Nanomagnetism in Biology and Medicine

Quentin Pankhurst

Deputy Director

London Centre for Nanotechnology

Outline

- Basic concepts
- Current applications
  - *Magnetic separation, MRI contrast agents, targeted drug delivery, hyperthermia treatments*
- Near-future applications
  - *Biomagnetic imaging and diagnostics*
  - *Magnetic actuation*
- Conclusions and prospects

Summary

- Magnetic nanoparticles are routinely used for cell and protein purification, and as contrast agents in MRI scanners
- Trials are under way for more far-reaching applications, including drug delivery and hyperthermia treatments for tumours
- There are many more potentially life-saving and/or wealth-creating applications, both *in vitro* and *in vivo*
- Magnetic tweezers and biomagnetometers are at proof-of-concept stage, and there are opportunities for technology transfer

Basic concepts

Why magnetic nanoparticles are useful in bio applications:

- Their size is smaller than or comparable to
  - *a cell (10-100 μm)*
  - *a virus (20-450 nm)*
  - *a protein (5-50 nm)*
  - *a gene (2 nm wide and 10-100 nm long)*
- They can be manipulated by a magnetic field gradient
  - *action at a distance*
- They can resonantly respond to a time-varying field
  - *energy transfer*

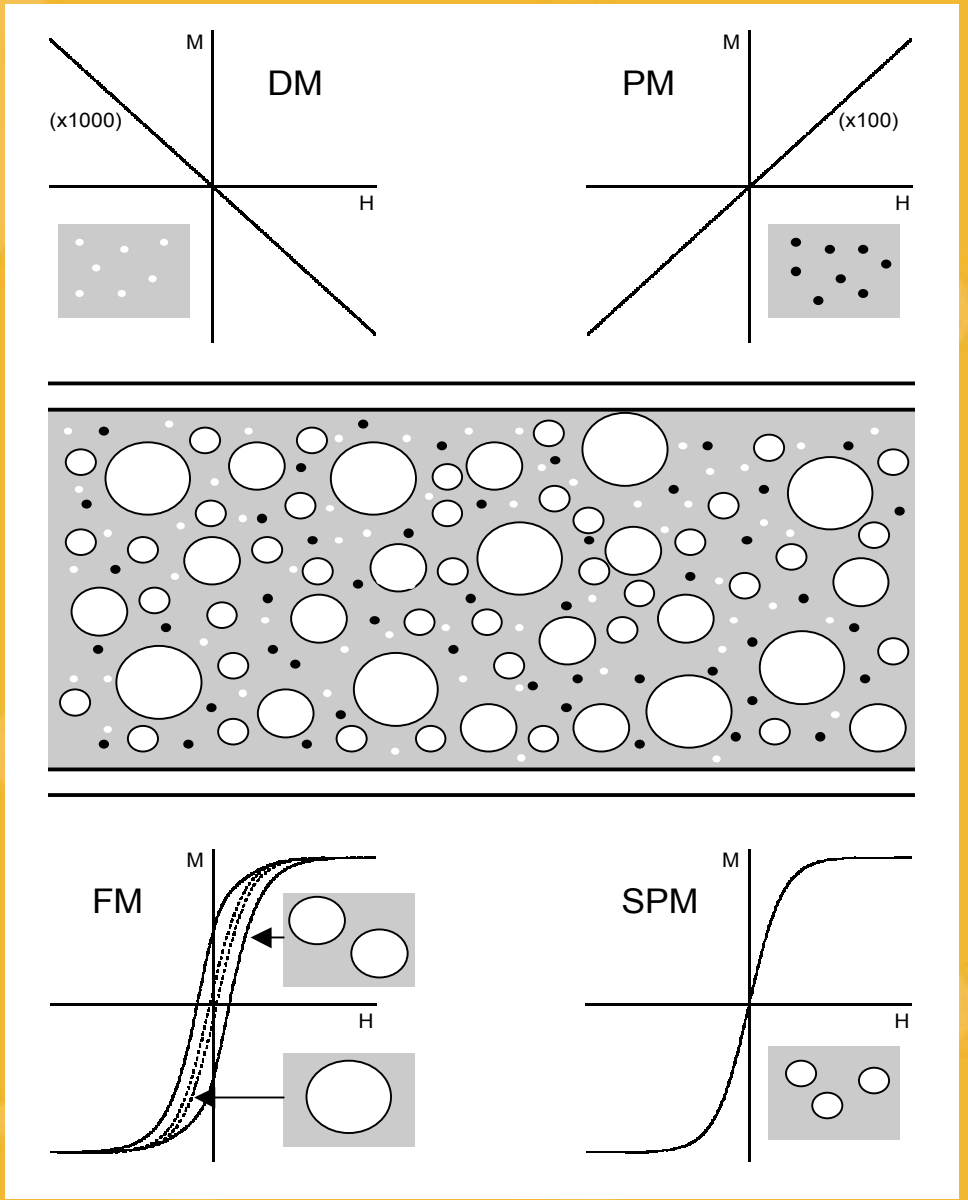
- M-H curves – hysteresis means *energy transfer*
- Magnetic field – gradient means forces and *action at a distance*

$$\boldsymbol{B} = \mu_o (\boldsymbol{H} + \boldsymbol{M})$$

$$\boldsymbol{M} = \chi \boldsymbol{H}$$

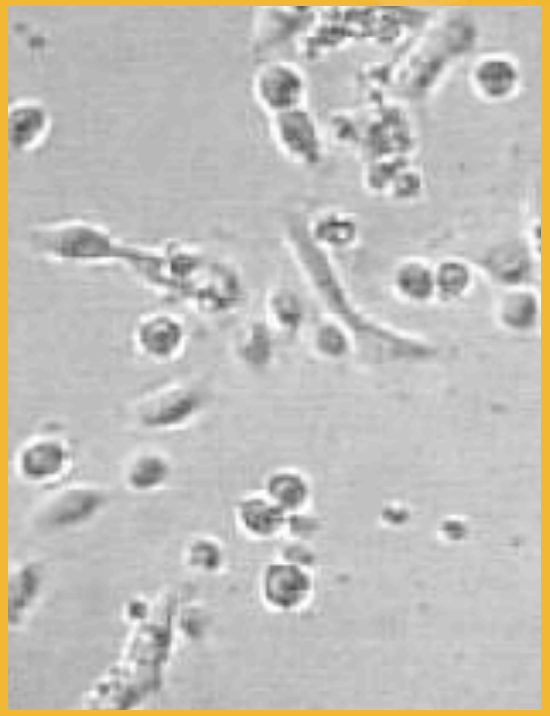
$$\boldsymbol{F}_m = (\boldsymbol{m} \cdot \nabla) \boldsymbol{B}$$

$$\boldsymbol{F}_m = V_m \Delta\chi \nabla (\tfrac{1}{2} \boldsymbol{B} \cdot \boldsymbol{H})$$

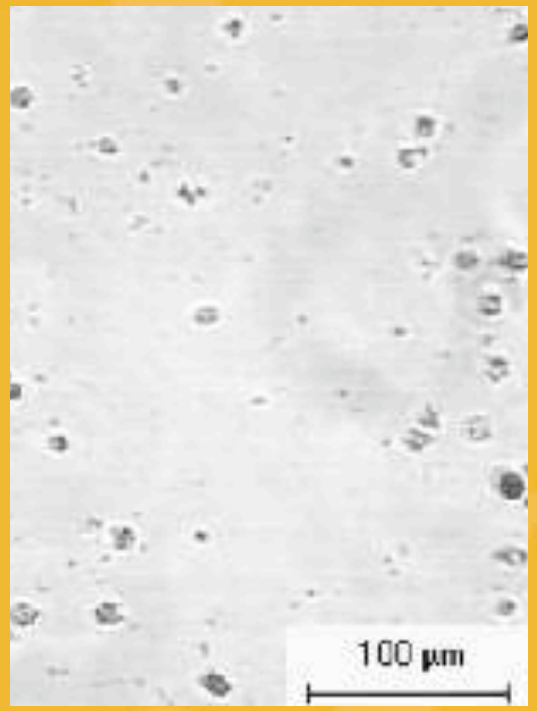


Biocompatibility

– *need to avoid toxicity of magnets that contain Fe, Co, Ni …*



before



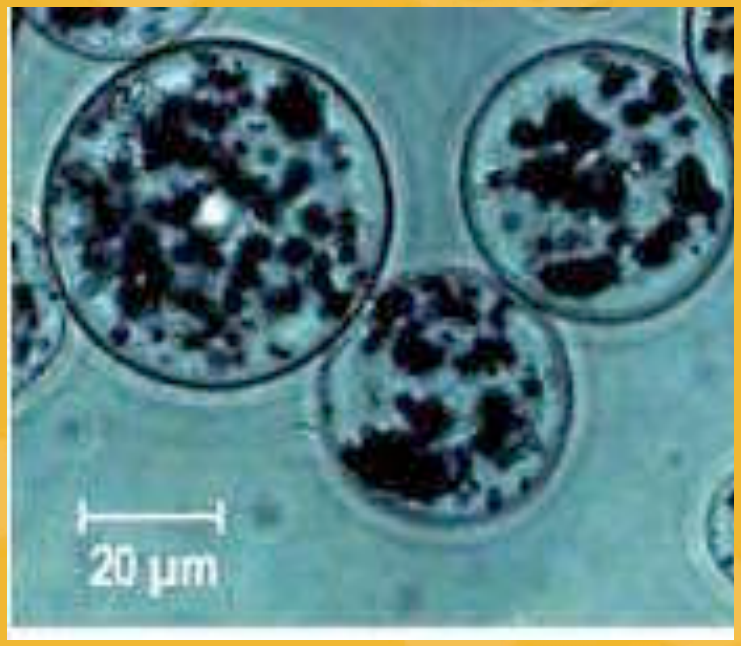
after

Treatment of human prostate cells with $FeCl_3$

Biocompatibility

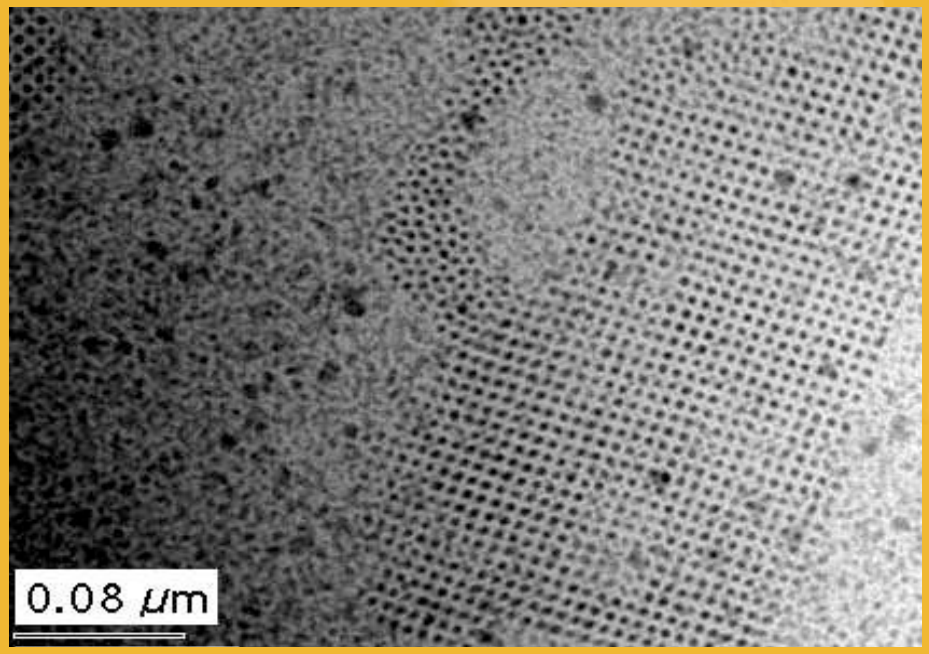
- *most of the current FDA approved (iron oxide or nickel) magnetic nanoparticles are encapsulated in dextran or agarose 'microbeads'*

Advanced Magnetics, USA	Combidex Endorem Feridex
Qiagen, USA	Ni-NTA
Miltenyi Biotec, Germany	MicroBeads
Micromod, Germany	Nanomag
Schering, Germany	Resovist

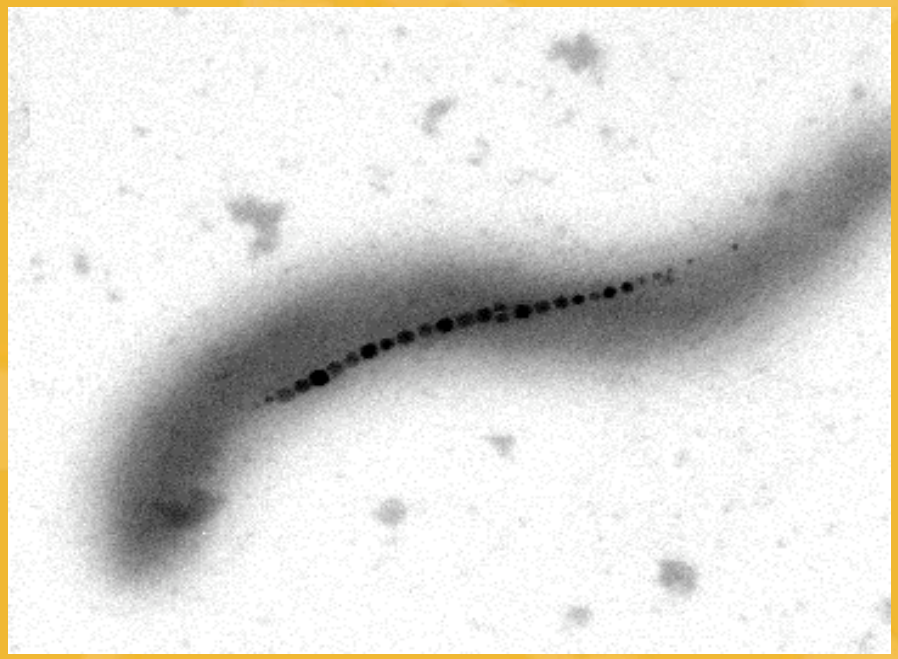


Biocompatibility

– *future trends …*



Co-Au core-shell –
Krishnan, Washington



Magnetosomes from bacteria –
Hergt, Jena

Current applications

Magnetic separation

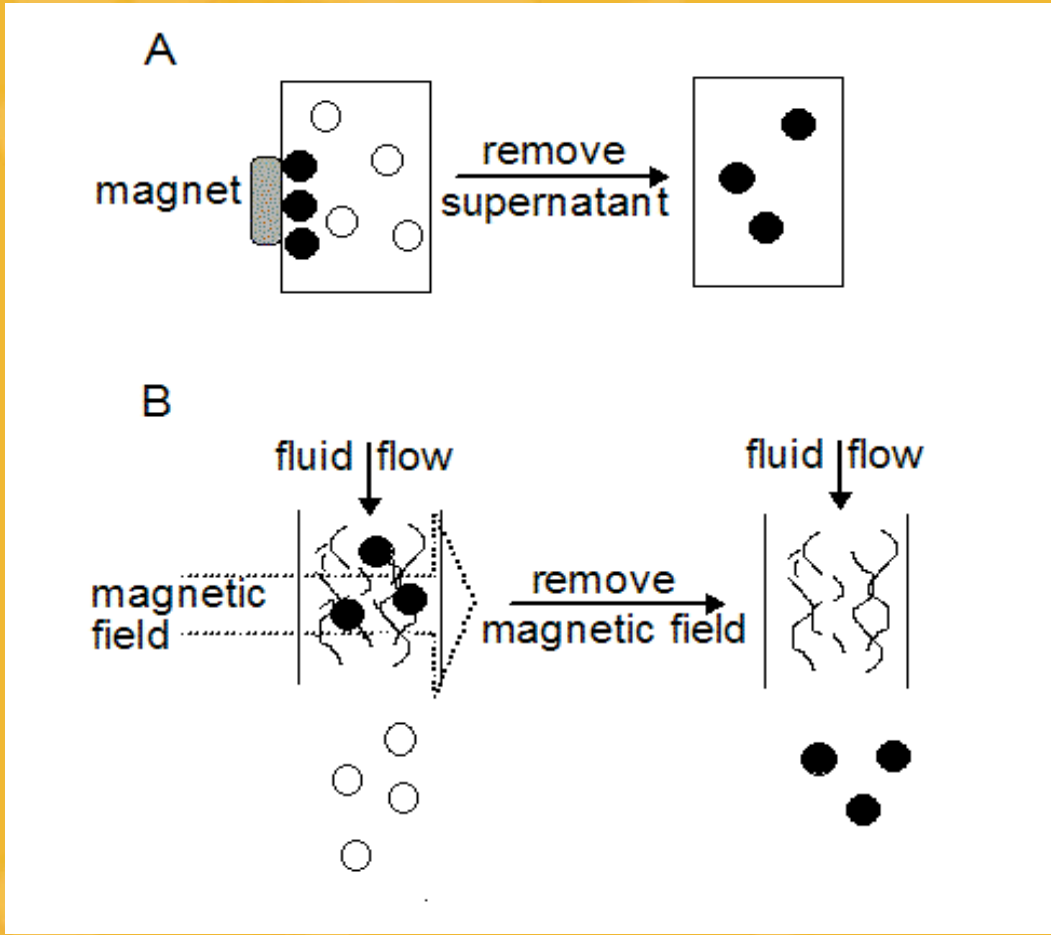
MRI contrast agents

Targeted drug delivery

Hyperthermia treatments

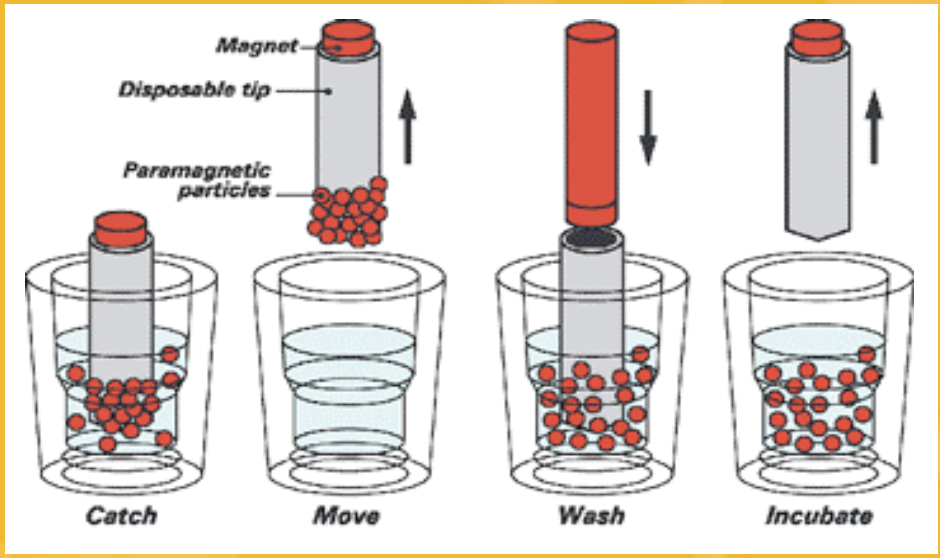
Magnetic separation:

- A route to concentrated samples
  - *tagging or labeling with magnetic material*
  - *separating out via fluid-based magnetic separation*



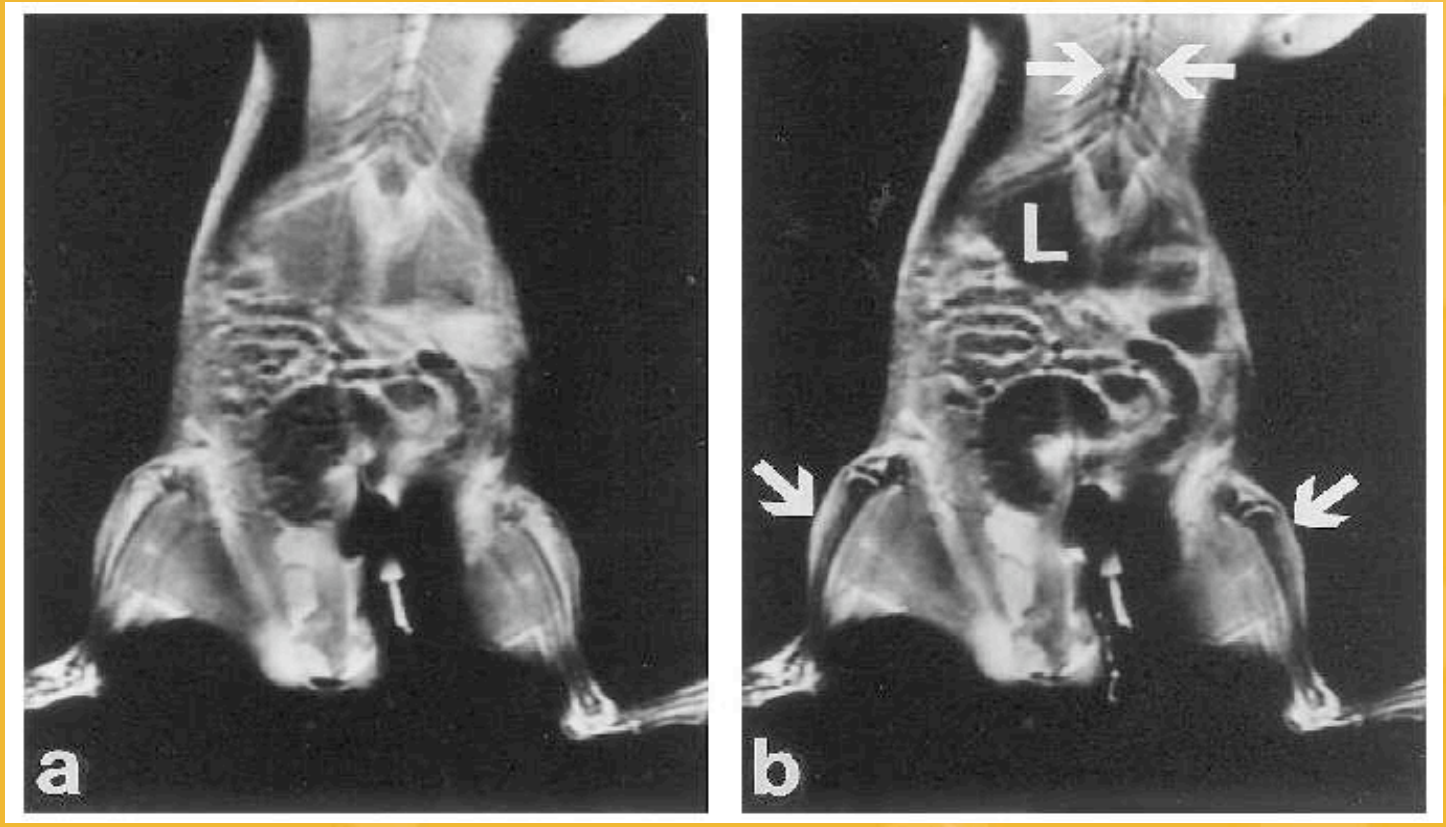
Magnetic separation:

- Thermo Labsystems' KingFisher magnetic separator
  - *'automated DNA purification'*



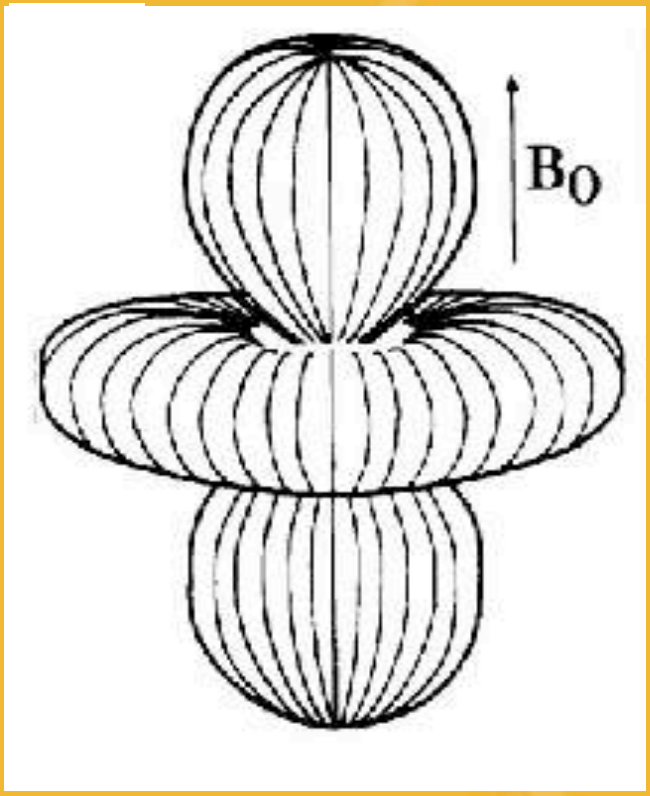
MRI contrast agents:

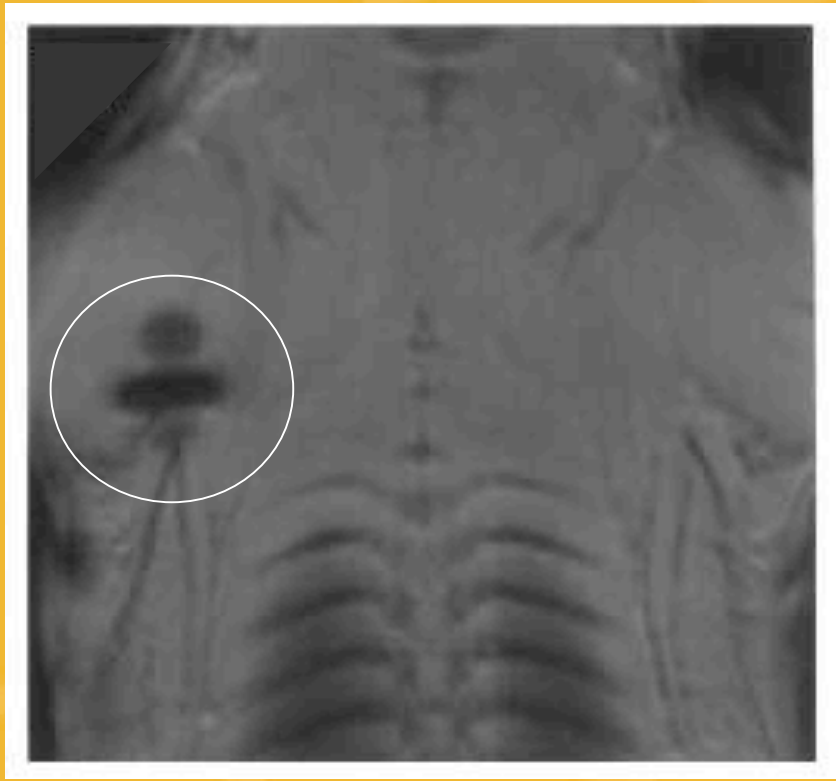
- Contrast enhancement for tissue mapping
  - *rat bone marrow uptake of magnetoliposome-PEG*



MRI contrast agents:

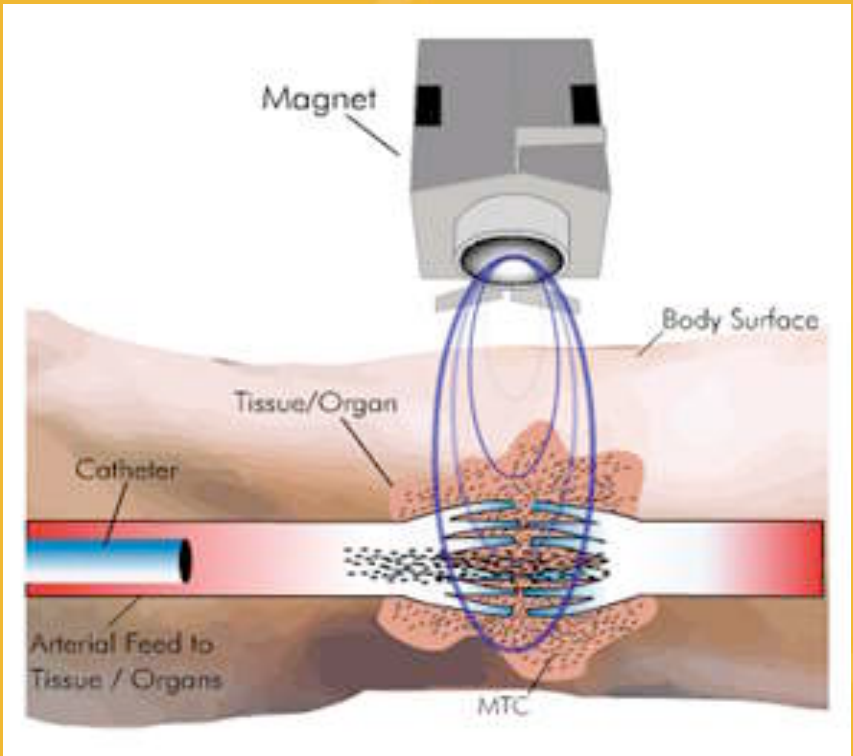
- Hypointensity artifacts in gradient echo MRI
  - *rat study of magnetic nanoparticles in left lymph node*





Targeted drug delivery:

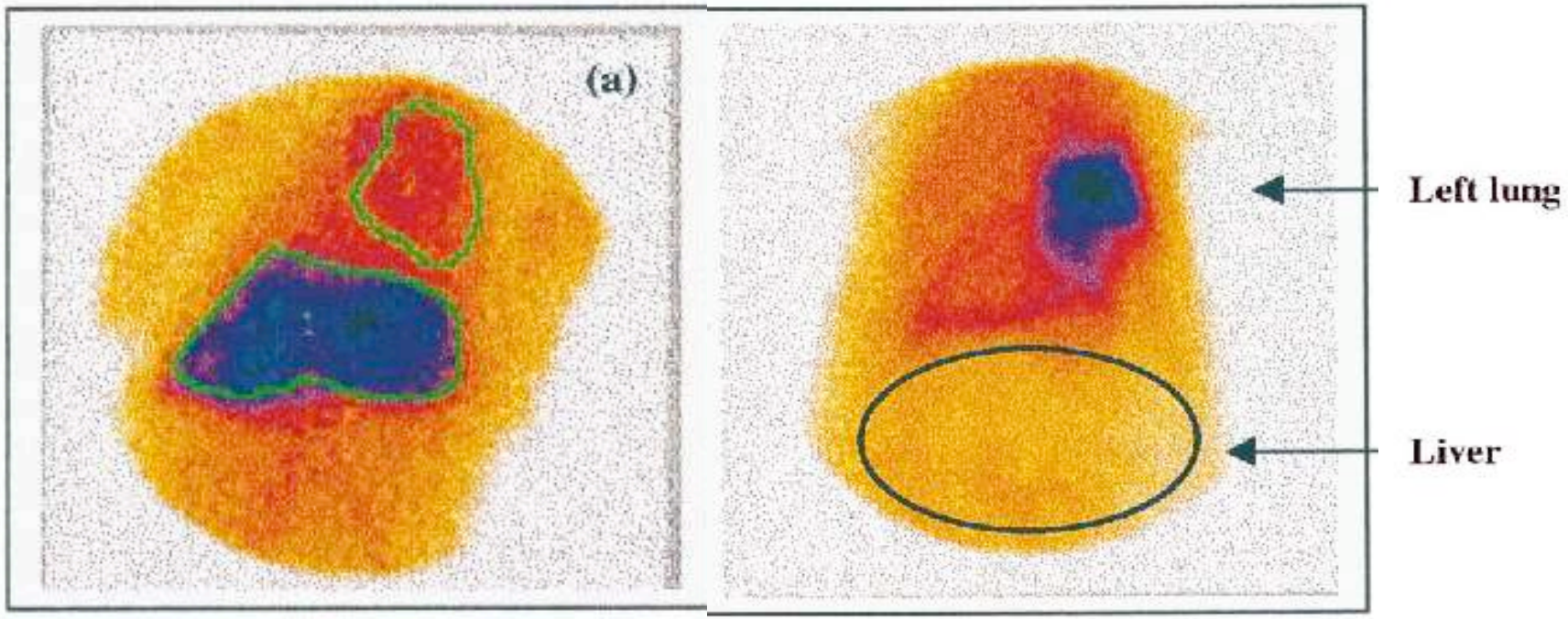
- Magnetic targeting and localisation
  - *reduce systemic distribution of drugs, with their side-effects*
  - *reduce the dosage required by localized targeting*



FeRx Inc.

Targeted drug delivery:

- Intra-arterial chemotherapy animal trials
  - *γ-camera images of swine 60 min after transfusion with ^{99m}Tc-MTC*



No magnet

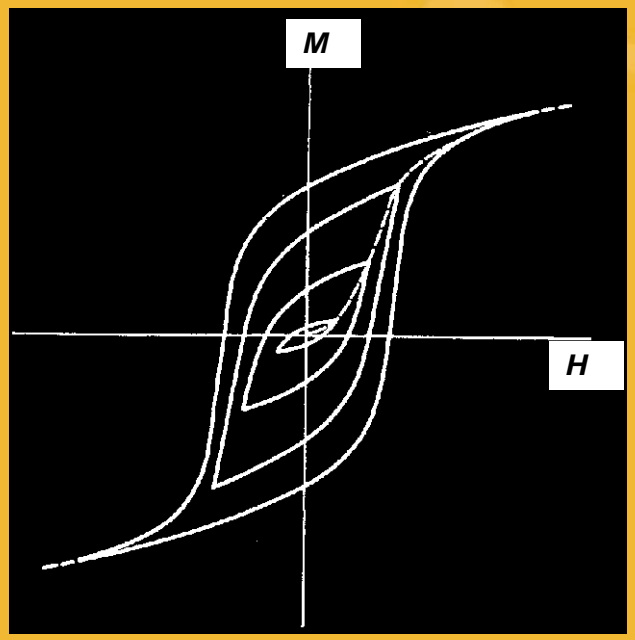
Magnet targeting left lung

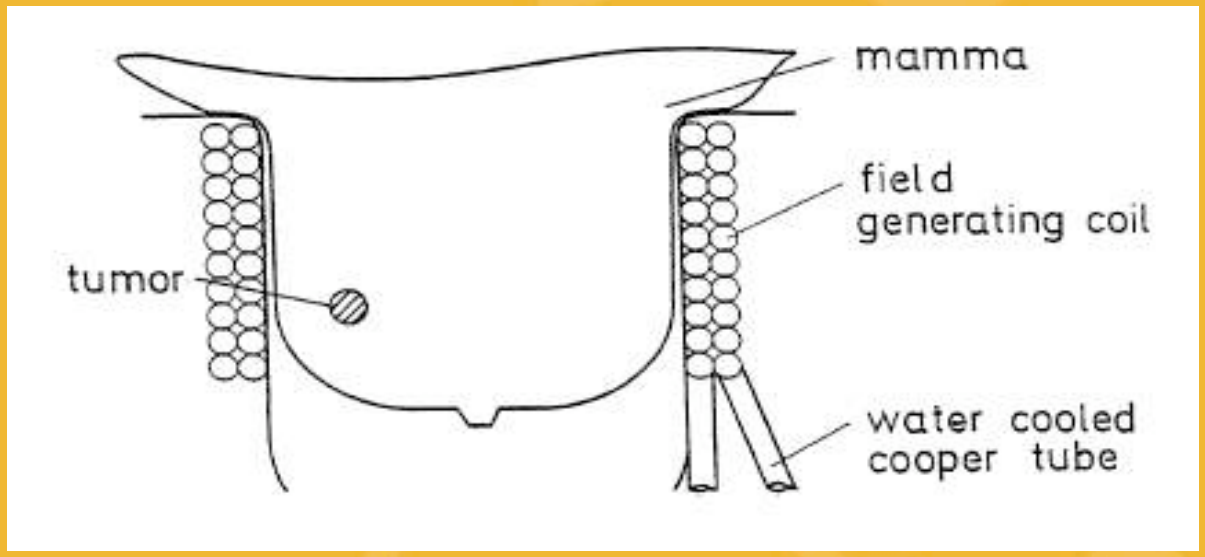
Targeted drug delivery:

- Clinical trials
  - *FeRx Inc. phase II/III trials started Jan02*
  - *1-2 μm Fe-loaded activated carbon microbeads*
  - *loaded with 20 wt.% doxorubicin for treatment of primary liver cancer (hepatocellular carcinoma)*
  - *5 kG field to localise*
  - *2 of 3 trials halted as no significant effect*
  - *third trial: 28 results to May04, median survival 63 weeks c.f. 43 weeks without targeting*

Hyperthermia treatments:

- Localised rf heating of tumour-injected magnetic particles





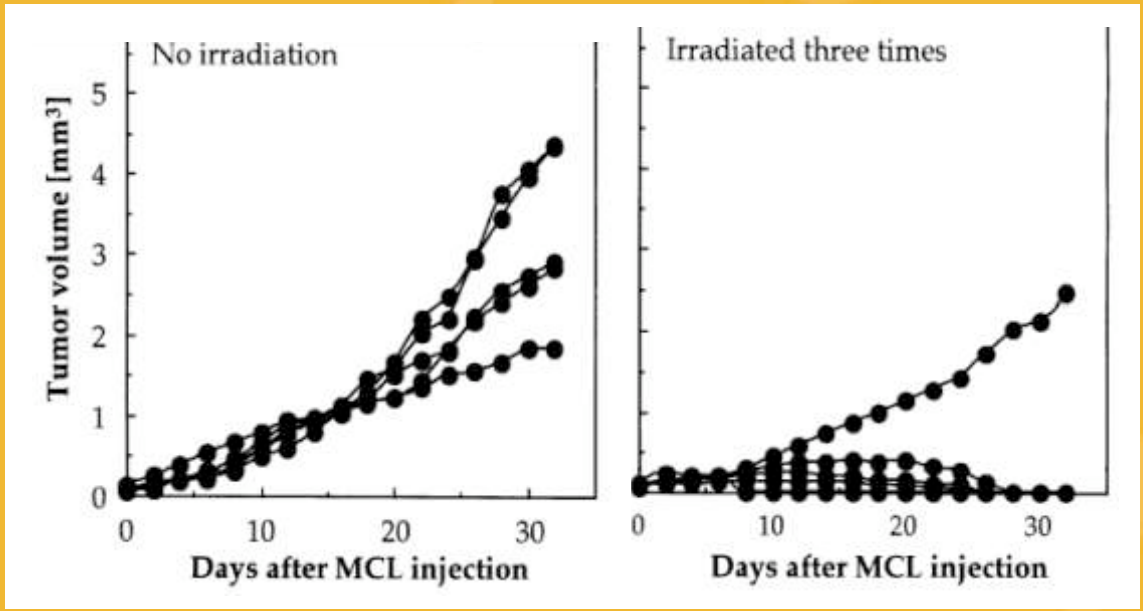
$$P_{FMP} = \mu_o \, f \oint H \, dM$$

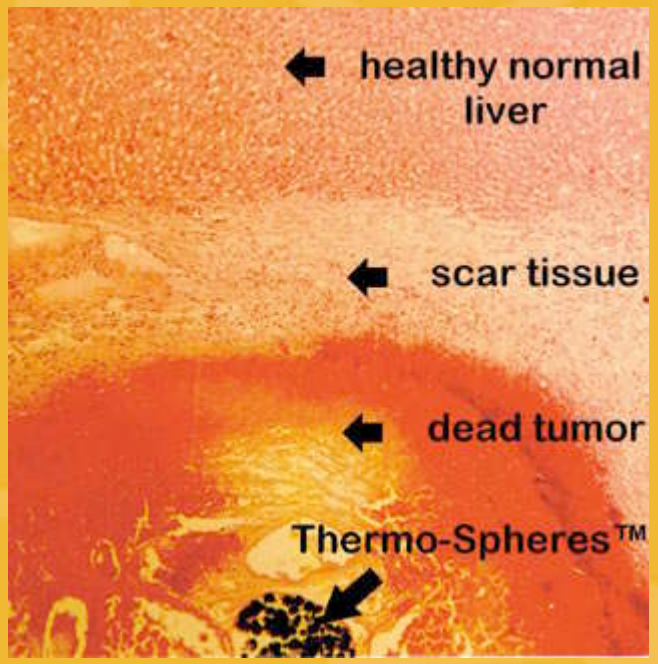
$$P_{SPP} = \mu_o \, \pi \, f \, \chi'' \, H^2$$

Schematic of breast carcinoma

Hyperthermia treatments:

- Promising results from animal trials





Sirtex Ltd.

Hyperthermia treatments:

- Clinical trials
  - *European Organization for Research and Treatment of Cancer, phase III trial*
  - *silane coated magnetite (Fe_3O_4) nanoparticles*
  - *direct injection into brain cancer (neurofibrosarcoma) tumours*
  - *200 G field at 100 kHz for 15 minutes to induce cell necrosis (45 °C)*
  - *12 patients treated to May04*
  - *mean survival 23 weeks c.f. 12 weeks without hyperthermia treatment*

Near-future applications

Biomagnetometry

Magnetic Actuation

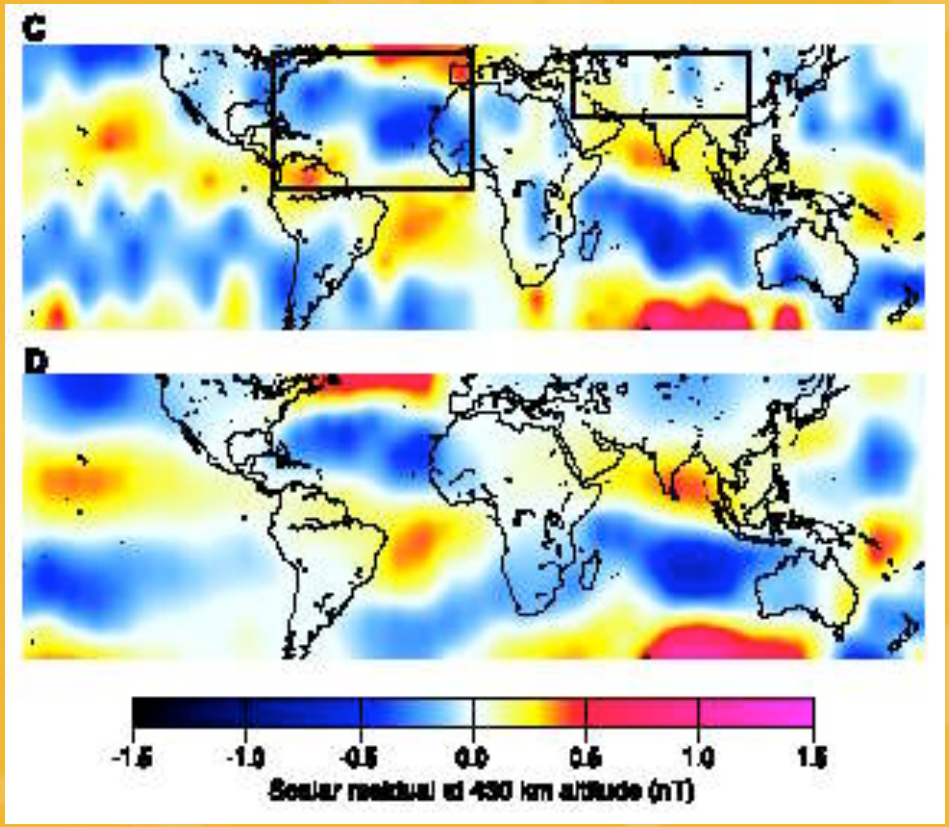
Biomagnetometry:

- Detecting and quantifying magnetic nanoparticles in vivo

Satellite Observations of Magnetic Fields Due to Ocean Tidal Flow

Robert H. Tyler,[1*] Stefan Maus,[2] Hermann Lühr[2]

Modern magnetic field sensors are incredibly sensitive



Biomagnetometry:

- The London-Houston biomagnetometer

  – *Combining* *(1) magnetic fingerprinting,*
  (2) magnetic field sensors and
  (3) magnetic biomarkers

  – *A range of diagnostic instruments to detect magnetic material*

  – *Examples:*
  tagged cancer cells or tumours
  iron overload diseases
  pharmacokinetics

Biomagnetometry:

- Potential for pharmacokinetics

Nanoparticles illuminate brain tumors for days under MRI

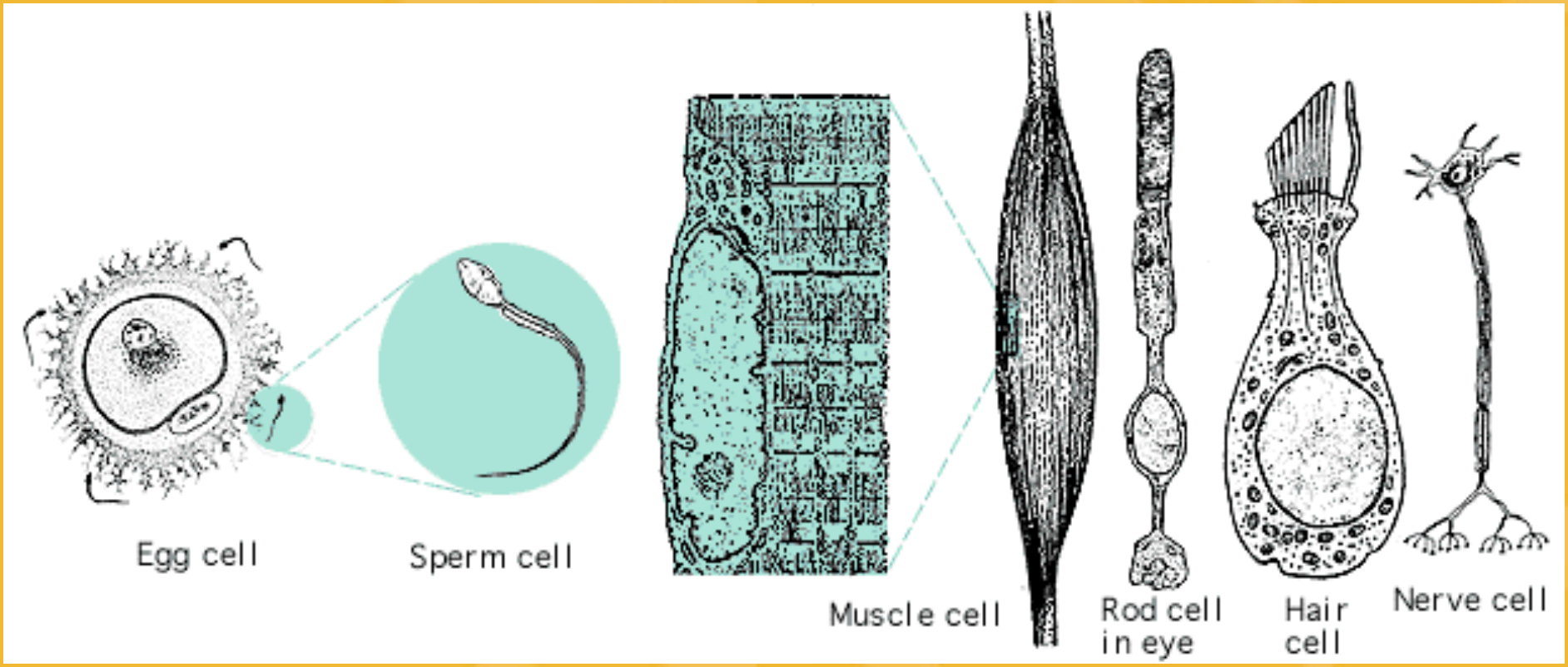
PORTLAND, Ore. - A research team from Oregon Health & Science University and the Portland Veterans Affairs Medical Center is demonstrating some of the world's first clinical applications for nanometer-size particles in the brain.

The OHSU scientists have shown that an iron oxide nanoparticle as small as a virus can outline not only brain tumors under magnetic resonance imaging, but also other lesions in the brain that may otherwise have gone unnoticed, according to a study published in the journal Neuropathology and Applied Neurobiology.

The iron oxide nanoparticle, ferumoxtran-10, can be viewed as a contrast agent under MR for more than 24 hours, sometimes as long as five days, said the study's lead author, Edward Neuwelt, M.D., professor of neurology and neurological surgery, OHSU School of Medicine, and the Portland VA Medical Center.

Magnetic actuation:

- Probing cellular function

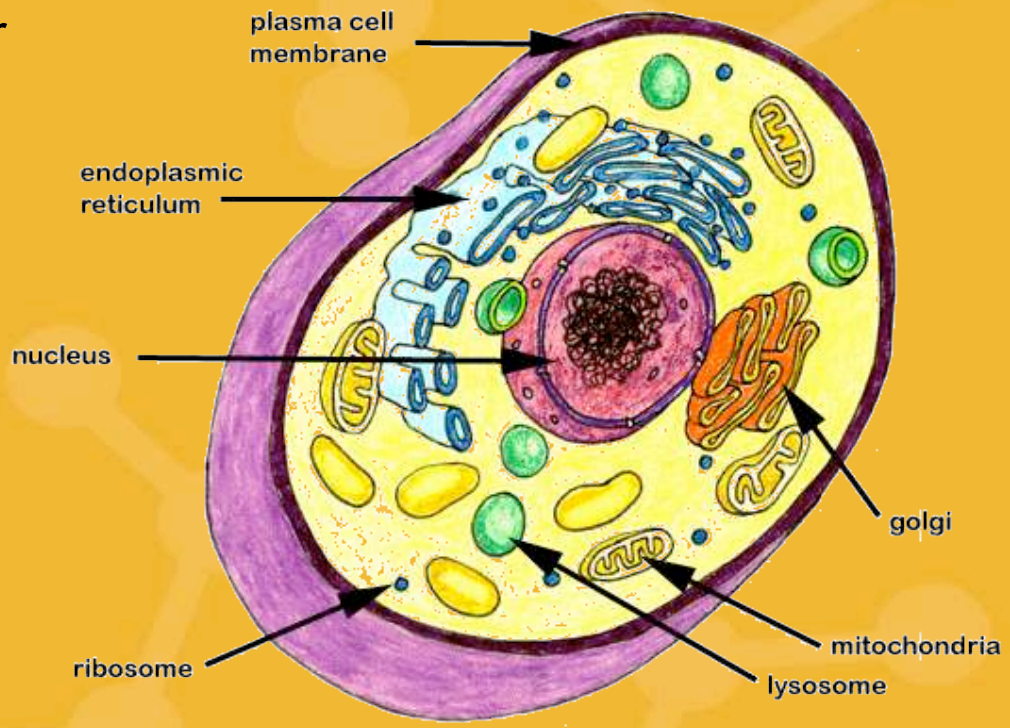


Magnetic actuation:

- Underlying concepts

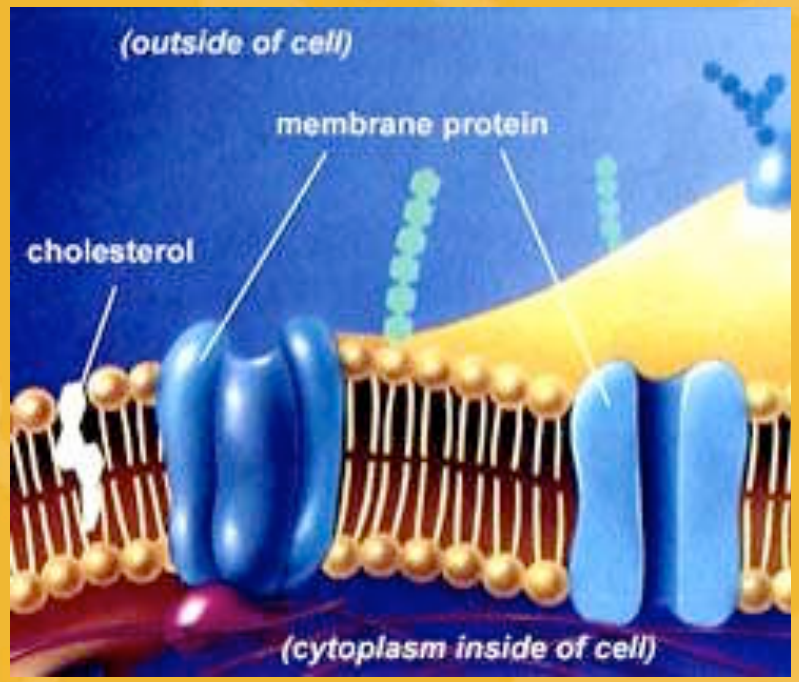
  – *Many biological processes occur in macromolecular complexes in the cell or at the plasma membrane.*

  – *By manipulating the position or activity of these complexes, we can control cell behaviour.*



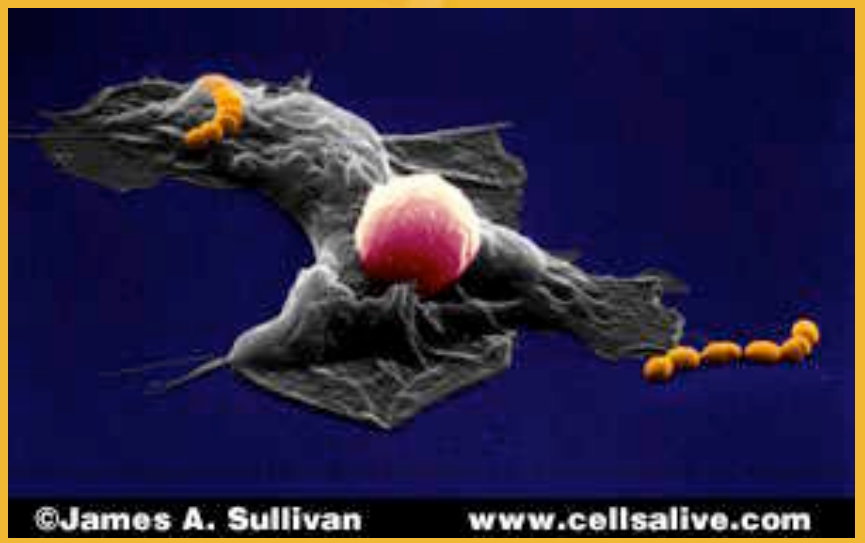
Magnetic actuation:

- Underlying concepts
  - *Magnetic nanoparticles can be coated with derivatised linker molecules that bind to selected bioactive molecules such as drugs, peptides, or proteins.*
  - *By manipulating these magnetically tagged molecules at the cell surface or within cells it would be possible to locally activate cell processes and cell signalling*

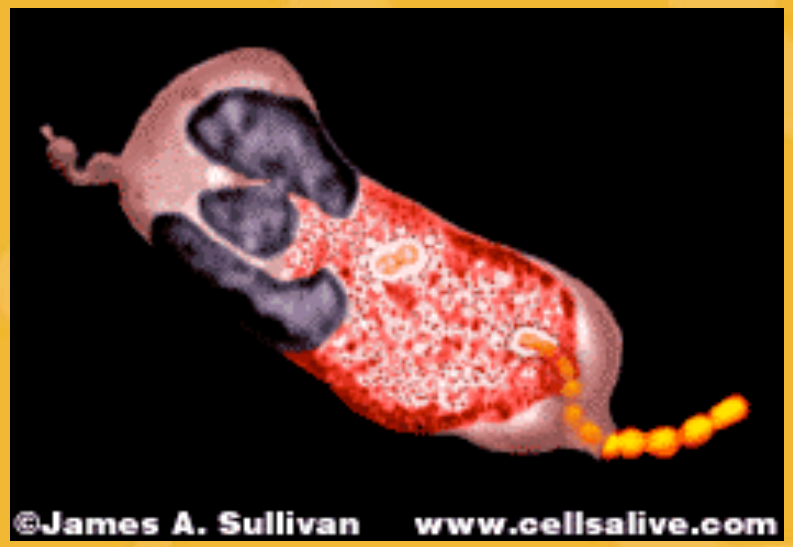


Magnetic actuation:

- Potential for more effective pharmacology
  - *probing drug delivery, specificity, functionality, effectiveness and kinetics at the cellular and sub-cellular level*



Human macrophage



White blood cell

Conclusions and Prospects

- Some biomedical applications are routine
  - *magnetic separation via cell and protein labelling*
  - *MRI contrast enhancement*
- Others are undergoing clinical trials with promising results
  - *targeted drug delivery*
  - *hyperthermia treatment of solid tumours*
- Others are at the proof-of-concept demonstrator phase
  - *magnetic tweezers*
  - *London-Houston biomagnetometer*
- There are many commercial opportunities in this field
  - *in vitro, as well as in vivo, in animals as well as humans*

BIOGENIC MAGNETITE PARTICLES IN ALZHEIMER'S DISEASE BRAIN TISSUE

Quentin Pankhurst

London Centre for Nanotechnology

ACKNOWLEDGEMENTS

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Gill Bates, Ben Woodman – Guy's Hospital

Jon Dobson – Keele

Andy Curtis, Chris Morris, John Burn – Newcastle

SUMMARY

Alzheimer's disease (AD) is the most common form of senile dementia, affecting millions of people across the world every year

After correcting for longevity, 60% of AD sufferers are women and 40% are men – the origin of this gender difference is not known

Tiny magnetic particles are present in all human brains, at very low levels, which we can measure using new methods

In our study we found that two-thirds of the women suffering from AD had abnormally large levels of magnetic particles in their brains

This draws attention to the role of iron in AD, and offers a potential diagnostic role for MRI brain scans

INTRODUCTION

Our hypothesis is:

'that the presence of magnetic biominerals in the brain can provide a diagnostic indicator of neurological diseases'

Our approach is:

To locate and characterise the magnetic material:

Established* – *histopathology (sectioning, staining, microscopy)

Current* – *in vitro SQUID magnetometry

Future?* – *in vivo magnetic resonance imaging (MRI)

or magneto-encephalography (MEG)

Our immediate goal is:

to establish whether magnetic materials are present in abnormal concentrations using *in vitro* SQUID magnetometry

HISTOPATHOLOGY

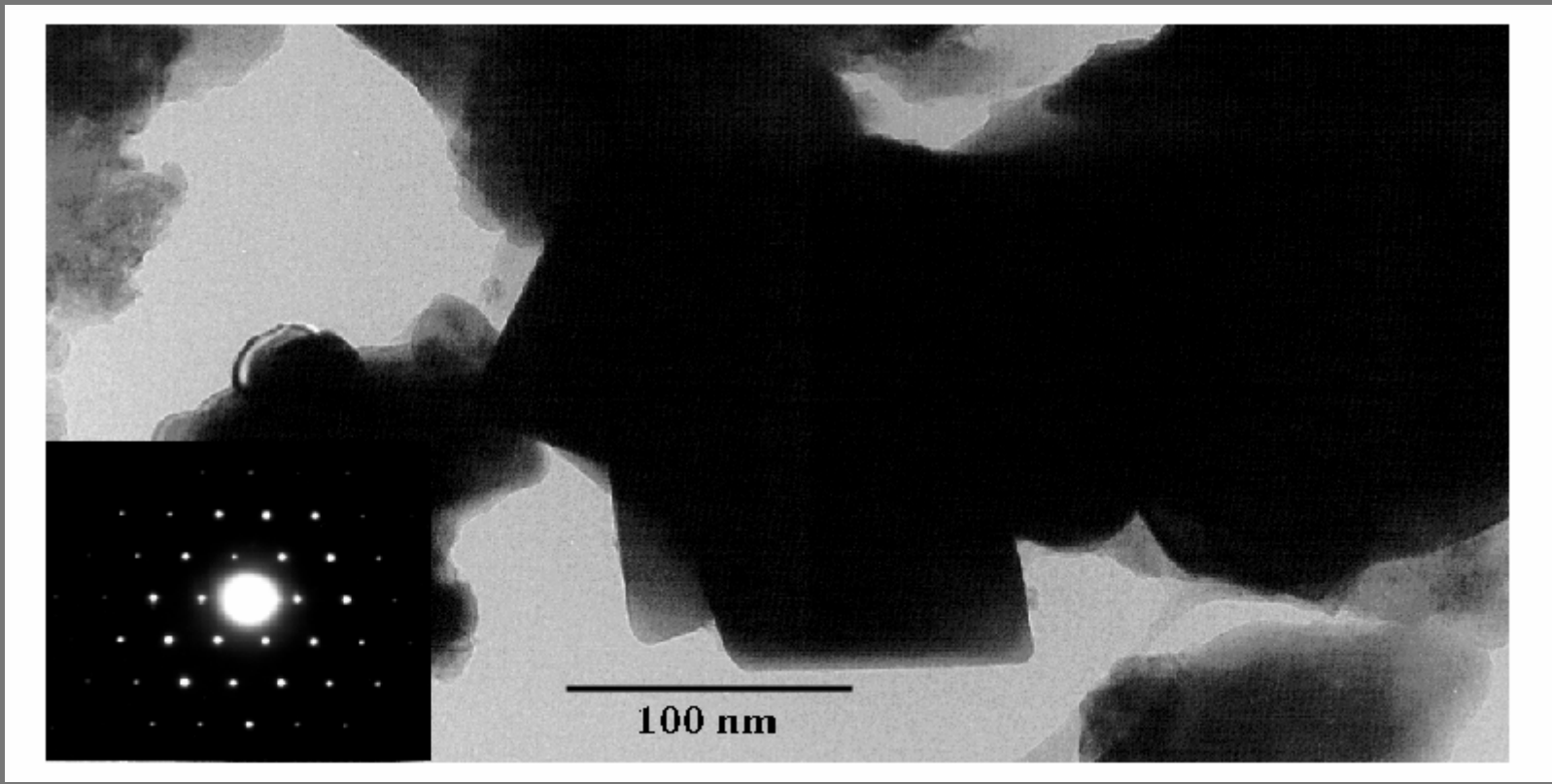
- **Perls' stain for iron in an AD shows an association of iron with the neurofibrillary tangles and plaques that characterise AD.**

AD (superior temporal gyrus)

Control

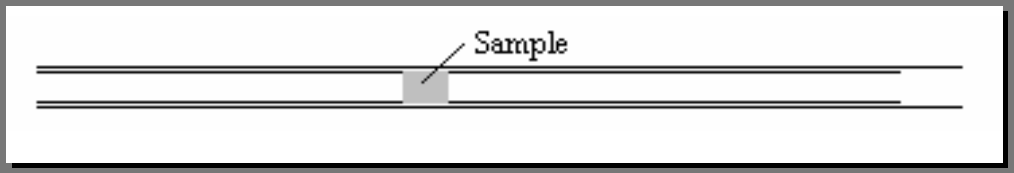
MAGNETIC EXTRACTION

- Recent work on magnetic extractions from the human hippocampus shows up magnetite/maghemite nanocrystals.



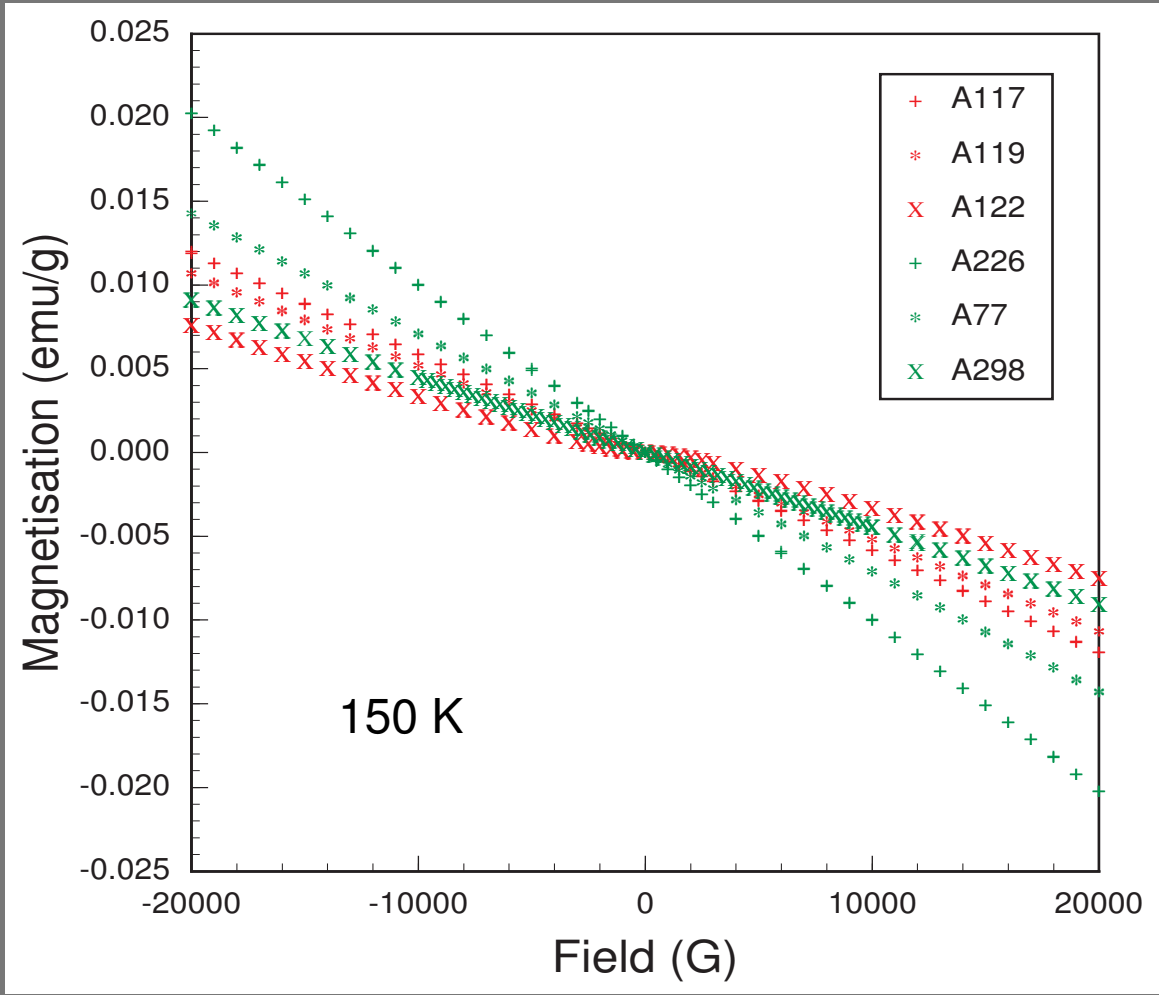
SQUID MAGNETOMETRY

- Superior temporal gyrus samples, preserved by freezing at -80 °C, ca. 1 gram by weight, supplied by MRC London Brain Bank.
  - *First cohort: six samples, all female.*
  - *Second cohort: twenty samples, ten male, ten female.*
- Tissues very dilute – ca. 200 ng/g magnetic material.
  - *Measure using an ultra-sensitive superconducting quantum interference device (SQUID) magnetometer.*
  - *Months of testing to arrive at a reliable measurement protocol.*



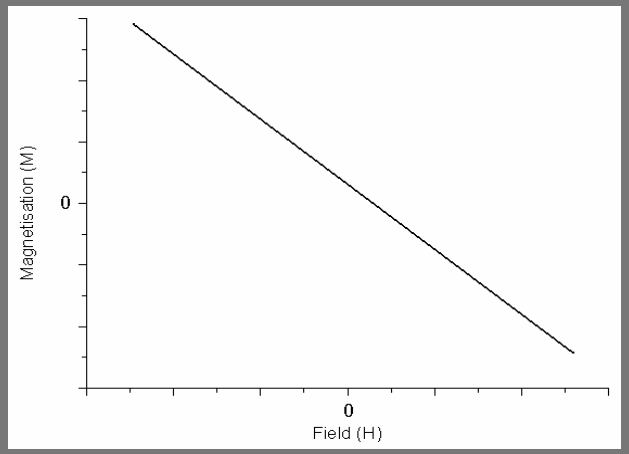
SQUID MAGNETOMETRY

- M-H curves dominated by the diamagnetic response of the tissue.



SQUID MAGNETOMETRY

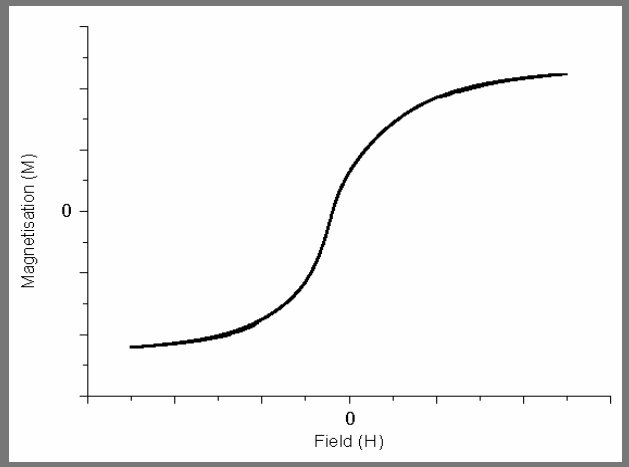
- **Model the M-H curves as a sum of three magnetic contributions.**



Diamagnetic tissue

linear, negative slope

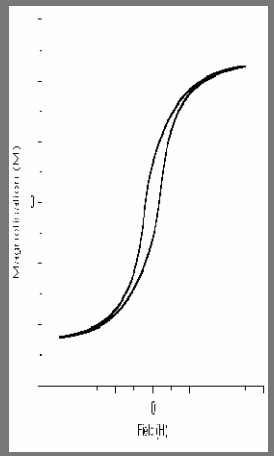
+



Superparamagnetic ferritin

constrained to that of human spleen ferritin

+

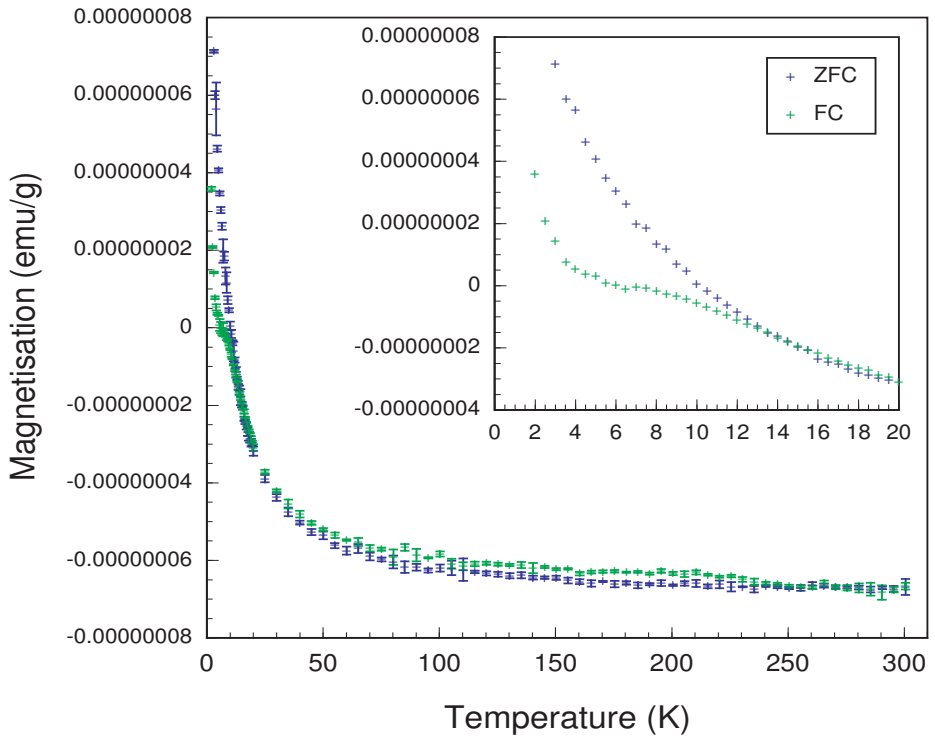


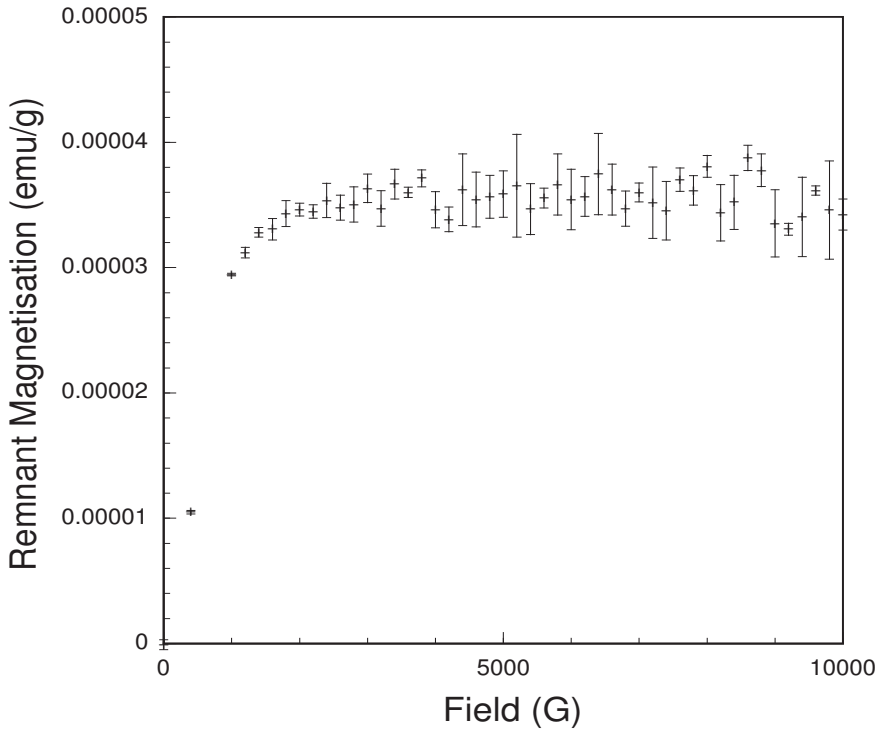
Ferrimagnetic magnetite

fitted, ignoring the small coercivity

SQUID MAGNETOMETRY

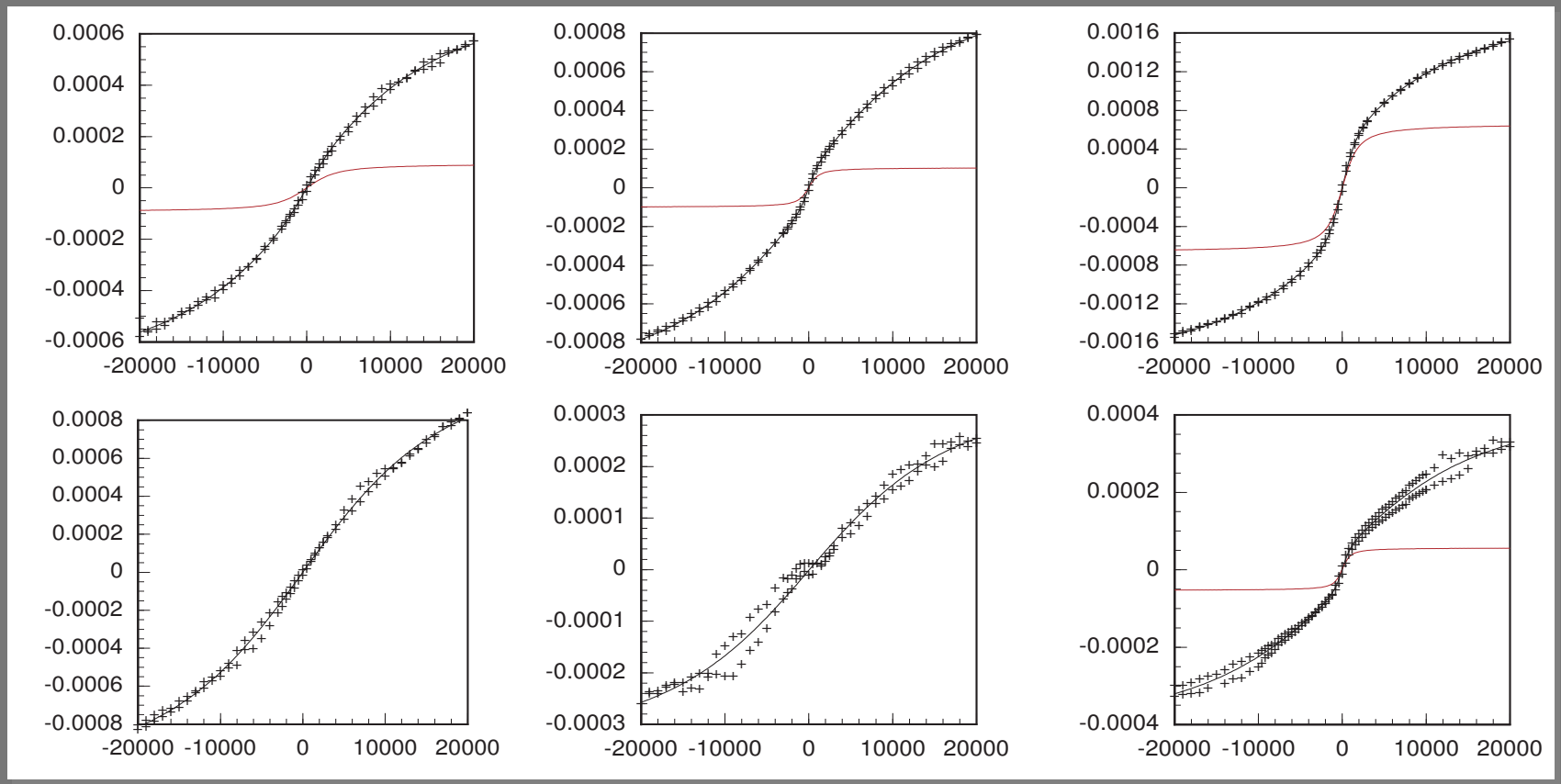
- M(T) shows a ferrihydrite blocking transition at 12 K.
- IRM shows the presence of magnetite and/or maghemite.





SQUID MAGNETOMETRY

- **Extracted M-H curves – fitted as ferritin plus magnetite.**



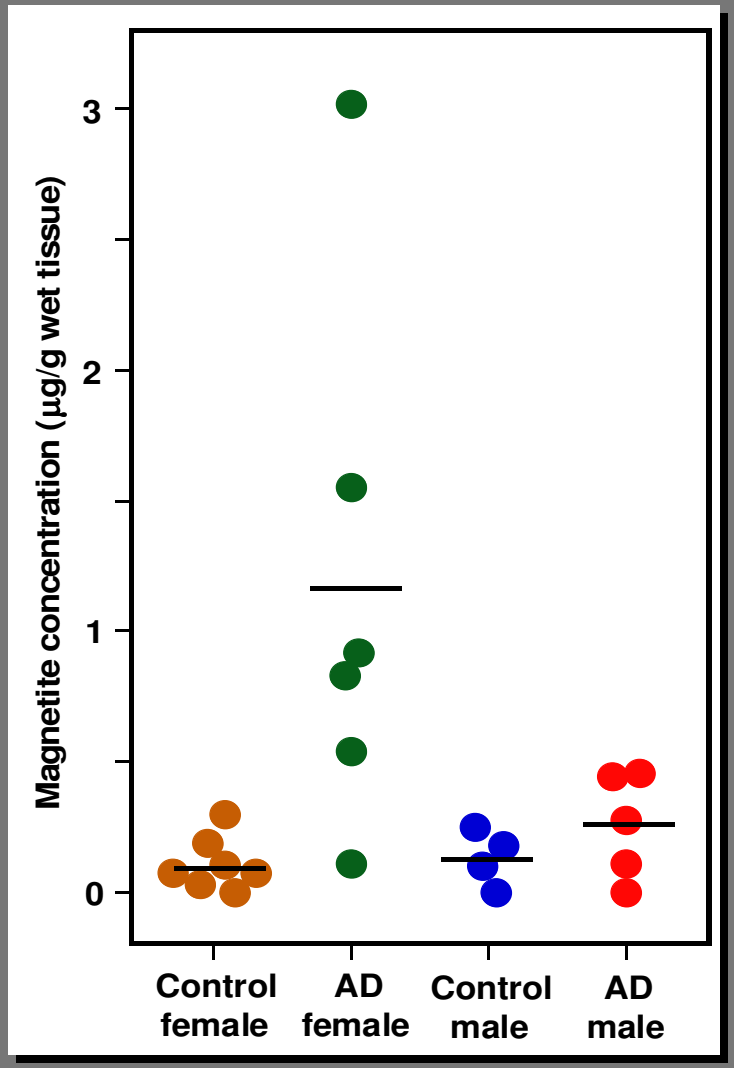
SQUID MAGNETOMETRY

- Even without case-by-case scrutiny, AD females clearly have more magnetite/maghemite than the others.

- Statistical analysis:
Mann-Whitney rank sum test.

- No differences between AD and control males, p = 0.286, nor between the male and female controls, p = 0.788.

- Significant differences between AD and control females, p = 0.005, and between the male and female AD subjects, p = 0.030.

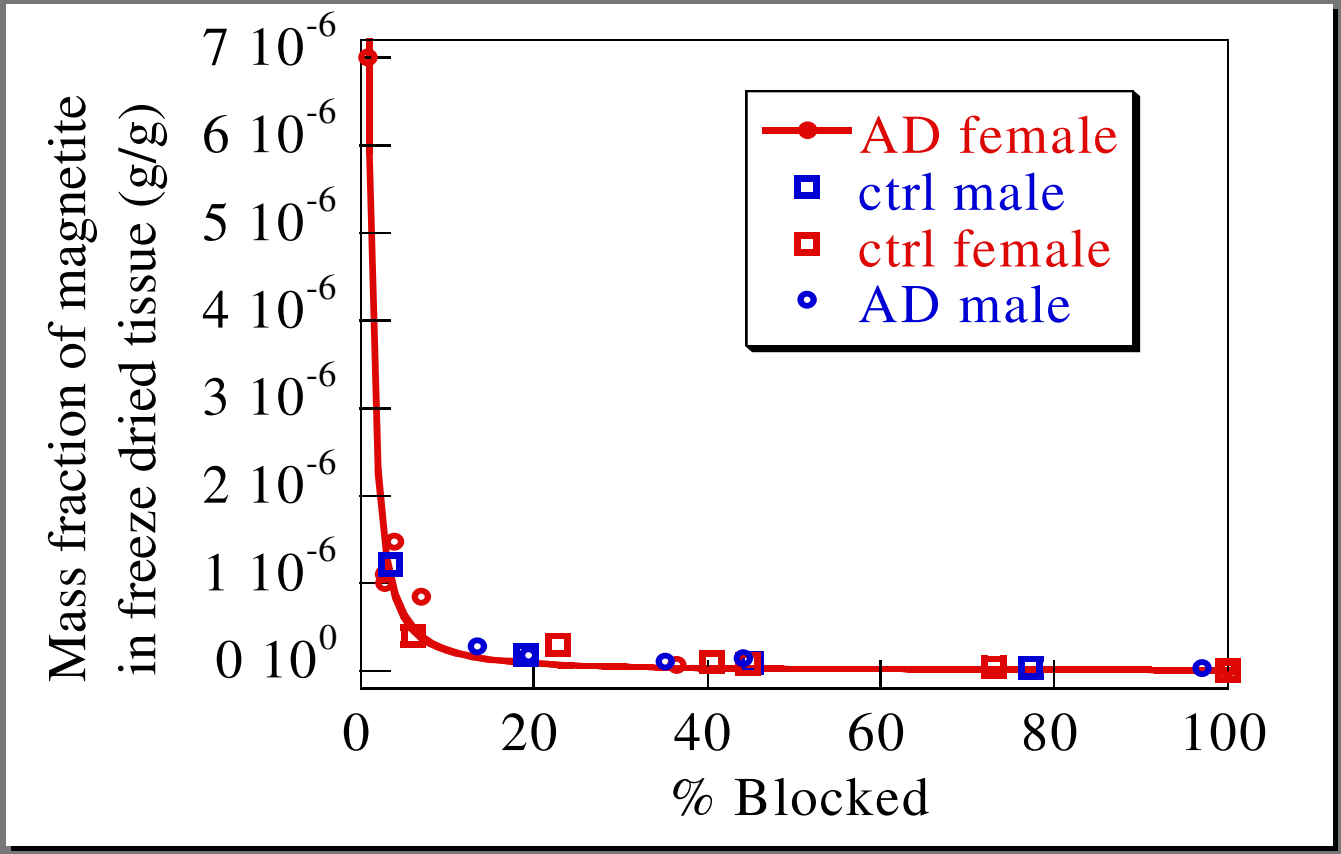


WHAT THIS MEANS

- There is a measurable and quantifiable differentiation between the pathogenesis of AD in men and women.
- There is a potential role for disrupted iron homeostasis in AD.
- There is support for the hypothesis that a malfunction in the iron biomineralisation cycle undertaken by the iron storage protein ferritin may be a significant factor in AD pathogenesis.

SQUID MAGNETOMETRY

- Across all tissue samples – male, female, AD and controls – see a correlation between the total magnetite concentration and the percentage of magnetite that is nanoscale i.e. < 50 nm in size.

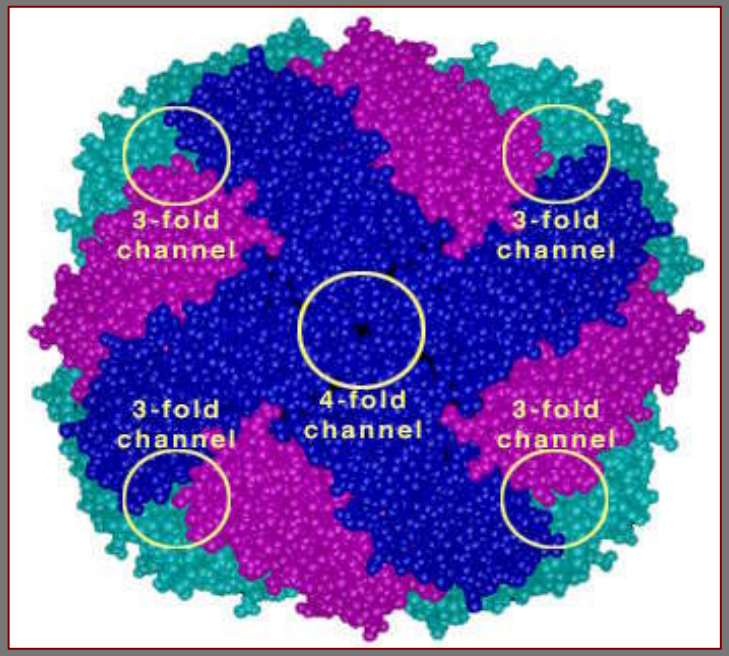


WHAT THIS MEANS

- **A possible answer to a 50 year old conundrum: why does the iron content increase in diseased tissue whereas the amount of ferritin does not?**

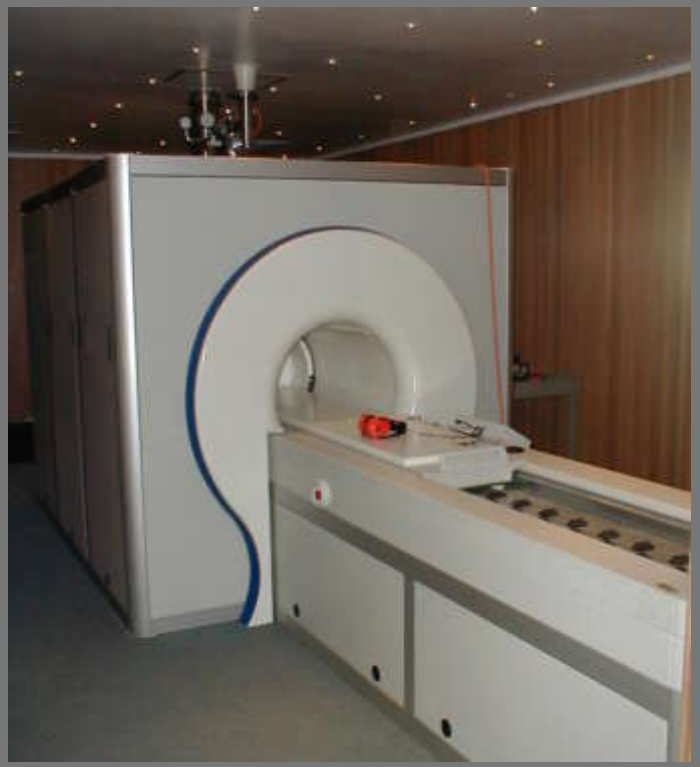
  - ***Propose the accelerated growth of nanoscale magnetite***

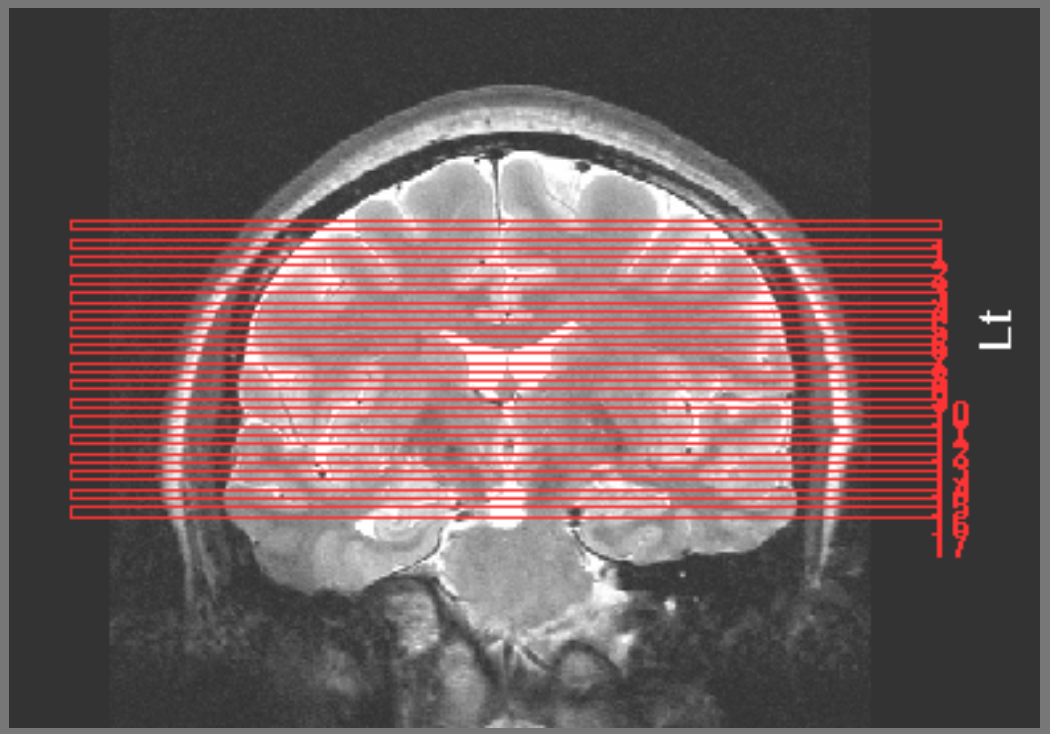
  - ***Conversion of the 8 nm sized ferrihydrite cores of the storage ferritin***



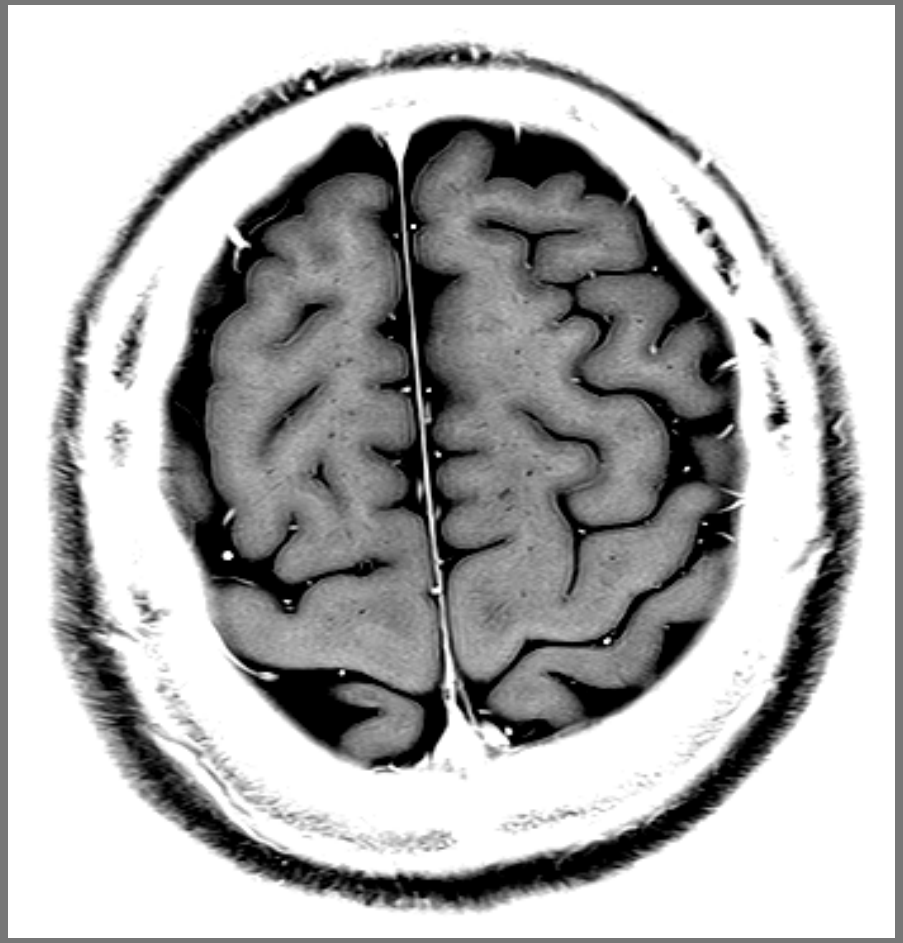
MRI SCANS

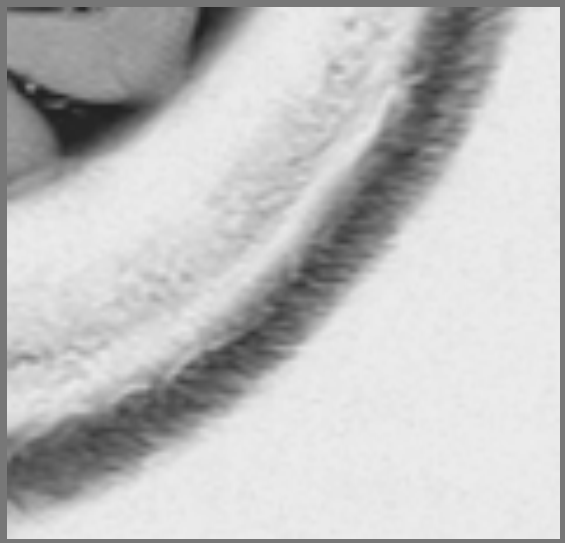
- New 4.7 T, 90 cm bore fast spin echo system at UCL.
  - *Resolution: 400 microns x 500 microns.*
  - *Relaxation Parameters: TE = 66 ms, TR = 3.5 s.*
  - *Scan Time: 17 slices (2 mm thick) in 6 minutes.*





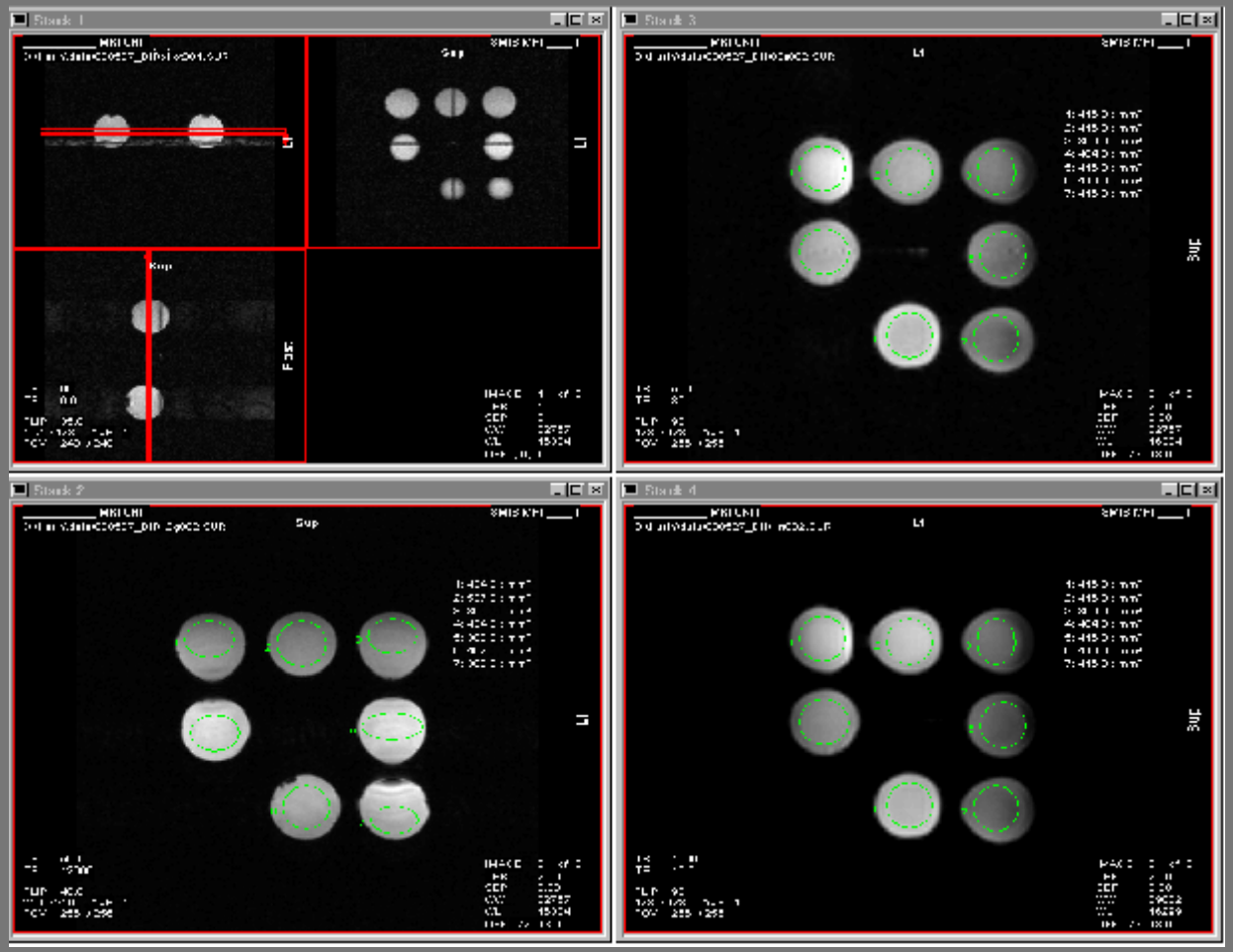
MRI SCANS





MRI SCANS

- We have started tests with ping-pong balls filled with different concentrations of water and ferritin.



CONCLUSIONS

- **Alzheimer's disease:**
  - *we find a measurable, statistically significant difference between magnetic nanoparticles in AD men and women*
  - *we propose an accelerated growth of nanoscale magnetite and/or maghemite in ferritin, and an increase in iron loading*

- **Further work:**
  - *further work on HD transgenic mice*
  - *continuing MRI studies*
  - *much more to learn from cross-disciplinary communicating*

FINAL THOUGHTS

- **So what have we learned?**

  - that biogenic magnetism is worth paying attention to, and may be an important clue to iron metabolisation malfunctions in the body

- **What is the scope for medical improvements?**

  - there may be diagnostic or even therapeutic implications, as evidenced by recent work on vitamins for AD treatment

- **What else is there to do?**

  - we have barely scratched the surface: there have been very few studies of biogenic magnetism

  - what happens to the ferritin in the liver, spleen or blood?

  - do anaemia sufferers get AD?