
James M. Gallo and Urs Hafeli

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Letter

We read with great interest the tandem papers on magnetic drug targeting by Lübbe et al. (1, 2). These papers present important, and in general, positive information relating to the safety of magnetic particles (ferrofluid) in vivo. Unfortunately, there is not a sufficient amount of data presented to support a number of claims, particularly those pertaining to the behavior of their ferrofluid. In addition, the historical perspective of magnetic drug targeting (1, 2) has neglected a number of papers, and in so doing, the authors paint a dimmer picture (prior to their studies) of this field of research than is warranted.

With respect to the latter, the overwhelming consensus of magnetic drug targeting is that magnetic particles can increase tumor drug concentrations and improve the therapeutic efficacy in preclinical models when compared to conventional drug administrations (3–5). The single study (6) of magnetic drug targeting in a large animal (dogs) that seemed to form the basis for the “discouraging data” label cannot so readily be classified. In fact, intraarterially administered radiolabeled magnetic albumin microspheres did show positive tumor localization (6). The indication by Lübbe et al. (1) that the plethora of problems associated with magnetic drug targeting, including difficulties related to the magnetic dosage forms, have not lead to further experimentation is totally inaccurate. A number of novel magnetic delivery systems have been developed (7–10), including those in which drug or ligand is adsorbed (11, 12), and, contrary to the authors’ statement that animal studies halted in the mid-1980s (page 4701), such studies have progressed (13–16). In fact, the first major clinical trial of magnetic targeting via an embolization strategy was reported in 1985 (17). A recent international meeting, “Scientific and Clinical Applications of Magnetic Carriers,” attests to the continued developments of biomedical applications of magnetic carriers (visit the Web page, http://www.ccf.org/cc/radonc/conferences/mag-carriers.html for a synopsis).

Numerous statements related to the uniqueness of their magnetic particles, such as, “The Ferrofluid that was used in this study did not necessitate a third compound as an intermediate” (page 4701), can readily be questioned. It is obvious from their description (for instance, see pages 4695 and 4698) that the ferrofluid consists of magnetite particles “surrounded with anhydroglucose” to which drug is adsorbed. This system definitely qualifies as a three-component system. Because of the qualitative descriptions and lack of data, the nature of the association (is it microencapsulated, hydrogen/Van der Waals, or covalent bonding?) between the magnetite and carbohydrate and its stability cannot be determined. The stability of the magnetite and carbohydrate will greatly impact on what fraction of the adsorbed drug is available for targeting to the tumor. Rapid dissociation of the drug-carbohydrate “complex” from the magnetite will severely limit the capacity to target drugs to tumors. Thus, the chemical nature of the ferrofluid, its stability, and the release rate of the drug are prerequisite data that are needed to support statements concerning the behavior of the ferrofluid.

The claim of magnetic localization and efficacy due to mechanical obstruction (page 4697) and claims related to the adsorptive capacity and release kinetics of the drug from the ferrofluid are problematic. One statement, “An important feature of the ferrofluid was its ability to separate from the drug whenever necessary” (page 4698), is somewhat unfathomable. How did they control drug release in vivo? Furthermore, the statement (page 4701) that 50% of the drug was released under the influence of the magnetic field cannot be supported. Without drug-tumor concentration measurements, both the drug concentration-time profile and the fraction of the dose reaching the tumor are unknown. Neither of these parameters can be inferred from in vitro studies. Although the mechanism of mechanical obstruction of the tumor vasculature may be desirable [in fact, Kato (18) developed the concept of chemomobilization years ago with different types of magnetic particles], it is difficult to see how this process was predominant following i.v. administration. To achieve an appreciable mass of magnetic particles at the tumor capable of vascular obstruction, the magnetic particles would have to overcome reticuloendothelial system clearance and systemic distribution due to the i.v. administration they reportedly used. Reticuloendothelial system clearance may be reduced due to the small diameter and hydrophilic carbohydrate coating, yet it is indicated (page 4698) that such a process occurred. Regardless of how their particles distributed to tissues and tumor, timed measurements of magnetite and drugs in the tissues, along with microscopic analyses, are needed for a comprehensive characterization of the in vivo disposition of the magnetite and drug.

We congratulate Lübbe and co-workers on advancing the field of magnetic drug targeting, particularly through the clinical investigation. At the same time, the mechanistic and pharmacokinetic aspects of magnetic drug targeting should not be inferred from tolerance and efficacy studies. To further advance this drug targeting strategy, a quantitative examination of the mechanisms that control distribution of magnetic particles to tumors and an understanding of how to optimize the associated factors are needed.

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References
LETTERS TO THE EDITOR


Reply

We thank Drs. Gallo and Hafeli (1) for their stimulating comments, and we are happy to respond to the questions they raise, specifically, their claims that “there is not a sufficient amount of data presented to support a number of claims, particularly those pertaining to the behavior of the ferrofluid,” and that we “neglected a number of papers” in the literature cited in our studies (2, 3). Drs. Gallo and Hafeli quote three papers in support of their claims (4–6). These three papers are very familiar to us; two of them were cited in our articles (2, 3). In fact, we believe those articles (4–6) support our claims that “valuable preclinical information” has been gained; yet, due to reasons partly discussed in our papers, overall data on magnetic drug targeting had been discouraging to the point that no clinical testing had been conducted.

The intraarterial administration of the various magnetic compounds close to or next to the tumor (in the tip of the rat tail with the tumor being a few centimeters more proximal in the tail) suggests, among other things, a partial embolization effect and not the necessity of strong magnetic fields. Although it remains subjective to judge the efficacy of all of those animal experiments, Dr. R. M. Morris from the Widder group (4) has indicated those problems in the application of their albumin/magnetic particle/drug compound in larger animal models (dogs) to us (personal communication). Yet, Gallo and Hafeli (1) are correct in that there was undoubtedly some effect on “positive tumor localization” in the successful animal experiments with intraarterially administered radiolabeled magnetic albumin microspheres. Our claim that “a number of problems have not lead to further experimentation” should be understood in terms of large animal and human experimentation. In this context, Gupta et al. (6), who is quoted by Gallo and Hafeli, have come to the very same conclusion as we have. On the other hand, it is correct that several novel magnetic delivery systems have been developed in the meantime. However, the first clinical trial that was mentioned by Gallo and Hafeli, the “magnetic targeting via an embolization strategy that was reported in 1985” was not drug targeting in its strong sense; instead, large particles had been applied solely to occlude blood vessels, an approach done by Russian scientists many years earlier for the occlusion of cerebral aneurysms and by others, who were cited in our preclinical paper [see literature (Refs. 21, 22) from Ref. 2].

Gallo and Hafeli point out that too few data were included on the ferrofluid used in our study. We regret that the information seemed to be “questionable.” We purposely did not include more information because this was not the focus of our articles. Our system does not need a third component the way other users define it; by this we mean that no other third compound is necessary for the drug and the particles to react. Rather, the carbohydrate coating is necessary for the stabilization of the ferrofluid particles anyway; yet, it is capable for adsorptive binding of cytostatic agents, as well as many other drugs, DNA-fragments, cells, and cytokines. By a third component we mean an albumin, starch, or other microsphere or matrix into which the magnetic particles plus the drug had been incorporated or to which it had been bound. In any of those, as well as in our system, a stabilizer surrounds the particles to prevent them, from among other things, sedimentation. With the exception of our fluid, in no other system is the direct and reversible binding via ionic and Van der Waals forces feasible.

The authors are correct in their statement that more data are necessary to understand the chemical nature of the binding as well as the quality of the desorption process, which is important in terms of the kinetics. As we indicate in our study, the bioavailability of the ferrofluid particles lies around 30 min. With a magnetic field application of 120 min and other physiologically relevant parameters (blood circulation time and flow, blood and tumor volume, vascular content), 50% of the drug epirubicin was adjusted to desorb within 60 min. Thus, the drug did not desorb too early or outside of the tumor. A publication specifically addressing those parameters, as well as their in vitro and in vivo measurement techniques, is in preparation. Briefly, the rat cremaster muscle was exteriorized such that the neurovascularly-intact microcirculatory bed could be visualized under the microscope with trans- and fluorescent epilumination techniques. Then, the ferrofluid was injected into the jugular vein while a magnet (0.2 tesla) was applied to a certain region of that preparation. Within that region (diameter of approximately 3 mm), we purposely included one large first-order arteriole and vein. This was one of our in vivo models to measure different times upon which a magnetic obstruction of the various vessels occurred. Because epirubicin possesses a fluorescent quality, we were also allowed to measure (by fluorescent light intensity) the amount of epirubicin that desorbed in vivo from the bound ferrofluid.

Thus, taken together, those as well as other data that Gallo and Hafeli rightly regard as necessary for full understanding do exist but have not been described in detail due to the other focus of our articles (2, 3). We hope that these comments clarify some of the issues raised.

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