Magnetic nanoparticles as possible theranostic agents

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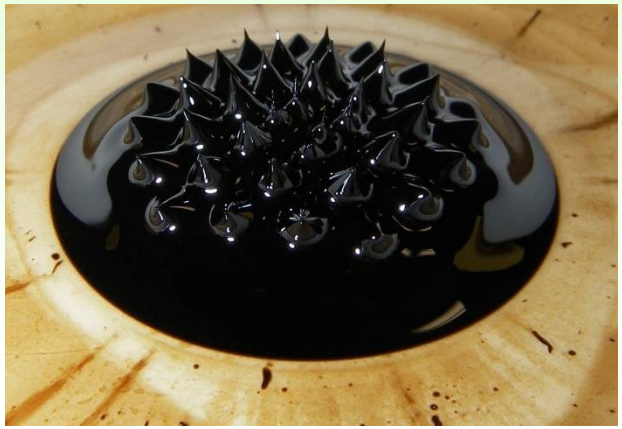
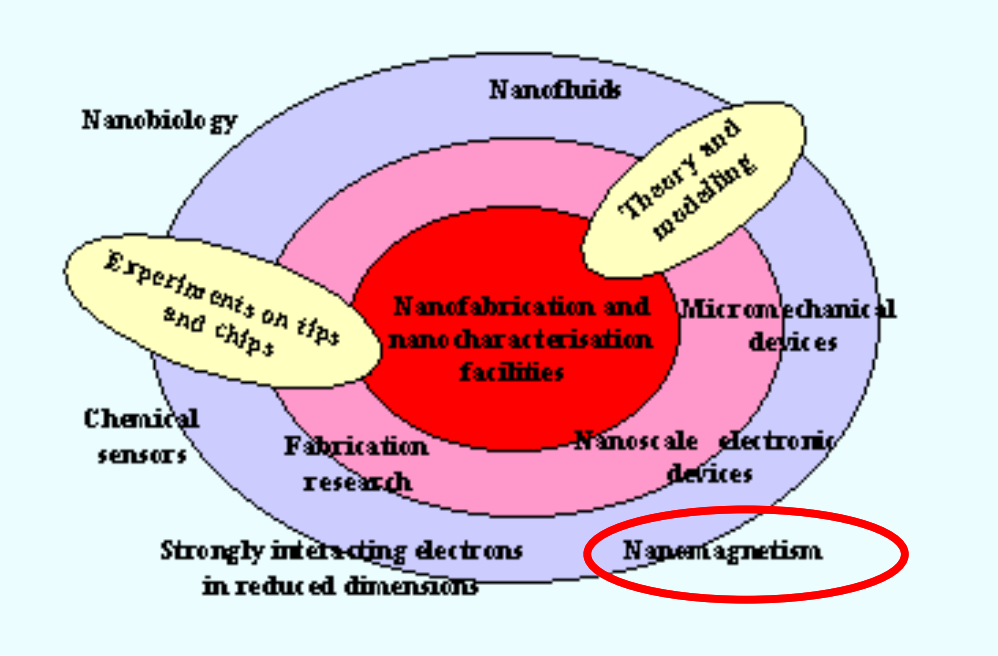
Actual funds : COST-EURELAX, INFN-PROTHYP

OUTLINE

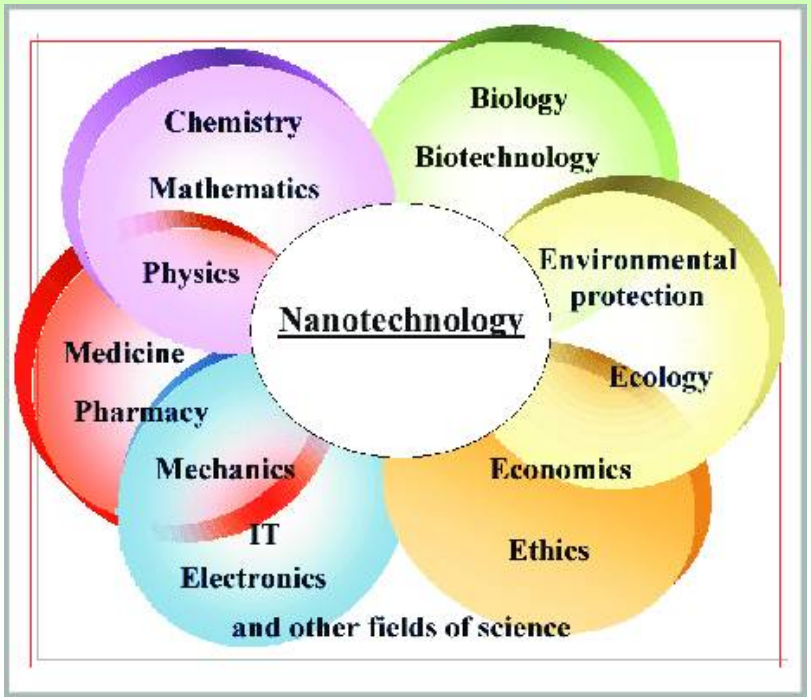
- **Brief intro to MNPs in medicine**
- **Applications : state of the art**
- **Novel samples : MRI and magnetic hyperthermia applicative results in-vitro and at preclinical stage (NOT EXHAUSTIVE !!)**
- **Future Issues**



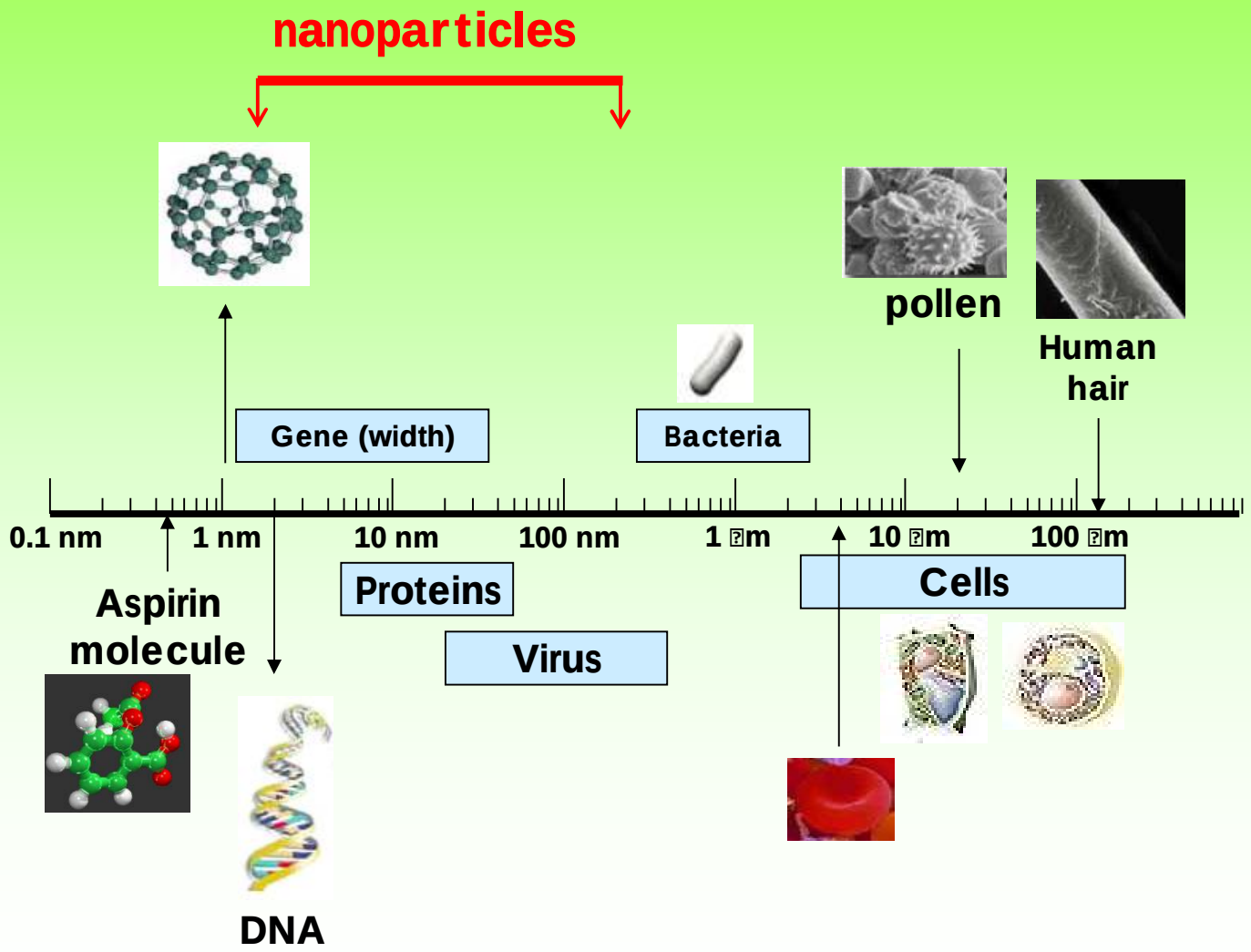
Nowadays : MNPs, interdisciplinarity and world interest



UCL Nanotechnology center

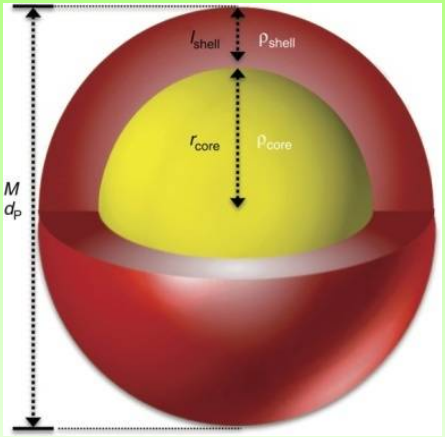


Why MNPs in biomedicine

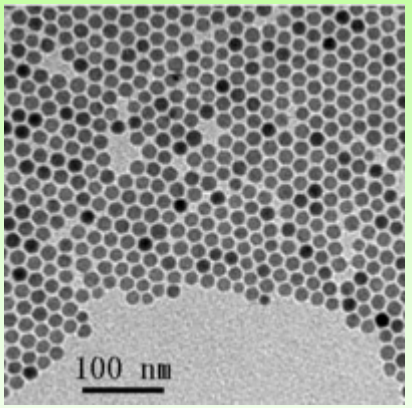


What are magnetic nanoparticles ?

Simplest form : magnetic core (often simple ferrites) + organic coating



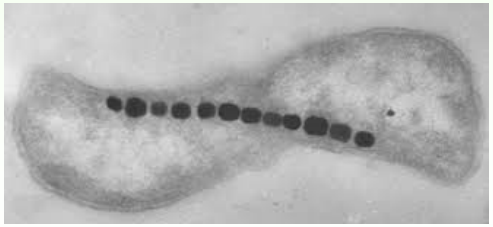
TEM

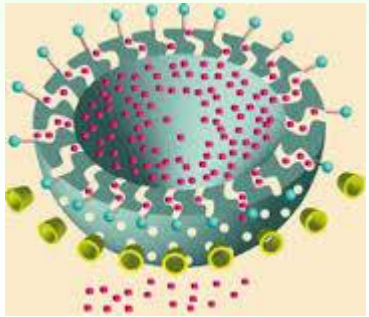


High monodispersity

*** Natural NPs (magnetosomes)**

*** Hollow / different shape**





Before looking at uses in biomedicine :

what about the relevant physico-chemical properties of magnetic nanoparticles ?

Microscopic parameters influencing the magnetic properties of magnetic NPs

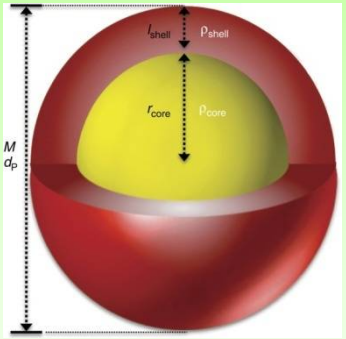
Size of magnetic core

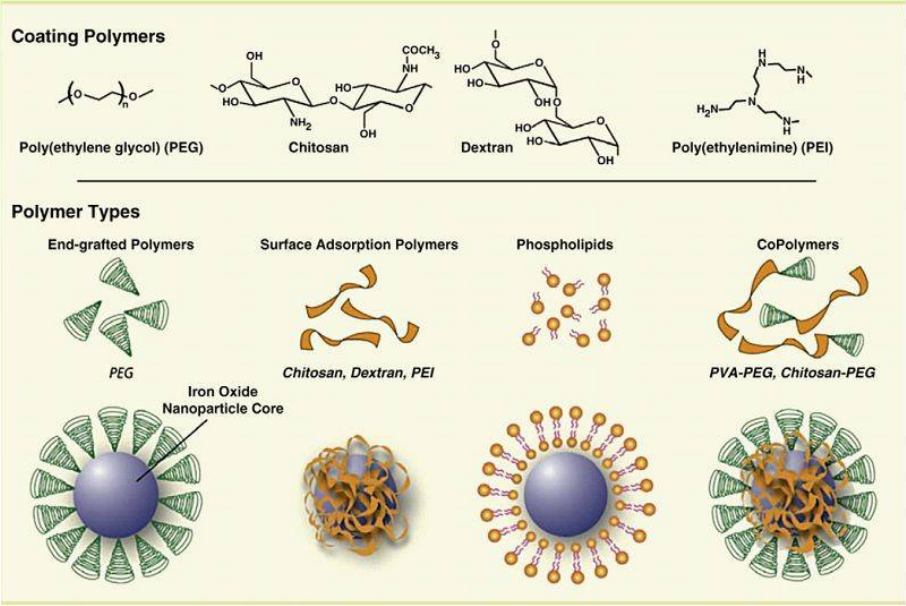
Magnetic energy and anisotropy

Kind of magnetic ion

Kind of coating

Shape of the nanoparticle





PARTICULARLY, WITHIN PHYSICAL PROPERTIES:

* «basic» magnetic properties

* Physics of “spin dynamics” (electron spin motion) for optimization of MRI and MFH efficiencies (biomed applications)

Spin dynamics in MNPs : “at least” 2 CRUCIAL correlation times

(I) Molecular/magnetization reversal by Brownian motion (η = solvent viscosity)

$$\tau_B = \frac{3\eta V}{k_B T}$$

(II) Magnetization reversal by thermal activation (Neel or VF time)

$$\tau_N = \tau_0 e^{\frac{KV}{k_B T}}$$

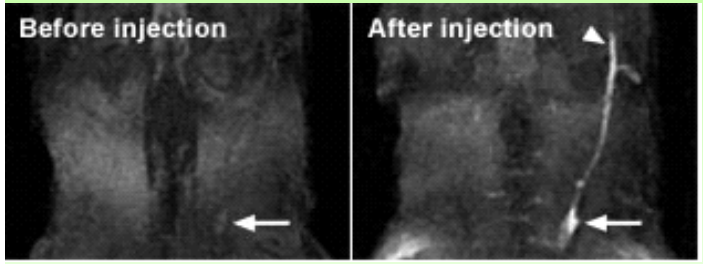
(III) Magnetization reversal Neel time changes suppressing the anisotropy barrier by a magnetic field

Globally : $1/\tau = 1/\tau_N + 1/\tau_B$

Uses of magnetic nanoparticles in biomedicine

Sensing (MRI, Sentimag, MEG-SQUID, Biosensors)

SENSING

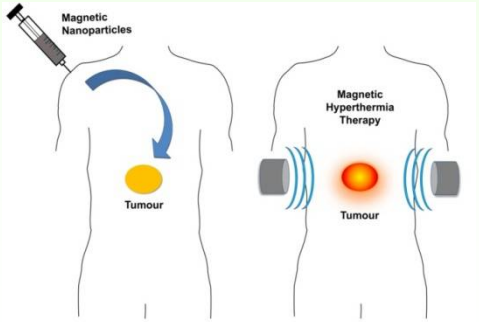


MOVING

Magnetic transport

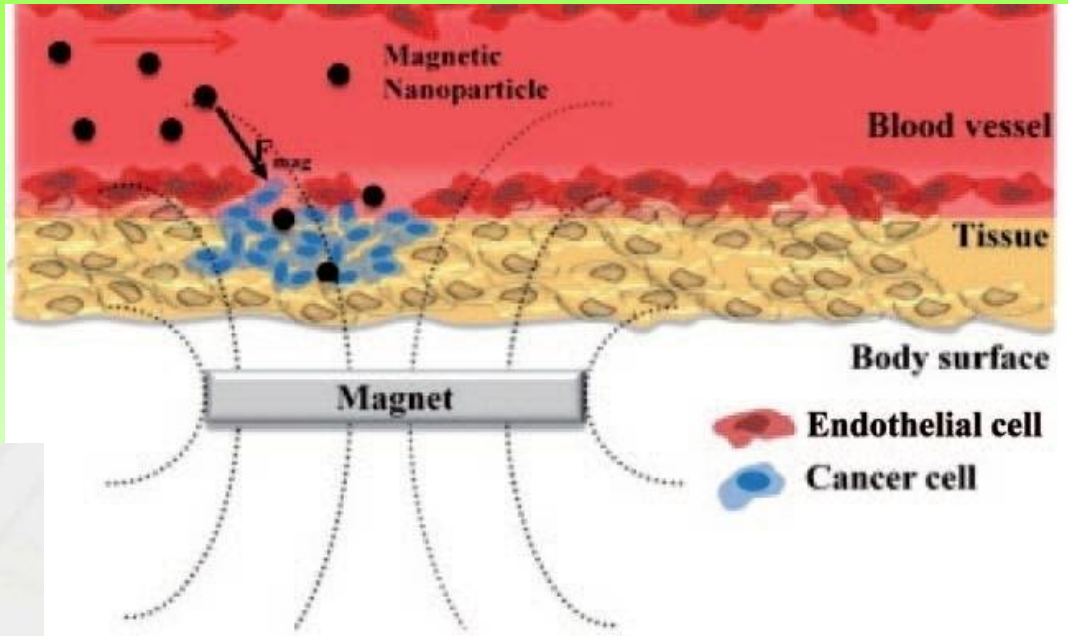
HEATING

Magnetic hyperthermia



Magnetic transport - NOT at (pre) clinical level

IV injection + local drug release (under pH change or external stimulus)



Forces on a magnetic nanoparticle:

$$F_m = (m \cdot \nabla) B$$

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

Hydrodynamic drag force:

$$F_d = 6 \pi \eta R_m \Delta v$$

Equating the two:

$$\Delta v = \frac{R_m^2 \Delta\chi}{9\mu_0\eta}\nabla(B^2) \quad \text{or} \quad \Delta v = \frac{\xi}{\mu_0}\nabla(B^2)$$

Magnetic Particle Imaging – MPI (preclinical)

1st MPI system
(Bruker-Philips, 2013)

It images the distribution of MNPs in biological tissues

http://www.philips.com/e/imalytics/productsnew/magneticparticle.html

Today SENTIMAG : a sensitive susceptometer

The Sentimag® is a Class IIa device, CE-approved for marketing and sales in Europe, and TGA-approved for Australasia.

Sentinel lymphnodes

MNPs

Key features and benefits of Sienna+®:

- Particle size optimised for filtration and retention by sentinel lymph nodes
- Simple storage and handling procedure, and significantly improved workflow compared with radioactive tracers
- Localisation can start after only 20 minutes following injection†
- Natural dark brown colour eliminates the need for separate dye injections
- Non-toxic, aqueous suspension dissipates naturally in the body
- Long shelf life
- Uniquely designed and calibrated for use with Sentimag®
- Compatible with Sysmex's One-Step Nucleic Acid Amplification (OSNA) assay (http://www.sysmex-lifescience.com/OSNA-assay-for-lymph-nodes-175-2.html)

Other applications/researches on MNPs

CNS diseases (e.g. Alzheimer, MS) :

- MNPs use for Imaging of involved molecules
- Role of ferritin and other ferrite-based endogen Fe systems in the disease

MNPs via oral administration

Today, focus on 2 techniques :

Magnetic Resonance Imaging

Magnetic Fluid Hyperthermia

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI)

Typical MRI apparatus for clinical use, magnetic field H = 1.5 Tesla

MNPs as contrast agents

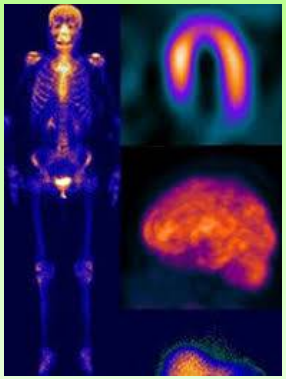
MRI Timeline

1946 MR phenomenon - Bloch & Purcell
1952 Nobel Prize - Bloch & Purcell
1950-70 NMR developed as analytical tool
1972 Computerized Tomography
1973 Backprojection MRI - Lauterbur
1975 Fourier Imaging - Ernst
1977 Echo-planar imaging - Mansfield
1980 FT MRI demonstrated - Edelstein
1986 Gradient Echo Imaging - NMR Microscope
1987 MR Angiography - Dumoulin
1991 Nobel Prize - Ernst
1992 Functional MRI
1994 Hyperpolarized ^{129}Xe Imaging
2003 Nobel Prize - Lauterbur & Mansfield

Imaging techniques : a short comparison

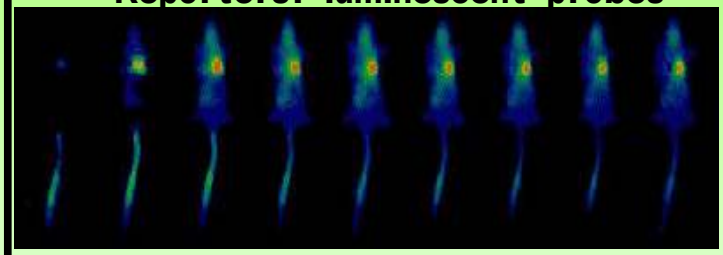
Nuclear Medicine:

- Poor spatial resolution
- Poor temporal resolution
- High sensitivity
- Reporters: radionuclides



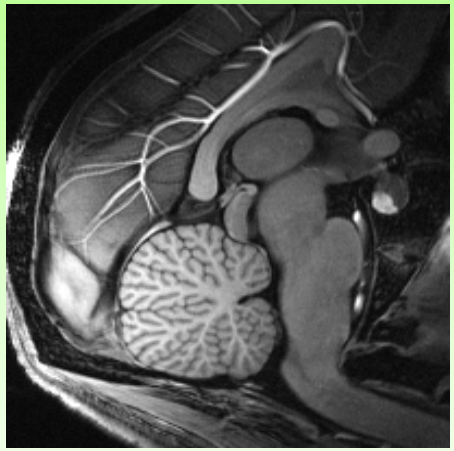
Optical Imaging:

- Poor spatial resolution
- Poor temporal resolution
- High sensitivity
- Reporters: luminescent probes



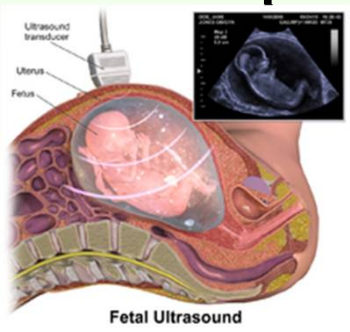
MRI :

- Non-invasive
- Good spatial resolution
- Good temporal resolution
- Low sensitivity



Ultrasounds

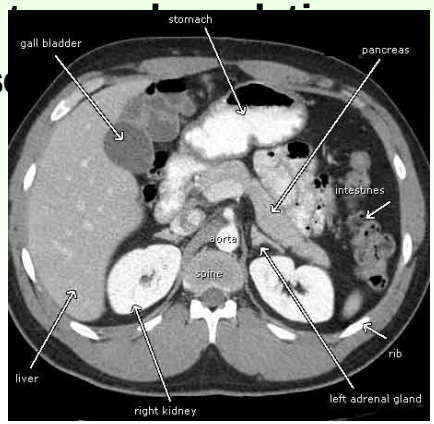
- Non-invasive
- Poor spatial resolution
- Good temporal resolution
- Low sensitivity
- Easy



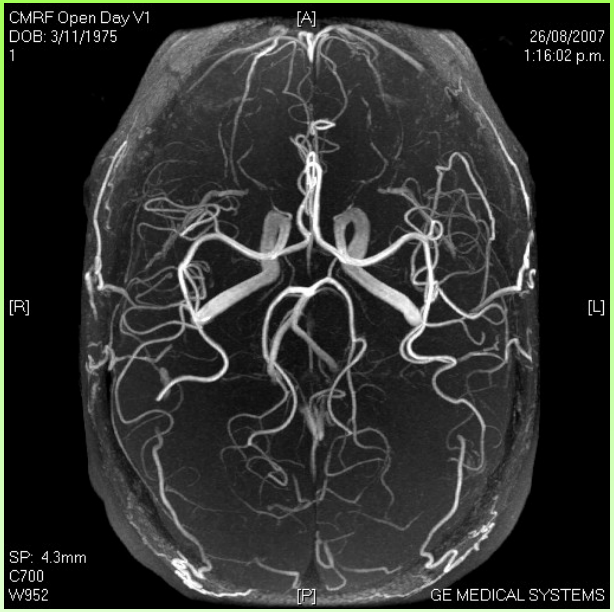
Fetal Ultrasound

X-Ray (CT):

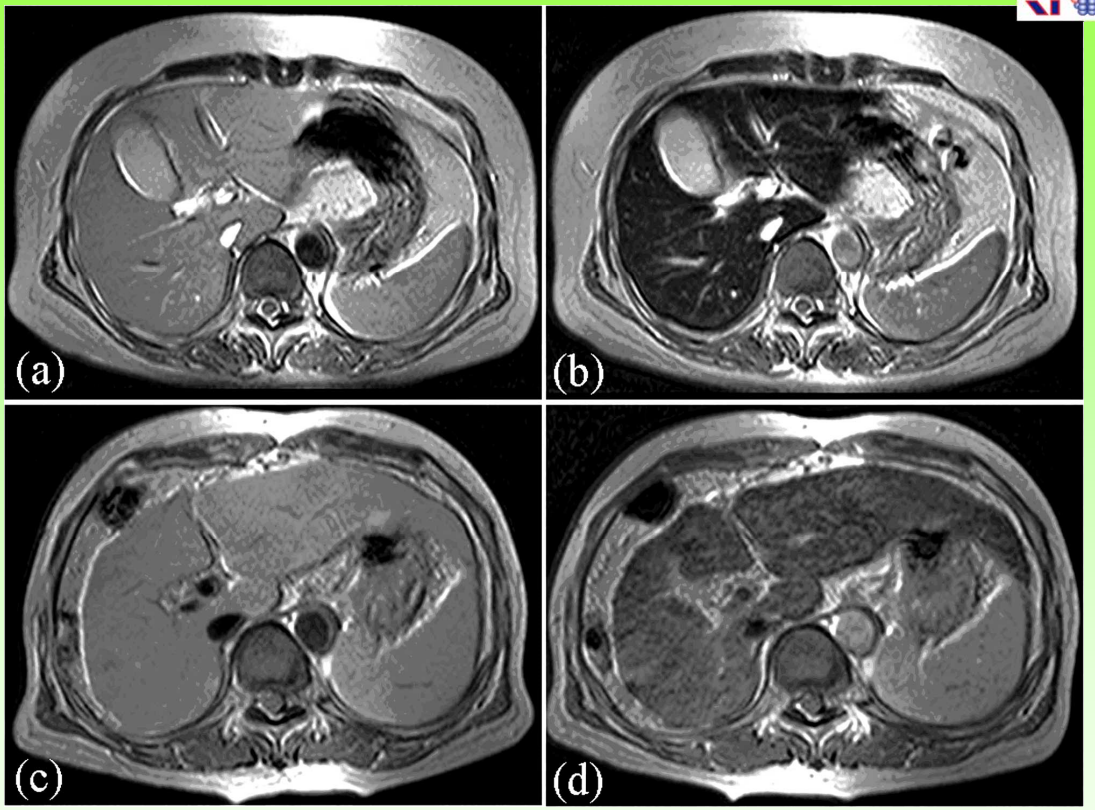
- Good spatial resolution
- Good
- Low s



MRI examples for NPs



Blood pool positive agents



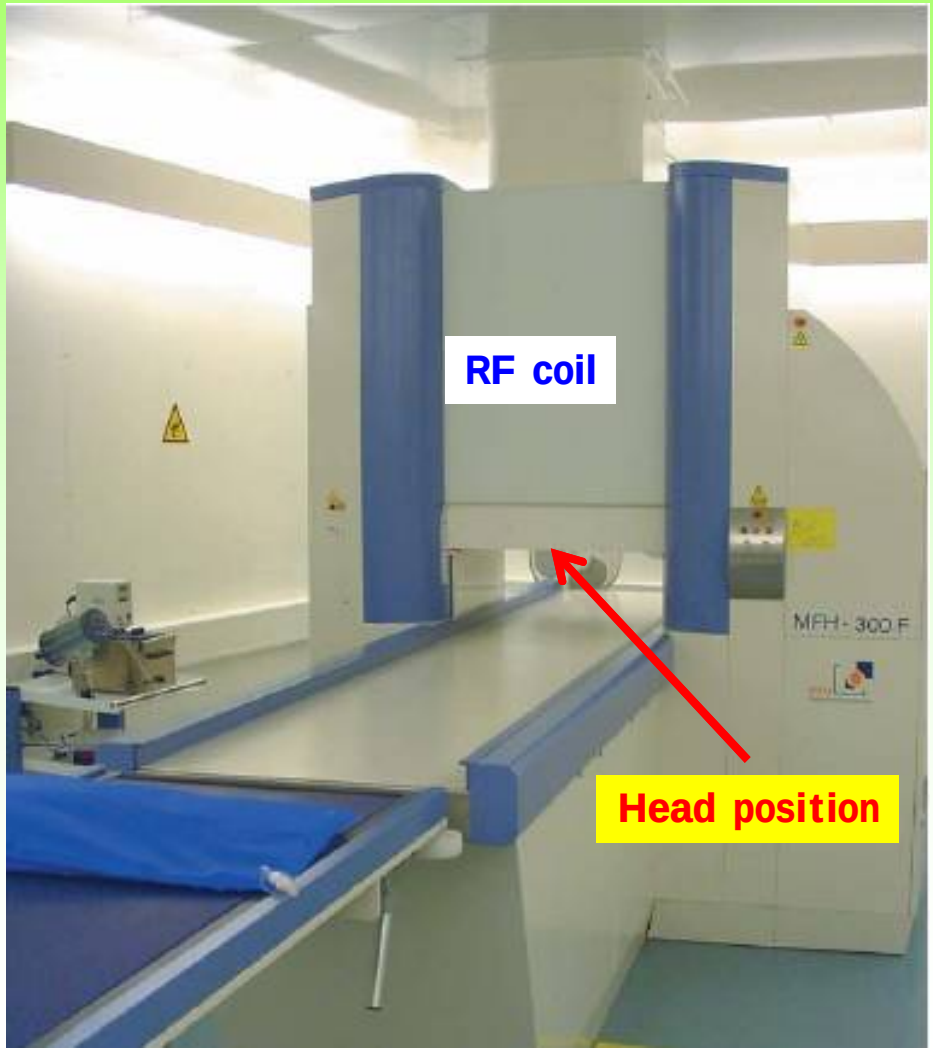
Negative agents (mostly MNPs)

Figure . - MR images on T2-weighted GRE sequence in a 51-year-old woman with chronic hepatitis (A and B) and a 65-year-old woman with liver cirrhosis (C and D) (Child-Pugh class B, score 8). Before (A and C) and after (B and D) administration of SPIO. Signal intensity reduction of liver parenchyma in a patient with cirrhosis (reduction-%LMR, 38.2%) is less than chronic hepatitis (reduction-%LMR, 73.8%).

Magnetic Fluid Hyperthermia (MFH)

Magnetic Fluid Hyperthermia (MFH) tumor treatment

Started a new study on glioblastoma multiforme in 2014, in USA and Germany Several german hospitals involved



• **Heating** through application of **AC magnetic field** via activation of 12 nm amino-silane coated Fe_3O_4 MNP directly implanted in the tumour mass at high doses (ca. 50 mg/cm^3)

• Typically : $\nu \sim 100$ kHz, amplitude 10 kA/m

• Minor side effects

Safety limits :

$H_0 f \leq 4.85\ 10^8$ Am^{-1}s^{-1} (*)

$50\ \text{kHz} \leq \nu \leq 1\ \text{MHz}$

(*) Depending on the radius of the exposed region

• Typical values of the reported **specific loss of power, SLP or SAR** (the energy converted into heat per mass unit) are : 10÷200 W/g [exceptions : 35 nm bacterial magnetosomes (960 W/g at 410 KHz and 10 kA/m); 16 nm γ-Fe_2O_3 N P (1650 W/g at 700 kHz and 24.8 kA/m, 300 W/g at 11 kA/m)]

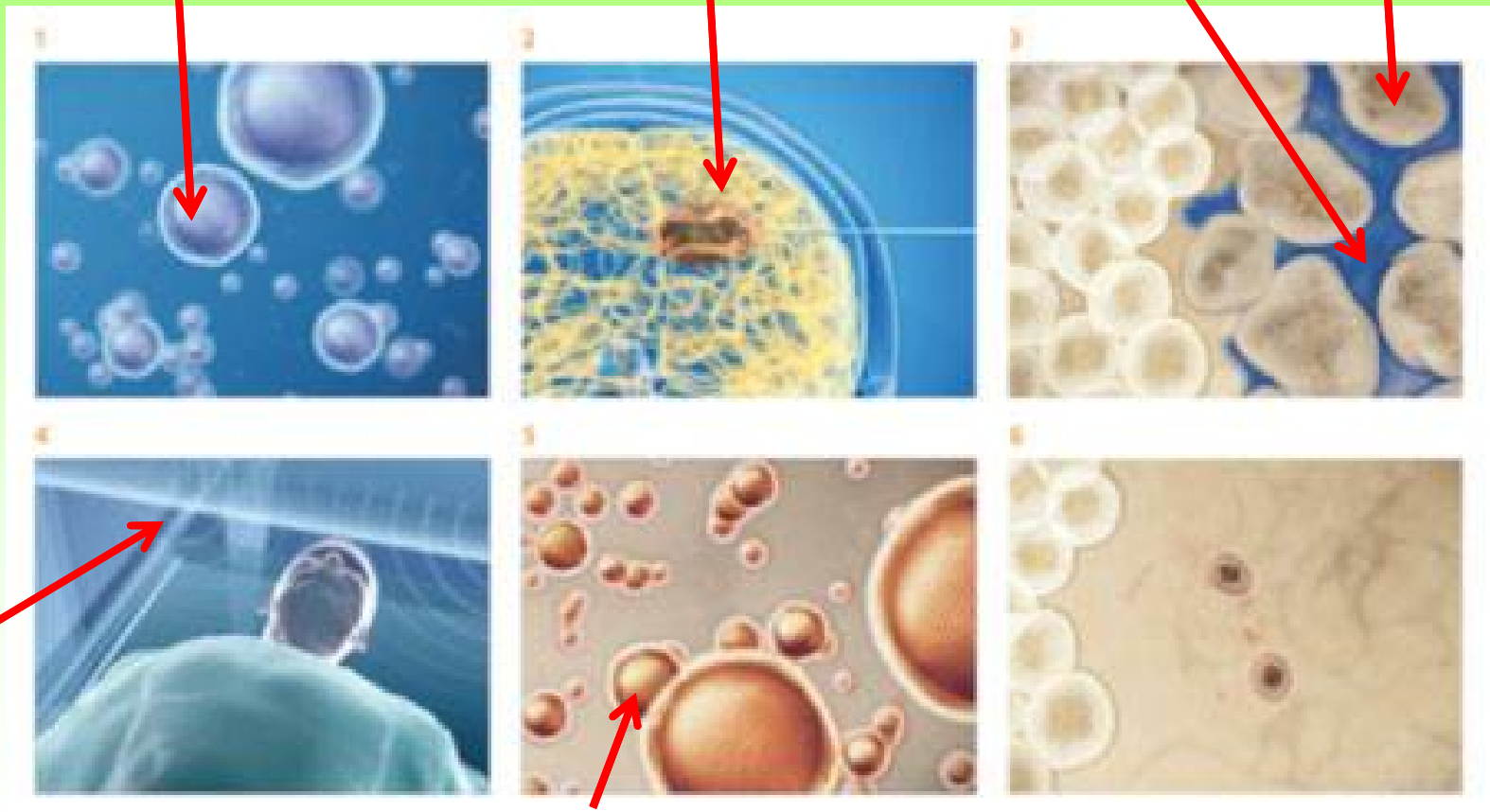
Magnetic Fluid Hyperthermia - Clinical applications

MNPs coated
With amminosilane

Direct injection in
the brain tumour

Tumour cells

ferrofluid



AMF

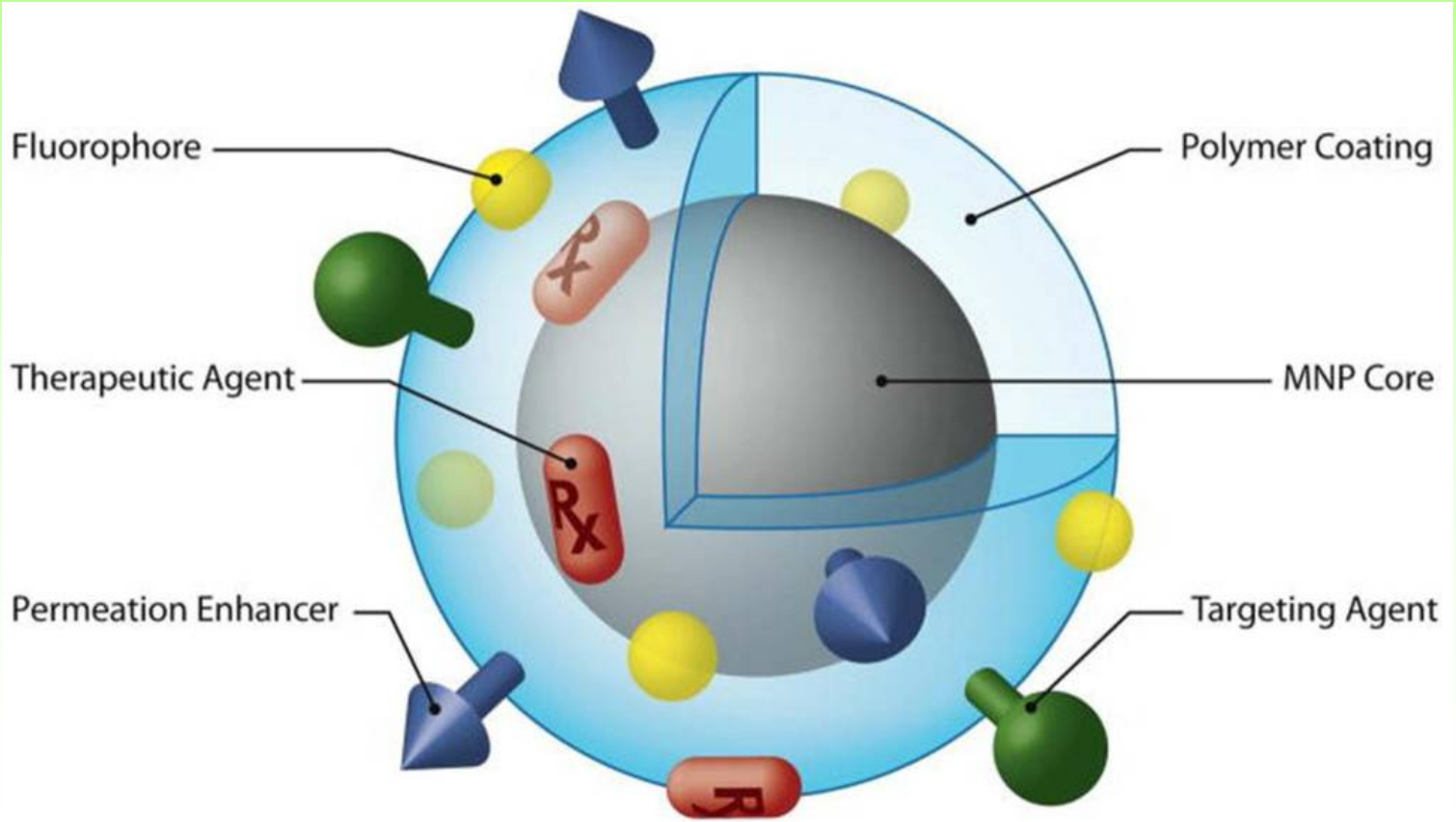
Heating – kill
tumour cells

Joining various techniques in a single object…..

The ideal task – novel systems: a single theranostic nano-object

Diagnostics : MRI CA, fluorescence

Therapy : Magnetothermia, drug release



Some details on MRI and MFH

Magnetic Resonance Imaging
MRI
with non-specific CA

STATE OF THE ART for novel systems

Diagnostics

Novel non-specific MRI contrast agents

Most of new CA for MRI
are "non-specific" (i.e. not targeting)
and so, two crucial questions …..

1) Fate of the MNPs ? Mostly in liver
if MNPs are not reduced in total size (and not only) !!!

2) Medical doctors are really interested ?

Or they just point to specific (i.e. targeting)
or multifunctional CA ??

ALERT : SAFETY & TOXICITY !!

"Tumour (disease) targeting" in clinics is actually almost prohibitive,

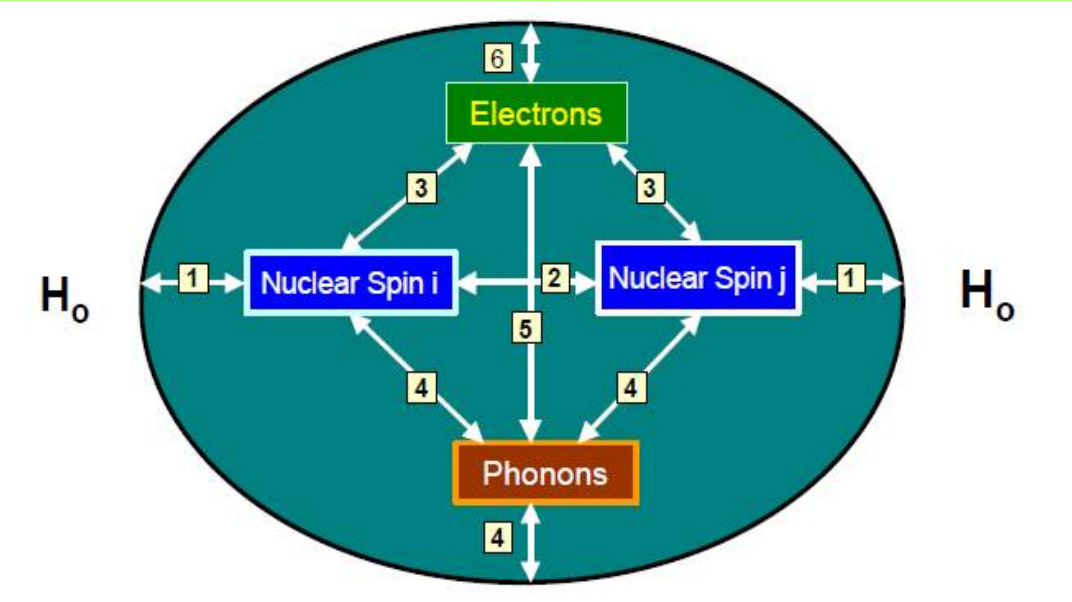
what could be the "industry" and clinicians interests ?

A "small" non-specific CA, with well controllable synthesis and with higher efficiency (relaxivity) than actual ones (lower costs, lower doses) BUT SAFE !

⇒ research about controlling the physical mechanisms/parameters that enhances the efficiency

What NMR TECHNIQUE accesses

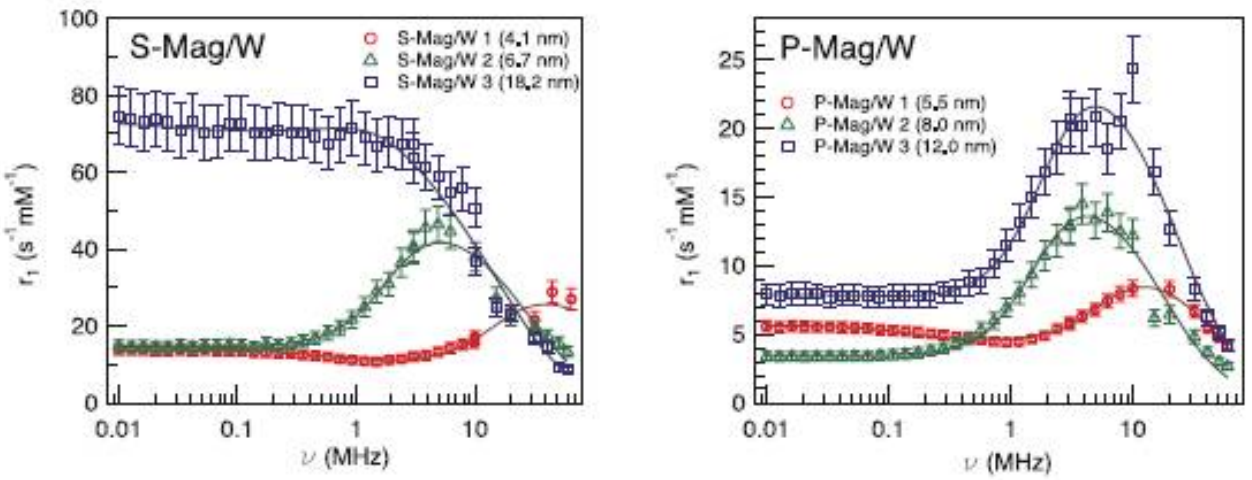
3 main NMR experimental parameters: spectrum, nuclear spin-spin relaxation time T_2, nuclear spin-lattice relaxation time T_1



- Nuclei are **LOCAL PROBES** ⇔ sensitive to hyperfine interactions
- **LOCAL MAGNETIC FIELDS AND DYNAMICS** can be studied

In MRI and NMR spectroscopy and "relaxometry", one is sensitive to magnetic properties, spin dynamics and molecular "motion"

New MRI CAs : importance of investigation of fundamental chemico-physical properties



e.g. :
NMR-D relaxometry
i.e. relaxivity vs field

IMPORTANT NOTE :

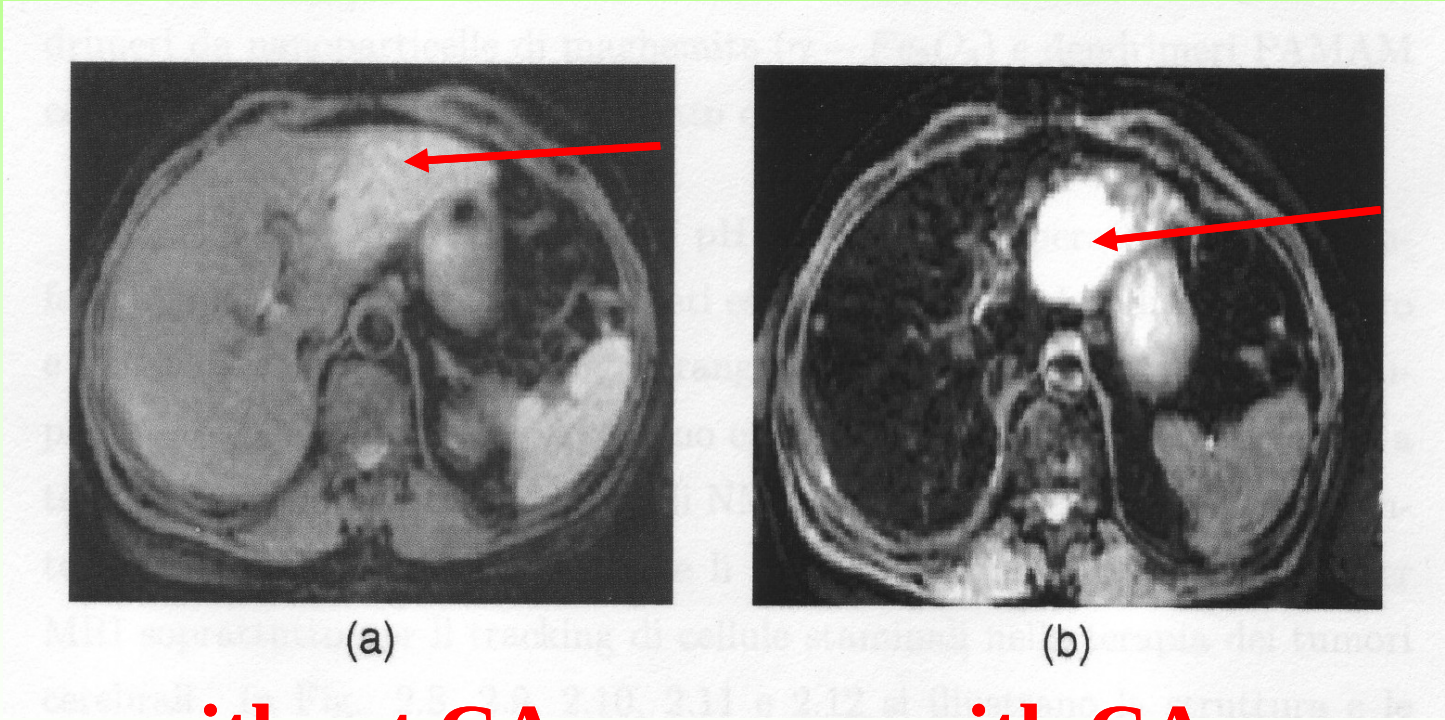
To improve the CA efficiency, need for a longitudinal r_1 and transverse r_2 predictive physical model of nuclear relaxation

"CLASSICAL EXAMPLE" of NPs- MRI-CA

Liver tumour detection by "negative" commercial SP-CA ENDOREM

- Generally the **negative CA** are based on **superparamagnetic nanoparticles**

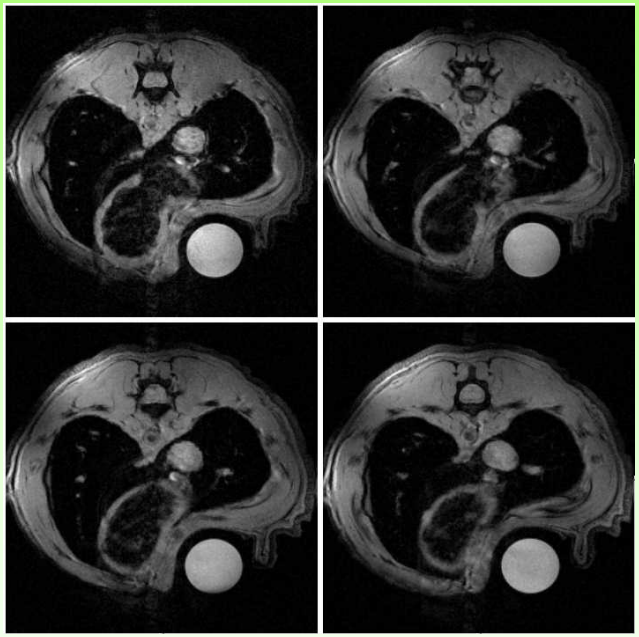
Rat's liver tumour



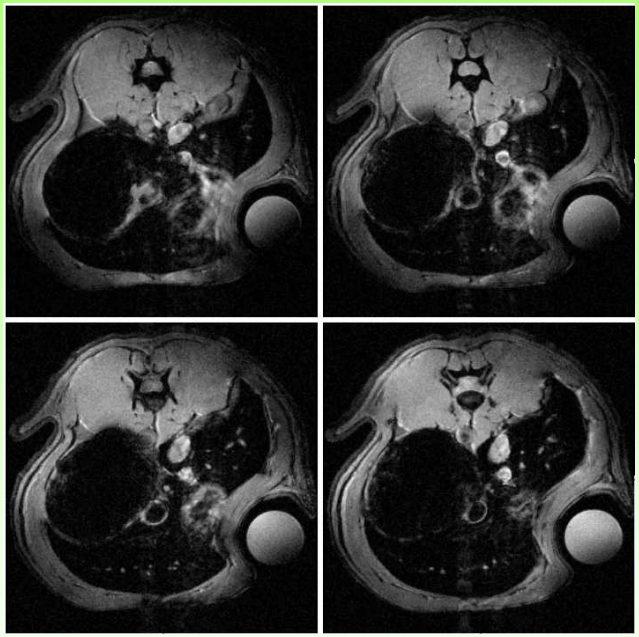
without CA **with CA**

MRI images with new CAs

MRI with novel Co-based ferrites on normal rats (Colorobbia)



Endorem



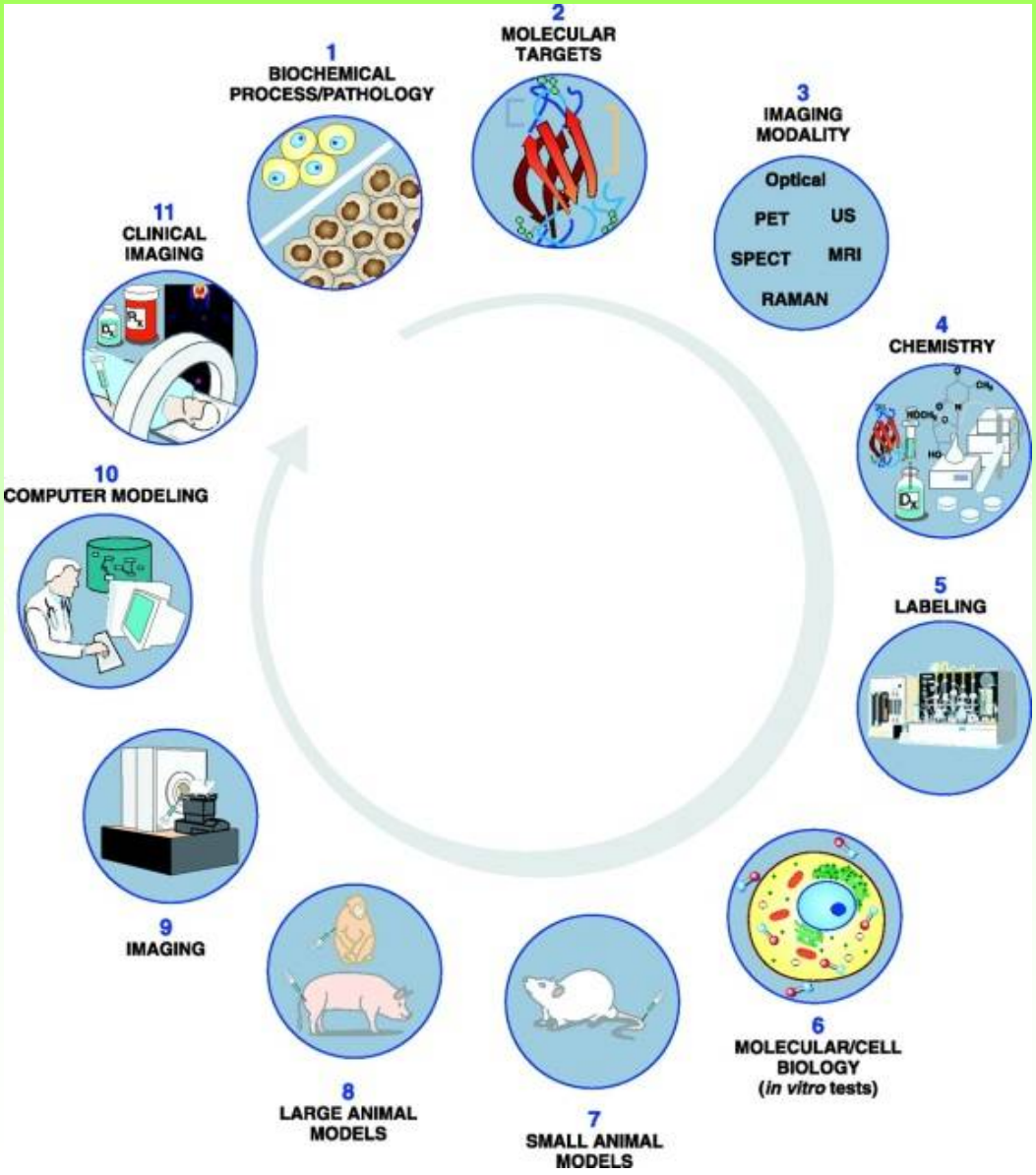
NBR1 (Colorobbia)

NBR1 is good for MR images (r_2 higher than for commercial compound)

M. Comes Franchini, A. Lascialfari, M. Corti, U. Guerrini, G. Baldi et al., *Small*, 2010

Molecular targeting, drug delivery and MRI

STATE OF THE ART - Targeting with MNPs
i.e. Molecular Imaging by MRI



For targeting, the surface functionalization is crucial !

A Plethora of papers

Verma et al. Journal of Nanobiotechnology 2013, 11:1
http://www.jnanobiotechnology.com/content/11/1/1

JOURNAL OF NANOBIOTECHNOLOGY

RESEARCH Open Access

Magnetic core-shell nanoparticles for drug delivery by nebulization

Navin Kumar Verma[1,2*], Kieran Crosbie-Staunton[1,2], Amro Satti[2,3], Shane Gallagher[2,3], Katie B Ryan[4], Timothy Doody[4], Colm McAtamney[2], Ronan MacLoughlin[5], Paul Galvin[6], Conor S Burke[7], Yuri Volkov[1,2†] and Yurii K Gun'ko[2,3†]

review

Magnetic nanoparticles as targeted delivery systems in oncology

Sara Prijic[1] and Gregor Sersa[2]

Radiol Oncol 2011; 45(1): 1-16.

Eur Biophys J (2006) 35: 446–450
DOI 10.1007/s00249-006-0042-1

BIOPHYSICS LETTER

Christoph Alexiou · Roswitha J. Schmid
Roland Jurgons · Marcus Kremer · Gerhard Wanner
Christian Bergemann · Ernst Huenges
Thomas Nawroth · Wolfgang Arnold
Fritz G. Parak

Targeting cancer cells: magnetic nanoparticles as drug carriers

Breast Cancers: MR Imaging of Folate-Receptor Expression with the Folate-Specific Nanoparticle P1133[1]

Radiology: Volume 255: Number 2—May 2010 ▪ radiology.rsna.org

www.medscape.com

Magnetic Nanoparticle-based Approaches to Locally Target Therapy and Enhance Tissue Regeneration *in vivo*

Richard Sensenig, Yulia Sapir, Cristin MacDonald, Smadar Cohen, Boris Polyak

Nanomedicine. 2012;7(9):1425-1442.

Nanomedicine www.futuremedicine.com

Targeted folic acid-PEG nanoparticles for noninvasive imaging of folate receptor by MRI

Ting-Jung Chen,[1] Tsan-Hwang Cheng,[2] Yu-Chin Hung,[1] Kuei-Tang Lin,[1] Gin-Chung Liu,[3,4] Yun-Ming Wang[1]
[1]Faculty of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan
[2]Department of Biological Science and Technology, Chung Hwa University of Medical Technology, Tainan County 717, Taiwan
[3]Department of Medical Imaging, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan
[4]Department of Radiology, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung 807, Taiwan

Journal of Biomedical Materials Research Part A

Lysosomal Membrane Permeabilization by Targeted Magnetic Nanoparticles in Alternating Magnetic Fields

Maribella Domenech,† Ileana Marrero-Berrios,‡ Madeline Torres-Lugo,† and Carlos Rinaldi†,§,⊥,*

VOL. 7 ▪ NO. 6 ▪ 5091–5101 ▪ 2013 ACSNANO www.acsnano.org

nature nanotechnology LETTERS
PUBLISHED ONLINE: 16 SEPTEMBER 2012 | DOI: 10.1038/NNANO.2012.146

M13-templated magnetic nanoparticles for targeted *in vivo* imaging of prostate cancer

Debadyuti Ghosh[1,2], Youjin Lee[1], Stephanie Thomas[3], Aditya G. Kohli[3], Dong Soo Yun[1], Angela M. Belcher[1,2,4]* and Kimberly A. Kelly[3]*

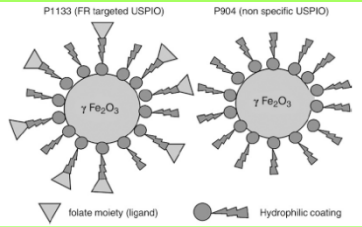
Pharmaceutics **2013**, *5*, 246-260; doi:10.3390/pharmaceutics5020246
OPEN ACCESS
pharmaceutics
ISSN 1999-4923
www.mdpi.com/journal/pharmaceutics

Article

Development of a Novel Lipophilic, Magnetic Nanoparticle for *in Vivo* Drug Delivery

Thomas Linemann, Louiza B. Thomsen, Kristian G. du Jardin, Jens C. Laursen, Jesper B. Jensen, Jacek Lichota and Torben Moos *

Some images about targeting



Meier et al. (also Guerbet)
MDA-MB-231 breast cancer

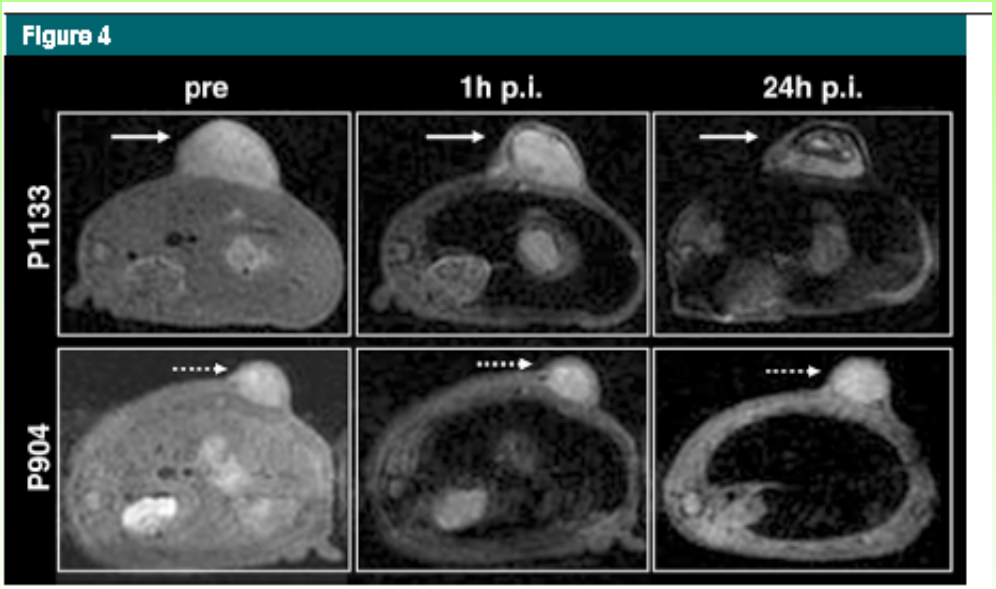
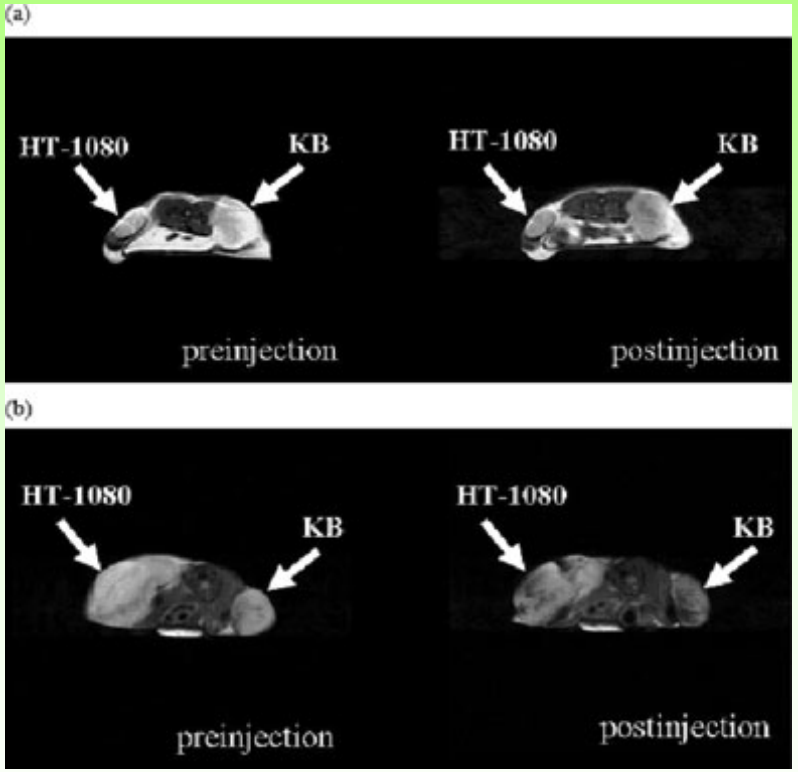


Figure 4: Axial T2-weighted spin-echo MR images (2000/18.8; flip angle, 90°) of two representative FR-positive MDA-MB-231 tumors (arrow) before injection (*pre*) and at 1 hour and 24 hours after injection (*p.i.*) of FR-targeted P1133 or nontargeted P904. Marked negative and inhomogeneous tumor enhancement is noted at 24 hours after injection of P1133 but not P904.

Chen et al.
KB cell, a human nasopharyngeal epidermal carcinoma cell line



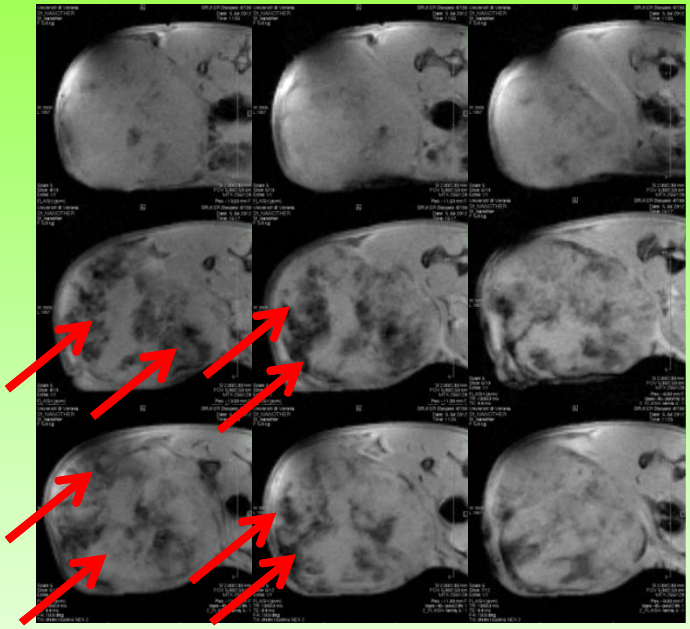
Targeting folate receptor !!

IEO Istituto Europeo di Oncologia

Milano, 09/04/2019

Some images about targeting : GE T2*W MRI

EU- FP7-Nanother

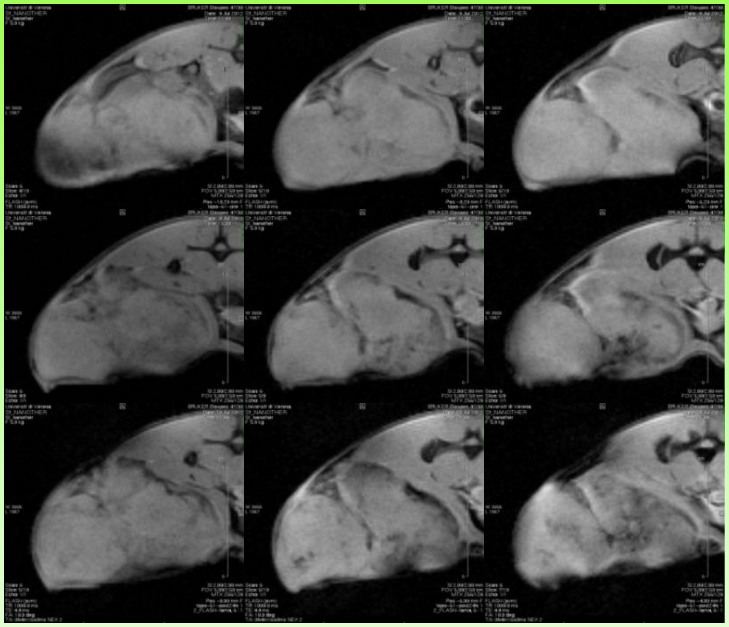


PRE

POST

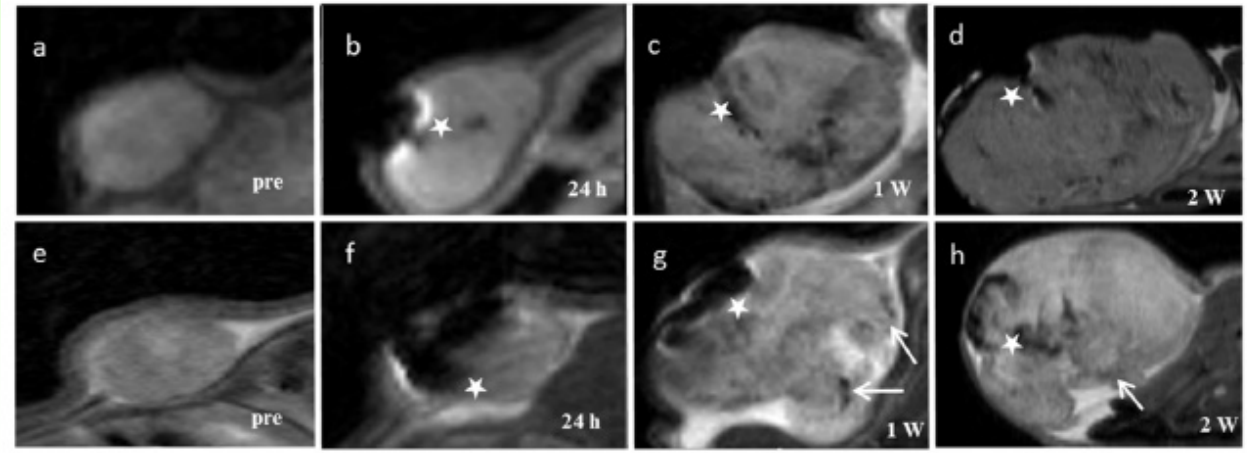
POST 24 H

MDA-MB-231 breast cancer



NPs with folic acid

NPs without folic acid



Magnetosomes (local injection)

AIRC project

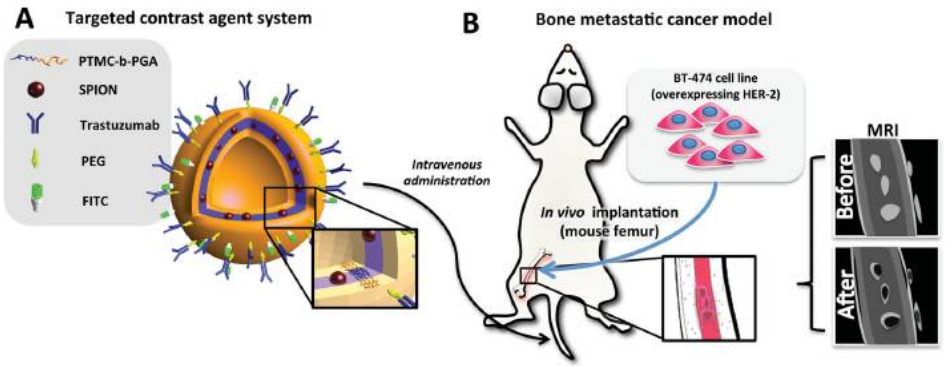
Other images about targeting

ADVANCED HEALTHCARE MATERIALS
www.advhealthmat.de
Materials Views
www.MaterialsViews.com

Antibody-Functionalized Magnetic Polymersomes: In vivo Targeting and Imaging of Bone Metastases using High Resolution MRI

Line Pourtau, Hugo Oliveira, Julie Thevenot, Yali Wan, Alain R. Brisson, Olivier Sandre, Sylvain Miraux, Eric Thiaudiere, and Sébastien Lecommandoux**

BT-474 breast cancer



within EU- FP7-Nanother

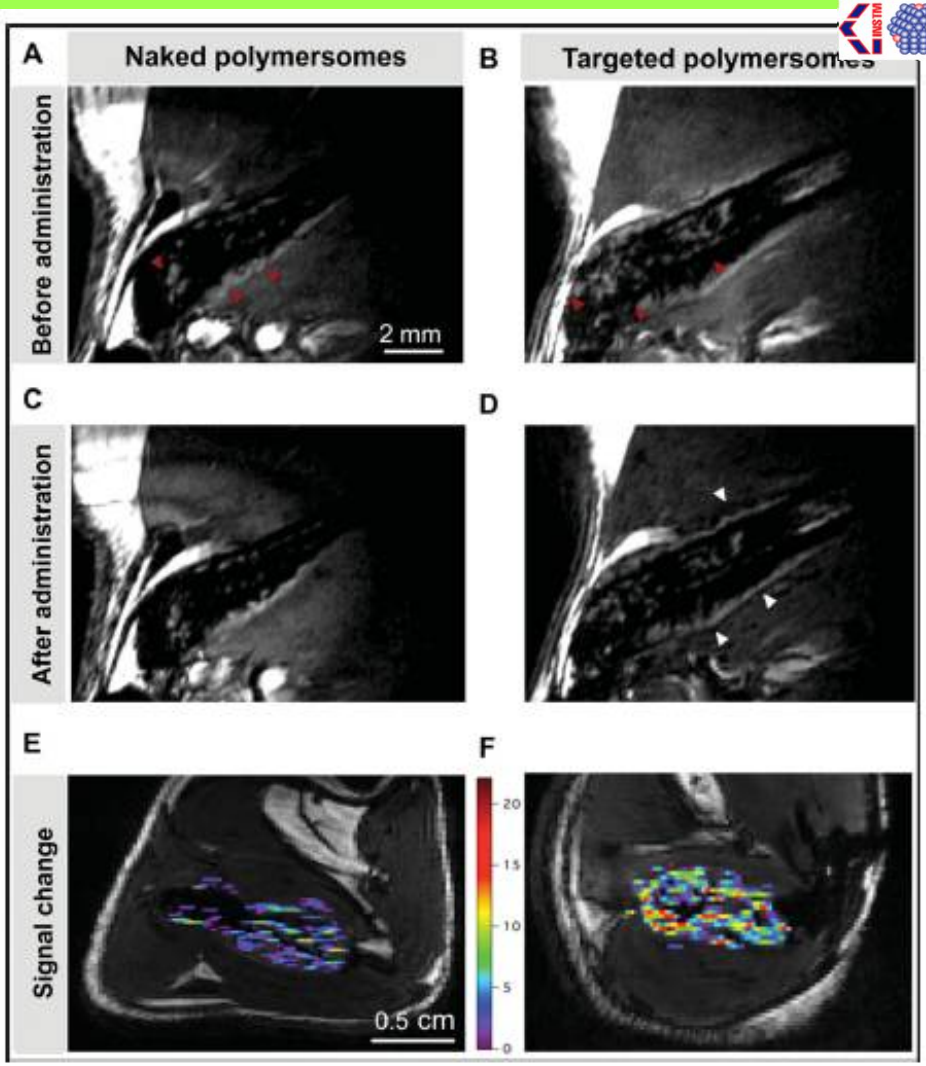


Figure 3. Bone BT-474 tumor targeting as assessed from high resolution 3D TrueFisp MRI. Extracted axial views and color map of relative signal change in percent brought by the injection of naked (A) or targeted (B) polymersomes. Longitudinal views before (C,D) and after (E, F) injection of naked (C, E) and targeted (D, F) polymersomes. Red arrows denote tumor tissue. White arrows denote contrast variations on tumor boundaries. Experiments were performed when the tumors reached a volume of 12 to 15 µl.

Multimodal Imaging

NOTE ON IMAGING :

dual or multiple IMAGING probes. Many "lab" examples

In vivo evaluation of 64Cu-labeled Magnetic Nanoparticles as a Dual-Modality PET/MR Imaging Agent

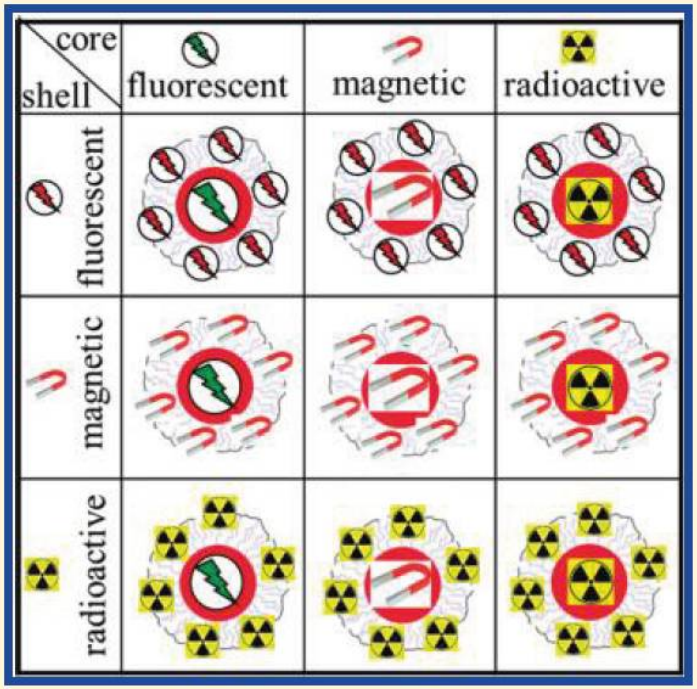
Authors:
Address: † Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia, USA

G. Bao et al.

analytical chemistry
PERSPECTIVE
pubs.acs.org/ac

Multifunctional Nanoparticles for Dual Imaging

Z. Ali,† A. Z. Abbasi,† F. Zhang,† P. Arosio,§ A. Lascialfari,§,⊥ M. F. Casula,¶ A. Wenk,‖ W. Kreyling,‖ R. Plapper,# M. Seidel,# R. Niessner,# J. Knöll,‡ A. Seubert,‡ and W. J. Parak*,†



Why ?

- **Optical and PET more sensitive (ideally few cells...)**
- **MRI less invasive**

Magnetic Fluid Hyperthermia
MFH

Actual status of Magforce MFH therapy for humans

Started a new study on glioblastoma multiforme in 2014, in USA and Germany

Several german hospitals involved

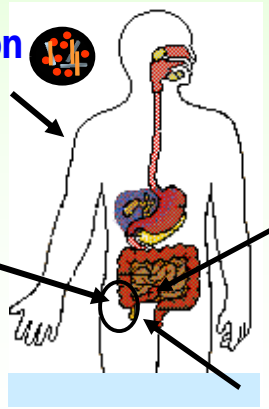
Problems of "integrating" this therapy alongside the more conventional hospital therapies

STATE OF THE ART
Magnetic Fluid Hyperthermia (MFH)

…… after and/or trying to go beyond

Jordan's clinical studies : a higher NPs-SAR and a better distribution of NPs inside the tumor

1. Injection

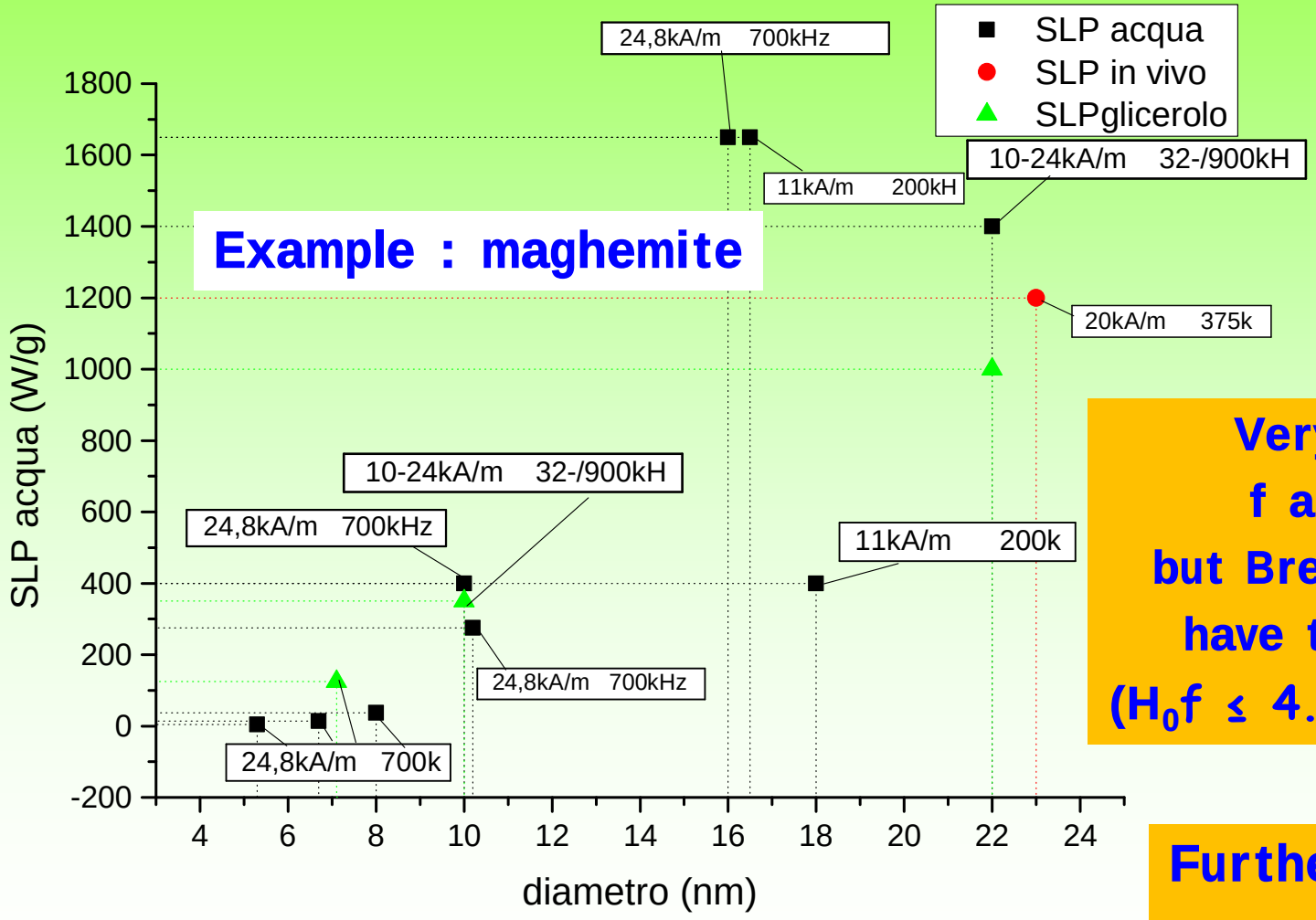


2. Localization to Tumor

3. External Activation with AC Magnetic Field

4. Heat Dissipation

In literature : by SAR not deep systematic characterization of MNPs for MFH

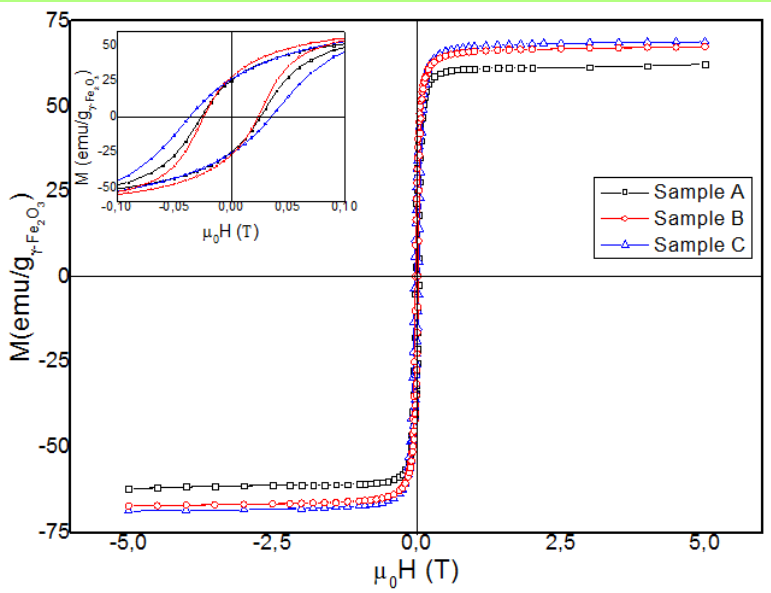


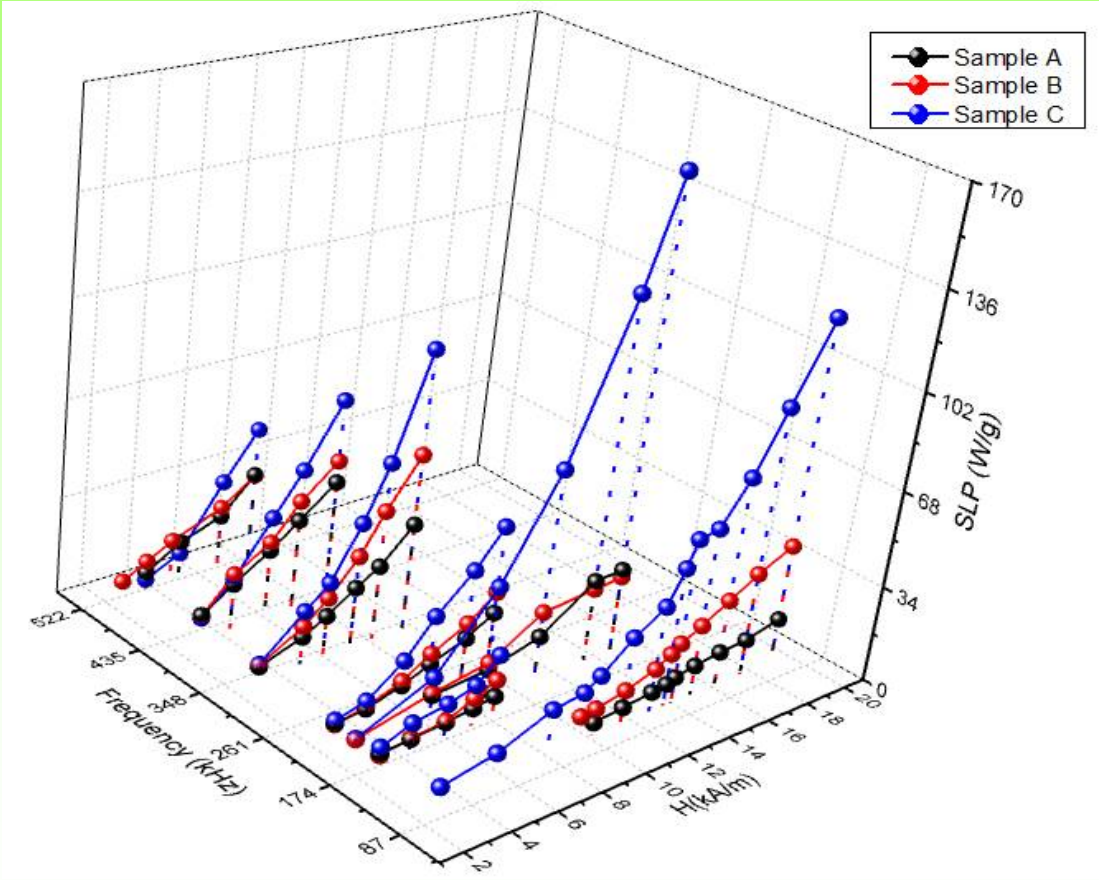
Example : maghemite

Very different f and H values but Brezovich criterion have to be satisfied ($H_0 f \leq 4.85\ 10^8\ Am^{-1}s^{-1}$)

Further problem : non-toxicity

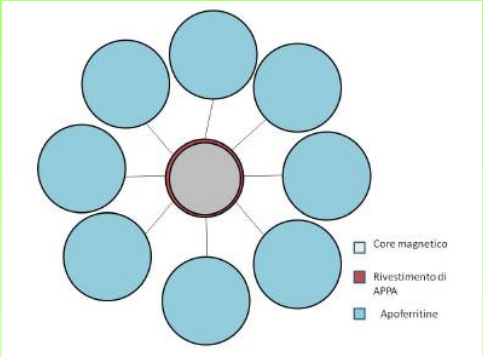
New MFH maghemite-based NPs : a starting point for systematic investigation of fundamental chemico-physical properties related to SAR



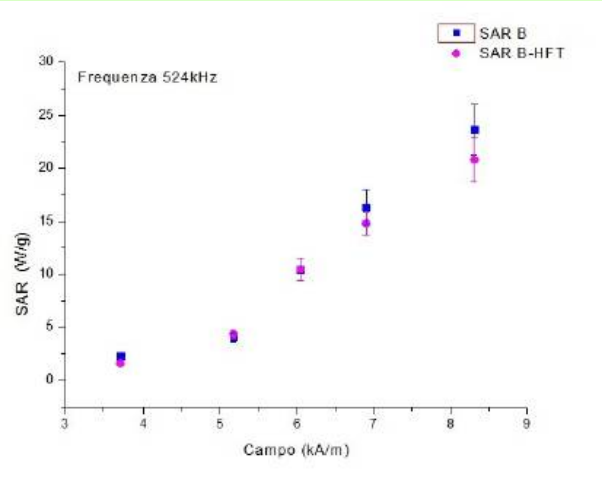


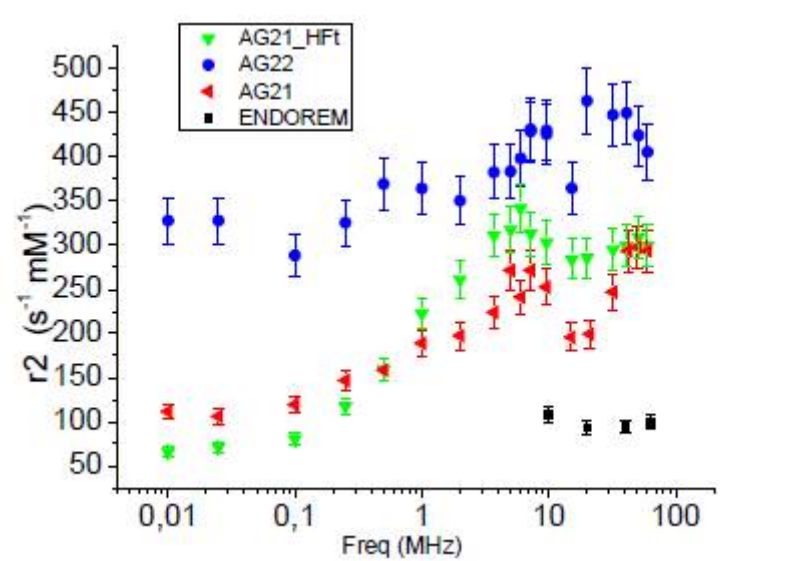
M. Cobianchi, A. Guerrini, M. Avolio et al., J. MMM (2017)

New MFH maghemite-APOFERRITIN-based THERANOSTIC systems



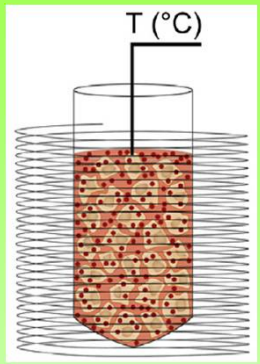
MRI & Hyperthermia agent





A. Guerrini, M. Avolio M. Basini et al., in preparation

FURTHER PROBLEM : The role of the medium



Human adenocarcinoma cells

Biomaterials 35 (2014) 6400–6411

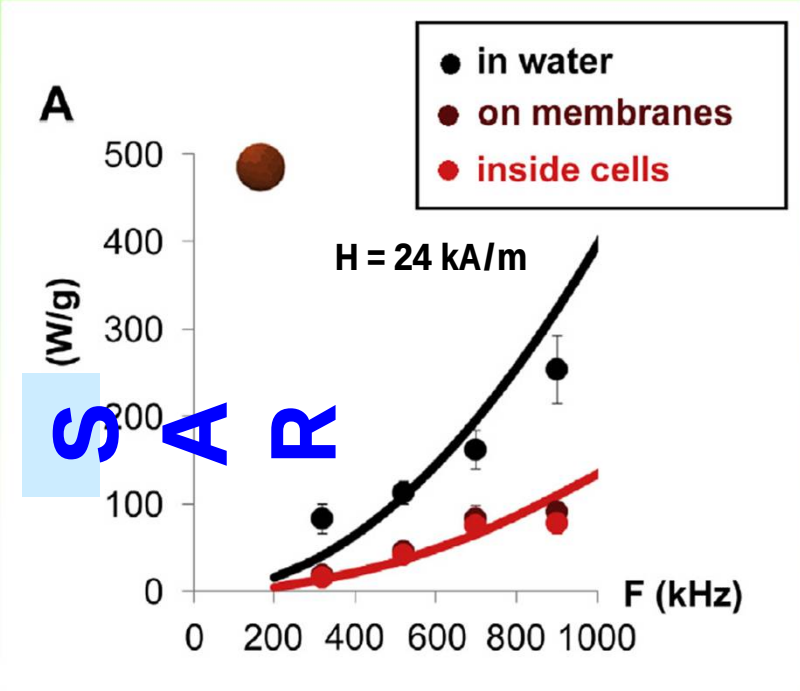
Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Magnetic hyperthermia efficiency in the cellular environment for different nanoparticle designs

Riccardo Di Corato [a], Ana Espinosa [a], Lenaic Lartigue [a], Mickael Tharaud [b], Sophie Chat [c], Teresa Pellegrino [d], Christine Ménager [e], Florence Gazeau [a], Claire Wilhelm [a,*]

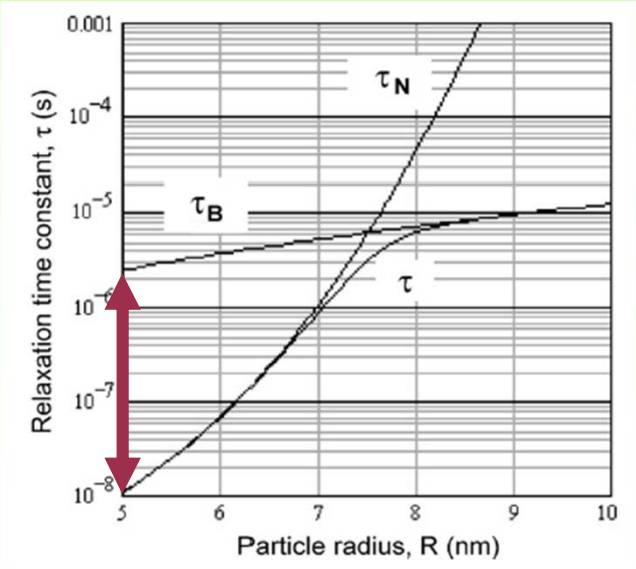


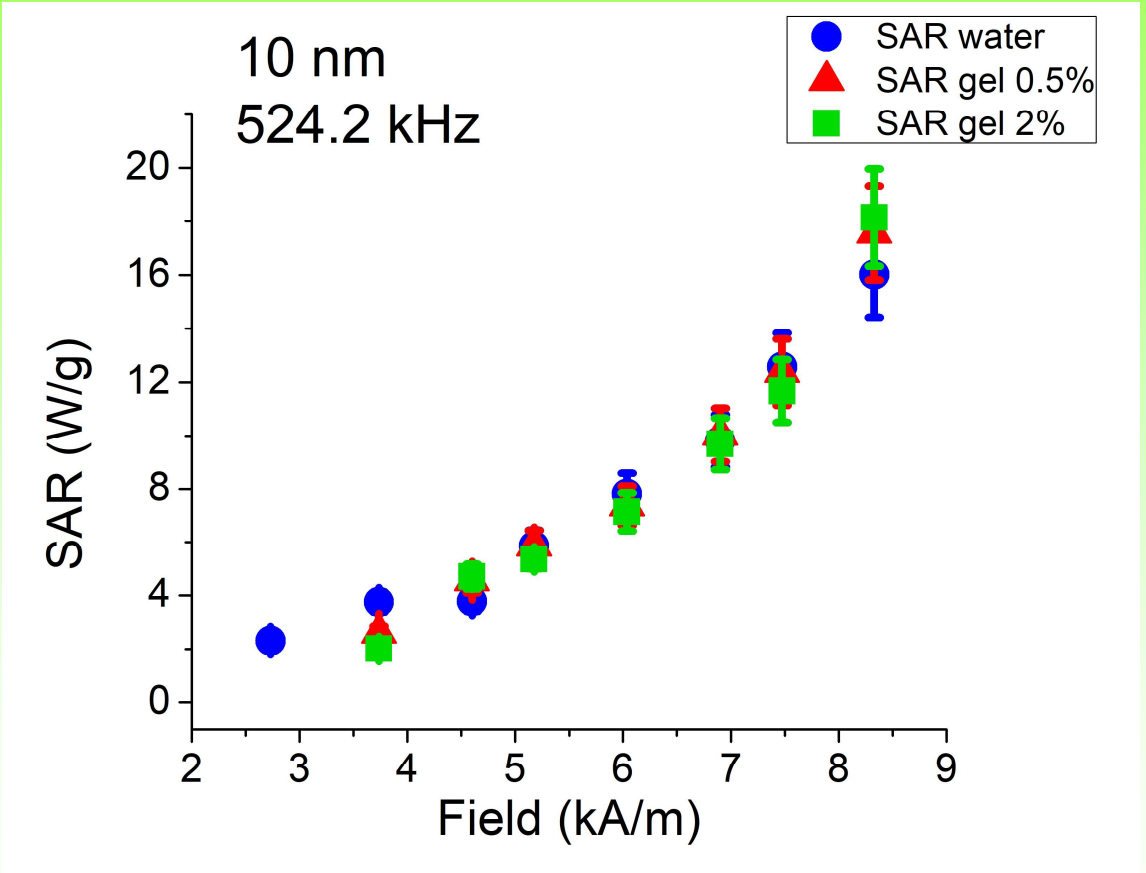
- **Maghemite, cobalt ferrite, iron oxide/gold dimers**
- **Spherical, nanocubes, nanoflowers**
- **10 to 250 nm**

«heating efficiency which occurs in cellular conditions can wipe put improvements observed when a material is tested in solution»

Results of NPs in gels

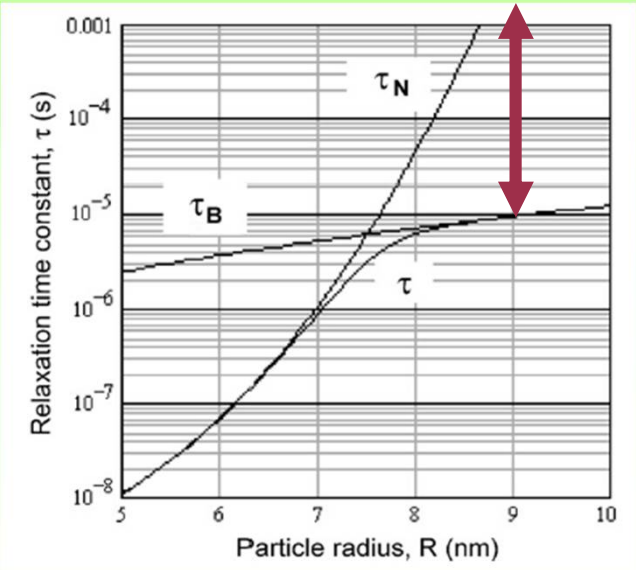
1. **10 nm: SAR is the same in gels and water samples**

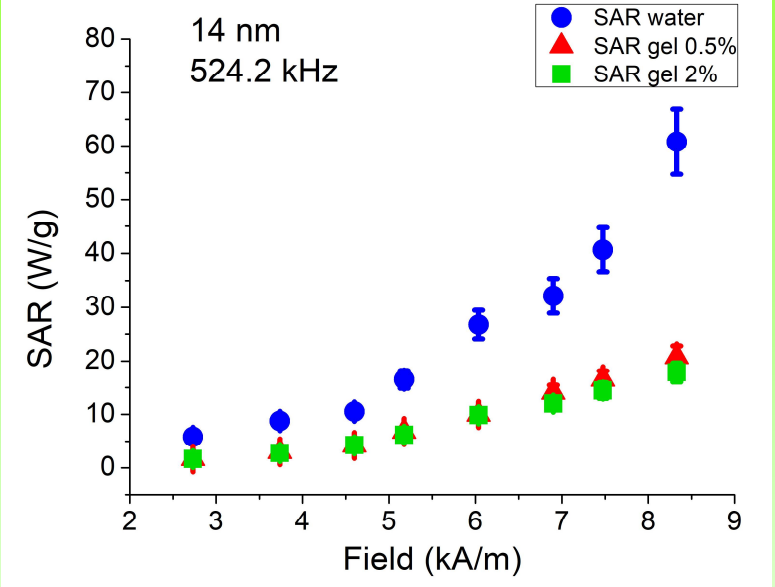


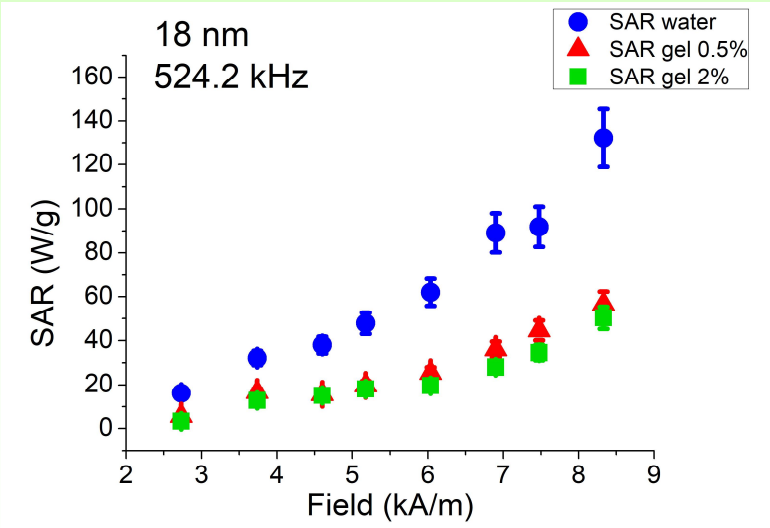


Results of NPs in gels

2. 14 and 18 nm: SAR fall in the two gels



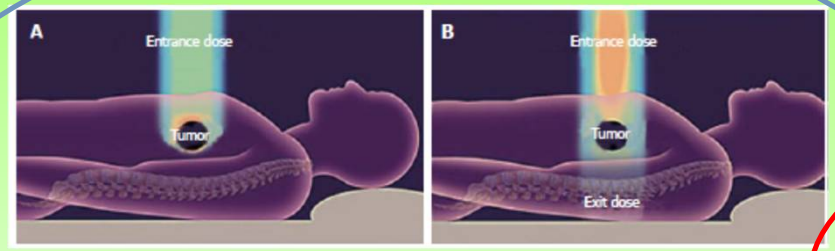




A particular case : combining MFH and hadron therapy

Combined therapies using magnetic NPs

INFN project HADROCOMBI



(A) targeted proton therapy deposits most energy on target;
(B) conventional radiation therapy deposits

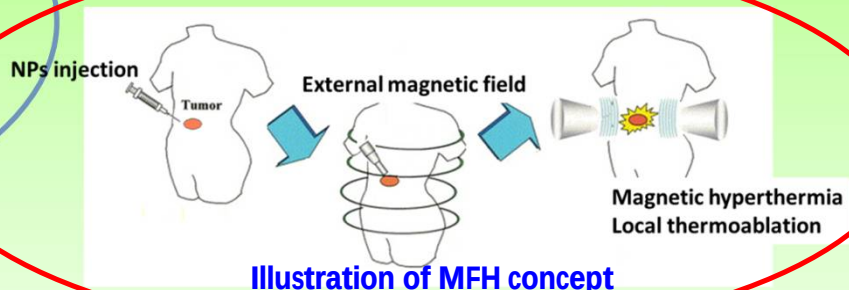


Illustration of MFH concept

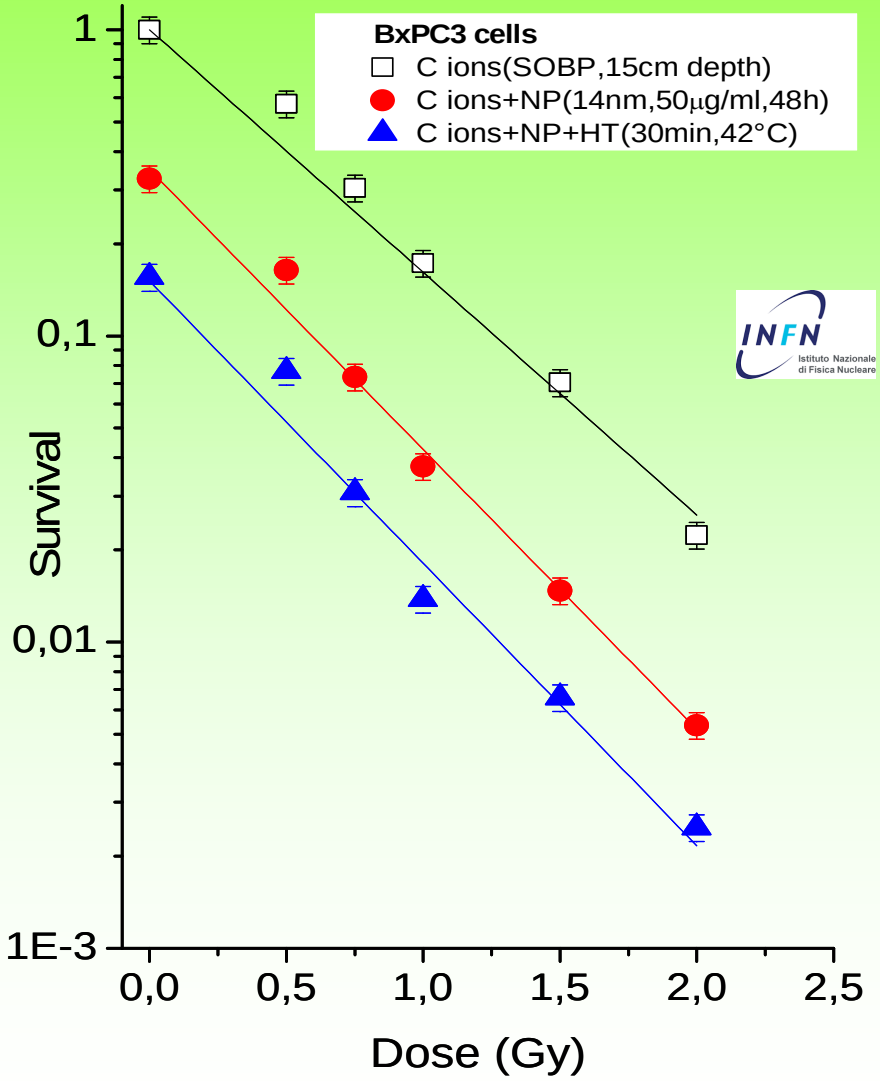
Hadron Therapy and Magnetic Hyperthermia are new and interesting treatments for cancers **where the "classical" therapies fail**.

The goal of the project is the investigation of the possible combined action of the two therapeutic techniques, for going one step beyond the state of art of pancreatic cancer therapy. X-rays irradiation will be used as control and comparison technique

Hadron therapy plus MF Hyperthermia

Preliminary results with carbon ions irradiation at CNAO-Pavia

* BxPC3 cells treated (or not) with MNPs
* Irradiated with hadrons. C ions, SOBP, 15 cm depth in water. 0 - 2 Gy.
* Successive hyperthermic treatment
* Two weeks of incubation at 37°C, then fixed and coloured for cells counting



Clonogenic survival :

- only hadrons
- hadrons and MNPs
- hadrons, MNPs and MFH

Conclusions (basics)

Basic physics and chemistry

* NMR T_1 model and experimental data tests needed for d > 20 nm, T_2 model needed
* Model for hyperthermia to be tested
* Surface spins effect to be clarified
* Solvent effect to be clarified (work partly in progress)
* Coating effect to b clarified
* Magnetic ion other than Fe ←→ TOXICITY ??
* Need for specific model if functionalization with drugs, fluo-molecules, antibodies/peptides, are implemented

……..

Crucial physical properties (linked/guided by biochemical ones)

* M(H) values at $T_{physiol}$ and above
* Dynamics (Brown, Neel) of M(H) at $T_{physiol}$ and above
* Role of surface spins, coating, solvent

Conclusions (applications)

Novel CA for MRI

- Several *non-specific systems* with high efficiency in contrasting images

Selective uptake in vivo (targeting/ Molecular Imaging)

- **Some NPs** (es. 15_Block-M-PTX-FA(115/15) with folic acid) are able to produce **a loss of signal in the tumor MDA-MB-231** (partly also in HT-29, early time), differently from the system WITHOUT folic acid. At longer time points, such effect remains. **Specific uptake in tumor tissue** was observed.

Therapy : intratumoral Magnetic Fluid Hyperthermia

- Some cases of diminution of tumour volume. Too low statistics. Too sparse data (several frequency and field values, also outside Brezovich criterion)

Other therapeutic effects (drug delivery)

- Driven by field, **some MNPs acts with drug.** In case of 15_Block-M-PTX-FA(115/15) with folic acid and PTX the increase rate of the tumour volume diminishes with IV injection

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14-18 settembre 2020

Thank you !

Any questions ??