Supplementary Material

Circulating Magnetic Microbubbles for Localized Real-Time Control of Drug Delivery by Ultrasonography-Guided Magnetic Targeting and Ultrasound

Beata Chertok[1,2,*] and Robert Langer[3,4,5,6]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, United States

[2]Department of Biomedical Engineering, College of Engineering, University of Michigan, Ann Arbor, MI, Unities States

[3]Department of Chemical Engineering, MIT, Cambridge, MA 02139, USA

[4]David H Koch Institute for Integrative Cancer Research, MIT, Cambridge, MA 02139, USA

[5]Institute for Medical Engineering & Science, MIT, Cambridge, MA 02139, USA

[6]Harvard-MIT Division of Health Sciences & Technology, Cambridge, MA 02139, USA

[*]Corresponding author: beata@umich.edu; Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, United States

1. Theoretical analysis of magnetic capture requirements

In order to capture a magnetic microparticle from the flowing blood, the magnitude of the magnetic force must be sufficient to pull the particle across the blood flow to the vessel wall against the opposing drag force. The criterion for the required magnetic force was previously derived as the following:[1]

$$F_m(N) > 7.5 \times 10^{-6} \left(\frac{R}{l}\right) \left(\frac{\mu}{\mu_0}\right) d_p v_L \qquad (1)$$

where:

F_m – the magnitude of magnetic force
R – capillary radius
l – length of a moderately "straight" capillary segment that lies within the magnetic field region
μ – the viscosity of blood
μ_0 – the viscosity of water
d_p – particle diameter
v_L – average linear flow velocity

The average linear blood flow velocity in a tumor capillary can be approximated according to the following equation: [2]

$$v_L = \frac{PV}{n}(\pi R)^{-2}\left(\frac{3V}{4\pi}\right)^{-2/3} \qquad (2)$$

where the average linear blood velocity in a single capillary (v_L) is a function of four parameters: blood perfusion of the tumor (P), tumor volume (V), microvessel density (n) and capillary radius (R).

Using equation (2) and physiological values (Table S1) to define the pathophysiology of a solid tumor, we calculated the characteristic capillary flow rate (v_L) of a solid tumor to be ~0.04 cm/s.

According to equation 1, for a tissue with a given microvascular morphology and blood perfusion, the magnetic force threshold required to achieve magnetic capture is a linear function of a microsphere's diameter. We calculated the threshold magnetic force for capturing magnetic microbubbles of 1 - 5 μm at a characteristic capillary flow rate of solid tumors (Figure S1).

Table S1. Characteristic values of microvascular morphology and blood perfusion for solid tumors

Parameter	Symbol	Units	Tumor	Reference
Tissue perfusion	*P*	ml/100g/min	40	[3]
Capillary radius	*R*	μm	10.5	[4]
Microvessel density	*n*	Vessels/mm^2	180	[5]
Tissue volume	*V*	μL	100	Present study
Viscosity of water	μ_0	P	8 x 10^{-3}	[1]
Viscosity of whole blood	μ	P	28 x 10^{-3}	[1]
Length of a capillary	*l*	μm	160	[1]

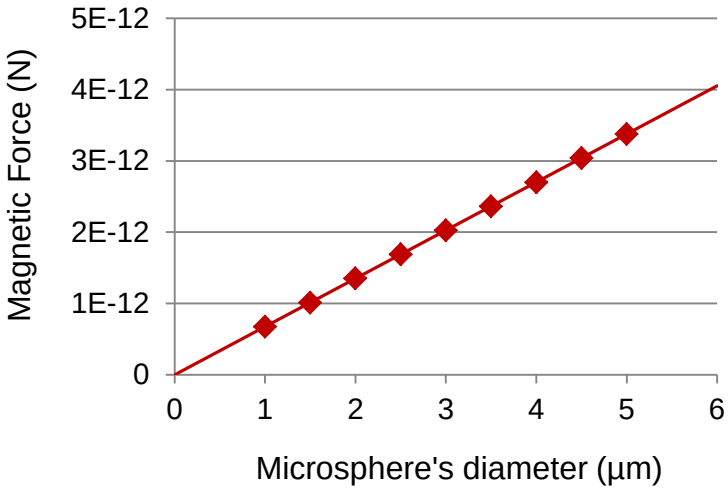

Figure S1. Magnetic force threshold required to capture magnetic microspheres from flowing blood at a characteristic capillary flow rate of solid tumors (~0.04 cm/s).

We next estimated the required magnetic moment of the microbubble to achieve magnetic capture under the experimental conditions: the magnetic flux and gradient of 0.9 T and 50 T/m, respectively. In an external inhomogeneous static magnetic field, with no external current density, the magnetic force on a particle is given by the following:[6]

$$\overrightarrow{F_m} = \nabla\left(\vec{\mathrm{m}} \cdot \vec{\mathrm{B}}\right) \tag{3}$$

where $\vec{m}$ is the particle magnetic dipole moment and $\vec{B}$ is the external magnetic field density.

Assuming alignment of the particle magnetic moments with the applied field, the magnetic force acting on a single particle simplifies to the following:

$$\overrightarrow{F_m} = m\nabla B \tag{4}$$

where $B = \left\|\vec{B}\right\|$, and m is the scalar magnetic moment.

To capture a 3-μm microbubble, a magnetic force of 2×10^{-12} N (Figure S1) would be required. Based on equation 4, to achieve a magnetic force of $>2\times10^{-12}$ N under the magnetic flux and gradient of 0.9 T and 50 T/m, respectively, a magnetic microbubble would need to exhibit a magnetic moment of $>4\times10^{-14}$ Am^2.

2. Estimation of microbubble's magnetic moment

In order to determine the value of m, we measured the induced magnetization of the heparinized iron oxide nanoparticles (MNPh) as a function of applied magnetic field using a Superconducting Quantum Interference Device (SQUID) (Figure S2). The induced magnetization of MNPh reaches saturation above the applied field of 0.7 T. Thus, under the experimental conditions (magnetic flux density and gradient of 0.9 T and 50 T/m, respectively) the scalar magnetic moment, m, can be approximated by the following:

$$m = M_{sat} \times w \tag{5}$$

where $\boldsymbol{M_{sat}}$ is the saturation magnetization , and $\boldsymbol{w}$ is the iron content (g Fe) of a single magnetic microbubble.

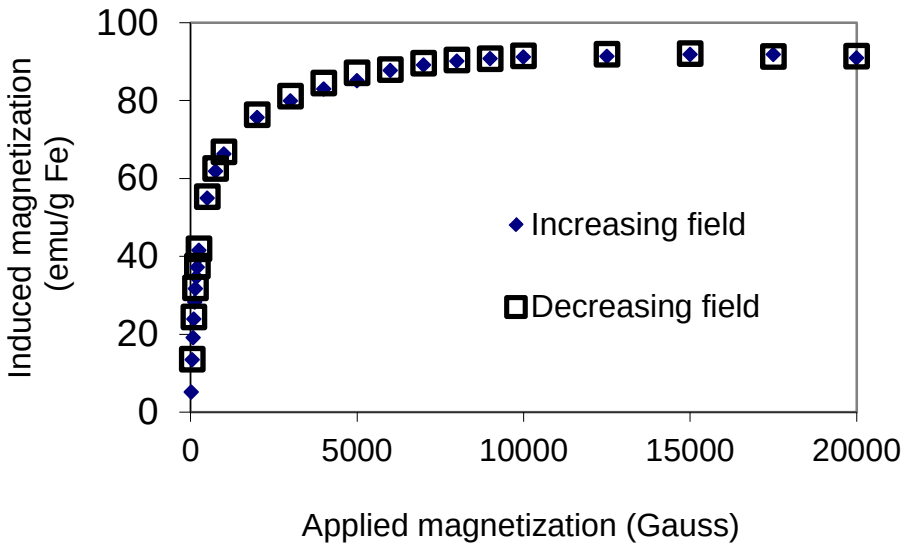

Figure S2. Induced magnetization of the heparinized iron oxide nanoparticles (MNPh) as a function of applied magnetic field

Magnetic moments of microbubbles with different MNPh contents were estimated according to equation 5 using experimentally determined microbubble's iron content (w, gFe/MB) and saturation magnetization (M_{sat}) of 90±3 emu/g Fe (Figure S2).

3. Purification of MagMB

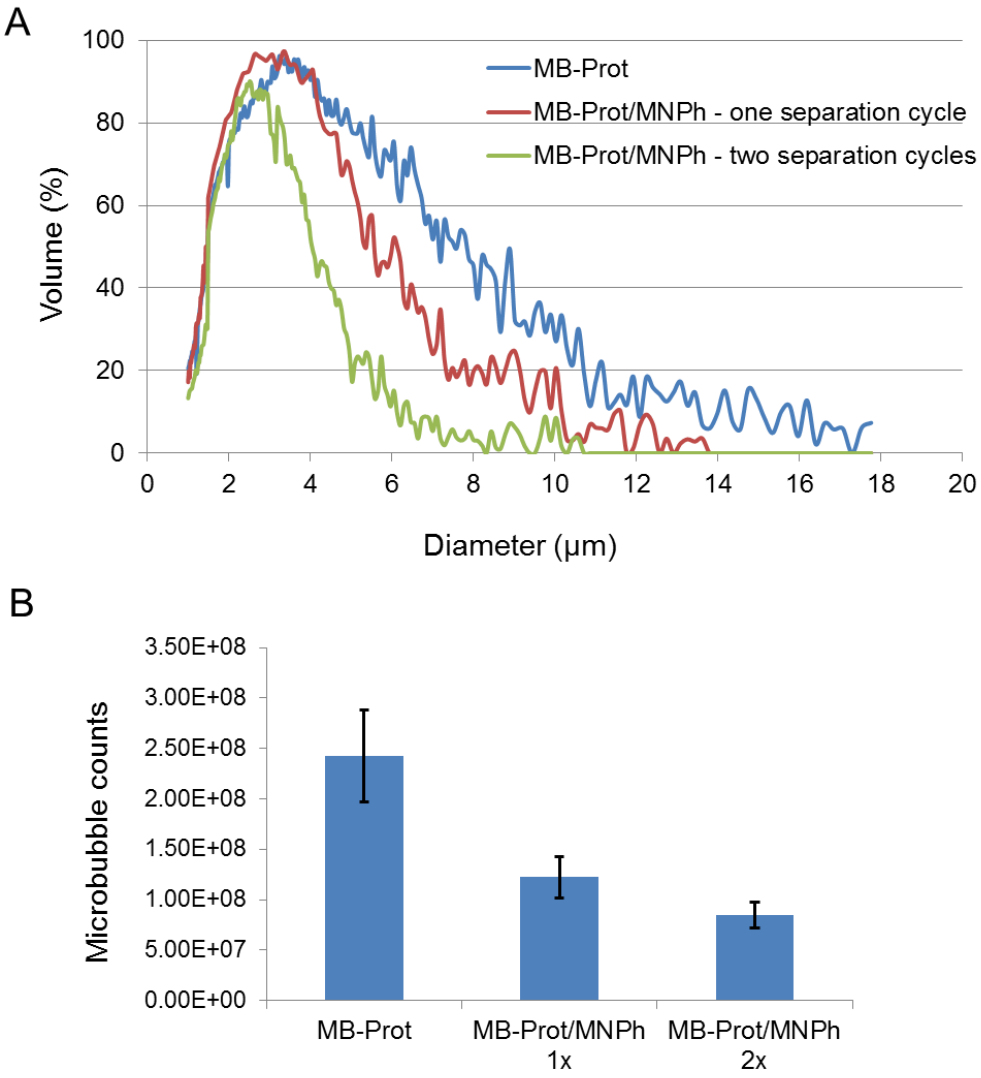

Figure S3. Representative size distributions and microbubble counts during the intermediate steps of MagMB purification. (A). Representative size distributions of protamine-functionalized microbubbles (MB-Prot) and magnetic microbubbles MB-Prot/MNPh after the first and the second purification cycles. (B). Representative microbubble counts for protamine-functionalized microbubbles (MB-Prot) and magnetic microbubbles MB-Prot/MNPh after the first (1 x) and the second (2 x) purification cycles.

4. Fluorescence imaging of tumors post administration of MagMB-Cy5.5

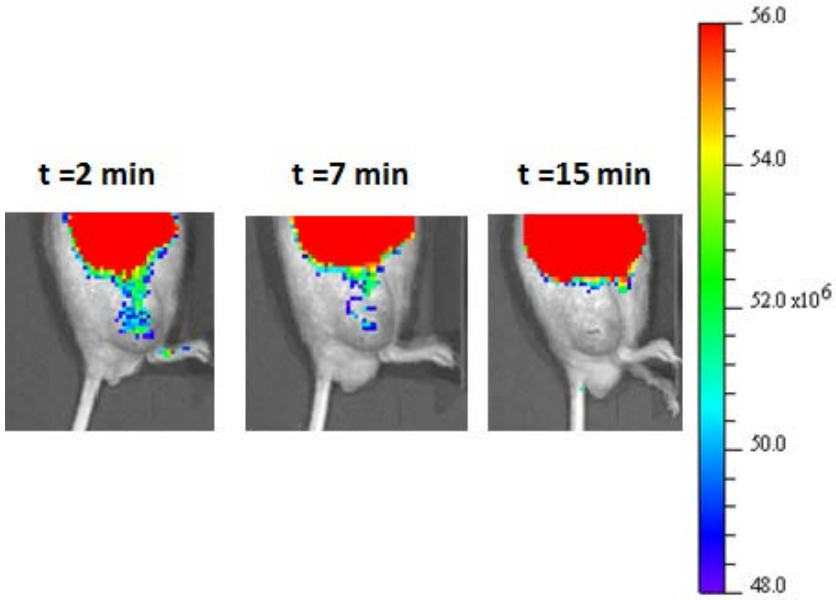

Figure S4. Representative kinetic sequence of fluorescence images acquired post administration of MagMB-Cy5.5. The colorscale is adjusted to visualize the fluorescence signal in the tumor. The color bar represents fluorescence radiance expressed in [photon/s/cm^2/steradian].

REFERENCES:

1. Driscoll CF, Morris RM, Senyei AE, Widder KJ, Heller GS. Magnetic targeting of microspheres in blood flow. Microvasc Res. 1984; 27: 353-69.
2. Chertok B, David AE, Huang Y, Yang VC. Glioma selectivity of magnetically targeted nanoparticles: a role of abnormal tumor hydrodynamics. J Control Release. 2007; 122: 315-23.
3. Fallowfield ME. Blood-Flow Distribution within Transplantable Tumors in the Mouse. European Journal of Cancer & Clinical Oncology. 1989; 25: 1683-8.
4. Pathak AP, Schmainda KM, Ward BD, Linderman JR, Rebro KJ, Greene AS. MR-derived cerebral blood volume maps: issues regarding histological validation and assessment of tumor angiogenesis. Magn Reson Med. 2001; 46: 735-47.
5. Clere N, Corre I, Faure S, Guihot AL, Vessieres E, Chalopin M, et al. Deficiency or blockade of angiotensin II type 2 receptor delays tumorigenesis by inhibiting malignant cell proliferation and angiogenesis. International Journal of Cancer. 2010; 127: 2279-91.
6. Chertok B, David AE, Yang VC. Magnetically-enabled and MR-monitored selective brain tumor protein delivery in rats via magnetic nanocarriers. Biomaterials. 2011; 32: 6245-53.