MRI Contrast agents

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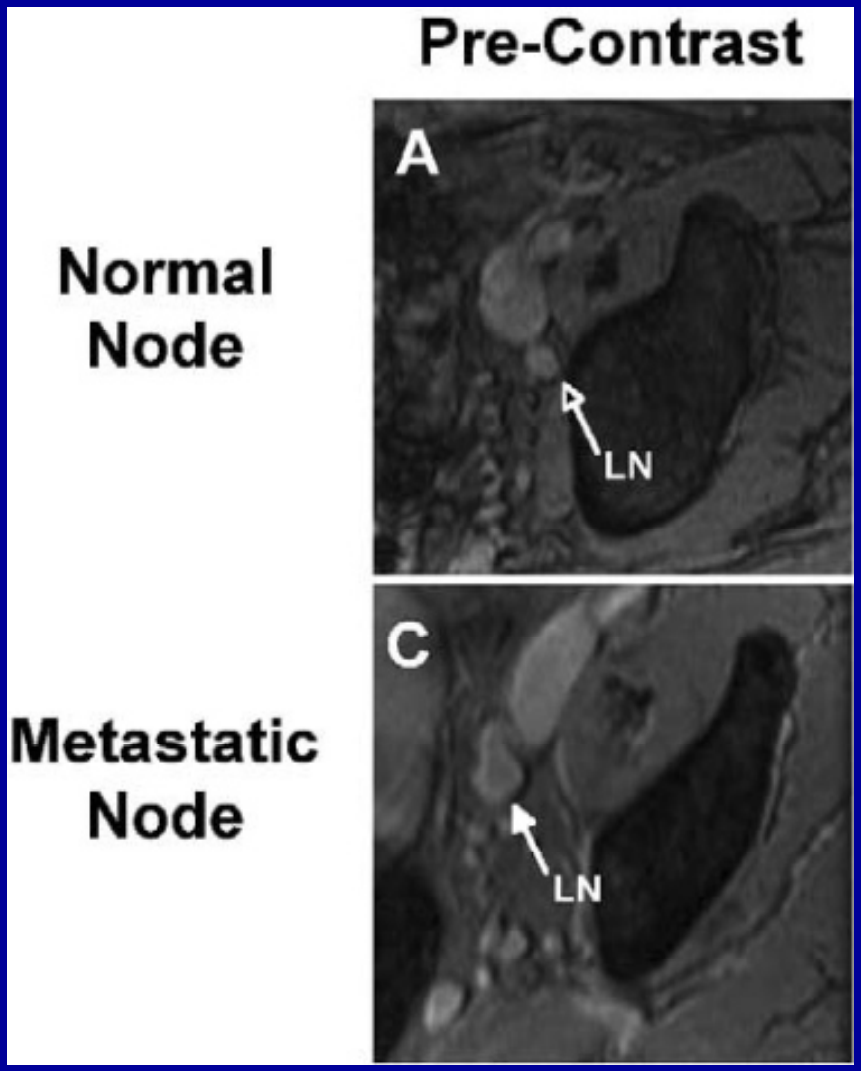
MRI

- Magnetic resonance imaging (MRI):
- A powerful non-invasive diagnostic imaging modality
- No use of ionizing radiation
- 3D reconstructed images
- High soft tissue contrast
- High spatial resolution

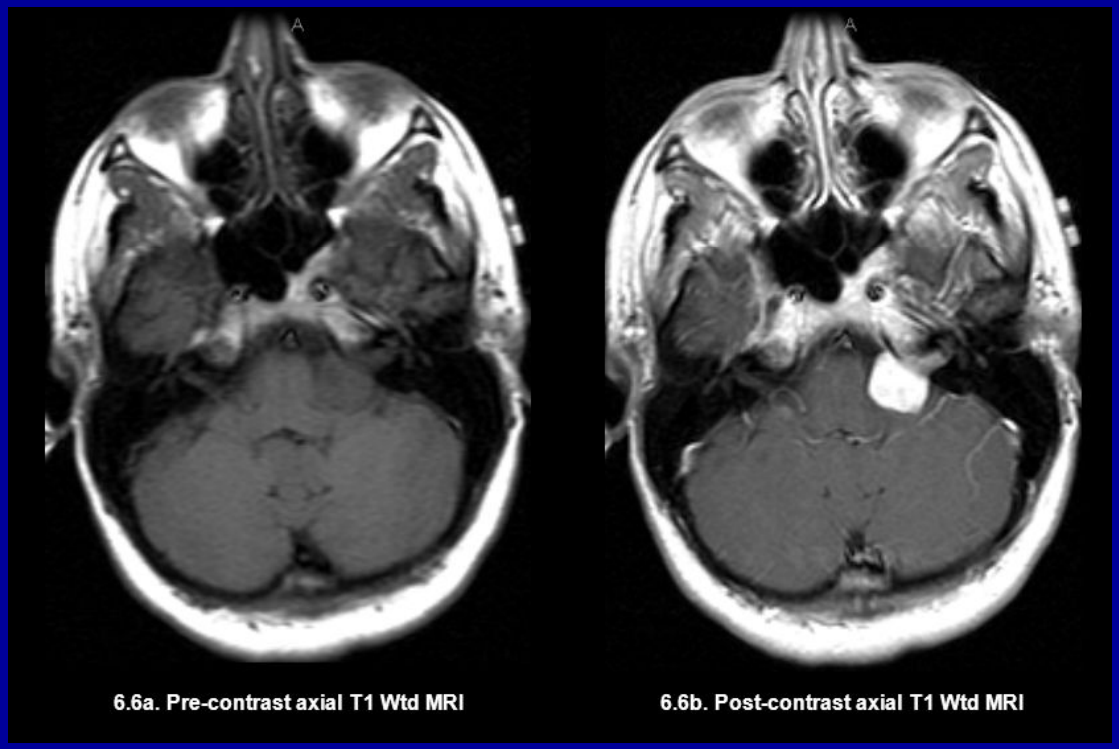
MR images contrast

- MRI contrast
- Inherent MRI contrast depends on:
- Relaxation times (T1 and T2)
- Proton density of the materials or tissues

MR images contrast



MRI contrast agents (CAs)



6.6a. Pre-contrast axial T1 Wtd MRI

6.6b. Post-contrast axial T1 Wtd MRI

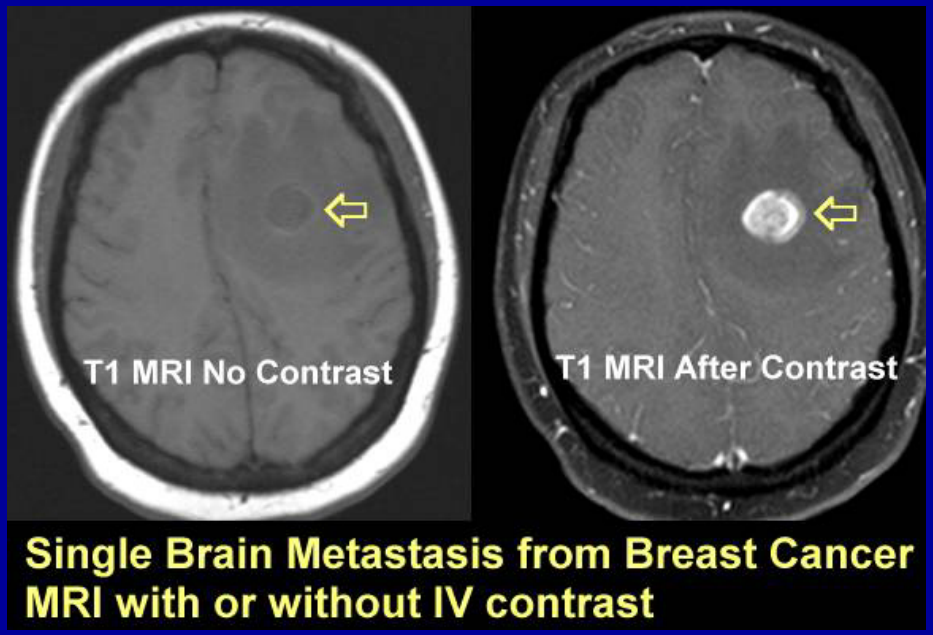
MRI contrast agents

- Paramagnetic
- Superparamagnetic
- Reduction of the proton relaxation times →
- Changes of signal intensity in the accumulated region

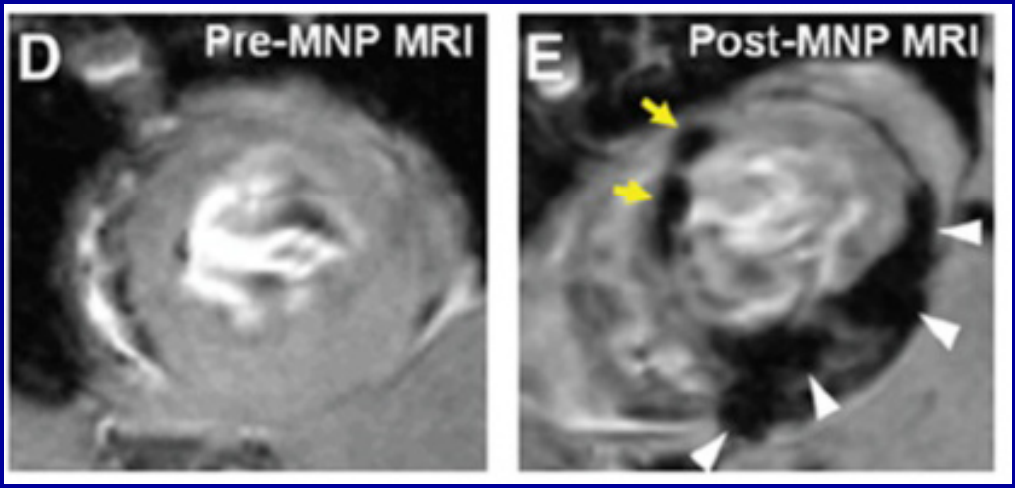
MRI Contrast agents

- Positive
- Negative

Positive contrast agents



Negative contrast agents



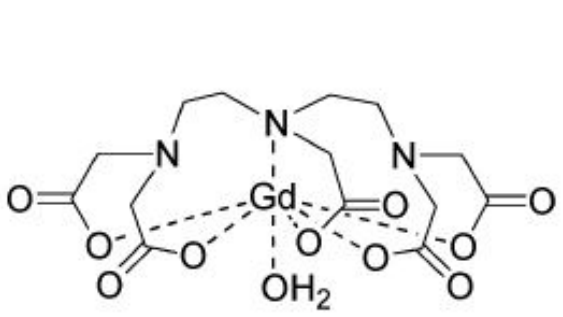
Gadolinium

- Gd:
  - Paramagnetic substance
  - Relatively large magnetic moment
  - Free Gd ions are cytotoxic and are retained in liver, spleen, and bone!
  - Attachment to a chelate

Gadolinium

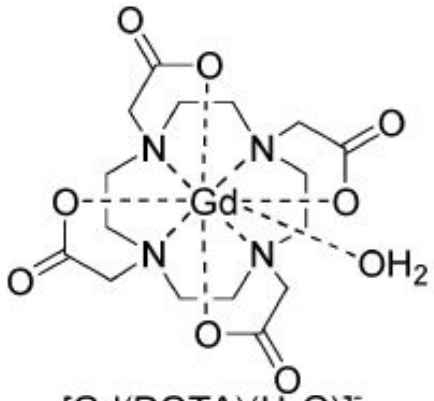
- The most common chelate in use is diethylene triaminepentaacetic acid (DTPA)
- Other chelates:
- HP-DO3A
- DTPA-BMA
- DOTA

Gadolinium based commercial contrast agents



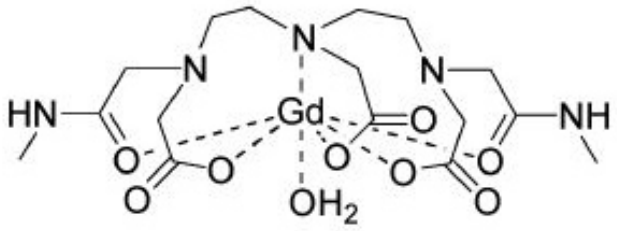
$[Gd(DTPA)(H_2O)]^{2-}$

(Magnevist: Berlex/Schering)



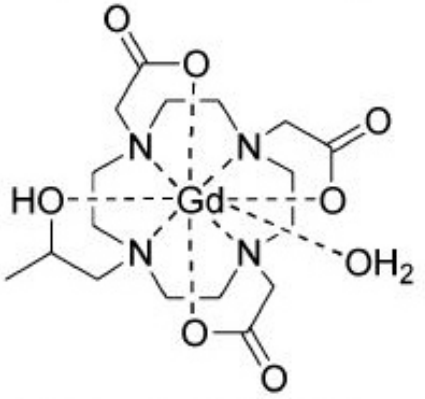
$[Gd(DOTA)(H_2O)]^{-}$

(Dotarem: Guerbet)



$[Gd(DTPA\text{-}BMA)(H_2O)]$

(Omniscan: Nycomed-Amersham)



$[Gd(HP\text{-}DO3A)(H_2O)]$

(Prohance: Bracco)

Figure 2. Common commercial Gd(III) contrast agents.

Nano Gd based CAs

- Recent advances in the field of nanotechnology have lead to the synthesize ultra-small crystals (2–10 nm diameter) containing large amounts of the Gd.
- High relaxivity
- Gd_2O_3

Manganese Based MR Contrast Agents

Mn properties

- A paramagnetic agent
- The second most powerful positive contrast agent for MRI after gadolinium.
- Manganese oxide

Iron oxide nanoparticles

Iron oxide nanoparticles

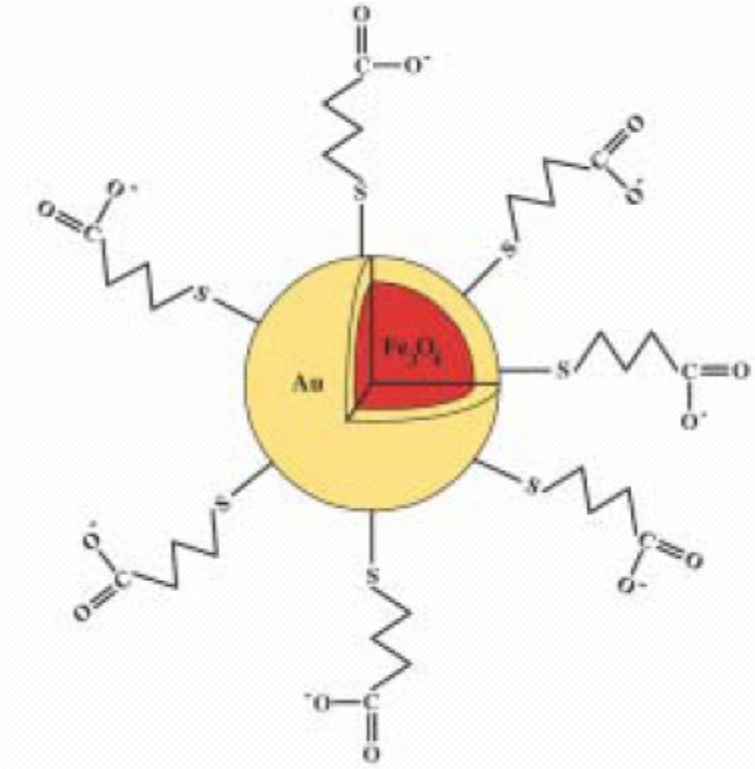
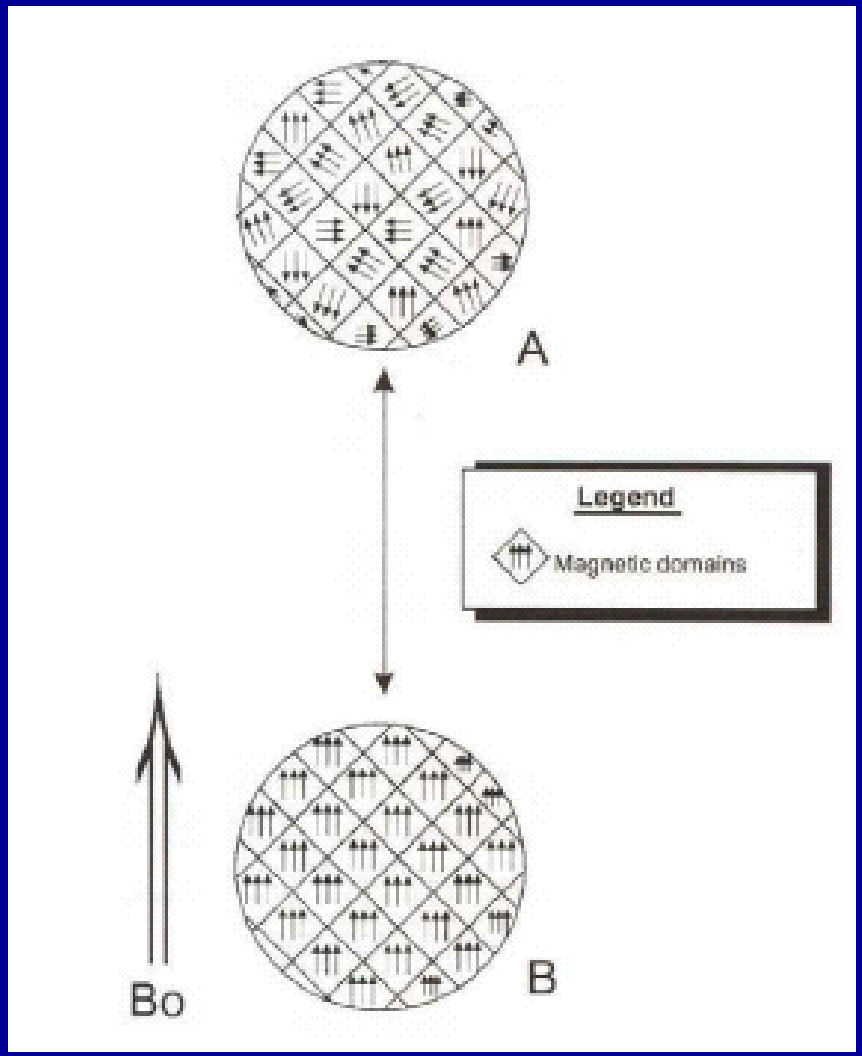


Fig. 1 Au coated ferrite nanoparticles can be attached to functional groups through Au-S bonds. (Credit: Charles O'Connor.)

Coating role

- Avoiding aggregation
- Chemical stability
- Reducing toxicity
- Biocompatibility

Superparamagnetism



Properties of iron oxide nanoparticles

- Superparamagnetic (SPM):
- Controlled by external magnetic fields
- High magnetic moment →
- Using with low doses in comparison with positive contrast agents

Classification

- According to the overall size of the nanoparticles:
- Diameter <50 nm: ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles
- Diameter >50 nm: superparamagnetic iron oxide (SPIO) nanoparticles
- Diameter >200 nm (sometimes several micrometers): large nanoparticles

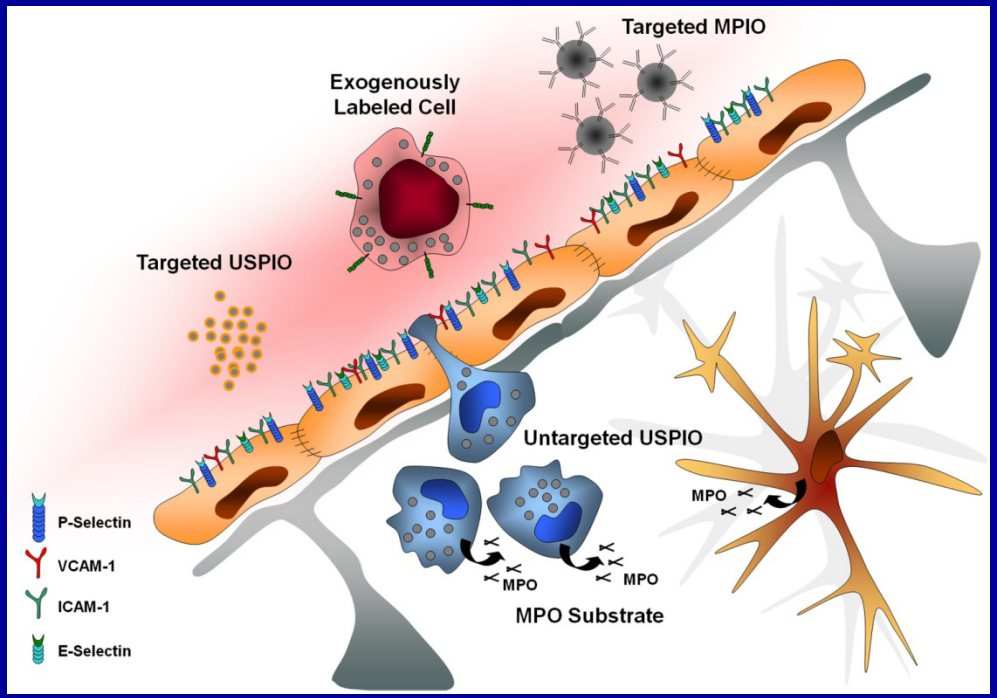
Iron oxide nanoparticles

- Reticuloendothelial system (RES)
- Targeting

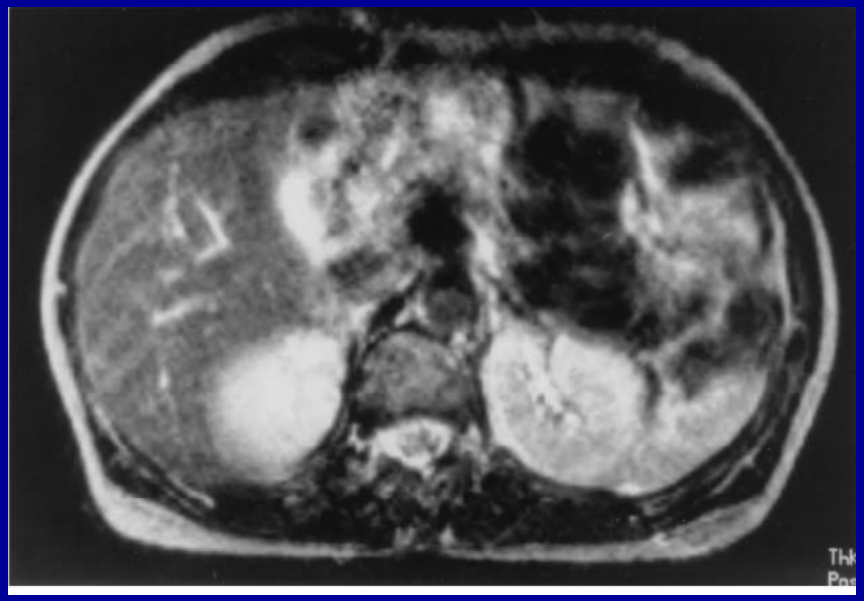
RES agents

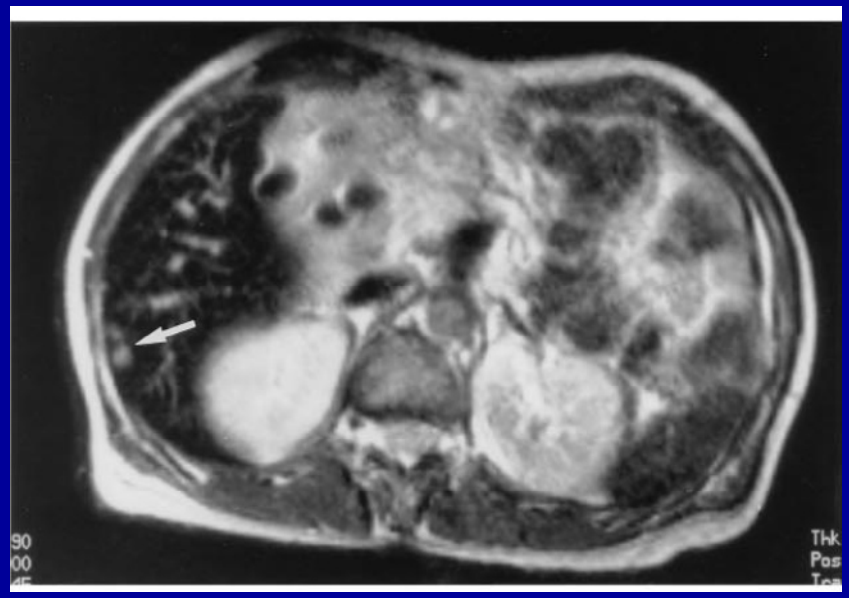
- Iron oxide particles have been evaluated as the reticuloendothelial system (RES) agents
- Using for imaging of:
- Liver
- Spleen
- lymph nodes
- bone marrow

Half-life


Targeted MPIO
Exogenously Labeled Cell
Targeted USPIO
Untargeted USPIO
MPO
MPO
MPO
MPO Substrate
P-Selectin
VCAM-1
ICAM-1
E-Selectin

Liver metastases



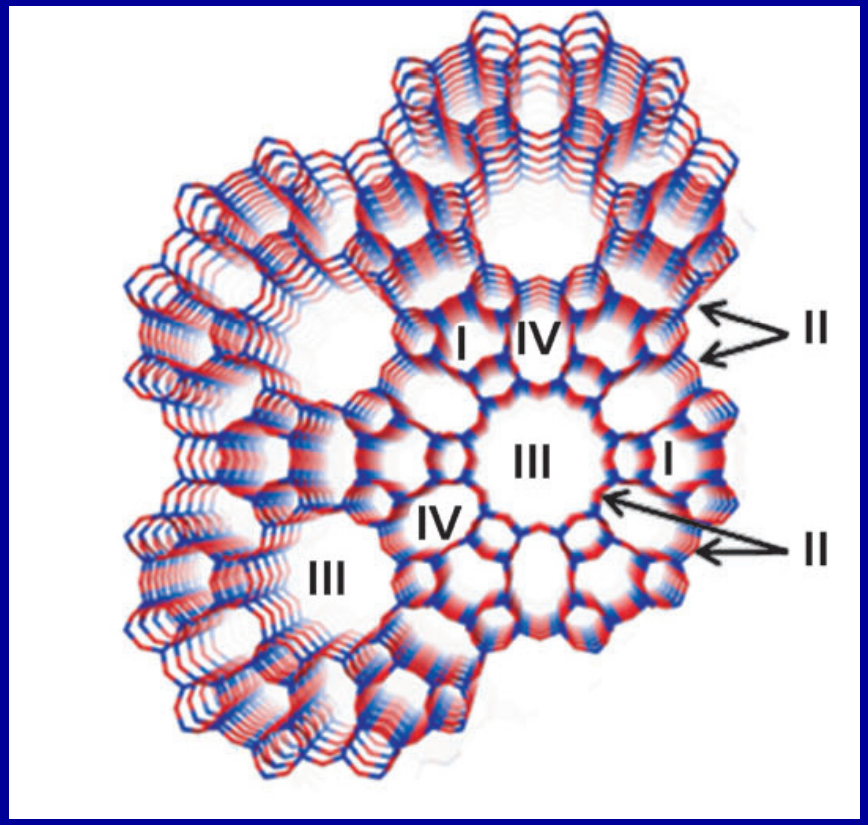


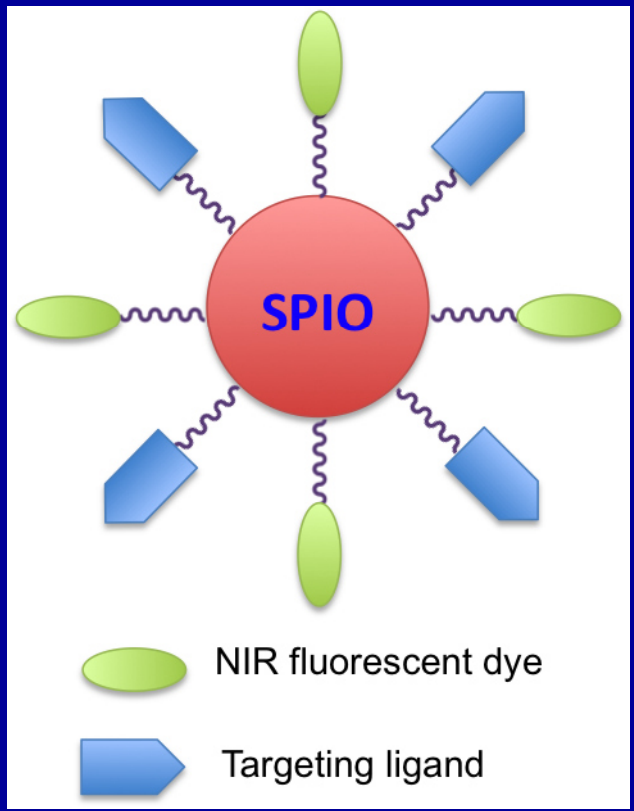
Bimodal and Multimodal agents

Multimodal agents

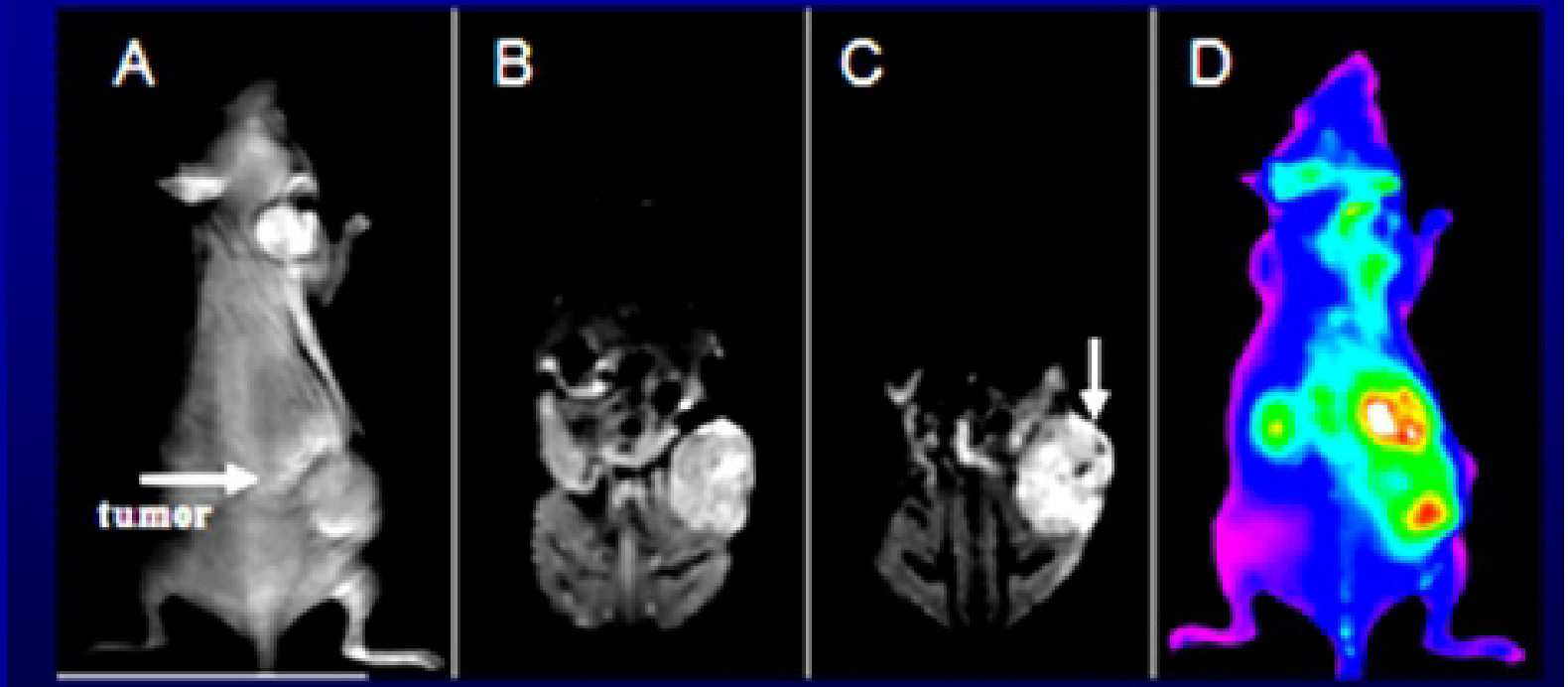
- Coordination complexes that produce MRI contrast in addition to serving as probes for other modalities are an active area of research.

Bimodal MR/optical imaging

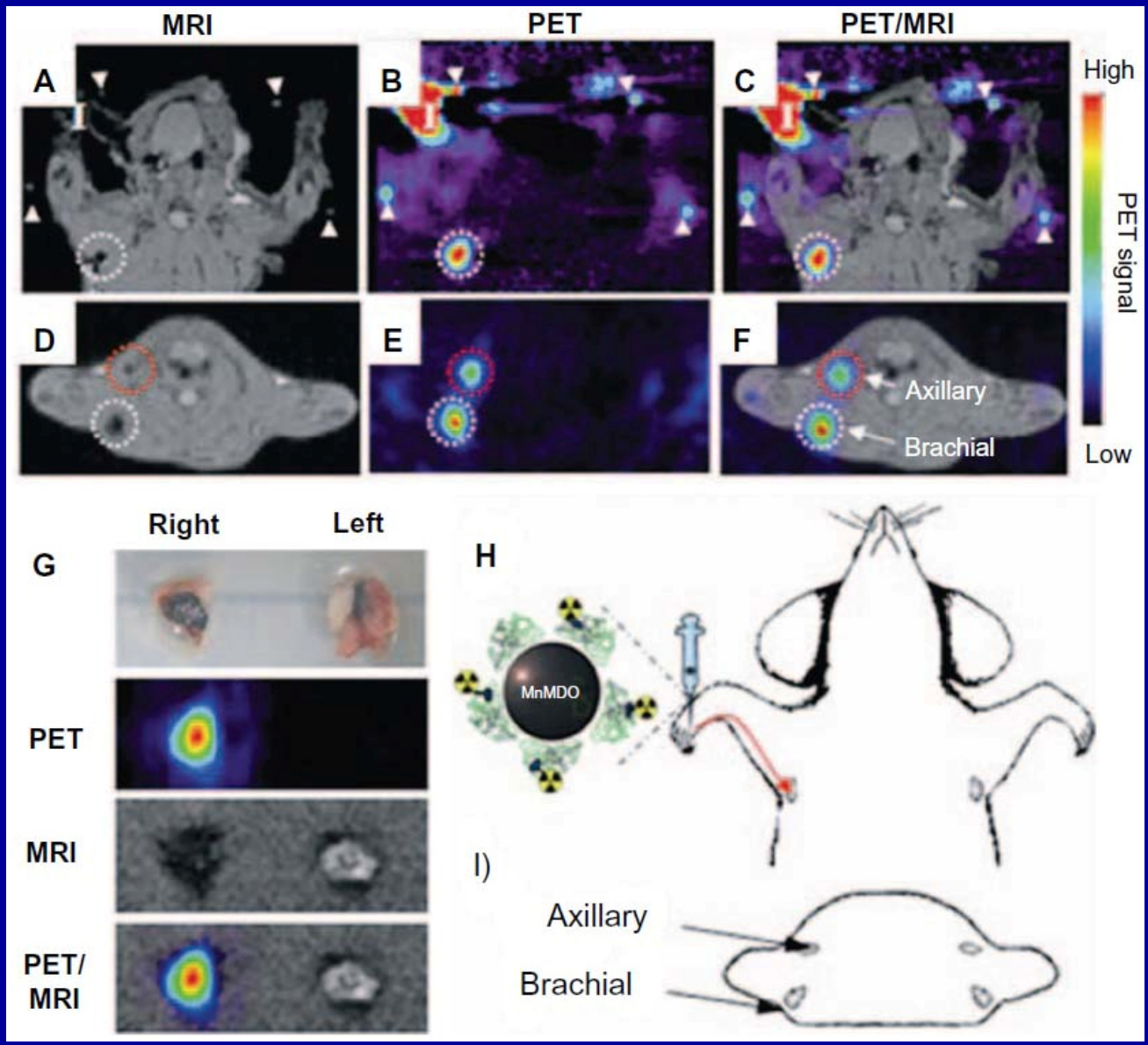




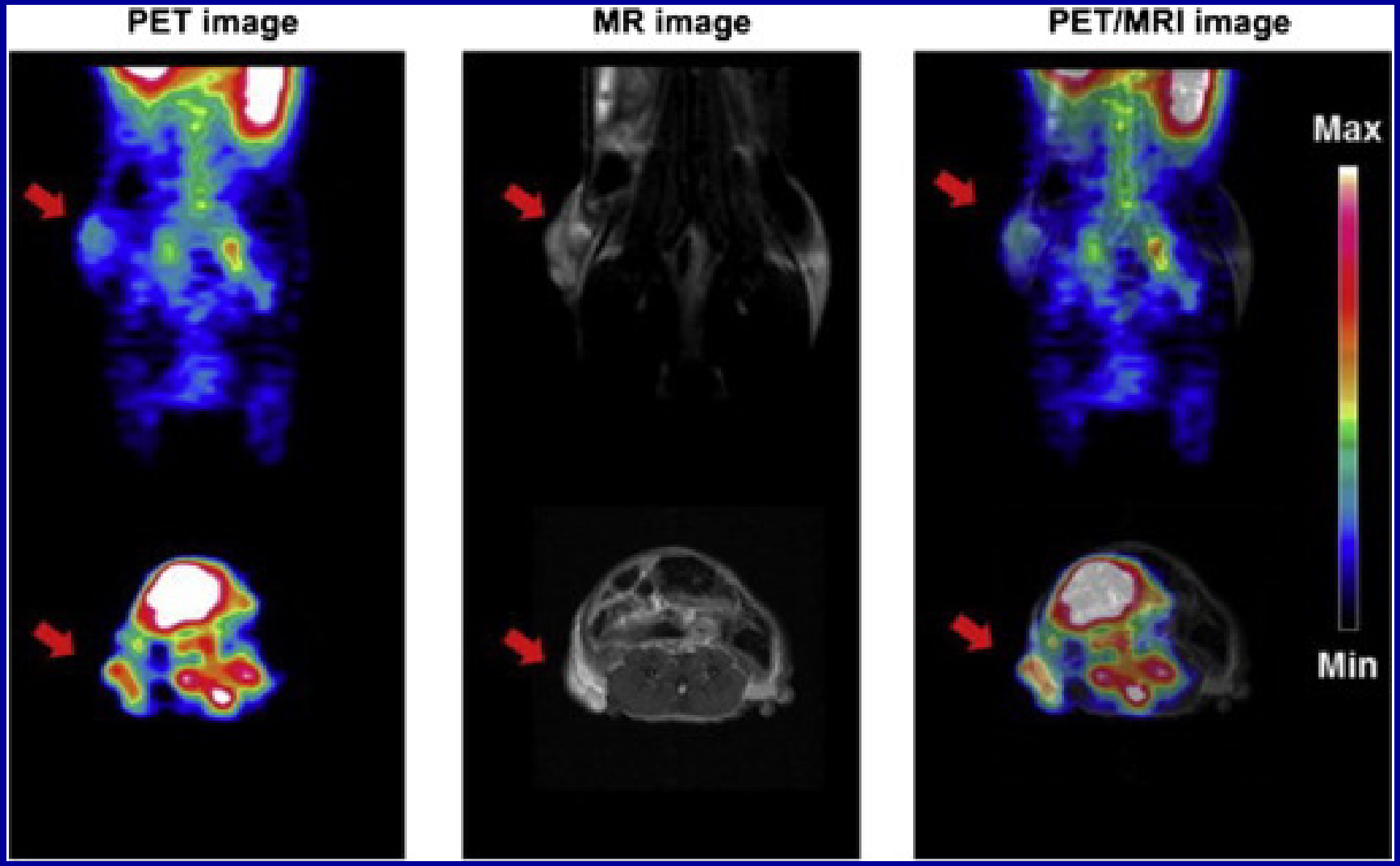
Bimodal MR/optical imaging for breast cancer imaging



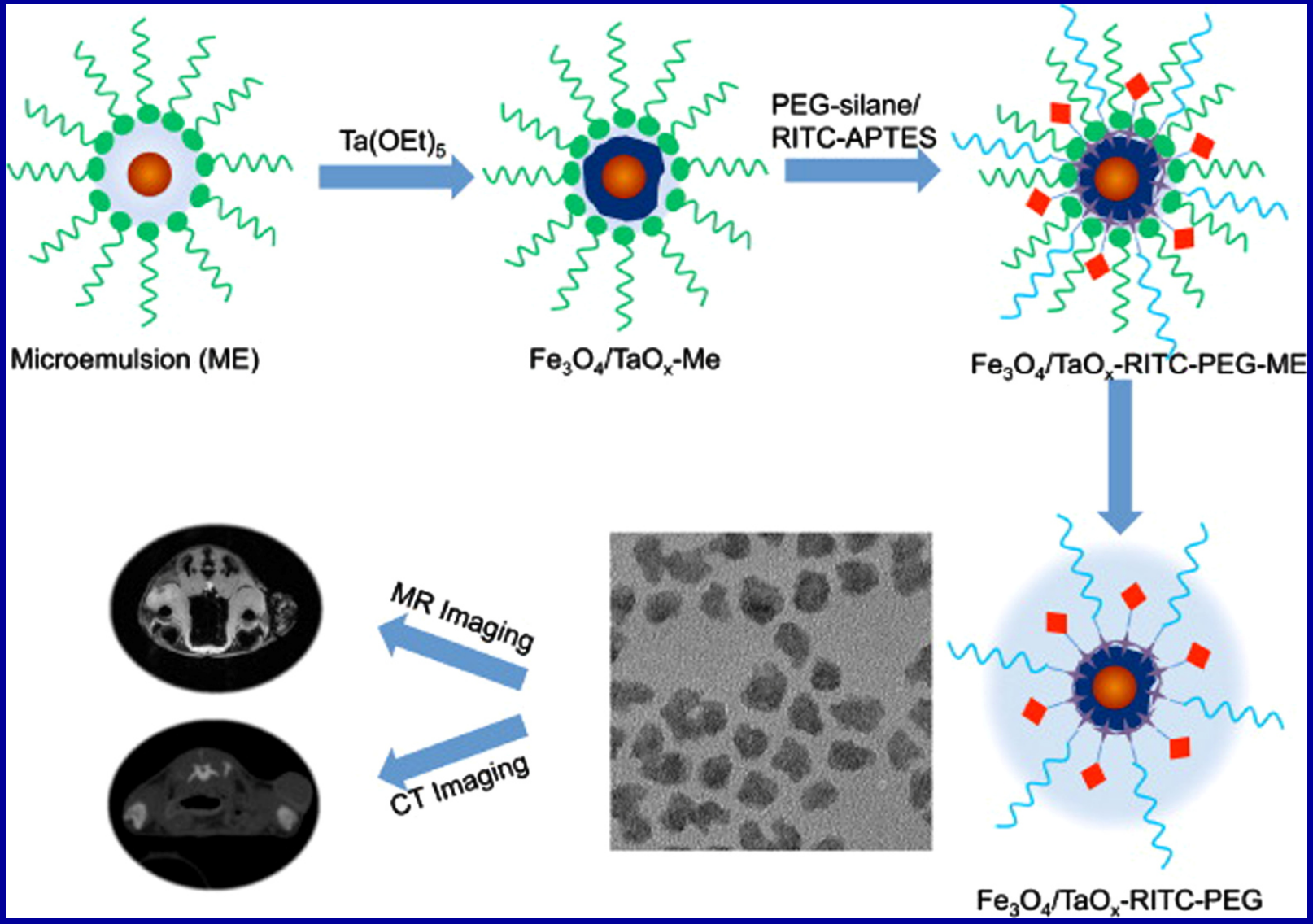
PET/MRI


MRI
PET
PET/MRI
A
B
C
D
E
F
High
PET signal
Low
Axillary
Brachial
Right
Left
G
PET
MRI
PET/
MRI
H
MnMDO
I)
Axillary
Brachial

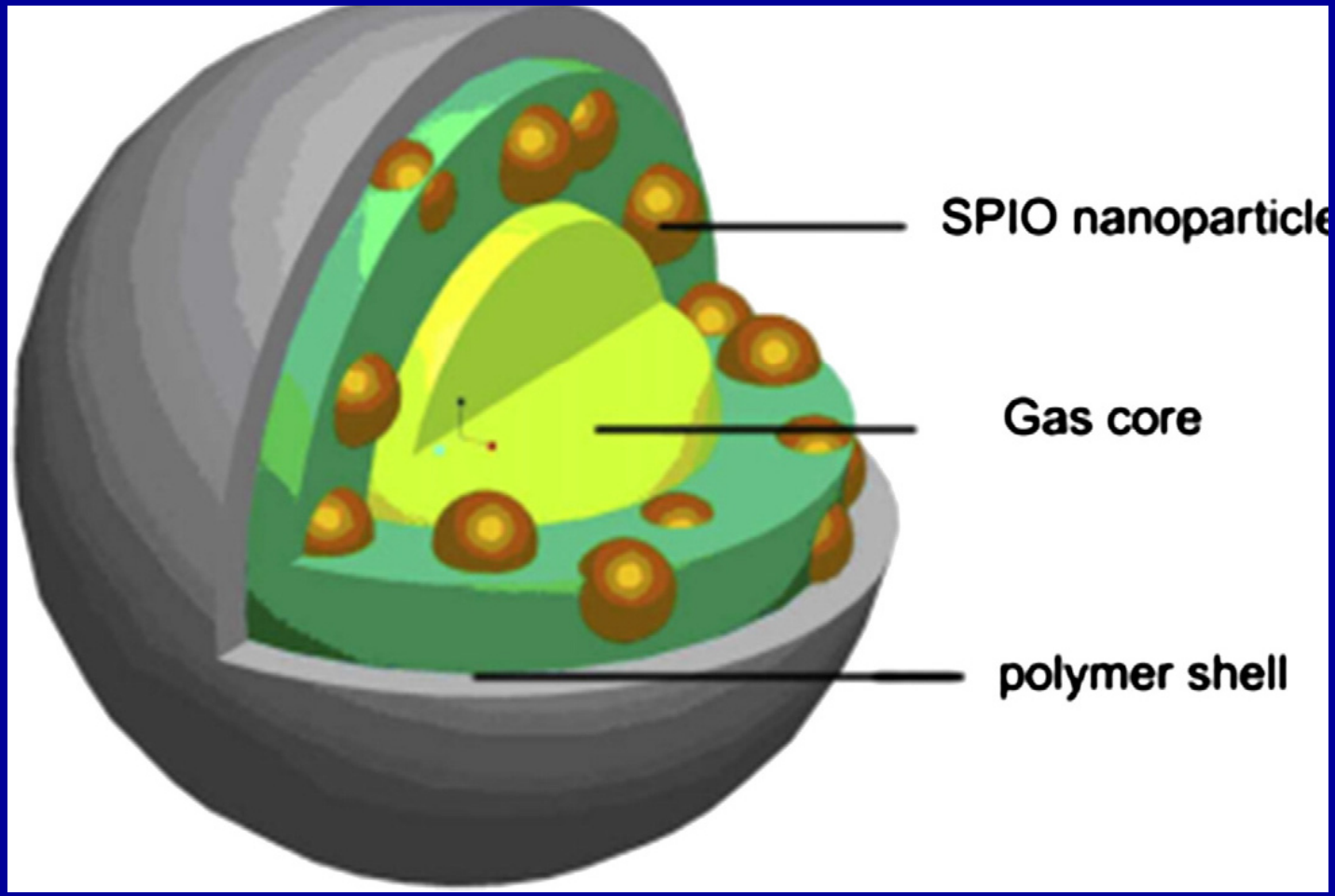
PET/MRI



MRI/CT


Ta(OEt)5
PEG-silane/
RITC-APTES
Microemulsion (ME)
Fe3O4/TaOx-Me
Fe3O4/TaOx-RITC-PEG-ME
MR Imaging
CT Imaging
Fe3O4/TaOx-RITC-PEG

MRI/Ultrasound



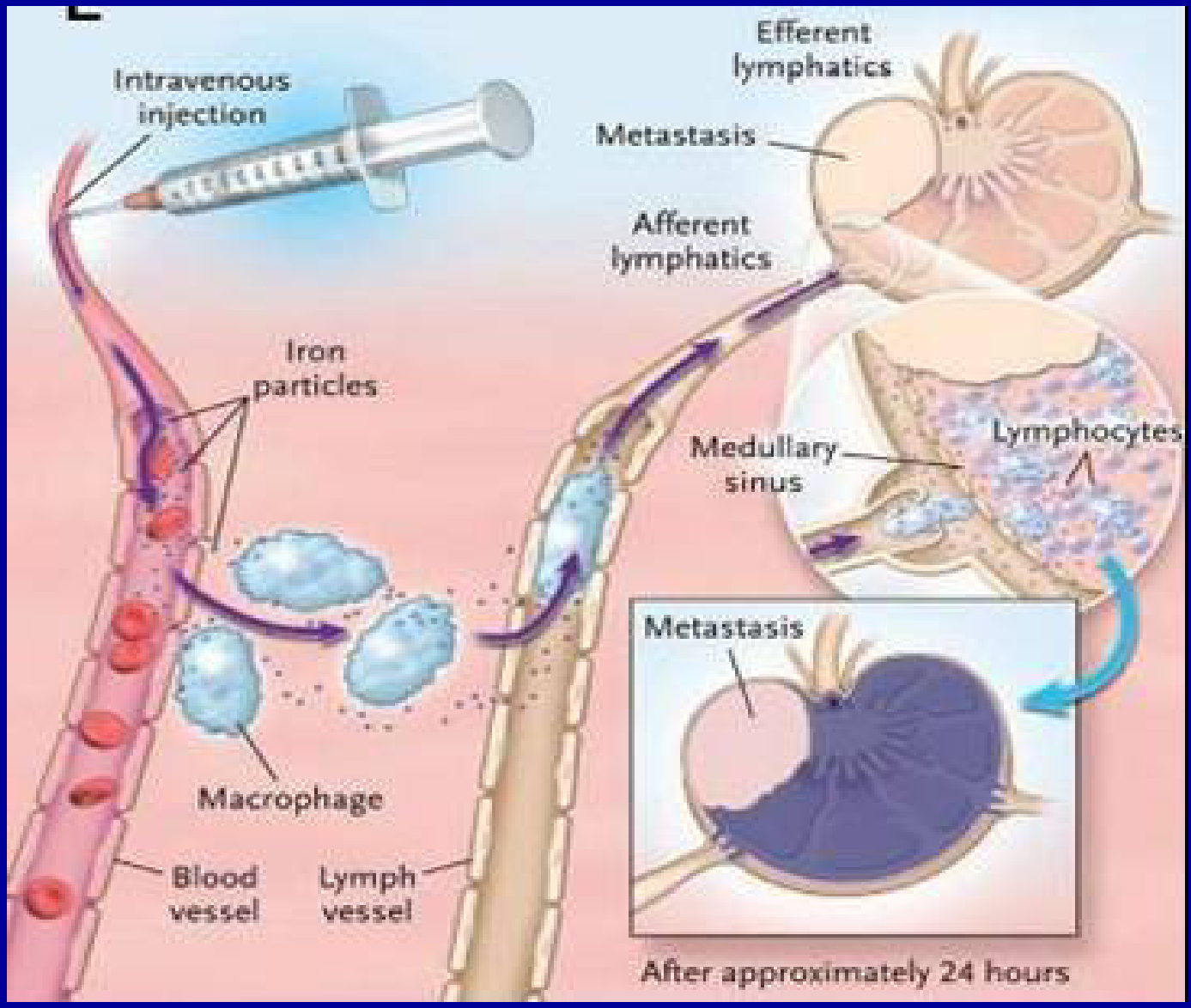
Nanoparticles applications

Cancer detection

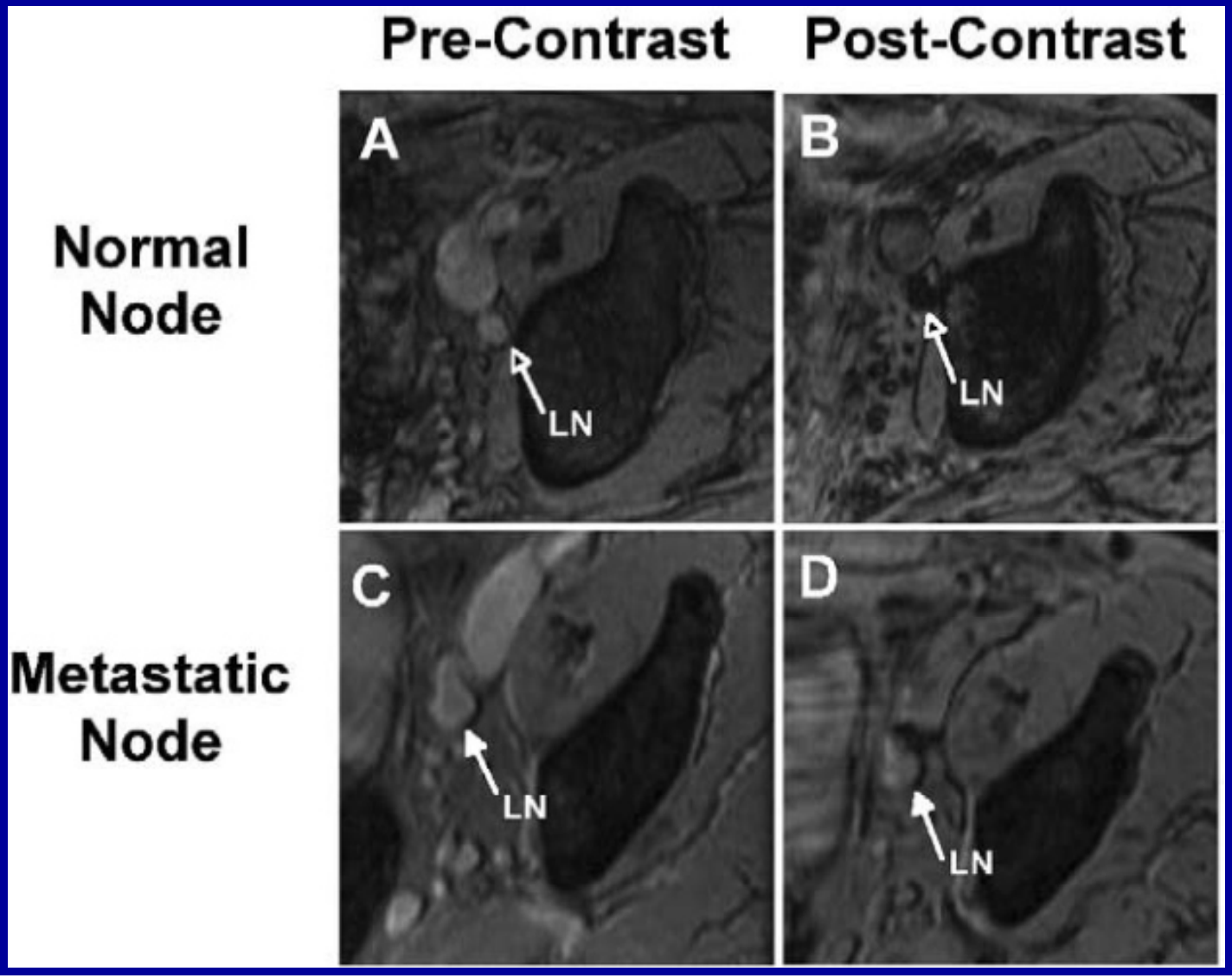
Cancer detection

- A typical clinical application of USPIOs is lymph-node imaging.
- The detection of lymph nodes is critical for:
- Accurate tumor staging
- The subsequent therapeutic planning

MR Lymphography



MR images of normal and metastatic lymph nodes

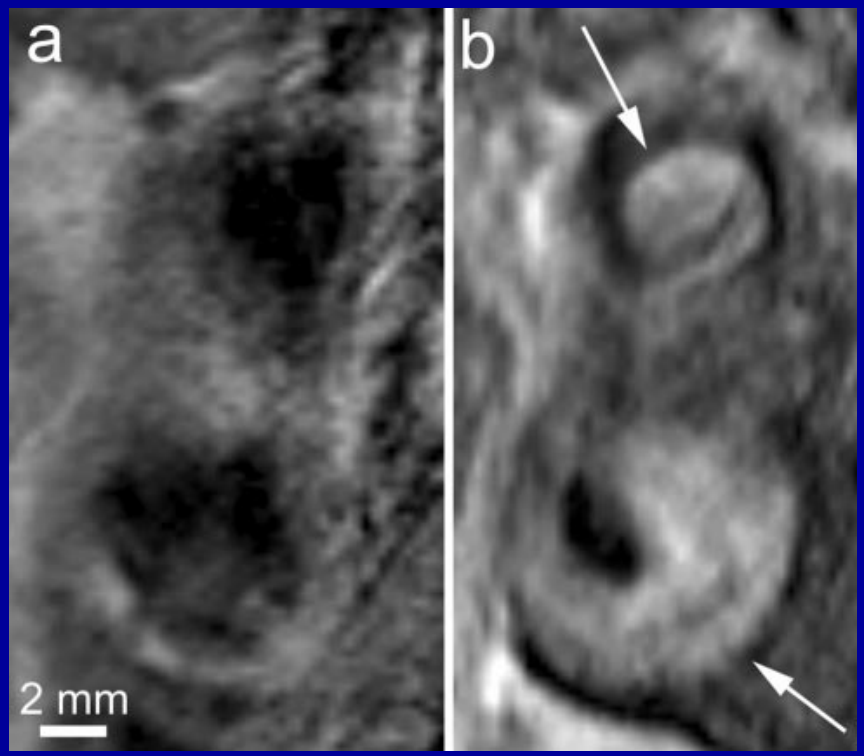


Inflammation/Infection

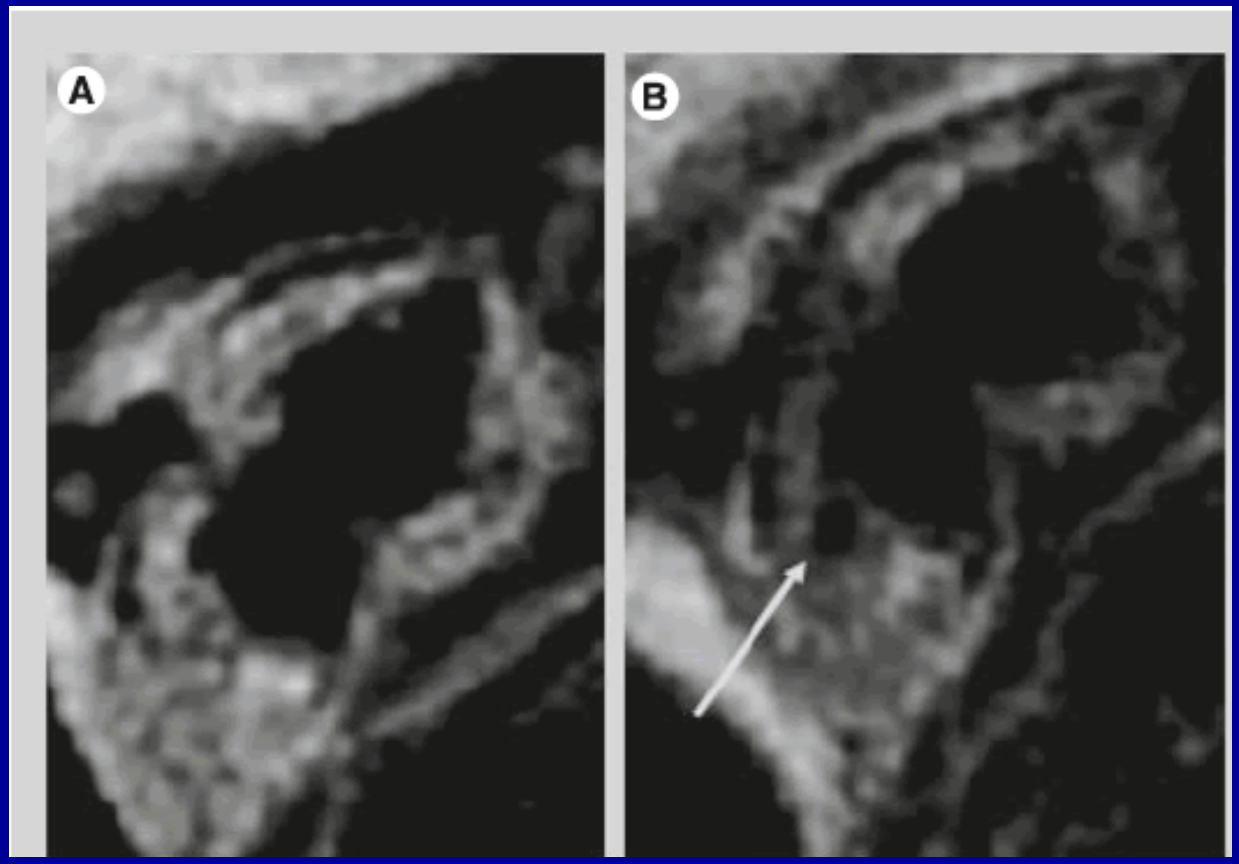
Inflammation

- Phagocytosis by macrophages of injected SPIONs results in hypointensity of macrophage-infiltrated tissues in contrast-enhanced MR images.

Detection of atherosclerotic plaques



USPIO imaging in carotid artery plaque



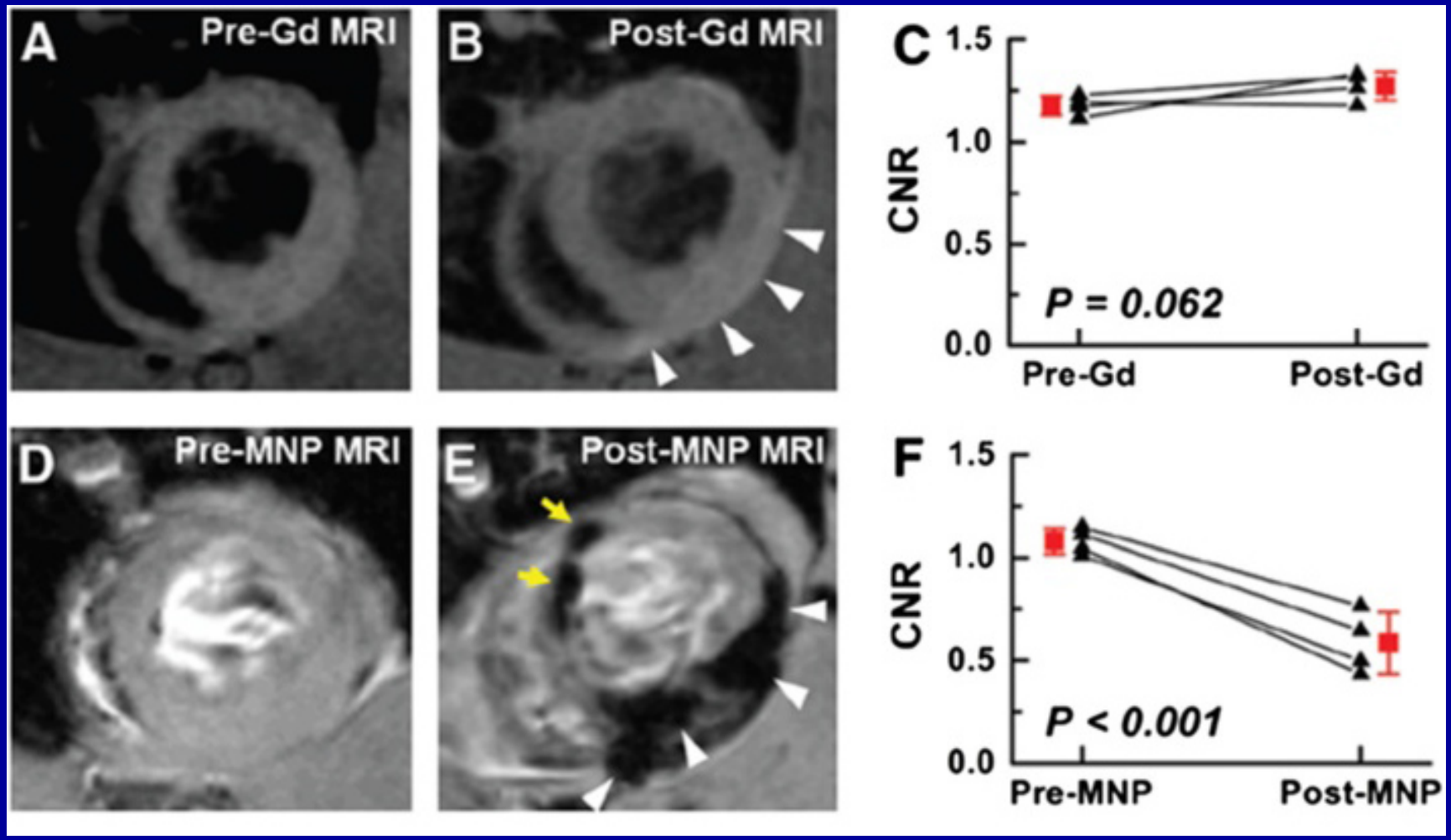
SPIONs applications in patients

- Both coronary and carotid plaques that take up SPIONs are more prone to rupture
- Abdominal aneurysms with increased SPION uptake are more likely to grow

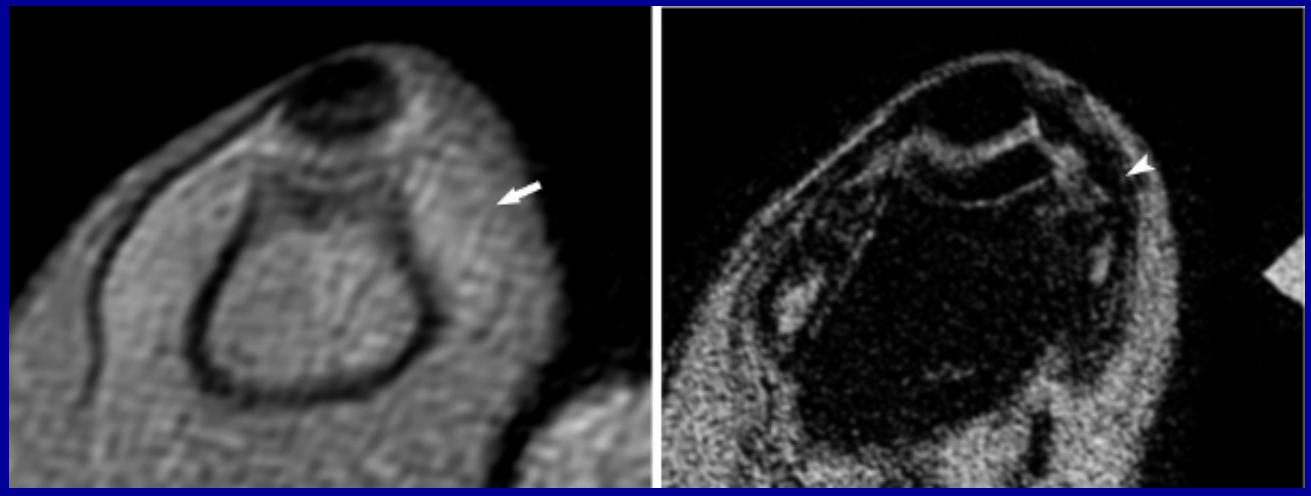
Inflammation

- **SPIONs in Cardiovascular magnetic resonance (CMR):**
- Assessment of myocardial infarction and myocarditis.

Inflammatory lesion in rat left ventricular wall with Gd and SPION



Septic arthritis



Tumor-associated macrophages (TAMs)

- Non-invasive imaging of TAMs using SPION:

1) Staging the inflammatory microenvironment of primary and metastatic tumors

2) Monitoring the treatment response of cancer patients treated with radiation and immunotherapy.

Other USPIO applications

- As positive contrast agent:
- MR angiography
- Perfusion imaging of brain, myocardium and kidney
- Tumor vascular imaging

Cancer therapy

Hyperthermia

Hyperthermia

- Hyperthermia therapy is a type of treatment in which body tissue is exposed to high temperatures to:

1) damage and kill cancer cells

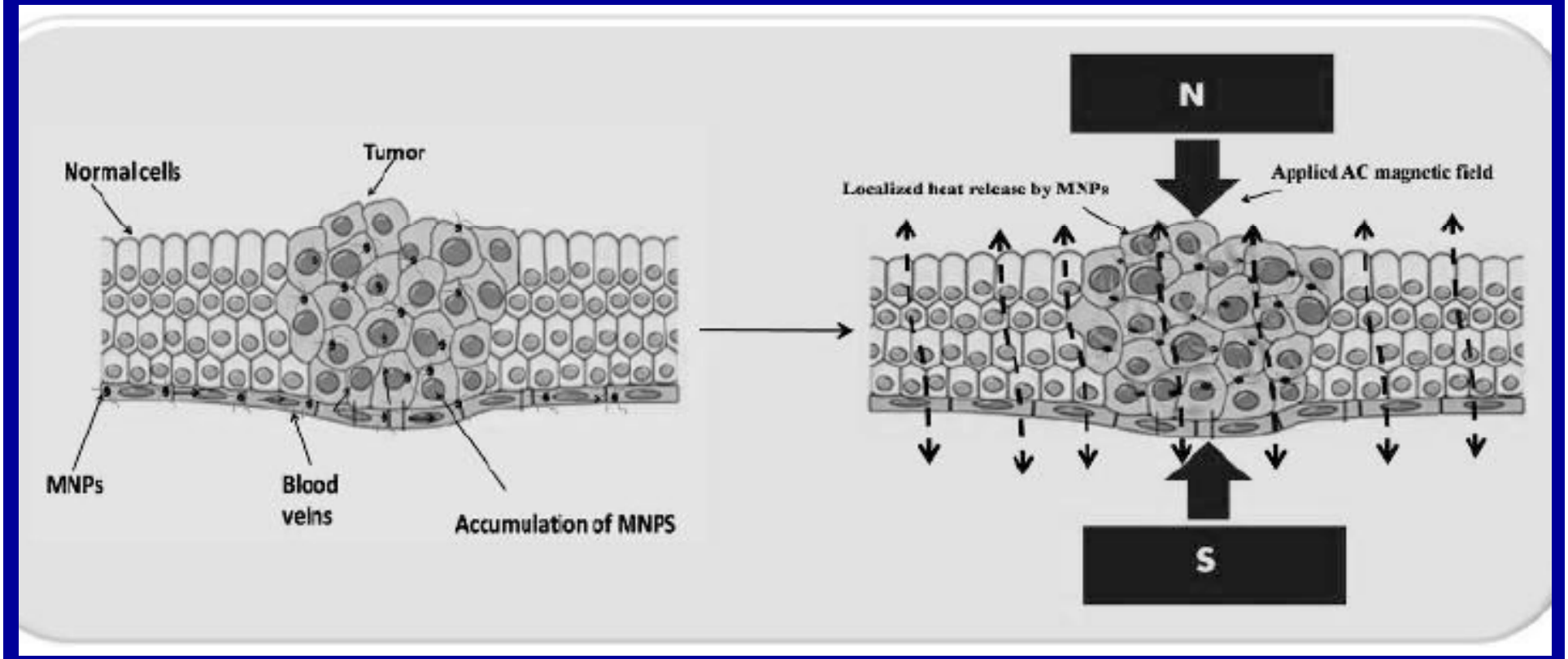
2) make cancer cells more sensitive to the effects of radiation and certain anticancer drugs.

- Temperature level: 41- 45 C

Hyperthermia

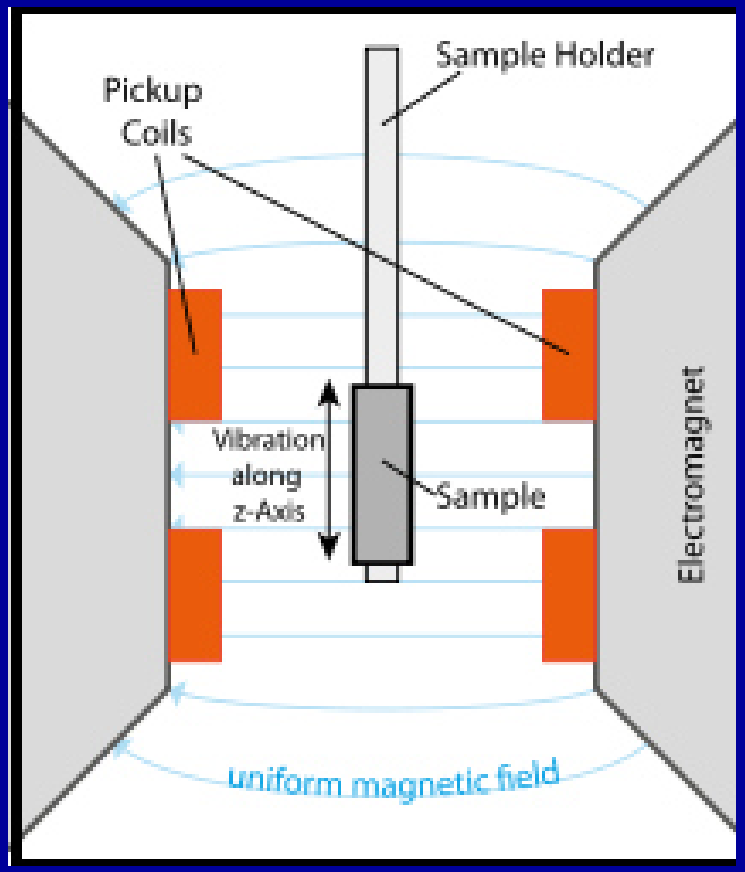
- External hyperthermia:
- The heat is applied from outside the body using various means such as microwaves, radiofrequencies, ultrasound etc.
- Internal hyperthermia:
- Certain foreign substances are inserted inside the body to act as sources of heat.

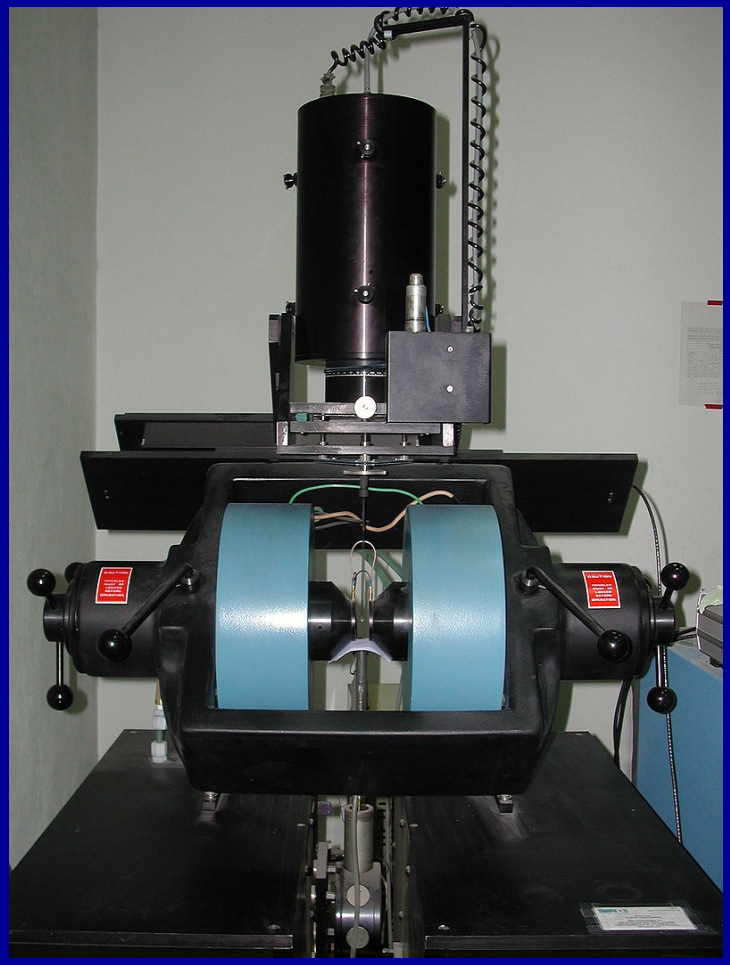
Hyperthermia

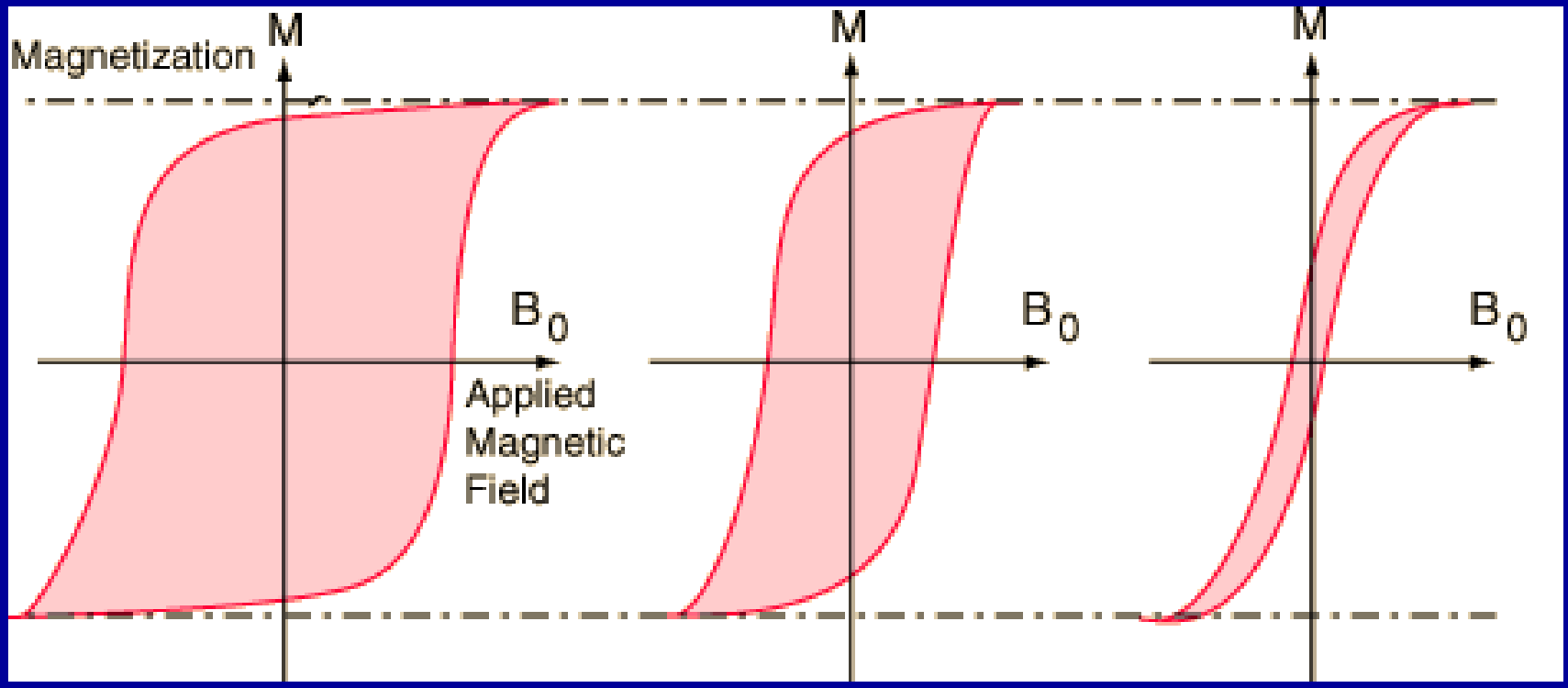


Magnetometry

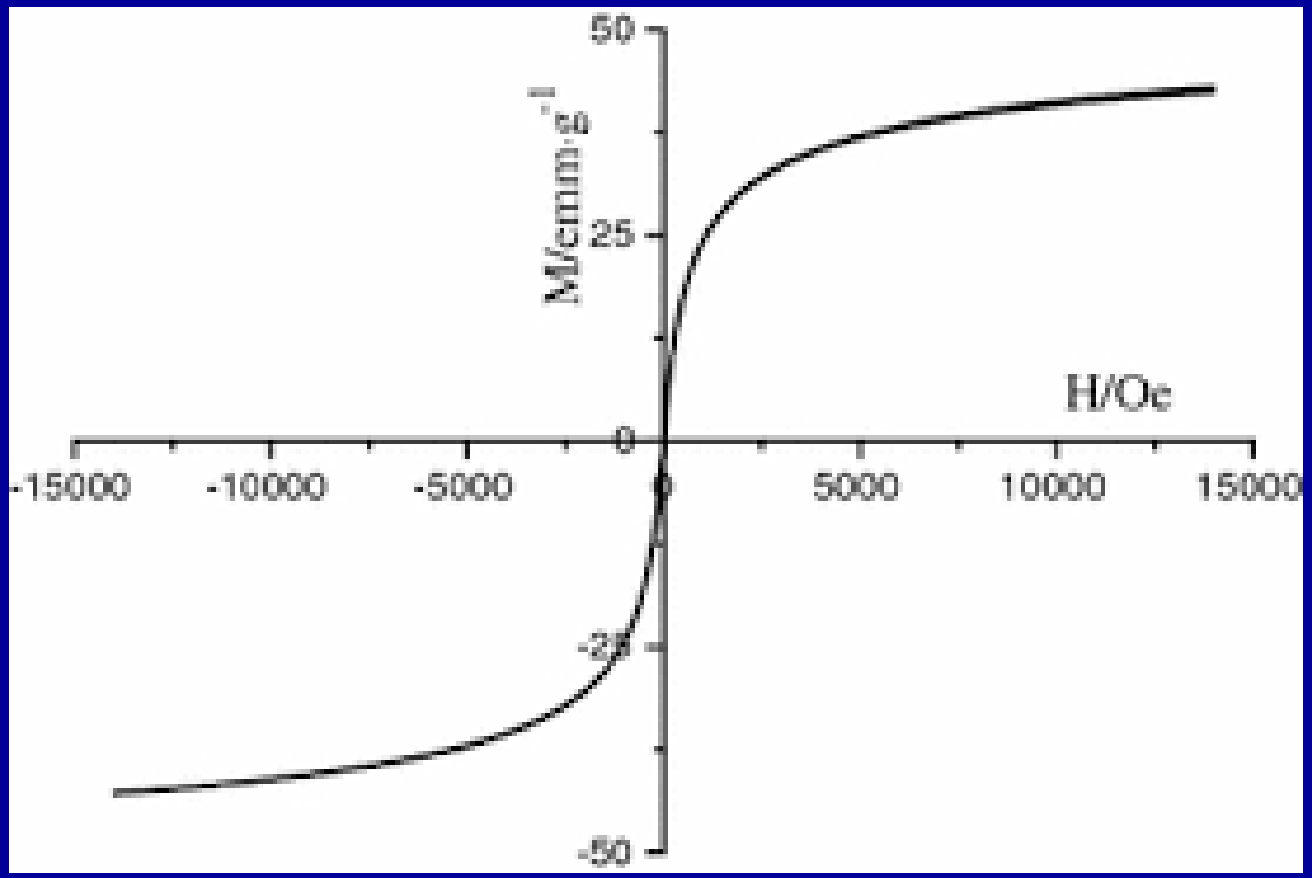
Vibrating sample magnetometer (VSM)





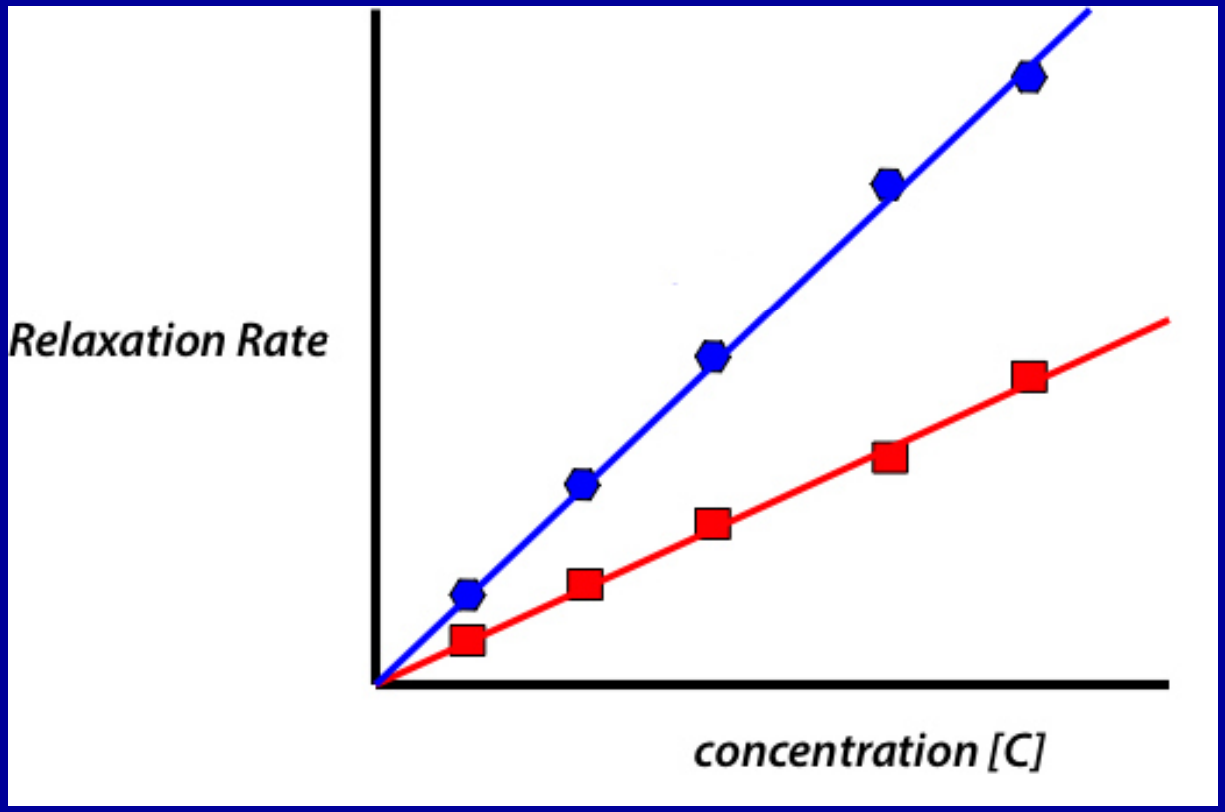

Magnetization
M
B0
Applied
Magnetic
Field
M
B0
M
B0

Superparamegnetic contrast agent magnetization curve

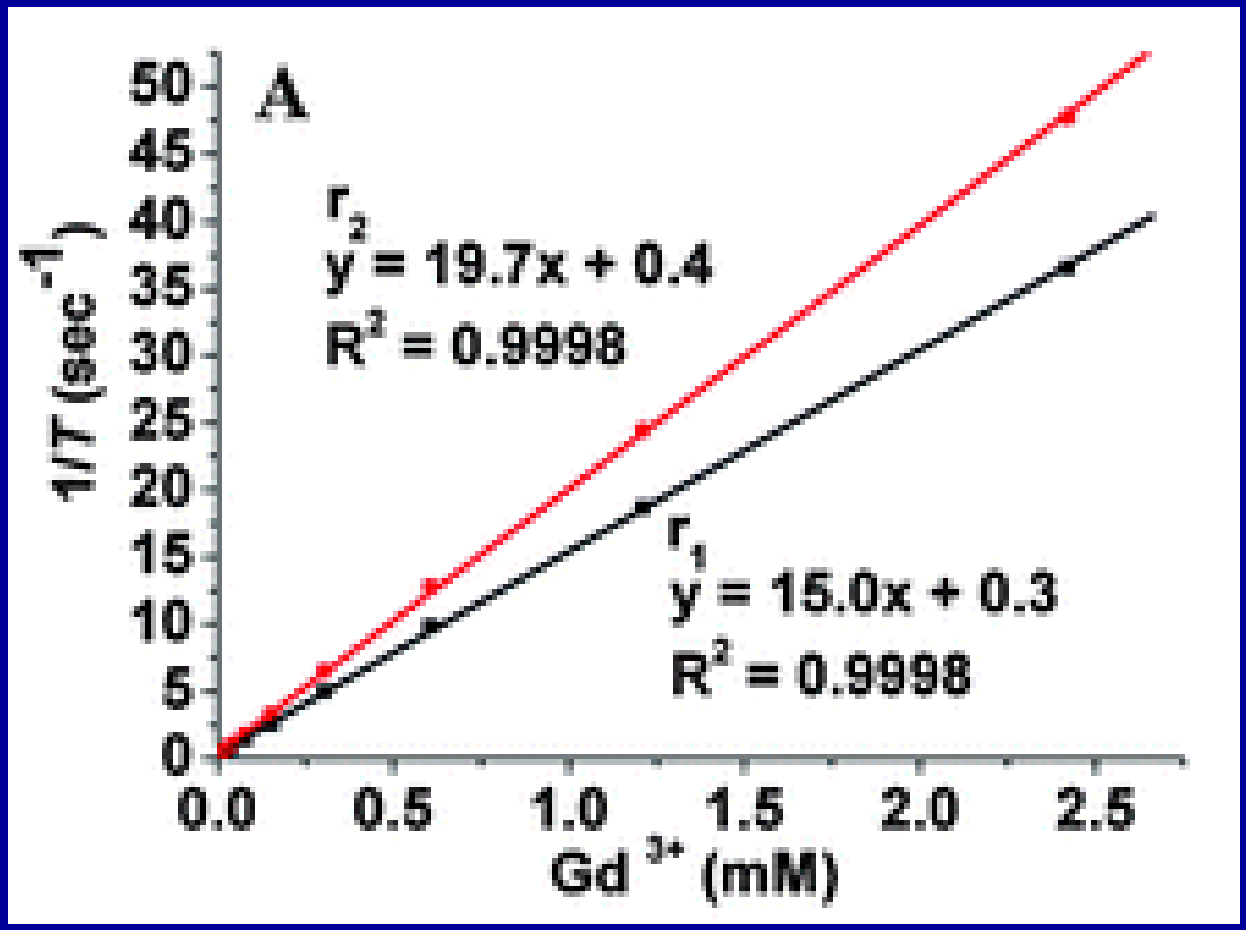


Relaxivity

Relaxivity



Relaxivity


A
r_2
y = 19.7x + 0.4
R^2 = 0.9998
r_1
y = 15.0x + 0.3
R^2 = 0.9998
1/T (sec^{-1})
Gd^{3+} (mM)
0
5
10
15
20
25
30
35
40
45
50
0.0
0.5
1.0
1.5
2.0
2.5

Relaxivity