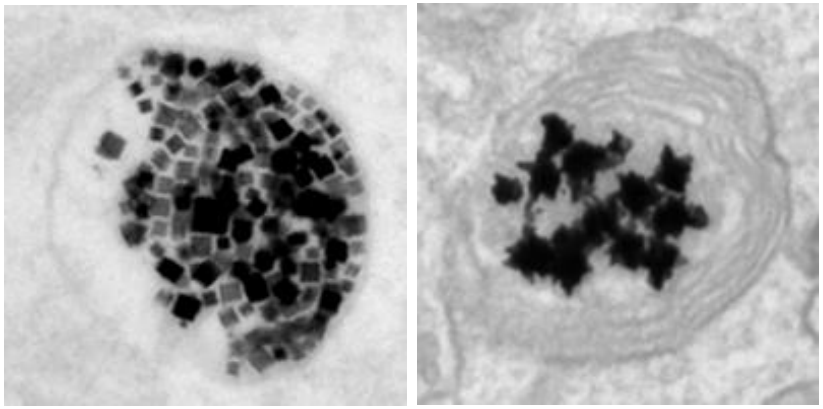
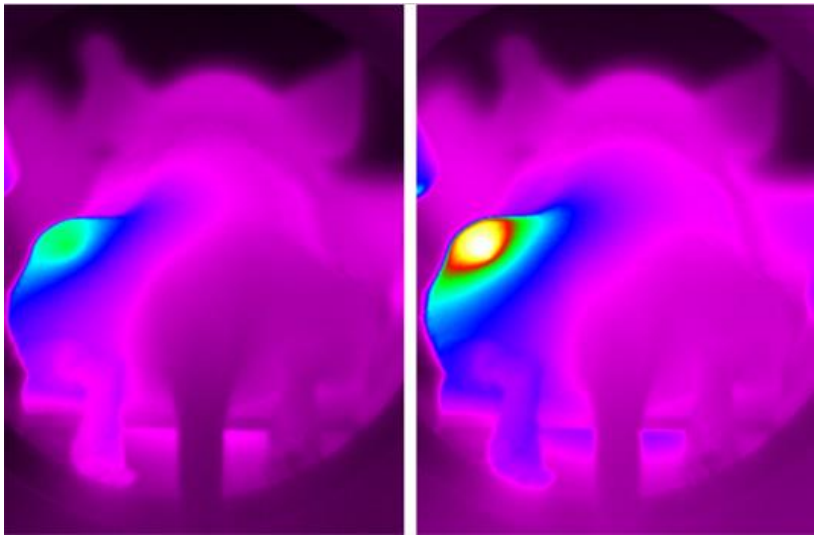
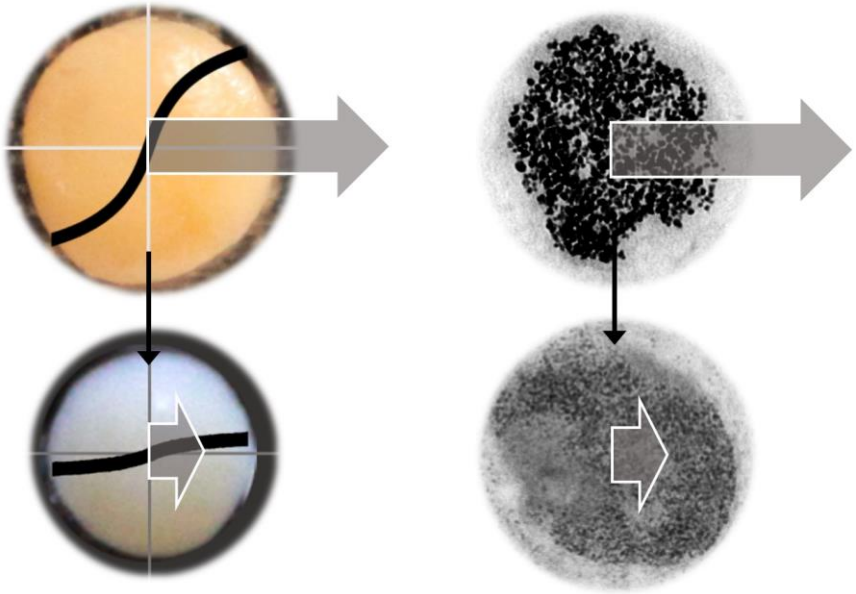
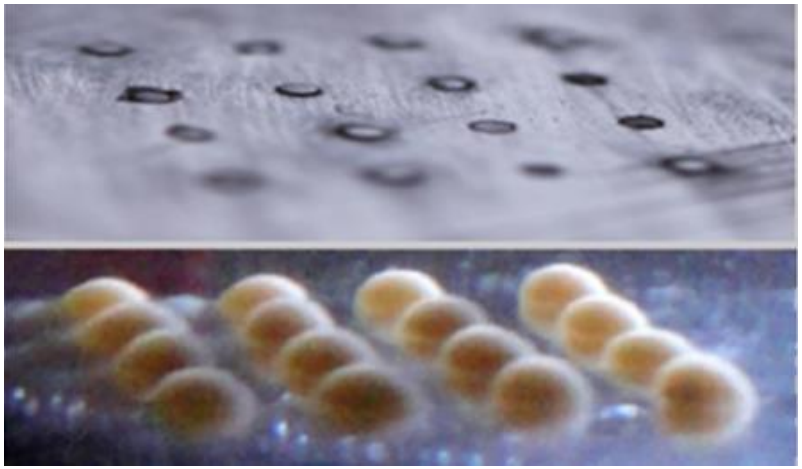
(Intra)cellular therapies using magnetic and/or plasmonic nanoparticles : from thermal cancer treatments to tissue engineering and biotransformations









Remote activation (light, magnetism, radiation) :
Towards **temporal** and **spatial** control of the therapeutic action

➡ **Nano-Magnetism & Nano-Plasmonics**

at the heart of **Nano-Bio-Medicine**

"**on-demand**" & "**at a distance**" therapies

PHENIX, Paris 6,
Christine Ménager
Ali Abou-Hassan

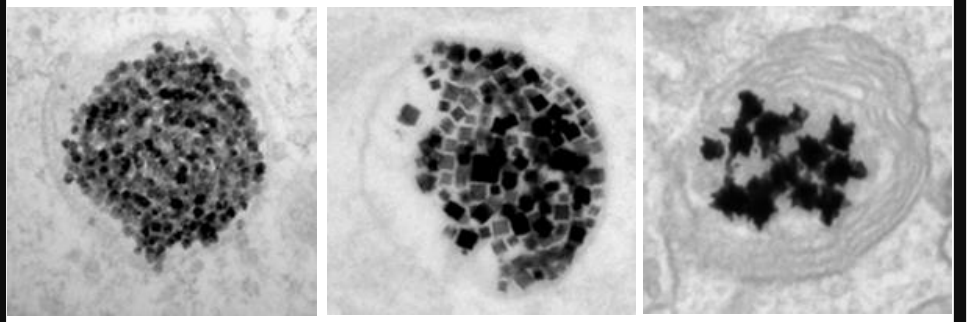
IIT Genova,
Teresa Pellegrino

biomaGUNE,
Javier Reguera
Luis Liz-Marzán

Thank you !

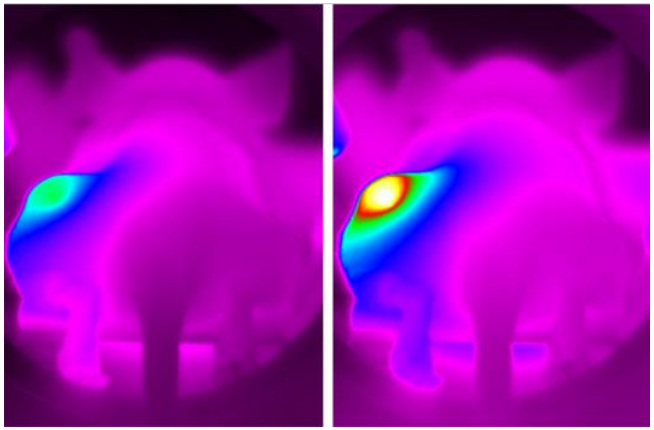
1 Thermal therapies

In situ **measurements of therapeutic efficiency**



2 Thermal therapies

Combined (synergistic) nano-therapies

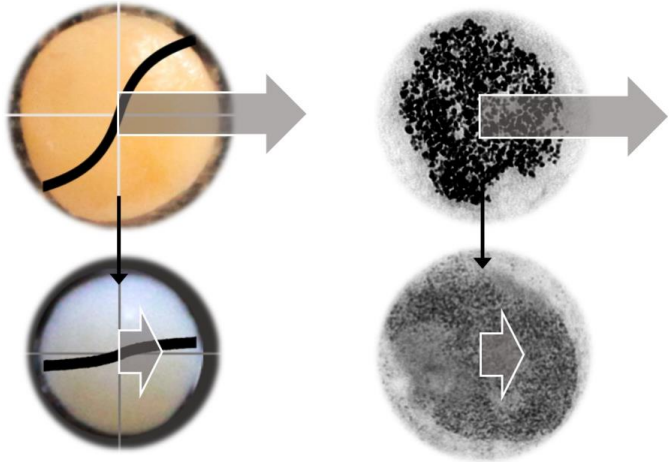


3 Tissue Engineering

Magnetic approaches to tissue mechanics, stimulation & engineering

4 Nano-Bio-Degradation in tissues

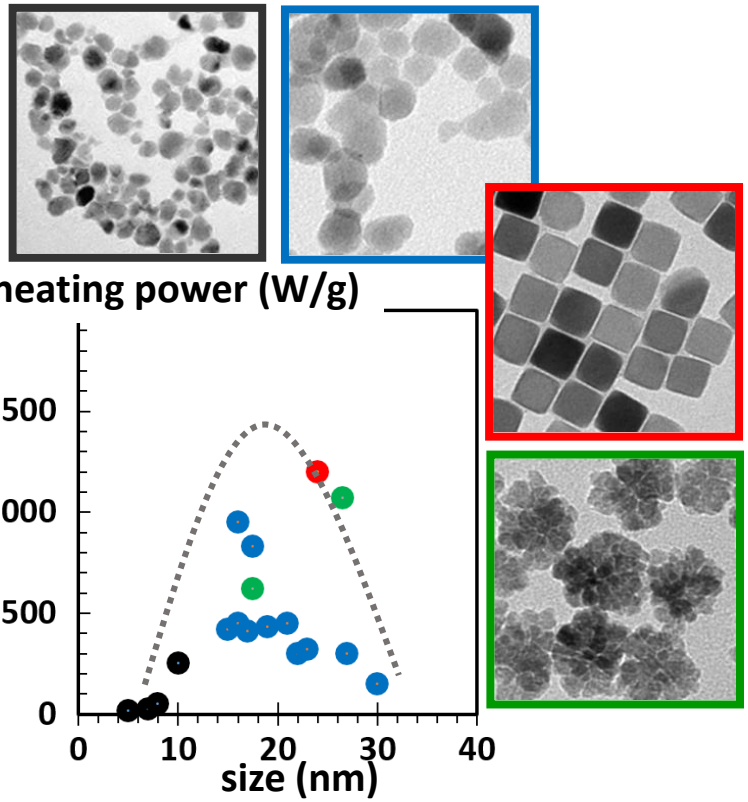
multiscale nanometrologies to track the nano-bio-fate



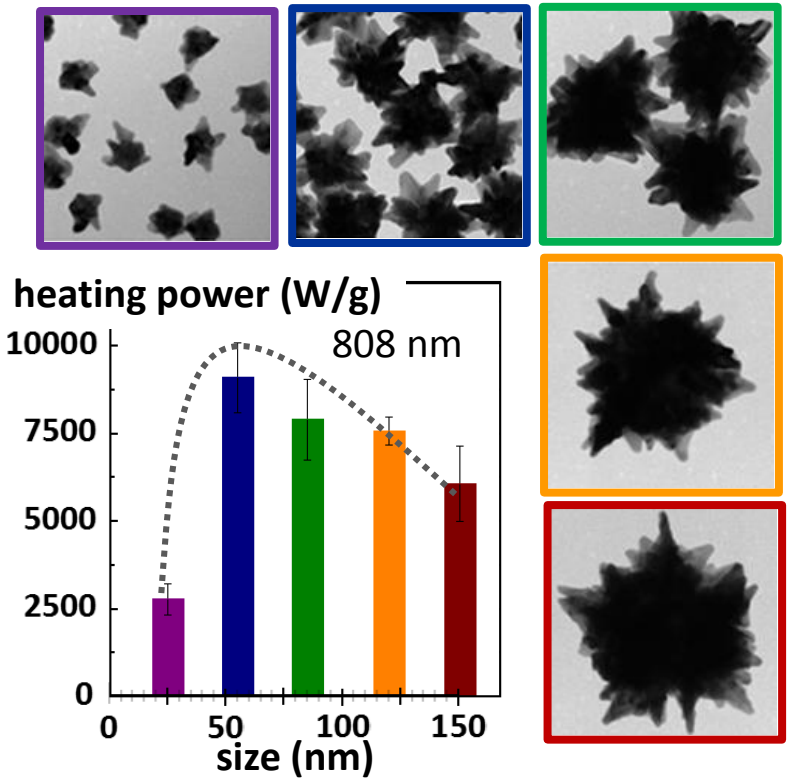
THERMAL NANO-THERAPIES :

CURRENT RESEARCH = to optimize heating efficiency, thanks to innovative designs

SIZE, MAGNETISATION
and ANISOTROPY
of magnetic nanoparticles
govern their heating capacities



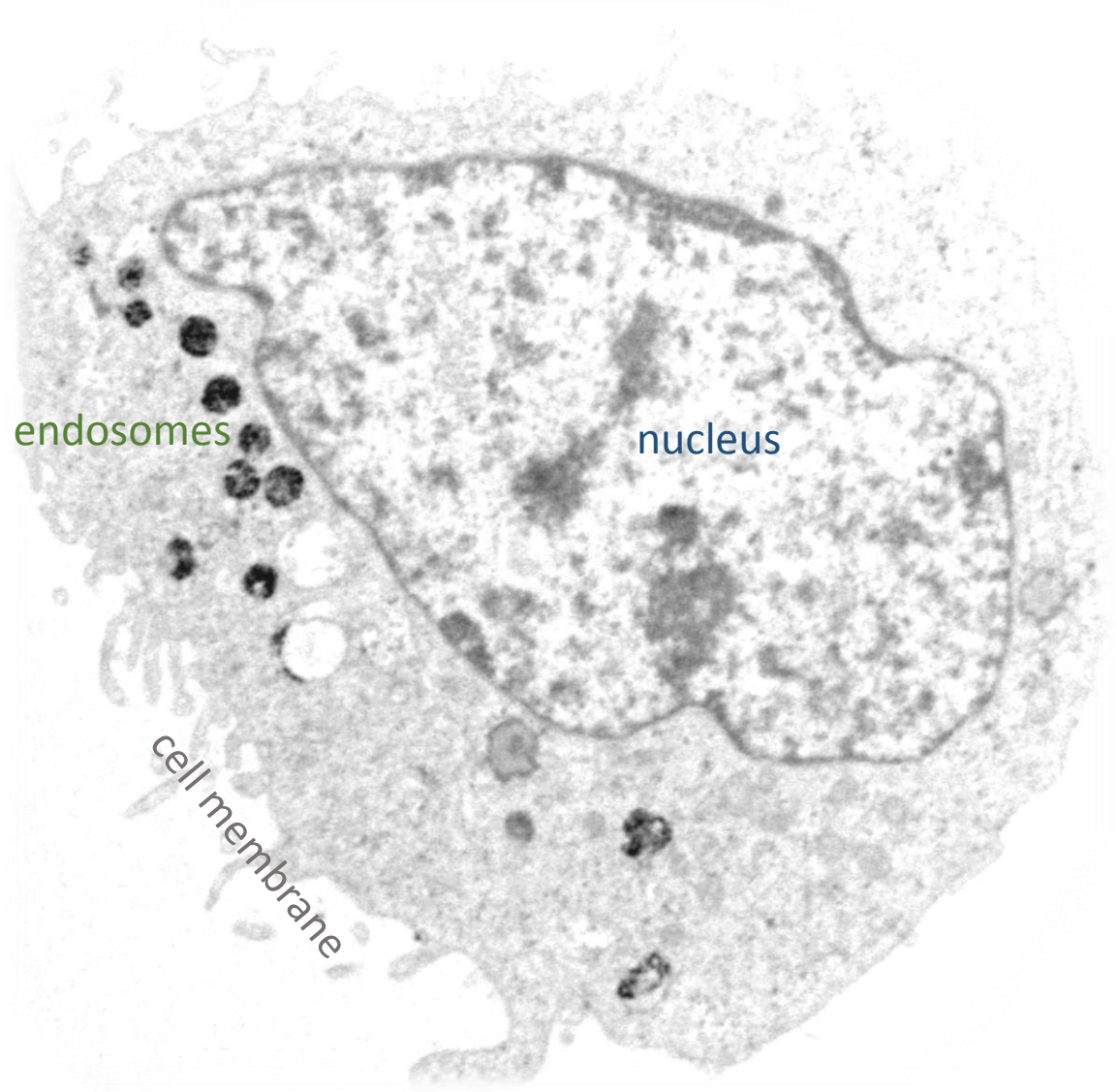
SIZE, DESIGN and
PLASMON BAND
of gold nanoparticles
govern their heating capacities



MEASURE of heating efficiency : in AQUEOUS DISPERSION

BUT THERAPEUTIC TARGET = CANCER CELL

& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

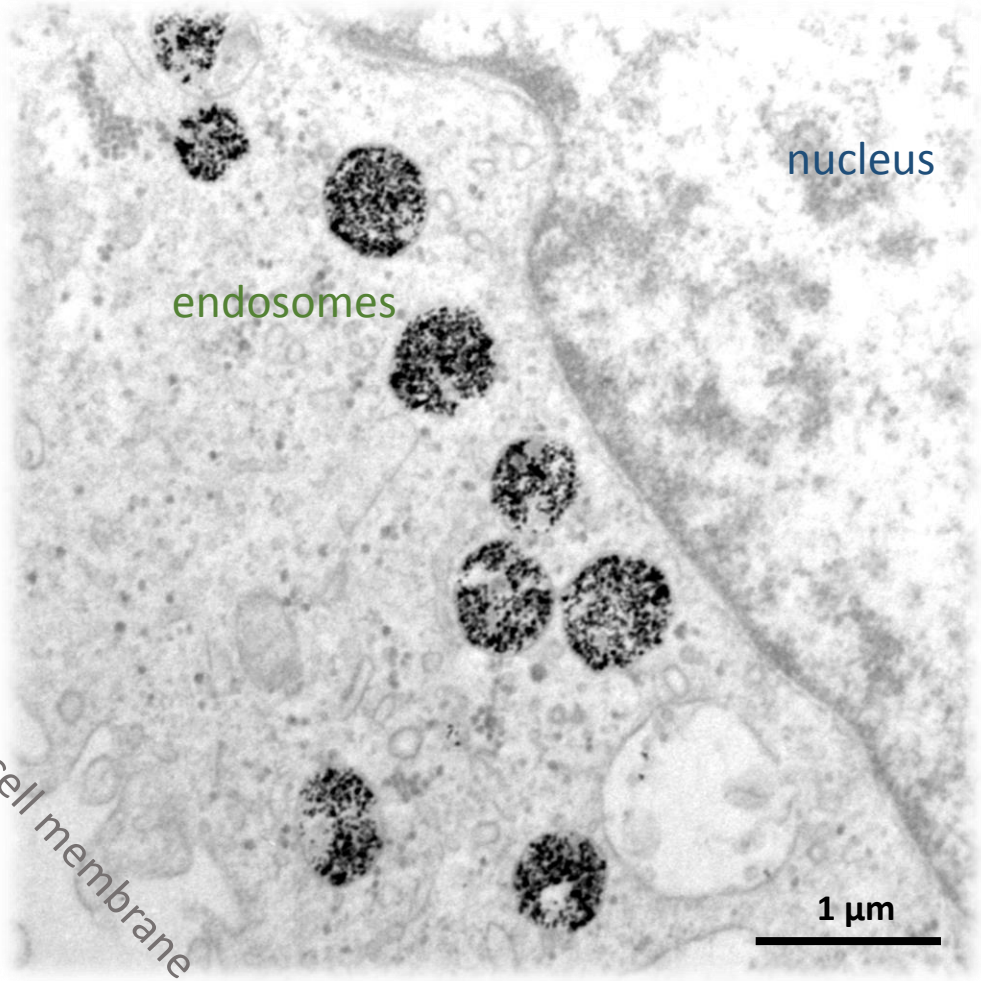


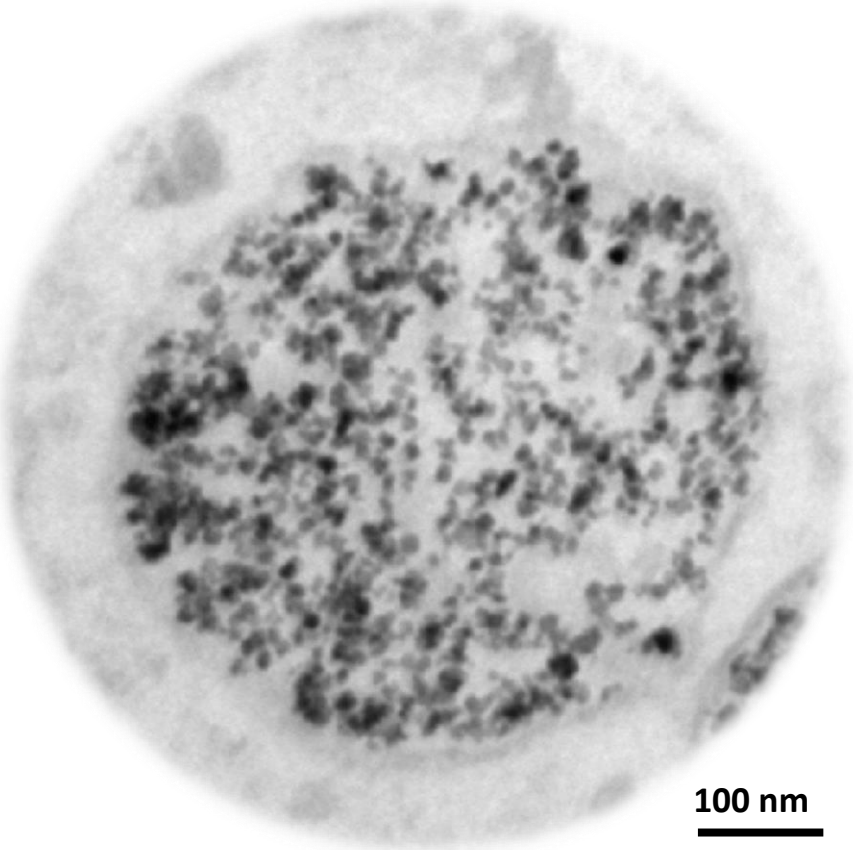
⚠ MEASURE of heating efficiency : in AQUEOUS DISPERSION

THERAPEUTIC TARGET = CANCER CELL

& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

→ **MAGNETIC NANOPARTICLES**

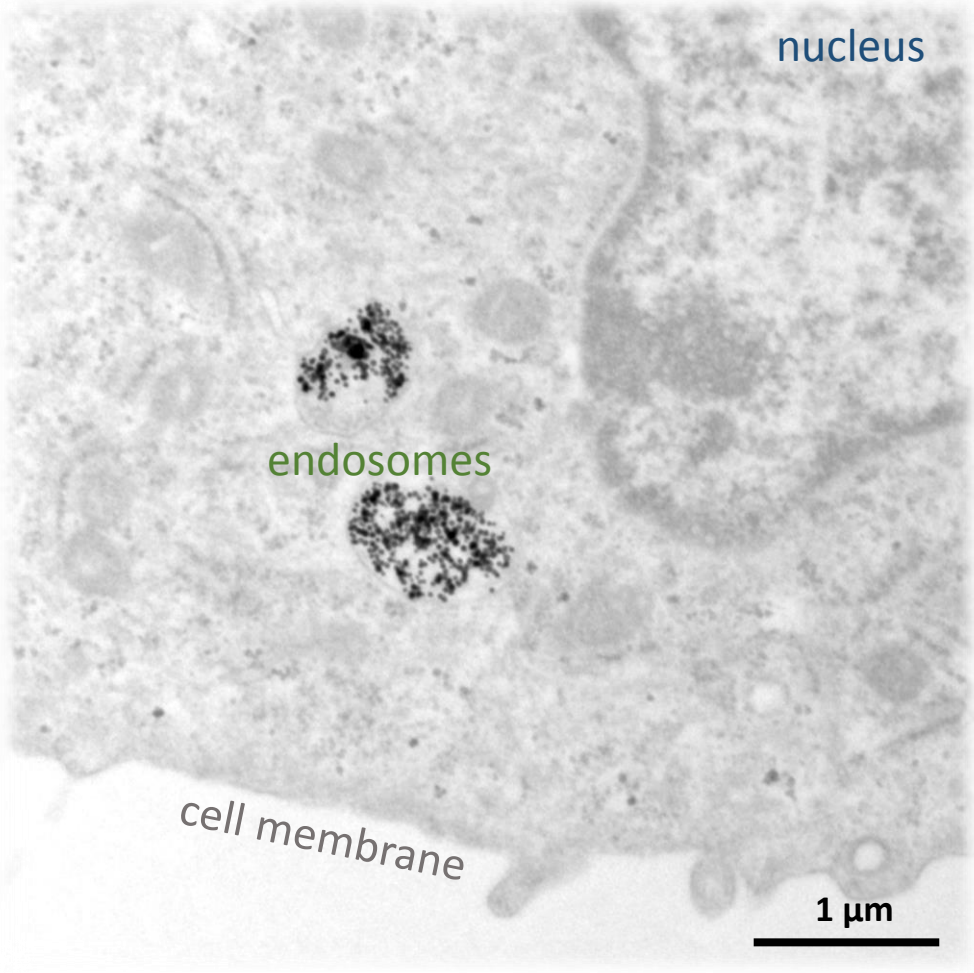


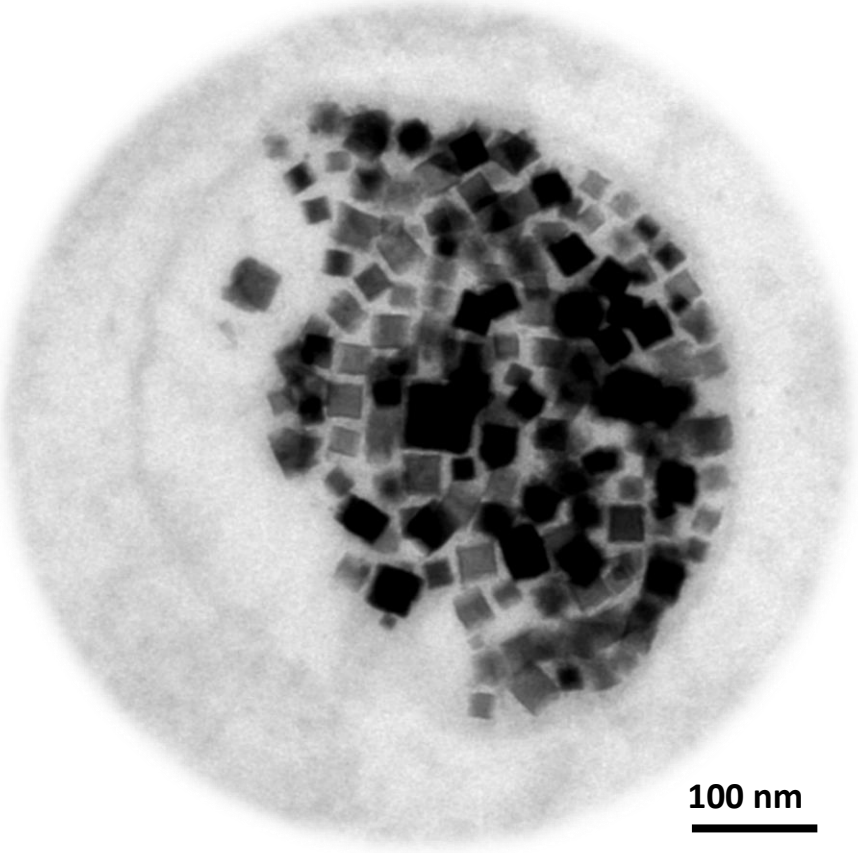


THERAPEUTIC TARGET = CANCER CELL

& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

→ **MAGNETIC NANOCUBES**

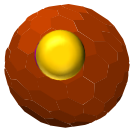


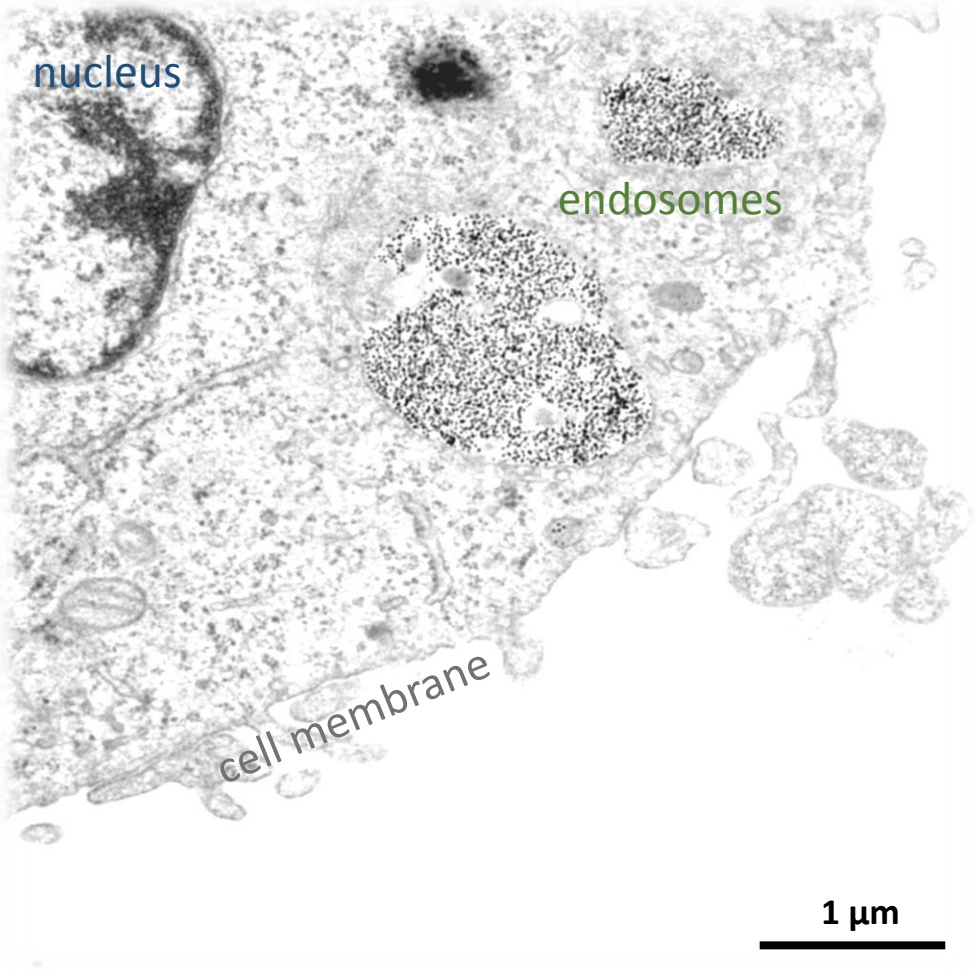


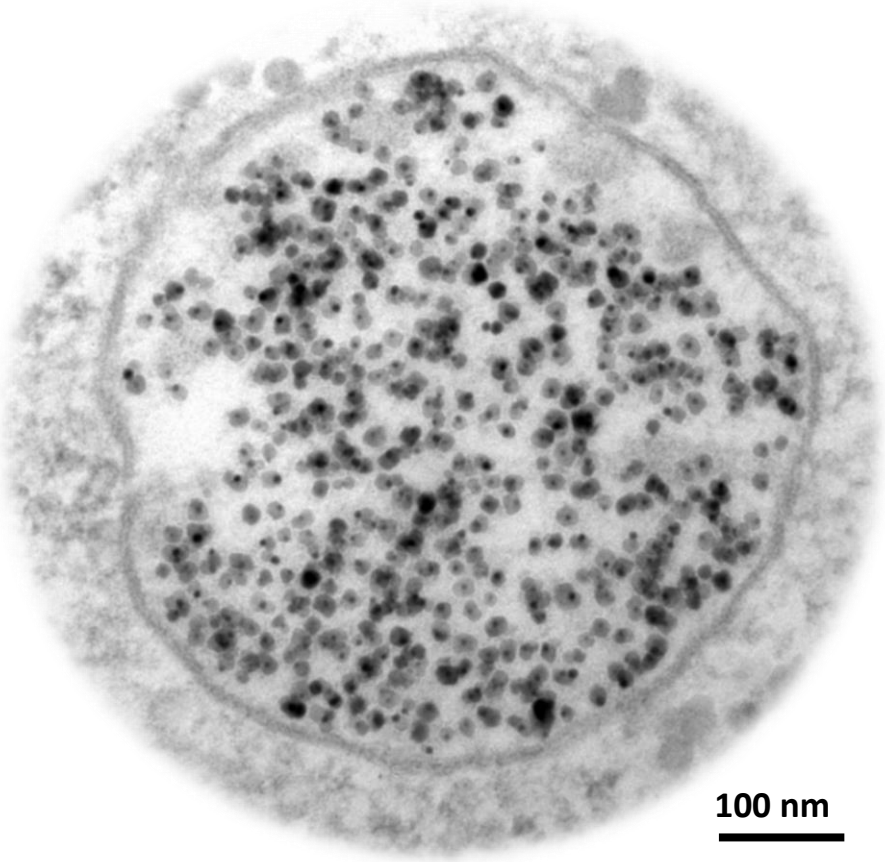
THERAPEUTIC TARGET = CANCER CELL

& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

→ **MAGNETIC NANODIMERS**



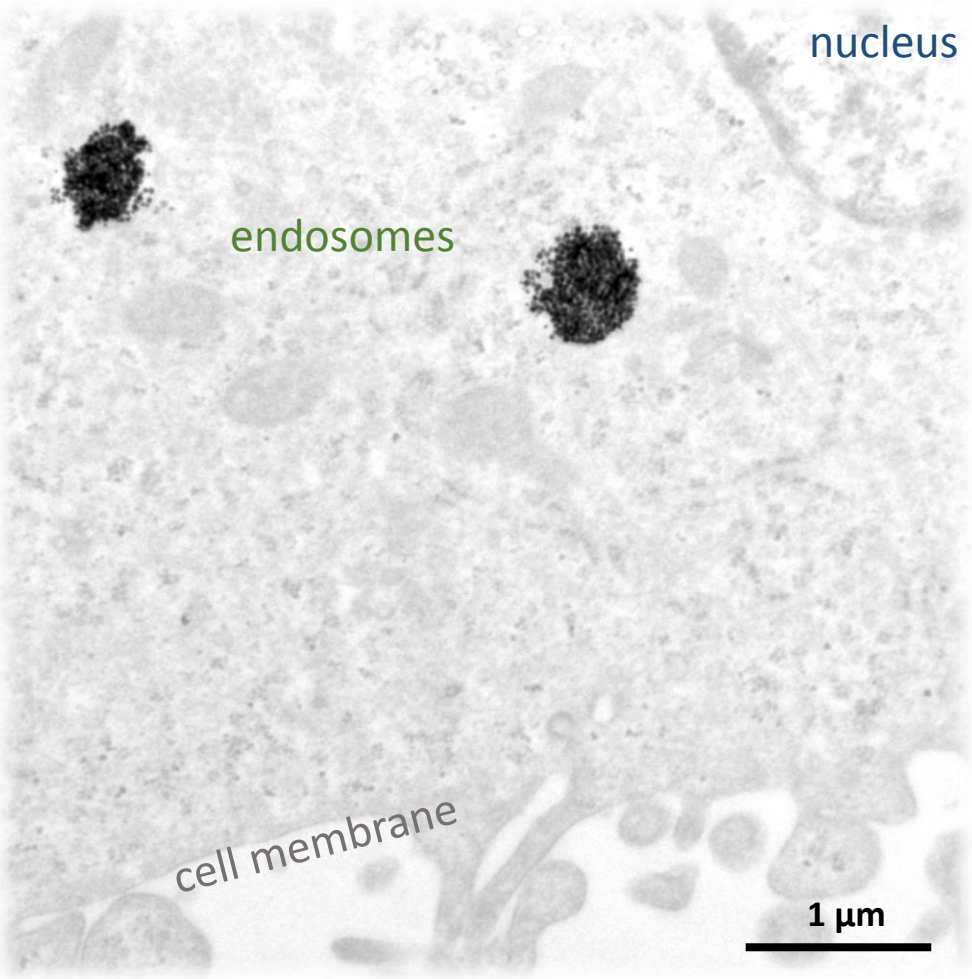


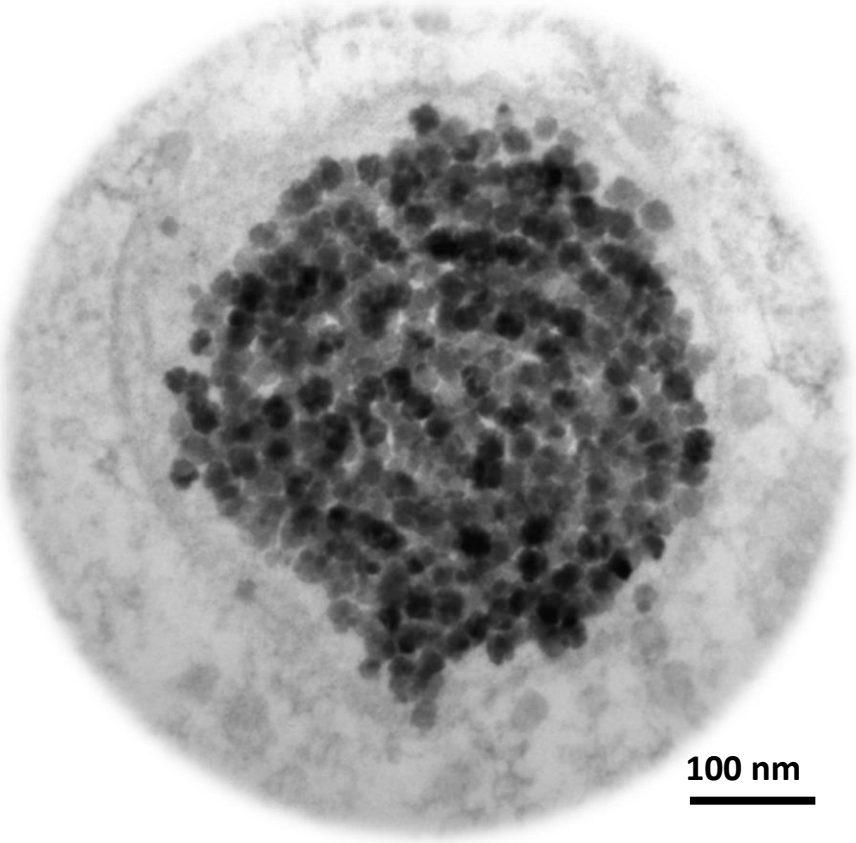


THERAPEUTIC TARGET = CANCER CELL

& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

→ **MAGNETIC NANOFLOWERS**

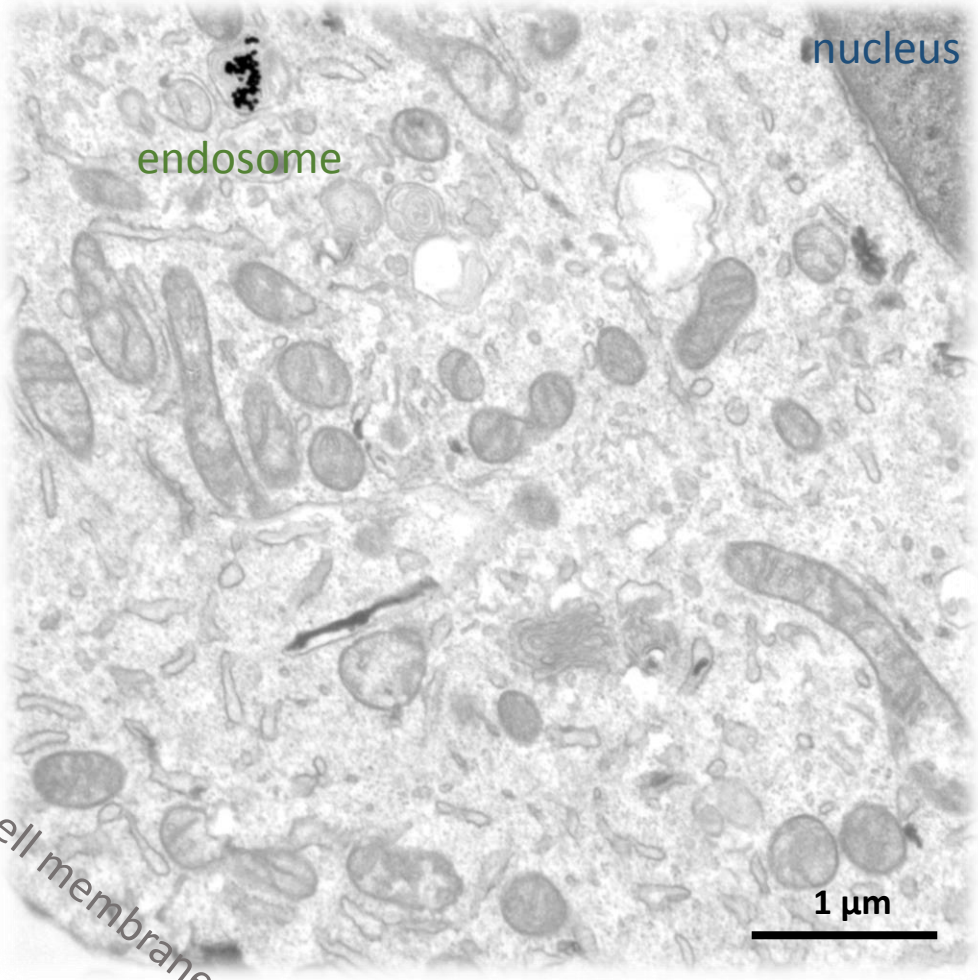


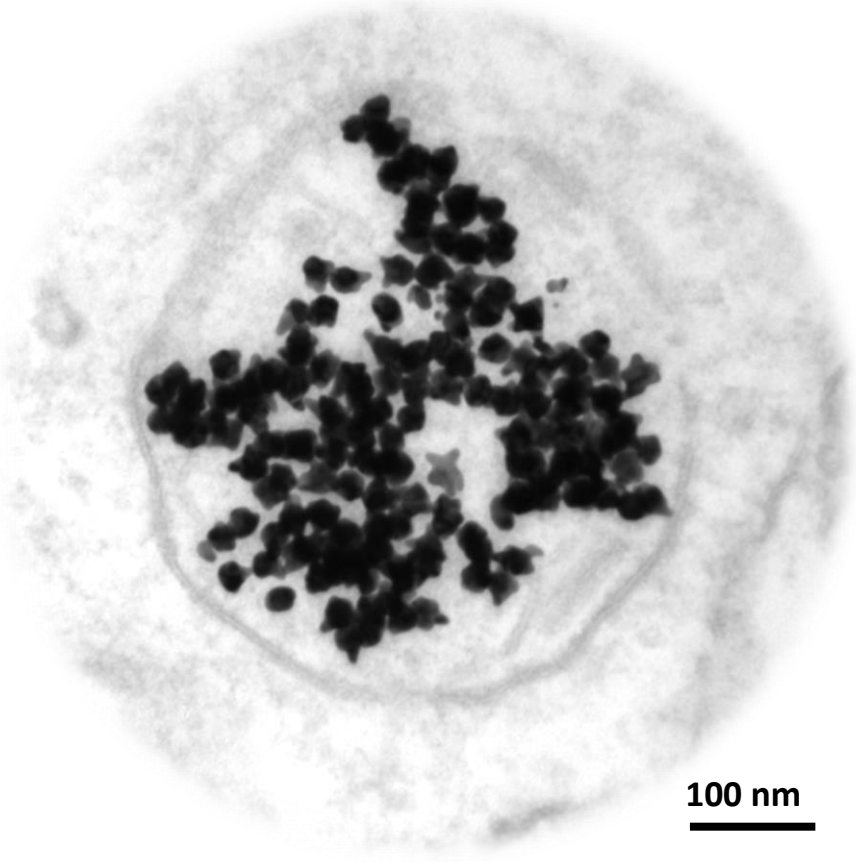


THERAPEUTIC TARGET = CANCER CELL

& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

→ **GOLD NANOSTARS (small)**

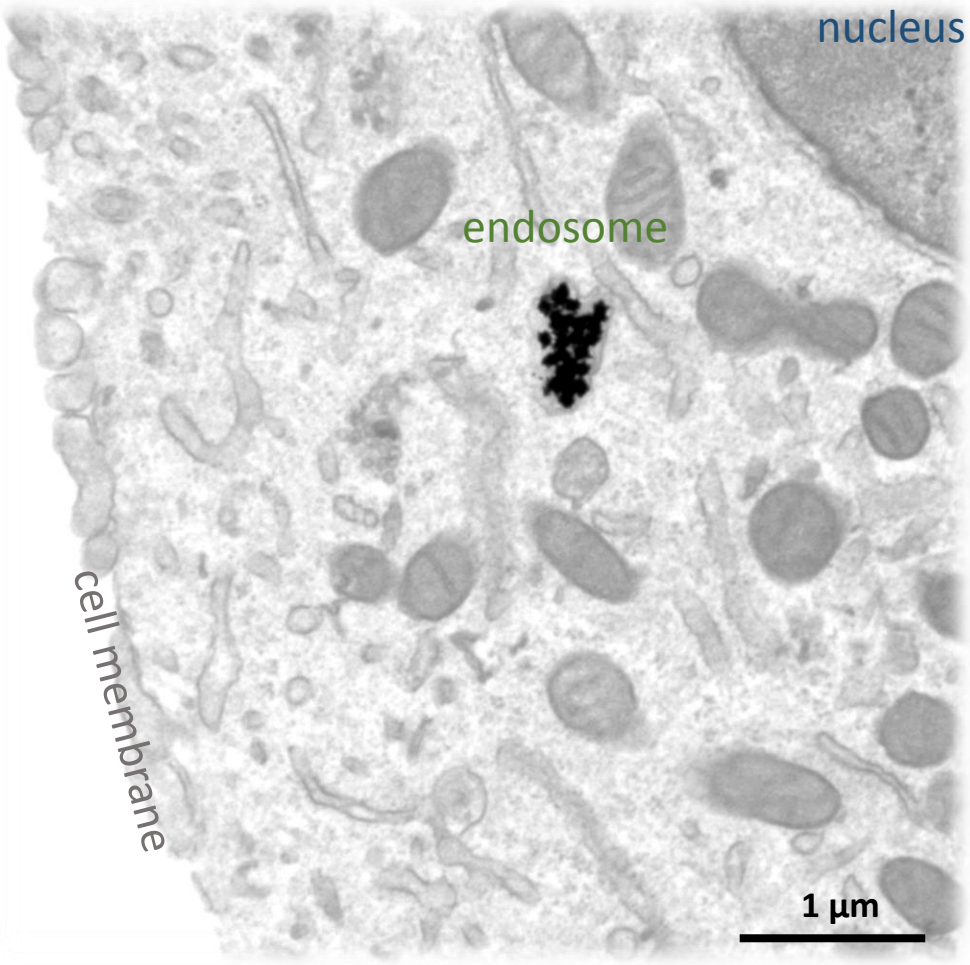


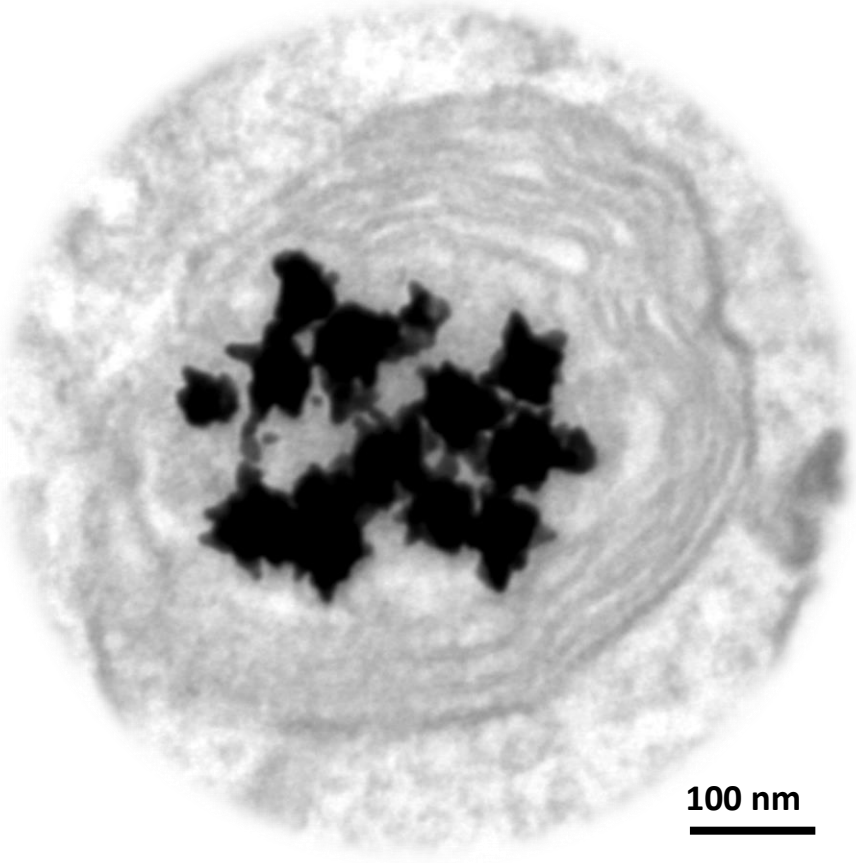


THERAPEUTIC TARGET = CANCER CELL

& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

→ **GOLD NANOSTARS (medium)**

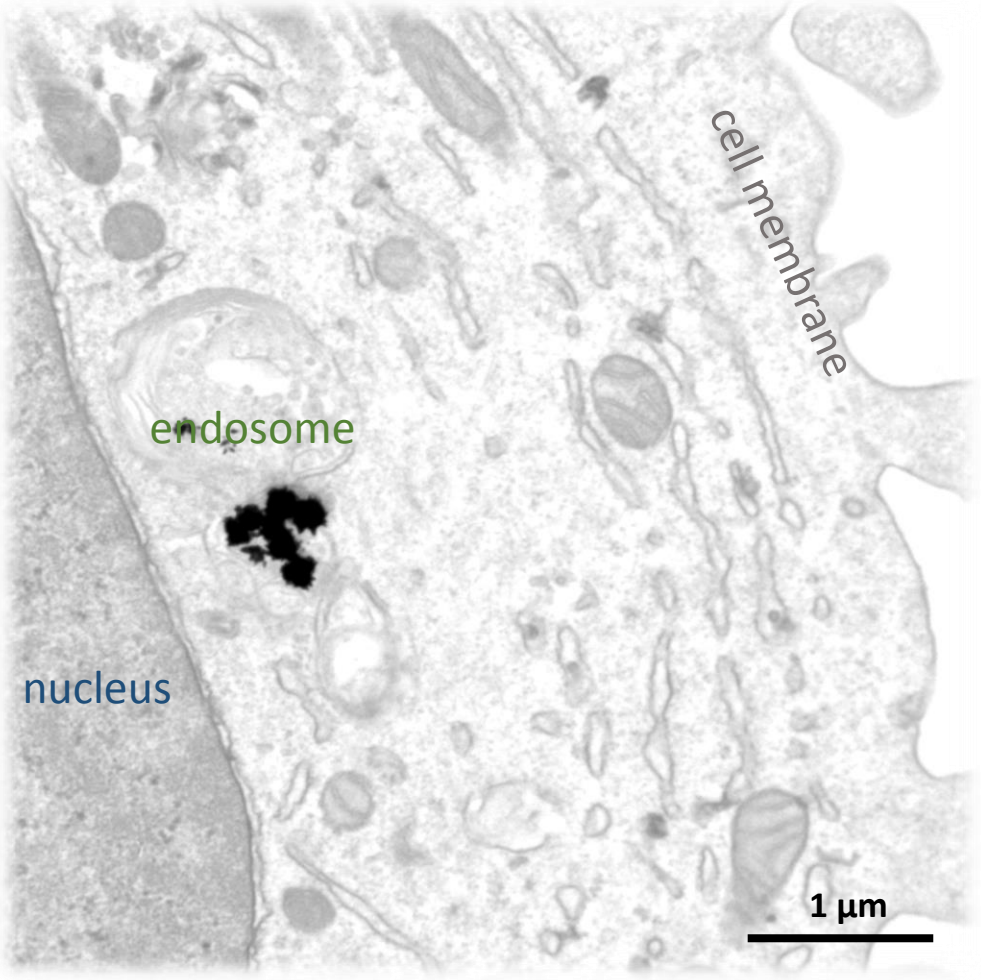


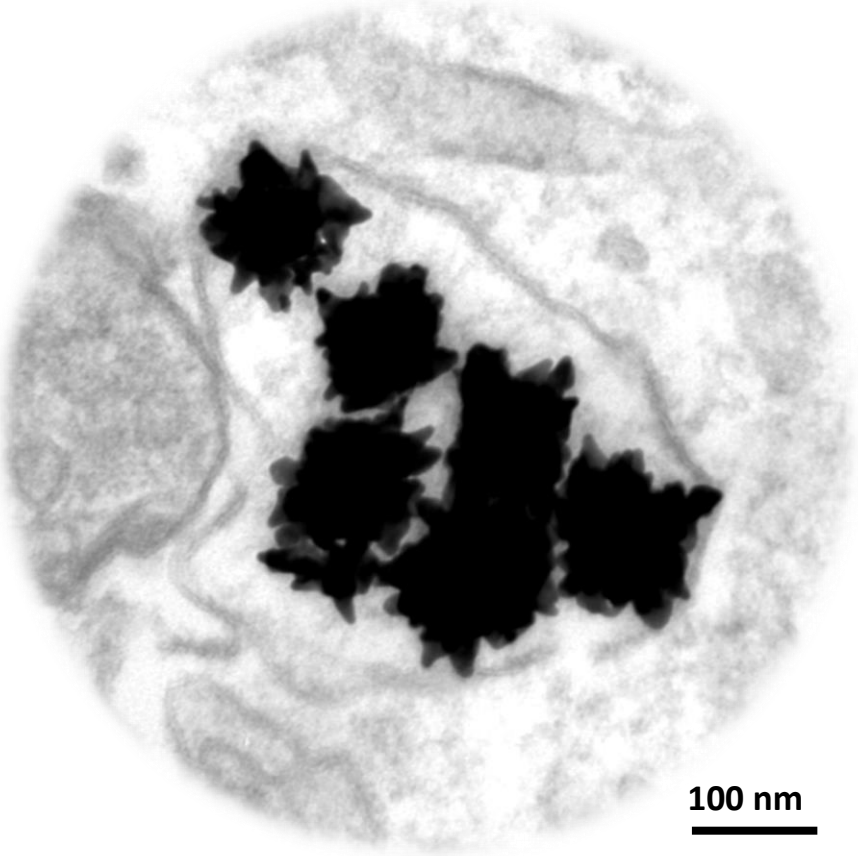


THERAPEUTIC TARGET = CANCER CELL

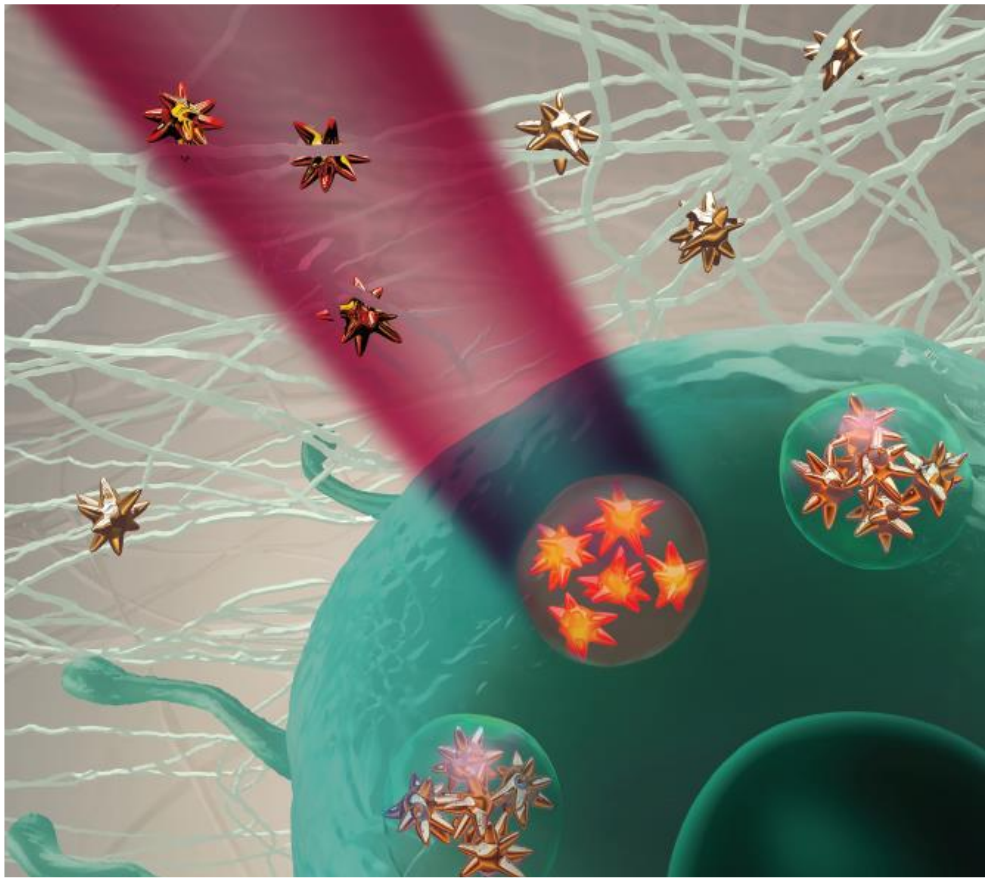
& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

→ **GOLD NANOSTARS (large)**

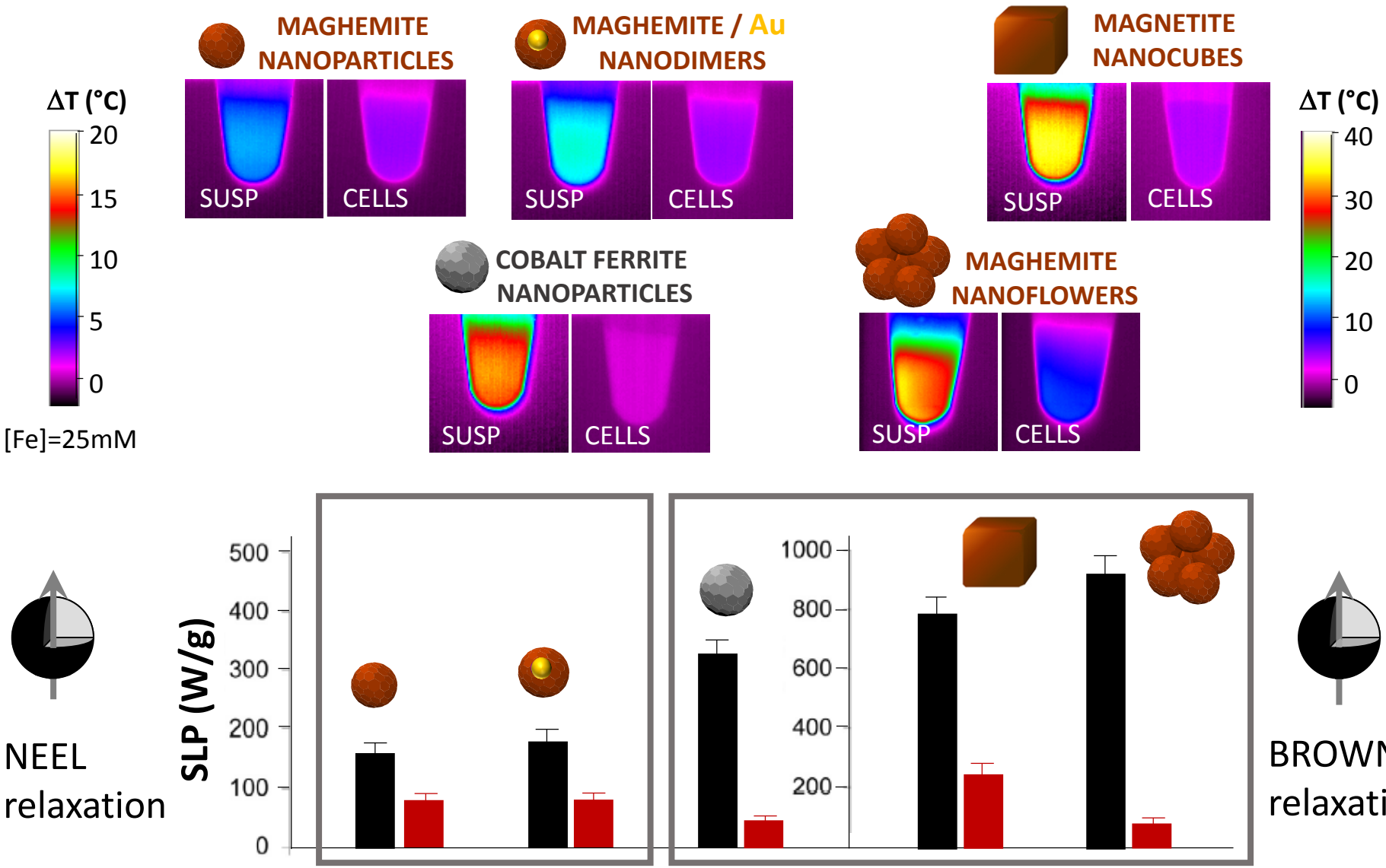




THERMAL THERAPIES EFFICIENCY INSIDE CANCER CELLS ?



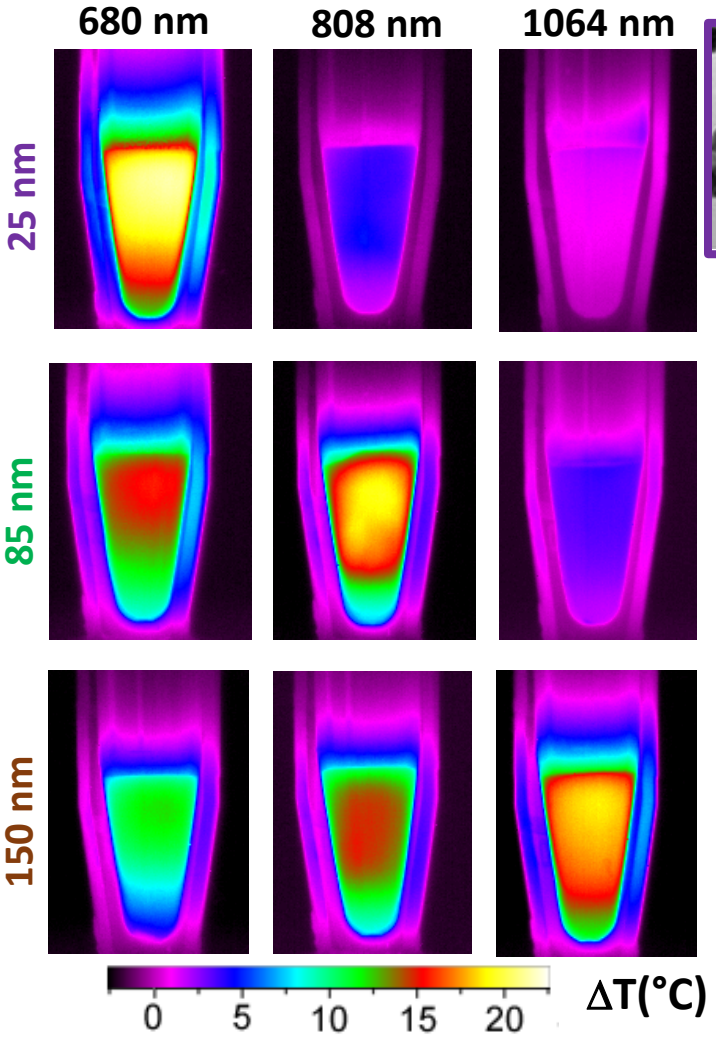
MAGNETIC HYPERTHERMIA INSIDE CANCER CELLS ?

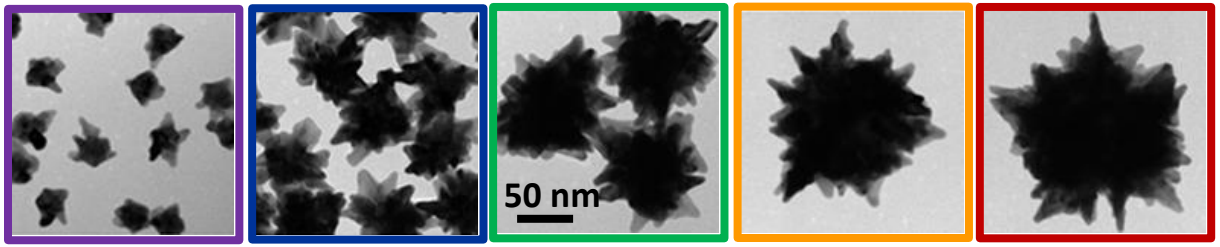


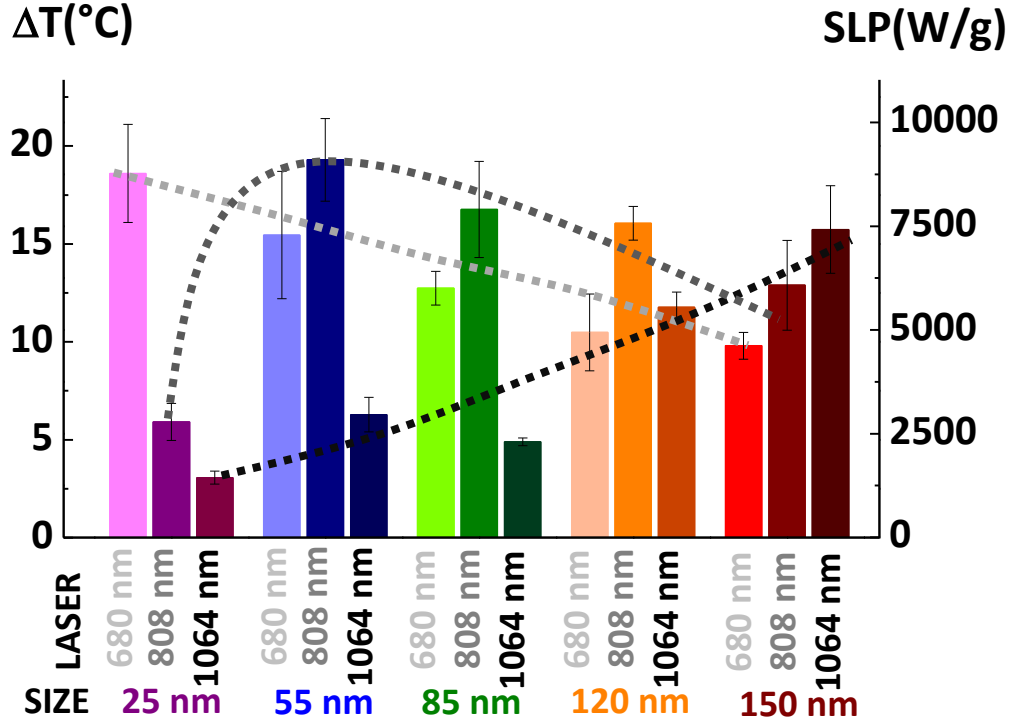
Magnetic hyperthermia efficiency in the cellular environment for different nanoparticle designs.
Di Corato R, Espinosa A, Lartigue L, Tharaud M, Chat S, Pellegrino T, Ménager C, Gazeau F, Wilhelm C
Biomaterials 24, 6400-6411 (2014)

PHOTOTHERMIA INSIDE CANCER CELLS ?

1. Measurements in aqueous dispersion



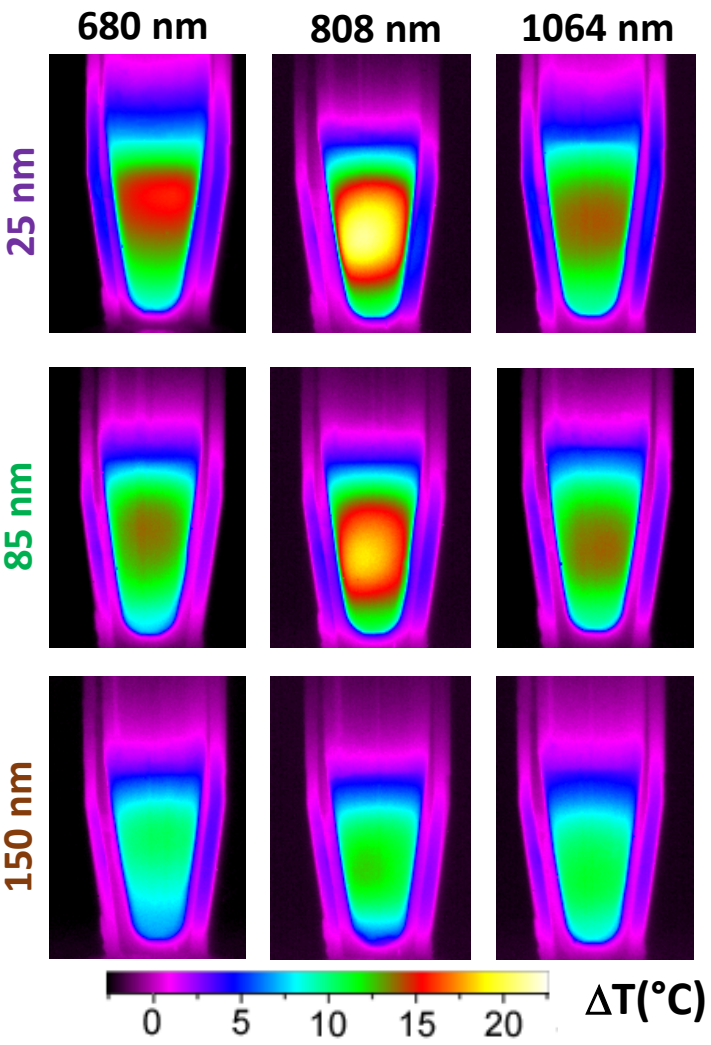


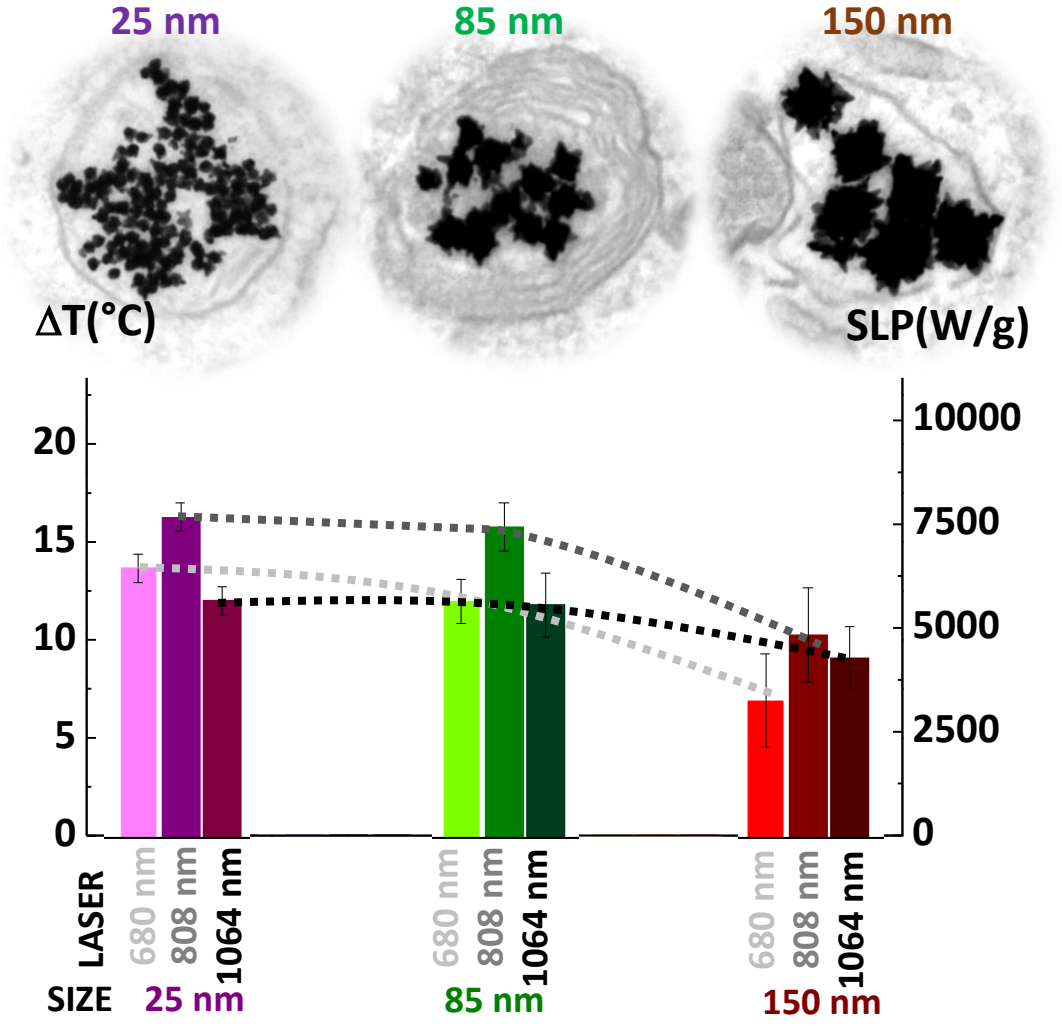


Cancer cell internalisation of gold nanostars impacts their photothermal efficiency in vitro and in vivo: towards a plasmonic thermal fingerprint in tumoral environment. Advanced HealthCare Materials 5, 1040–1048 (2016)
Espinosa A, Silva AKA, Sánchez A, Grzelczak M, Péchoux C, Desboeufs K, Liz-Marzan L, Wilhelm C.

PHOTOTHERMIA INSIDE CANCER CELLS ?

2. Measurements on internalized nanostars





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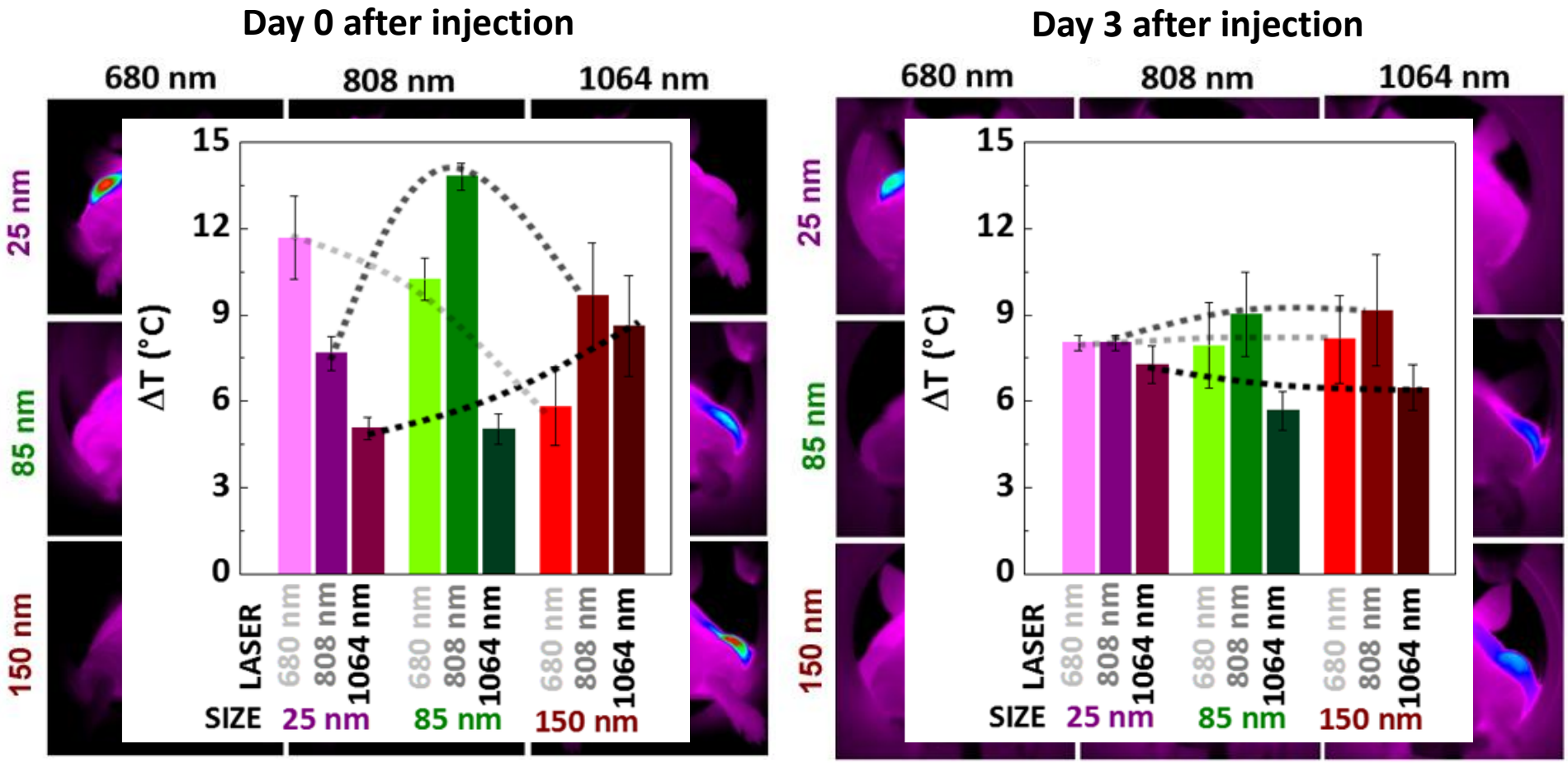
PHOTOTHERMIA INSIDE CANCER CELLS ?

3. Measurements in vivo inside tumors



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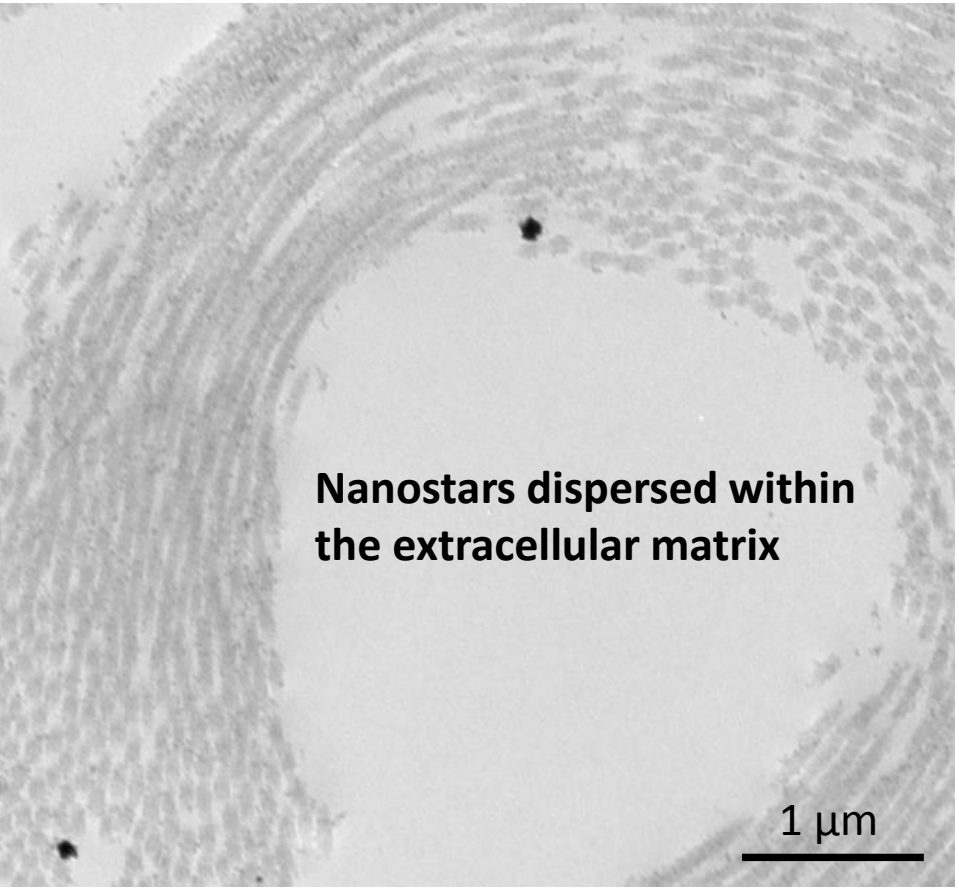
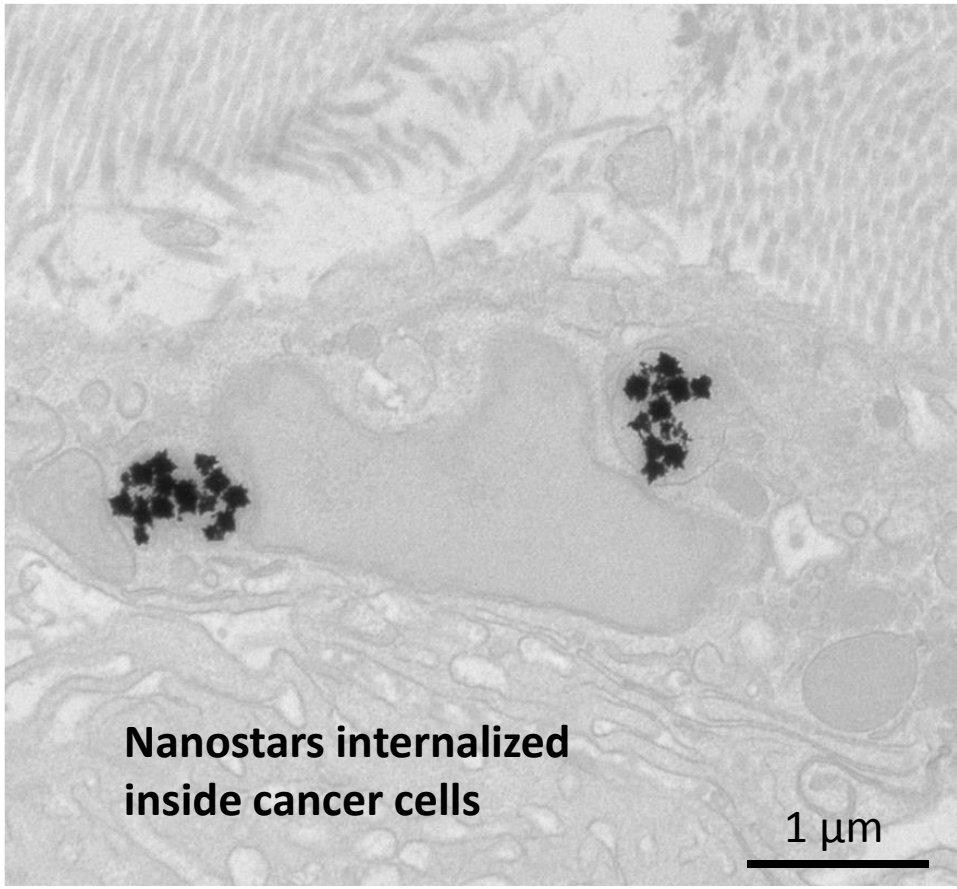
PHOTOTHERMIA INSIDE CANCER CELLS ?

3. Measurements in vivo inside tumors

Day 0 after injection



Day 3 after injection



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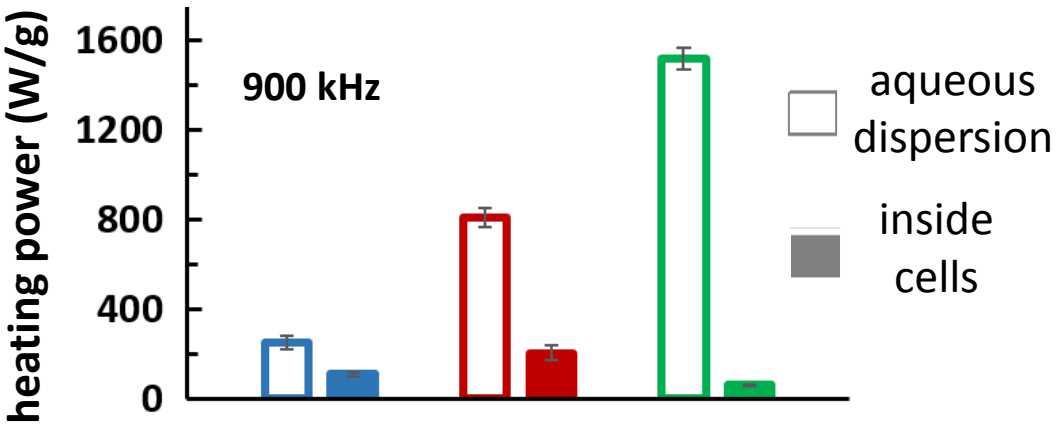
Espinosa A, Silva AKA, Sánchez A, Grzelczak M, Péchoux C, Desboeufs K, Liz-Marzan L, Wilhelm C.

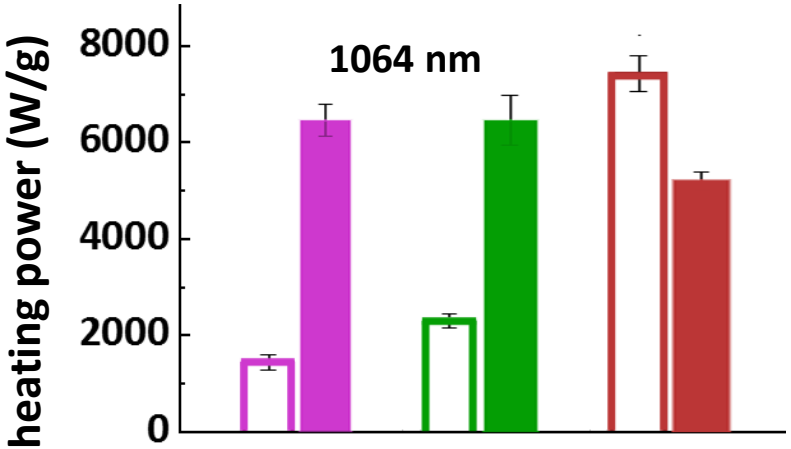
***In situ* measurements** in the biological target environment:
physical (thermal) fingerprints of therapeutic efficacy

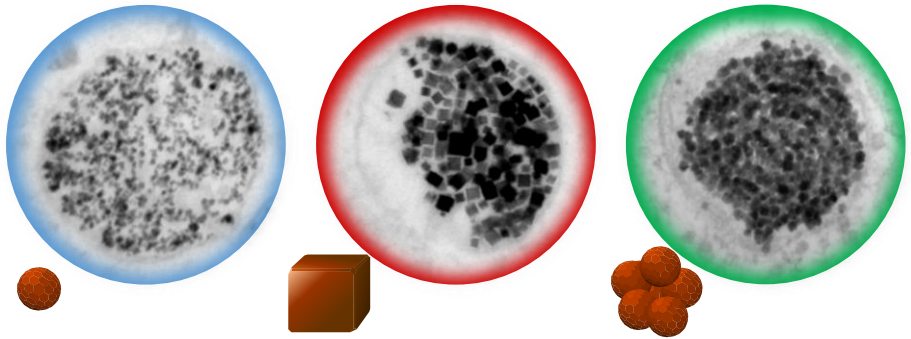
Nanoparticles internalization by cancer cells impact their heating efficiency

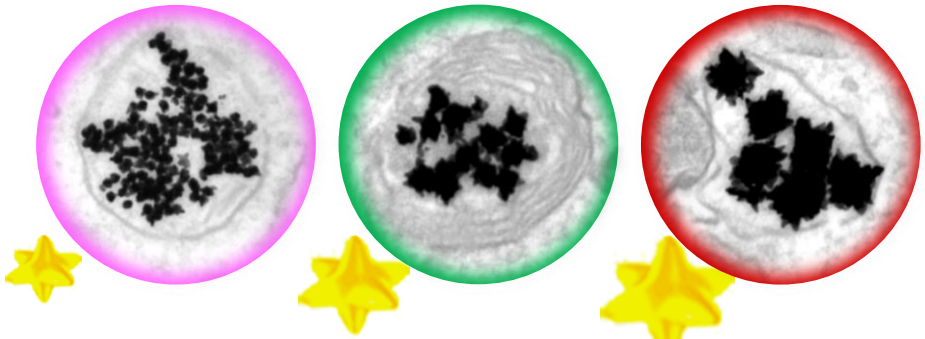
MAGNETIC HYPERTHERMIA
with iron oxide nanoparticles :
Systematic decrease after cell internalization; more pronounced for Brown relaxation.

PHOTOTHERMIA with gold nanoparticles :
Cell internalization can either increase or decrease photothermal efficiency depending on size and laser excitation



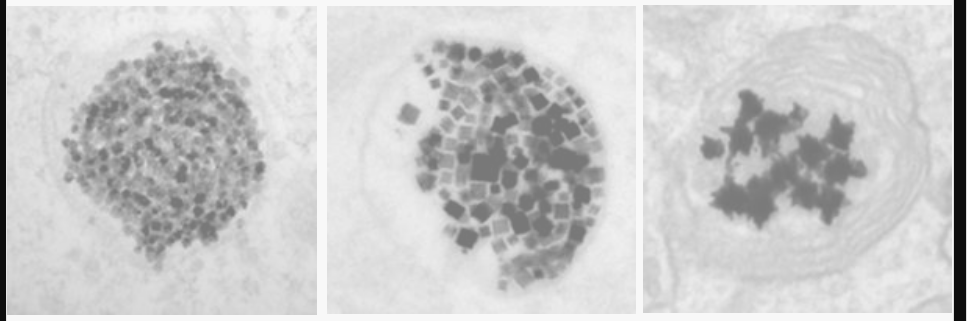






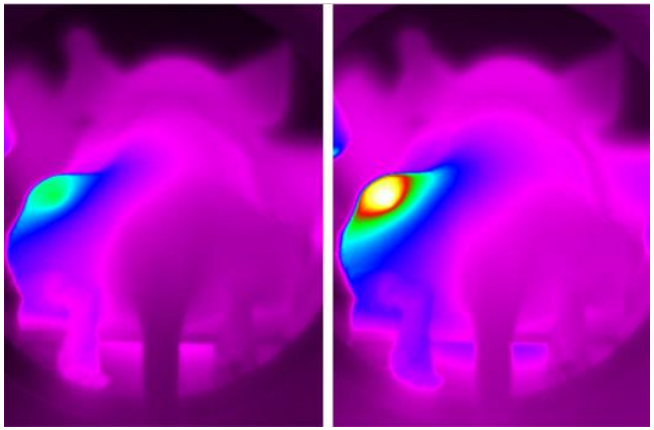
1

In situ measurements of therapeutic efficiency



2

Combined nano-therapies

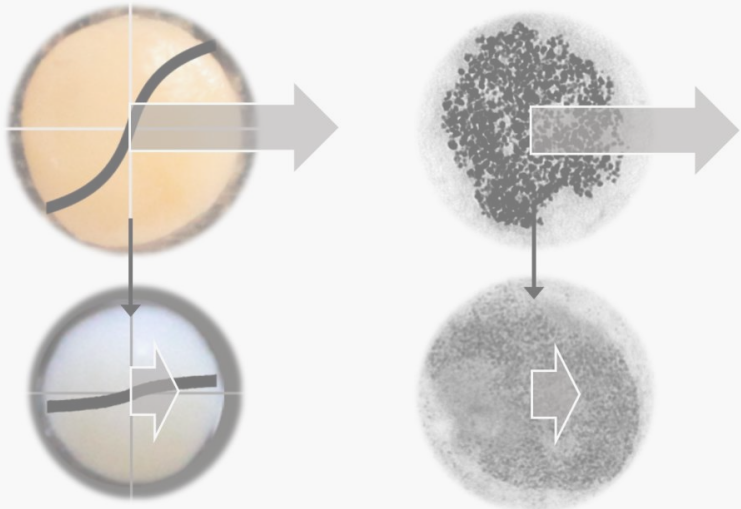


3

Magnetic tissue engineering

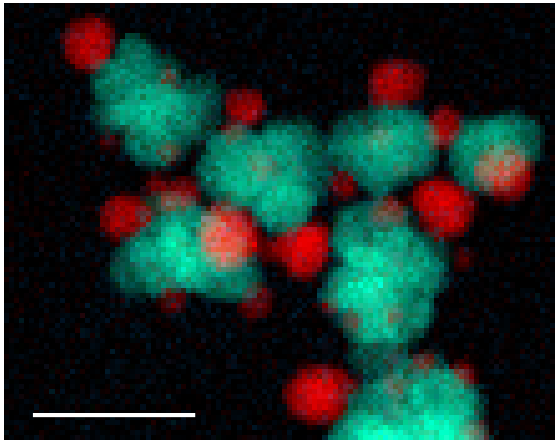
4

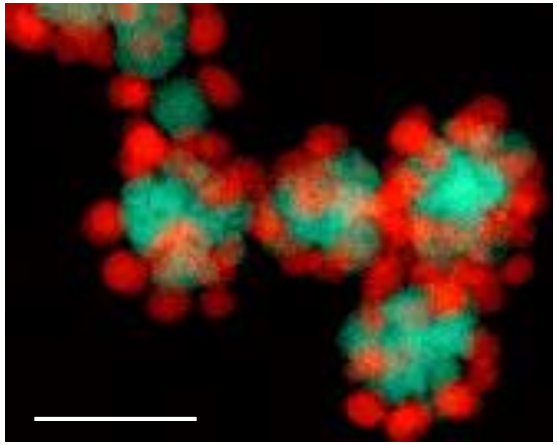
Nano-Bio-Degradation in tissues

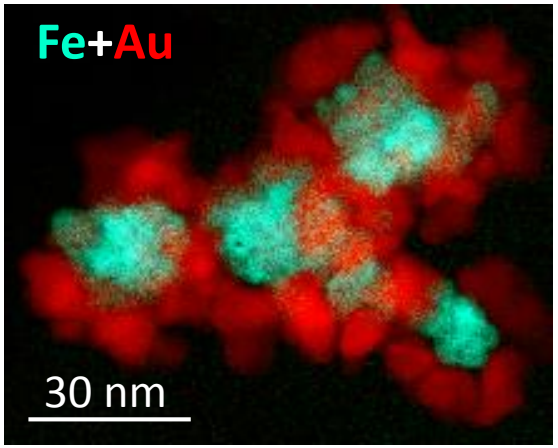


COMBINED THERMAL NANO-THERAPIES

strategy 1 = Magneto-Plasmonic NANOHYBRID

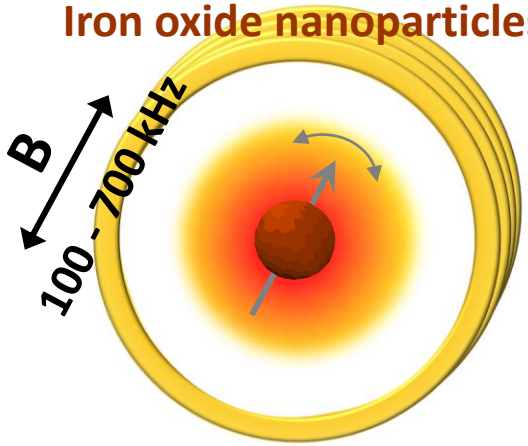






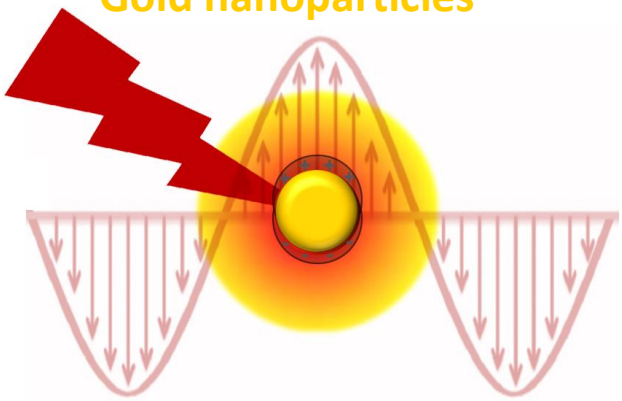
MAGNETIC HYPERTHERMIA

Iron oxide nanoparticles



PHOTOTHERMIA

Gold nanoparticles

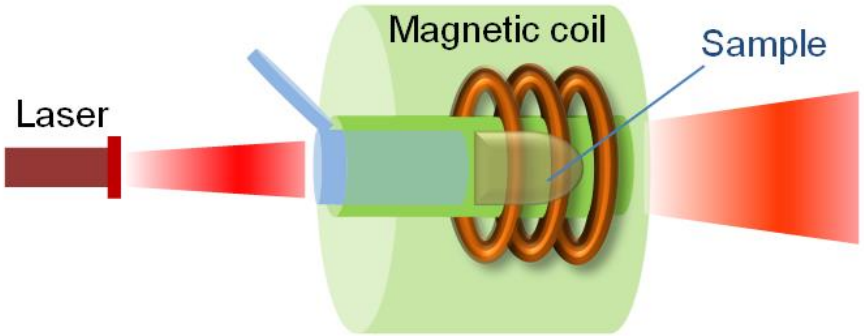


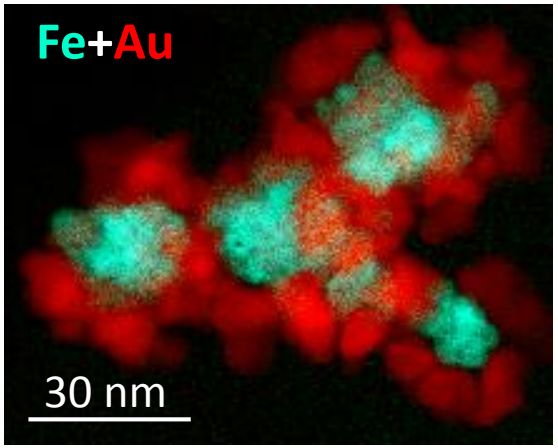
CURRENT CHALLENGE FACING THERMAL THERAPIES : INCREASE THE HEATING / DECREASE THE DOSE

Can magneto-plasmonic nanohybrids efficiently combine photothermia with magnetic hyperthermia ?
Espinosa A, Bugnet M, Radtke G, Neveu S, Botton GA, Wilhelm C, Abou-Hassan A. Nanoscale, 7, 18872 (2015)

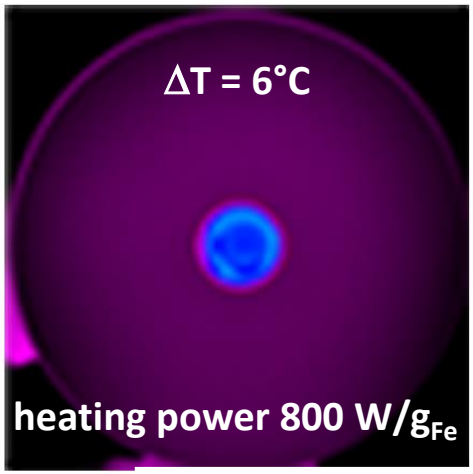
COMBINED THERMAL NANO-THERAPIES

strategy 1 = Magneto-Plasmonic NANOHYBRID

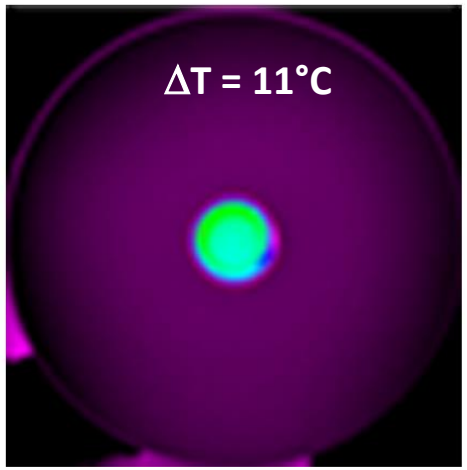




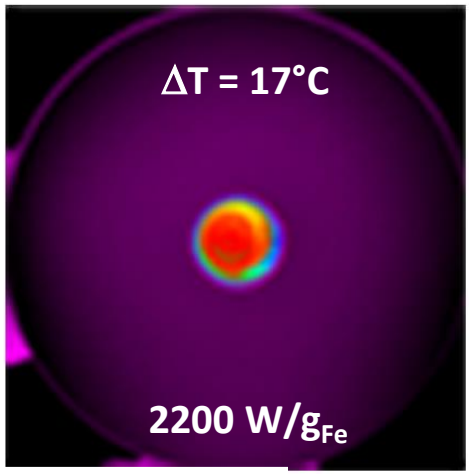
MAGNETIC HYPERTHERMIA



PHOTOTHERMIA



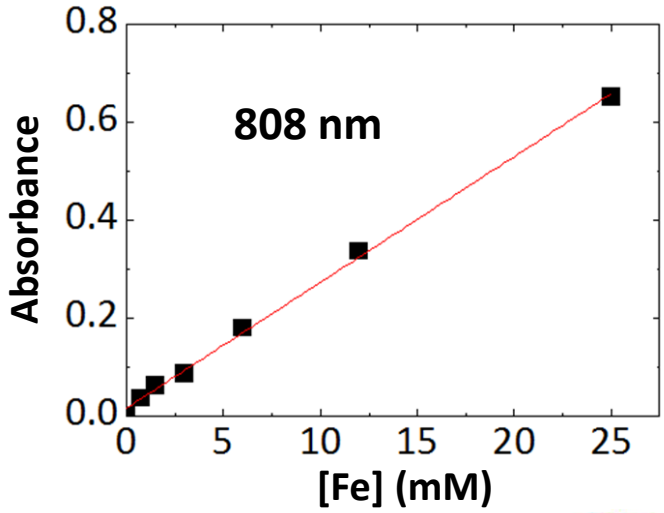
MAGNETO-PHOTO-THERMIA



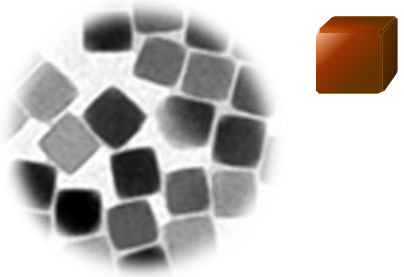
Can magneto-plasmonic nanohybrids efficiently combine photothermia with magnetic hyperthermia ?
Espinosa A, Bugnet M, Radtke G, Neveu S, Botton GA, Wilhelm C, Abou-Hassan A. Nanoscale, 7, 18872 (2015)

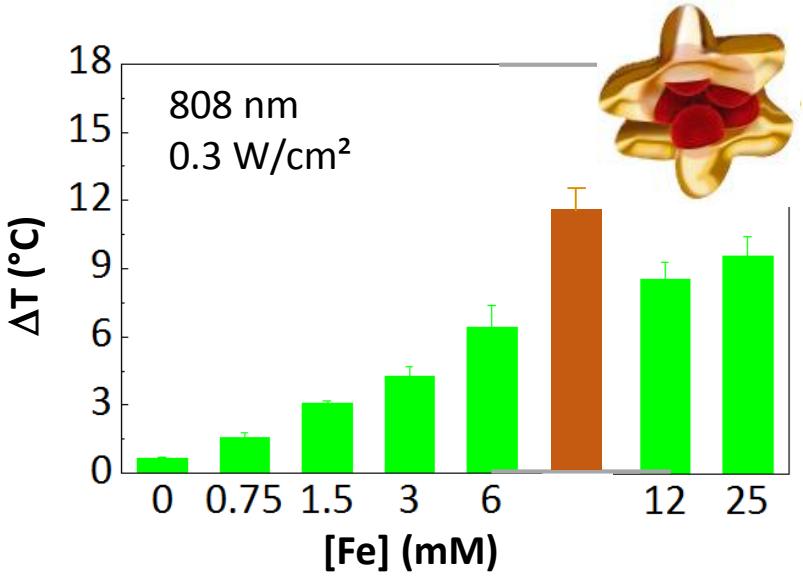
MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY ?

strategy 2 = Iron oxide nanoparticles only



MAGNETITE Nanocubes

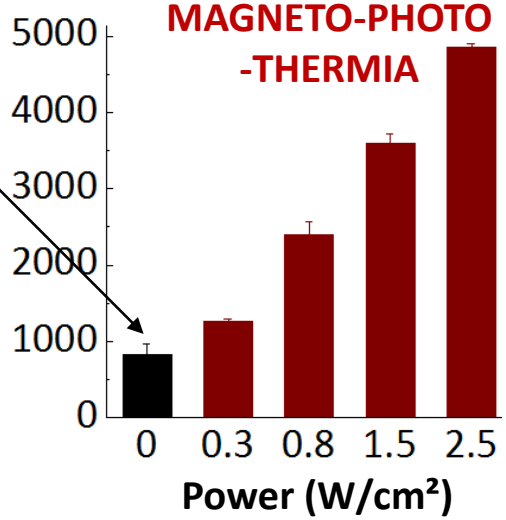




Heating power
SLP (W/g_{Fe})

MAGNETIC HYPERTHERMIA only

MAGNETO-PHOTO -THERMIA

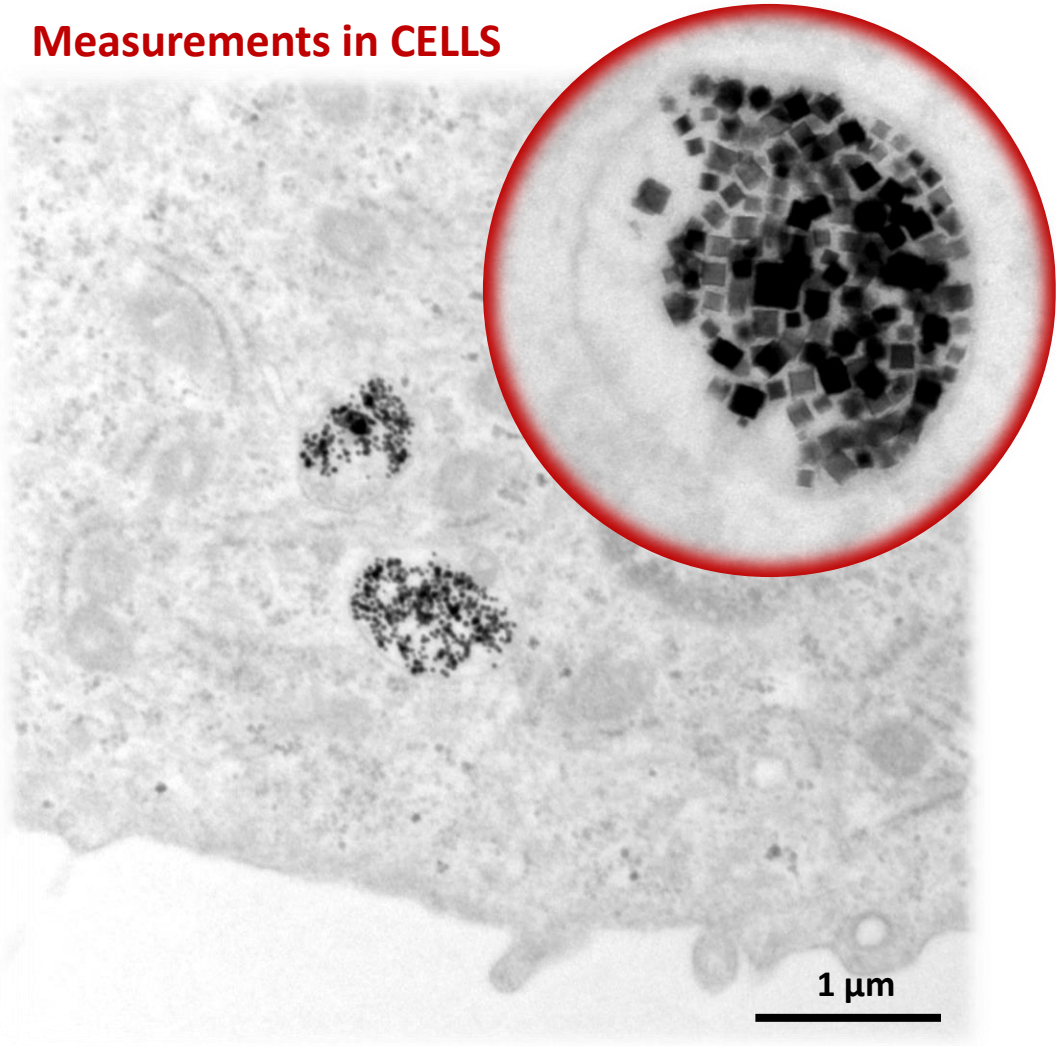


Duality of Iron Oxide Nanoparticles in Cancer Therapy: Amplification of Heating Efficiency by Magnetic Hyperthermia and Photothermal Bimodal Treatment. ACS nano, 10, 7627- 38 (2016)
Espinosa A, Di Corato R, Kolosnjaj-Tabi J, Flaud P, Pellegrino T, Wilhelm C.

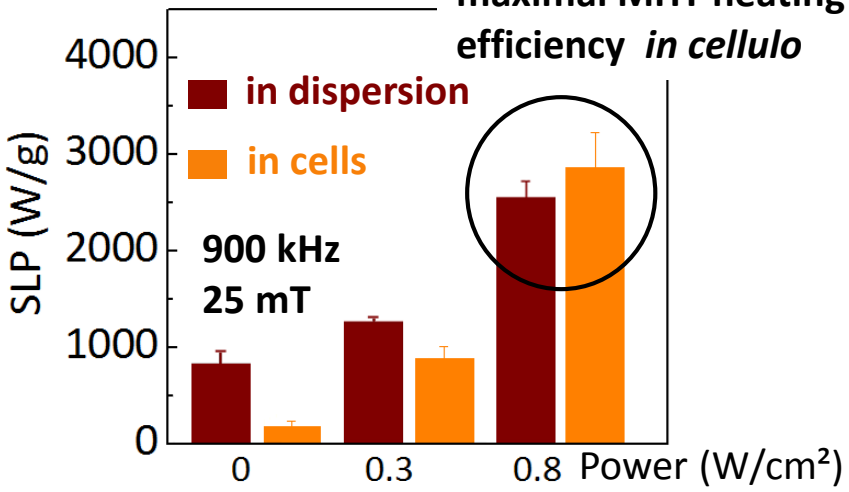
MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY ?

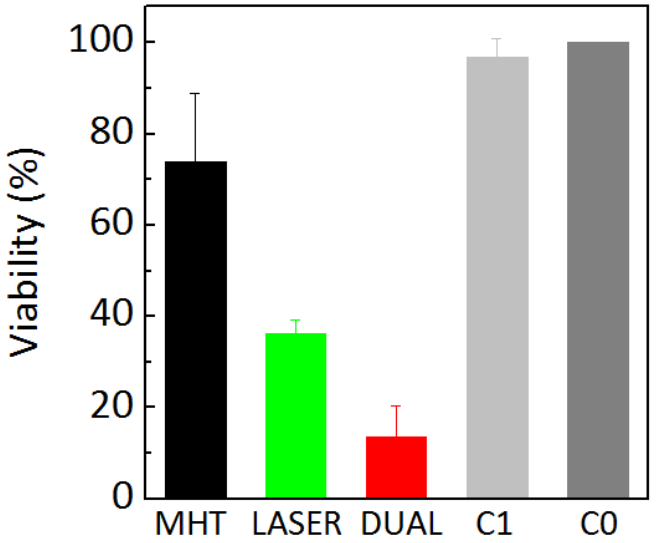
strategy 2 = Iron oxide nanoparticles only

Measurements in CELLS



Laser restores maximal MHT heating efficiency *in cellulo*





Duality of Iron Oxide Nanoparticles in Cancer Therapy: Amplification of Heating Efficiency by Magnetic Hyperthermia and Photothermal Bimodal Treatment. ACS nano, 10, 7627- 38 (2016)

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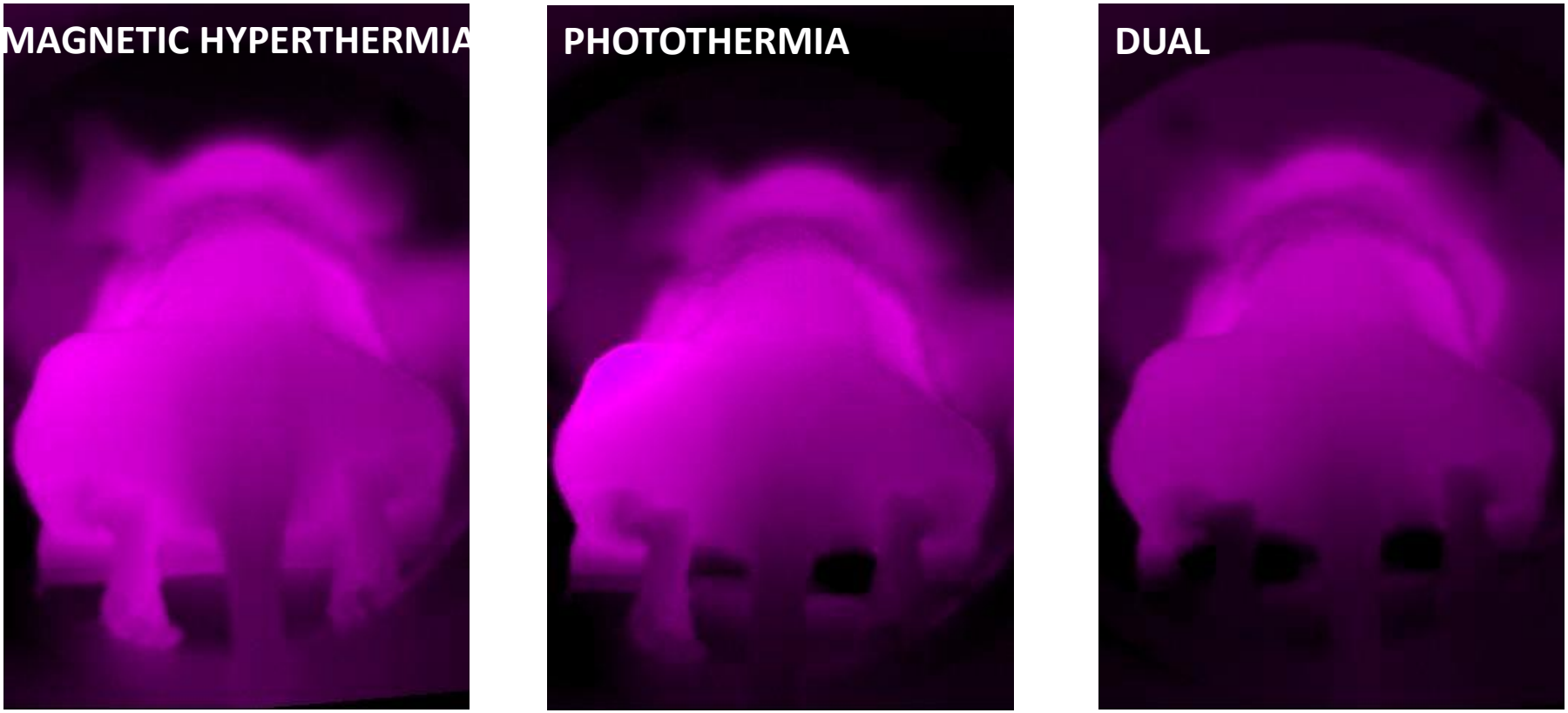
MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY ?

strategy 2 = Iron oxide nanoparticles only

TREATMENT in TUMORS : CUMULATIVE HEATING



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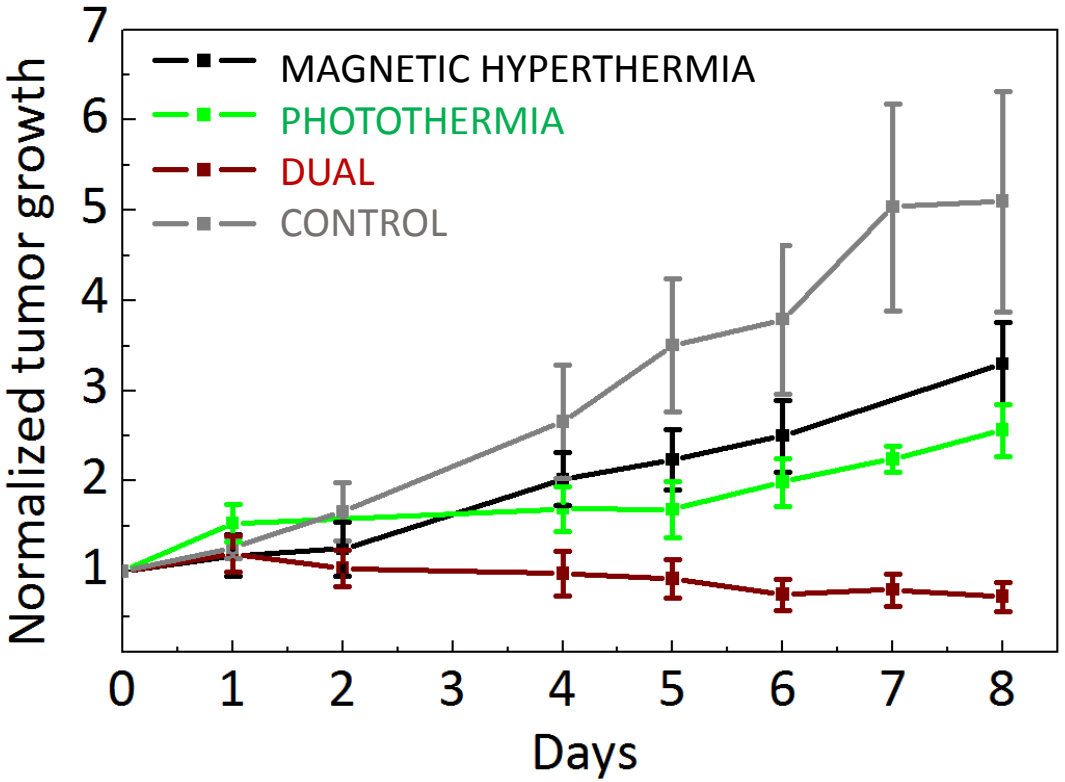
MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY ?

strategy 2 = Iron oxide nanoparticles only

TREATMENT in TUMORS: TUMOR REGRESSION / ABLATION



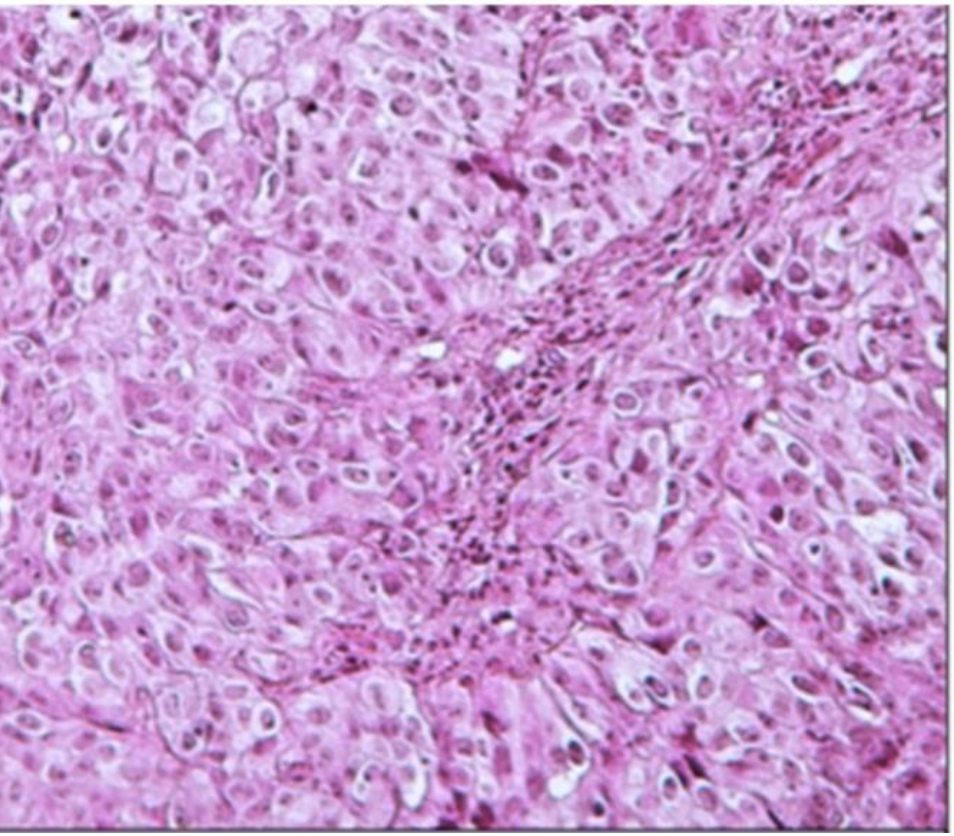
Duality of Iron Oxide Nanoparticles in Cancer Therapy: Amplification of Heating Efficiency by Magnetic Hyperthermia and Photothermal Bimodal Treatment. ACS nano, 10, 7627- 38 (2016)
Espinosa A, Di Corato R, Kolosnjaj-Tabi J, Flaud P, Pellegrino T, Wilhelm C.

MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY ?

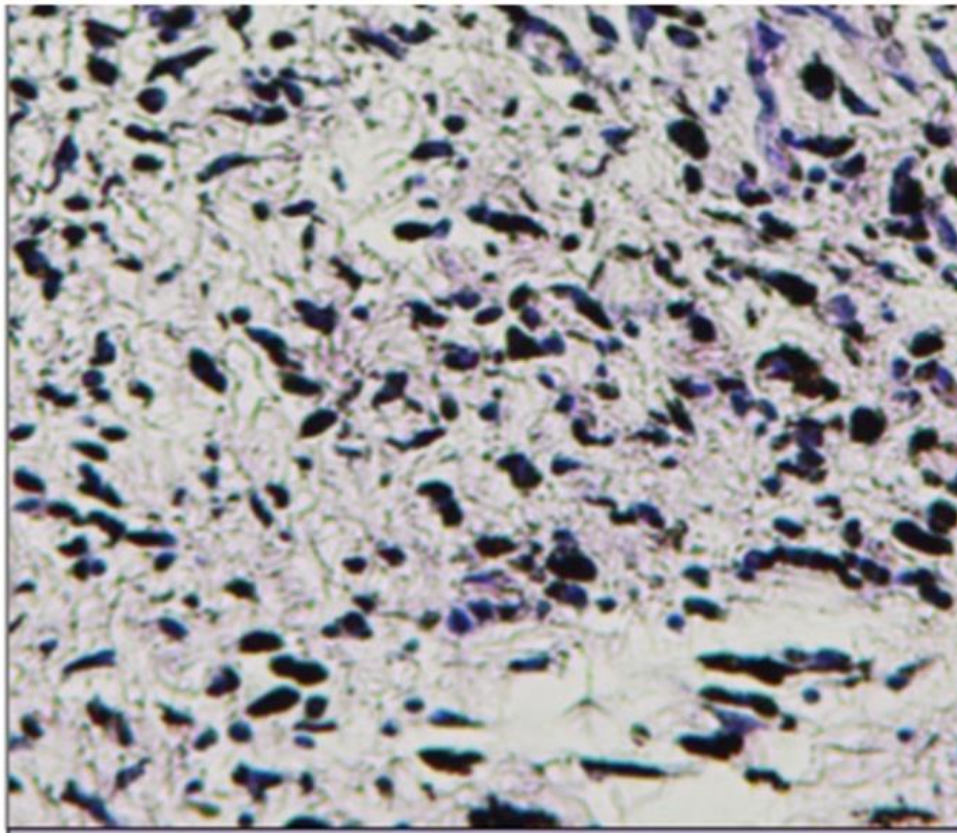
strategy 2 = Iron oxide nanoparticles only

TREATMENT in TUMORS: TUMOR REGRESSION / ABLATION

complete tumor eradication



CONTROL (no injection, no hyperthermia)



DUAL

Duality of Iron Oxide Nanoparticles in Cancer Therapy: Amplification of Heating Efficiency by Magnetic Hyperthermia and Photothermal Bimodal Treatment. ACS nano, 10, 7627- 38 (2016)
Espinosa A, Di Corato R, Kolosnjaj-Tabi J, Flaud P, Pellegrino T, Wilhelm C.

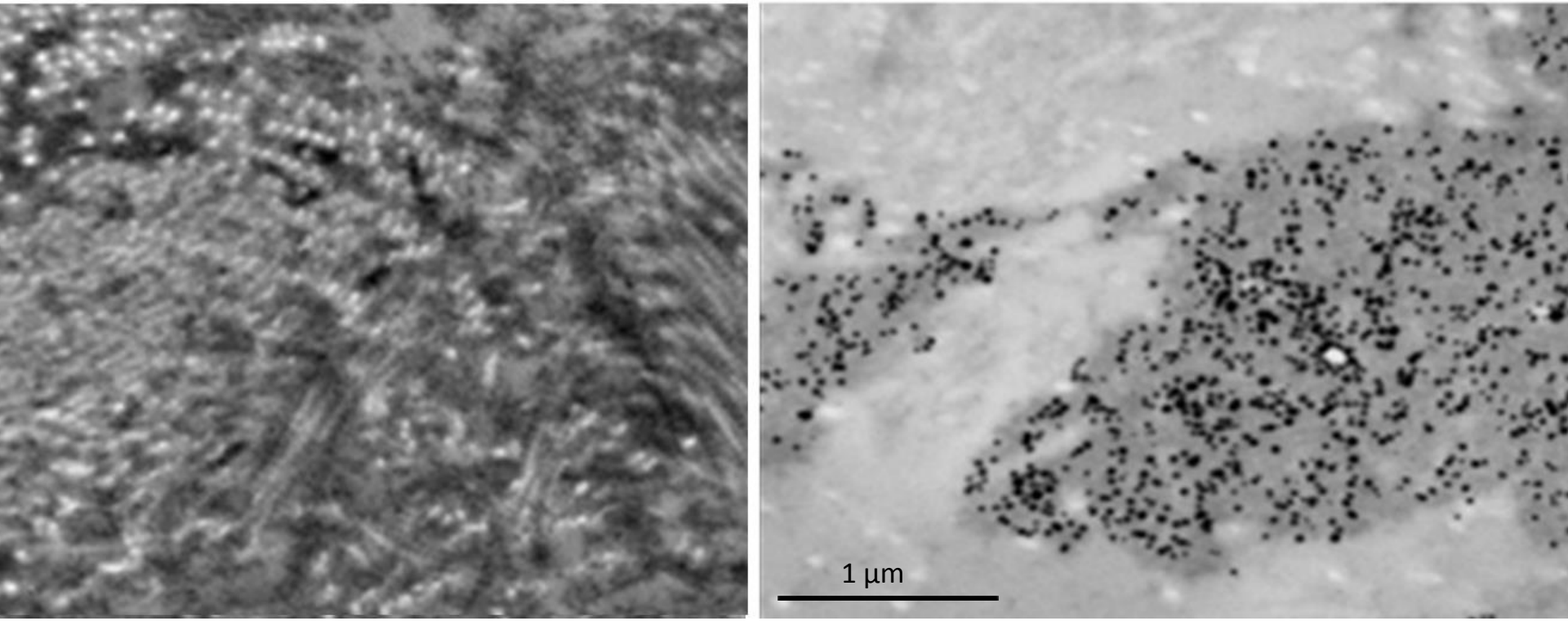
MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY ?

strategy 2 = Iron oxide nanoparticles only

TREATMENT in TUMORS: MASSIVE DAMAGES TO THE EXTRACELLULAR MATRIX

organized collagen fibers

denatured collagen fibers



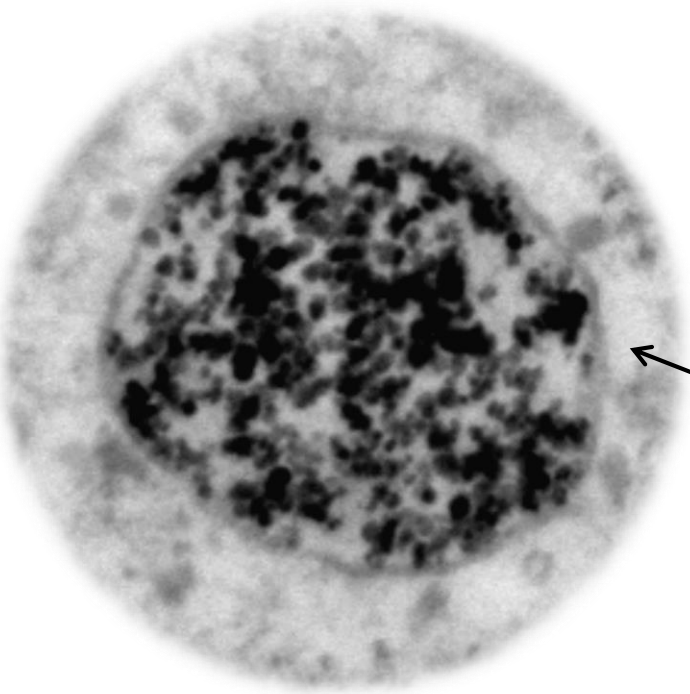
CONTROL (no injection, no hyperthermia)

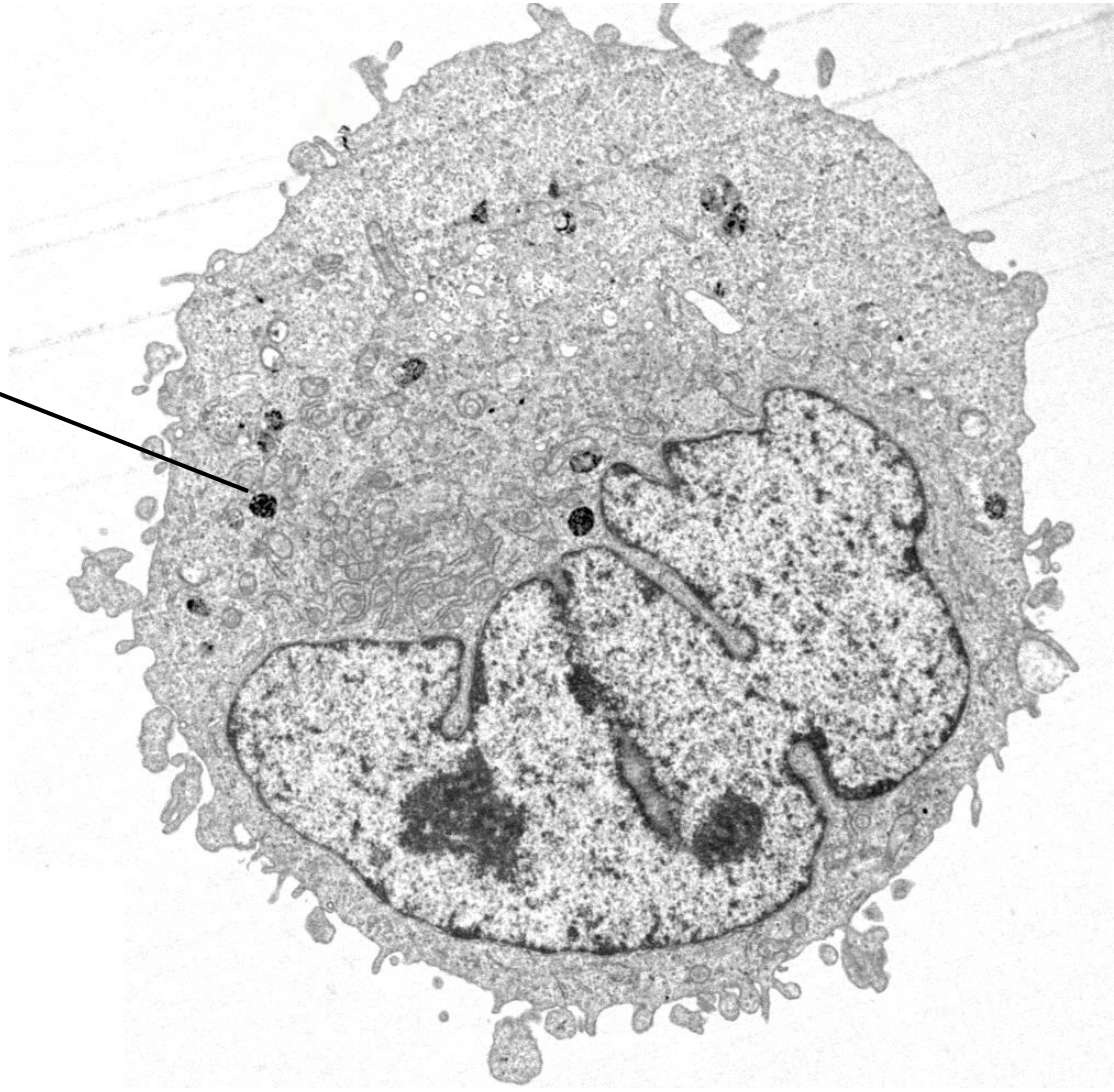
DUAL

Duality of Iron Oxide Nanoparticles in Cancer Therapy: Amplification of Heating Efficiency by Magnetic Hyperthermia and Photothermal Bimodal Treatment. ACS nano, 10, 7627- 38 (2016)
Espinosa A, Di Corato R, Kolosnjaj-Tabi J, Flaud P, Pellegrino T, Wilhelm C.

INTRACELLULAR NANOPARTICLES :

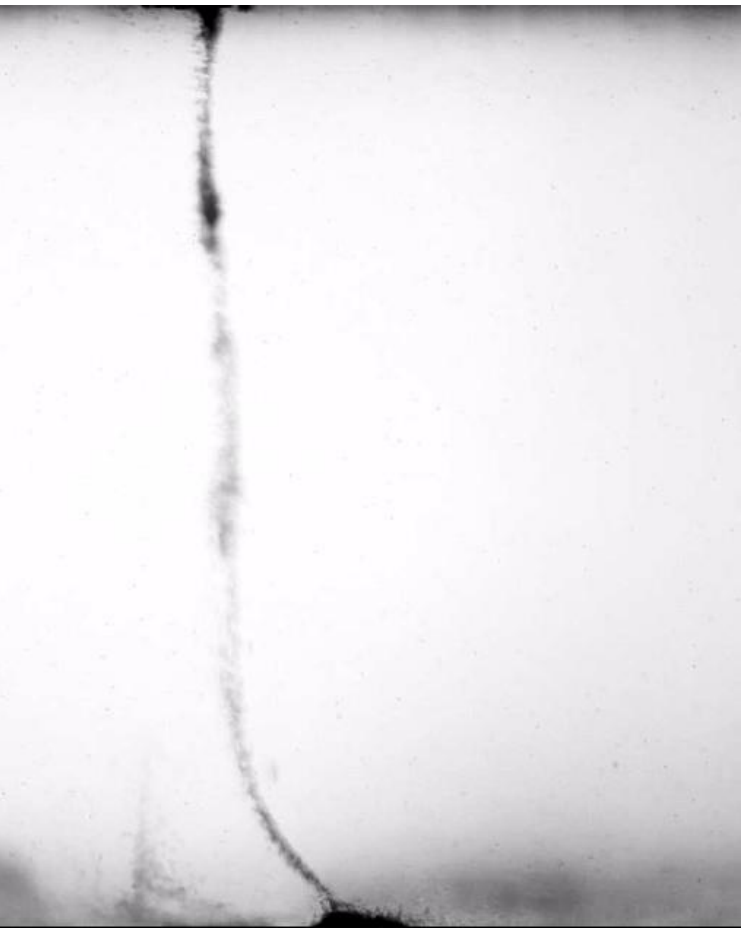
- Import inside the cells their (**multiple**) functions = **COMBINED THERAPIES**
- BUT internalization can impact their thermal efficiency = ***IN SITU*** **MEASUREMENTS**





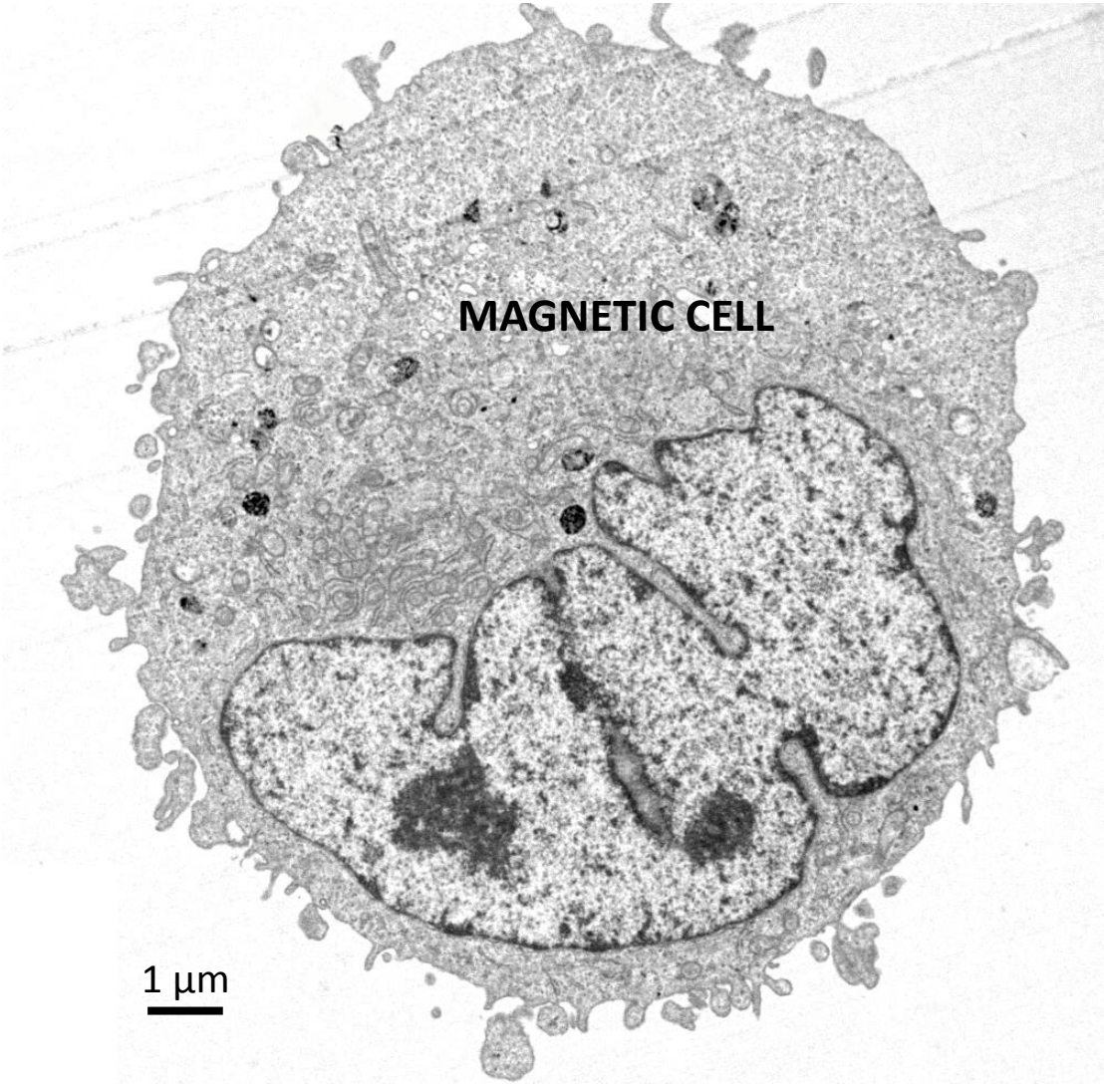
INTRACELLULAR NANOPARTICLES :

→ Provide the cells with sufficient magnetization to manipulate single cells



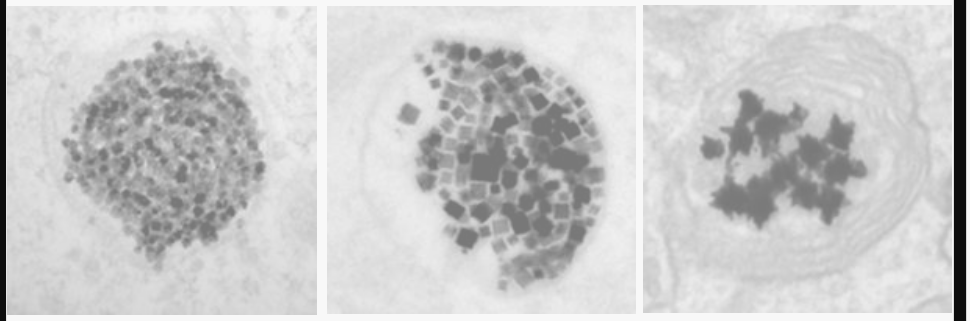
0.1 mm

MICRO-MAGNET



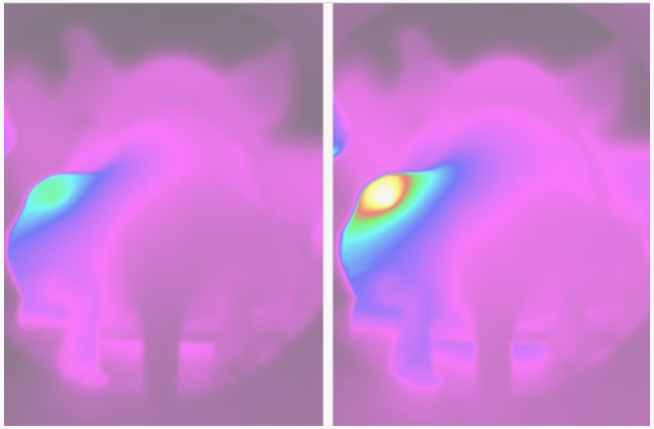
1

In situ measurements of therapeutic efficiency



2

Combined nano-therapies

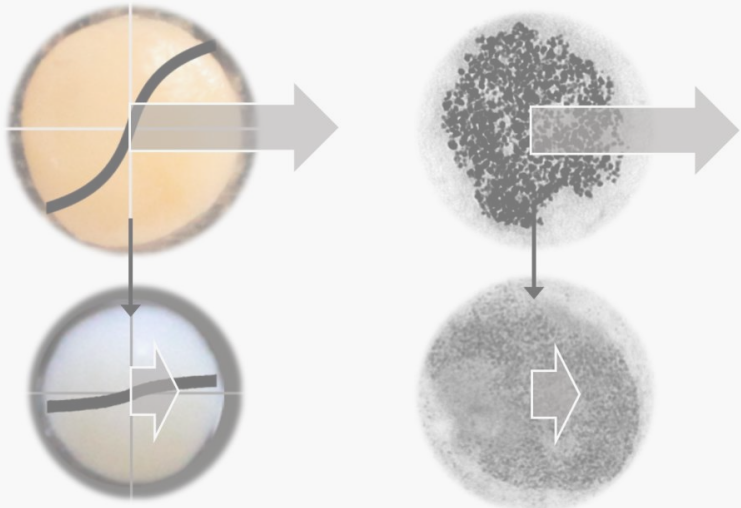


3

Magnetic tissue engineering

4

Nano-Bio-Degradation in tissues

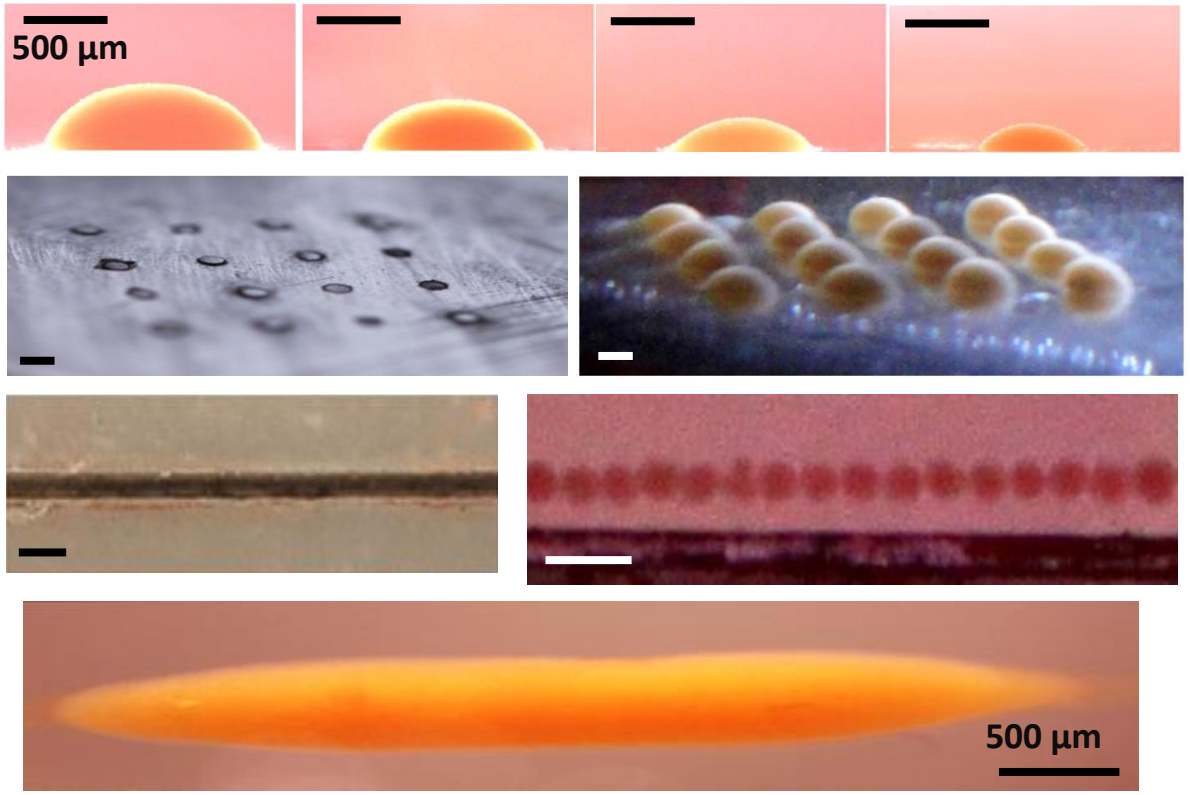


MAGNETIC CELLS MANIPULATION FOR TISSUE ENGINEERING

Magnetic cells aggregation

to build TISSUES

Various shapes and sizes



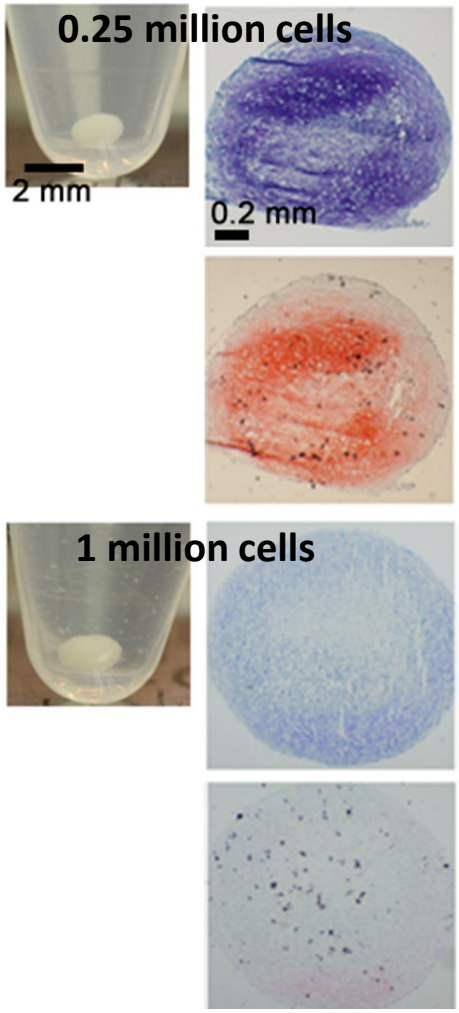
MAGNETIC TISSUE ENGINEERING

Advanced Materials **00342 (2013)** *Patent* WO2013030393 (**2013**)

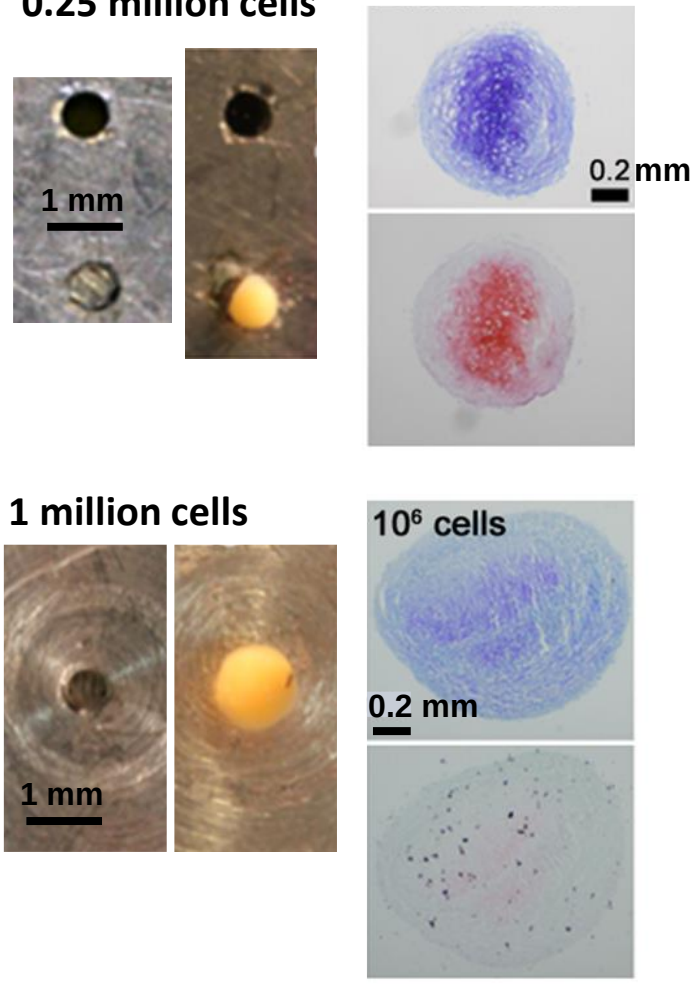
MAGNETIC CARTILAGE TISSUE ENGINEERING

LIMIT : aggregate size

Aggregation by centrifugation



Magnetic aggregation



No improvement compared to centrifugation

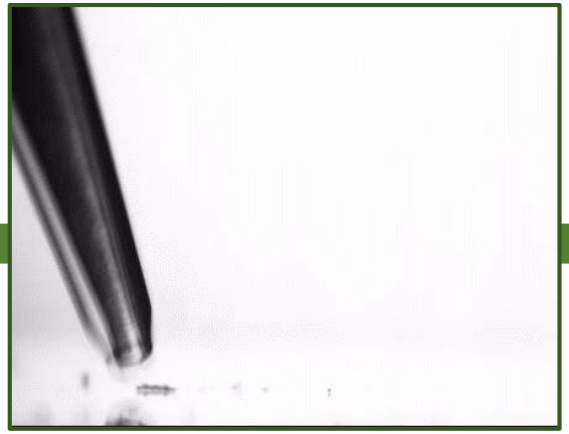
Magnetic forces promote stem cell differentiation, aggregates fusion and tissue building.
Fayol D, Frasca G, Le Visage C, Gazeau F, Luciani N, Wilhelm C. *Advanced Materials*, 25, 2611 (2013)

MAGNETIC CARTILAGE TISSUE ENGINEERING

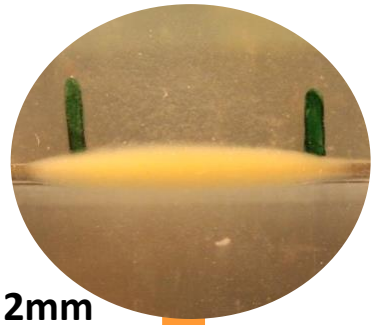
LIMIT : aggregate size

magnetic line

2mm

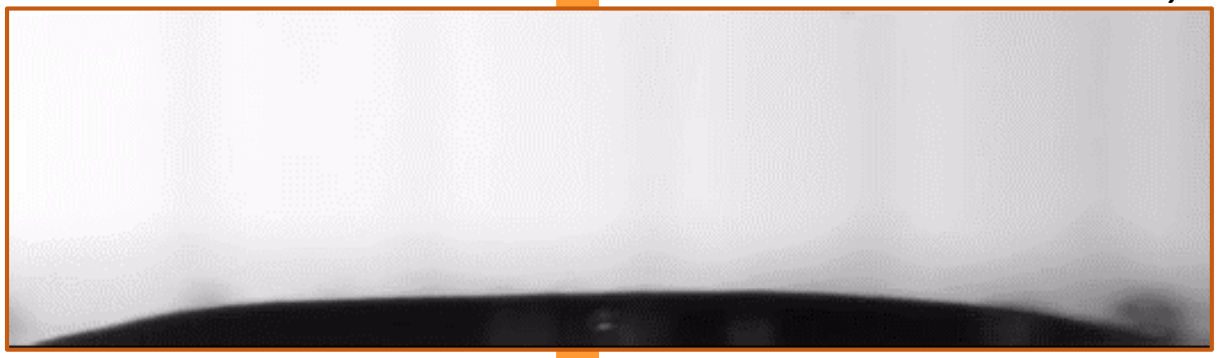


1 million cells



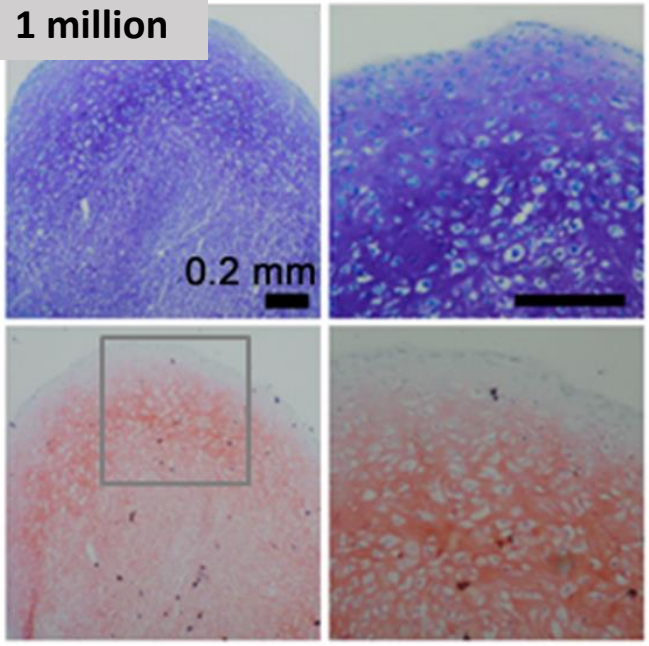
2mm

3 days



2mm

1 million



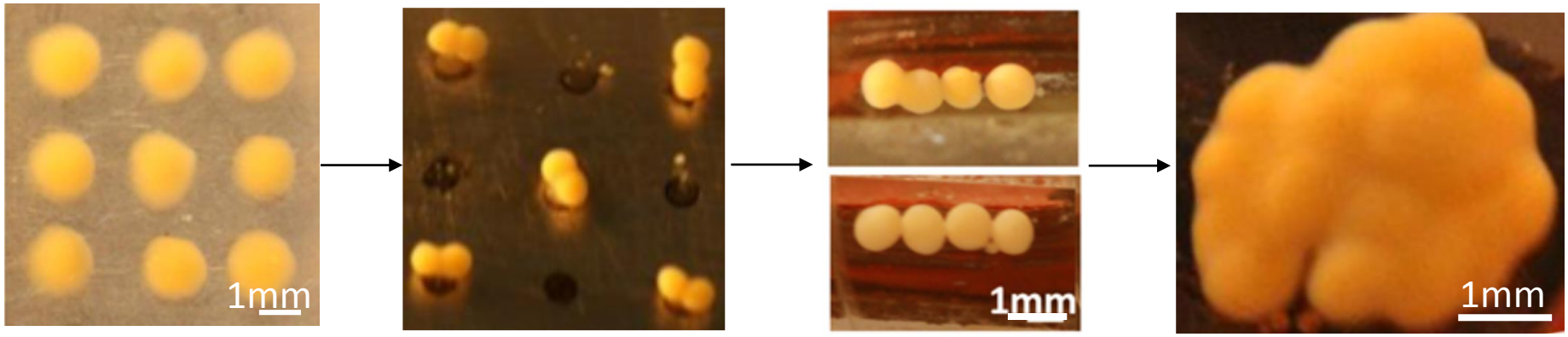
Magnetic forces promote stem cell differentiation, aggregates fusion and tissue building.
Fayol D, Frasca G, Le Visage C, Gazeau F, Luciani N, Wilhelm C. *Advanced Materials*, 25, 2611 (2013)

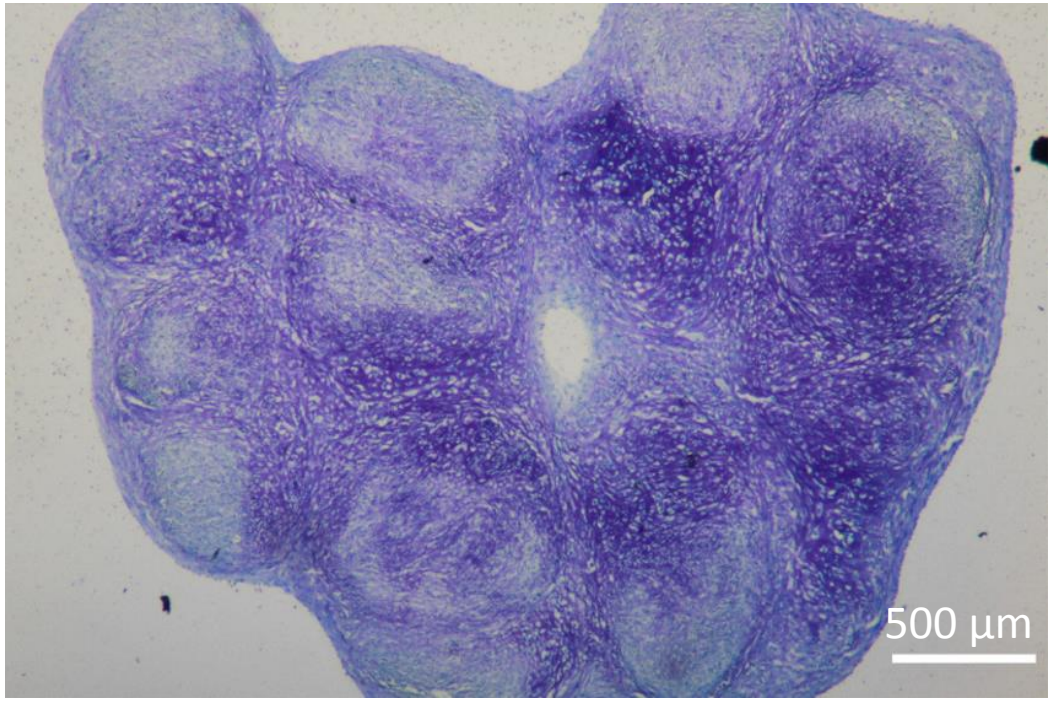
TISSUE-ROD SELF-BENDING : Shape transition was triggered by the initially non-homogeneous cell compaction

Magnetic engineering of stable rod-shaped stem cell aggregates: circumventing the pitfall of self-bending. Fayol D, Du V, Reffay M, Luciani N, Bacri J-C, Gay C, Wilhelm C. *Integrative Biology*, 7, 170-177 (2015)

MAGNETIC CARTILAGE TISSUE ENGINEERING

Sequential formation of 3D thick cartilage tissues



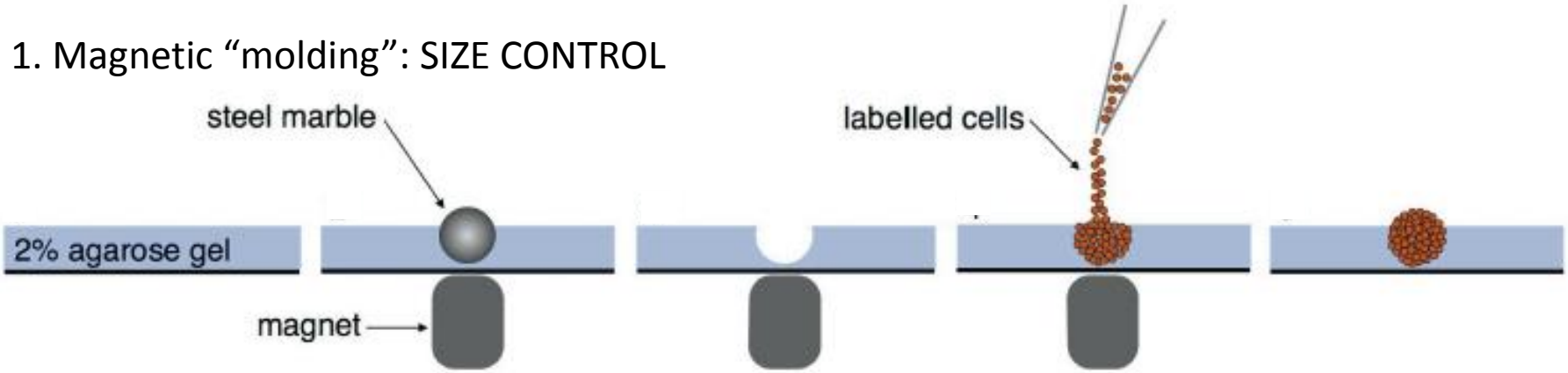


Patent. Methods for aggregation and differentiation of magnetized stem cells. WO2013030393 (2013)

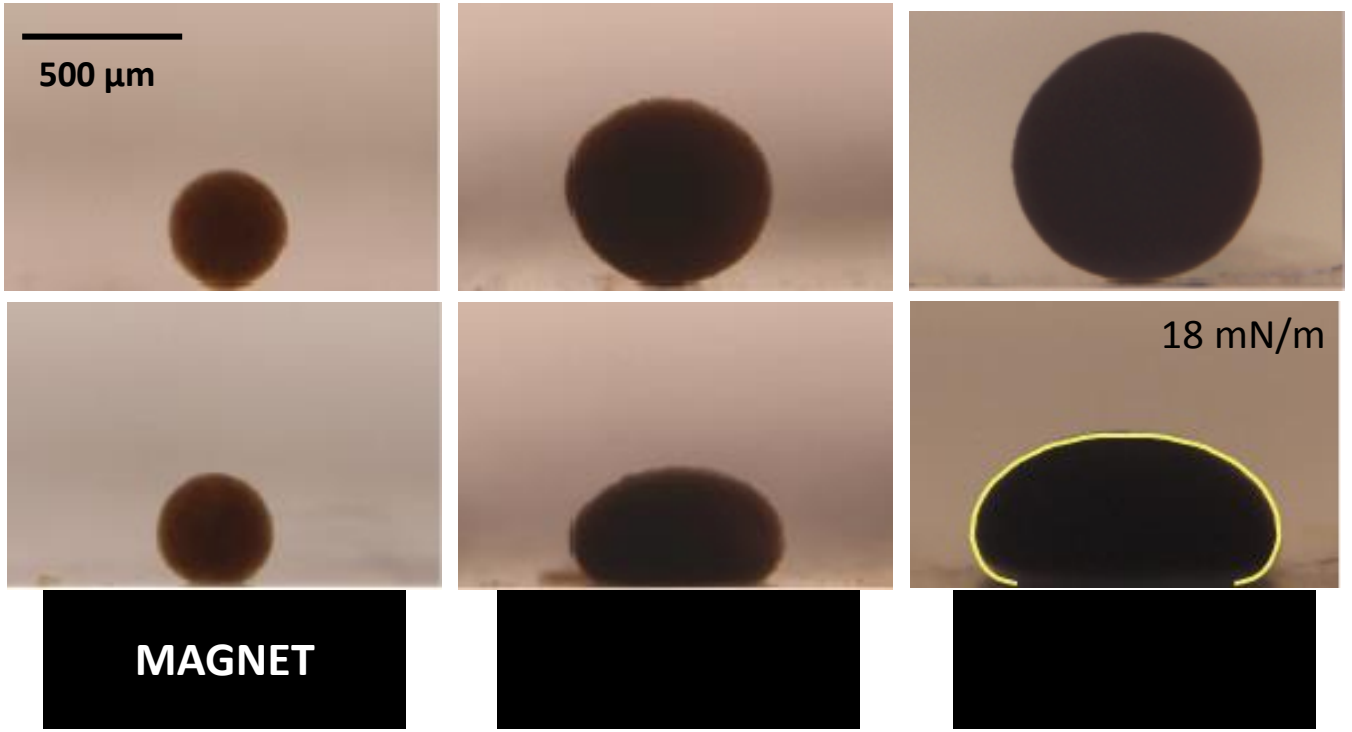
Magnetic forces promote stem cell differentiation, aggregates fusion and tissue building.
Fayol D, Frasca G, Le Visage C, Gazeau F, Luciani N, Wilhelm C. *Advanced Materials*, 25, 2611 (2013)

MAGNETIC SPHEROIDS IN BIOPHYSICS

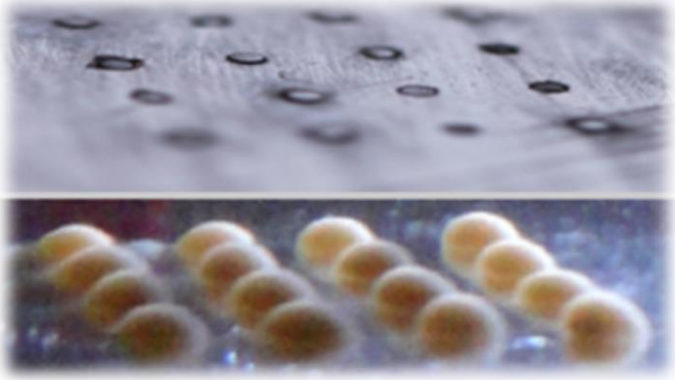
1. Magnetic “molding”: SIZE CONTROL

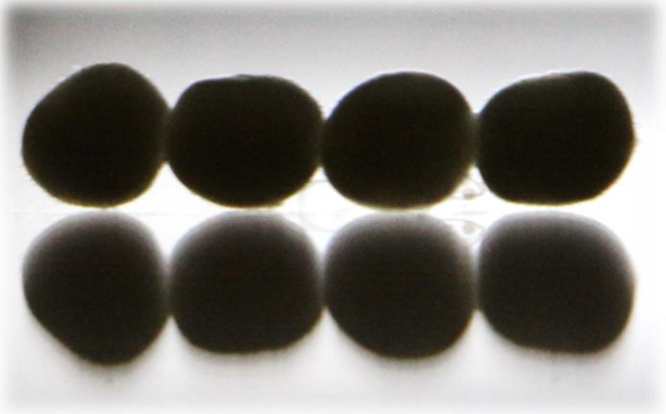


2. Magnetic “supergravity” to flatten the spheroids and retrieve the surface tension



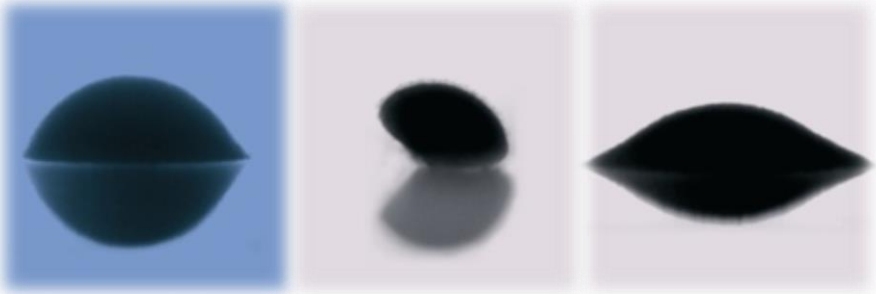
Magnetic flattening of stem-cell spheroids indicates a size-dependent elastocapillary transition.
Mazuel F, Reffay M, Du V, Bacri J-C, Rieu J-P, Wilhelm C. *Phys Rev Lett*, 114, 098105 (2015).

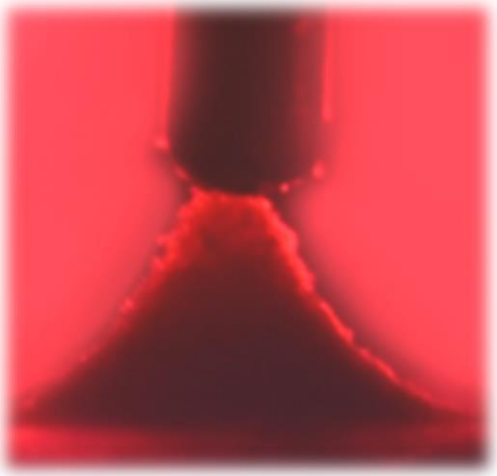




MAGNETIC approaches to tissue engineering and manipulation, in which **magnetic forces** are created **intracellularly** on **internalized magnetic nanoparticles** and used to **manipulate single cells** within a **3D construct**, allow

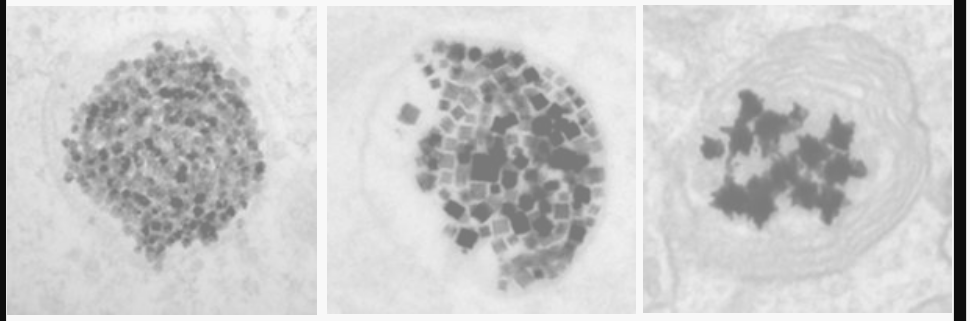
producing 3D organized artificial tissues with an inherent capacity for further physical stimulation





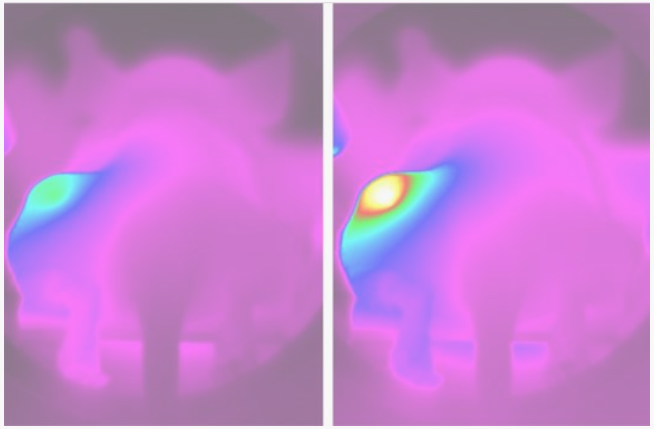
1

In situ measurements of therapeutic efficiency



2

Combined nano-therapies

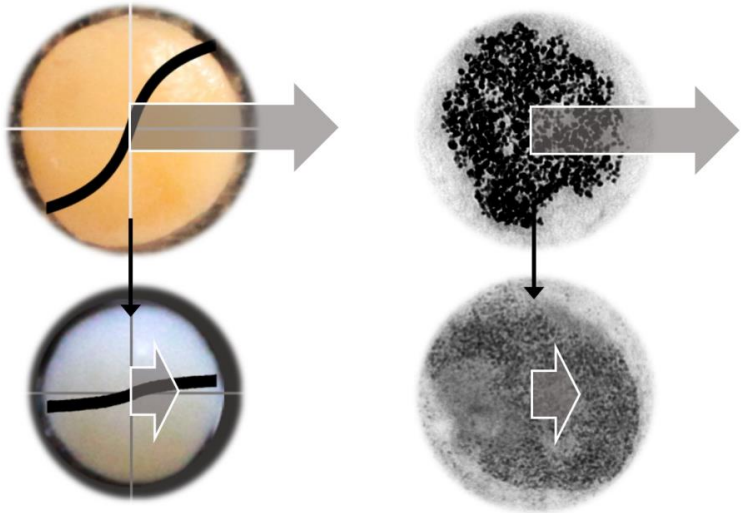


3

Magnetic tissue engineering

4

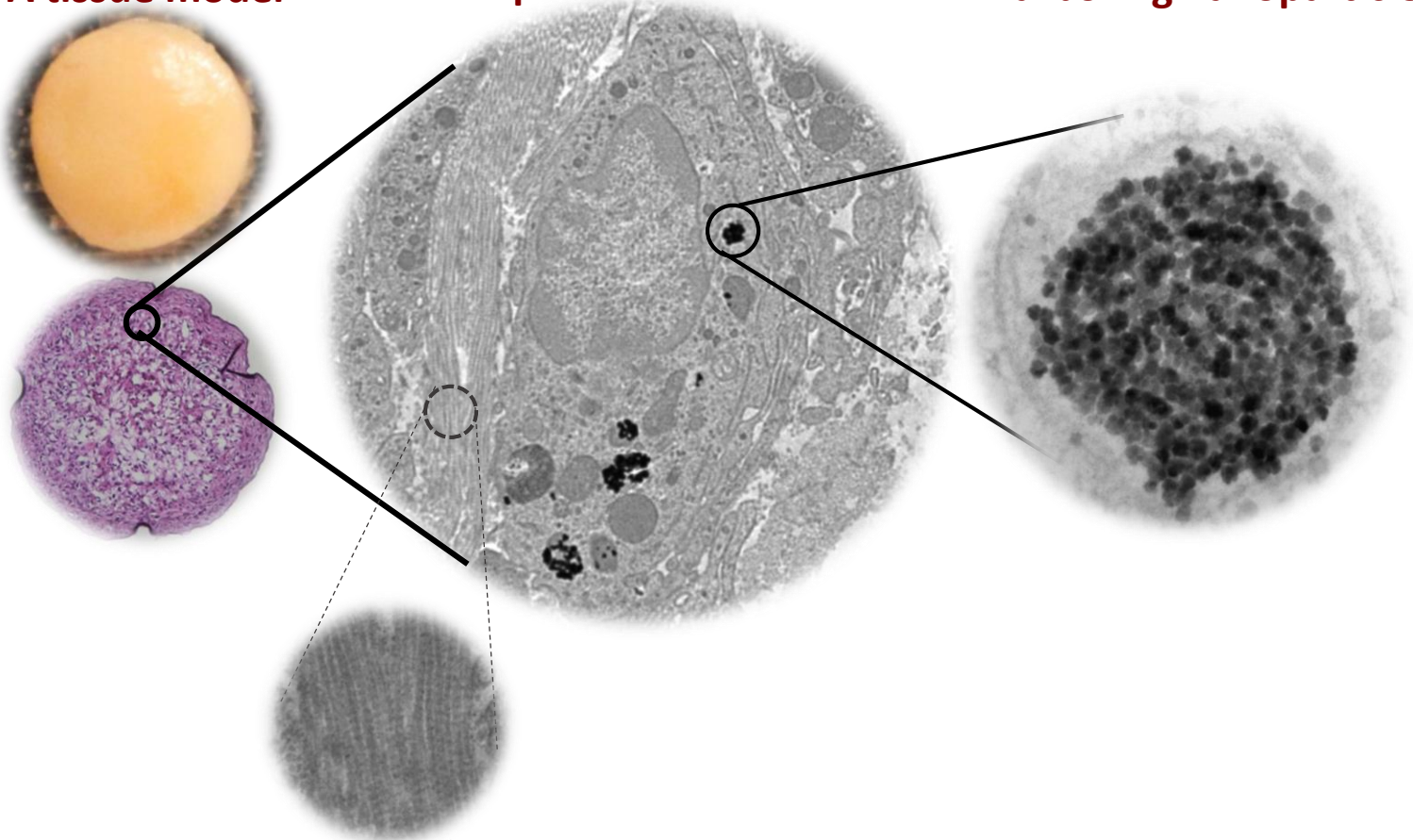
Nano-Bio-Degradation in tissues



REMAINING ISSUE : WHAT IS THE TISSULAR FATE OF THE NANOPARTICLES ?

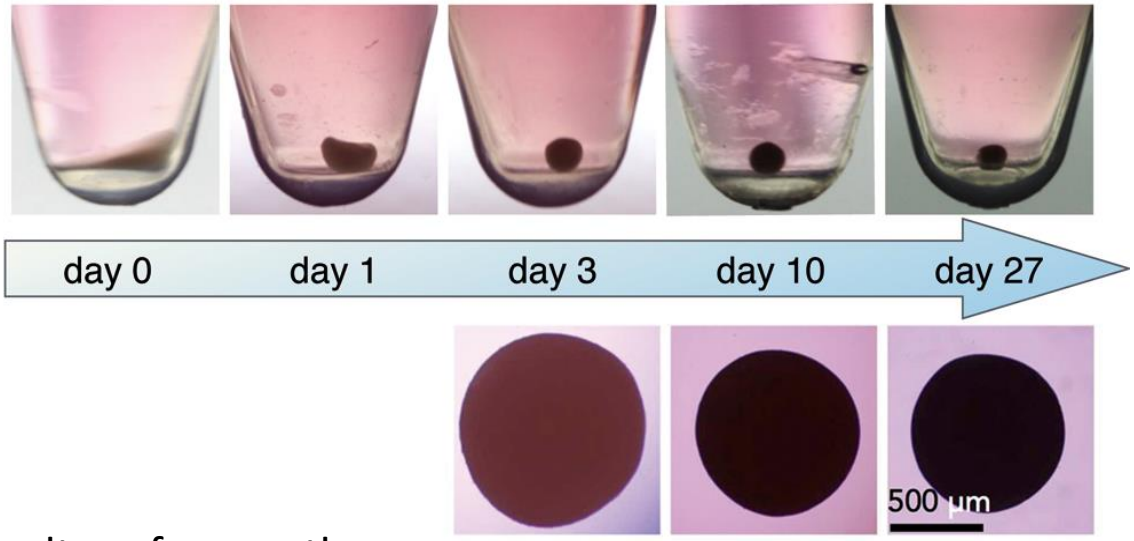
Quantitative, **multiscale nanometrologies** to track the **transformation – degradation** of **nanoparticles in tissue environments**

SPHEROIDS:
A tissue model **composed of stem cells** **harboring nanoparticles**

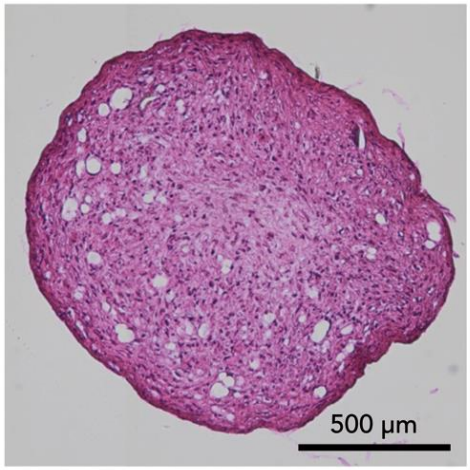


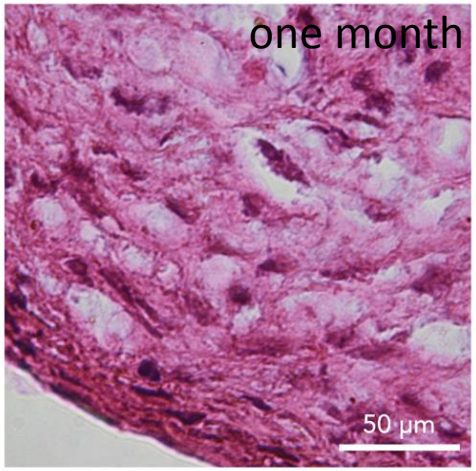
collagen fibers

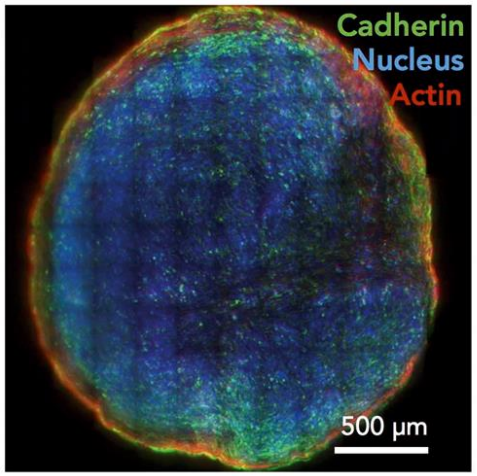
Multicellular spheroids to monitor (intra)cellular nano-transformations during tissue maturation

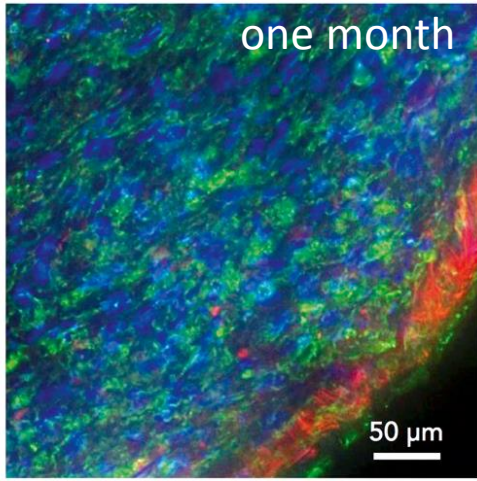


A viable tissue in culture for months



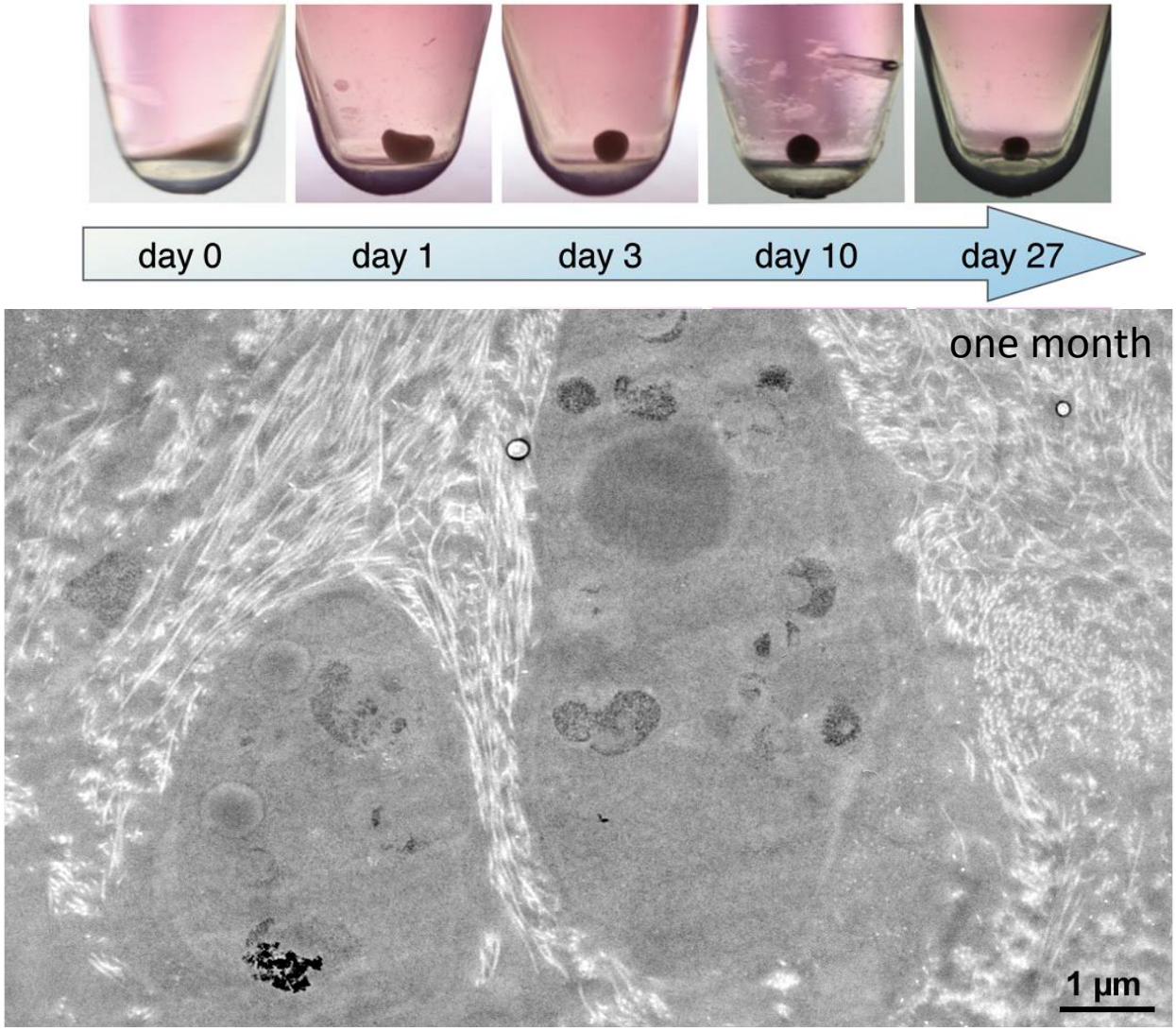






Massive Intracellular Biodegradation of Iron Oxide Nanoparticles Evidenced Magnetically at Single Endosome and Tissue Levels. Mazuel F, Espinosa A, Luciani N, Michel A, Le Borgne R, Desboeufs K, Motte L, Pellegrino T, Reffay M, Lalatonne Y, Wilhelm C. *ACS nano*, 10, 7627-7638 (2016).

Multicellular spheroids to monitor (intra)cellular nano-transformations during tissue maturation



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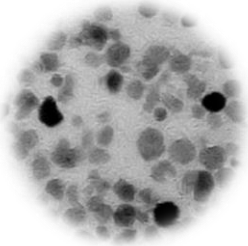
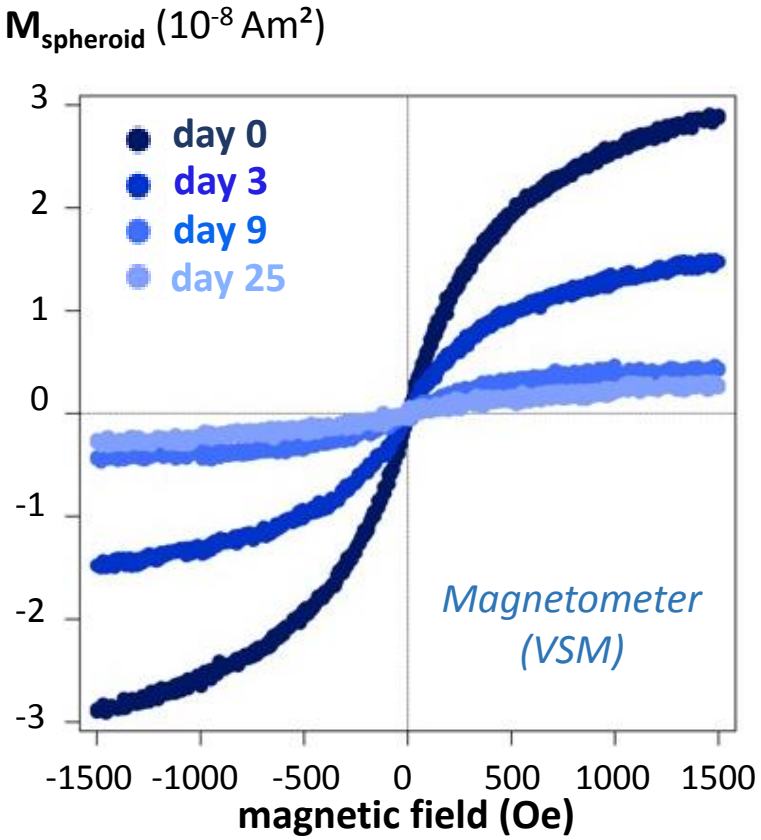
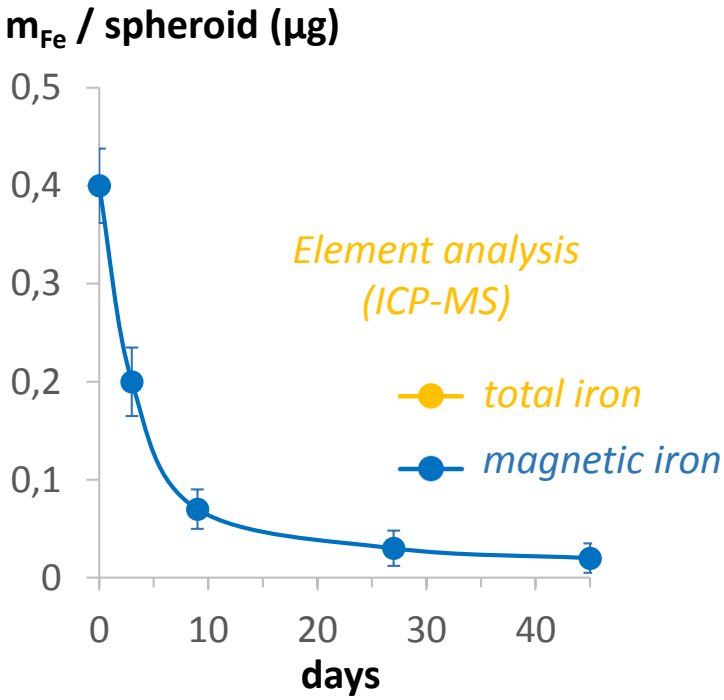
Magnetic quantitative signature of (intra)cellular nano-transformations at the tissue scale

Iron oxide nanoparticles







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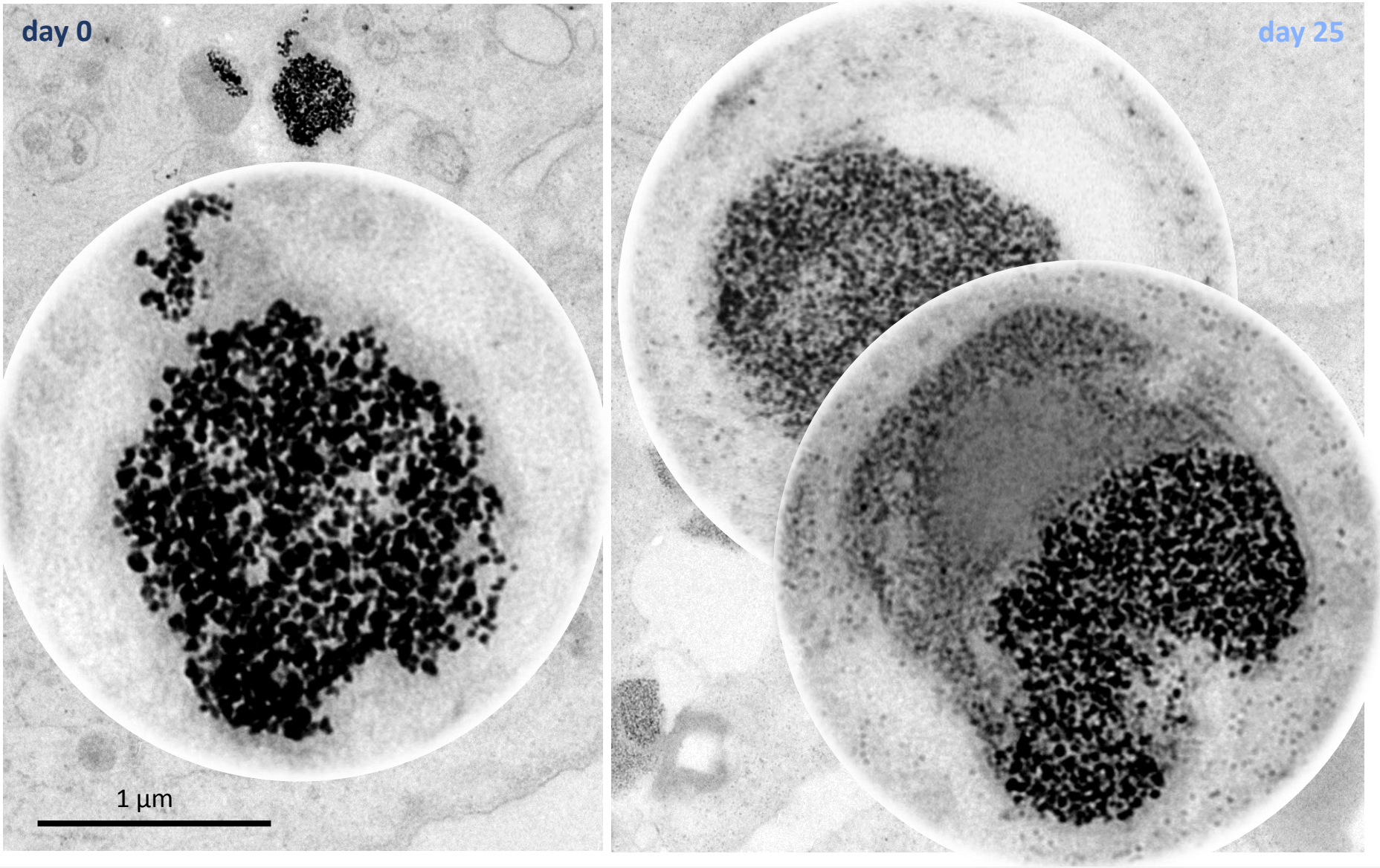
Nanoscale signature of (intra)cellular nano-transformations



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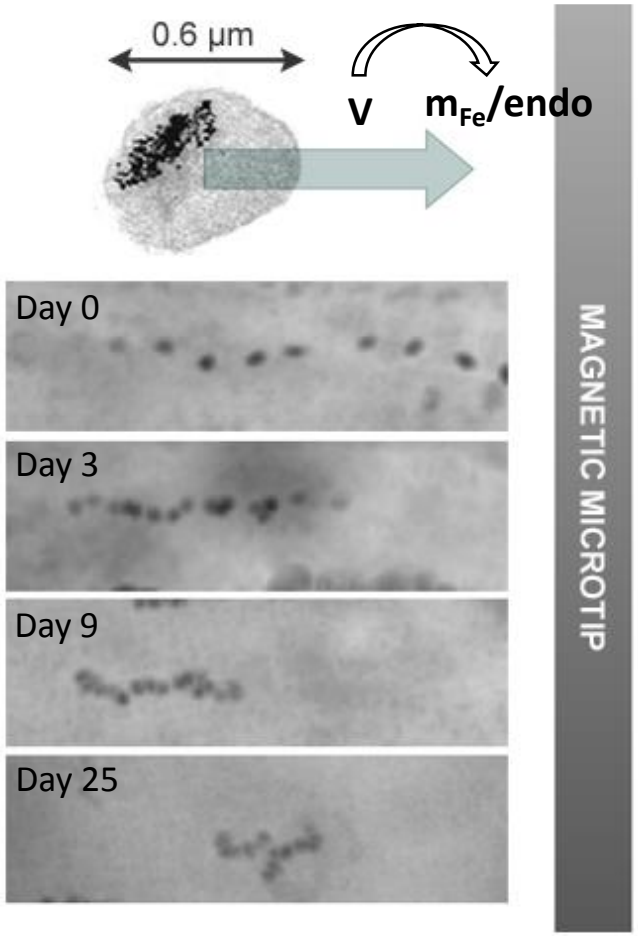
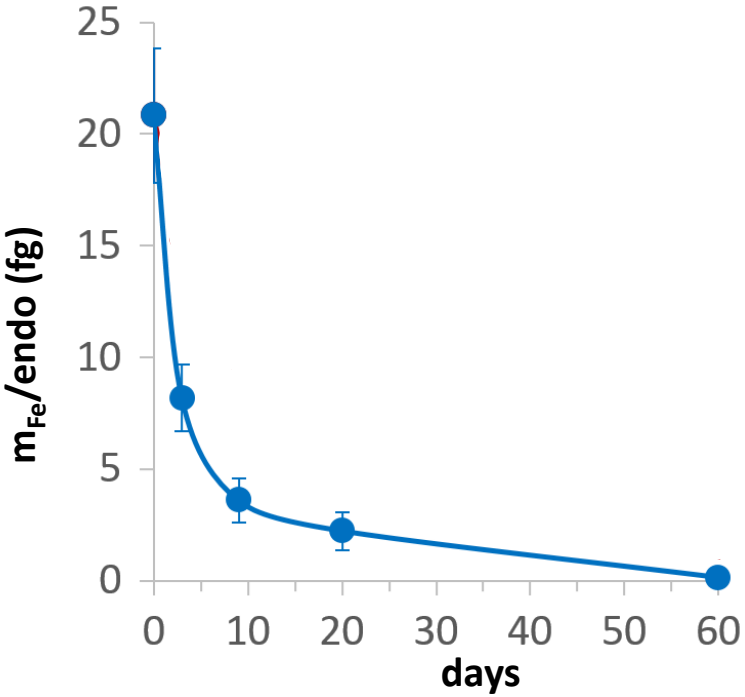
Intra-ENDOSOMAL degradation

magnetic purification of nanoparticles-loaded endosomes





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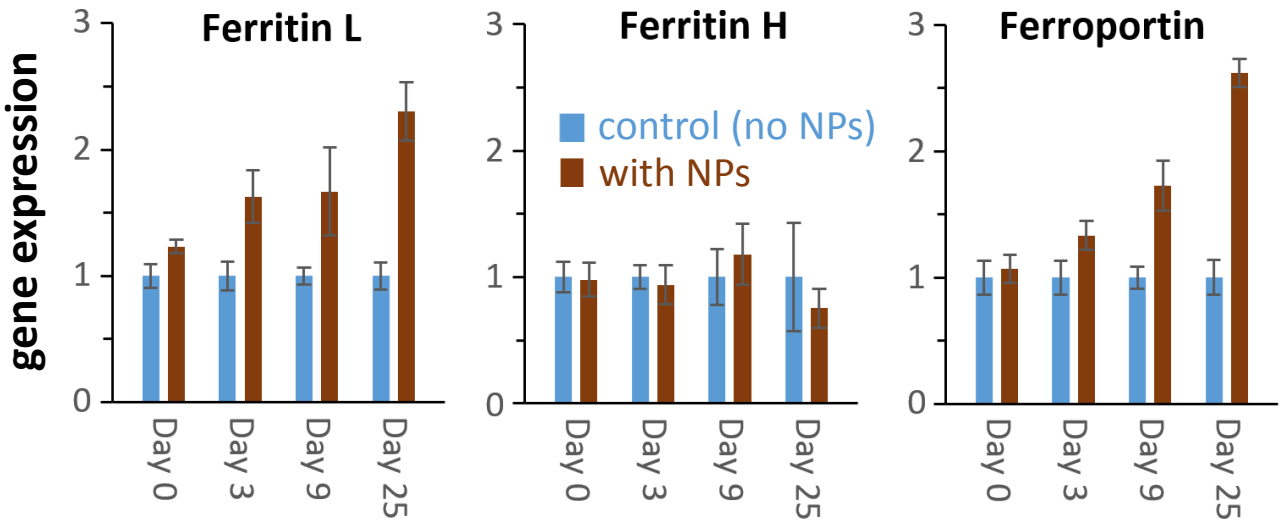
Biological monitoring of iron homeostasis



Only Ferritin Light chain (iron binding and nucleation of the iron core) and **Ferroportin** (iron transport from the inside to the outside) are slightly **overexpressed**.

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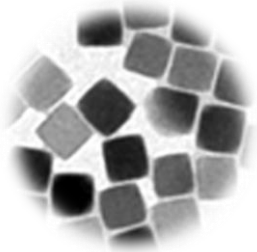
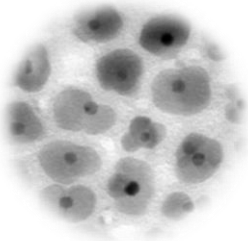
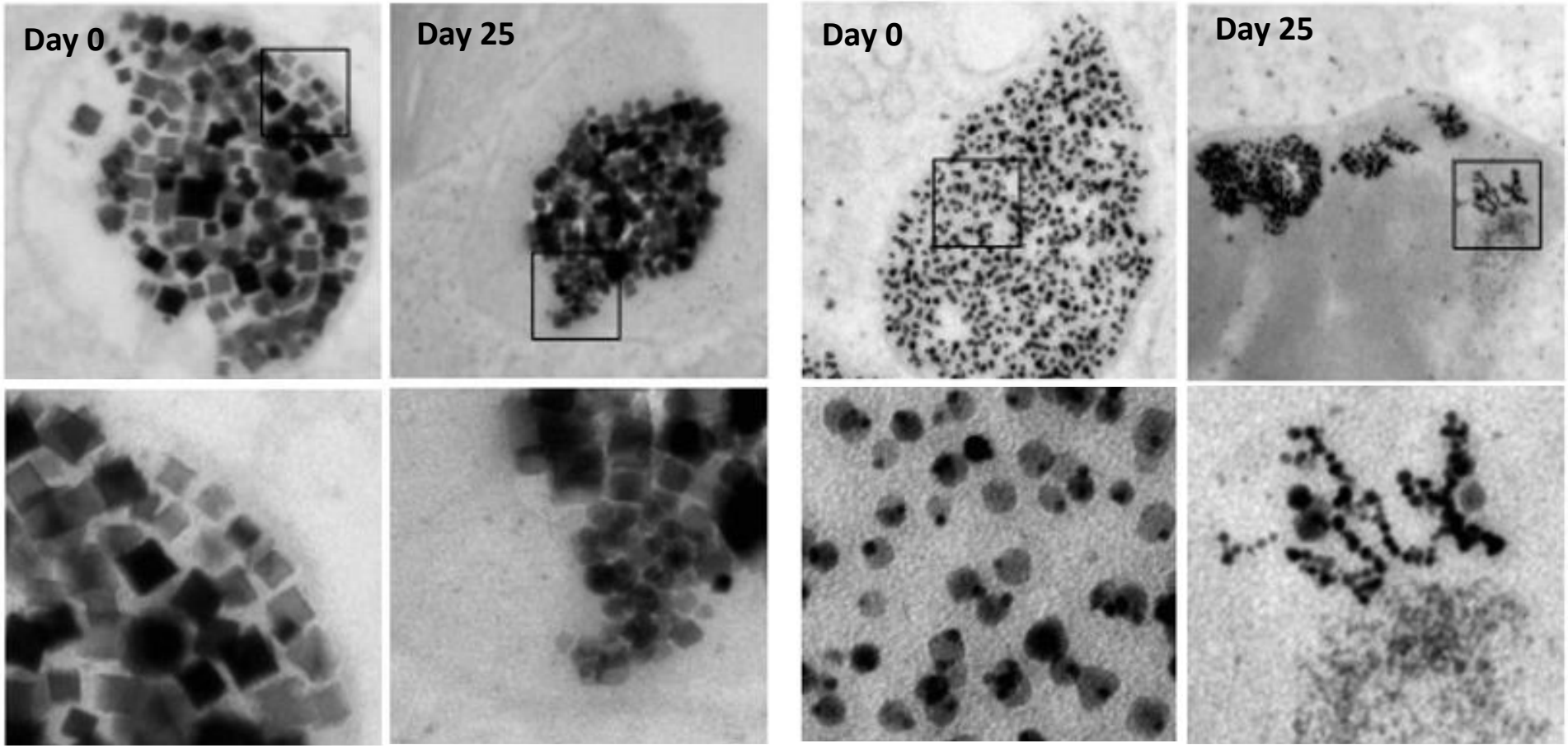
A model to be used with any magnetic nanoparticles



Nanocubes or Nanodimers as shape or composition probes to monitor their degradation at the nanoscale within the tissue





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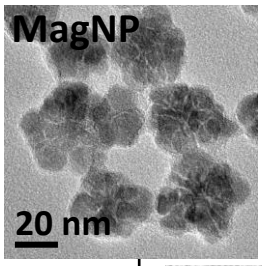
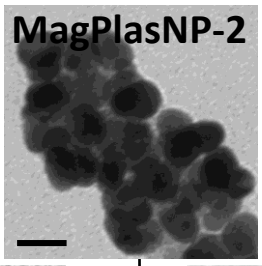
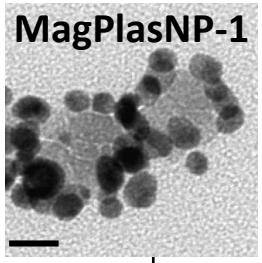
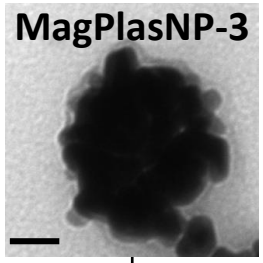
A model to be used with any magnetic nanoparticles

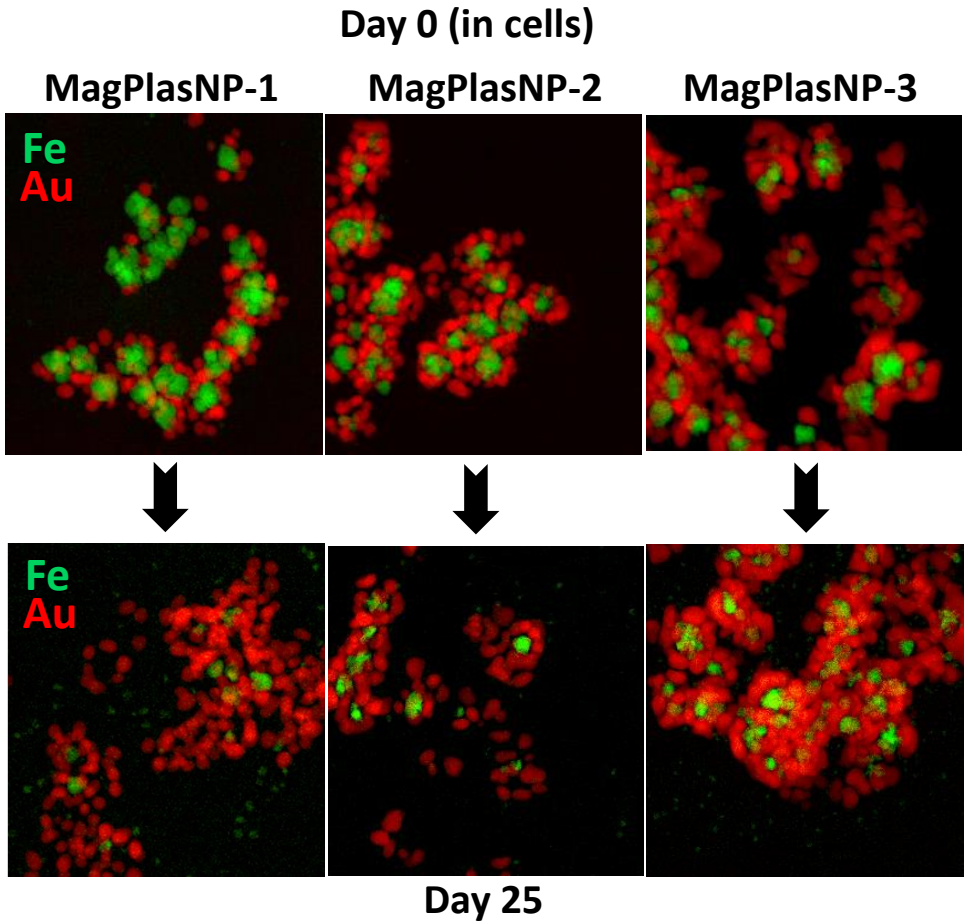
→ Gold can serve as a shield to prevent iron degradation











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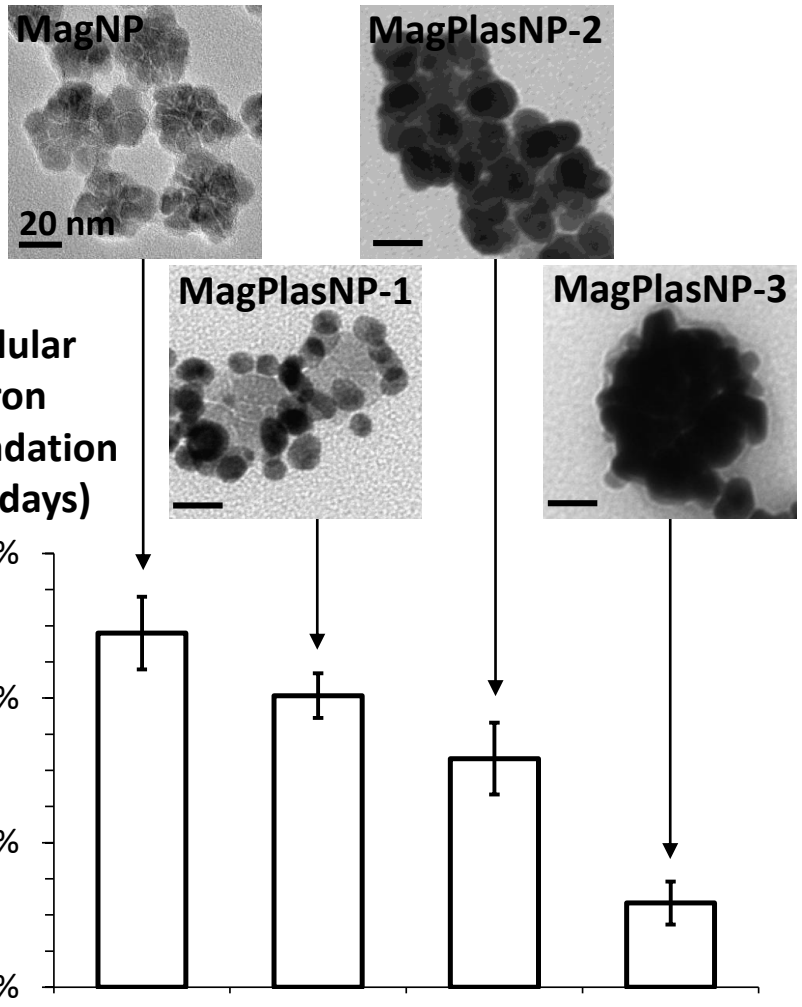

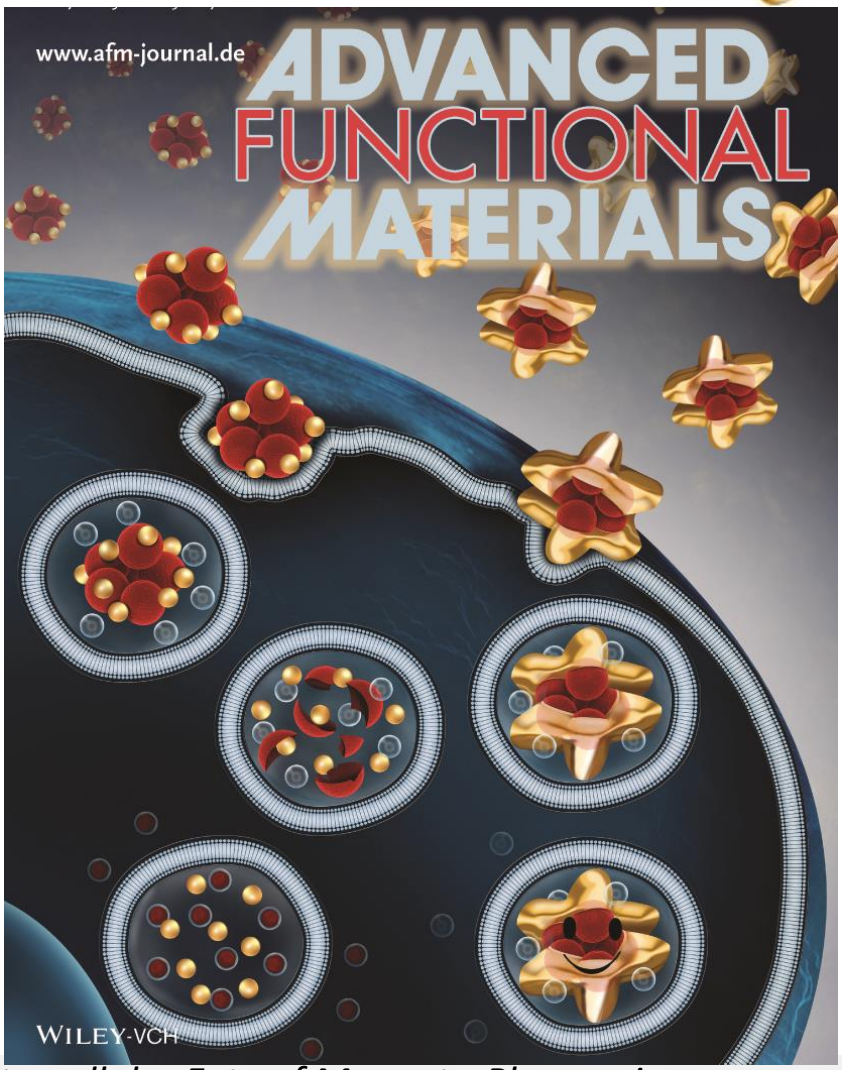

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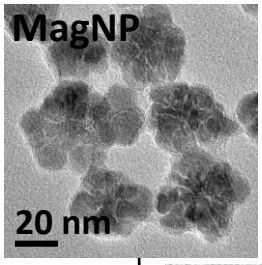
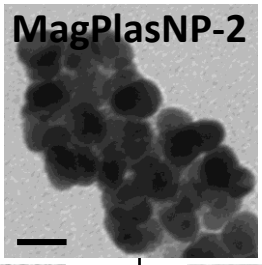
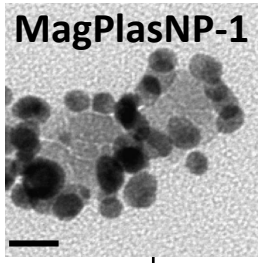
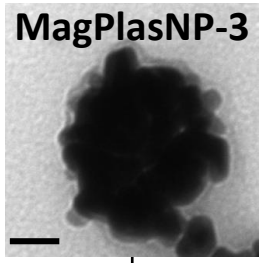
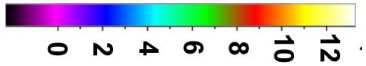


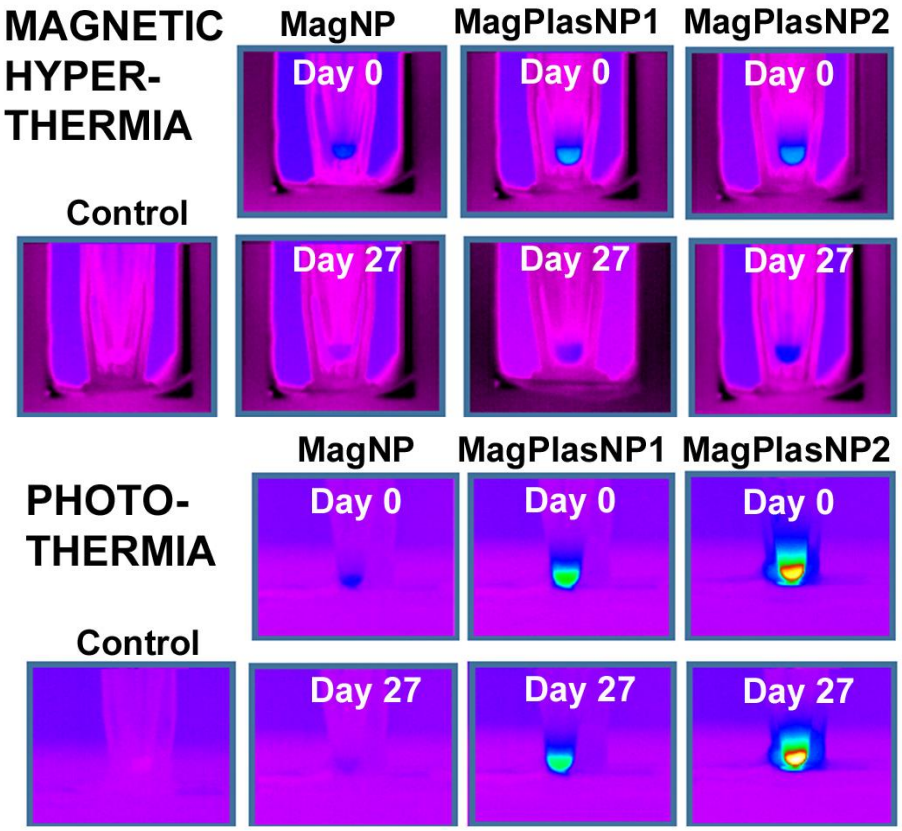






→ Magneto-Thermal Metrics to monitor biodegradation in situ





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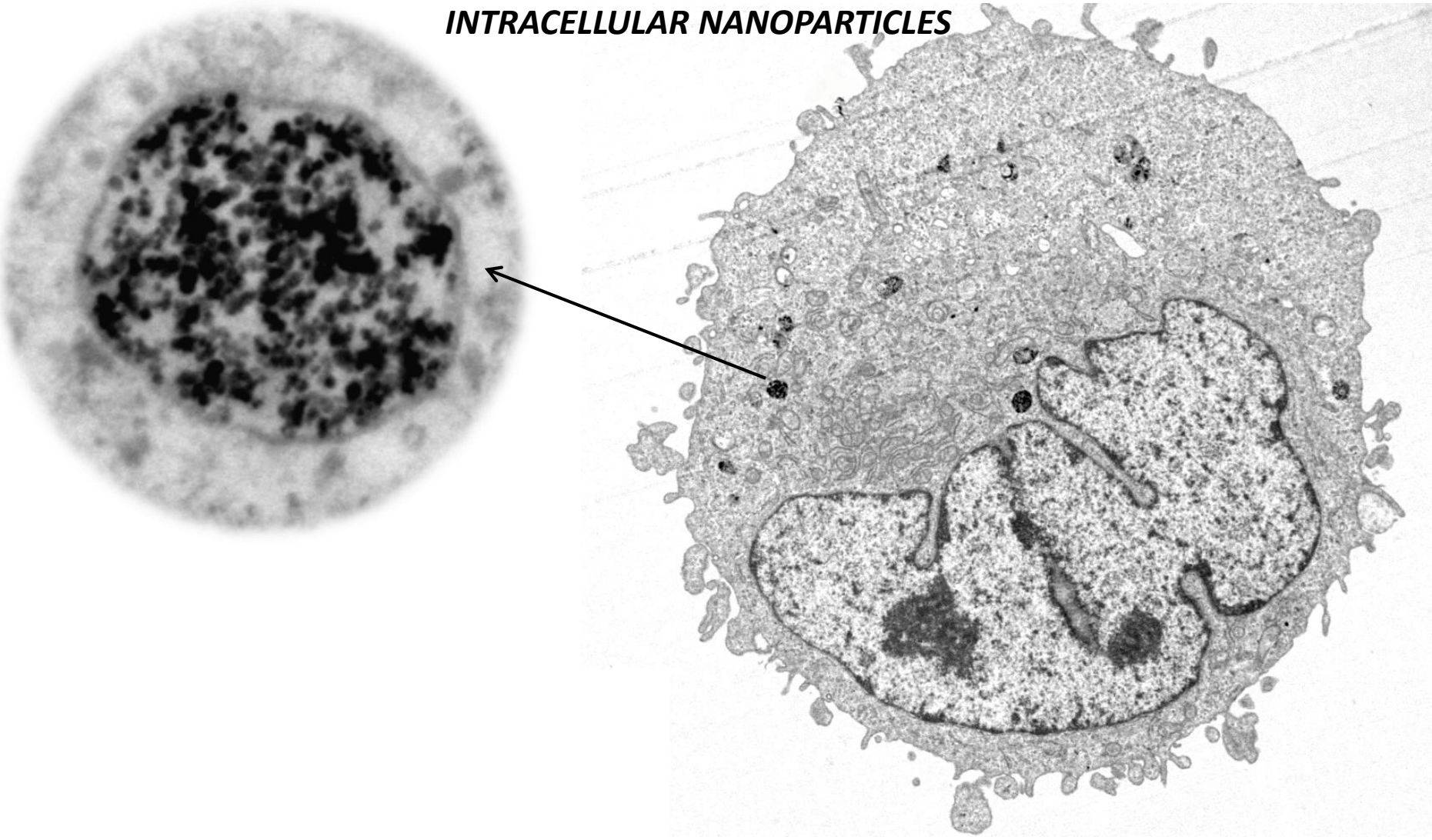
One take-home message …

INTRACELLULAR NANOPARTICLES



Nanomaterials import inside the cells their (multiple) functions : **COMBINED THERAPY / MAGNETIC TISSUE ENGINEERING**

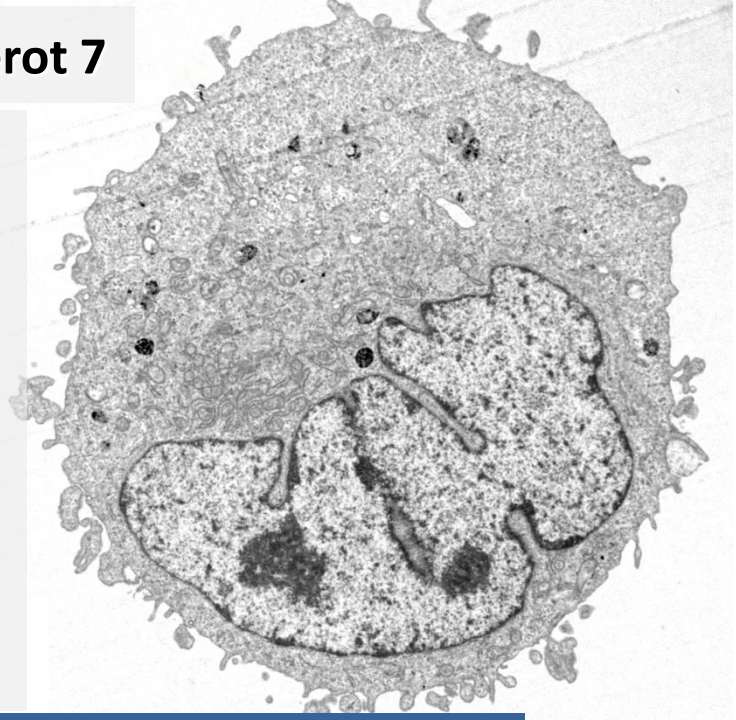
BUT internalization can impact their (thermal) therapeutic efficiency: ***IN SITU*** **MEASUREMENTS**

AND they can experience massive **INTRACELLULAR LYSOSOMAL DEGRADATION**

MSC UMR 7057, CNRS & University Paris Diderot 7

Nathalie Luciani, **Myriam Reffay**, **Amanda Silva**

Ana Espinosa, **Riccardo Di Corato**, Alberto Curcio, Sophie Richard, Aurore Van de Walle; postdocs; Anouchka Plan, Gaetan Mary, phD students; **François Mazuel**, phD 2016; **Vicard Du**, phD 2015; Kelly Aubertin, phD 2014; **Delphine Fayol**, phD 2012; Michael Levy, phD 2011; Guillaume Frasca, phD 2010, Damien Robert, phD 2010;



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NanoSciences ILE-DE-FRANCE

SEVENTH FRAMEWORK PROGRAMME

AGENCE NATIONALE DE LA RECHERCHE ANR

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