

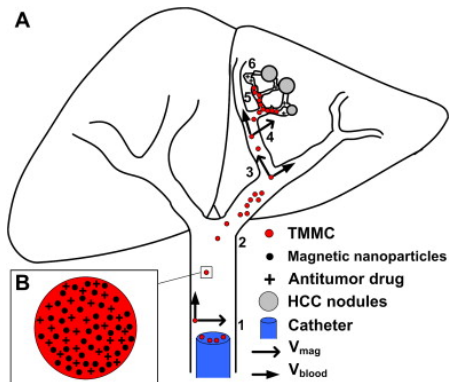
Directing cell therapy to anatomic target sites *in vivo* with magnetic resonance targeting

Munitta Muthana¹, Aneurin J. Kennerley^{2,*}, Russell Hughes³, Ester Fagnano¹, Jay Richardson¹, Melanie Paul¹, Craig Murdoch⁴, Fiona Wright¹, Christopher Payne⁵, Mark F. Lythgoe⁵, Neil Farrow⁶, Jon Dobson⁷, Joe Conner⁸, Jim M. Wild⁹ & Claire Lewis³

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.

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

- ▶ in vivo (rat)
- ▶ prove increased anti-tumour effects

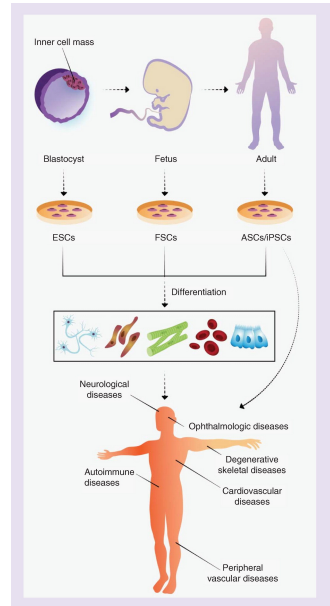


Cell based Therapy - Overview

Cell therapy = injection of living cells into patient

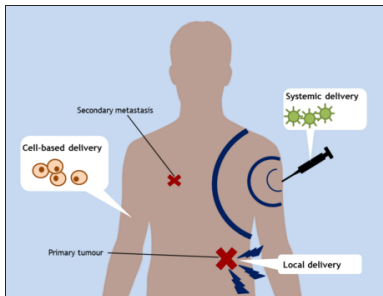
Cell based therapies can be used to treat various diseases:

- ▶ infarcted myocardium
- ▶ spinal cord injury
- ▶ cerebral ischaemia
- ▶ neurodegenerative diseases (Alzheimer's, Parkinson's)
- ▶ cancer



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

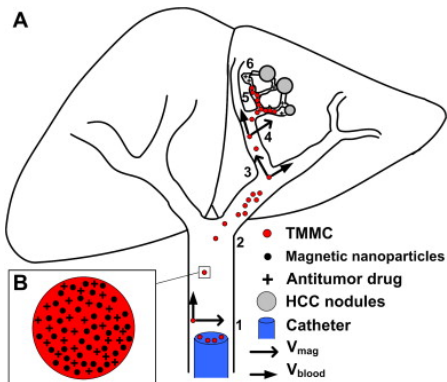
- ▶ reduces therapeutic efficacy
- ▶ can induce side effects in other body locations



Need to find ways to precisely target the tumour cells

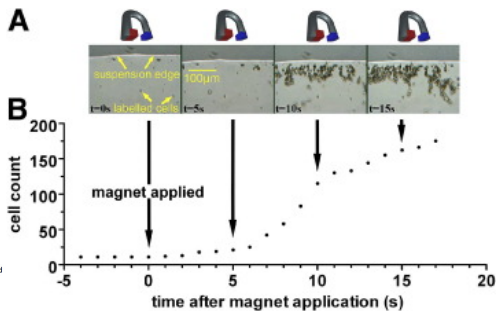
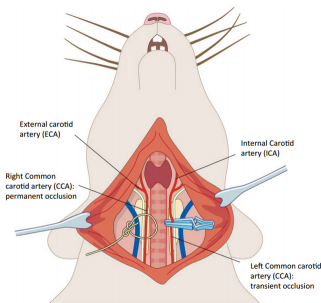
Magnetic Resonance Targetting can drive macrophages to tumour location

- ▶ special gradient sequence applied to move cells to desired target
- ▶ can interleave with imaging sequence to read particle location



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

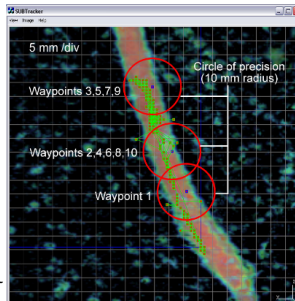
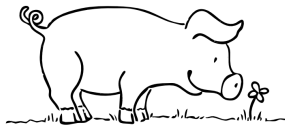
Location - common carotid artery



Kyrtatos et al., 2009

But only works for superficial tissues

Other study used MRI machines to steer magnetic bead in pigs

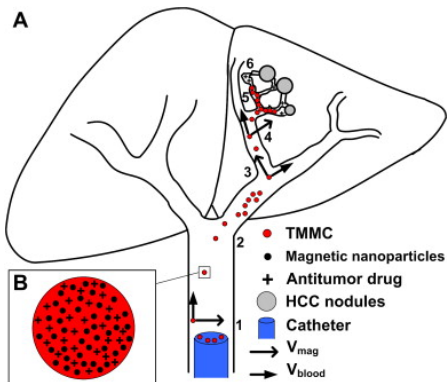


A Chanu, Martel S, IEEE Eng Med Biol Soc, 2007

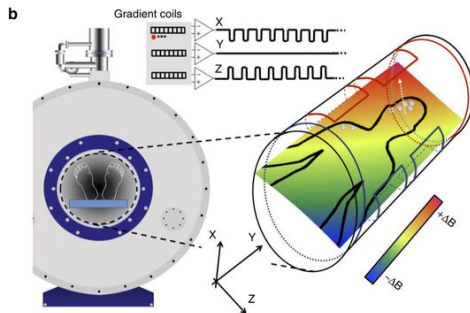
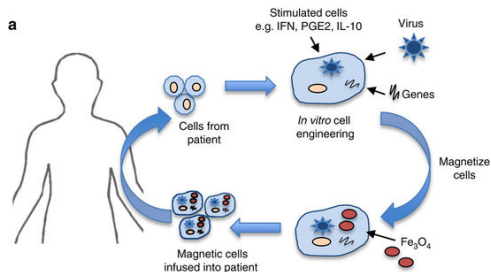
But not attempted using smaller particles such as magnetic induced cells.

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

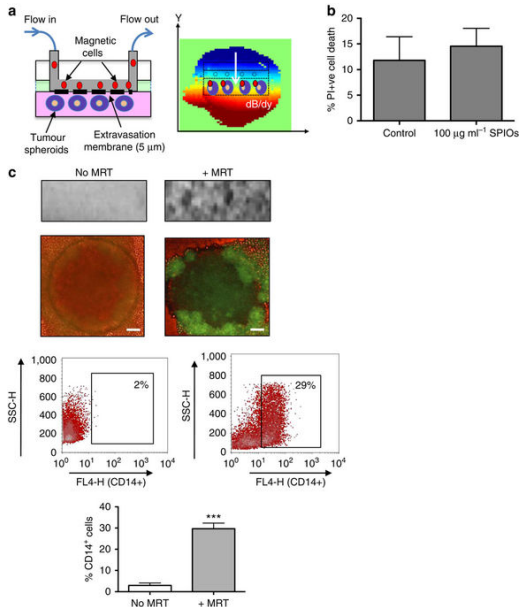
- ▶ in vivo (rat) using MR machine
- ▶ prove increased anti-tumour effects



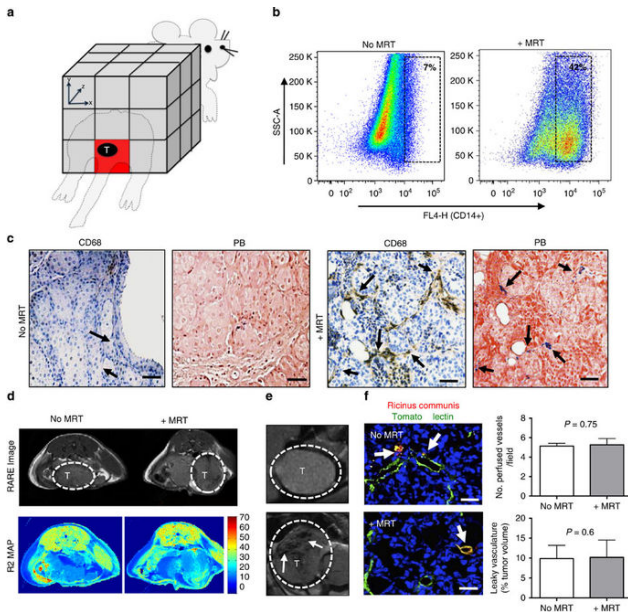
Methods - Magnetic Resonance Targetting of therapeutic cells



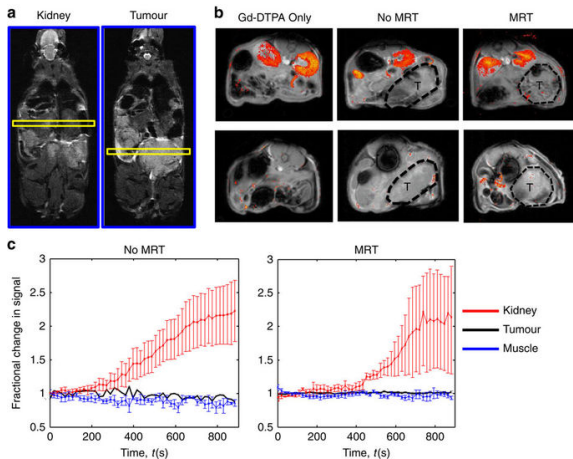
In vitro MRT of magnetised particles results in increased uptake in tumor model



In vivo MRT leads to increased uptake in tumor areas

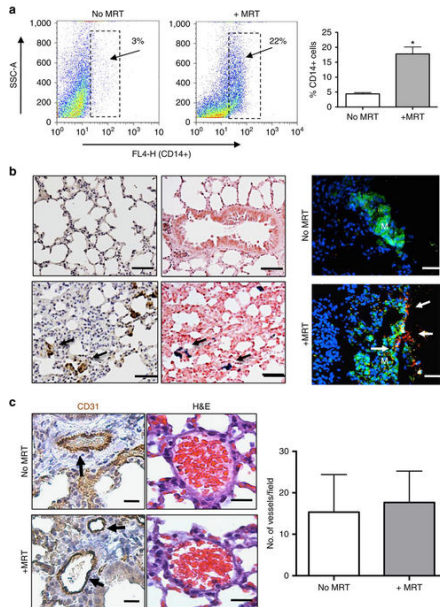


MRT does not affect the vasculature



Change in signal in kidney suggests vasculature remained intact

MRT can also steer macrophages into lung metastases



MRT increases anti-tumour effects of macrophages

