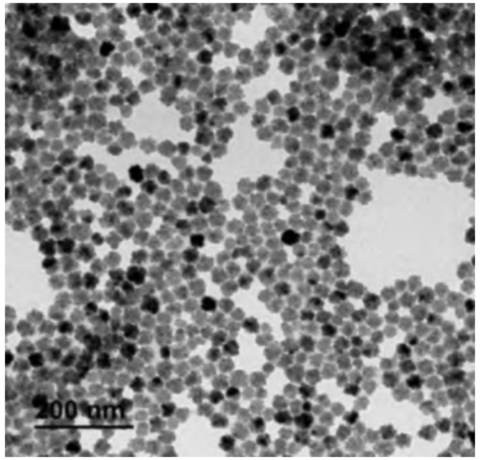
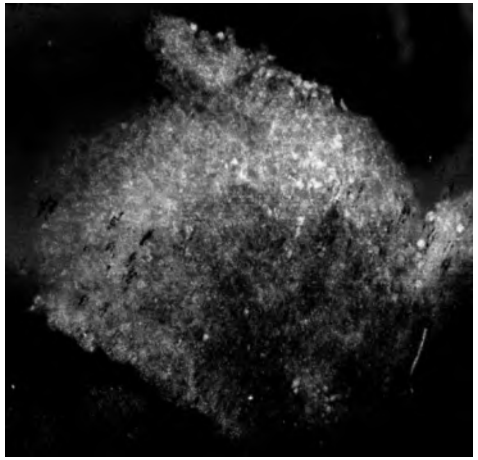
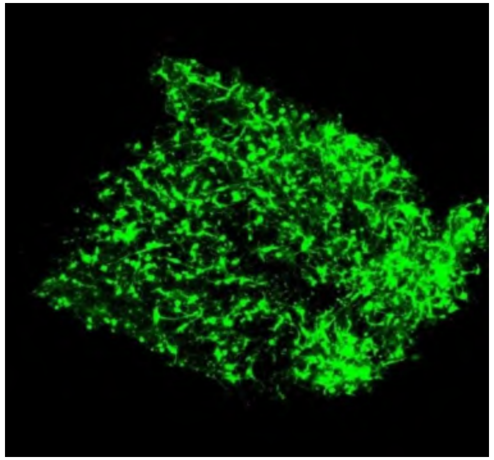
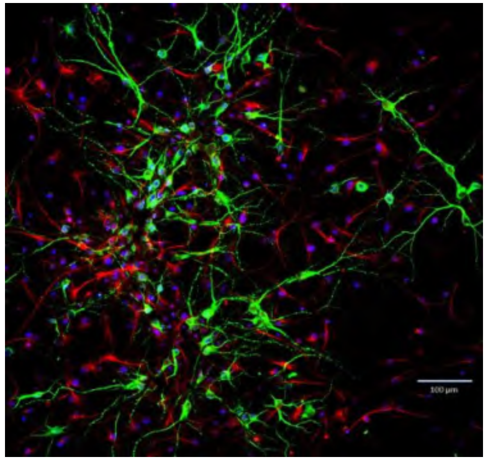
Nanomagnetism for Oncology

María del Puerto Morales

Instituto de Ciencia de Materiales de Madrid, ICMM/CSIC
Materiales para Medicina y Biotecnología



By Daniel Pastrana

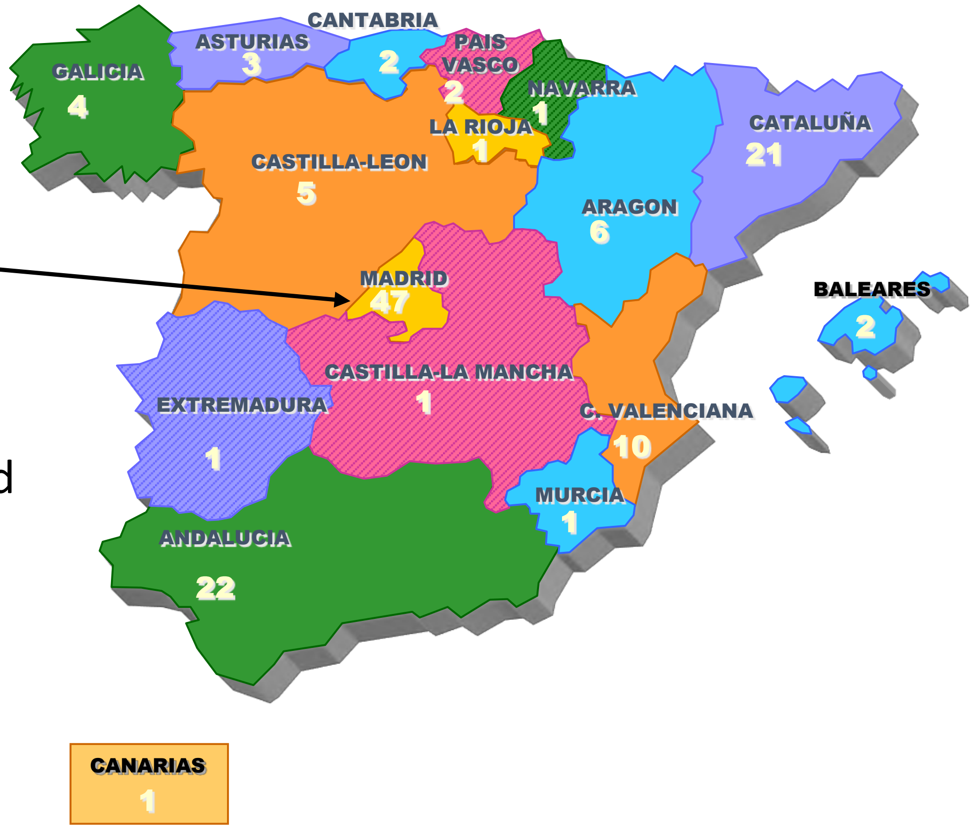
European School on Magnetism 2023, La Cristalera, Madrid, Spain

CSIC
CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

Instituto de Ciencia de Materiales de Madrid



Dept. de Energía, Medioambiente y Salud



Grupo de Materiales para la Salud

Materials for Medicine and Biotechnology Group (MaMBIO)

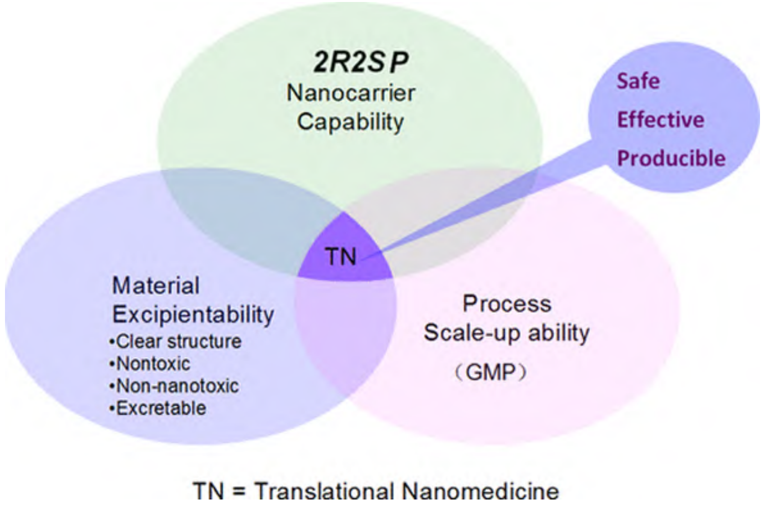
icmm CSIC

Materials for Medicine and Biotechnology Group (MaMBIO)

icmm CSIC

MAMBIO research focus

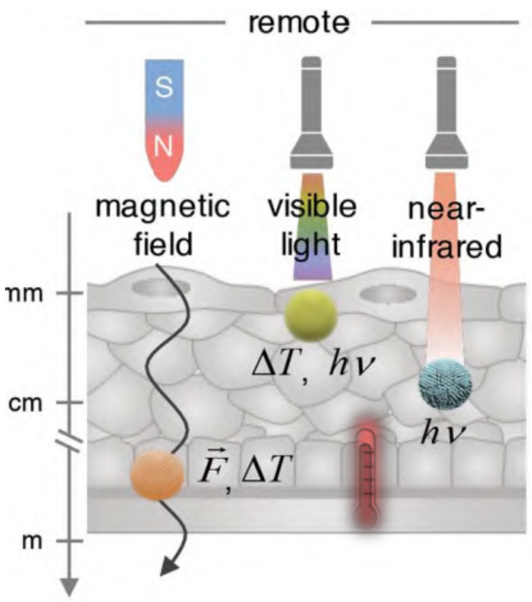
Synthesis methods



Development of safe, effective and reproducible synthesis methods

J. Colloid Interf. Sci., 608, 2022, 1585
Cryst. Growth Des. 2023, 23, 59
Nanomaterials 2021, 11(8), 2059

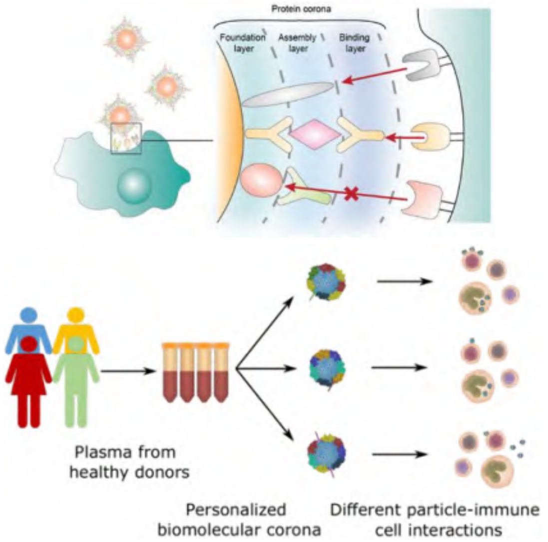
Smart nanomedicines



Nanothermometry
Remote control

ACS Mater. Interfaces 12 (2020) 4295
Nano letters 21 (17), 7213-7220, 2021
Journal of Cleaner Production 308, 17, 2021

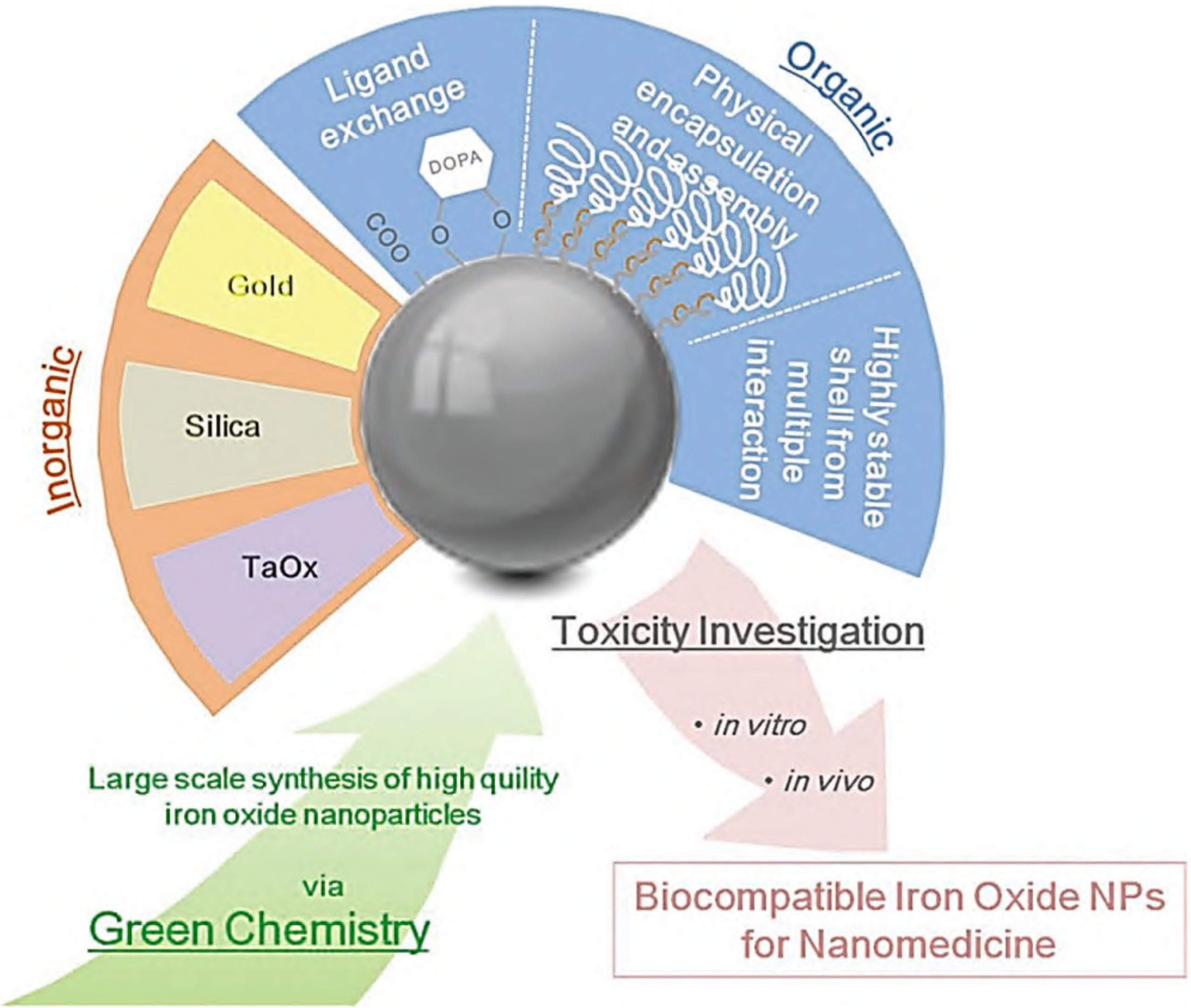
Nano–bio interactions



Nanoparticle Interactions with Cells

Journal of Nanobiotechnology 20, 1-23, 2022
Biomaterials 281 (2022) 121365
Cancers 13 (18), 4583, 11, 2021

Magnetic iron oxide nanoparticles



Small 2013, *9*, No. 9–10, 1450–1466

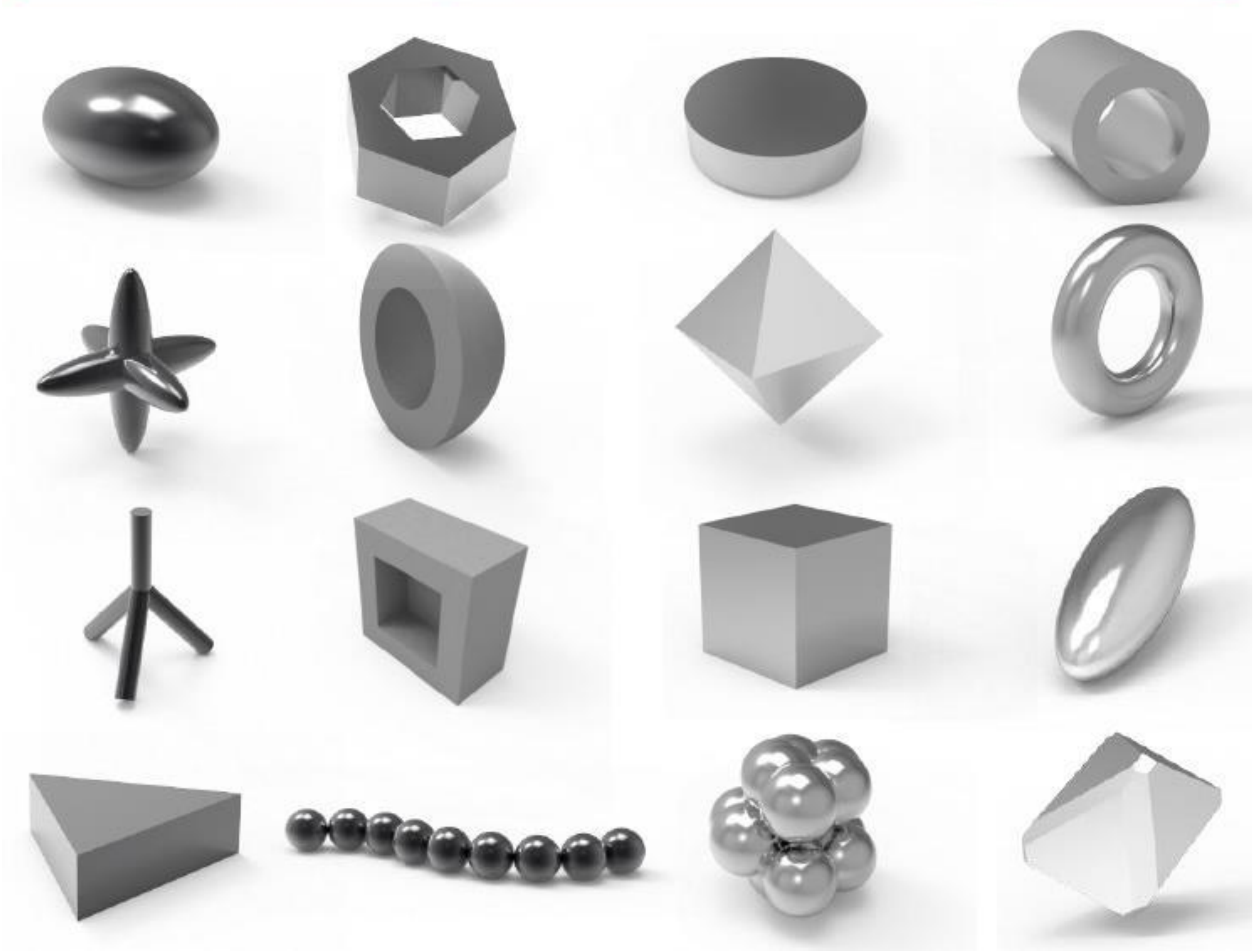
Chem. Soc. Rev., 2012, 41, 4306

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

Design strategies for shape-controlled magnetic iron oxide nanoparticles
Roca A.G., Gutiérrez L., Gavilán H., Fortes Brollo M.E., Veintemillas-Verdaguer S., Morales M.P. Advanced Drug Delivery Reviews; 138: 68 - 104. **2019**. 10.1016/j.addr.2018.12.008.

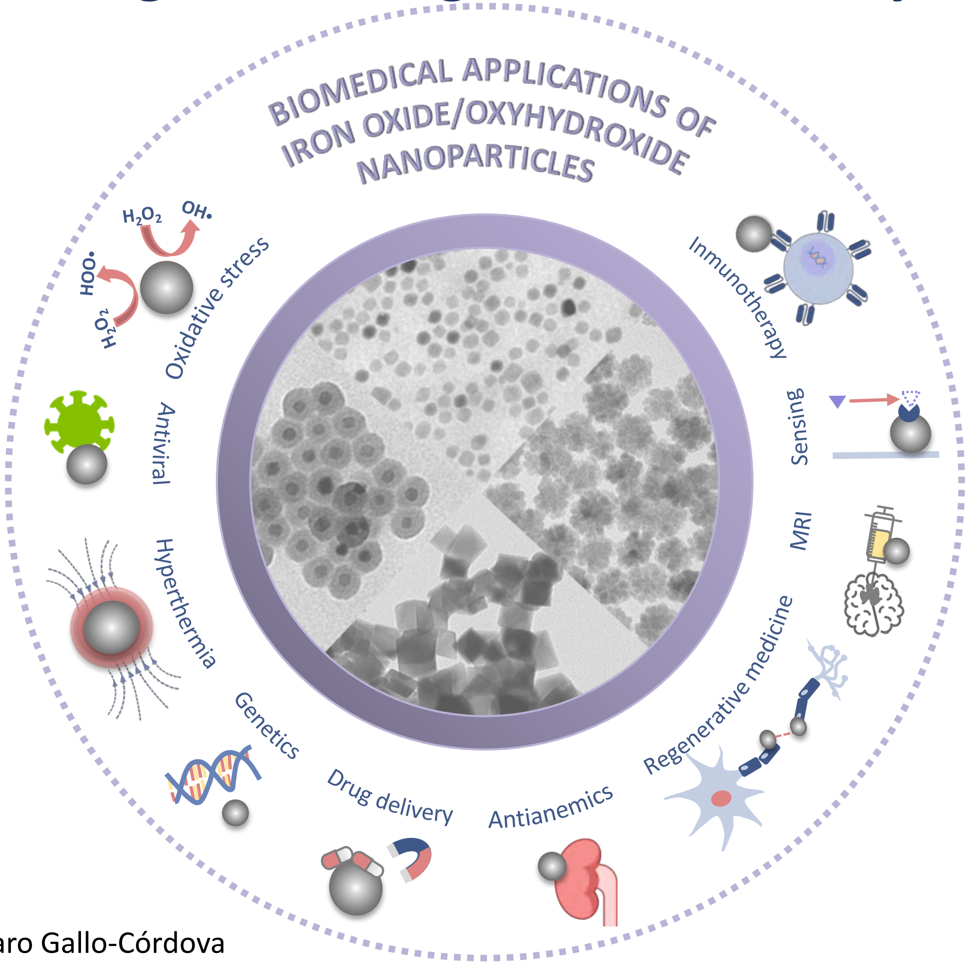
Magnetic iron oxide nanoparticles

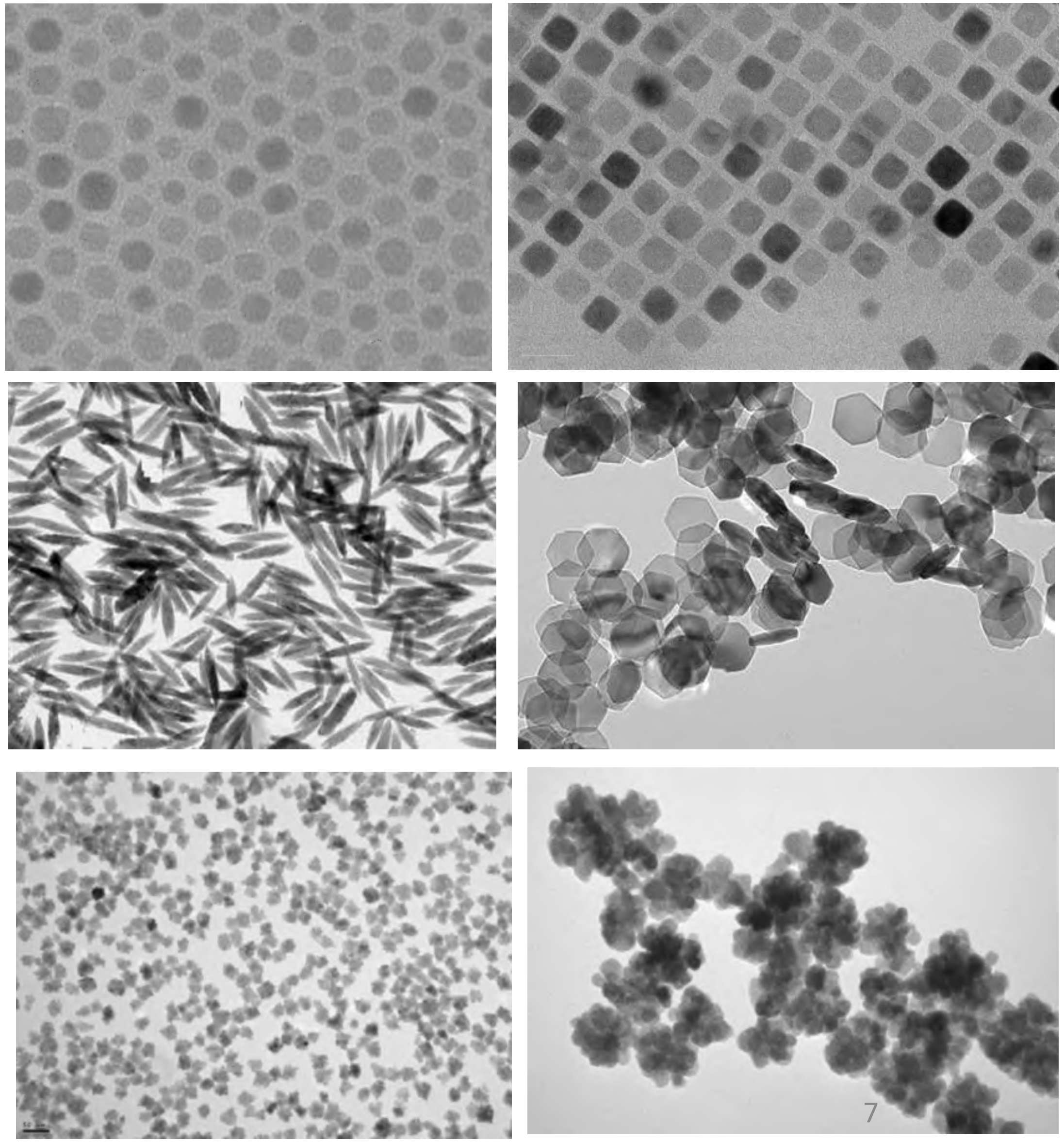


Advanced Drug Delivery Reviews; 138: 68 - 104. **2019**. 10.1016/j.addr.2018.12.008.

Magnetic iron oxide nanoparticles

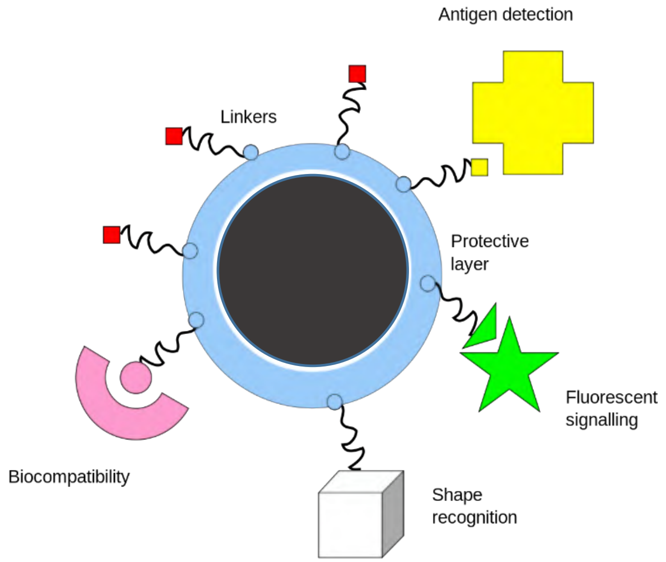
Biocompatible and biodegradable
Customizable in size/shape/funcionalization
Responsive to magnetic fields
Targetable drug and cell delivery

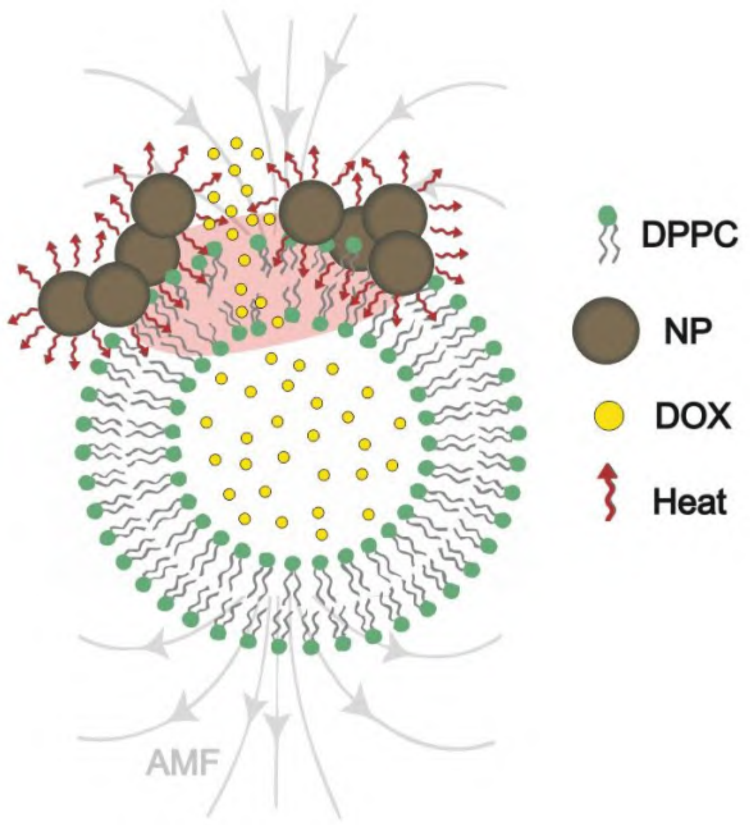


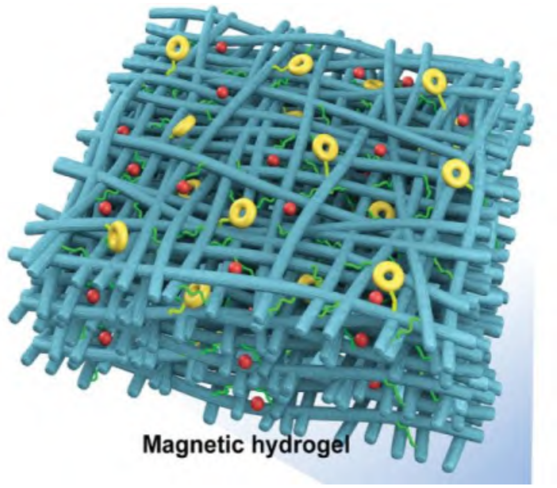


Scheme done by Dr Álvaro Gallo-Córdova

Designing Smart Nanomaterials







NPs coating

Magnetoliposomes

Magnetic hydrogels

Projects in the last 10 years

1. MAG4Spinal- Bio-implantes magnéticos inteligentes para regeneración neural: Aplicación a la médula espinal lesionada, (2021-2024)

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2. MULTIFUN- Multifunctional Nanotechnology for selective detection and Treatment of cancer, FP7-NMP-2010-LARGE-4, (2011-2015)

3. NANOMAG- Nanometrology Standardization Methods for Magnetic Nanoparticles, Project No.604448, FP7-NMP-2013-LARGE-7, EU, (2013-2017).

4. HOTZYMES- Redesigning biocatalysis: Thermal-tuning of one-pot multienzymatic cascades by nanoactuation, H2020-FETOPEN (2019-2022).

5. BYAXON - Towards an active bypass for neural reconnection, H2020-FETOPEN (2014- 2017).

6. MARGO- MAxillofacial bone Regeneration by 3D-printed laser-activated Graphene Oxide scaffolds. FLAG–ERA JTC 2019 –2023

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7. NESTOR- Nanomaterials for Enzymatic Control of Oxidative Stress Toxicity and Free Radical Generation (RISE, 2021-2025).

8. HYPELIGNUM- Exploring wooden materials in hybrid printed electronics, HORIZON-CL4-DIGITAL EMERIGING 2022-2026.

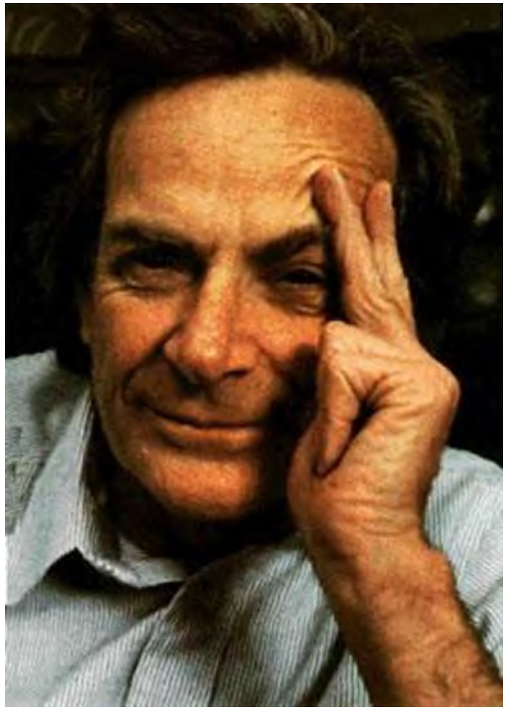
9. IMAGINE- Implementing MAgnetic targeting of nano-Guided ImmuNE cells, ESF 2022-2024

10. PIEZO4SPINE- Piezo-driven theramesh: A revolutionary multifaceted actuator to repair the injured spinal cord, HORIZON-EIC-2022-PATHFINDEROPEN-01, 2023-2027.

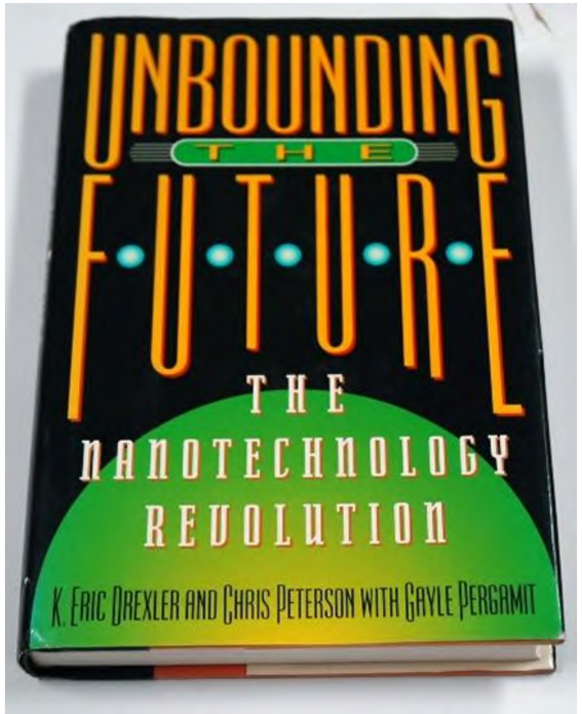
OUTLINE

1. Nanomedicine
2. Advantages of magnetic nanoparticles
3. Requirements for bioapplications
4. Applications
   - ✓ Diganosis: MRI
   - ✓ Therapy: Drug delivery, Hyperthermia
   - ✓ Nanoactuators/nanomotors
5. Nanotoxicity
6. Synthesis routes
7. Final remarks

NANOMEDICINE



Richard Feynman (1959)



"A friend of mine (Albert R. Hibbs) suggests a very interesting possibility for relatively small machines. He says that, although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and ``looks'' around.... It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately-functioning organ.

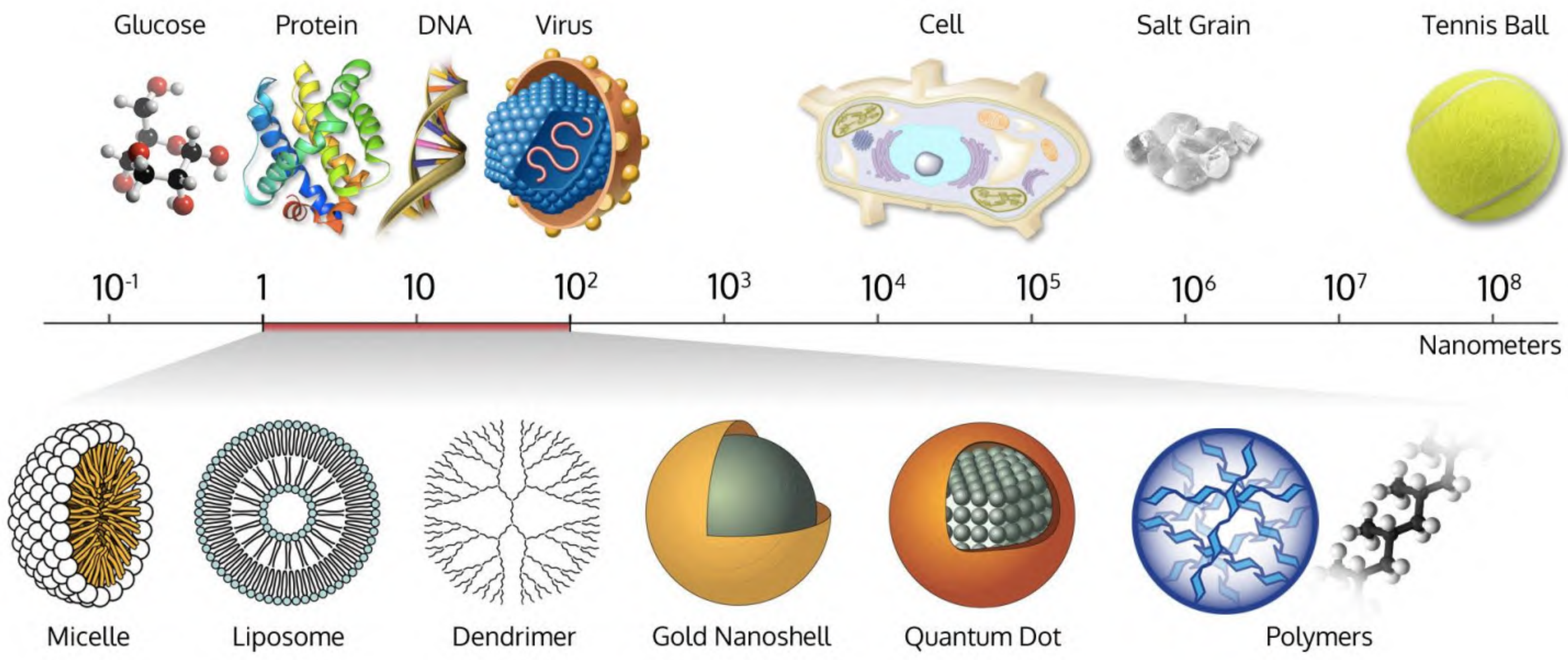
How do we make such a tiny mechanism? I leave that to you...

The Word Nanomedicine

K. Eric Drexler,
Chris Peterson y
Gayle Pergamit (1991)

Financial support for Nanomedicine Initiatives, first released in late 2003

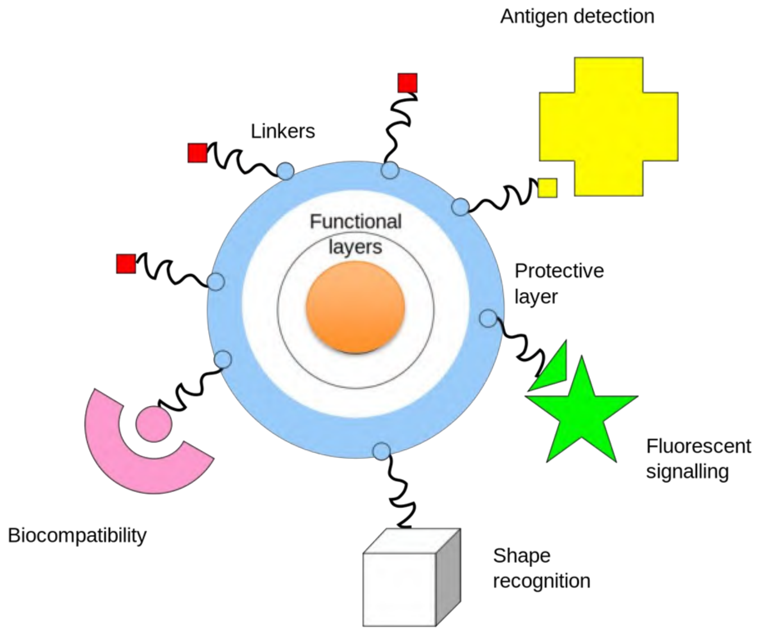
Nanomedicine



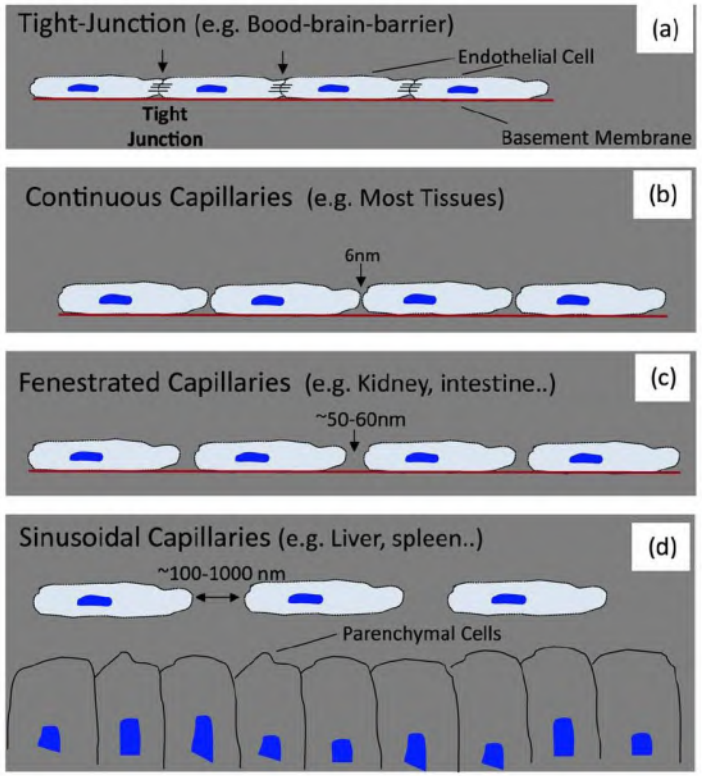
Tamaño 1-100 nm

Nanomedicine is the application of nanotechnology to medicine

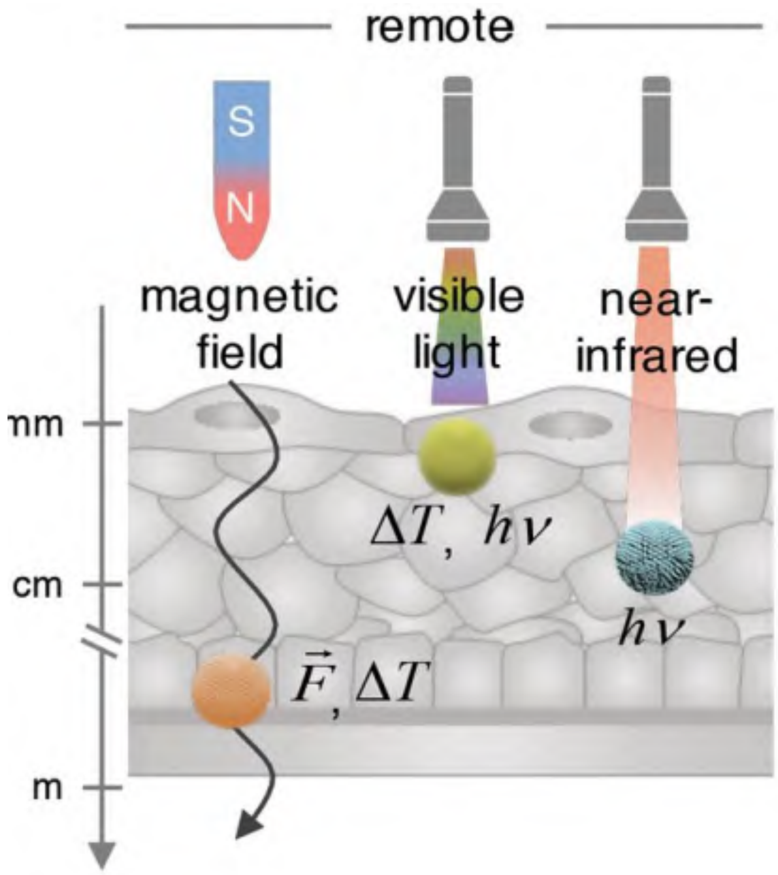
Nanomedicine



Functionalized



Cross barriers

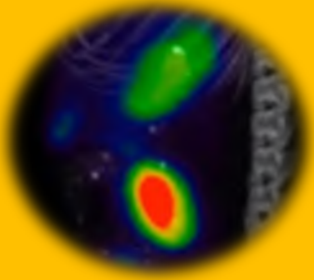


Respond to stimuli

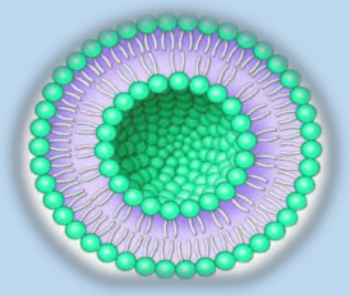
Nanomedicine

Diagnosis

Molecular Imaging



Nano-drugs

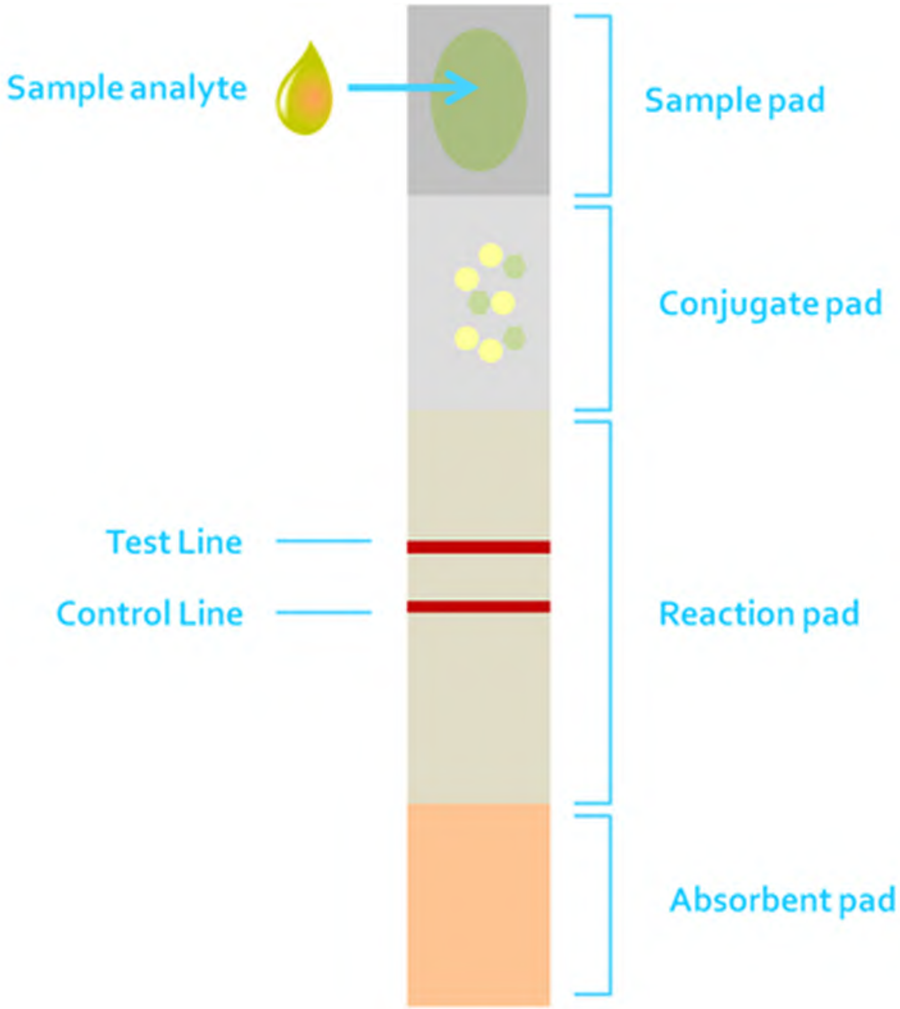


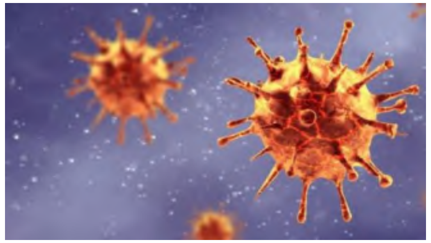
Vaccines

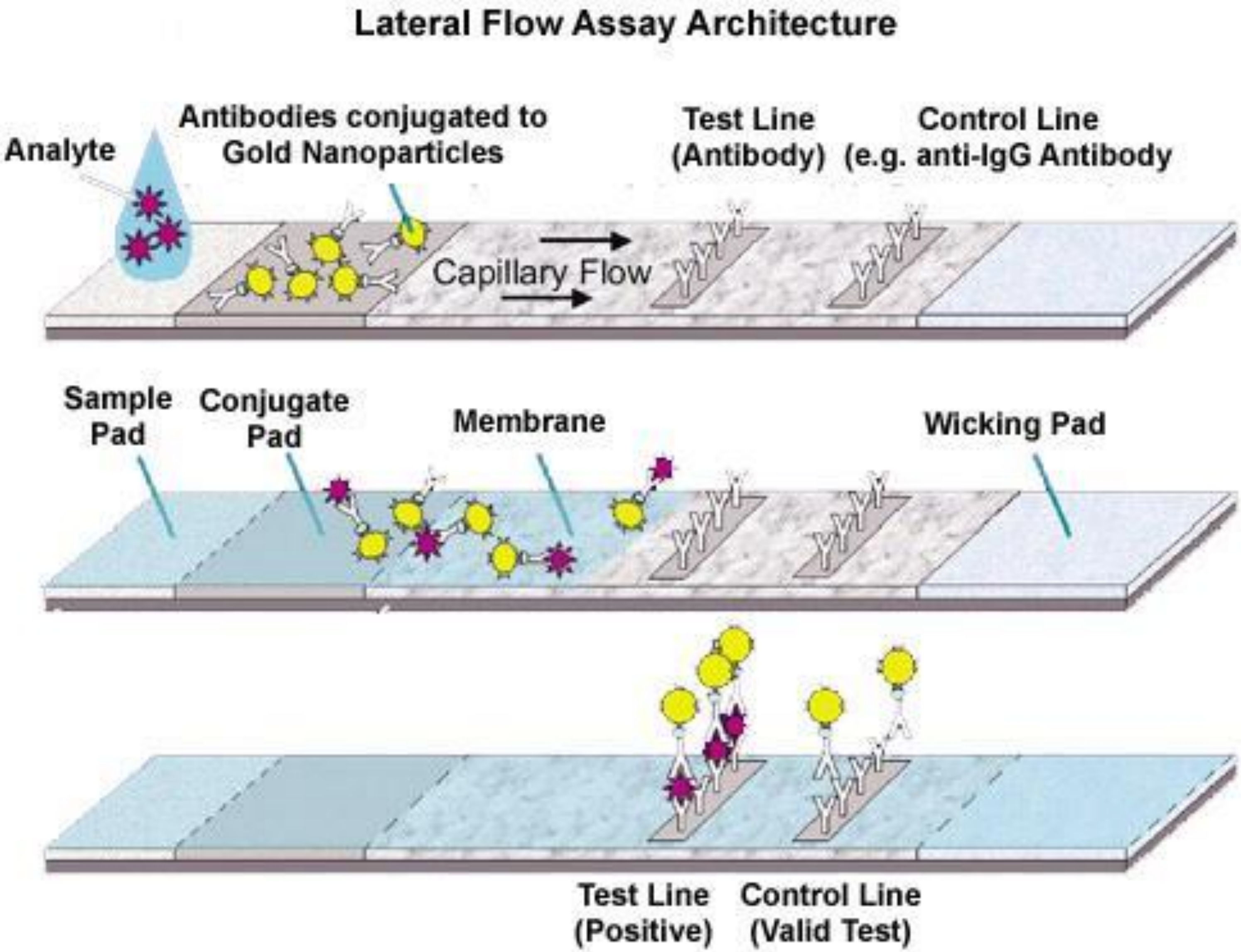
Regenerative Medicine

Nanomedicine is the process of diagnosing, treating, and preventing disease and traumatic injury, relieving pain, and preserving and improving human health, using molecular tools and molecular knowledge of the human body.

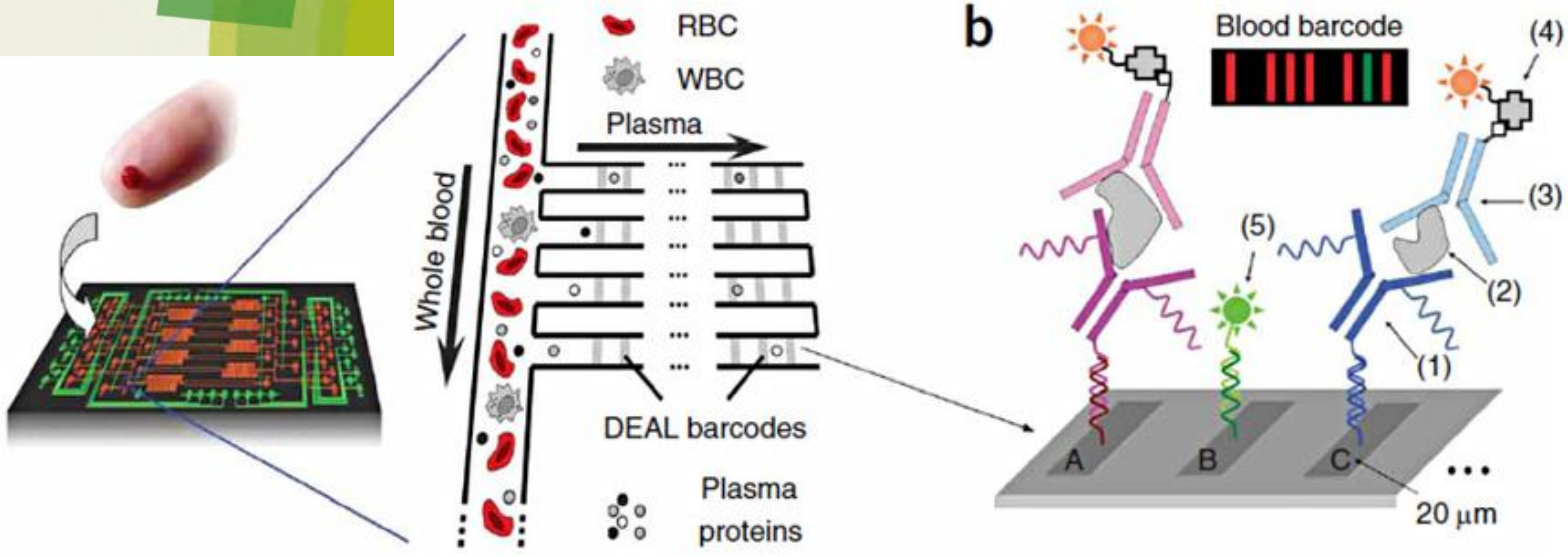
Diagnosis


Sample analyte
Sample pad
Conjugate pad
Test Line
Control Line
Reaction pad
Absorbent pad

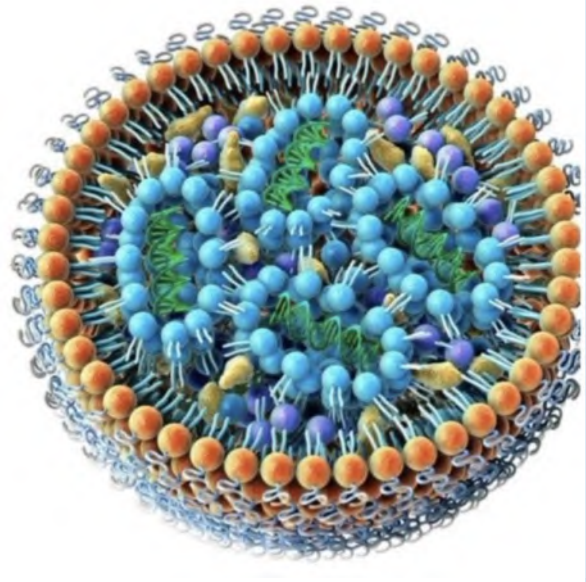




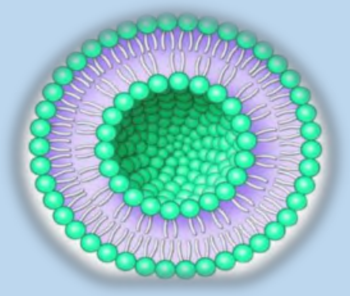
Lateral Flow Immunoassay. https://www.cytodiagnostics.com/pages/lateral-flow-assay



Cancer biomarkers
Alzheimer, VIH…



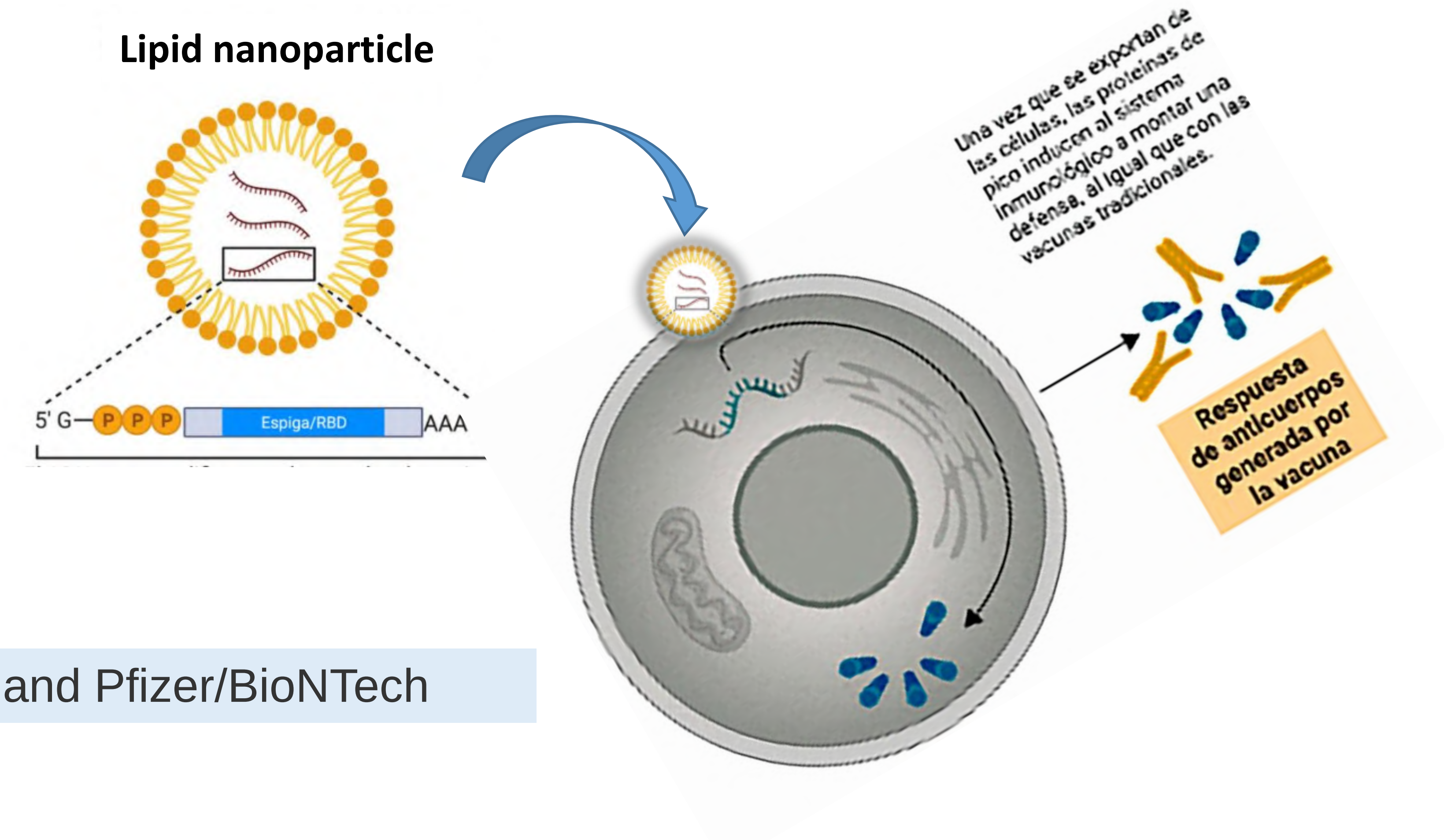
Nano-drugs



Vaccines

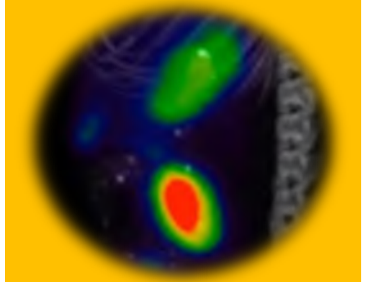
Vaccines

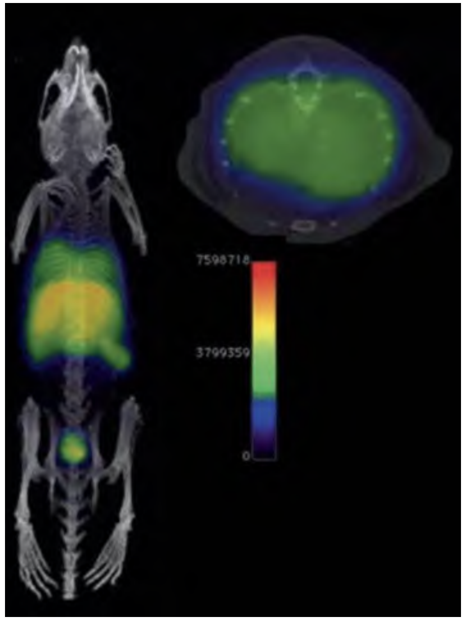
mRNA Vaccine : use messenger RNA, or mRNA, to trigger the immune system to produce protective antibodies.

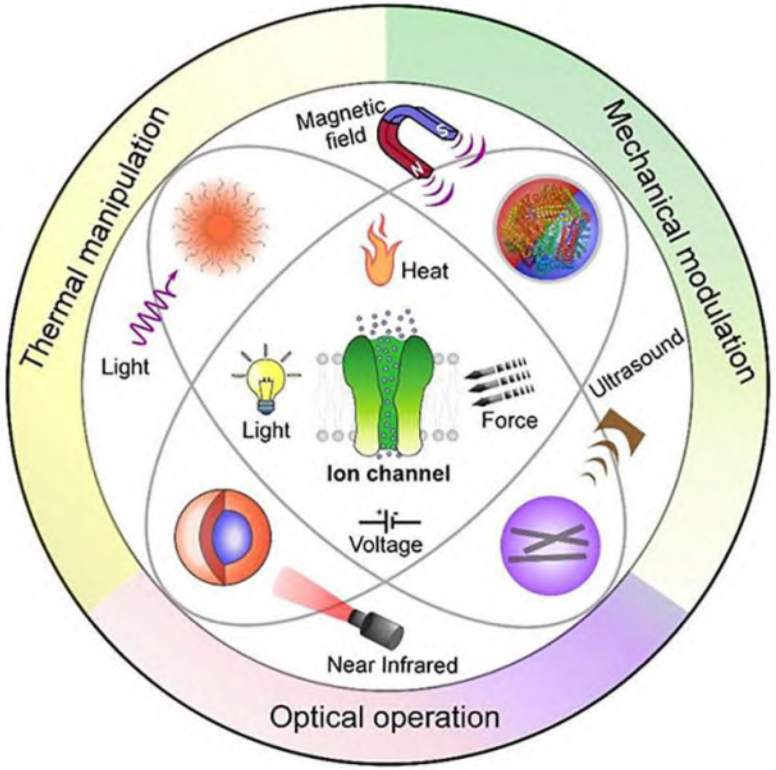


Moderna and Pfizer/BioNTech

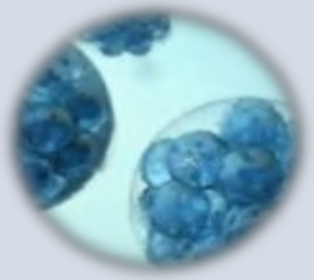
Molecular Imaging





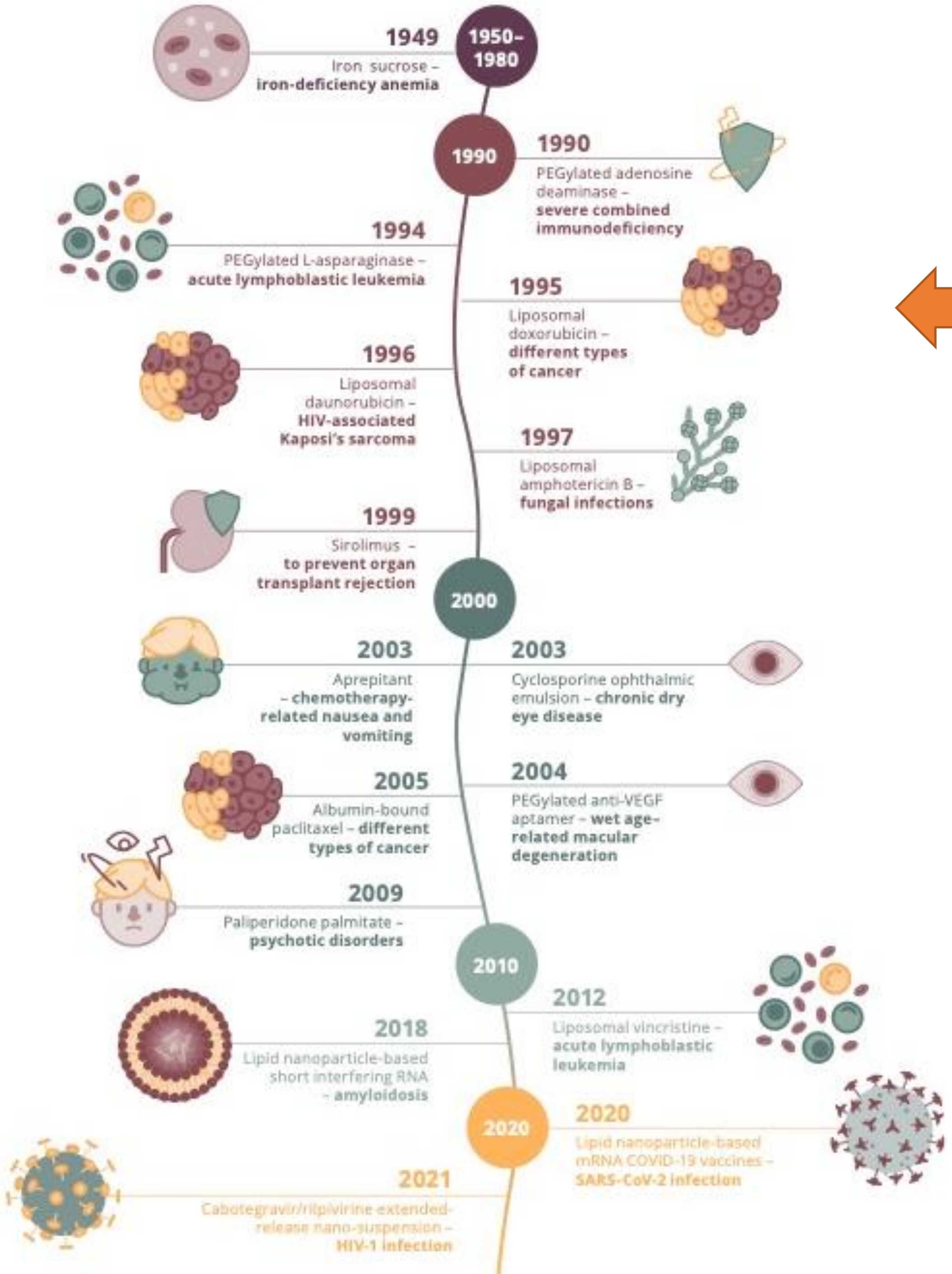


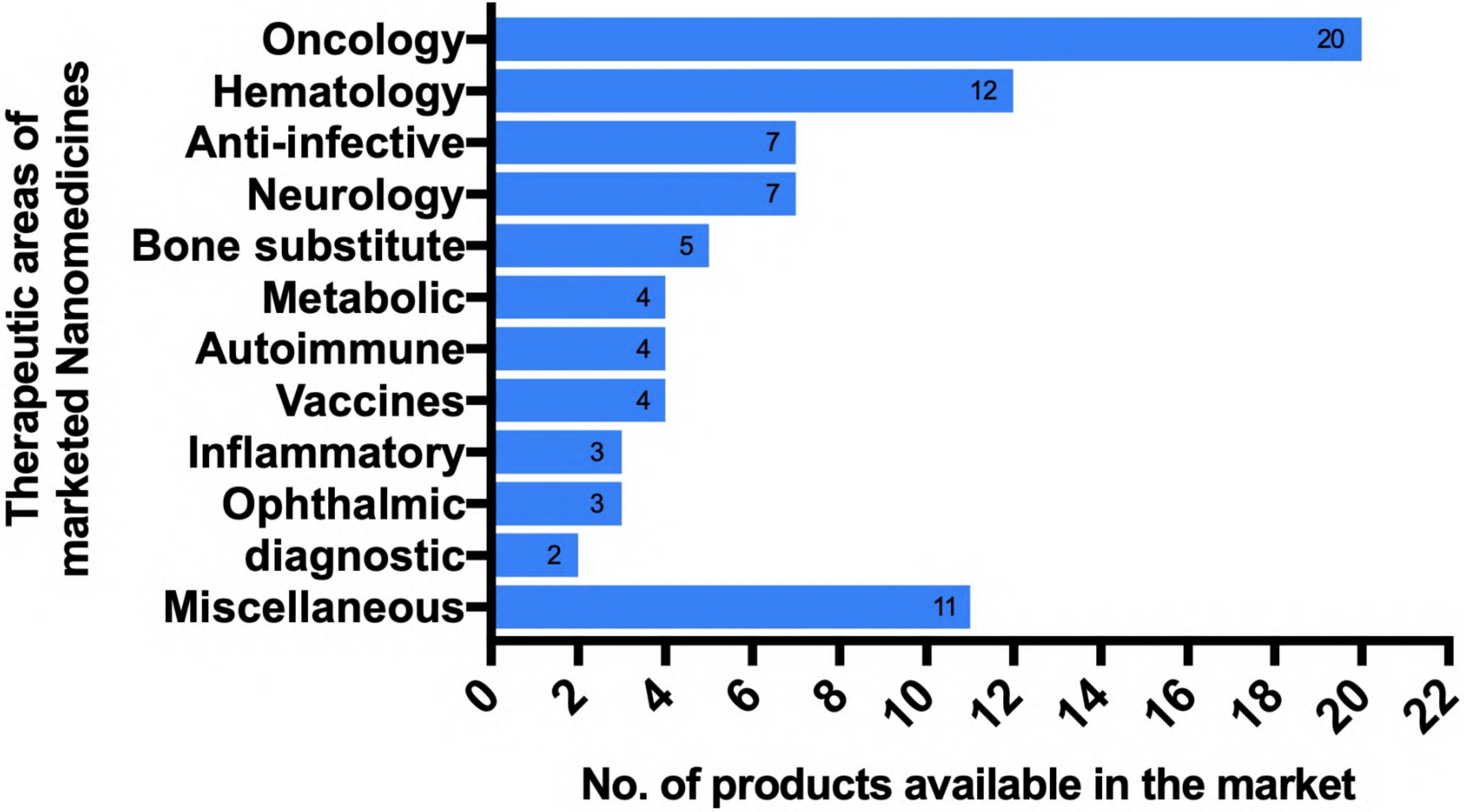
Regenerative Medicine



State of the art

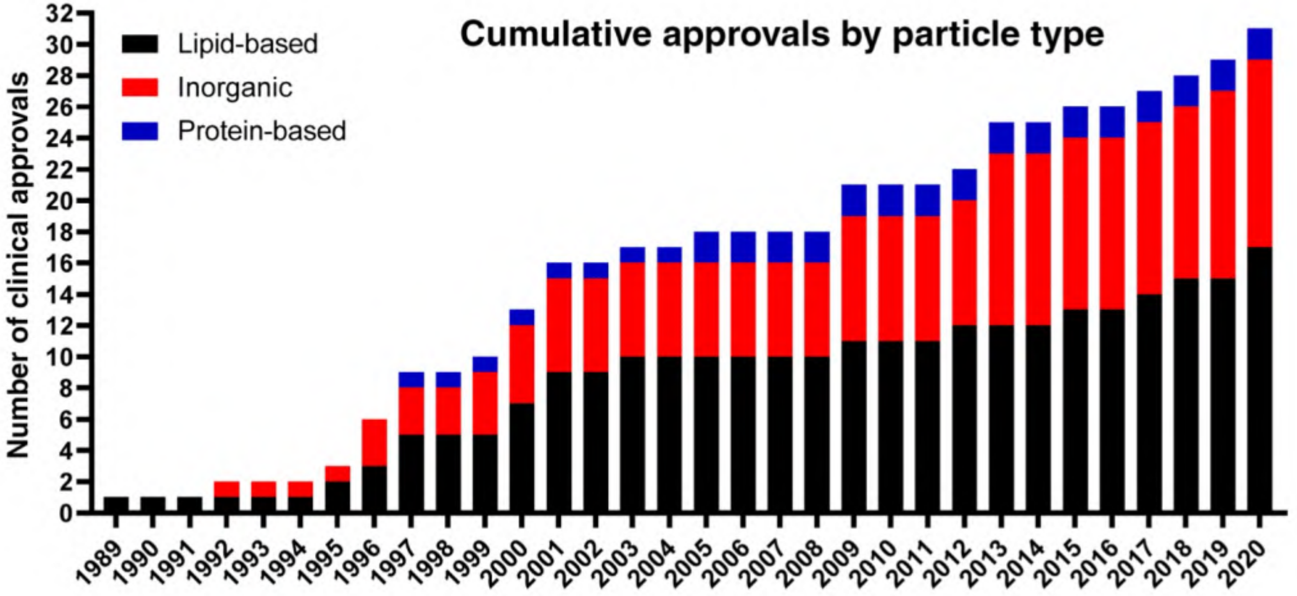
MILESTONES IN THE HISTORY OF NANOMEDICINES

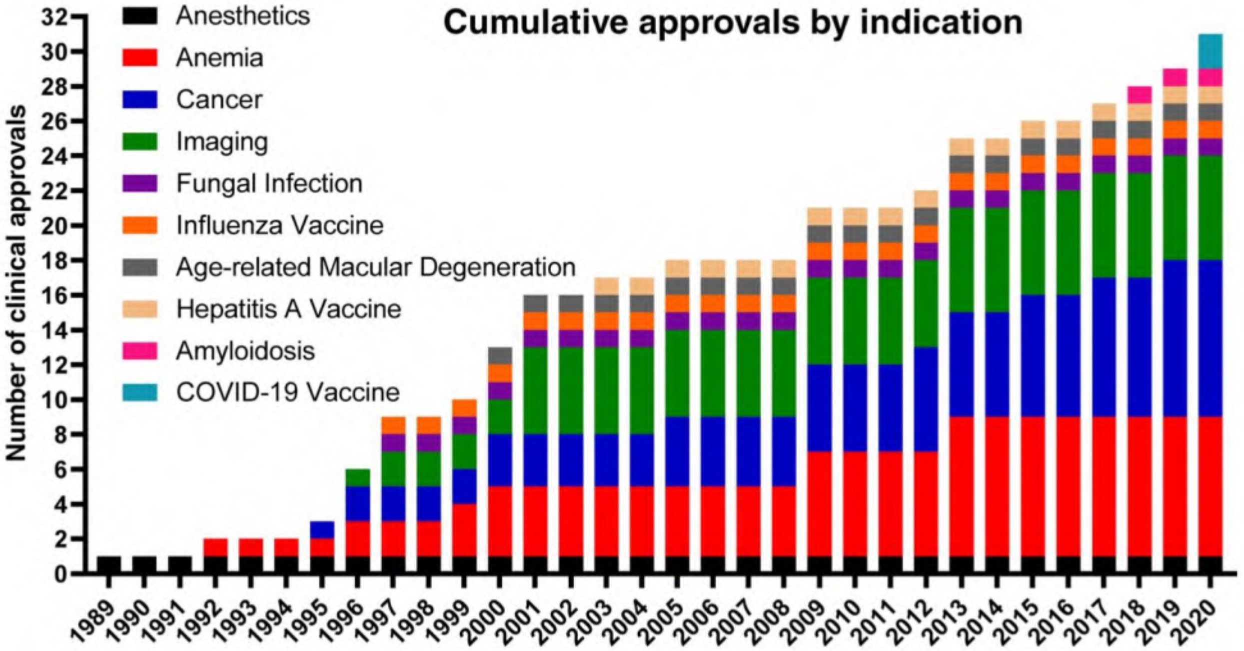




https://doi.org/10.1016/j.jconrel.2020.07.007

https://doi.org/10.3390/ pharmaceutics14010106





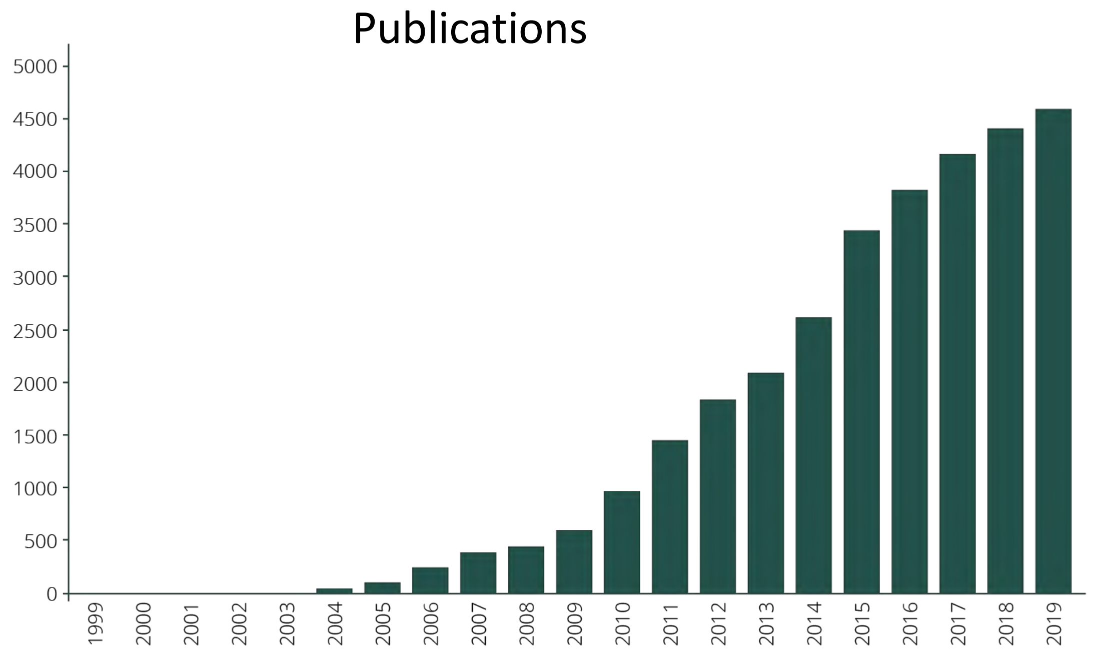
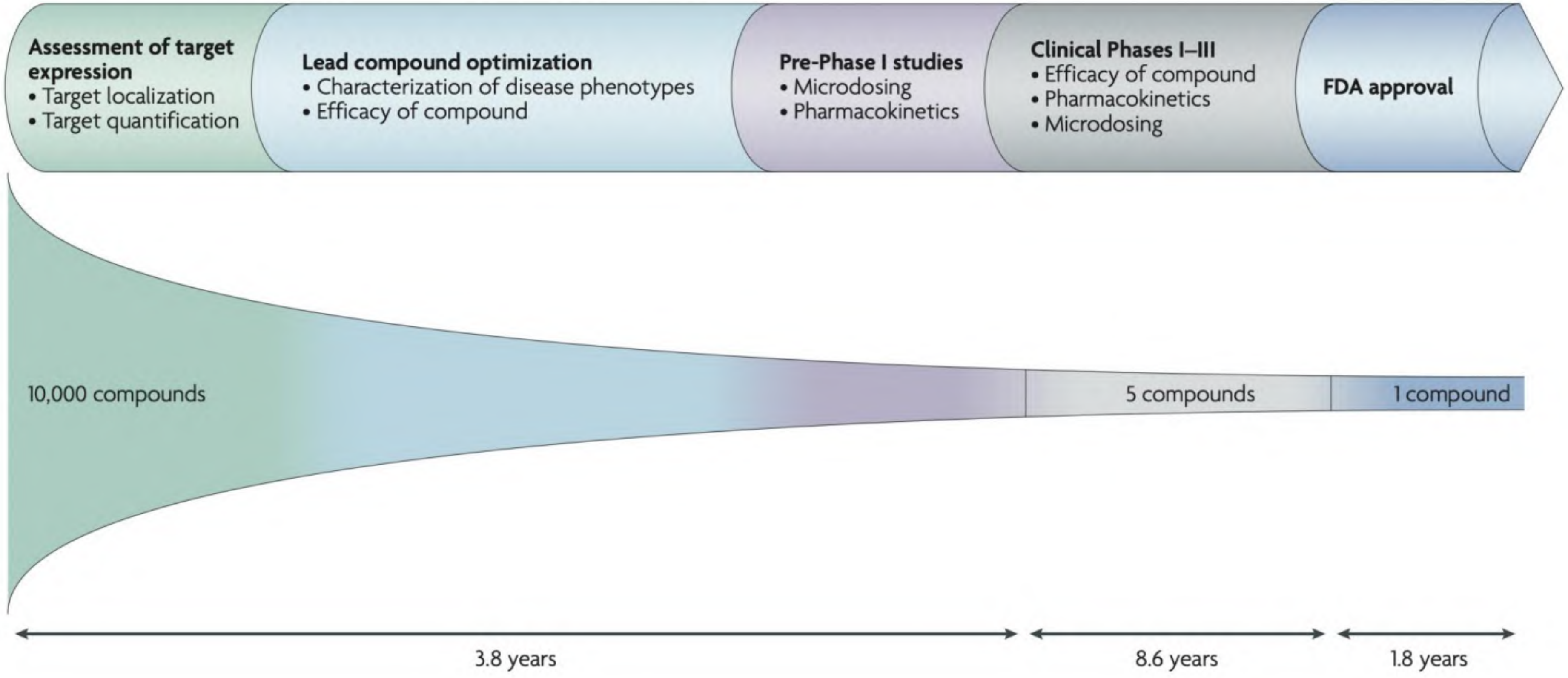
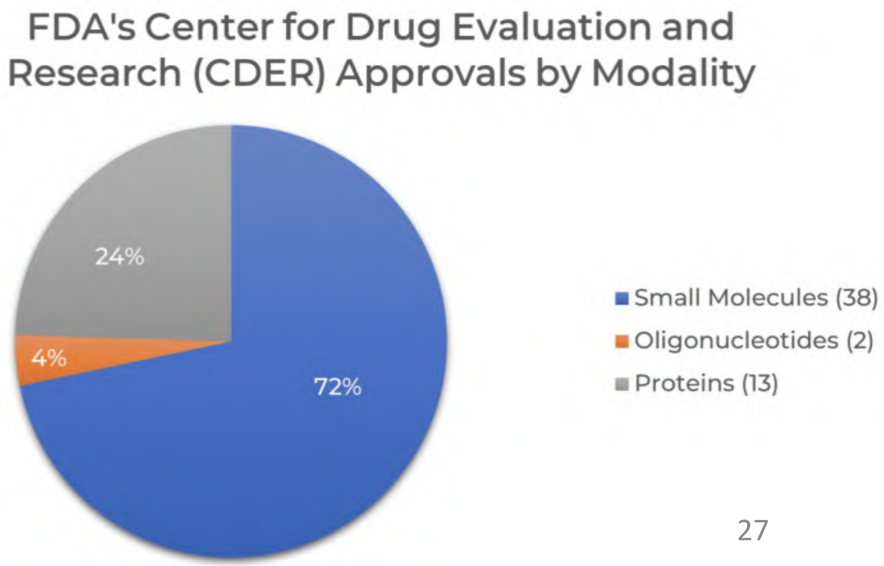


Figure 2. Indexed publications on the topic of nanomedicines from 1999-2019 [From 9].

DOI: 10.1002/btm2.10246


Assessment of target expression
• Target localization
• Target quantification
Lead compound optimization
• Characterization of disease phenotypes
• Efficacy of compound
Pre-Phase I studies
• Microdosing
• Pharmacokinetics
Clinical Phases I–III
• Efficacy of compound
• Pharmacokinetics
• Microdosing
FDA approval
10,000 compounds
5 compounds
1 compound
3.8 years
8.6 years
1.8 years


FDA's Center for Drug Evaluation and Research (CDER) Approvals by Modality
24%
4%
72%
Small Molecules (38)
Oligonucleotides (2)
Proteins (13)

Nanosystems in medicine

Materials
Nano-porous
Nano-crystals
Nano-reinforced
Nano-structured surfaces

Properties
Tissue ingrowth, transport of substances
Physical, electrical, optical, mechanical properties
Mechanical properties, Biocompatibility

Applications

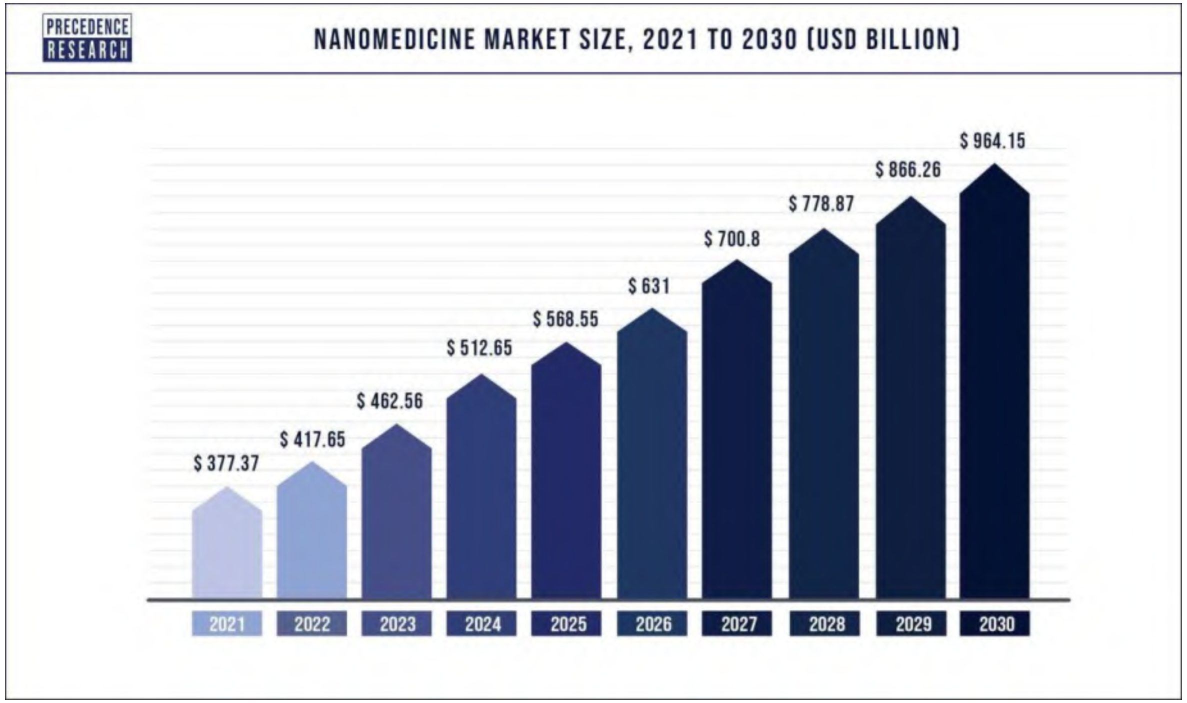
- Surgery
- Therapy
- Diagnostics
- Biosensors/biodetection
- Implantable materials/devices: Tissue engineering
- Textiles and wound care products
- Drug/gene delivery materials and devices

Bandages with silver nanoparticles
Curad® (www.curadusa.com)

antibacterial agent.

Nanotechnology and heath care, huge potential and some risks.

Global Market for Nanoparticles



Drug delivery

- Drug release control
- Drug solubility problems
- DNA carriers
- Tissue regeneration

Areas: Cancer
Neurodegenerative
Cardiovascular
Infection

Nanoparticles in Biotechnology, Drug Development & Drug Delivery (BIO113B) by Jackson Highsmith, and **Nanotechnology in Medical Applications: The Global Market (HLC069B)** by Paul Evers. For more information, visit www.bccresearch.com. and www.drug-dev.com.

Oncology

High mortality without effective treatment

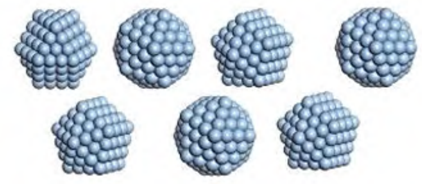
Consequences: The oncology market is the third largest pharmaceutical market, behind the cardiovascular and central nervous system therapy areas.

Treatment of cancer with traditional medicine involves surgery, ionizing radiation, and chemotherapy

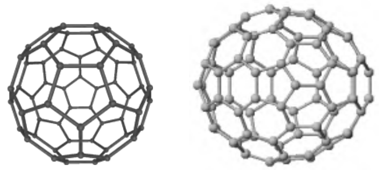
These treatments affect both tumors and healthy tissue.

Consequences: Multi-billion markets in medical and palliative expenses because systemic toxicity and undesirables side effects.

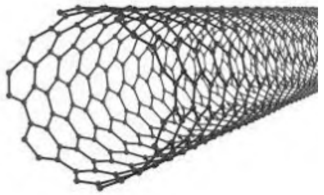
Nanosystems



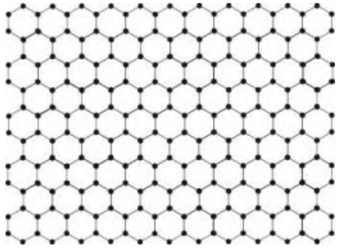
nanopartículas metálicas, semiconductoras,…



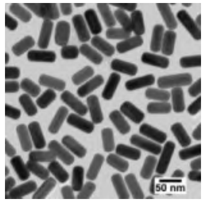
C_{60},C_{84},…



nanotubos de carbono



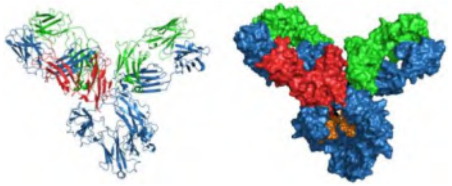
grafeno



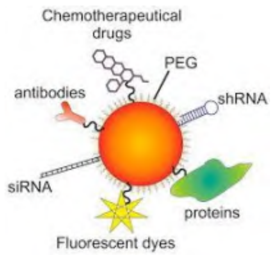
nanobarras,…

ADN

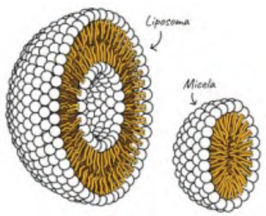
nanocontenedores de ADN



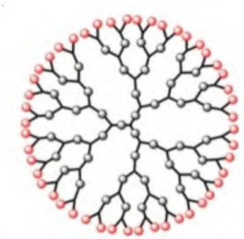
proteínas



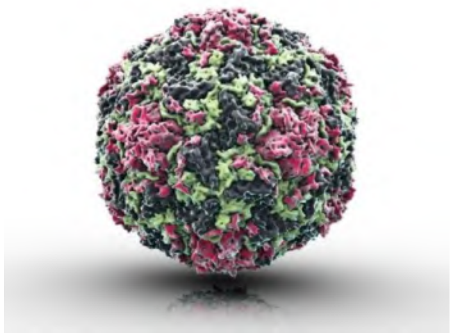
Nanopartículas funcionalizadas



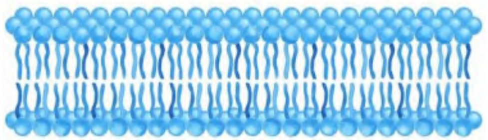
liposomas, micelas



dendrimeros



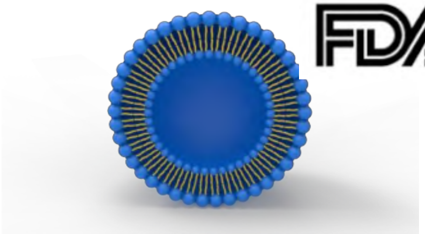
cápsidas virales



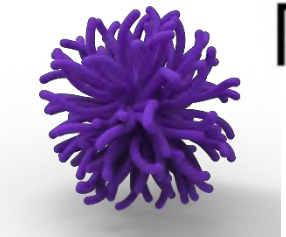
membranas

¿¿Toxicicity??

Nanoparticles in clinical phases

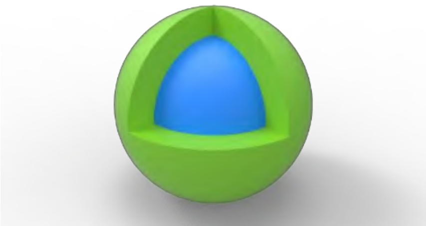


Liposomas
Encapsulación de fármacos hidrofóbicos y protección de degradación prematura

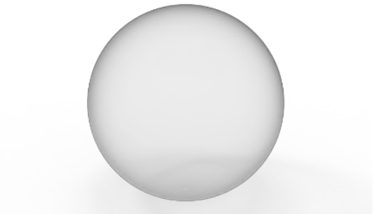


NPs poliméricas
Transporte de fármacos y liberación con diferentes estímulos (pH, temperatura, degradación).

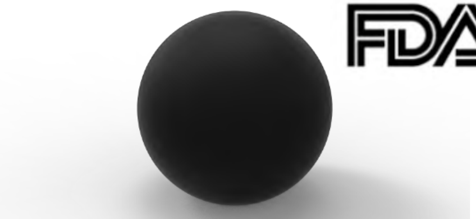
NPs de Oro
Diagnóstico por imagen, terapia fototérmica



Quantum dots
Propiedades ópticas para imagen



NPs Sílice
Transporte de fármacos (porosidad controlada)



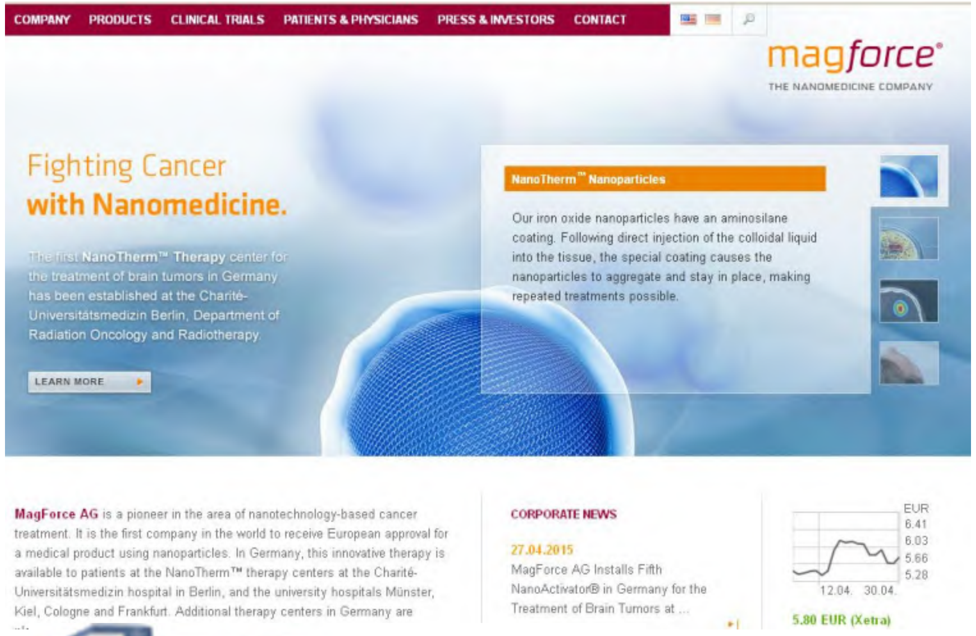
NPs Magnéticas
Imagen/transporte/trata miento

Commercial products

Abraxane®

(nanoparticle albumin-bound paclitaxel)

ABRAXANE is a prescription medicine for breast cancer that has spread to other parts of the body. ABRAXANE is used after treatment with combination chemotherapy has stopped working, including anthracyclines, if appropriate, or when the cancer has come back within 6 months of treatment after surgery.



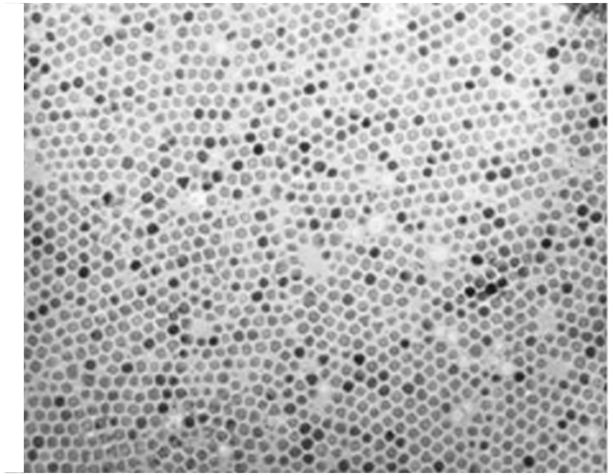
http://www.magforce.de/en/home.html

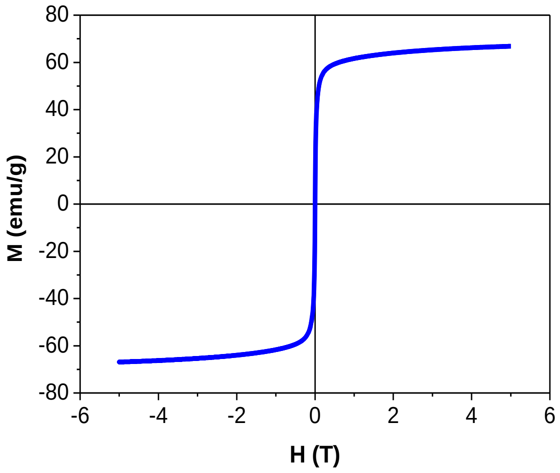
Nano-Formulations approved by different regulatory agencies

Product	Nanosystem	Application	Status	Company
Doxil (Barenholz, 2012)	Doxorrubicin encapsulated in PEG liposomes	Ovarian cancer	Approved 11/17/1995	Ortho Biotech (JNJ)
Myocet (Waterhouse et al., 2001)	Doxorrubicin encapsulated in liposomes	Metastatic Breast Cancer	Approved in EU and Canadá	Sopherion Therapeutics, LLC in EEUU, Cephalon, EU
DaunoXome (Forssen, 1997)	Doxorrubicin encapsulated in liposomes	Kaposi's sarcoma associated to HIV	Approved in E.E.U.U	Galen Ltd.
ThermoDox (Dromi et al., 2007)	Doxorrubicin encapsulated in liposomes	Breast cancer and liver cancer in the first stages	Approved 2013	Celsion
Abraxane (Guarneri et al., 2012)	Nanoparticles in albumine-paclitaxel	Different kinds of cancer	Approved 1/7/2005 FDA21660	Celgene
Rexin-G (Gordon and Hall, 2010)	MicroRNA-122 encapsulated in liposomes	Sarcoma, osteosarcoma, pancreatic cancer…	Approved in Filipinas, Phase II y III in E.E.U.U	Epeius Biotechnologies Corp.
Oncaspar (Avramis ,Tiwari 2006)	PEG Asparaginase	Acute lymphoblastic leukemia	Approved 24/06/2006	Enzon Pharmaceuticals, Inc
Resovist (Hamm et al., 1994)	Nanoparticles of iron oxide coated with Carboxydextran.	Liver and spleen NMR contrast agents	Approved in Europa 2001	Bayer Schering Pharma AG
Feridex (Weissleder et al., 1989)	Nanoparticles of iron oxide coated with Dextran	Liver and spleen NMR contrast agents	Approved FDA in E.E.U.U 1996	Berlex Laboratories
Endorem (Weissleder et al., 1989)	Nanoparticles of iron oxide coated with Dextran	Liver and spleen NMR contrast agents	Approved in Europa	Guerbet

Advantage of using magnetic materials

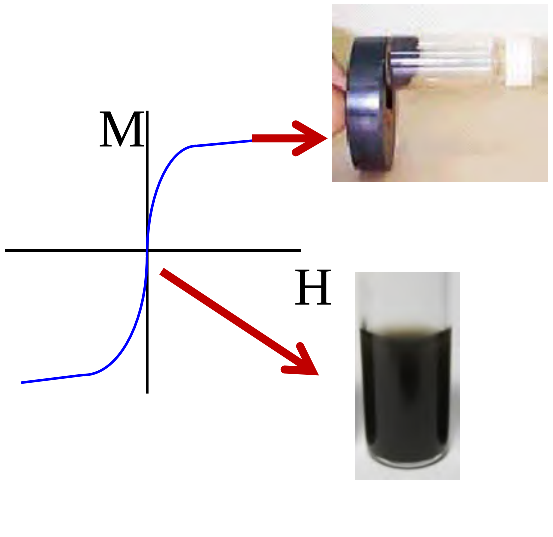
Advantages of magnetic materials



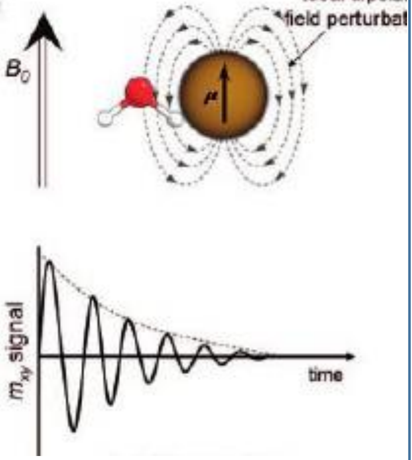


<100 nm

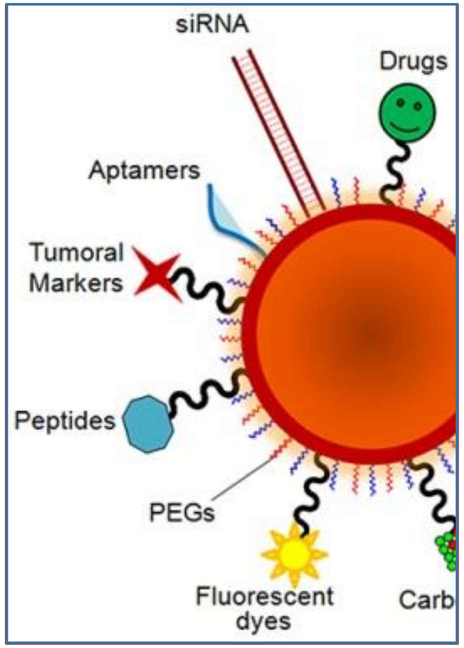
Magnetic colloids

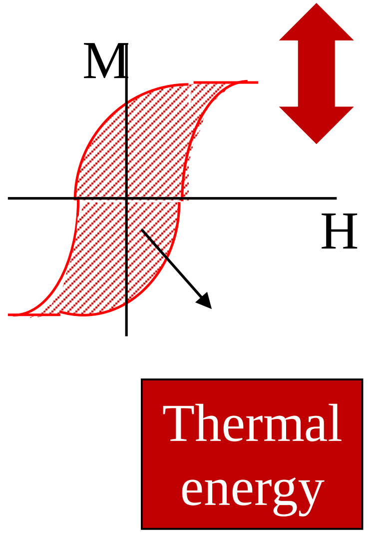


Response to a magnetic field

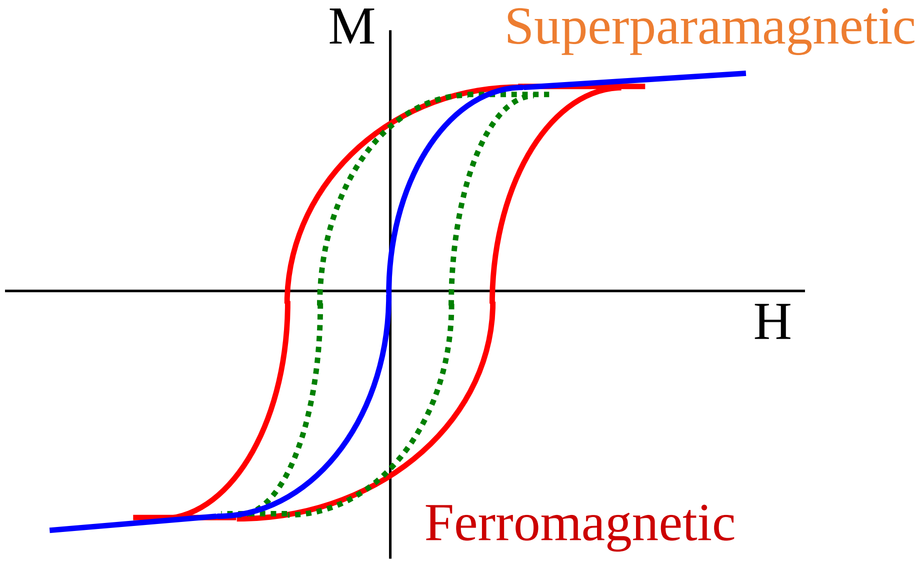


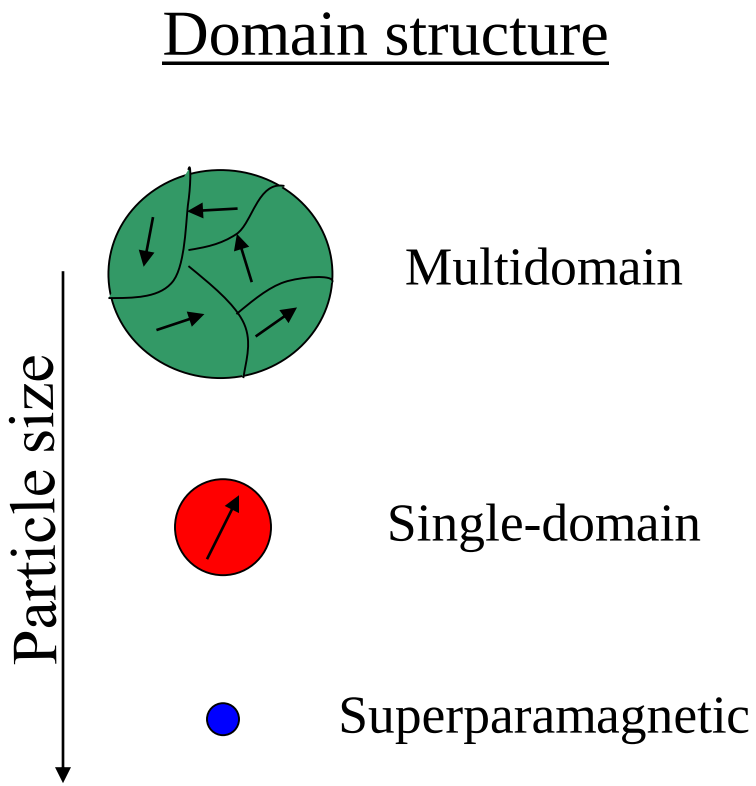
Alter NMR signal





Particle Size

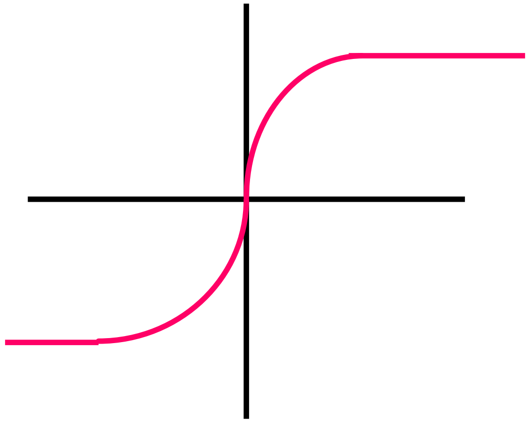




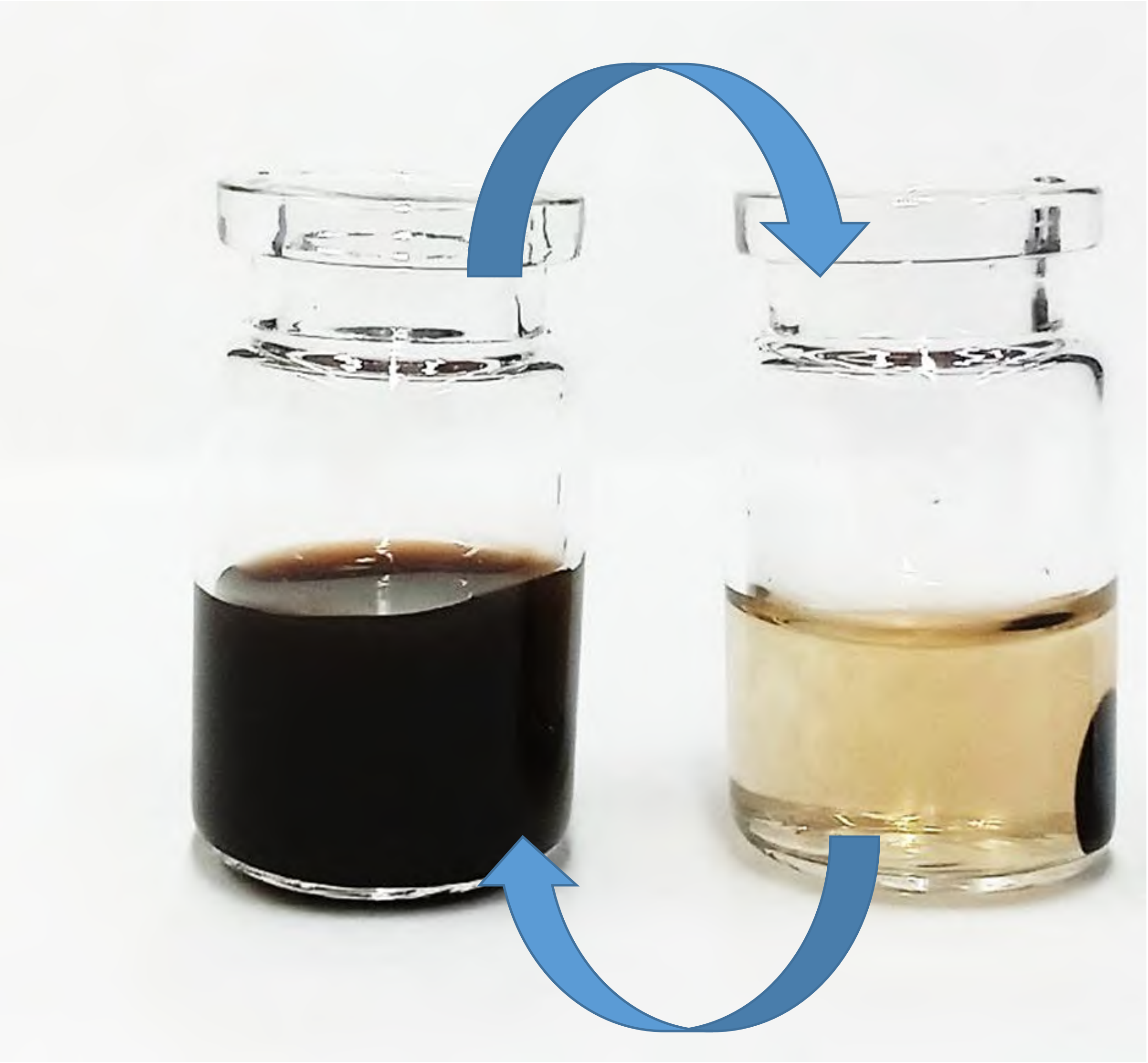
The shape of the loops are determined in part by the particle size

at the nanoscale….

Superparamagnetism

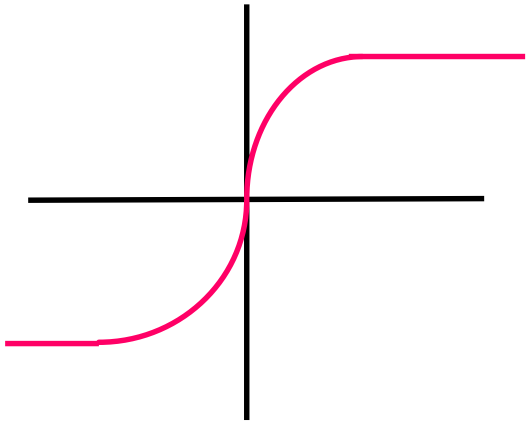


Static magnetic field



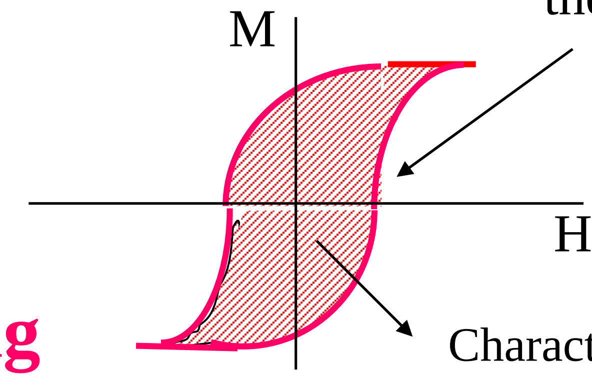
at the nanoscale….

Magnetic hyperthermia

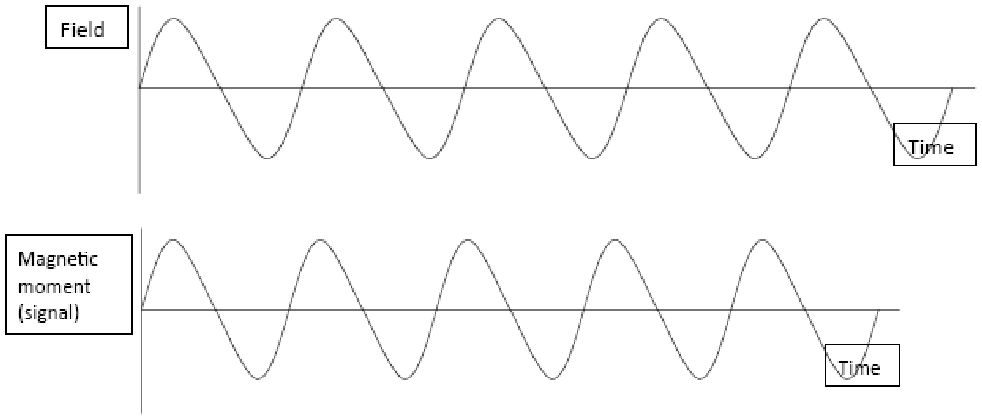


Alternating magnetic field

Delivered by the applied field



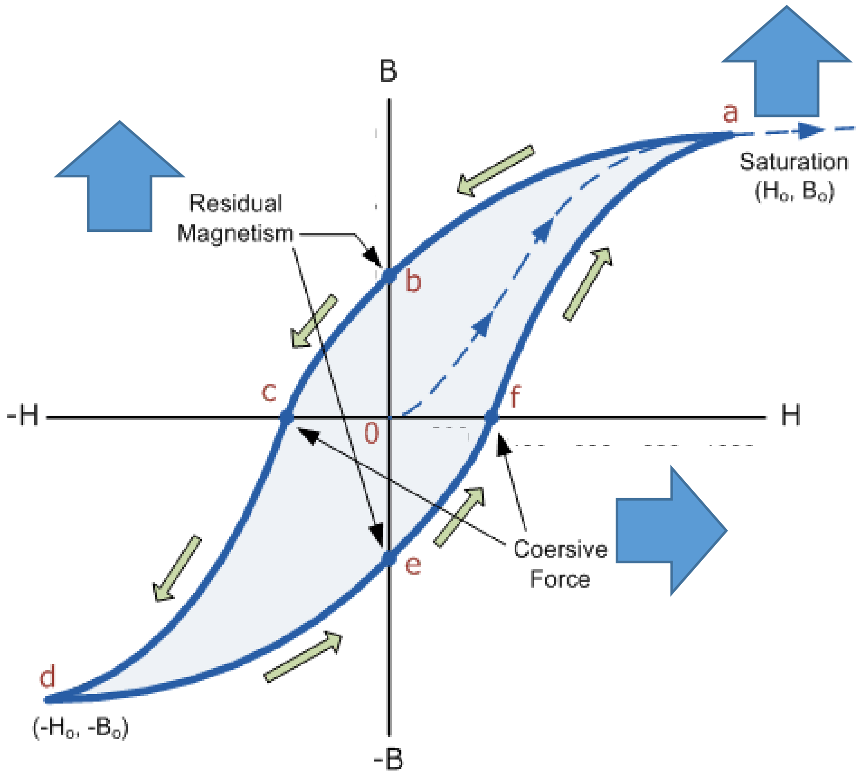
Characterised by area enclosed by the hysteresis loop



Thermal energy

Heating power= $\mu_0.\pi.f.H^2.X''$

Maximizing the heating with magnetic nanoparticles



Ferromagnetic

Heat dissipated grows with:

- Saturation Magnetization (M_S)
- Remanent Magnetization (M_R)
- Coercive Field (H_C)

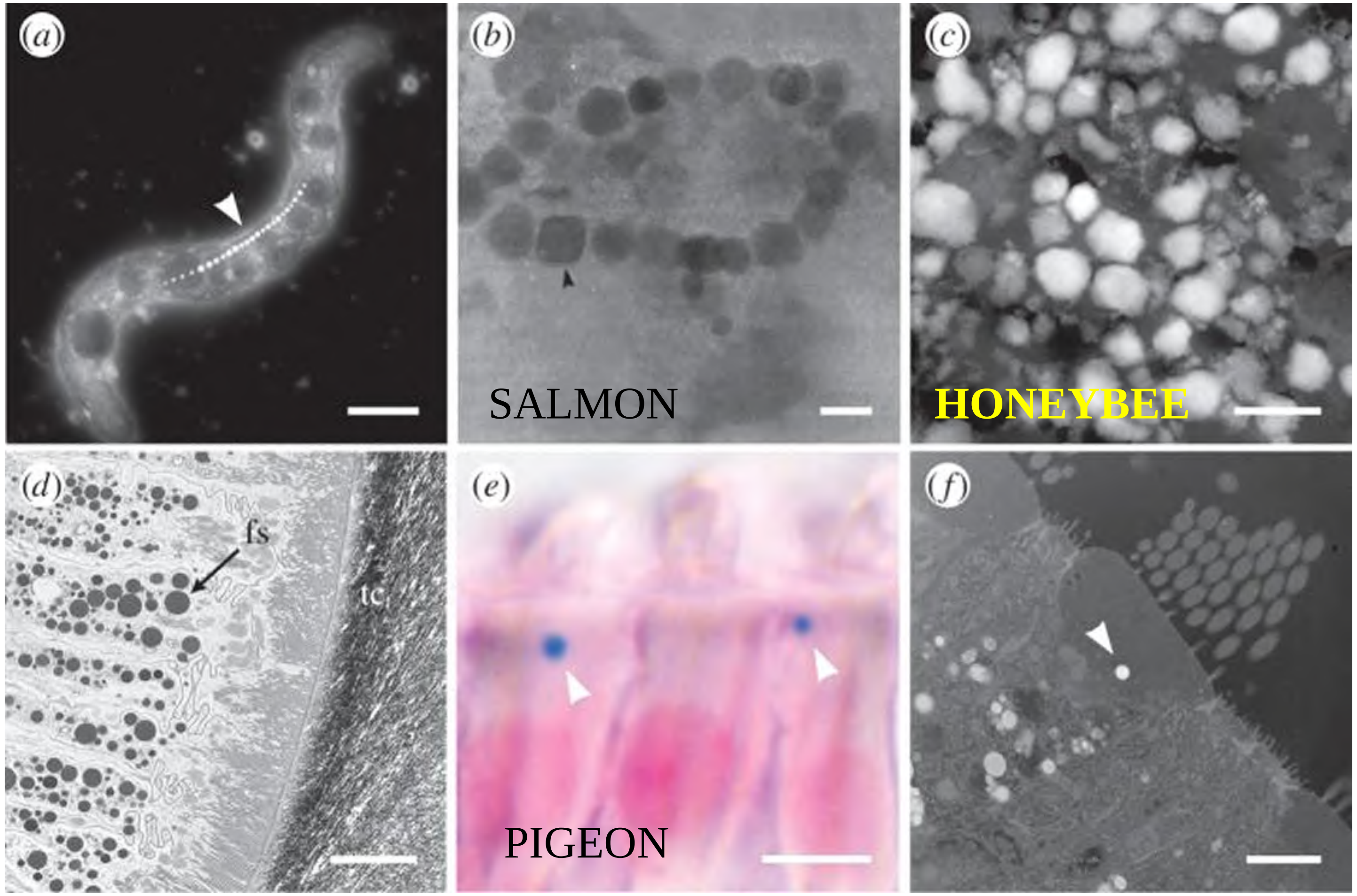
Larger particle size

Doping

Iron oxide Nanoparticles

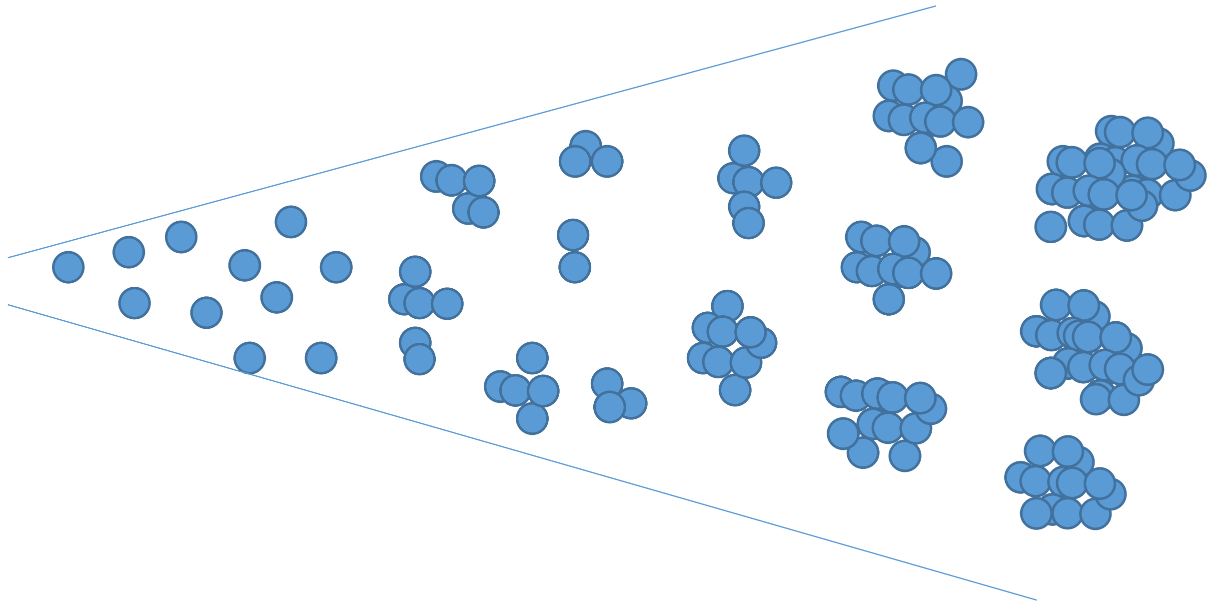
Living organisms

Magnetotactic bacteria



Aggregation

Primary particles | Partially aggregate | Aggregates



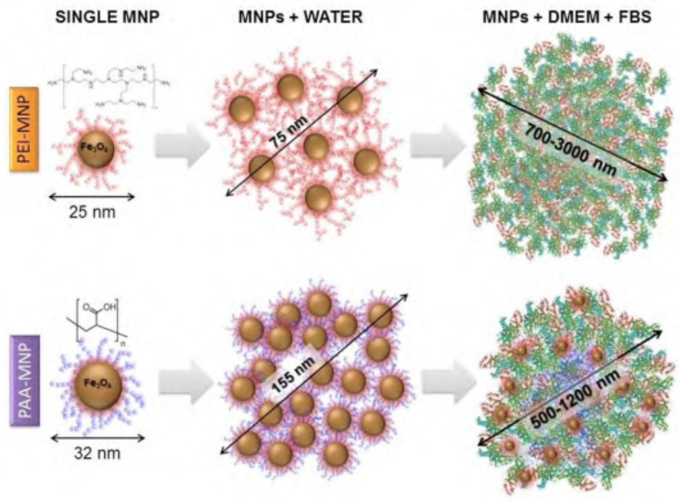
Surface area decreases with increasing aggregation

The measured size increases with aggregation

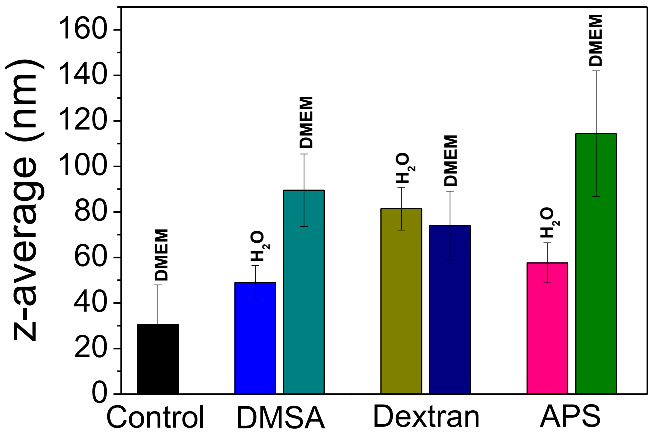
Control aggregation !!

Aggregation: NP-biosystems

Cell Culture media

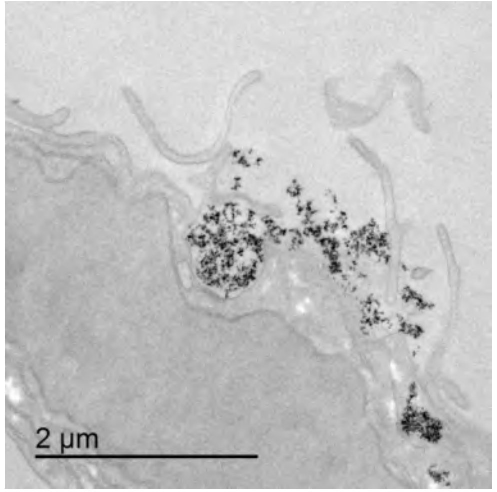


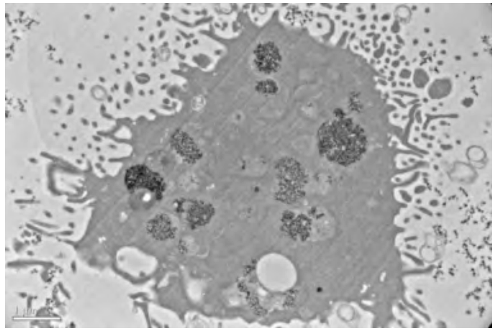
http://nanomagnetism.blogspot.com.es/

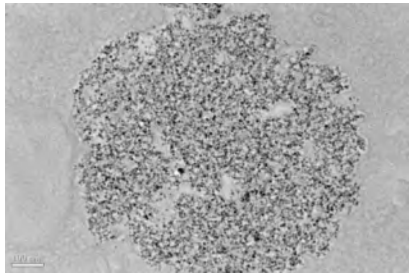


Nanoscale, 2013, 5, 11428-11437

Cell uptake

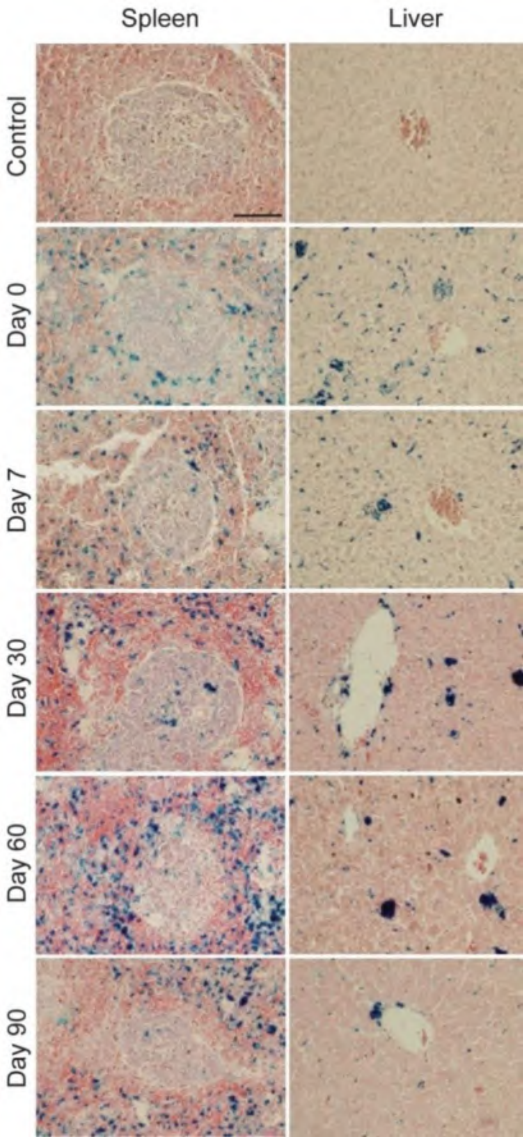






Nanomedicine: Nanotechnology, Biology, and Medicine, 10 (2014) 733–743

Tissue diffusion

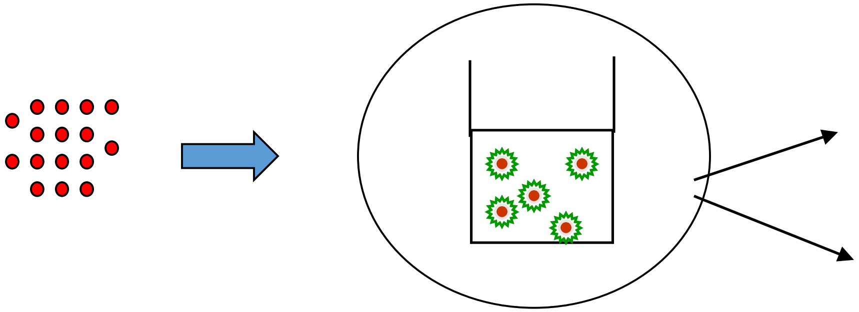


Journal of Controlled Release 171 (2013) 225–233

Requirements

Nanoparticles for biomedical applications

NANOPARTICLES | **COLLOIDAL SUSPENSIONS** | **APPLICATIONS** | **REQUIREMENTS**



In vitro

In vivo

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

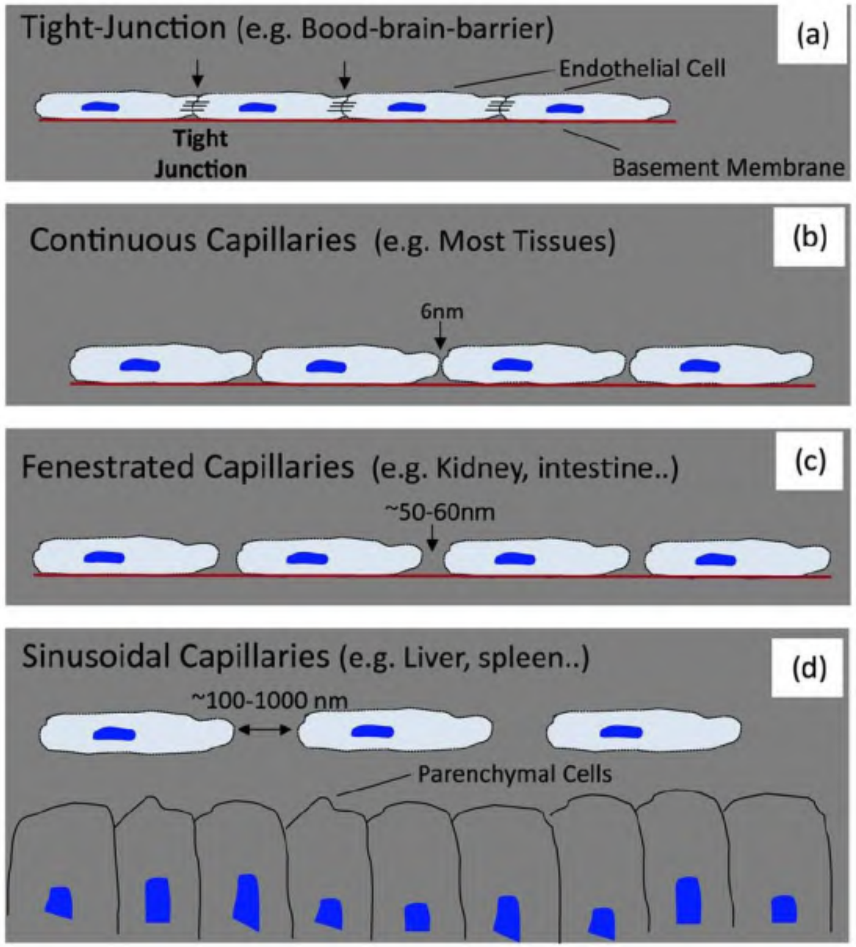
No toxic!!

- Stable
- Biocompatible
- Reversible

P. Tartaj et al. J. Phys. D: Appl. Phys., (2003) R182
Roca et al, . J. Phys. D: Appl. Phys., (2009)
S. Laurent et al, Chem. Rev., 108, 2064 (2008)

Nanoparticles for biomedical applications

Biology barriers



Blood capillaries

Gaps between endothelial cells

2 nm

6 nm

50 nm

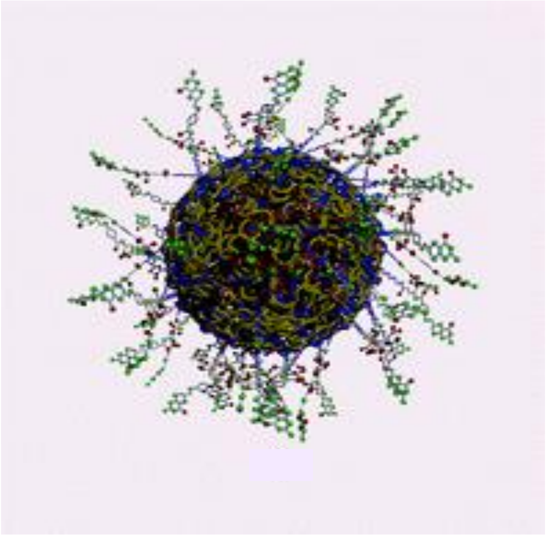
> 100 nm

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

Nanoparticles for biomedical applications

Surface

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



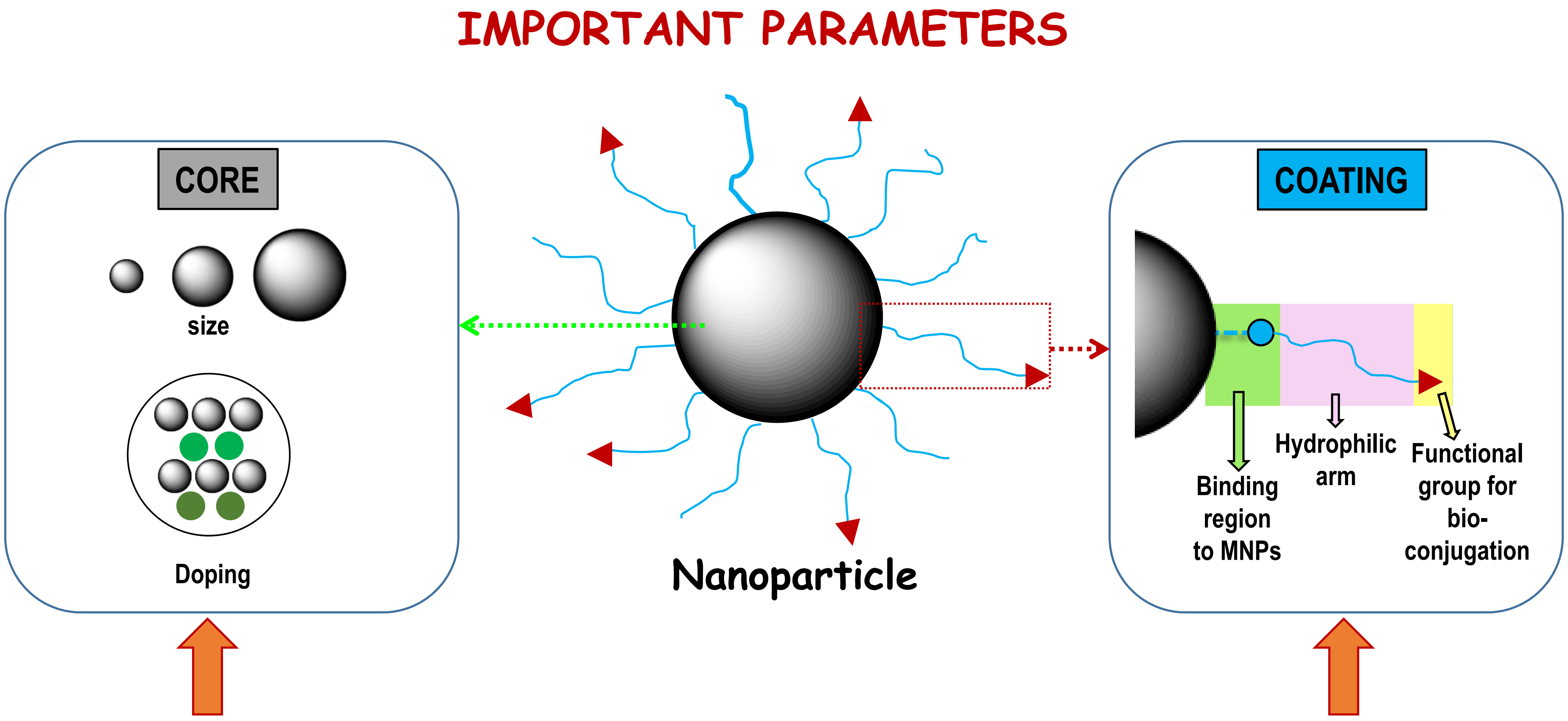
=> **Biocompatible** = **Hydrophilic coating** make the particle look friendly to the immune system

- 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

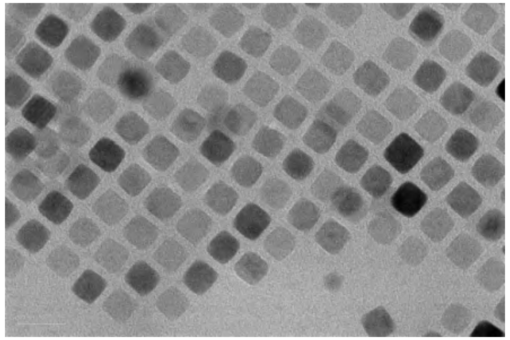
Design a Nanoparticle for each application

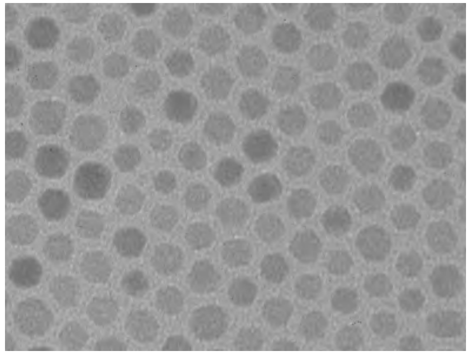


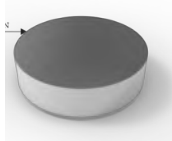
- Different core size
- Different core composition

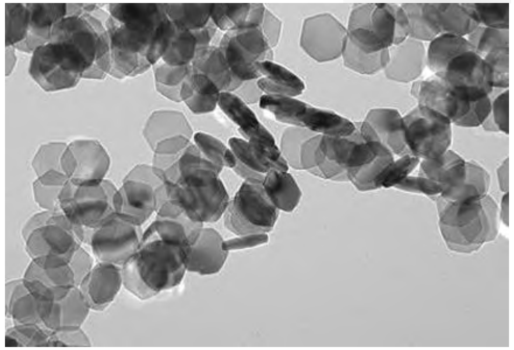
- Biocompatible polymers
- Colloidal stability
- Strong anchoring
- > MNPs blood life-time
- Core protection

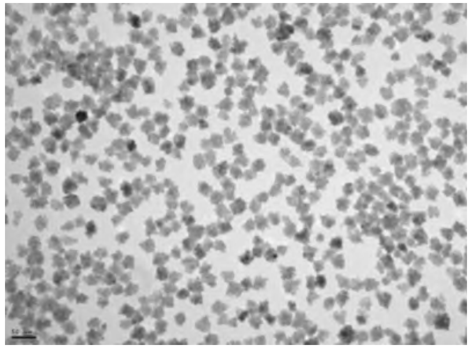
Comparison with other morphologies

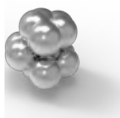


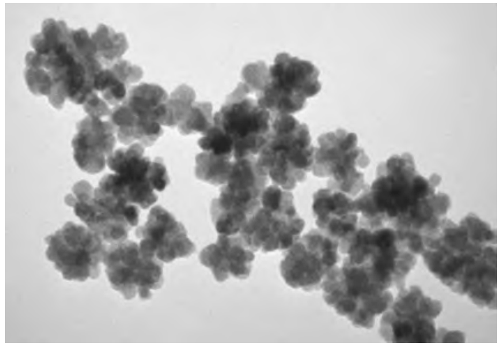


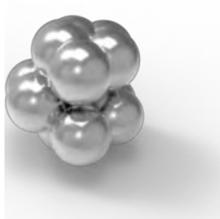


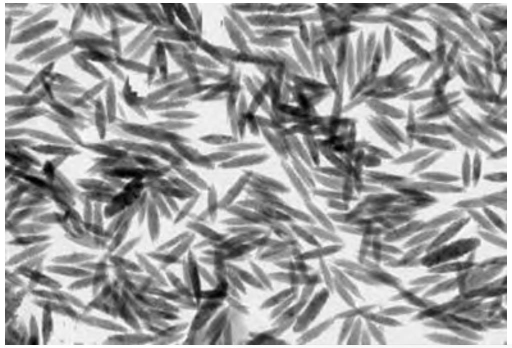




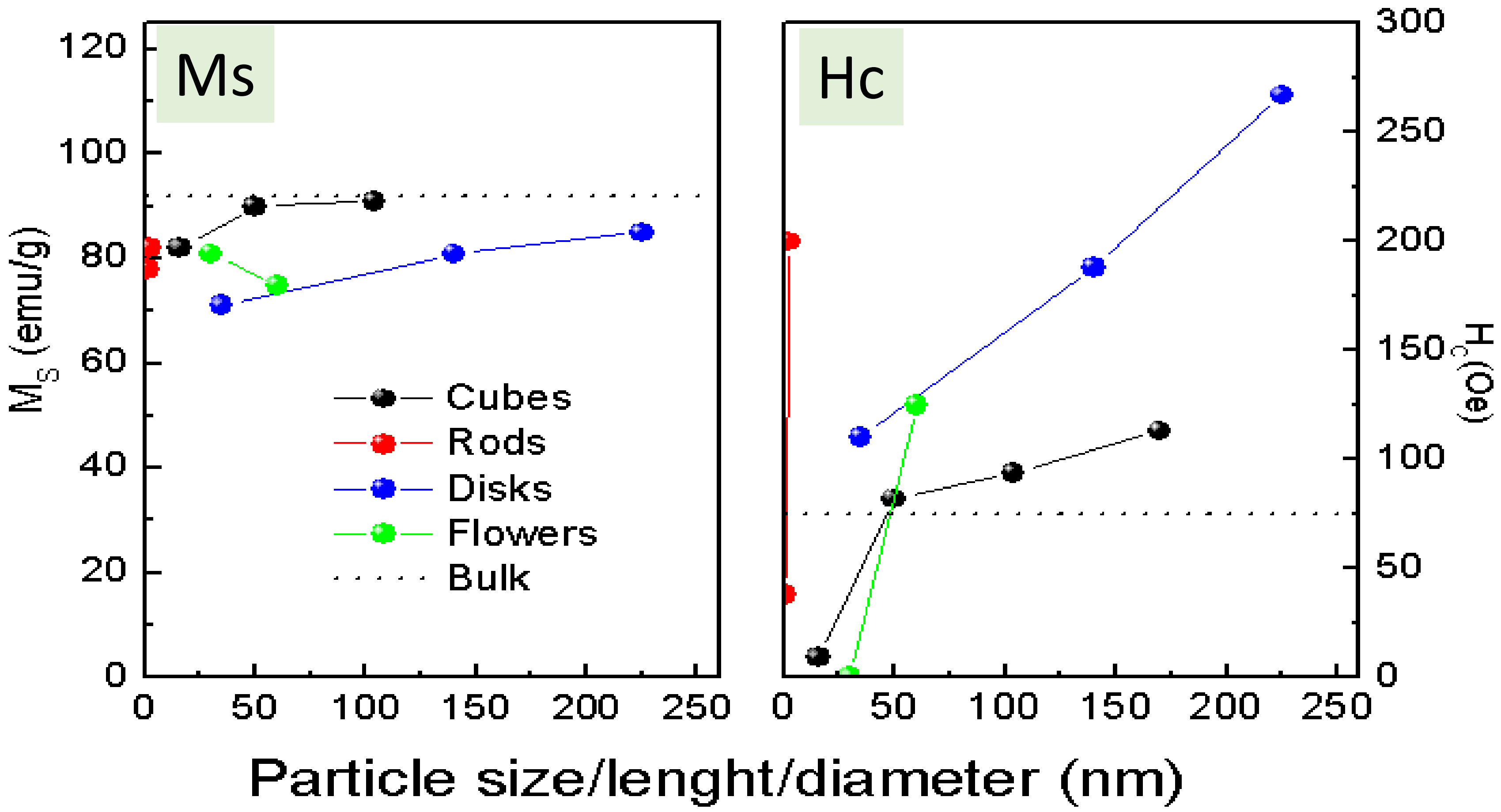




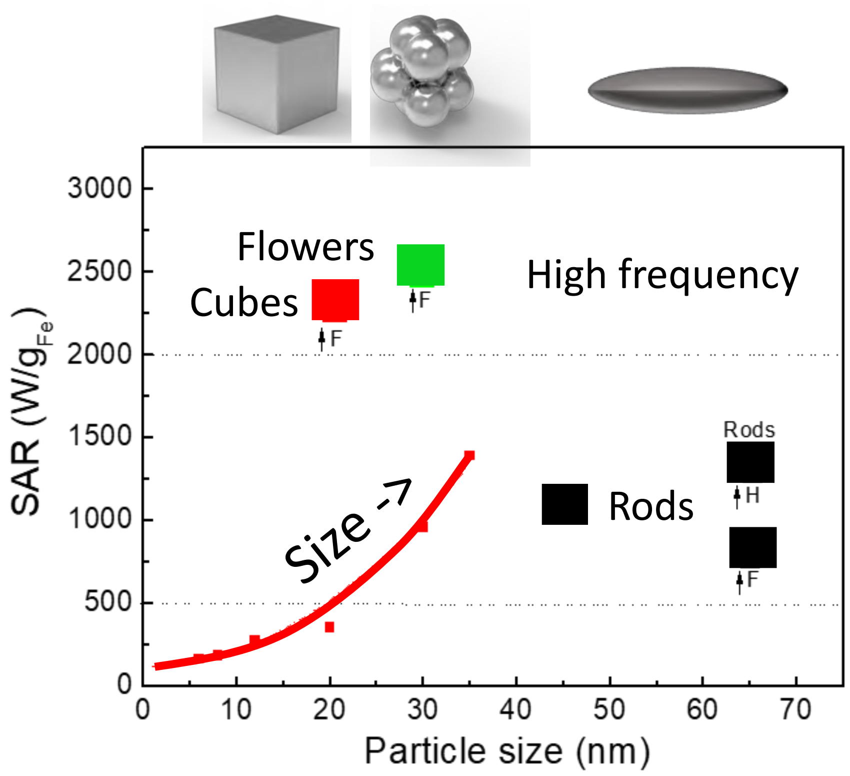




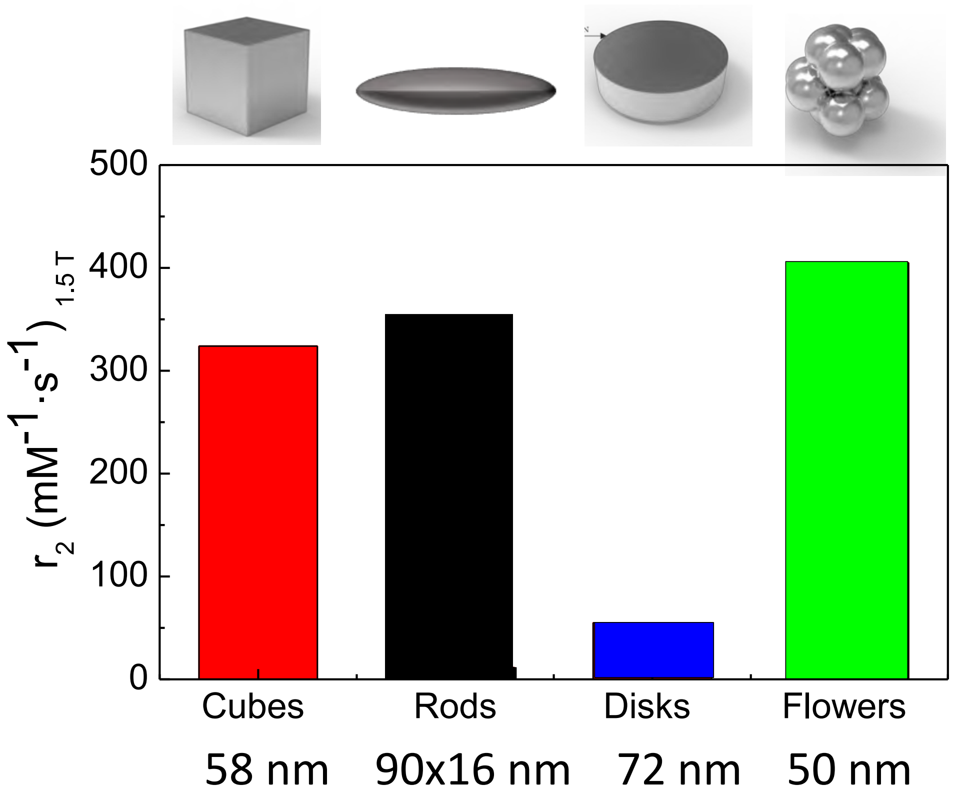
Comparison with other morphologies



Heating capacity



NMR relaxivity

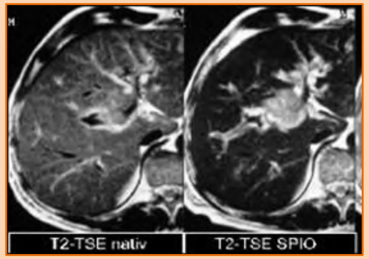


Design Strategies for Shape-Controlled Magnetic Iron Oxide Nanoparticles, Roca et al., Adv. Drug Delivery Rev. 2019

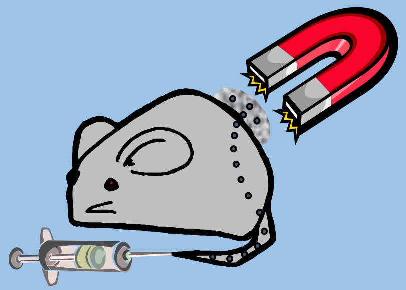
Applications

Applications

Contrast agents



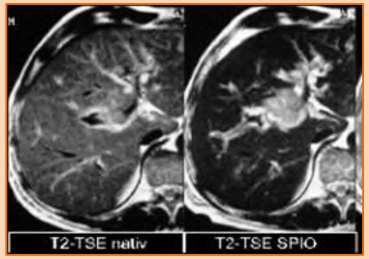
Drug Delivery



Hyperthermia

NMR Imaging

Contrast agents



The most powerful technique for diagnosis

Nobel Prize 2003

Paul C. Lauterbur and Sir Peter Mansfield

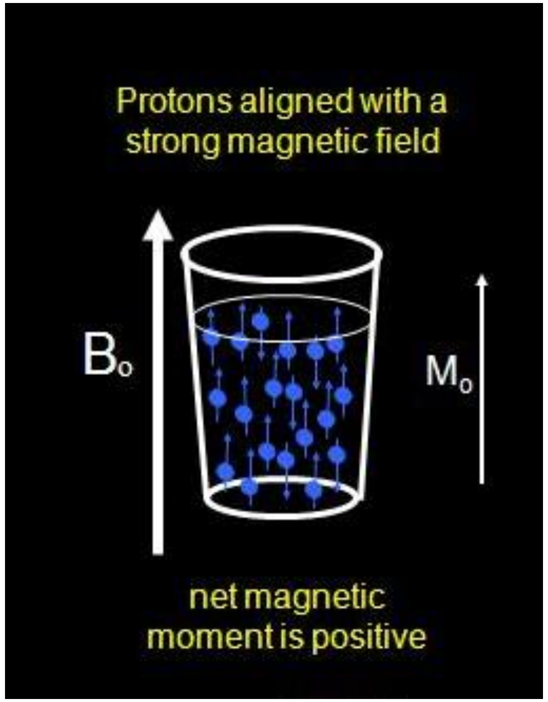
"for their discoveries concerning magnetic resonance imaging"

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

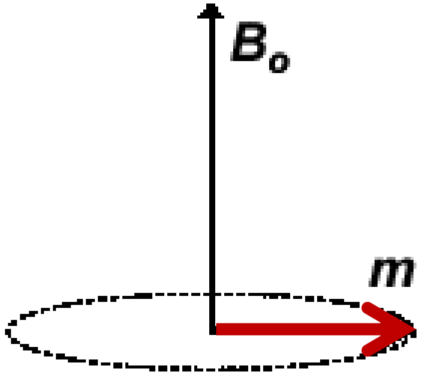
Instead: it is a technique that combines a large magnetic field and some radio frequency antennas

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

NMR Imaging



high-frequency electro-magnetic pulse



protons out of alignment

"resonance" signal as the proton goes back into alignment

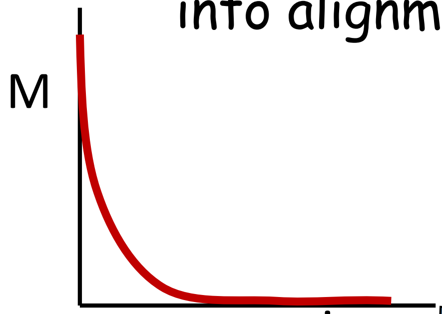
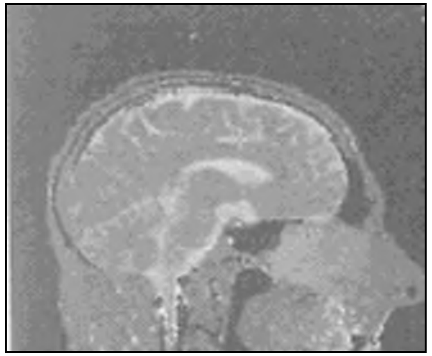
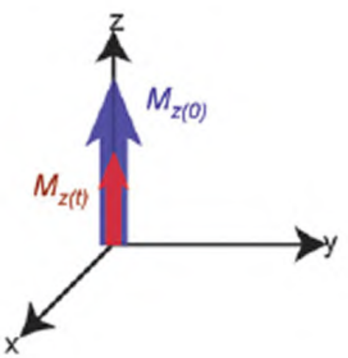


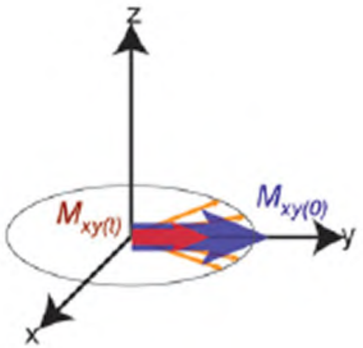
image reflects the water protons in the patient and their chemical association with proteins



NMR Imaging

T1





T2

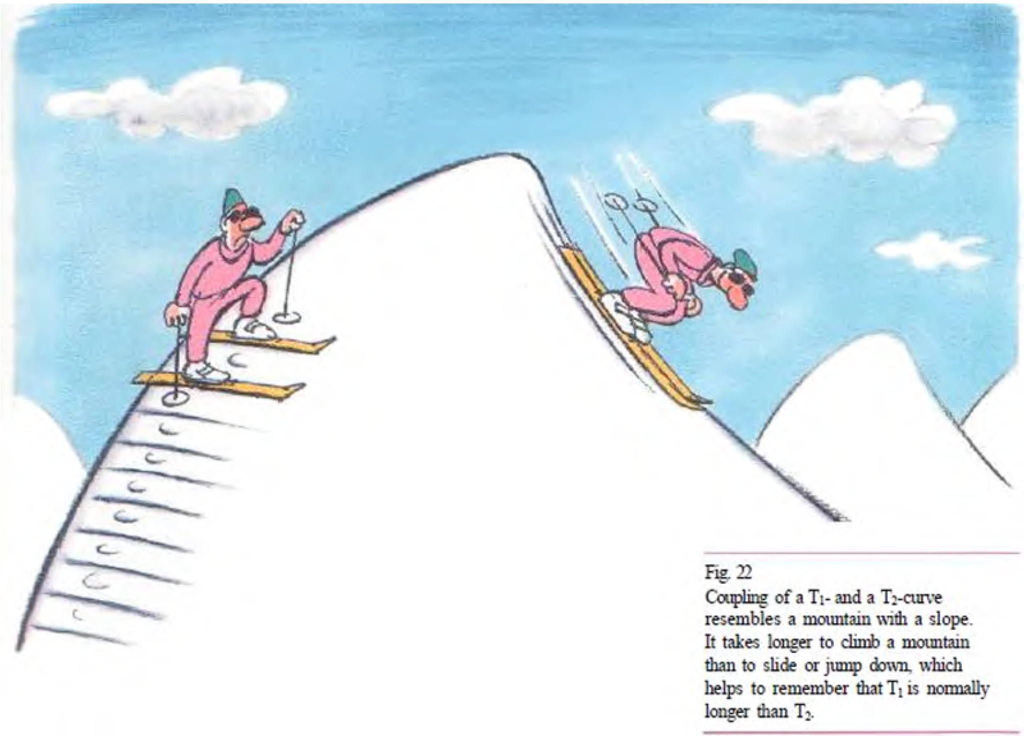
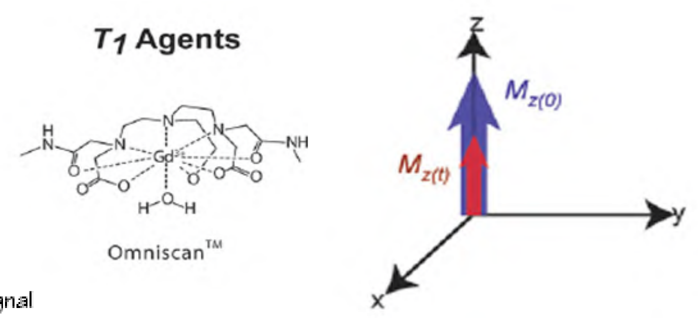
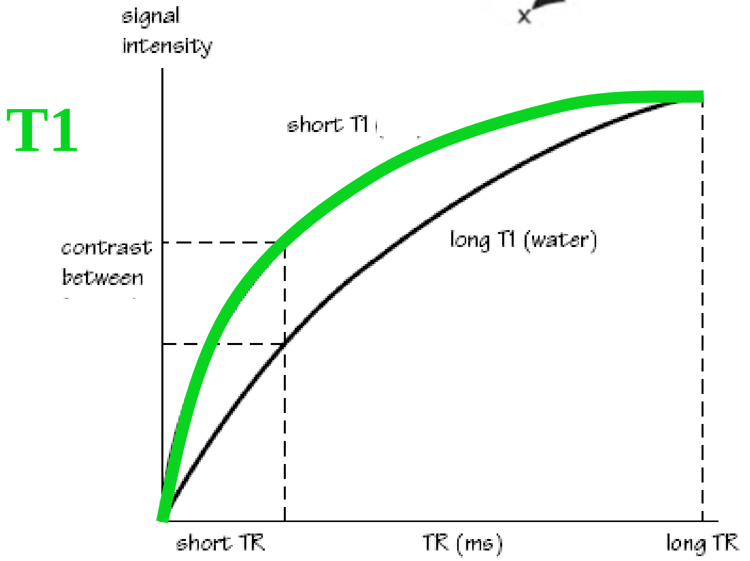


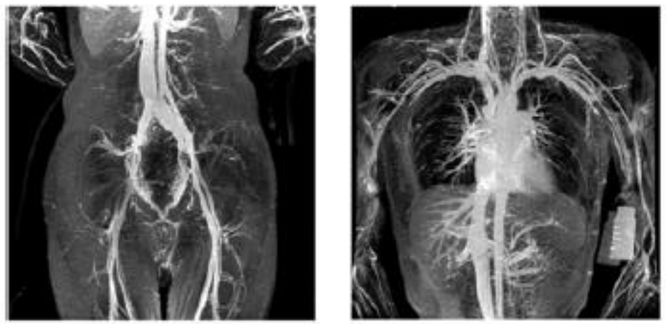
Fig. 22
Coupling of a T_1- and a T_2-curve resembles a mountain with a slope. It takes longer to climb a mountain than to slide or jump down, which helps to remember that T_1 is normally longer than T_2.

MRI made easy

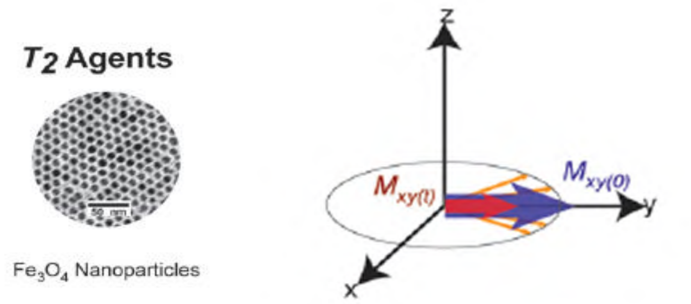
NMR Imaging

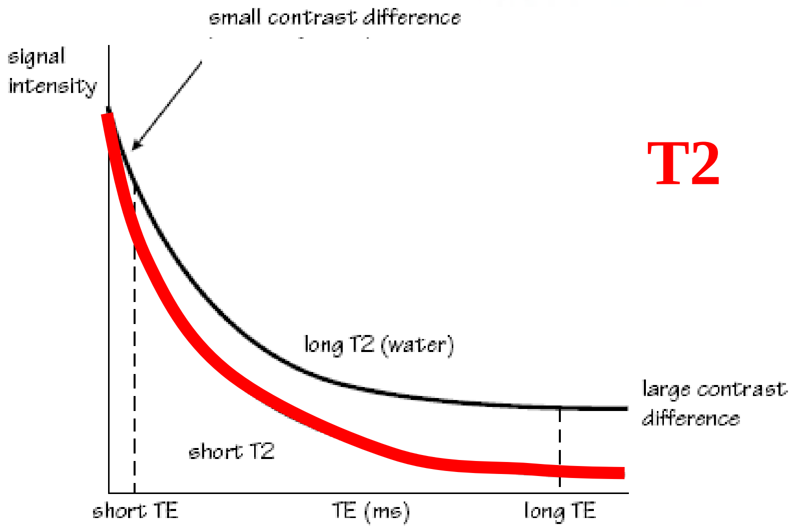


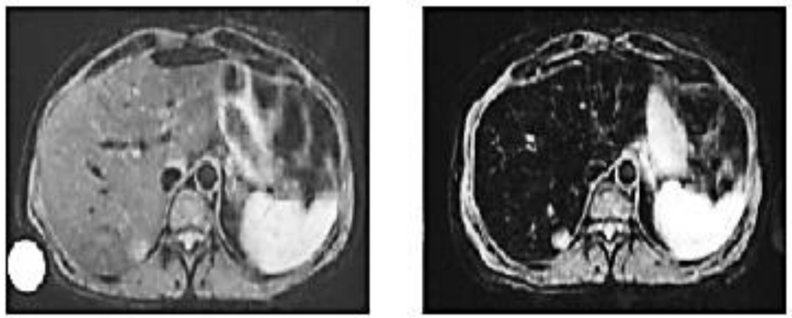




Positive contrast





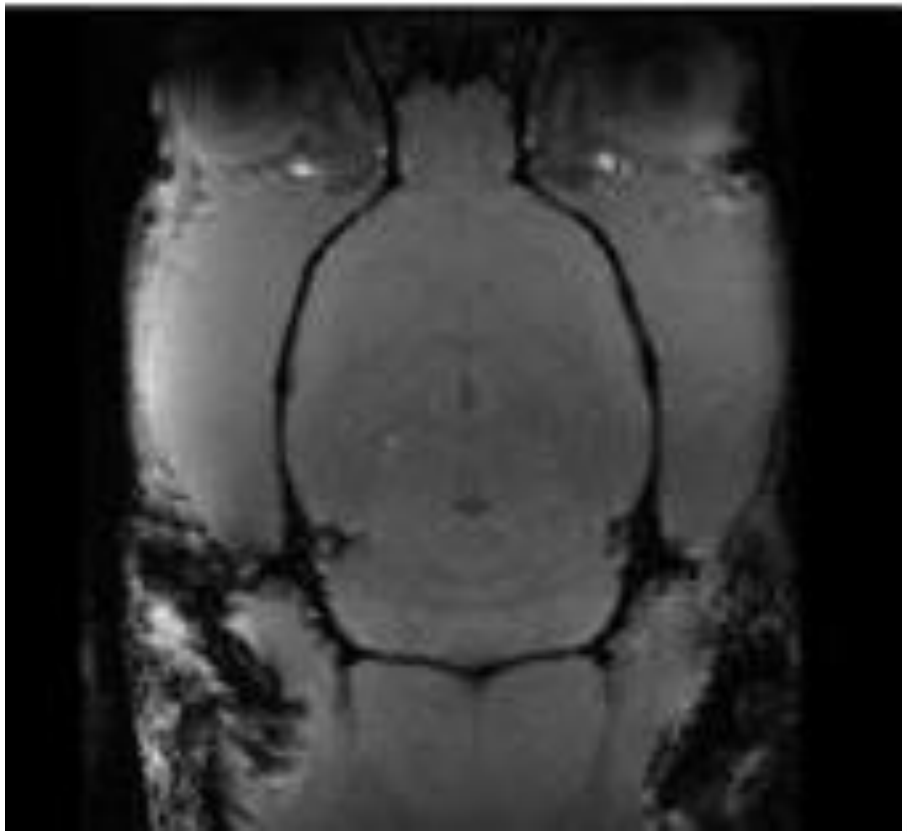


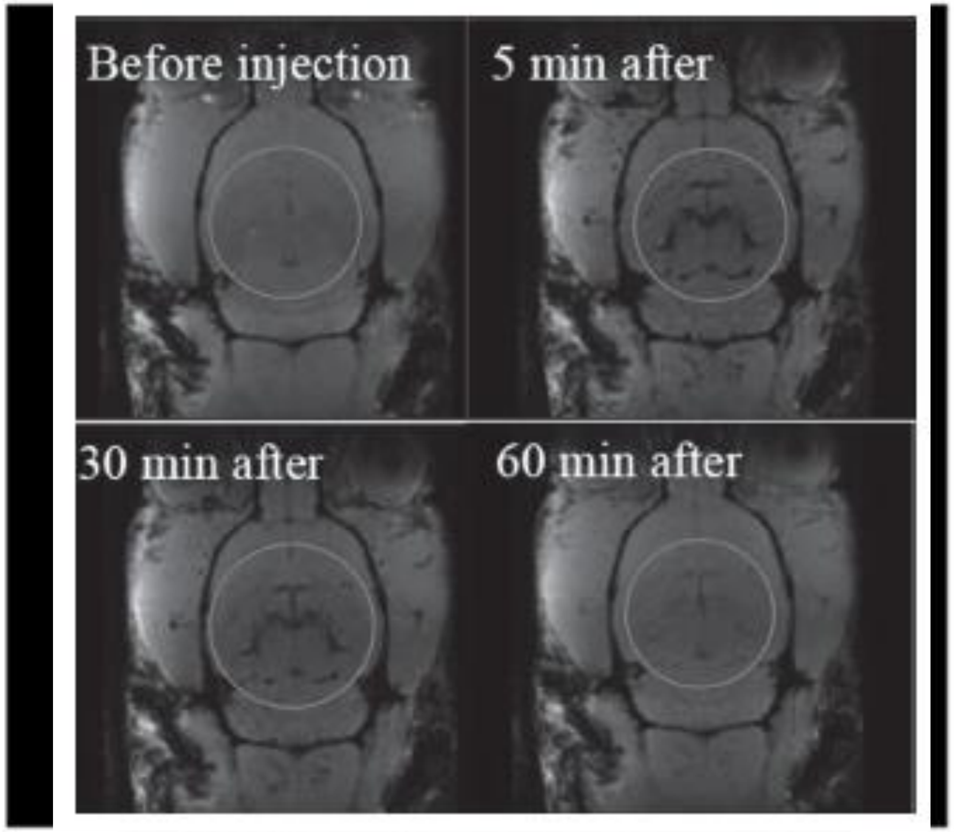
Negative contrast

Contrast agent for T2 NMR Imaging

USPIO

NMR IMAGING OF RAT BRAIN DURING 1 HOUR





Arrowheads (*Yellow*)- Third Ventricle
Arrows (*white*)- Lateral Ventricle
Arrowheads (*blue*)- Recess *Inferior Colliculus*

R. Mejias et al., Nanomedicine 2010

Problems

Black signal in the image is difficult to distinguish in several pathologies showing a natural hypo-intense area due to **calcium deposits**, **bleeding** or **other metals** that might be present.

Contrast agents for T1 NMR imaging

Microwave synthesis and functionalisation

Extremely fast and reproducible synthesis of nanoparticles

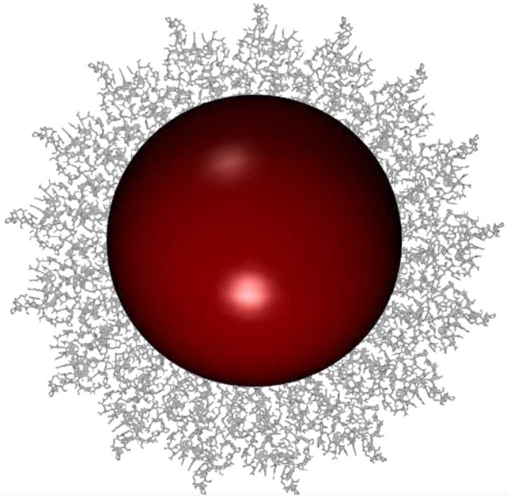
$FeCl_3$

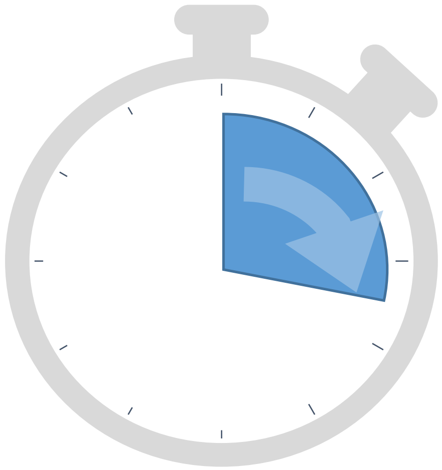
Polymers / Molecules

(Sodium Citrate)

water

100 ºC / 10 min → Hydrazine

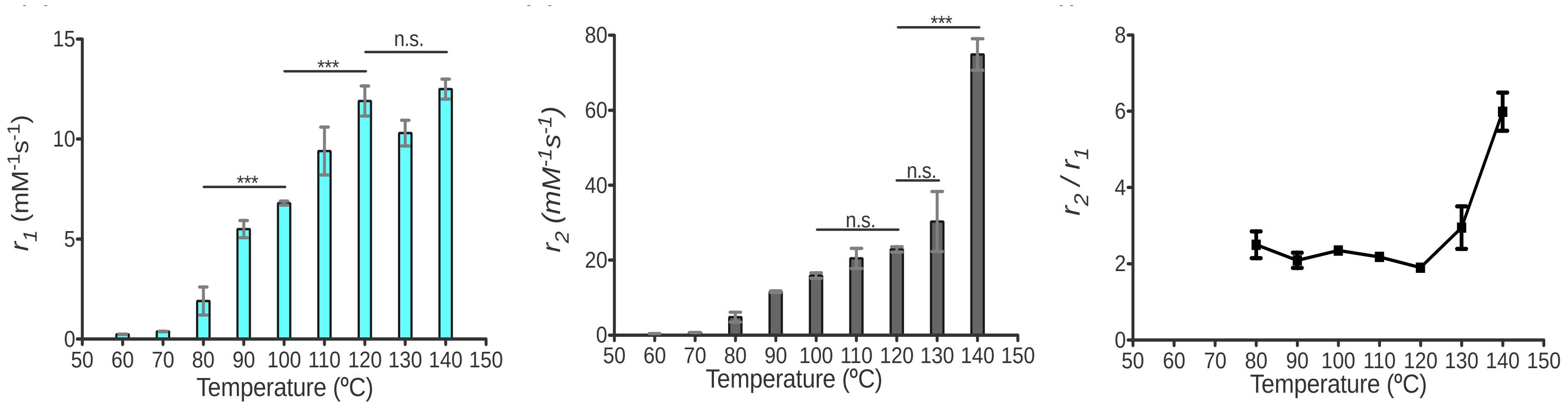


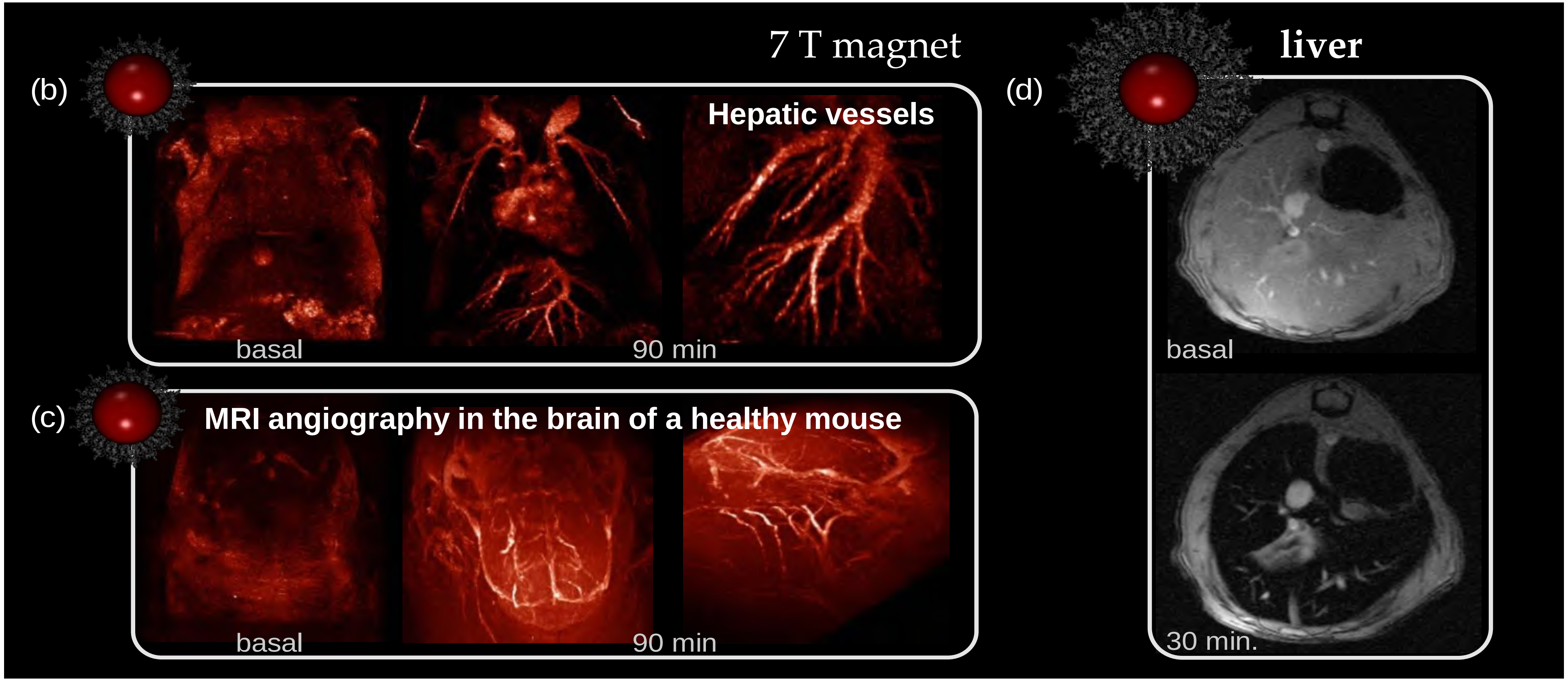


Pellico et al. Contrast Media & Molecular Imaging, 2016
Langmuir 33 (39), 10239-10247, 2017
ACS Omega, 42, 2719-2727, 2019

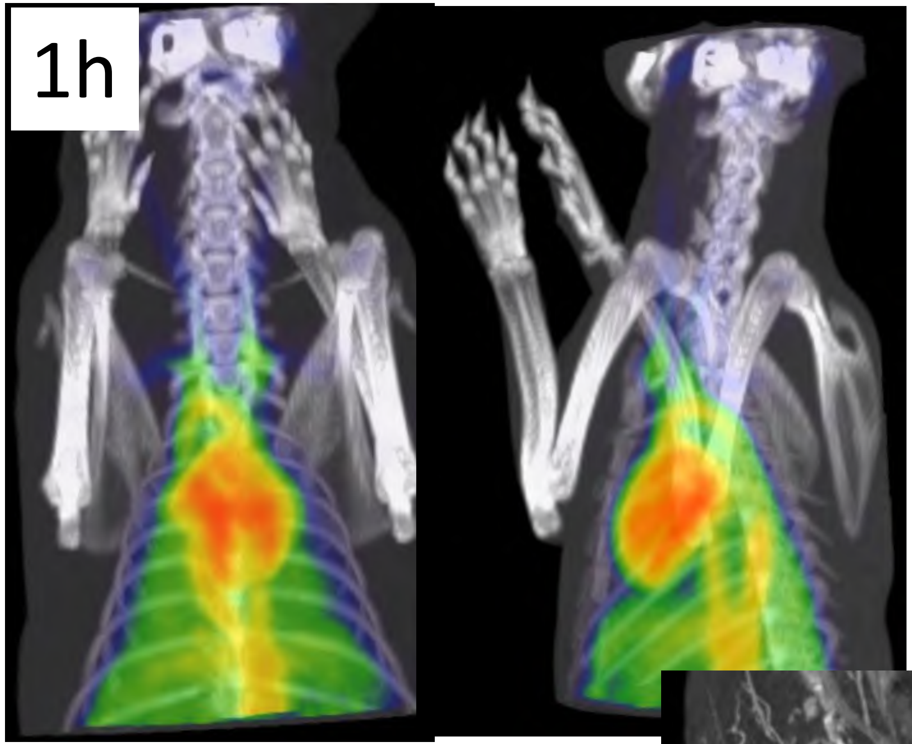
240 W for 10 min at 60, 70, 80, 90, 100, 110, 120, 130, and 140 ºC

Contrast agent for T1 NMR Imaging

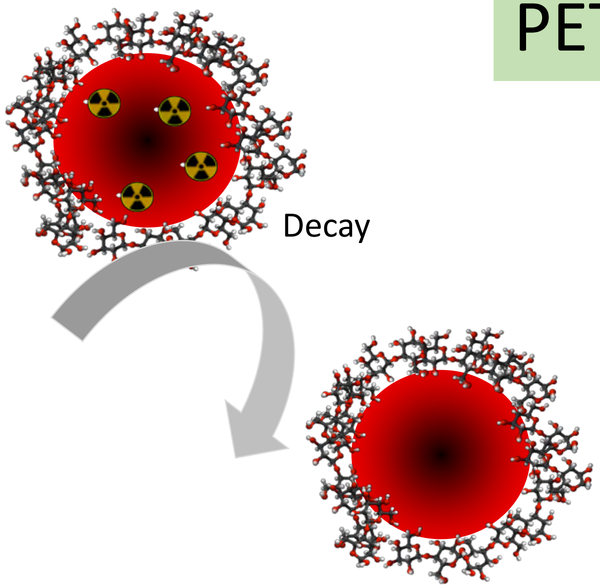


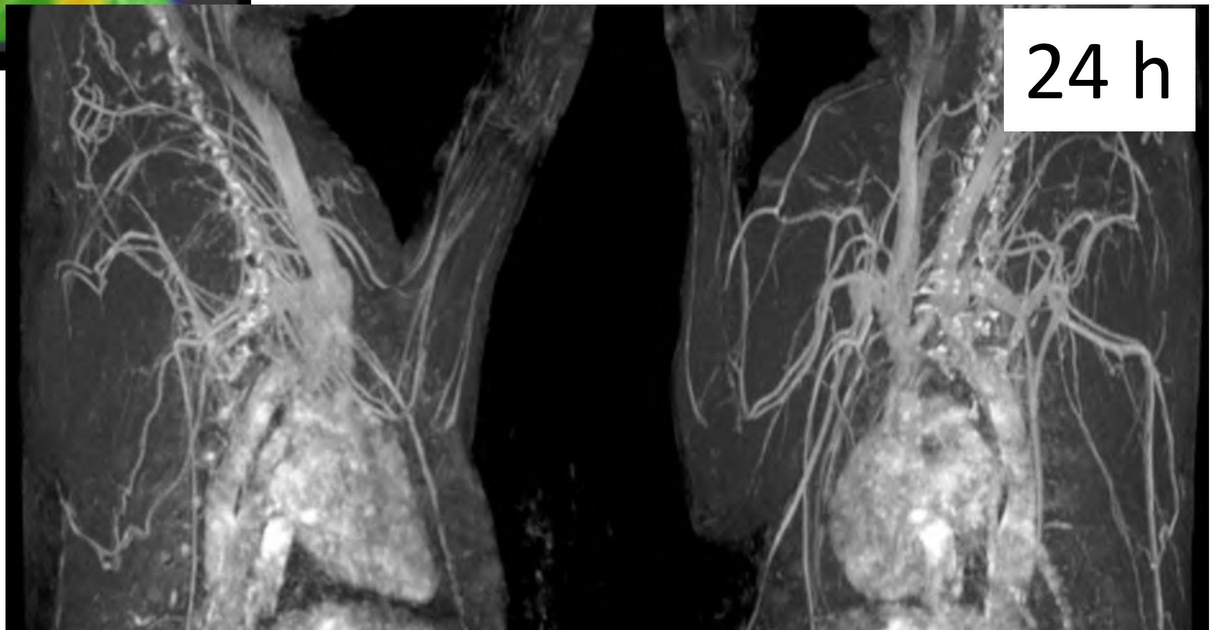


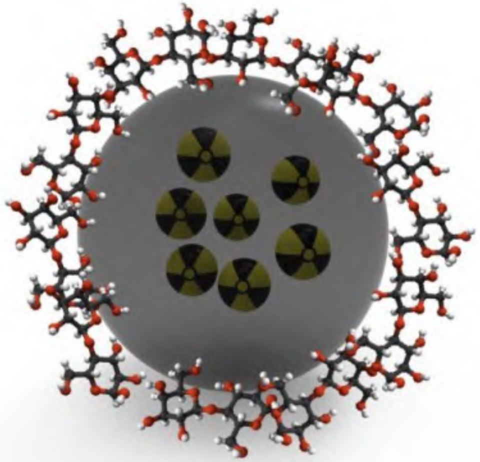
Magnetic nano-radiotracers



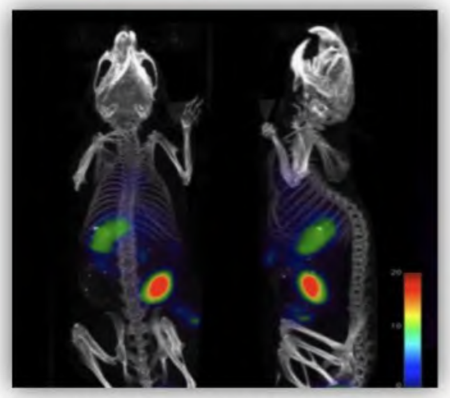
PET + MRI





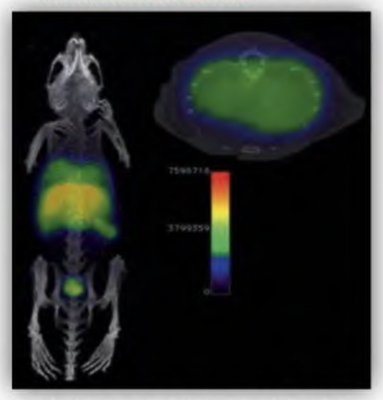


Tumour PET



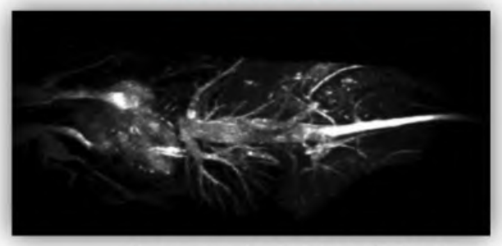
Contrast Media Mol. Imaging ***2016***, *203.*

Inflammation PET



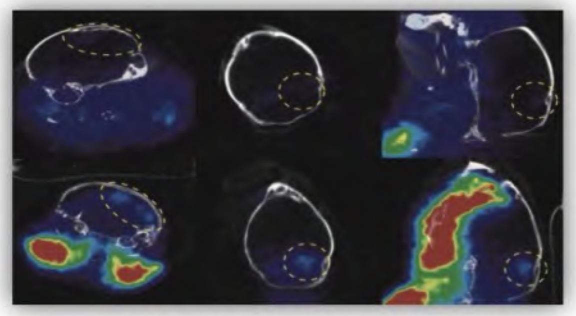
Sci. Rep. ***2017***, *7, 13242.*

MR angiography



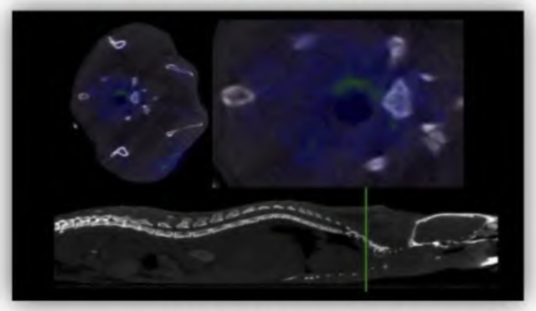
Langmuir. ***2017***, *10239*

Brain thrombi PET



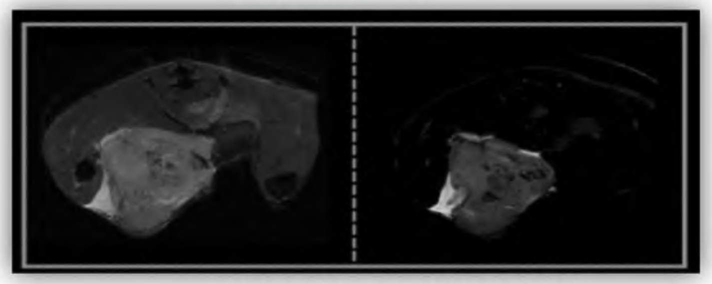
Nanoscale. ***2020***. *12, 22978*

Atherosclerosis PET



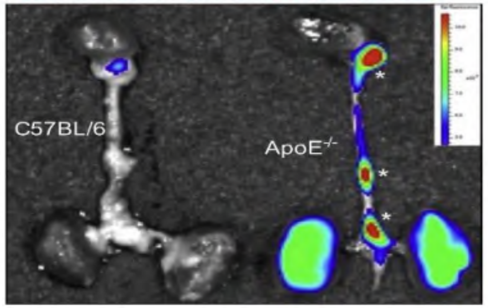
Nanomedicine NBM. ***2019***, *26.*

Tumour MRI



ACS Omega. ***2019***, *2719*

Atherosclerosis Fluoresc.



Nanomedicine NBM. ***2018***, *643.*

NanoMedMol
Nanomedicine and Molecular Imaging group
IQM Instituto de Química Médica
ciberes Centro de Investigación Biomédica en Red Enfermedades Respiratorias
fherranz@iqm.csic.es

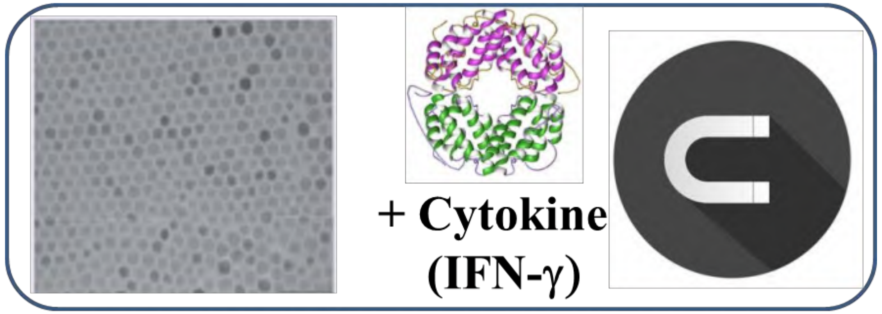
Twitter: @F_Herranz
@NanoMedMol

Comparison of MPI with common clinical imaging modalities

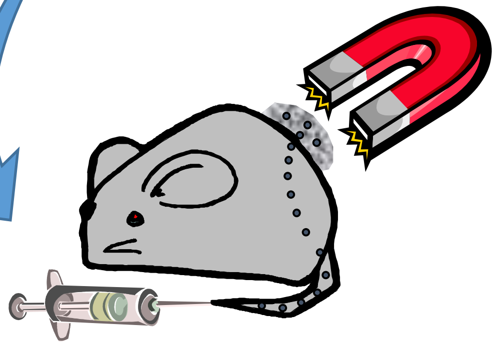
Modality	Ultrasound	CT	MRI	PET	SPECT	MPI
Main clinical applications	Structural imaging	Structural imaging	Structural imaging	Tracer imaging	Tracer imaging	Tracer imaging
Spatial resolution	1 mm	<1 mm	1 mm	4 mm	3–10 mm	1 mm
Temporal resolution	<1 second	Seconds	Seconds to hours	Minutes	Minutes	<1 second to minutes
Contrast agents/tracers	Microbubbles	Iodine	Gadolinium, iron oxide particles	Radioactive tracers	Radioactive tracers	Iron oxide particles
Sensitivity	Low	Low	Low	High	High	High
Patient risk	Heating and cavitation	Radiation	Heating and peripheral nerve stimulation	Radiation	Radiation	Heating and peripheral nerve stimulation
Cost	Low	Medium	High	High	Medium	Medium

AJNR Am J Neuroradiol. 2019 Feb; 40(2): 206–212.

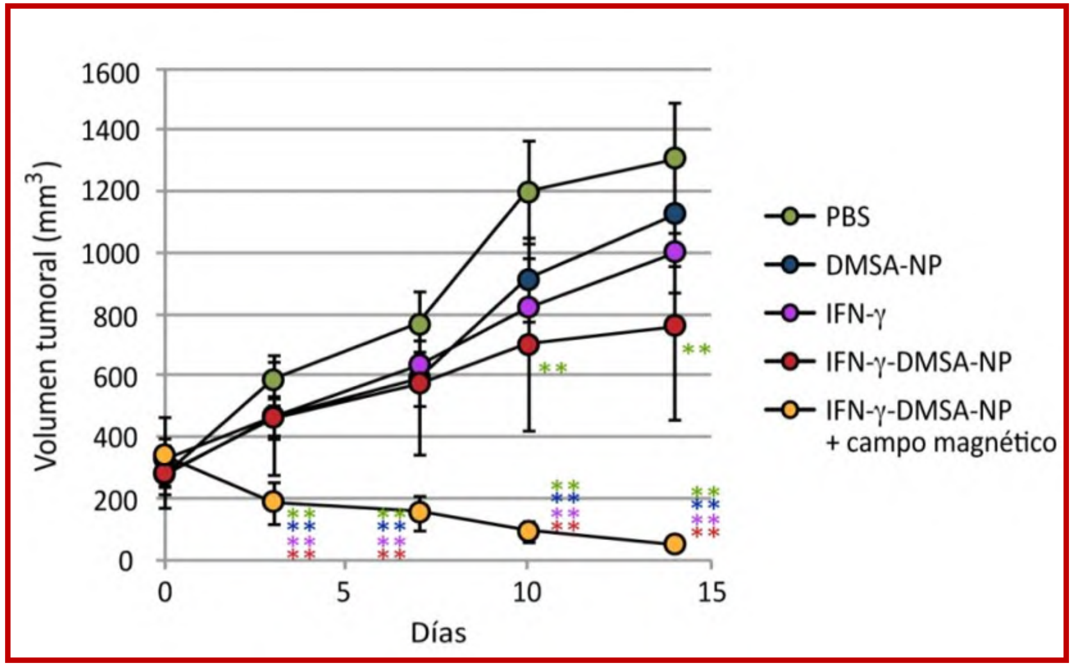
Inmunoterapia



Activa el sistema inmune



Administración local

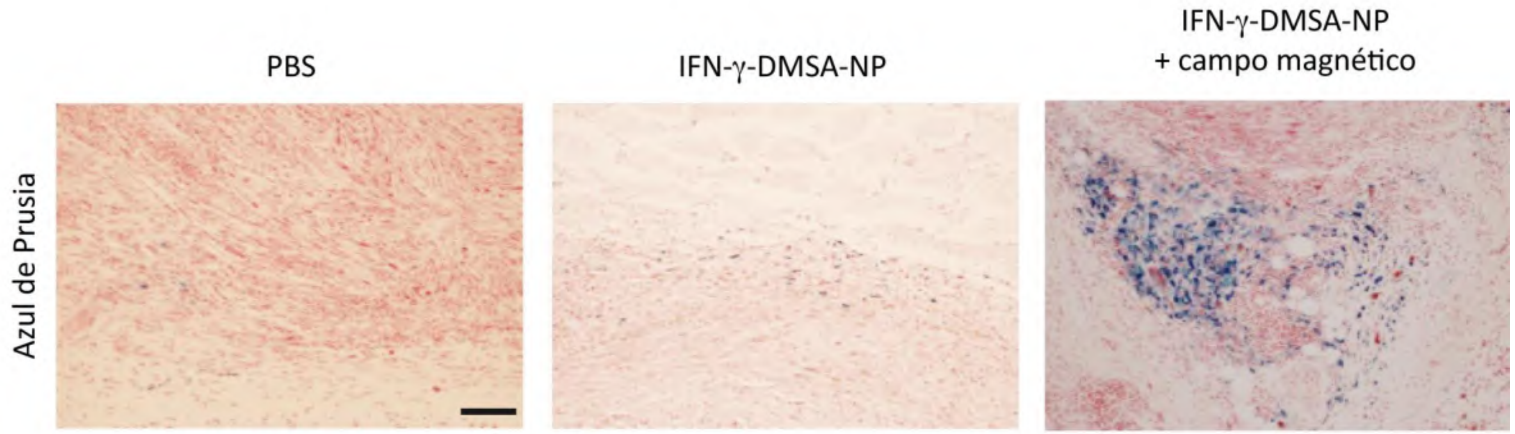


CNB
CENTRO NACIONAL DE BIOTECNOLOGIA

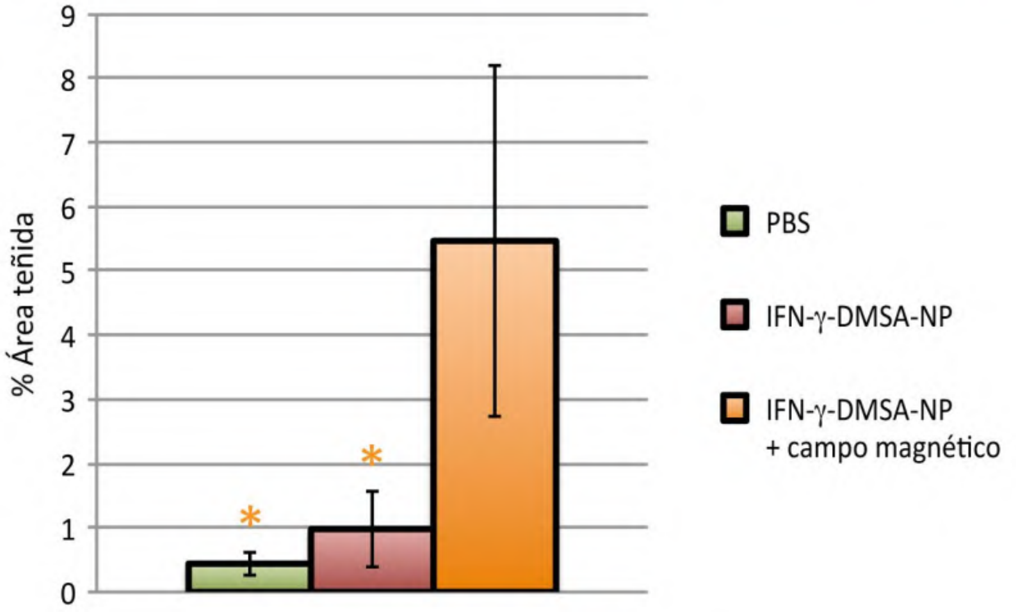
R. Mejias et al, Biomaterials 2011, 2015

Biodistribution in vivo: Non-magnetic methods

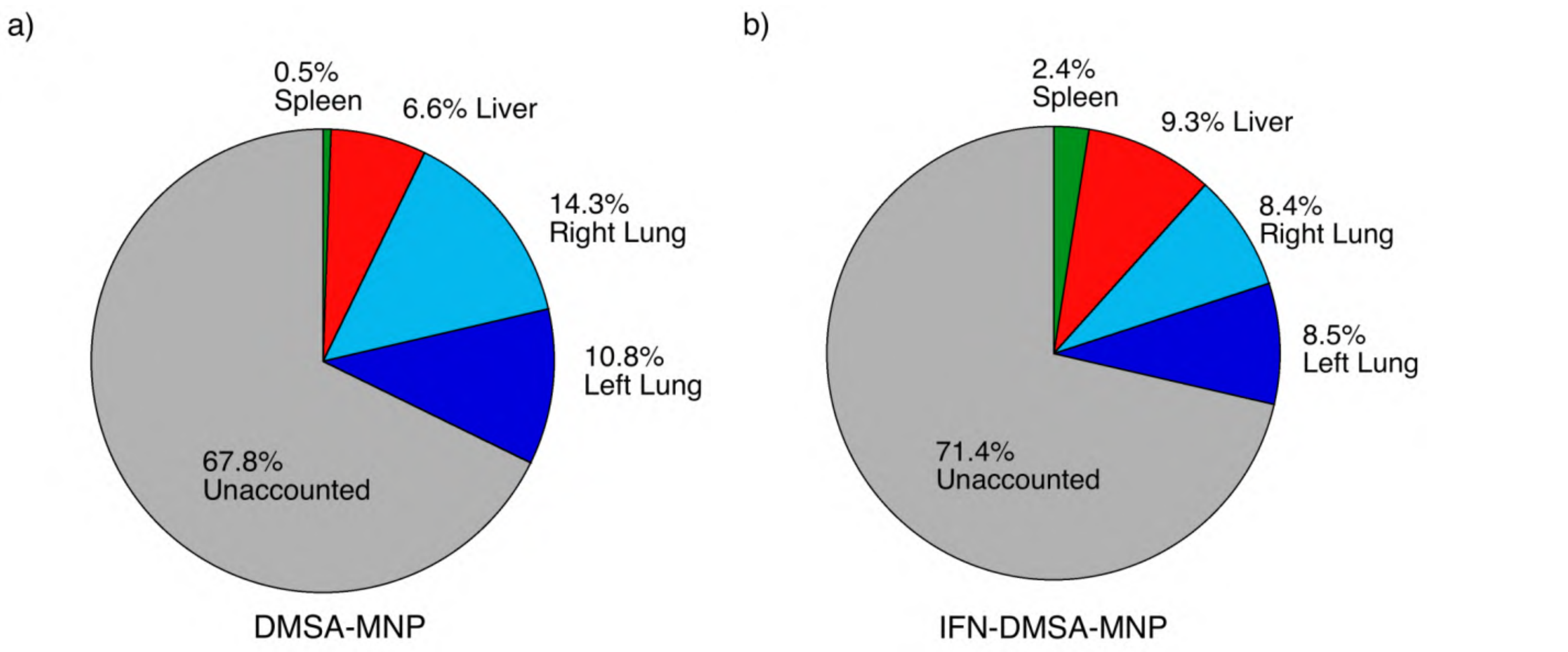
NP in the tissue
Prusian blue



Barra de escala: 100 μm

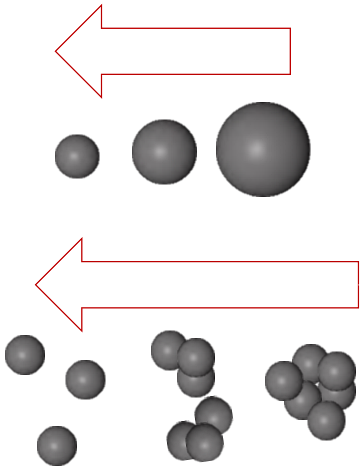


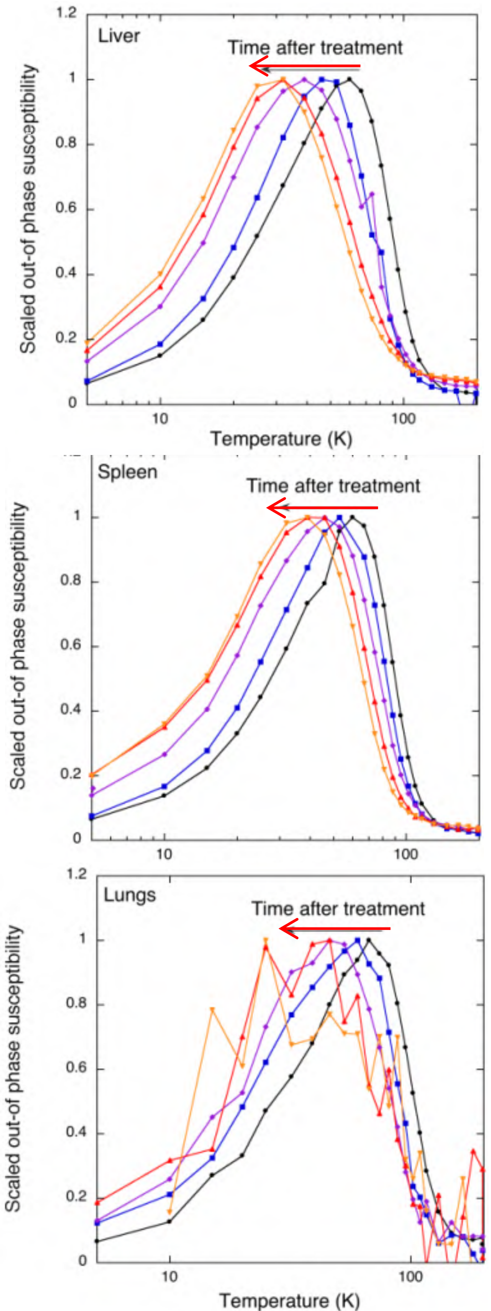
Detection, identification and quantification of NP in biosystems

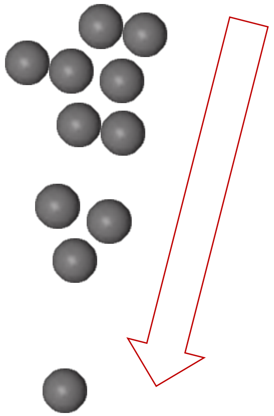


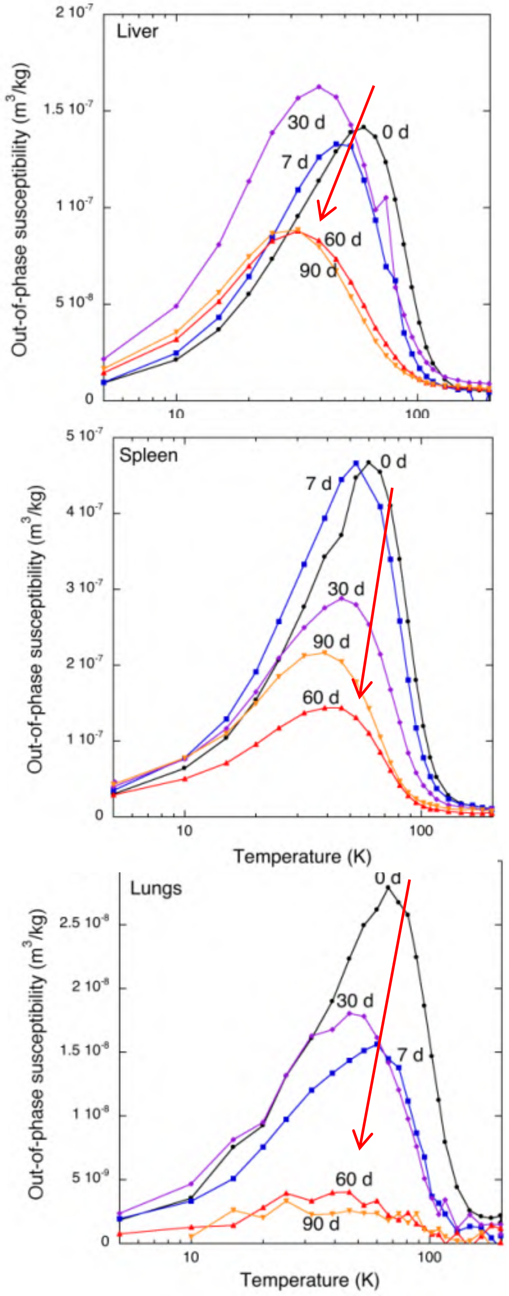
Multiple doses (same dose, twice a week for two weeks)
10% of the total injected iron (1200μg).
30% of the iron administered in the last injection to the animal

Long term particle transformations









Long term biodistribution, biotransformation and toxicity of dimercaptosuccinic acid-coated magnetic nanoparticles

R. Mejías, L. Gutiérrez, G. Salas, S. Pérez-Yagüe, T. M. Zotes, Fr. J. Lázaro, M. P. Morales, D.F. Barber

Journal of Controlled Release 171 (2013) 225–233

Efficiency of the drug carrier and effects on tumor size.

Inyección subcutanea de 2,5x10^6 células Pan02

Días: -7 0 3 7 10 14

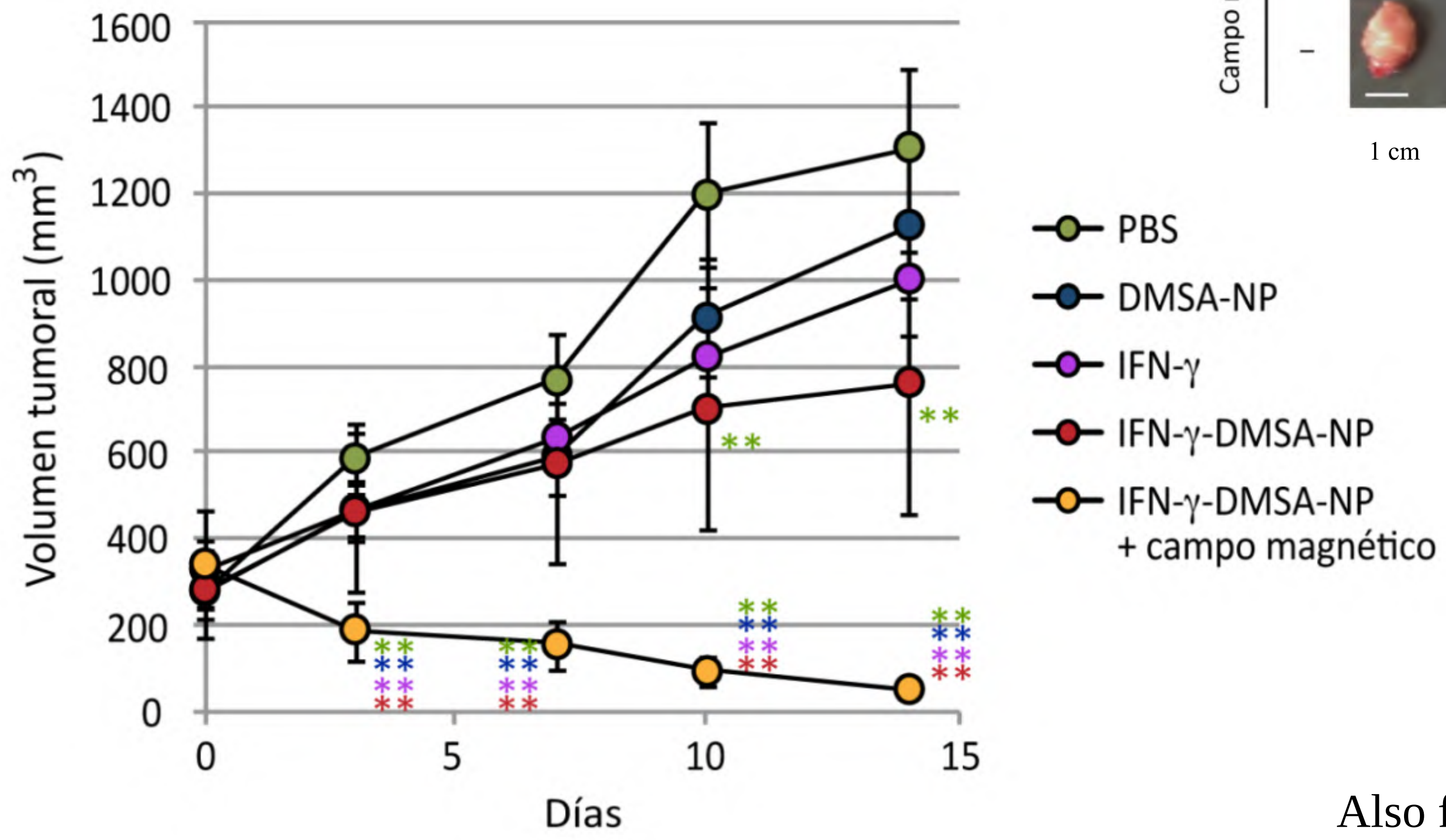
Eutanasia y extracción de tumores:
Tamaño
Presencia de nanopartículas
Niveles de IFN-γ
Inmunohistoquímica

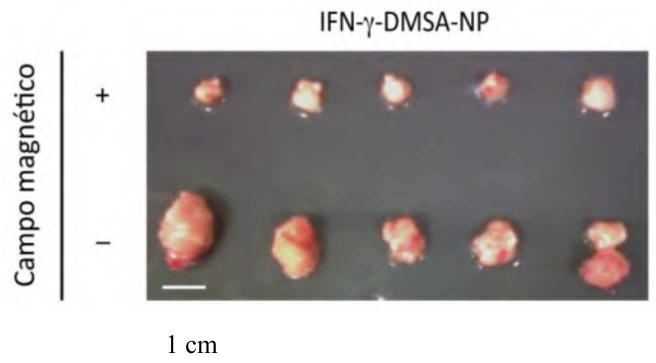
PBS (Control) + campo magnético externo
DMSA-NP (300 μg Fe) + campo magnético externo
IFN-γ (10000 UI) + campo magnético externo
IFN-γ-DMSA-NP (300 μg Fe + 10000 UI) + campo magnético externo
IFN-γ-DMSA-NP (300 μg Fe + 10000 UI)

(0,4 T; 1 h)

Efficiency of the drug carrier and effects on tumor size.

Tumor size



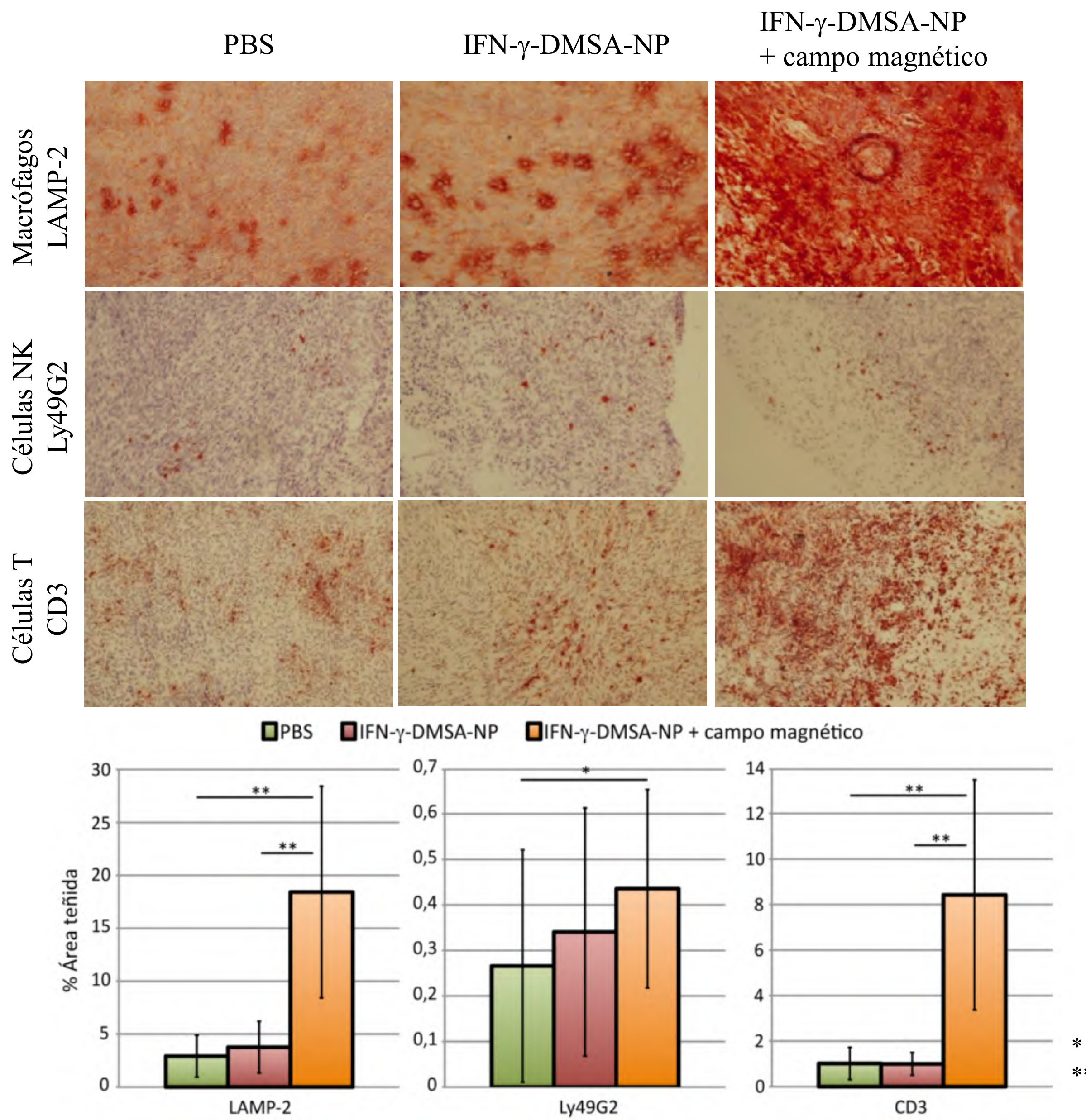


Also for induced tumours
with 3-methylcholanthrene (MCA)

R.Mejías, Biomaterials 32, 2938, 2011

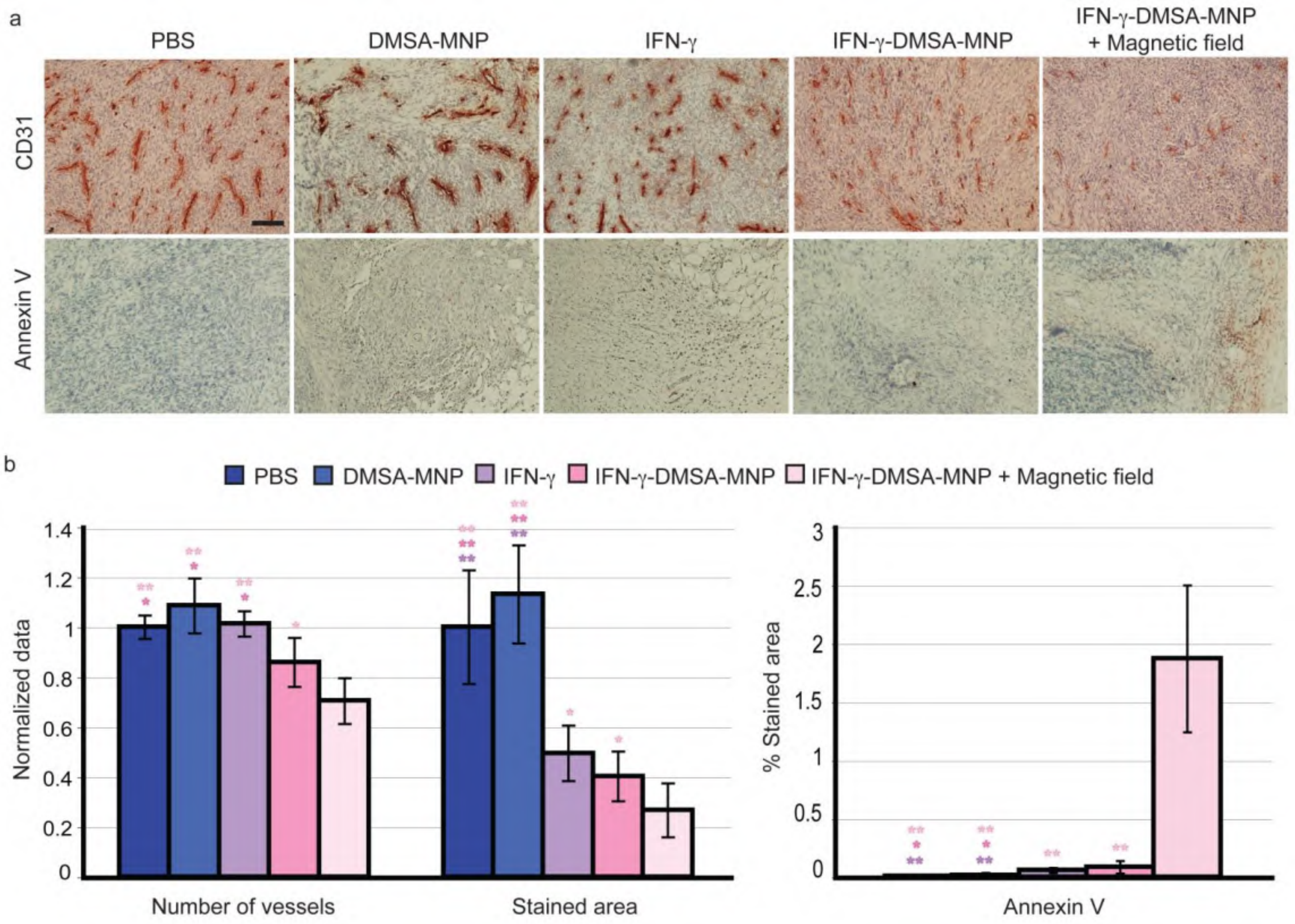
Efficiency of the drug carrier and effects on tumor size.

Inmunology response



* p < 0,05
** p < 0,001

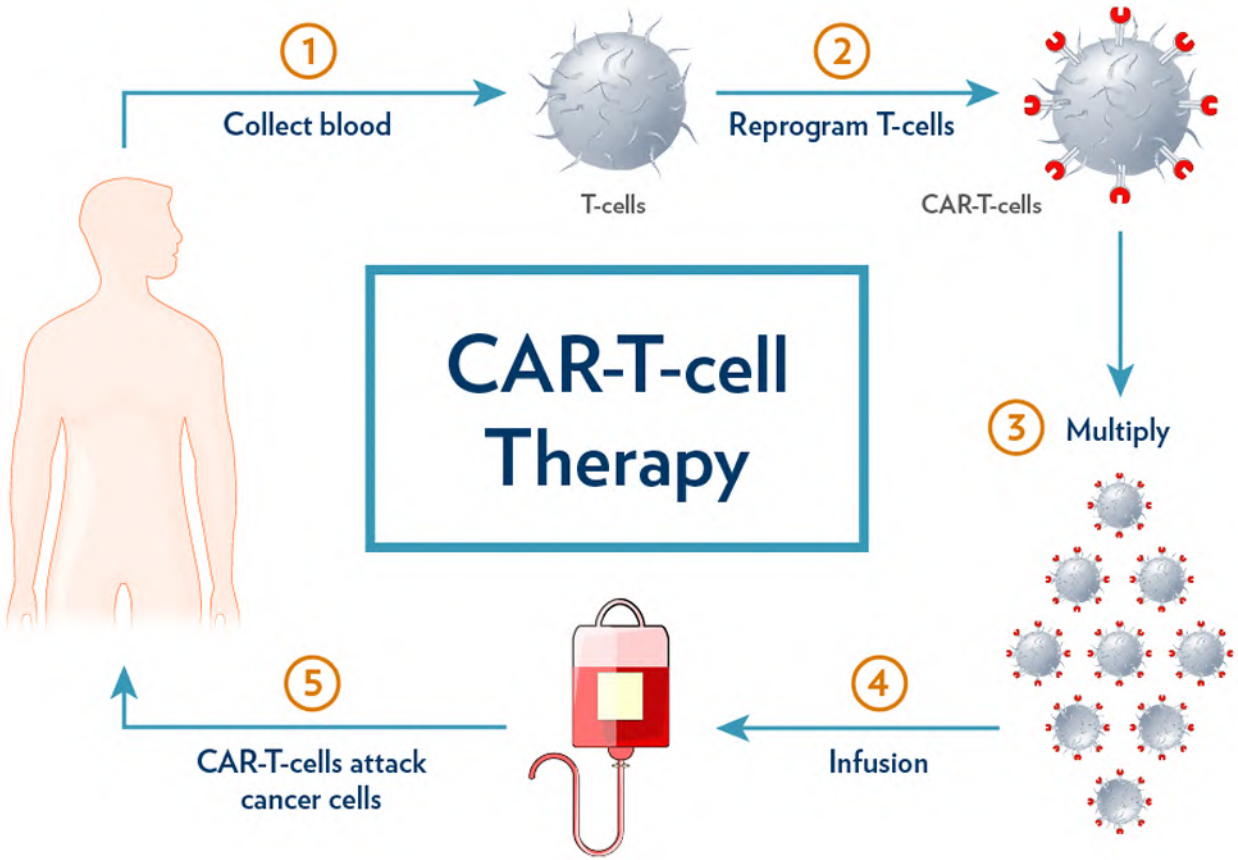
Immune response



Tumor vascularization and tumor cell apoptosis.

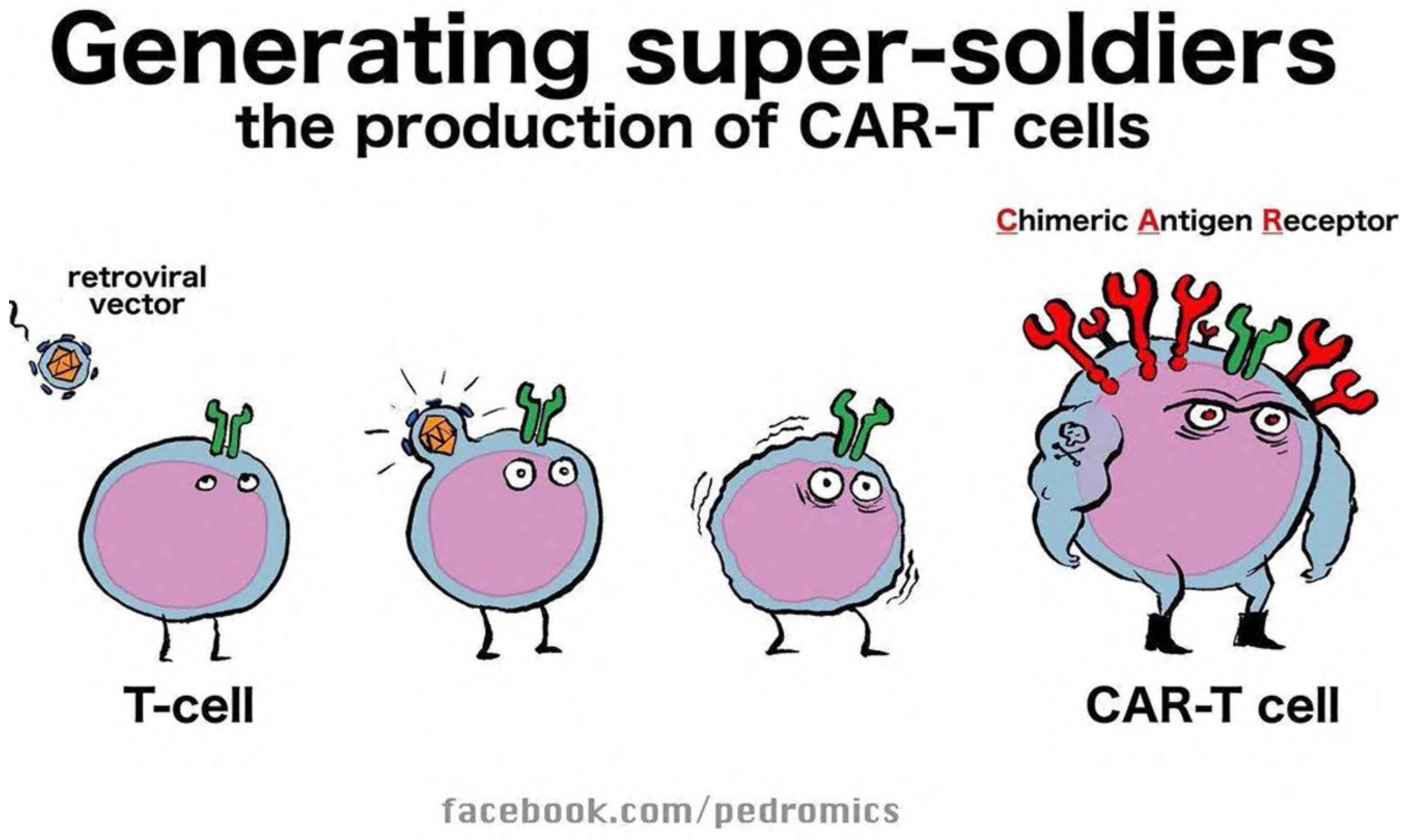
Implementing MAgnetic targeting of nano-Guided ImmuNE cells

IMAGINE



https://medicine.musc.edu/departments/surgery/news-and-announcements/2021/june/car-t-cell-therapy-research

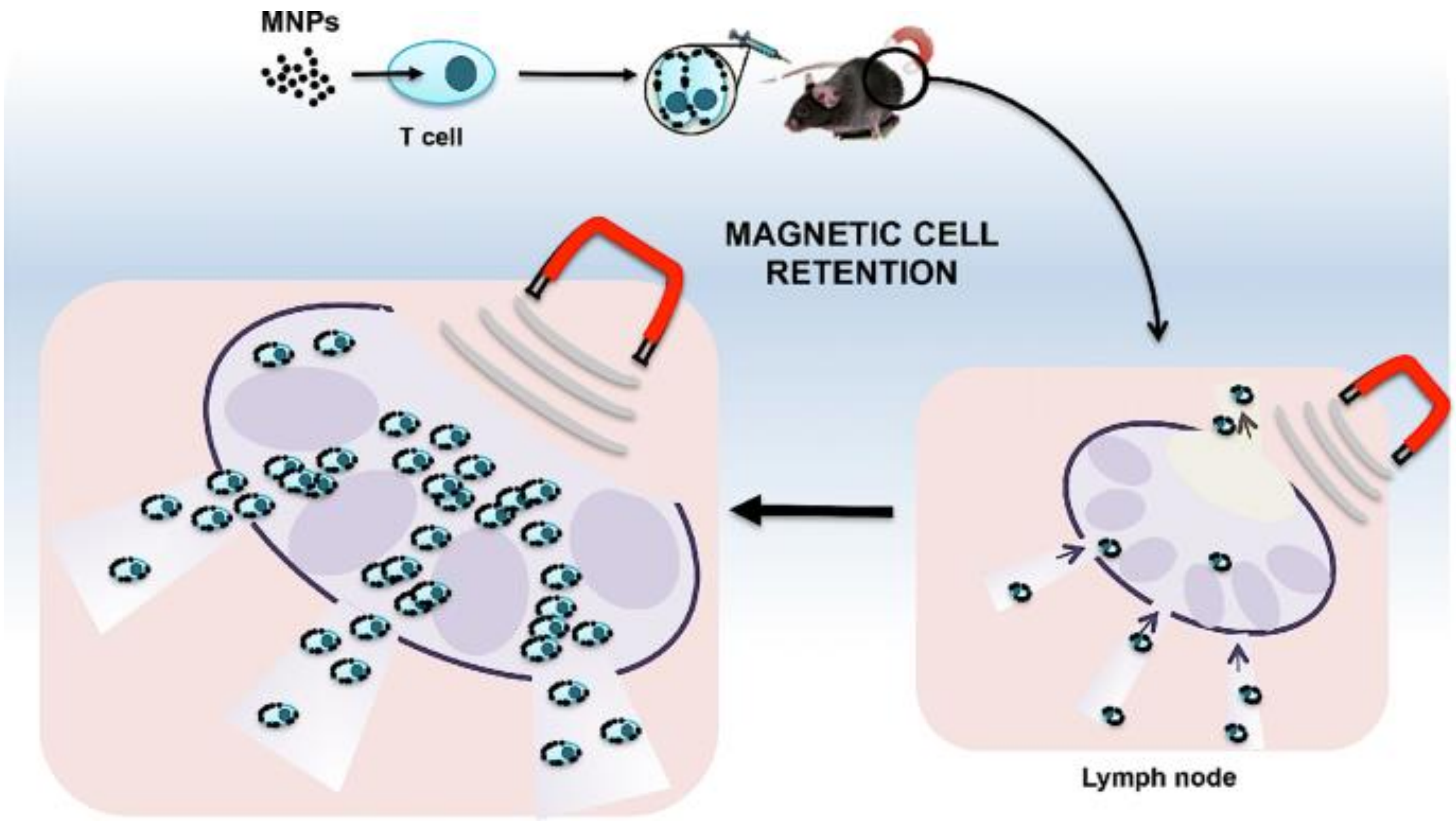
Implementing MAgnetic targeting of nano-Guided ImmuNE cells



https://medicine.musc.edu/departments/surgery/news-and-announcements/2021/june/car-t-cell-therapy-research

Implementing MAgnetic targeting of nano-Guided ImmuNE cells

CAR T and TCR cells loaded with magnetic nano-vehicles will be targeted to the tumour site

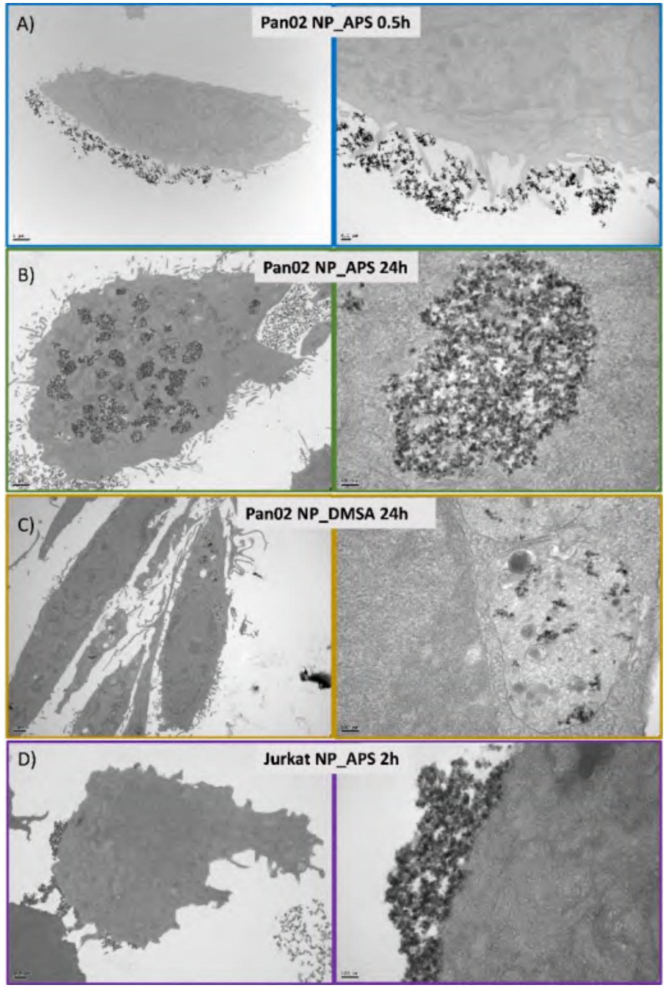


[Journal of Nanobiotechnology](#) **volume 17**, 14 (2019)

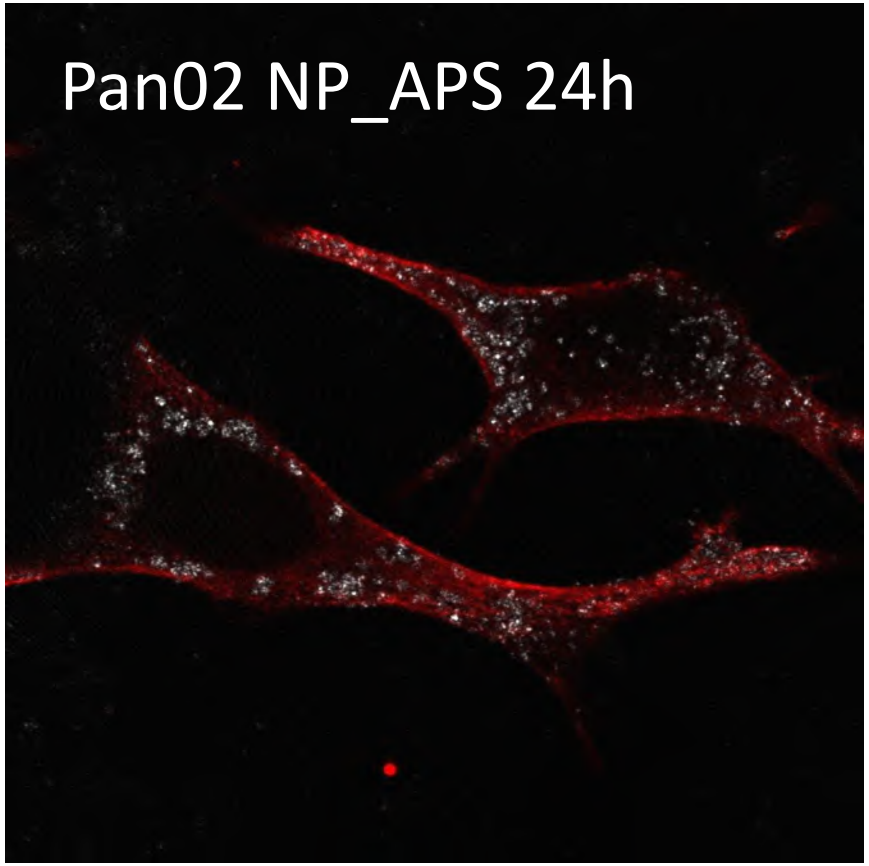
OBJECTVES

- NPs with a high magnetic moment per particle
- Sustainable synthesis method

Pan02 and Jurkat cells labelling



Lysosomal compartments

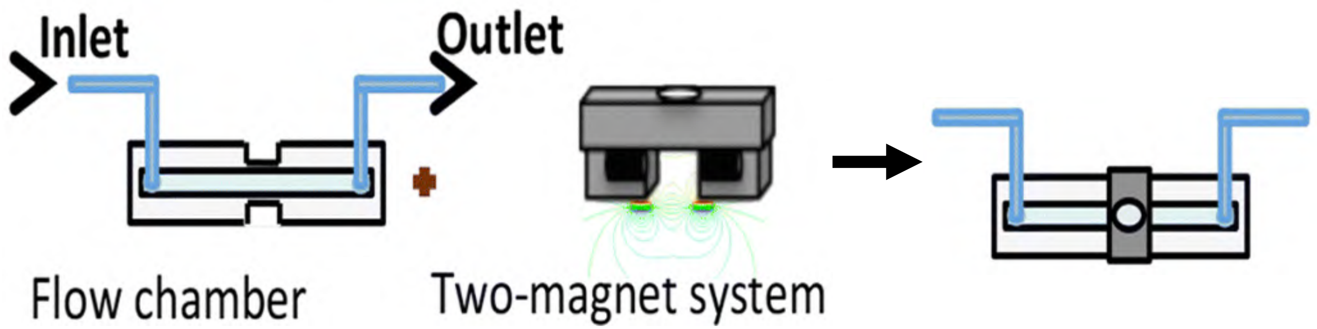


Cell membrane

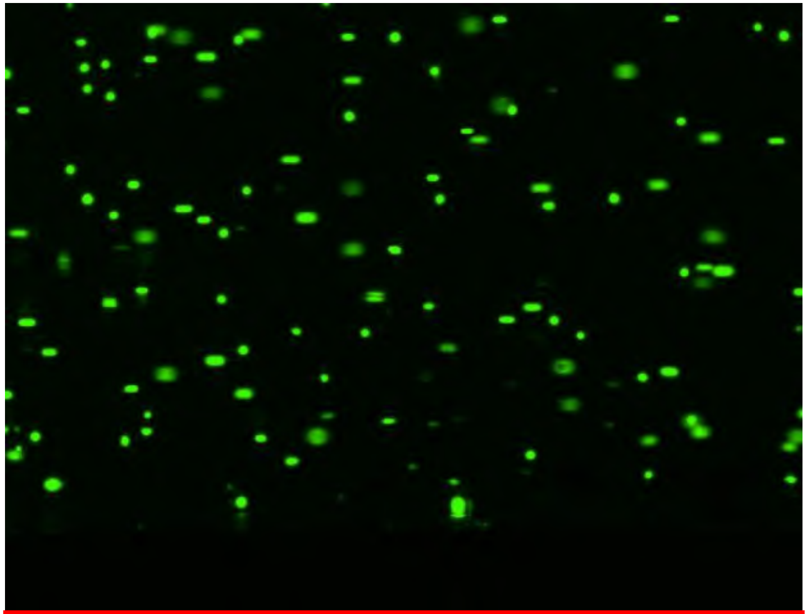
Two distinct aggregation systems in a natural way

Magnetic properties of nanoparticles as a function of the spatial distribution on liposomes and cells
M. E. F. Brollo, et al, Phys. Chem. Chem. Phys., 2018,20, 17829

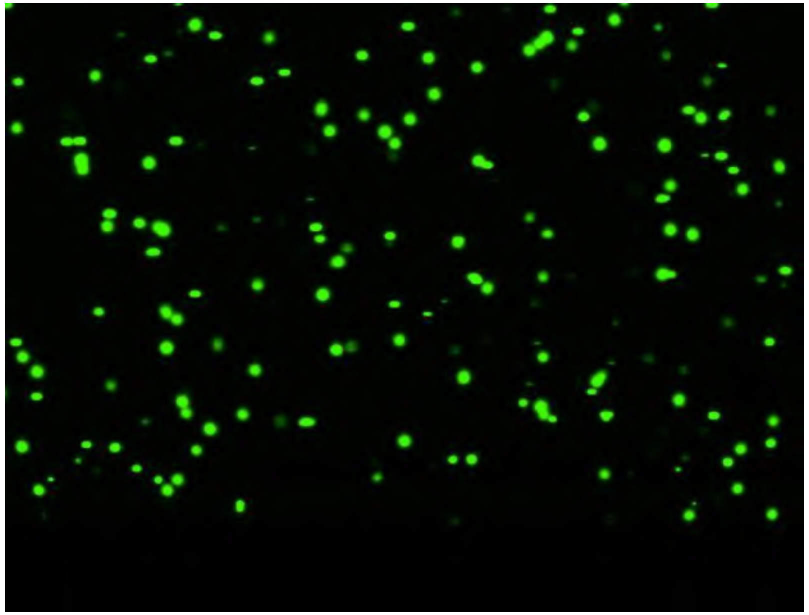
Jurkat cells labelling



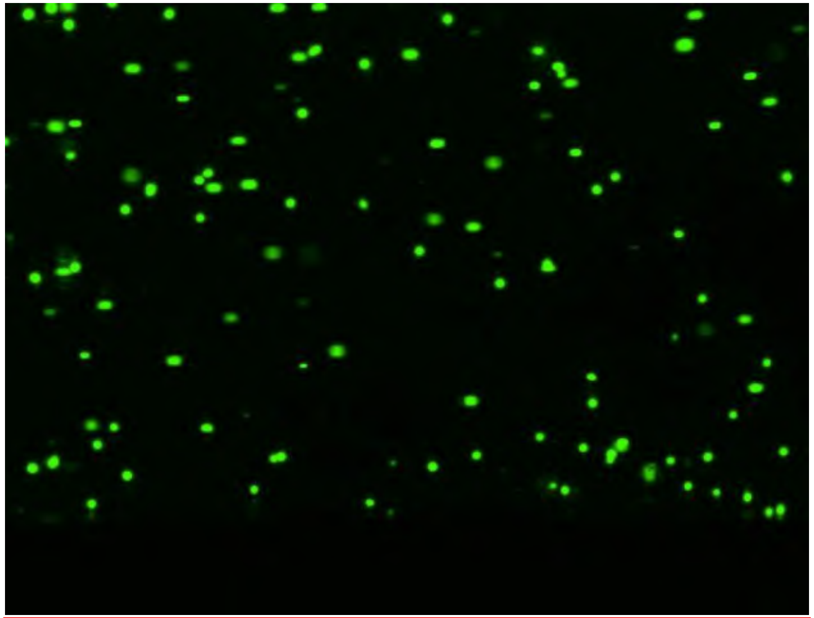
	B (T)	Radius (mm)	Length (mm)
Magnet A	1.45	8	6



Control
NO MNPs

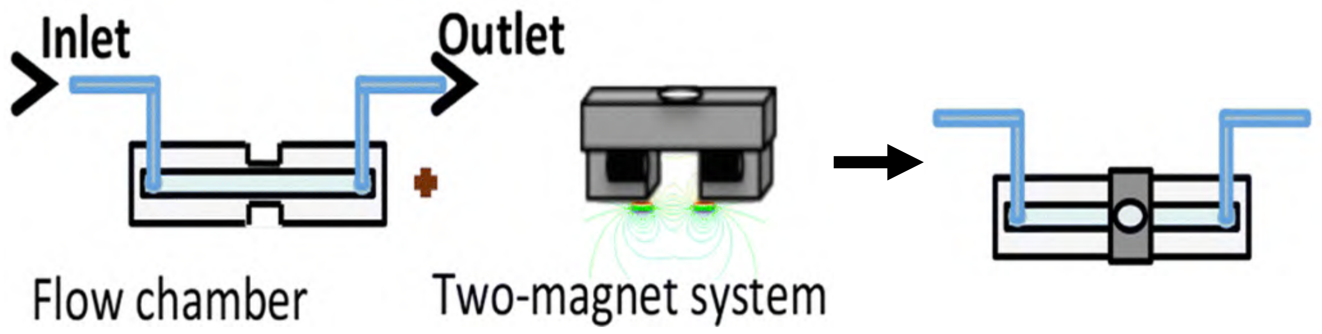


COP12-APS
200 µg/ml

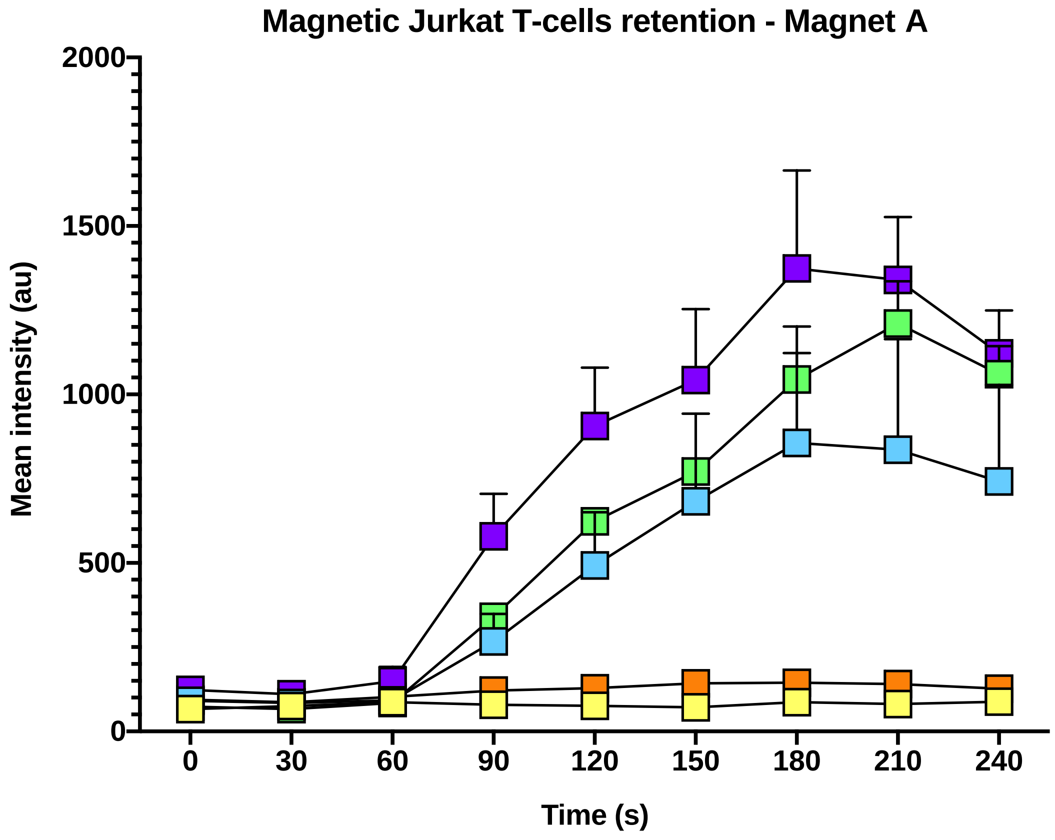


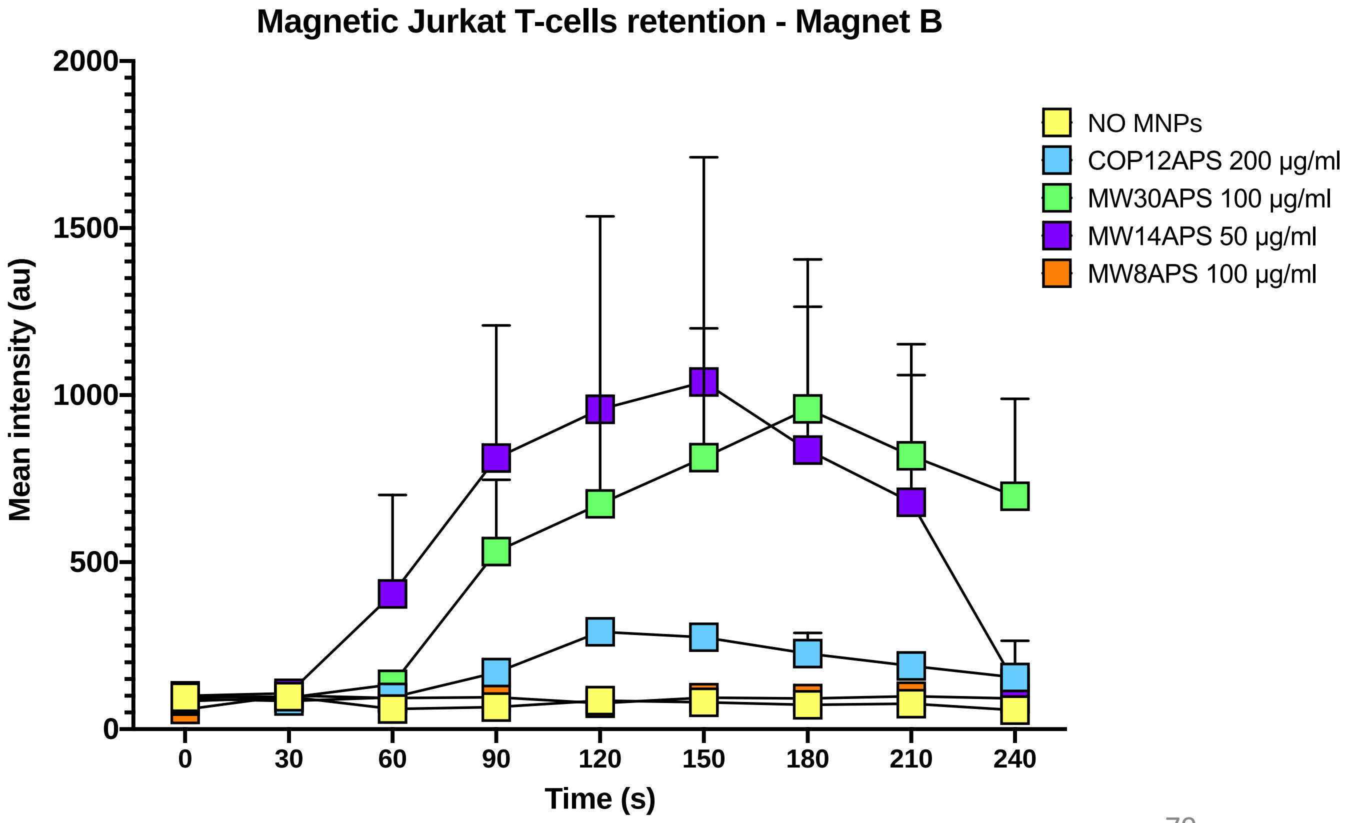
MW30-APS
100 µg/ml

Jurkat cells labelling



	B (T)	Radius (mm)	Length (mm)
Magnet A	1.45	8	6

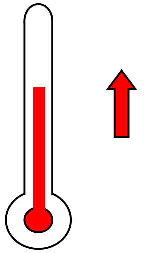




In vivo tests are in progress

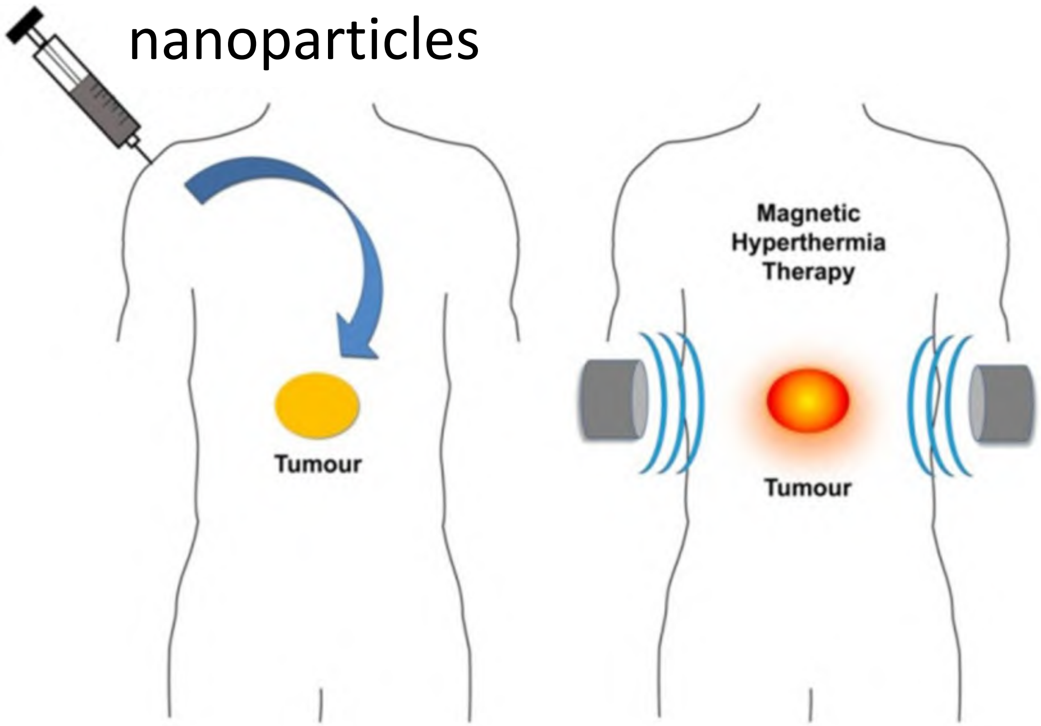
Hyperthermia

What is magnetic hyperthermia?



42-43ºC

Magnetic nanoparticles



Magnetic field

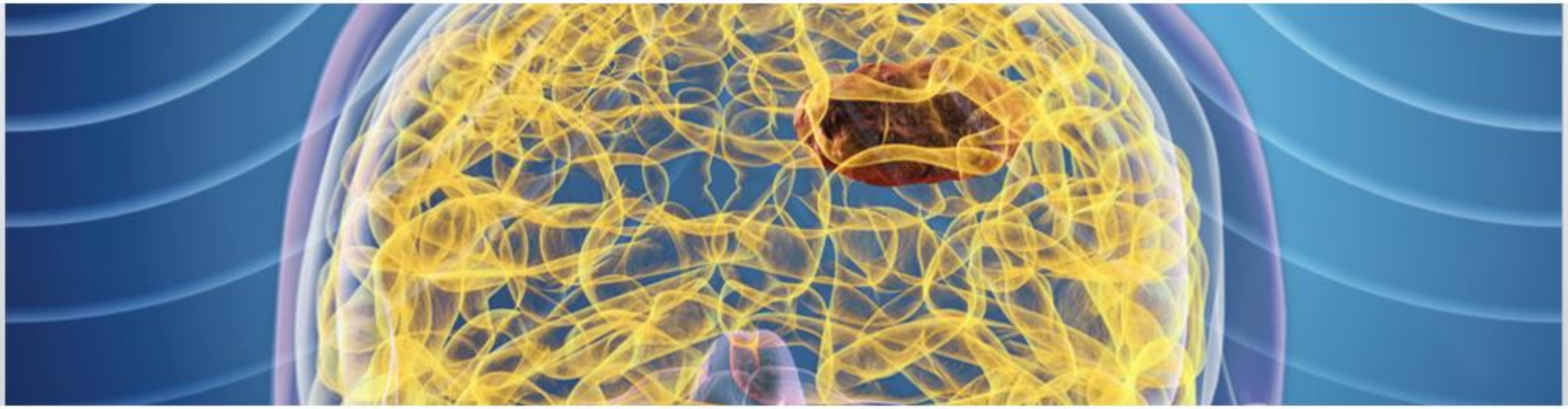
Targeting of a tumor with the help of magnetic nanoparticles in the presence of external alternating magnetic field that causes production of heat through Néel-relaxation loss due to rapid **changes in the direction of magnetic moments**

http://technologytimes.pk/post.php?id=9852

Magnetic hyperthermia

COMPANY PRODUCTS CLINICAL TRIALS RESEARCH PRESS & INVESTORS CONTACT

magforce®
THE NANOMEDICINE COMPANY



NanoTherm™ therapy
NanoTherm™
NanoPlan®
NanoActivator®

Fighting cancer more effectively and with fewer side effects

HOW DOES NANOTHERM™ THERAPY WORK?

NanoTherm™ therapy is a new approach to the local treatment of solid tumors. The method is based on the principle of introducing magnetic nanoparticles directly into a tumor and then heating them in an alternating magnetic field. At approximately 15 nanometers in diameter, the nanoparticles, which are suspended in water, are extremely small (a nanometer is one millionth of a millimeter), and comprise an iron oxide core with an aminosilane coating. The particles are activated by a magnetic field that changes its polarity up to 100,000 times per second, generating heat.

MED CERT

Compliant with European Standard

NanoTherm™

Magnetic hyperthermia

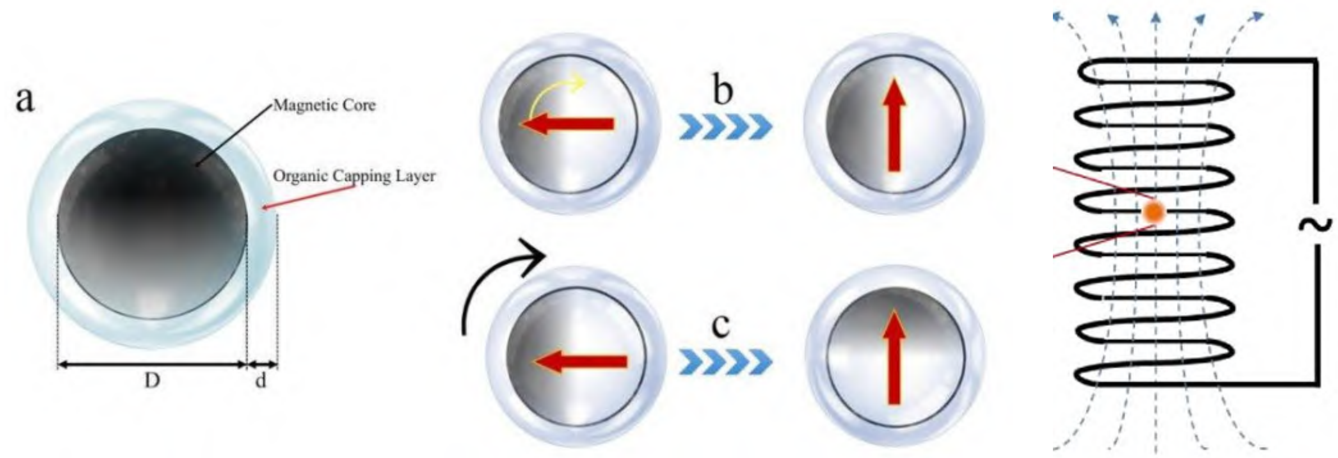
- Overview
- New glioblastoma study
- Patient Information
- Physicians' Information
- Publications
- Contact

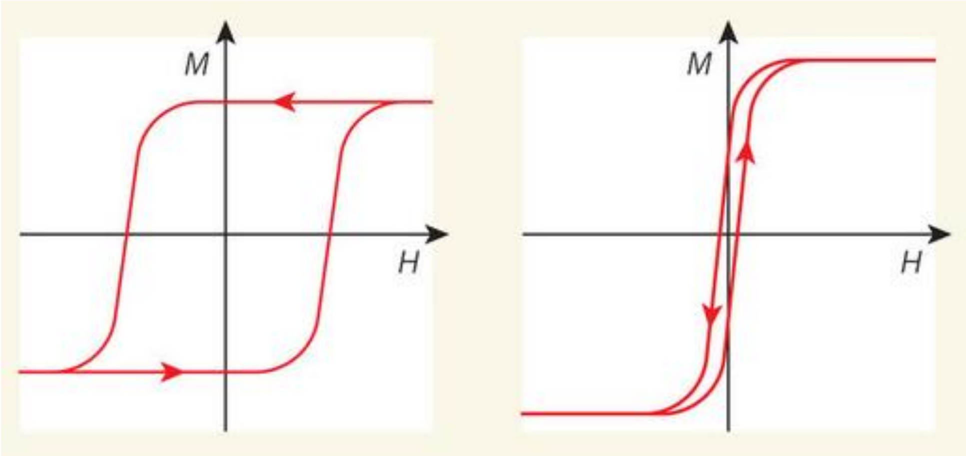
Growing nanomedicine into a cancer therapy of the future

CLINICAL TRIALS/ TUMOR TYPES	STATUS OF TRIALS Phase I Feasibility study	Phase II Efficacy study	
Glioblastoma multiforme			EU Regulatory Approval
Prostate carcinoma			
Pancreatic carcinoma			

Study results

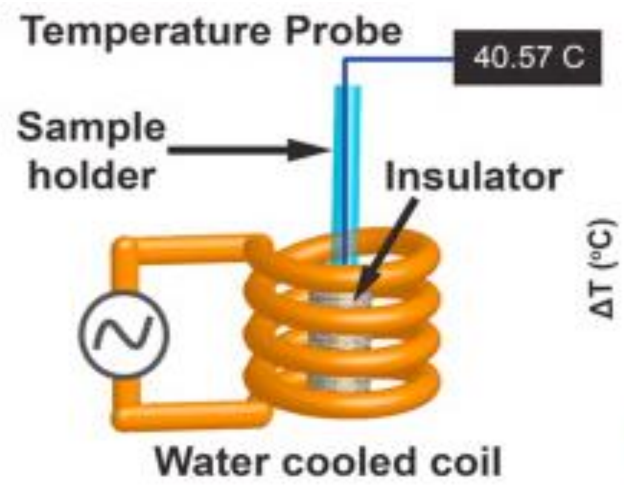
Magnetic hyperthermia

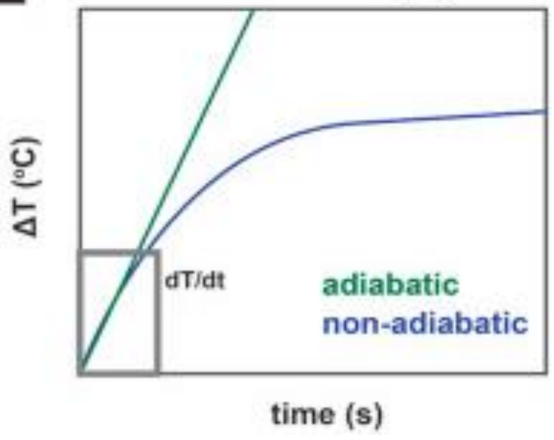


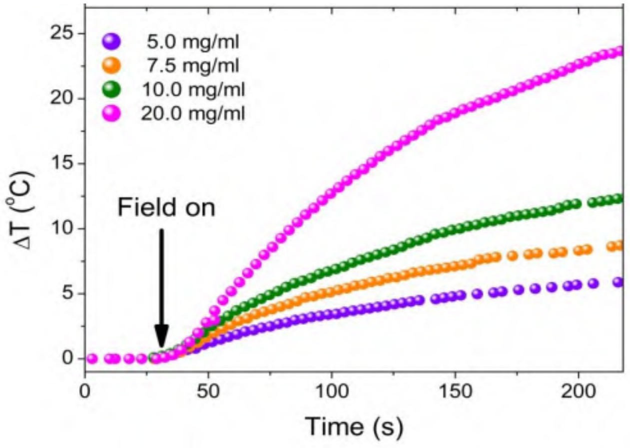


Maximum hysteresis loss ∝ Ms. Hc ∝ Heat

What we actually measure







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

$Cm = 4.185\ Jg^{-1}\ K^{-1}$

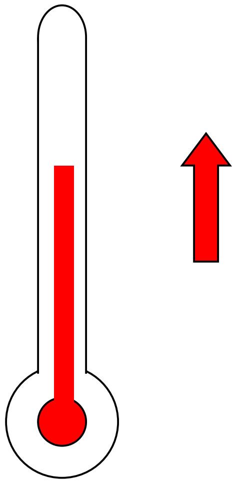
$\emptyset = mgFe/mL$

https://doi.org/10.1016/j.pnsc.2016.09.004

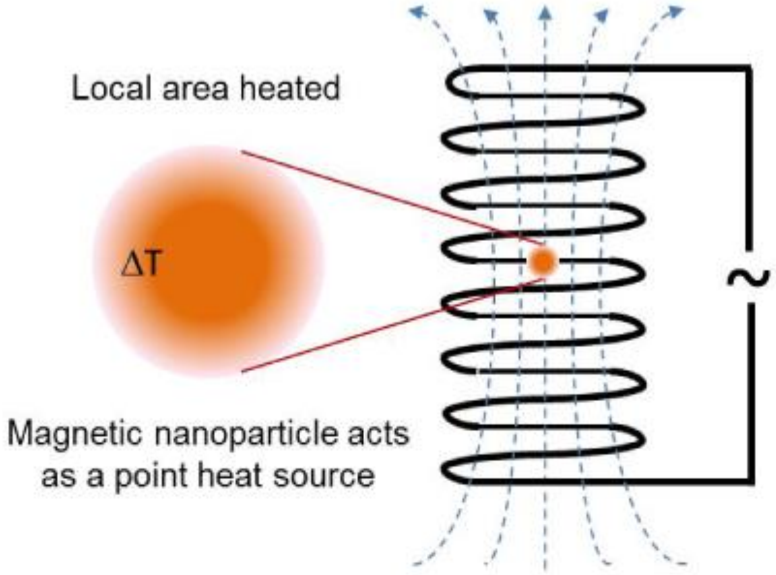
Magnetic hyperthermia

The heat is due to changes in the direction of magnetic moments

Alternating magnetic field



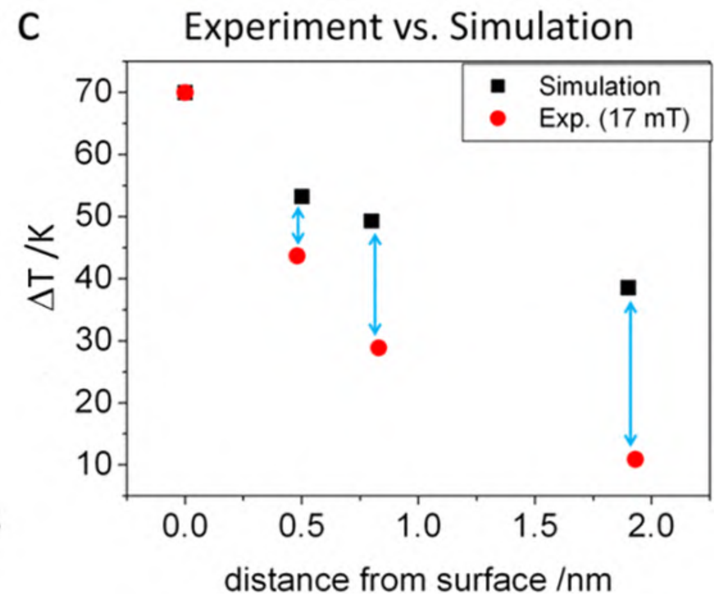
42-100ºC



Control of spatial extent of heating is still an unsolved challenging task

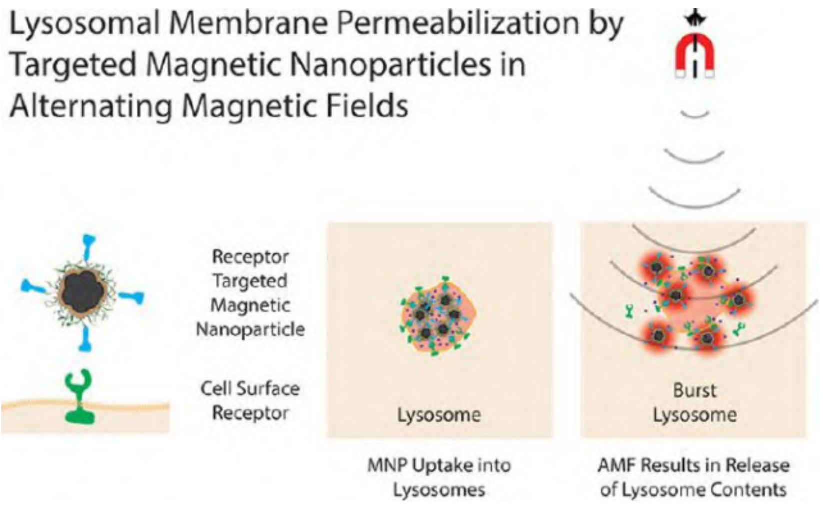
Malekigorji M, Curtis ADM, Hoskins C (2014) The Use of Iron Oxide Nanoparticles for Pancreatic Cancer Therapy. J Nanomed Res 1(1): 00004. DOI: [10.15406/jnmr.2014.01.00004](https://doi.org/10.15406/jnmr.2014.01.00004)

Thermal damage



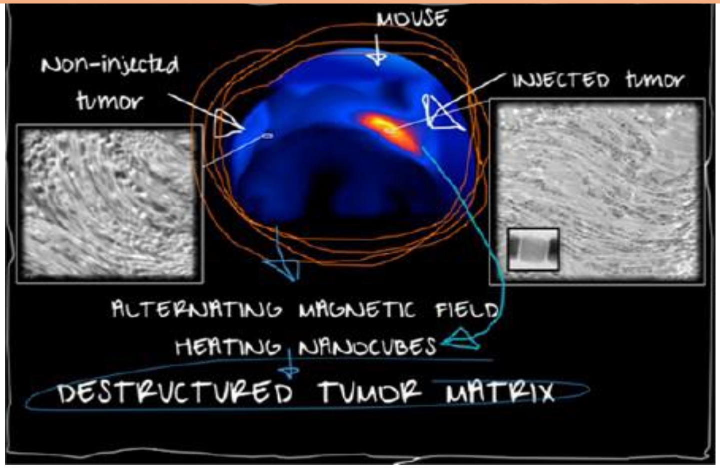
Heat generated is limited to the immediate proximity of the nanoparticle surface.

Non-thermal damage



Mechanical damage

Improve drug penetration

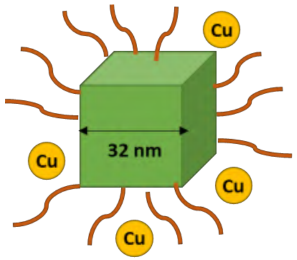


Hyperthermia could be used to locally modify tumor stroma and thus improve drug penetration

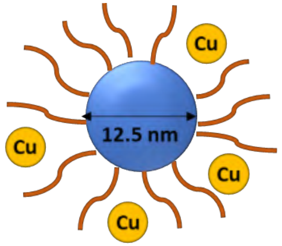
ACS Nano 2013, 10.1021/nn405356r
Angewandte Chemie · December 2013
Nano Lett. 2013, 13, 2399−2406

Surface heating measurements with fluorescent Proteins

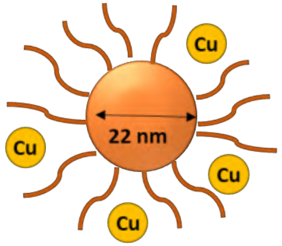
Particles



$CSIC5\text{-}c/Cu^{2+}$



$CSIC9\text{-}c/Cu^{2+}$

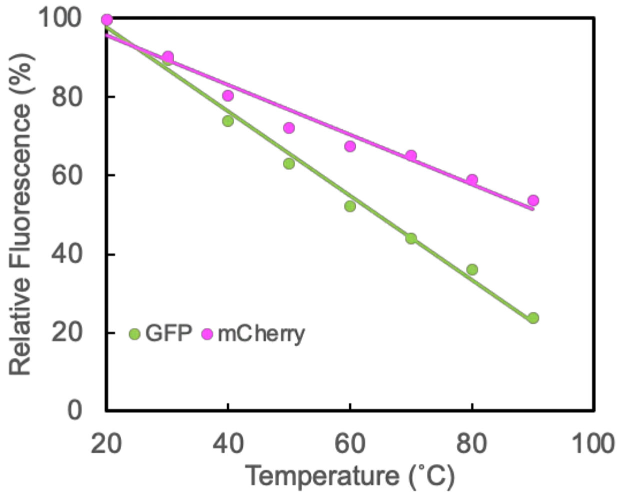


$CSIC14\text{-}c/Cu^{2+}$

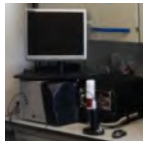
Proteins

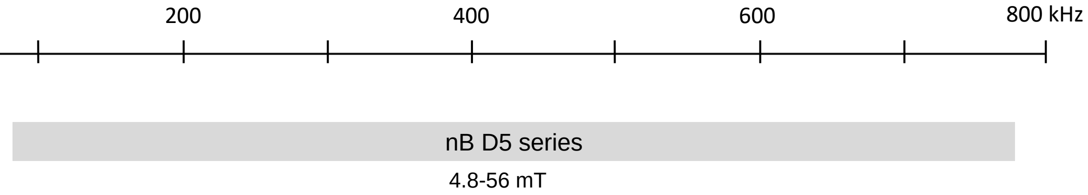
	GFP	mCherry
Origin of protein sequence	Aequorea victoria	Discosoma sp.
Heterologous host	E.coli	E.coli
Tag	His-tag	His-tag
Mutations	His-tag at N-terminus	His-tag at N-terminus
Quaternary structure	Monomeric	Monomeric
Molecular weight	29 kDa	30 kDa
Isoelectric point	6,37 (Theoretical)	6,01 (Theoretical)
Extinction coefficient (280 nm) (M^{-1} x cm^{-1})	19035 (Theoretical)	34380 (Theoretical)
PDB ID	1GFL	2H5Q

Fluorescent intensity vs T°C



AMF Applicator

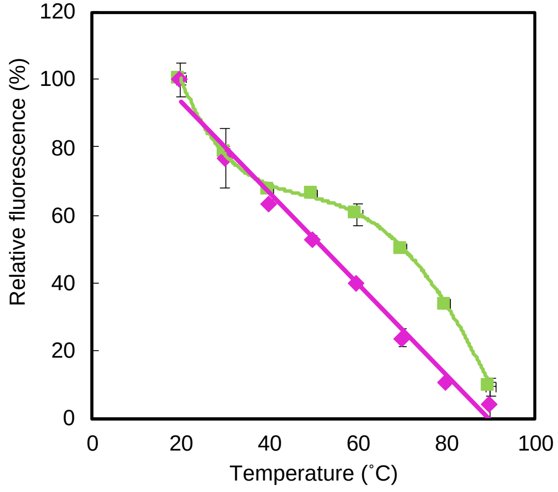




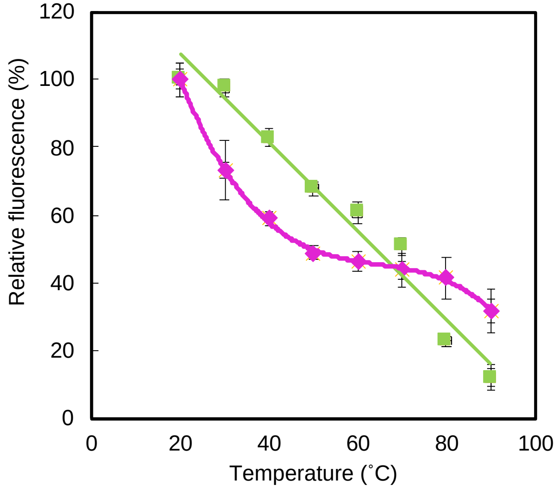
Surface heating measurements with fluorescent Proteins

CALIBRATION CURVES

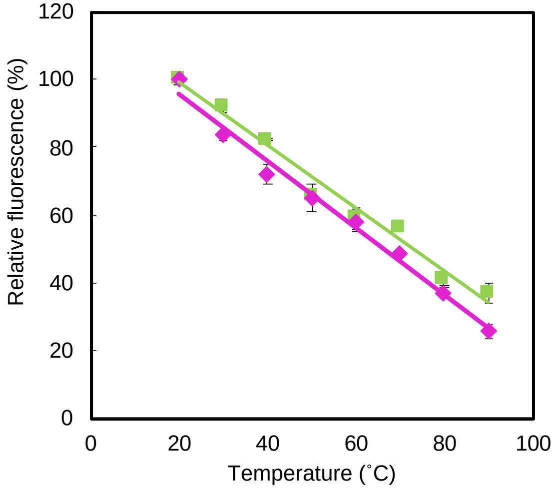
CSIC-9



CSIC-14



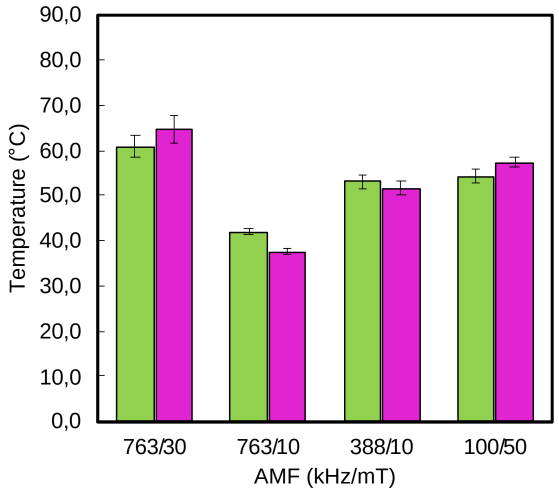
CSIC-5



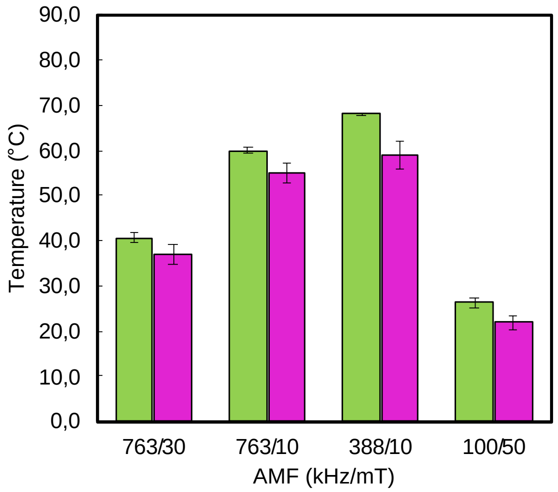
Global heating

LOCAL HEATING ESTIMATIONS vs AMF conditions

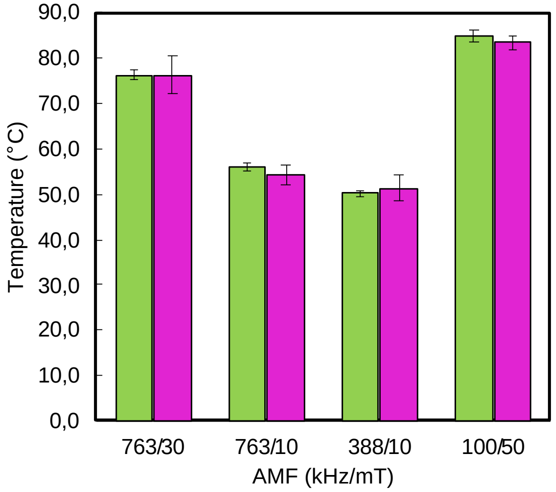
CSIC-9



CSIC-14



CSIC-5

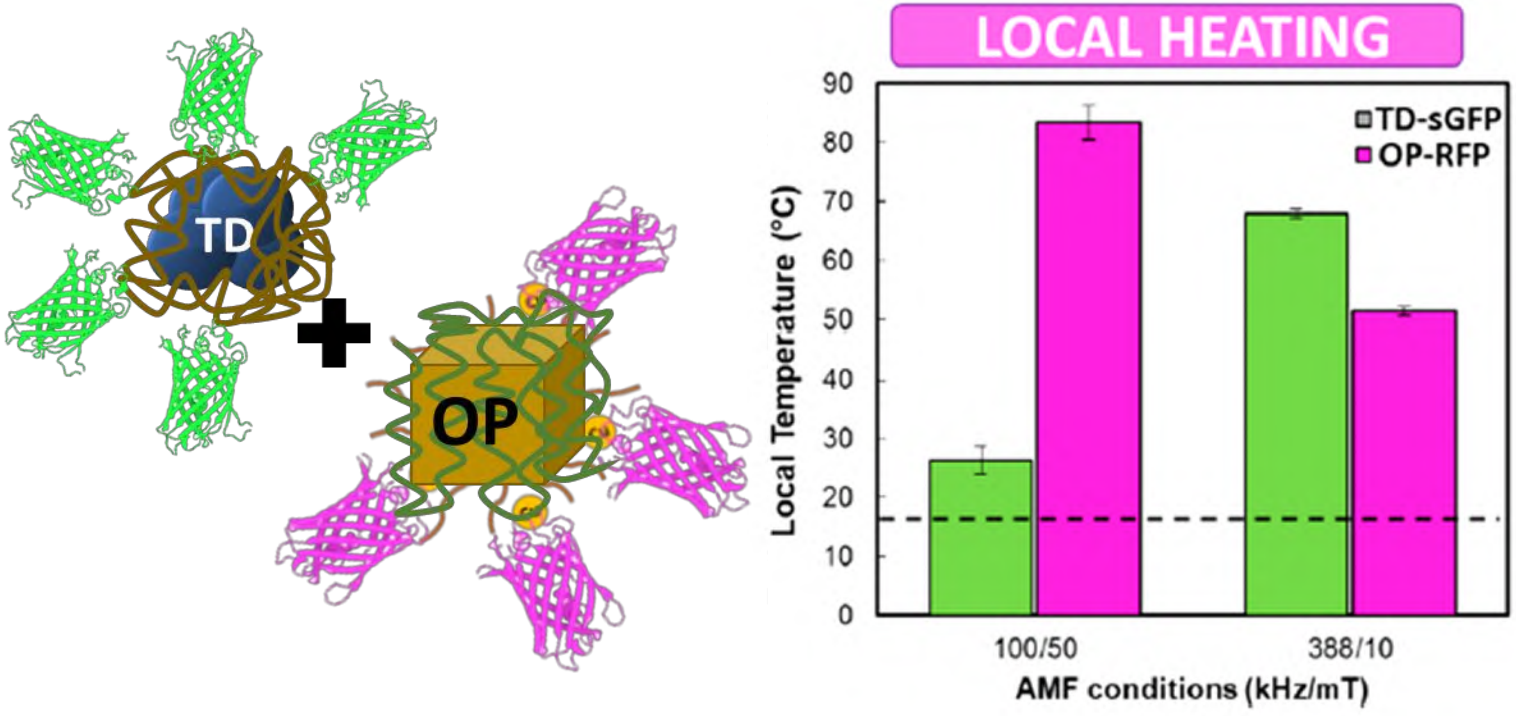


AMF heating

High Frequency – Low Field

High Field – Low Frequency

Temperatures at the nanoscale vs global heating



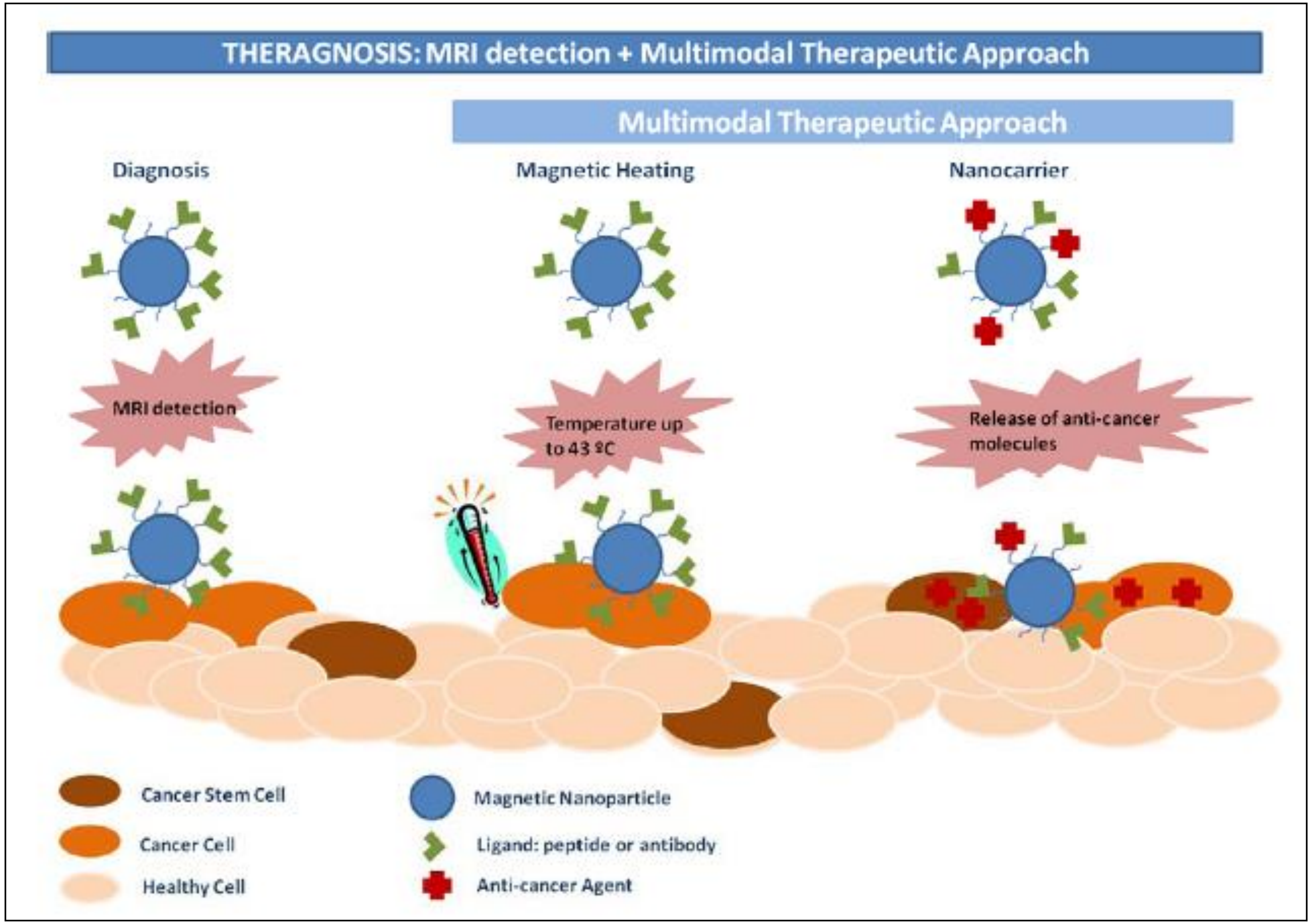
No change in solution temperature

Ovejero et al. (2021) **Nano Lett.** 21, 7213−7220

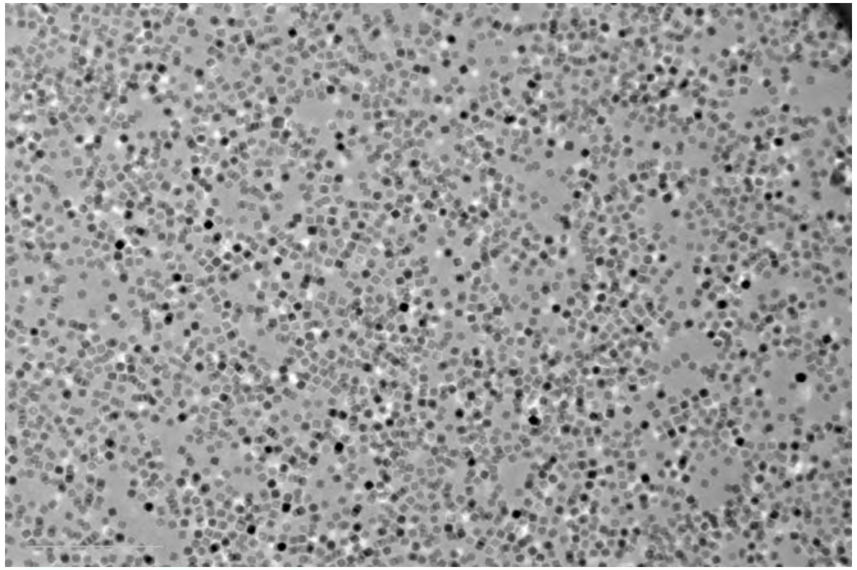
Multifunctional Nanotechnology for selective detection and Treatment of cancer

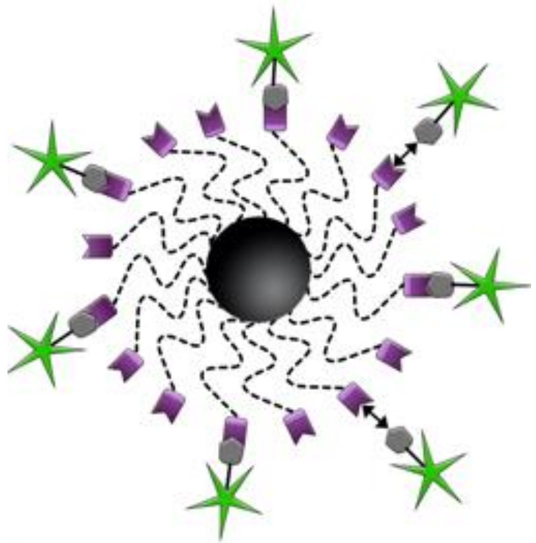
multifun

Multifunctional Nanotechnology for
selective detection and Treatment of cancer



Multifunctional Nanotechnology for selective detection and Treatment of cancer





Pancreatic Cancer

Cancer Cells

Targeting markers & ligands

EGFR & LARLLT peptide
Nucleolin/Nucleophosmin&NUCANT

Therapeutic Modalities:

Magnetic heating
NUCANT
SiRNA (Bcl-2)
Gemcitabine or PM001183

Cancer Stem Cells

Targeting markers & ligands

CD44 & antibody
Search high select. Markers

Therapeutic Modalities :

Magnetic heating
NUCANT
miRNA-145 mimic
Gemcitabine or PM001183

Breast Cancer

Cancer Cells

Targeting markers & ligands:

Her-2 & MARAKE peptide
Nucleolin/Nucleophosmin & NUCANT

Therapeutic Modalities:

Magnetic heating
NUCANT
SiRNA (Bcl-2)
Fluorouracile or PM001183

Cancer Stem Cells

Targeting markers & ligands

CD44 & antibody
Search high select. Markers

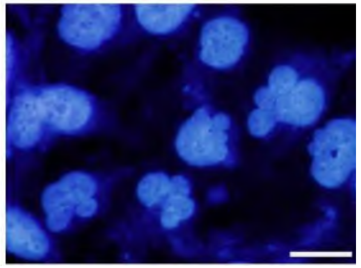
Therapeutic Modalities:

Magnetic heating
NUCANT
miRNA-145 mimic
Fluorouracile or PM001183

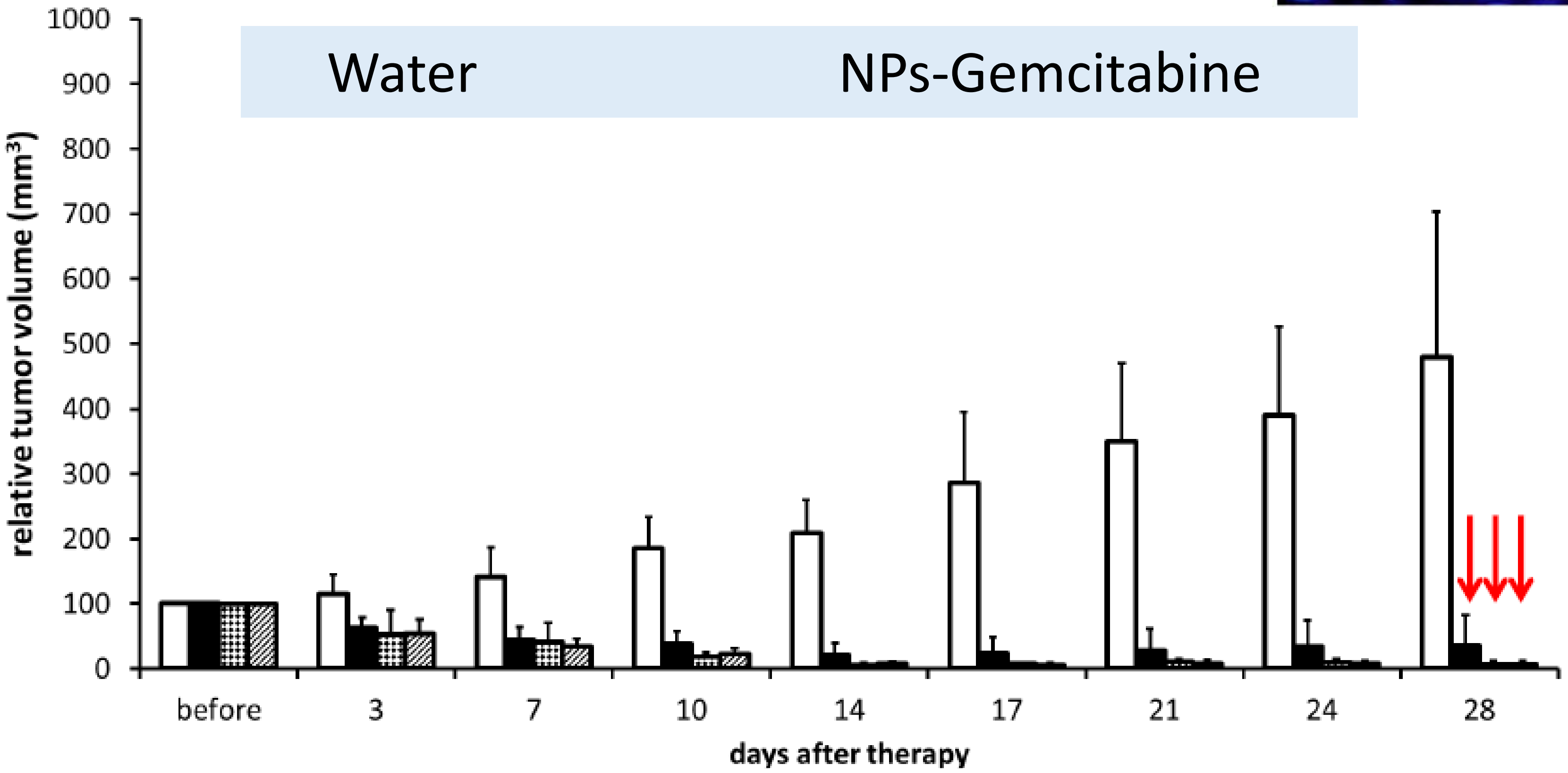
1	ATOS ORIGIN SOCIEDAD ANONIMA ESPANOLA
2	FUNDACION CENTRO NACIONAL DE INVESTIGACIONES ONCOLOGICAS CARLOS III
3	UNIVERSITE PARIS XII - VAL DE MARNE
4	AGENCIA ESTATAL CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS
5	FYZIKALNI USTAV AV CR V.V.I
6	FUNDACION IMDEA NANOCIENCIA
7	INSTITUT NATIONAL DES SCIENCES APPLIQUEES DE TOULOUSE INSAT
8	KING'S COLLEGE LONDON
9	LIQUIDS RESEARCH LTD
10	SOLUCIONES NANOTCNOLOGICAS SL
11	PEPRIC NV
12	PHARMAMAR, S.A.U.
13	THE PROVOST FELLOWS & SCHOLARS OF THE COLLEGE OF THE HOLY AND UNDIVIDED TRINITY OF QUEEN ELIZABETH NEAR DUBLIN
14	UNIVERSITY COLLEGE CORK, NATIONAL UNIVERSITY OF IRELAND, CORK
15	Universitätsklinikum Jena
16	THE UNIVERSITY OF MANCHESTER

multifun

Effect of the magnetic Field



Pancreatic cancer (BxPC-3)



NoCanTher 2017-21

Magnetic hyperthermia

Vall d'Hebron enrolls the first patient in a clinical trial designed to treat locally advanced pancreatic cancer with nanoparticles

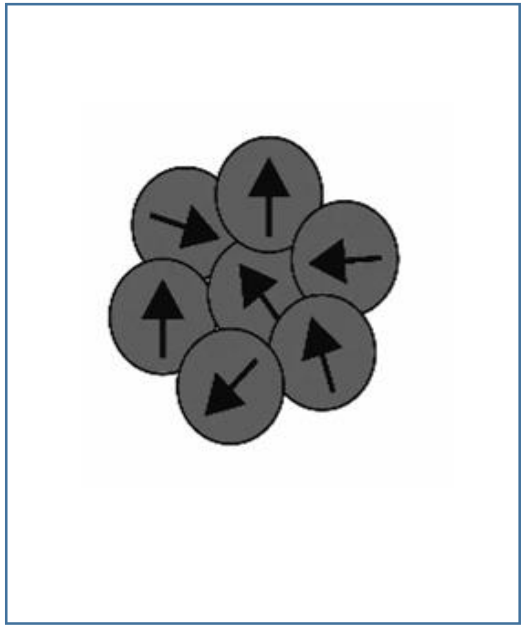
18/03/2022

The NoCanTher project has designed a new technology that combines the injection of nanoparticles into the cancer with the application of hyperthermia to locally advanced pancreatic tumors.

https://www.vallhebron.com/en/news/news/vall-dhebron-enrolls-first-patient-clinical-trial-designed-treat-locally-advanced-pancreatic-cancer-nanoparticles

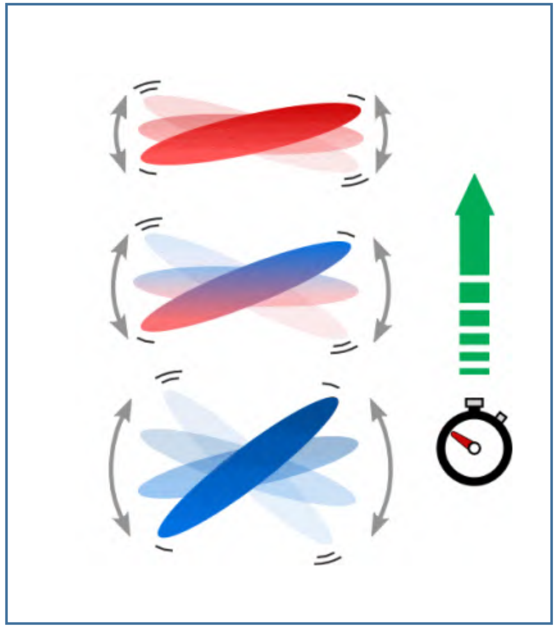
Hyperthermia

Improving the heating by tuning anisotropy and interactions



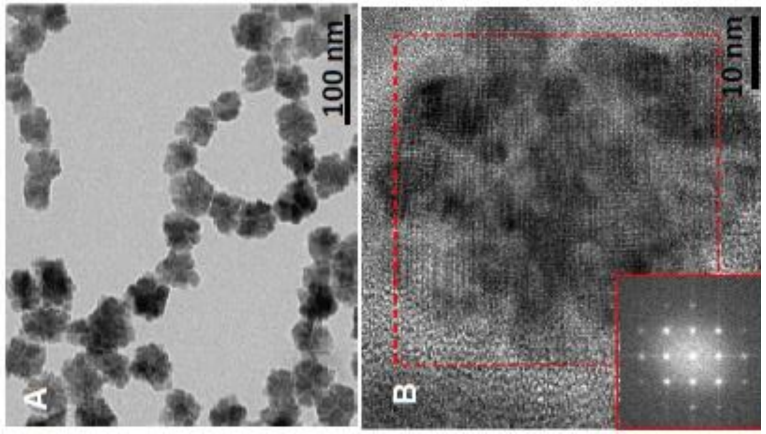
Exchange interactions

Dipolar interactions

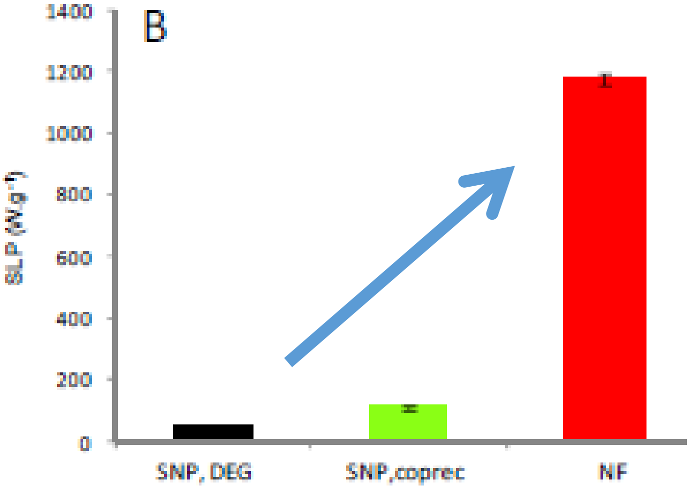


Synergy
Heat release-Mechanical

Magnetic hyperthermia in vitro



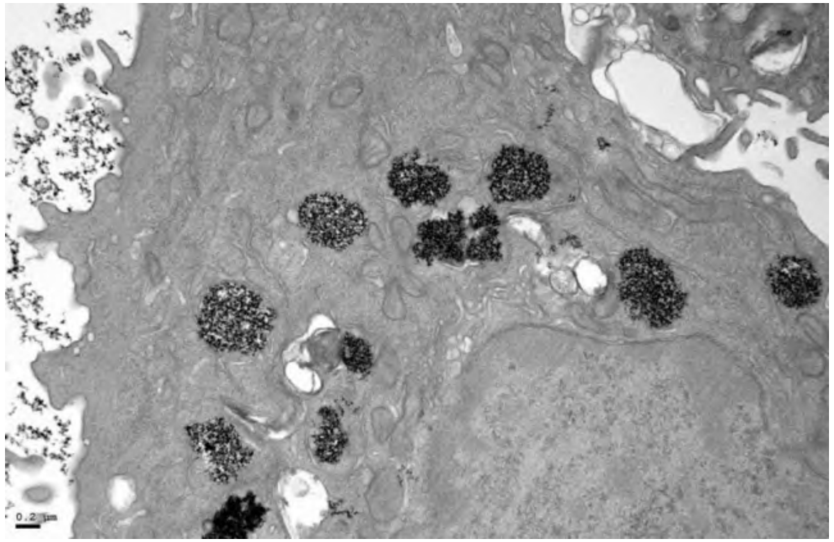
L. Lartigue, F. Gazeau et al., ACS Nano (2012)

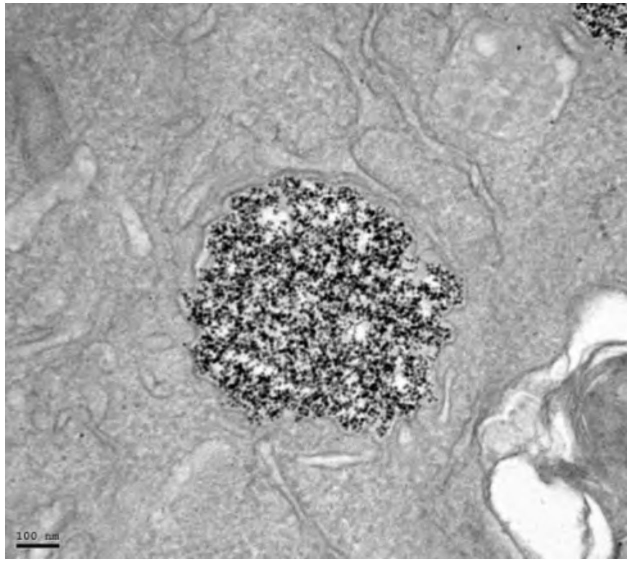


SAR drops to 1/10 Intra-cellular

Biomaterials 35, 6400 (2014)

Nanoparticles-cells (Pan02) in vitro

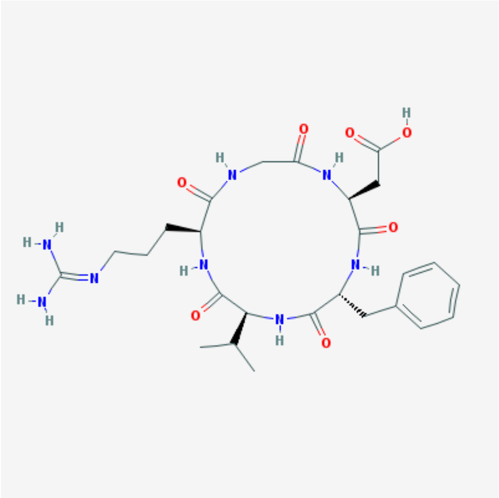


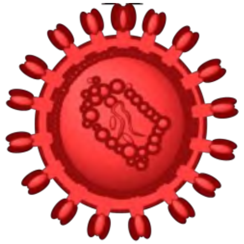


ACS APPLIED MATERIALS & INTERFACES, 11, 340-355, 2019

Optimizing flower coating

RGD
(biological targeting)



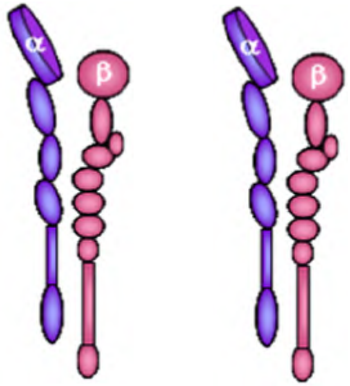


U87MG cells

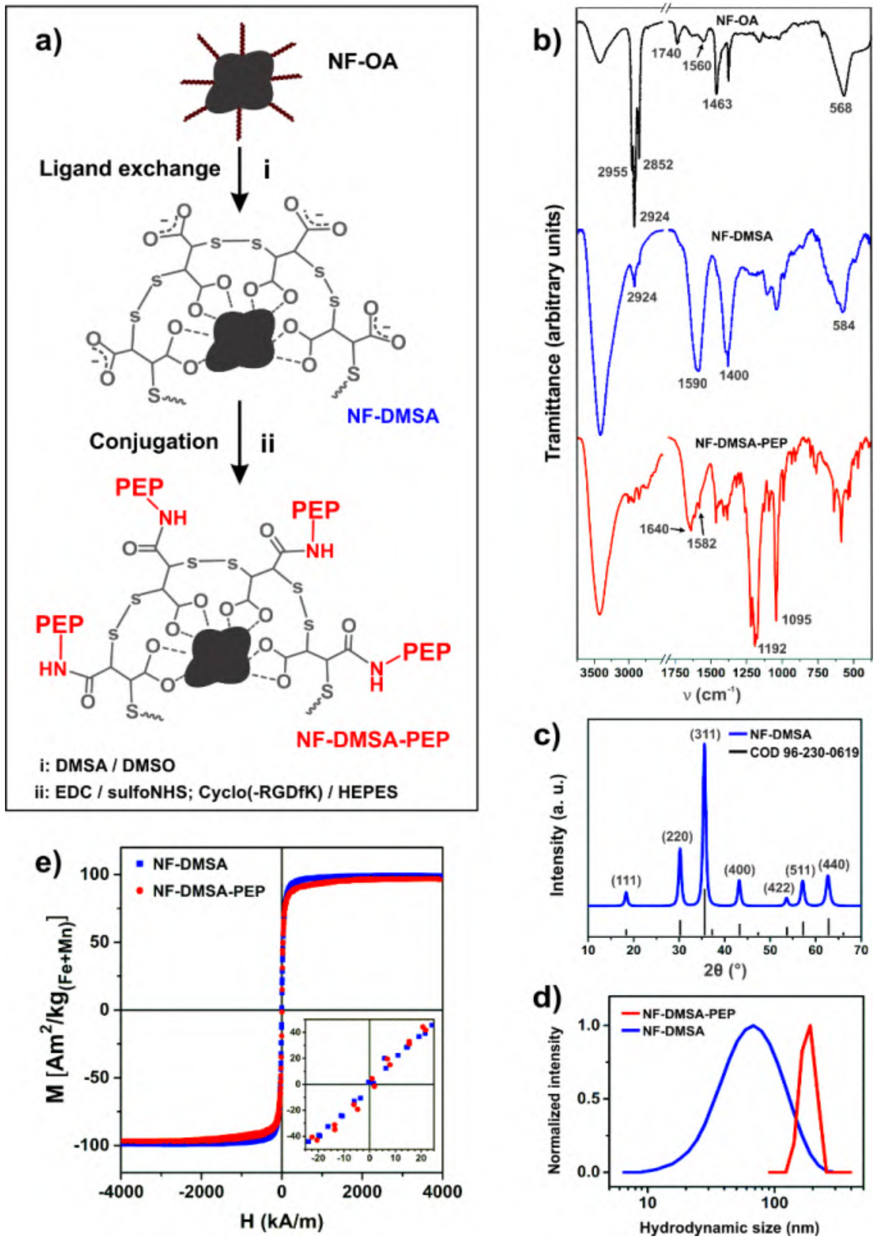
Human primary Glioblastoma cell line

$\alpha_v\beta_3$-integrin

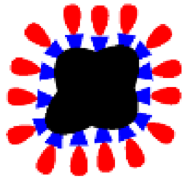
Cell adhesion molecule that is overexpressed in tumor vasculature and invasive tumor cells.



Optimizing flower coating



NF-DMSA

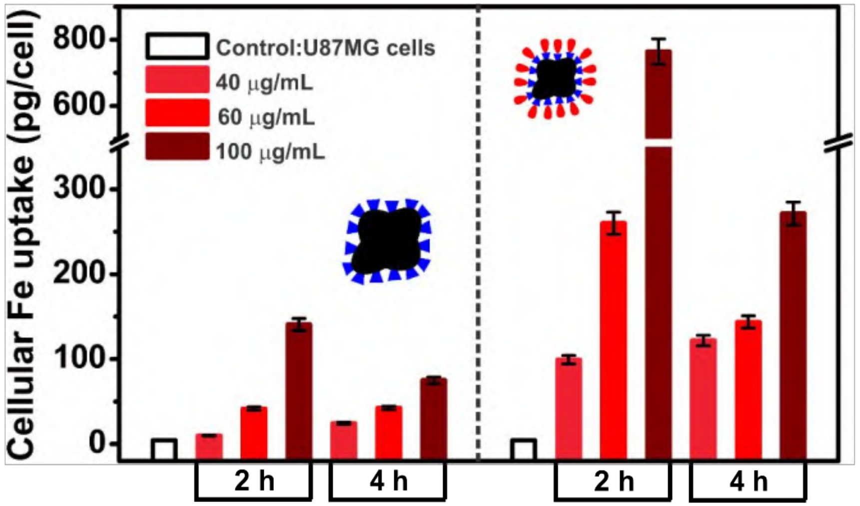


NF-DMSA-PEP

Flower-like Mn-doped magnetic nanoparticles functionalized with RGD-ligand to efficiently induce intracellular heat after AMF-exposition triggering glioma cell death. S. Del Sol-Fernández et al, ACS Applied Materials and Interfaces 2019

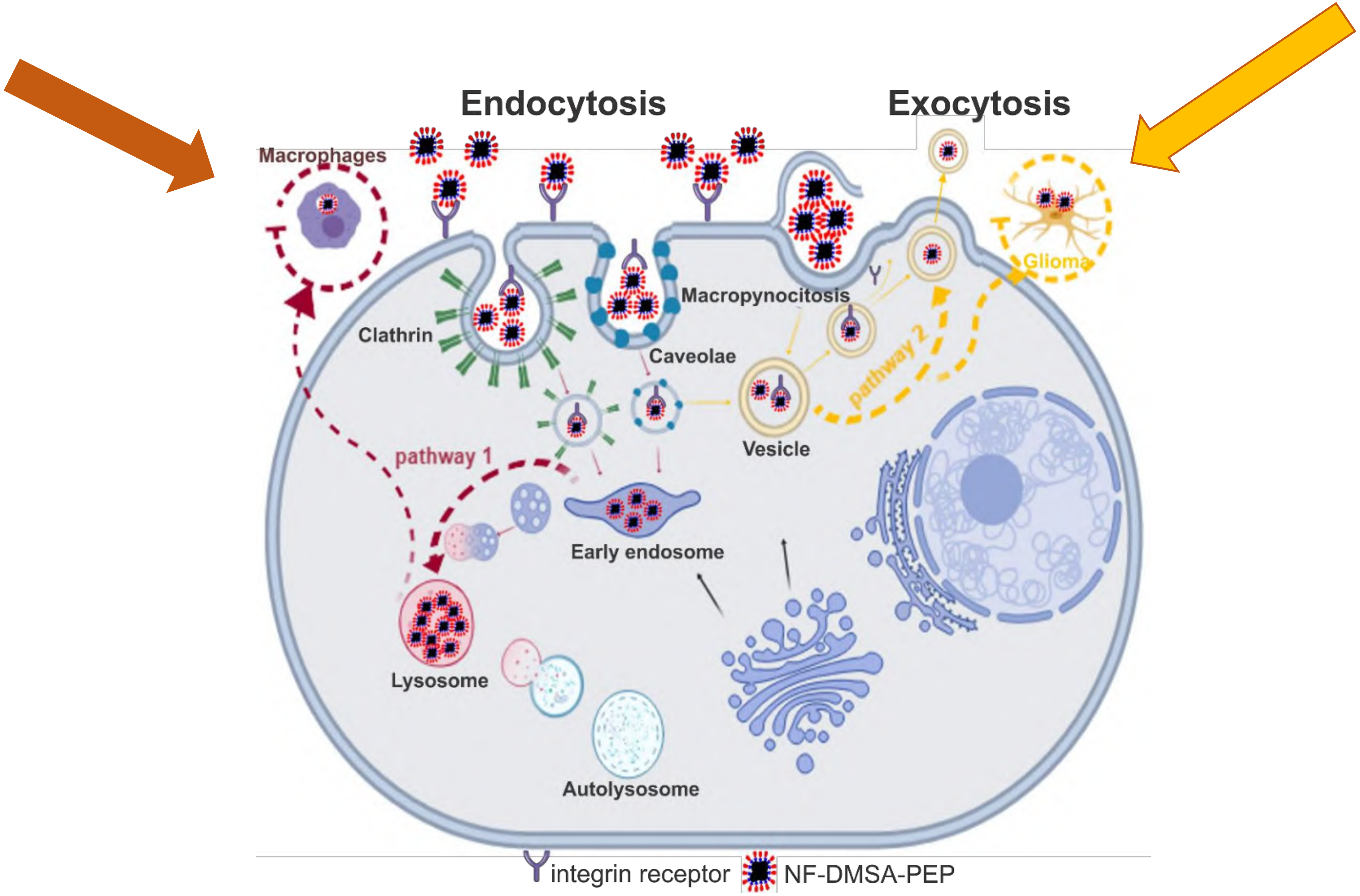
Optimizing flower coating

a)



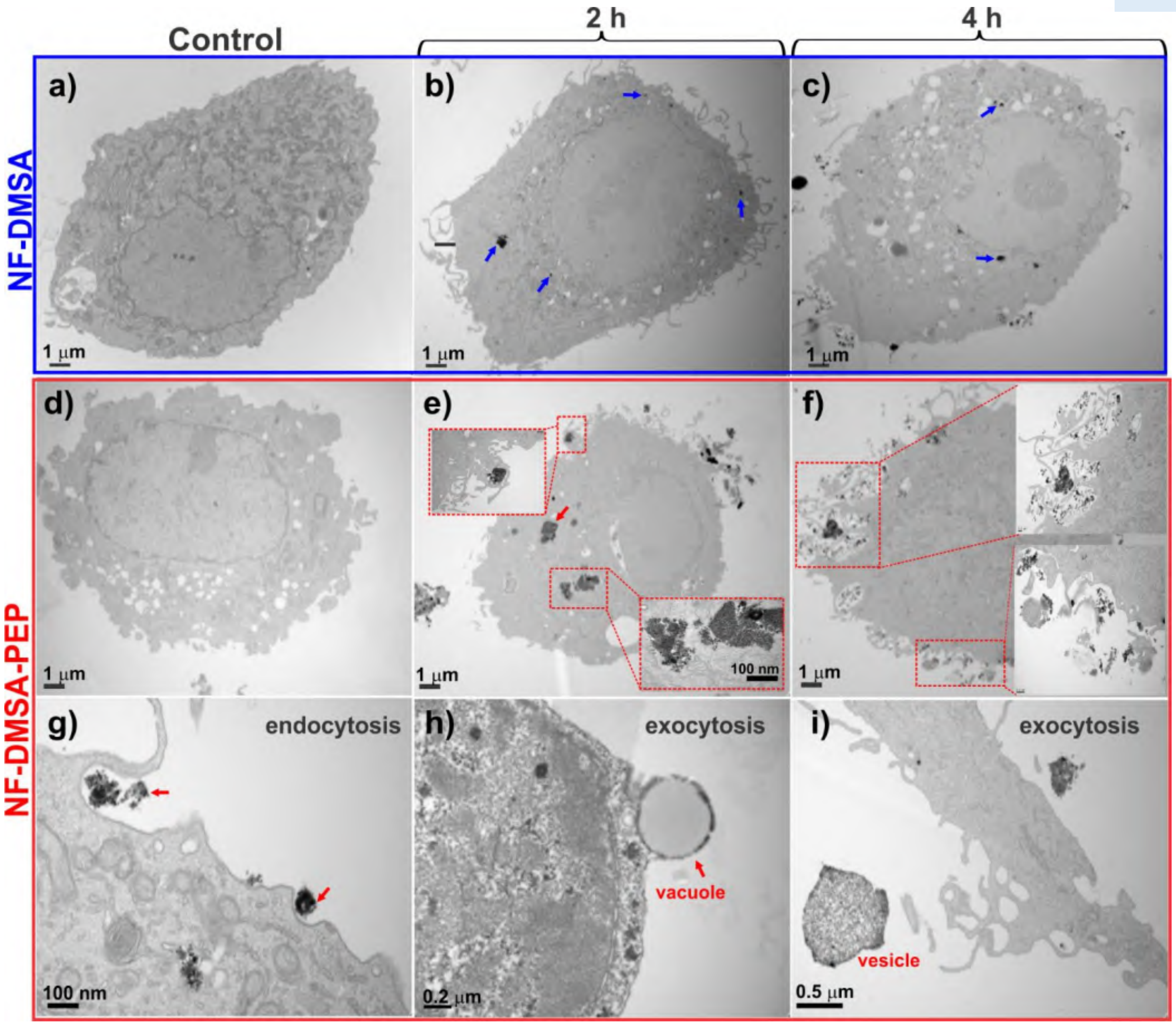
U87MG cells

Optimizing flower coating

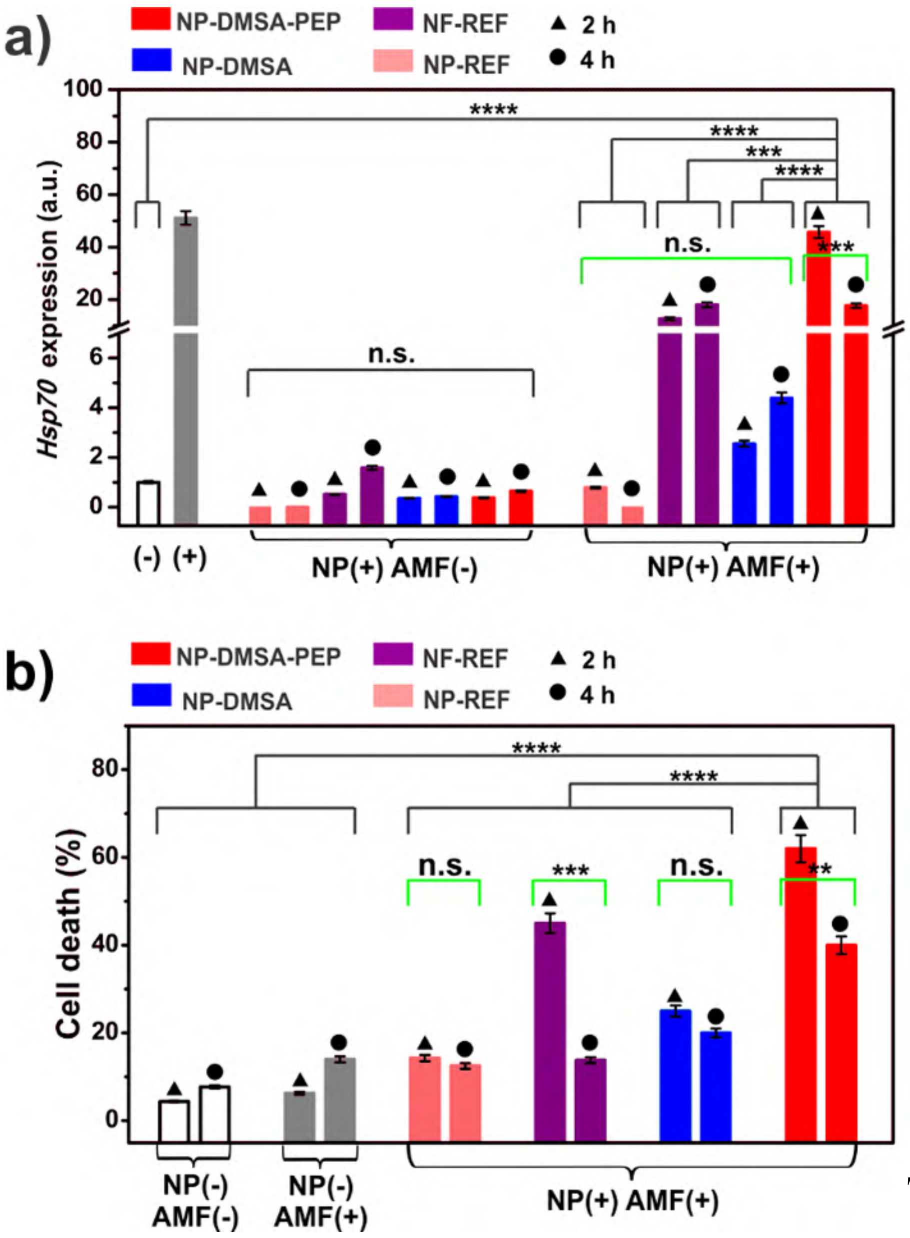


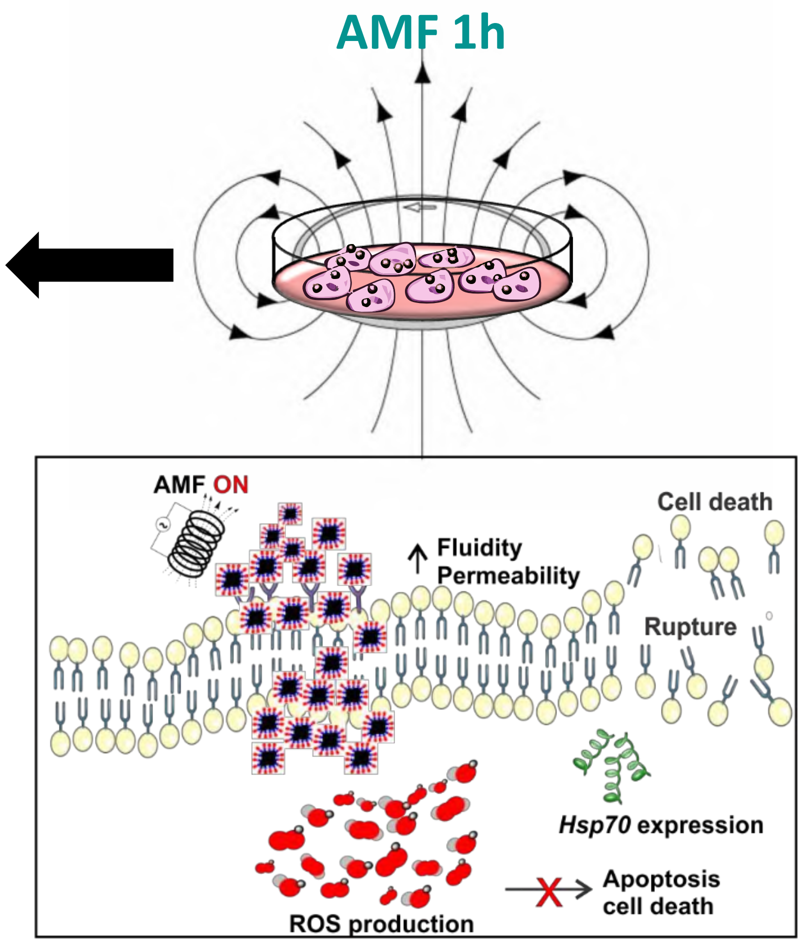
Optimizing flower coating

U87MG cells



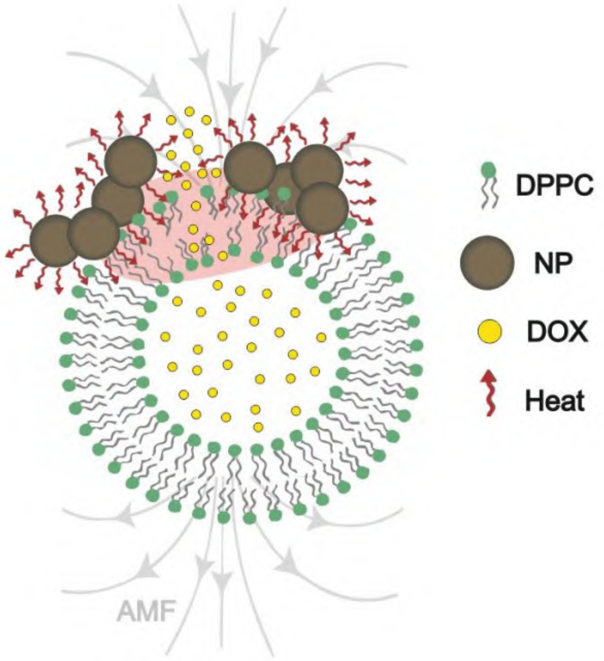
Optimizing flower coating

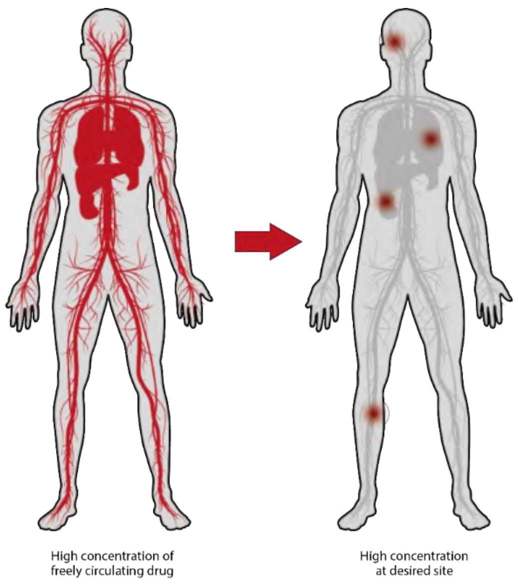




Trypan Blue

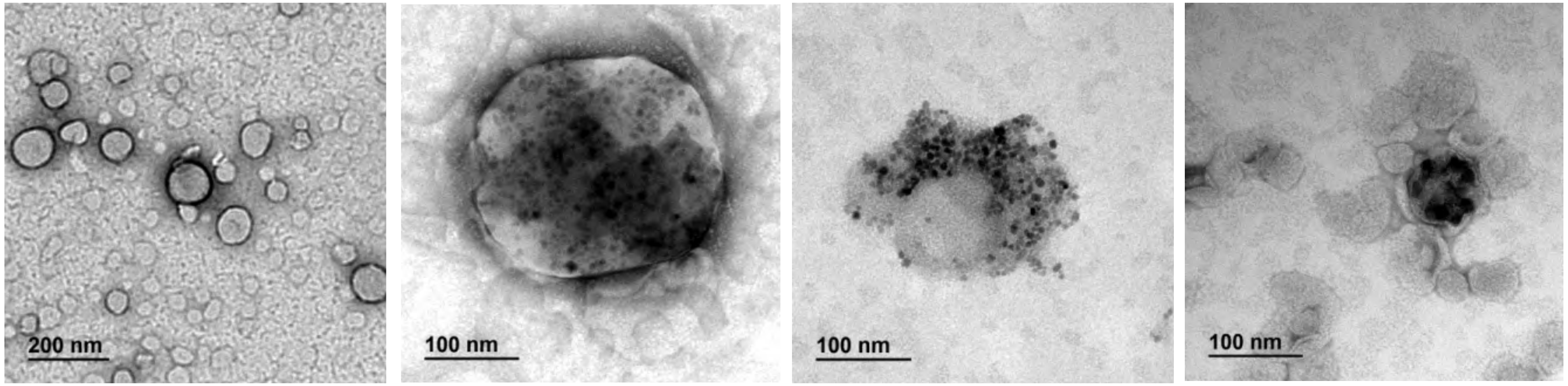
Magnetoliposomes



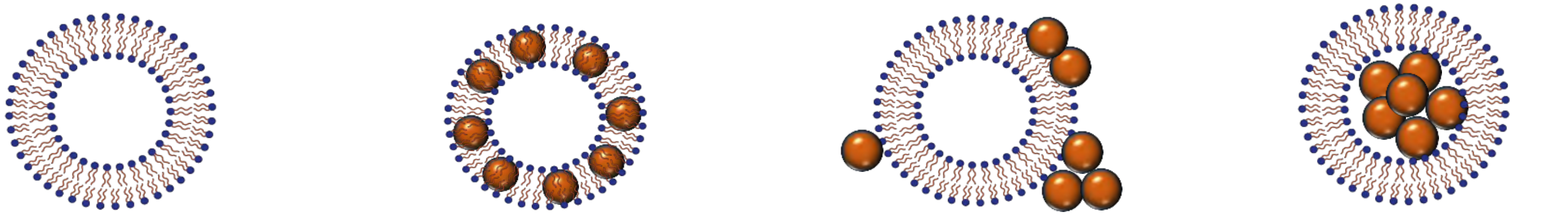


Problem: Remote control

Magnetoliposomes

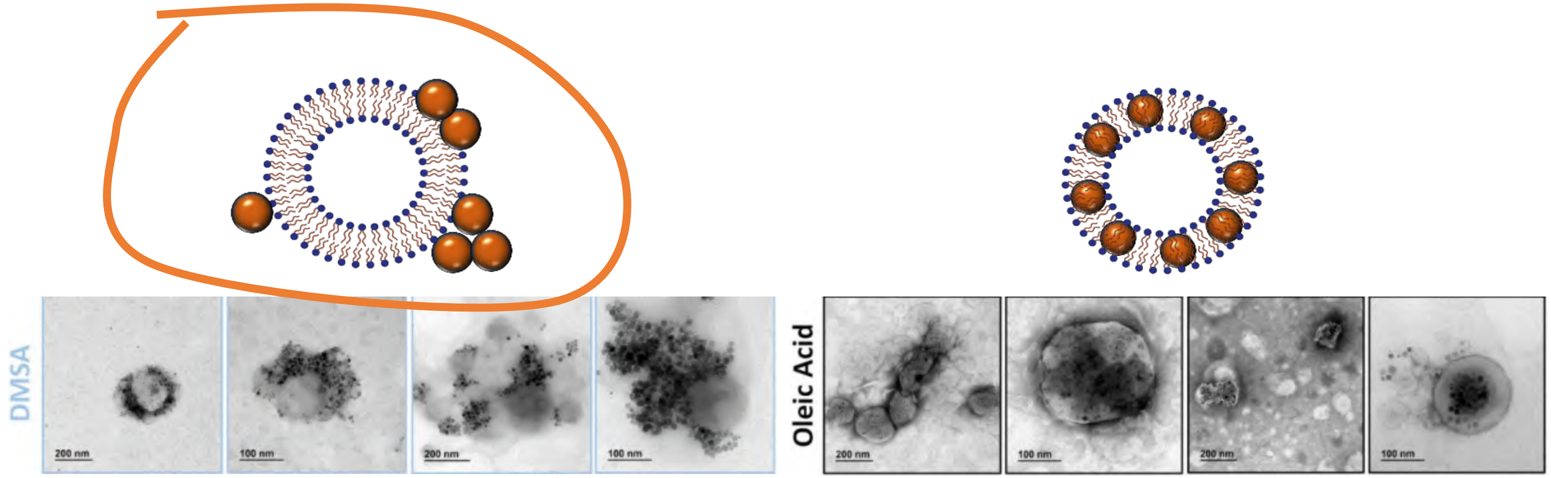


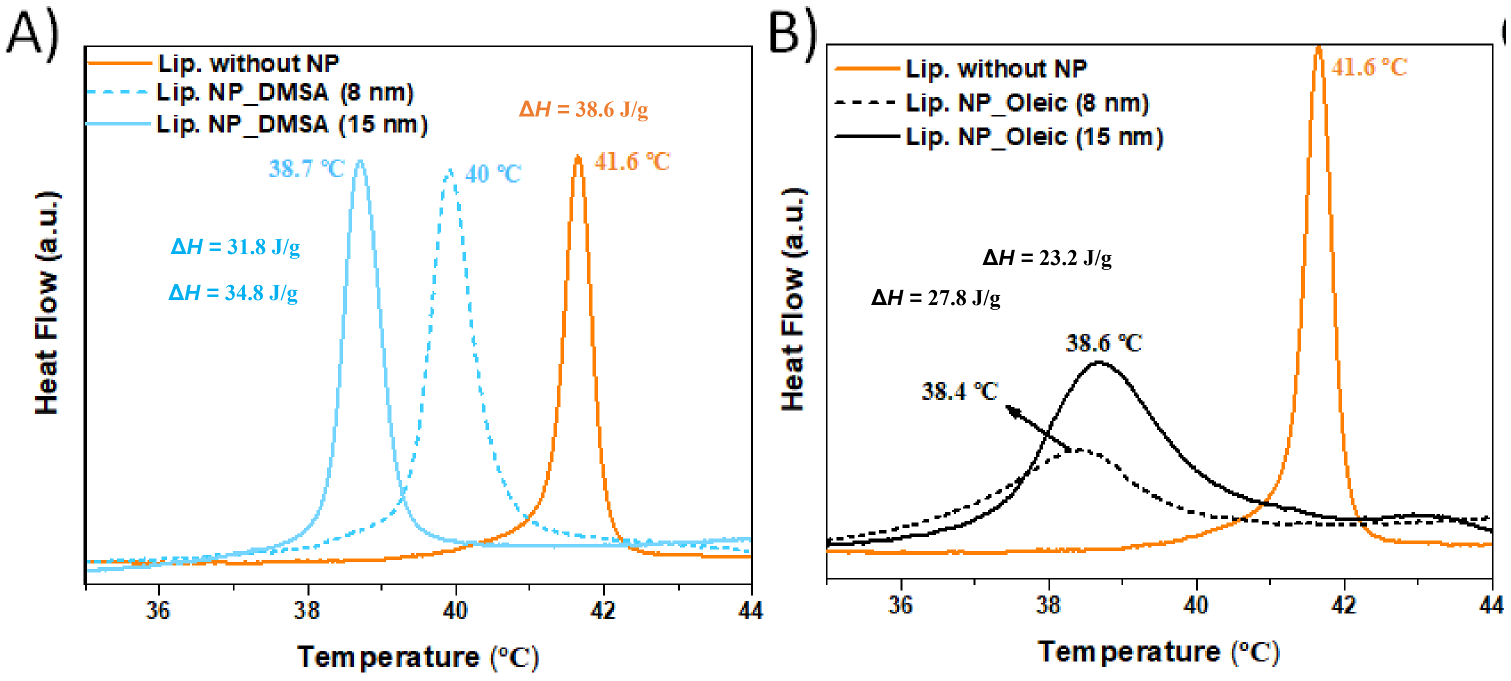
Without Particles | **Particles coated with oleic acid** | **Particles coated with DMSA** | **Particles coated with APS**



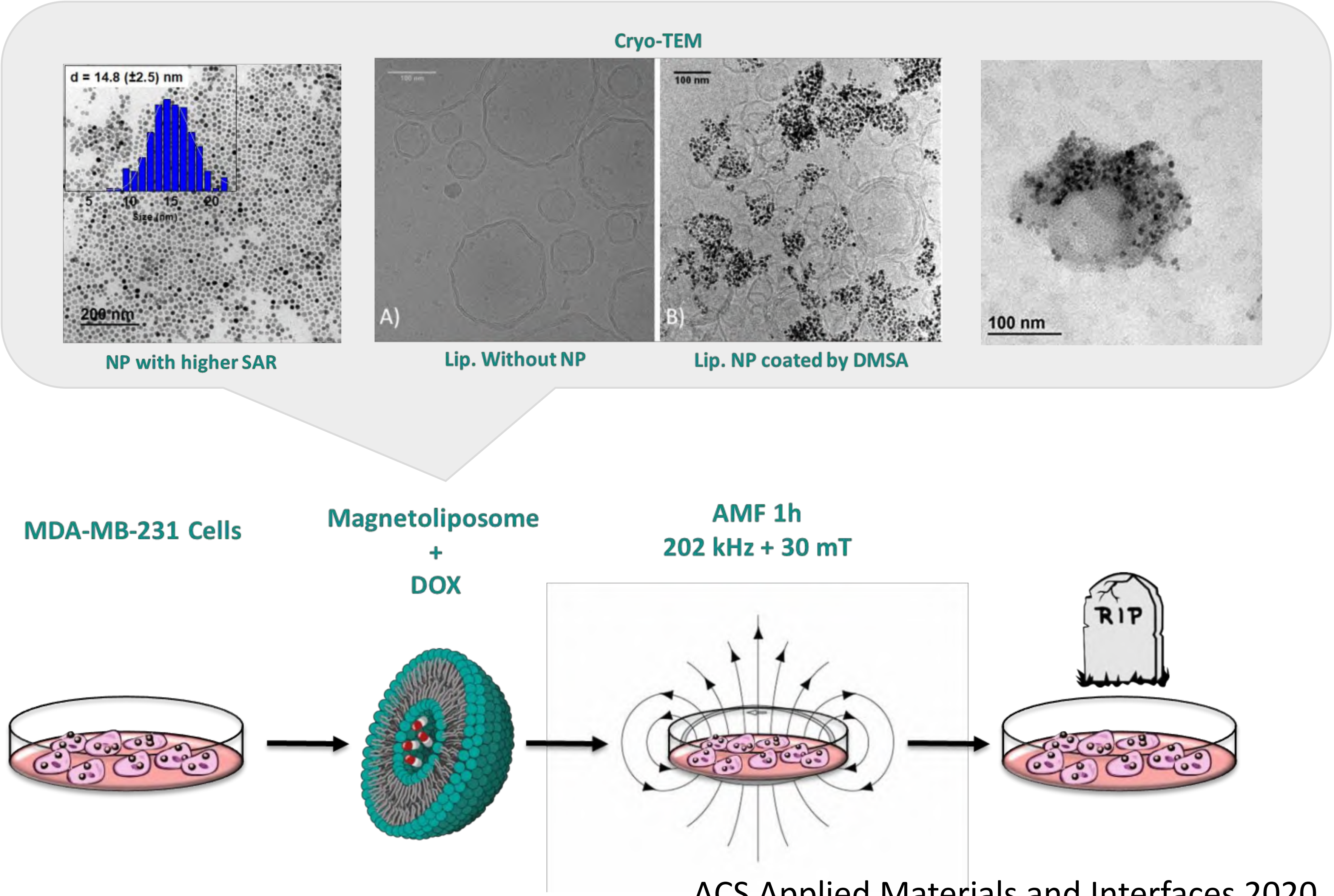
M. E. F. Brollo, P. H. Flores, L. Gutiérrez, C. Johansson, D. F. Barber and M. P. Morales, Phys. Chem. Chem. Phys., 2018, DOI 10.1039/C8CP03016B
M.E. F. Brollo et al., ACS Materials and Interfaces 2019.

Magnetoliposomes



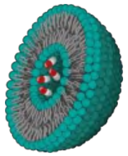


Magnetoliposomes

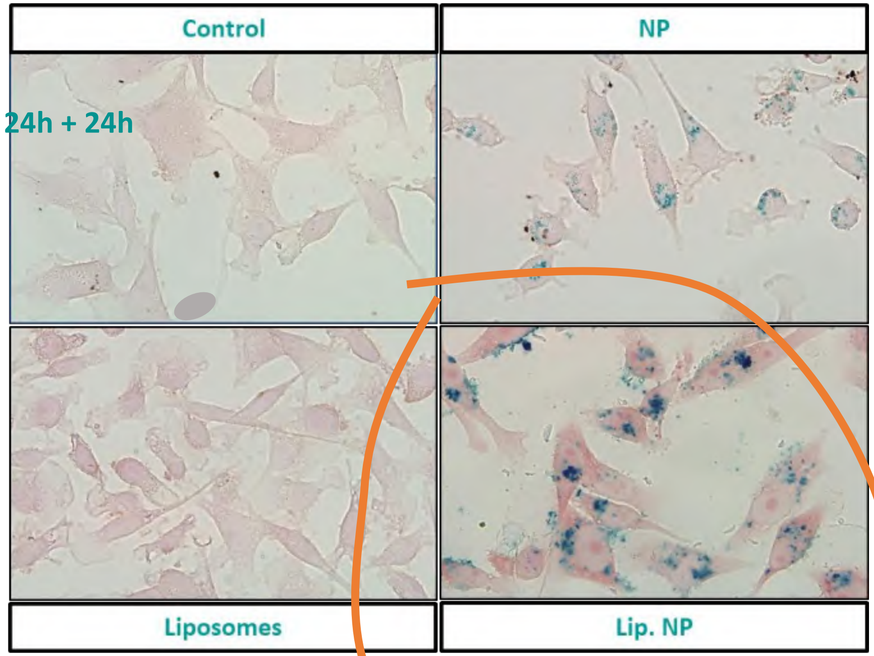


ACS Applied Materials and Interfaces 2020

Magnetoliposomes



MDA-MB-231 cells uptake



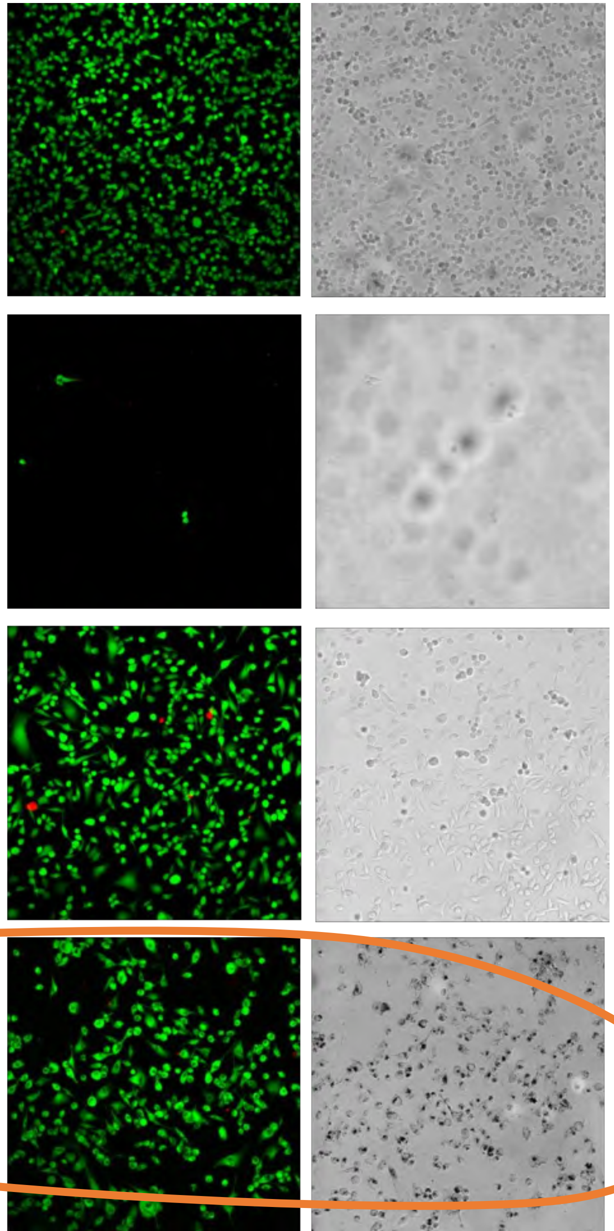
100% labelling

Control

DOX

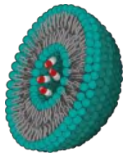
Lip. DOX

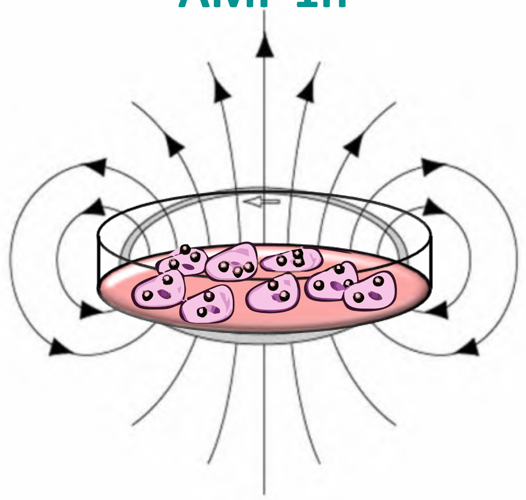
Lip. NP DOX



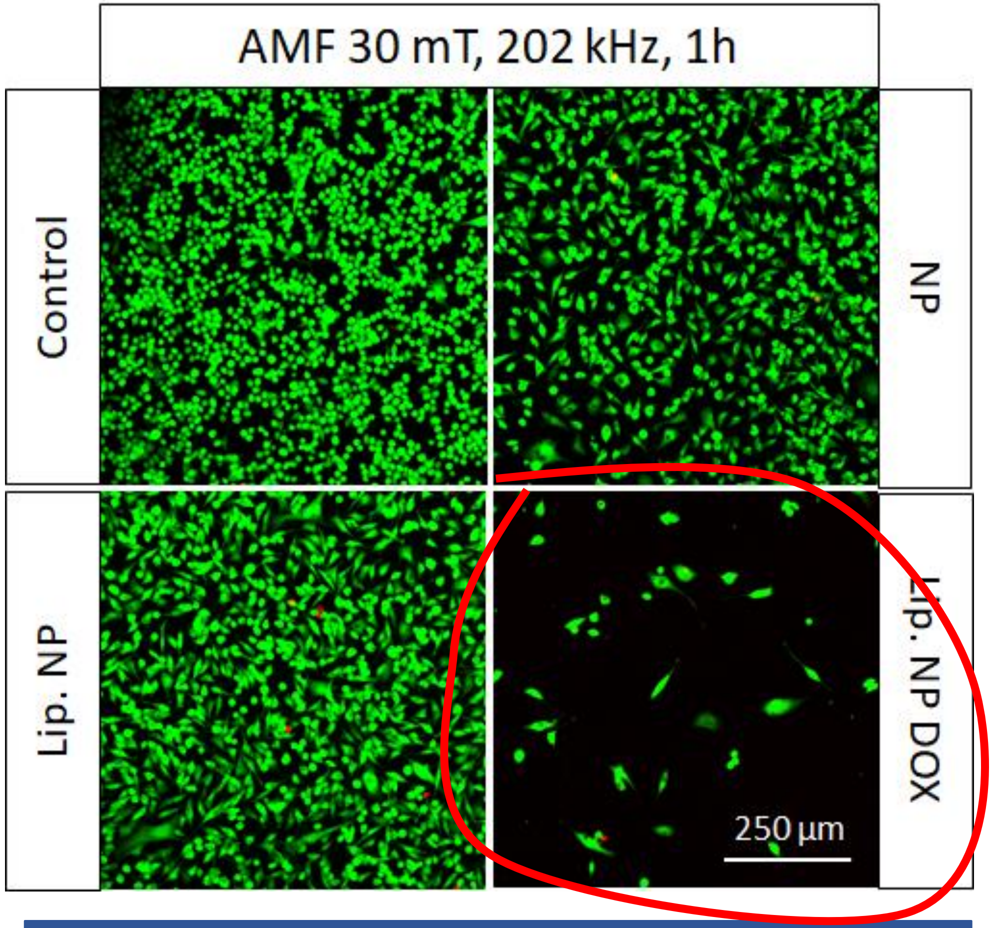
icmm
Instituto de Ciencia de Materiales de Madrid

Magnetoliposomes



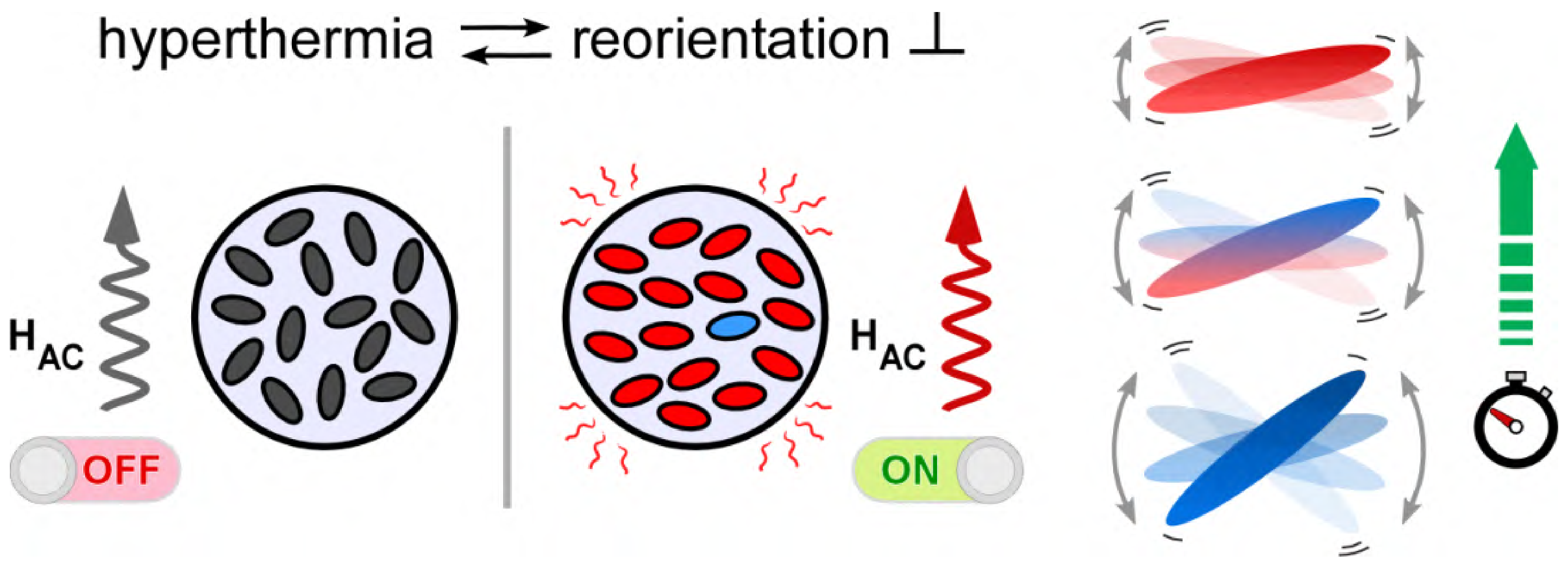


AMF 1h



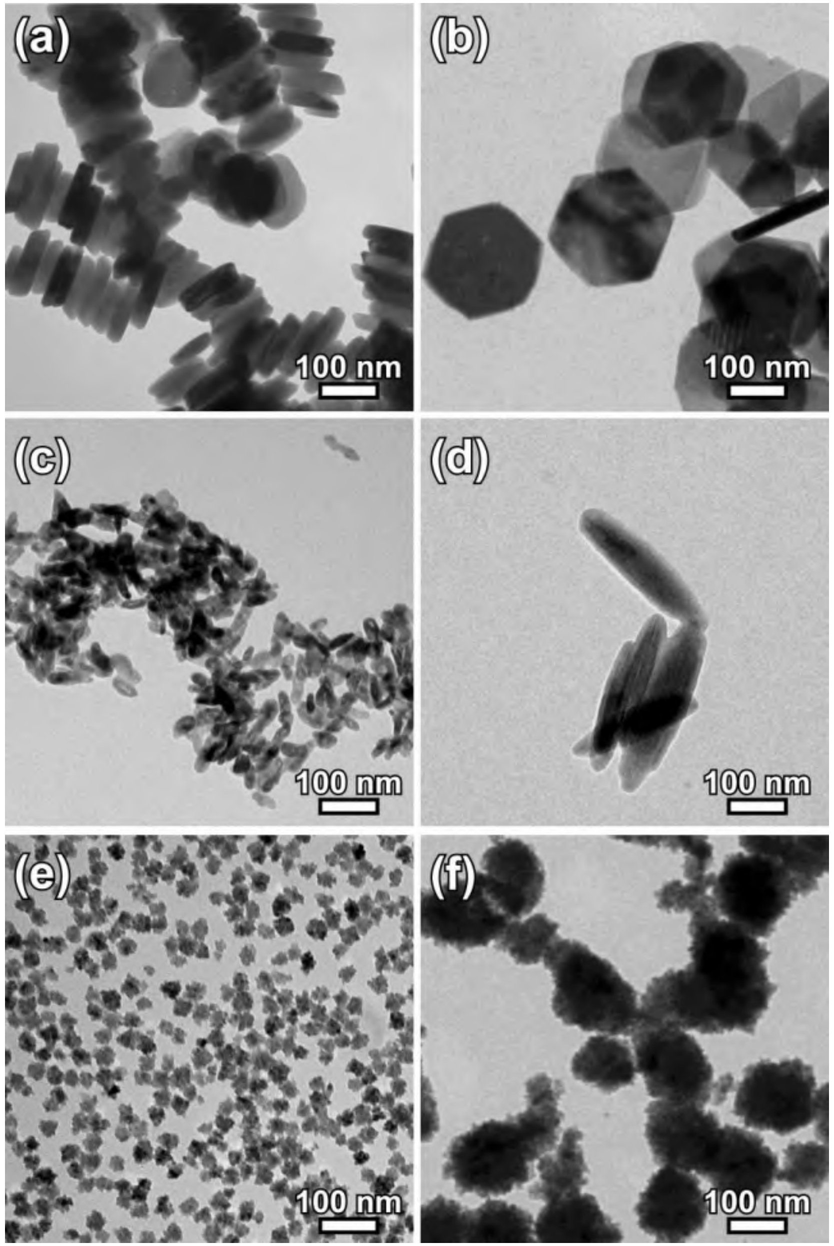
Remote Drug release control

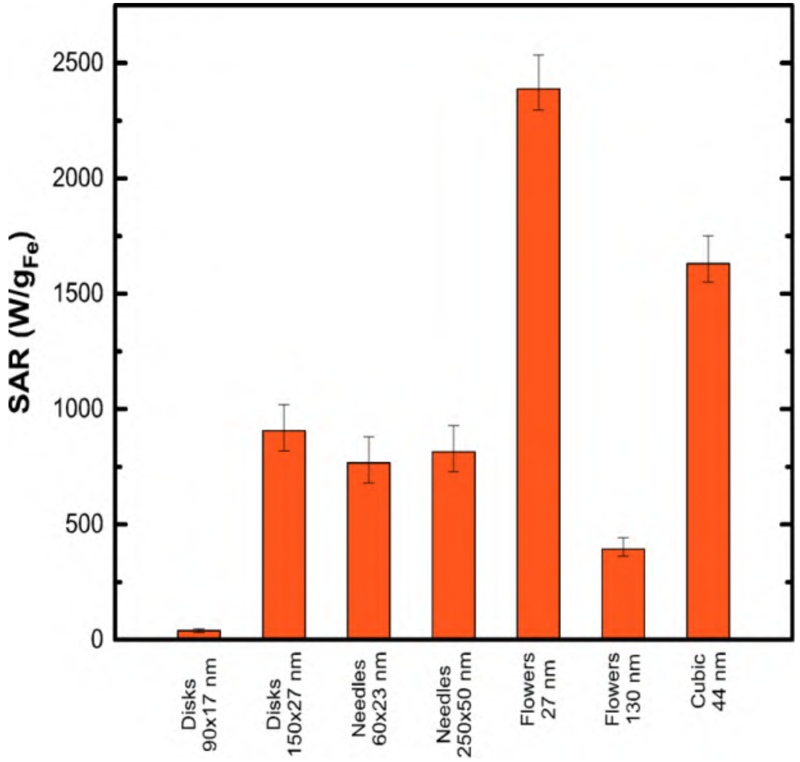
ACS Applied Materials and Interfaces 2020



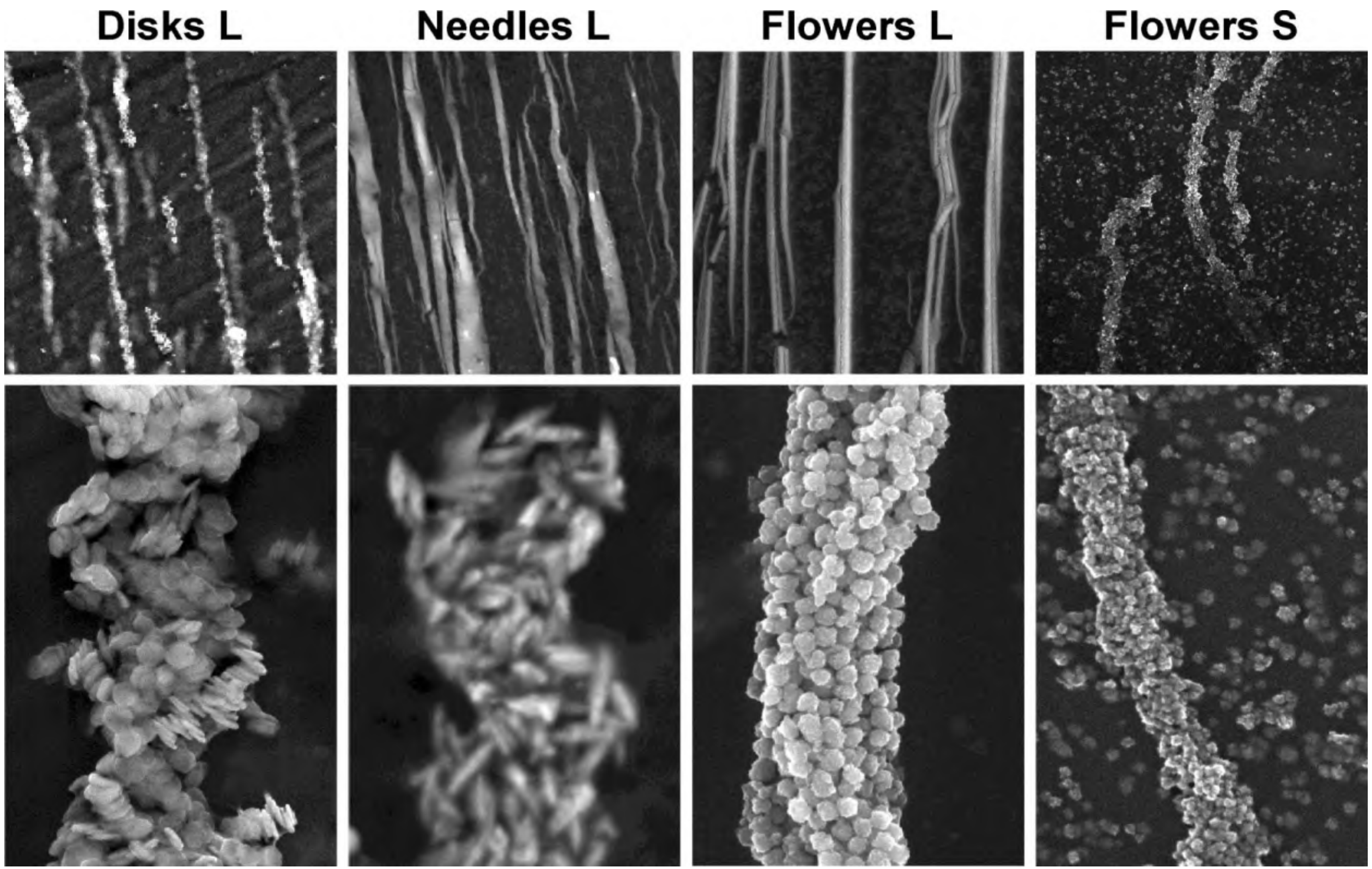
Time-dependent perpendicular-reorientation process induced by the hyperthermia AC field on the magnetic rods

Comparison with other morphologies

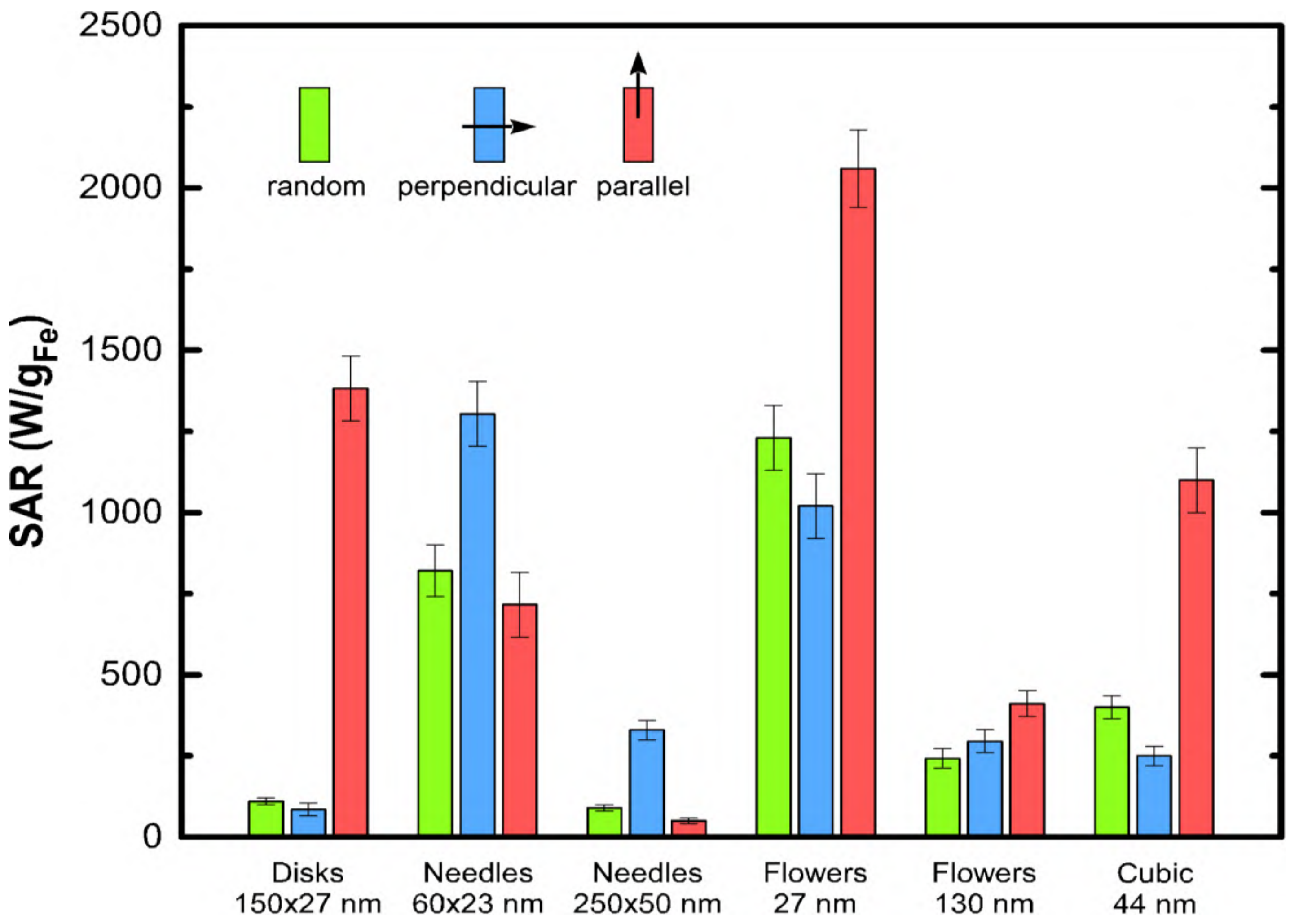




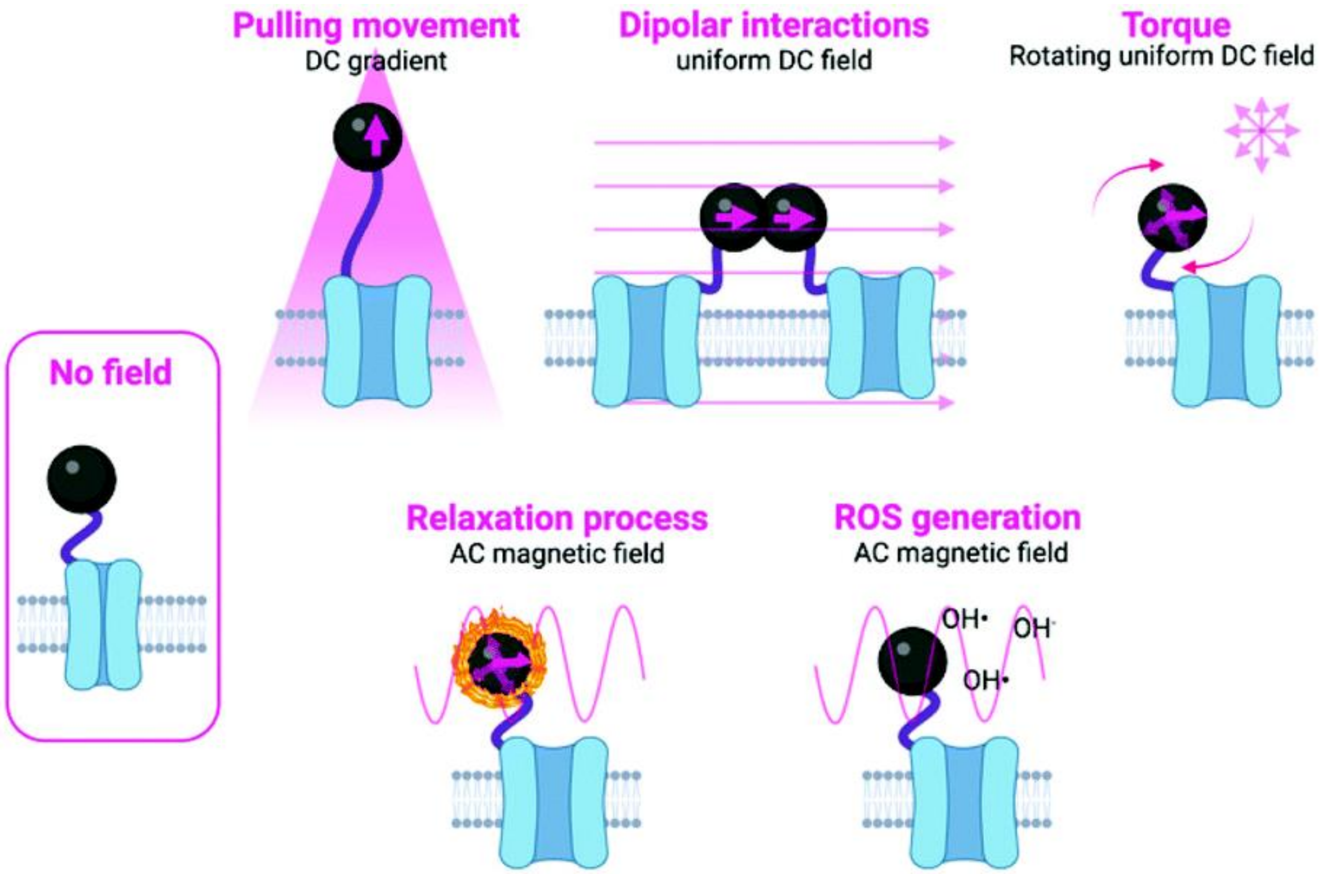
Comparison with other morphologies



Comparison with other morphologies



Magneto-mechanical and magneto-thermal stimulation to activate cell functions

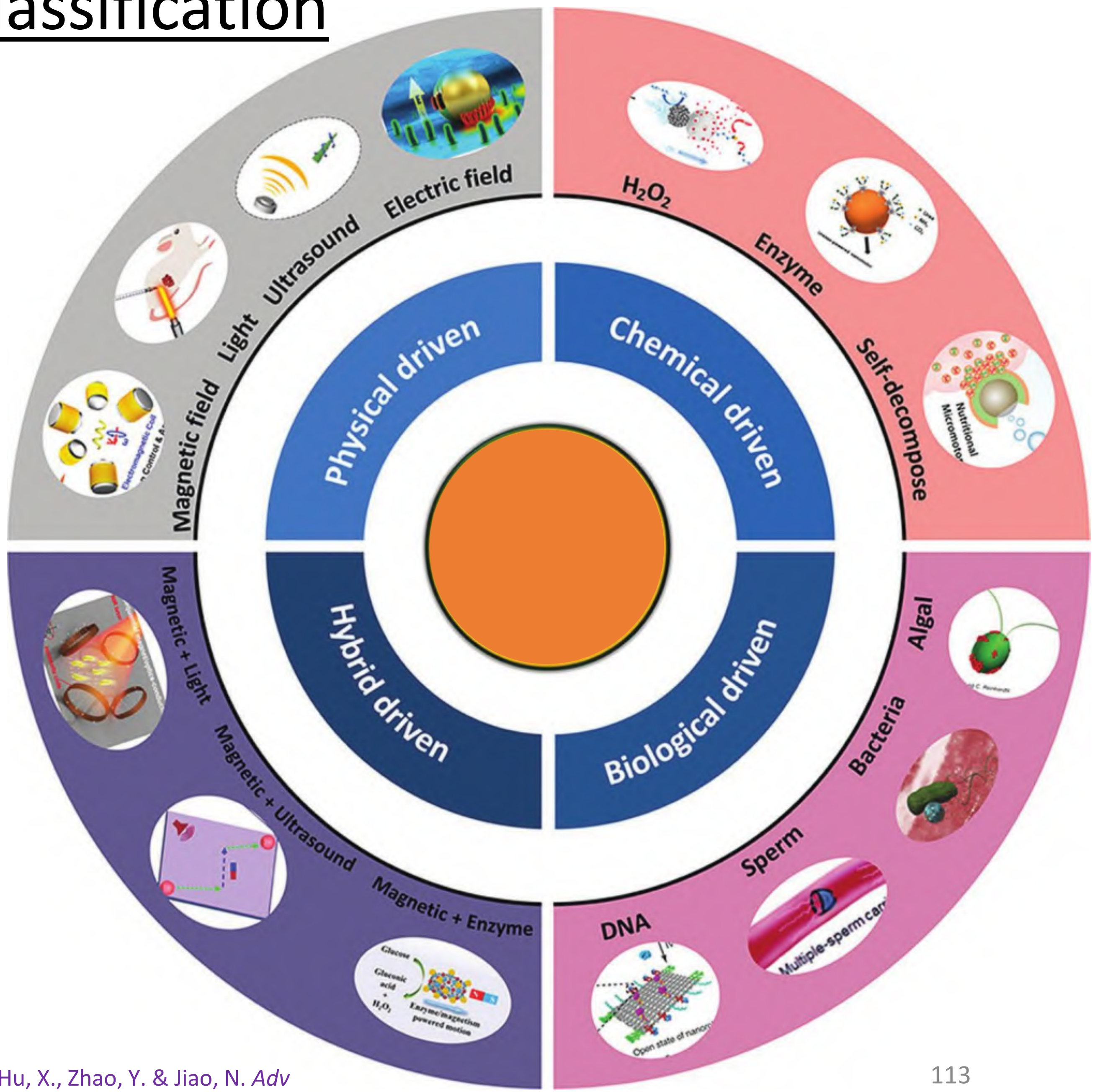


Susel Del Sol et al, Nanoscale, 2022, 14, 2091–2118

Nano-motors: definition and classification

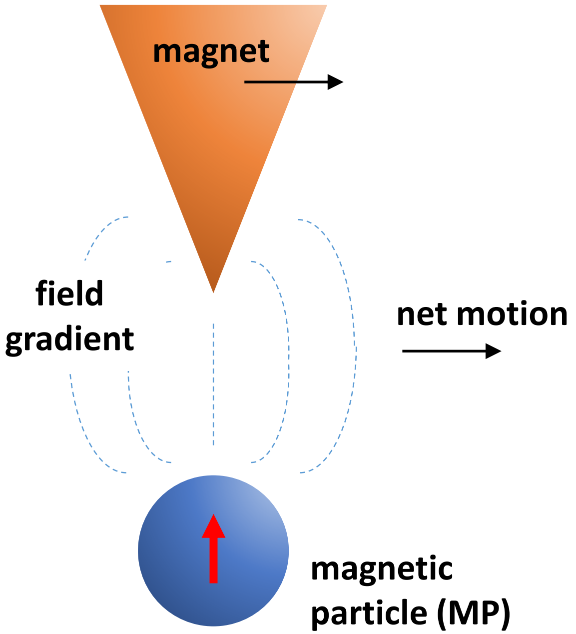
- Initial research inspired by living organisms.
  - Nano-motors convert different sources of energy into mechanical work, leading to translational or rotational movement.

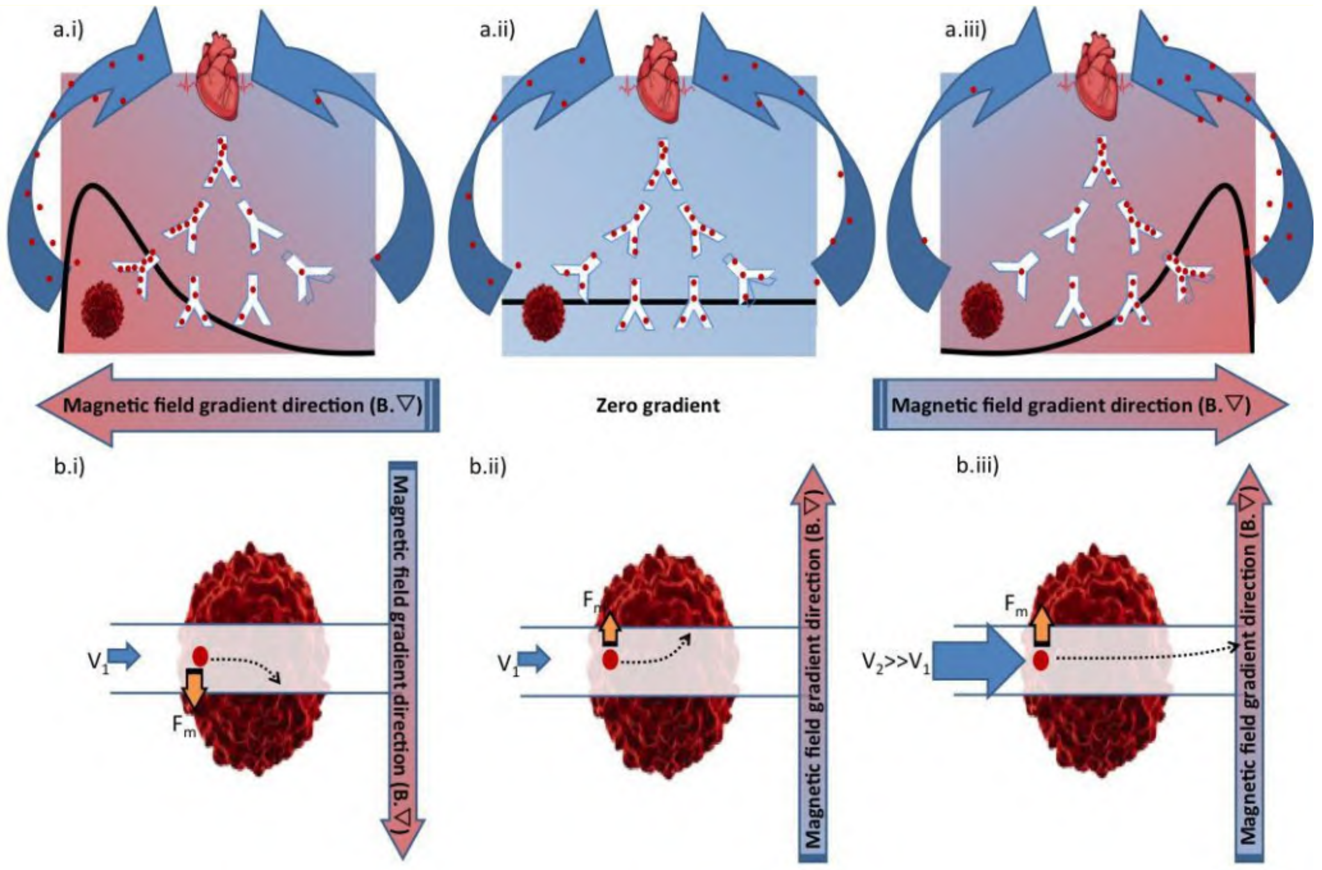
- Classification:
  - Physically-driven motors
    - Require source of external energy
    - Light
    - Ultra-sound
    - Magnetic field
    - Electric field
  - Chemically-driven motors
    - carry fuel to drive environmentally triggered autonomous locomotion.
  - Hybrid-driven motors
  - Biologically-driven motors



Li, M., Hu, X., Zhao, Y. & Jiao, N. *Adv Materials Technologies* 2201928 (2023)

Nanoparticle targeting using the magnetic field gradients





- Magnetic Force due to magnetic field gradient:

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

- Magnetic Resonance Targeting (using MRI scanners)
- Macrophages loaded with oncolytic virus + **Magnetosomes**

M. Muthana et. al., Nature communications 6, 8009 (2015)

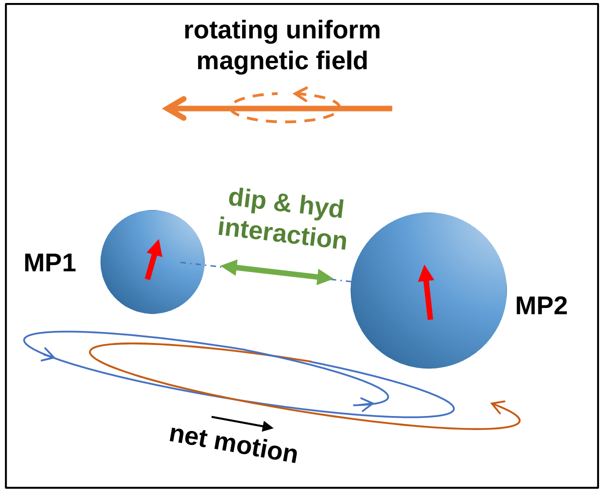
Nanoncolytics

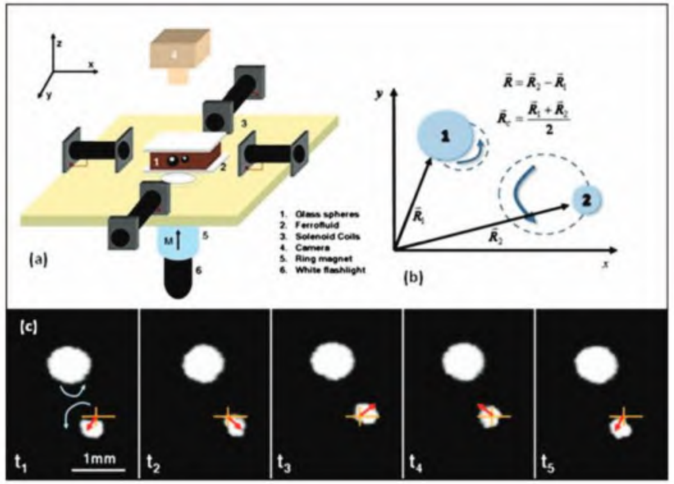
CANCER RESEARCH UK

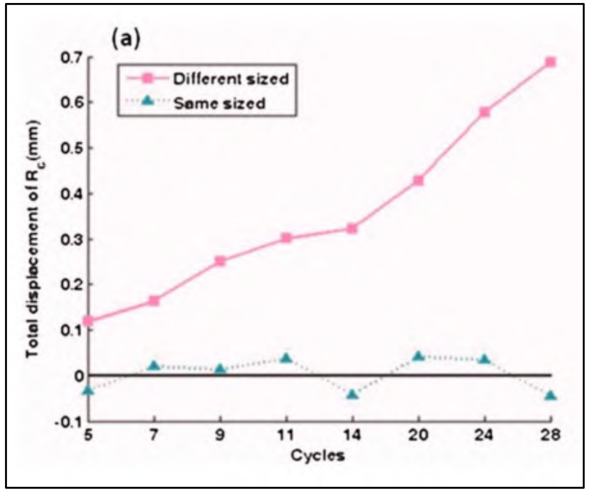
Rotating Magnetic field driven n/m motors (torque-based)

Torque driven motion $\vec{T} = \vec{m} \times \vec{B}$

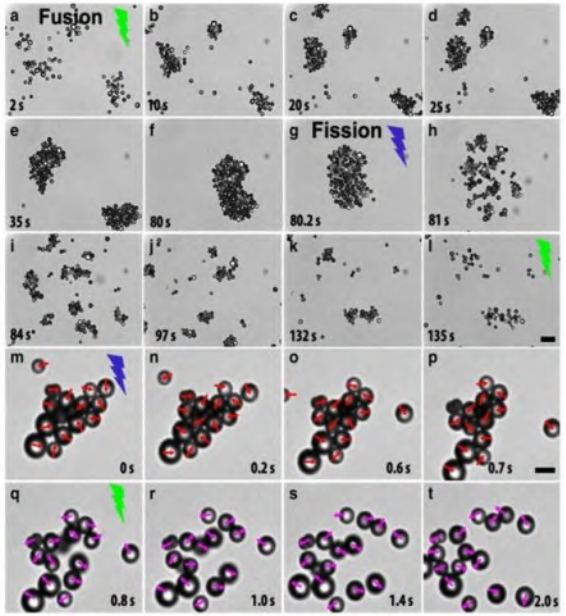
Particle synchronisation



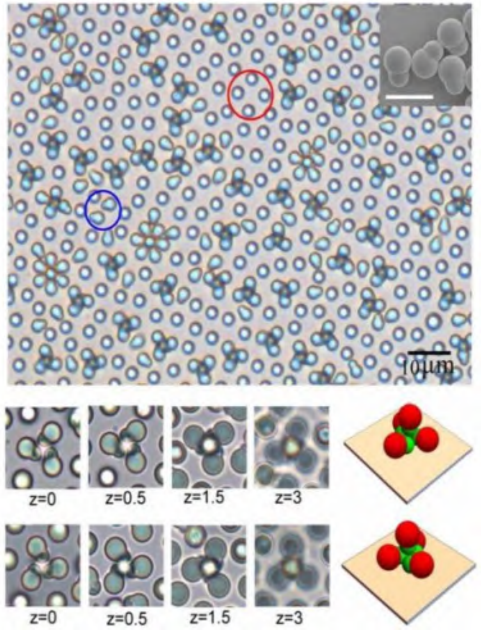




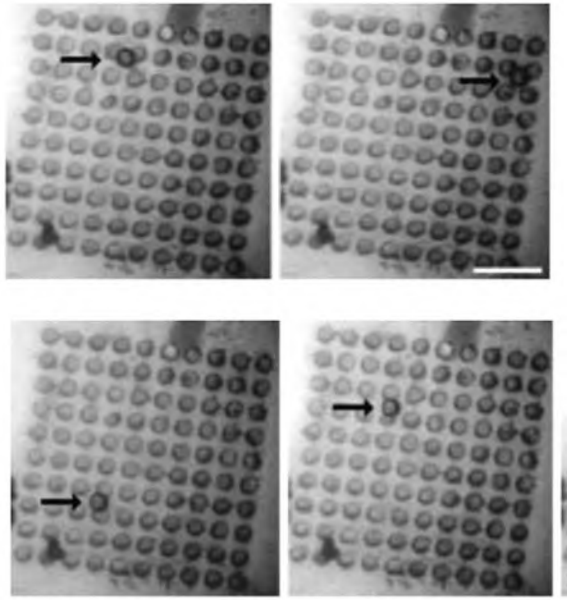
Swarming



Motors as assembled particles



Substrate assisted transport

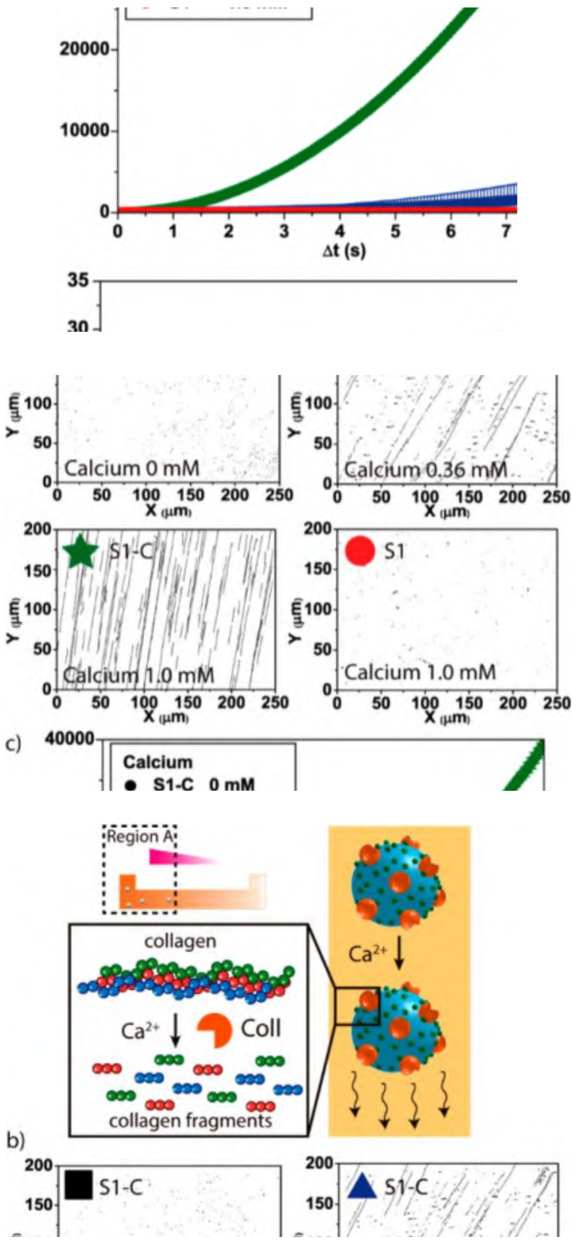


Bhat, S., Kurzweg, T. P., Guez, A. & Friedman, G. *Applied Physics Letters* **94**, 224105 (2009).

Fusi, A. D. *et al.* *Angewandte Chemie* **135**, (2023).

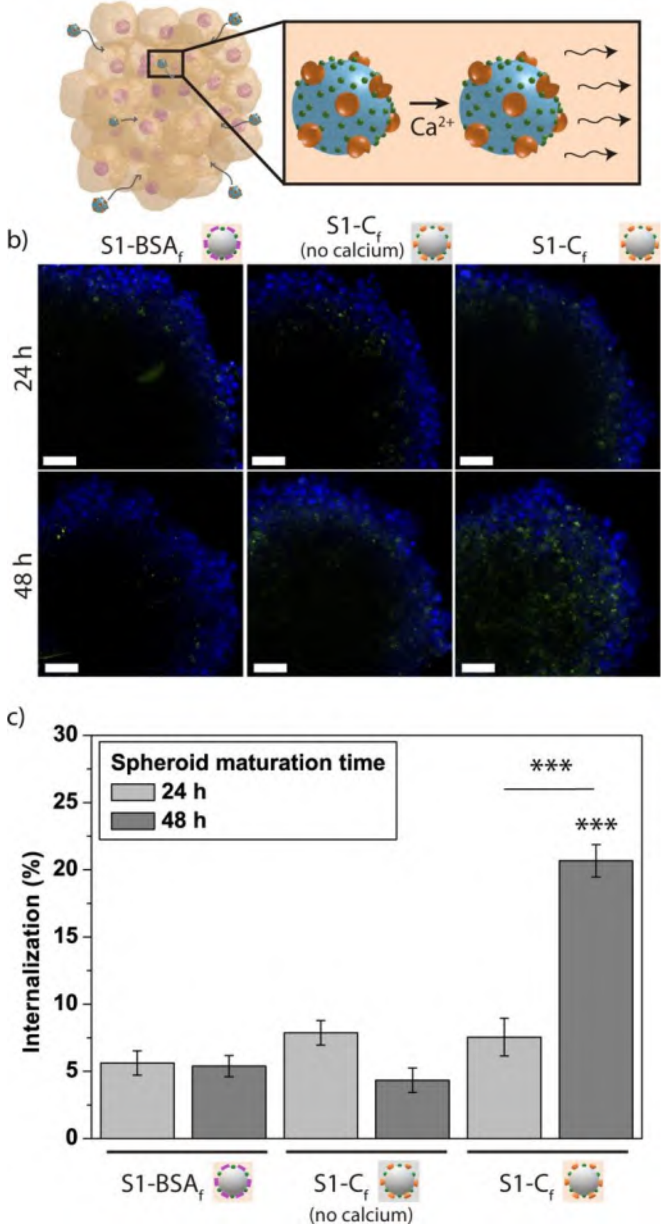
Yellen, B. B., Hovorka, O. & Friedman, G. *PNAS* **102**, 8860–8864 (2005).

“Swimming”



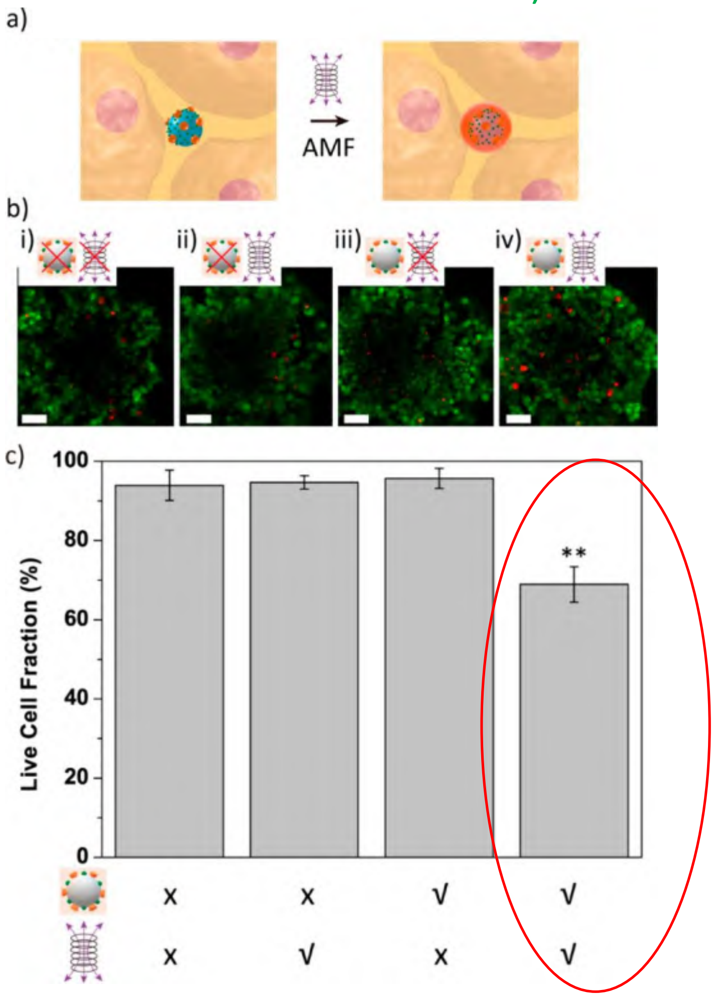
Cell spheroid penetration

human primary osteogenic sarcoma cell line



Hyperthermia

AMF (f = 476.7 kHz, 23 mT) for 30 min.

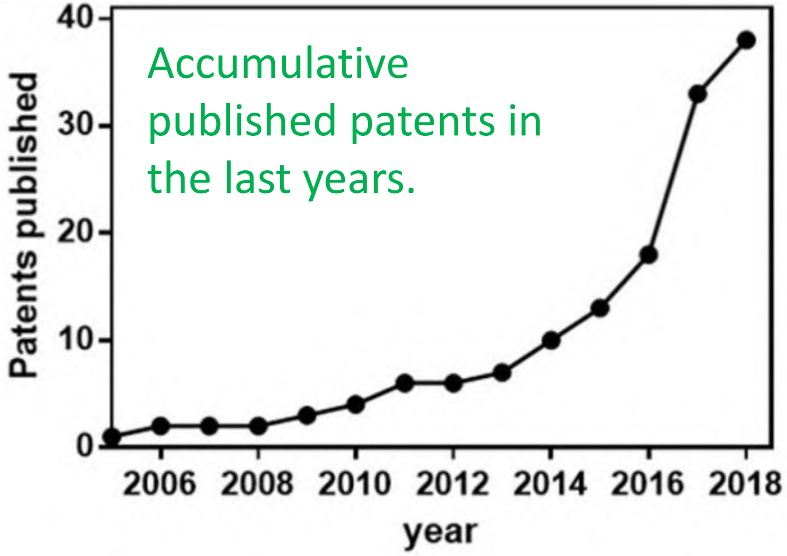


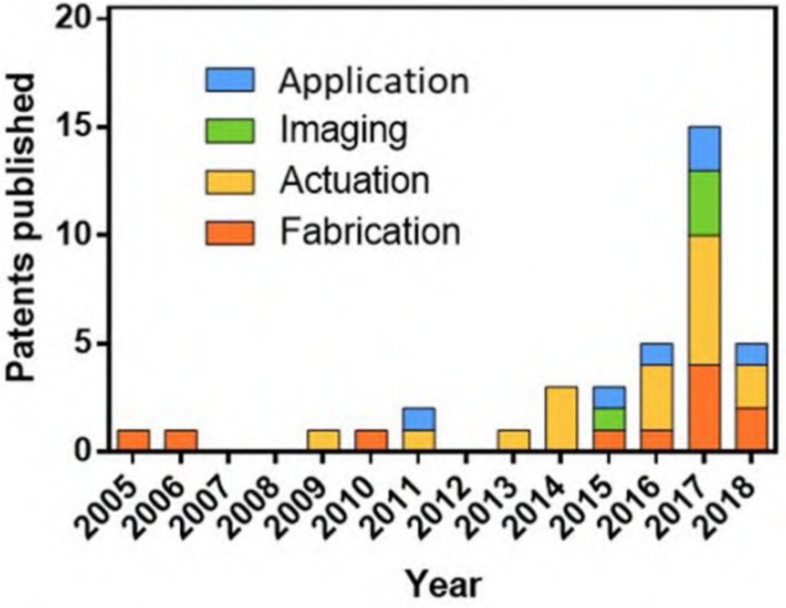
- Best cell treatment if using motor + hyperthermia.

Intellectual Property and Commercialization

- No clinical trials so far (as of 2018)

- A few active companies working toward the commercialization of nanorobots for use in medical applications (as of 2018)
    - Aeon Scientific, Swiss Magnetibox, Weingberg medical physics, …





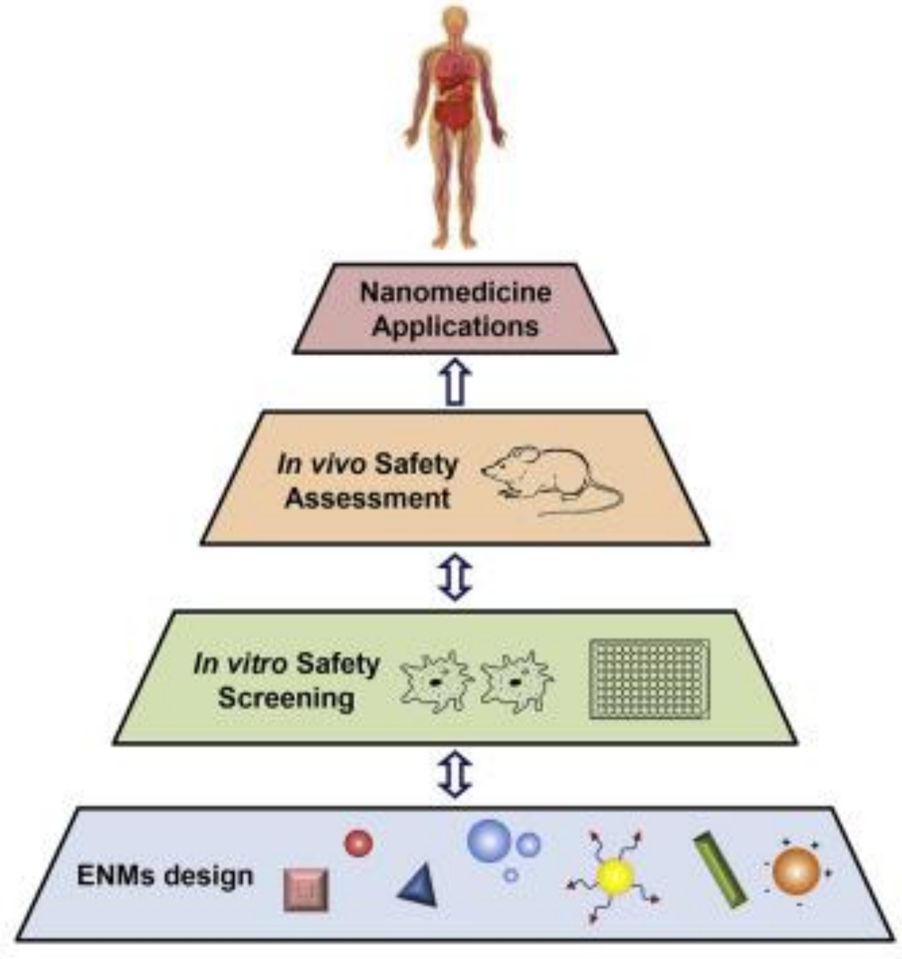
Patents considering the application per year.

Soto, F. & Chrostowski, R., *Front. Bioeng. Biotechnol.* **6**, 170 (2018).

- Challenges to be addressed toward tangible translation to market: Mass fabrication, Standardization of the methodologies and reproducibility, actively consider the commercialization outlook,…

Nanotoxicity

Nanotoxicity



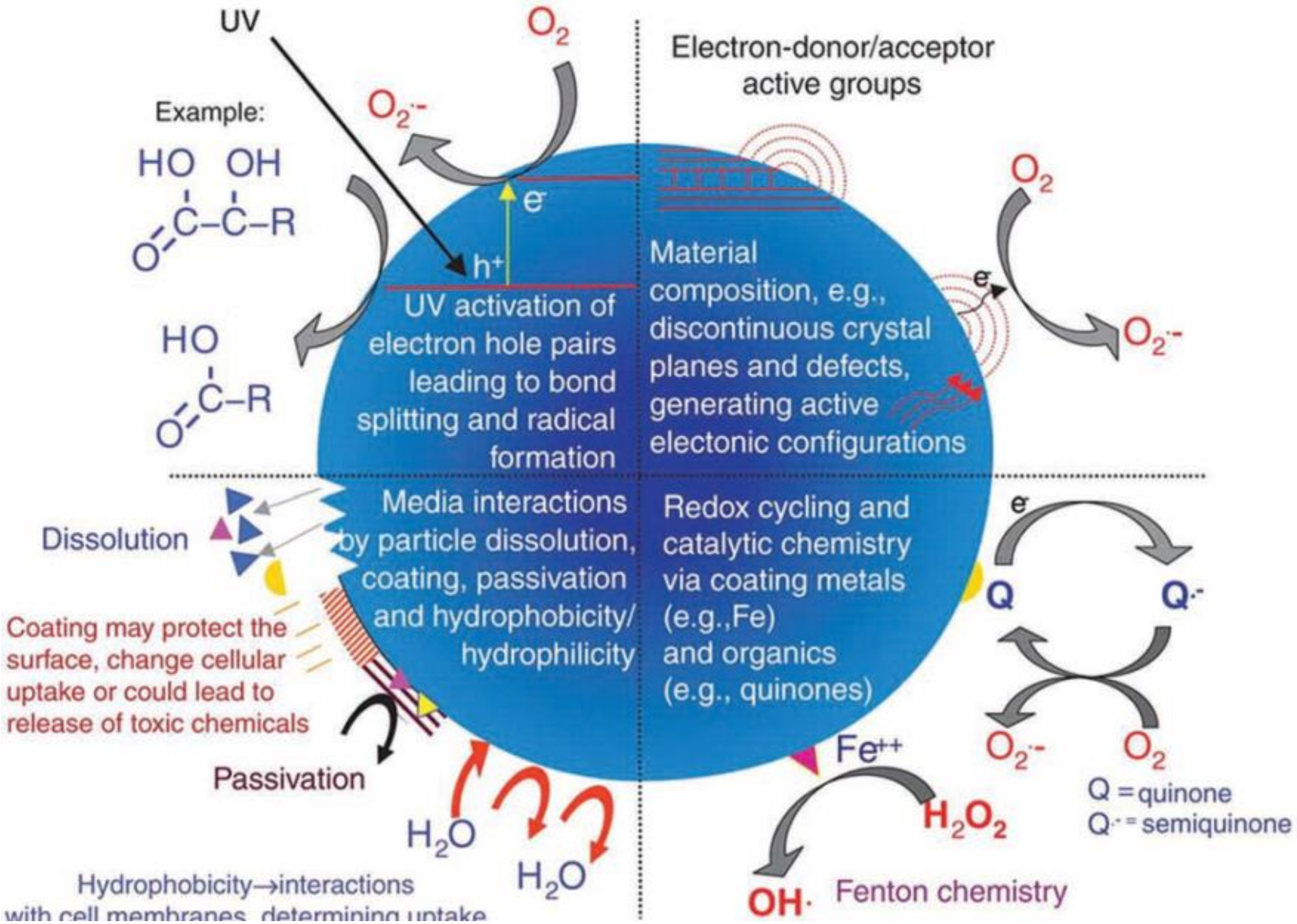
Biodistribution and degradation

Interaction with cell, tissues

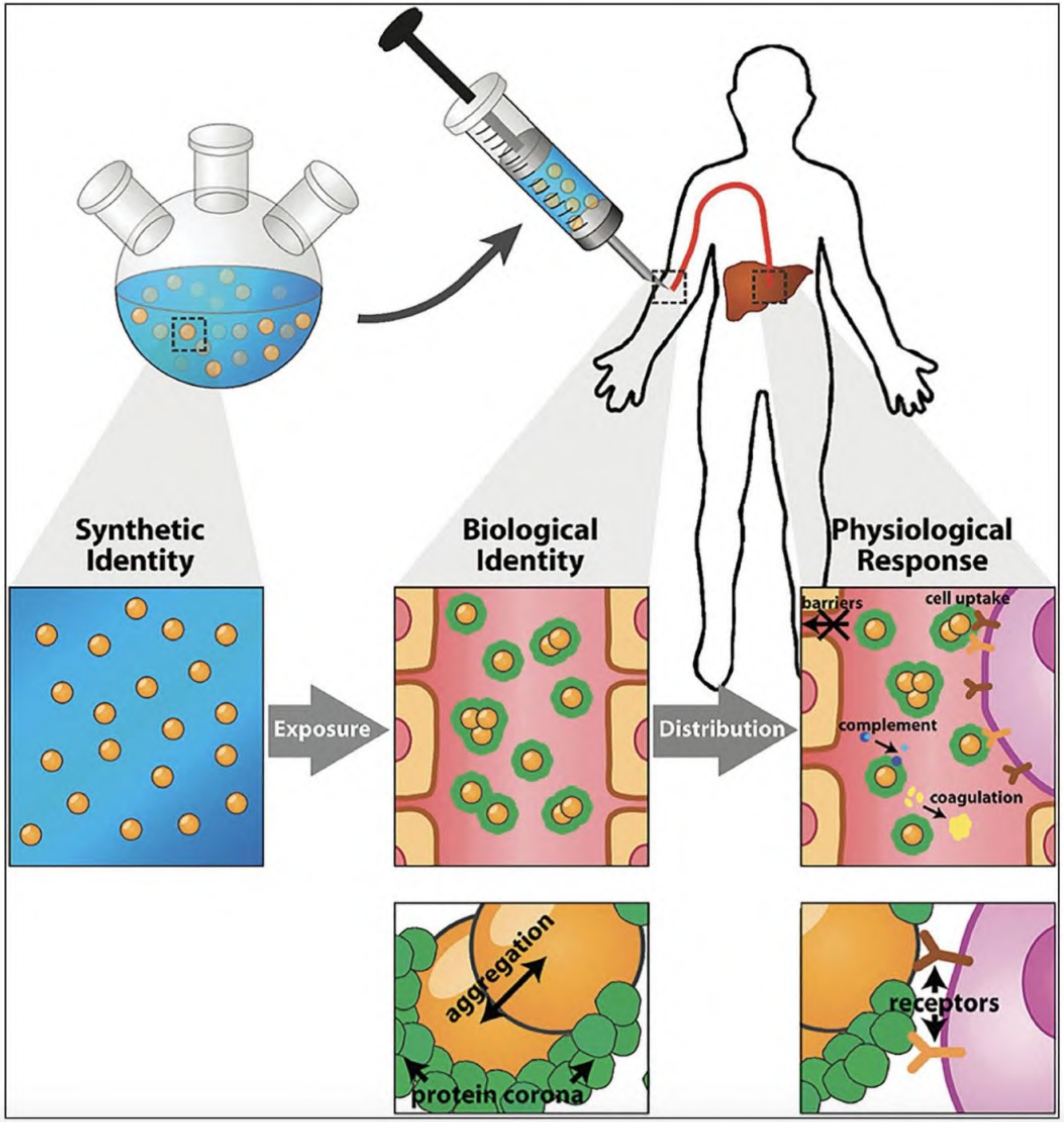
Facilitating Translational Nanomedicine via Predictive Safety Assessment

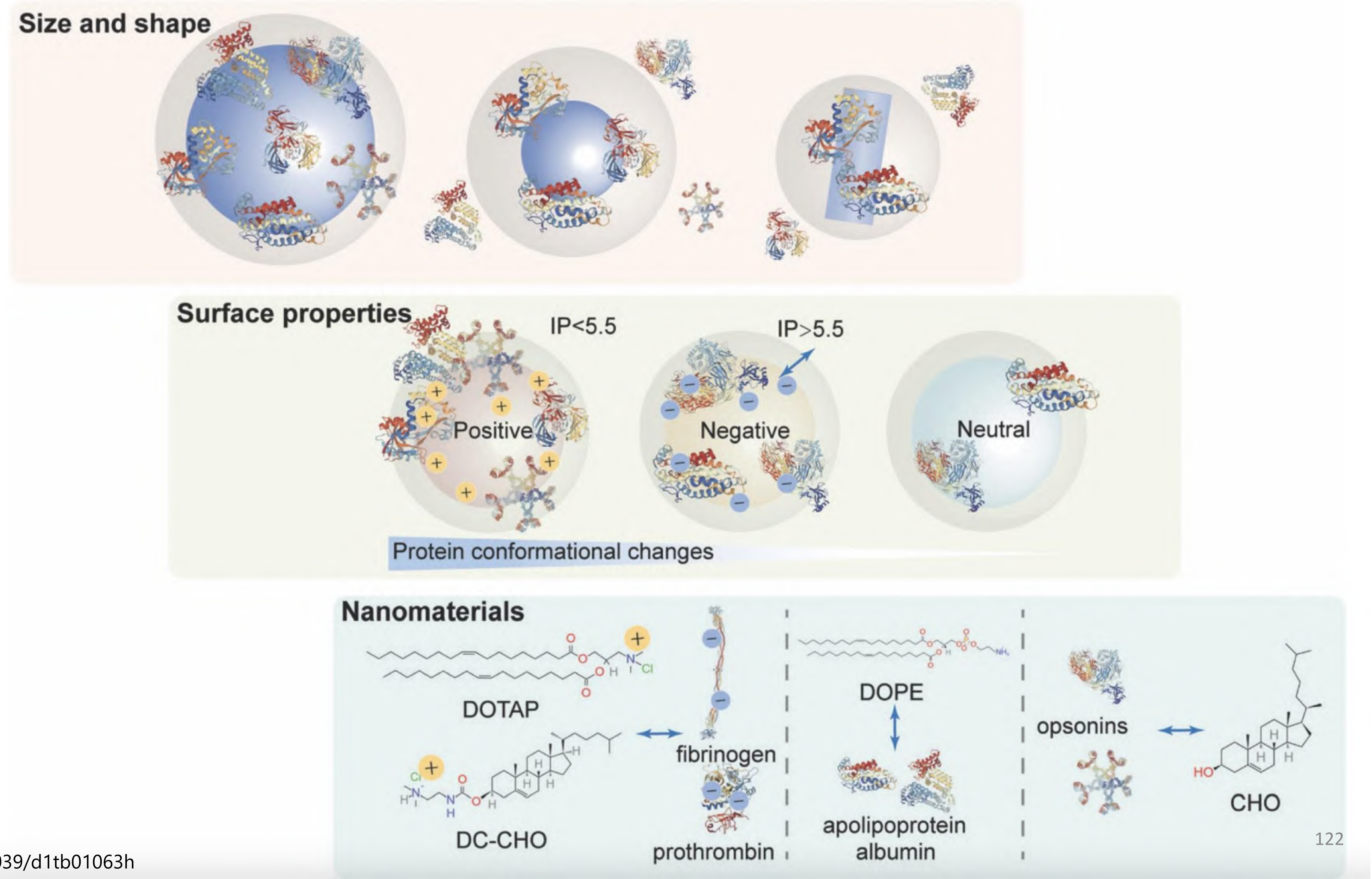
DOI: http://dx.doi.org/10.1016/j.ymthe.2017.03.011

Interaction with cell

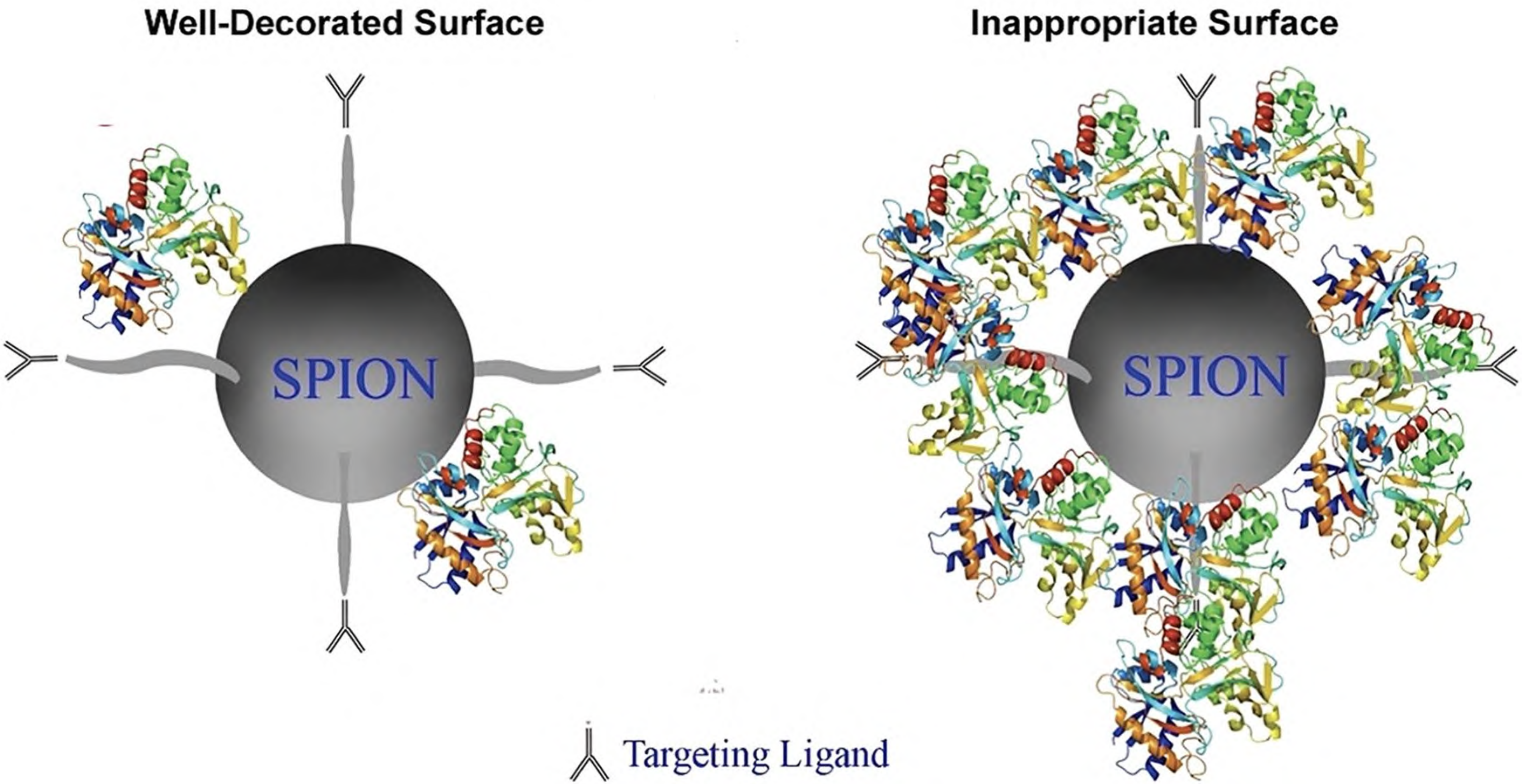


A. Nel , T. Xia , L. Mädler , N. Li, *Science* **2006** , *311* , 622
.

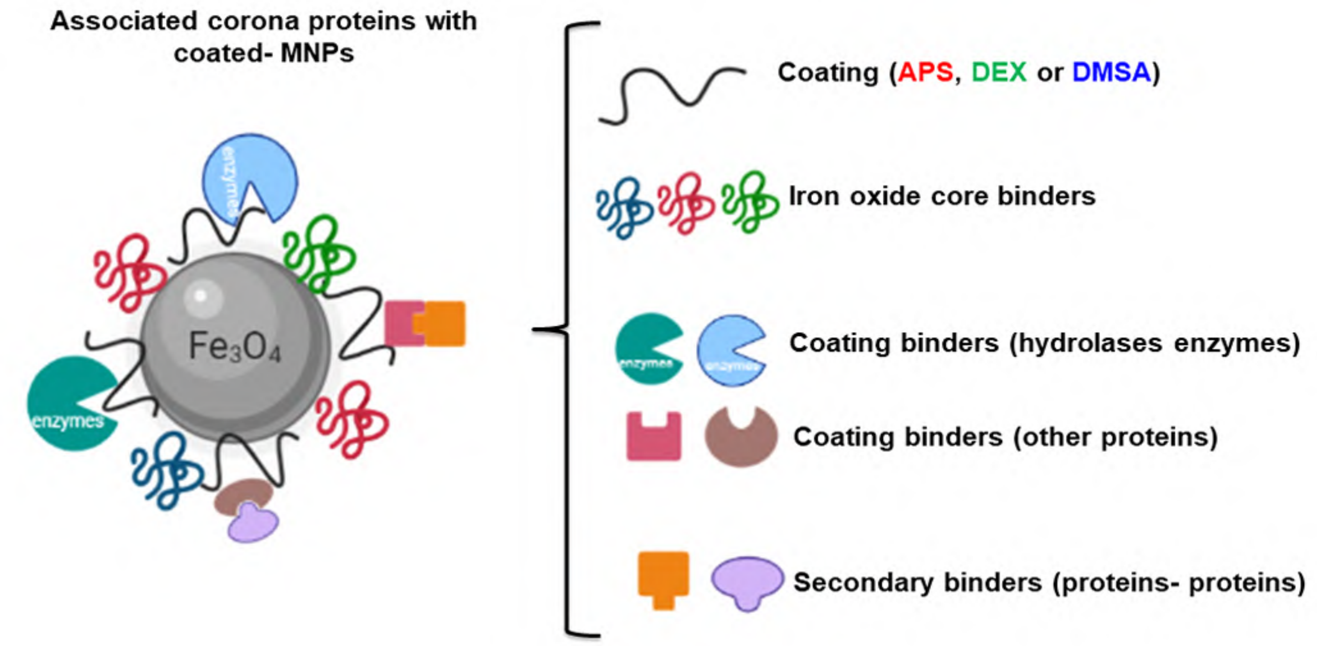

Synthetic Identity
Biological Identity
Physiological Response
Exposure
Distribution
barriers
cell uptake
complement
coagulation
aggregation
protein corona
receptors

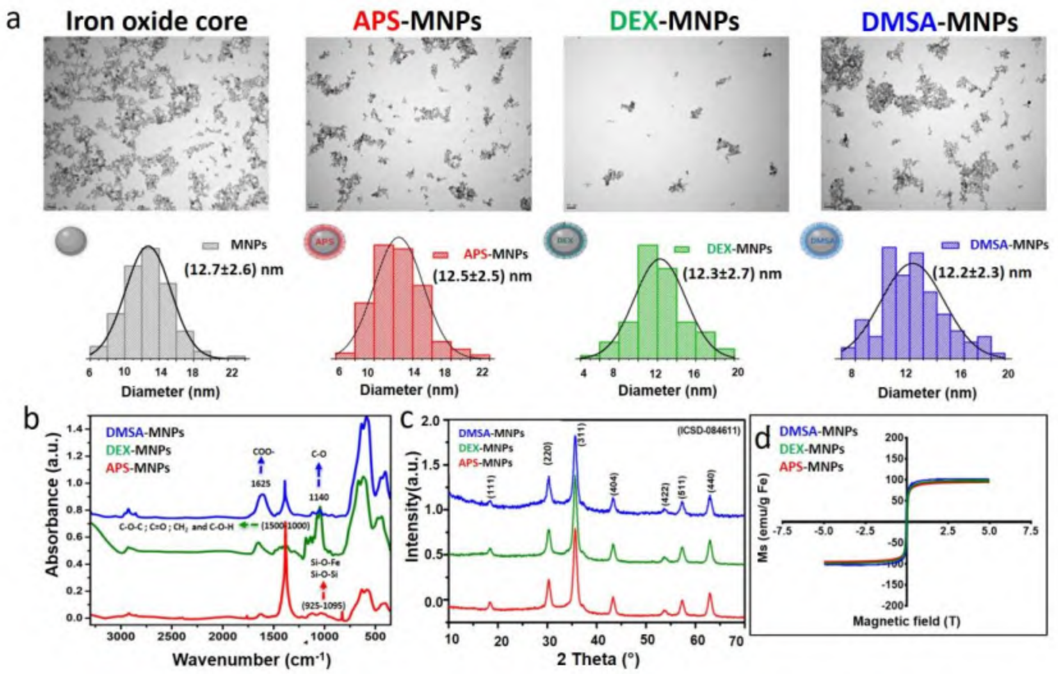


DOI: 10.1039/d1tb01063h

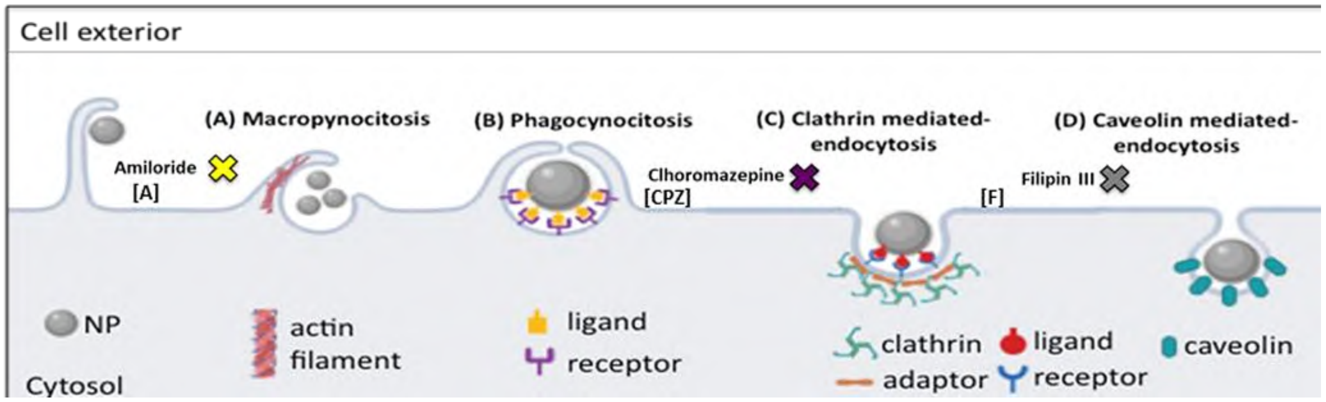

Well-Decorated Surface
Inappropriate Surface
SPION
SPION
Targeting Ligand

Interacciones Nano–bio y bioprocesado in vitro and in vivo





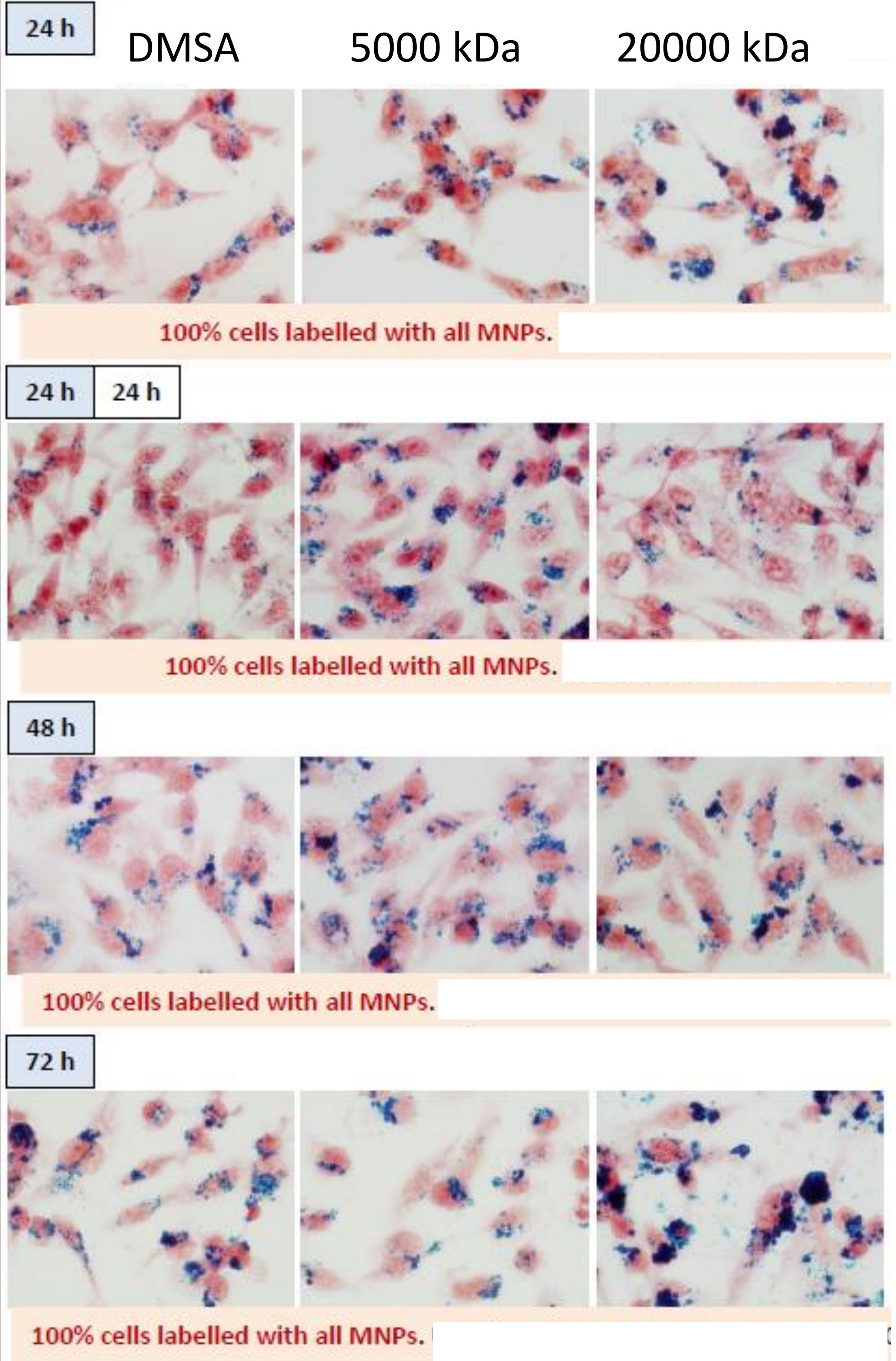
Corona composition affects the mechanisms cells use to internalize nanoparticles



ACS Applied Materials & Interfaces 2021 13 (7), 7924
Biomaterials 2022

CNB CENTRO NACIONAL DE BIOTECNOLOGÍA

Cell interaction

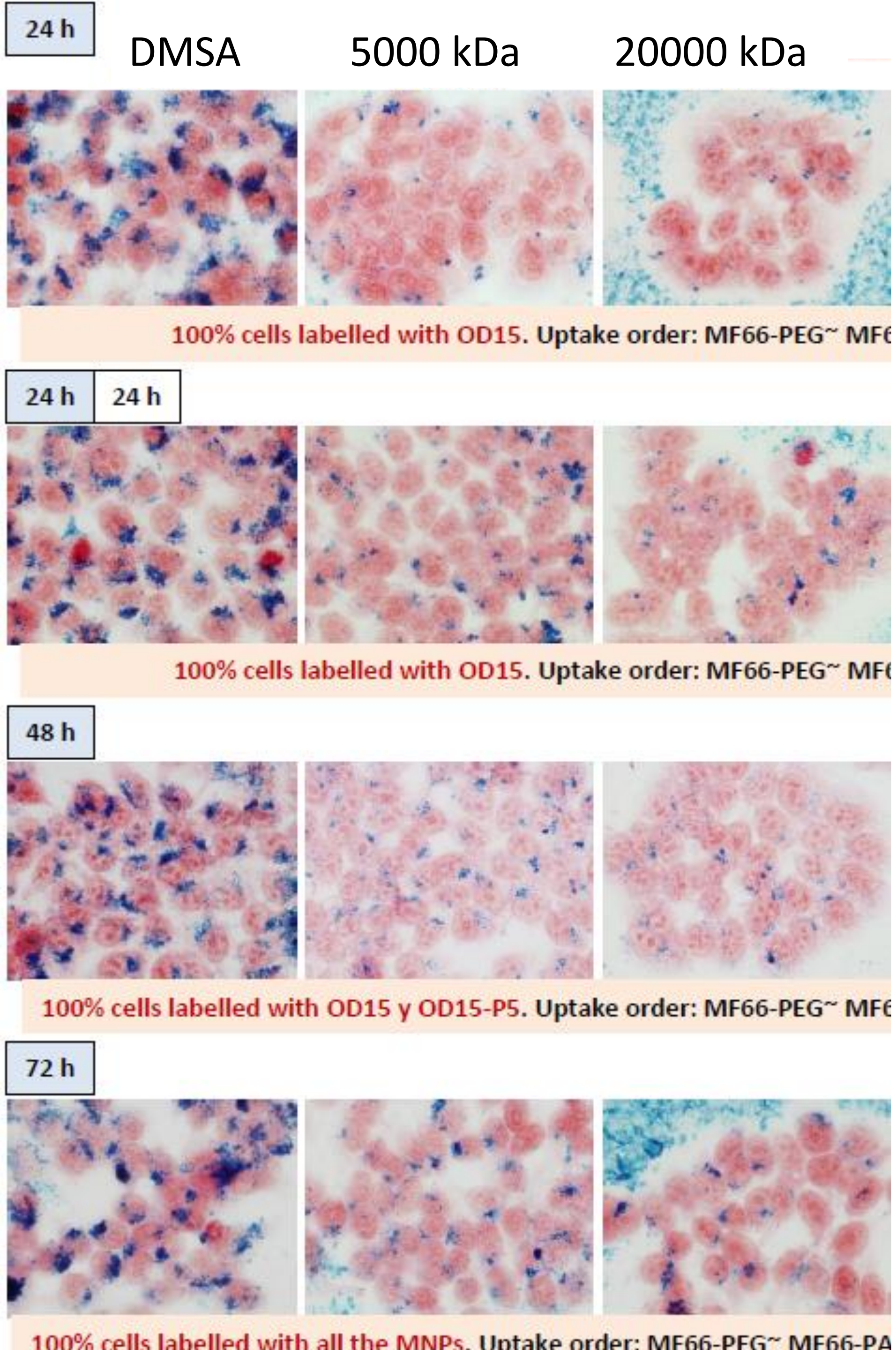


MDA Breast cancer cells

100%
24 h

Time of incubation

Angeles Villanueva , UAM

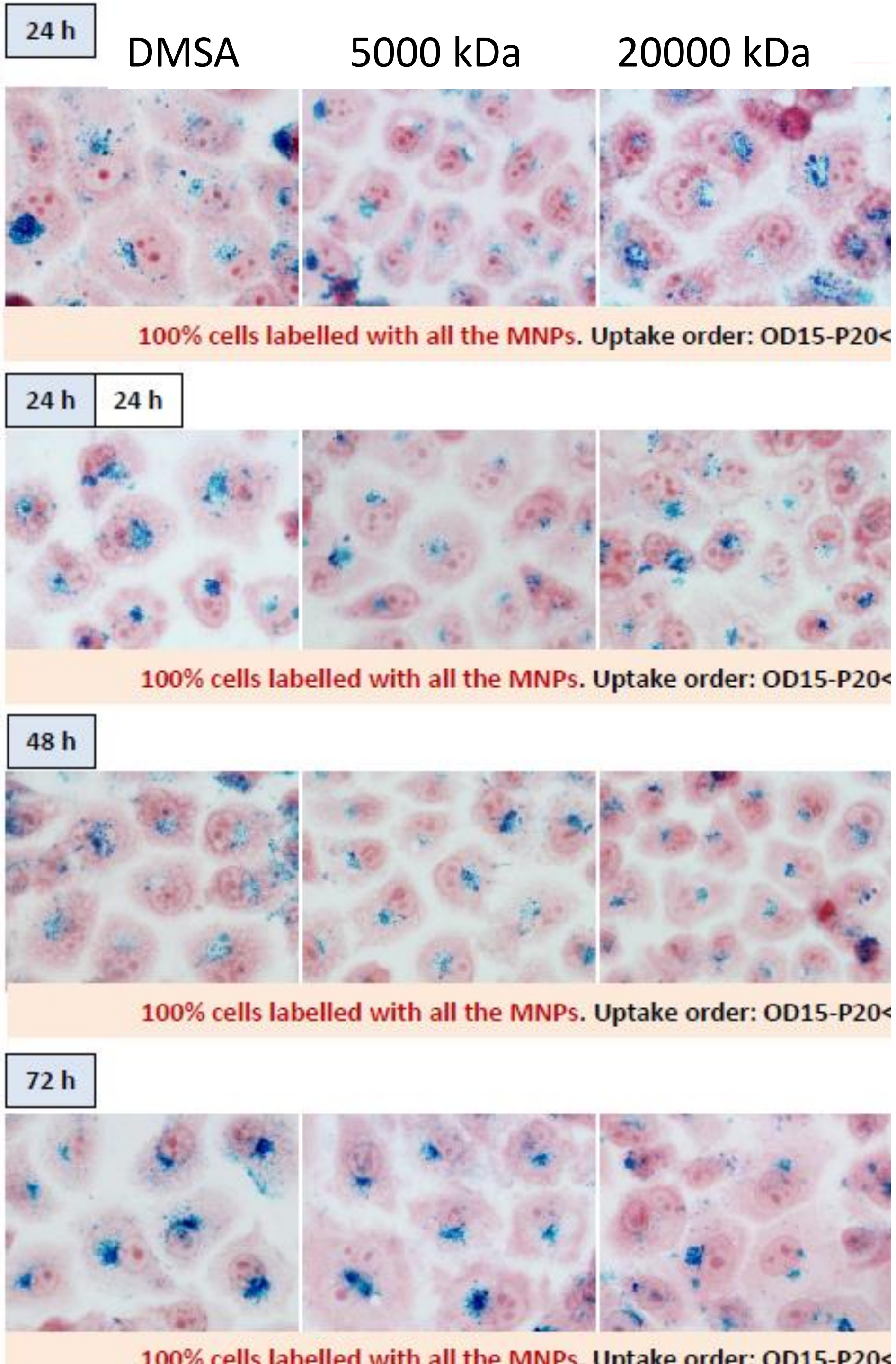


Time of incubation

MCF Breast cancer cells

100%
72 h

Angeles Villanueva , UAM

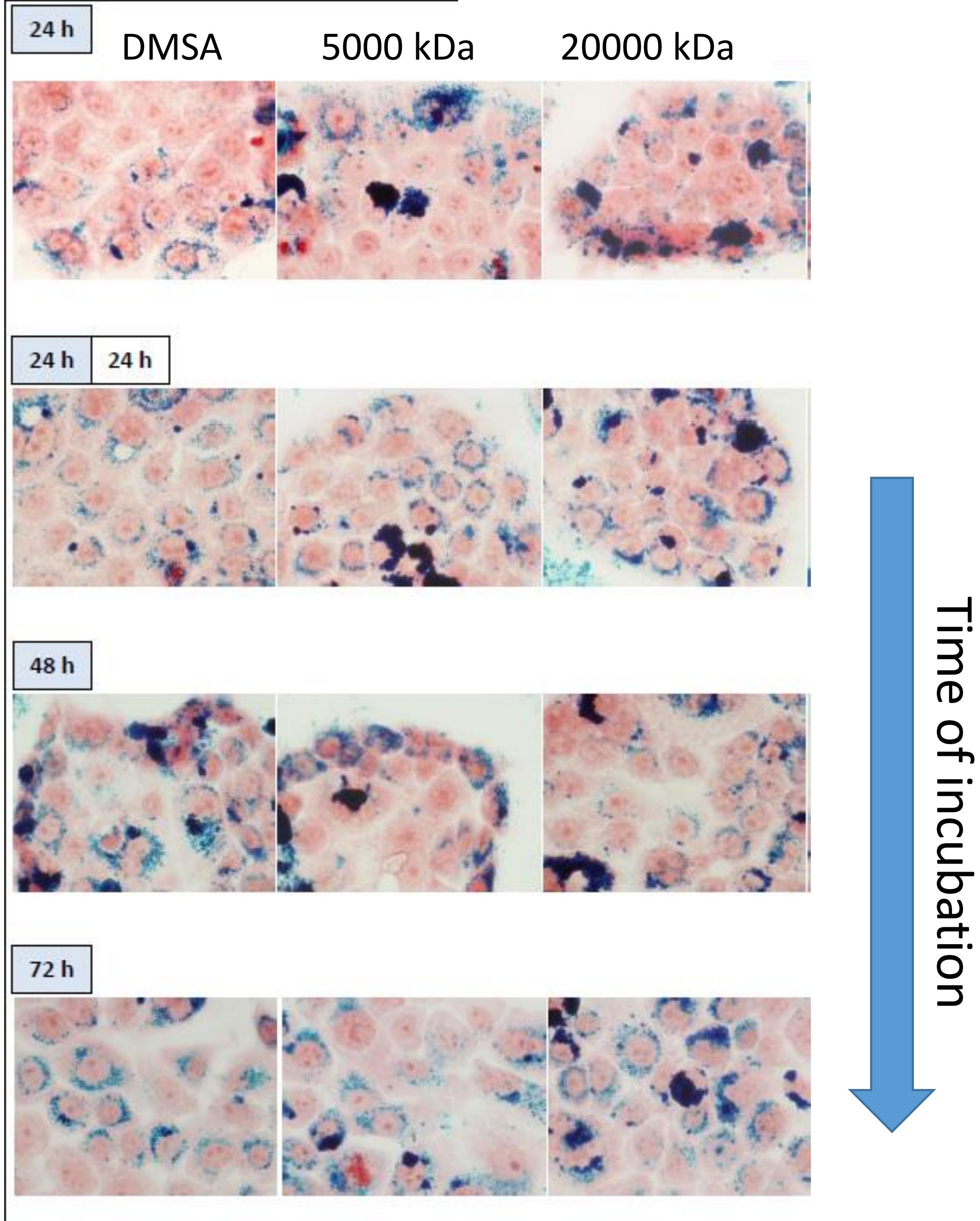


Time of incubation

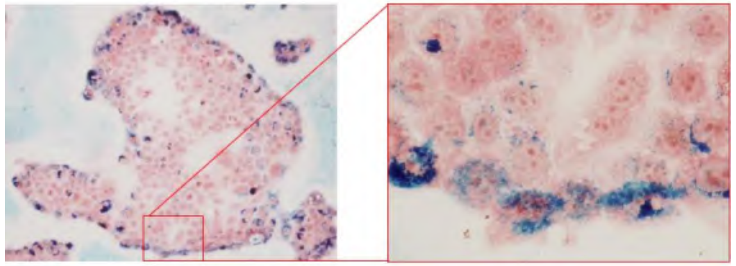
PANC-1 Pancreatic cancer cells

100%
24 h

Angeles Villanueva , UAM



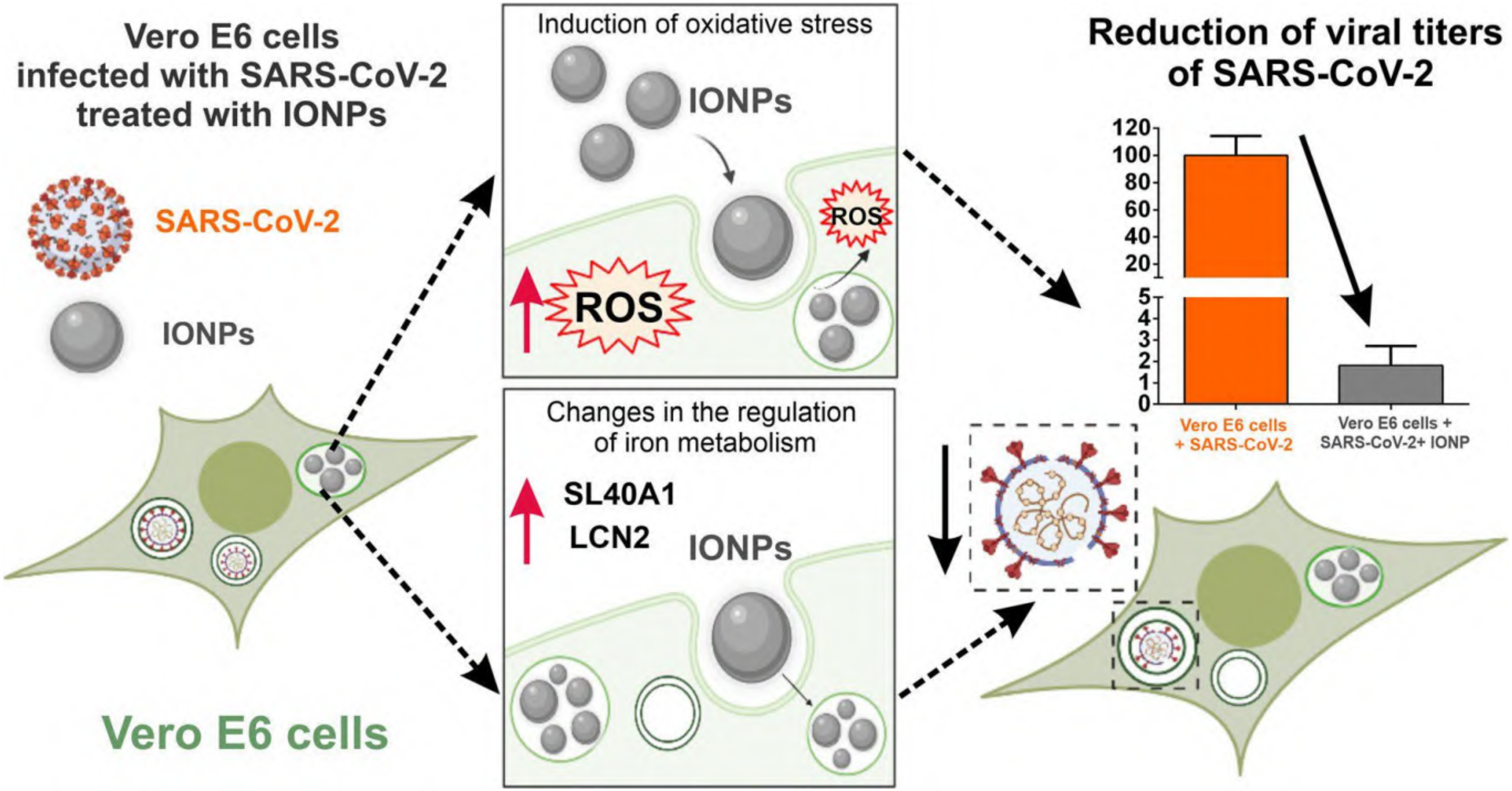
BxPC-3 Pancreatic cancer cells



Uptake only in microcolony periphery

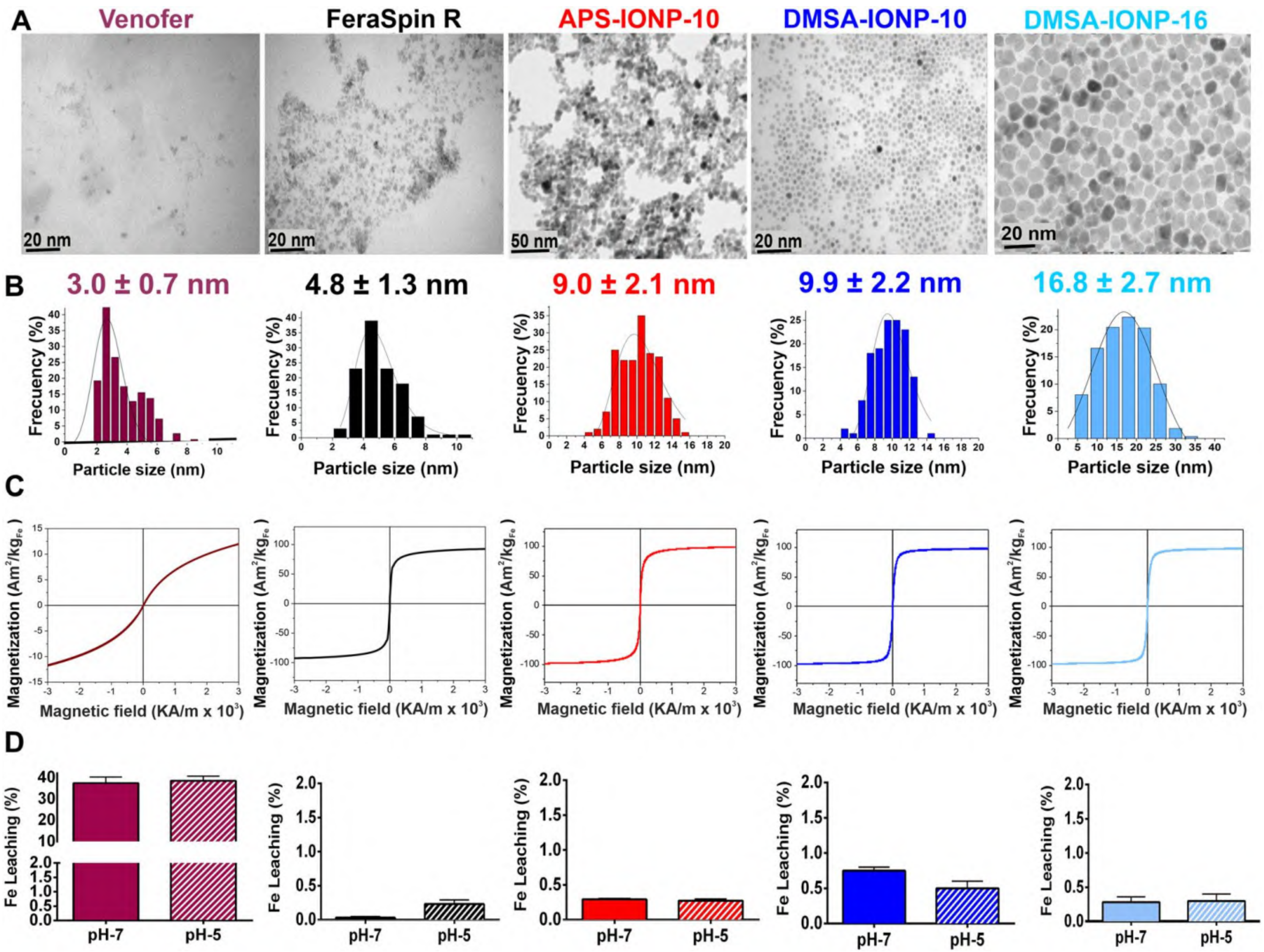
Angeles Villanueva , UAM

Iron oxide and iron oxyhydroxide nanoparticles impair SARS-CoV-2 infection of cultured cells



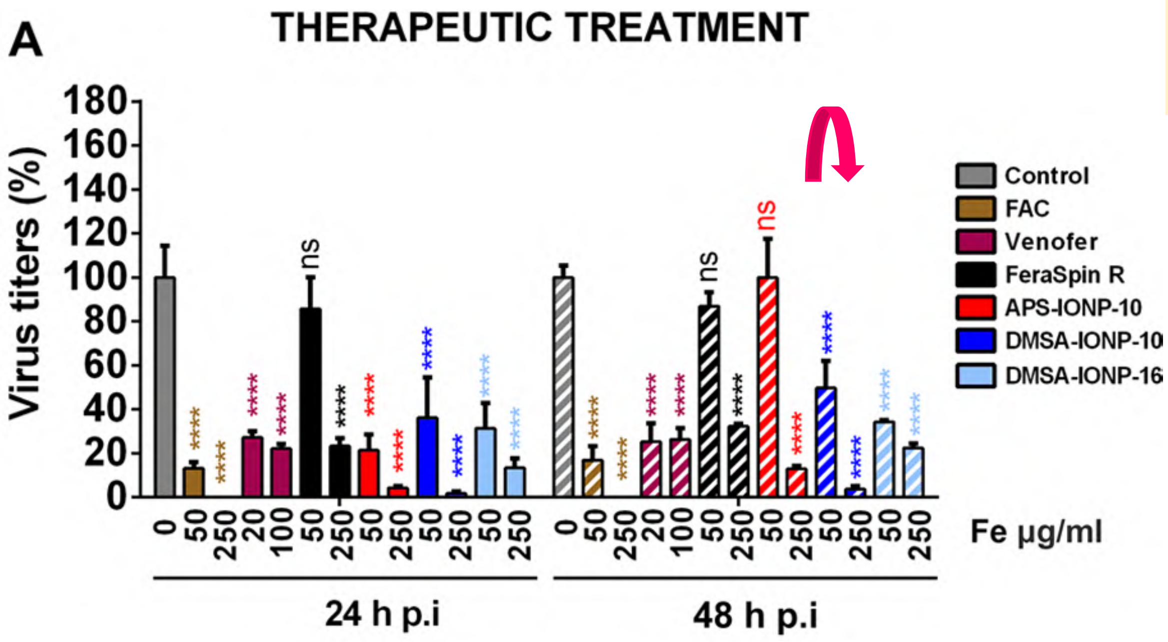
DeDiego *et al. Journal of Nanobiotechnology (2022) 20:352*
https://doi.org/10.1186/s12951-022-01542-2

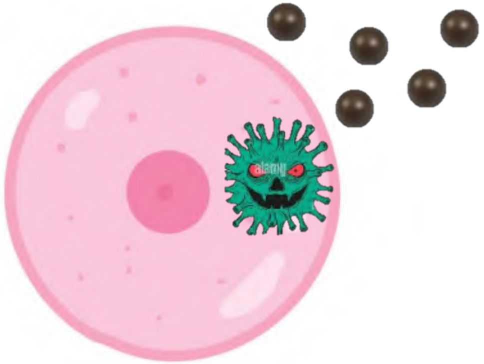
The treatment with IONPs affects oxidative stress and iron metabolism, influencing virus replication and production.



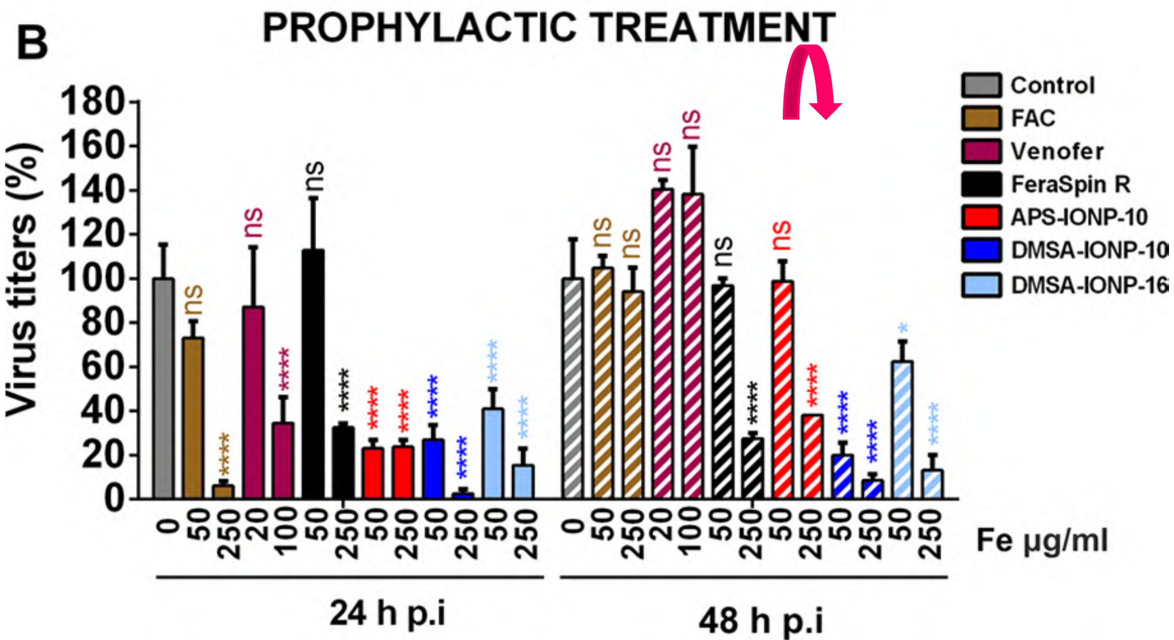
A
Venofer
FeraSpin R
APS-IONP-10
DMSA-IONP-10
DMSA-IONP-16
20 nm
20 nm
50 nm
20 nm
20 nm
B
3.0 ± 0.7 nm
4.8 ± 1.3 nm
9.0 ± 2.1 nm
9.9 ± 2.2 nm
16.8 ± 2.7 nm
Frecuency (%)
Particle size (nm)
C
Magnetization (Am²/kg_Fe)
Magnetic field (KA/m x 10³)
D
Fe Leaching (%)
pH-7
pH-5

Post-treatment and pre-treatment of cells with IONPs reduces SARS-CoV-2 production.



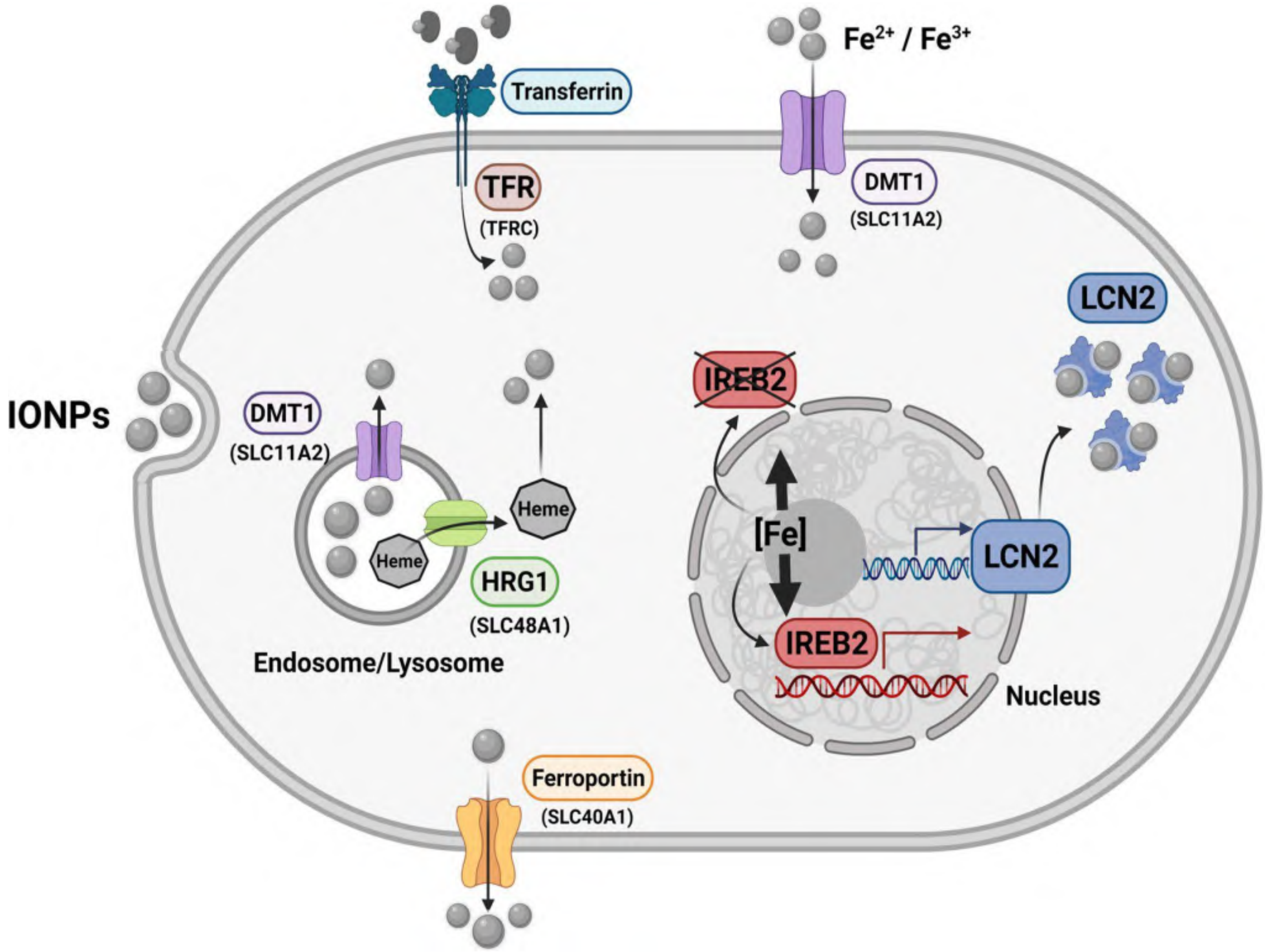


Vero E6 cells were infected with SARS-CoV-2 and the cells were treated IONPs



Vero E6 cells were treated with IONPs and 24 h after treatment, the cells were infected with SARS-CoV-2

The treatment of cells with IONPs affects oxidative stress and iron metabolism to different extents, likely influencing virus replication and production.



DeDiego *et al. Journal of Nanobiotechnology (2022) 20:352*
https://doi.org/10.1186/s12951-022-01542-2

The increasing use of magnetic nanoparticles as important nanomaterials for technology, research and industrial applications emphasized the need for analyzing the environmental impact of the nanoparticles and the synthesis methods.

Balancing safety and functionality in the different stages of the innovation process

- Identify the risk for a specific application
- Safe nanomaterials/ Safe production/ Safe storage and transport

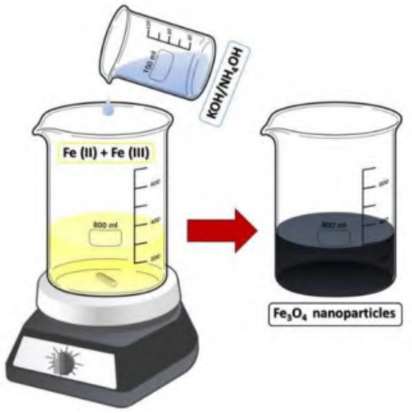
Claudia Som et al. NanoBiomat 2019

Development of safe, effective and reproducible synthesis methods

Advanced in the use of Green Chemistry for the synthesis of the nanomaterials

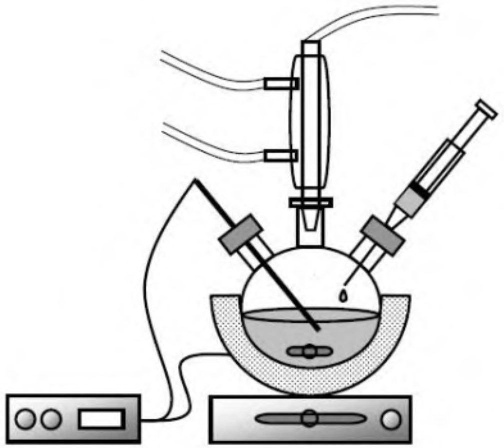
Iron oxide nanoparticles synthesis

Coprecipitation



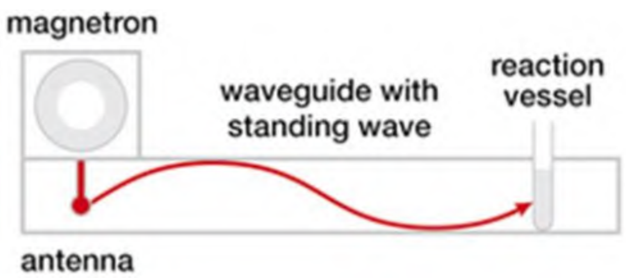
- ✓ Commercially used
- ✓ Fast
- ✓ Scale up
- ✗ Broad size distribution
- ✗ Size limitation

Thermal decomposition



- ✓ Control of size and shape
- ✓ Narrow size distribution
- ✓ High crystallinity
- ✗ Time consuming
- ✗ Toxic residues
- ✗ Price
- ✗ Reproducibility

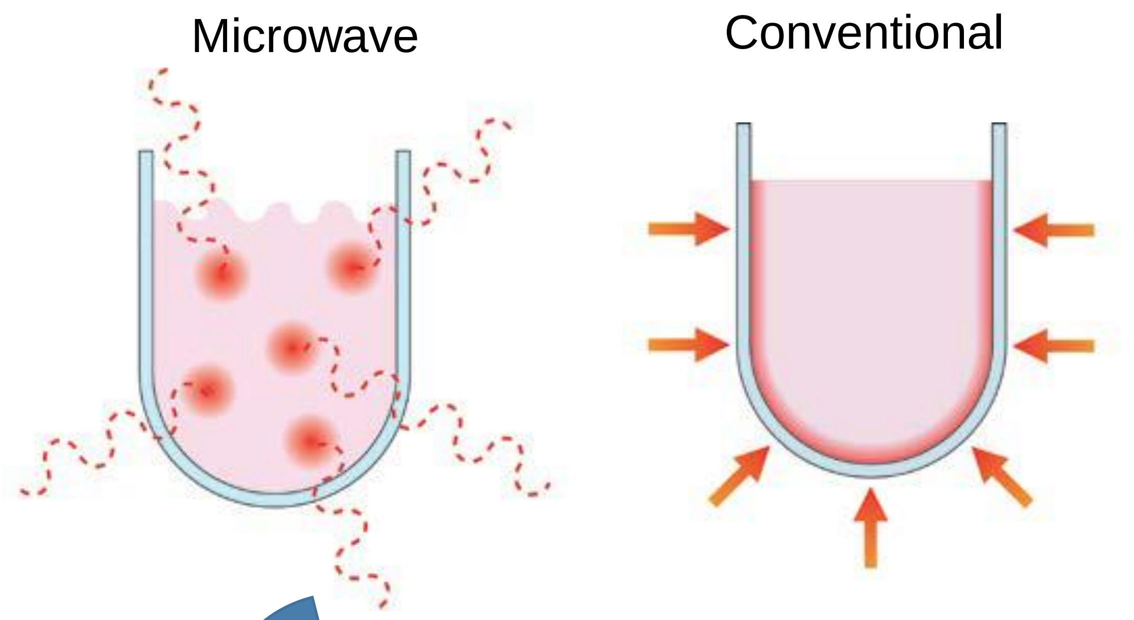
Microwave assisted

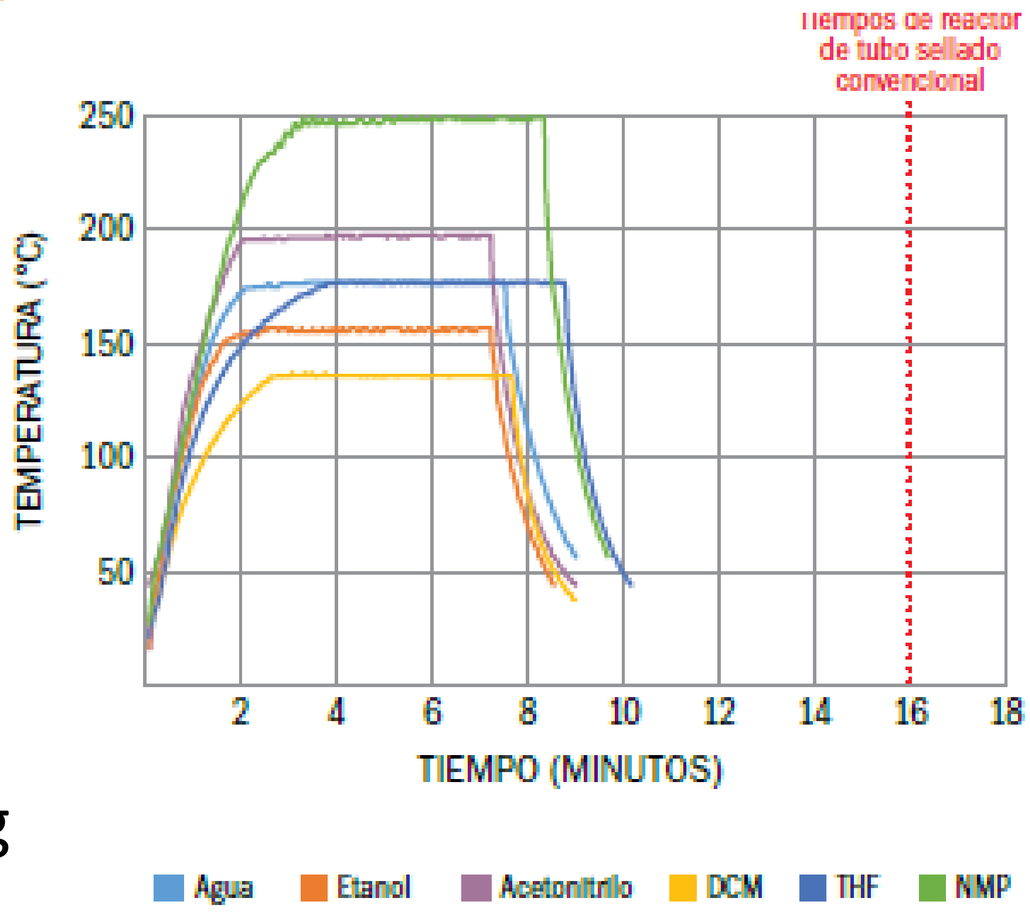


- ✓ Reproducibility
- ✓ Fast
- ✓ Straightforward
- ✓ Narrow size distribution
- ✓ Efficient heating
- ✗ Size limitation
- ✗ Scale up limitations

New insights in the structural analysis of maghemite and (MFe2O4, M= Co, Zn) ferrite nanoparticles synthetized by Microwave assisted - Polyol process, Gallo A.; Mater. Chem. Front., 2020, 4, 3063. DOI: 10.1039/d0qm00460j

More efficient heating





Faster and homogeneous heating and larger yields

Safer reagents and solvents

Reaction media Alcohol Water

Microwave Synthesis

Uses dielectric heating to form the particles instead of heat transfer

f = 2.45 GHz

Advantages:

- Faster process
- Homogeneus heating inside the sample
- High reproducibility
- Low Polydispersity
- Effective Heating
- Clean and user friendly
- Versatile

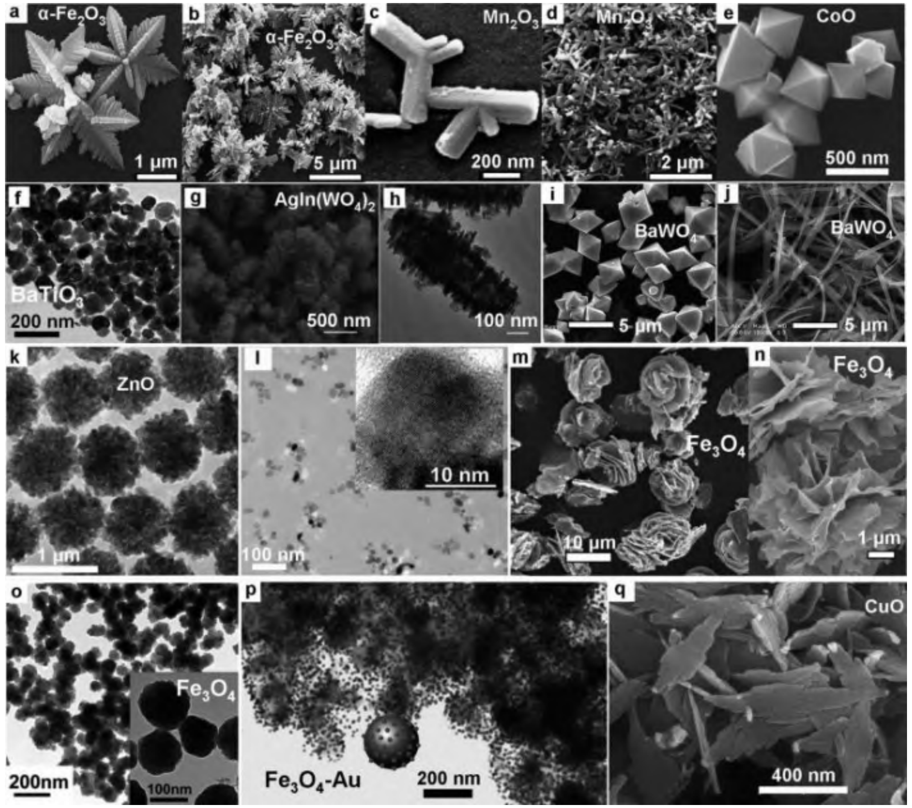
Disadvantages:

- Can't heat up to 300ºC (equipament security)
- Not up to 170ºC if working with H_2O
- Low yield, since the maximum volume is 20 ml

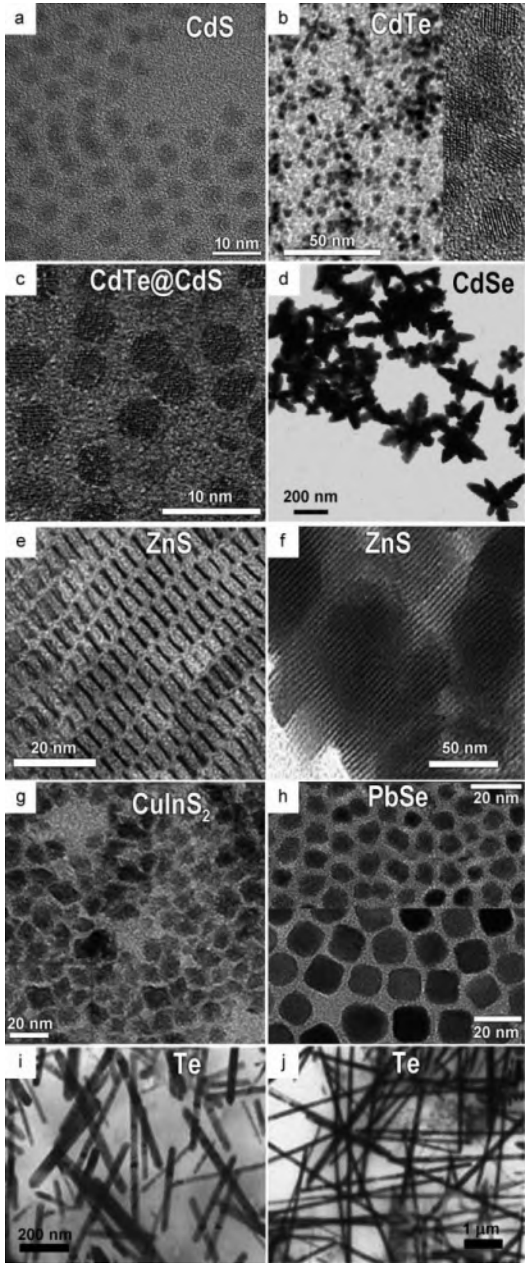
Monowave 300, Anton Paar

In the literature…

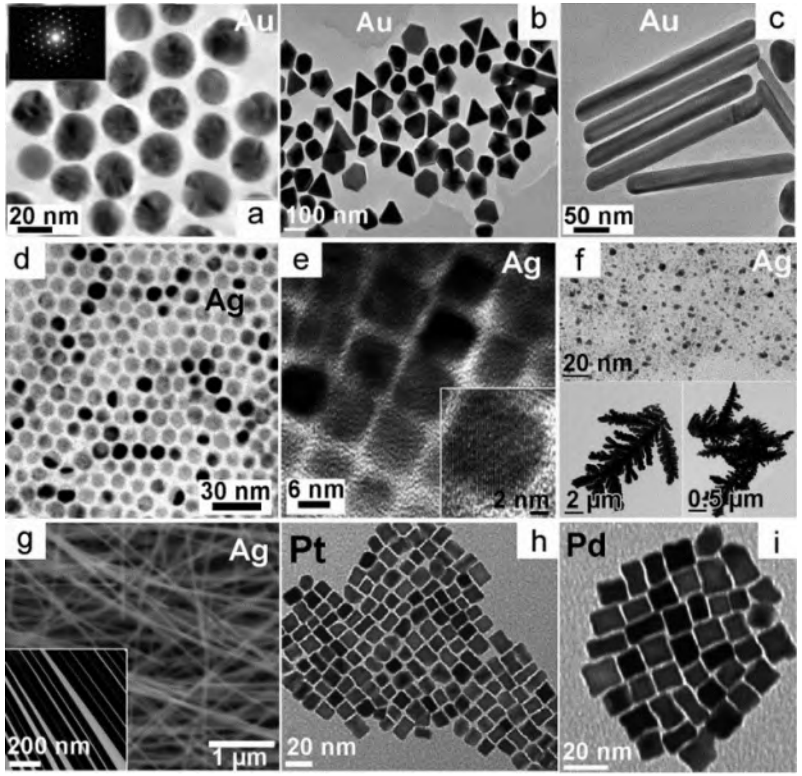
transition-metal oxide NCs



semiconductor NCs



single-composition metal NCs



P. D. Cozzoli, C. O. Kappe et al.
Angew. Chem. Int. Ed. 2011, 50, 11312 – 11359

Microwave synthesis and functionalisation of small iron oxide nanoparticles for MRI T_1 contrast agents

$FeCl_3$

Polymers / Molecules

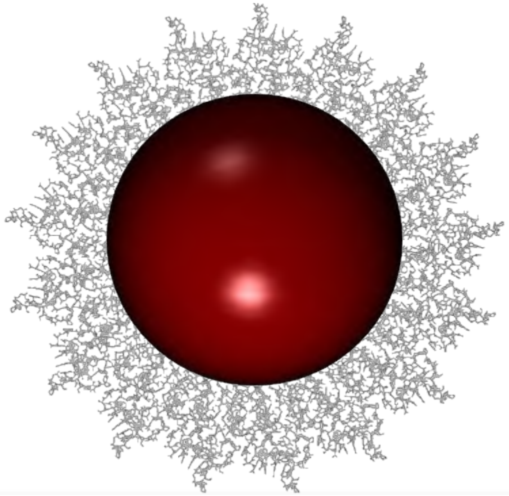
(Sodium Citrate)

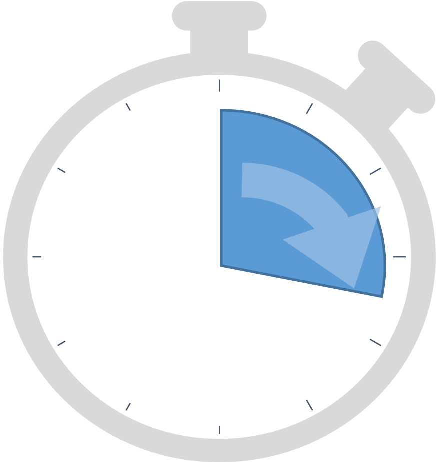
water

100 ºC / 10 min

→

Hydrazine





cnic

IQM CSIC

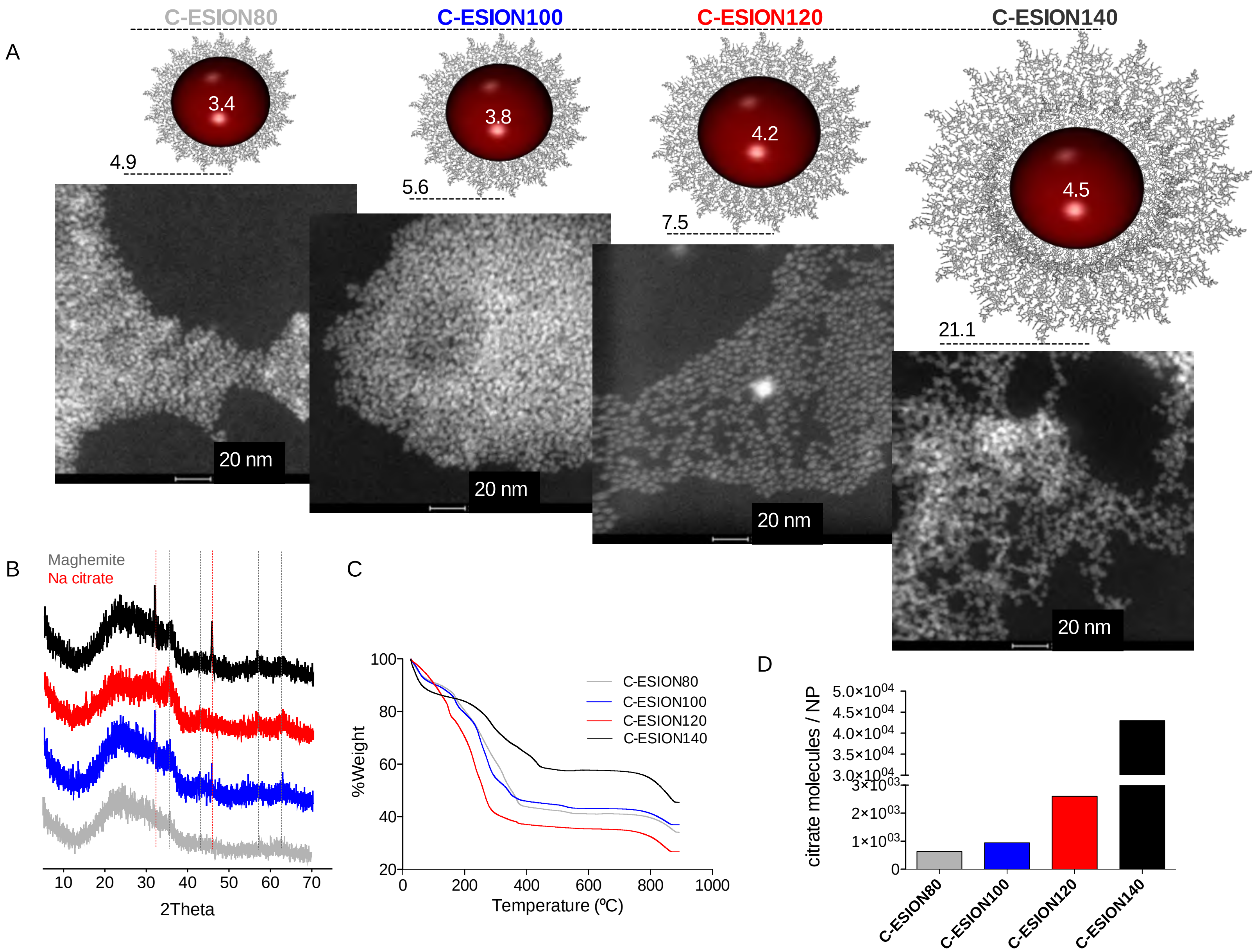
Instituto de Química Médica

Consejo Superior de Investigaciones Científicas

Pellico et al. Contrast Media & Molecular Imaging, 2016
Langmuir 33 (39), 10239-10247, 2017
ACS Omega, 42, 2719-2727, 2019

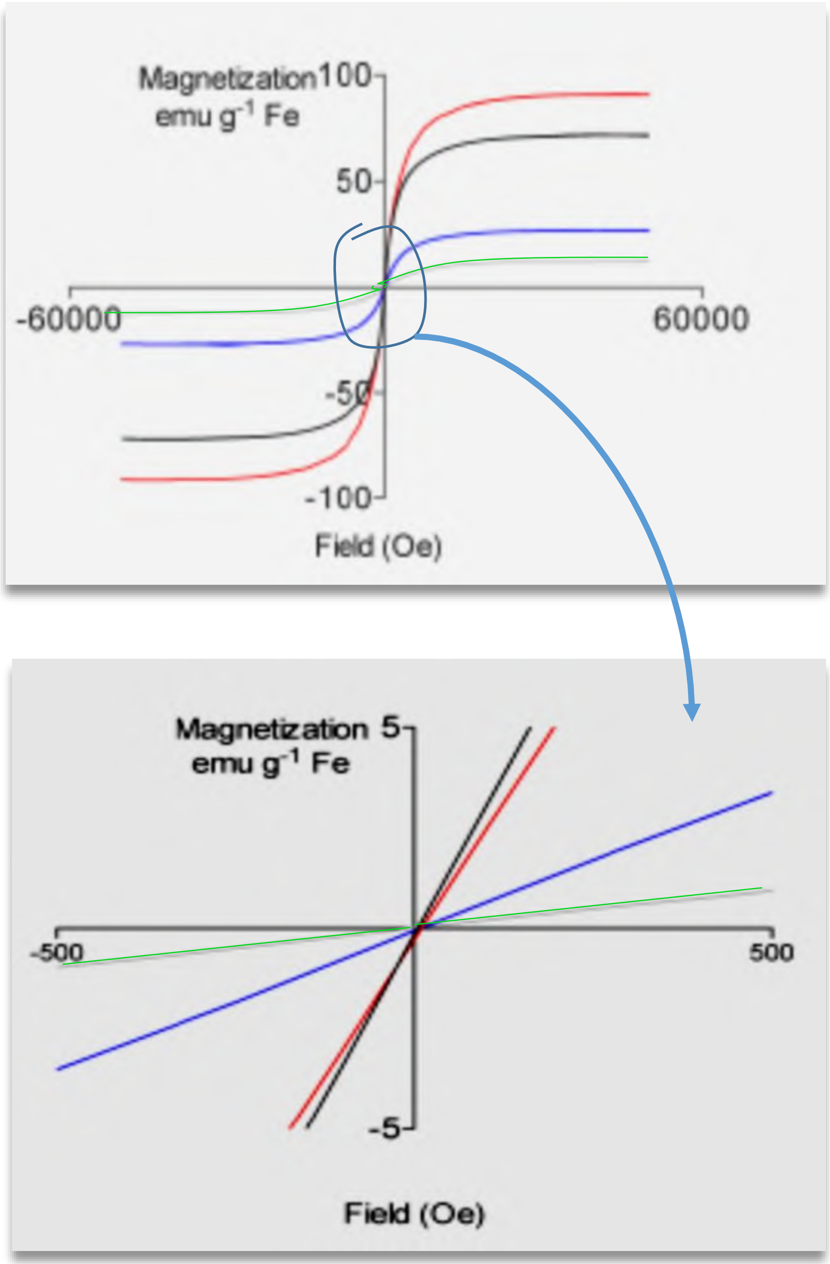
240 W for 10 min at 60, 70, 80, 90, 100, 110, 120, 130, and 140 ºC

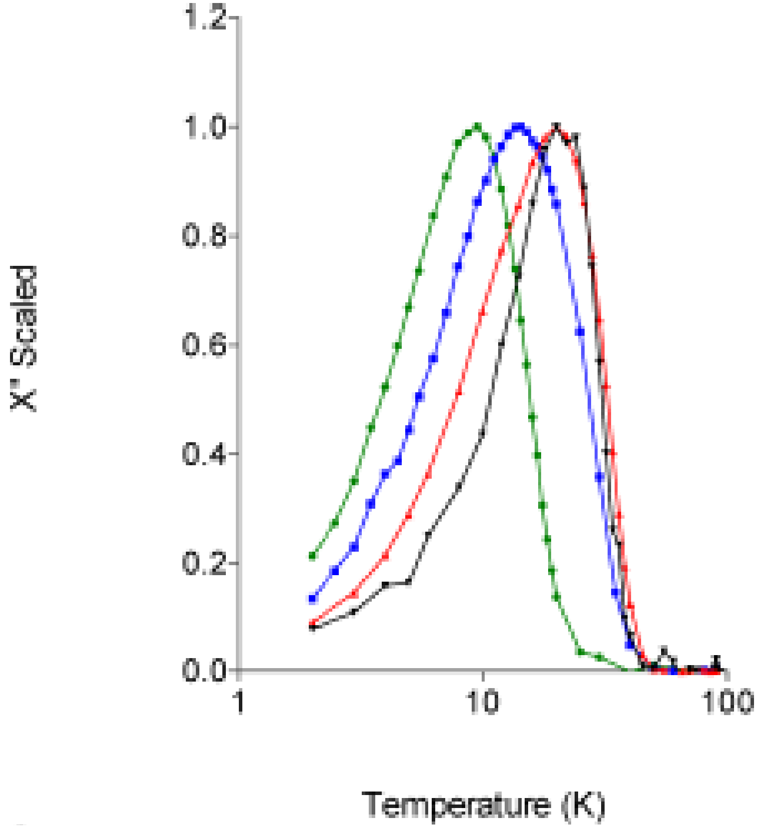
Structural characterisation



Langmuir 33 (39), 10239-10247, 2017

Magnetic characterisation





M (emu/g Fe)-80ºC

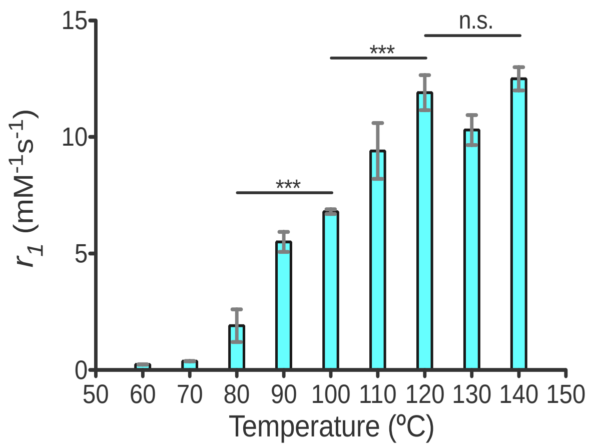
M (emu/g Fe)-100C

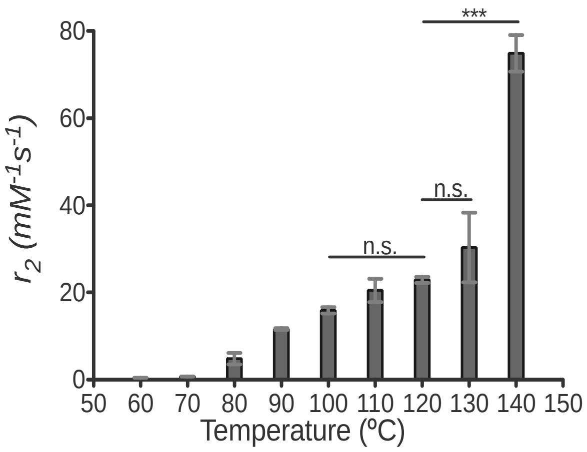
M (emu/g Fe)-120C

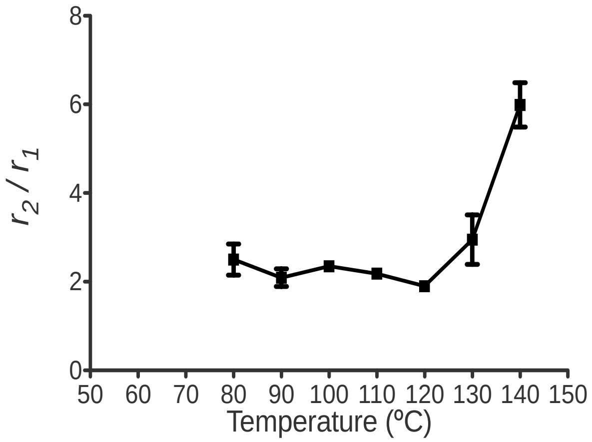
M (emu/g Fe)-140C

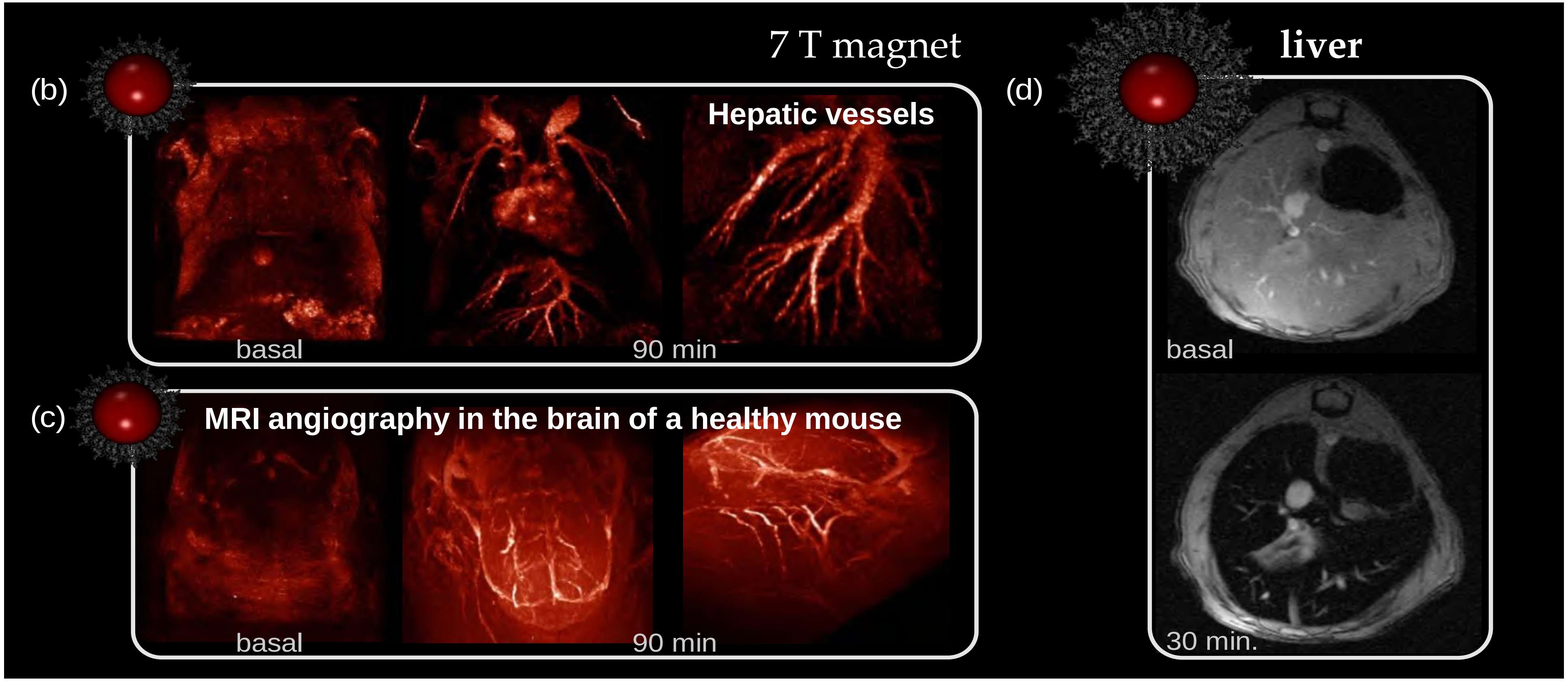
Langmuir 33 (39), 10239-10247, 2017

Relaxometric characterisation

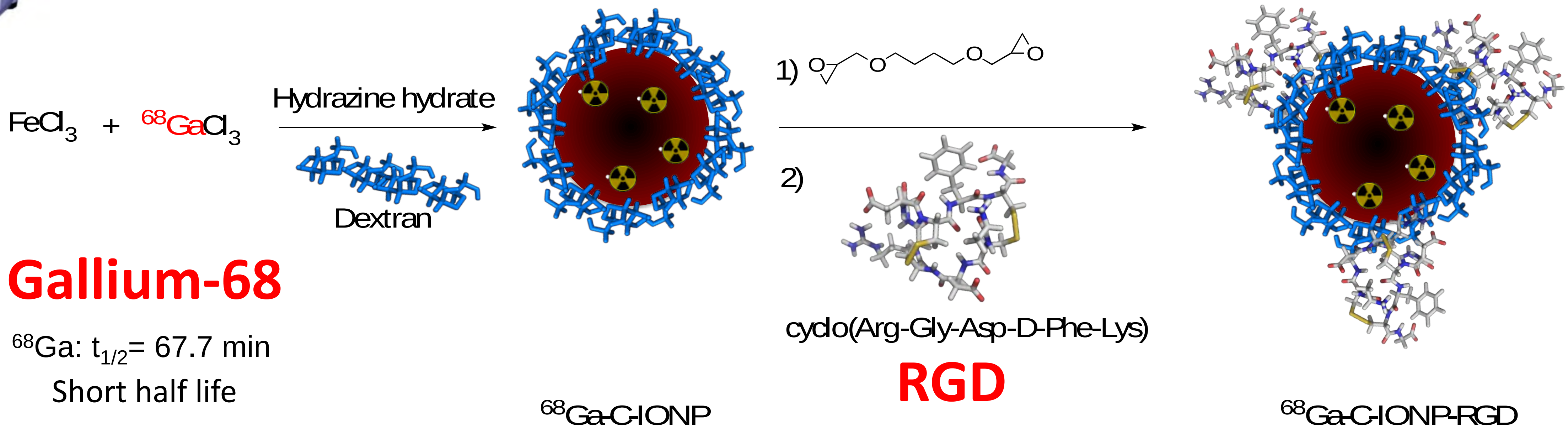








Applications in Molecular Imaging



Gallium-68

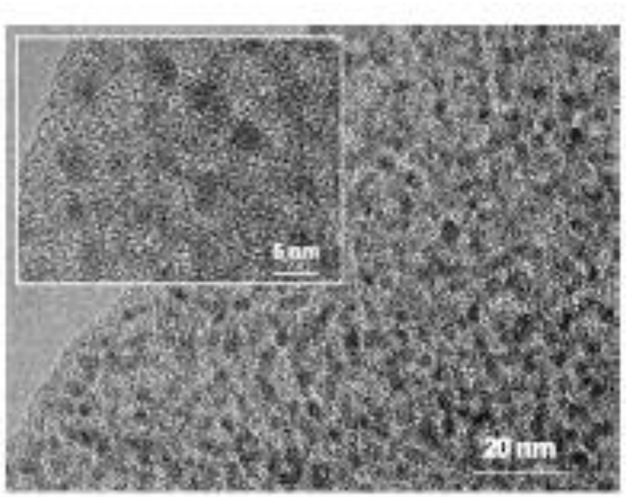
^{68}Ga: $t_{1/2}$= 67.7 min

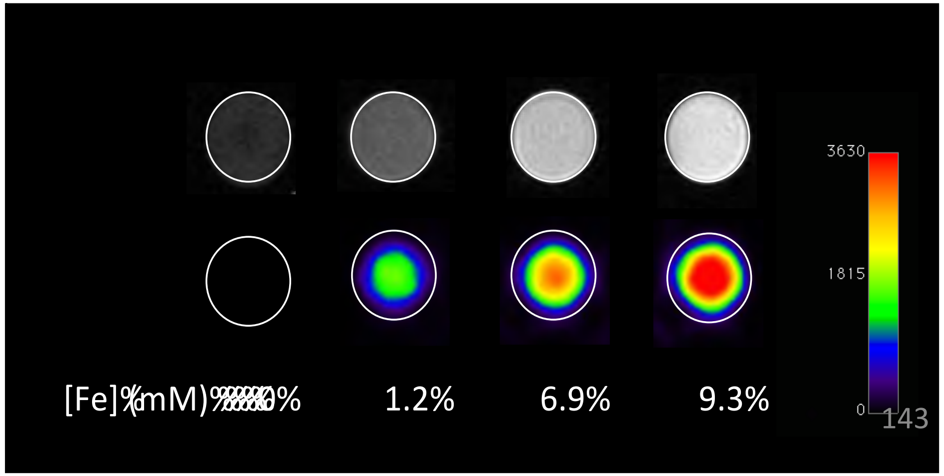
Short half life

DLS= 20.6 ± 2.4 nm

TEM= 2.2 ± 0.2 nm

The % of Ga relative to Fe is 0.294 ± 0.008





Microwave synthesis of large iron oxide nanoparticles for cell labelling

Fe (acetate)$_2$
POLYOL

170 ºC / 2 h →

Green Rust
WATER

100 ºC / 3-10 min →

Magnetic nanoparticles
8-15 nm

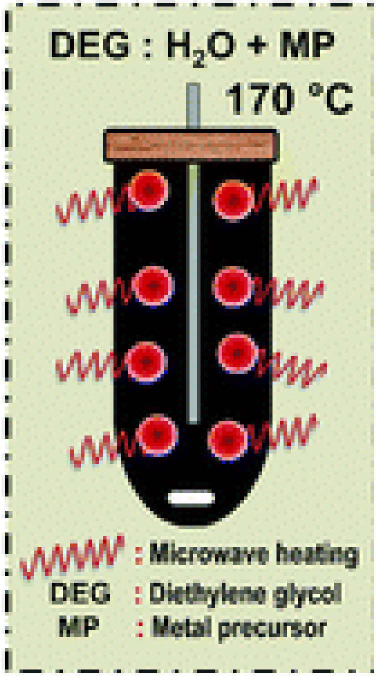
Magnetic nanoparticles
30 nm

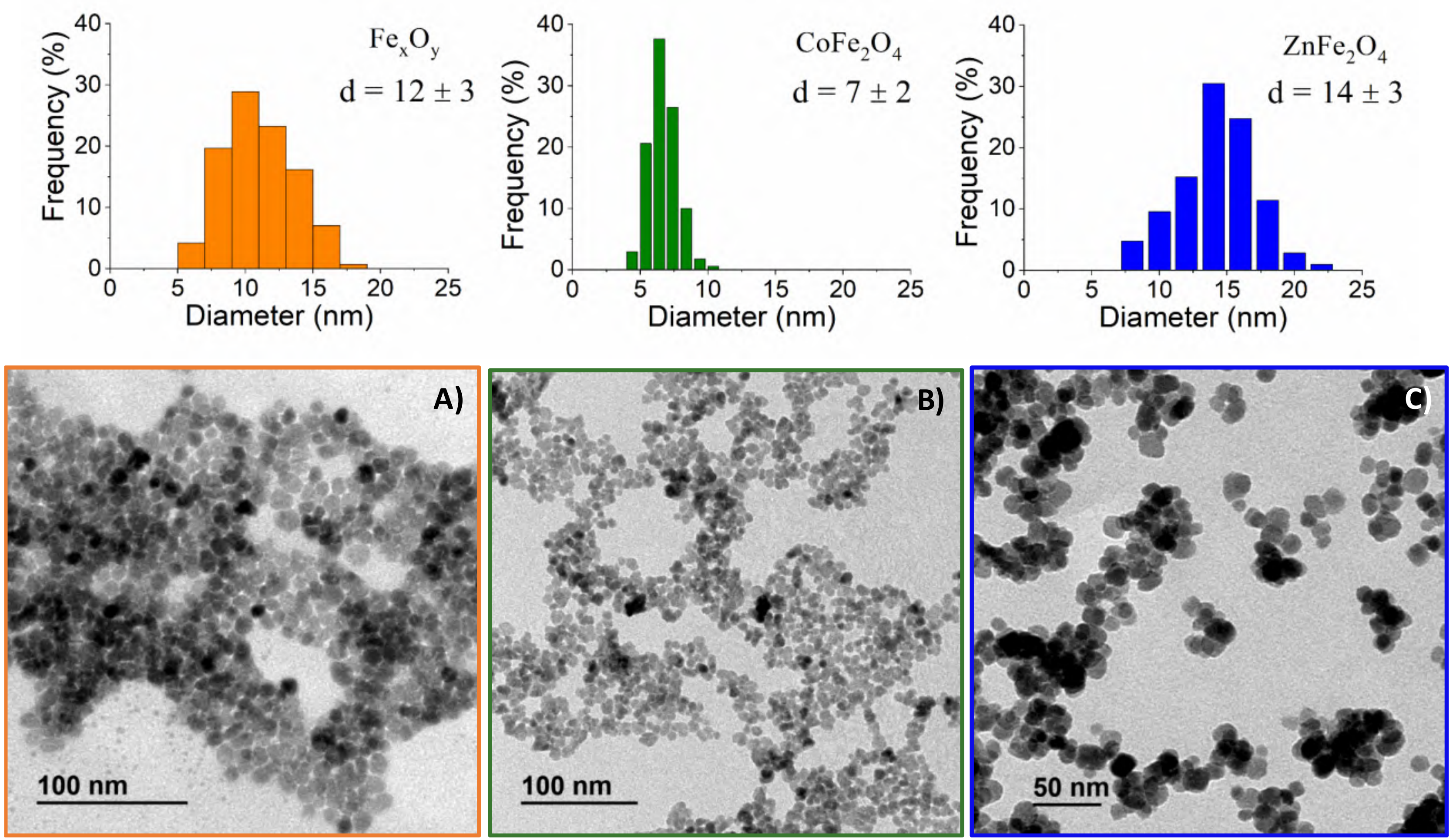
Mater. Chem. Front., 2020, 4, 3063

Nanomaterials 2021, 11, 1052

Nanomaterials, 2022, 12, 3304

Polyol media

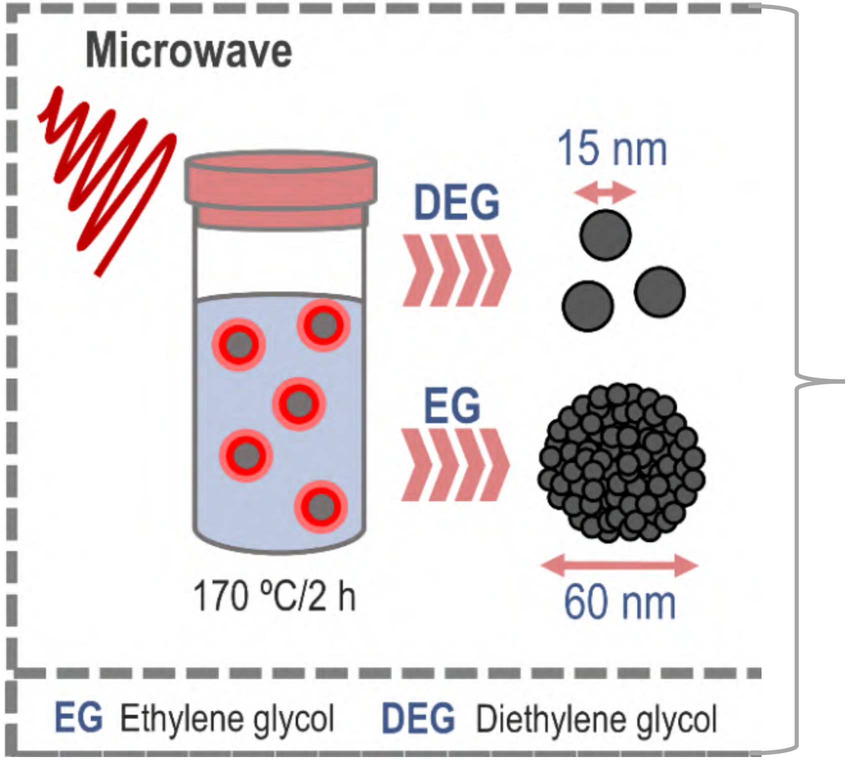


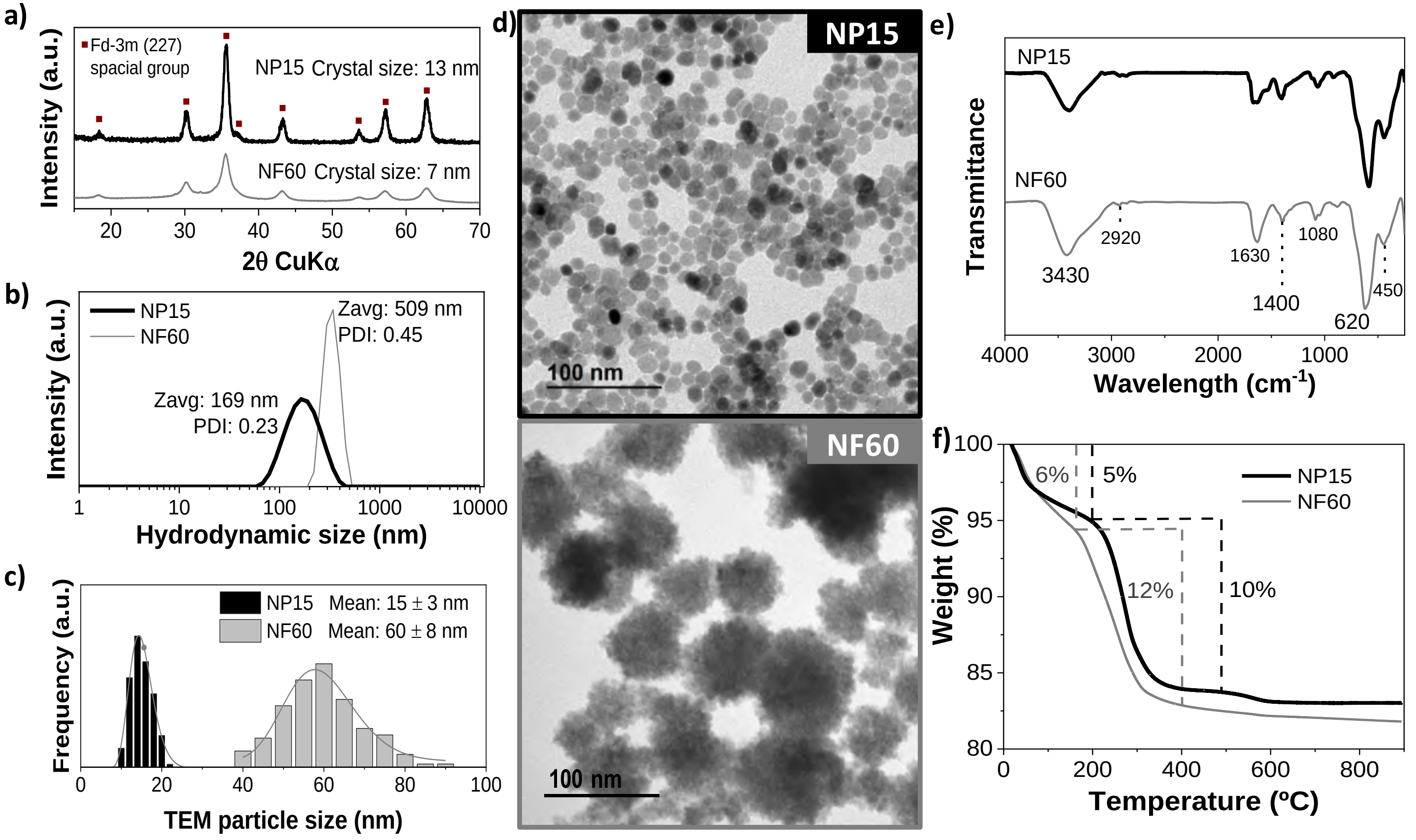


Particles size control up to 15 nm and introduction of Co and Zn

Mater. Chem. Front., 2020, 4, 3063.

Polyol media

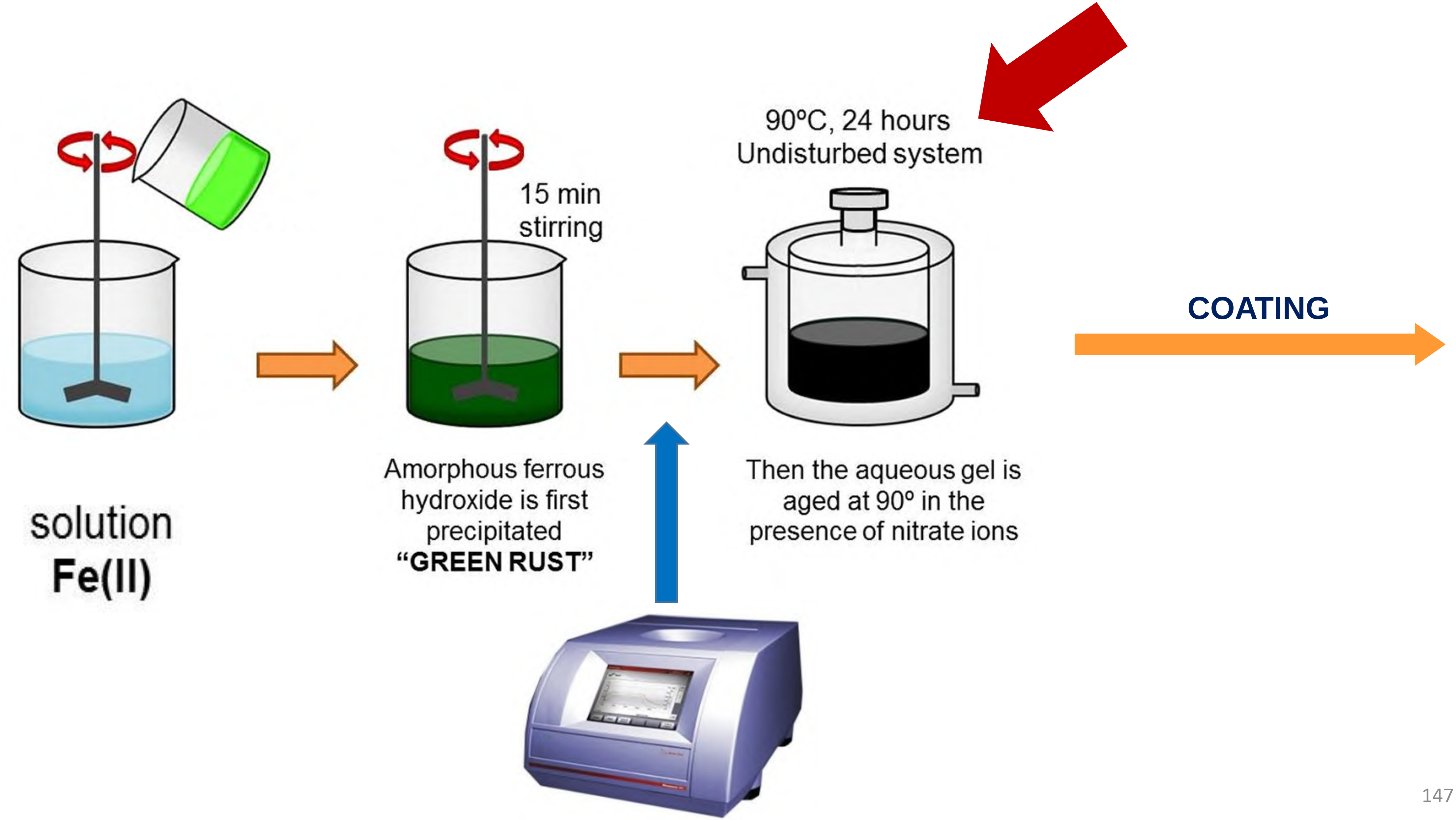




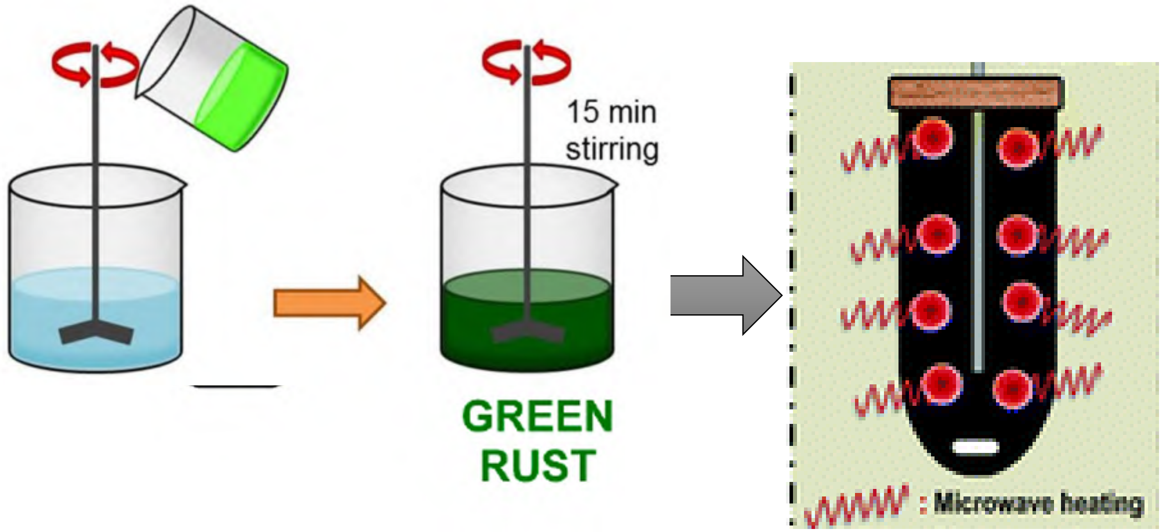
Aggregation control

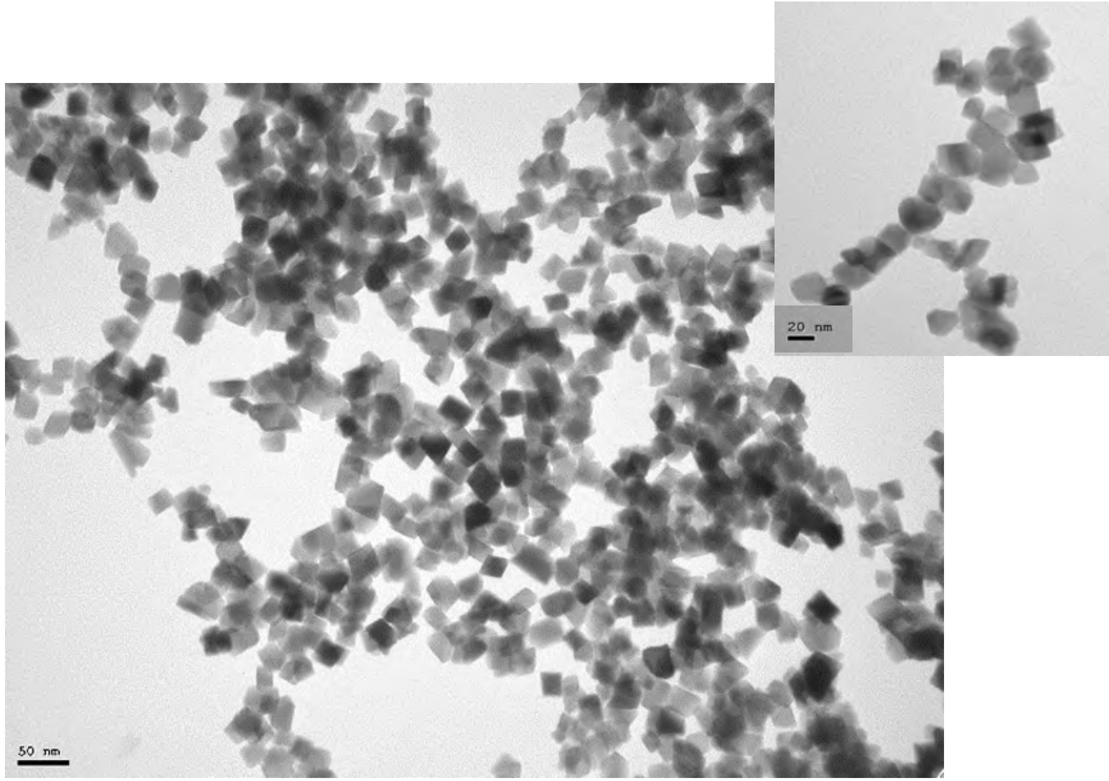
Nanomaterials 2021, 11, 1052.

Oxidative precipitation in water



Oxidative precipitation in water





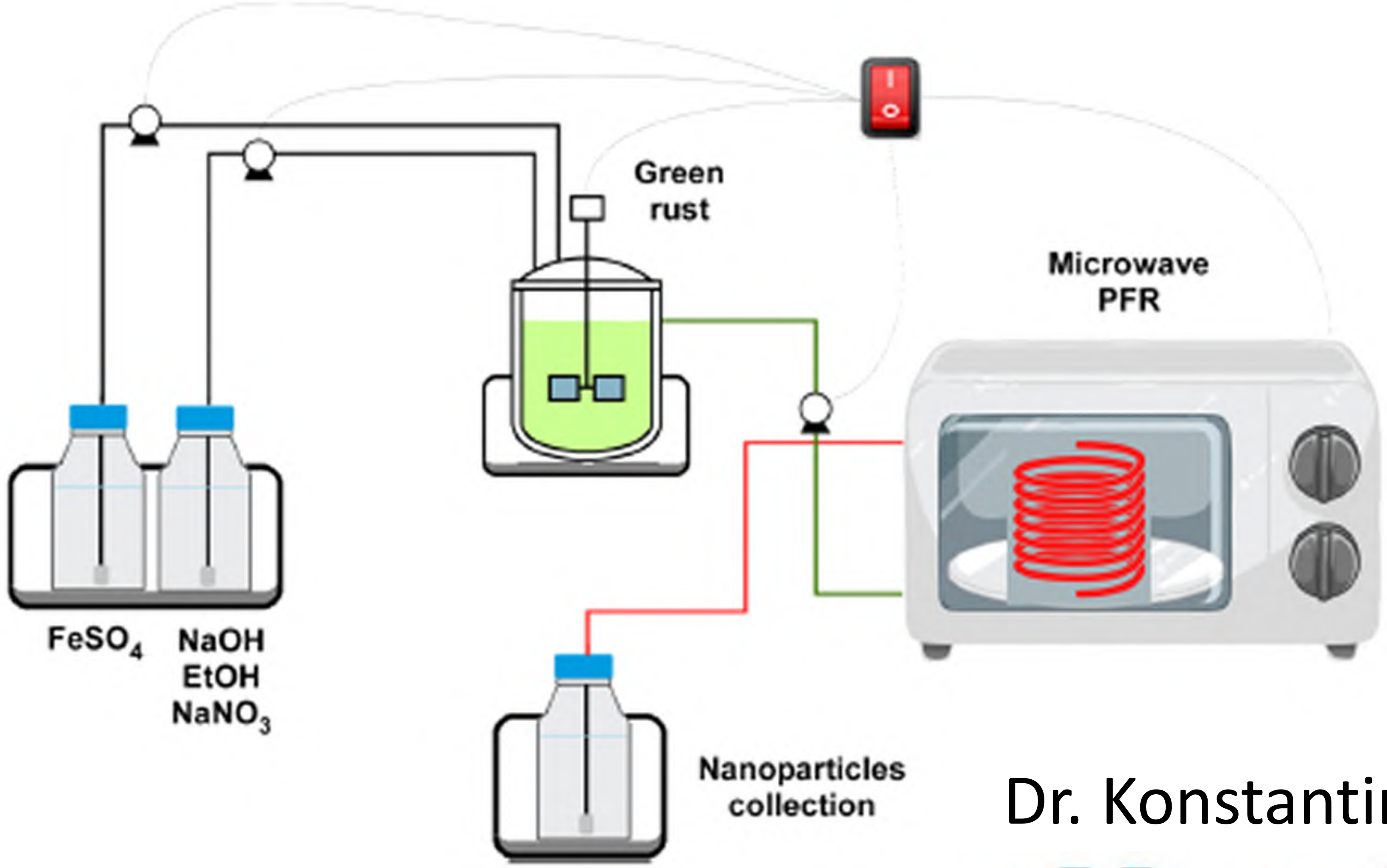
TESTED PARAMETERS

Fe(II) Concentration 0.2-0.05 M	Green Rust Curing time 7 min- 8 hours	→	Microwave Heating time 1 hours- 3 min	Microwave temperature 90-115ºC

Magnetic nanoparticles
20-30 nm
at 0.1 M in 3 min/113ºC

Microwave heating in batches

Continuous production of iron oxide nanocrystals in water



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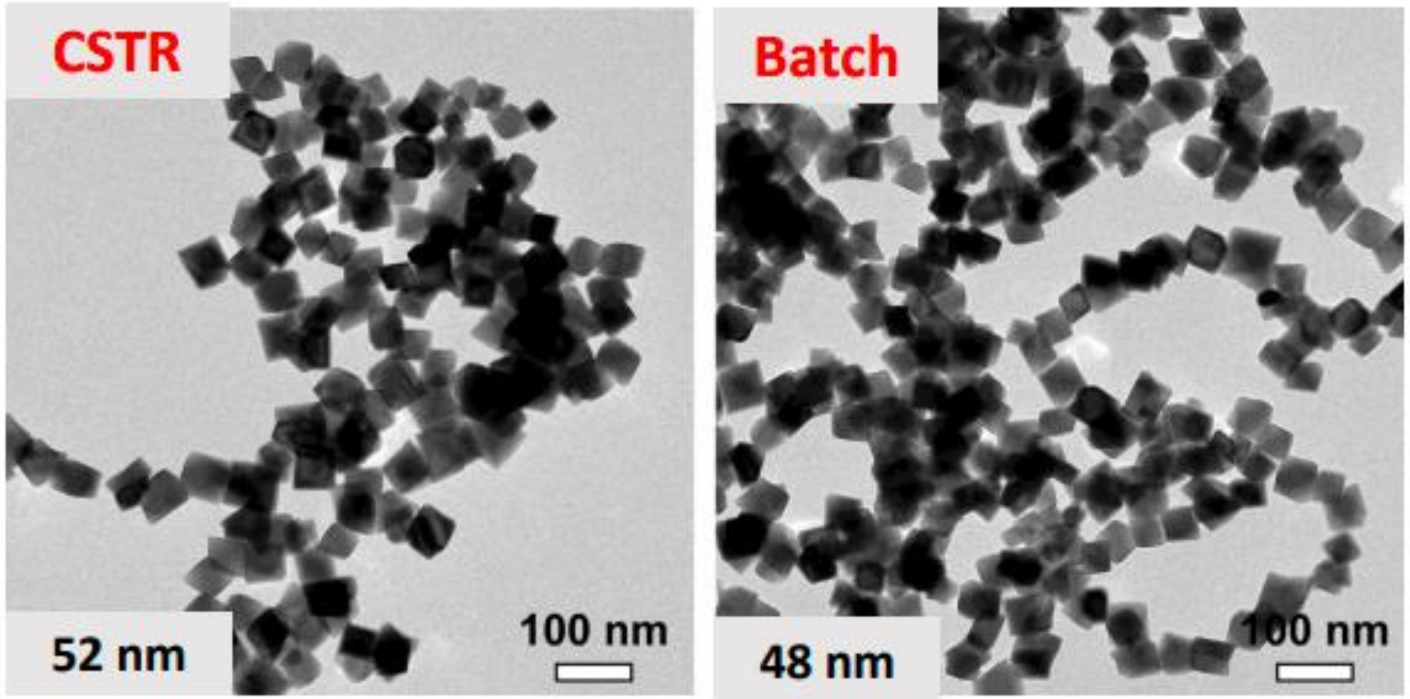
Viability of the continuous operation of microwave synthesis



Microwave-assisted continuous-flow process

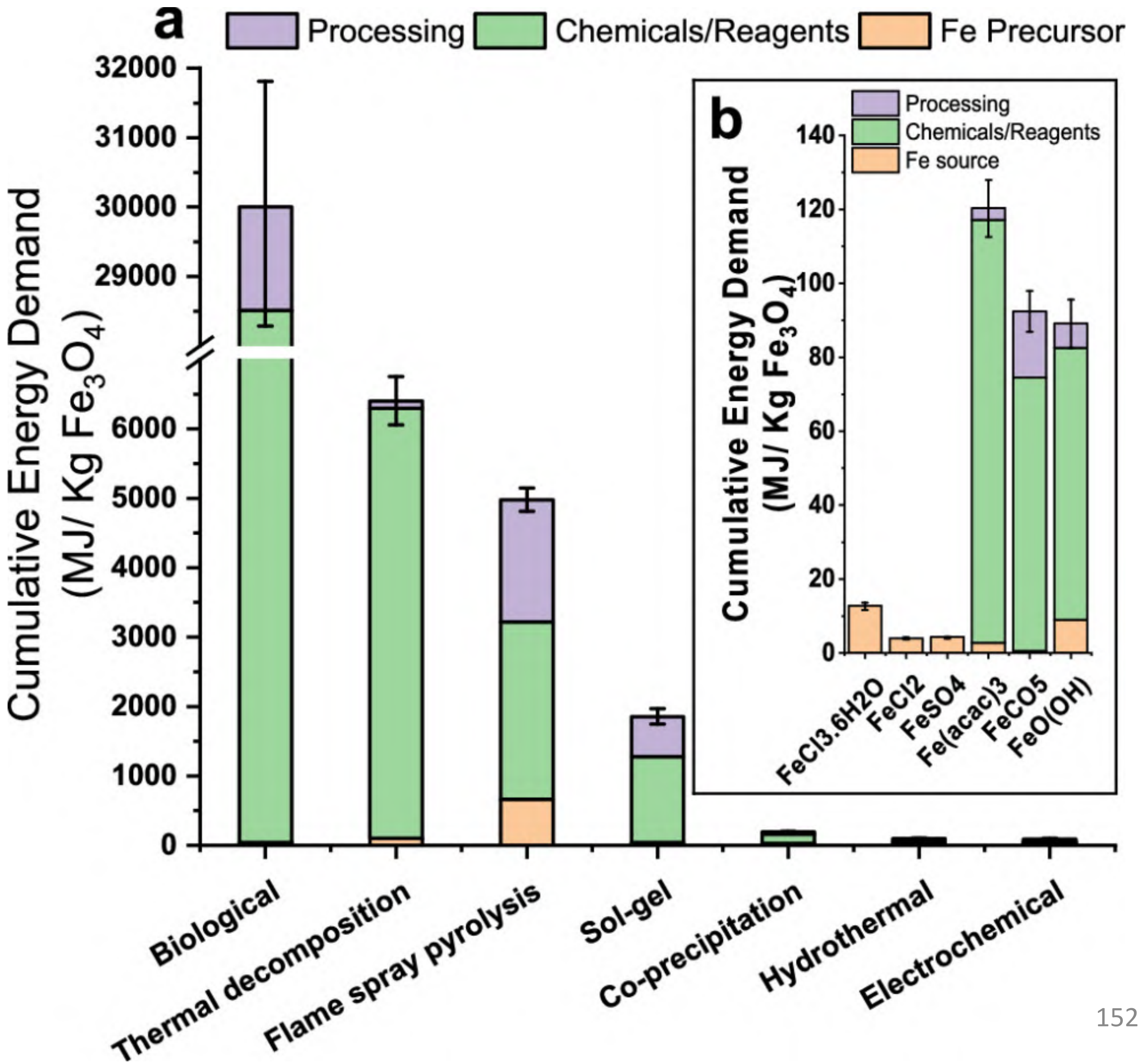
0.1 M $FeSO_4$ @ 90 °C

Ethanol 15 % v/v

Retention time 10 min

Sustainability and cost of Fe_3O_4 production

- Process contribution to environment
- Energy demand in life cycle



Rahman et al. ACS Sustainable Chem. Eng. (2022) 10:3155

Conclusions

Magnetic nanoparticles constitute promising nanomedicine tools.

The size and the shape of the nanoparticles is a way to control its anisotropy, the nanoparticle assembly and their movement, heating or mechanical response to a remote stimuli.

The advances in magnetic nanotechnology applied to medicine rely on the precise control of the nanoparticle performance in the cellular and in vivo environment.

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