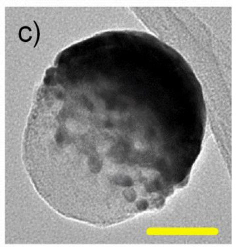
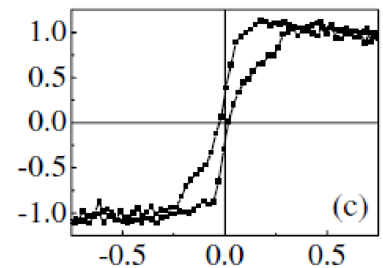
# Magnetoplasmonic Nanocapsules as Wirelessly Controlled Nanotherapies





**JOSEP NOGUÉS**



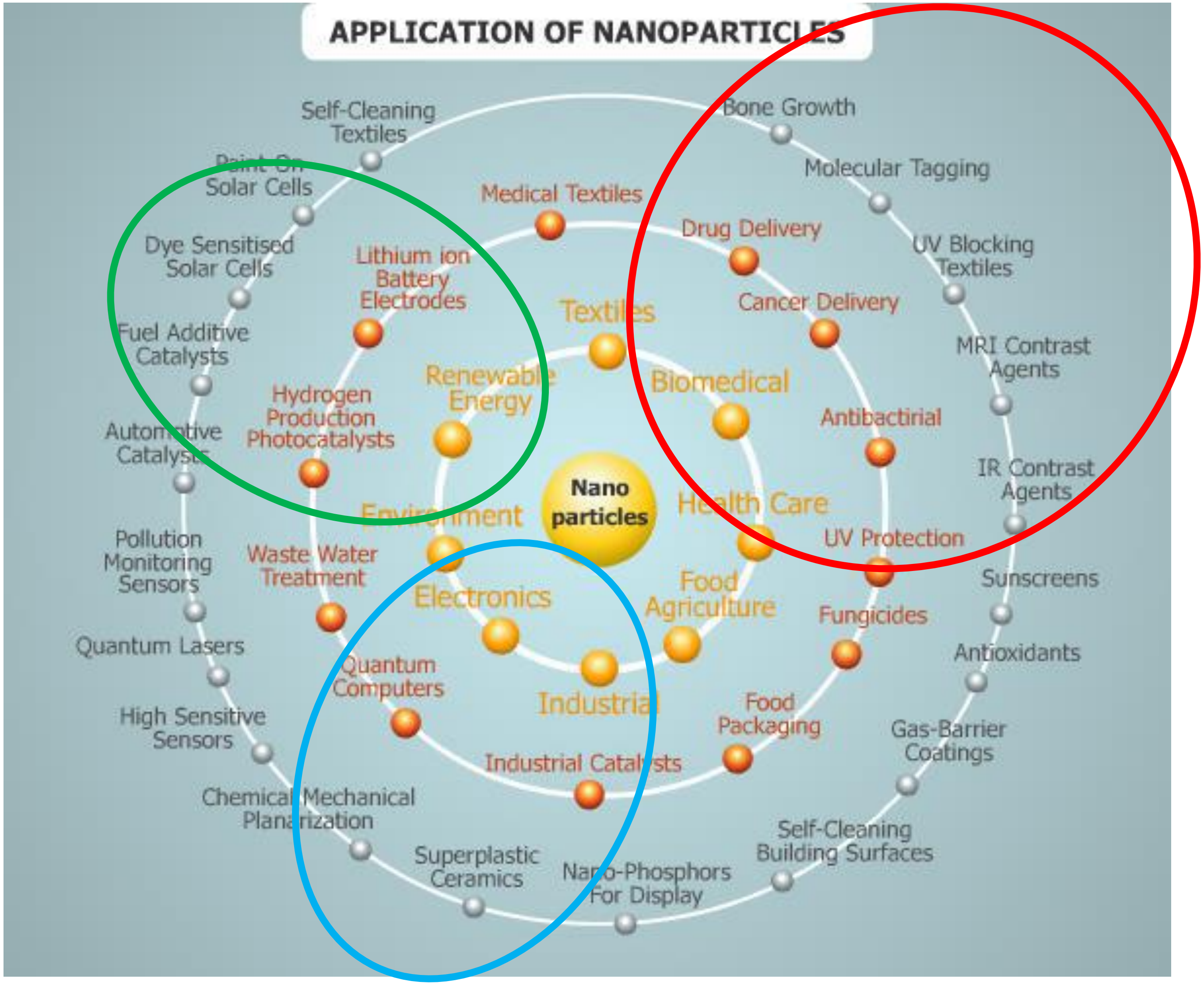
*Catalan Institute of Nanoscience and Nanotechnology (ICN2), Barcelona, Spain*

*ICREA, Barcelona, Spain*



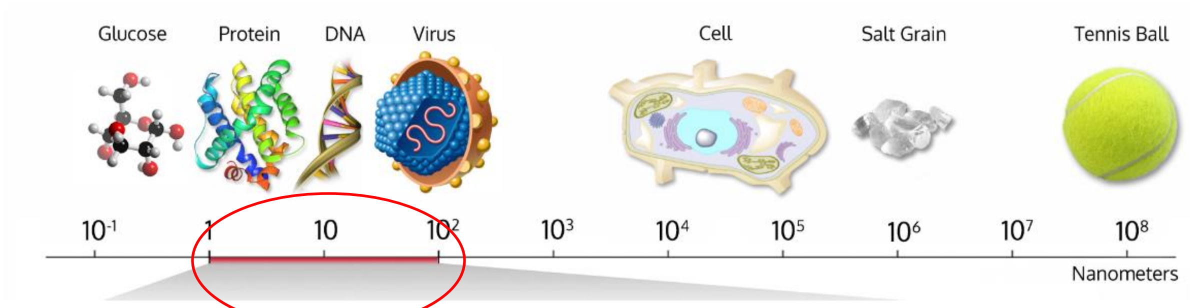
Thanks to the grant PID2022-138588OB-C32 funded by MCIN/AEI/10.13039/501100011033

# Applications of Nanoparticles



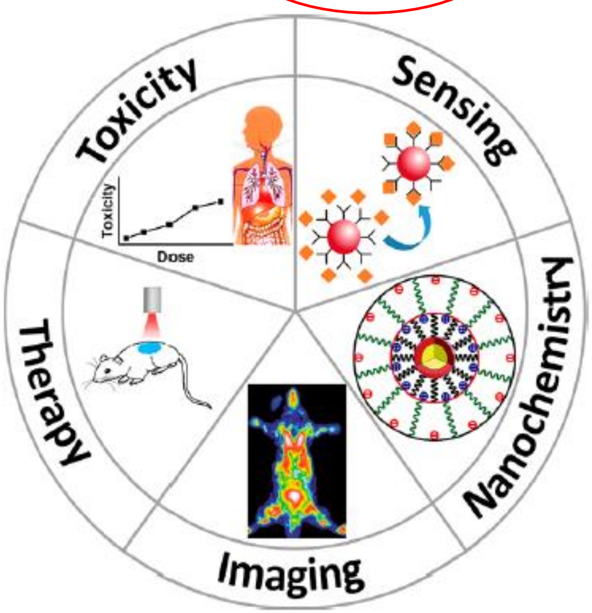

K. Sowjanya, Res. Rev.: J. Med. Health Sci. 4(3) (2015)

# Magnetic Nanoparticles for Biomedical Applications




**Nanometric size**

**Easy interactions with bilogical matter**




Most studies biomedical studies of **magnetic nanoparticles** are on **iron oxide nanoparticles**

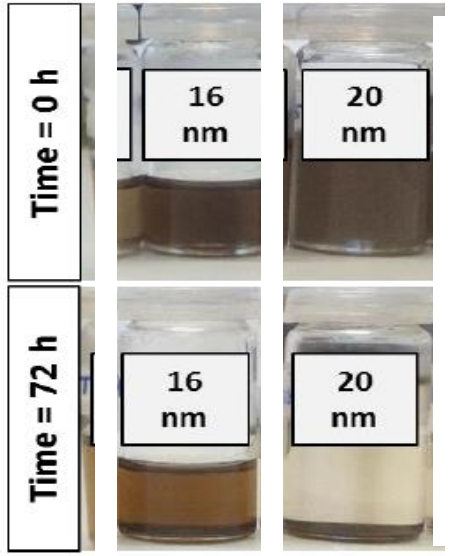
However, **colloidally stable iron oxide nanoparticles** are **difficult to manipulate** using magnetic fields

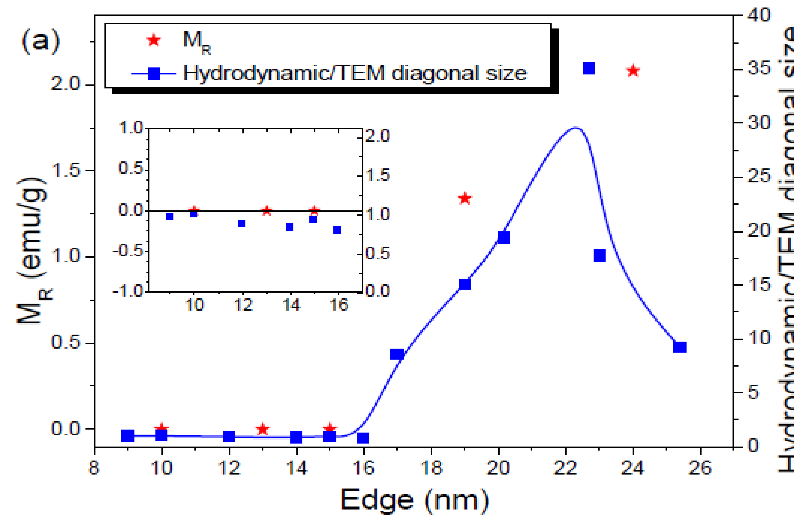
G. Chen, Chem. Rev. 2016, 116, 2826–2885

# Magetic Nanoparticles for Biomedical Applications

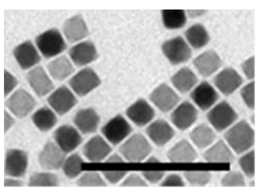
Most biomedical applications use **iron oxide** nanoparticles

If the partciles are too large they aggregate and their properties worsen

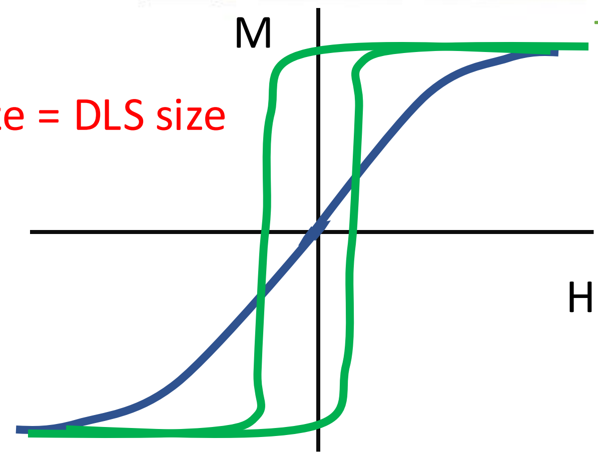


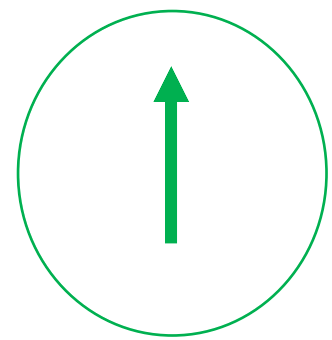

ferromagnetic – intearcations -aggregation

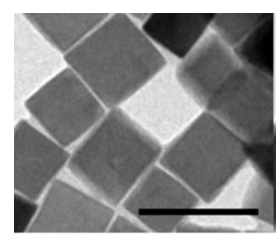


TEM size = DLS size



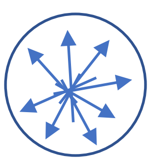

TEM size << DLS size





Stable moment

Moment fluctuates

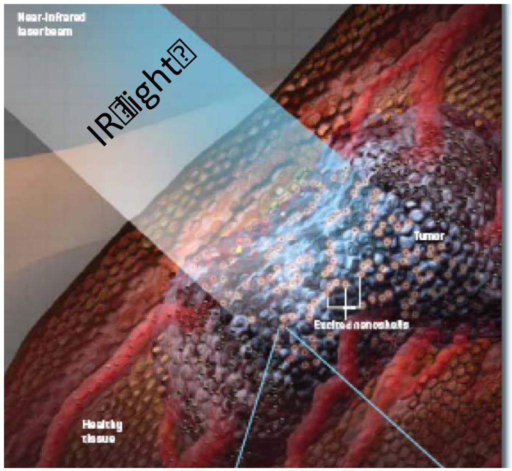


Superparamagnetic – no intearcations – colloidally stable

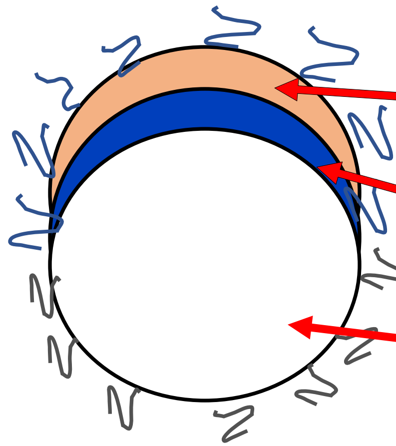
J. Muro-Cruces, ACS Nano **2019**, *13*, 7716

# Magnetoplasmonic nanodomes for Photo-Thermal Therapy control

## MAGNETIC CONTROL OF CANCER THERAPIES WITH NIR LIGHT




### NANODOMES



Au PLASMONIC , $SiO_2$

Fe, Co MAGNETIC “PLASMONIC”

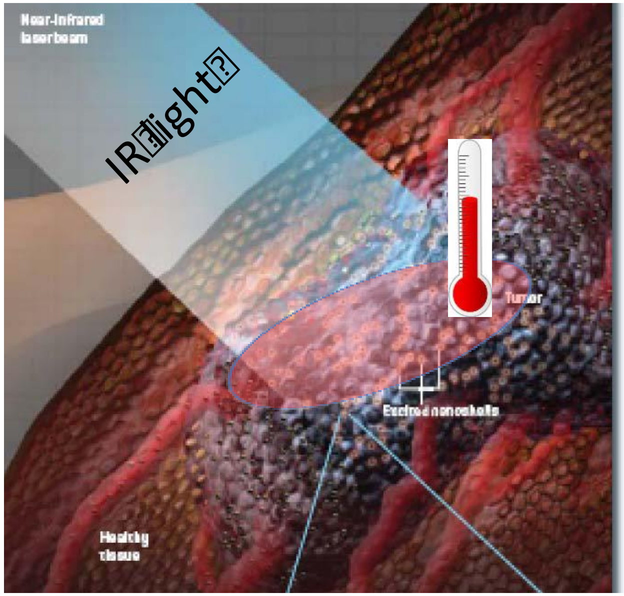
Polystyrerne
Biodegradable PLGA

**MAGNETIC**
- High magnetization
- Nuclear magnetic resonance contrast
- Strong Magnetic manipulation

**PLASMONIC**
- Damped plasmonic behavior
- Large absorption in the NIR
- Large photothermal effect

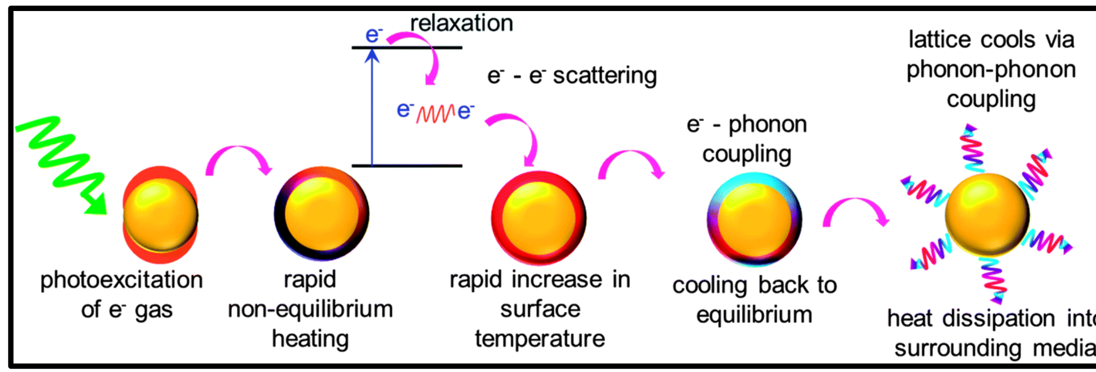
# Introduction: nanoparticles for optical hyperthermia

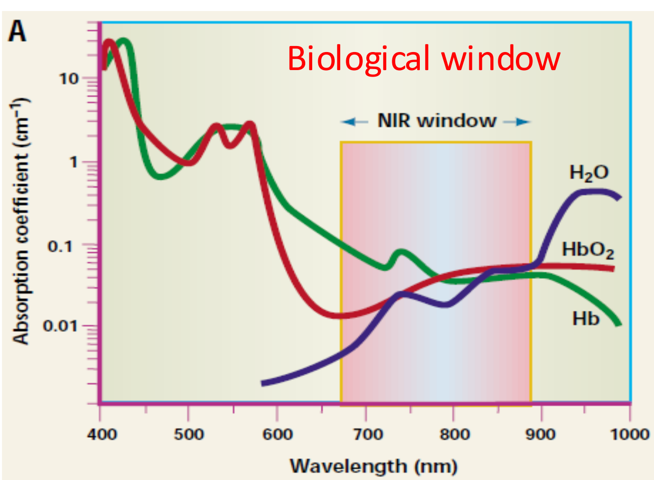
## Hyperthermia with light (NIR)

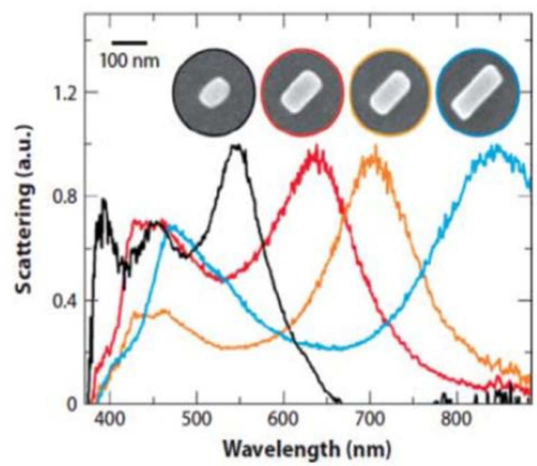


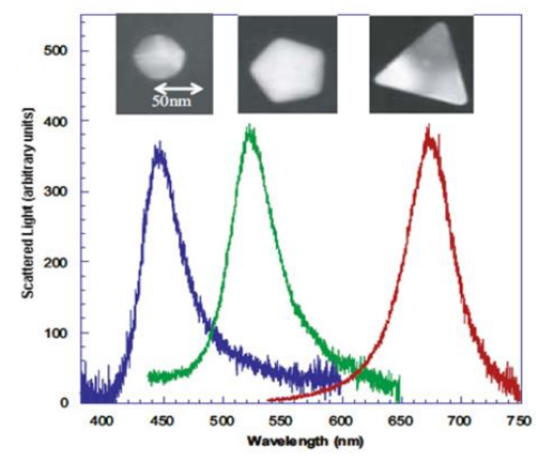

Nanoparticles with light absorption

Localized surface plasmon resonance (Au, Ag)



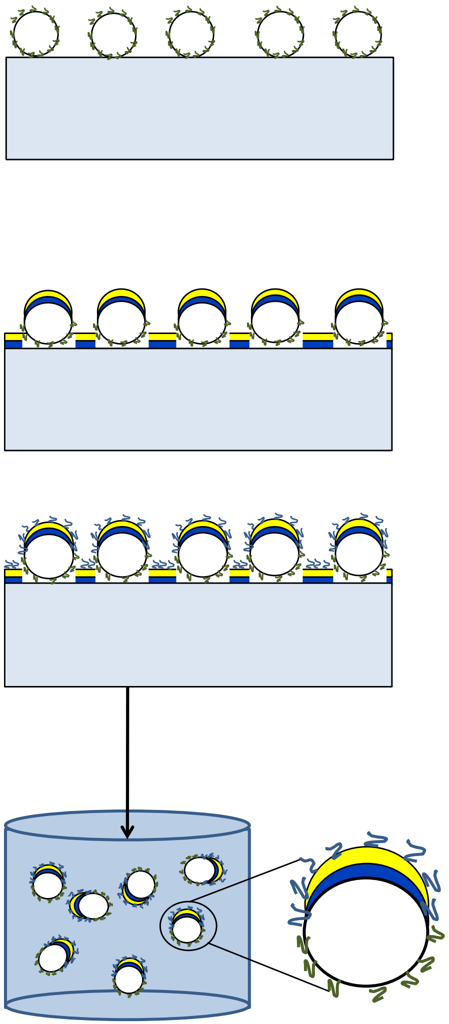



# Magnetoplasmonic nanodomes fabrication

**Beads Polystyrene or PLGA** (diameter 100 nm) as template



a) **Electrostatic self-assembly 4-inch Si wafer**

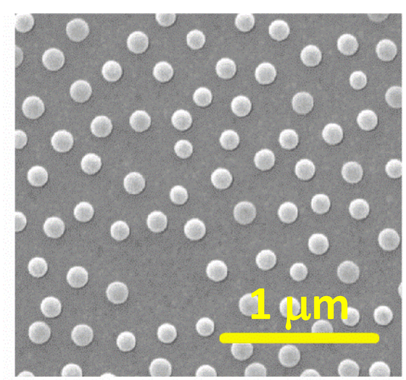
b) **e-beam physical vapor deposition**

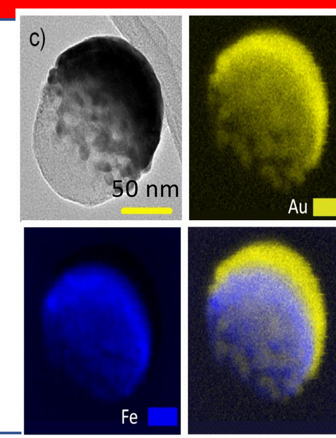
c) **Functionalization Negative poly-electrolytes Proteins, DNA, lipids...**

d) **Transfer into water solution by ultrasonication**

## Advantages

- **Fabrication in vacuum -> no need of toxic organic solvents**
- **Direct functionalization on the wafer**
- **Direct dispersion in water based solutions**
- **High colloidal stability**
- **Highly tunable magnetic and optical properties**




**4 inch wafer ->** $1.3 \cdot 10^{11}$ particles

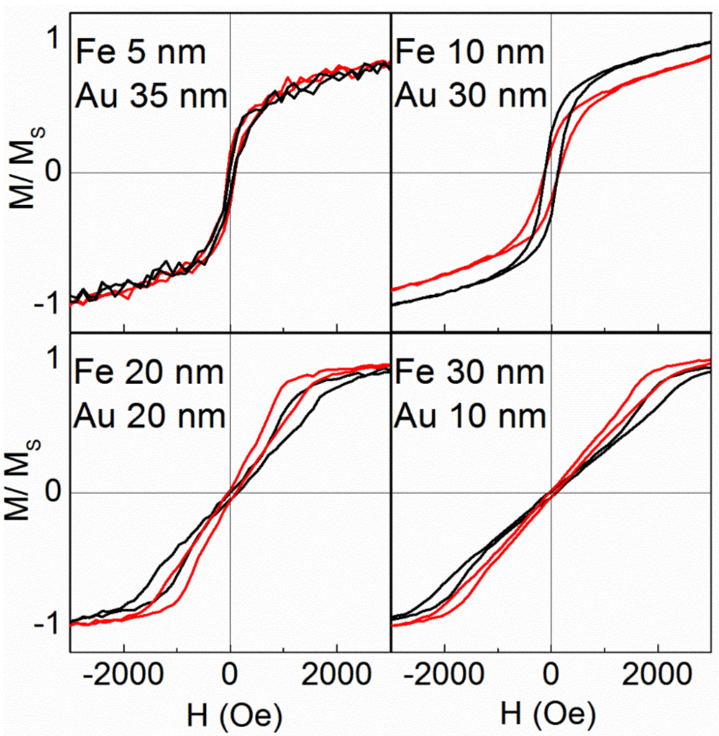
**600 µg/wafer and scalable**

# Au/Fe Magnetoplasmonic nanodomes

## Magnetic characterization -> Tunable magnetic properties

$M_s$ ($Fe^0$) = 2.2 T
$M_s$ ($Fe_3O_4$) = 0.6 T

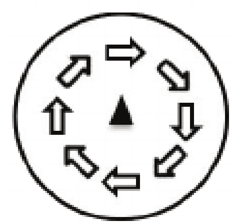
**Ferromagnetic with in-plane magnetization**




**1 ND = 500 iron oxide 10 nm particles**

**Single domain**

**Thick Au capping layer**



**Magnetic Vortex**

Circular arrangement of in-plane magnetization

**Zero remanence**

**From DLS measurements**

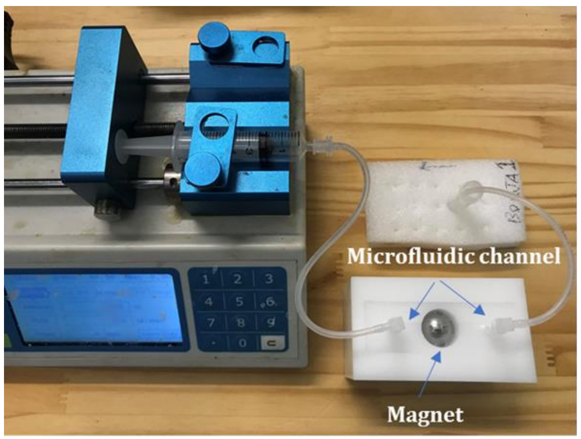
| Zeta potential | size | PDI |
|---|---|---|
| -20 mV | 130 nm | 0,08 |

- **Minimal magnetic dipolar interaction**
- **High colloidal stability**
- **Strong magnetic manipulation**

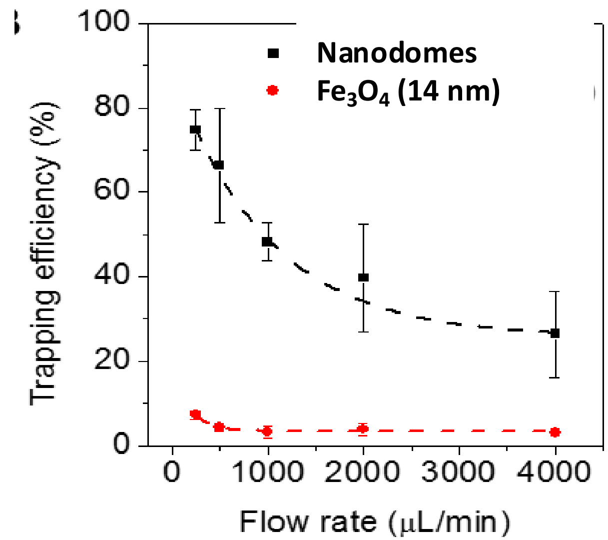
Z. Li, Appl. Mater. Today 12 (2018) 430

# Au/Fe Magnetoplasmonic nanodomes

**Magnetophoretic trapping ->** $F_m = V(M \bullet \nabla)B$




Absrorption

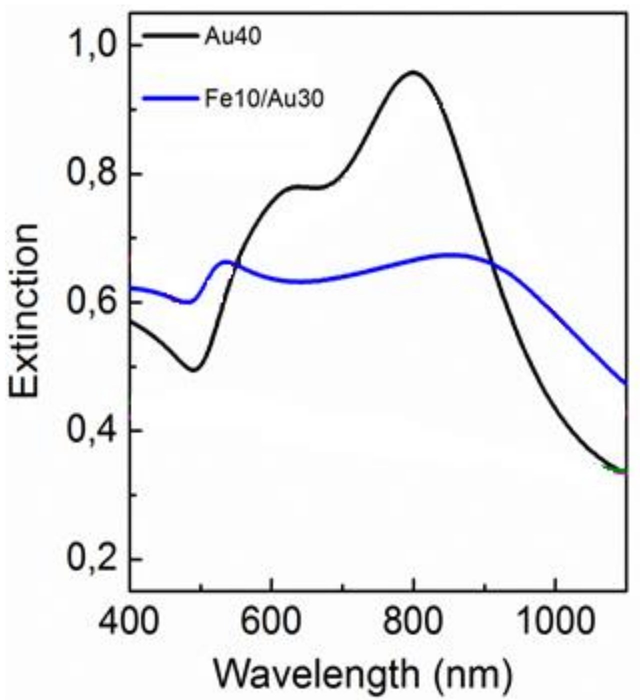


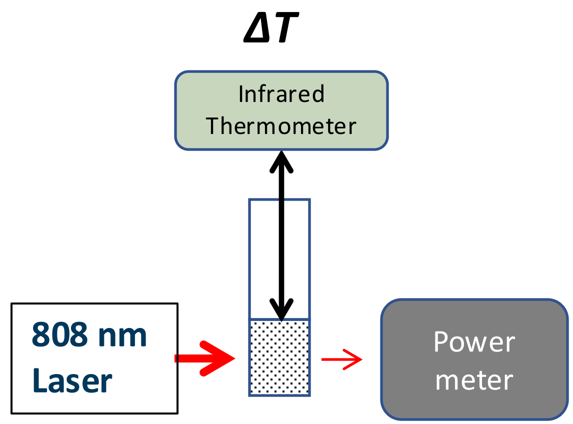

(blood in mice 90 μL/min - 1800 μL/min)

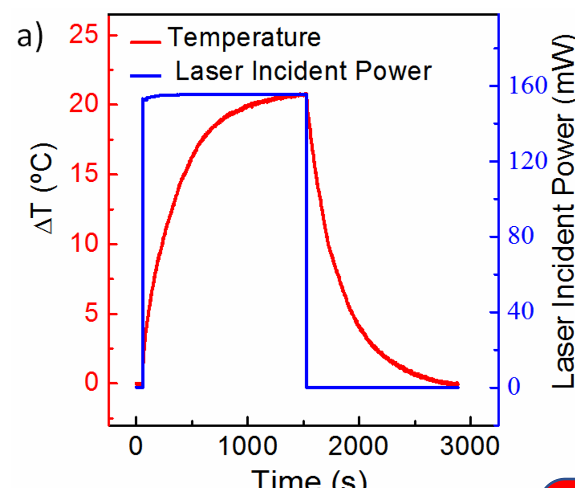
**The trapping efficiency of the nanodomes is much better than that of superparamagnetic nanoparticles**

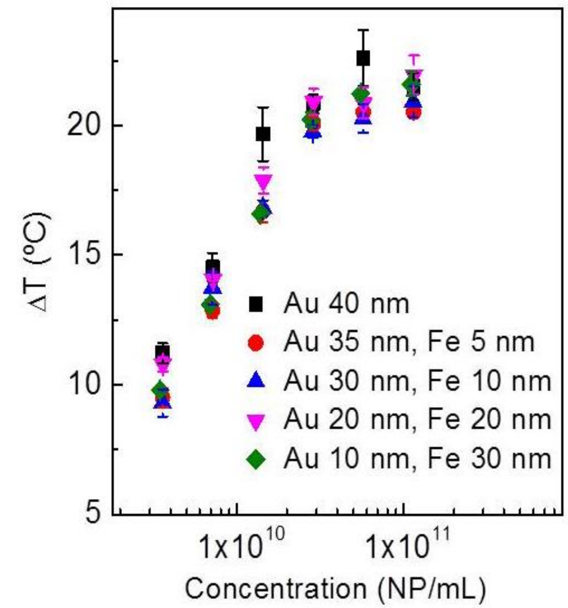
# Au/Fe Magnetoplasmonic nanodomes

## Tunable optical properties -> efficient optical heating




***ΔT*** increases with nanodomes **concentration**

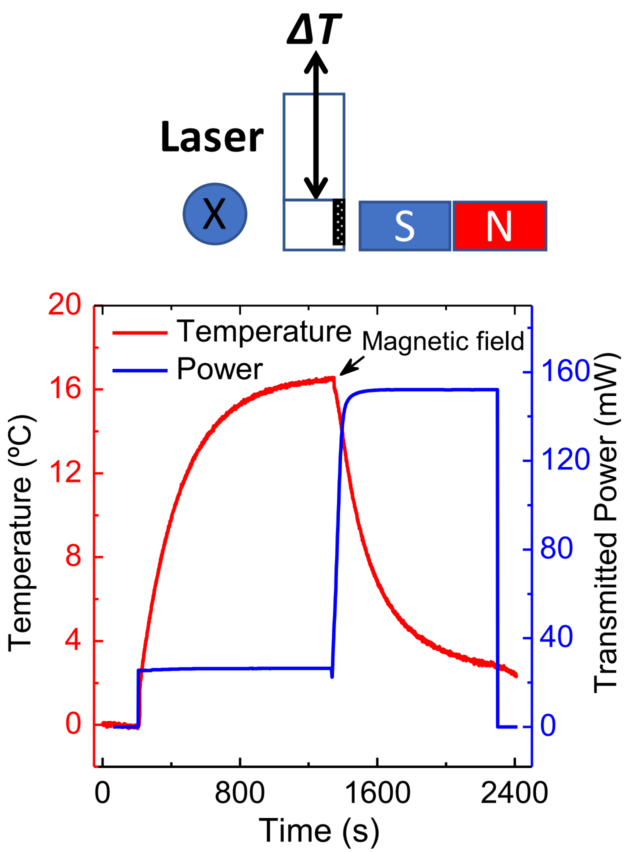
**Strong phtothermal effect**

Z. Li, Appl. Mater. Today 12 (2018) 430

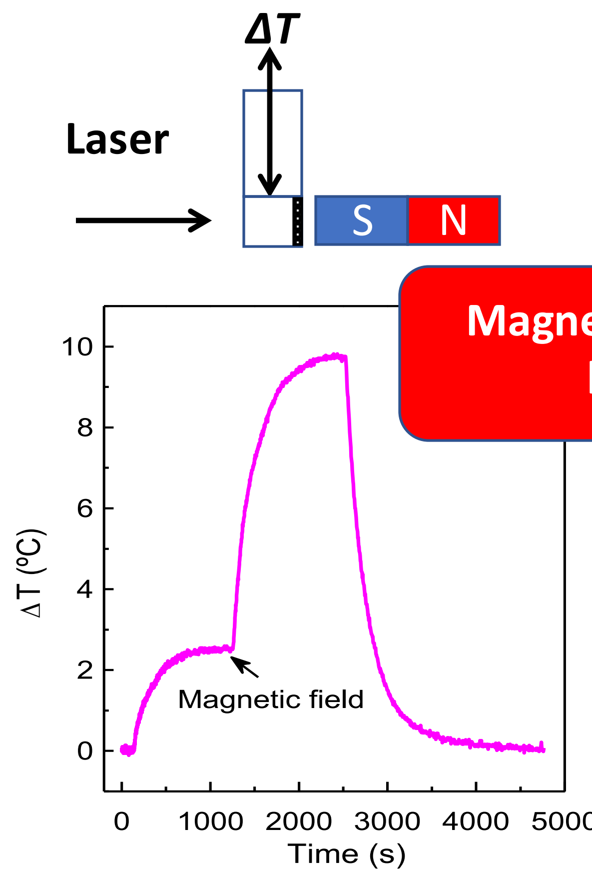
# Au/Fe Magnetoplasmonic nanodomes

## Control of Phtothermal Effect with Magnetic Field

**Particles attraction outside of the optic path**




**Particles attraction in the optic path**

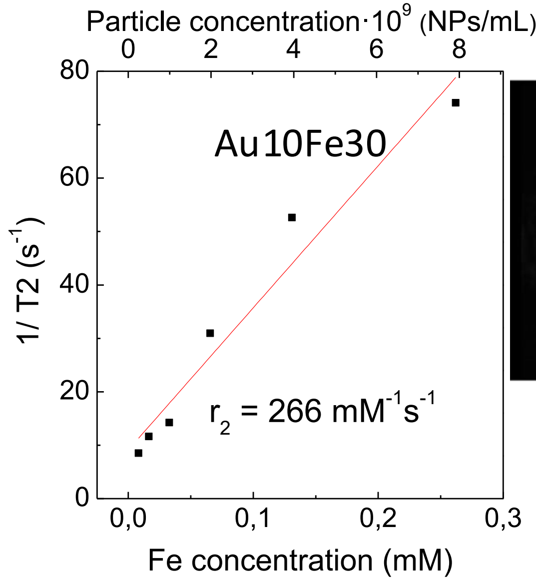


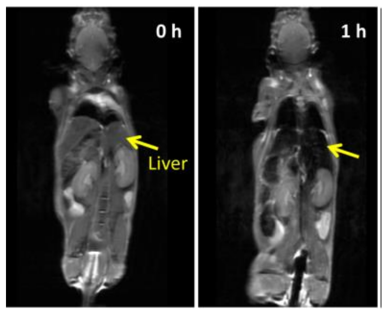

**Magnetic enhanced heating**

Z. Li, Appl. Mater. Today 12 (2018) 430

# Au/Fe Magnetoplasmonic nanodomes for imaging

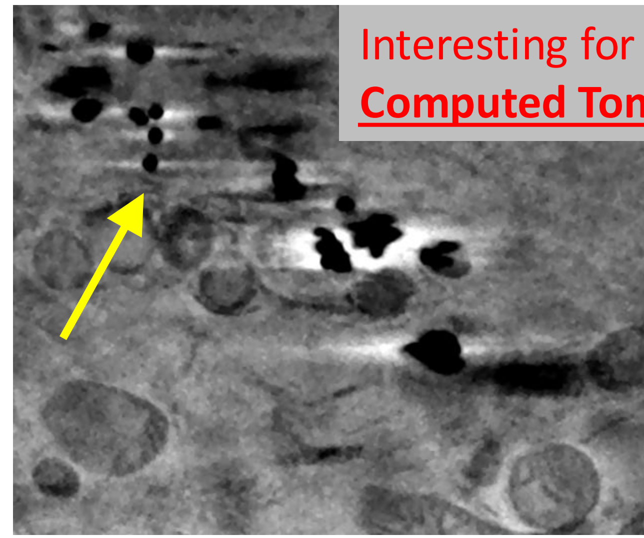
## Nuclear Magnetic Resonance – $T_2$ contrast



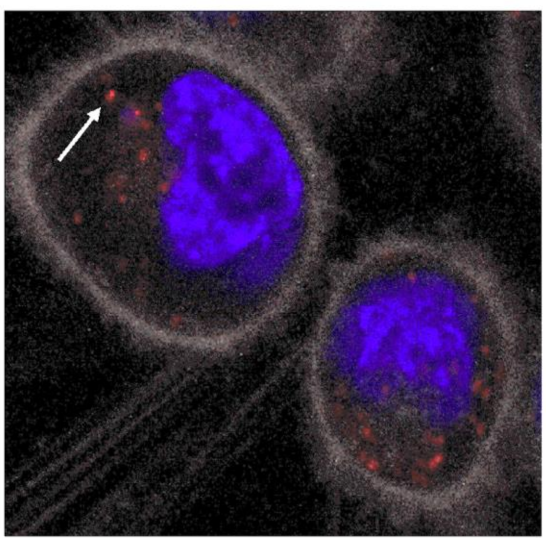



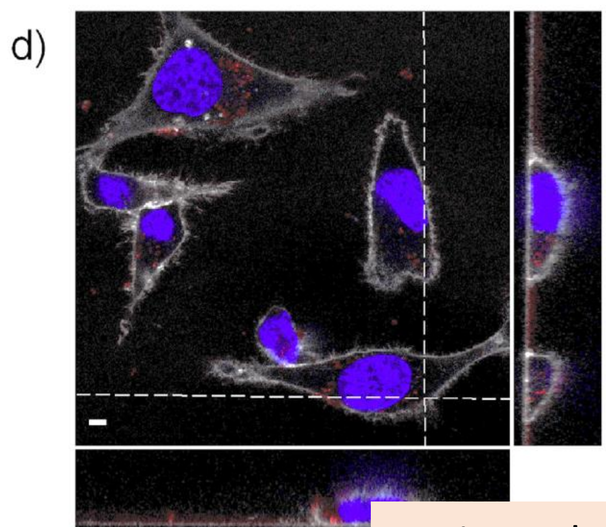

Resovist – 176 $mM^{-1}s^{-1}$

## X-ray microscopy of frozen cells



Interesting for
**Computed Tomography**






## Confocal microscopy

Using fluorescent polystyrene beads

Z. Li, Appl. Mater. Today 12 (2018) 430

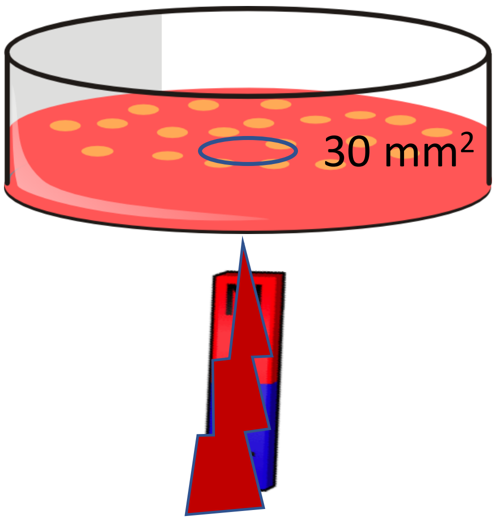
# Au/Fe nanodomes for amplified Photo-thermal Therapy

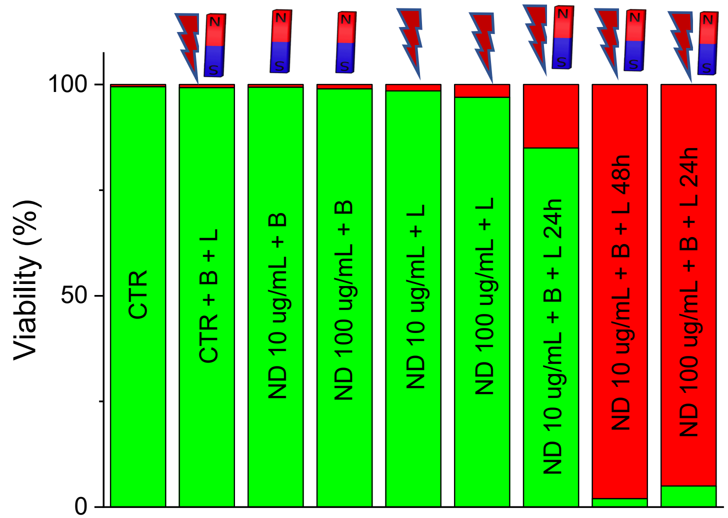
**HeLa cancer cells + Fe20/Au20 nanodomes**

3 h incubation with cells with/without magnetic concentration

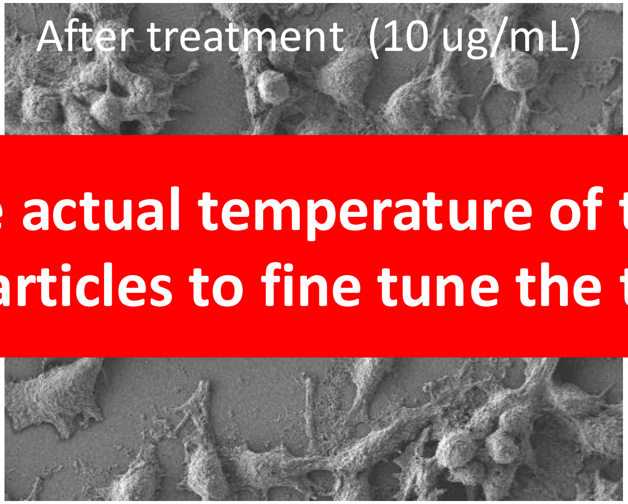
**Irradiation conditions:**

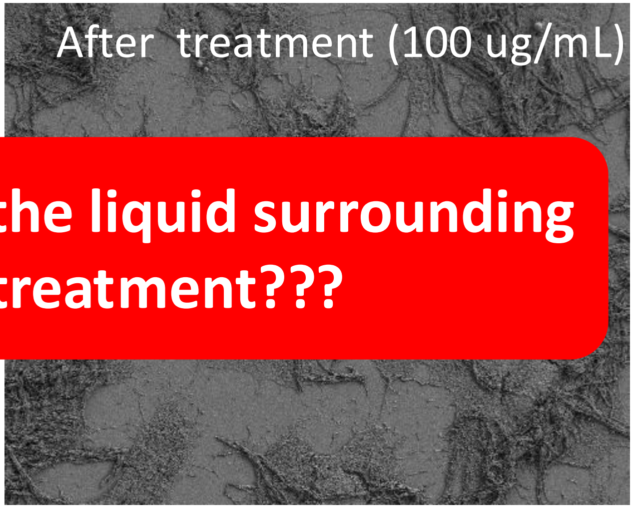
808 nm laser, 5 W/cm$^2$, 30 min







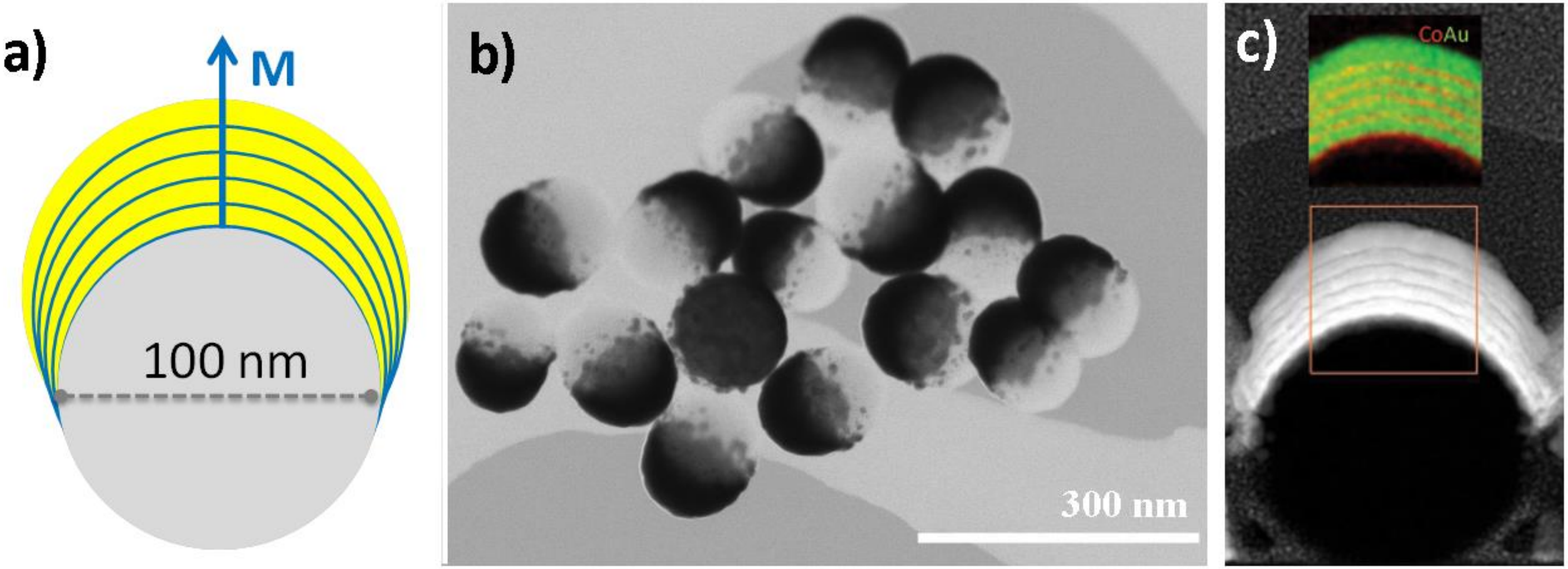




**Which was the actual temperature of the liquid surrounding the particles to fine tune the treatment???**

# Au/Co nanodomes nano-heater/thermometers

**Simultaneous nano-heating-thermometry**

Magnetoplasmonic multilayer **(Co 1 nm + Au 6 nm)*5 + Au 5 nm**

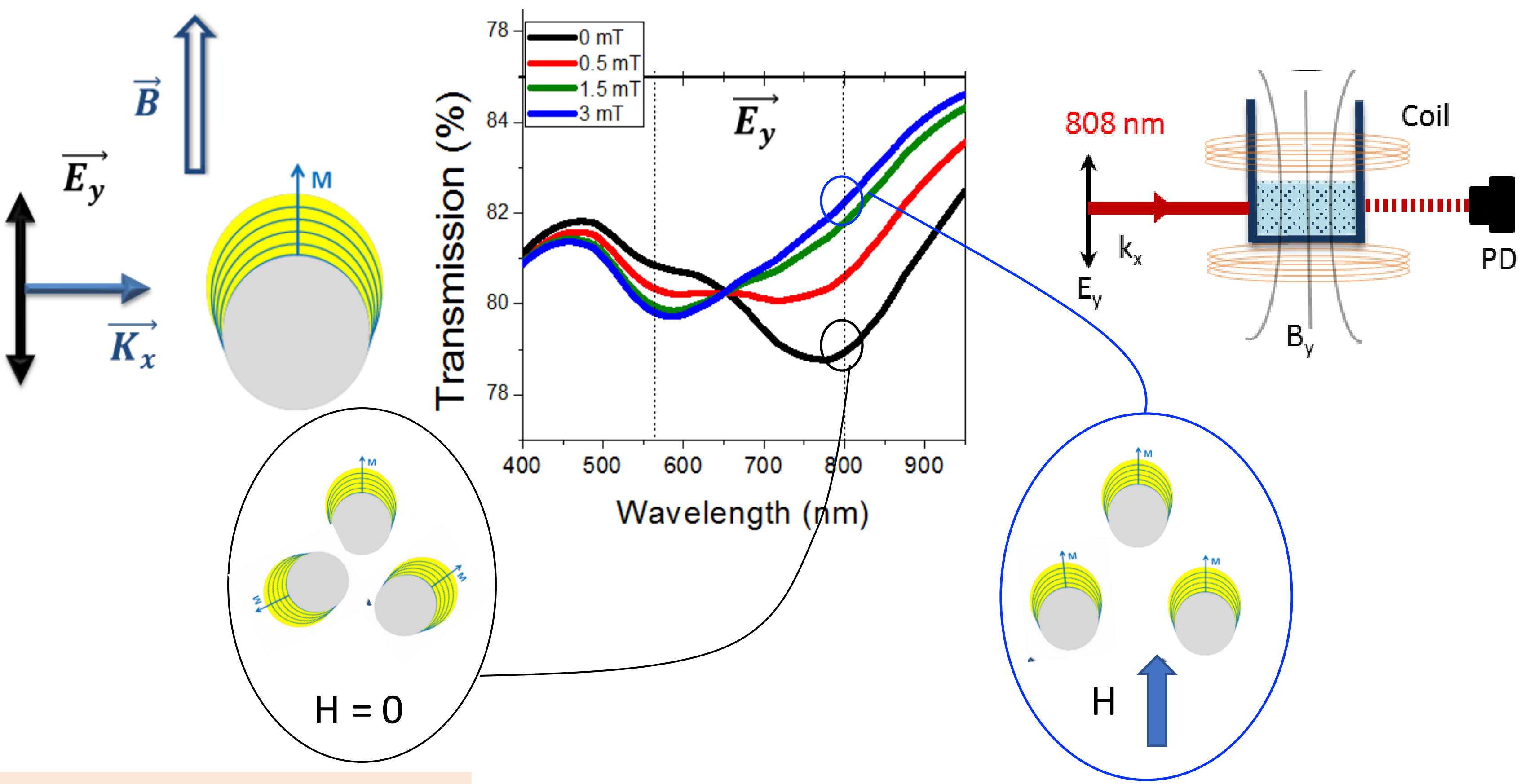



Nanoparticles with high magnetic and optical anisotropies
**-> Strong magnetochromic effects**

# Nanodomes nano-heater/thermometers

## Magnetochromic effect

Color change in the colloidal dispersion under a magnetic induction B (0-2 mT)

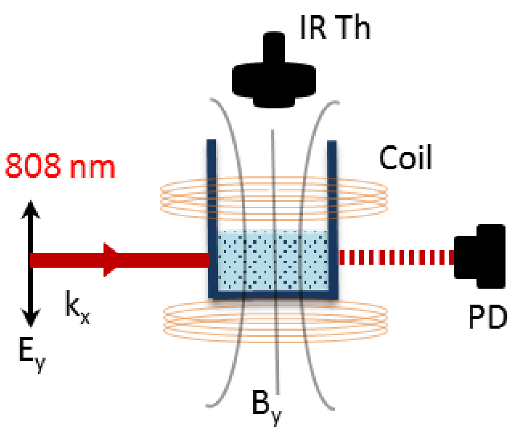


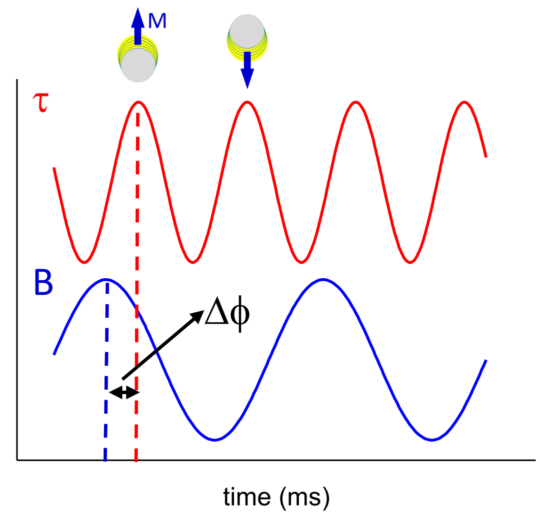

Z. Li, Small 14 (2018) 1800868

# Nanodomes nano-heater/thermometers

## Dynamic Magnetochromic effect due to particle rotation

Intensity modulation under low alternating magnetic induction **(B = 2mT)**



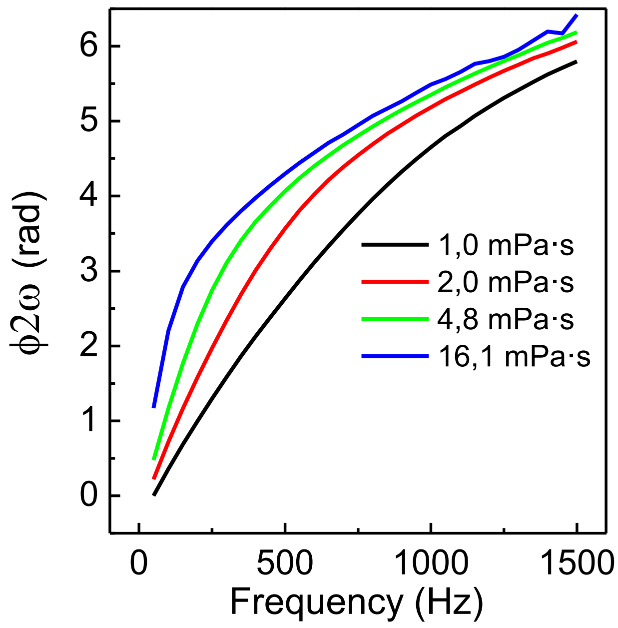

The transmission has **2ω** reponse

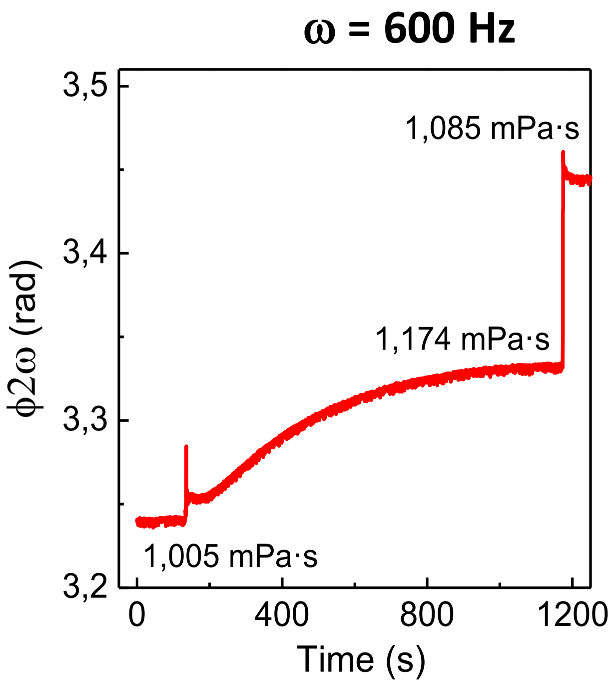
There is **Phase Lag** delay due to **viscosity**

# Au/Co nanodomes nano-heater/thermometers

## Detection of viscosity variations around the particles

Viscosity increase in water/glycerol solutions



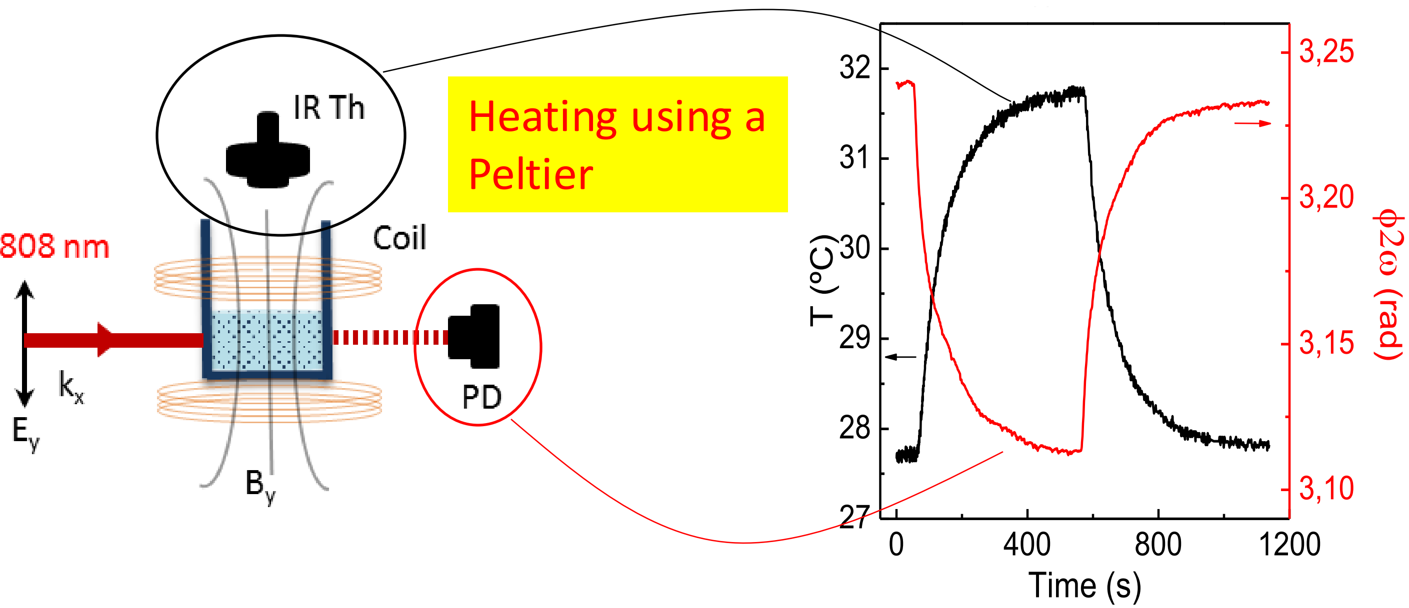




**Real-time detection of viscosity variations**
**Limit of detection of 0.0016 mPa.s!!**

# Au/Co nanodomes nano-heater/thermometers

**Detection of temperature variations around the particles**

Viscosity **decreases** when temperature around the particles **increases**




Phase-temperature calibration

**Real-time detection of temperature variations**
**Limit of detection of 0.05 ºC!!**

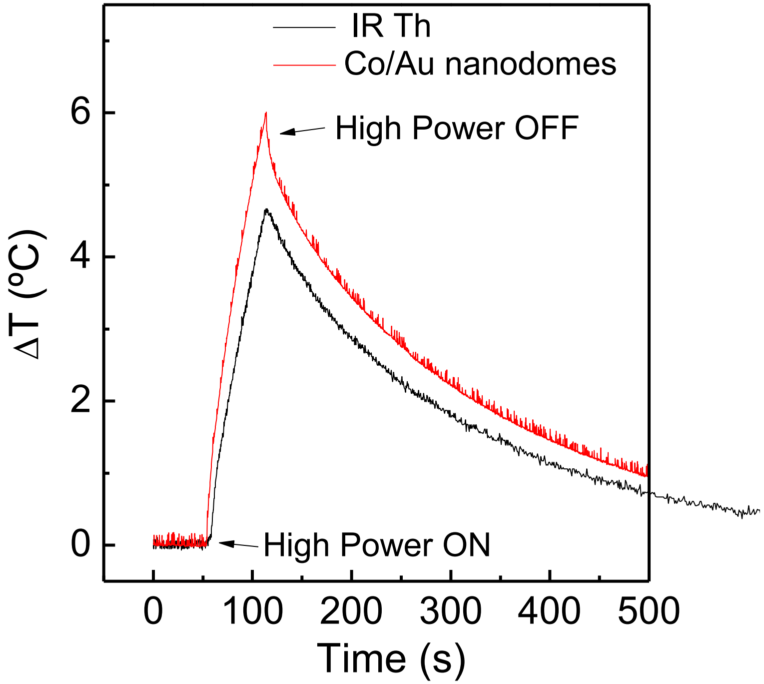
Z. Li, Small 14 (2018) 1800868

# Au/Co nanodomes nano-heater/thermometers

**Simultaneous optical heating and temperature detection**

Viscosity decrease when particles are optically heated

Collimated Laser (3 mm)



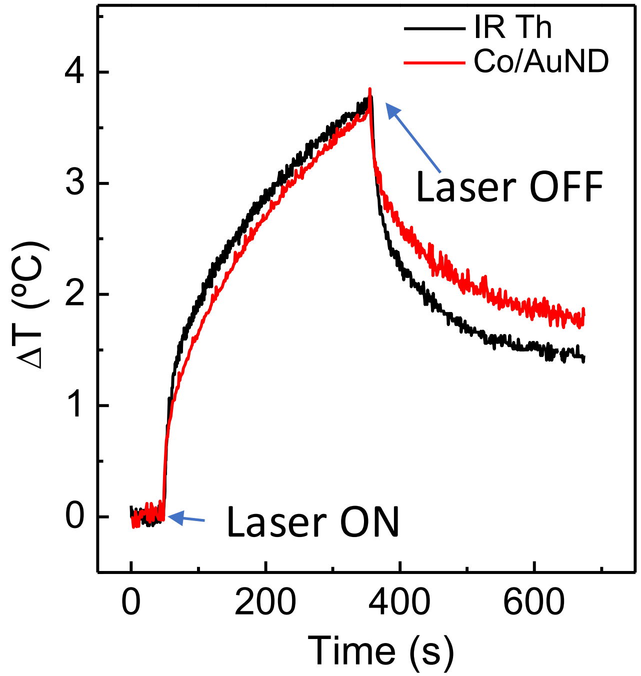

**Real-time detection of temperature due to plasmonic heating**

Z. Li, Small 14 (2018) 1800868

# Au/Co nanodomes nano-heater/thermometers

**Simultaneous optical heating and T detection in monocyte dispersions**

$6 \cdot 10^6$ cells/mL -> very high optical scattering -> **20 fold reduction of transmitted light** **<u>but no effect on the phase!!</u>**

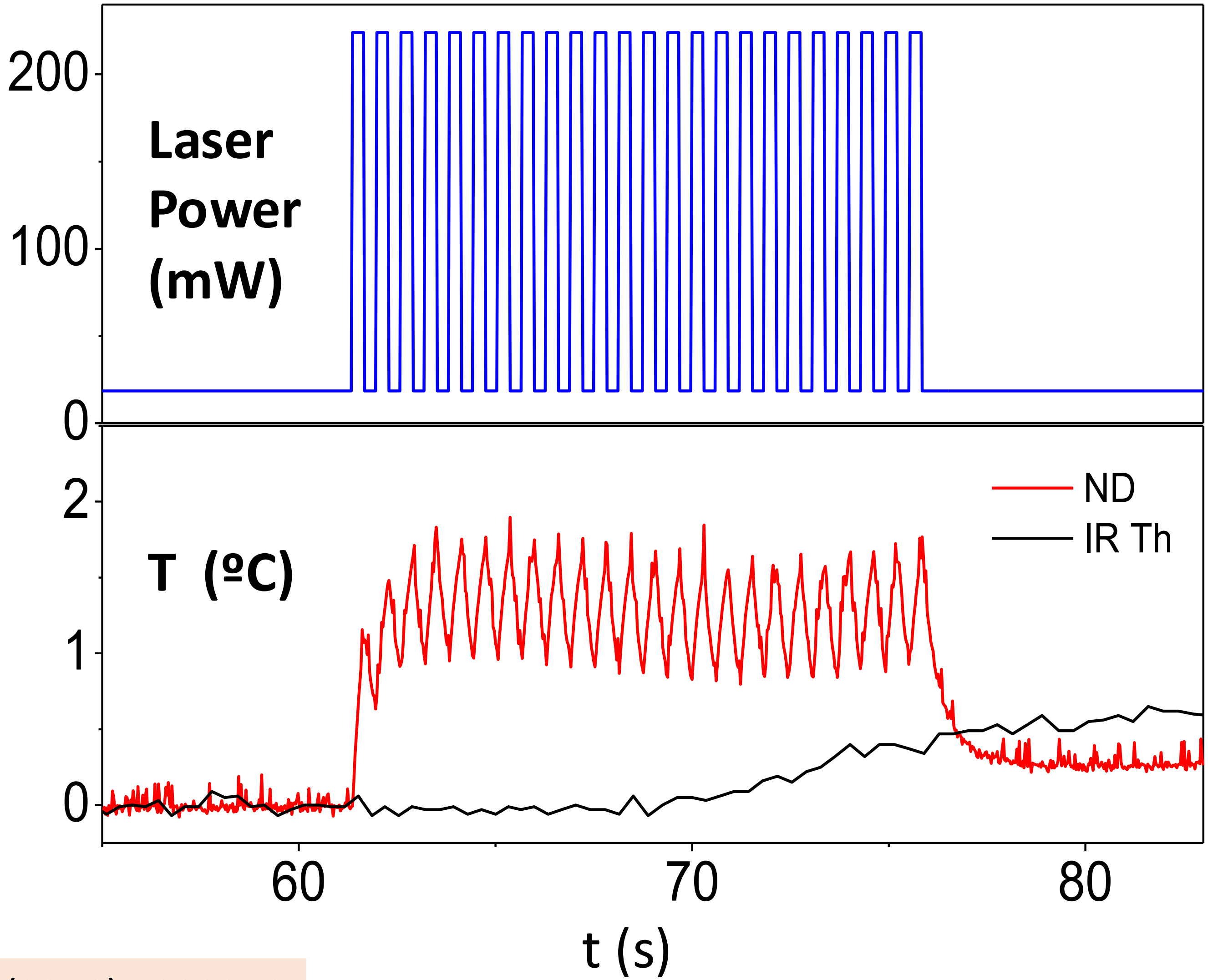



**Real-time detection of plasmonic heating in <u>highly dispersive</u> medium**

**Also possible with Au/Fe nanodomes (detection limit 0.1 ºC)**

# Au/Co nanodomes nano-heater/thermometers

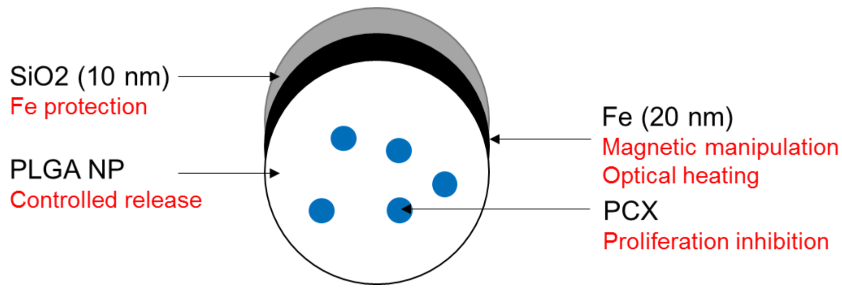
**Fast detection of temperature variations in focused laser**

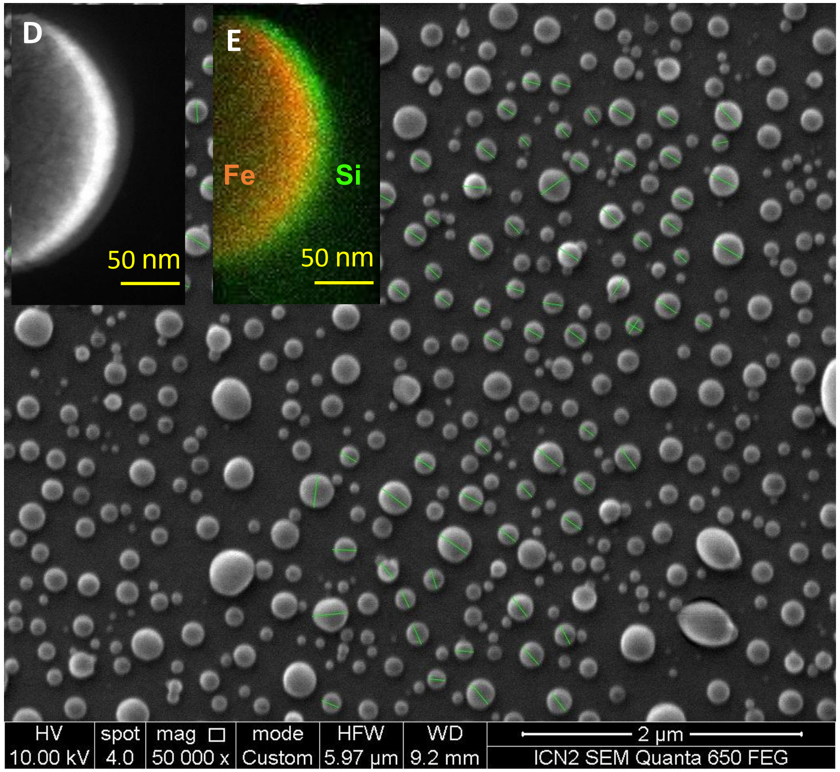



Z. Li, Small 14 (2018) 1800868

# In vivo durg delivery using Nanodomes

## Fabrication




Use of **biodegradable** poly-lactic-co-glycolic-acid (**PLGA**) beads

Fill the PLGA beads loadeswith **anticancer drug paclitaxel** (PCX) (emulsification – evaporation)

Use **$SiO_2$ as capping layer** instead of Au

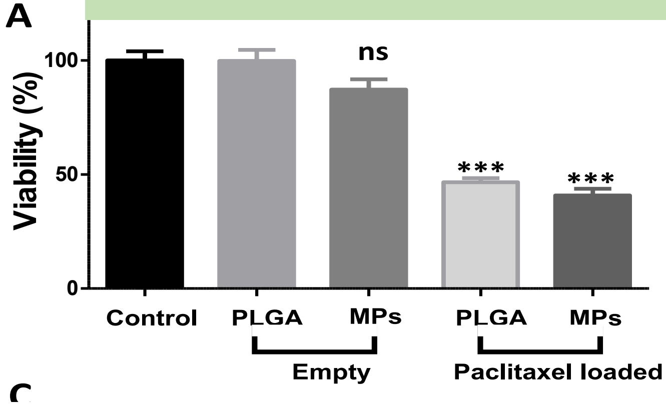
**Fe** has a **damped plasmonic behavior** thus it has a large absorption of light in the NIR range, consequently, it can induce **strong photothermal effects**

A. Fluksman, ACS Nano 17 (2023) 1946

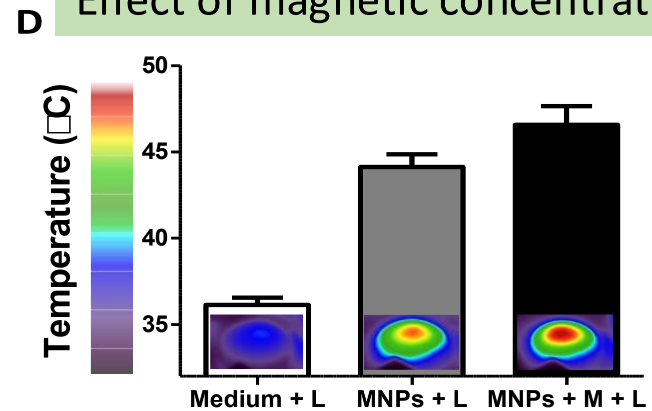
# In vivo durg delivery using Nanodomes

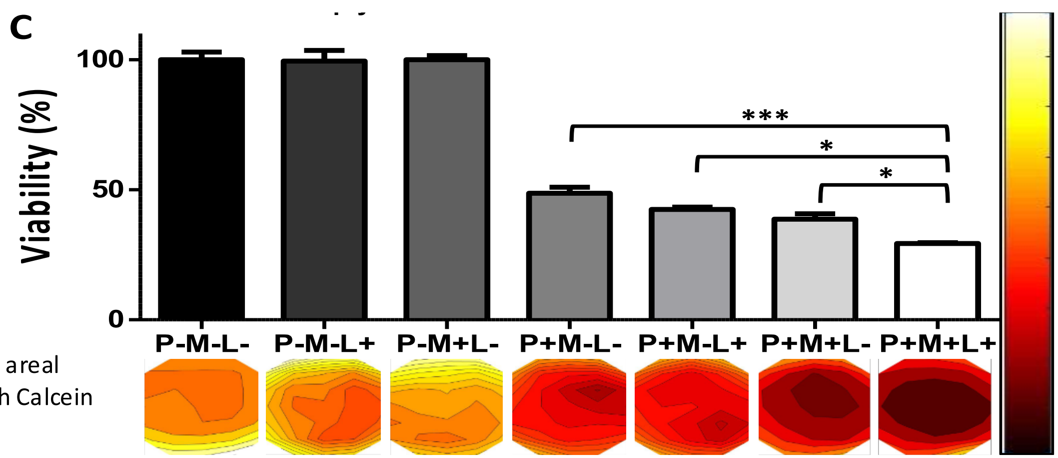
## **In-vitro studies** (MDA-MB-231 cells)

Effect of PCX without actuation




Effect of magnetic concentration on ΔT




fluorescence areal scanning with Calcein AM staining

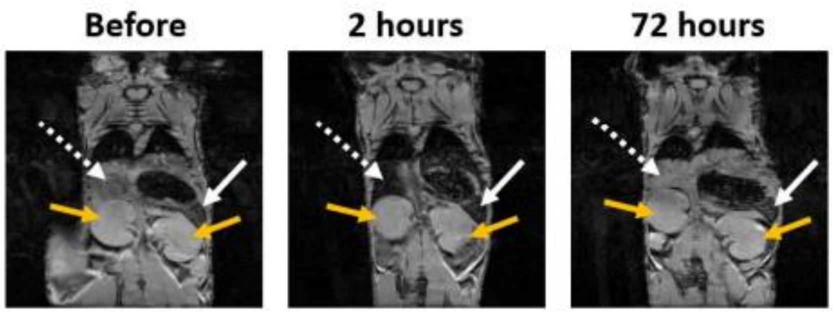
Effect of **full** actuation

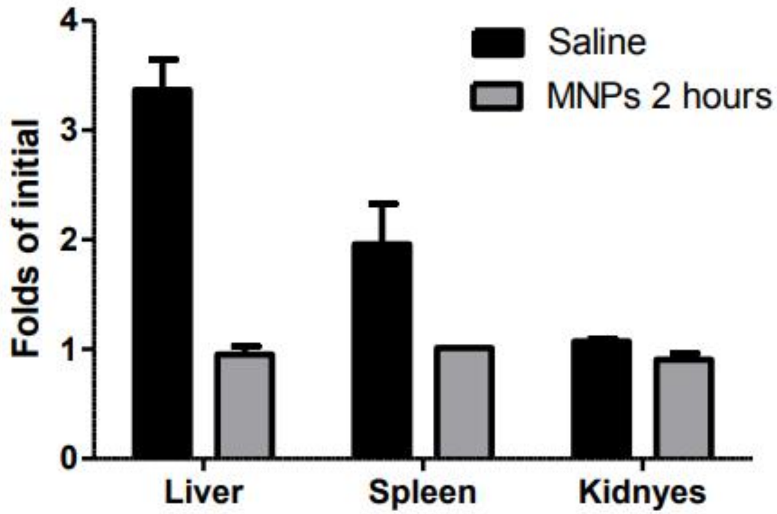
**Magnetic concentration impoves the phothermal effect**

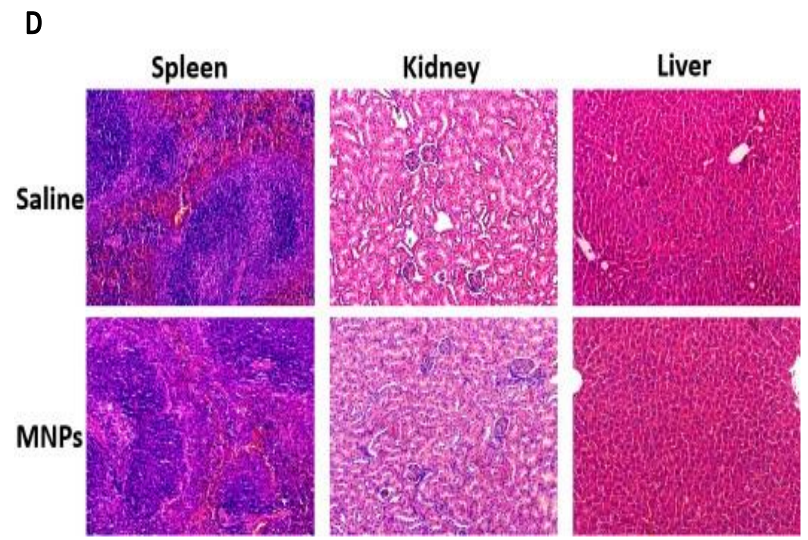
**Laser + magnetic concentration reduces significantly the cell viability**

# In vivo durg delivery using Nanodomes

## Study of the biodistribution using MRI

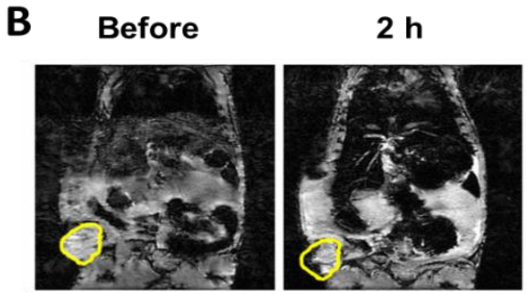


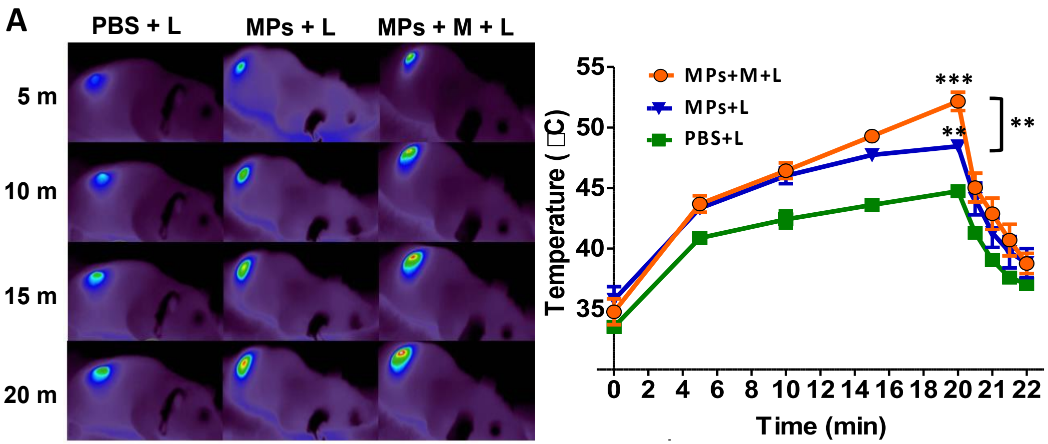



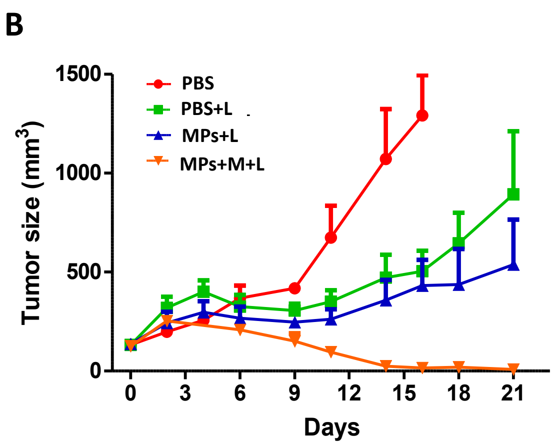




- Accumulation of the particles in the lever and spleen
- The particles are cleared from the body after 72 h
- No major changes in the organs after the injection of nanoparticles

# In vivo durg delivery using Nanodomes




## In-vivo therapy

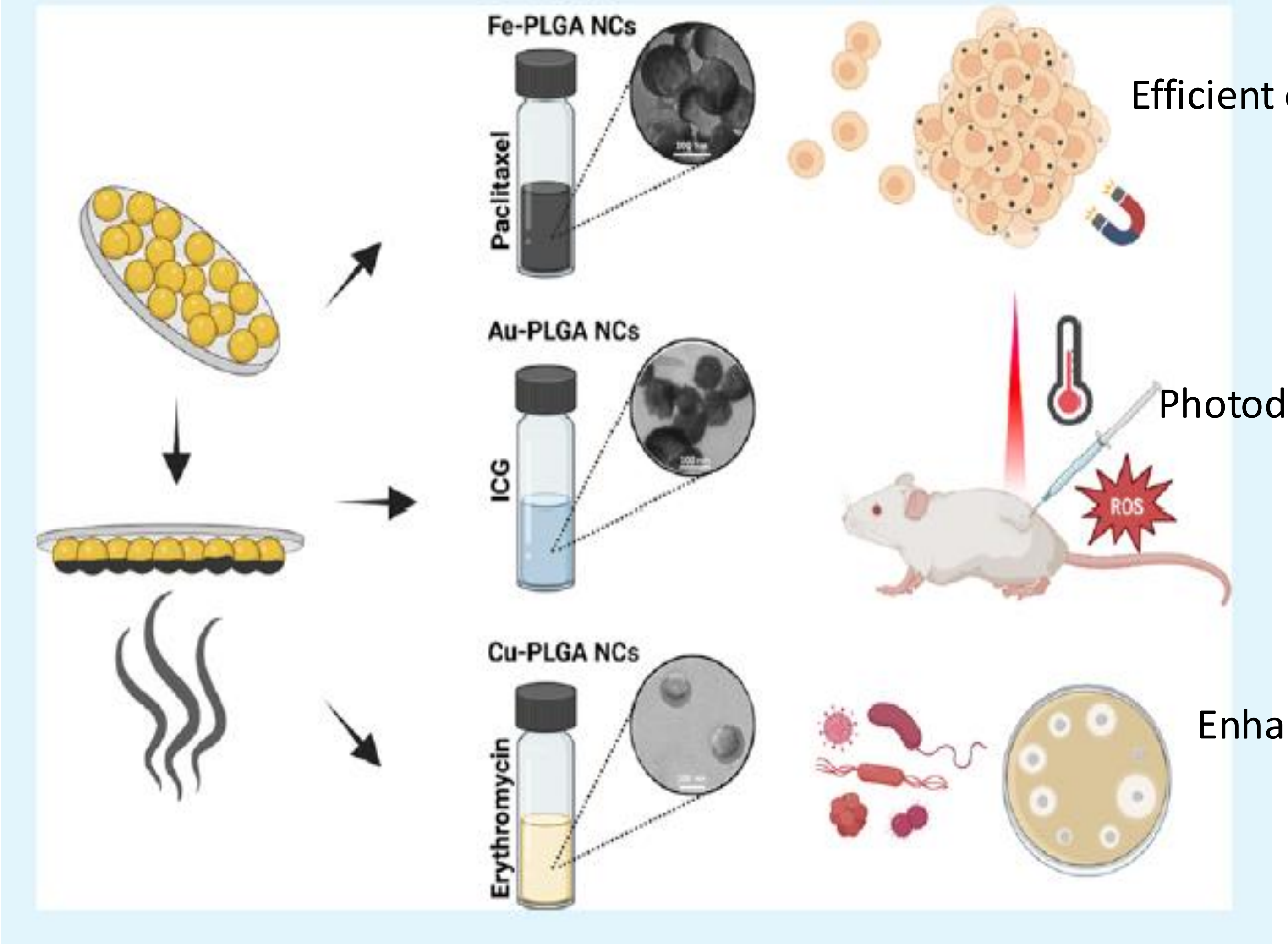
- **Ultralow concetration**: 1 mg/kg of nanodomes containg only 8 µg/kg of paclitaxel (**100-500** times lower)
- 2 h **magnetic concentration** using a permanent magnet (magnetic actuation increases the concentration in the tumor between **2.4** and **4** times)
- **Single** 20 min **laser actuation** (808 nm, 0.95 W/cm$^2$) in day 1

**Drug loaded nanodomes with magnetic concentration and NIR-laser irradiation are very effective in eradicating the tumor even at ultralow concentacion of drugs**

A. Fluksman, ACS Nano 17 (2023) 1946

# Extension of the Nanodome Concnept

**The nanodomes concept can be extended to a virtually infinite combination of capping materials (with different functionalities) and drugs**



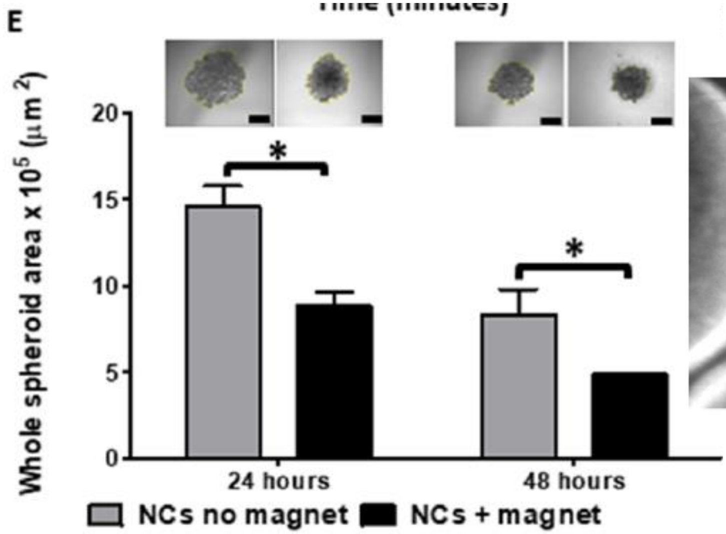

Efficient cancer spheroid assembly

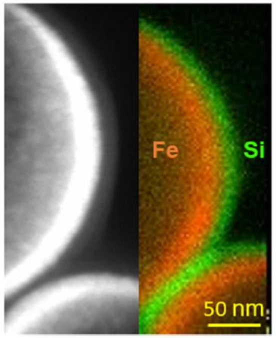
Photodynamic cancer treatment
Fluorescence imaging

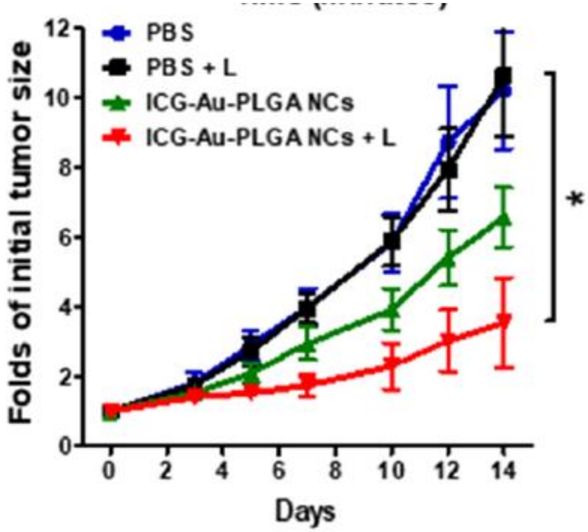
Enhanced antibacterial activity

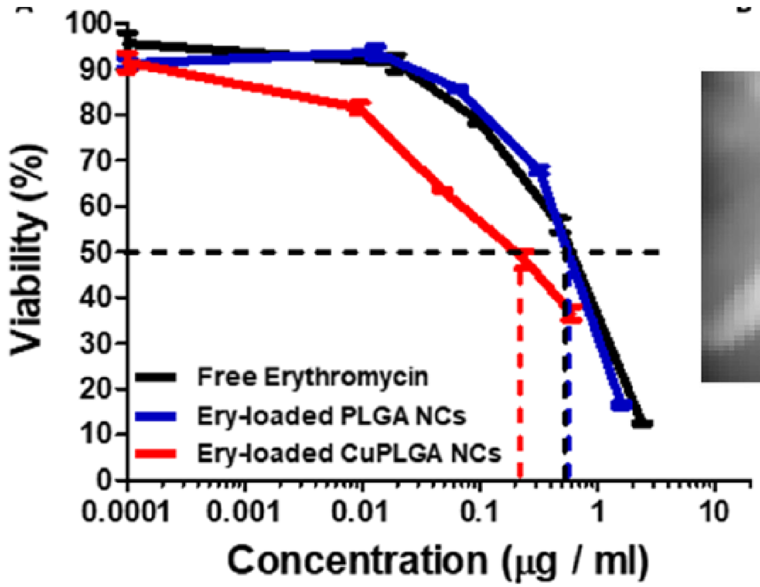
A. Fluksman, ACS Appl. Mater. Interfaces 2023, 15, 50330

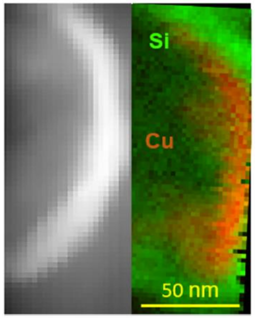
# Extension of the Nanodome Concnept

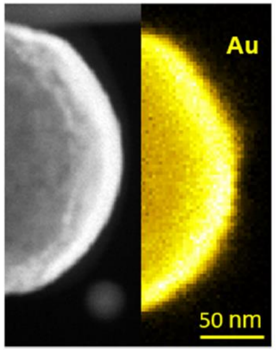



A. Fluksman, ACS Appl. Mater. Interfaces 2023, 15, 50330

# Conclusions

ICN2 Institut Català de Nanociència i Nanotecnologia

EXCELENCIA SEVERO OCHOA

- **Nanodomes to control photo-thermal therapies**
  - **Strong nanomagnets & nanoheaters**
  - **Multimodal imaging (NMR, CT, fluorescence)**
  - **Very high efficiency photo-thermal therapy by magnetic manipulation**
- Biodegradable drug-loaded nanodomes for in-vivo therapy
  - **Drug loaded nanodomes with magnetic concentration and NIR-laser irradiation are very effective in eradicating tumors**
- Nanodomes concept
  - **The nanodomes concept can be extended to a virtually infinite combination of capping materials (with different functionalities) and drugs**

A. Fluksman, ACS Appl. Mater. Interfaces 2023, 15, 50330
"Modular Drug-Loaded Nanocapsules with Metal Dome Layers as a Platform for Obtaining Synergistic Therapeutic Biological Activities"

## A. Lafuente, A.G. Roca

*Catalan Institute of Nanoscience and Nanotechnology (ICN2)*
*Barcelona, Spain*

## A. Flucksman, O. Benny

The Hebrew University of Jerusalem, Jerusalem, Israel

## J. Sort, C. Nogués

*Universitat Autònoma de Barcelona, Barcelona, Spain*

## B. Sepúlveda

Instituto de Microelectrónica de Barcelona, Bellaterra, Spain