ARTICLE

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Directing cell therapy to anatomic target sites *in vivo* with magnetic resonance targeting

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Cell-based therapy exploits modified human cells to treat diseases but its targeted application in specific tissues, particularly those lying deep in the body where direct injection is not possible, has been problematic. Here we use a magnetic resonance imaging (MRI) system to direct macrophages carrying an oncolytic virus, Seprehvir, into primary and metastatic tumour sites in mice. To achieve this, we magnetically label macrophages with super-paramagnetic iron oxide nanoparticles and apply pulsed magnetic field gradients in the direction of the tumour sites. Magnetic resonance targeting guides macrophages from the bloodstream into tumours, resulting in increased tumour macrophage infiltration and reduction in tumour burden and metastasis. Our study indicates that clinical MRI scanners can not only track the location of magnetically labelled cells but also have the potential to steer them into one or more target tissues.

MEDICAL ROBOTS

Beyond imaging: Macro- and microscale medical robots actuated by clinical MRI scanners

Sylvain Martel

Magnetic resonance actuation has potential for use in medical therapies.

Macro- and microrobots that can be actuated by magnetic resonance imaging (MRI) have been pursued over the past 10 years. MRI scanners have been used to provide tetherless actuation for applications ranging from microscale therapeutic agents along predefined trajectories in the vasculature and macroscale magnetic components to implement systems such as MRI-actuated motors and needle inserters. MR actuation also inspired the use of a relatively new imaging modality known as magnetic particle imaging (MPI) to actuate magnetic devices (*1*) by exploiting the gradient between a region known as the field free point (FFP) and the surrounding magnetic sources. Because MPI exploits the nonlinear magnetization response below the saturation magnetization of tracers that occurs in the FFP, the spatially selective MPI-based actuation of helical objects, as described by Rahmer *et al.* (*2*) in this issue of *Science Robotics*, is achieved by repositioning the FFP to create a lower magnetization region where magnetic torque actuation can occur.

The first in vivo proof of concept of MRI-

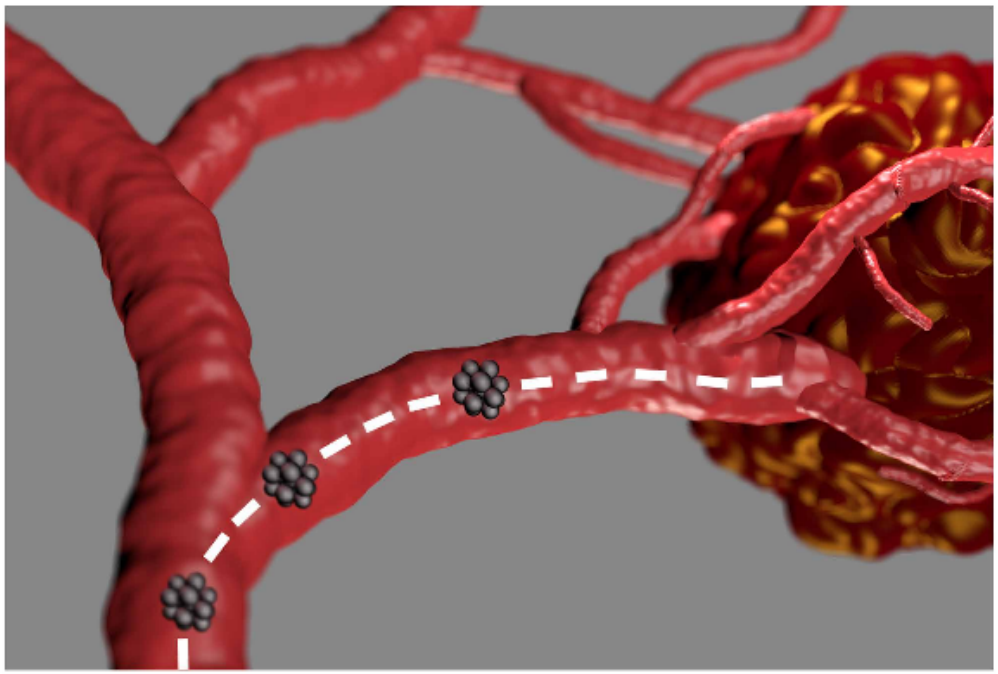
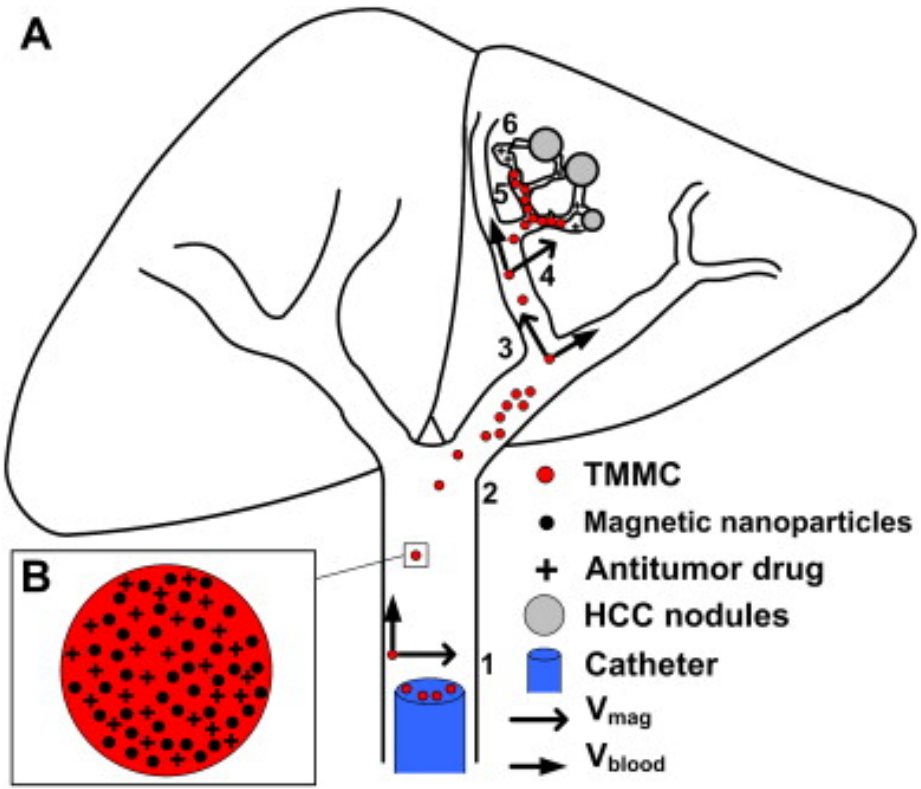


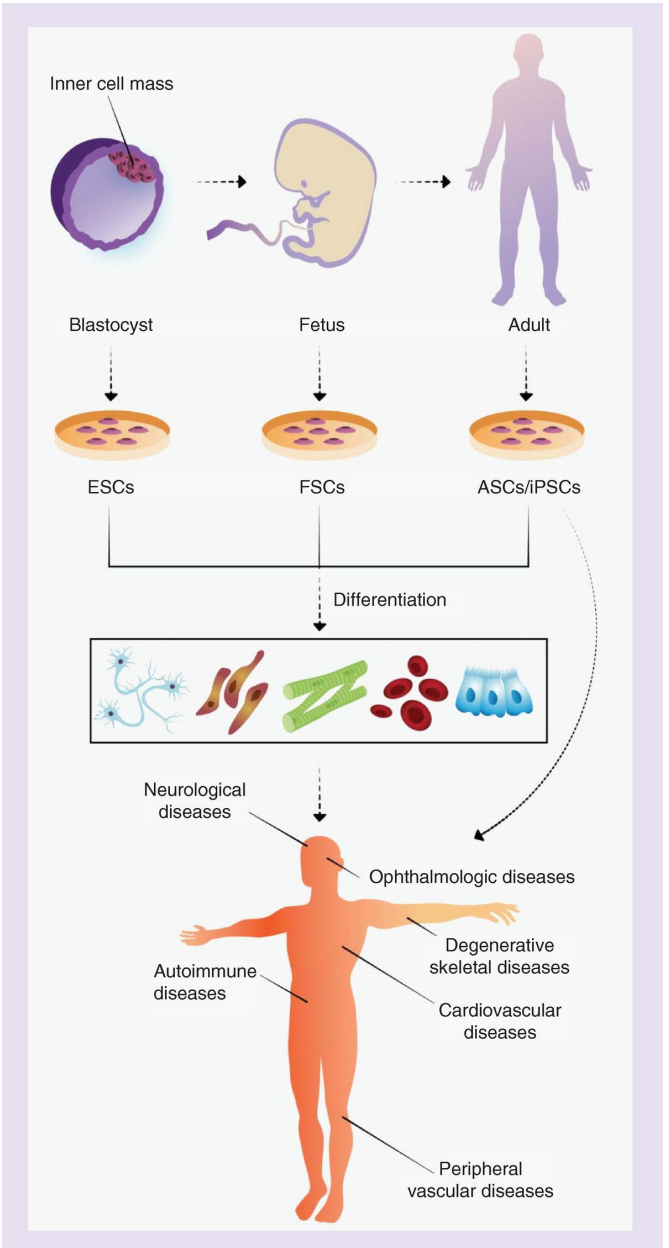
Fig. 1. Combining the imaging capability of MRI with magnetic resonance actuation offers great potential for medical robotics ranging from the micro- to the macroscale. [Credit: Dumitru Loghin, NanoRobotics Laboratory, Polytechique Montréal]

Aim: Use MRI to non-invasively steer therapeutic cells to tumors



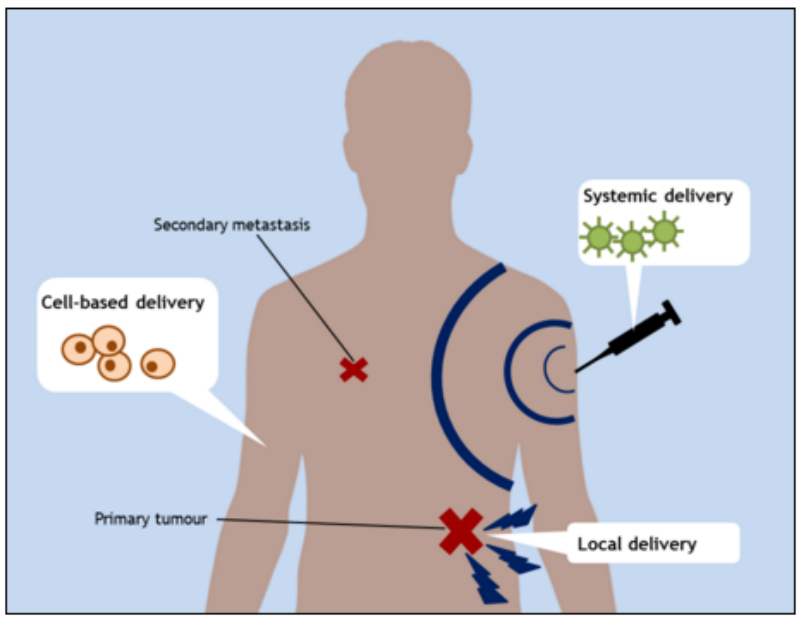
Cell based Therapy - Overview

Cell therapy = injection of living cells into patient



Need to deliver cell-based therapies *systemically*

- disease not confined to one site
- tissue inaccessible by direct injection



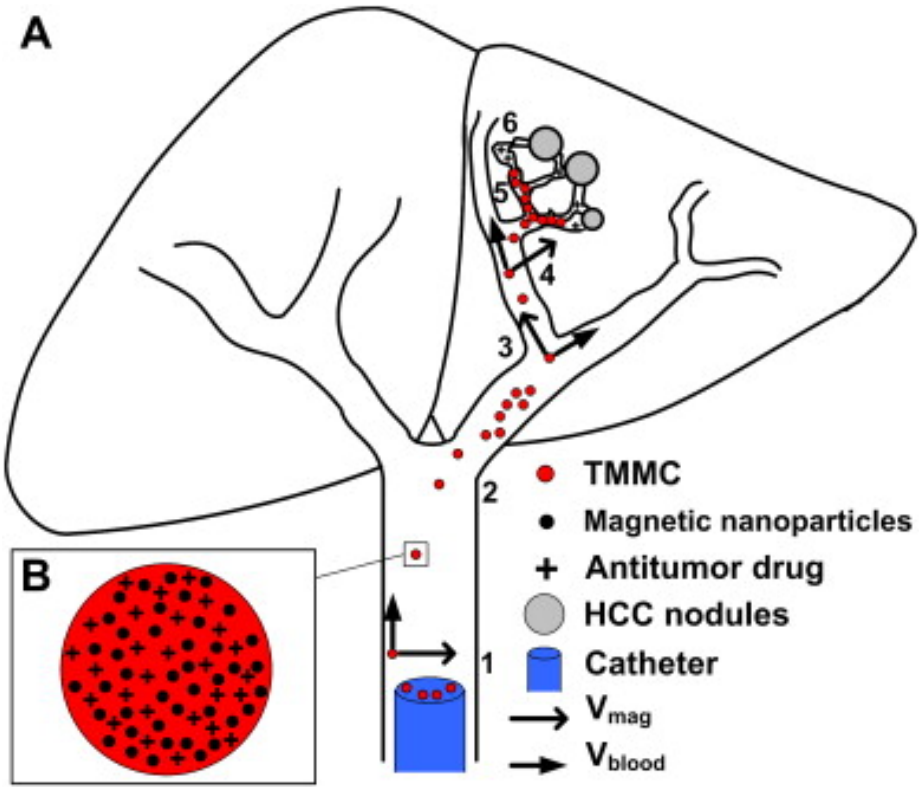
Therapeutic chemicals lack precise targetting of tumour cells

- reduces therapeutic efficacy
- can induce side effects in other body locations: hair loss, nausea, tissue damage

- Current approaches for targetting exploit different properties of tumour cells
- Need to find more precise ways to target tumour cells

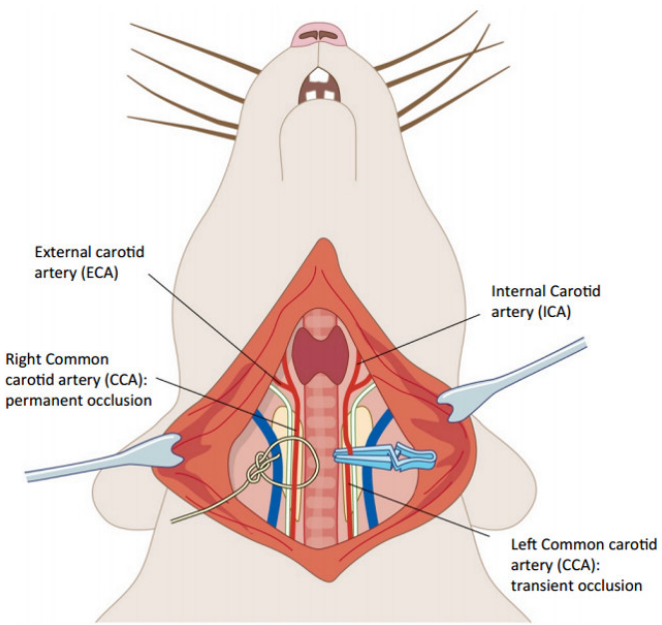
Magnetic Resonance Targetting can increase spatial targetting of tumour cells

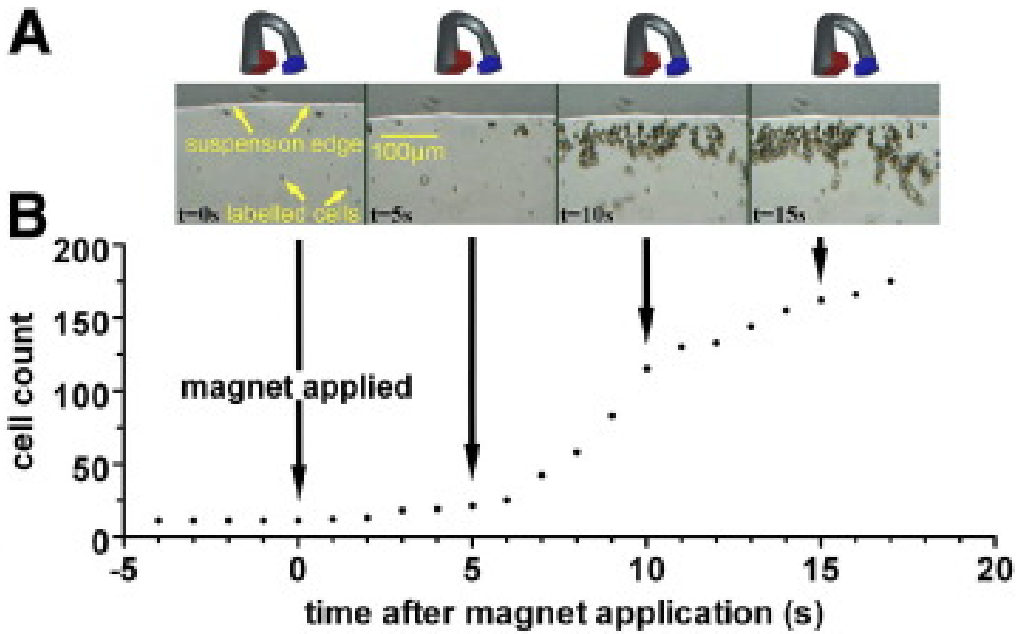
- magnetic forces drive macrophages to tumour location



Previous studies used external magnet to attract cells to tumor in rat

Location - common carotid artery

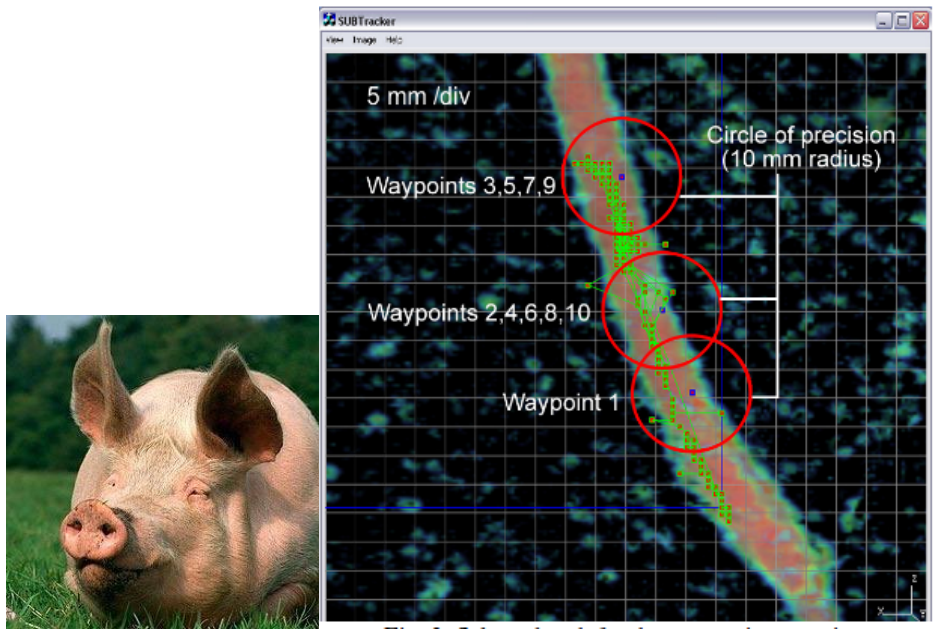




Kyrtatos et al., 2009

But only works for superficial tissues

Other study used MRI machines to steer magnetic bead in pigs

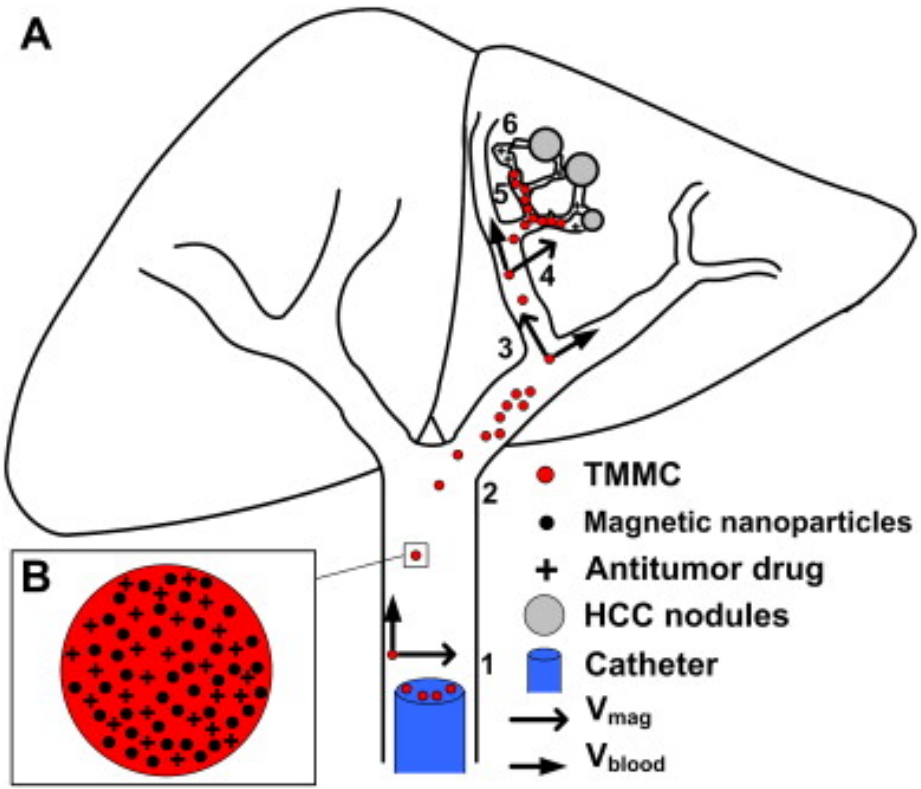


A Chanu, Martel S, IEEE Eng Med Biol Soc, 2007

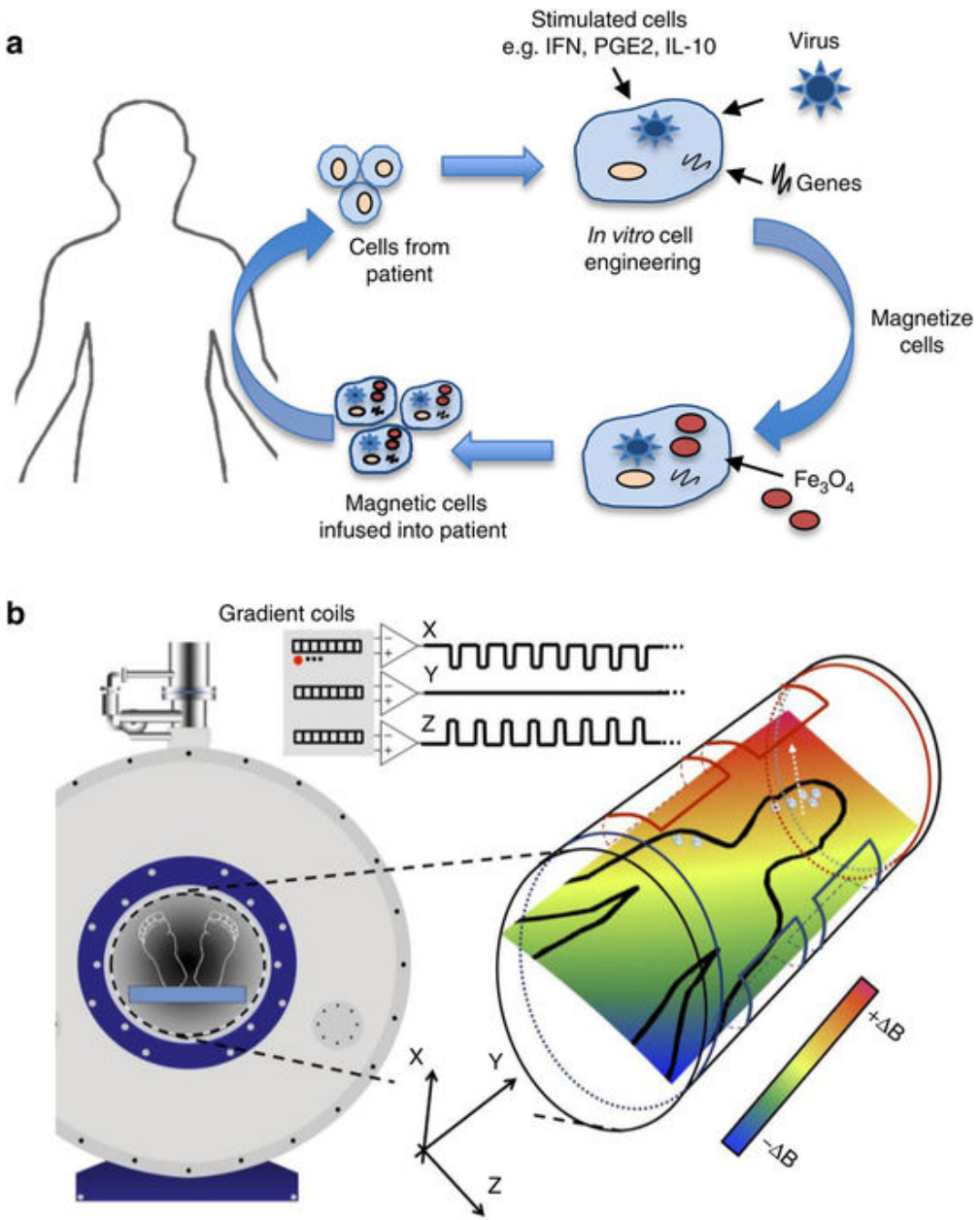
But not attempted using smaller particles such as magnetic induced cells.

Aim: Use MRI to non-invasively steer therapeutic cells to tumors

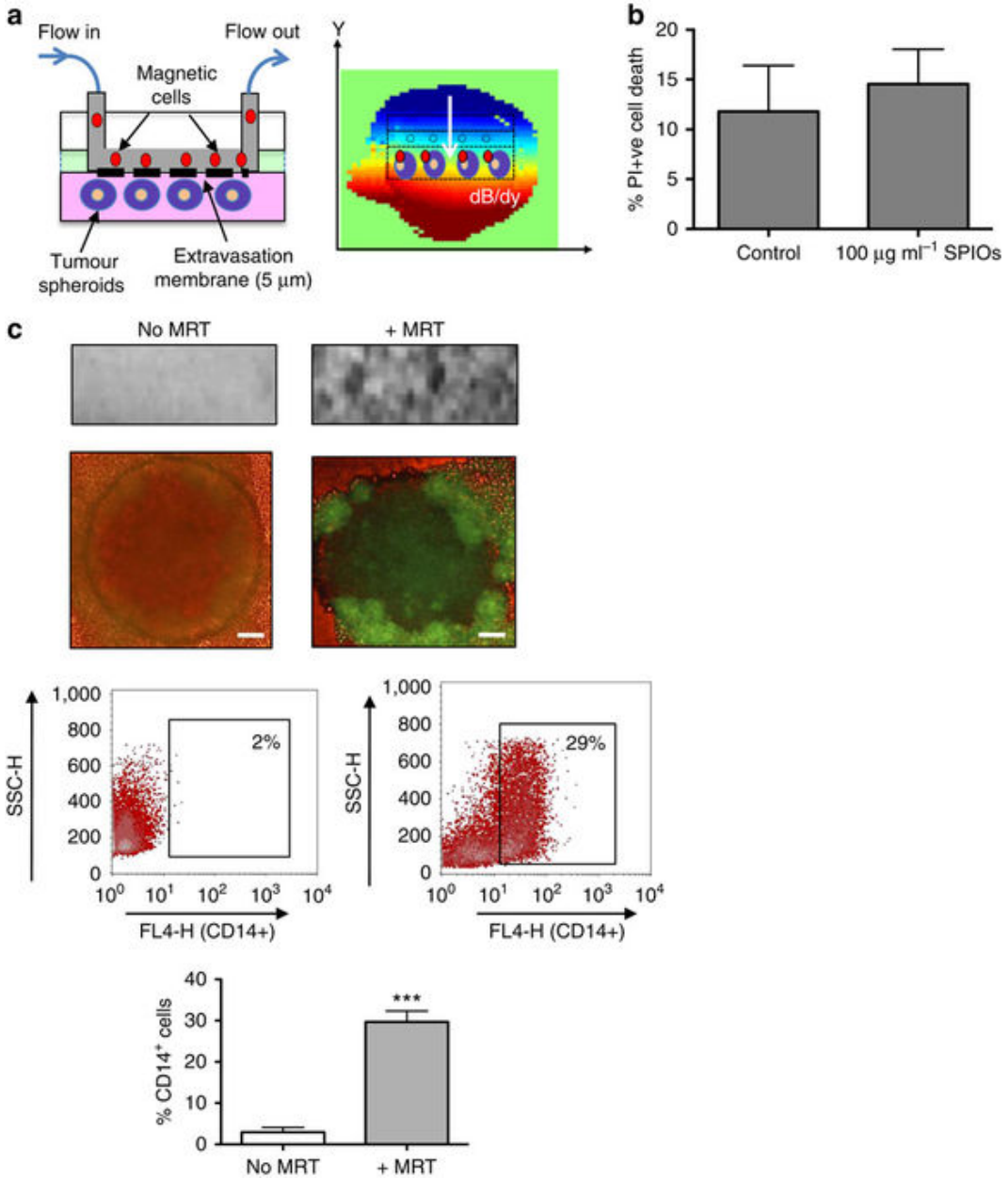
- in vivo (rat) using MR machine
- prove increased anti-tumour effects



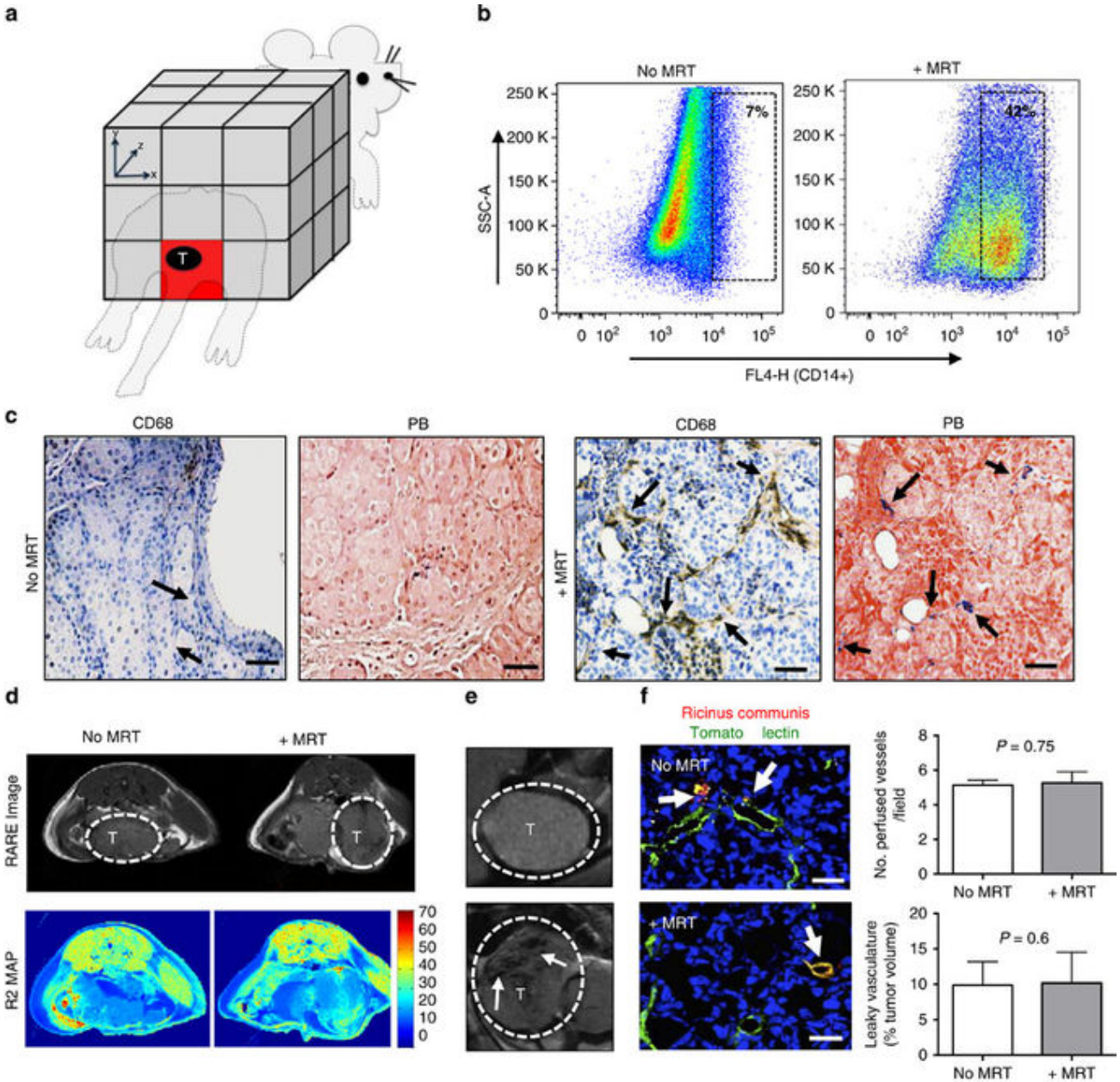
Methods - Magnetic Resonance Targetting of therapeutic cells



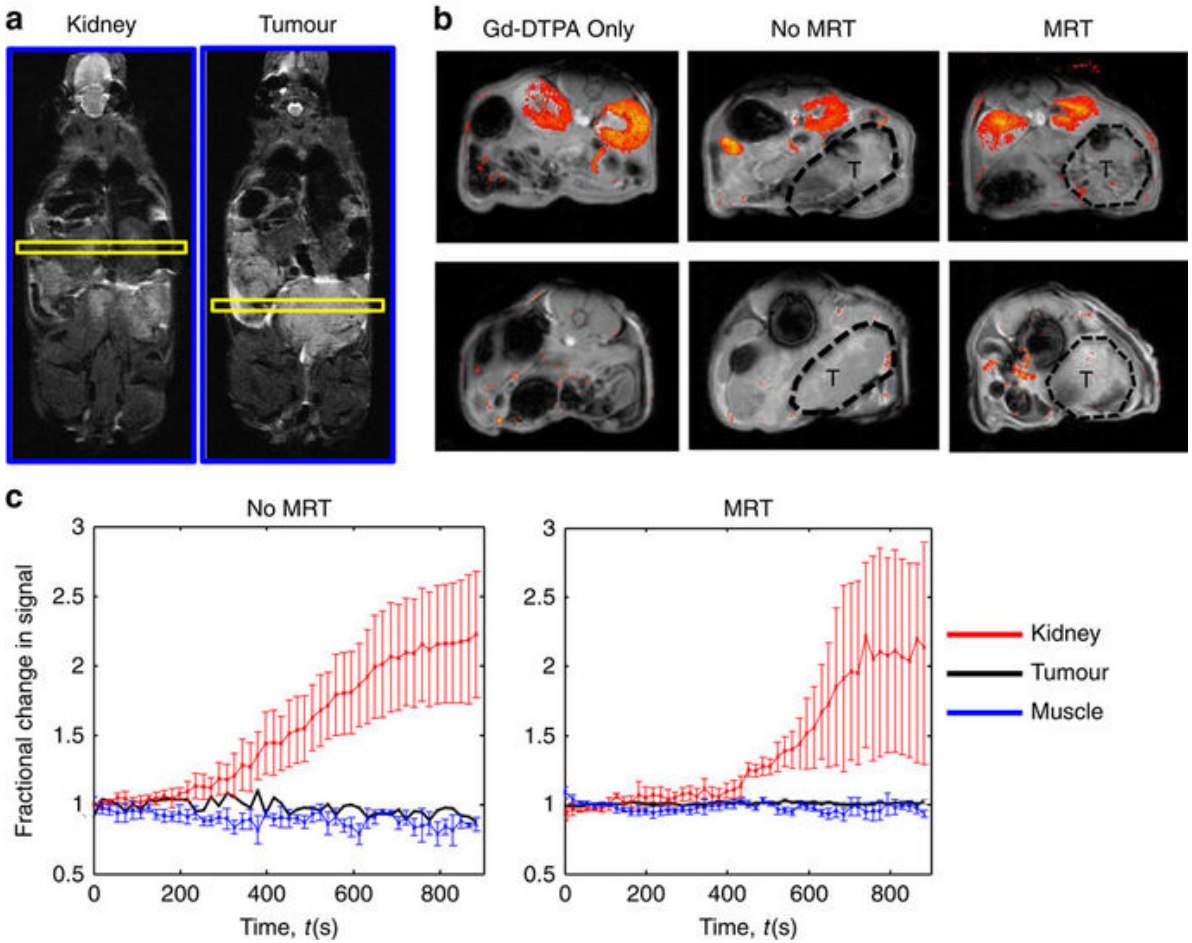
In vitro MRT of magnetised particles results in increased uptake in tumor model



In vivo MRT leads to increased uptake in tumor areas

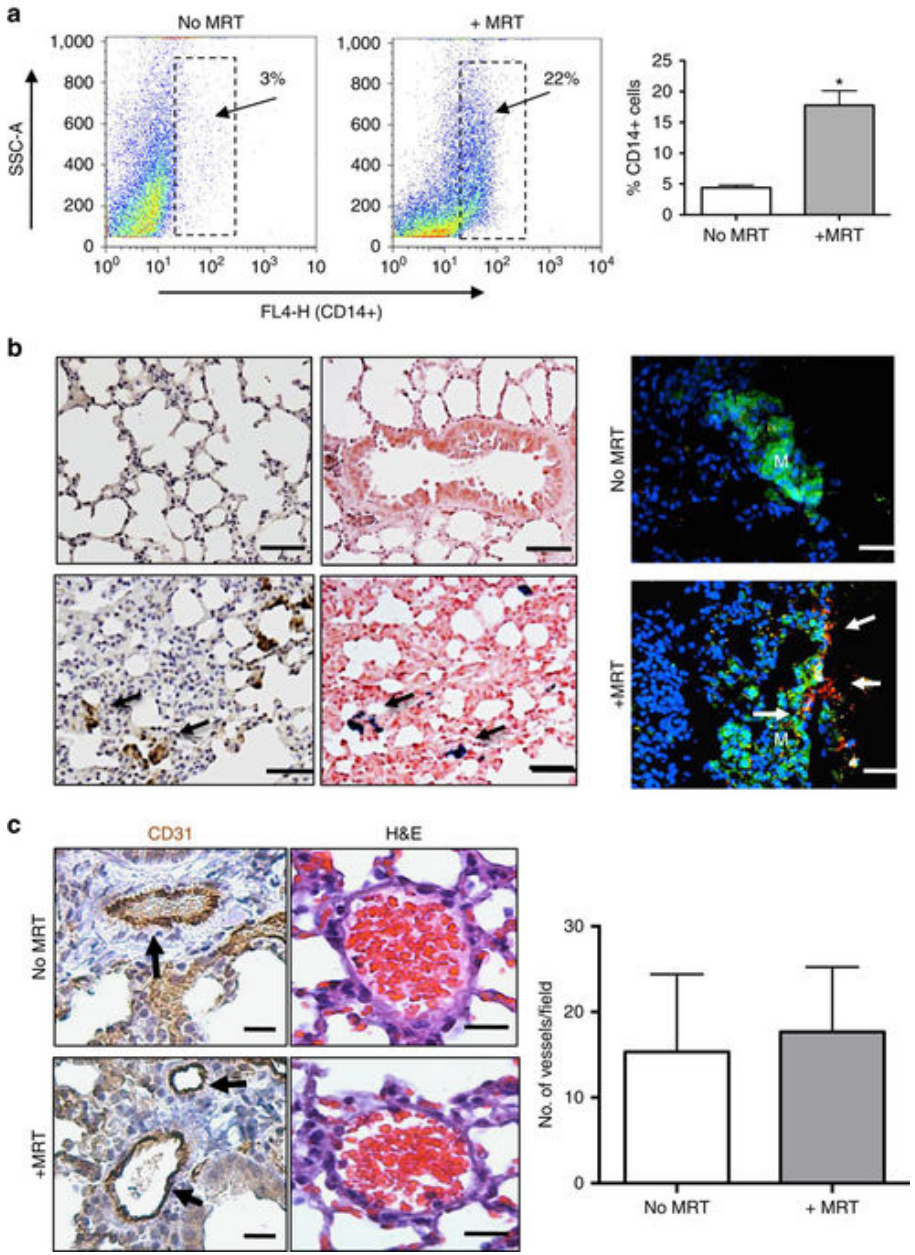


MRT does not affect the vasculature

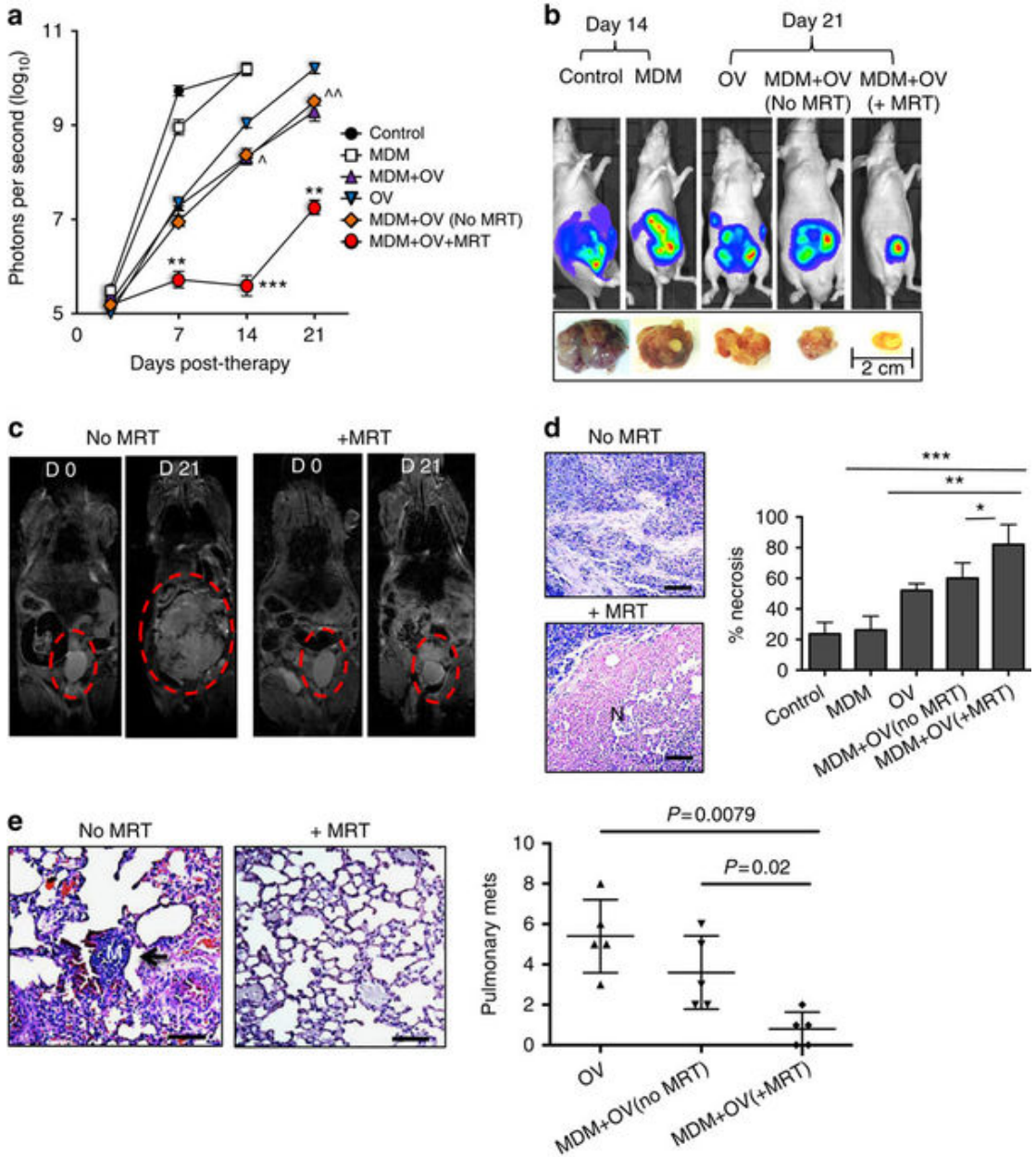


Change in signal in kidney suggests vasculature remained intact

MRT can also steer macrophages into lung metastases



MRT increases anti-tumour effects of macrophages



Discussion

Impact:

- First study to prove MRT *aids treatment of tumours*, in vivo

Limitations:

- MR gradient directions were known a-priori (no imaging required)

SCIENTIFIC REPORTS

OPEN

Simultaneous steering and imaging of magnetic particles using MRI toward delivery of therapeutics

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Magnetic resonance navigation (MRN) offers the potential for real-time steering of drug particles and cells to targets throughout the body. In this technique, the magnetic gradients of an MRI scanner perform image-based steering of magnetically-labelled therapeutics through the vasculature and into tumours. A major challenge of current techniques for MRN is that they alternate between pulse sequences for particle imaging and propulsion. Since no propulsion occurs while imaging the particles, this results in a significant reduction in imaging frequency and propulsive force. We report a new approach in which an imaging sequence is designed to simultaneously image and propel particles. This sequence provides a tradeoff between maximum propulsive force and imaging frequency. In our reported example, the sequence can image at 27 Hz while still generating 95% of the force produced by a purely propulsive pulse sequence. We implemented our pulse sequence on a standard clinical scanner using millimetre-scale particles and demonstrated high-speed (74 mm/s) navigation of a multi-branched vascular network phantom. Our study suggests that the magnetic gradient magnitudes previously demonstrated to be sufficient for pure propulsion of micron-scale therapeutics in magnetic resonance targeting (MRT) could also be sufficient for real-time steering of these particles.

... Using specialised MRI sequences

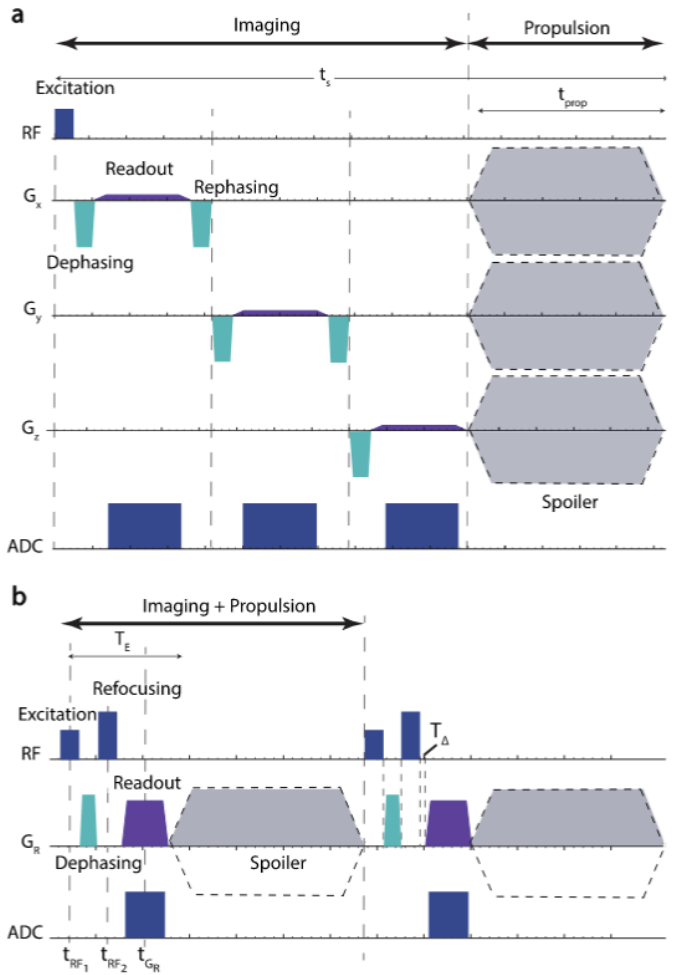

Figure 1. MRI pulse sequences for imaging and steering. (**a**) Alternating imaging and propulsion. Imaging is performed along the three axes of the MRI coordinate frame using a gradient echo pulse sequence. (**b**) Proposed simultaneous imaging and propulsion. Imaging and propulsion are performed along a single desired direction. *RF* = Radio Frequency excitation, *ADC* = Analogue to Digital Converter Sampling.

General discussion about MRT

Open questions:

- Could it be used to navigate in other body networks?
- Do MR scans have enough resolution for accurately *mapping* vessel pathways?
- Same for accurately *navigating* particles through pathway?
- Do we need to modify current MR scanners to make it work better?

Obstacles in further MRT development:

- restricted access to clinical MR scanners
- lack of expertise in robotics community to develop and implement MR sequences
- protexted source codes