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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 epiillumination 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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We would like to thank Drs. Gallo and Hafeli for their knowledgable contribution, and we congratulate them for their past work on magnetic fluids for use in clinical application.

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