFPEG 1000 samples Weight ratio of modification substance to magnetite content e g PVP/Fe_3O_4 from 0 25 to 1 had not significant influence on cytotoxicity These results are meant to be the ground for utilization of magnetic fluids in cancer treatment

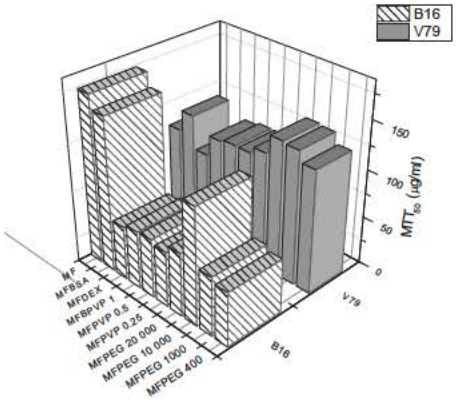

Figure 1 Cytotoxic effect of different magnetic fluids tested on two cell lines B16 and V79

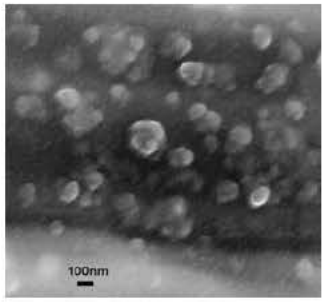

Figure 2 SEM image of nanoparticles in MFBSA

Acknowledgments This work was supported by Ministry of Education Agency for Structural Funds of EU in frame of projects 26220120021 and 26220220005 and 26110230097, VEGA 0041, 0045, Slovak Research and Development Agency – contracts No APVV-0742-10 and APVV-99-026505

Magnetic field visualization in applications to magnetic cell separation and drug targeting

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Due to a highly non-linear dependence of the magnetic force on distance from the magnet, it is difficult to develop an intuitive understanding of the magnetic particle behavior in suspensions exposed to magnetic fields. Such understanding is important in developing new designs of the magnetic cell separators and for magnetic drug targeting. The existing closed-form formulae for various shapes of permanent magnets and computer algebra software allows to visualize the directions of the magnetic forces acting on the magnetically labeled cells and magnetic drug carriers in suspension and their accretion inside the magnetic separators and blood vessels based on various magnetic field and flow parameters, such as square of the local B field (B^2, directly proportional to the magnetostatic energy density in free space, visualized as a heat map), gradient of B^2 (directed along the lines of force acting on a paramagnetic particle) and the B^2 isosurface (approximating the envelope of magnetic accretion of paramagnetic cells and drug carrier in the separators and blood vessels, see Figure). Comparison of the grad B^2 magnitude scaled by the difference in magnetic susceptibility between dispersed and the continuous phase with the local shear stresses due to the flow of viscous fluid allows to model the magnetic cell and drug carrier accretion shape deformation due to the varying flow rate through the separator and the blood vessels. A number of combinations of permanent magnets and magnetic cell and magnetic drug carriers flow geometries were modeled for their relevance to practical applications providing vivid images of the field-particle interactions.

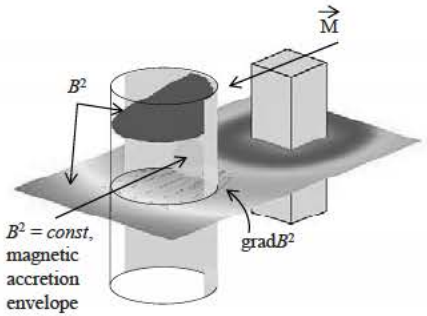

Illustration of magnetic precipitation (pink) of paramagnetic particles from flowing suspension in a tube exposed to a rectangular permanent magnet magnetized across its long axis (as indicated).

Synthesis of SiO2-coated magnetic nanolabels with controlled surface properties

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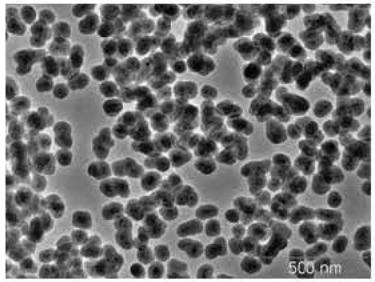
Magnetic particles (MP) have become very popular in scientific research as labels. They are stable unlike fluorescent labels and safe as compared to radioactive agents. Possibility of quantitative detection of magnetic nanoparticles (MP) *in vivo* can be beneficial for many biomedical applications, especially because MP are already approved for injection in humans. Contrary to optical labels, magnetic nanoparticles can be specifically detected integrally in blood, organs, etc. [1, 2]

Here, we set a goal to create a set of magnetic nanoparticle labels with tunable in a wide range physicochemical properties (size, ζ -potential, etc.). Such a set can be handy for selecting the proper label for the particular target – a large protein, a nanoparticle, an organelle, a cell, or any other target that needs to be traced. Possibility to use the nanolabel that would not change the biological behavior of the target, e.g., its pharmacokinetic properties such as biodistribution and half-life in blood, would be very attractive for biomedical research and applications.

We synthesized set of SiO_2-coated MNP with different ζ -potentials from -80 mV to +10 mV and sizes ranging from 20 nm to 1 μm. As magnetic cores, we used superparamagnetic magnetite nanoparticles synthesized by co-precipitation of Fe^{2+} and Fe^{3+} salts under alkaline conditions at 80 C. Then, particles stabilized with sodium citrate or carboxymethyl-dextran were coated with silica. By variation of different parameters during synthesis we controlled the silica shell thickness from 2 nm to 1000 nm. The synthesis route of these particles was optimized for detection by non-linear magnetization in ac magnetic field [1,2]. We should note, that silica shell does not influence the magnetic signals of the magnetic cores. For characterization of the nanoparticles we used dynamic light scattering and transmission electron microscopy.

The surface of the particles has been functionalized with carboxy- and amino-groups for further conjugation with biomolecules. For that we used modification of the surface with (3-Aminopropyl)triethoxysilane and with succinic anhydride. Variation of ζ-potential of nanolabels was controlled by anhydride concentration.

The synthesized set of particles was used in the preliminary studies regarding possibility to track different biological targets with magnetic nanolabels *in vitro* and *in vivo*.



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2. M. Nikitin, M. Torno, H. Chen, A. Rosengart, P. Nikitin, J Appl Phys 103, 07A304 (2008)

Electrospun Magnetic Nanofibre Mats – A New Bondable Biomaterial Using Remotely Activated Magnetic Heating

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Electrospinning is a useful method to prepare nanosized fibers (see **Fig. 1**). The process can be used to incorporate many different things into the fibres, for example drugs (Sill 2008), and use the fibres then for tissue engineering and technical applications.

Our aim was to see if we could make magnetic nanofibre mats where the fibres could be melted together by remote heating induced in an alternating electromagnetic field. Such a method would be useful to precisely bond layers made from different (polymeric) materials in places where access is limited (inside the body, near implants, technically inside a 3-dimensional box).

For this purpose the biodegradable polymer poly(caprolactone) (MW 65 kDa) and 33 weight% of magnetic Fe_3O_4 nanoparticles were electrospun into a 0.2 mm thick mat. Sandwiched between two non-magnetic 1 mm thick mats, magnetic heating was induced in an alternating magnetic field of 25 kA/m and 400 kHz. Fibre optic measurements showed a fast increase to over 90 °C (see **Fig. 2**), which completely melted the magnetic mat between the non-magnetic mats. The energy dispersed was as calculated from heating curves to be about 11 J to melt a mat of 100 mg. A specific heating power of about 3 W/g for the complete sandwich mat and about 35 W/g for the magnetic heating layer within the sandwich was thus reached. This energy should be sufficient to fuse mats under more realistic conditions that take the contribution of heat dissipation to the surrounding into account.

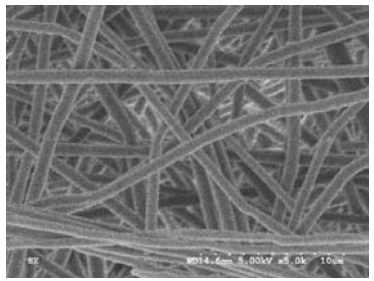

Fig. 1. Scanning electron microscopy picture of PCL nanofibres containing 5% Fe_3O_4.

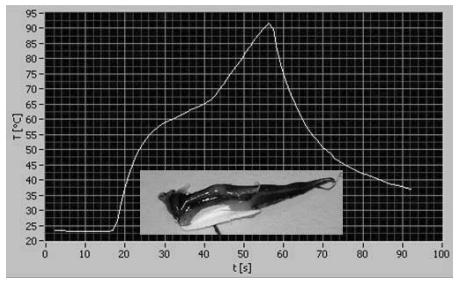

Fig. 2. Heating curve and result of melting together of magnetic and non-magnetic PCL nanofibre mats (insert).

References: Sill TJ, von Recum HA (2008). *Electrospinning: Applications in drug delivery and tissue engineering*. Biomater **29**, 1989-2006.

Acknowledgments: Eike Dohmen for discussions about magnetothermal bonding; and a discovery grant from the Natural Sciences and Engineering Research Council (NSERC) in Canada for funding.

Efficient magnetic recycling of covalently attached enzymes on carbon-coated metallic nanomagnets

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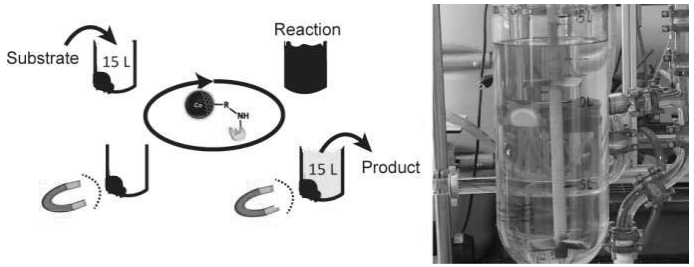
In the pursuit of robust and reusable biocatalysts for industrial synthetic chemistry, nanobiotechnology is currently taking a significant part. The recent synthesis of magnetic nanocomposites opened new possibilities in biocatalysis and enzymes have been immobilized on different magnetic supports. However, the inability of the current magnetic carriers to be efficiently recycled from large volumes impedes their further usage in industrial processes. The development of such a core/ shell-enzyme nanomaterial with a very high magnetic saturation (> 150 emu/g) enables us to efficiently perform magnetic biocatalysis and very quickly (< 30 s) separate the enzyme from solution in large volumes (15 L) by utilizing a modified Büchi-glass reactor with a built-in magnetic filter. The nanoparticles used are composed of a metallic (cobalt) core surrounded by a graphene layer which gives a further possibility for functionalization due to the known chemistries on carbon surfaces. The Carbon coated cobalt nanoparticles (Co/C) were found to be a practically useful enzymatic support due to their high surface area/volume ratio (30 nm in size), beneficial magnetic properties of the core and the possibility of covalent surface chemistry.

In this study the Co/C nanoparticles were chemically functionalized (diazonium chemistry), activated for bioconjugation (N, N-Disuccinimidyl carbonate) and subsequently used in enzyme immobilization. Three enzymes: β-glucosidase, α-chymotrypsin and lipase B were successfully covalently immobilized on the magnetic nanosupport. The enzyme-particle conjugates retained about 28-55 % of the specific enzymatic activity, showed increased storage stability and were efficiently recycled from milliliter to liter scales in short recycle times.



Schematic representation of the catalyst recycling on a large scale (left); product formation after magnetic catalyst removal (right)

Hyperthermia Effect of Non-spherical Magnetic Nanoparticles under Alternating Magnetic Field

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Magnetic nanoparticles offer attractive possibilities in many bio-medical applications [1-3] They have controllable sizes ranging from a few nanometers up to tens of nanometers, which places them at dimensions that are smaller or comparable to those of a cell (10–100мм), a virus (20–450 nm), a protein (5–50 nm) or a gene (2 nm wide and 10–100 nm long) This means that they can 'get close' to a biological entity of interest The particles can be coated with biological molecules to make them interact with or bind to a biological entity, thereby providing a controllable means of 'tagging' or addressing it

Under the action of magnetic field of high frequency, fine magnetic particles can produce a local heating (hyperthermia effect) Oscillating field can induce rotating motion of the particles This motion can destroy membranes of the biological cells if the particles have been attached on the membranes due to the biological coating Both these effects can be used for destruction of tumor cells and cancer therapy

We present results of theoretical modeling of the heat production in a suspension of the fiber ferromagnetic particles under the action of the linearly polarized oscillating magnetic field We suppose that the particles are situated in the Maxwell viscoelastic liquid with the Maxwell time τ_V of the viscoelastic relaxation Two mechanisms of the heat production, namely, the particle rotations in the liquid as well as its internal remagnetization are considered We study effect of the particle shape, its magnetic properties and rheological properties of the carrier liquid on the intensity of the heat production by the particles

Mathematically this model presents a system of nonlinear differential equation of the particle rotating and its internal remagnetization under the alternating magnetic field These equations have been solved numerically; intensity of the power production in suspension of the particles has been calculated The figures show the results of calculations of intensity of the power production of suspensions of the iron particles in water as a function of the frequency of the field oscillations In Fig 1 the lines 1 and 2 present results for the particles with a permanent moment, determined in experiments of [1] and Maxwell liquids (τ_v= 5×10-2 sec); 3 and 4- the particle with internal remagnetization in the Newtonian (τ_v=0) and in the Maxwell liquids (τ_v= 5×10^{-2}sec), respectively

In Fig 2**,** the power dissipation vs the field frequency, same as in Fig 1 for the particle with the field-induced magnetization lines 1 and 2: the particle aspect ratio (i e the ratio of the major axis to the minor one) *r* =5 2 and 8 6 respectively These results demonstrate effect of the particle internal remagnetization and its shape on the efficiency of the heat production in the suspension of the fiber-like particles

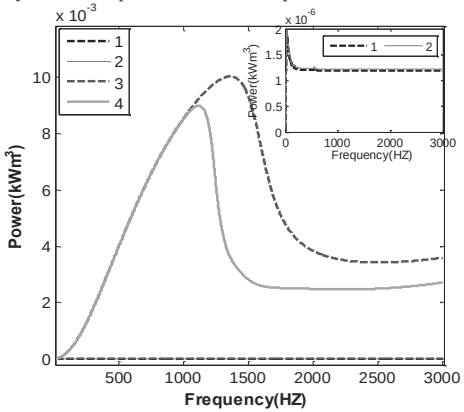

Fig 1

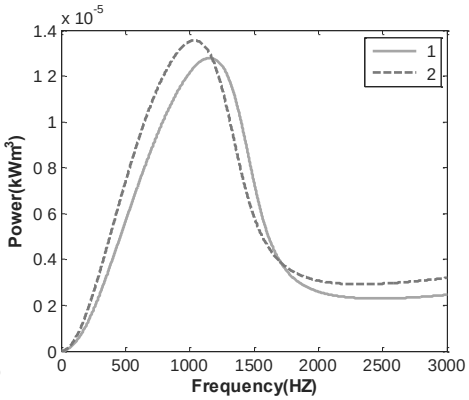

Fig 2

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SENSOR SYSTEMS

DYNOMAG AC SUSCEPTOMETER

DynoMag is a portable, easy to use AC susceptometer. It measures the real and imaginary components of the AC susceptibility in a wide frequency range. The instrument enables determination of the dynamic magnetic properties of liquids, powders or solid samples.

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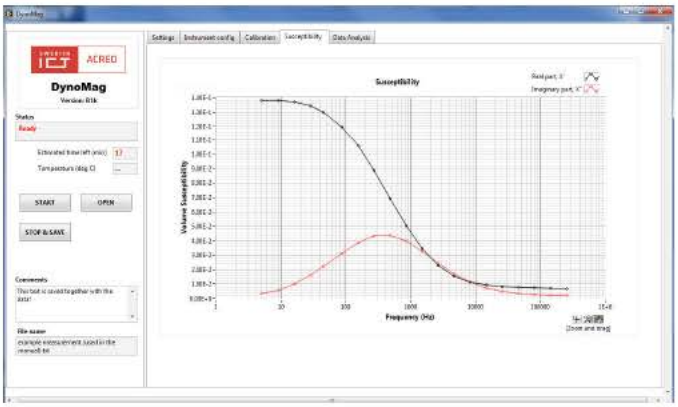
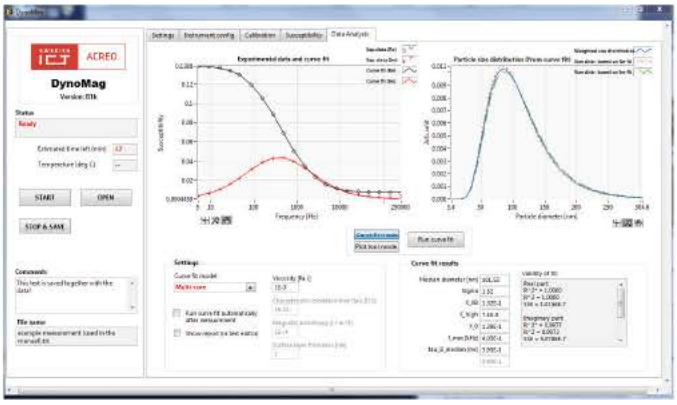
Typical application areas include:

- Measurement of size distribution of magnetic nanoparticles (MNP)
- Quality control during synthesis and manufacturing of MNP
- Studies of binding reactions of biomolecules to the surface of MNP



A DynoMag measurement of the AC susceptibility versus frequency for magnetic nanoparticles dispersed in a liquid (Chemicell FluidMag cobalt-ferrite). The decrease in real part and the maximum in imaginary part of the susceptibility around 400 Hz is due to Brownian relaxation of the nano-particles. The residual non-zero real susceptibility above 10 kHz comes from fast Néel relaxation.



A fit to the measured data in the left figure. With the analysis package you can fit your experimental DynoMag data and determine the particle size distribution from the Brownian relaxation as well as Néel relaxation of single core particles.

Property	Value	Comments
Frequency interval	1 Hz - 500 kHz	Measurement accuracy is lower below 5 Hz
Excitation field	0.5 mT = 5 G	The magnetic field strength is constant below 1 kHz, falling off at higher frequencies
Volume susceptibility resolution	1*10^-5	The value is the standard deviation of the volume susceptibility, measured at 1 kHz, with an excitation filed of 5 G and a time constant (measurement time) of 1 s.
Sample size	Cylindrical sample holder with volume 0.2 cm^3	The sample volume can be customized to smaller volumes than 0.2 cm^3
Measurement time	Typically around 15 minutes	Depends on the number of data points chosen, 15 minutes is for 20 points
Operating temperature	Normal lab temperatures	

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MSI AUTOMATION, INC.-- 2014--

Magnetic Hyperthermia System for Nano Particle Heating/Nano Carrier Cancer Drug Release

5.0, 10+ KW / 150-500 kHz SYSTEM

SUMMARY: (1) TARGETED NANOPARTICLE HEATING HAS SHOWN PROMISE AS A MEANS TO CAUSE TUMOR ABLATION, IMPROVE AUTO-IMMUNE RESPONSE AND INITIATE CANCER CELL DEATH @ 42-46C.
(2) TARGETED MAGNETIC HEATING TO RELEASE A NANO CARRIER CANCER DRUG IN PROXIMITY TO THE TUMOR. WHEN USED IN CONJUNCTION WITH CHEMOTHERAPY, RESULTS ARE SUPERIOR TO CHEMOTHERAPY ALONE AND WITH LESS HARMFUL EFFECT ON HEALTHY TISSUE AND ORGANS.

Induction Heating System Features:

A. **MAGNETIC POWER INTENSITY: Up to 30-60 kA/METER***
B. **BENCH MOUNT OR FULLY MOBILE POWER SUPPLIES**
C. **COLOR TOUCH SCREEN** OPERATOR CONTROLS.
D. **PROGRAMMABLE TEMPERATURE CONTROLLER**
E. **REMOTE PC CONTROL** via ETHERNET or RS 232/485
F. **POWER AND FREQUENCY** DISPLAY.
G. **SOLID STATE ELECTRONICS**
H. **HEATING COIL SIZES: 25-125 mm**
I. **STANDARD FREQUENCY RANGE: 150 – 450 kHz**

OPERATOR CONTROL:
UNIQUE TO MSI AUTOMATION'S MAGNETIC HYPERTHERMIA SYSTEM IS A SOPHISTICATED ON-BOARD COMPUTER AND **COLOR TOUCH SCREEN DISPLAY**. VITAL FUNCTIONS OF THE UNIT ARE DISPLAYED IN REAL TIME.

INTERFACE FEATURES: WITH THE USE OF A FIBER OPTIC TEMPERATURE SENSOR, IT IS POSSIBLE TO UTILIZE THE BUILT-IN TEMPERATURE CONTROLLER TO MEASURE, REACH AND HOLD TEMPERATURES WITHIN SPECIFIED LIMITS. ETHERNET CAN BE USED FOR EXTERNAL LAPTOP PC CONTROL.

Recent Articles citing MSI's system's use in Hyperthermia:

1. http://pubs.acs.org/doi/pdfplus/10.1021/jp905776g
2. http://www.rsc.org/Publishing/Journals/JM/article.asp?doi=b713775c
   (Most recent)
3. http://dx.doi.org/doi:10.1016/j.ijpharm.2013.09.032
4. http://www.sciencedirect.com/science/article/pii/S0378517313008788

PHOTO: MEASURING FLUID TEMPERATURE WITH A **FIBER OPTIC SENSOR**. THE SAME SENSOR CAN BE INSERTED IN SOFT TISSUE FOR ANIMAL STUDIES DURING HYPERTHERMIA TRIALS. SOFTWARE IS INCLUDED FOR REAL-TIME CHARTING OF THE TEMPERATURE RISE.

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Advanced biomagnetic separation equipment

Sepmag Systems

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E-08290 Cerdanyola del Vallès
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sepmag®

You have already selected the right magnetic bead for your application. Now what?

SEPMAG A125ml

Before going into production, you need to ask yourself:

- **How will I scale-up the magnetic separation process?**
- **How will I guarantee reproducibility?**
- **How will I validate?**

In-vitro diagnostic (IVD) and other biotech companies functionalize magnetic beads and subsequently aliquot them into smaller kits, aiming to have perfect reproducibility of every single test.

Using traditional magnetic separators, not all beads experience similar conditions: some beads are fully magnetized, while others may experience weak and variable magnetization. Often, some beads even experience an excessive magnetic force that is potentially damaging to both the bead and its attached biomolecule.

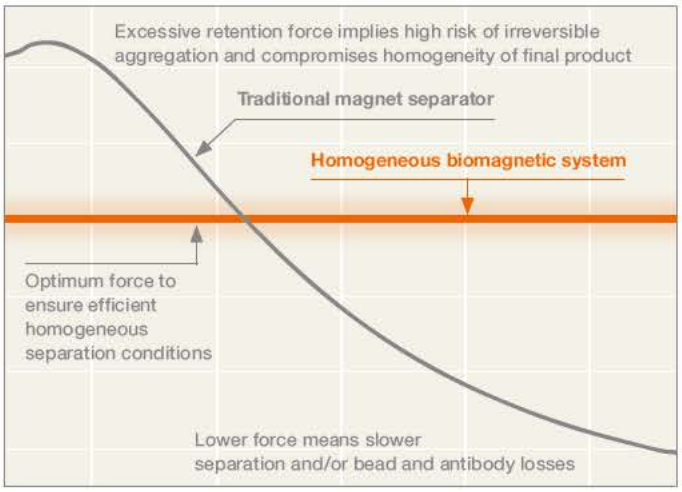

Diagram showing the variable force a bead experiences in a conventional magnet (grey) compared with the homogeneous force experienced in a Sepmag homogeneous biomagnetic system (orange).

SEPMAG Q1L with Quality Control Recording (QCR)

Sepmag systems provide your company with:

1. **Homogeneous separation conditions. Eliminate assay variability.**
2. **Highest recovery of biomolecules and beads.**
3. **Full scalability from 1µl to 50l.**
4. **Safe operation.**
5. **Process monitoring.**

Ordering information

Family	Model	Volume
A	SEPMAG A125ml	1-125 ml
A	SEPMAG A250ml	1-250 ml
LAB	SEPMAG LAB1x15ml	15 ml
LAB	SEPMAG LAB1x25ml	25 ml
LAB	SEPMAG LAB3x25ml	3x25 ml
Q	SEPMAG Q250ml	250 ml
Q	SEPMAG Q500ml	500 ml
Q	SEPMAG Q1L	1,000 ml
Q	SEPMAG Q2L	2,000 ml
Q	SEPMAG Q5L	5,000 ml
Q	SEPMAG Q10L	10,000 ml
Q	SEPMAG Q15L	15,000 ml
Q	SEPMAG Q20L	20,000 ml

Customized systems available on request.

Check how Sepmag can help your biomagnetic separation process: www.sepmag.eu

Sepmag Systems
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STREM Chemicals, Inc.

Metals • Inorganics • Organometallics • Catalysts • Ligands • Nanomaterials • Custom Synthesis • cGMP

Corporate Headquarters, Newburyport, MA, USA

cGMP kilo-lab manufacturing suites

Corporate Overview

Strem Chemicals, Inc., established in 1964, is an employee-owned company that manufactures and markets specialty chemicals of high purity. Its clients include academic, industrial and government research and development laboratories as well as commercial scale businesses in the pharmaceutical, microelectronics, chemical and petro- chemical industries.

Strem's corporate headquarters is located in Newburyport, 38 miles (60km) north of Boston. This facility occupies 48,000 sq. ft. (4,460 m^2). The European headquarters and warehouse are located in Bischheim, France.

Experience in Manufacturing High Quality Chemicals

A wide variety of fine chemicals are available with a special emphasis on organometallics, catalysts, ligands and nanomaterials. Quality is the most critical component of all products and services. Most products are of high purity, typically at 99%, while some are as high as 99.9999% metals purity.

Custom Synthesis and cGMP Production

Custom synthesis services and process development are conducted under the strictest confidence. The variety of chemicals manufactured for Strem's catalog of chemicals for research provides access to a wide span of technical expertise, in both inorganic and organic synthesis. Reaction capabilities for custom synthesis include:

- Alkylation
- Amination
- Ammonolysis
- Asymmetric synthesis
- Carbonylation
- Carboxylation
- Chiral chemistry
- Dehydrogenation
- Formylation
- Friedal-Crafts reactions
- Grignard reactions
- High Pressure reactions
- Hydroformylation
- Hydrogenation
- Liquid ammonia reactions
- Organometallic reactions
- Phosphorylation
- Quaternization
- Reduction, Catalytic

For pharmaceutical applications, manufacturing is conducted under current Good Manufacturing Practices (cGMP) in kilo-lab suites. This capability has been available since 1988. Complete documentation is provided, including validation and stability studies. Active Drug Master Files (DMF's) are also maintained in N. America and Europe. Strem's cGMP facilities are FDA inspected.

ChemStewards® CERTIFIED FACILITY

Strem Chemicals is a member of SOCMA (Society of Chemical Manufacturers and Affiliates) and is committed to the ChemStewards® program.

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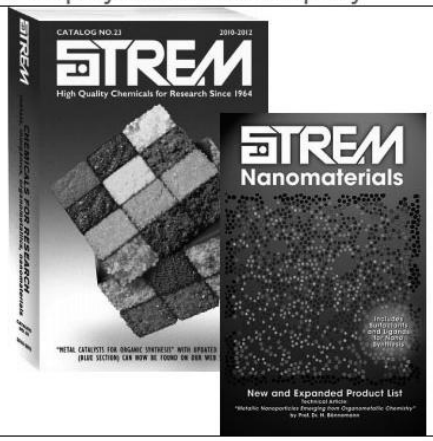
an employee-owned company

Magnetic Fluids

Since 1964



- Request our *New* Catalog #23 at www.strem.com

Strem's nanomaterials manufacturing activities began in 2004 when it licensed technology developed by Prof. Dr. Boennemann at the Max-Planck Institute in Germany. This technology allowed for the manufacture of a variety of metal-based nanoparticles including colloids and magnetic fluids. In 2008 Strem expanded its US-based nanomaterials initiative and established a Nanochemistry Laboratory at the Institut de Science et d'Ingenierie Supramoleculaires (ISIS) of the University of Strasbourg, France. It is headed by Dr. Nina Matoussevitch, an experienced Nanochemist. Dr. Matoussevitch's lab works closely with Strem's US facility and Prof. Dr. Helmut Boennemann, Strem's nanoconsultant. The goal of the Nano facility is to serve R&D groups worldwide with custom-made nanostructured materials.

Strem's product offering now includes nanoparticles of many transition metals, precious metals as well as metal oxides, mixed-metal oxides and magnetic fluids. Nanocatalysts are also available.

"Selected Strem Nanoproducts" – Magnetic Fluids

27-0001 HAZ	**Cobalt magnetic fluid in kerosene with AOT [sodium dioctylsulfosuccinate] and LP4 [a fatty acid condensation polymer] (8.2% vol%)** ca. 10 nm (mean particle size); black fluid	1ml 5ml 25ml
27-0023 HAZ	**Cobalt nanoparticles coated with AOT [sodium dioctylsulfosuccinate]** 10-12 nm; black waxy material	1g 5g
27-0028	**Cobalt nanoparticles (surfaced modified with L-cysteine ethyl ester), ethanol wet** ~10nm; black pwdr. (wet with ethanol)	250mg 1g
27-0026 HAZ	**Cobalt nanoparticles, toluene wet** 10-12 nm; black suspension	1g 5g
26-0011 HAZ	**Iron-cobalt nanoparticles** 5-8 nm; black pwdr.	250mg 1g
26-0020	**Iron-cobalt nanoparticles (surfaced modified with L-cysteine ethyl ester), ethanol wet** ~10nm; black pwdr. (wet with ethanol)	250mg 1g
26-0022 NEW→ HAZ	**Iron oxide magnetic fluid in kerosene coated with oleic acid (7-9 vol% of magnetite)** black, viscous liq.	2ml 10ml
26-0024 NEW→ HAZ	**Iron oxide magnetic fluid in kerosene coated with oleic acid (15-18 vol% of magnetite)** black, viscous liq.	2ml 10ml
26-0026 NEW→ HAZ	**Iron oxide magnetic fluid in kerosene coated with oleic acid (20-23 vol% of magnetite)** black liq.	2ml 10ml
26-0030 NEW→	**Iron (II,III) oxide (Magnetite) aqueous magnetic fluid [2.5 vol%(~12 wt%), Ms = 10-11 kA/m]** *[1317-61-9]* Fe_3O_4; black solid (water suspension)	2ml 10ml
26-0032 NEW→	**Iron (II,III) oxide (Magnetite) aqueous magnetic fluid [3.5 vol%(~17 wt%), Ms = 15-16 kA/m]** *[1317-61-9]* Fe_3O_4; black solid (water suspension)	2ml 10ml
26-0036 NEW→	**Iron (II,III) oxide (Magnetite) aqueous magnetic fluid [7.0 vol%(~35 wt%), Ms = 30-31 kA/m]** *[1317-61-9]* Fe_3O_4; black solid (water suspension)	2ml 10ml

Visit www.strem.com for new product information and searchable catalog.

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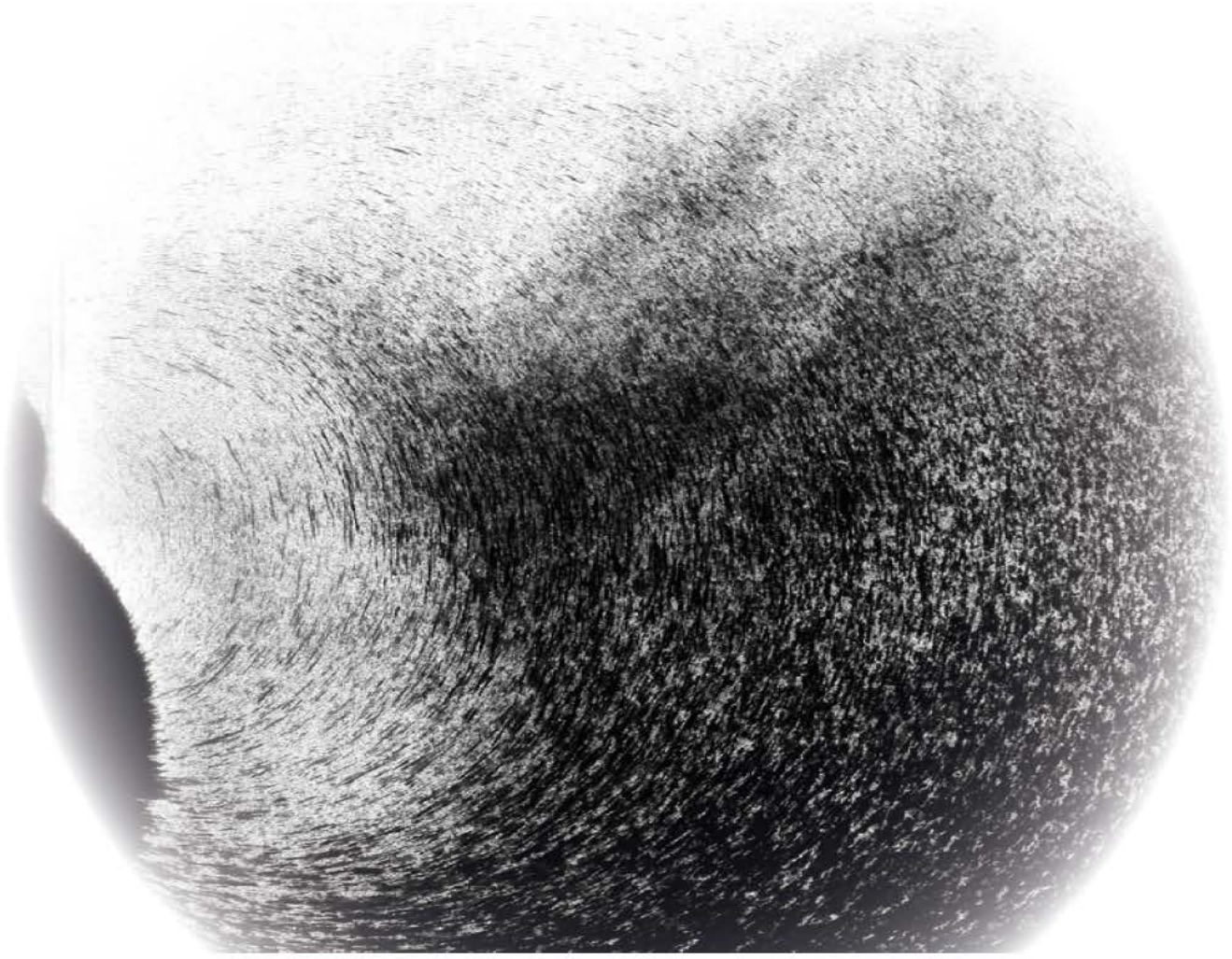
Incredibly fast



Carbon coated metal nanomagnets

Pick up an application booklet at our booth!

TurboBeads®
the *fastest* magnetic separation

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Uut	Fl	Uup	Lv	Uus	Uuo

Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

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Anteo Diagnostics

The Surface Coating Company

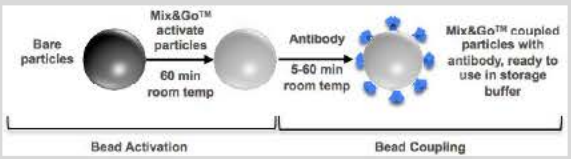
anteo diagnostics

Mix&Go – Truly Universal Protein Binding

- Gentle yet strong due to unique chelation-based binding
- Binds to glass, plastics, metal oxides, gold surfaces
- Ideal for particles of all sizes and materials
- Fast, stable, easy

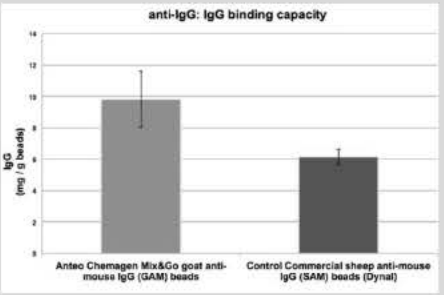
Mix&Go on Magnetic Particles

Fast Coupling



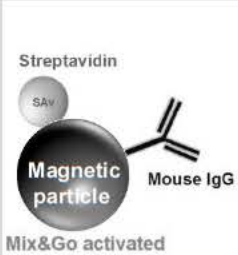
COUPLING TECHNOLOGY	ACTIVATION TIME	COUPLING TIME	TOTAL TIME
MIX&GO	1 HR RT	1 HR RT	2 HRS
AMIDE	0.5 HR RT	16 HRS RT	17 HRS
TOSYL	5 MINS (PRE-ACTIVATED)	16-24 HRS 37°C	24 HRS

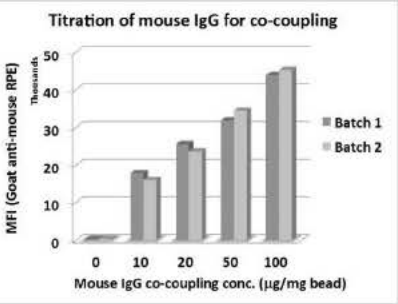
High Binding Capacity



Antibody coupled to Mix&Go particles can be used for IP or purification. Mix&Go activated magnetic particles have higher antibody binding capacity than commercially available particles.
Comparison of antibody binding capacity of Mix&Go α-mouse magnetic particles (3mm, Chemagen) and Dynal sheep α -mouse IgG beads.

Co-Coupling

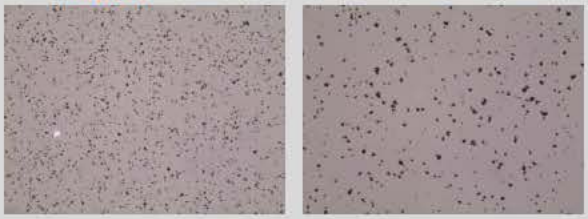




Streptavidin and mouse IgG were co-coupled to Mix&Go activated magnetic particles (200 nm, EMD Millipore) simultaneously. Mix&Go activated magnetic particles can bind to streptavidin and mouse IgG simultaneously. The coupling amount of mouse IgG is controlled by a simple IgG titration step during the co-coupling process.

No Aggregation

Mix&Go Particles | Commercial Particles



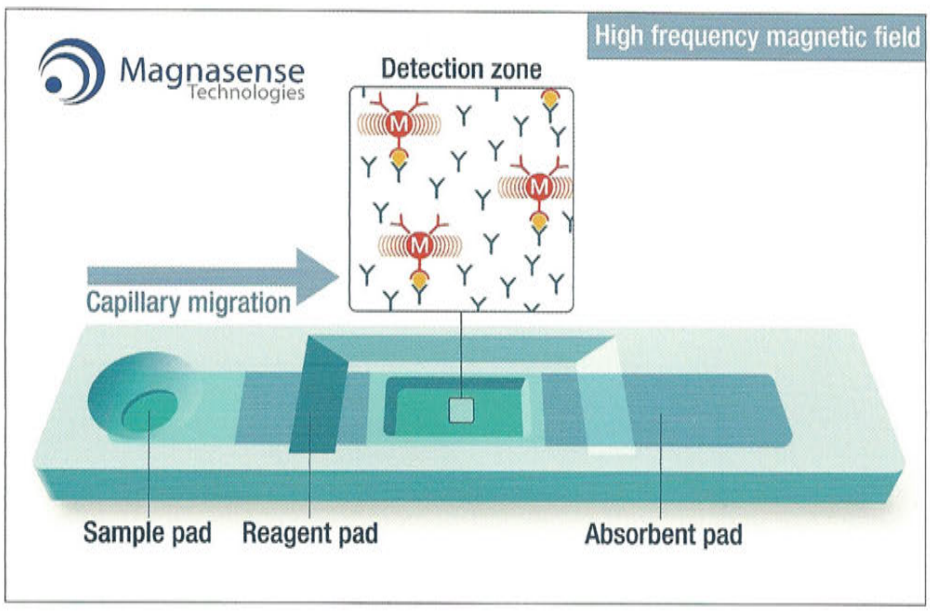
Particles from a leading provider where coated with Mix&Go and GM-CSF as capture antibody and compared to the commercial tosylated version. At 40x magnification Mix&Go particles are evenly dispersed with little to no aggregation.

Contact

Charlie Huang, Head, New Technologies Group , charlie.huang@anteodx.com
Joe Maeji, CSO, joe.maeji@anteodx.com

Magnasense Technologies

Magnasense has developed a patented point of care diagnostics system utilizing antibody labeled magnetic particles. With analyte-specific disposable test cartridges, this versatile technology provides affordable, accurate, and quantitative test results within minutes.



Unique Combination of Features

- Quantitative
- Flexible
- Affordable
- Compact
- Rapid
- Easy to use
- Direct data transfer

Point of Care Diagnostics

The Magnia® reader combines maximum sensitivity with ease of use.

The innovative combination of paramagnetic particles as labels combined with direct electronic measurement facilitates a low-cost, compact, portable instrument.

The system is compatible with gene-probe and immunoassays and both sandwich and competitive assay formats. The great stability of the end-point facilitates multiplexing.

Assays for C-Reactive Protein and infectious diseases have been developed.

Magnasense Technologies is looking for partners to develop the technology further. If you are looking for a more sensitive and precise rapid assay format, we look forward to hearing from you.

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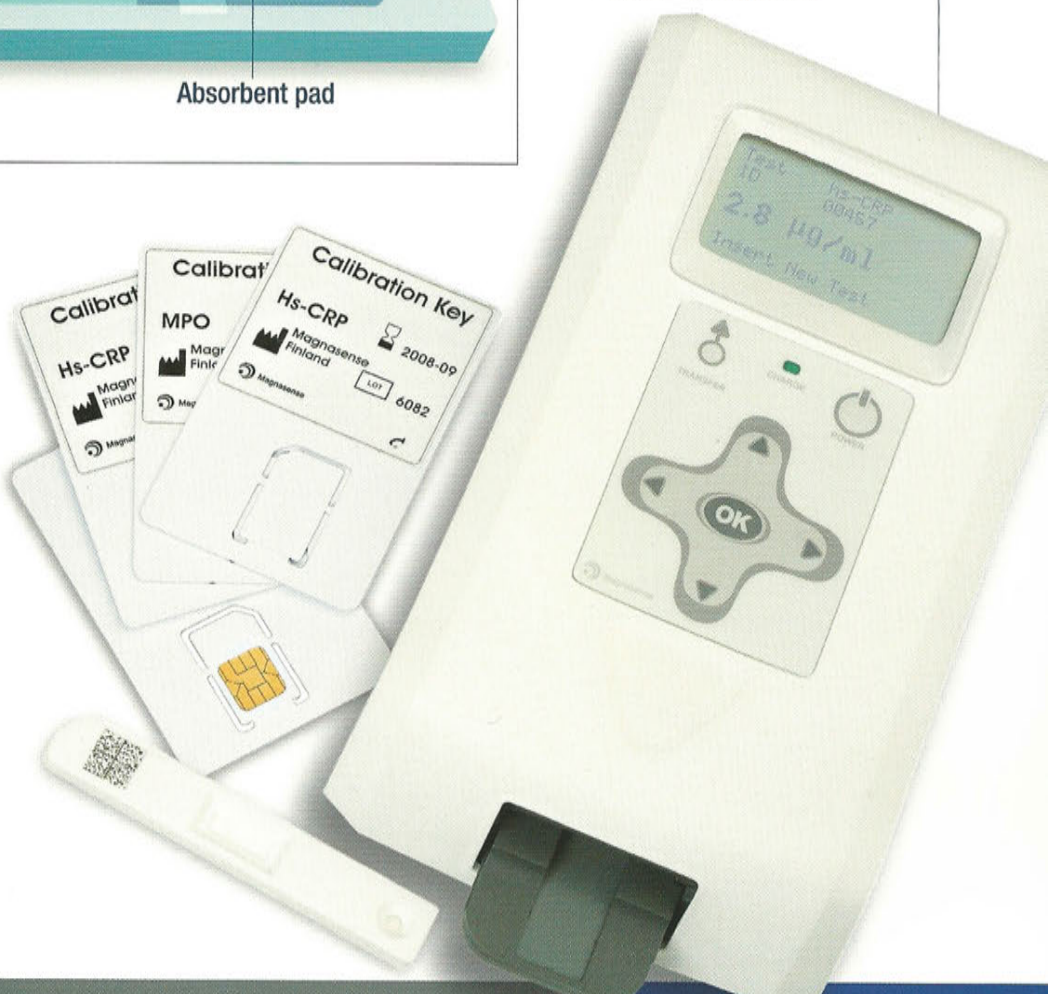

Technology for Diagnostics at Point of Care

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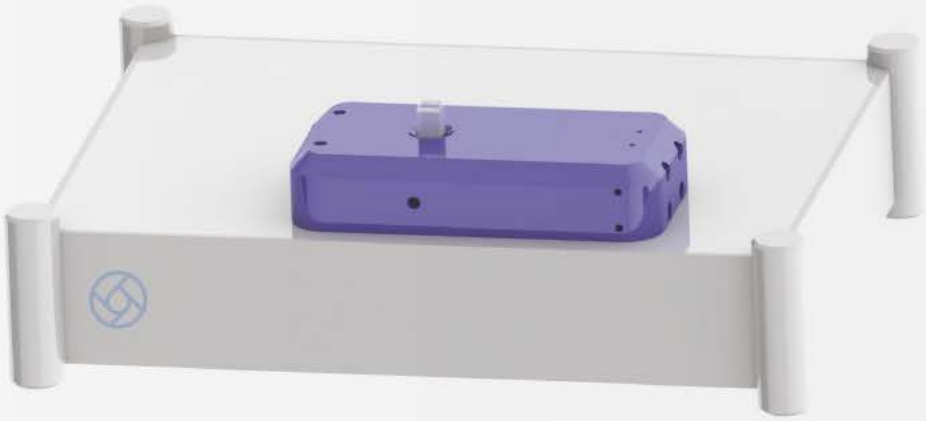
DIAGNOSTICS

BluSense Diagnostics develops innovative biosensing devices which provide high sensitivity biomarker detection in blood

SenseMag Research Grade System



For the R&D market we developed SenseMag, a portable and fast instrument to measure the dynamics of magnetic nanoparticles

- To provide a simple read-out for magnetic nanobead-based agglutination assays
- To accurately determine & quantify magnetic nanoparticle clustering
- To analyze your particles in each phase of surface conjugation & functionalization processes
- To study the interaction of nanoparticles with cells, bacteria, amplified DNA strands, proteins, etc.

info@blusense-diagnostics.com

11th

International Conference on the Scientific and Clinical Applications of Magnetic Carriers

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