Preparation and Biomedical Applications of Magnetic Nanoparticles

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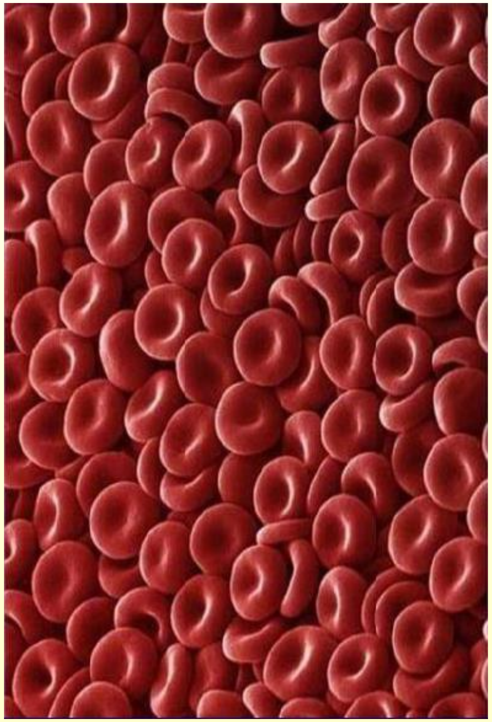
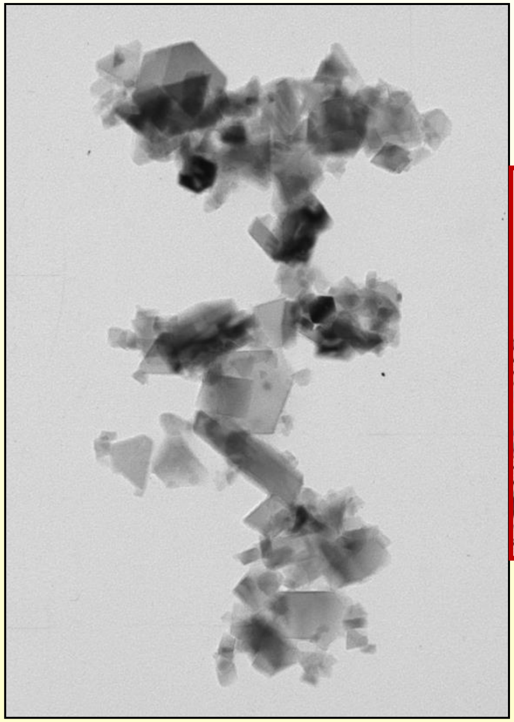
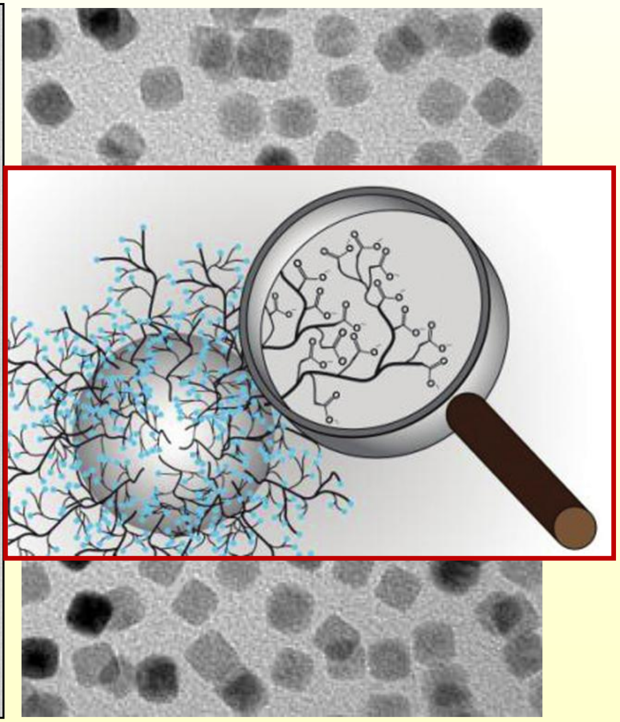
http://www.icmm.csic.es/csc







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Preparation and Biomedical Applications of Magnetic Nanoparticles

Summary

1- What are magnetic nanoparticles?
2- Requirements for biomedical applications
3- Basic principles in magnetism
4- Biomedical applications
  in vitro
  in vivo

5- Synthesis routes
  in solution
  aerosol
6-Example

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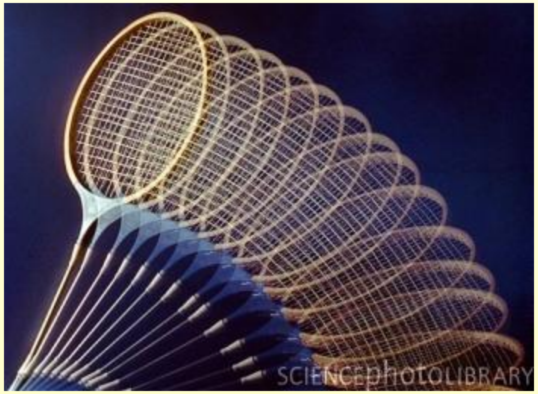
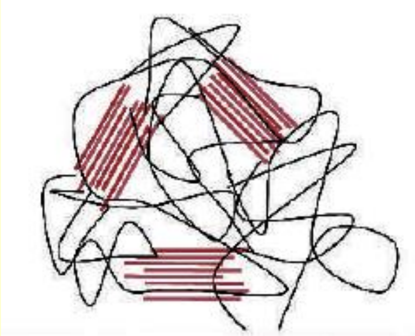
Nanotechnology

Particles

Films

Composites





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Improving Smelly Socks

ARC Outdoors, ArcticShield Socks

Incorporate 19-nanometer antimicrobial silver particles within their fibers.

A comfortable synthetic fiber sock with permanent resistance to odor and fungus.

Magnetic nanoparticles

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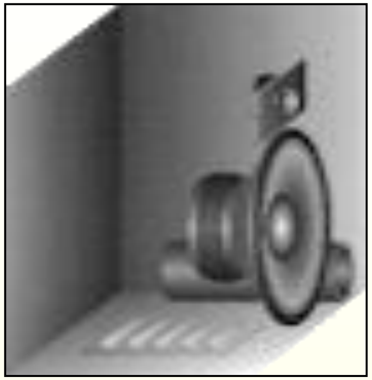
Magnetic nanoparticles

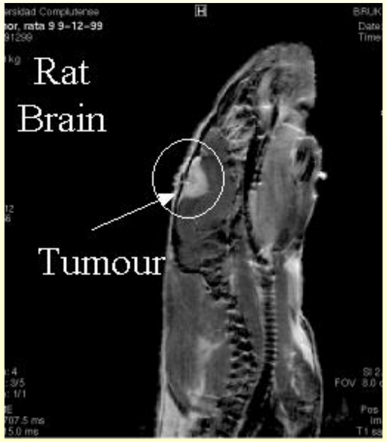
Inks



Loud speakers

Barcodes

Magnetic recording media



NMR Contrast agents

2004

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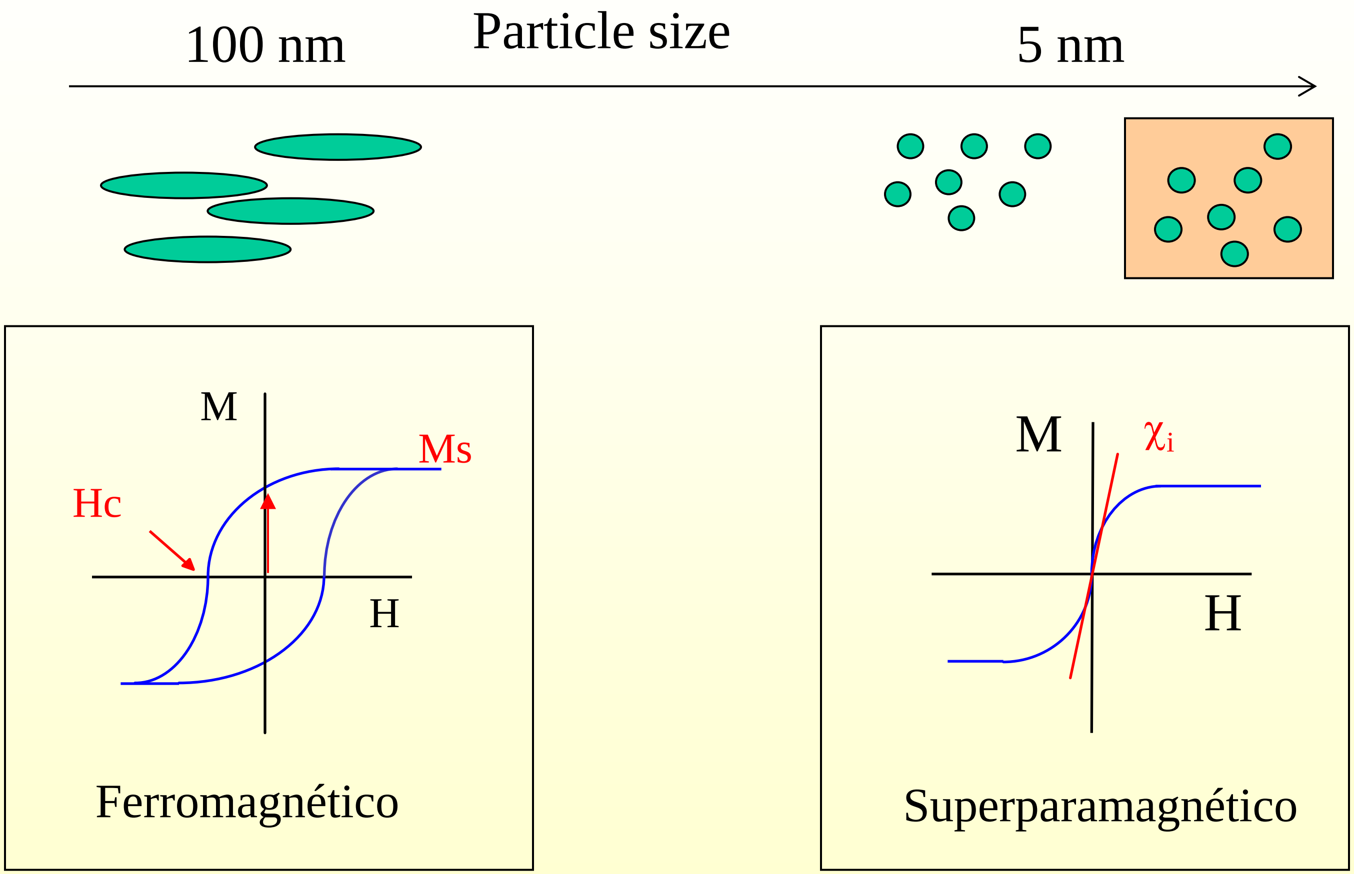
Formulaciones aprobadas por las diferentes agencias regulatorias.

Producto	Nanosistema	Indicación	Status	Compañía
Doxil (Barenholz, 2012)	Doxorrubicina encapsulada en liposomas PEGilados	Cáncer de ovarios	Aprobado 11/17/1995 FDA50718	Ortho Biotech (adquirida por JNJ)
Myocet (Waterhouse et al., 2001)	Doxorrubicina encapsulada en liposomas No PEGilados	Cáncer de mama metastásico	Aprobado en Europa y Canadá, en combinación con ciclofosfamida	Sopherion Therapeutics, LLC en América del Norte y Cephalon, Inc. en Europa
DaunoXome (Forssen, 1997)	Daunorrubicina encapsulada en liposomas	Tratamiento de sarcoma de Kaposi avanzado asociado al VIH	Aprobado en E.E.U.U	Galen Ltd.
ThermoDox (Dromi et al., 2007)	Doxorrubicina encapsulada en liposomas (liberación mediada por calor)	Cáncer de mama y primeras etapas de cáncer de hígado	Aprobación esperada para el año 2013	Celsion
Abraxane (Guarneri et al., 2012)	Nanopartículas de albúmina-paclitaxel	Diferentes tipos de cáncer	Aprobado 1/7/2005 FDA21660	Celgene
Rexin-G (Gordon and Hall, 2010)	MicroRNA-122 encapsulado en liposomas	Sarcoma, osteosarcoma, cáncer de páncreas, y otros tumores sólidos	Aprobado en Filipinas, Fase II y III en E.E.U.U	Epeius Biotechnologies Corp.
Oncaspar (Avramis and Tiwari, 2006)	Asparaginasa PEGilada	Leucemia linfoblástica aguda	Aprobado 24/06/2006	Enzon Pharmaceuticals, Inc.
Resovist (Hamm et al., 1994)	Nanopartículas de óxido de hierro recubiertas de carboxidextrano	Agentes de contraste para hígado y bazo	Aprobado en Europa en 2001	Bayer Schering Pharma AG
Feridex (Weissleder et al., 1989)	Nanopartículas de óxido de hierro recubiertas de dextrano	Agentes de contraste para hígado y bazo	Aprobado por la FDA en E.E.U.U en 1996	Berlex Laboratories
Endorem (Weissleder et al., 1989)	Nanopartículas de óxido de hierro recubiertas de dextrano	Agentes de contraste para hígado y bazo	Aprobado en Europa	Guerbet

Patrick Couvreur et al., Chem. Rev. 112, 5818, 2012

He was the first to develop nanometric capsules able to penetrate cells to deliver medicine

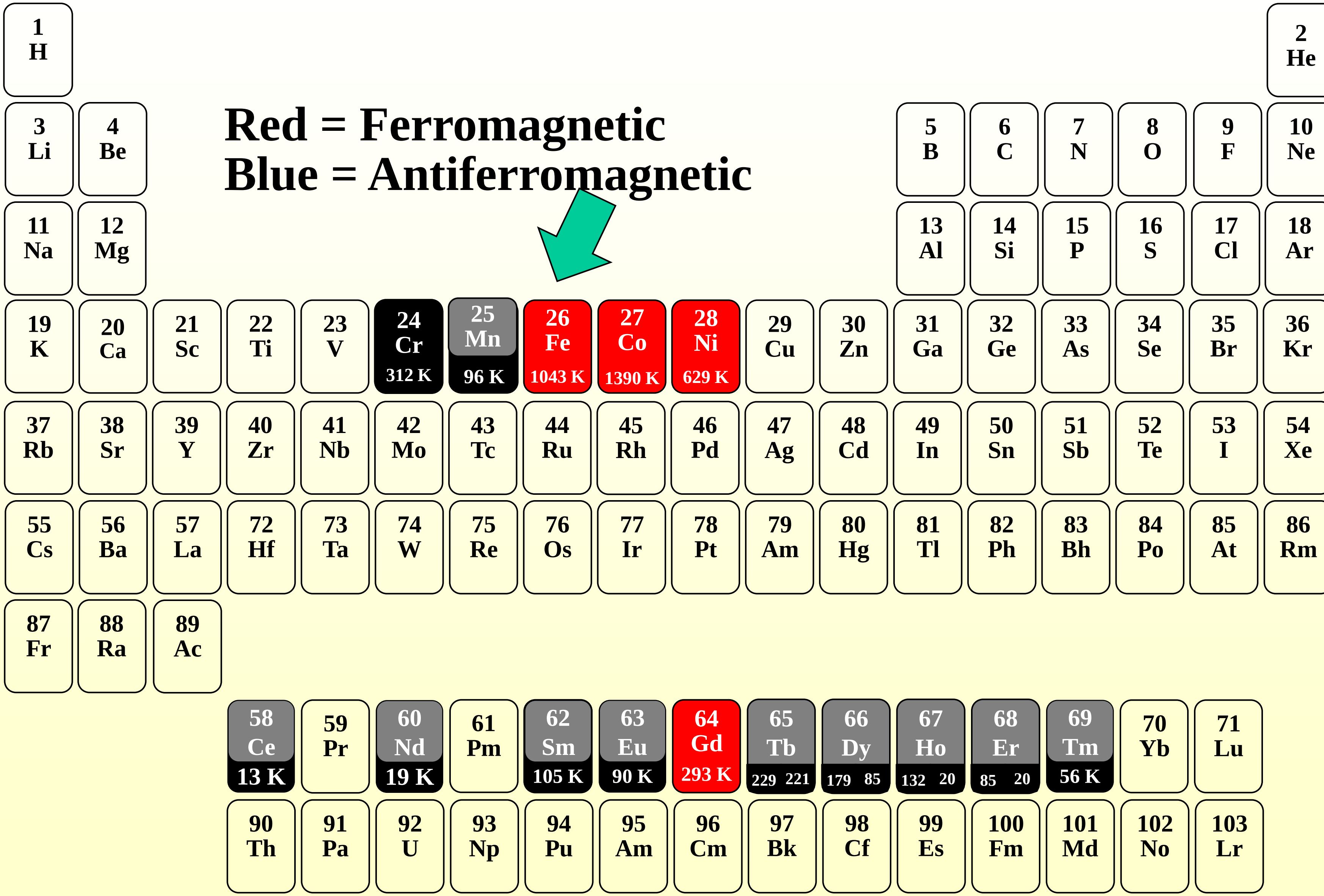
Magnetic nanoparticles



Magnetic recording

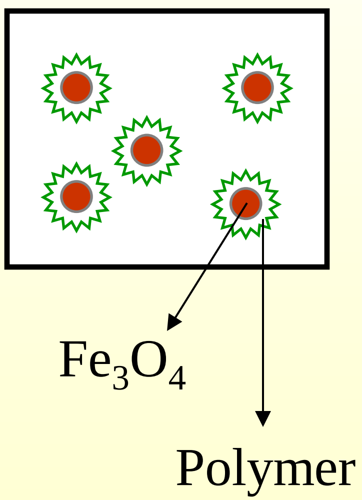
Sensors

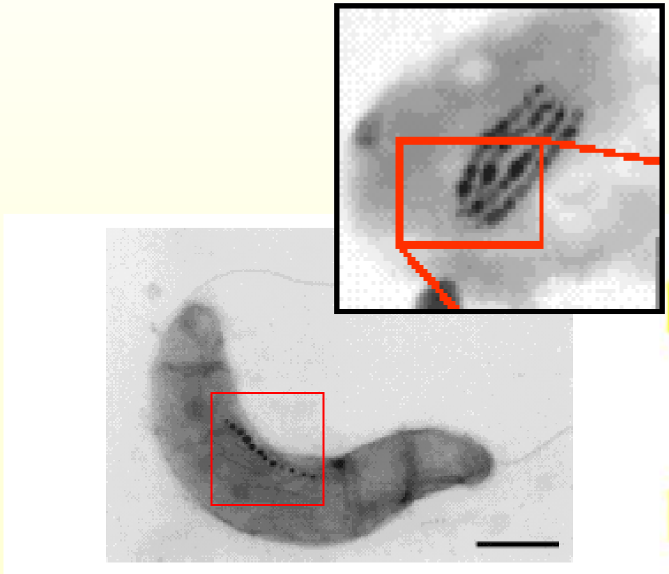
Magnetic nanoparticles



Magnetic nanoparticles

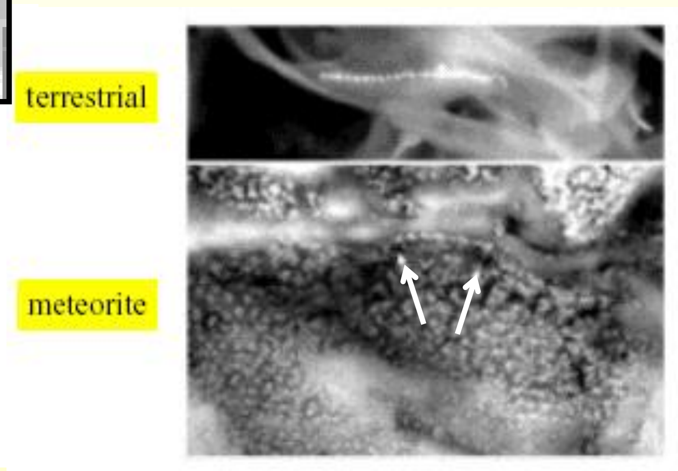
MAGNETIC NANOPARTICLES ⇔ LIVING SYSTEMS





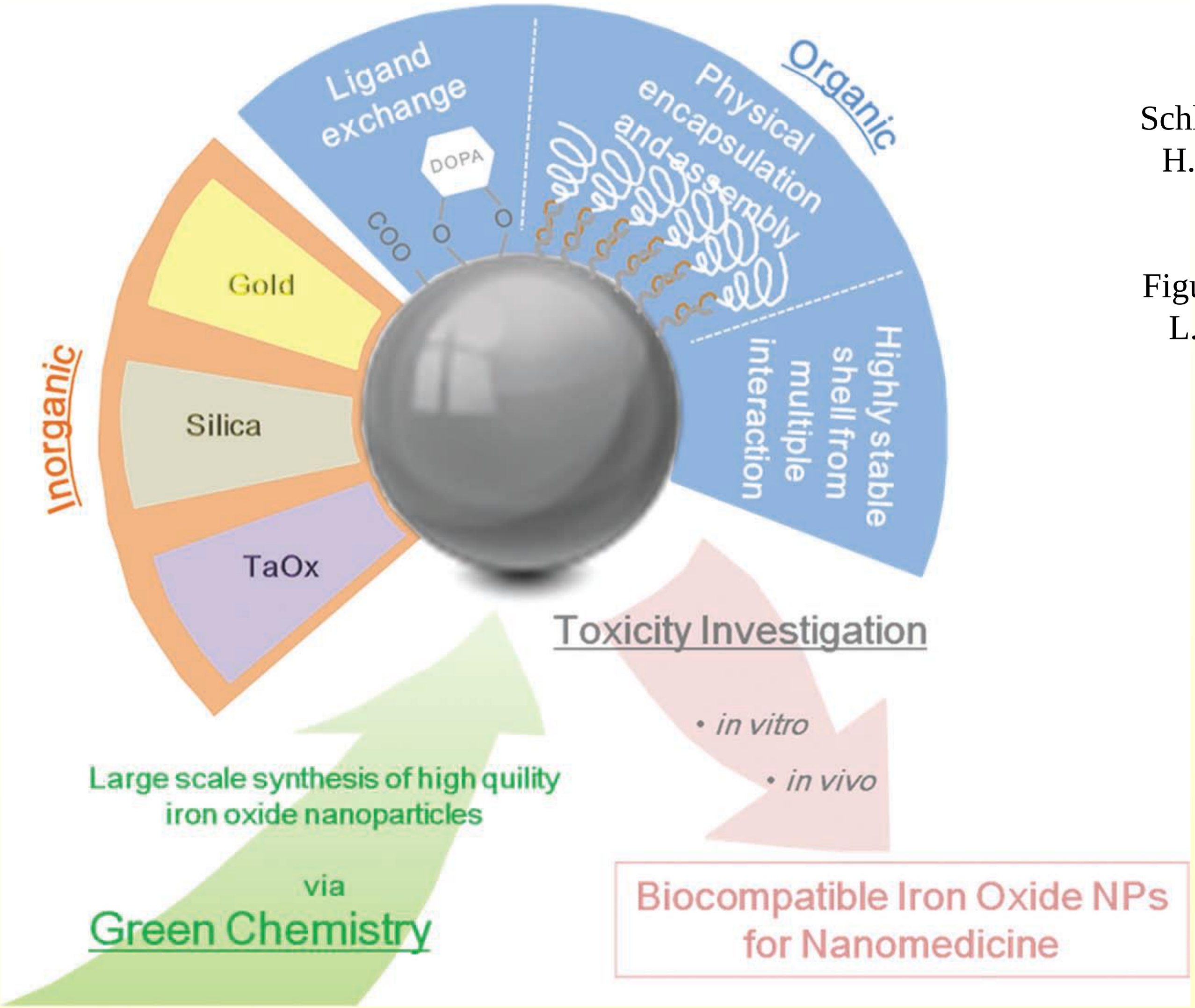
Magnetotactic bacteria

For orientation



Life in Mars?

Magnetic nanoparticles



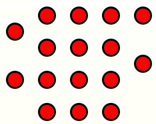
Chem. Soc. Rev., 2012, 41, 4306

Schladt, T. D.; Schneider, K.; Schild, H.; Tremel, W. *Dalton transactions* 2011, *40*, 6315

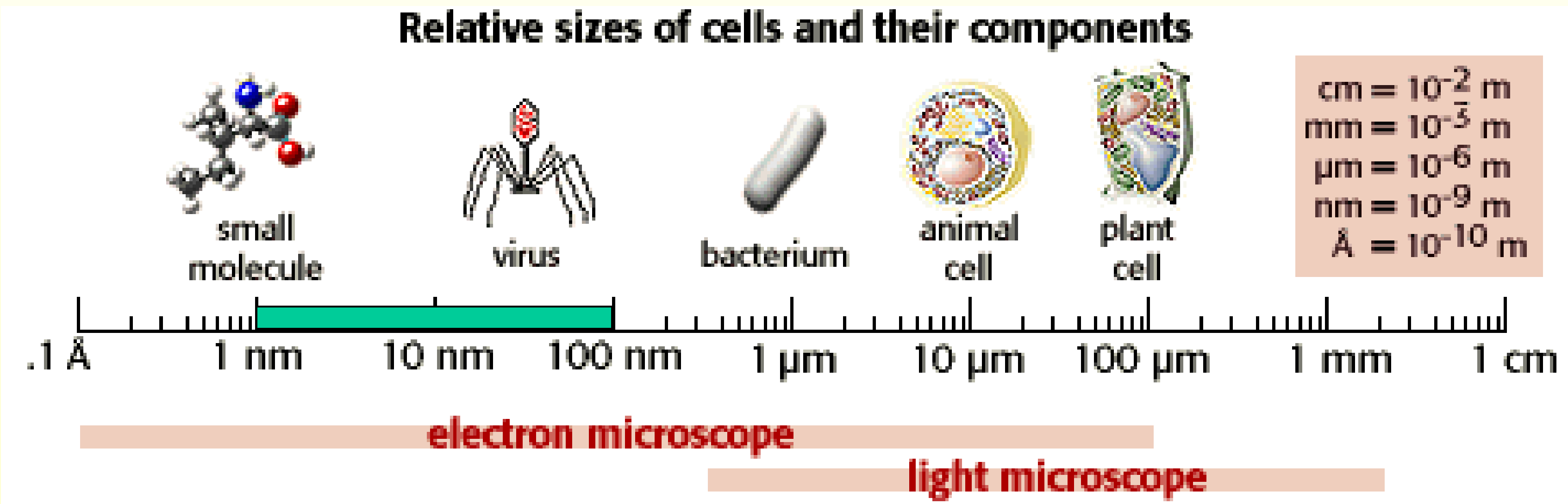
Figuerola, A.; Corato, R. Di; Manna, L.; Pellegrino, T. *Pharmacological Research* 2010, *62*, 126

Chemical Design of Biocompatible Iron Oxide Nanoparticles for Medical Applications, *Daishun Ling a nd Taeghwan Hyeon* , **Small** 2013, *9*, No. 9–10, 1450–1466,

Magnetic nanoparticles



Nanometer => **Size**: Get close to a biological entity of interest
=> **Surface**: Bind a biological entity
=> **Properties**: Manipulated by a magnet



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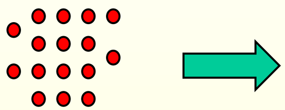
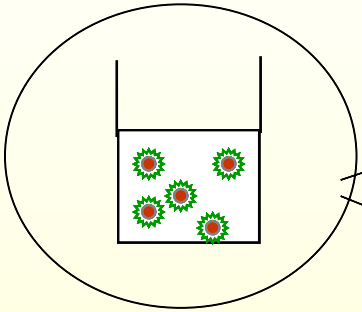
Requirements for biomedical applications

NANOPARTICLES



No toxic!!

COLLOIDAL SUSPENSIONS



- Stable
- Biocompatible
- Reversible

APPLICATIONS

In vitro

In vivo

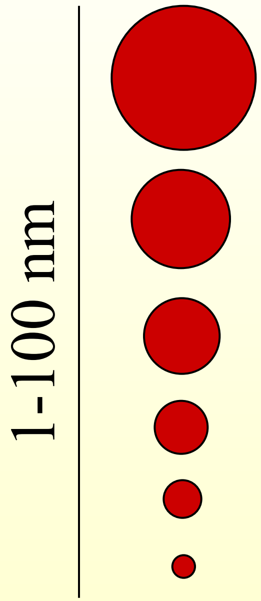
REQUIREMENTS

- **Size**
- **Surface**
- **Properties**

Requirements for biomedical applications

Size

5-50 nm = Ideal diameter for most forms of therapy

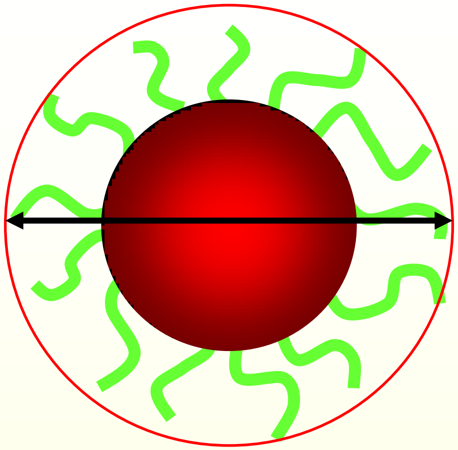


Detected by the immune system and eliminated

Remain in the body long enough to be circulated through the blood stream

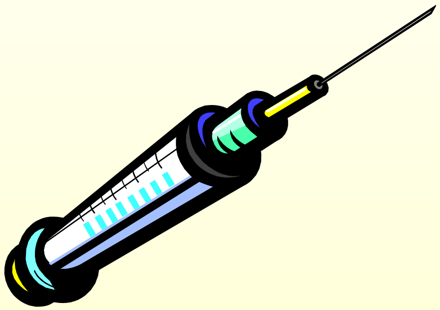
Small response to a magnetic field

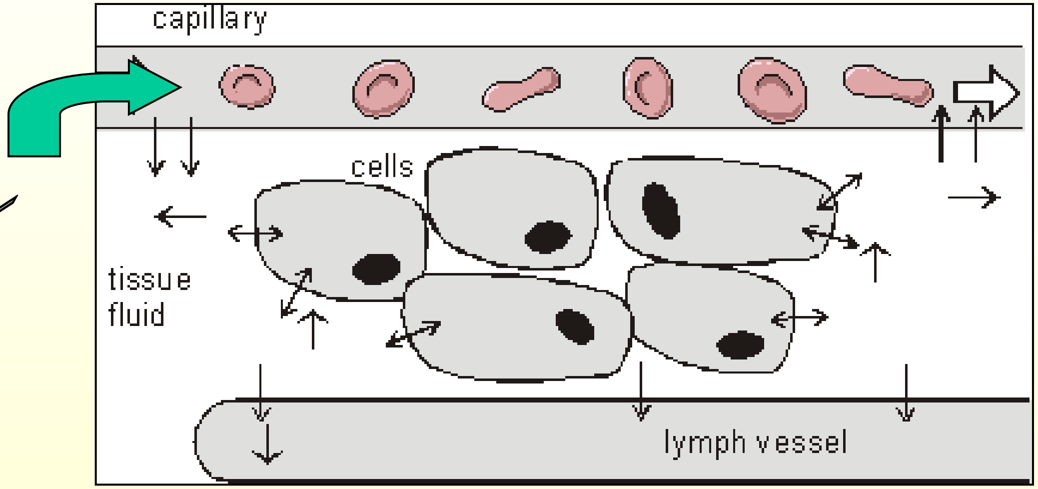
Requirements for biomedical applications

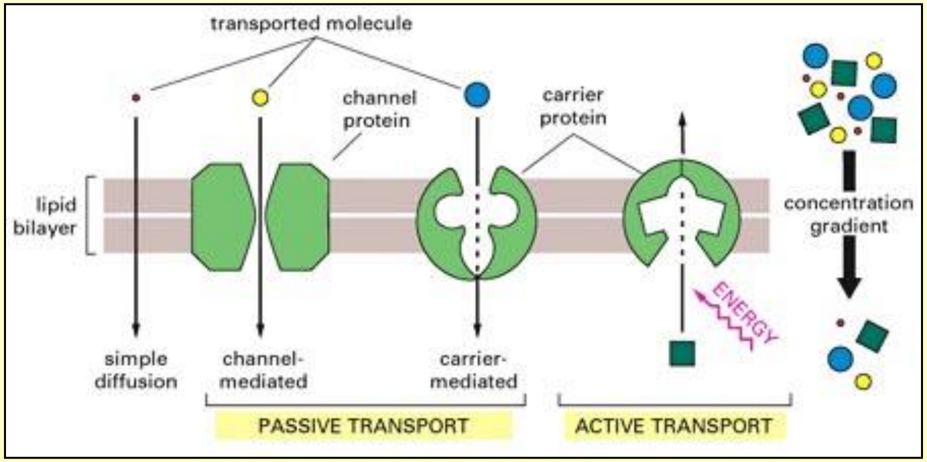


Hydrodynamic size

Core + Molecules around

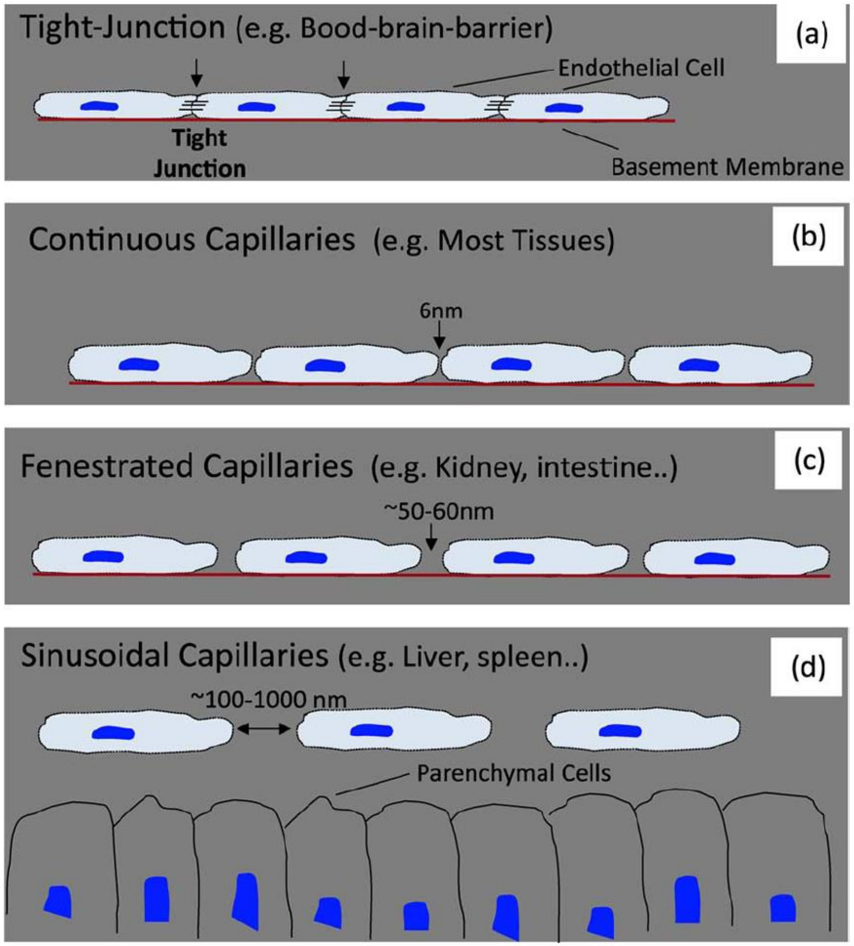






Requirements for biomedical applications

Biology barriers



Blood capillaries

Gaps between endothelial cells

2 nm

6 nm

50 nm

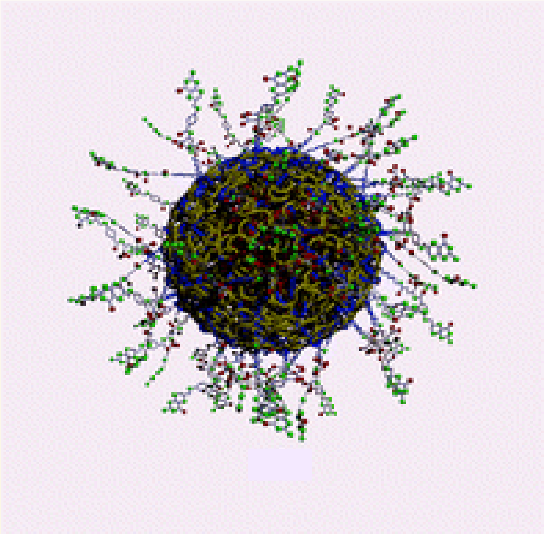
> 100 nm

Y. Okuhata, *Adv. Drug Del. Rev., vol. 37, pp. 121–137, 1999.*

Requirements for biomedical applications

Surface

Modification of the particle´s surface to make it biocompatible and specific



=> **Biocompatible** = **Hydrophilic coating** make the particle look friendly to the immune system

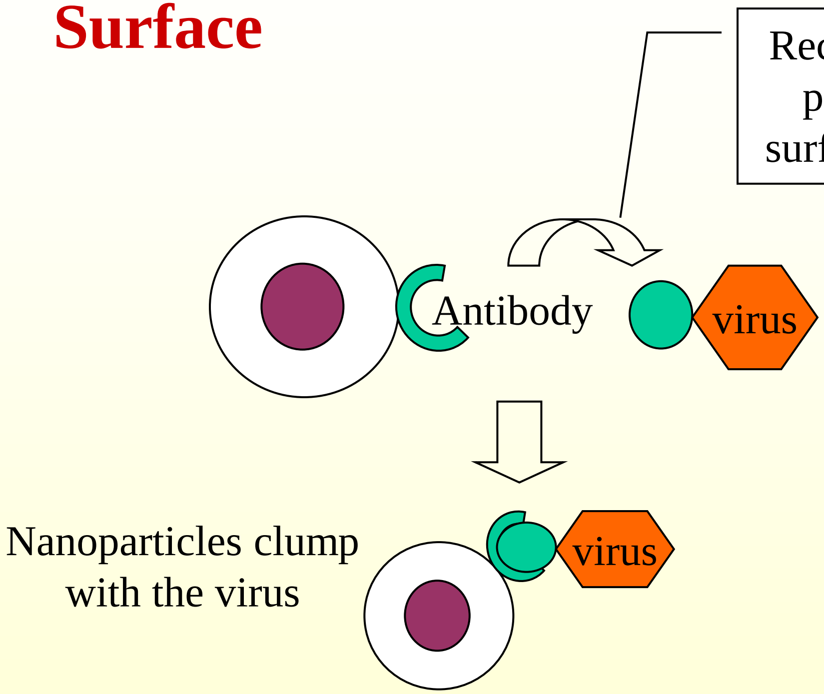
- Polymer
- Inorganic

=> **Specific** = Coated with a **biological entity** to make the particles function in a specific manner

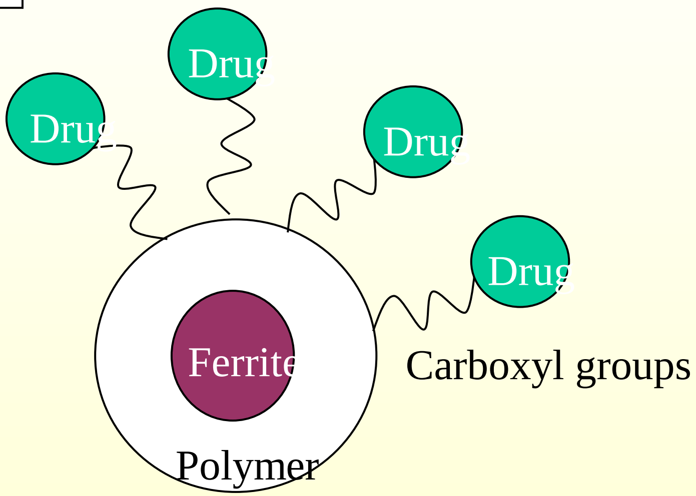
=> **Carrier =** to transport and deliver a biological active agent

Requirements for biomedical applications

Surface



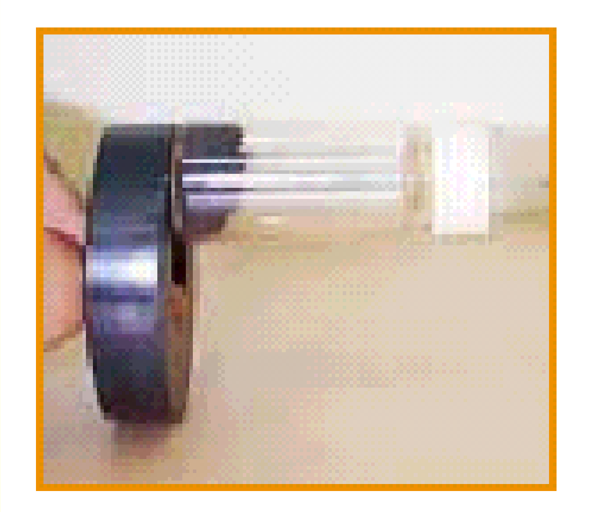
Detect virus in body fluids

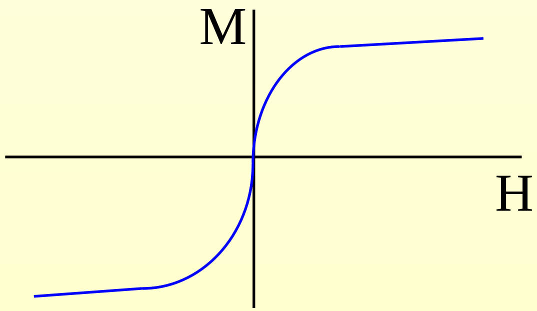


Recognise and destroy a cancer cell

Requirements for biomedical applications

Magnetic properties





- They must **constantly and rapidly “flip” magnetic states.**
  => Mr=0

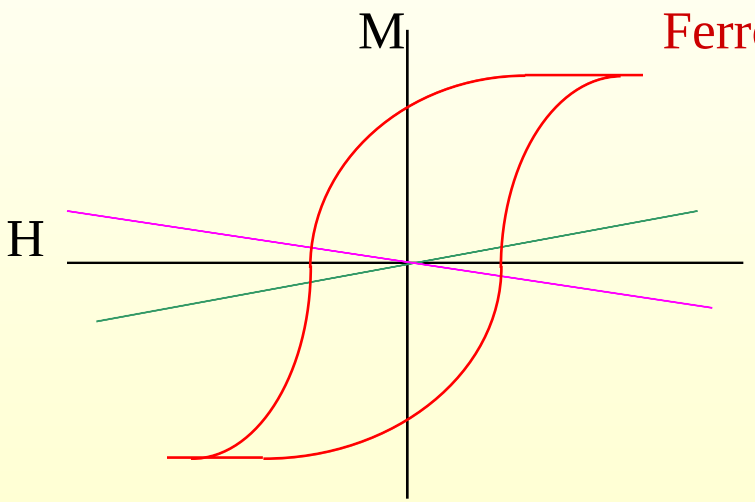
- **Saturation magnetisation** (Ms) should be **strong enough** to be manipulated by an external magnetic field

- **Resonant respond** to a time-varying magnetic field should be enough to heat up.

Basic principles in magnetism

All materials are magnetic to some extent with their magnetic response depending on their atomic structure and temperature

Ordered magnetic states
M = 10^4 times larger



Ferromagnetic, ferrimagnetic and antiferromagnetic

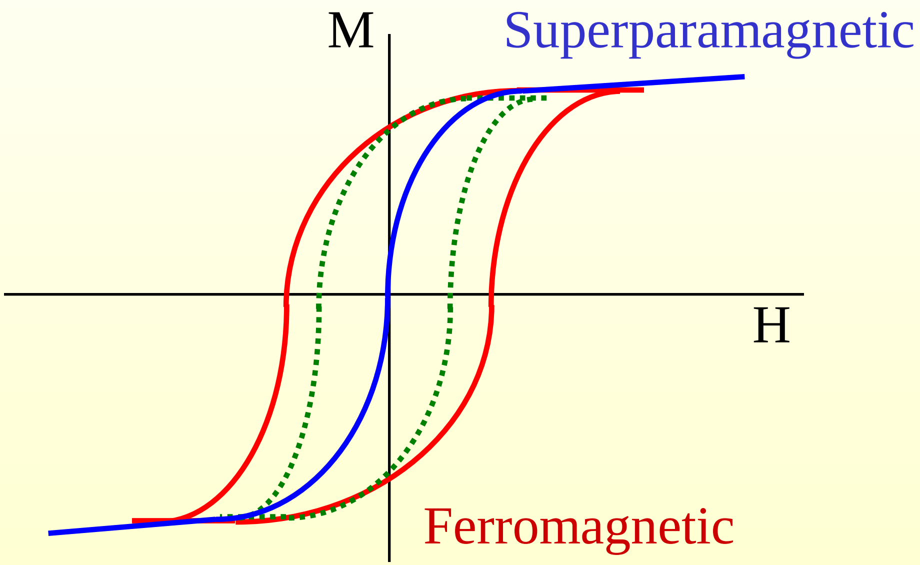
Paramagnetic

Diamagnetic

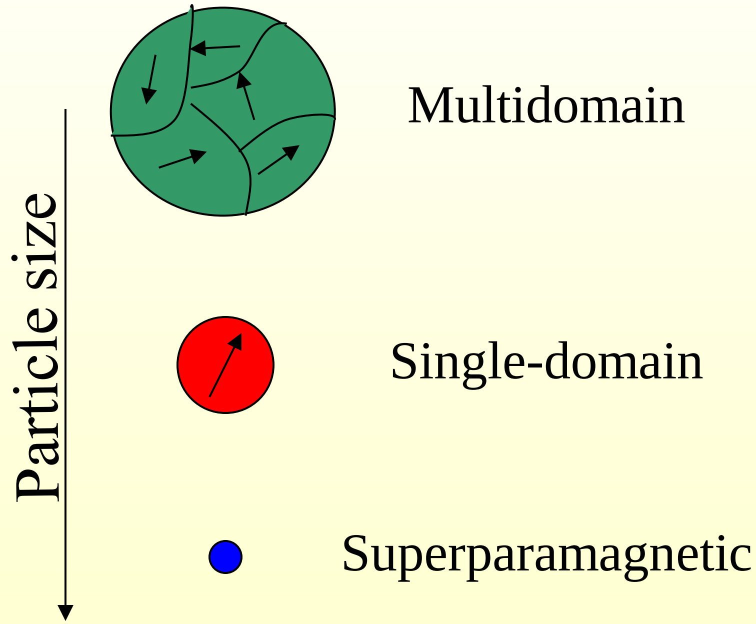
Little magnetism, only in the presence of a magnetic field

Basic principles in magnetism

The shape of the loops are
determined in part by the particle size



Domain structure



Basic principles in magnetism

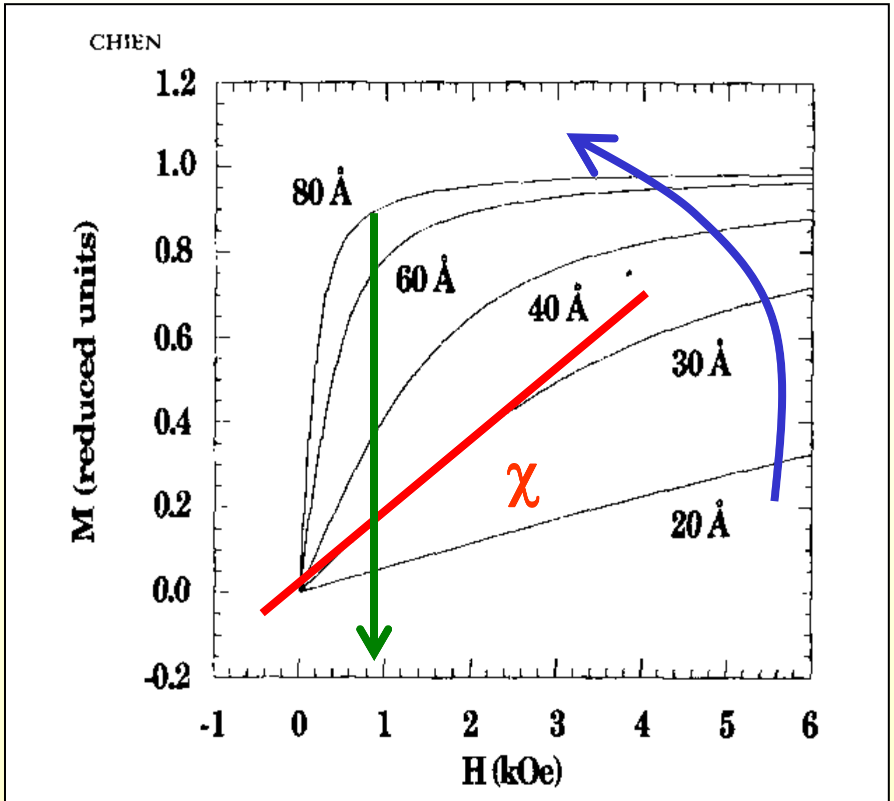
Superparamagnetism

Particle size

- Magnetic behaviour

$$\chi \approx \frac{VM_S^2}{3k_BT}$$

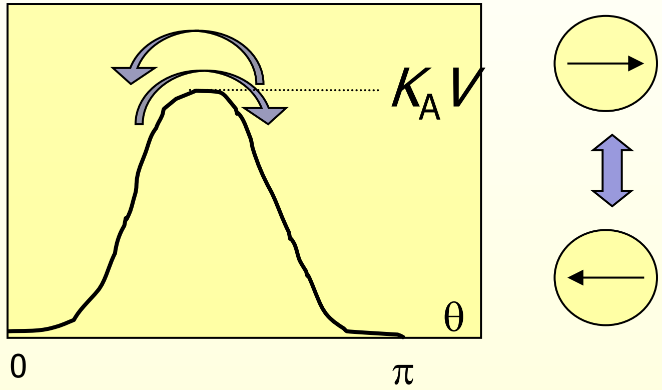
- Saturation field



ure 7 Calculated magnetization behavior at T = 300 K of Fe particles of various sizes

Basic principles in magnetism

Superparamagnetism



Jump frequency

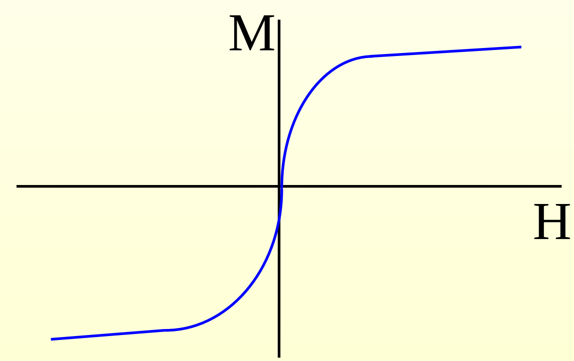
$$\upsilon = \tau_0^{-1} \exp\left(-\frac{K_a V}{k_B T}\right)$$

Relaxation time

$$\tau = \tau_0 \exp\left(\frac{K_a V}{k_B T}\right)$$

Small particle size

$$\Delta E = K_a V \approx k_B T$$



No particle aggregation

Reversible behaviour

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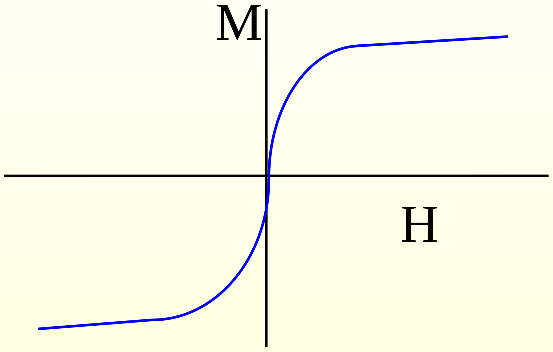
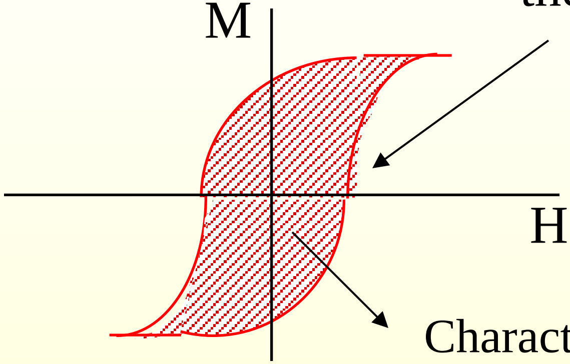
Basic principles in magnetism

Ferromagnetism



Alternating magnetic field

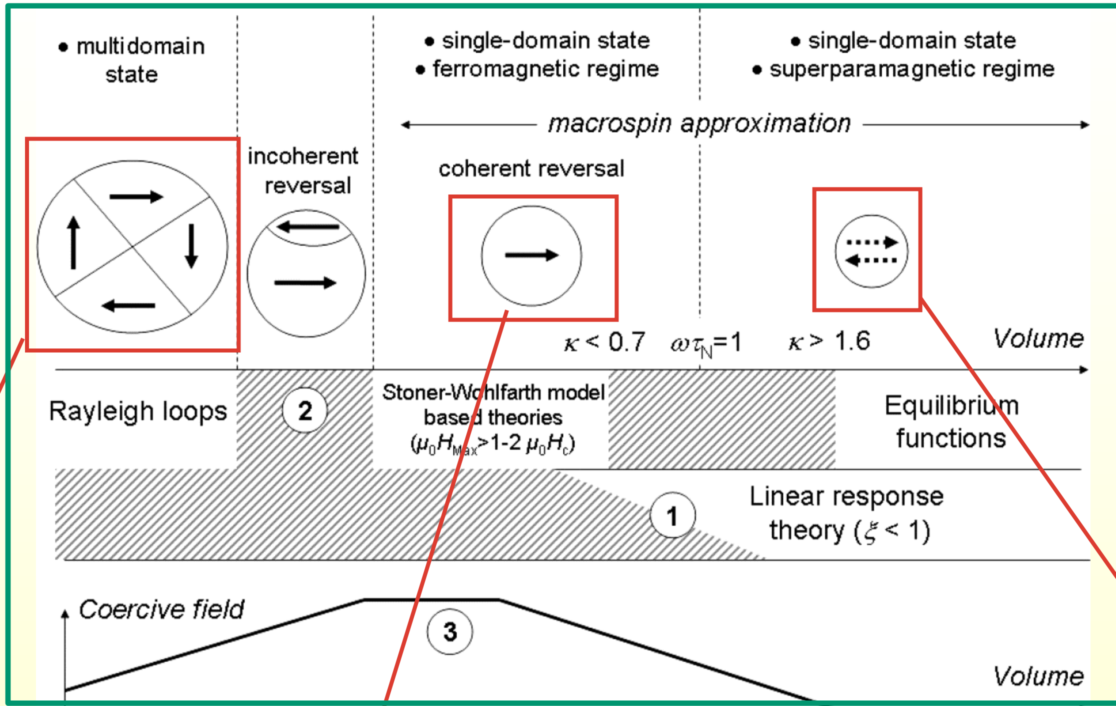
Delivered by the applied field



Characterised by area enclosed by the hysteresis loop

Thermal energy

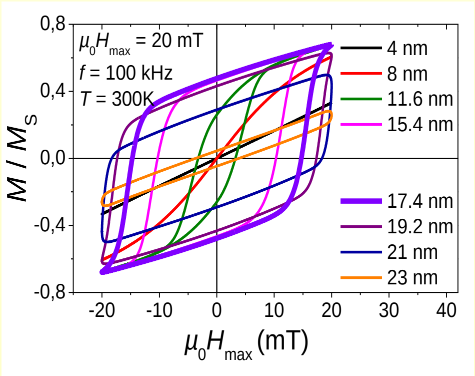
Basic principles in magnetism



- Drop of coercive field→ less efficient
- No prediction possible

-No hysteresis→ no interest
- Analytical calculation : Langevin…

- Open hysteresis loops→**optimized nanoparticles**
- Analytical calculations : Stoner-Wohlfarth model



J. Carrey et al. J. Appl. Phys. 110, 039902 (2011)

Biomedical applications

- In vitro → Diagnostic → **Separation/selection**

- In vivo
  - → Diagnostic → **NMR imaging**
  - → Therapeutic → **Drug targeting**, **Hyperphermia**

Gene delivery

Tissue regeneration (cell labelling)

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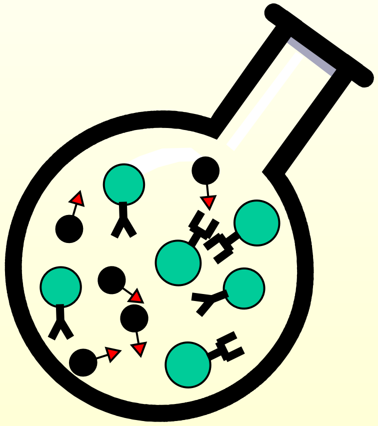
Biomedical applications

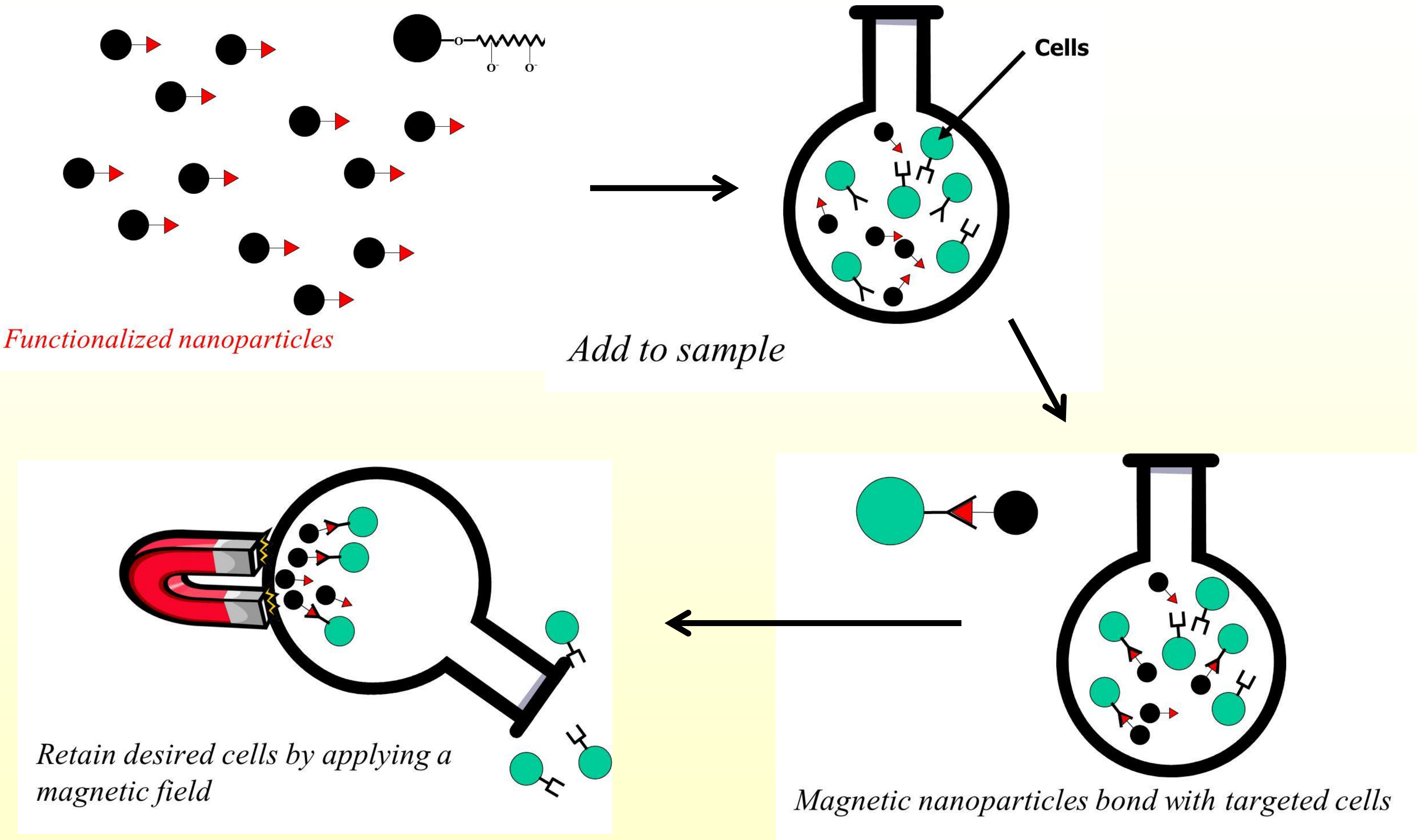
Separation/selection

- Goal: Separate/detect/isolate one type of cell from others, often when the target is present in very small quantities



Reduce the time
Detect lower concentrations

Separation/selection



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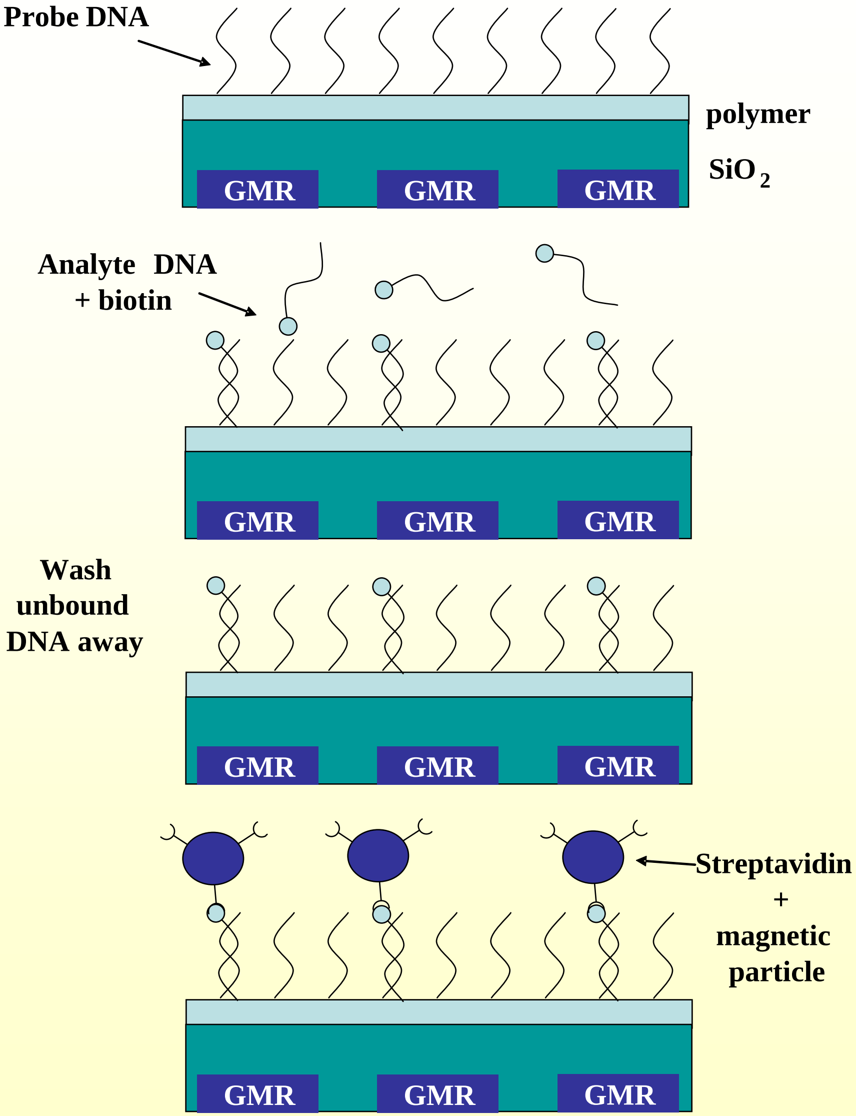
Separation/selection



Magnetic Sorting/Detection

- **High sensitivity**
- **Multiple analytes at one time**
- **Hand-held**
- **Lightweight**
- **Fast**
- **Potential for single-bead detection**

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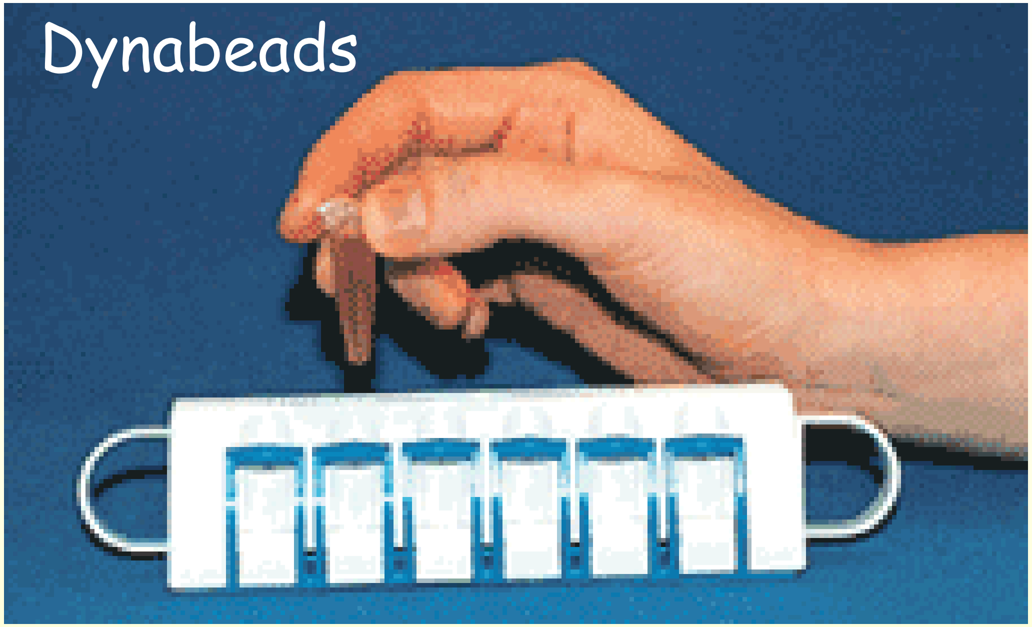
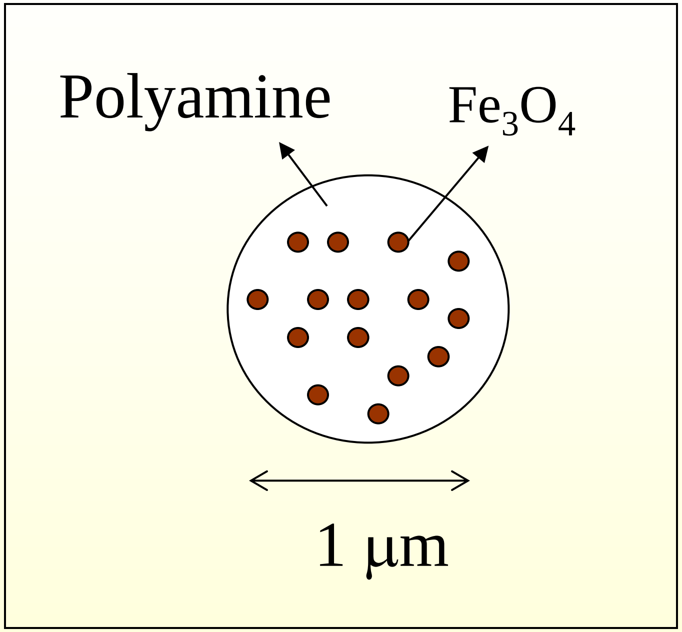
Biomedical applications

Separation/selection





Separación y purificación

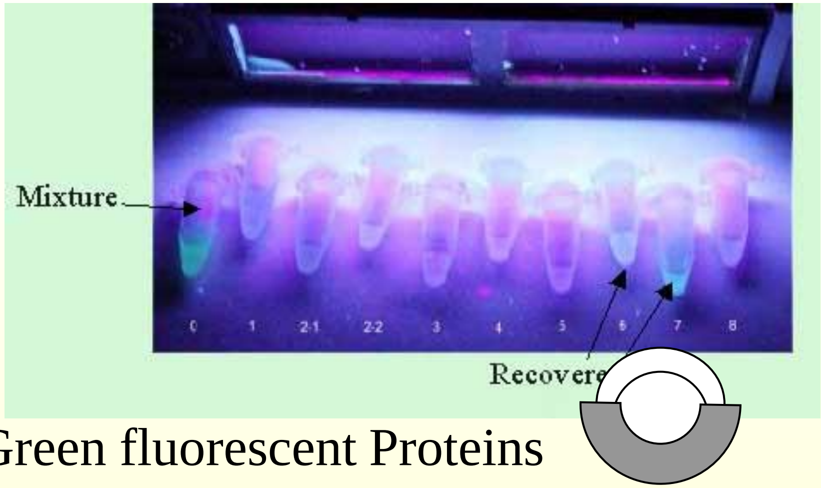
- ✓ Detection of proteins at 10^{-18} M = Prostate-specific antigen (PSA)
- ✓ Detection of DNA at 10^{-21} M

6 orders of magnitude more sensitive

J-M. Nam, C. S. Thaxton, C. A. Mirkin, Science, 301 (2003) 1884.
J-M. Nam, S. I. Stoeva, C. A. Mirkin, J. Am.Chem. Soc., 126 (2004) 5932

Biomedical applications

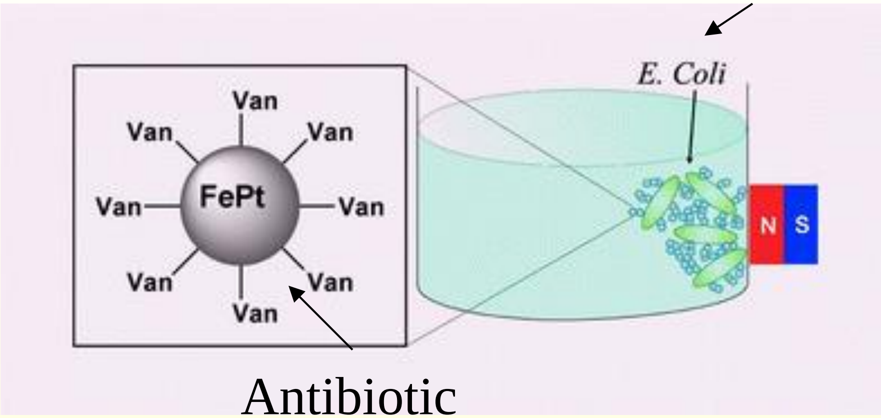
BIOMOLECULE SEPARATIONS



Green fluorescent Proteins

FOOD QUALITY CONTROL

Bacteria



Antibiotic

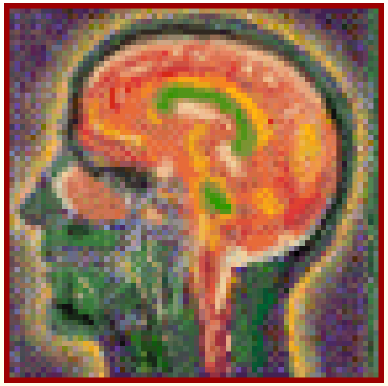
WATER PURIFICATION (Ar, Pb…)

884 millones = Personas que carecen de acceso a fuentes de abastecimiento de agua potable (una de cada ocho)

Yavuz, C. T. Prakash, A. Mayo, J. T.; Colvin, V. L. Chemical Engineering Science 2009, 64, 2510-2521;

Yavuz, C.T., Mayo, J.T., Yu, W.W. et al. Low-field magnetic separation of monodisperse Fe3O4 nanocrystals. Science 10 (2006)
Environ Geochem Health DOI 10.1007/s10653-010-9293-y
Mohan and Pittman 2007

NMR IMAGING



The most powerful technique for diagnosis

Nobel Prize 2003
Paul C. Lauterbur and Sir Peter Mansfield
"for their discoveries concerning magnetic resonance imaging"

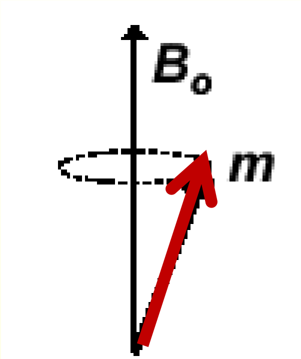
Advantage: not use X-Rays nor any other type of "ionizing" radiation

Instead: it is a technique that combines a large magnetic field and some radio frequency antennas

Measure the relaxation rate of protons in the atoms of water within the patient from their excited state to the ground state

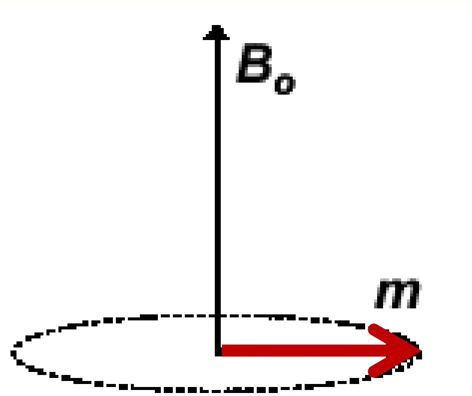
NMR imaging

magnetic field



protons of water "line-up"

high-frequency electro-magnetic pulse



protons out of alignment

"resonance" signal as the proton goes back into alignment

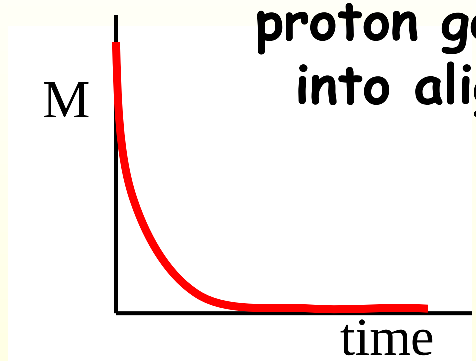
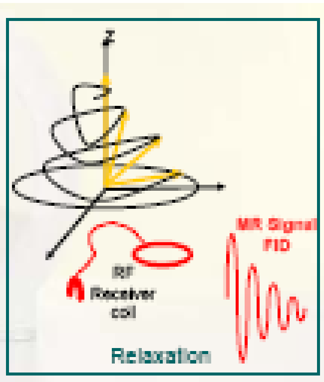
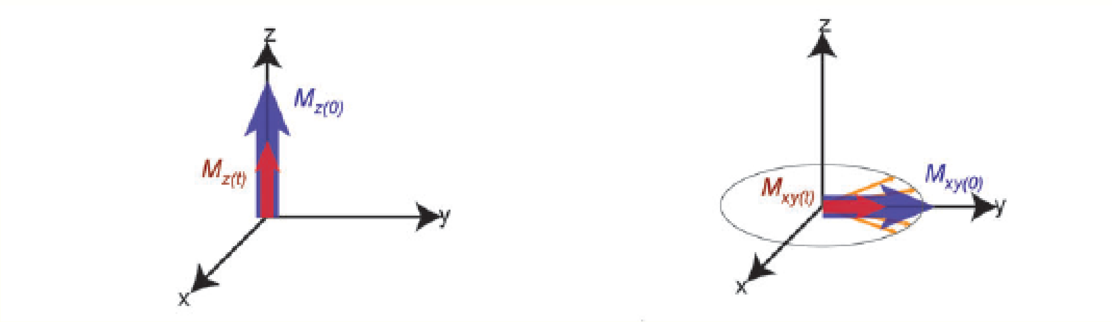


image reflects the water protons in the patient and their chemical association with proteins

NMR imaging





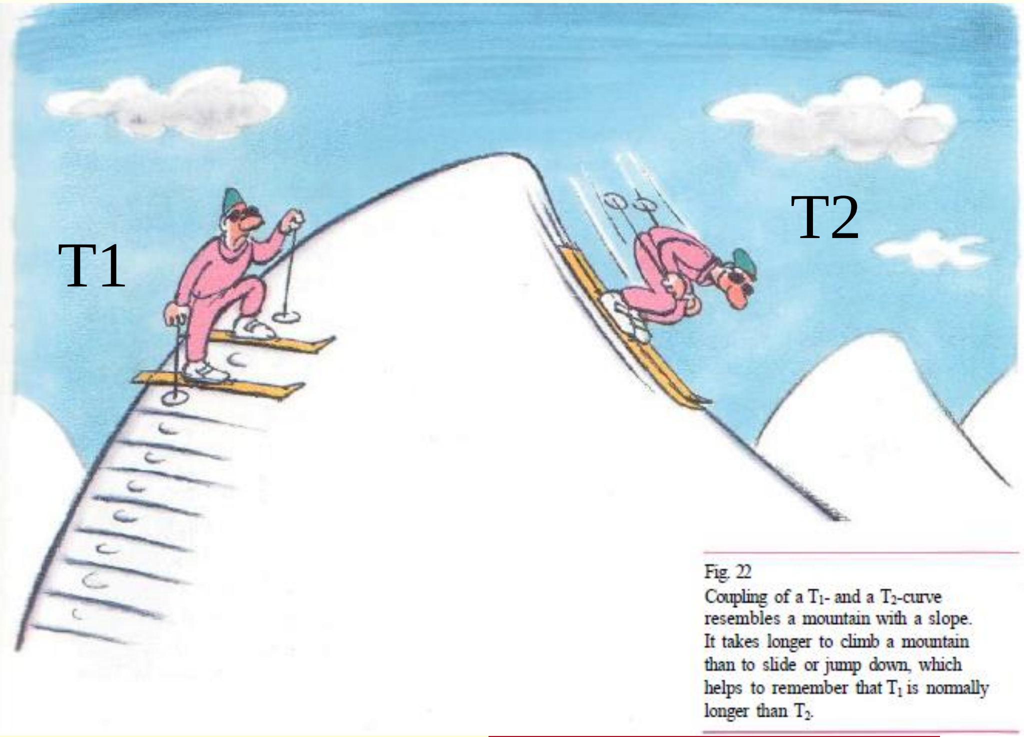
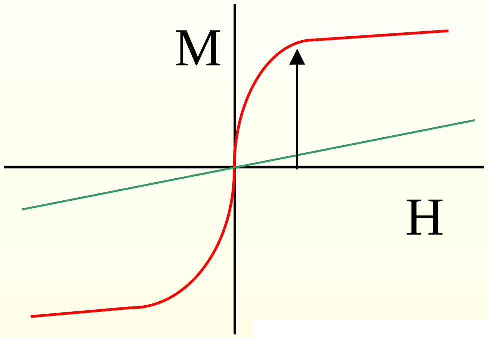


Fig. 22
Coupling of a T_1- and a T_2-curve resembles a mountain with a slope. It takes longer to climb a mountain than to slide or jump down, which helps to remember that T_1 is normally longer than T_2.

MRI made easy

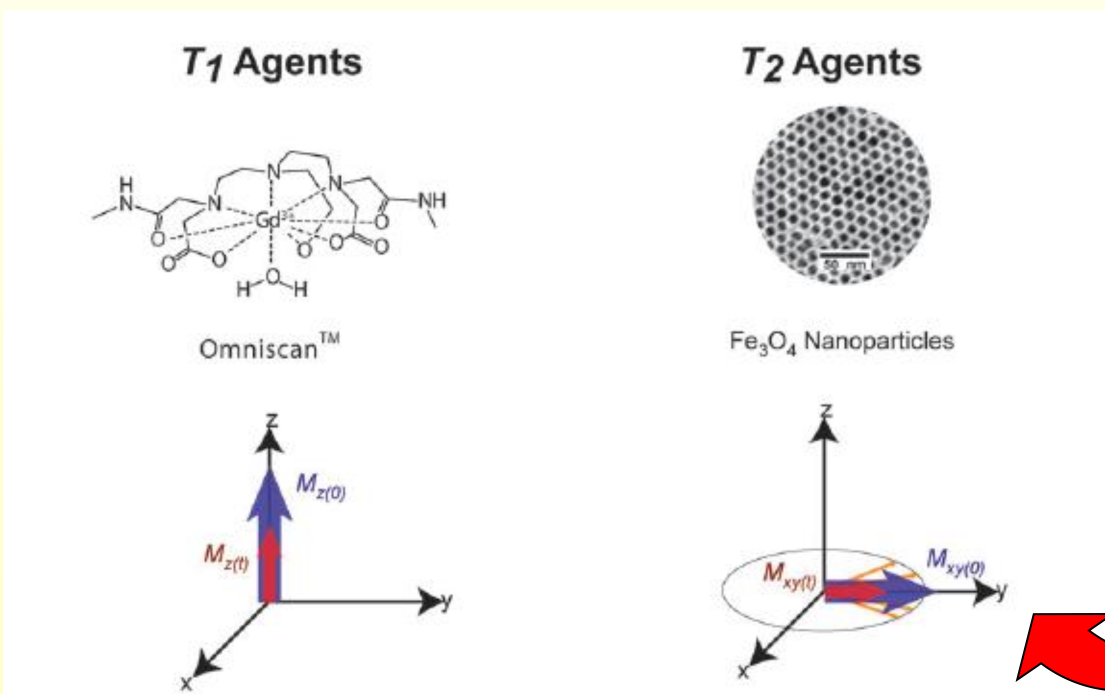
Contrast agents for NMR imaging

Enhance the contrast between normal and diseased tissues, indicate organ function or blood flow



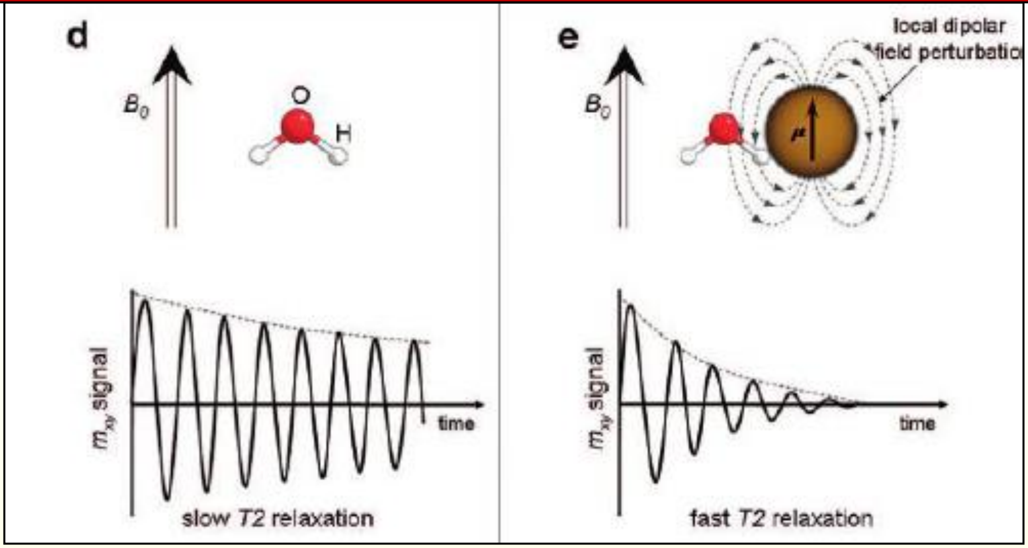
Superparamagnetic => **Magnetic nanoparticles**

Paramagnetic => Gd, Dy



- Magnetic moment 10^4 times larger
- 80-90% saturation at lower field

Contrast agents for NMR imaging



Cheon et al, ACCOUNTS OF CHEMICAL RESEARCH 1630-1640 December 2008 Vol. 41, No. 12

Shorter relaxation (T_2)
=> **Darker** in the MRI

$$\frac{1}{T_2} = R_2 = \frac{\left(\frac{64\pi}{135000}\right) \gamma^2 N_A M \mu^2}{r\, D}$$

NP magnetic moment

Concentration (mole.L^{-1})

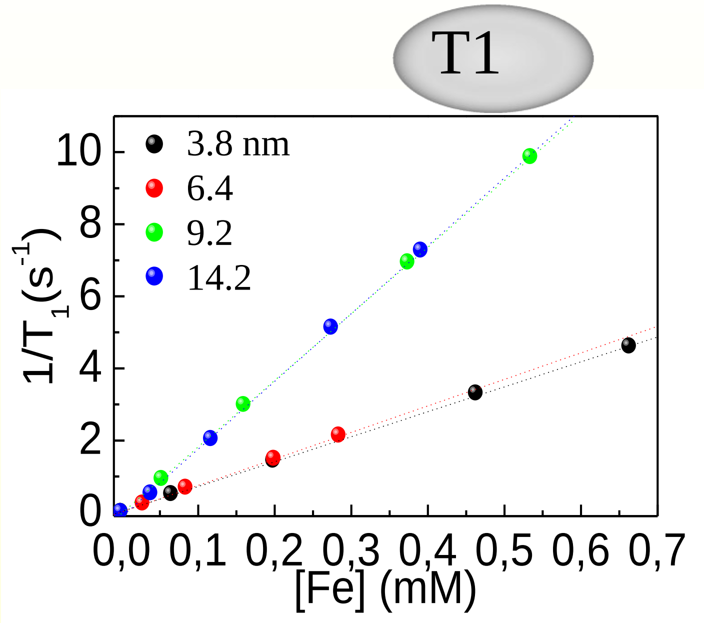
NP radio

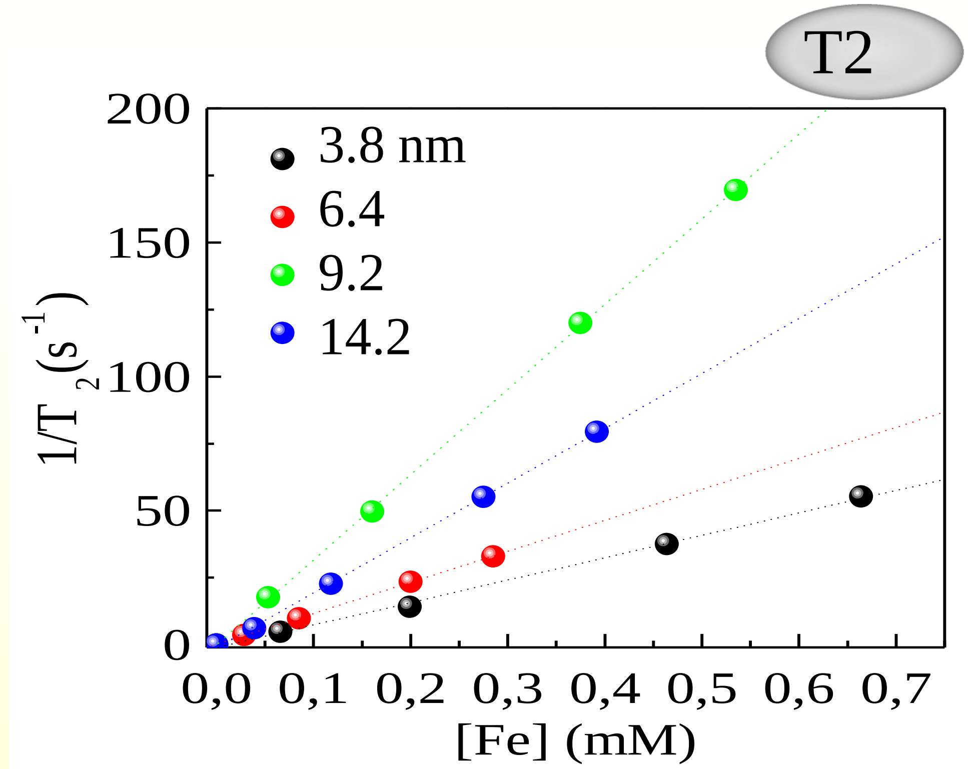
Diffusion coefficient of water molecules

The chemistry of contrast agents in Medical magnetic resonance imaging, André E. Merbach and Eva Toth, Wiley, 2001

Contrast agents for NMR imaging

MINISPEC MQ60 (37 º C, 1.5 T)





$$1/T_{1,2} = 1/T^0_{1,2} + r_{1,2}[Fe]$$

$r_{1,2}$ = Relaxivity constant

Measurement of the efficiency of the contrast agent

$1/T_2$ = $R_{1,2}$ = Inverse of the relaxation time

[Fe] = Concentration of iron in mmol l^{-1}

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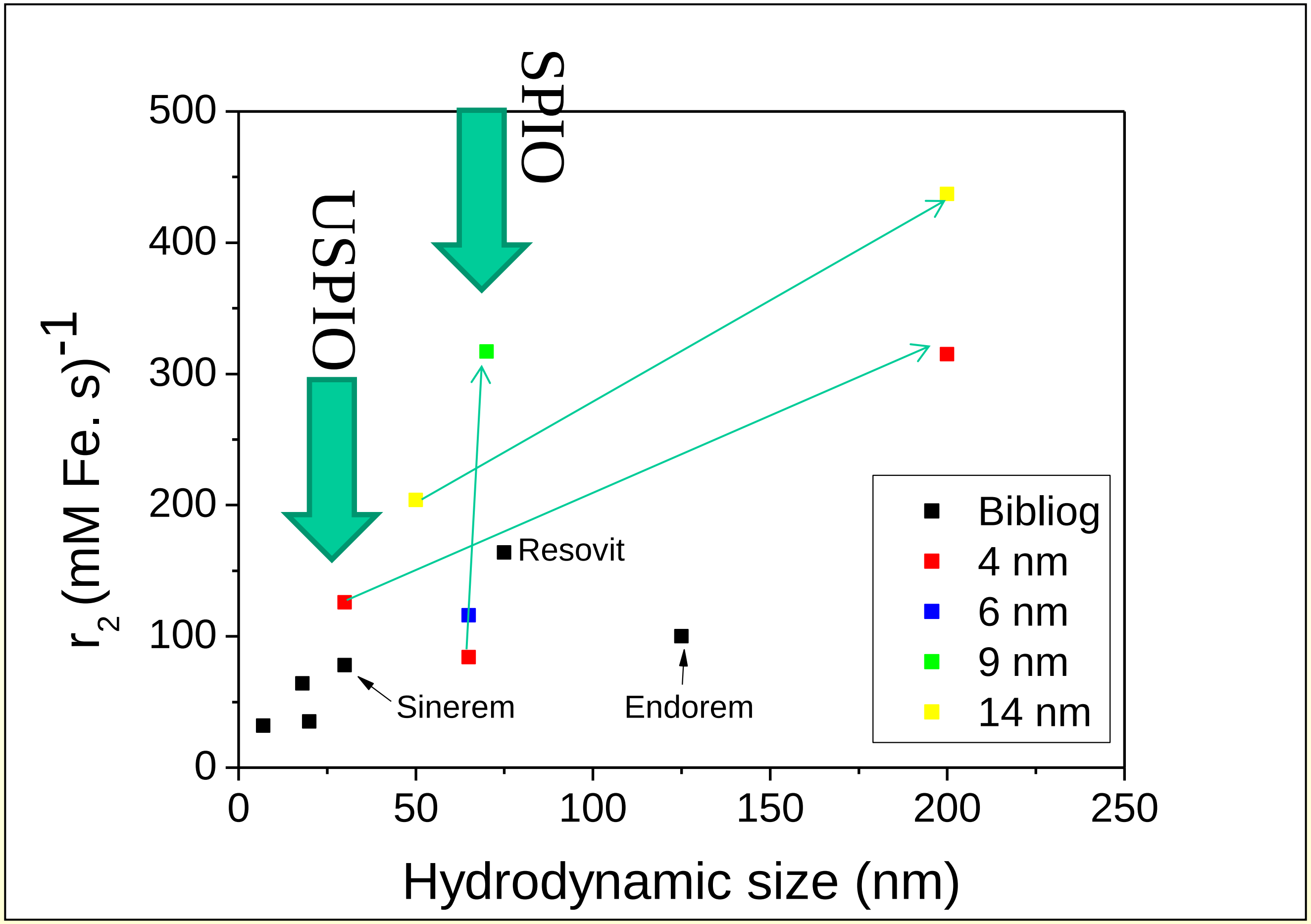
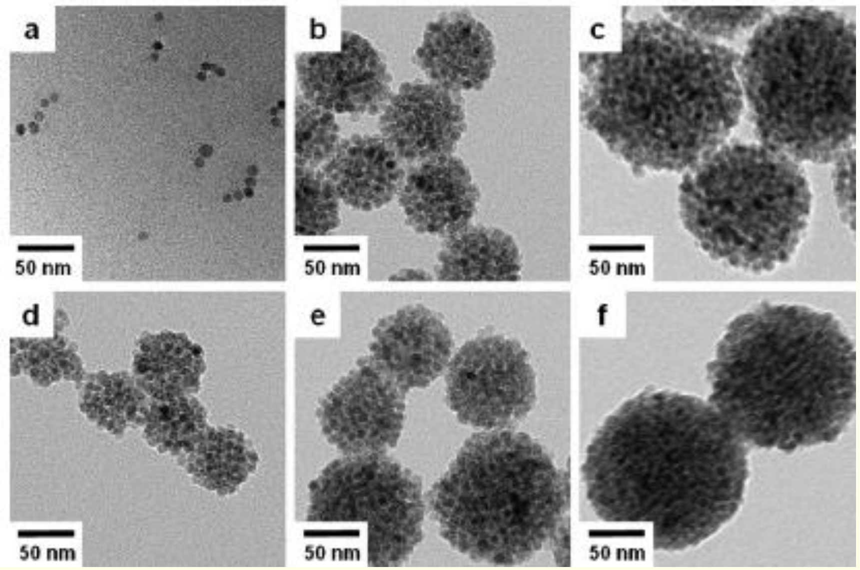
Contrast agents for NMR imaging

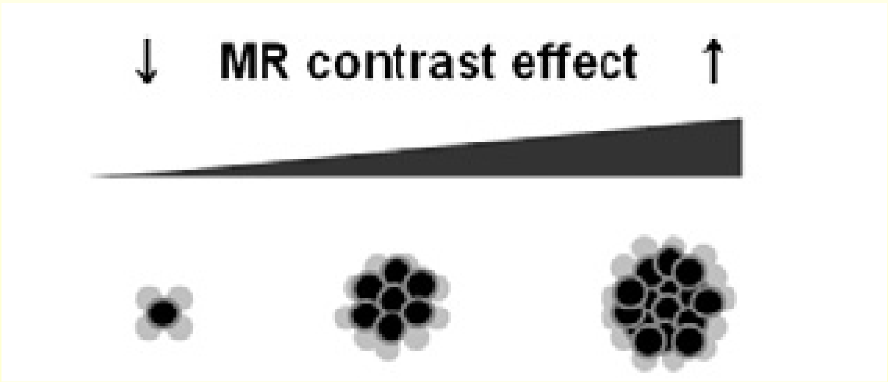
Commercial products = 5-10 nm



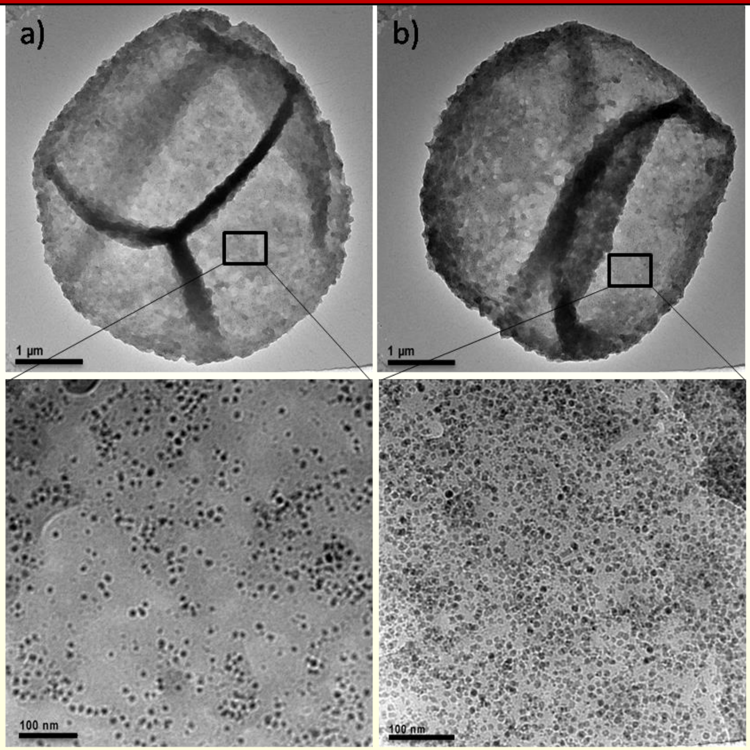
High crystalline particles lead to high relaxivity values

Contrast agents for NMR imaging





S.-B. Seo et al. / Journal of Colloid and Interface Science 319 (2008) 429–434



↑ MR contrast effect ↓

Azhar Zahoor AbbasiJ. Phys. Chem. C 2011, 115, 6257

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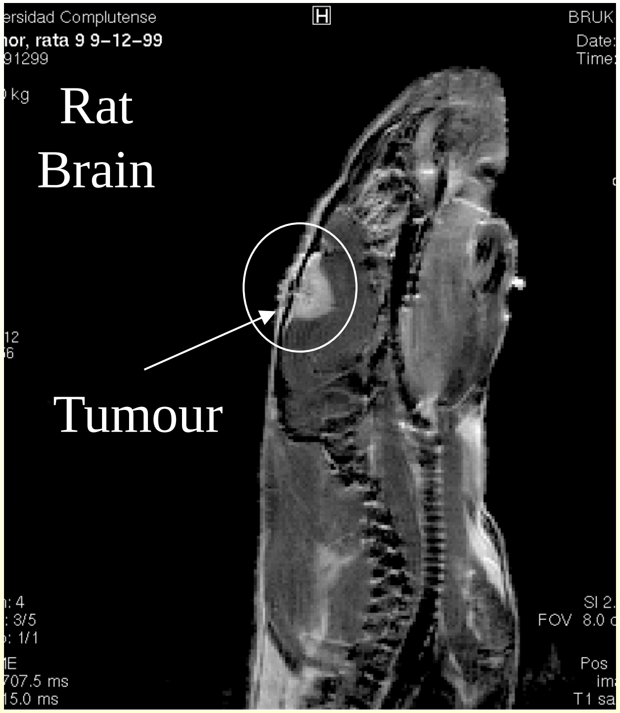
Contrast agents for NMR imaging

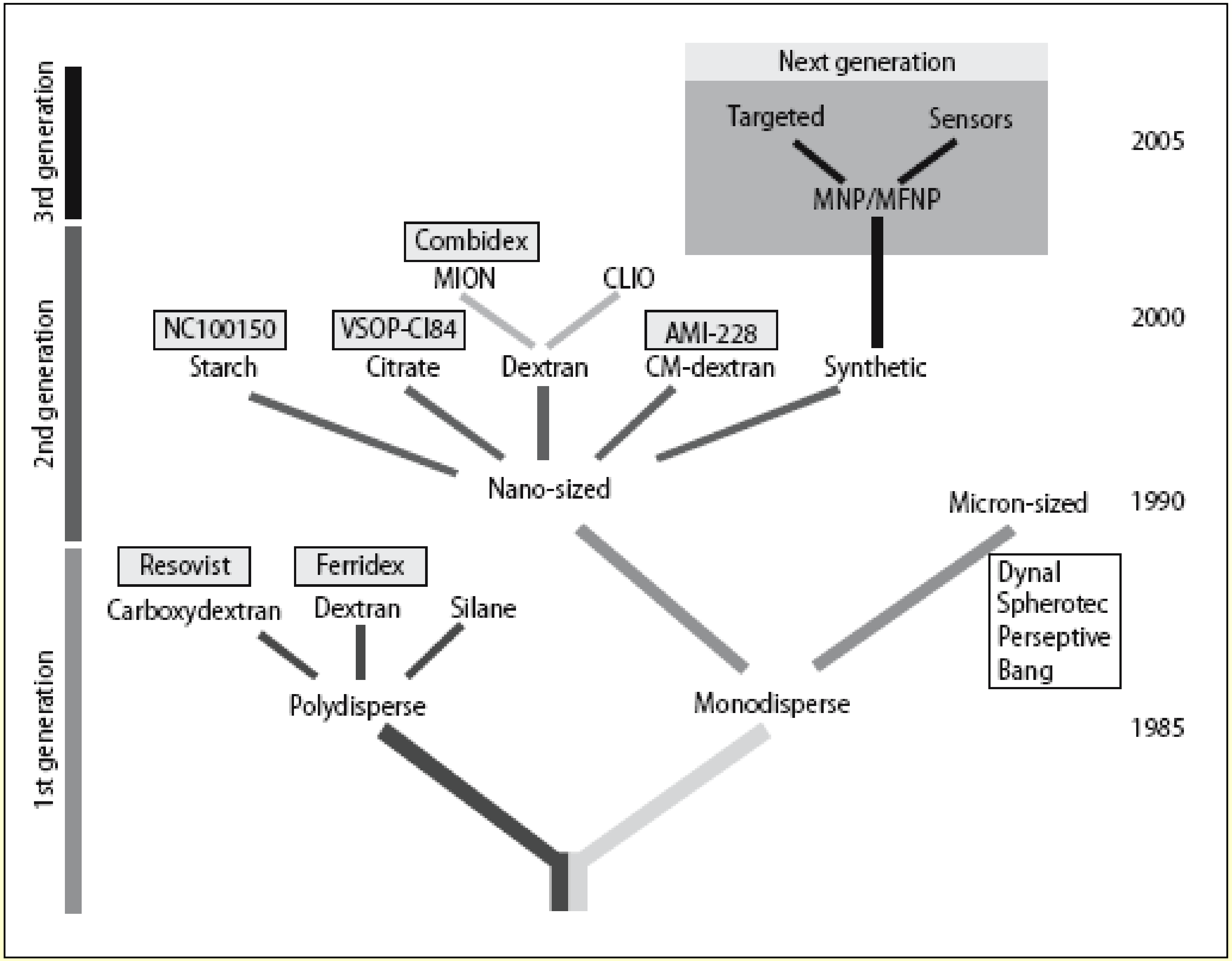


Lymph node metastasis

Tumour cells prevent the flow of macrophages and magnetic nanoparticles do not get to them => no decrease in signal intensity => appeared as **bright spots**

R. Weissleder et al. 2001 *Angew. Chem.*, Int. Ed. **40** 3204

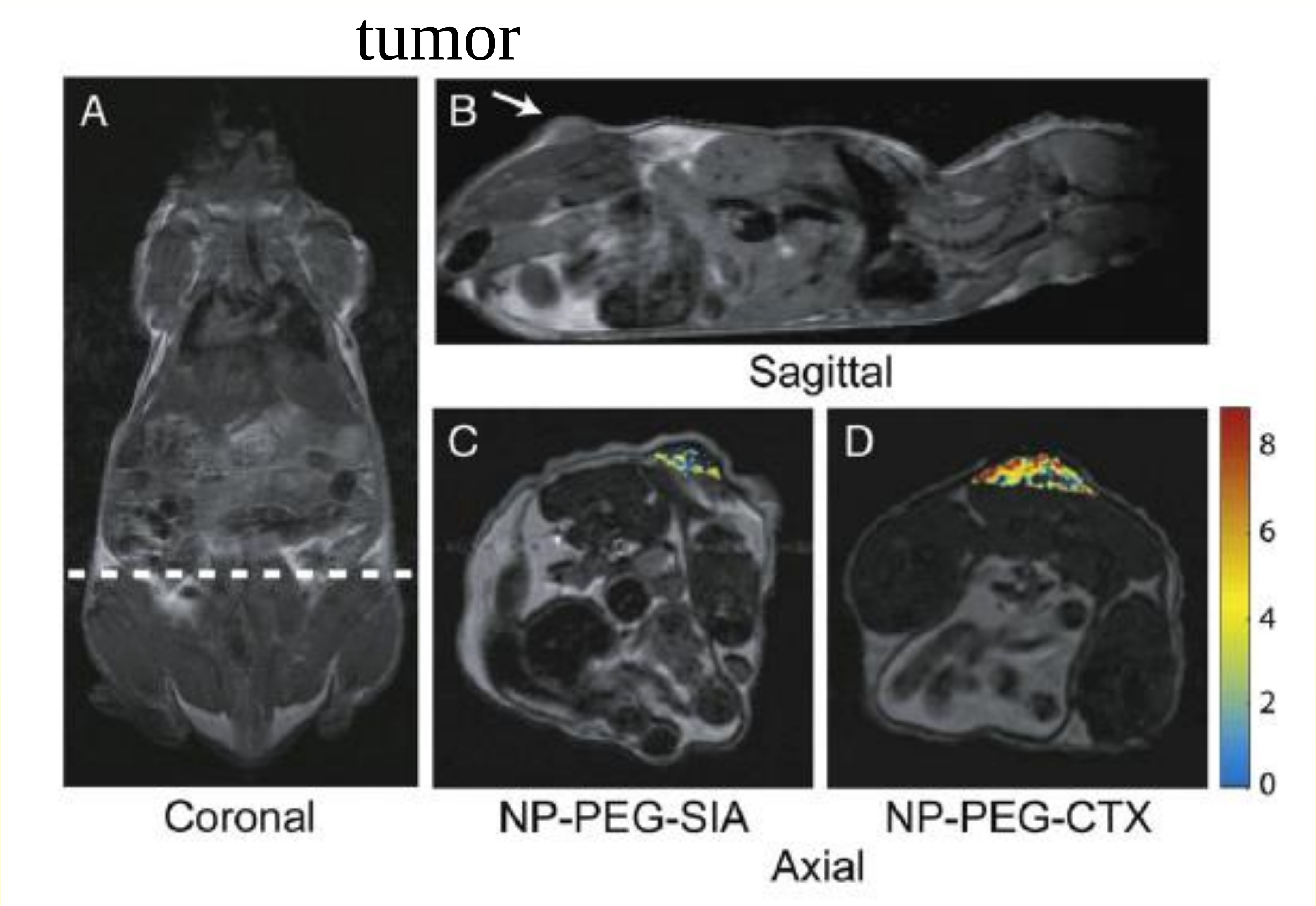
Contrast agents for NMR imaging



Ralph Weissleder

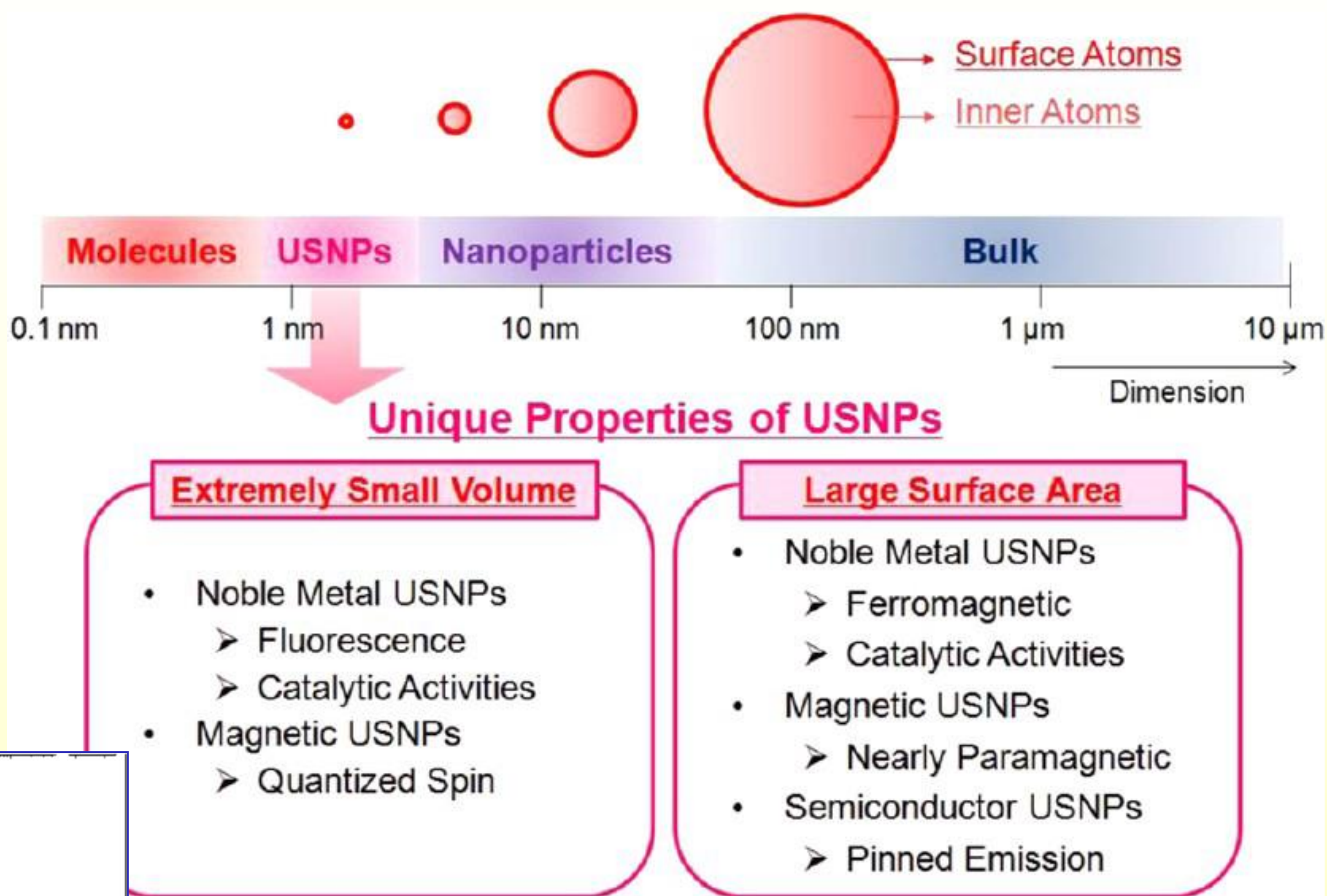
Basic Res Cardiol 103:122–130 (2008)

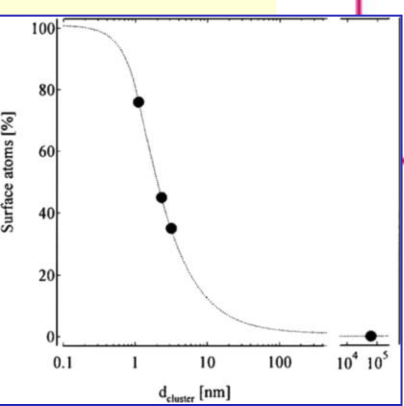
Contrast agents for NMR imaging



C. Sun et al. / Advanced Drug Delivery Reviews 60 (2008) 1252–1265

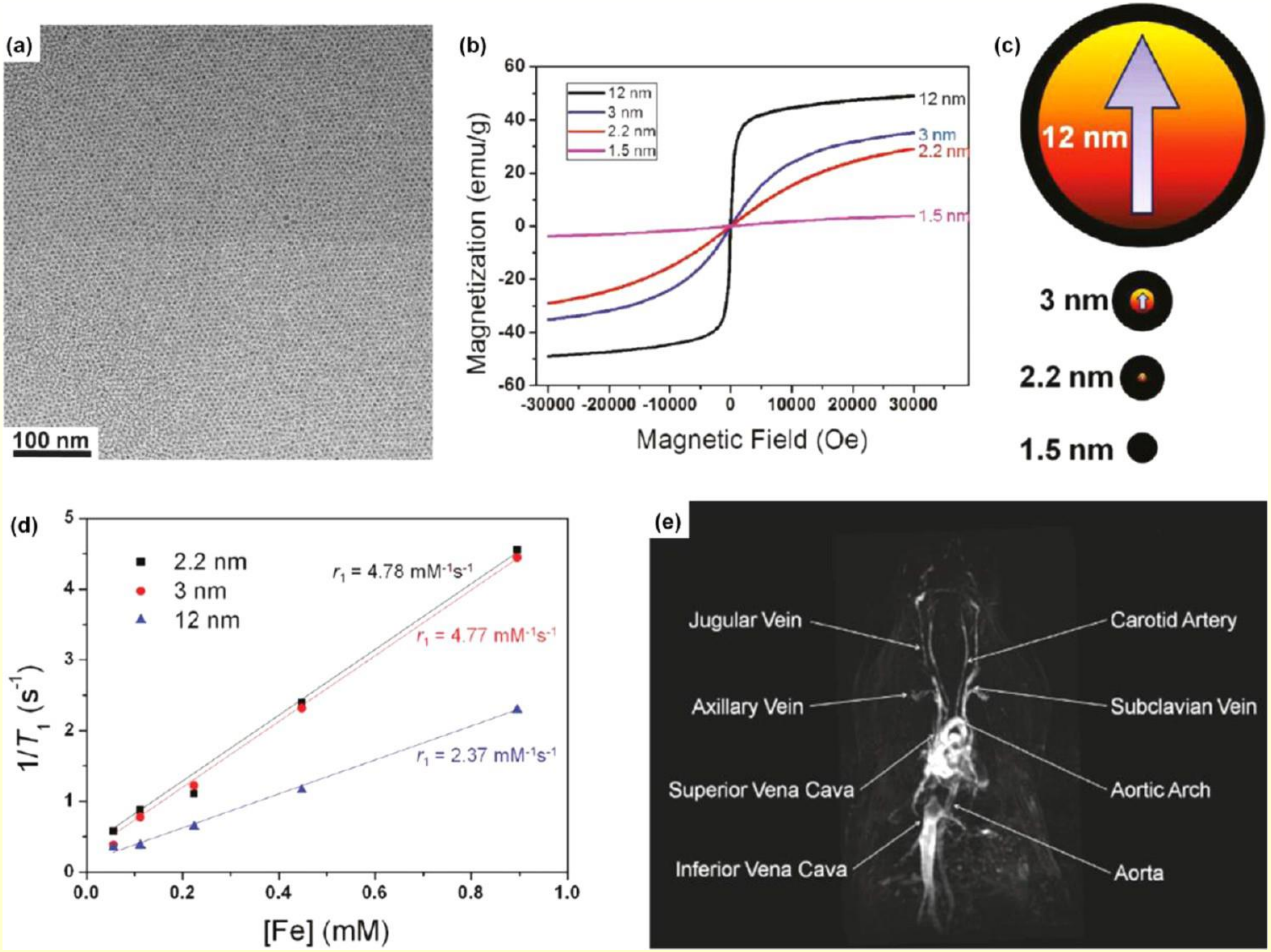
Contrast agents for NMR imaging





dx.doi.org/10.1021/cm402225z | Chem. Mater. 2014, 26, 59−71

Contrast agents for NMR imaging



Kim, B. H.; et al., J. Am. Chem. Soc. 2011, 133, 12624.

NMR imaging

Table 1. Imaging techniques and related contrast agents.

Imaging technology	Contrast agents	Spatial resolution	Toxicity	Sensitivity	Time Resolution
X-ray CT	Iodinated contrast material	sub-mm	Nephrotoxic	mM	1–2 s
MRI	Gadolinium-based	sub-mm	Nephrogenic systemic fibrosis	mM for Gd-based nM for Fe-based	1–2 s
PET/SPECT	Radioactively labelled agents	mm	Dosimetric exposure	pM	min

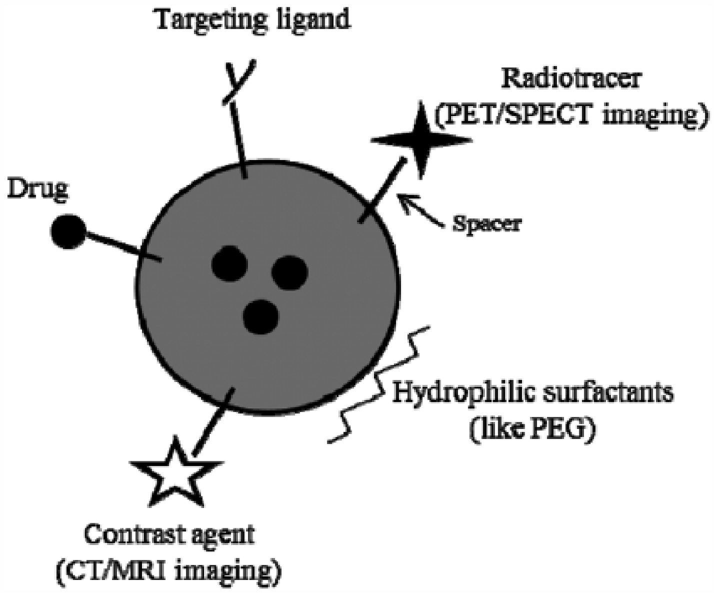


Figure 2. *Multi-functionalized NPs.* Graphical representation of multifunctional NP for molecular imaging (functionalized with contrast agents for CT/MRI, with radiotracer for PET/SPECT), for drug delivery (functionalized with drug molecules incorporated within the core of NP or conjugated to the surface), for specific targeting (functionalized with specific ligands) and for stealth (hydrophilic surfactants). Spacer/linker molecules are also indicated.

Biomedical applications

- In vitro → Diagnostic → **Separation/selection**

- In vivo
  - → Diagnostic → **NMR imaging**
  - → Therapeutic
    - **Drug targeting** ⇐
    - **Hyperphermia** ⇐

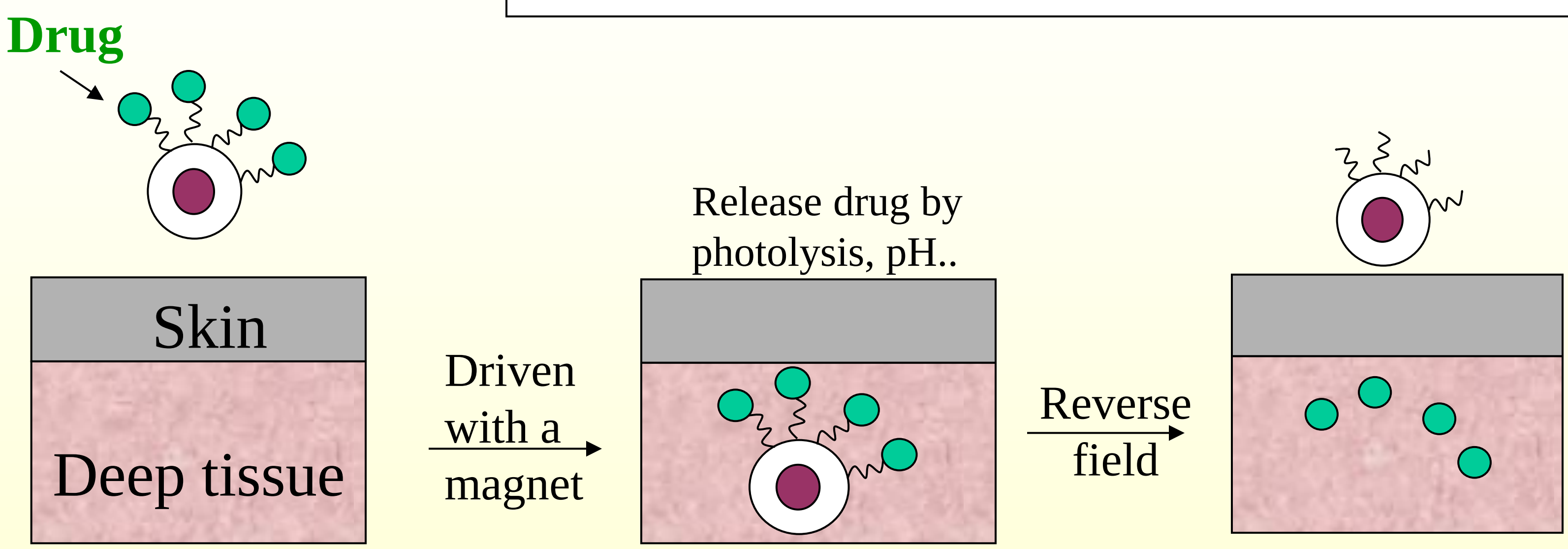
Gene delivery

Tissue regeneration (cell labelling)

Biomedical applications

DRUG DELIVERY

Targeting of a drug immobilised on magnetic nanoparticles under the action of an external magnetic field.

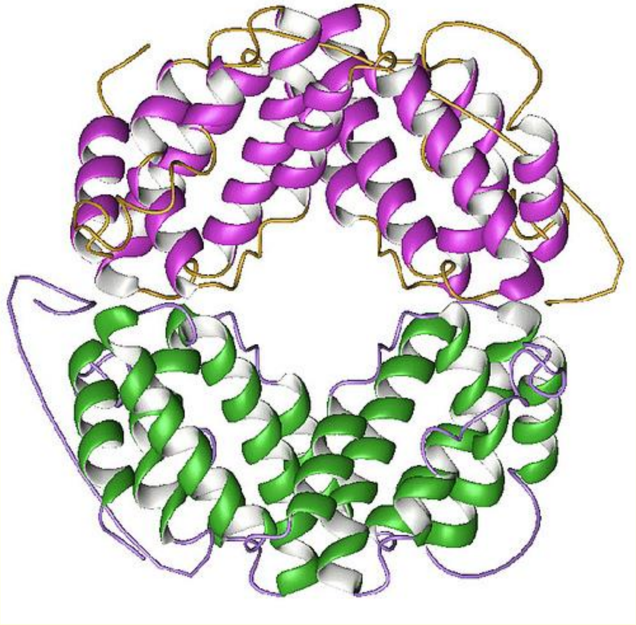


- **Specific** -> Reducing side effects
- **High local concentration** -> Reducing the dosage
- **Problem** -> Field strength

→ Human preliminary test

Drug delivery

Cytokine IFN-γ



Cancer inmunotherapy : Activating immune response to removal primary tumor and prevent metastases.

Cytokine: small protein produced by macrophages and T lymphocytes

Activity:

- Activate macrophages production
- Induce cancer cell apoptosis

IFN-γ the most effective cytokine in tumor elimination

Magnetic nanoparticles: Controlled local release of cytokines

CNB

R. Mejías, Journal of Controlled Release 130,168, 2008

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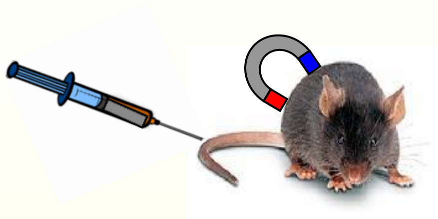
Drug delivery



Inyección subcutanea de 2,5x10^6 células Pan02

Días: -7 | 0 | 3 | 7 | 10 | 14

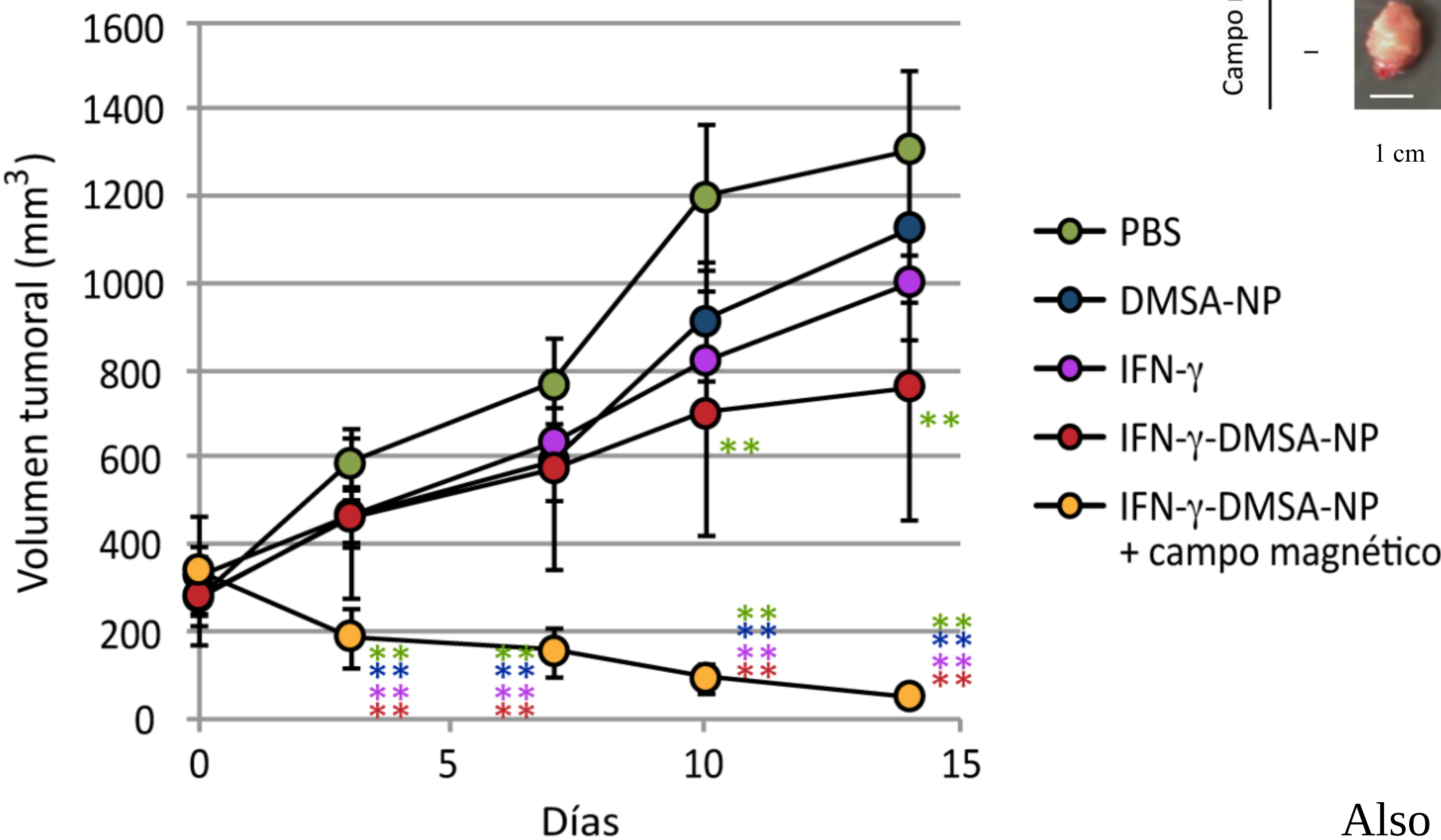
Eutanasia y extracción de tumores:
Tamaño
Presencia de nanopartículas
Niveles de IFN-γ
Inmunohistoquímica

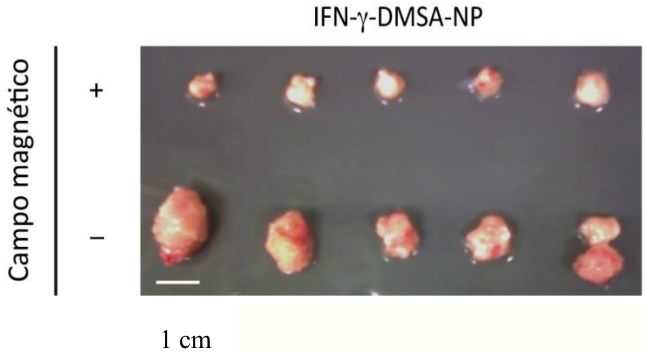
PBS (Control) + campo magnético externo
DMSA-NP (300 μg Fe) + campo magnético externo
IFN-γ (10000 UI) + campo magnético externo
IFN-γ-DMSA-NP (300 μg Fe + 10000 UI) + campo magnético externo
IFN-γ-DMSA-NP (300 μg Fe + 10000 UI)

(0,4 T; 1 h)

Drug delivery

Tumor size





Also for induced tumours
with 3-methylcholanthrene (MCA)

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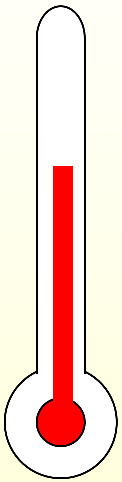
Biomedical applications

HYPERTHERMIA

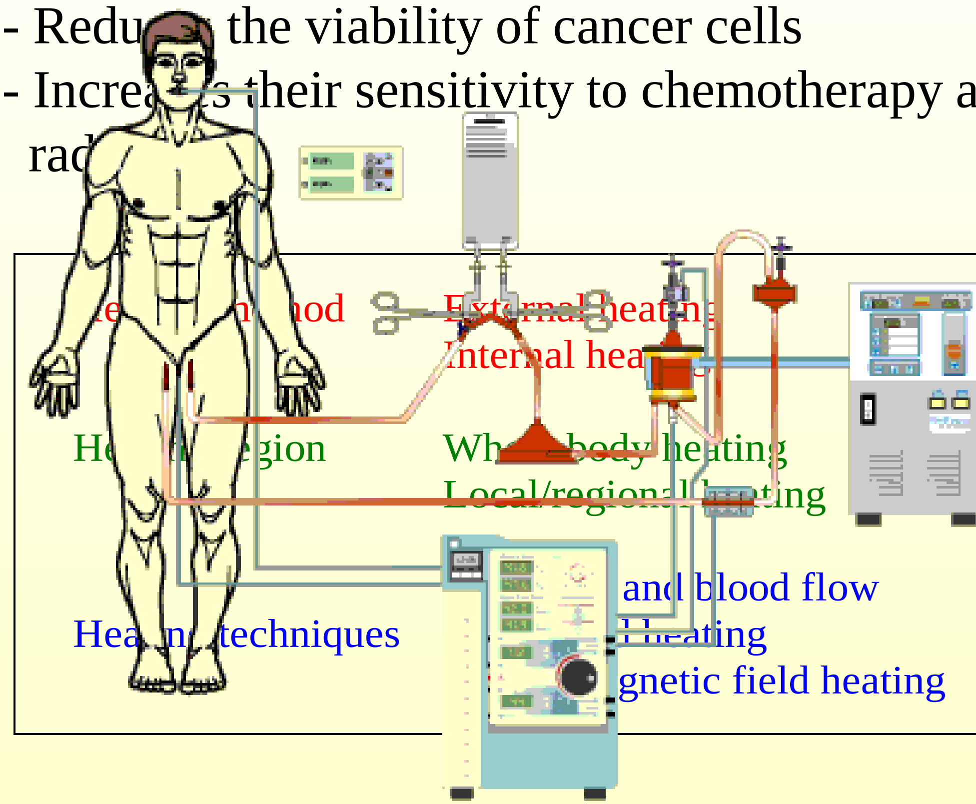
Heating of a target tissue to the temperatures between 42-43 ºC



42-43ºC

- Redu... the viability of cancer cells
- Incre... their sensitivity to chemotherapy and rad...

Conventional Hyperthermia



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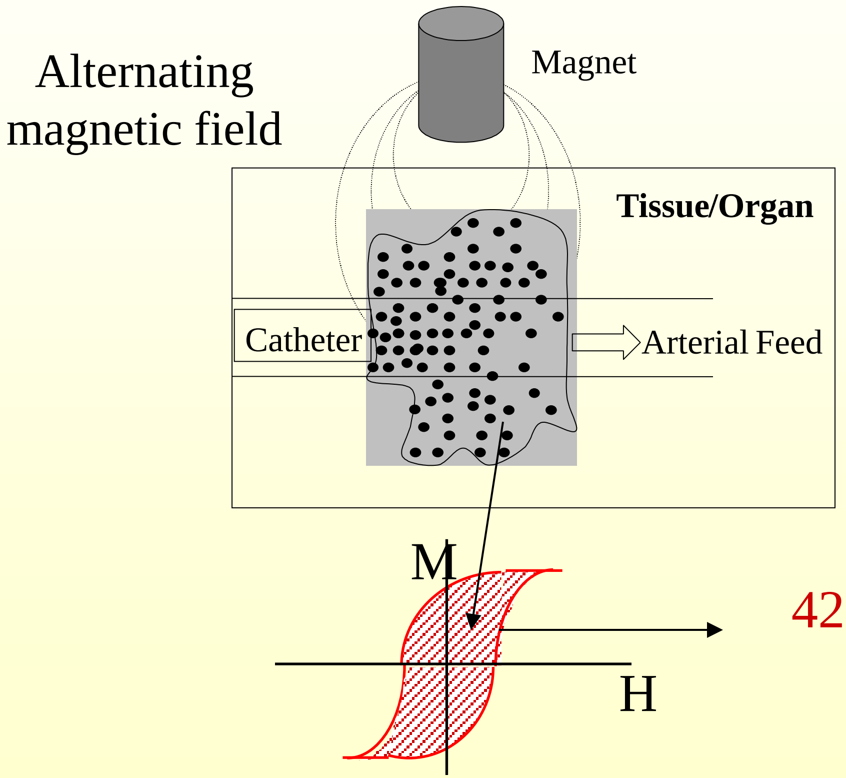
Biomedical applications

HYPERTHERMIA



Advantages of using magnetic nanoparticles

- Avoid heating healthy tissues

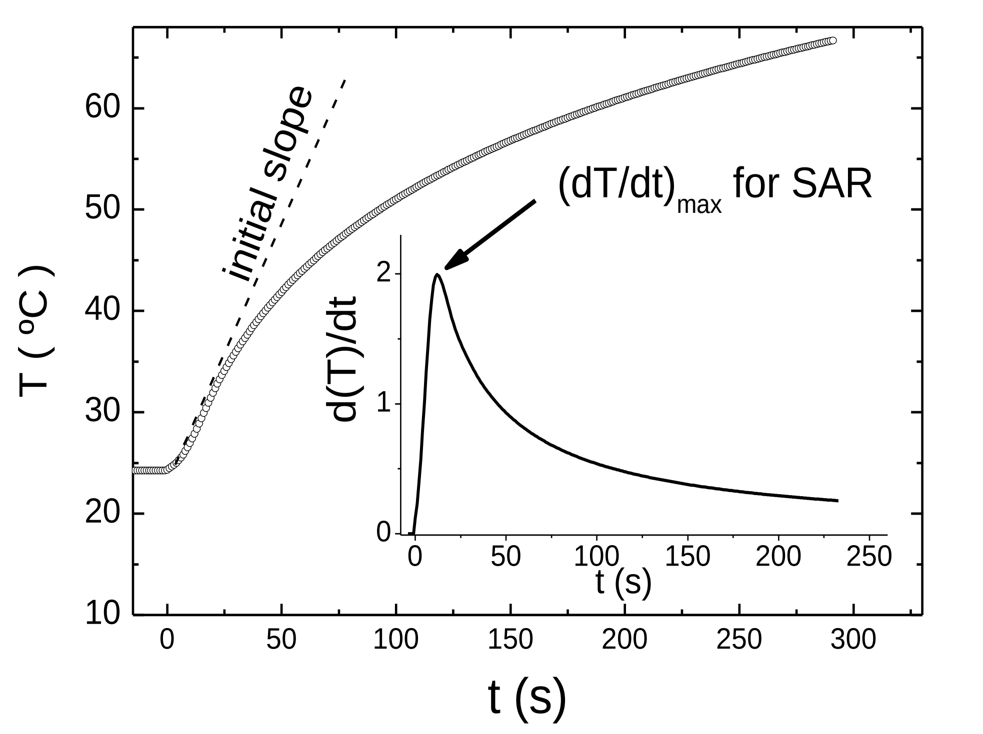
- Combining other therapies
  Targeting radionuclides

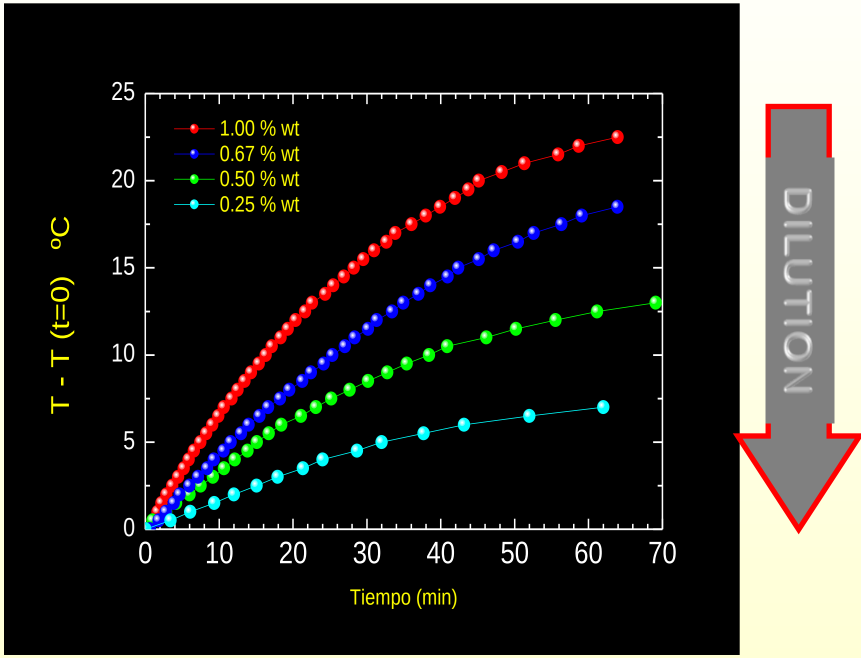
42ºC / 30 min ➡ Cancer is destroyed

Goya et al, Current Nanoscience 2008, 4, 1-16

Nearly complete regression of tumors via collective behavior of magnetic nanoparticles in hyperthermia, C L Dennis et al., Nanotechnology 20 (2009)

WHAT WE ACTUALLY MEASURE…

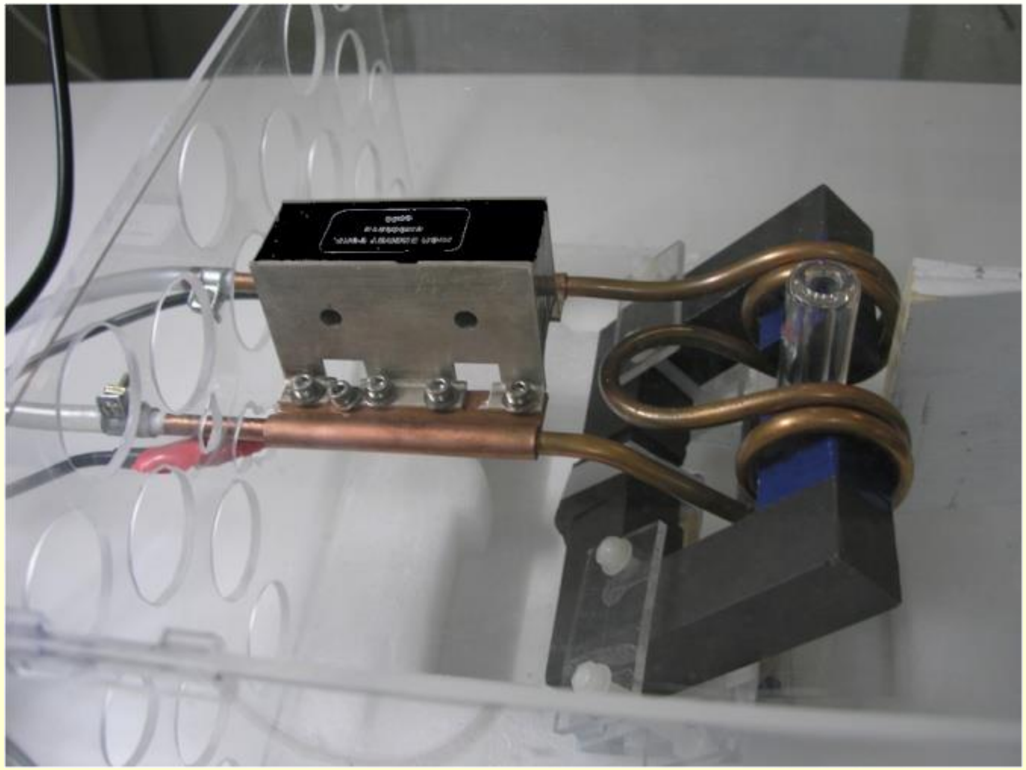




Magnetite nanoparticles 30 nm in diameter

Hyperthermia

SAR = Specific Absorption Rate= Specific loss power
= Power absorbed by unit mass of the magnetic material



$$SAR = C_m\ \phi(\Delta T/\Delta t)$$

C_m=specific heat capacity of the sample

$\phi = m_{ff}/m_{ox}$

Field Amplitude = 10kA/m
Frequency = 249 kHz

Gerardo F. Goya, *Instituto Universitario de Investigación en Nanociencia de Aragón (INA).*

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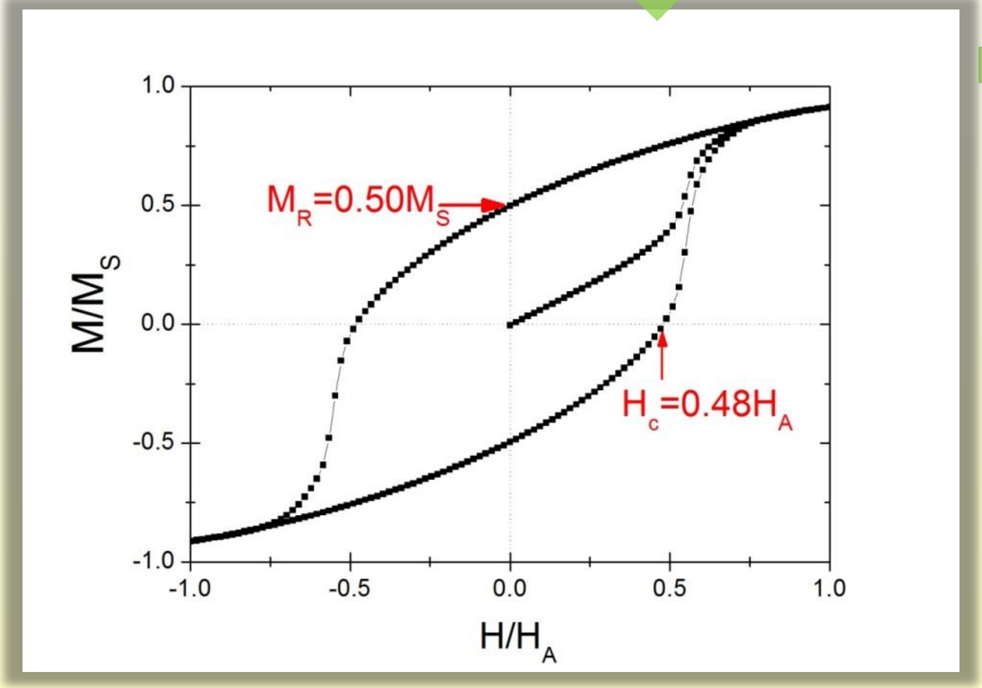
Hyperthermia

- Magnetic particles under an AC field will rise T
- Heat dissipated → area M(H) curve: Hysteresis Losses (HL)



Serantes et al.

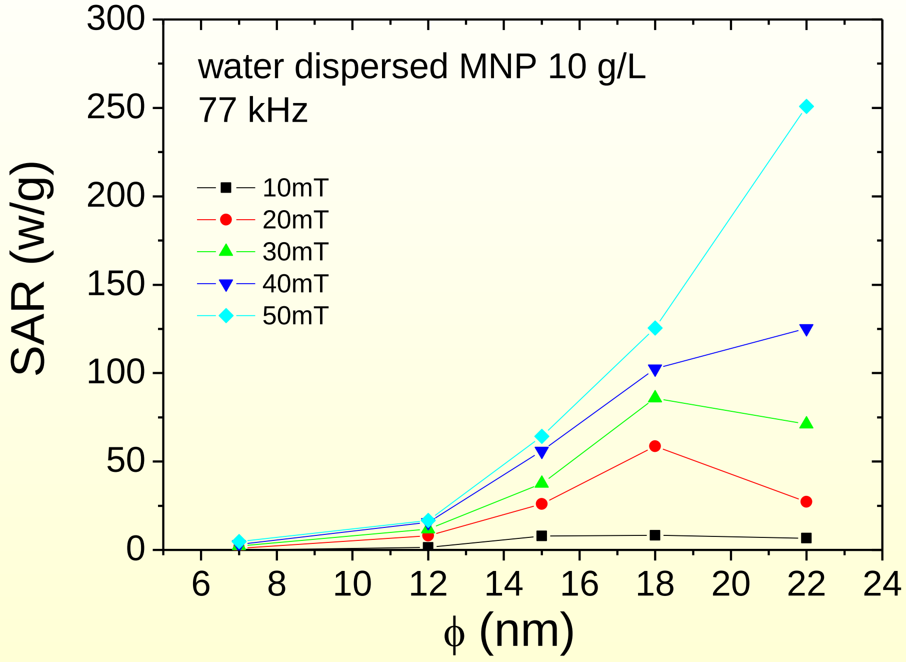
Specific Absorption Rate (SAR)

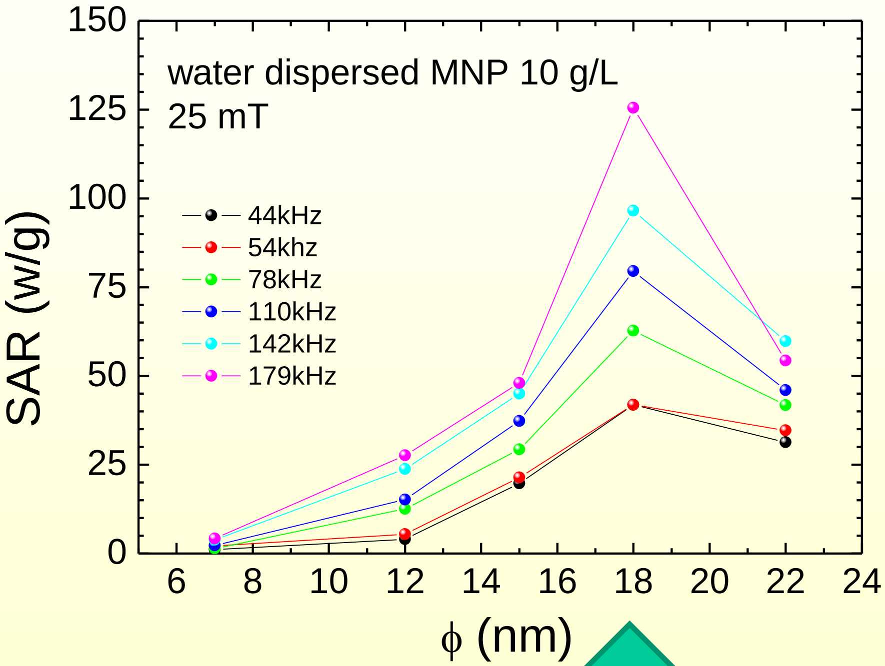
Heat can kill the tumour!

EFFECT OF THE PARTICLE SIZE

Heating efficiency

Specific Absorption Rate (SAR)





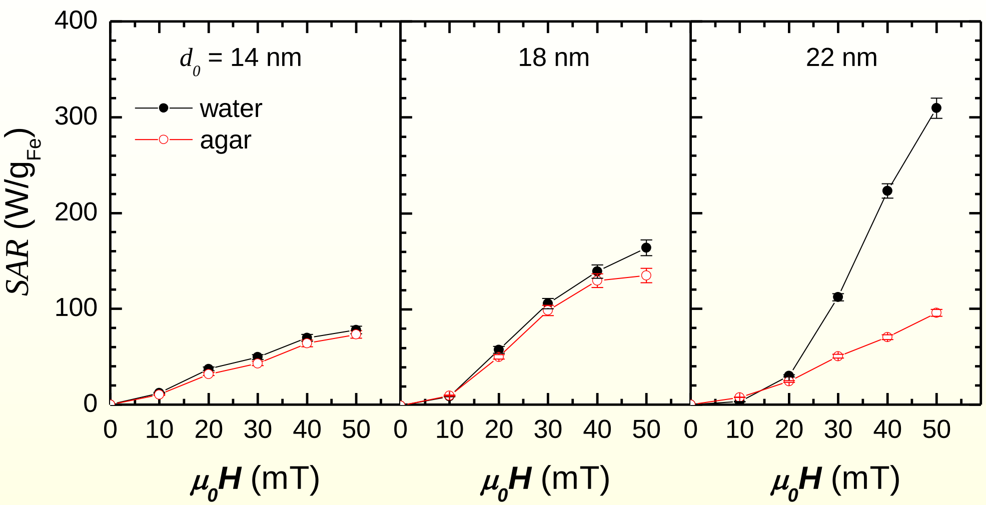
100 W/g, 250 Oe, 100 kHz

multifun

IMDEA Nanoscience (Madrid)

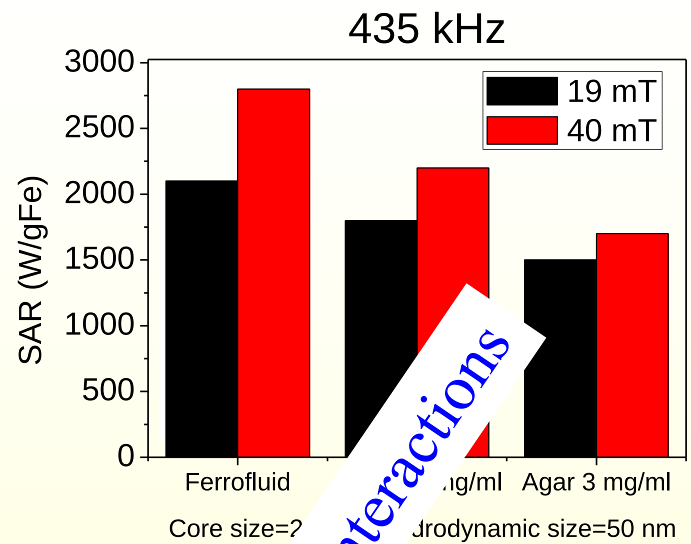
EFFECT OF THE MEDIA VISCOSITY

VISCOSITY



Frequency (77 kHz).

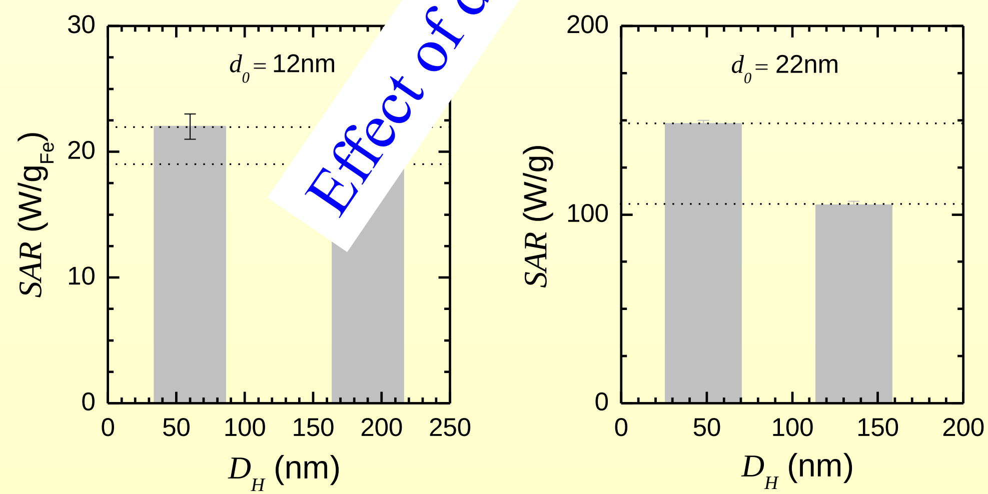
CONCENTRATION



5 kA/m and 30 kA/m

Effect of dipolar interactions

AGGREGATION



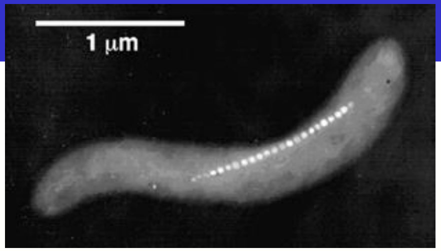
Physical rotation for sizes over 18 nm

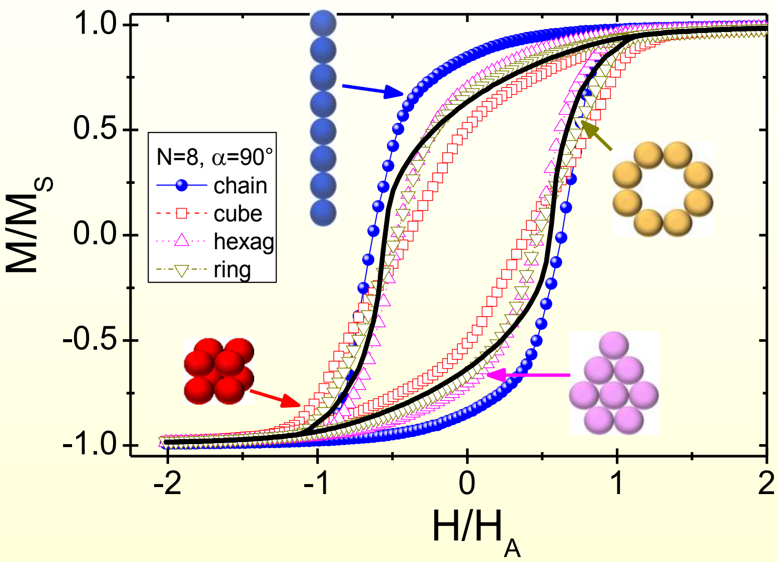
IMDEA Nanoscience (Madrid), INSA (Toulouse) and UHJ (Jena)

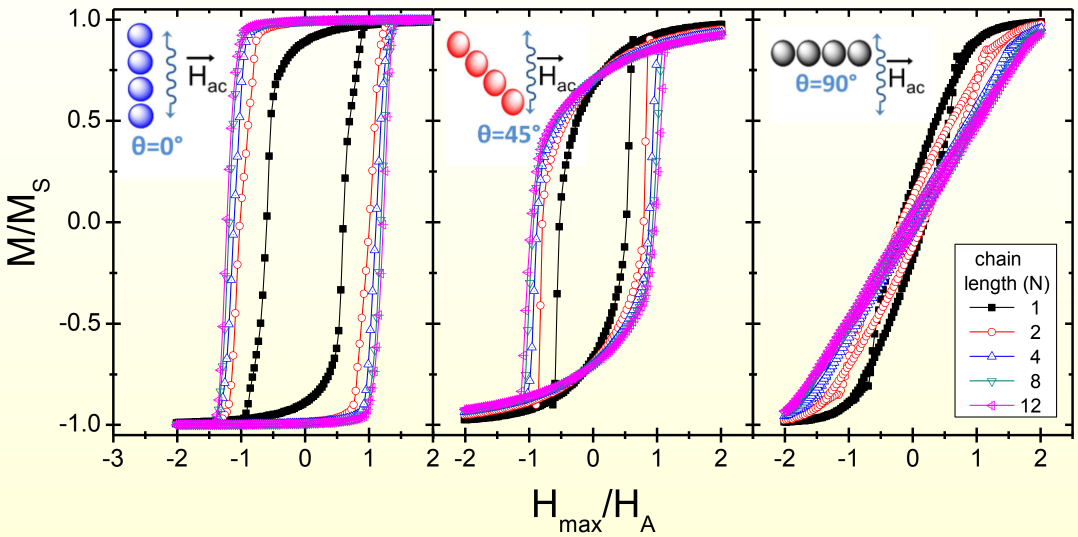
multifun

NANOPARTICLE ASSEMBLING

David Serantes, I. Conde-Leborán, D. Baldomir, K. Simeonidis, M. Angelakeris, Ò. Iglesias, O. Chubykalo-Fesenkoa and C. Martínez-Boubeta







- The highest area M(H) curve is attained for chain-like shape
- Dependence of area M(H) curve on ***chain length and orientation***

- What happens in real situations, with variable viscosity conditions?

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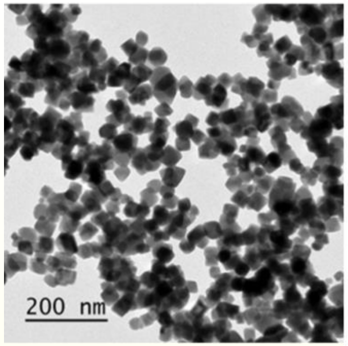
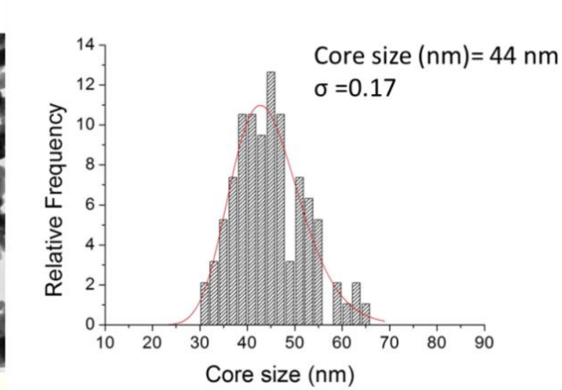
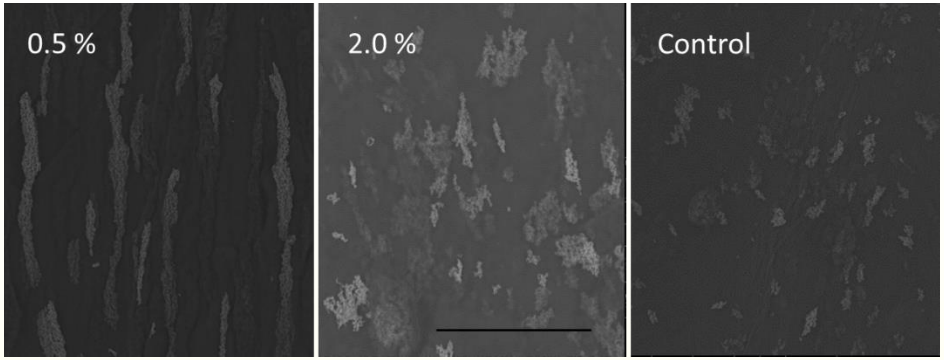
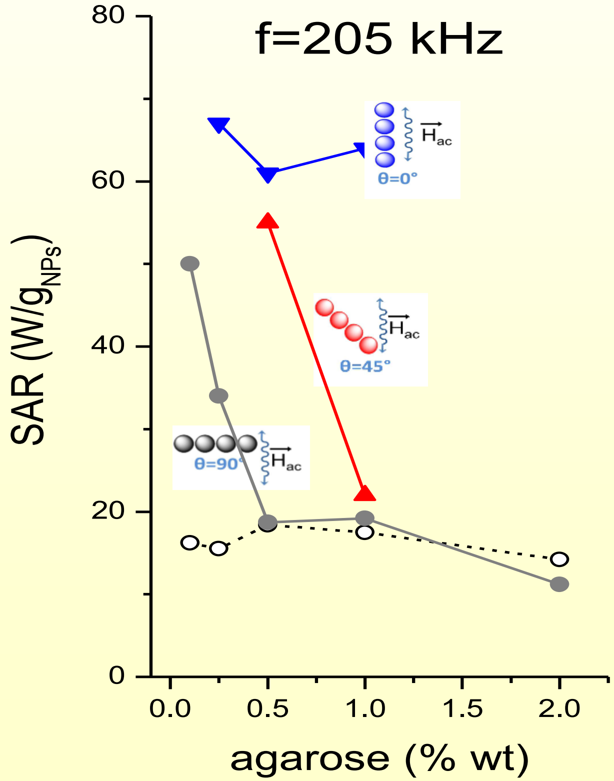
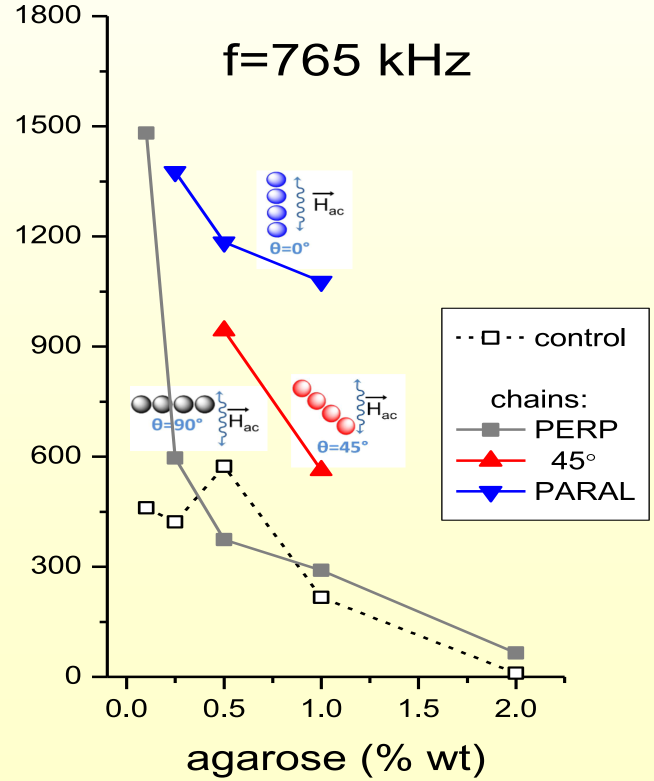
NANOPARTICLE ASSEMBLING











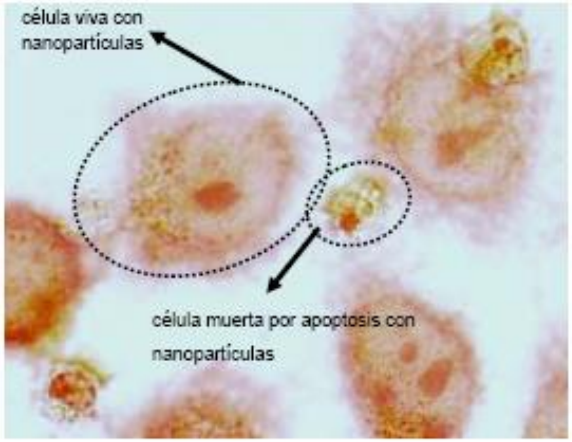
✓ **chaining allows to reduce the dosage of NPs for hyperthermia treatment.**

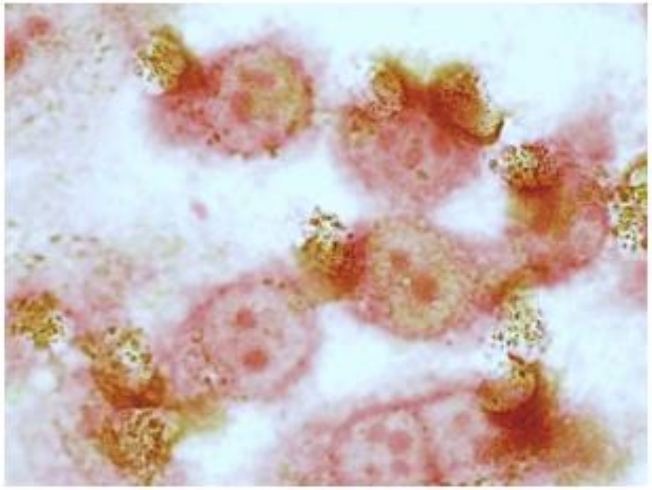
Hyperthermia: Aminodextran coated particles

UAM-IMA

Nanopartículas ferromagnéticas recubiertas de dextrano aminado (cargadas positivamente) DX 0.5 mg/mL 3h de incubación + campo magnético 100 kHz 150 Gauss durante 30 min. Las células se mantuvieron en el incubador y se procesaron 24h después del tratamiento. Tinción con rojo neutro y Hoechst.

Dx (catiónico)

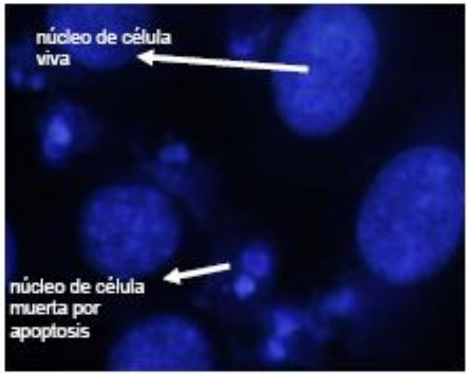


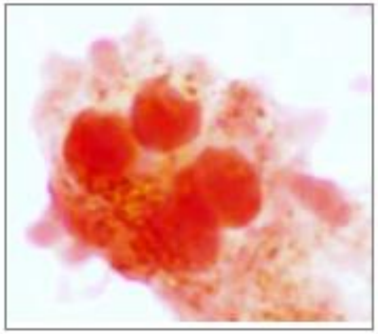


Resultados:

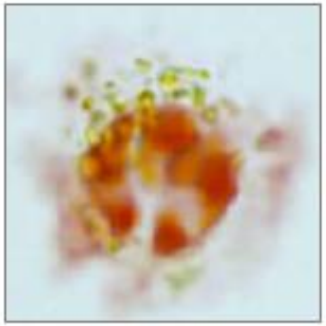
Un % significativo de las células han muerto por apoptosis y se observa: disminución del tamaño celular, redondeamiento y el núcleo condensado y fragmentado.

Las células contienen en su interior nanopartículas (color amarillo-marrón)

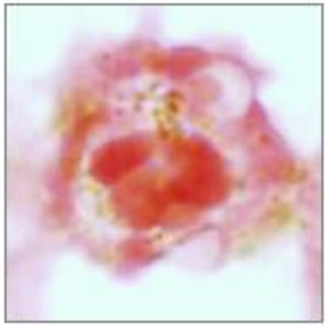




Apoptosis



Apoptosis



Apoptosis

Ingrid Hilger at al, Nanotechnology 20 (2009) 395103

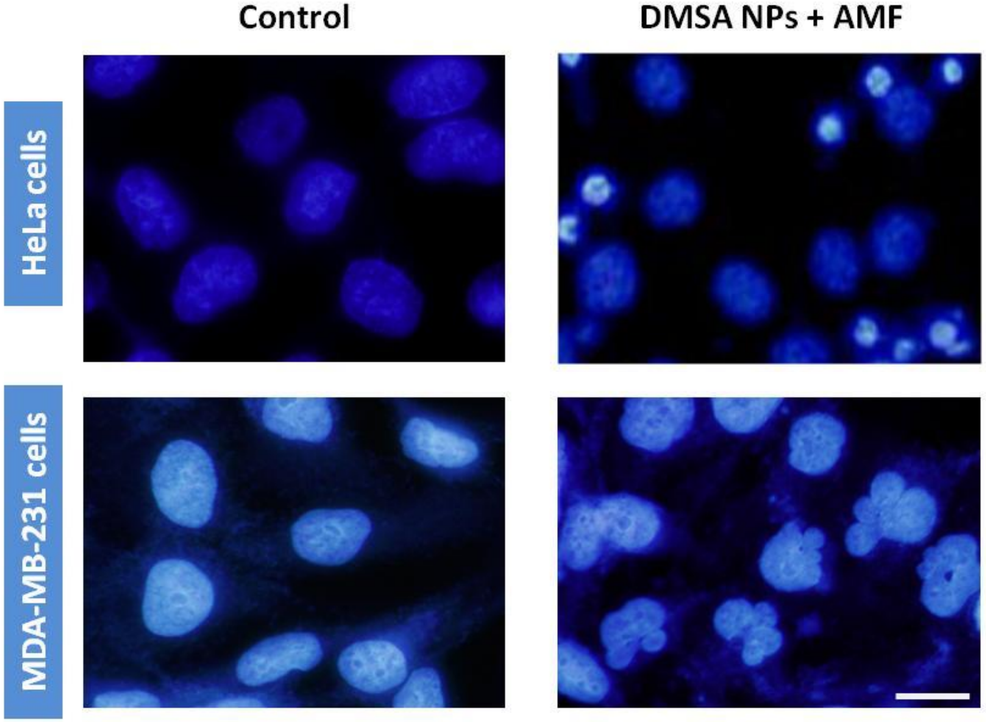
Hyperthermia: DMSA coated particles

UAM-IMDEA

HeLa and MDA-MB-231 cells (stained with Hoechst 33258) were incubated with DMSA coated NPs, and exposed to an AC magnetic field (AMF).

24 h after the treatment apoptotic cells (HeLa) and giant and multinucleated cells (MDA-MB-231) were observed.

DMSA (anionic)



AMF conditions: 161 kHz, 210 G, 15 min exposure (HeLa cells), 225 kHz , 150 G , 45 minutes exposure (MDA-MB-231 cells).

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Hyperthermia

Table 3. Summary of nanoparticle features favoring MRI and/or magnetic hyperthermia applications.

MRI (contrast)	Nanoparticle feature	Magnetic hyperthermia (heating)
+	High magnetization (size and surface coating)	+
+	SPIO	-
+	USPIO	-
+/-	Large size (core diameter >10 nm)	+
+	Sequestration by MPS	-
-	Long plasma half-life (targeting)	+
+	Short plasma half-life (targeting)	-

+: Favoring feature/parameter; -: Disfavoring feature/parameter; MPS: Monocyte phagocyte system; SPIO: Superparamagnetic iron oxide; USPIO: Ultrasmall superparamagnetic iron oxide.

Ingrid Hilger et al., Nanomedicine 2012

http://www.magforce.de/en
http://www.youtube.com/watch?v=BZLmD3SOR_Y
http://www.clinicaltrials.gov/ct2/show/study/NCT00003052
http://www.mhaus.org/

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Preparation and Biomedical Applications of Magnetic Nanoparticles

Summary

1- What are magnetic nanoparticles?
2- Requirements for biomedical applications
3- Basic principles in magnetism
4- Biomedical applications
    in vitro
    in vivo

5- Synthesis routes
    in solution
    aerosol
6-Example

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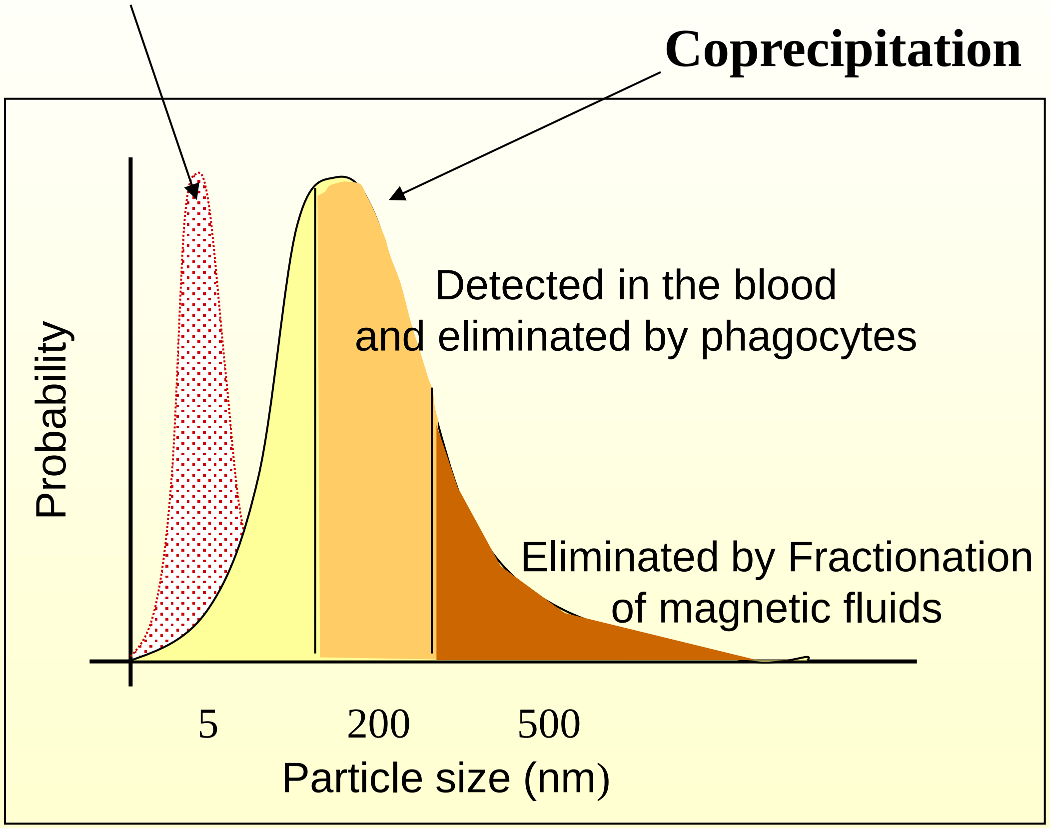
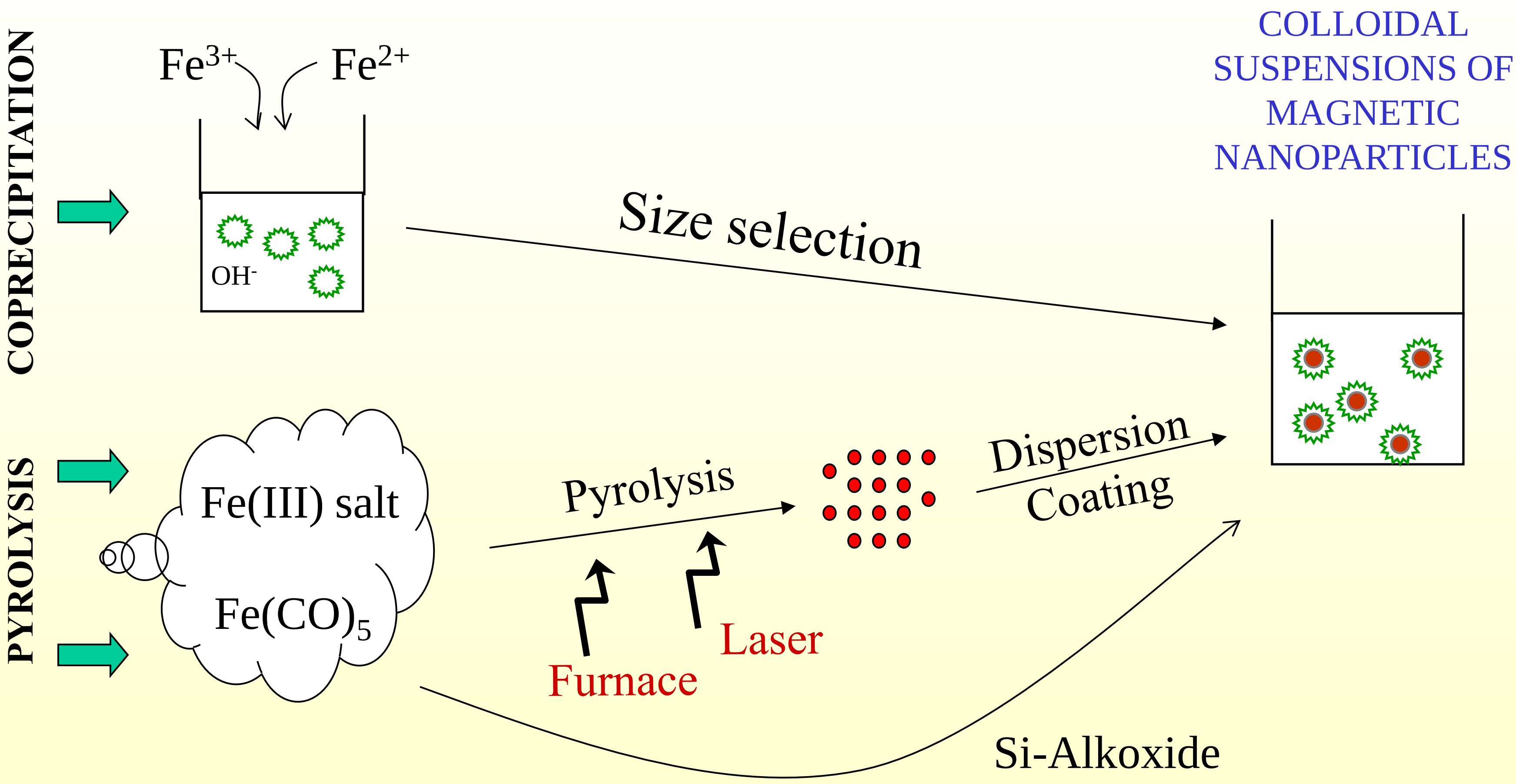
Synthesis of magnetic nanoparticles

UNIFORM NANOPARTICLES



In the case of contrast agents prepared by coprecipitation, upon application, only a small number of particles contribute to the desired magnetic effect.

Synthesis of magnetic nanoparticles



A:G. Roca et al. J. Phys. D:Apply Phys., 42, 224002, 2009

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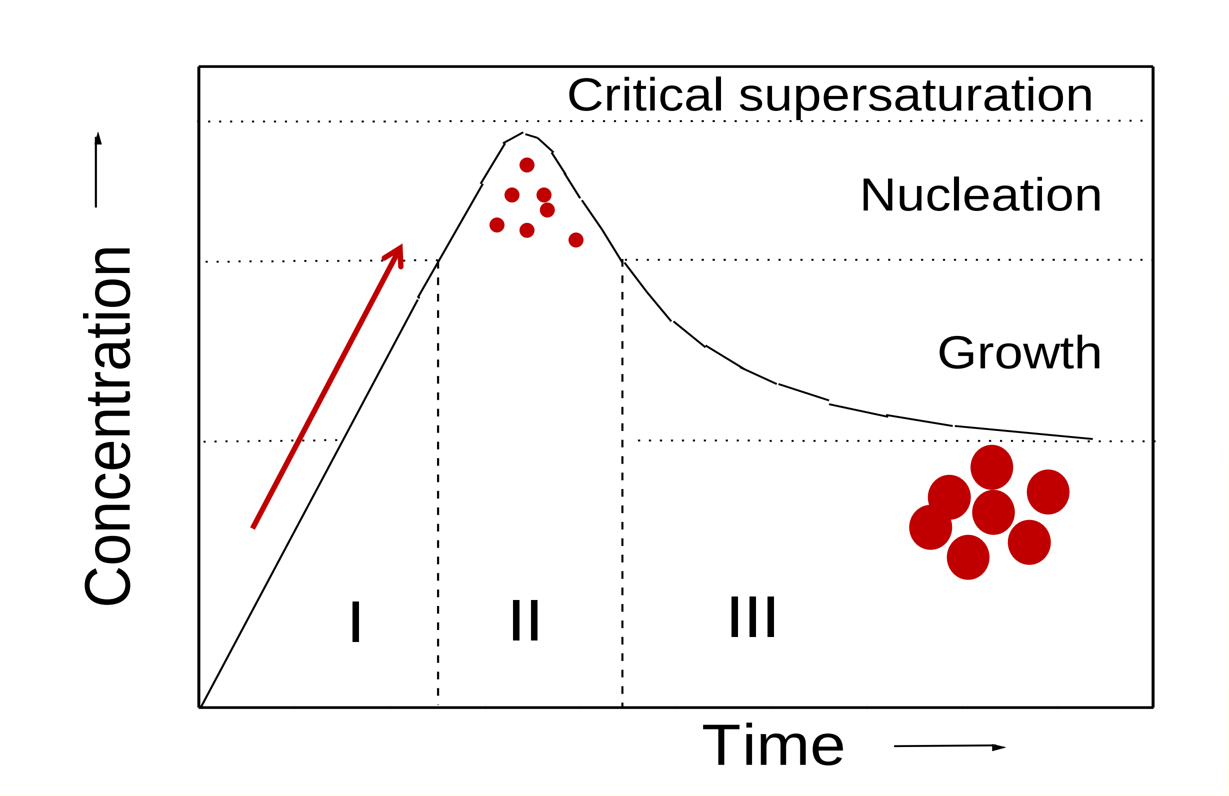
Synthesis of magnetic nanoparticles



Modelo Clásico
LaMer and Dinegar

Synthesis and Characterization of Nanoparticles: Synthesis of Inorganic Nanoparticles,
Gorka Salas, Rocio Costo and María del Puerto Morales
Part I, Vol. 4 Nanobiotechnology, Inorganic Nanoparticles vs Organic Nanoparticles
edited by J.M. de la Fuente and V. Grazu, 2012 Elsevier Ltd, FRONTIERS OF NANOSCIENCE, Series, Editor: R. E. Palmer, UK.

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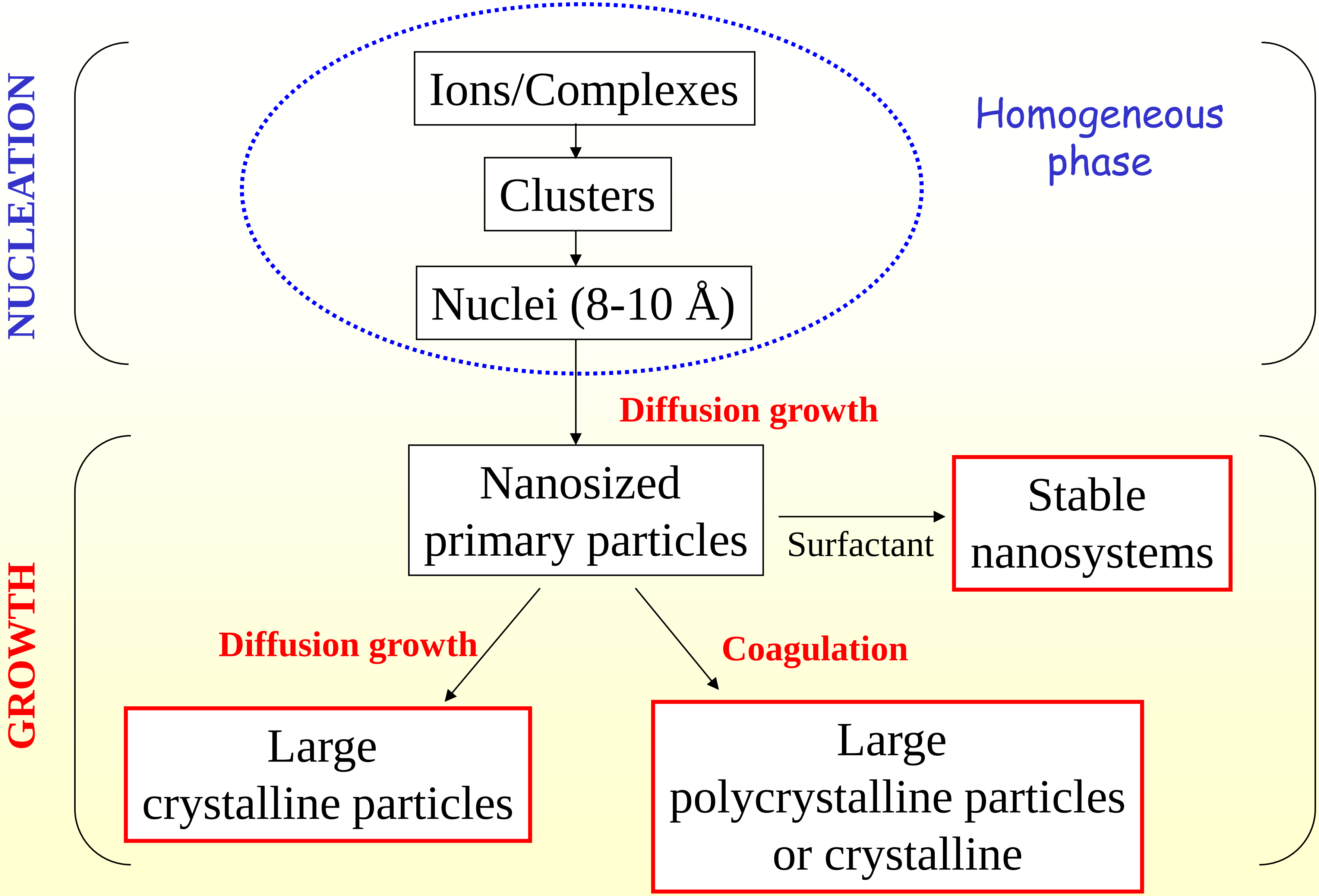

NUCLEATION
Ions/Complexes
Clusters
Nuclei (8-10 Å)
Homogeneous phase
GROWTH
Diffusion growth
Nanosized primary particles
Surfactant
Stable nanosystems
Diffusion growth
Coagulation
Large crystalline particles
Large polycrystalline particles or crystalline

Synthesis of magnetic nanoparticles

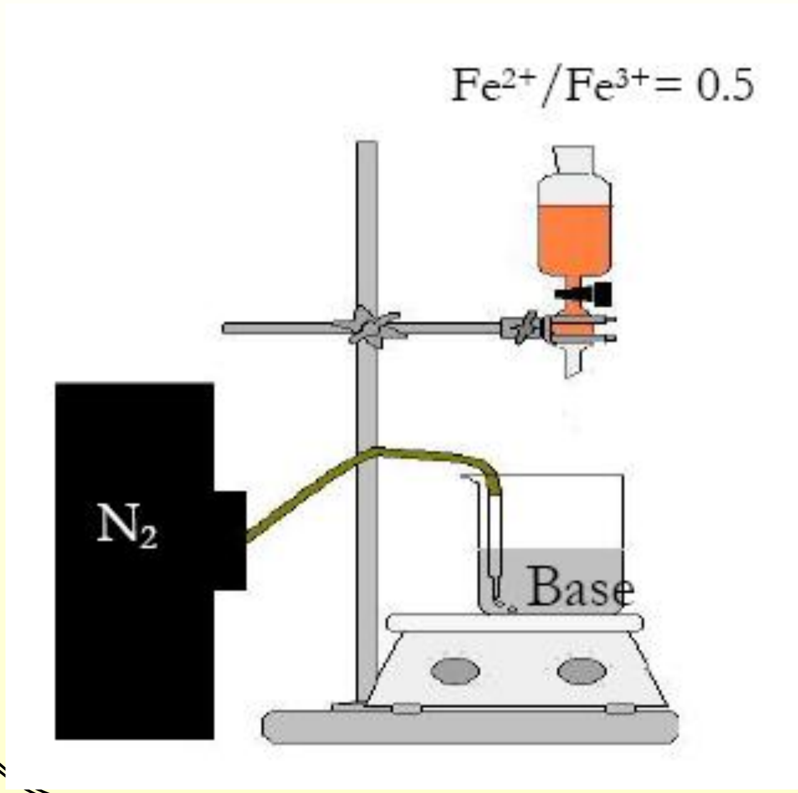
TABLE 2.1 Summary Comparison of the Synthetic Methods.

Synthesis Method	Reaction Time	Solvent	Surface-Capping Agent	Sizes	Size Distribution	Shape Control	Yield
Coprecipitation	Minutes	Water	No	2–15	Broad	Not good	Medium
Thermal decomposition	Hours–days	Organic compound	Yes	4–30	Very narrow	Very good	Medium
Polyol process	Hours	Polyglycol	Yes	5–150	Narrow–broad	Good	Medium
Microemulsion	Hours	Organic compound	Yes	5–50	Narrow	Good	Low
Spray pyrolysis	Seconds	Water and volatile solvents	No	2–10	Broad	Not good	High
Laser pyrolysis	Milliseconds	Gases	No	2–10	Very narrow	Good	High

Synthesis and Characterization of Nanoparticles: Synthesis of Inorganic Nanoparticles,
Gorka Salas, Rocio Costo and María del Puerto Morales
Part I, Vol. 4 Nanobiotechnology, Inorganic Nanoparticles vs Organic Nanoparticles edited by J.M. de la Fuente and V. Grazu, 2012 Elsevier Ltd, FRONTIERS OF NANOSCIENCE, Series, Editor: R. E. Palmer, UK.

Método convencional

Sal de Fe(II) y Fe(III)

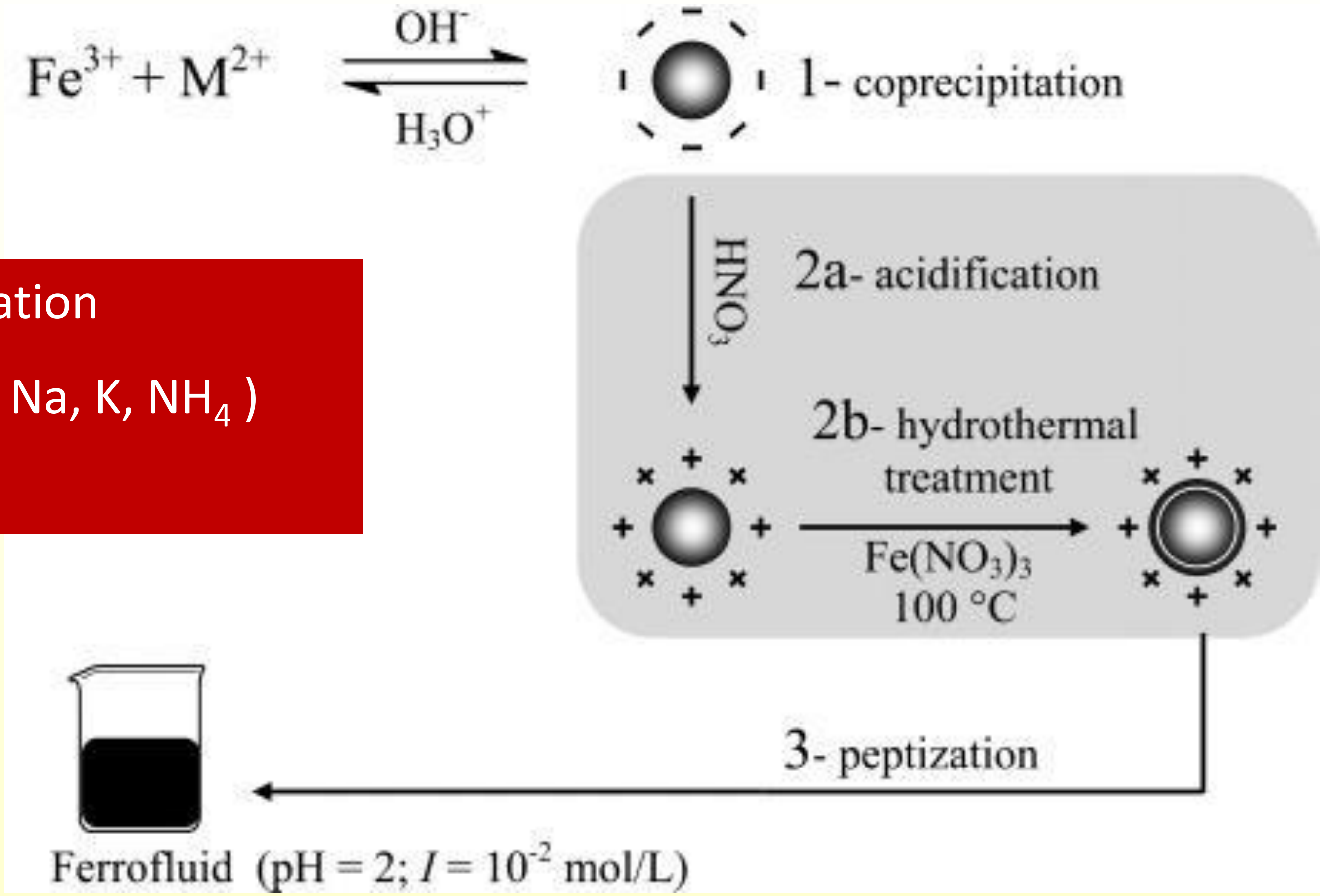


- Concentration
- Temperature
- Atmosphere
- Stirring

Fe_3O_4 (Magnetite)

Coprecipitation

- Salt concentration
- Nature of M (Na, K, NH_4)
- Temperature



R. Massart, IEEE Trans. Magn. Magn., 17, (1981) 131 and J.Chem.Phys. 84, 967 (1987)

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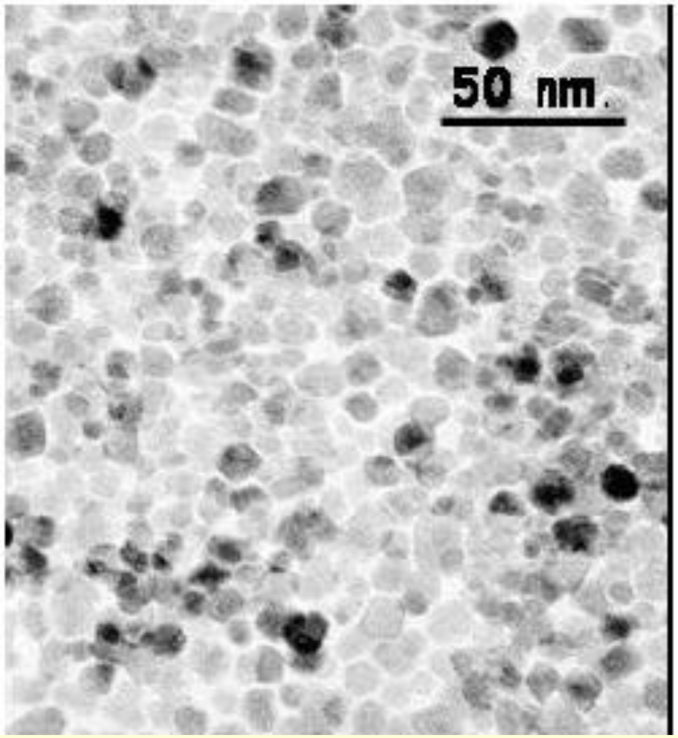
Synthesis by precipitation in water

Coprecipitation



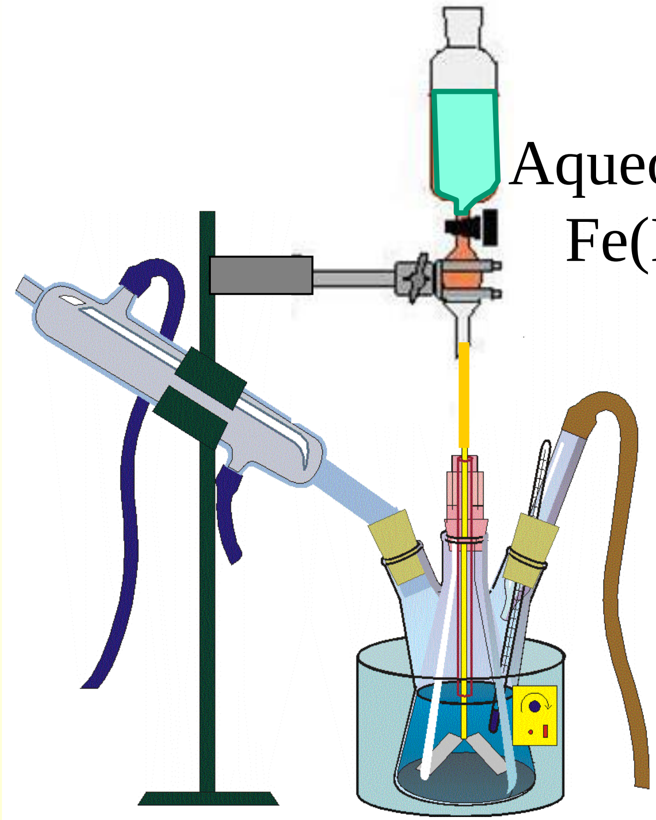
KOH	C1
Size XRD (nm)	8.4
Size TEM (nm)	9 ± 3.9
M_{50kOe} (emu/g sample)	45
χ (emu/g sample · kOe)	52
Hex 5 K (Oe)	0
% C	0
% weight loss (TG)	3.5

Fe_3O_4 Nanoparticles with sizes between 2-12 nm

J. P. Jolivet, in Metal Oxide Chemistry and Synthesis: From Solutions to Solid State, Wiley, New York, 2000.

Synthesis by precipitation in water

Sal de Fe(II)



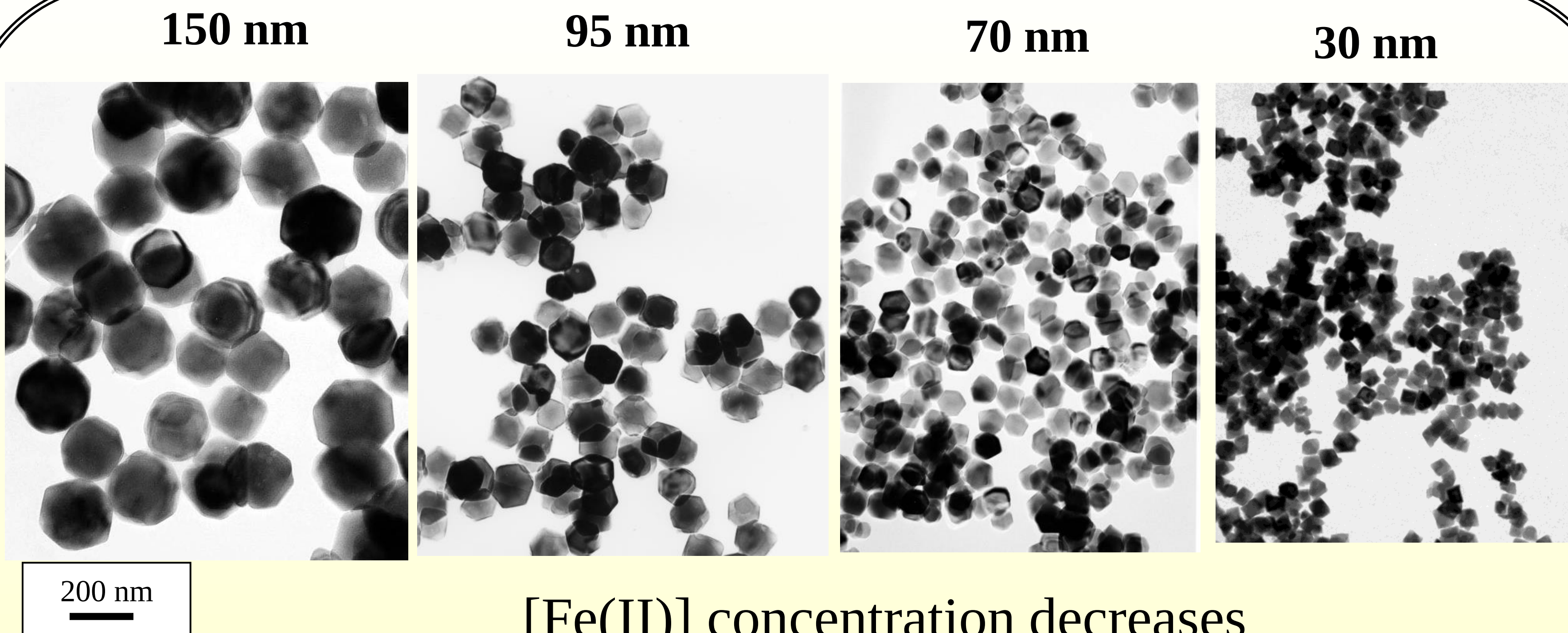
Aqueous solution
Na(OH) + KNO_3

$90^{o}C \pm 0.1$
24 hours

Undisturbed system

Synthesis by precipitation in water

Oxidation control



[Fe(II)] concentration decreases →

$[OH]_{exc}$ increases from 0.0002 M to 0.02 M →

Particle size decreases from 300 nm to 30 nm

M. Andres et al. J. Phys. D:Appl. Phys., 2008

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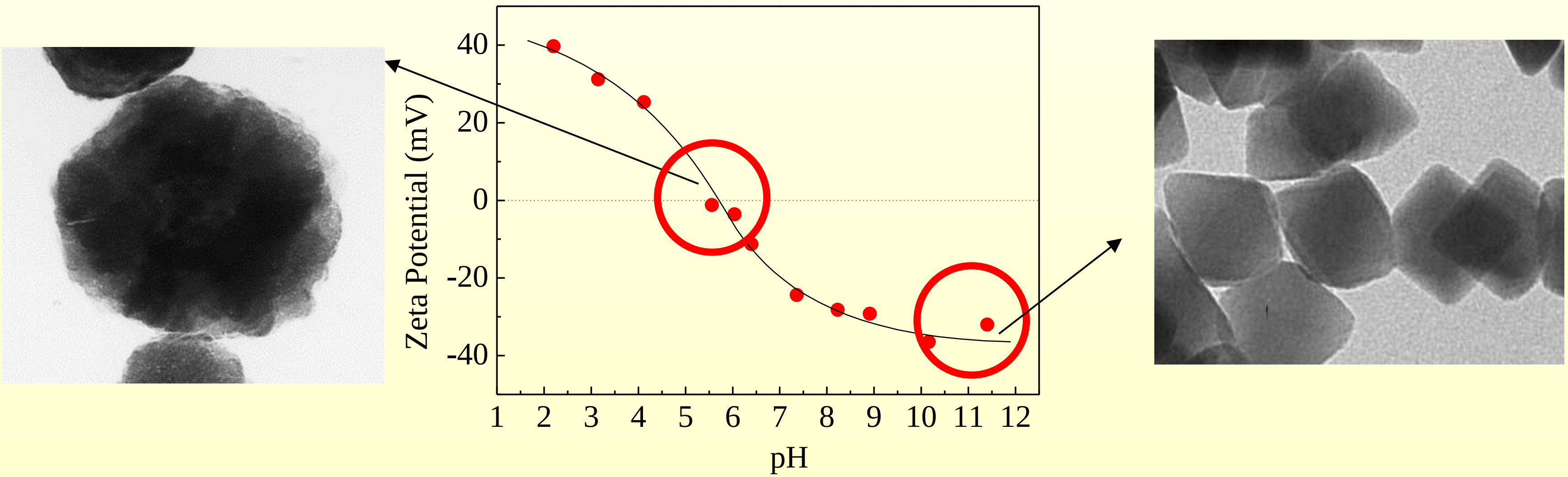
PARTICLE SHAPE

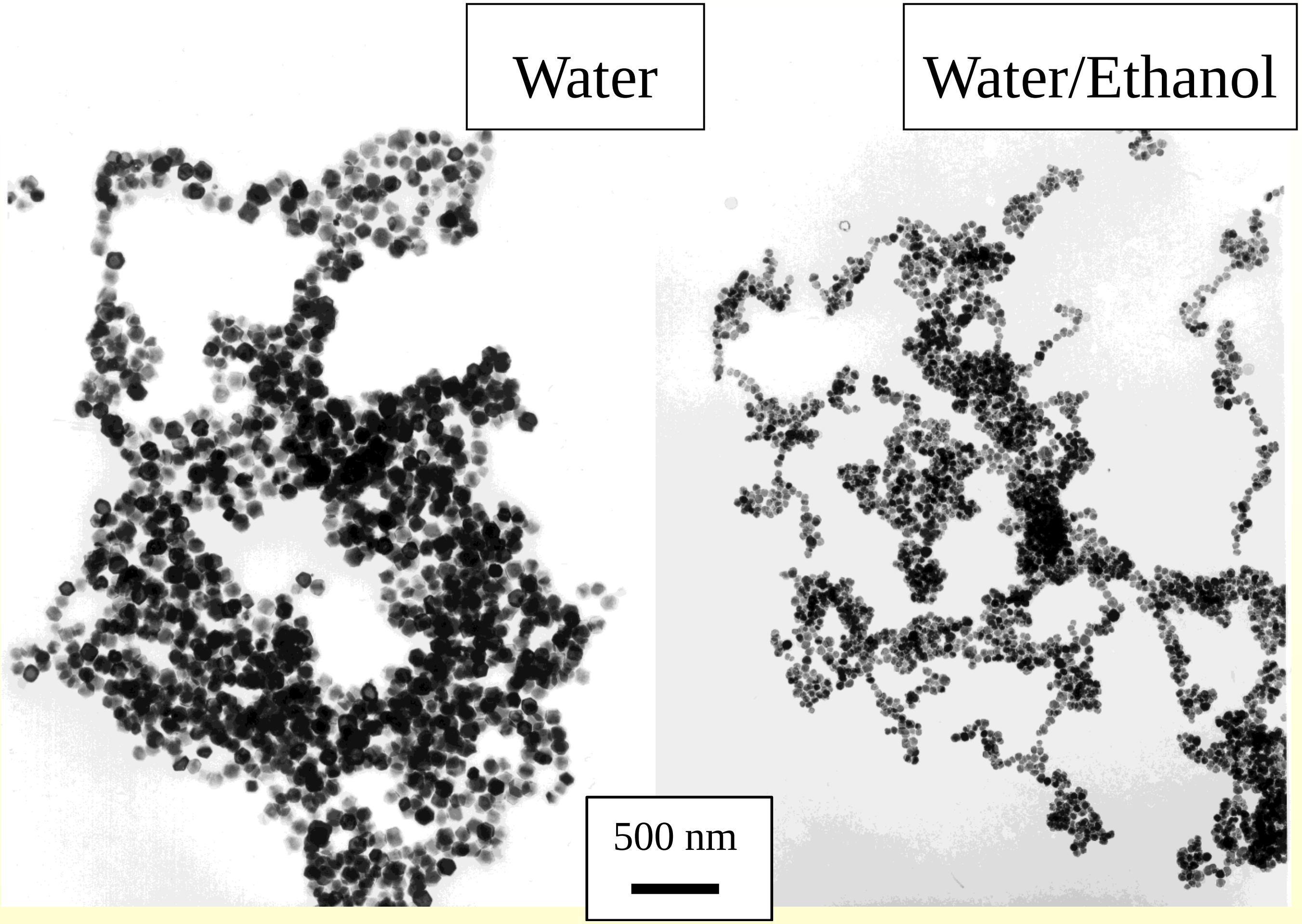
- At pH 6, electrostatic repulsion between the primary particles is small and coagulation of the very small primary particles would be expected to take place

- However, in excess of OH-, particles are of cubic morphology with a well-defined habit, which suggests a direct crystal growth mechanism.



SURFACE CHARGE FOR MAGNETITE

Synthesis by precipitation in water



Introduction of ethanol in the media lead to a important reduction in particle size

Marciello, J. Mater Chem. 2014 in press

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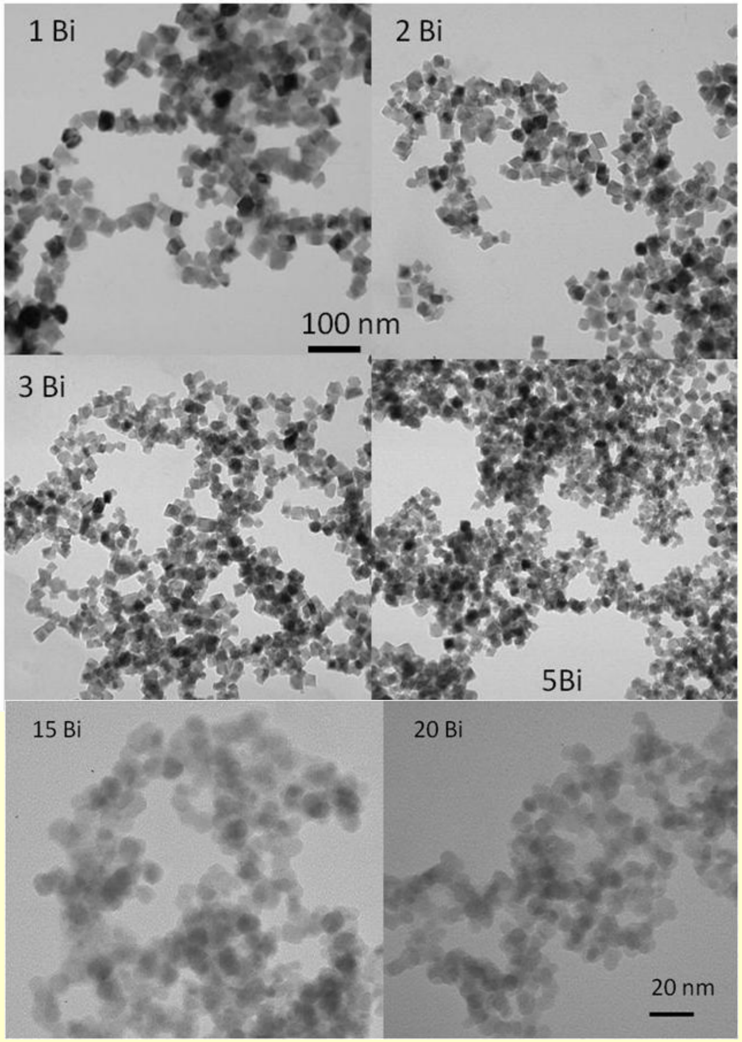
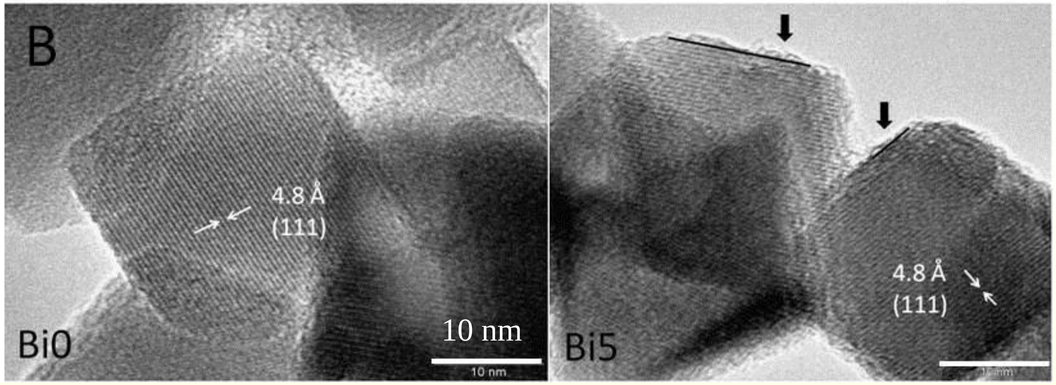
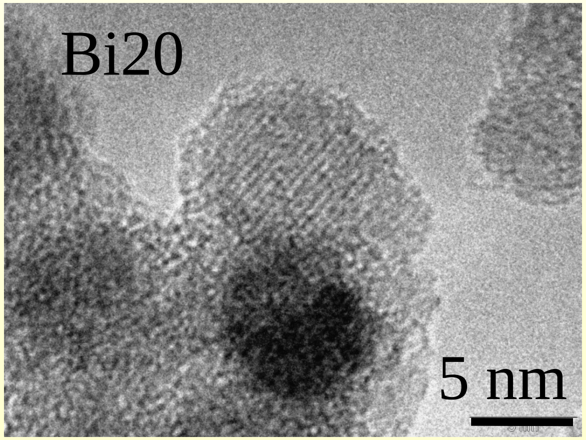
Hyperthermia + Dual imaging agent (NMR + CT)

Core/Shell Magnetite/Bismuth Oxide Nanocrystals with Tunable Size, Colloidal, and Magnetic Properties







Chem. Mater. 2012, 24, 319−324

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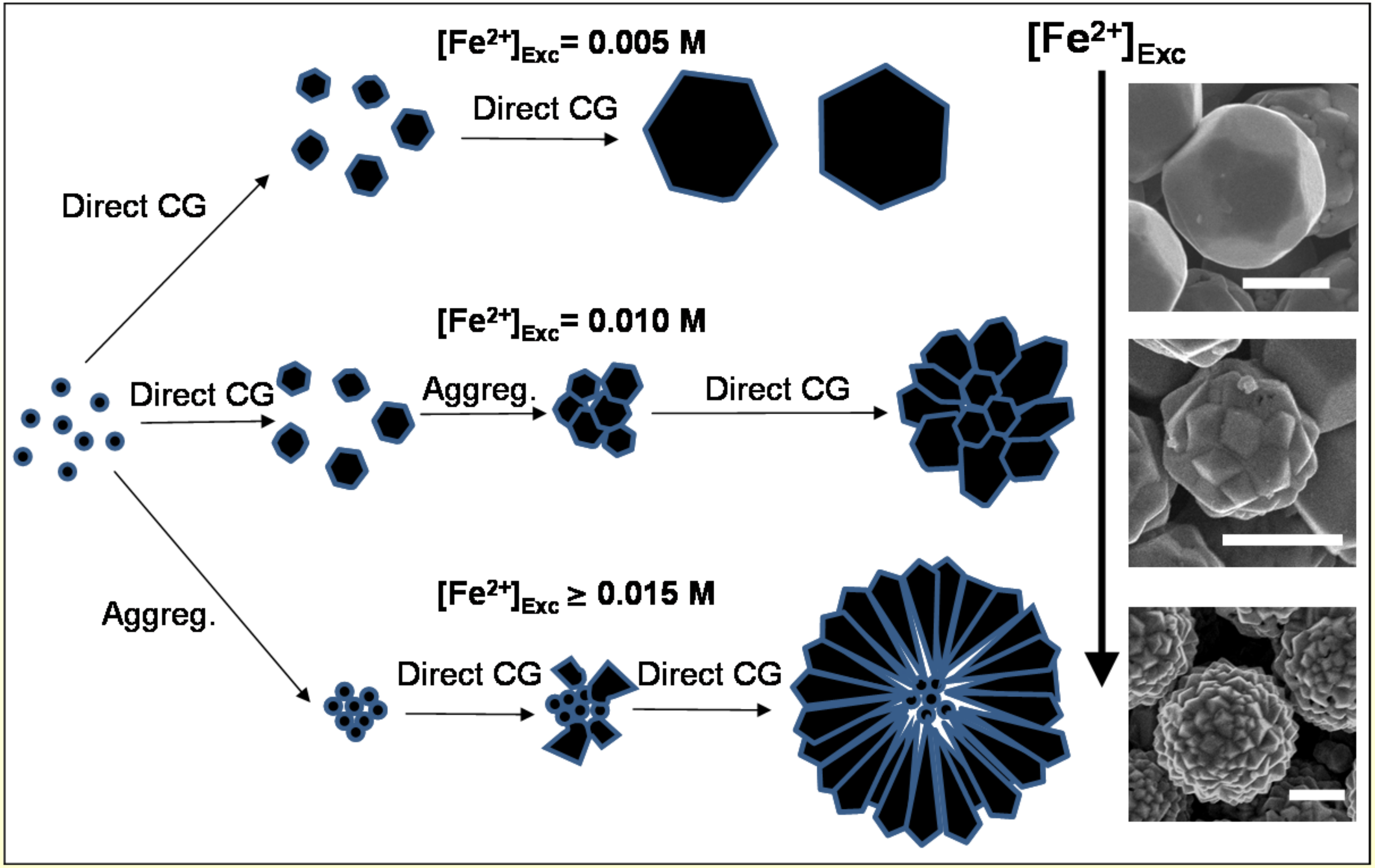
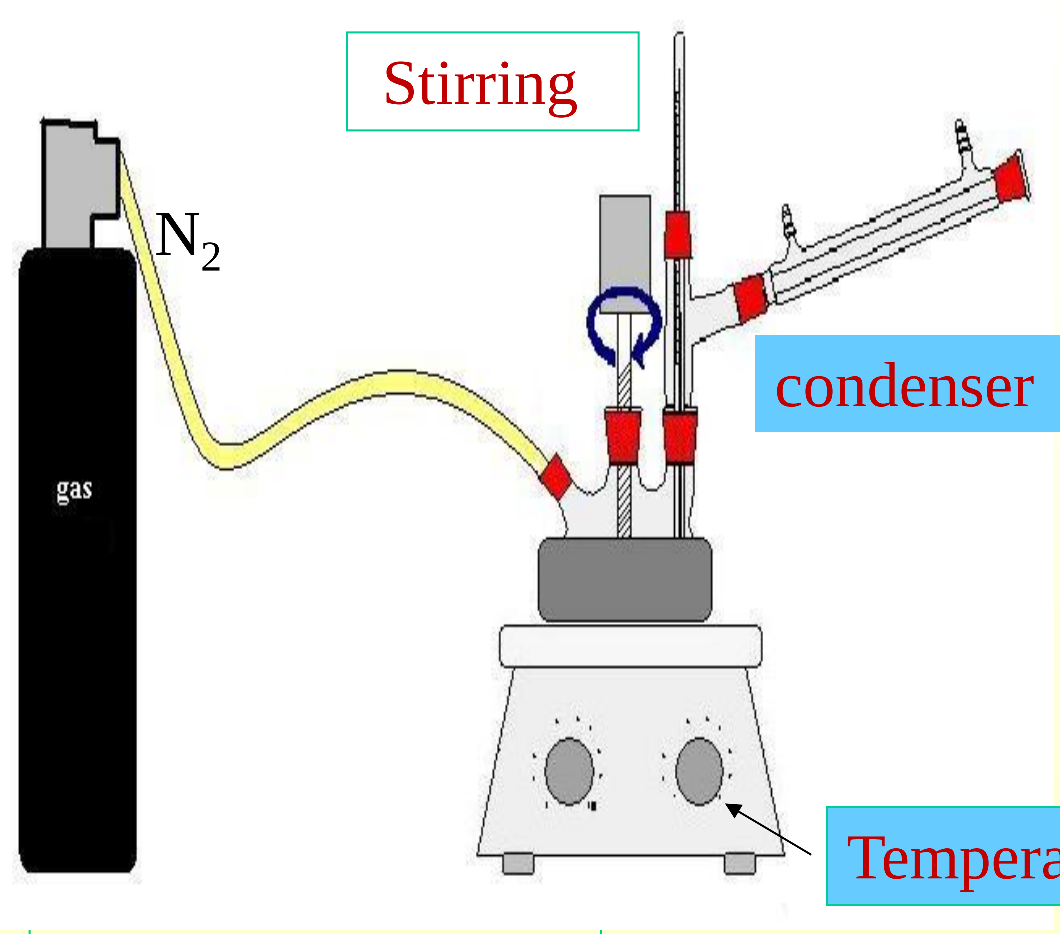
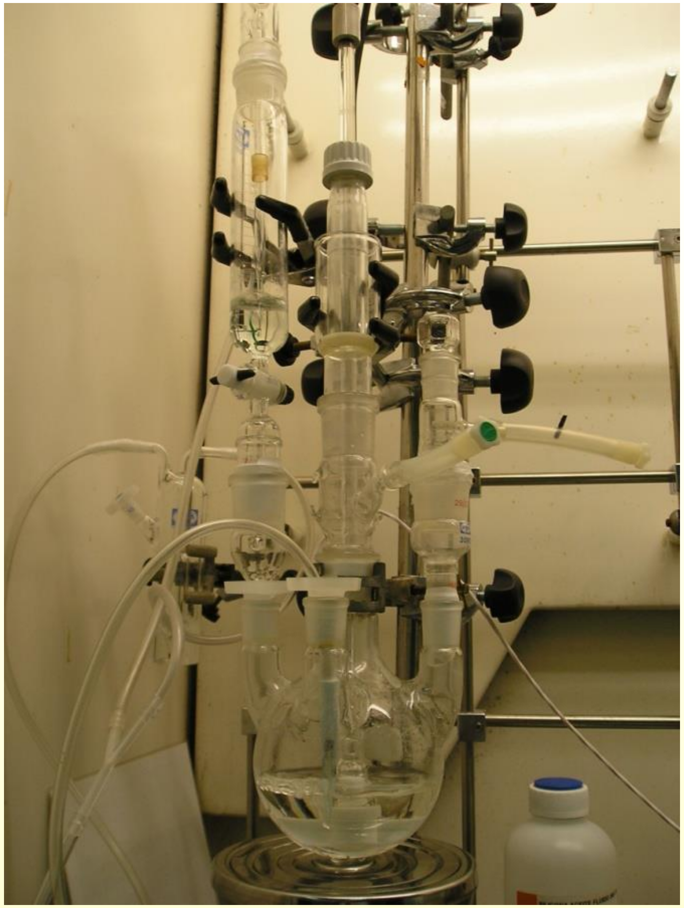
Synthesis by precipitation in water



Rodríguez-González, B.; Vereda, F.; de Vicente, J.; Hidalgo-Álvarez, R. *J. Phys. Chem. C* **2013**, 117, 5367

High temperature decomposition of organic precursors





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High temperature decomposition of organic precursors

Composition	Crystal structure	Diameter [nm]	Capping agent [a]
Fe	bcc	3.0–9.3	OA, LA, HAc, HAm
ε-Co	fcc	3.5–17	OA, LA, TOP
Co	hcp	2.0–12	OA, TOP, TBP, TOPO
Ni	fcc	5.0–13	OA, TOA, TOPO
FePt	fcc, fct	3.0–17	OA, OAm
CoPt	fcc, fct	7.0	ACA, HDA
γ-Fe_2O_3	fcc	3.0–25	OA, SA
Fe_3O_4	fcc	8.0–30	OA
CoO	fcc	~8	TOP
$CoFe_2O_4$	fcc	2.0–12	OA

Synthesis of Monodisperse Spherical Nanocrystals
Jongnam Park, Jin Joo, Soon Gu Kwon, Youngjin Jang, and Taeghwan Hyeon
Angew. Chem. Int. Ed. 2007, 46, 4630 – 4660

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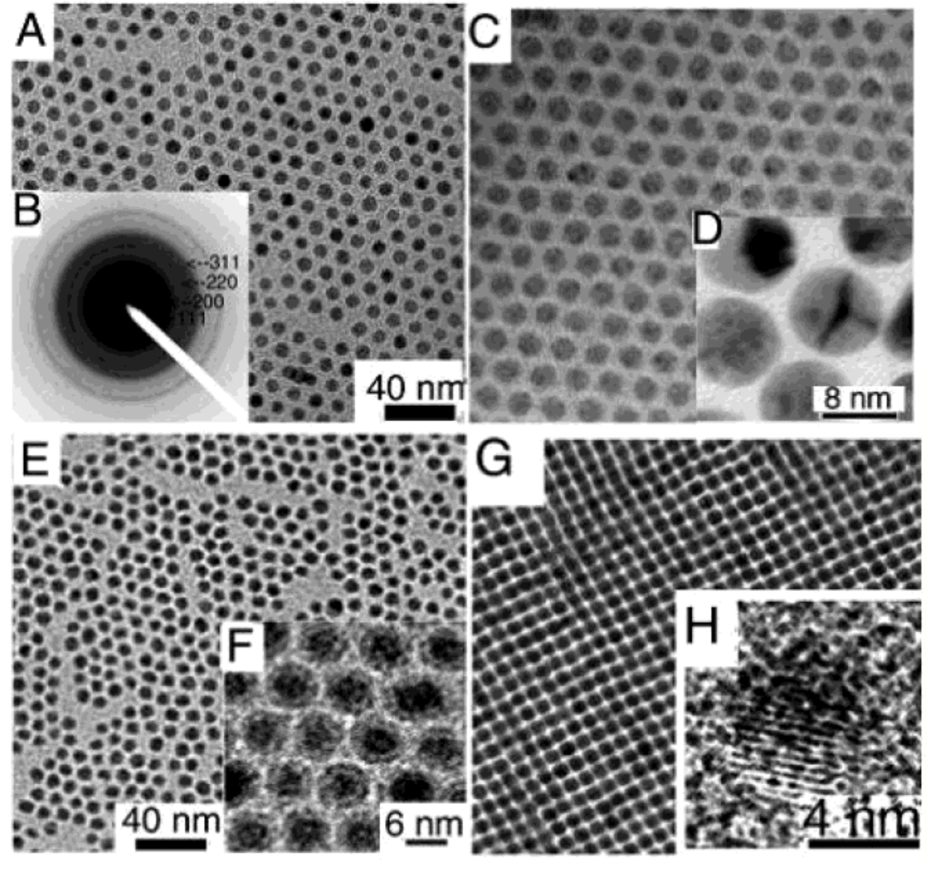
High temperature decomposition of organic precursors

8 nm Co-Ni
alloy nanoparticles

8 nm **Co**
nanoparticles



6 nm **Fe**
nanoparticles

6 nm **FePt**
nanoparticles

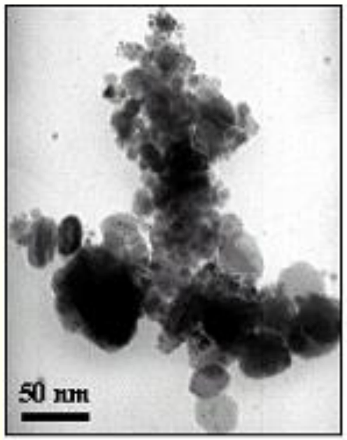
Sun and Murray et al. 2000 Science, 287, 1989

High temperature decomposition of organic precursors

Surfactant

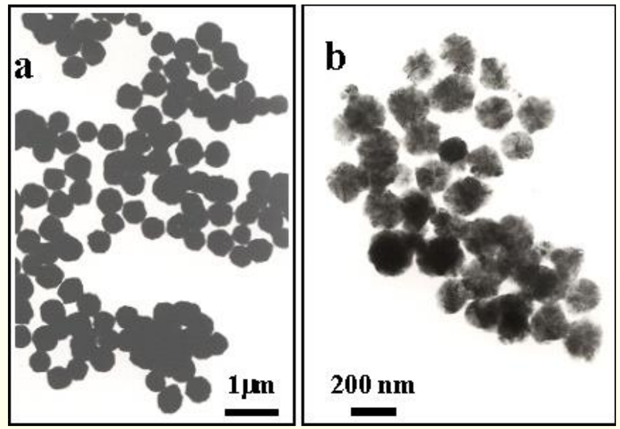
Co

No surfactant



Seeds: Ag

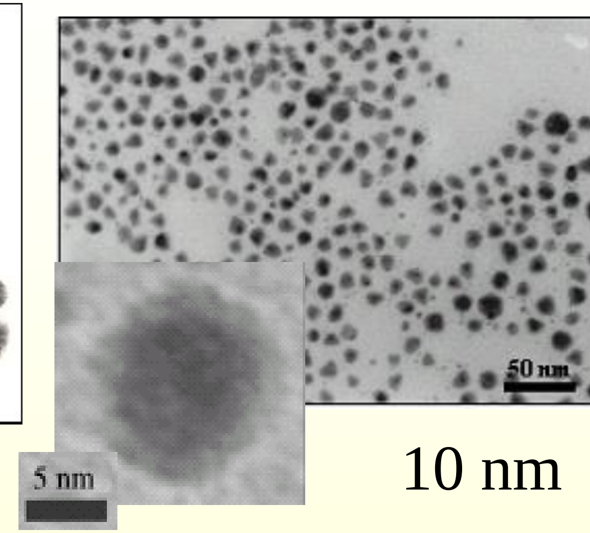
Pt



500 nm

100 nm

Pt + oleico

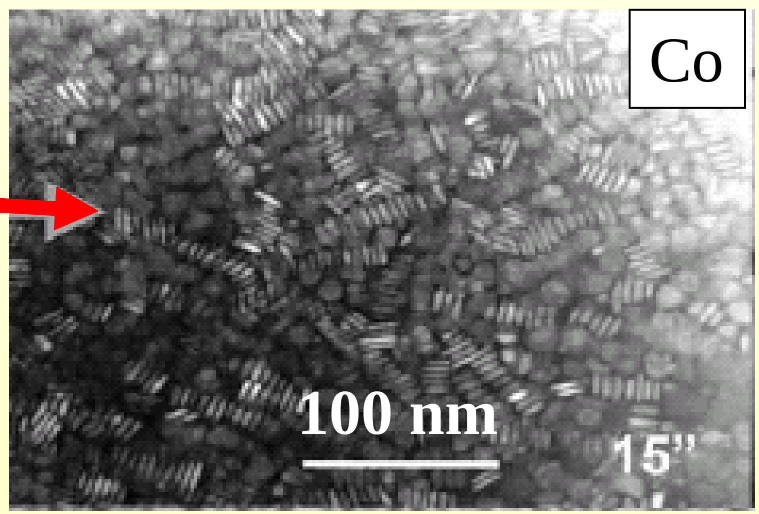


10 nm

Nanotechnology 14, 268, 2003 and
Nanotechnology 15, S293, 2004

$Co_2(CO)_8$

Oleic acid
+
TOPO

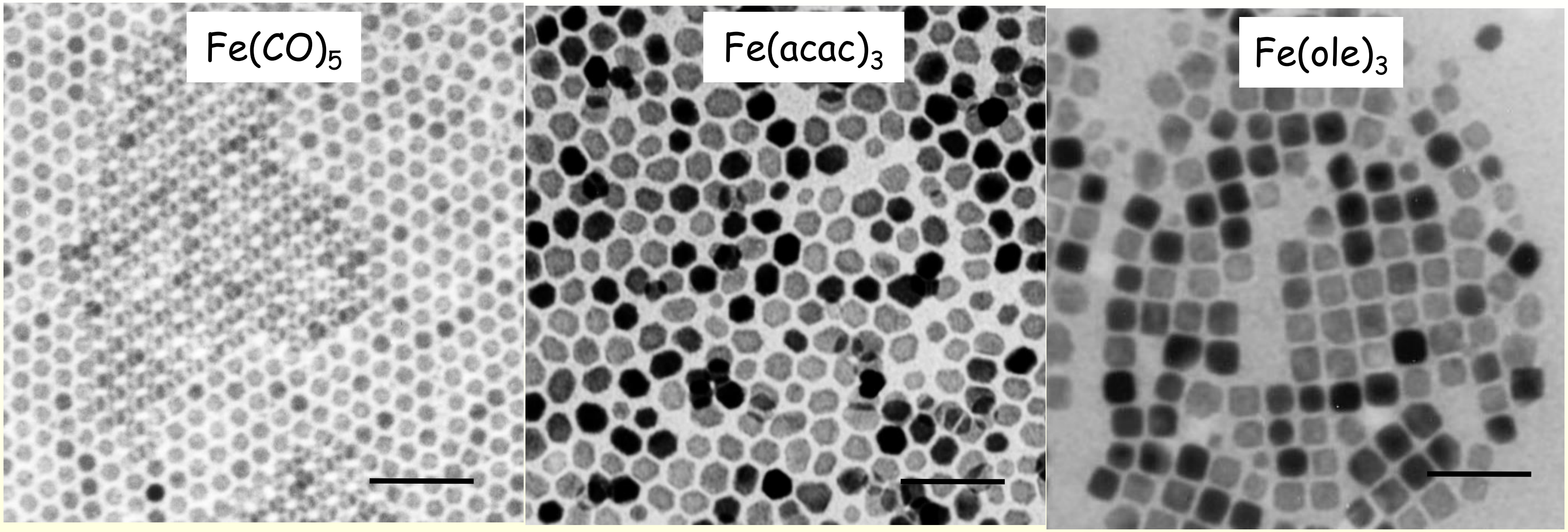


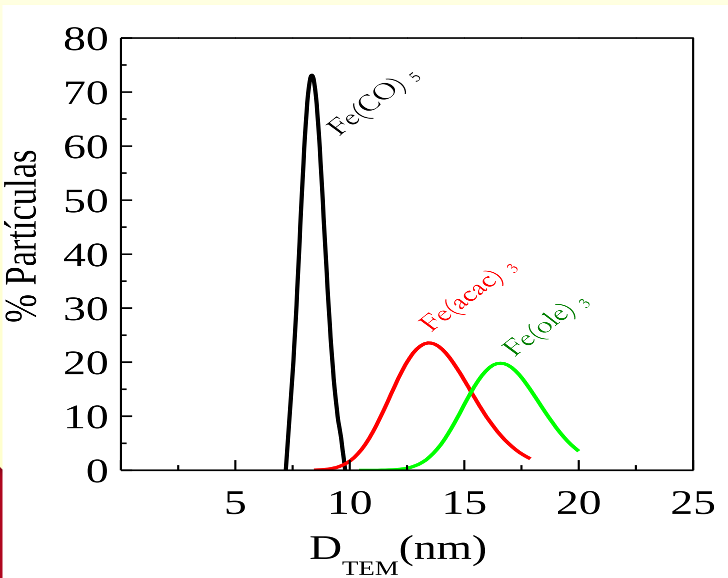
V.F. Puntes et al., Science 291 (2002) 2115

Effect on particle size and shape

High temperature decomposition of organic precursors

Precursor **Fe_3O_4**





$Fe(acac)_3$+ a.oleico ⇄ $(Fe\text{-}oleico)_x$+ subproducts

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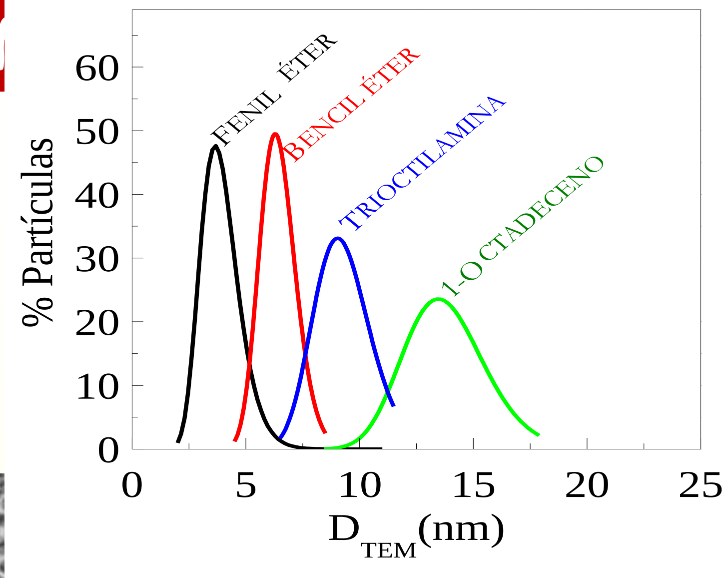
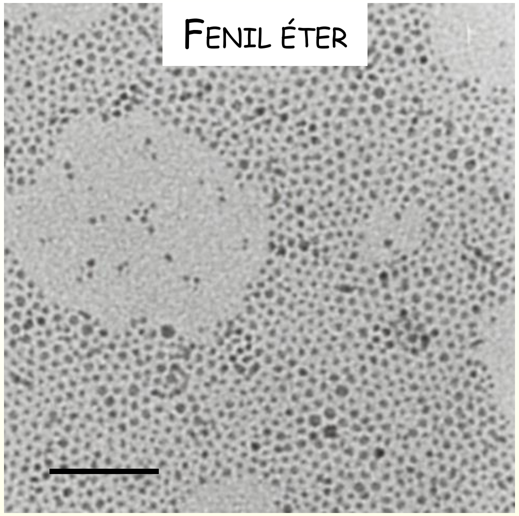
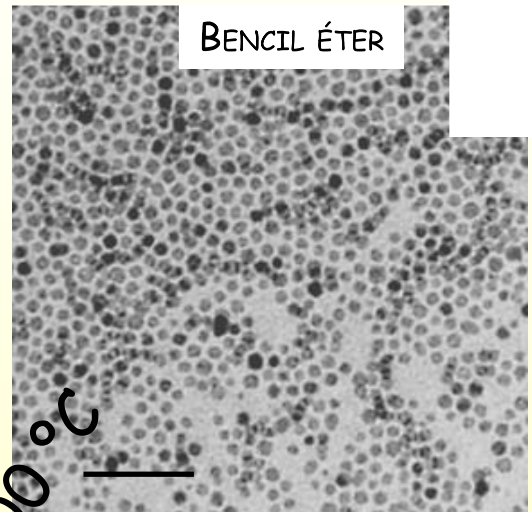
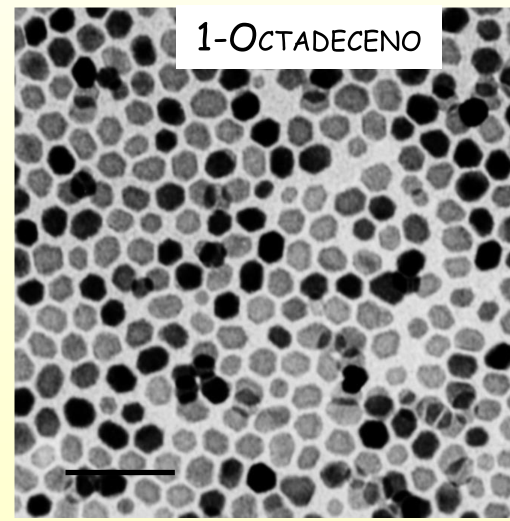
High temperature decomposition of









254 °C

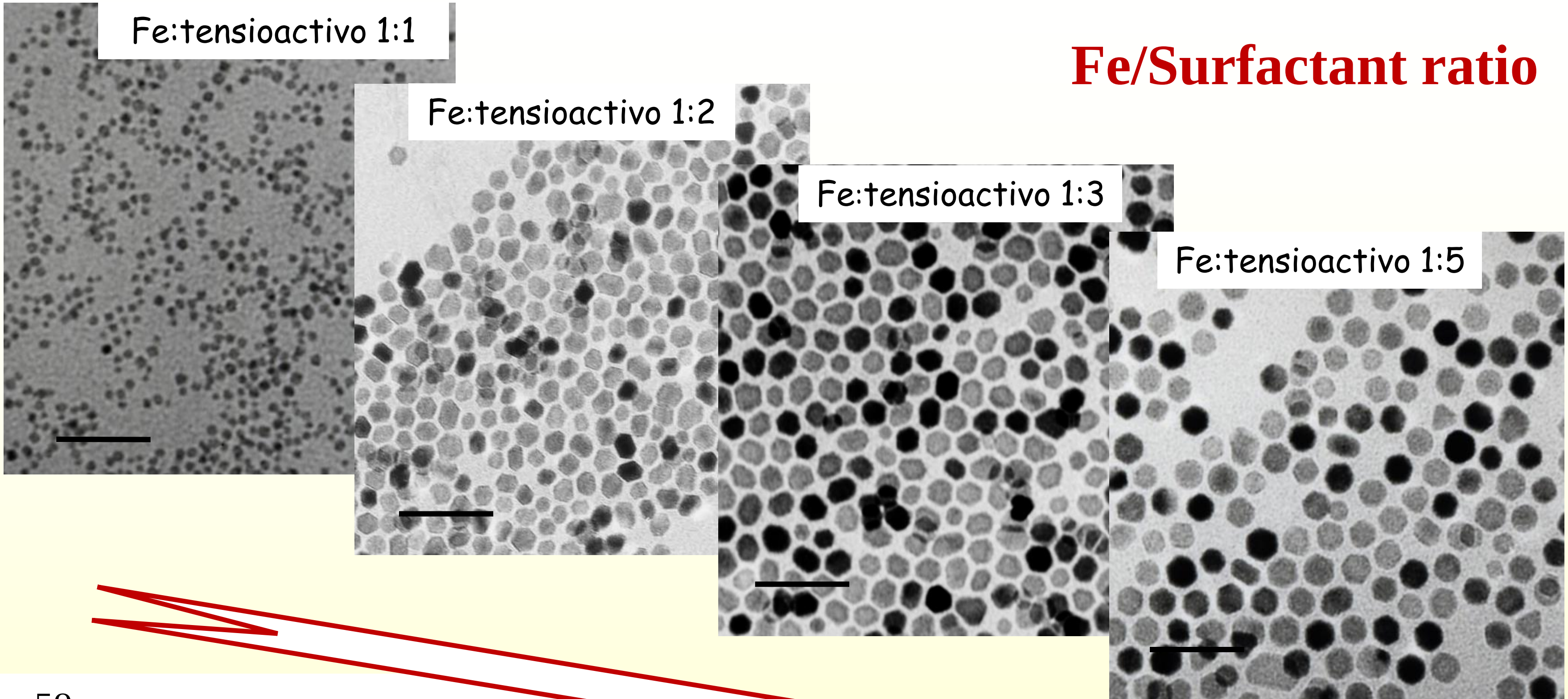
300 °C

320 °C

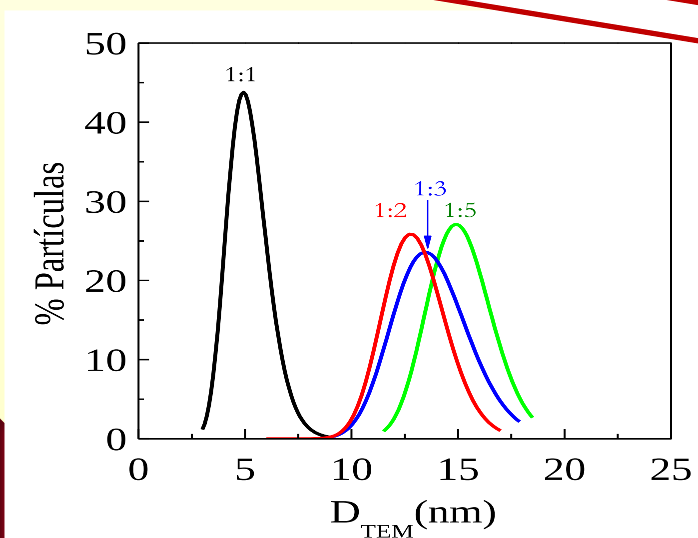
Boiling point

Solvent

High temperature decomposition of organic precursors



Fe/Surfactant ratio



Fe(acac)$_3$+ a.oleico ⇄ (Fe-oleico)$_x$ + subproductos

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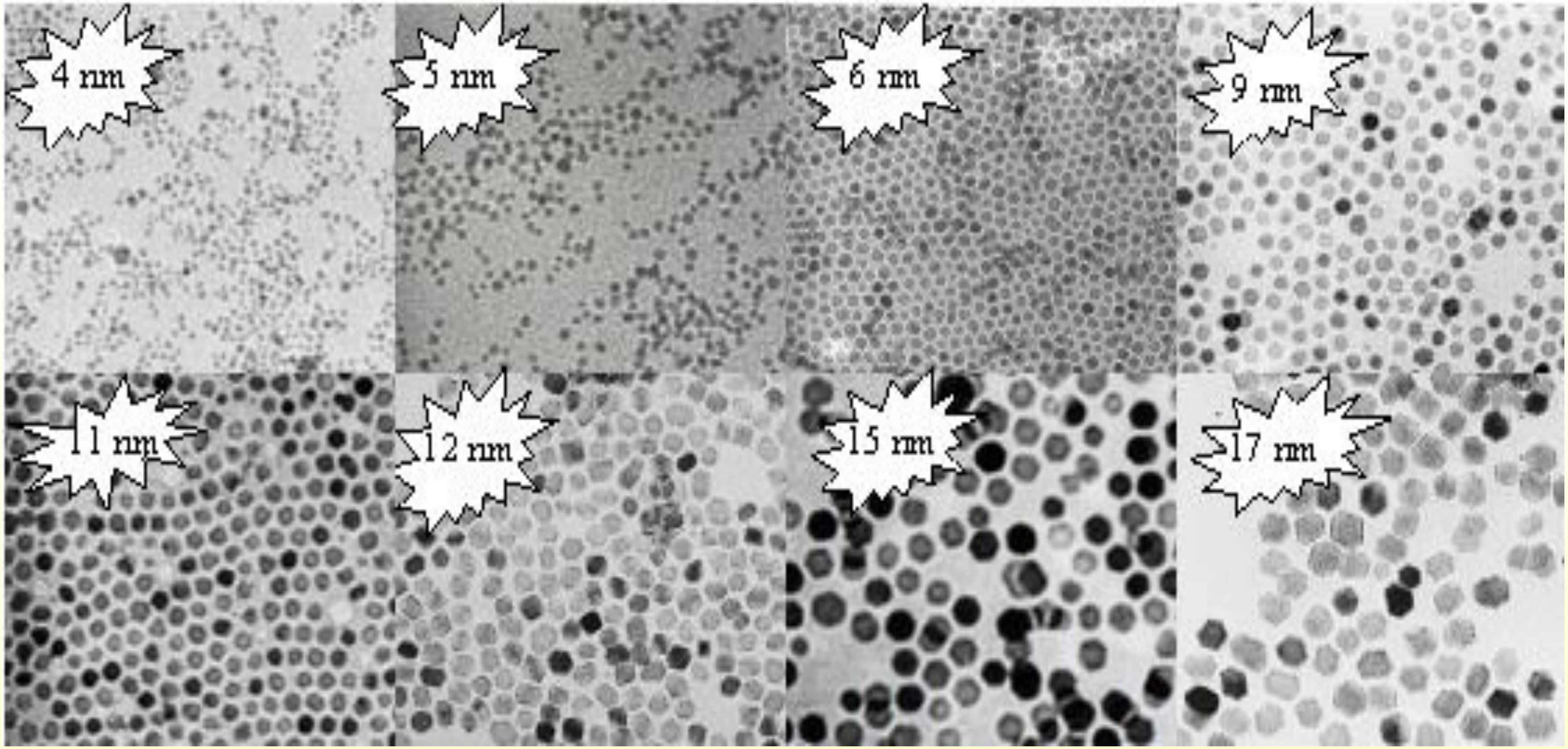
High temperature decomposition of organic precursors

Size control



Iron oxide nanoparticles showing one nanometer increments in diameter

Roca, A. G. et al *Nanotechnology* **2006**, *17*, 2783-2788.

IEEE TRANSACTIONS ON MAGNETICS, 42, 3025 (2006)

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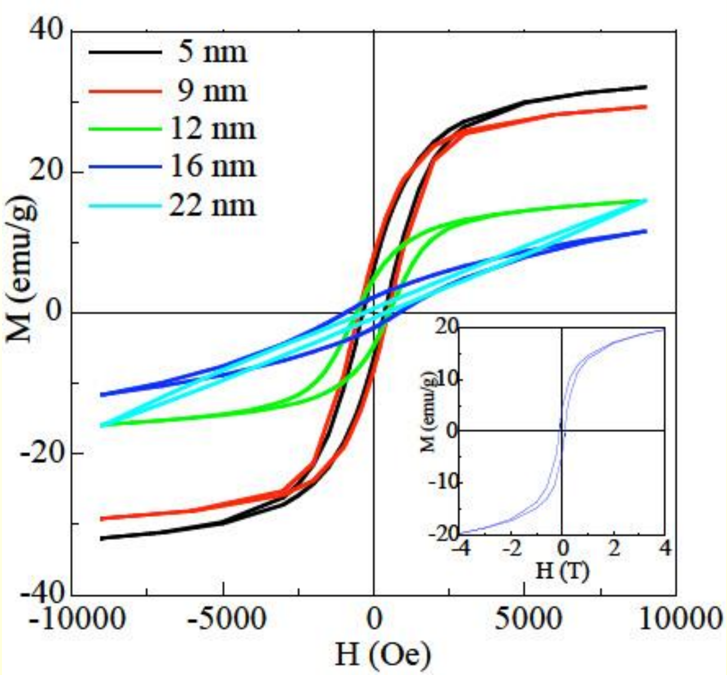
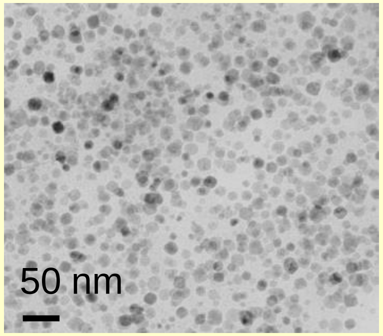
High temperature decomposition of organic precursors

Problems: low Ms at larger sizes

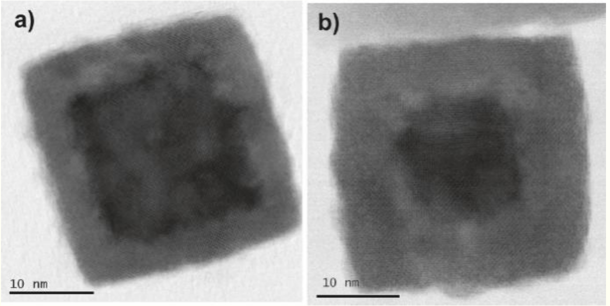


Park, J. *et al. Nat. Mater.* **2004**, *3*, 891-895



Broad size-distribution

Other phases

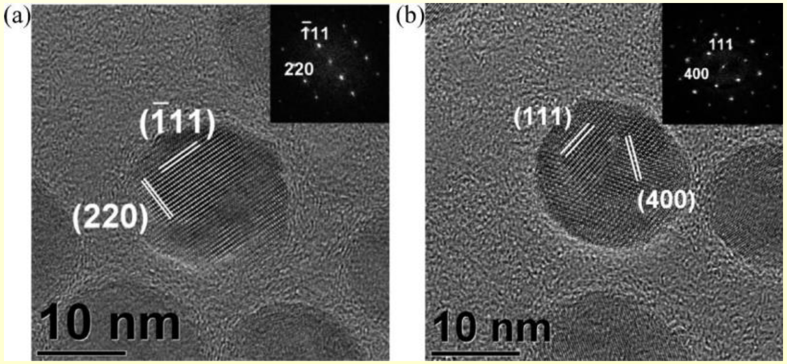


wüstite-spinel core-shell structure

FeO γ-Fe_2O_3/Fe_3O_4

Pichon et al *Chem. Mater.* **2011**, *23*, 2886-2900

Structural imperfections



|Chem. Mater. 2011, 23, 4170–4180

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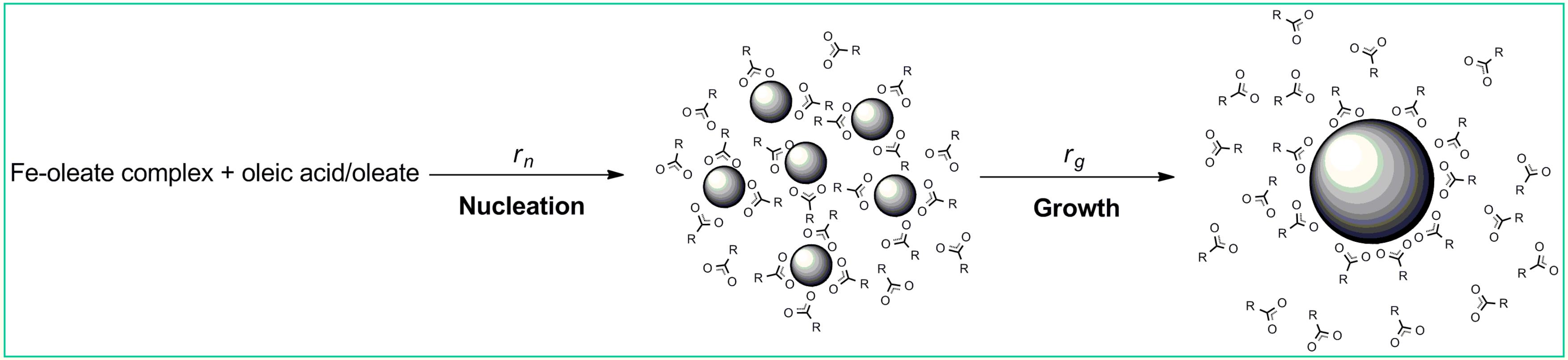
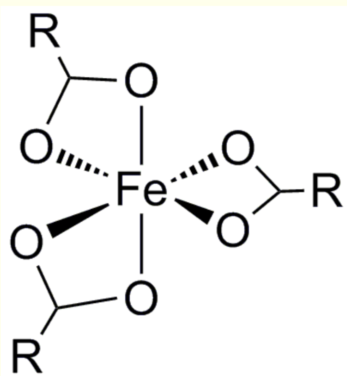
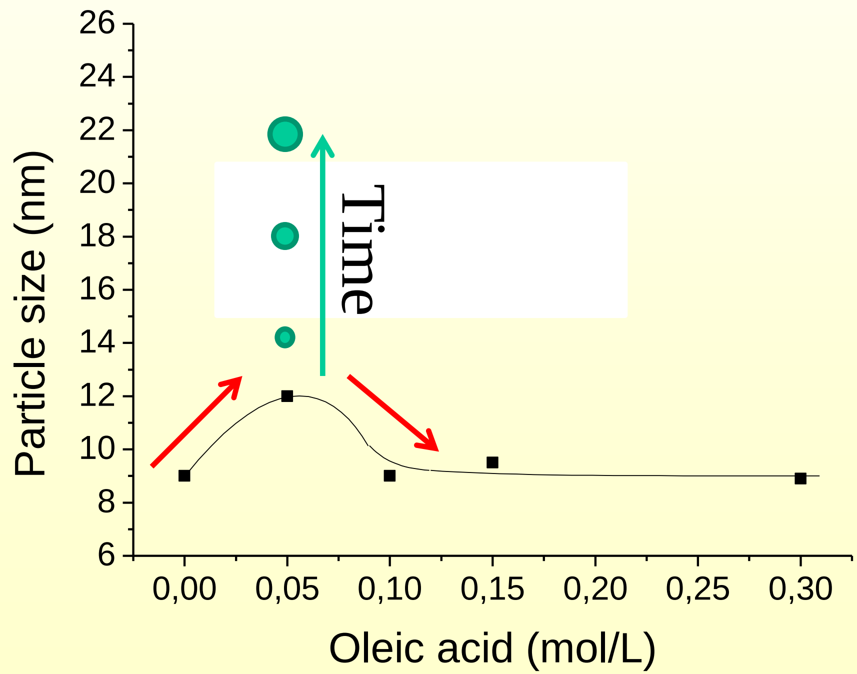
Iron oleate as precursor







J. Mater. Chem. 22, 21065 (2012).

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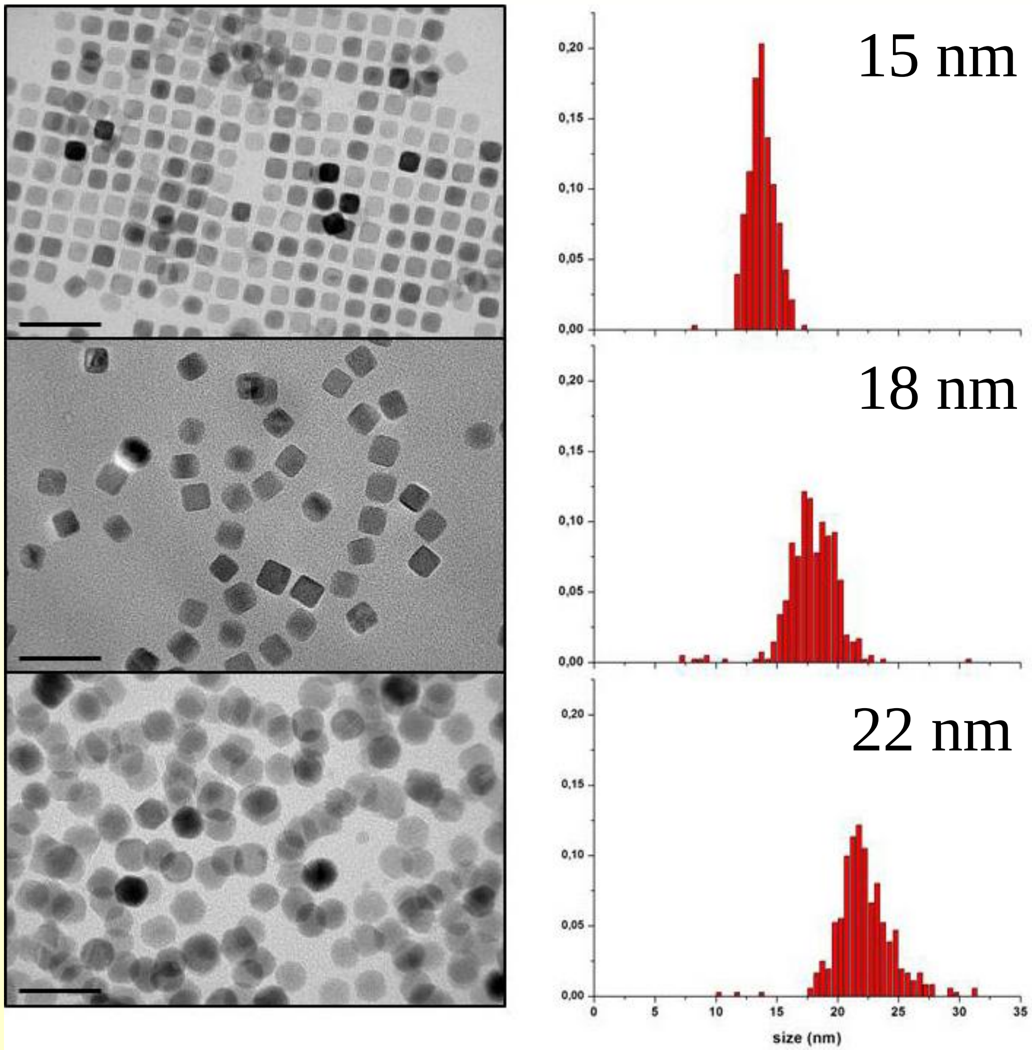
High temperature decomposition of organic precursors

Iron oleate as precursor + longer reaction times + No stirring



σ = 9%

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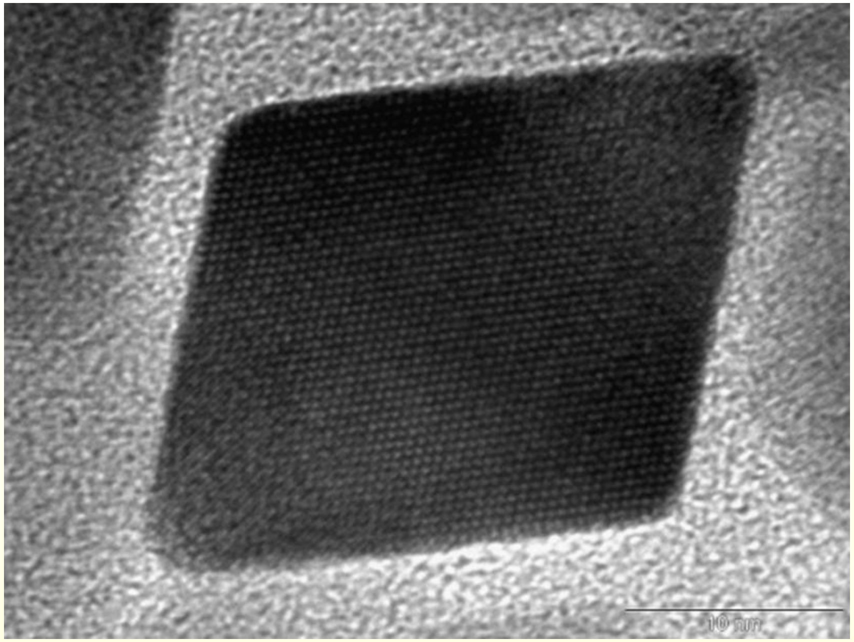
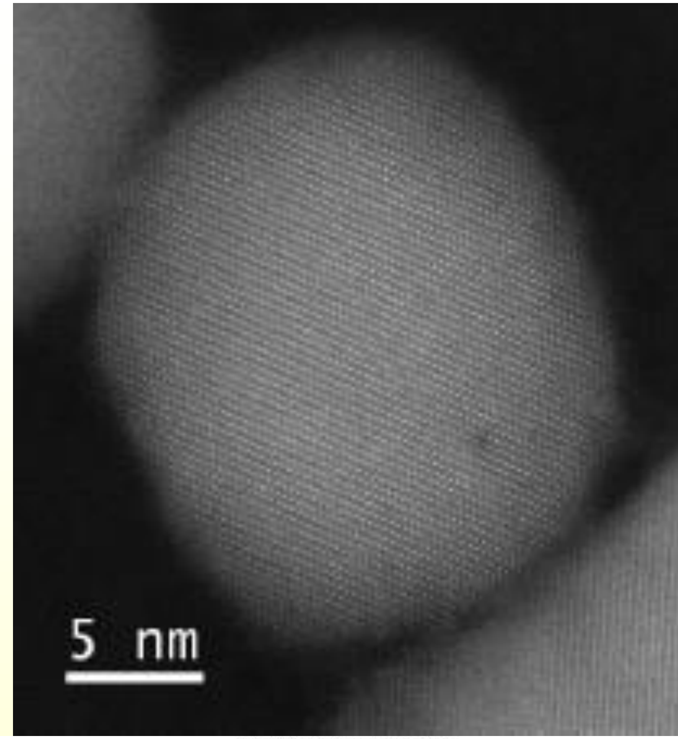
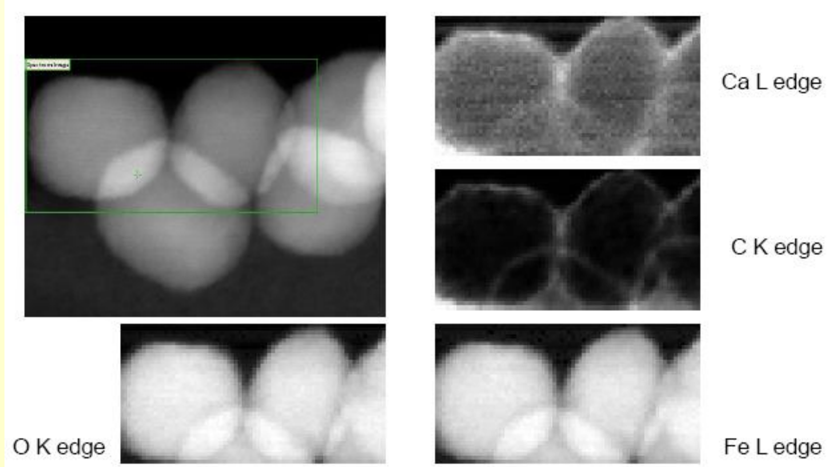
HIGH QUALITY NANOCRYSTALS

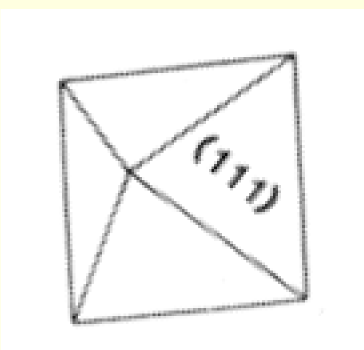


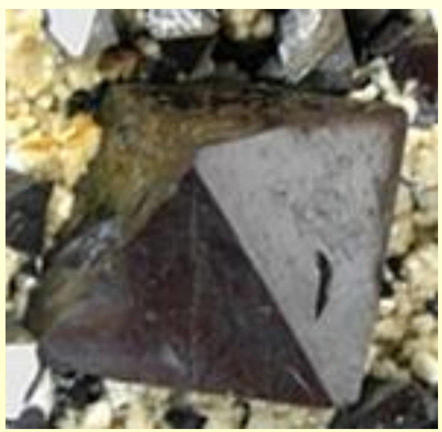
M. Varela, UltraSTEM200 2 200 kV, Oak Ridge National Laboratory



EELS elemental maps

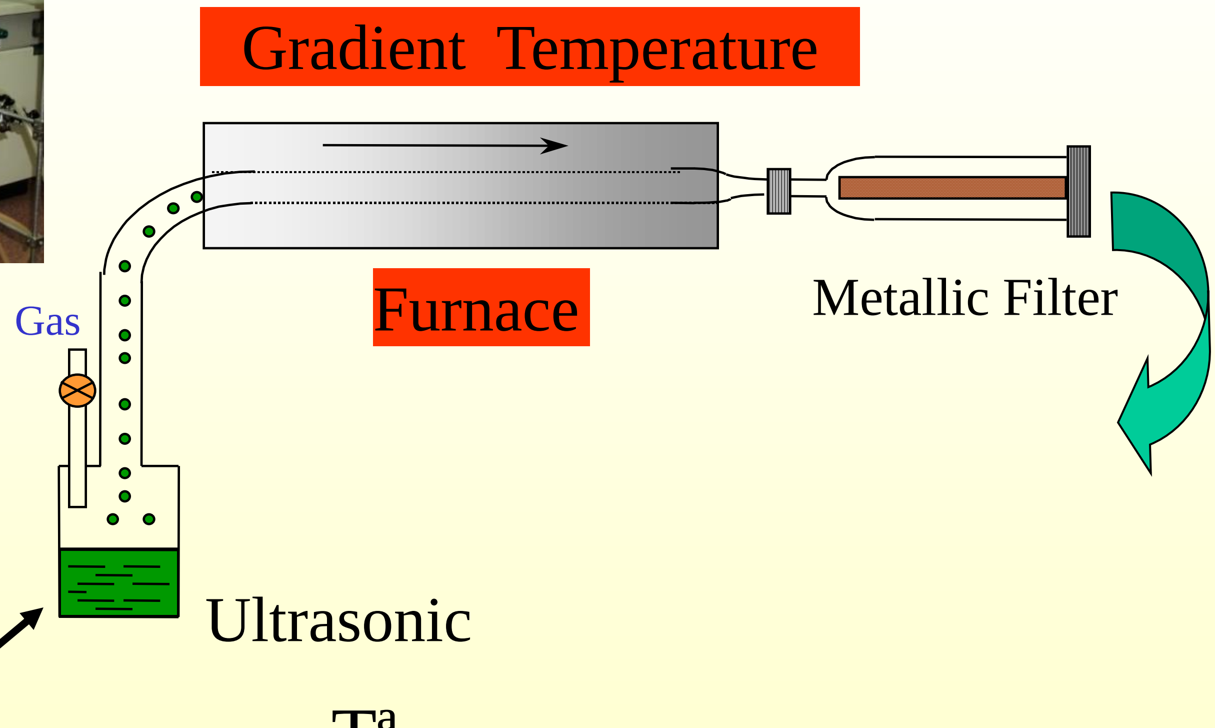






Magnetita: octaedro de 1.8 cm.
Cerro Huañaquino (Bolivia)

SPRAY PYROLYSIS METHOD



$Fe(NO_3)_3$ Solution $\xrightarrow{T^a}$ γ-Fe_2O_3

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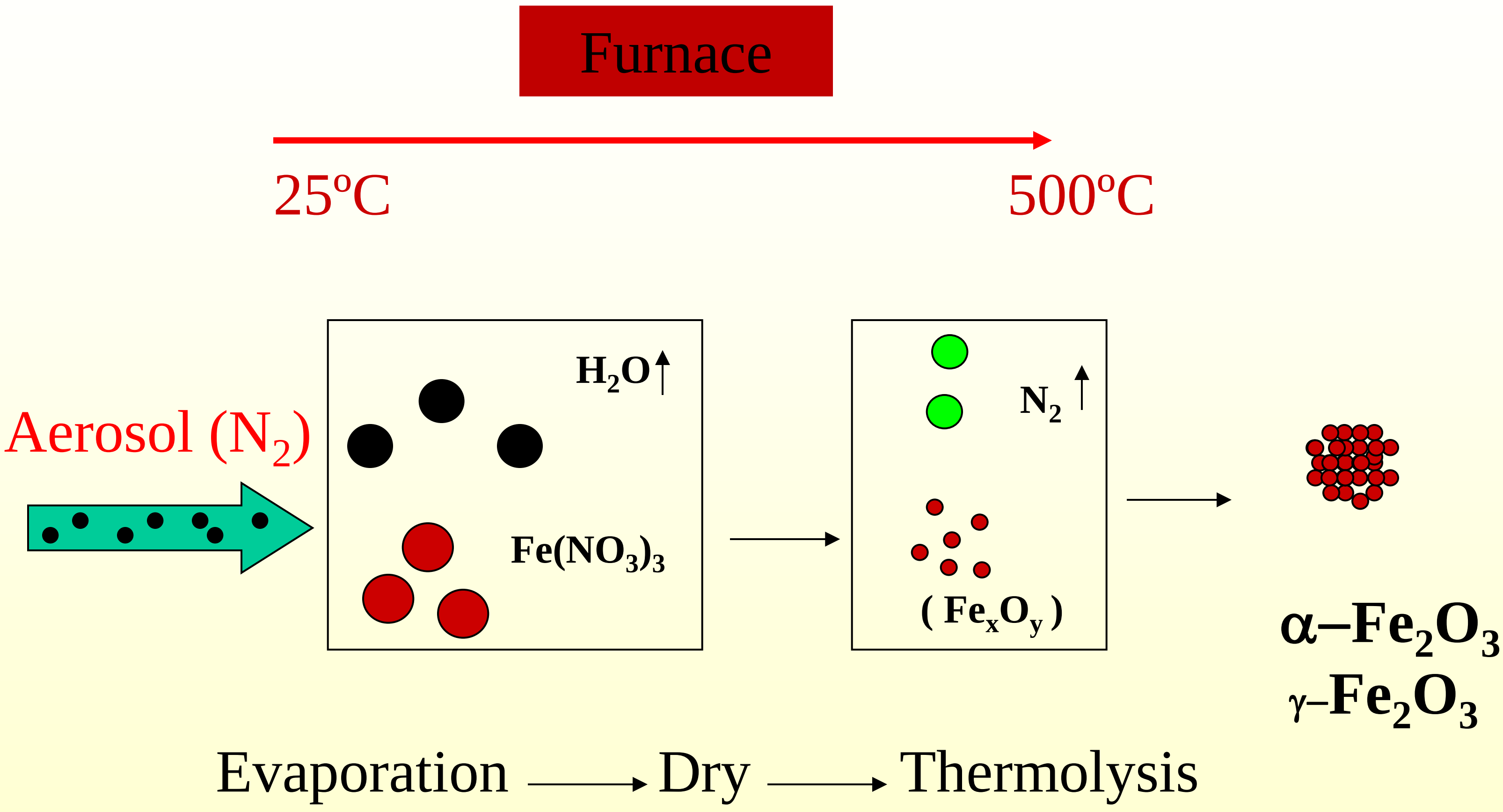
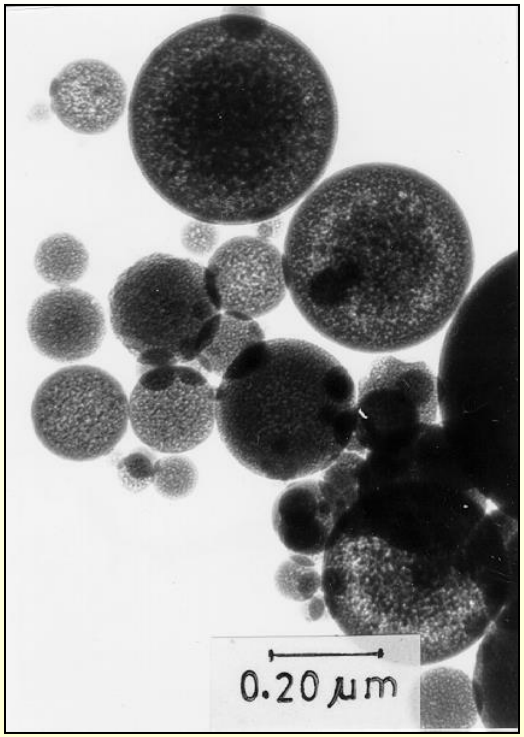
SPRAY PYROLYSIS METHOD

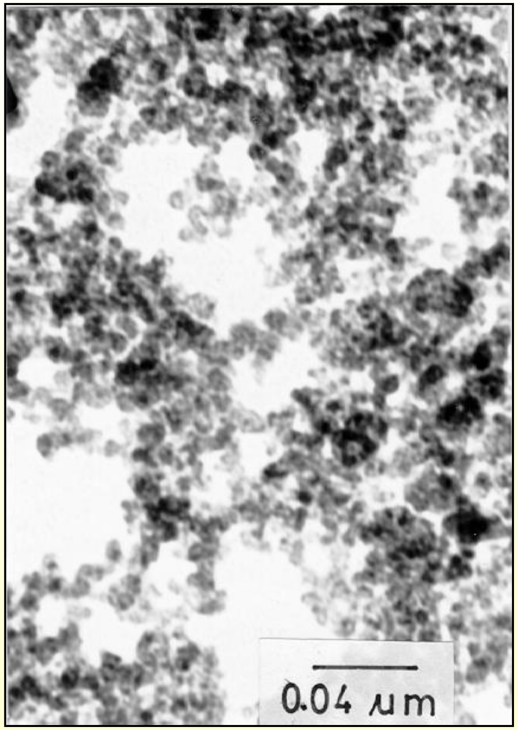


SPRAY PYROLYSIS METHOD

γ-Fe_2O_3

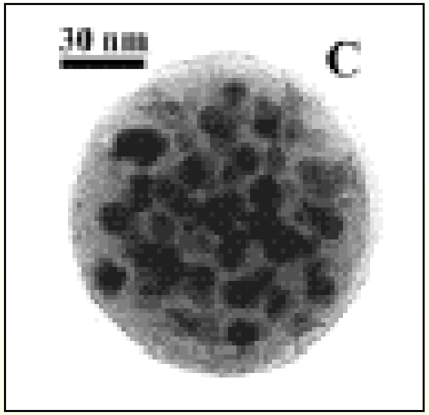


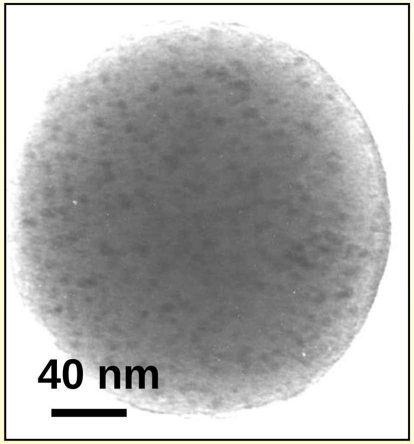
Nitrates



Acetylacetonate

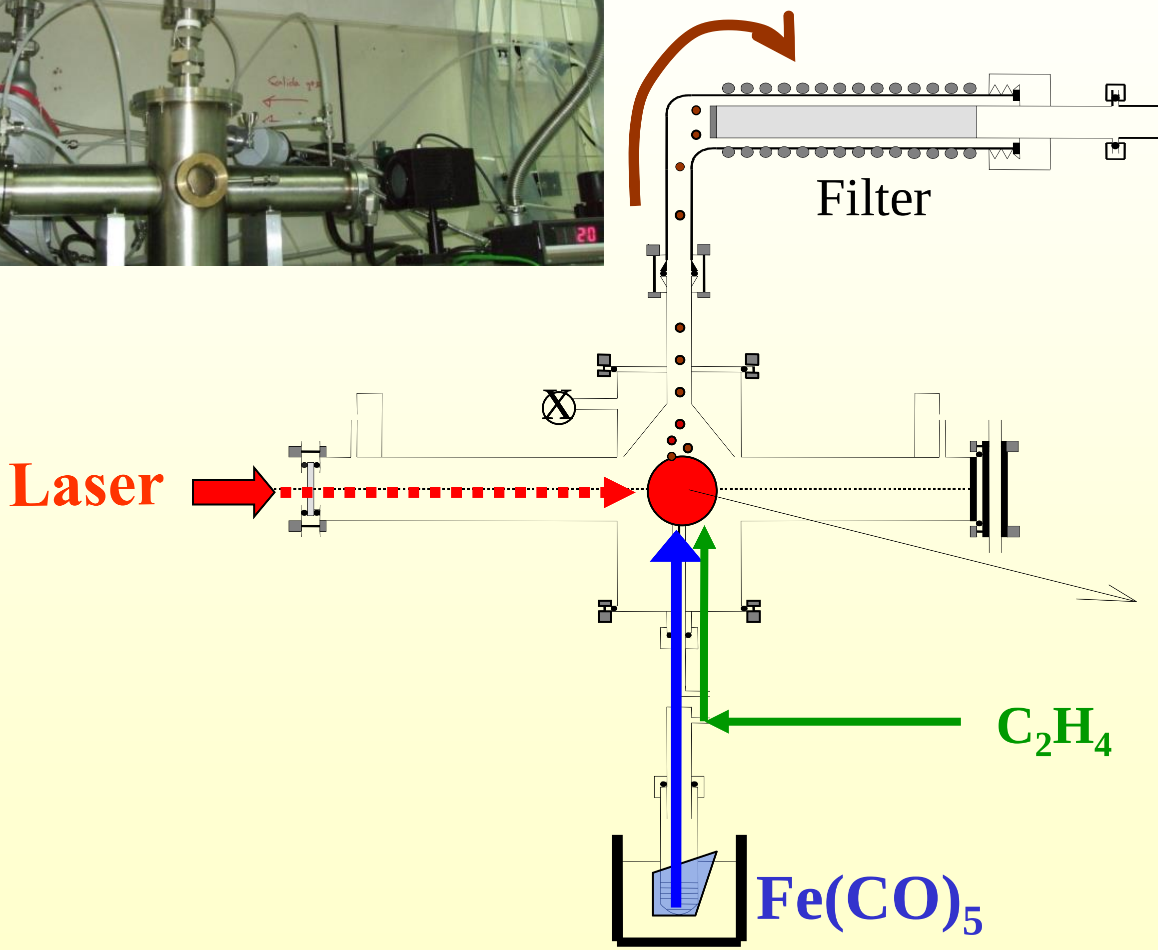
γ-Fe_2O_3/SiO_2





P. Tartaj et al. J. Amer. Chem. Soc., **125**, 15754-15755 (2003).
P. Tartaj et al , Adv. Mater., **16**, 529 (2004).

Laser Pyrolysis



S. Veintemillas-Verdaguer, O. Bomati-Miguel and M.P. Morales. **Scripta Mater**., 47, 589-593 (2002)

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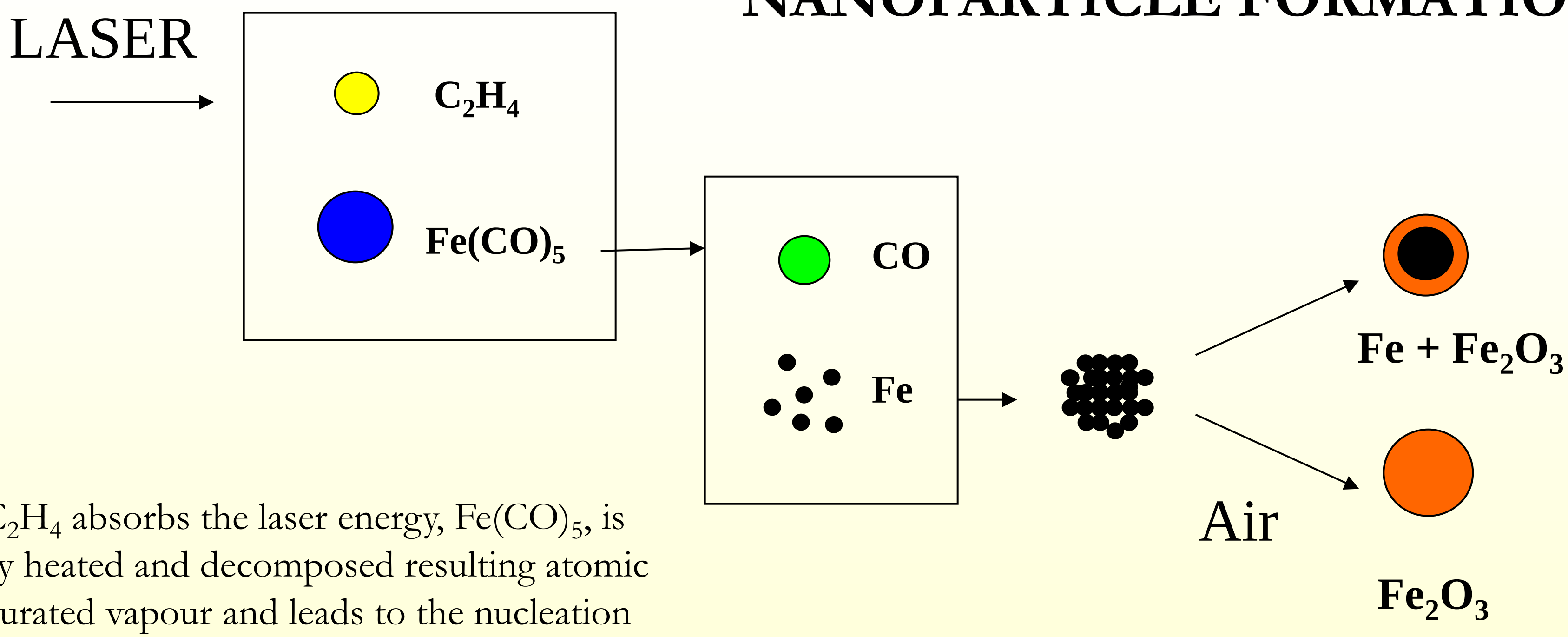
Laser Pyrolysis

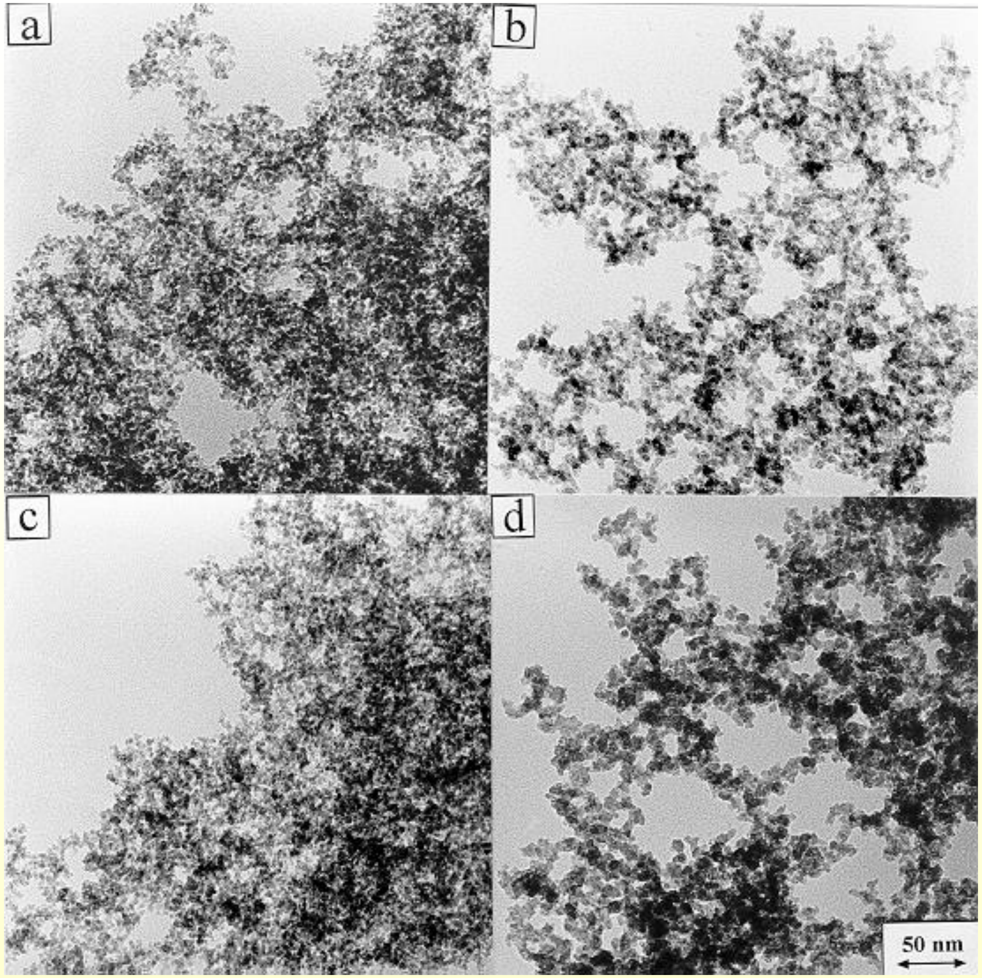
MECHANISM OF NANOPARTICLE FORMATION



The C_2H_4 absorbs the laser energy, $Fe(CO)_5$, is rapidly heated and decomposed resulting atomic Fe saturated vapour and leads to the nucleation and growth of iron metal nucleus

To stabilise the powders, a mixture of air and ethylene can be introduced together with the iron pentacarbonyl (hard oxidation) or after the laser pyrolysis (soft oxidation).

Laser Pyrolysis

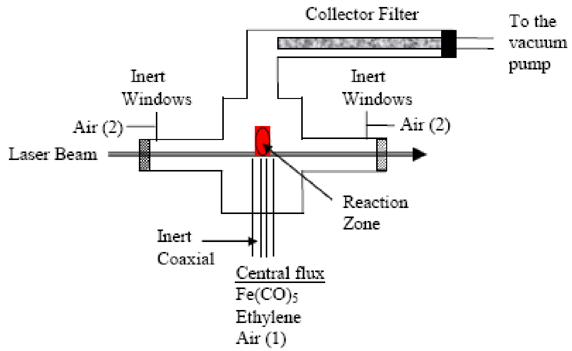


Increasing size as increasing precursor temperature and therefore the concentration of iron atoms in the reaction cell

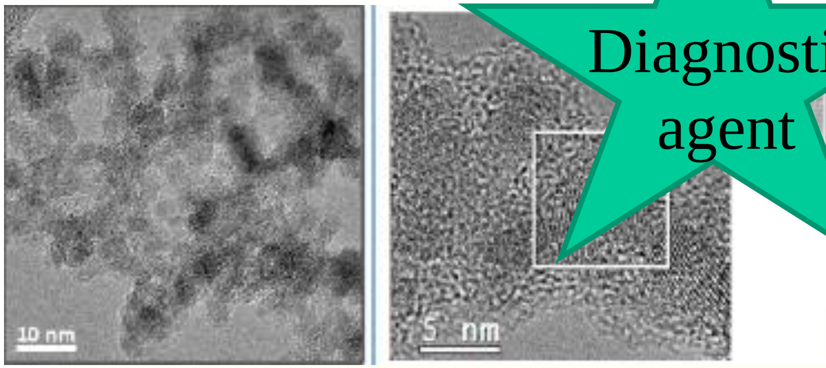
γ-Fe_2O_3 Nanoparticles with sizes between 3-5 nm

FP VI/ BONSAI: Bio-imaging with Smart Functional Nanoparticles

Preparation of magnetic iron oxide nanoparticles by laser pyrolysis



The Laser Pyrolysis technique enables the continuous production of uniform iron oxide nanoparticles induced by the fast laser heating of iron pentacarbonyl in an oxidant environment.



Diagnostic agent

< 5 nm

Acid treatment

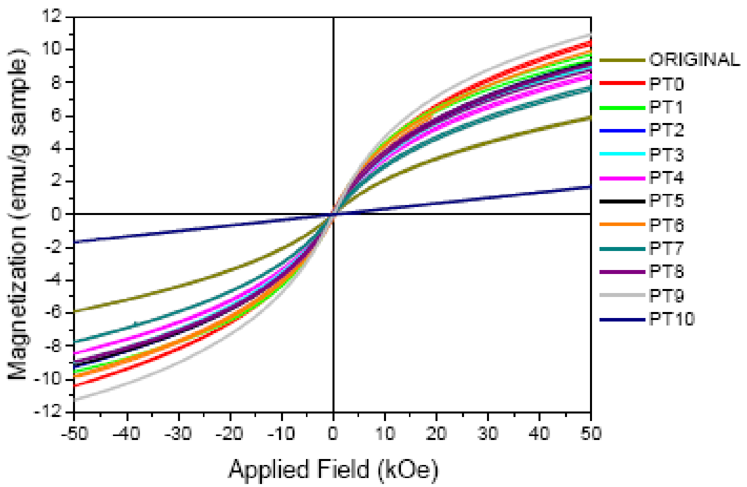


Figure 4.10: Magnetic curves at room temperature for all the samples. Sample named PT10 corresponds to PT10-30. . Sample PT11 presents a large amount of akaganeite and it has not been included in the graph.

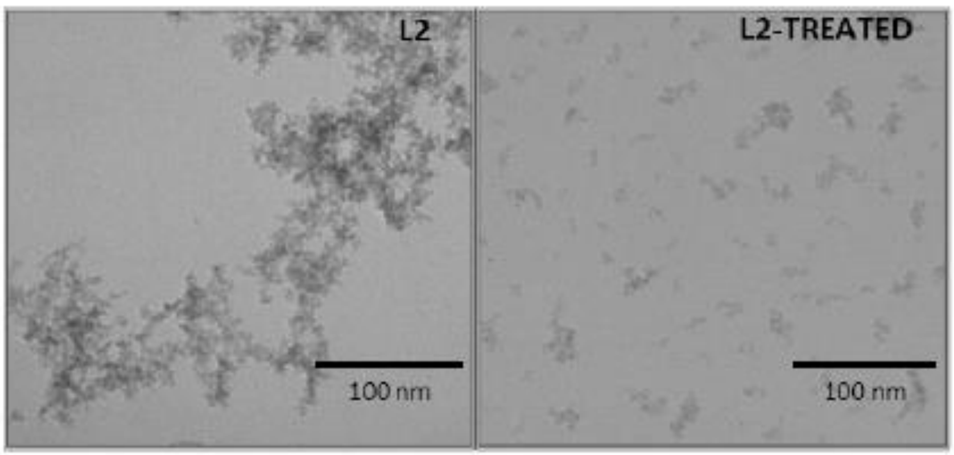


Figure 4.20: Low resolution TEM images of the original sample (L2) on the left and the sample after the acid treatment (L2-TREATED) on the right.

Costo et al. Langmuir 2012, 28, 178–185

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Surface Modification

Hydrophilic coating (polar - H_2O)

- ✓ Avoid aggregation
- ✓ Avoid no specific adsorption of proteins
- ✓ Low toxicity
- ✓ Selectivity
- ✓ Allow further functionalization

In general,
small, neutral, hydrophilic
=> Longer blood circulation times

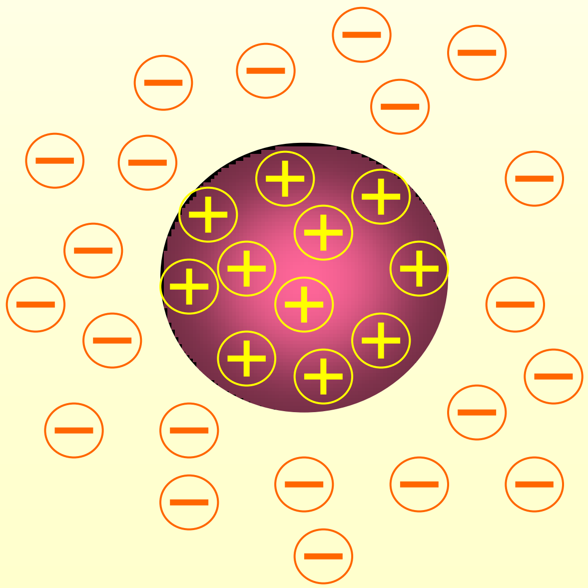
Electrostatic and Steric Stabilisation

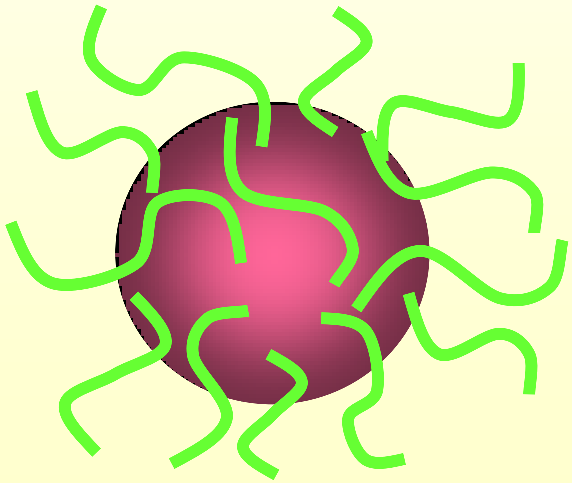
ELECTROSTATIC

- Easy to measure the controlling parameter (zeta potential)
- Reversible
- May only require change in pH or ion concentration

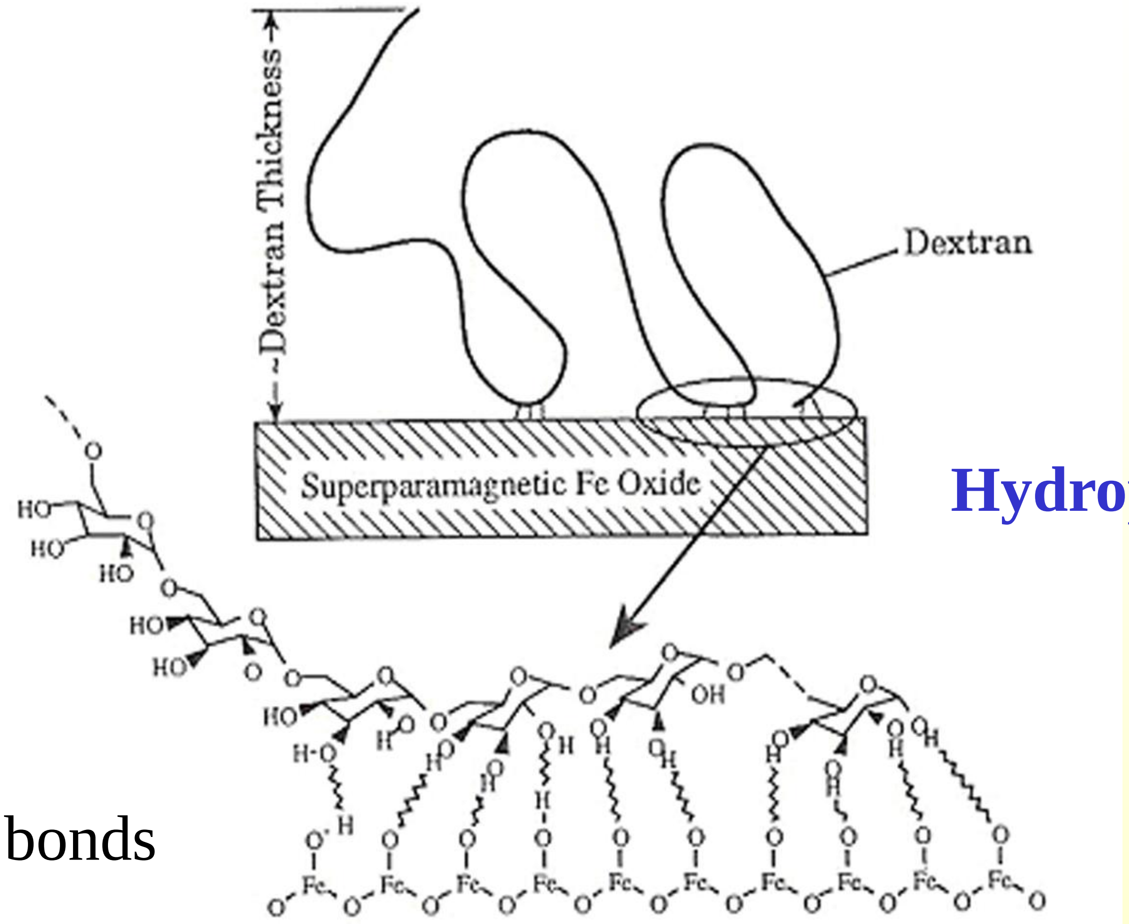
STERIC

- Simple, but limited options
- Irreversible
- An extra component





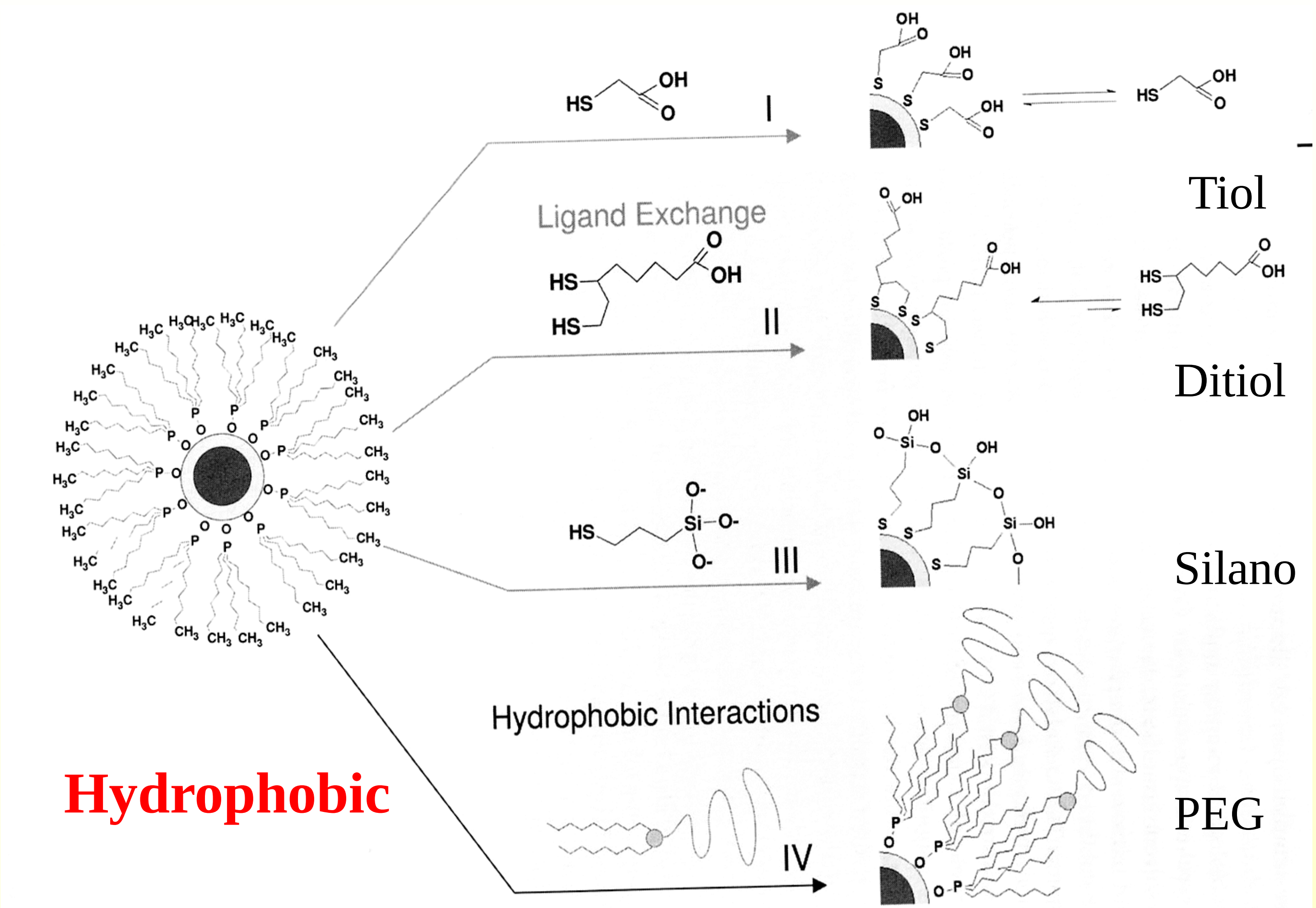
Adsorption



Hydrophilic

Hydrogen bonds

Ligand exchange or anphyphilic molecules



Hydrophilic

Small 2011, *7*, No. 22, 3113–3127

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Surface Modification

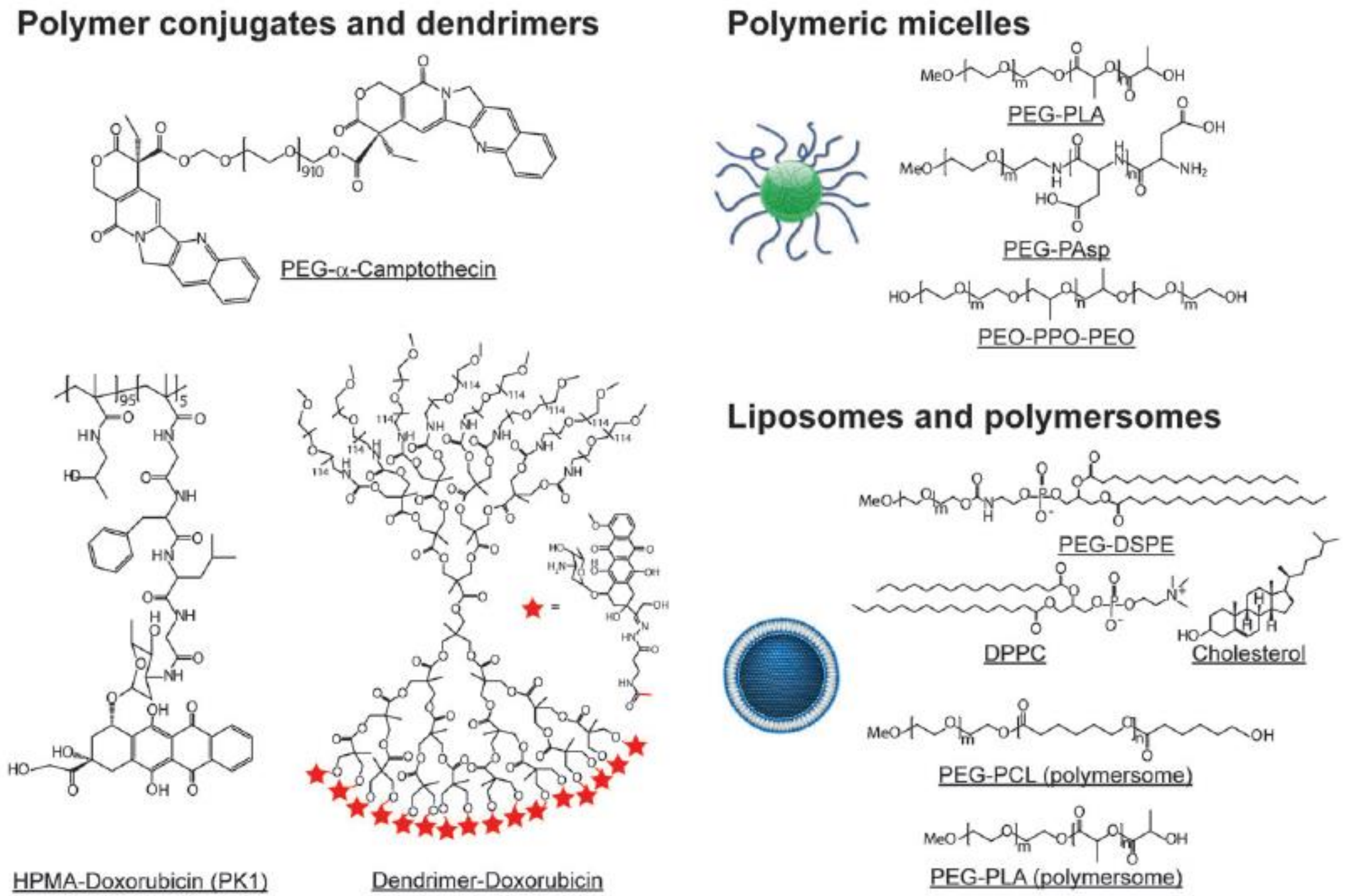


Fig. 4 Schematic illustration of chemical structures of representative polymer conjugates and dendrimers (*left*), polymeric micelles (*top right*), and liposomes and polymersomes (*bottom right*).

Biodegradable poly(D,L-lactic-*co-glycolic acid) (PLGA)*

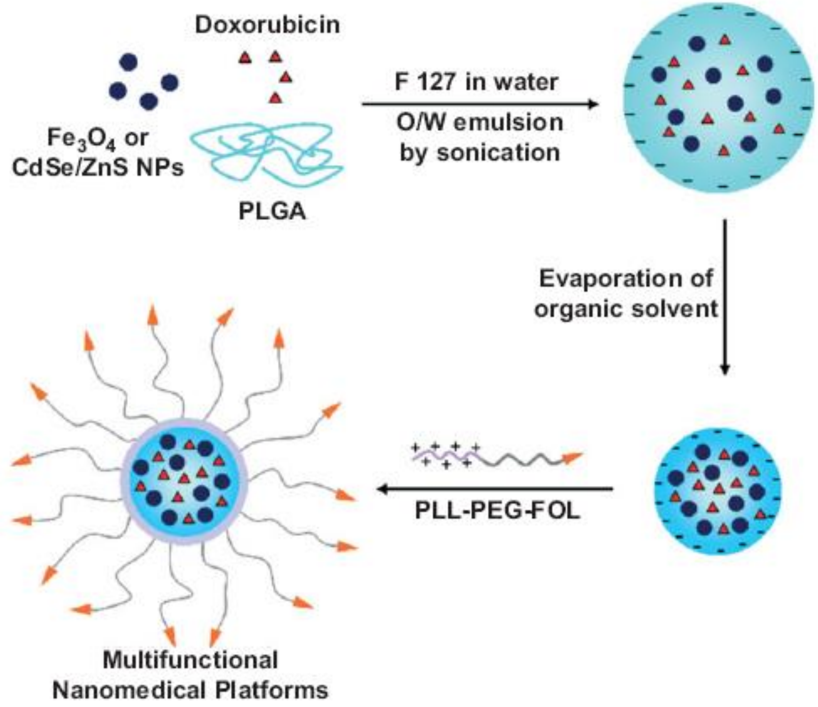


Figure 1. Synthetic procedure for the multifunctional polymer nanoparticles.

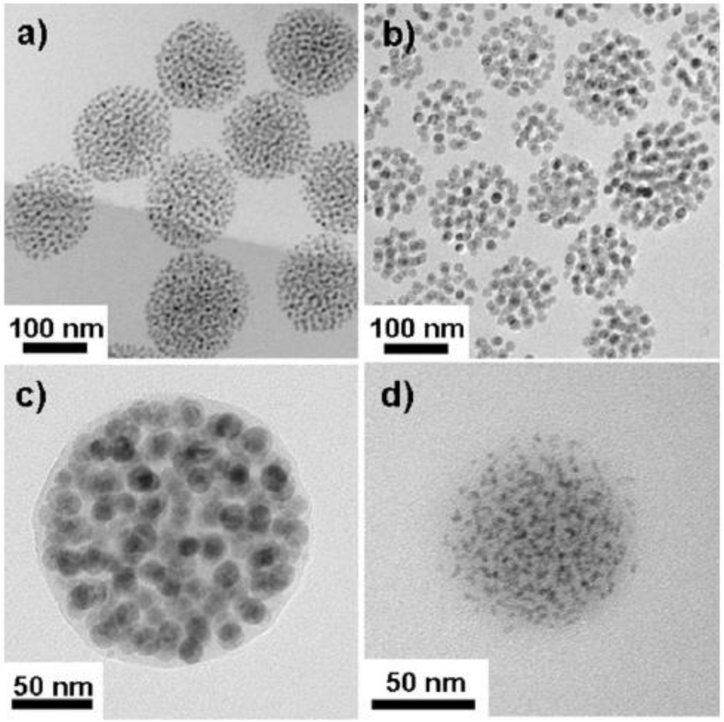


Figure 2. TEM images of PLGA(MNP/DOXO) nanoparticles embedded with a) 7-nm, and b), c) 15-nm Fe_3O_4 nanocrystals, and d) PLGA(QD/DOXO) nanoparticles embedded with 3-nm CdSe/ZnS nanocrystals.

Hydrophobic nanocrystals, DOXO, and PLGA in methylene chloride was poured into an aqueous solution containing F127, ultra-sonication, organic solvent was evaporated at room temperature by mechanical stirring and subsequently washed with deionized water several times.

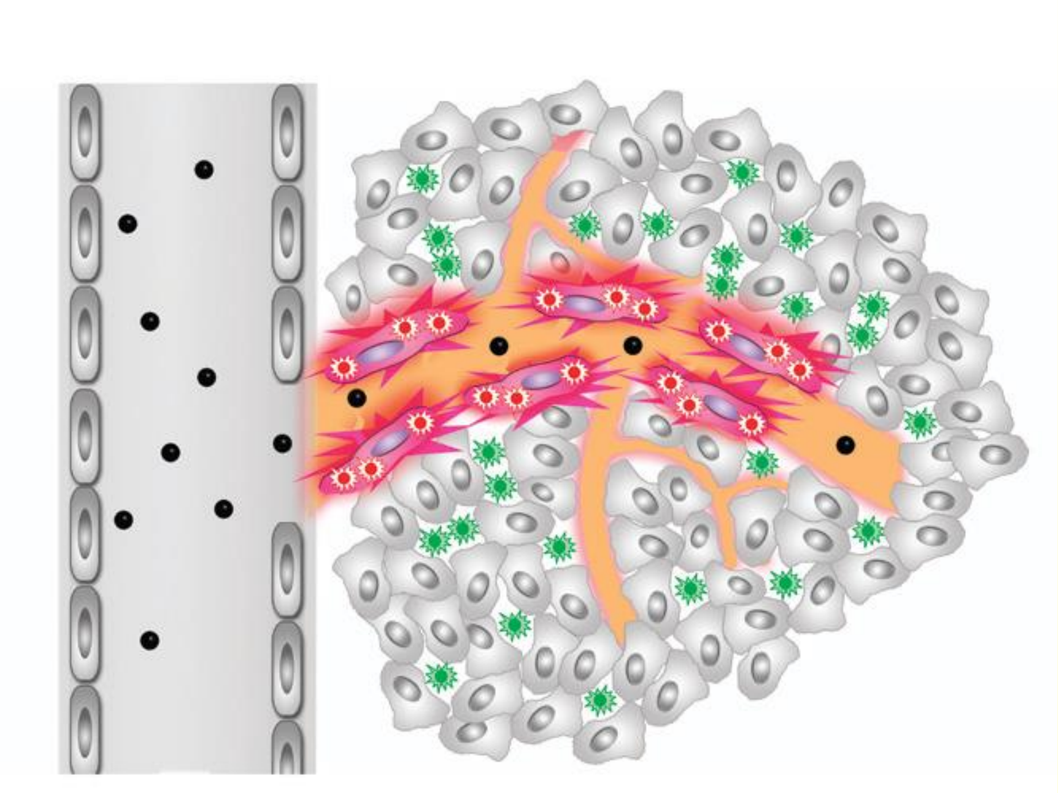
Adv. Mater. ***2008, 20, 478–483***

Surface Modification

Lighting up tumours : Detection of a wide range of tumours remains a challenge in cancer diagnostics.

pH-responsive polymeric nanomaterial

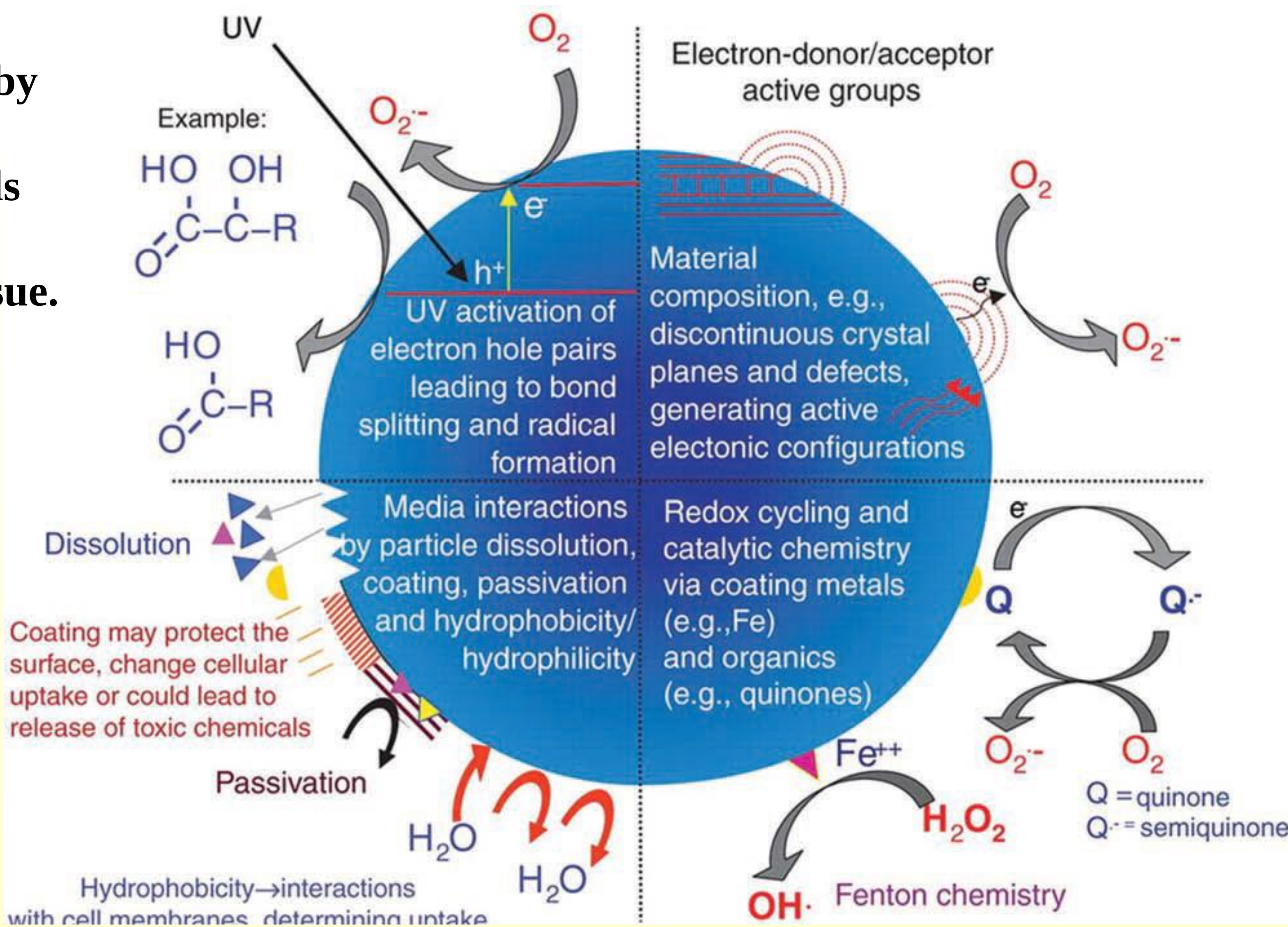
Highly fluorescent monomers within the acidic milieu of tumours (pHe, 6.5–6.8) or endocytic vesicles (pHi, 5.0–6.0) of the tumour endothelium.



PROBLEMS

- Nanoparticle-cell interactions
- Biodistribution

Possible mechanisms by which nanomaterials interact with biological tissue.

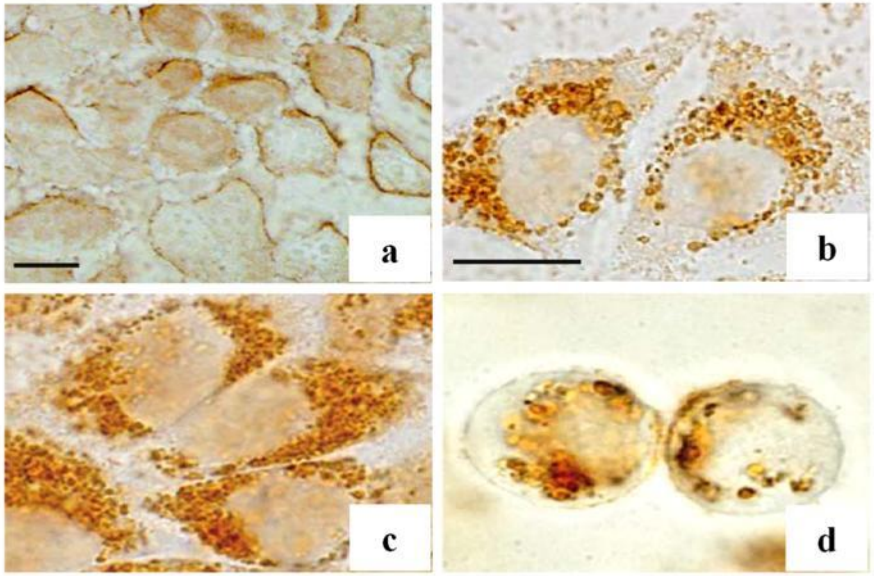


Material composition, electronic structure, bonded surface species (e.g., metalcontaining), surface coatings (active or passive), and solubility, including the contribution of surface species and coatings and interactions with other environmental factors (e.g., UV activation).

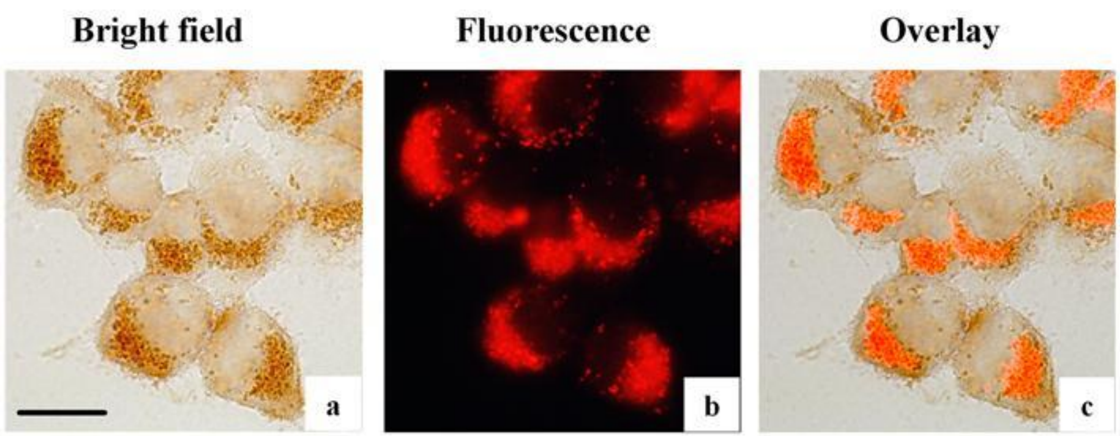
A. Nel , T. Xia , L. Mädler , N. Li , *Science* **2006** , *311* , 622 .

Interaction with cells

Internalization



In endocytic compartments



Lyso tracker red

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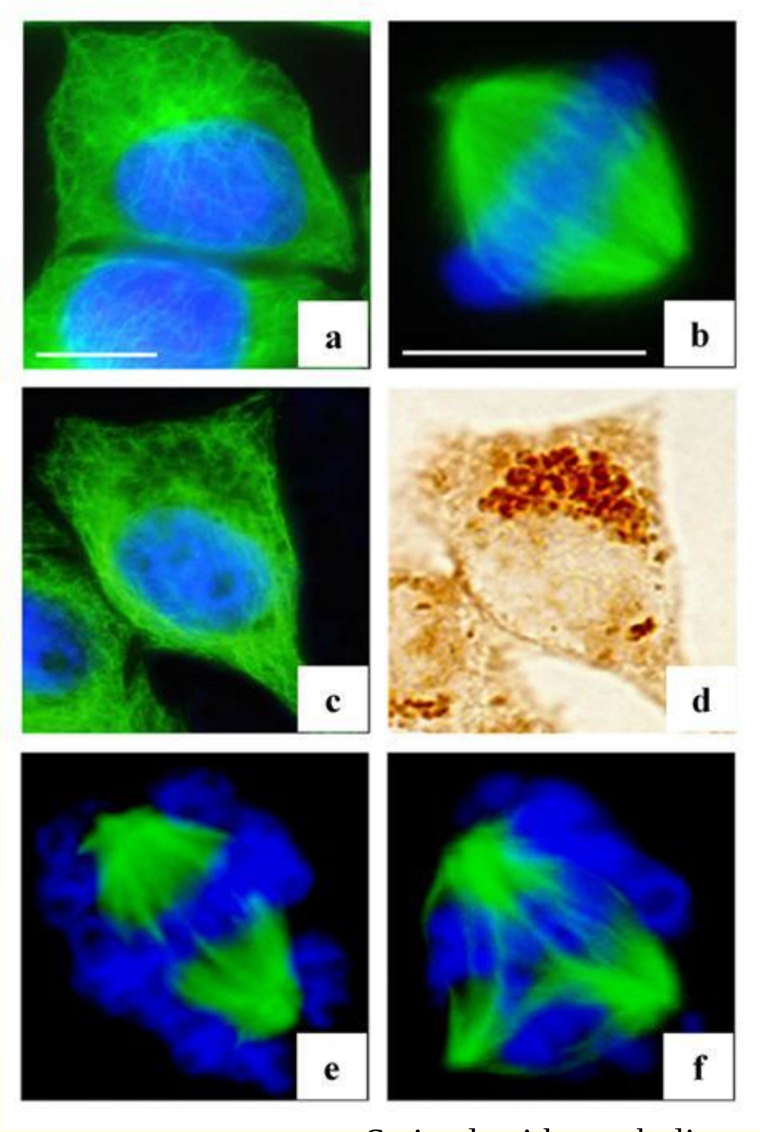
Cytotoxicity

Depending on the coating

Microtubules (green)
DNA (blue)



CONTROL

DMSA (-) , APS (+)

HEPARINE

Stained with α-tubulin

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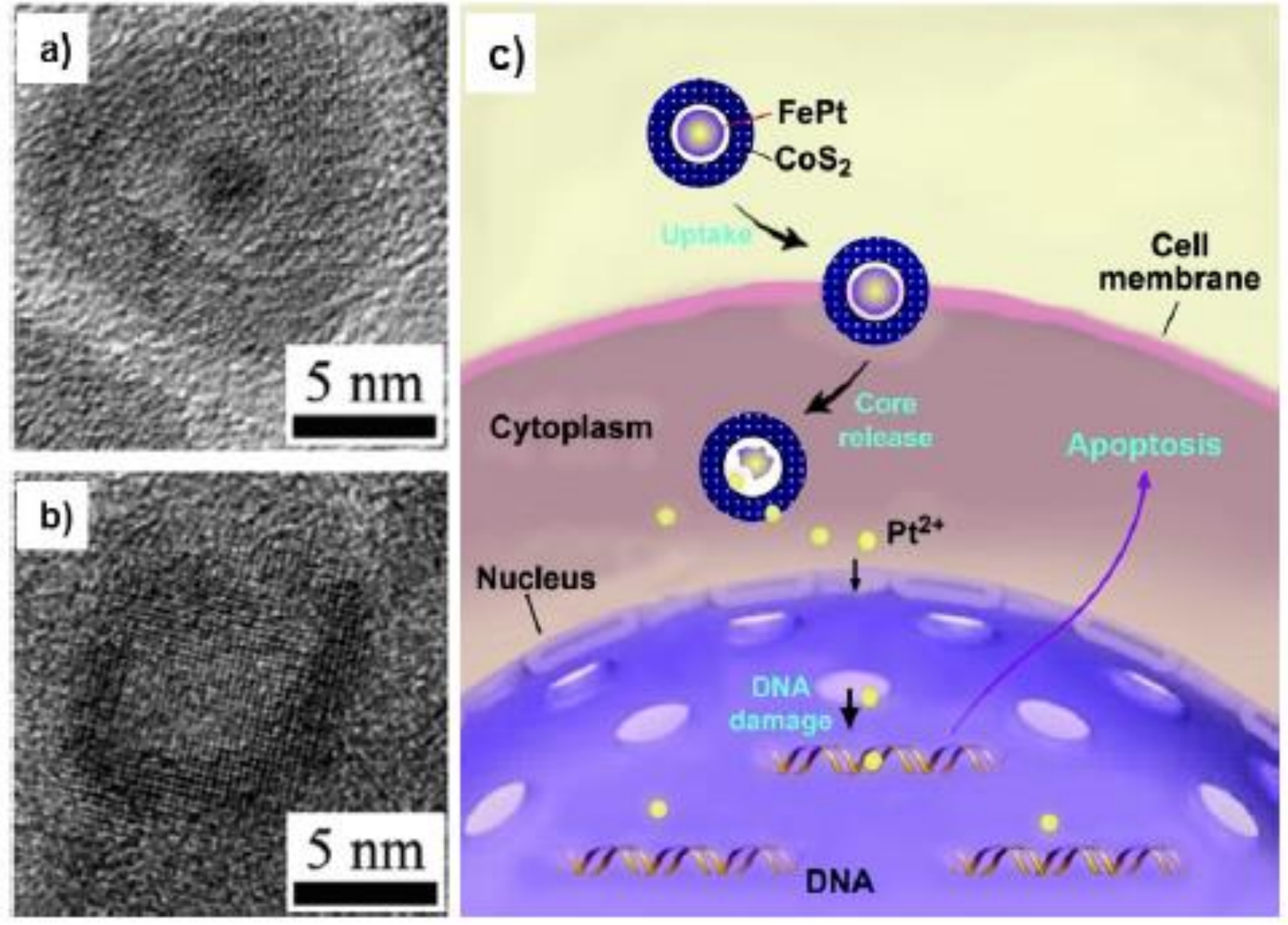
Interaction with cells

FePt@CoS2 yolk–shell nanocrystals dispersed in deionized water

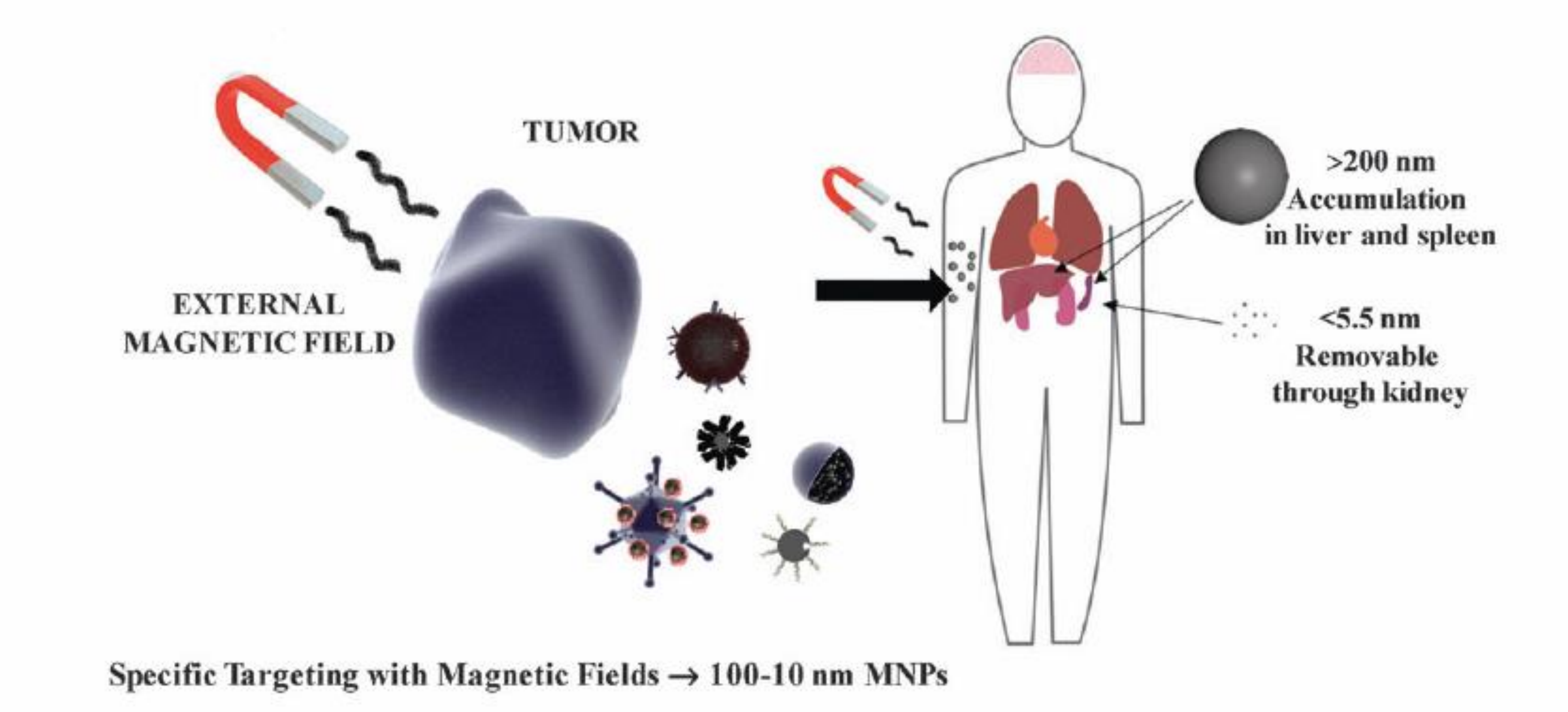
Hollow CoS2 nanocrystals without FePt cores are dispersed in the mitochondria after cell uptake.



After cellular uptake, FePt nanoparticles are oxidized to give Fe3+ and Pt2+ ions (yellow). The Pt2+ ions enter the nucleus and mitochondria, bind to DNA and lead to apoptosis.

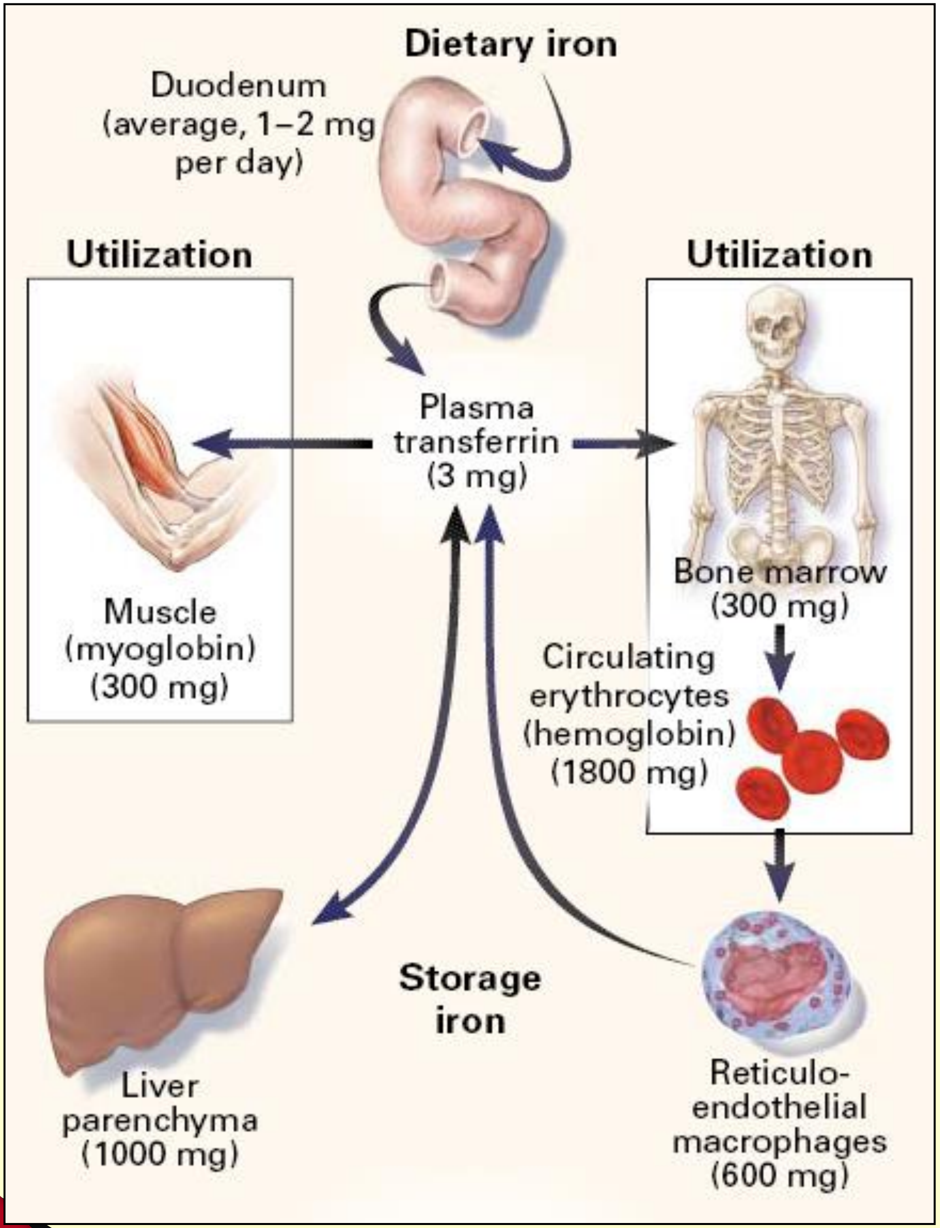
Gao J, Liang G, Zhang B, Kuang Y, Zhang X and Xu B 2007 . J. Am. Chem. Soc. 129 1428–33

Problem: Biodistribution



A SYSTEM FOR CONTROLLED LOCAL DRUG RELEASE IN CANCER THERAPY

Problem: Biodistribution



100 mg Fe => Endorem
(1-5 mg/Kg)

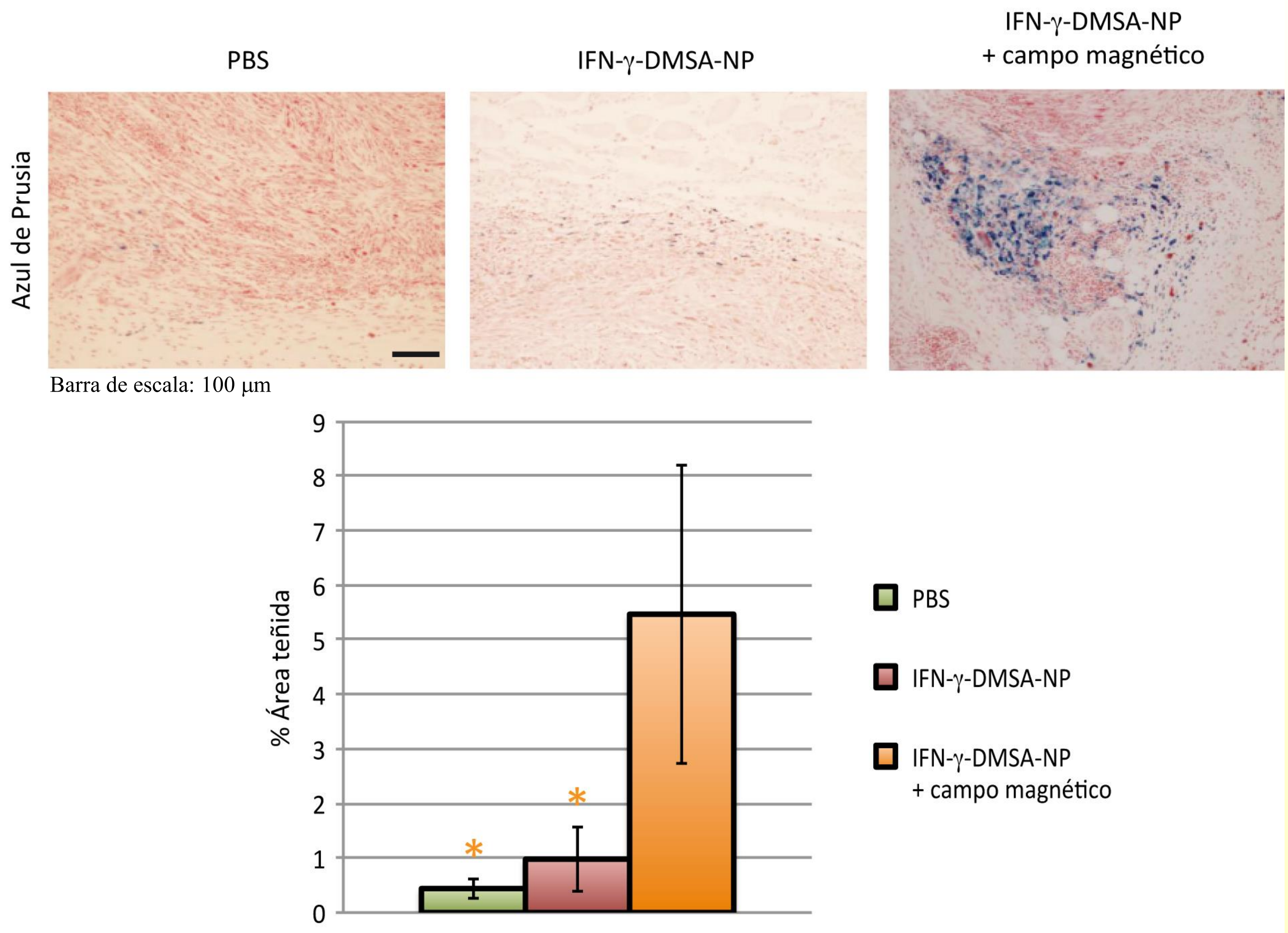
Distribution of Iron in Adults

NANCY C. ANDREWS

The New England Journal of Medicine
Volume 341 Number 26, 1986, 1999

Detection, identification and quantification of NP in biosystems

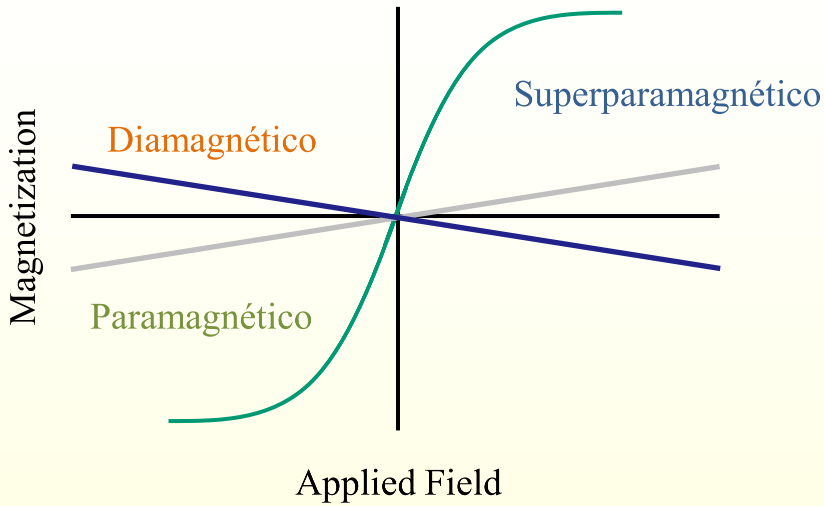
NP in the tissue
Prusian blue



Detection, identification and quantification of NP in biosystems

Magnetization curves

Magnetic methods



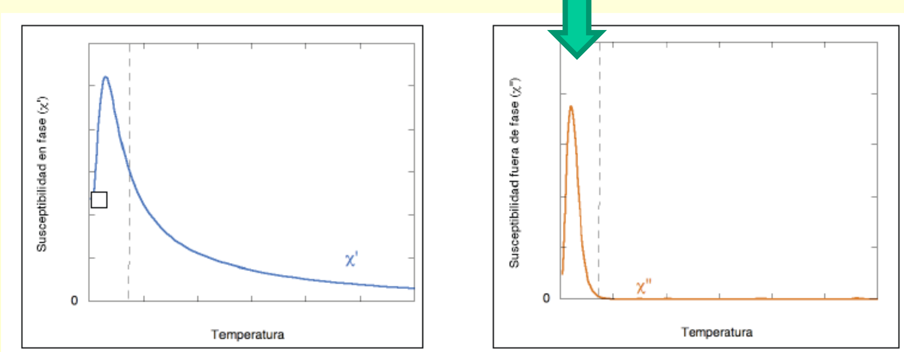
NP

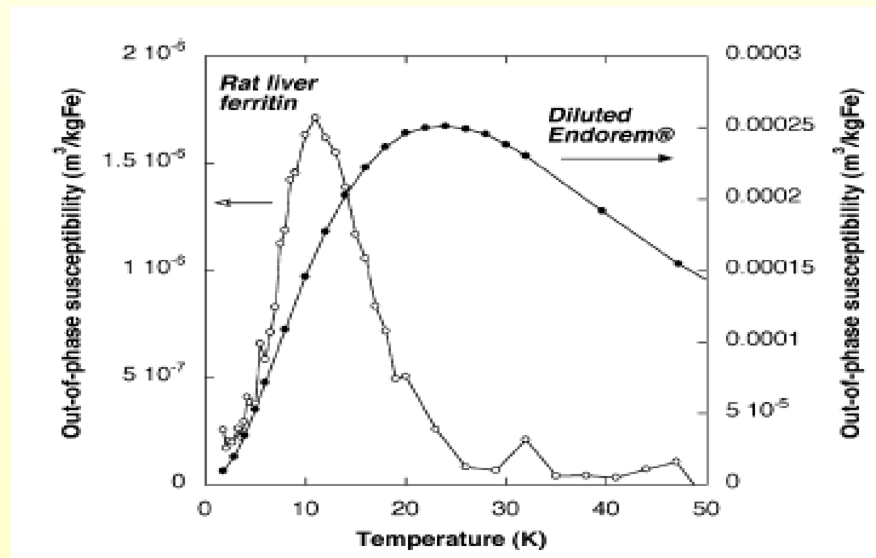
Ferritin, hemoglobine

Tissues…

AC Susceptibility

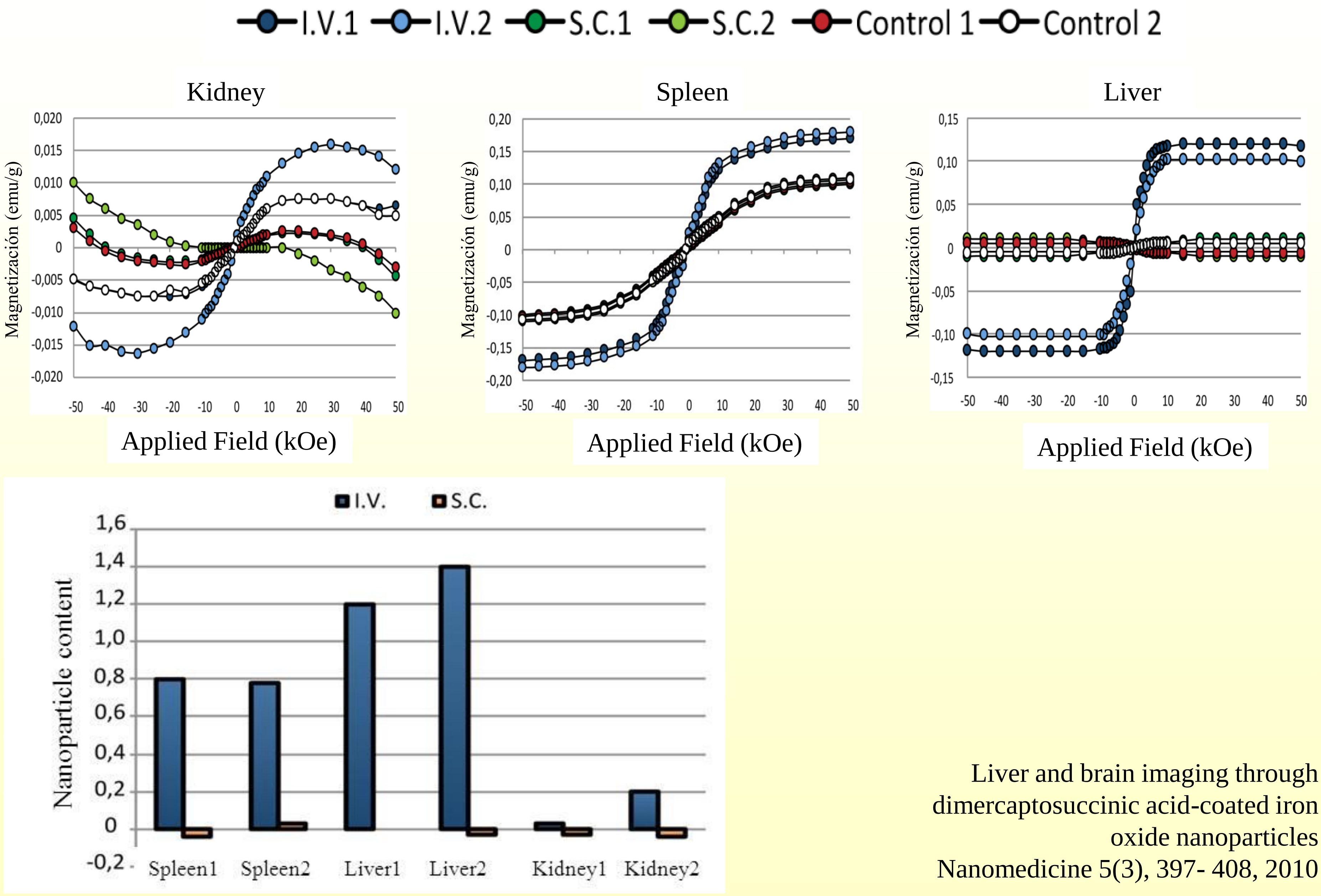
NP





Francisco Lázaro et al. 2007 J. Magn. Magn. Mater. 311 460–3

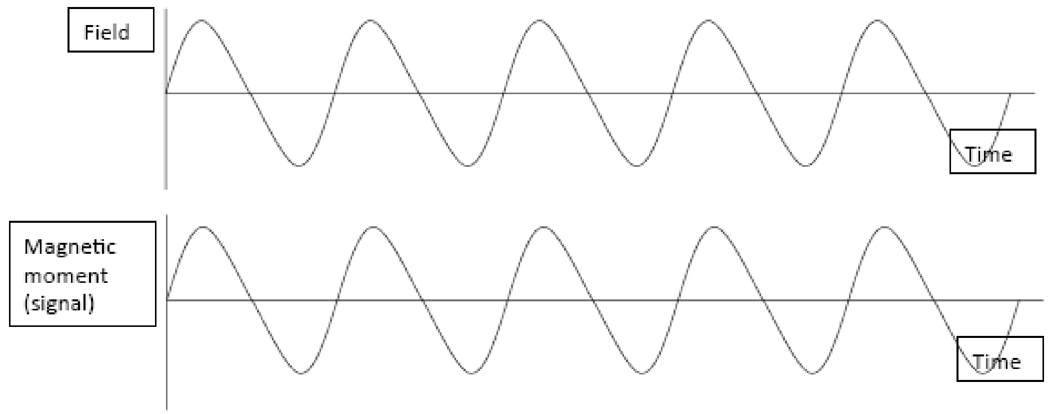
Detection, identification and quantification of NP in biosystems



Liver and brain imaging through dimercaptosuccinic acid-coated iron oxide nanoparticles
Nanomedicine 5(3), 397- 408, 2010

Detection, identification and quantification of NP in biosystems

AC Magnetic Susceptibility



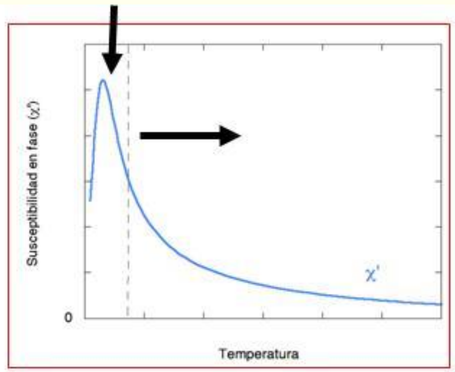
In-phase susceptibility (χ')

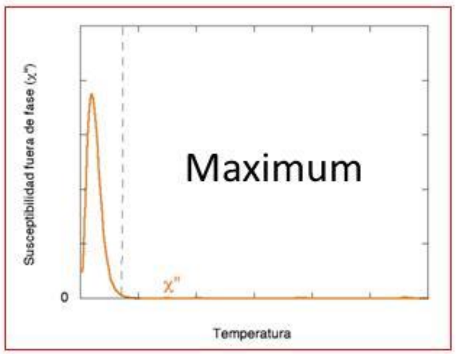
Out-of-phase susceptibility (χ'')

<u>Nanometric particles</u>

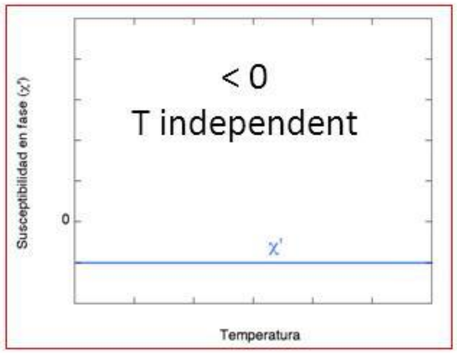
Hight Temperature: Curie Law

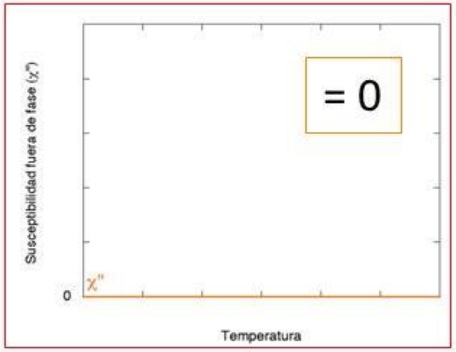
Low Temperature: Relaxation





<u>Diamagnetic contribution</u>





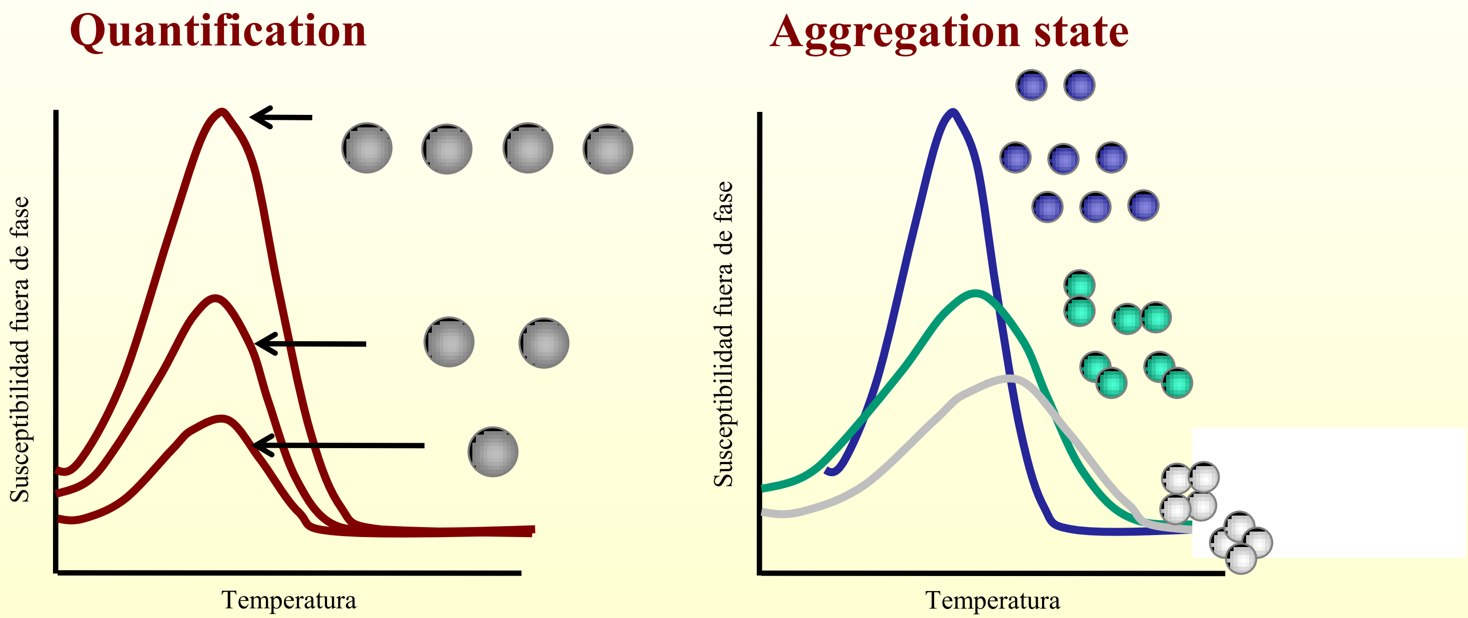
García-Palacios J.L., Advances in Chemical Physics (2000) 112, 1-210

Detection, identification and quantification of NP in biosystems

AC Magnetic Susceptibility

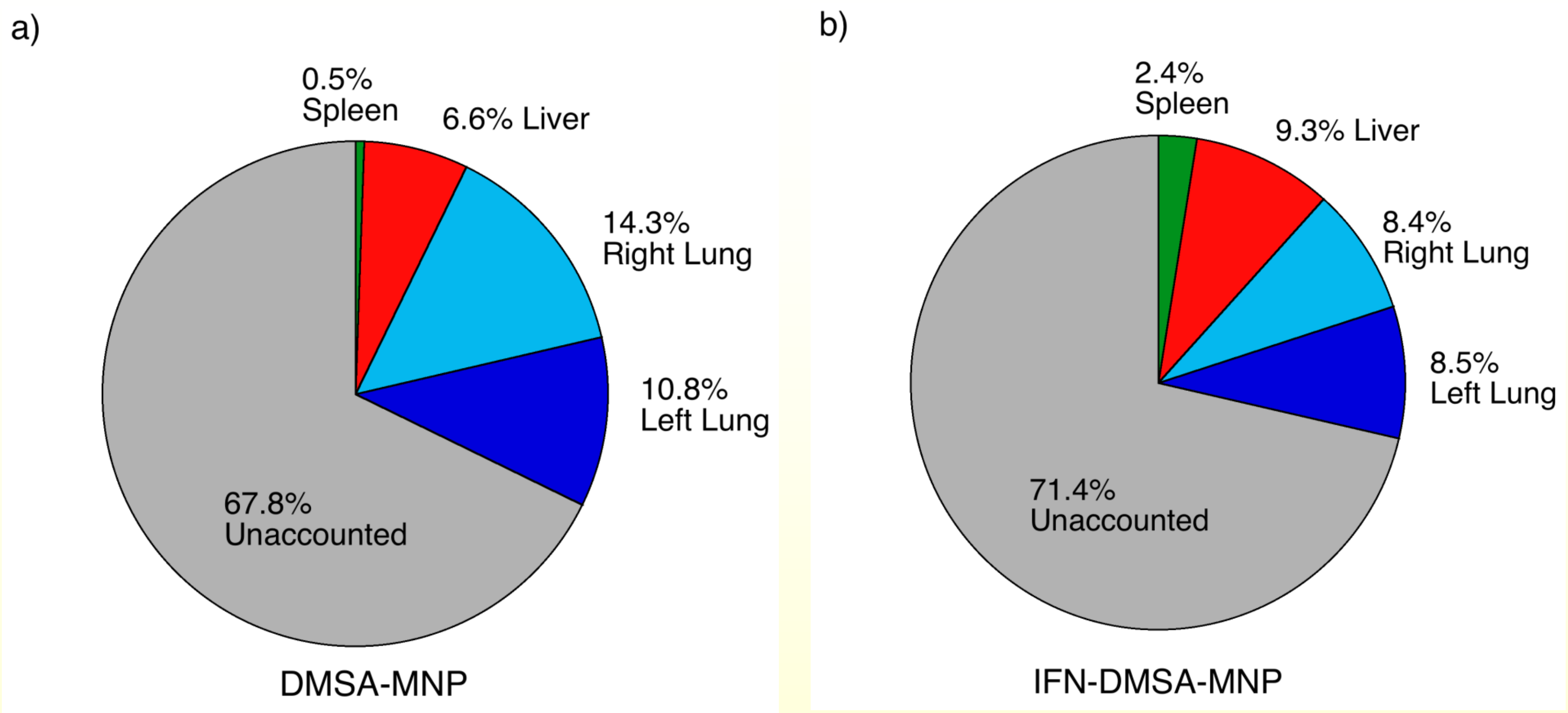
Out-of-phase susceptibility (χ'')

Size, Crystallinity, Aggregation



With the appropriated standards it is possible to calculate the amount of the total iron that is in the form of the magnetic nanoparticles.

Detection, identification and quantification of NP in biosystems



Percentage of the magnetic nanoparticles from the last MNP administration found in each organ. Values have been calculated from the total amount of iron found in each whole tissue in the form of MNP and the total amount of injected iron in the last administration.

AC Magnetic susceptibility study of in vivo nanoparticle biodistribution,
Gutierrez et al. Phys. D: Appl. Phys. 44 (2011) 255002

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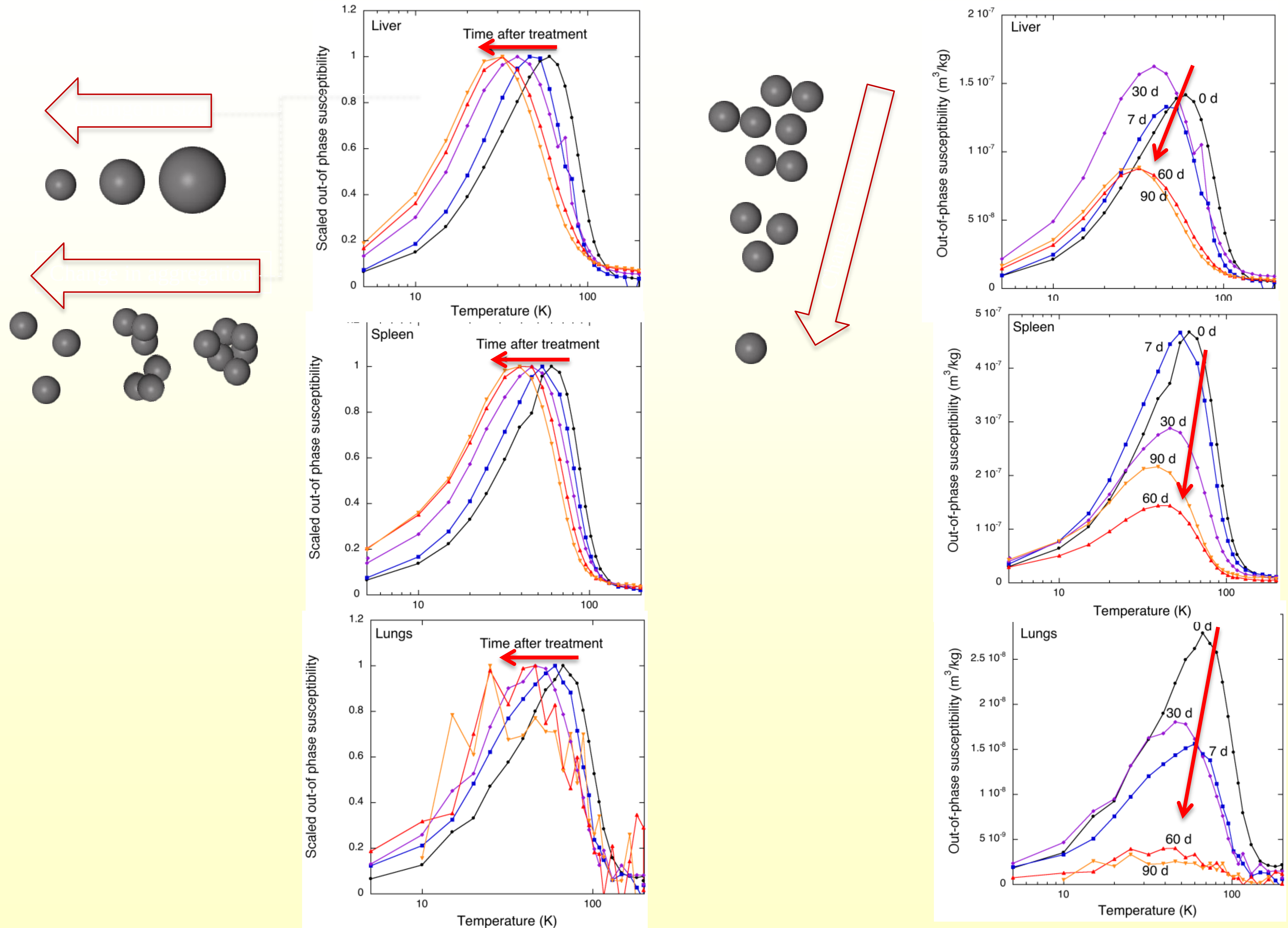
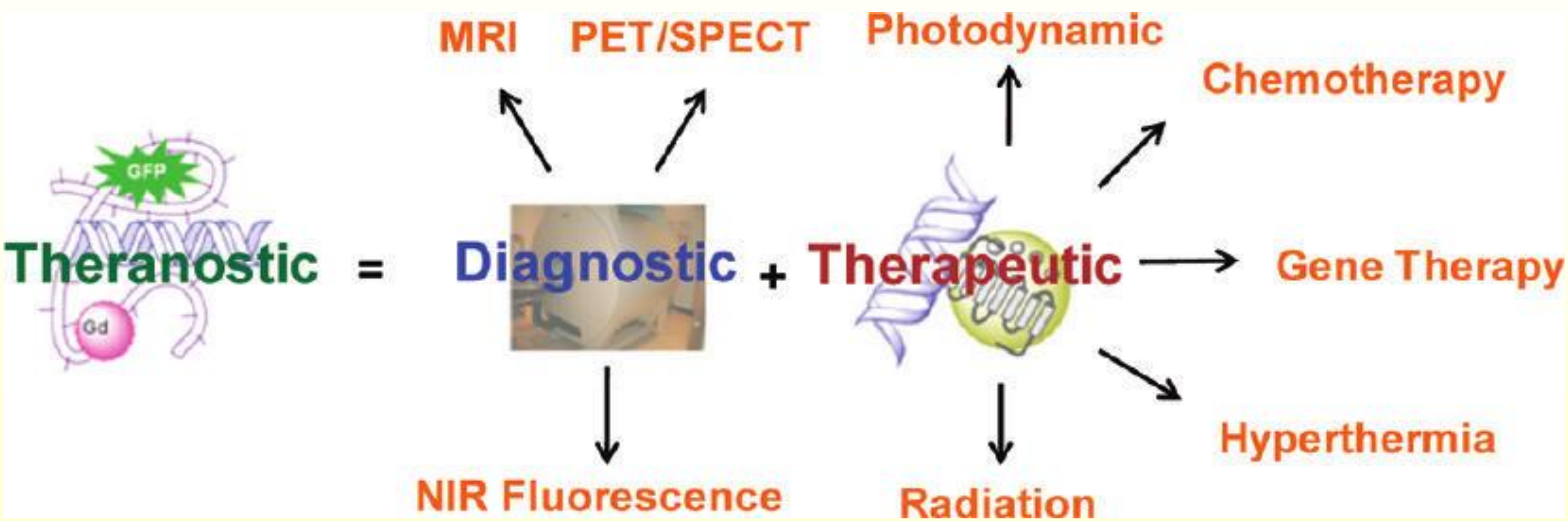
Long term particle transformations



Ideal

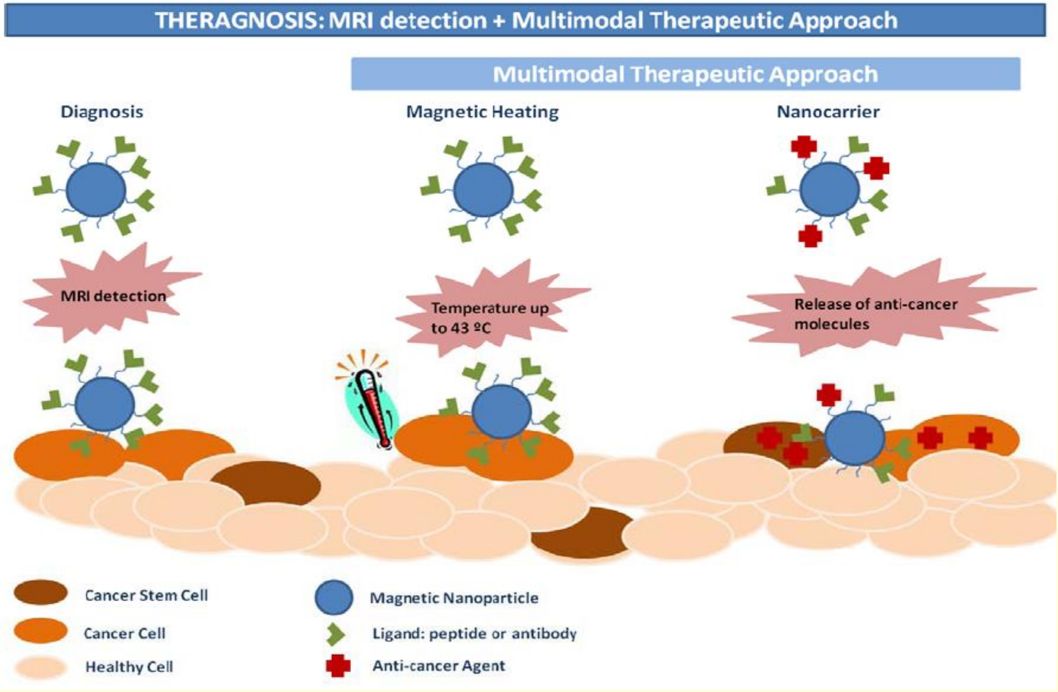


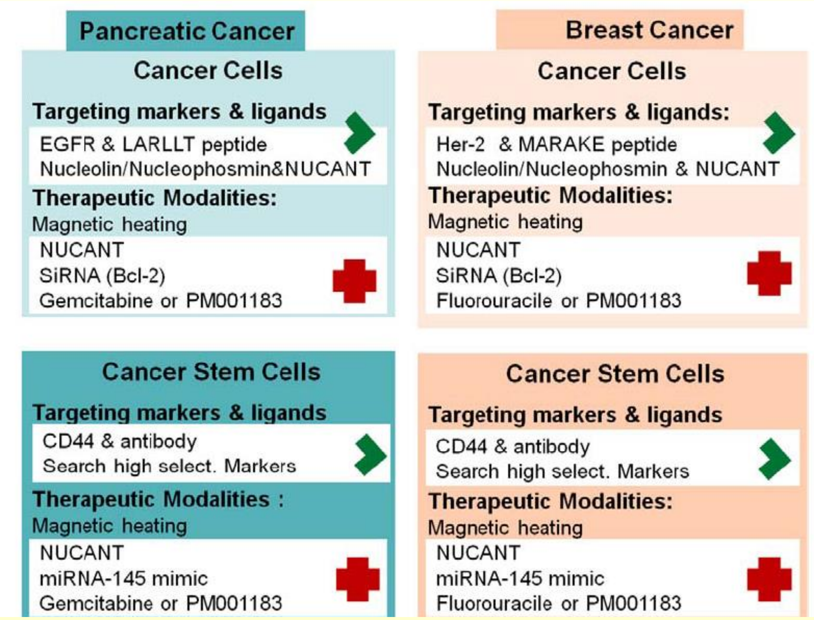
Bioconjugate Chem. 2011, 22, 1879–1903

FP VII/ MULTIFUN: Multifunctional nanotechnology for selective detection and treatment of cancer

multifun

> 10 nm





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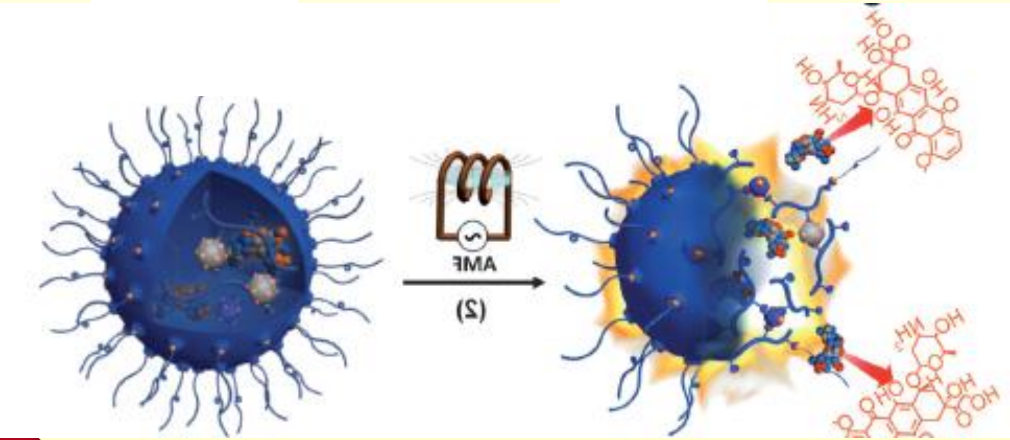
MAIN THEMES TACKLED IN MULTIFUN

- **Large scale production** of biocompatible iron oxide nanoparticles with optimal magnetic features.
- Functionalization of nanoparticle for **selective targeting** and for carrying different anticancer agents (i.e. drugs, sRNA, peptides)
- Implementation of **multimodal nanoparticle-based therapeutic** approach by combining heating capabilities and anticancer agents.
- **Toxicity and biodistribution** of nanoparticles in animal models (mice and pigs).
- Development of new **equipments for heat treatment and the detection-**quantification of nanoparticles in tissues, blood and urine.

Combine hyperthermia and drug delivery



J. Cheon *Ang. Chem. 2013*

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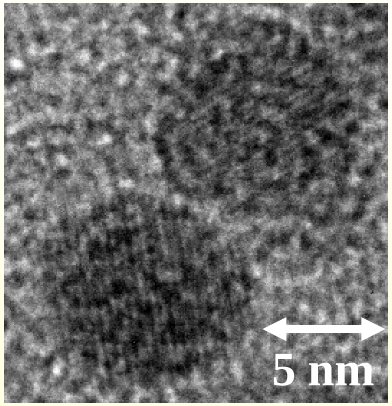
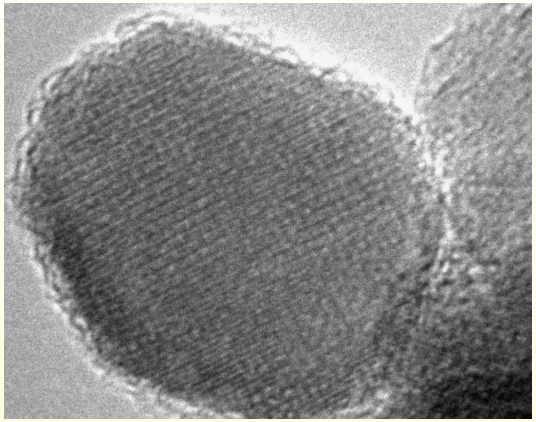
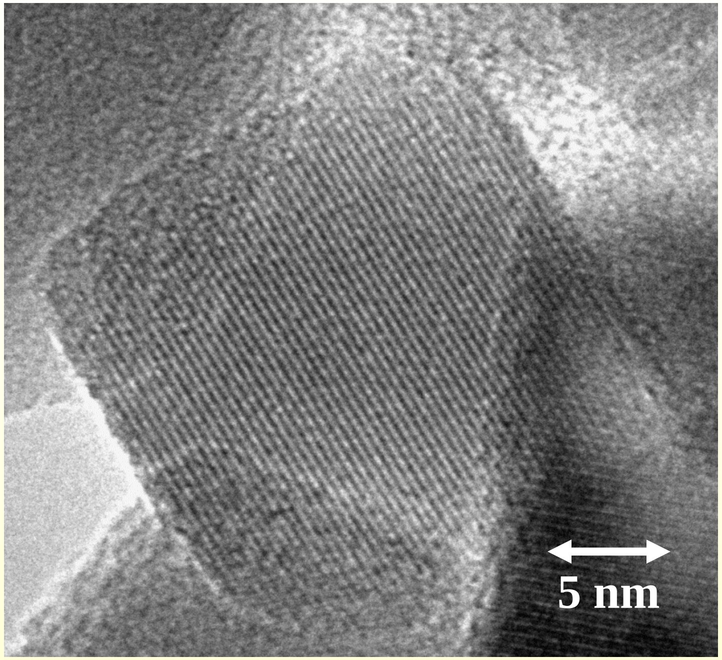
NANOPARTICLES AND NANOCRYSTALS OF IRON OXIDE

NANOPARTICLES





NANOCRYSTALS



High surface energy
Round shapes

MORE ORDERED

Lower surface energy
Less rounded shapes

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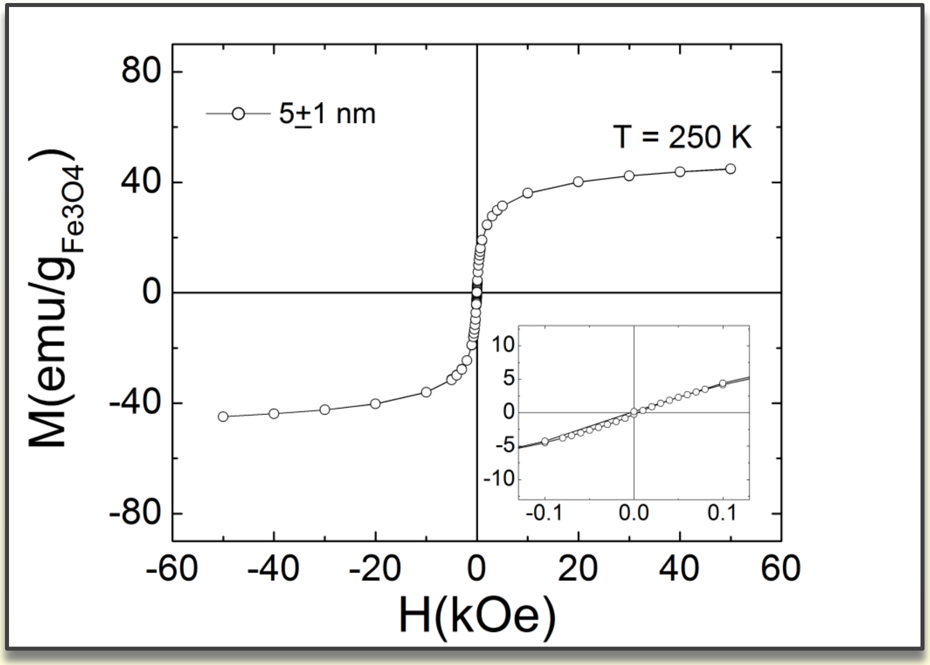
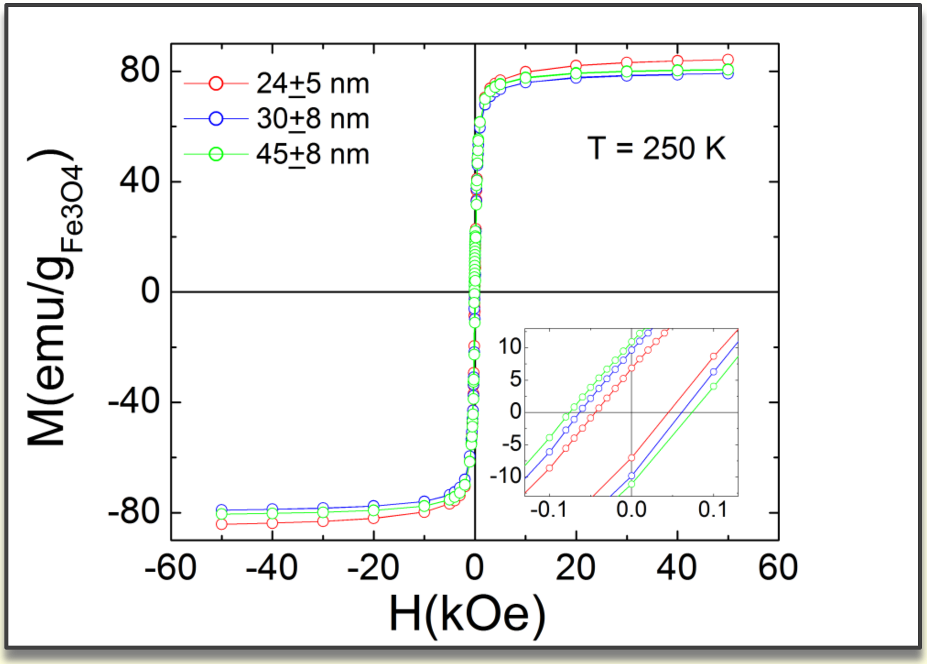
NANOPARTICLES AND NANOCRYSTALS OF IRON OXIDE



Nanoparticles

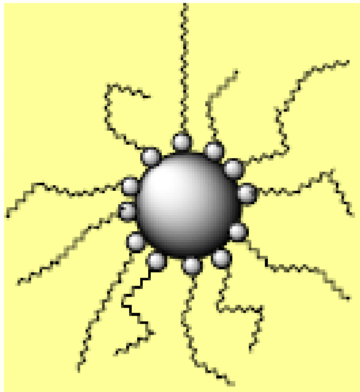


Nanocrystals

BETTER MAGNETIC RESPONSE

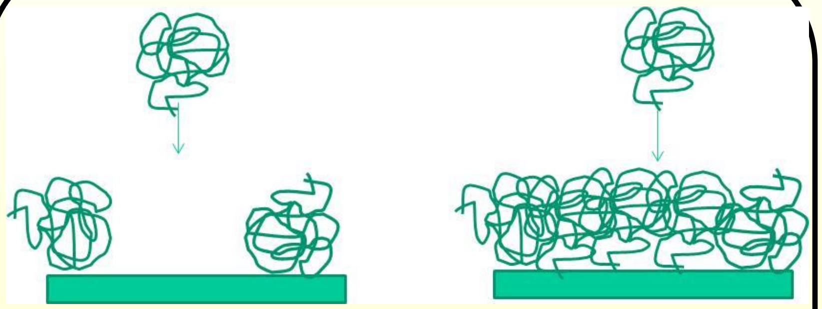
Maximum Heating efficiency and NMR contrast

LONG CIRCULATING AGENTS = POLYMERS = PEG

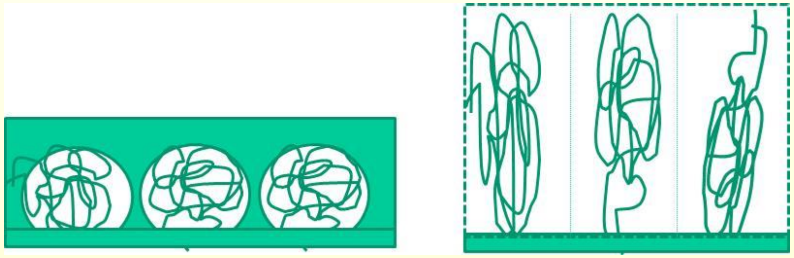


PROBLEMS

Polymerizability
End-group reactivity
Aggregation/Stability



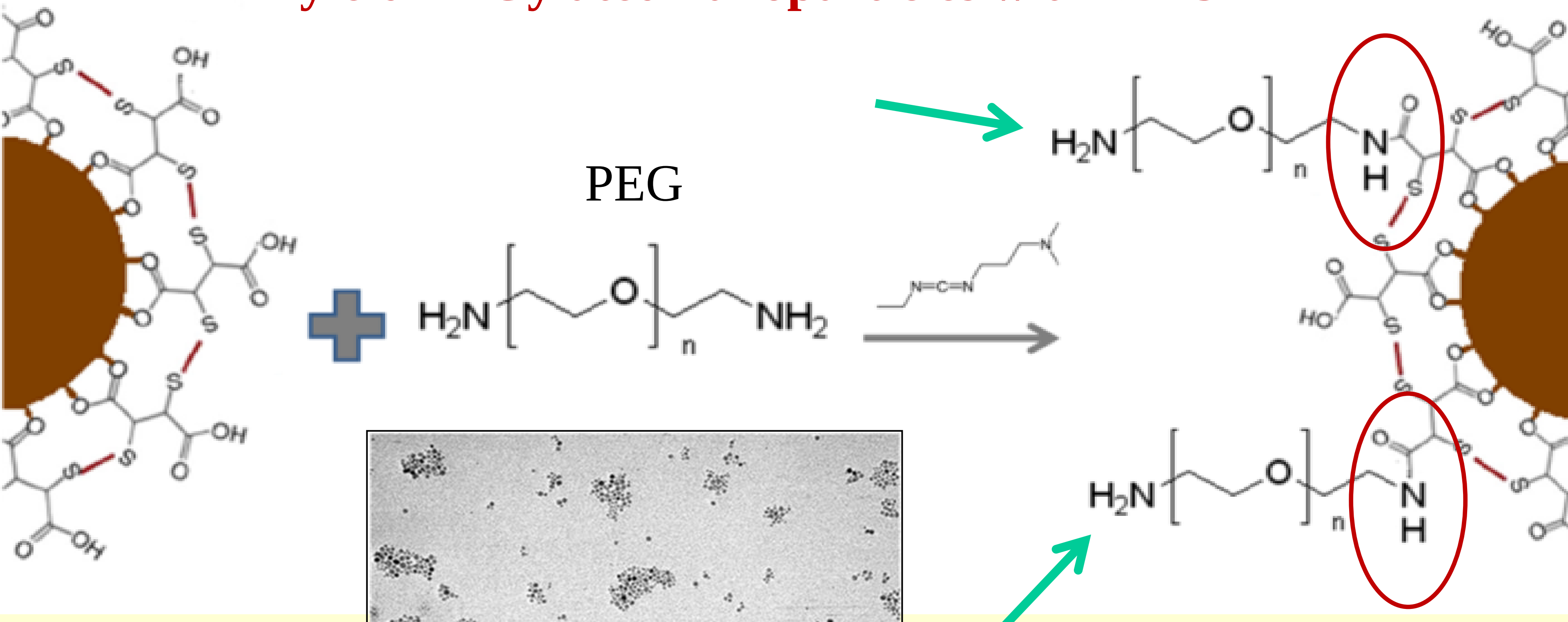
Grafting Density
(in the case of NPs
depend on geometry)

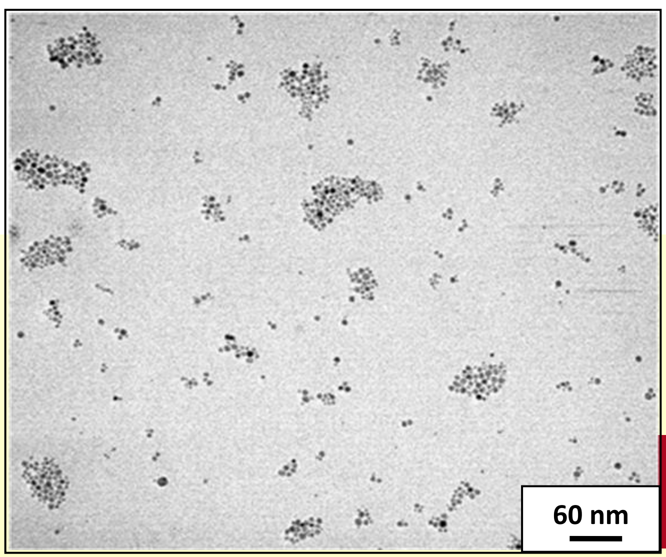


Conformations of
surface-attached polymers

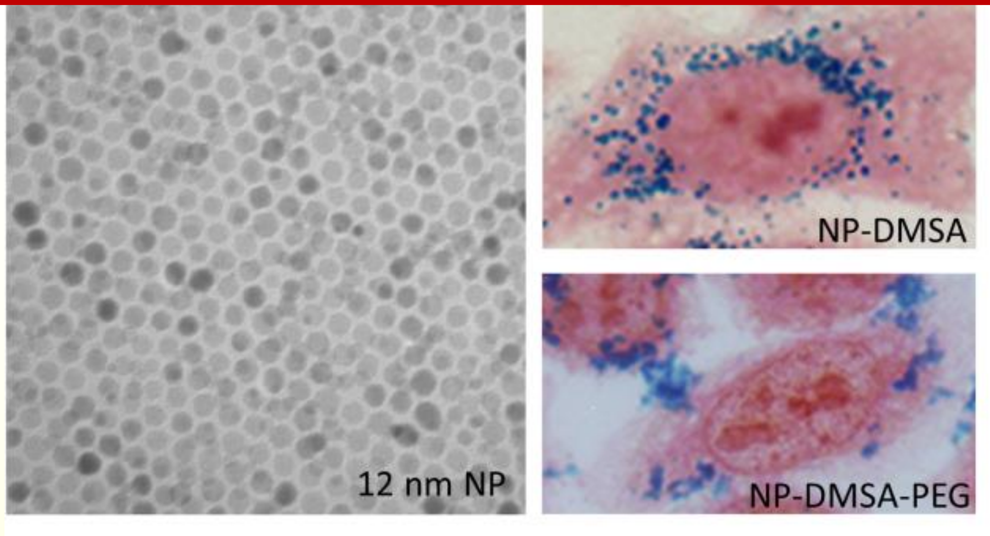
LONG CIRCULATING AGENTS = POLYMERS = PEG

The different amine functionalized PEGs were attached to NP(Fe)-DMSA via EDC-mediated coupling reaction to yield PEGylated nanoparticles with DMSA





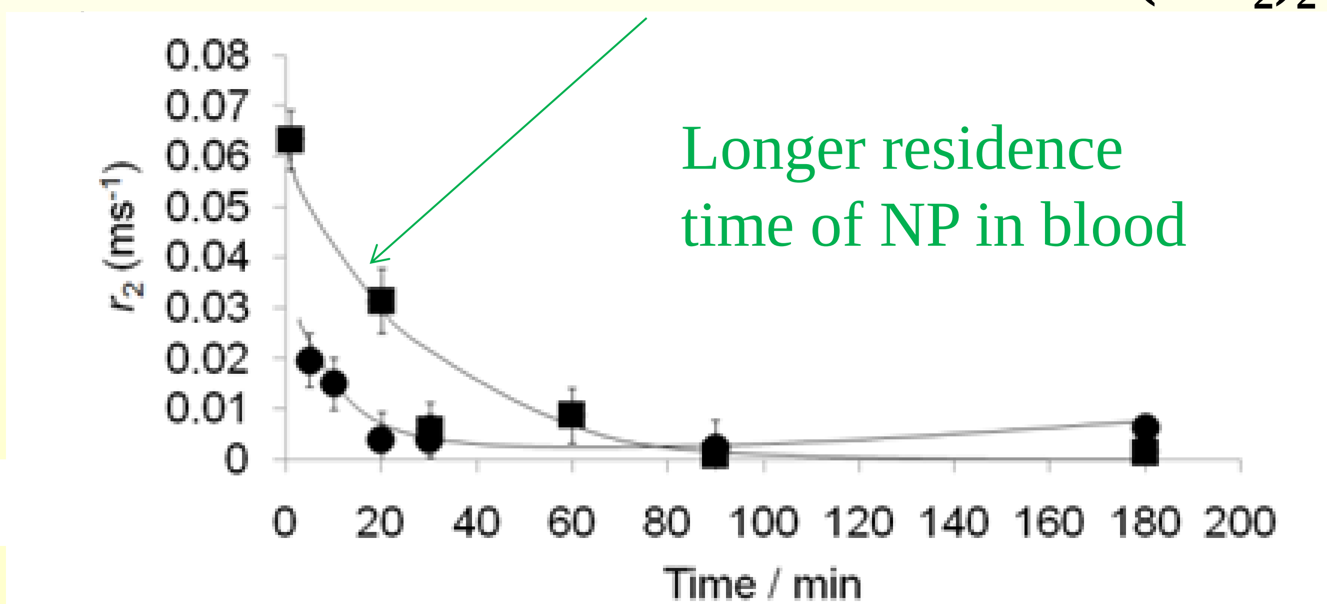
LONG CIRCULATING AGENTS



No cell uptake

NP-DMSA-PEG-$(NH_2)_2$

Longer residence time of NP in blood



A. Ruiz, et al., Nanoscale, 2013, 5, 11400–11408

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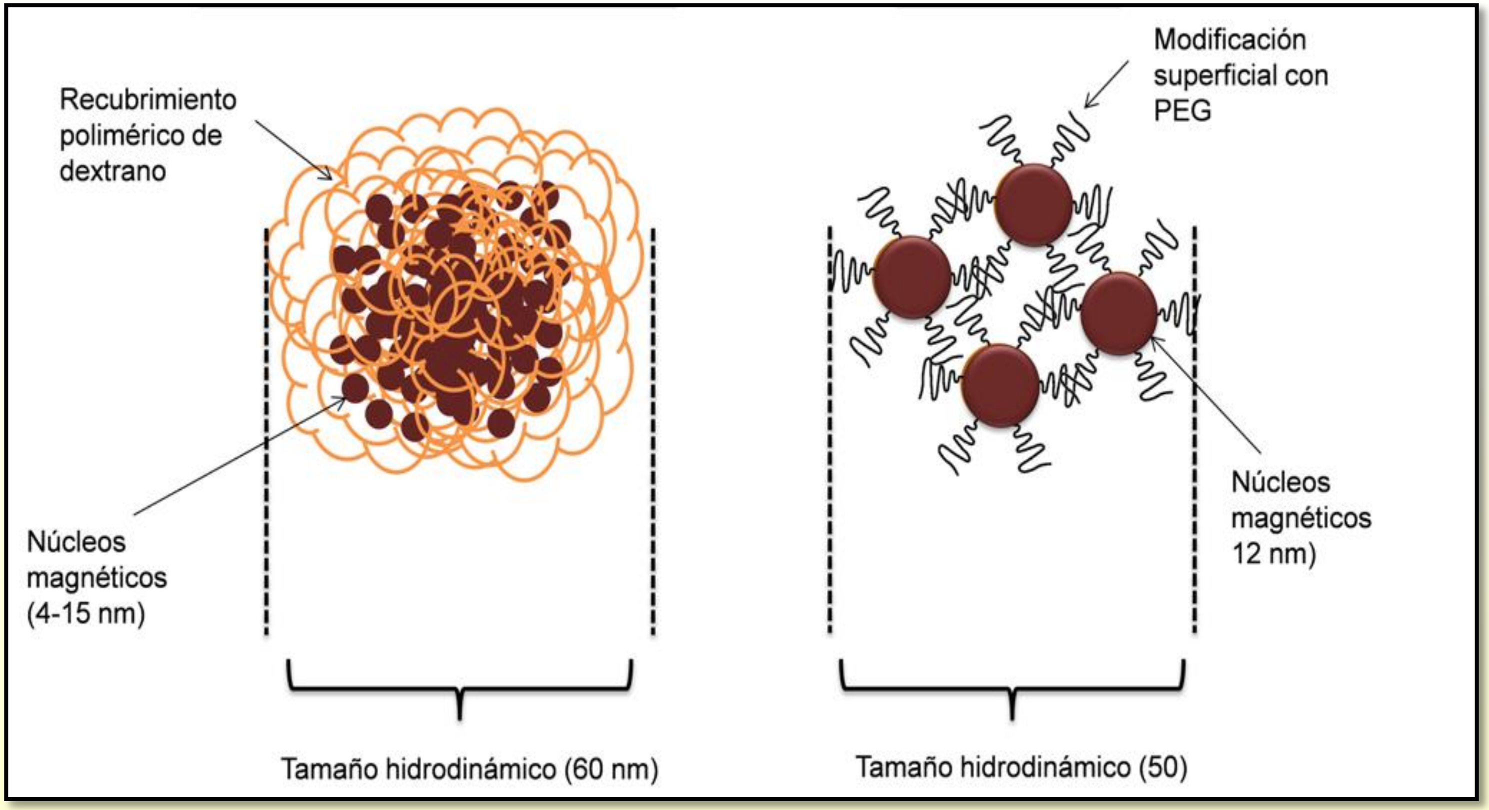
NanoMag:

Nanometrology Standardization Methods for Magnetic Nanoparticles (Nov 2013-2017)



The NanoMag project is to improve and redefine existing analyzing methods and in some cases, to develop new analyzing methods for magnetic nanostructures.

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CONCLUSIONS

- **Magnetic nanoparticles could help to improve clinical practice in the treatment of cancer**, most probably in synergy with other conventional treatments. Significant advances in the field have been made.

- There already exist methods to obtain magnetic nanoparticles with the appropriate properties, bearing in mind that these **properties must be optimized** to suit the magnetic field and application frequency that will be used.

- We have to developed not only magnetic nanoparticles with **good heating capacities**, but also with good colloidal properties, **long blood circulation time** and grafted ligands able to facilitate their specific internalization in tumor cells.

- More systemic and **long-term toxicological studies** are required before the translation of any nanoprobe to clinical adaptation.

- **Other applications of magnetic nanoparticles** are in gene therapy and cell labelling for tissue regeneration.

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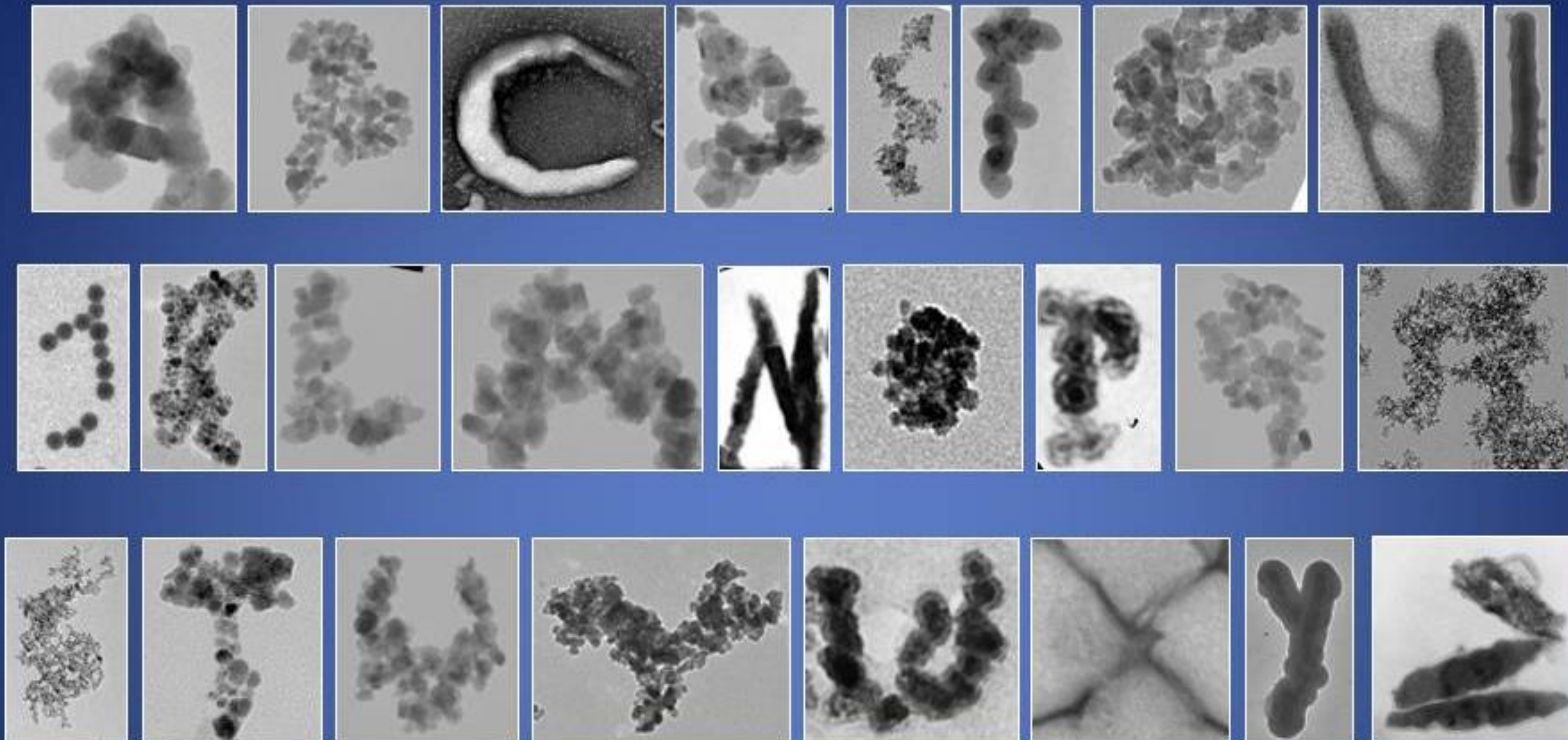

Gracias por vuestra atención

Pictures by: M. P. Morales[1], A. G. Roca[2], M. Ibrahim[3], © L. Gutiérrez[1,3]

[1]Insituto de Ciencia de Materiales de Madrid ICMM-CSIC, Spain, [2]The University of York, UK, [3]The University of Western Australia, Australia, 2012