

Biomedical Applications of Magnetic Nanoparticles

Quentin Pankhurst

Healthcare Biomagnetics Laboratory
University College London

UCL HEALTHCARE BIOMAGNETICS LABORATORY



UCL

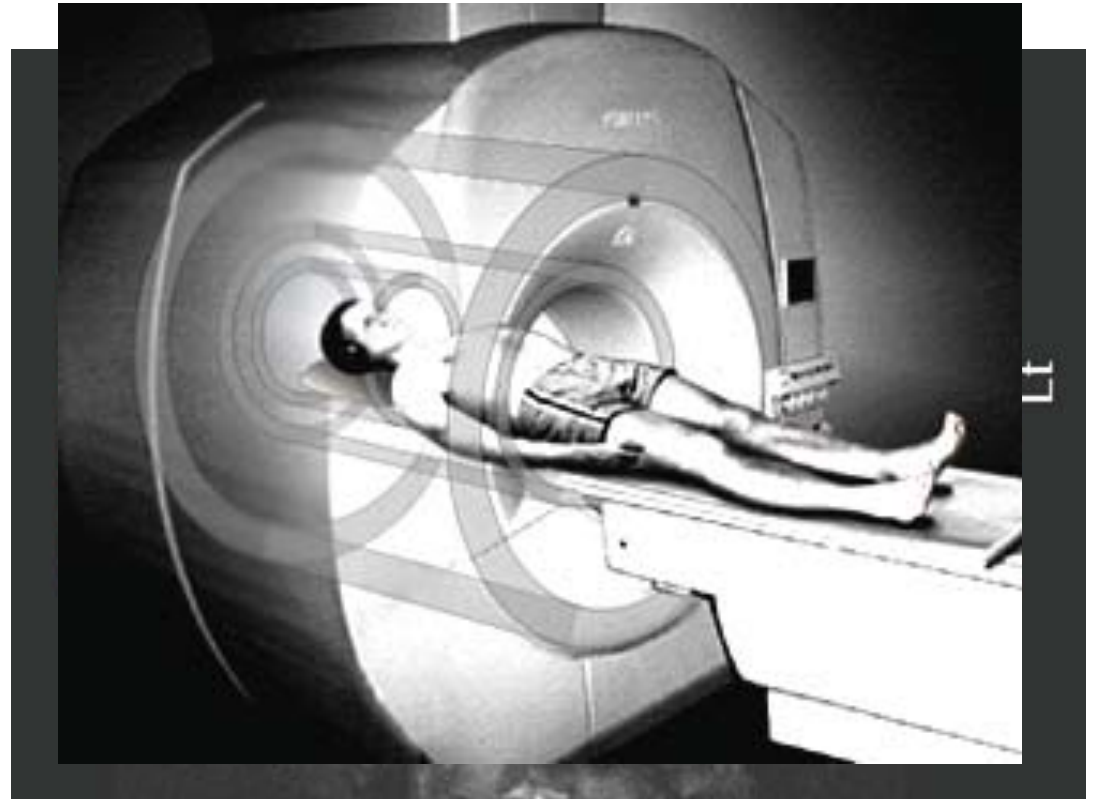
Biomedical Applications of Magnetic Nanoparticles

Quentin Pankhurst



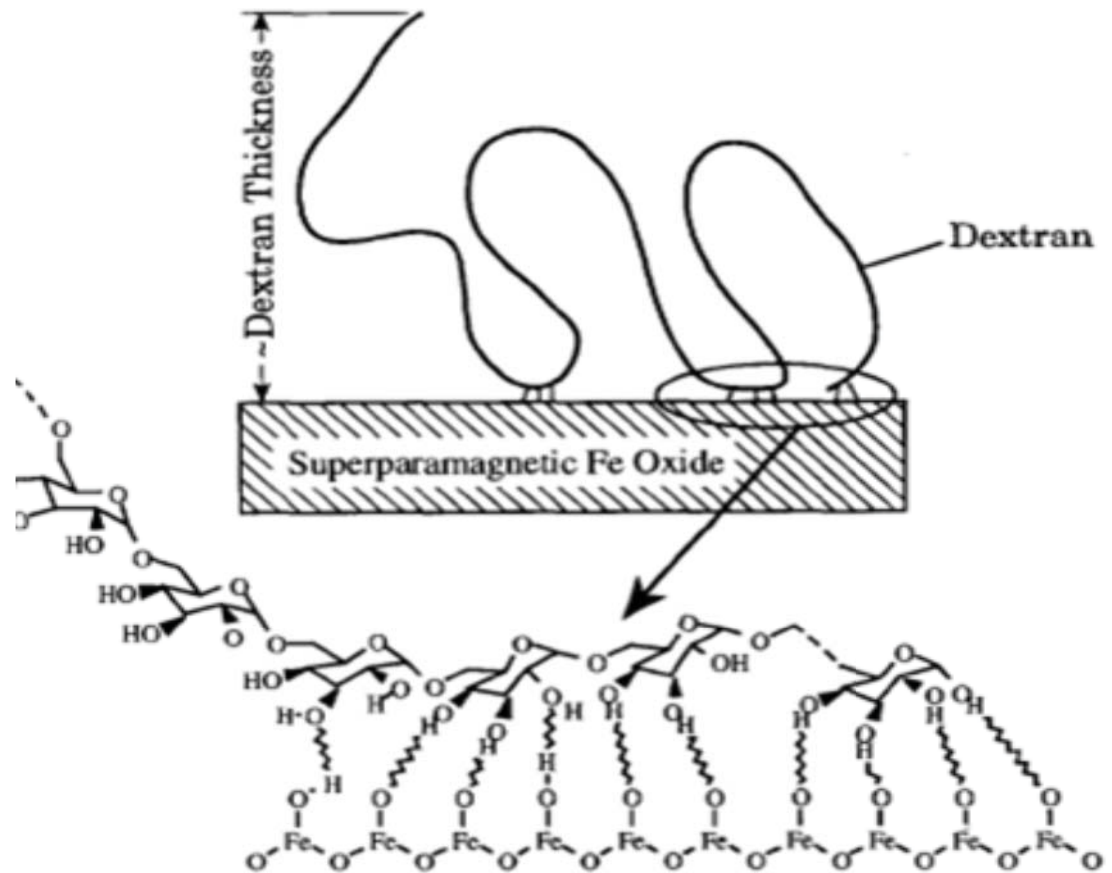
**RESONANT
CIRCUITS LTD**

Magnetic Nanoparticles: MRI



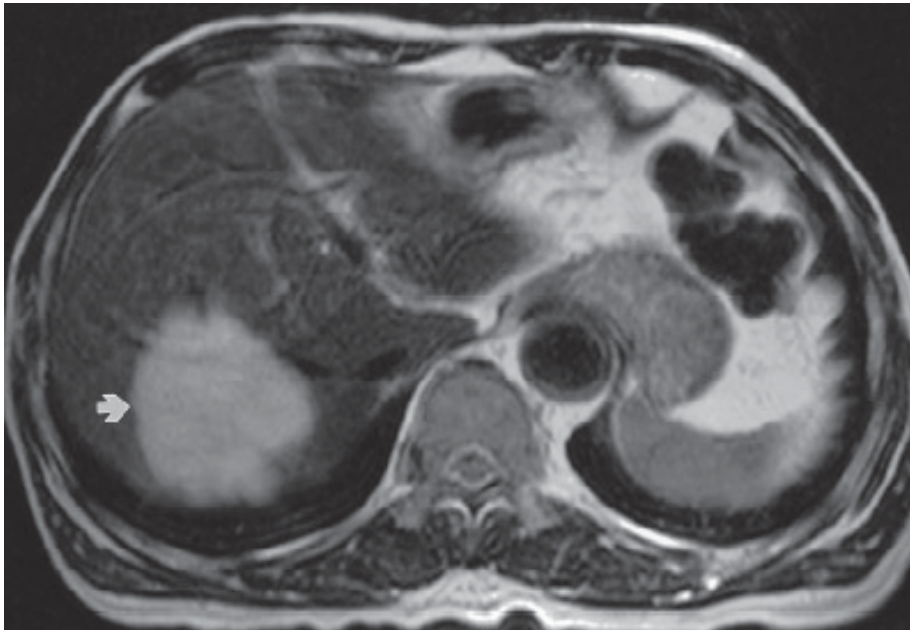
Magnetic resonance imaging (MRI)

Magnetic Nanoparticles: MRI

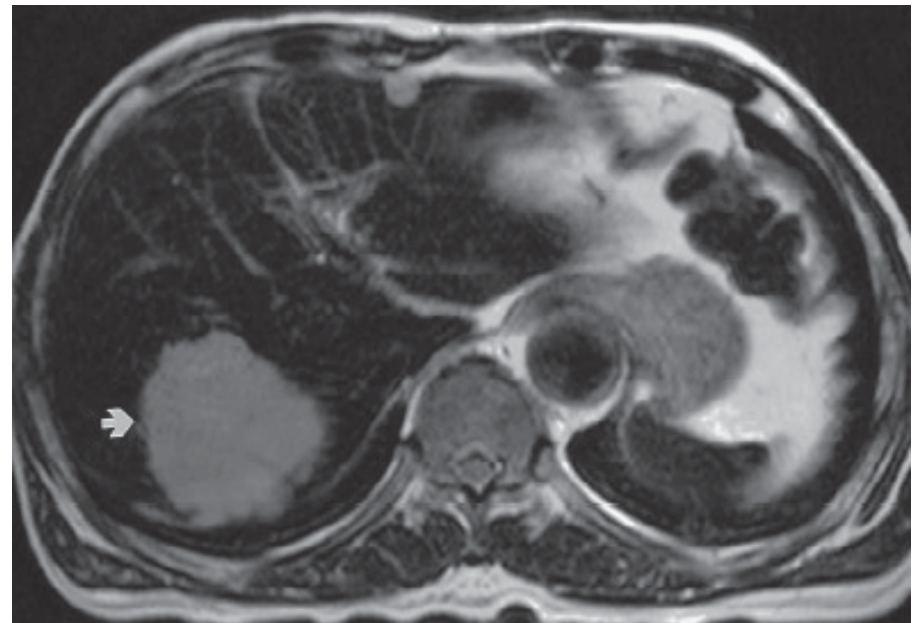


Magnetic Nanoparticles: MRI

Before contrast



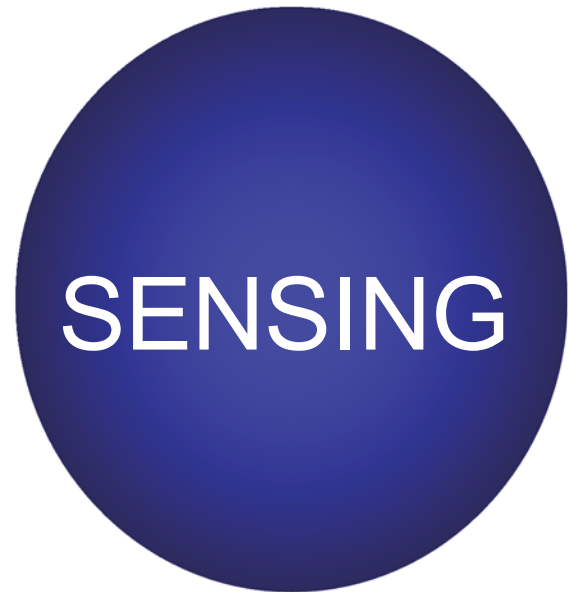
After contrast



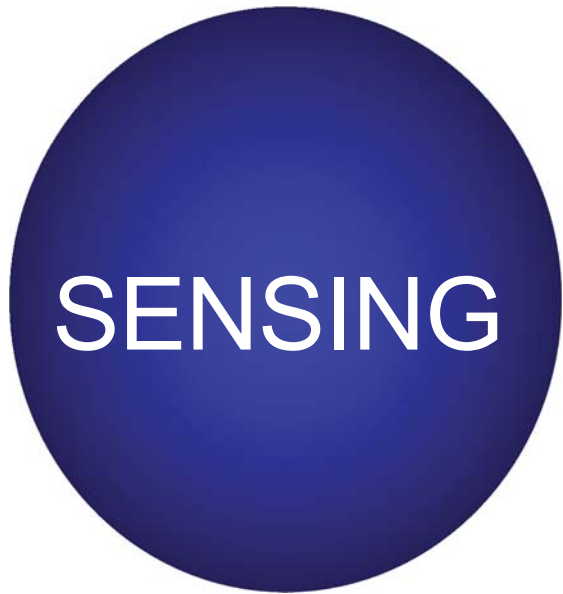
Magnetic Nanoparticles

- 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 actuated by a magnetic field gradient
 - *action at a distance*
- They can resonantly respond to a time-varying field
 - *energy transfer*

Healthcare Biomagnetics



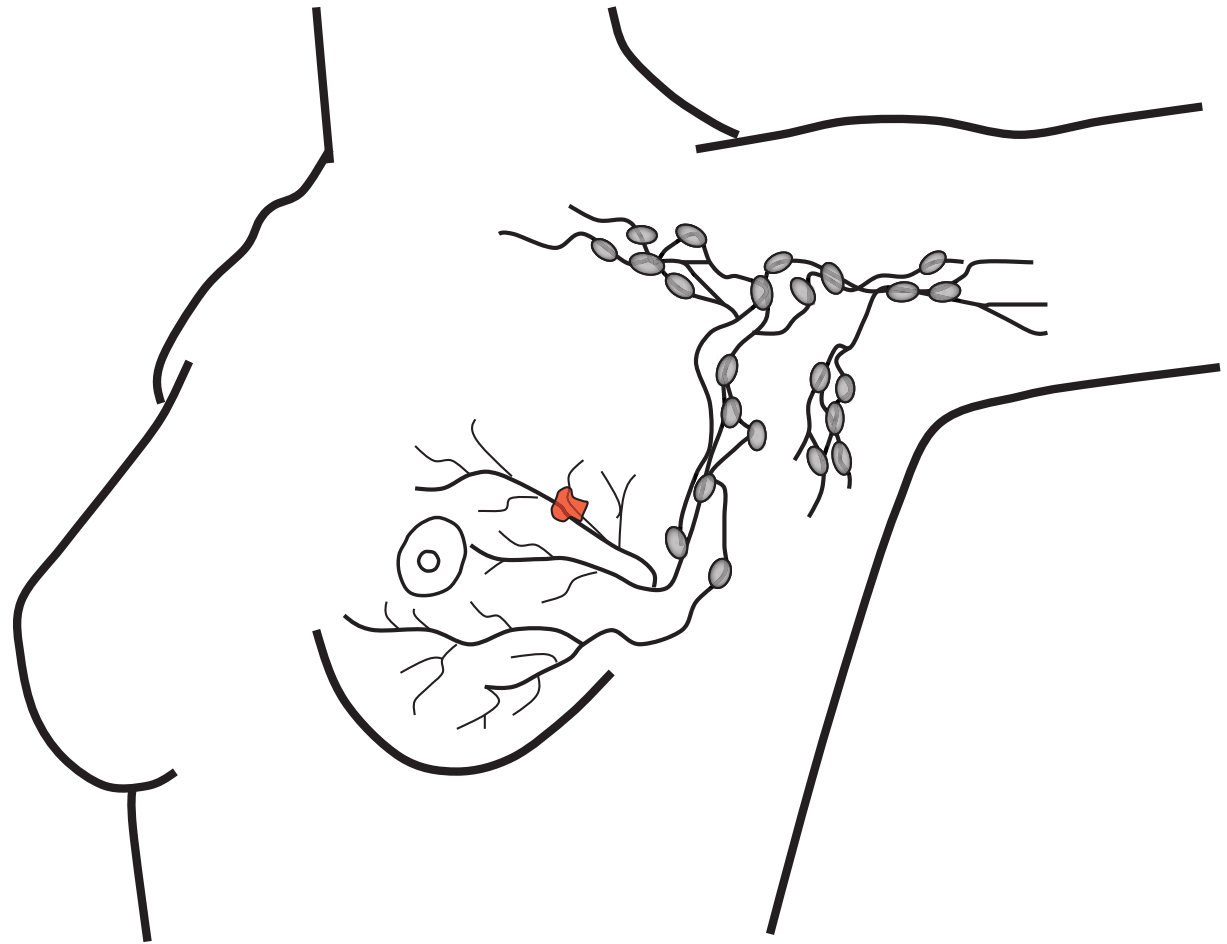
Healthcare Biomagnetics



- **Simon Hattersley**
- **Audrius Brazdeikis**
- **Michael Douek**
- **Eric Mayes**

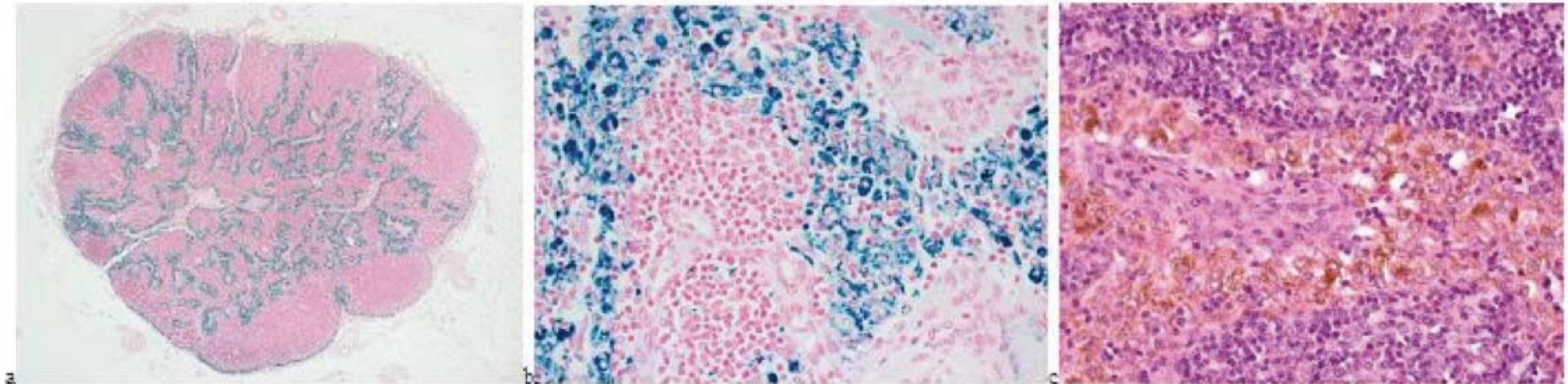
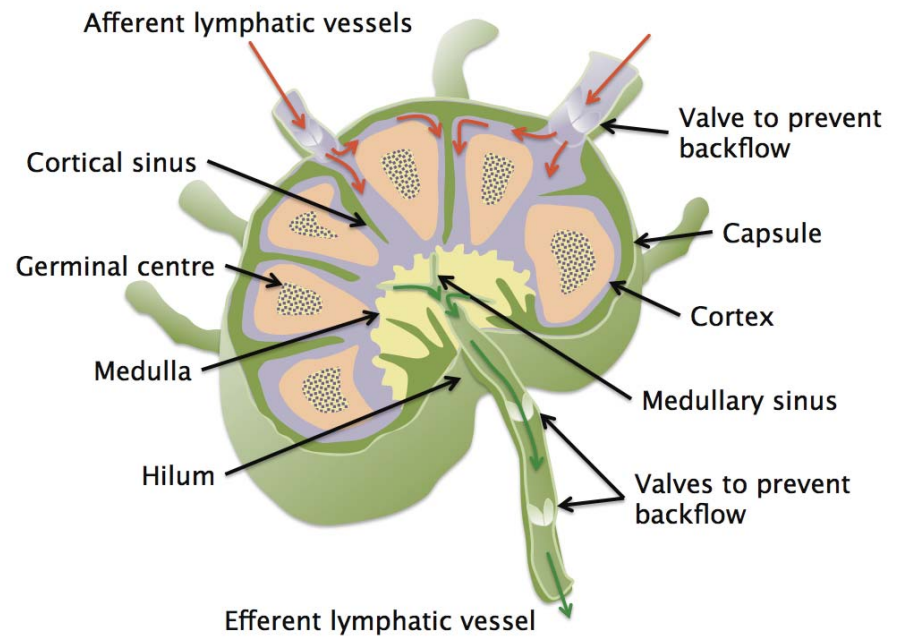
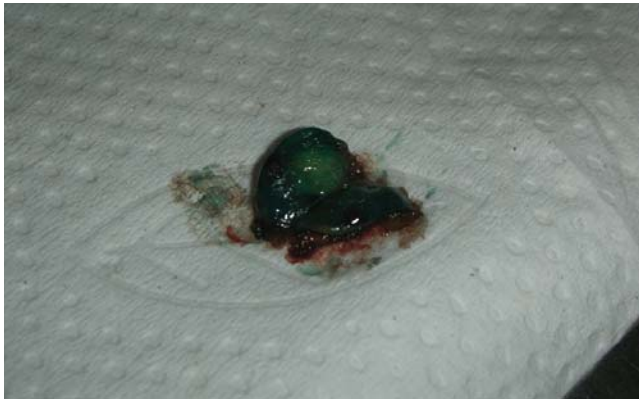


- *Staging of treatment.*
- *First metastases form in lymph nodes in the armpit.*
- *Sentinel lymph node biopsy performed.*



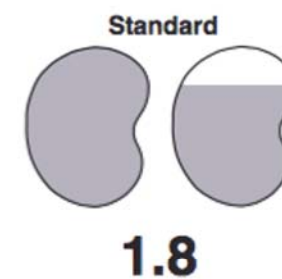
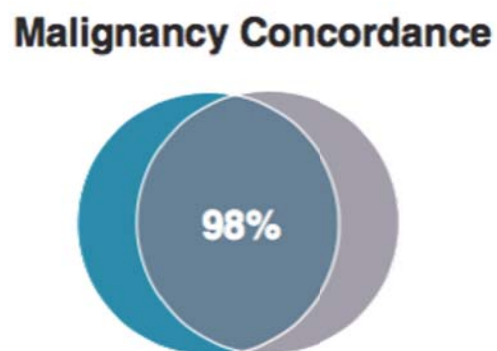
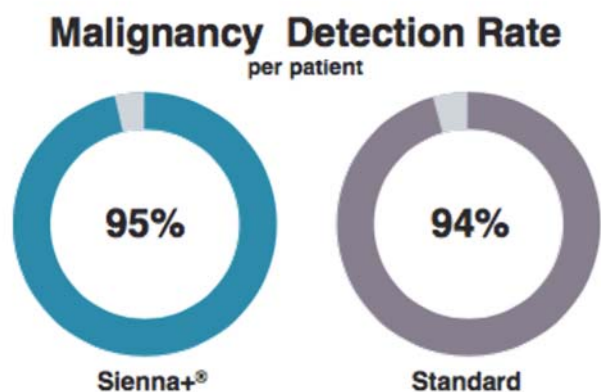
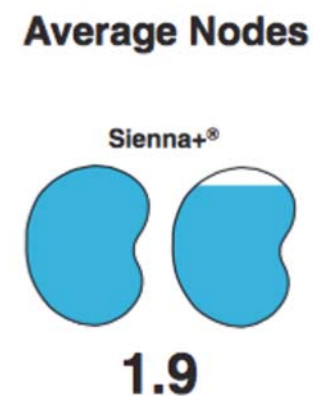
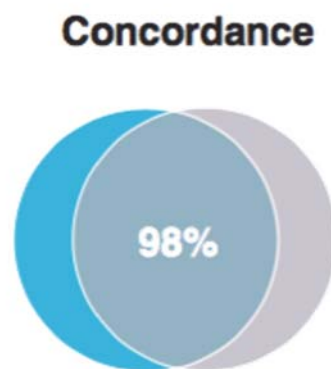
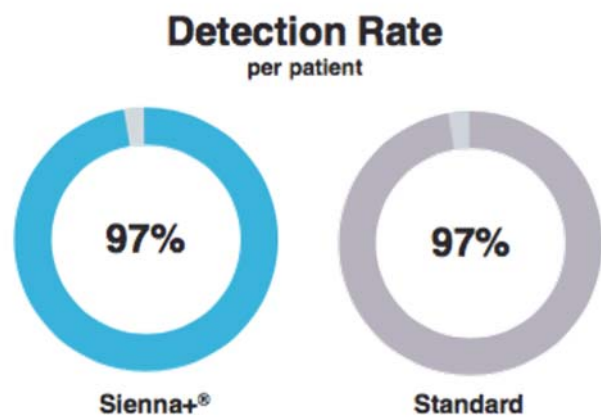
endomag⁺







Results of 1,000+ patients show equivalence with current practice:



endomag⁺

In USA have FDA approval for SentiMag with both Sienna+ (IDE) and Magseed (PMA).



sienna⁺
Plus

magseed⁺

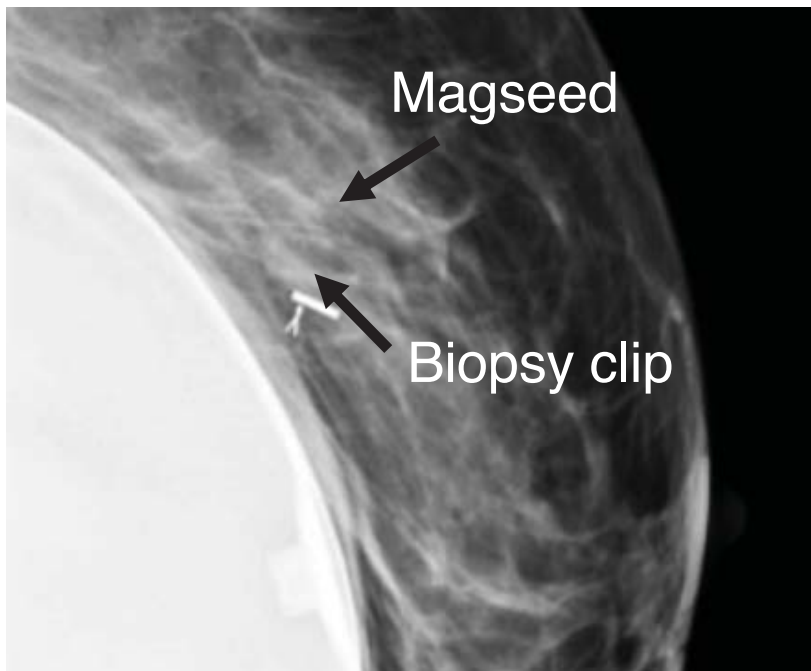
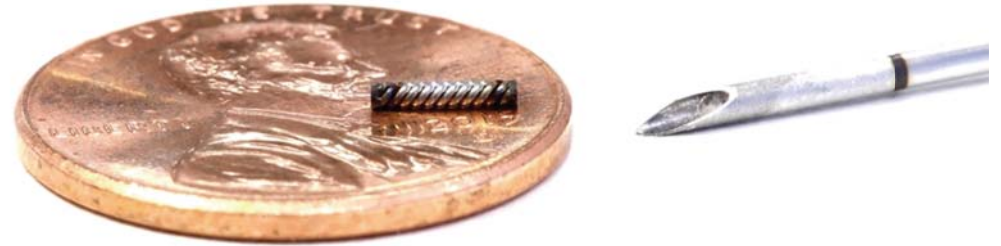


sentimag⁺

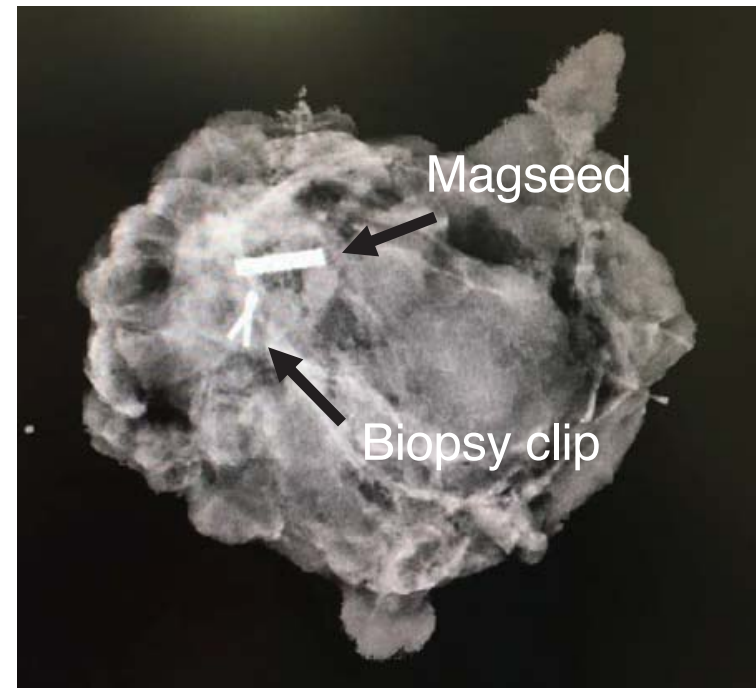




MagSeed: for impalpable lesion localisation.

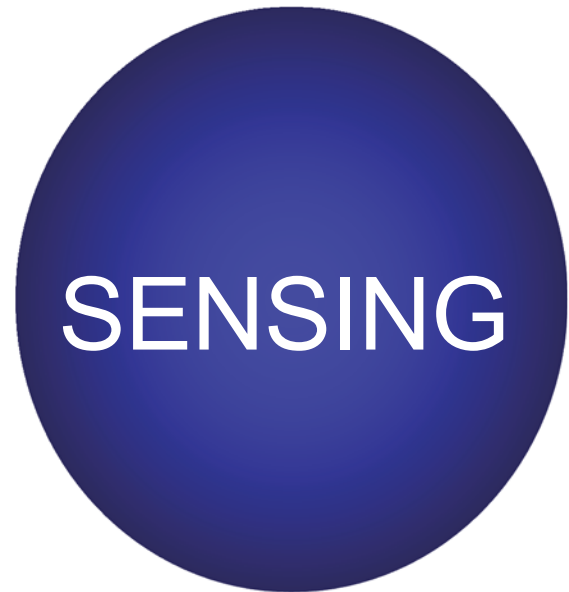


Mammogram



Excised lesion

Healthcare Biomagnetics



Healthcare Biomagnetics

- **Paul Southern**
- **Simon Hattersley**



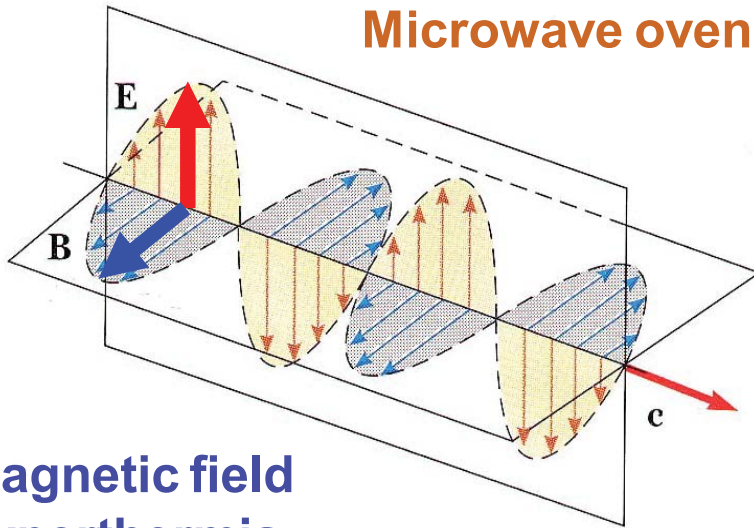
**RESONANT
CIRCUITS LTD**

HEATING



RESONANT
CIRCUITS LTD

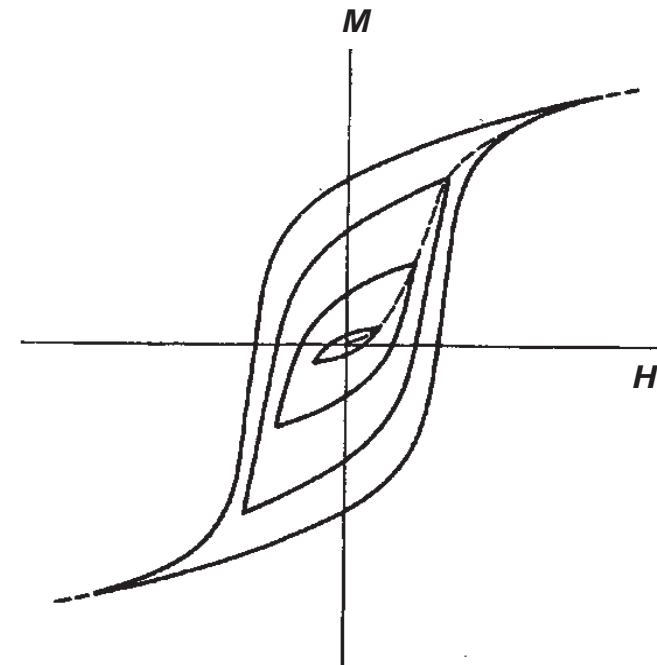
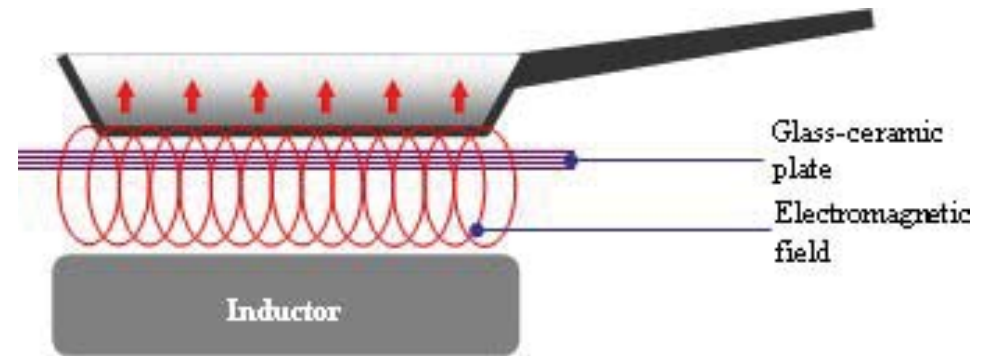
Microwave oven



Magnetic field
hyperthermia

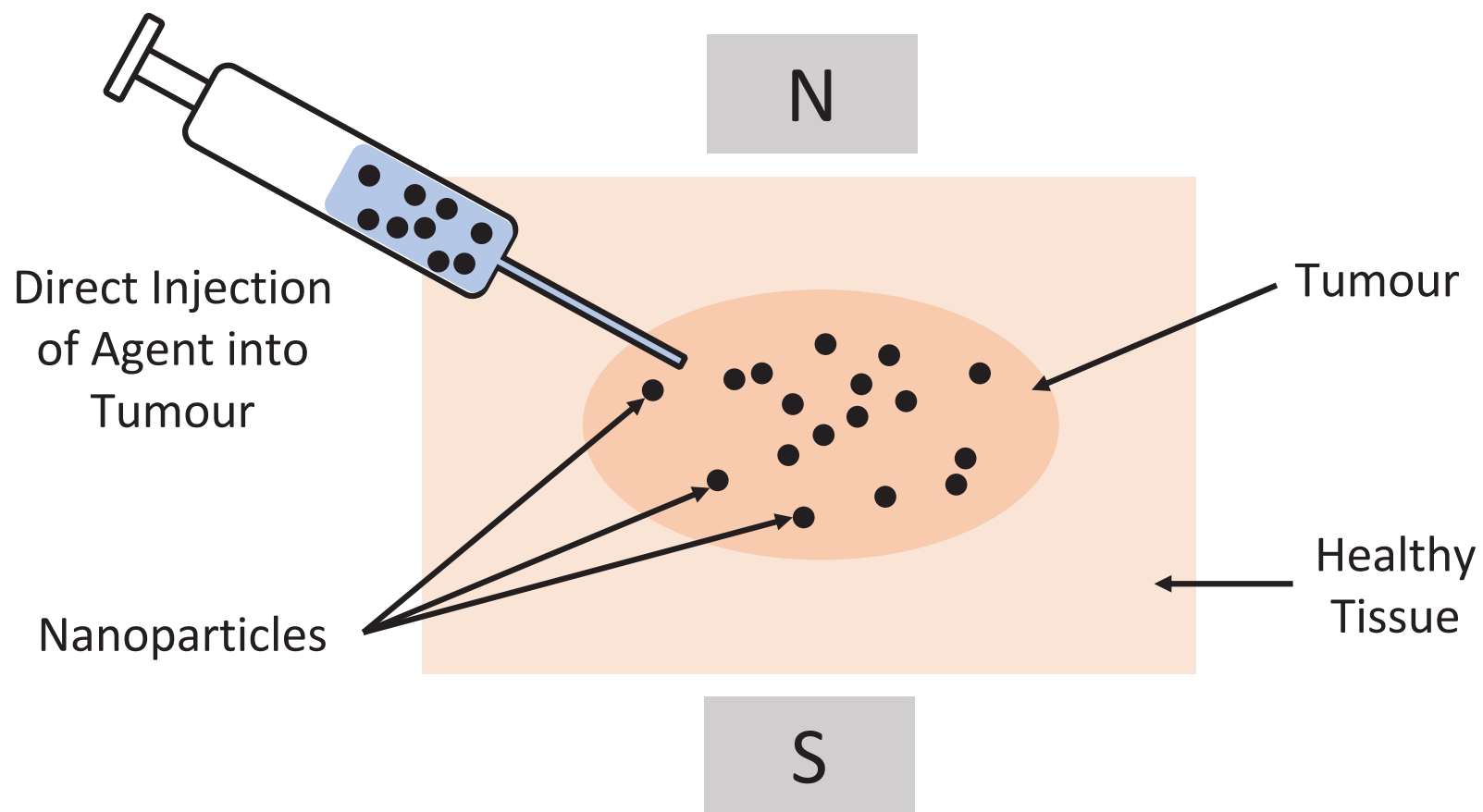
$$P_{FMP} = \mu_o f \oint H dM$$

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



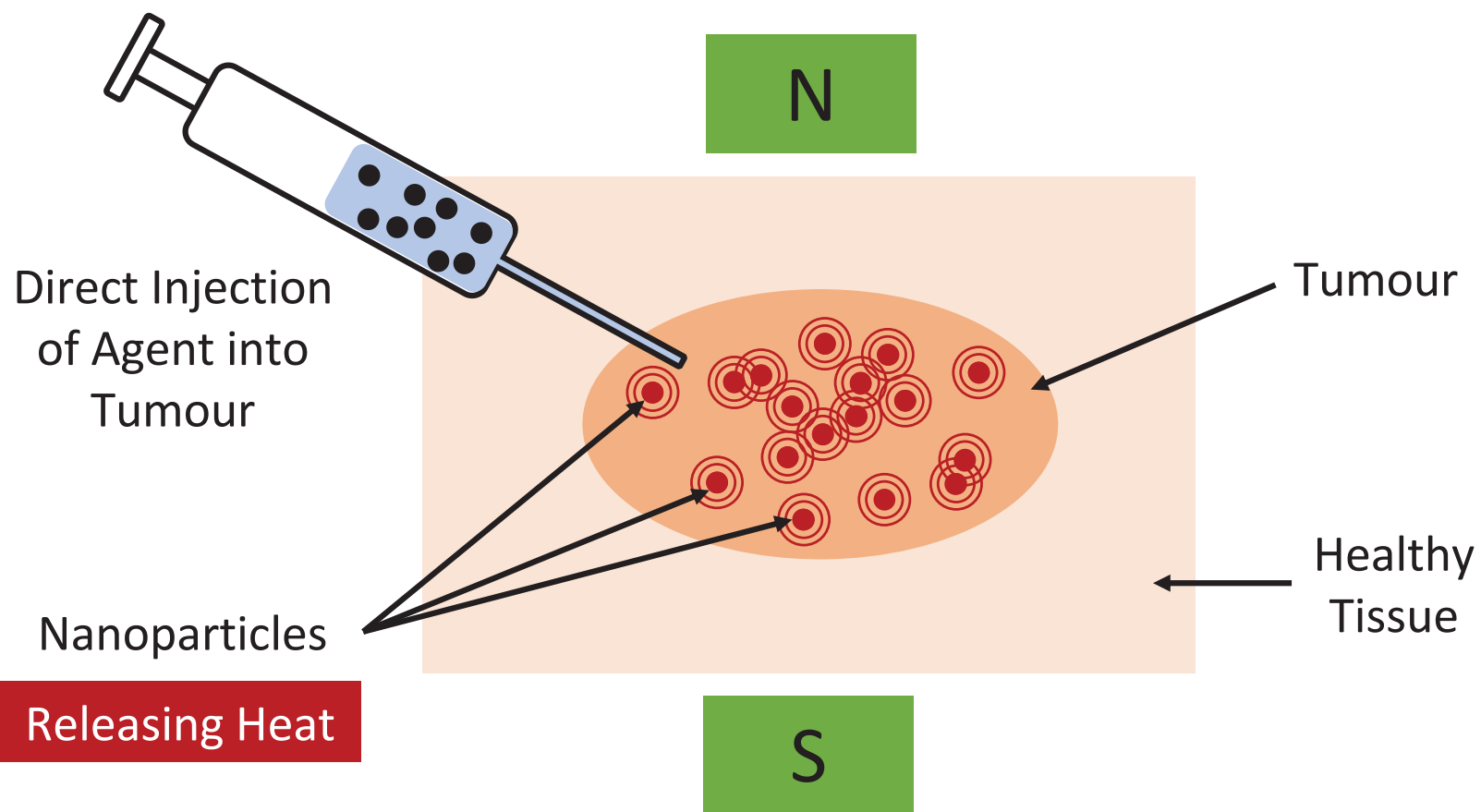


RESONANT
CIRCUITS LTD



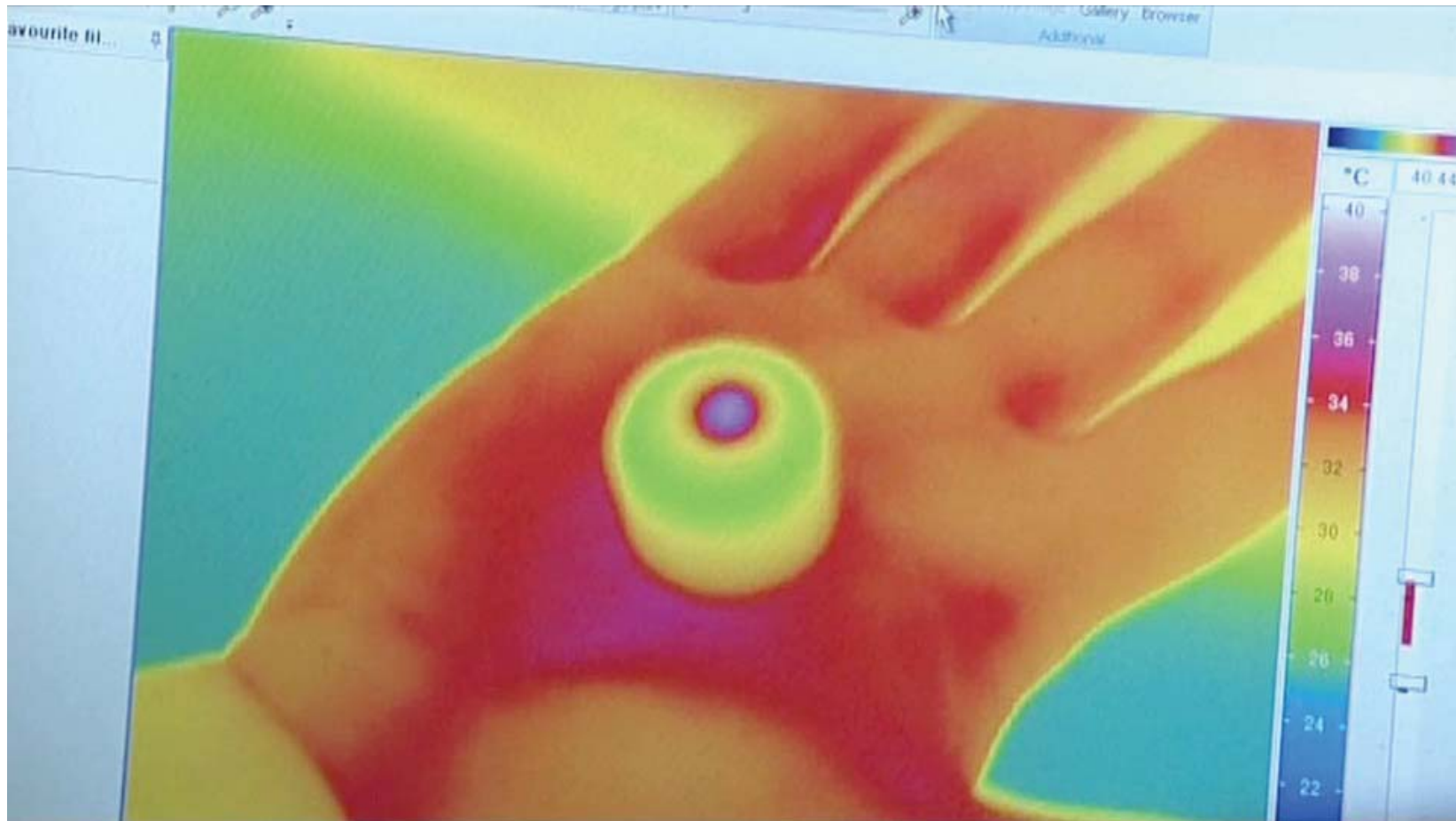


RESONANT
CIRCUITS LTD





RESONANT
CIRCUITS LTD





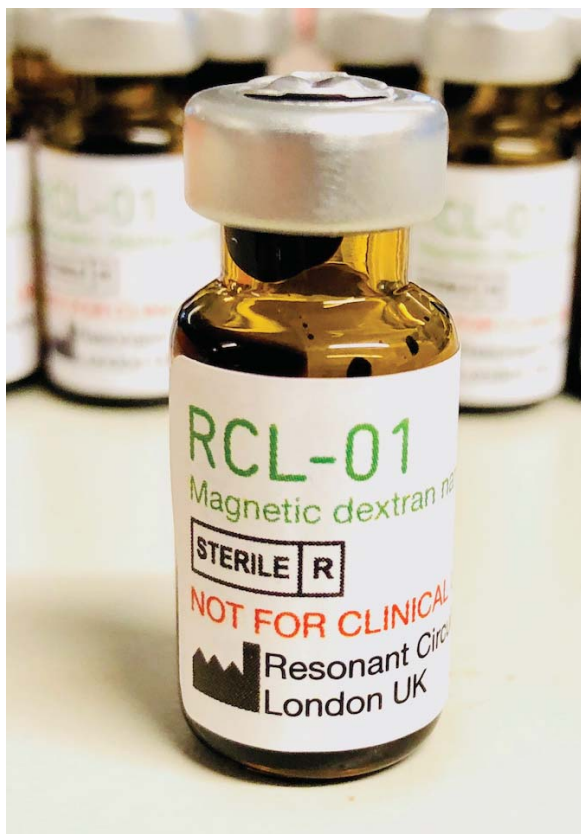
**RESONANT
CIRCUITS LTD**



www.resonantcircuits.com



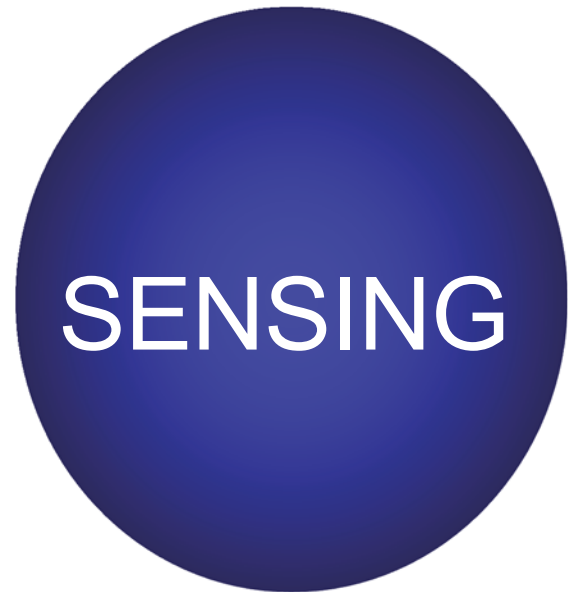
**RESONANT
CIRCUITS LTD**



Parameter	Result
Mean particle diameter (Z-average, nm)	149
Polydispersity index (PI)	0.26
Particle concentration (mg/ml)	188
Iron concentration (mg _{Fe} /ml)	72
Osmolality (mOsmol/kg)	299
AC-Susceptibility (25 kHz, 10 ⁻³ m ³ /kg _{Fe})	10.2
ILP (nHm ² /kg _{Fe})***	5.1
Endotoxin concentration (EU/ml)*	0.4
Microorganism contamination (cfu/ml)**	<1

www.resonantcircuits.com

Healthcare Biomagnetics



Healthcare Biomagnetics

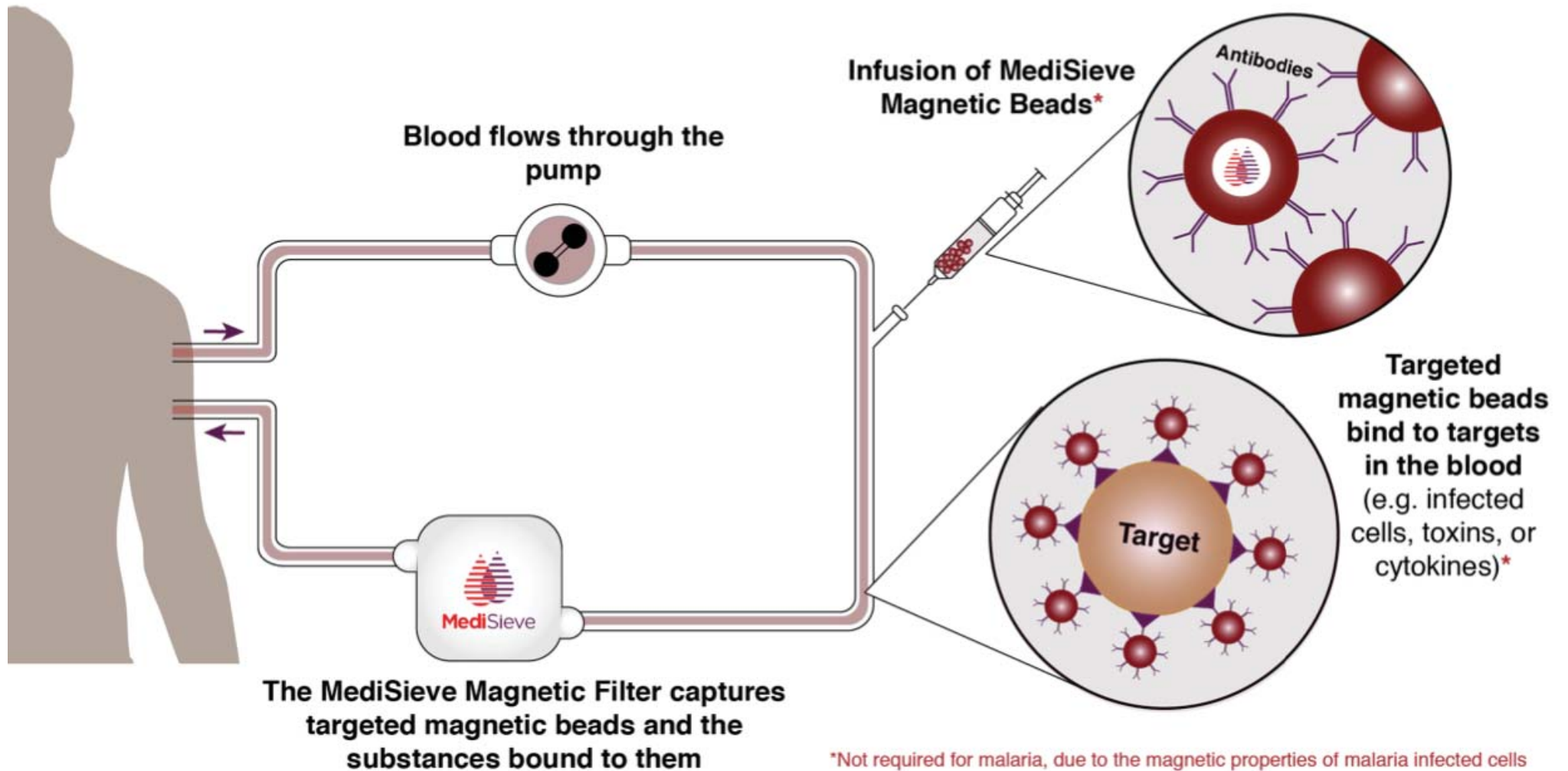


MOVING

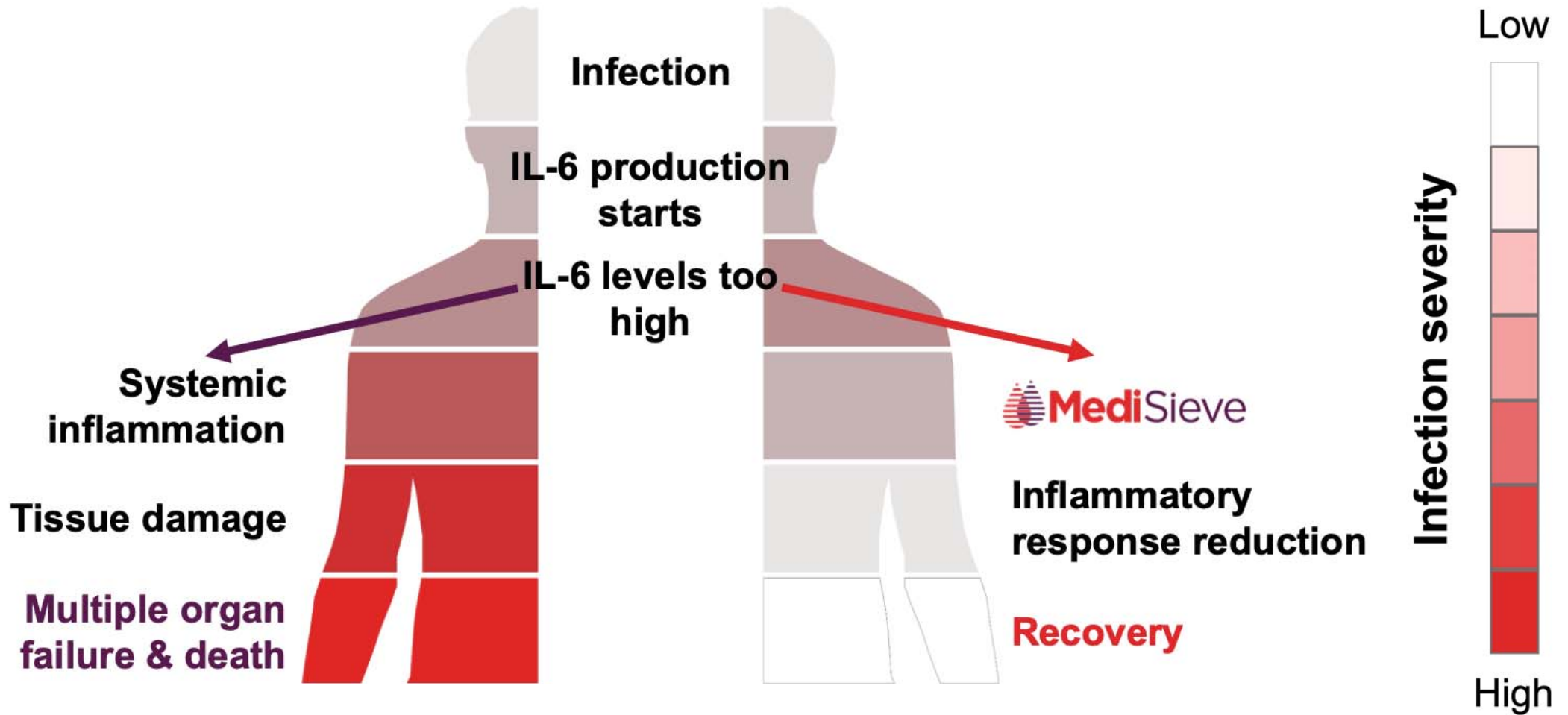
- **George Frodsham**
- **Cristina Blanco-Andujar**
- **Will Twigger**

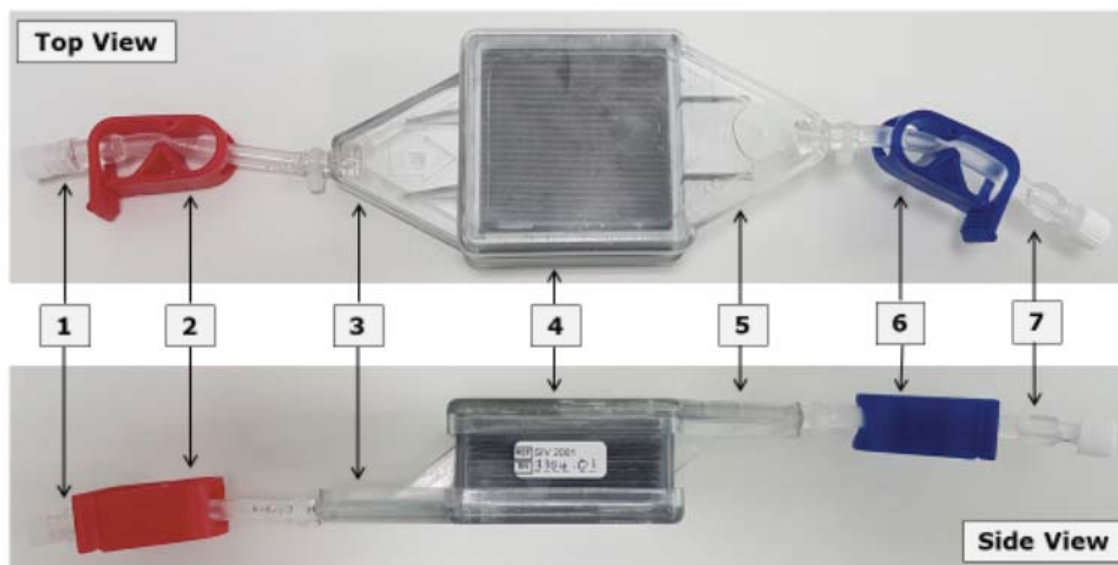


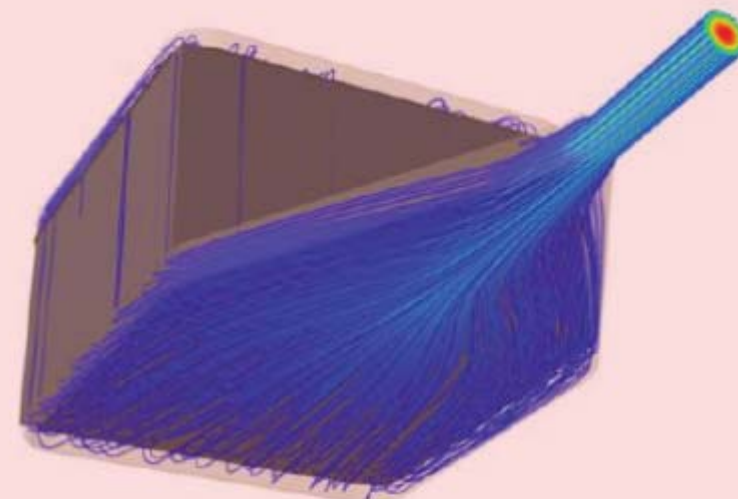
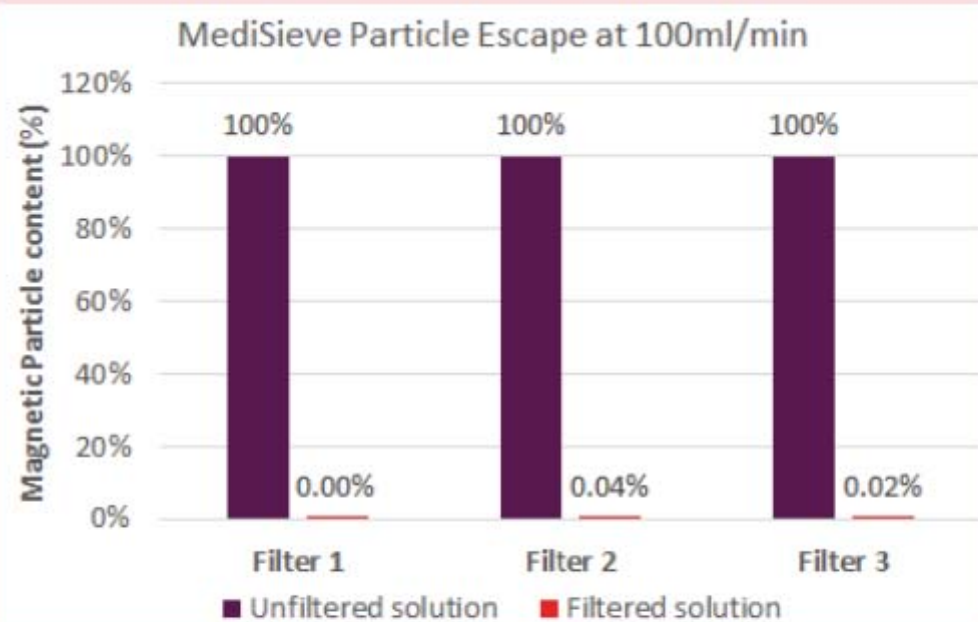
MediSieve



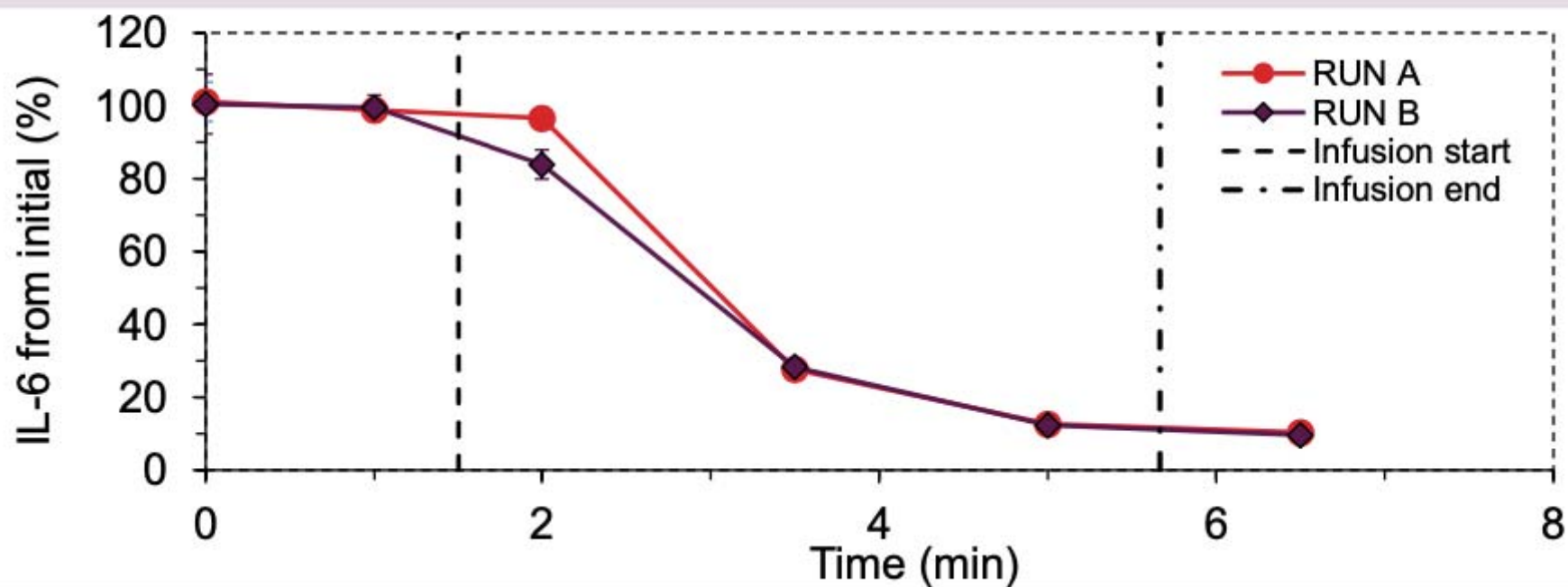
*Not required for malaria, due to the magnetic properties of malaria infected cells







Flow 100ml/min

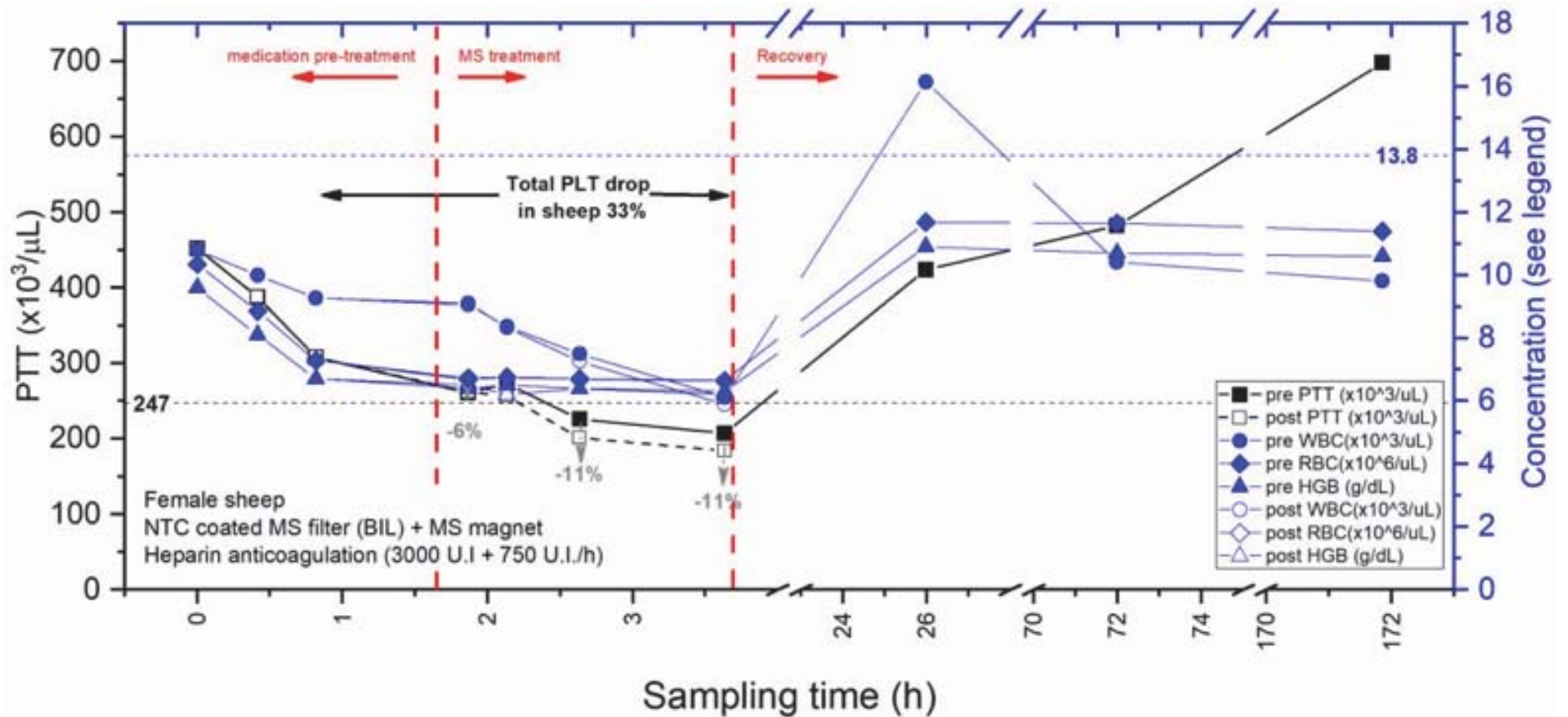




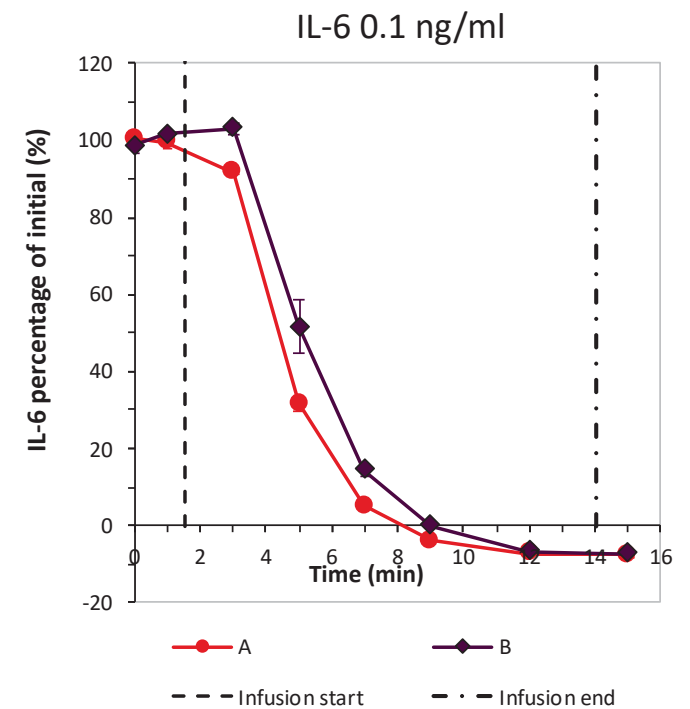
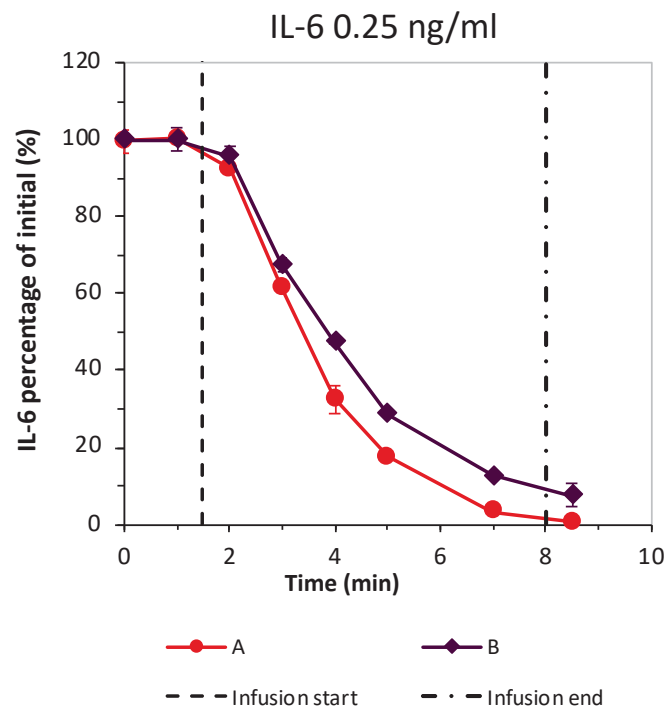
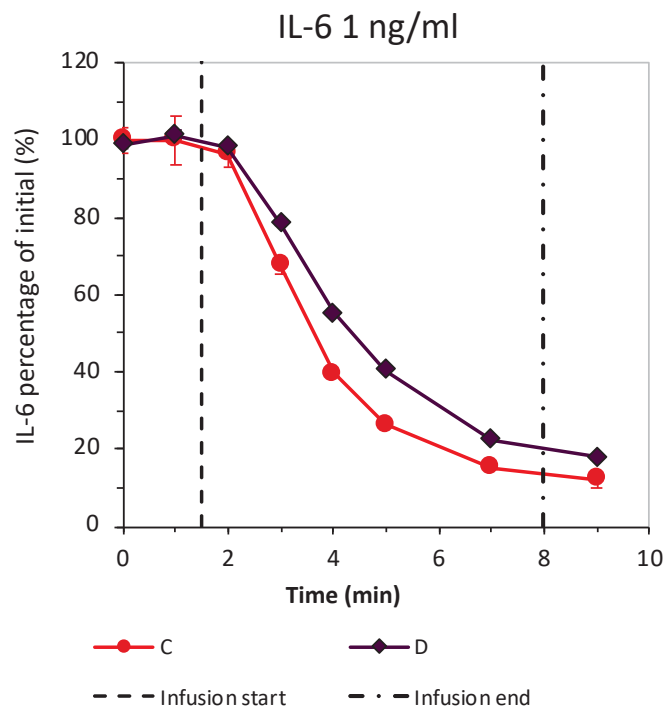


MediSieve

No adverse events during full procedure on sheep (GLP)



Removing IL-6 from Human Blood




IL-6 levels in COVID-19

IL-6 levels in sepsis

Towards Clinical Translation



IN VIVO
TRACKING

STABILITY

STANDARDS

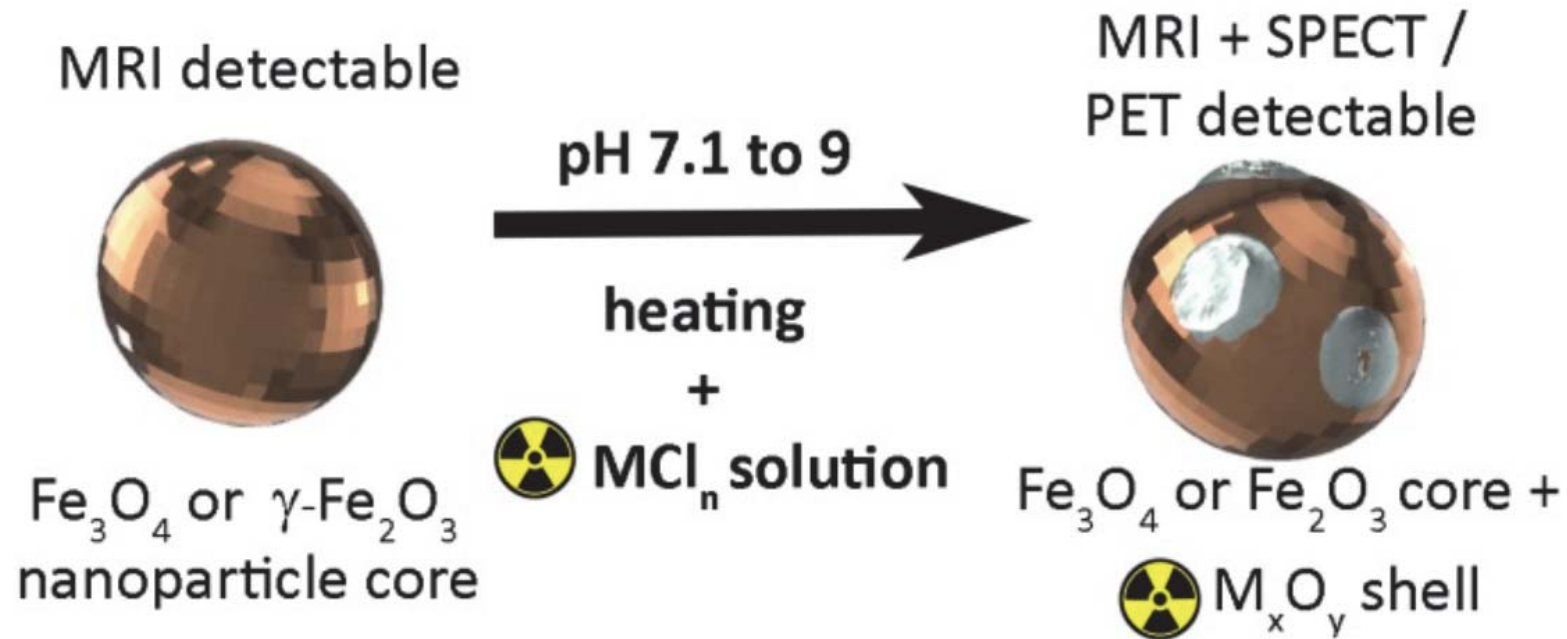
Towards Clinical Translation



IN VIVO
TRACKING

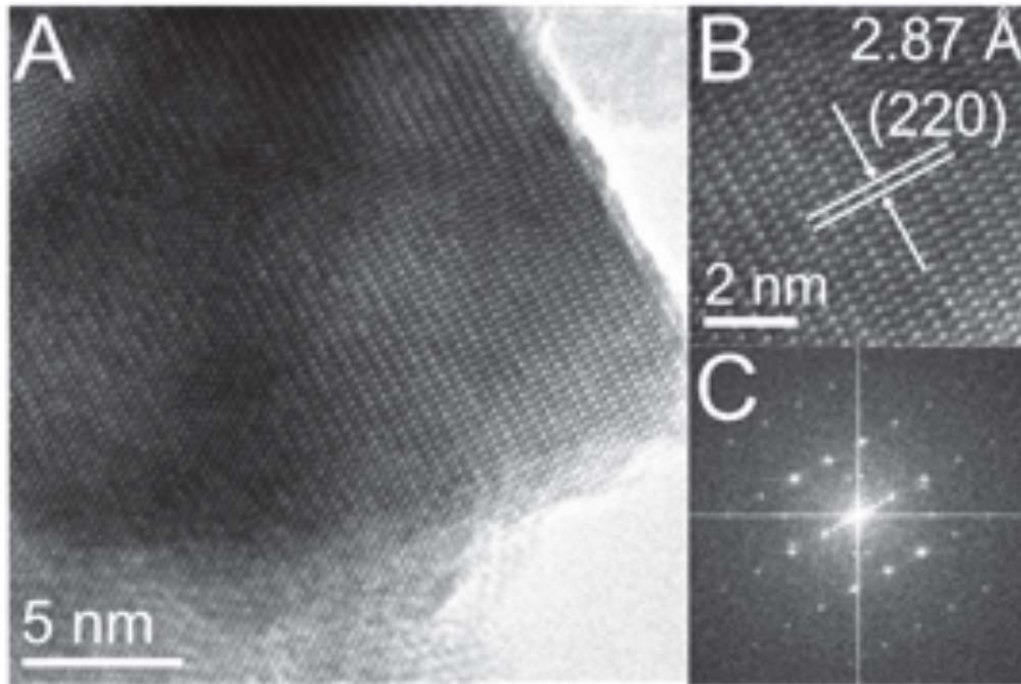
- **Stephen Patrick**
- **Joseph Bear**
- **Mark Lythgoe**

Surface Radio-Mineralisation:

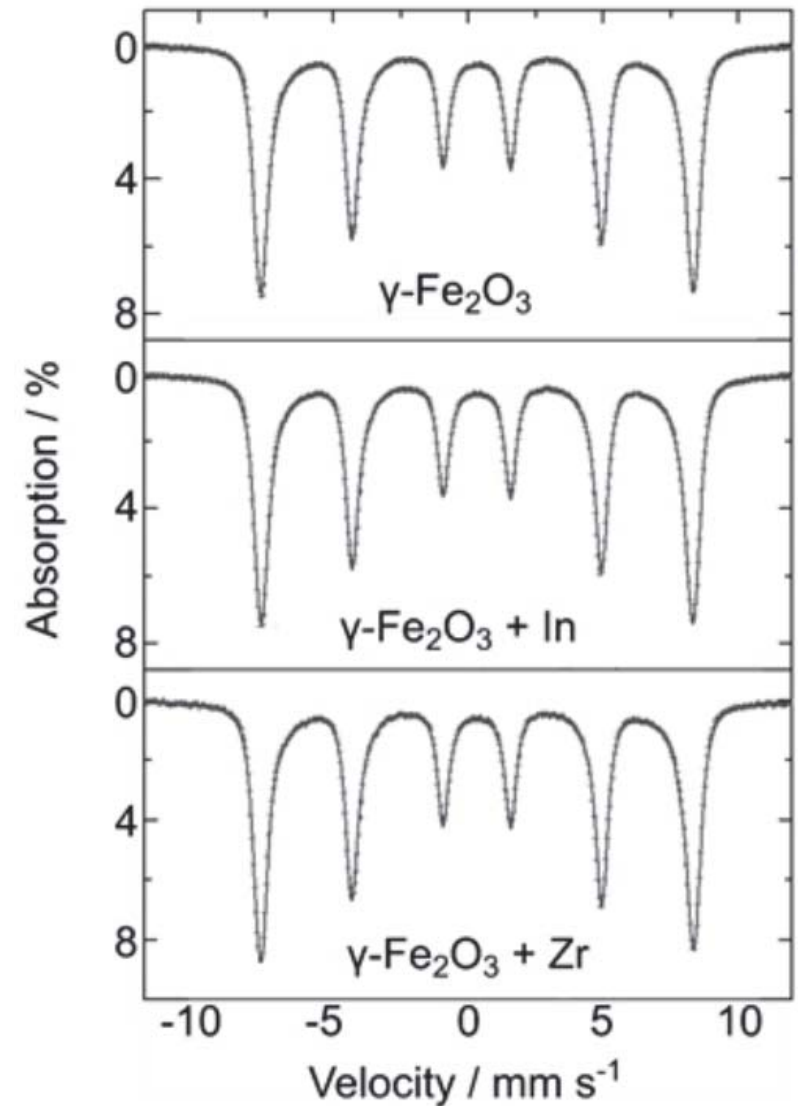


.. of iron oxide magnetic nanoparticles (or cores) with the radionuclides ^{111}In ($t_{1/2} = 67$ hours) and ^{99}Zr ($t_{1/2} = 3.3$ days).

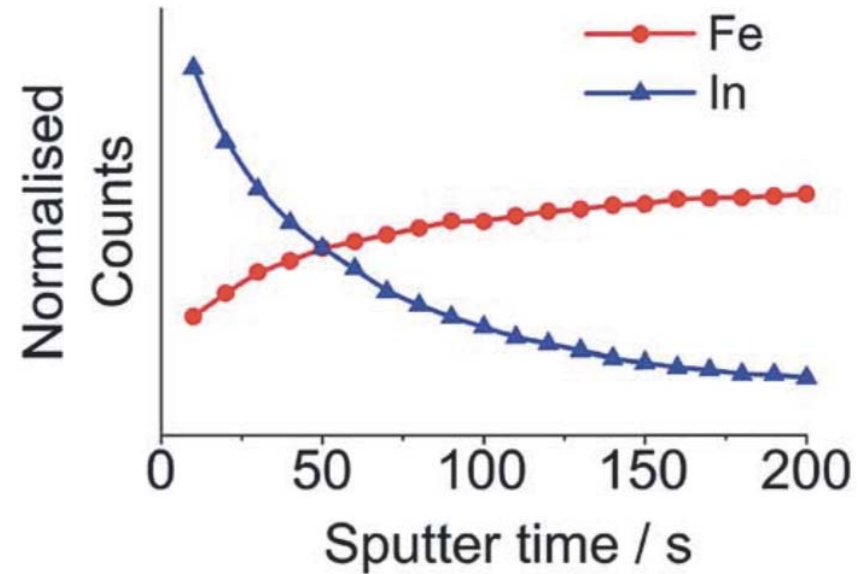
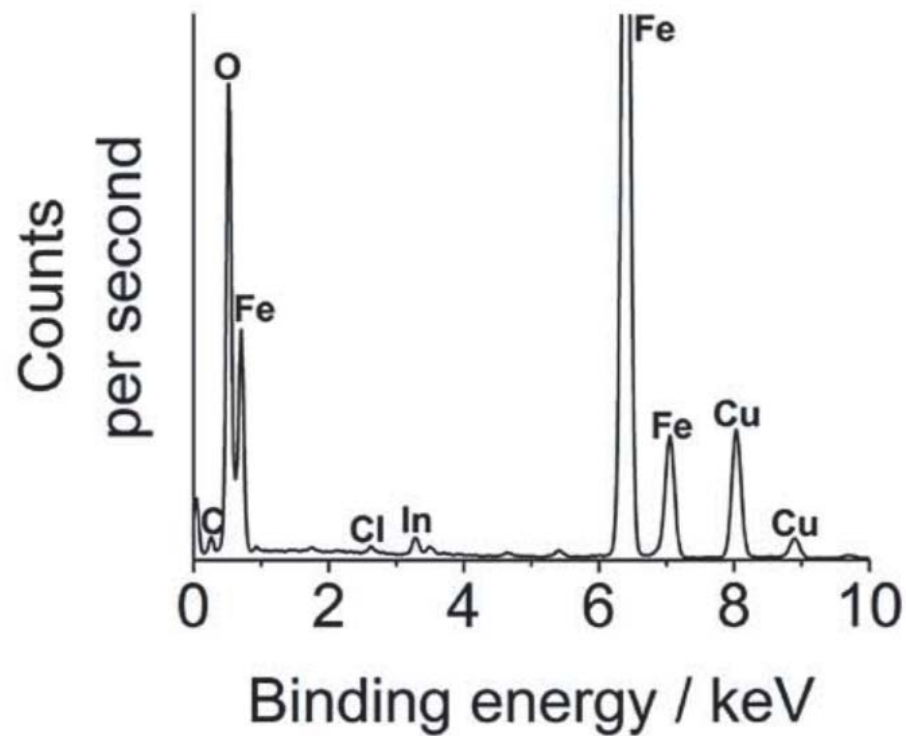
Surface Radio-Mineralisation:



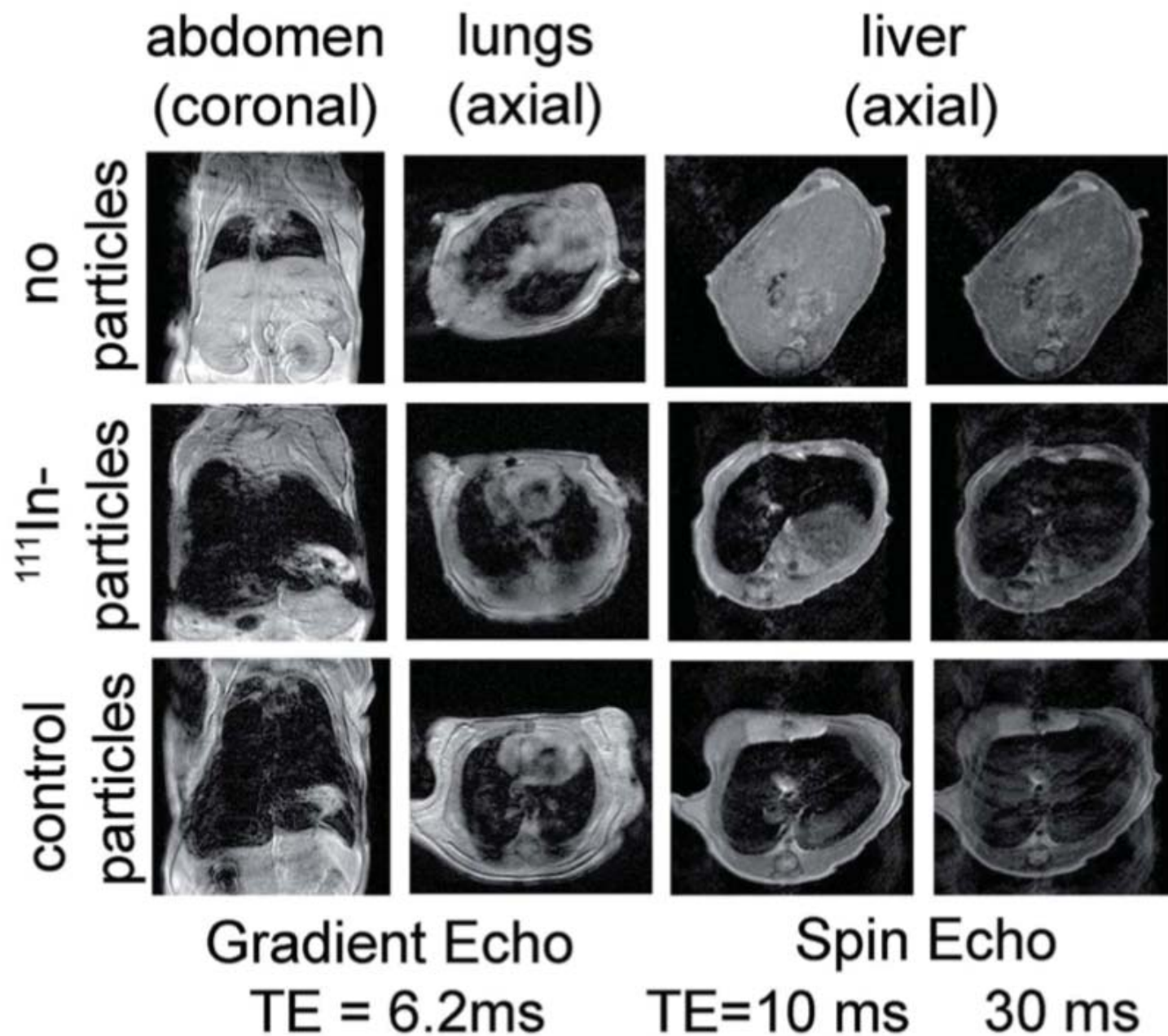
- *HRTEM and Mössbauer data for bare maghemite particles*



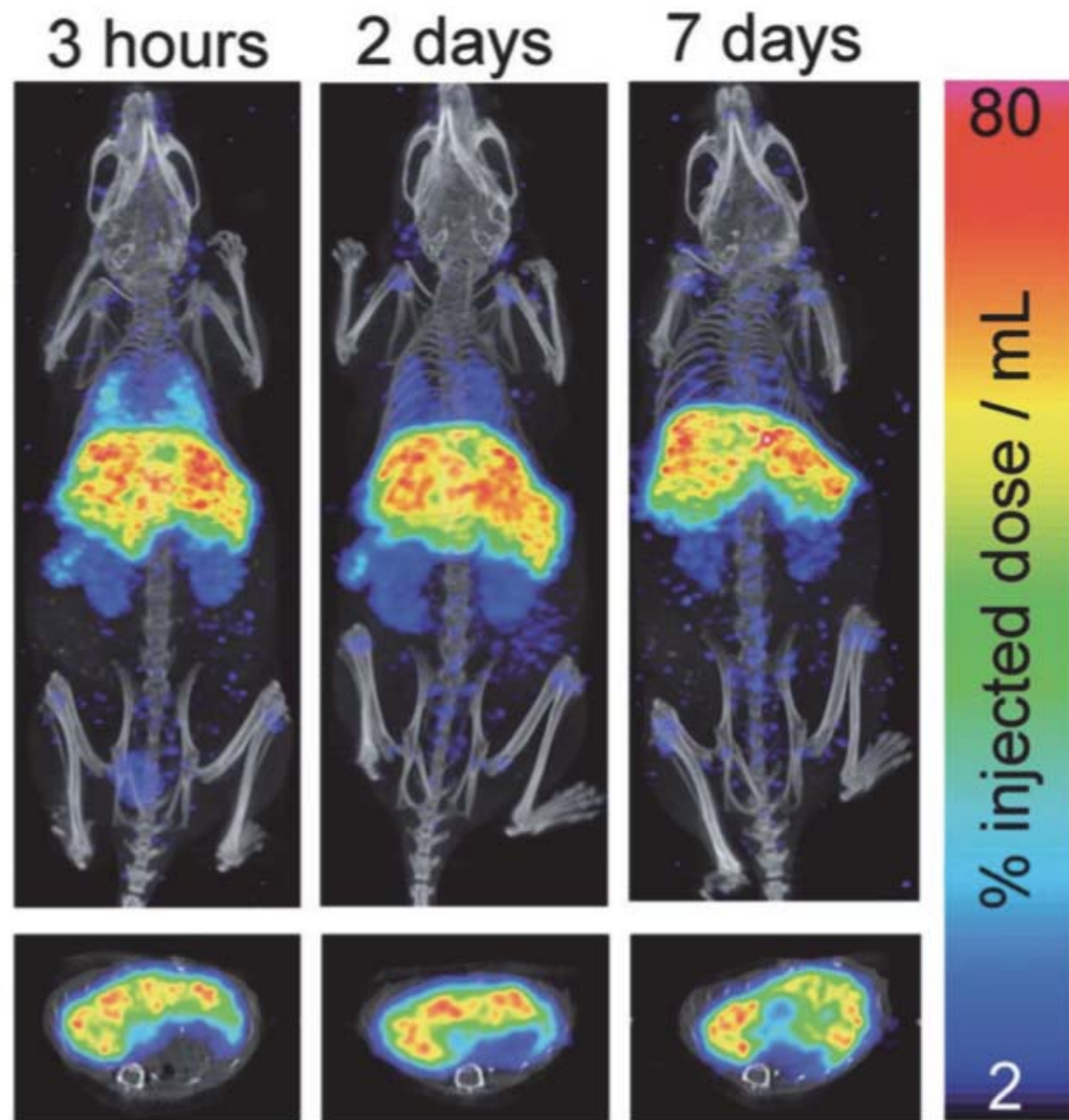
Surface Radio-Mineralisation:



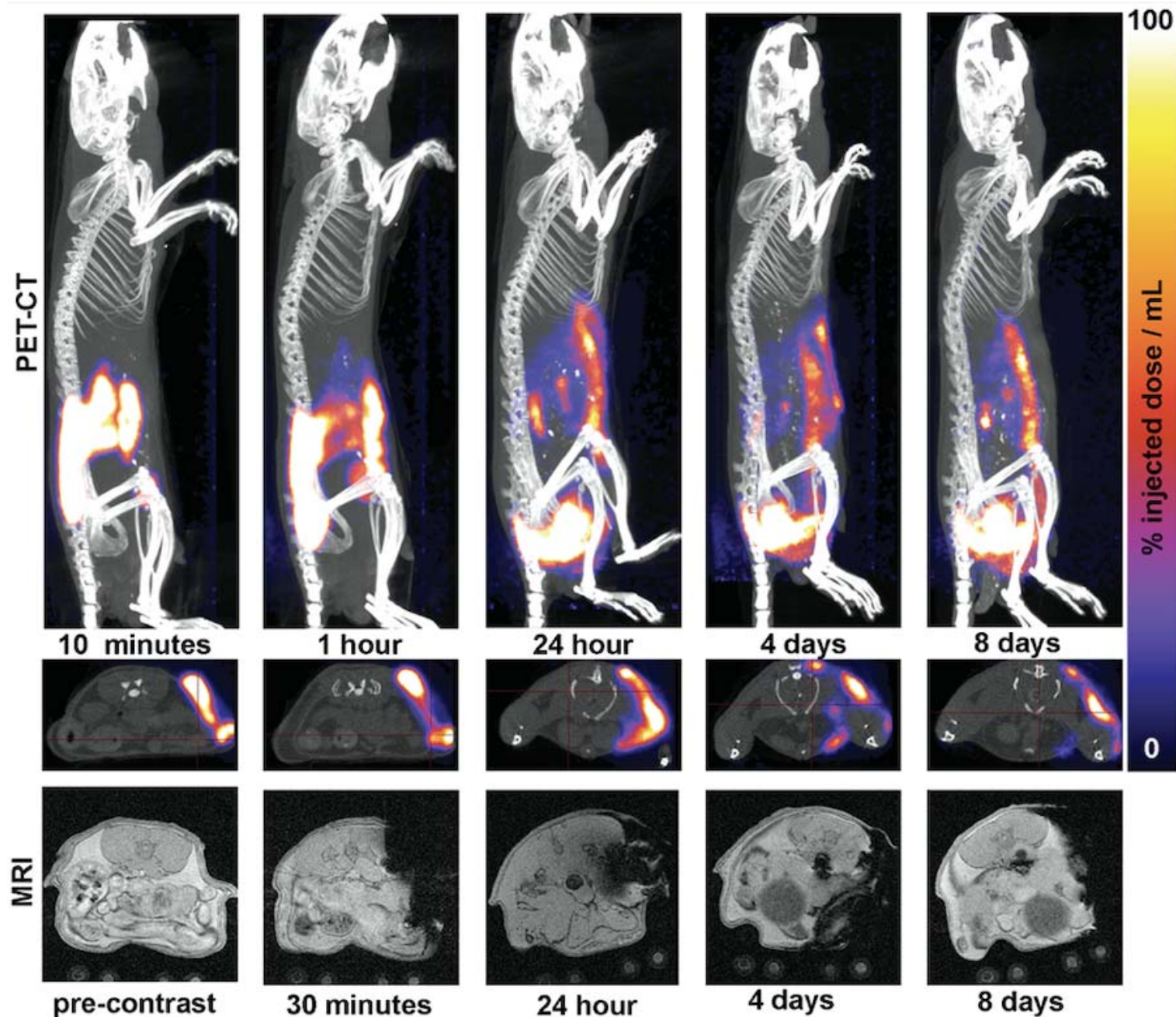
- *EDS & ToF-SIMS data for In-labelled γ -Fe₂O₃*



*SPECT-CT
imaging*



*Sub-
cutaneous
injection of
 ^{89}Zr -labelled
RCL-01*



Towards Clinical Translation



Towards Clinical Translation

- Uwe Steinhoff
- Christer Johansson
- Daniel Baumgarten
- James Wells
- Paola Tiberto
- Alex Price

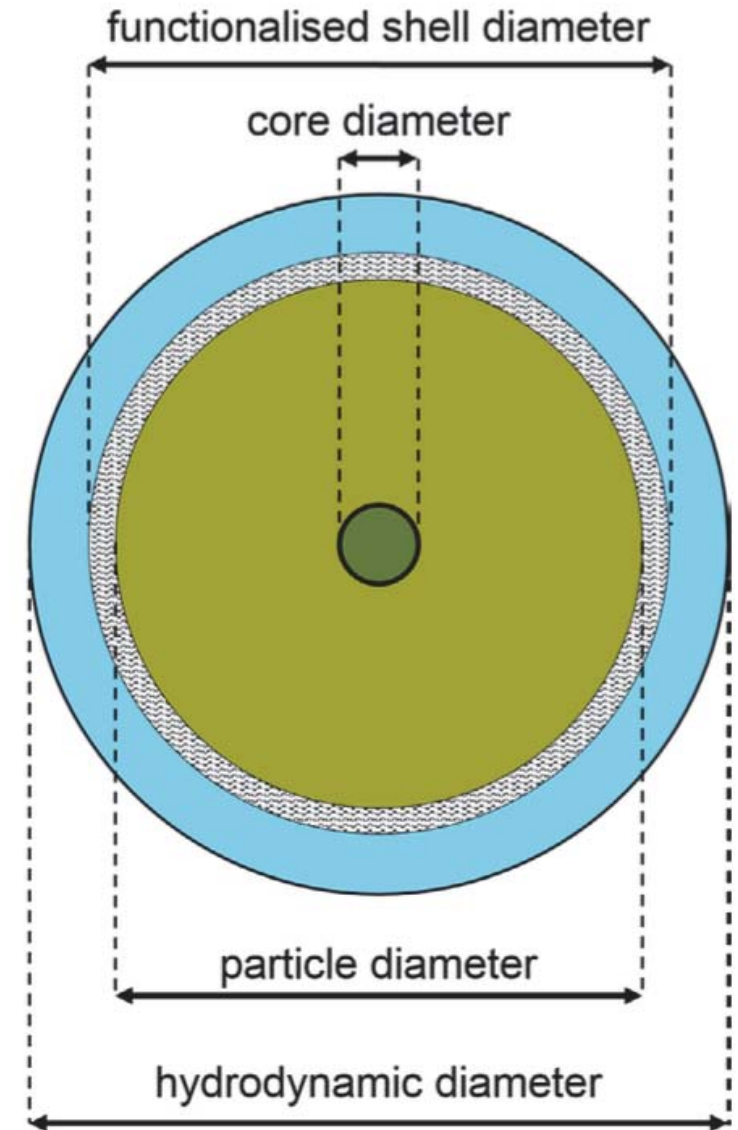


STANDARDS

NanoMag Project:

Single-core
magnetic
nanoparticle

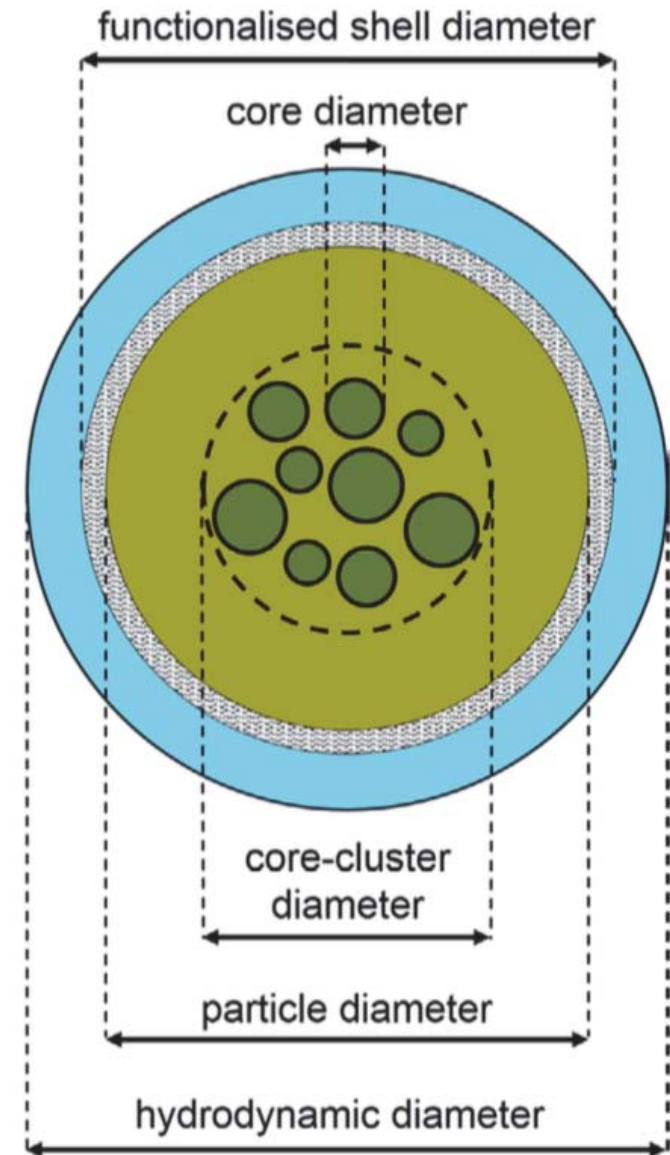
- *Terminology for magnetic nanoparticles:*



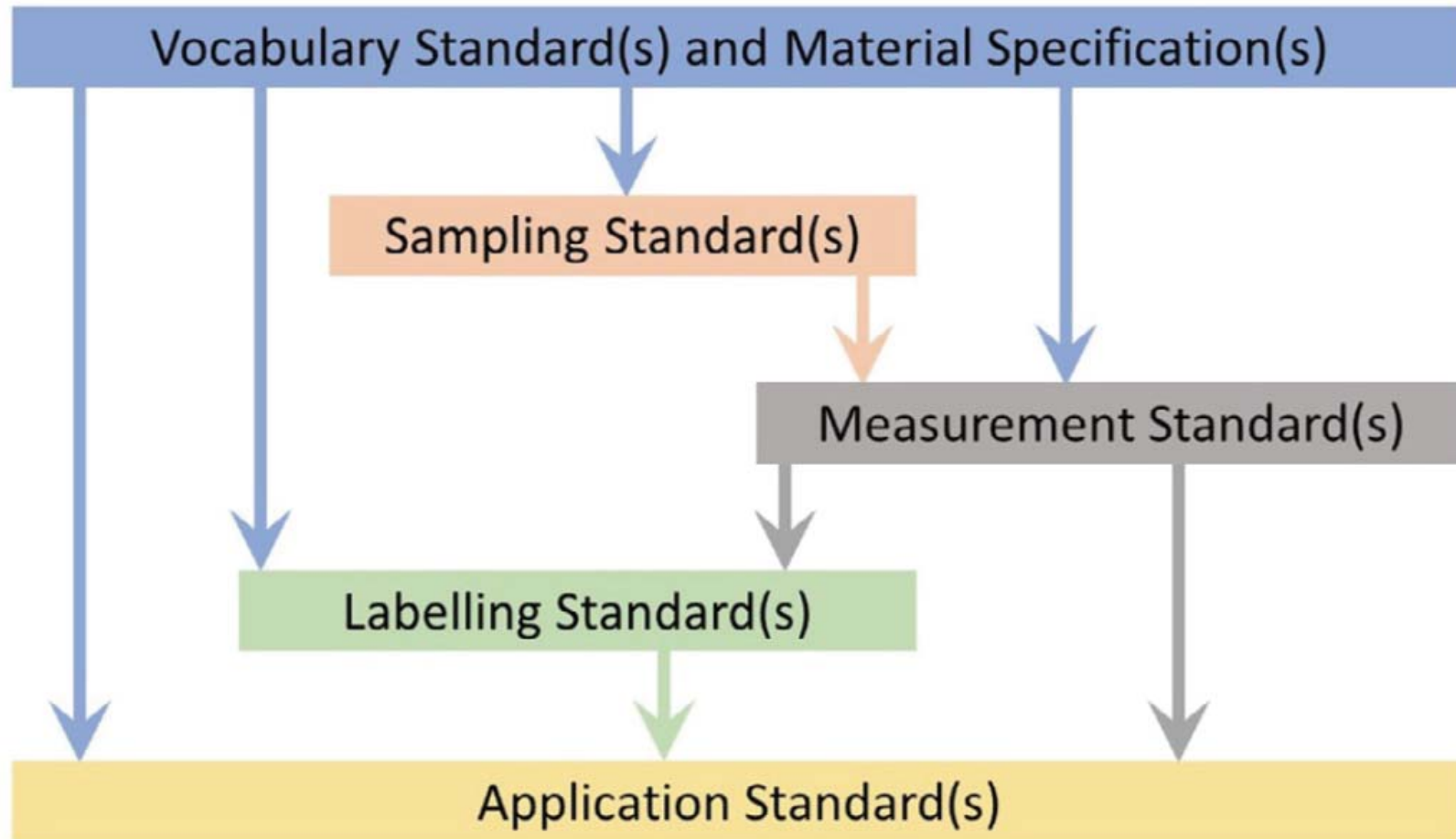
NanoMag Project:

Multicore
magnetic
nanoparticle

- *Terminology for magnetic nanoparticles:*



NanoMag Project:



- *A road map for standardisation.*

MagNaStand Project:

- *Coordinating & representing the EU contribution to two new ISO definitions standards:*

ISO 19807-1 : Magnetic Nanosuspensions

ISO 19807-2 : Magnetic Microbeads



EMPIR



The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

MagNaStand Project:

- *ISO 19807-1 includes definitions relevant to magnetic field hyperthermia:*

Magnetic field hyperthermia : the process where a time varying magnetic field of frequency f and amplitude H_0 results in a temperature T increase of a magnetic nanosuspension.

Specific Loss Power (SLP) : is in magnetic field hyperthermia the heating power of a magnetic nanosuspension per unit mass in response to a time varying magnetic field of frequency f and amplitude H_0 .

MagNaStand Project:

- *The definition of SLP include three notes:*

Note 1 to entry : *The unit mass can relate to the whole nanosuspension, to the solid content or to other compartments of the nanosuspension. It should be indicated which mass is used in reporting the SLP.*

Note 2 to entry : *In addition to the SLP, the intrinsic loss power (ILP) may be reported, which is given by the equation: $ILP = SLP / (f \cdot H_o^2)$*

Note 2 to entry : *When reporting the SLP or ILP parameter, also the initial temperature of the magnetic nanosuspension before the heating as well as frequency f and amplitude H_o of the excitation field should be indicated.*

Towards Clinical Translation



IN VIVO
TRACKING

STABILITY

STANDARDS

Towards Clinical Translation

(a) Magnetite



(b) Maghemite



STABILITY

- Lara Bogart
- Geraldo da Costa
- Jeppe Fock

Magnetite or maghemite?



Magnetite, Fe_3O_4



Maghemite, $\gamma\text{-Fe}_2\text{O}_3$

Magnetite or maghemite?

- *Both magnetite and maghemite comprise a cubic lattice of close-packed oxygen atoms in an ABCABC stacking sequence, within which there are octahedral and tetrahedral sites at which the iron atoms may sit.*
- *They have a spinel type unit cell of 32 oxygen atoms with 8 tetrahedral (A) and 16 octahedral (B) sites available for occupation by the cations.*
- **Magnetite:** $(\text{Fe}^{3+})_{\text{tet}} [\text{Fe}^{3+} \text{Fe}^{2+}]_{\text{oct}} \text{O}_4$
- **Maghemite:** $(\text{Fe}^{3+})_{\text{tet}} [\text{Fe}^{3+}_{5/3} \square_{1/3}]_{\text{oct}} \text{O}_4$

Magnetite or maghemite?

At the nanoscale:

- *Magnetometry – nearly identical, within error.*
- *XRD – really hard, especially with fine particles.*
- *XAFS, XANES – OK if you have the samples and the beamtime, but expensive.*
- *Chemical, colorimetry – OK but needs skill as it requires full dissolution without changing the oxidation state of the Fe ions.*

Why it matters:

- *In biomedical applications, a key question is whether the nanoparticles are magnetite or maghemite?*
- *This stems from the **redox activity** of the material.*
- *This is related to the Fenton reaction:*



*which promotes the formation of the highly reactive **hydroxyl radical**, $\bullet\text{OH}$.*

.. although the story is not quite so simple ..

Why it matters:

- *A related reaction is the Haber-Weiss reaction, a two-step (catalytic) process:*



where the second step is the Fenton reaction.

The net reaction is:

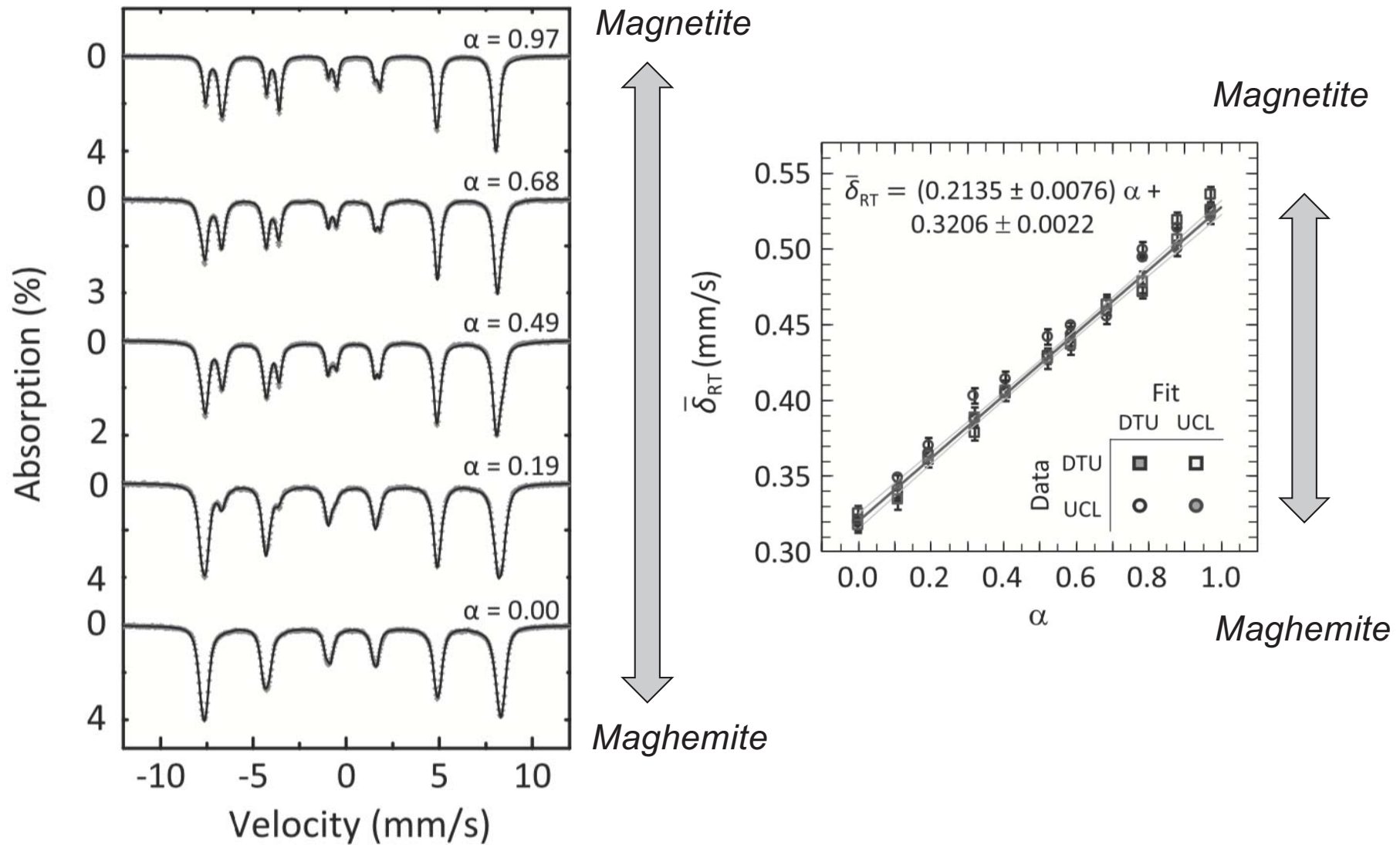


*which converts the relatively unreactive $\bullet\text{O}_2^-$ superoxide into the highly reactive $\bullet\text{OH}$ **hydroxyl radical**.*

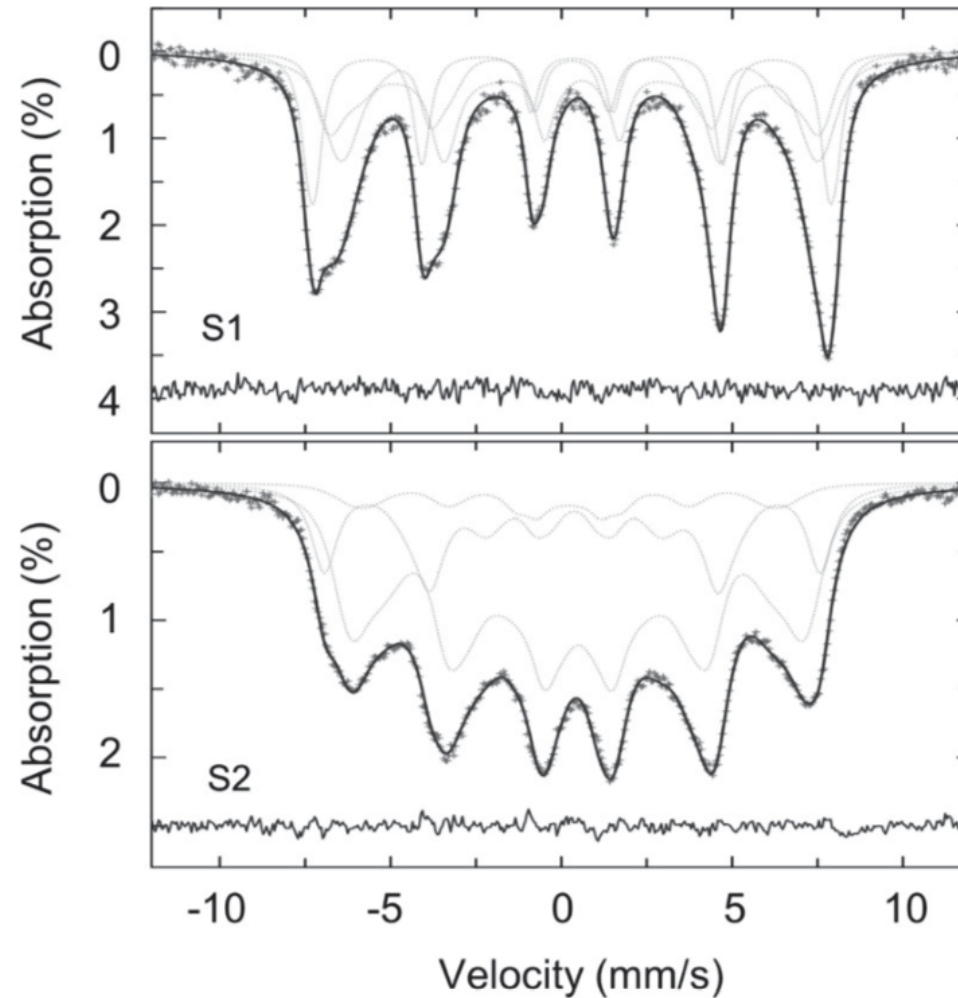
Why it matters:

- *The production of ROS is a part of **normal healthy** cellular function, e.g. in mobilising ion transport.*
- *They also promote **wound repair** (platelets release ROS to recruit more platelets) and to mediate apoptosis after ischaemia (heart attack or stroke).*
- *But they can also cause **cell death** – especially the $\bullet\text{OH}$ hydroxyl radical – which removes electrons from any molecule in its path, turning that molecule into a free radical and so propagating a chain reaction.*
- *In any case, it is **important to know** the charge state of the iron oxide nanoparticles, and to know whether this is stable over time.*

Our solution – the COG Method:



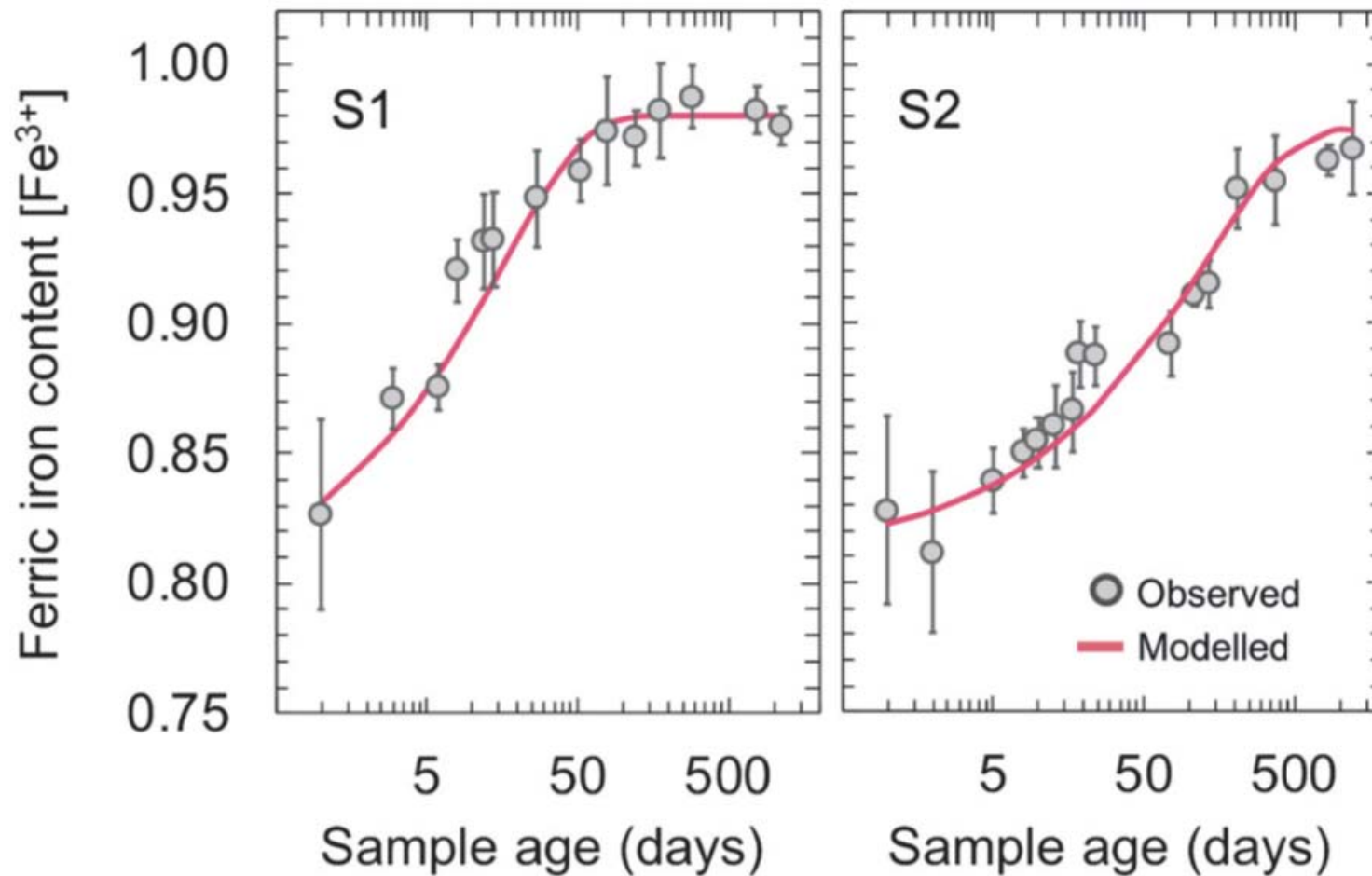
Monitoring environmental ageing:



Monitoring environmental ageing:

S1: Anaerobic

S2: Aerobic



Monitoring environmental ageing:

Sample	Diffusion Constant (m ² /s)
S1: Anaerobic synthesis nanoparticles	3.0×10^{-24}
S2: Aerobic synthesis nanoparticles	0.5×10^{-24}
Comparison: micron-sized iron oxide particles	13.0×10^{-24}

Healthcare Biomagnetics



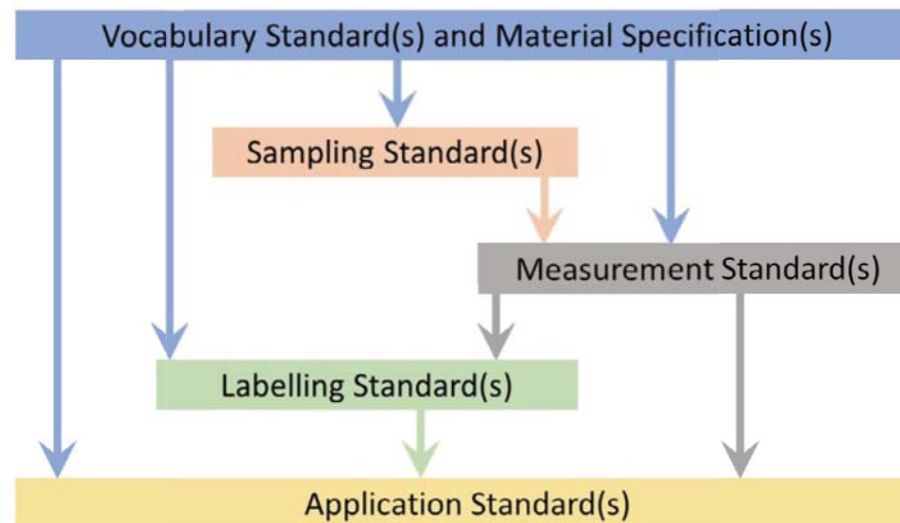
Towards Clinical Translation



(a) Magnetite



(b) Maghemite



Thank you!