August 2006

SPIO agents undergo scrutiny for cell tracking

Researchers weigh alternatives while they search for optimal ferric material

By: Paula Gould

Nanosized superparamagnetic iron oxide (SPIO) carriers are assuming a key role in MR-guided cell tracking. But are SPIO-based nanoparticles really the right material for the job? Alternative agents should not be overlooked, according to scientists at the 6th International Conference on Scientific and Clinical Applications of Magnetic Carriers held in Krems, Austria, in May. Radiology researchers remain unconvinced that a replacement for SPIO is required.

SPIO-based MRI contrast can be used in smaller concentrations than gadolinium agents. This quality makes the iron oxide preparations more suited to labeling human cells than conventional contrast. SPIO agents are also believed to have a good safety profile, given that their main constituent-iron-is already present in the body. Having done their job, biodegrading SPIO agents are recycled naturally.

But iron oxide is not necessarily the optimal material for MR-based cell tracking, according to Nguyen T.K. Thanh, Ph.D., a Royal Society university research fellow and lecturer at the Center for Nanoscale Sciences at the University of Liverpool in the U.K. Its effect as a contrast agent is limited by the inherent magnetic susceptibility of its constituent components, magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3).

"Increasing the size of the SPIOs is one way to increase the MR contrast. However, in many circumstances, this is not desirable. For instance, larger particles are more easily removed by the immune system," she said.

Taeghwan Hyeon, Ph.D., director of the National Creative Research Center for Oxide Nanocrystalline Materials at Seoul National University in Korea, is similarly doubtful about the long-term dominance of iron oxide for MR-guided cell tracking, but for different reasons. SPIO nanoparticles operate as T2-weighted contrast. That is, SPIO-labeled cells appear as dark holes on MRI. This "negative contrast" can be confused with local magnetic field inhomogeneities resulting from pathologic conditions, Hyeon said. Blooming artifacts can also sometimes obscure anatomy adjacent to the labeled cells. Their presence could reduce the accuracy of MR-guided cell tracking, if the cells' spread or precise location cannot be seen clearly.

"Eventually, T1 contrast agents will prevail over iron oxide-based T2 contrast

agents for cell tracking," he said.

Jeff Bulte, Ph.D., a professor of radiology at the Johns Hopkins University School of Medicine, is not swayed by the scientists' arguments against SPIO. Several teams, including one at Johns Hopkins, are developing techniques that would produce bright signal, or positive contrast, from SPIO-labeled cells (see Molecular Imaging Outlook 2005;3:1-3). More important, several SPIO-based agents have already been approved for clinical use.

"A lot of materials scientists seeking to work in my lab say, 'I can make these novel magnetic particles that we can use as MR contrast agents instead.' I am not that interested. Can I buy it? Can someone else repeat the studies easily? Is there rigorous quality control? No. The agent I use is a clinical product, what we are going to use in patients, and what we have already used in patients," he said.

Bulte accepts that SPIO-based agents may have some disadvantages. For instance, rapidly dividing cells can be monitored only for a finite length of time. Labeling of nonphagocytic cells has also traditionally been a lengthy process, though Johns Hopkins researchers may have overcome this drawback. Their magnetoelectroporation (MEP) technique, during which cells and an MR agent are subjected to rapid electrical pulses, completes cell labeling in milliseconds, with no loss of cellular function (Walczak P, Kedziorek DA, Gilad AA, et al. Mag Reson Med 2005;54:769-774).

Johns Hopkins investigators are also pushing ahead with MR tracking of phagocytic cells, which take up SPIO spontaneously. They are assembling research protocols for monitoring the fate of SPIO-labeled dendritic cells administered as a "cancer vaccine." This research will build on trials conducted at the University of Nijmegen in the Netherlands that demonstrated the importance of accurate injection (De Vries IJ, Lesterhuis WJ, Barentsz JO, et al. Nat Biotech 2005;23:1407-1413). This time, Bulte aims to use MR-compatible catheters so that injection of the dendritic cells can be monitored by real-time MRI, not ultrasound.

"Knowing precisely where your cells are injected is clinically very important if cell therapy is to go mainstream over the next five or 10 years. I want to emphasize that," Bulte said.