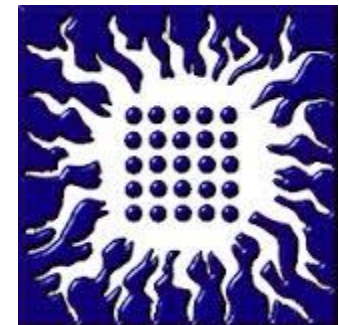


# Design of novel magnetic nanostructures for targeted tumour therapy @MagBioVin Project

Erzsébet Illés

N. Knezevic, A. Mrakovic, D. Peddis, M. Perovic, M. Boskovic, V. Kusigerski,  
S. Vranjes-Djuric, V. Spasojevic, B. Antic, Z. Prijovic

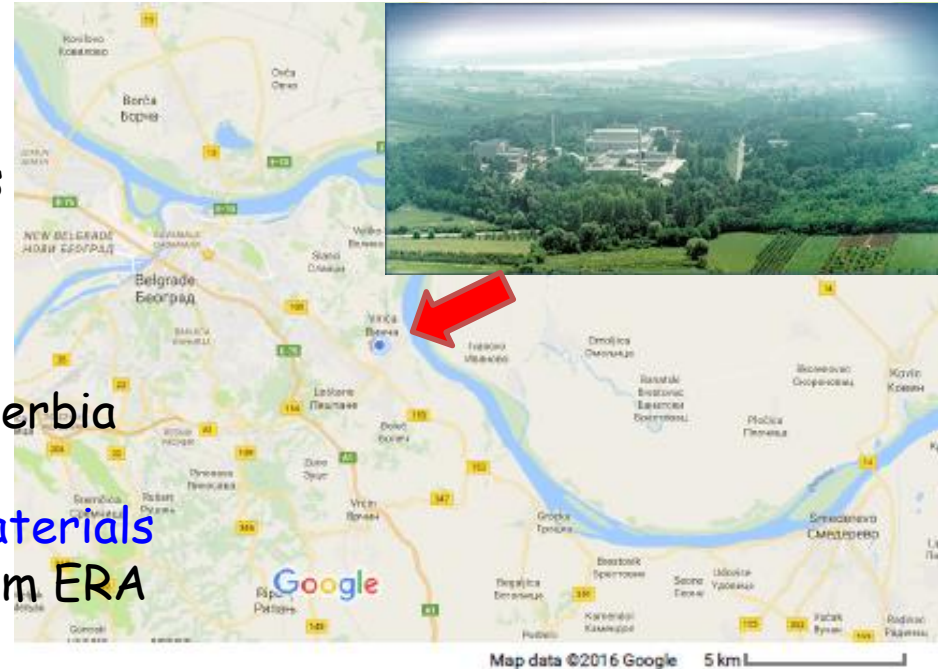
"Vinča" Institute of Nuclear Sciences, Belgrade, Serbia



*"VINČA" INN (Institute of Nuclear Sciences)  
CONDENSED MATTER PHYSICS LABORATORY - 020*

*„Strengthening of the MagBioVin Research and Innovation Team for Development of Novel Approaches for Tumour Therapy based on Nanostructured Materials“*

- FP7-ERA Chairs (2014-2019)
- one of the first 11 supported proposals
- 5 years, ~2.4 M EUR
- Vinča Institute of Nuclear Sciences, Serbia  
**VINCENT Center of Excellence for Knowledge-based multifunctional materials**  
+ postdocs, senior researchers from ERA
- Consortium: Serbia - Spain, France, Slovenia, Slovakia  
industrial partners, academic research groups
- Aim of the project:  
**design of new „activated“ magnetic nanoparticles for biomedicine**  
magnetic hyperthermia, drug delivery, radiolabeling - therapy and diagnostics
- Web: <http://www.vincent.org.rs/en/project/magbiovin-fp7-erachairs-pilot-call-2013>
- Social media: <https://www.facebook.com/magbiovin/>



VINCENT Center of Excellence for Knowledge-based multifunctional materials

## Department of Theoretical and Condensed Matter Physics

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Dr. Vladan Kusigerski, senior scientist  
Dr. Bratislav Antic, senior scientist  
Dr. Jovan Blanusa, senior research associate  
Dr. Natasa Jovic, senior research associate  
Dr. Marija Perovic, research associate  
Marko Boskovic, research assistant

## Department of Radioisotopes

Dr Sanja Vranješ - Đurić, senior scientist



Dr. Davide  
Peddis



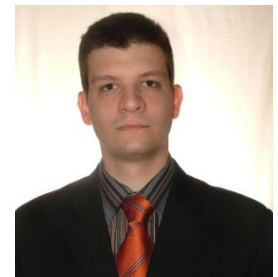
Dr. Nikola  
Knezevic



Dr. Ana  
Mrakovic

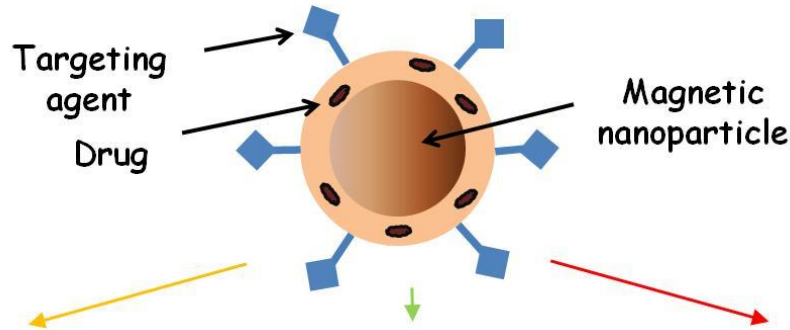


Milos  
Ognjanovic



Aleksandar  
Vukadinovic

Financial support: MAGBIOVIN / FP7 - ERAChairs - Pilot Call - 2013



**Therapy + diagnostics**

## THERANOSTICS

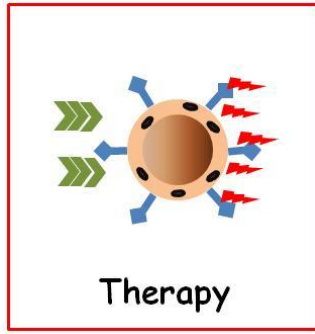
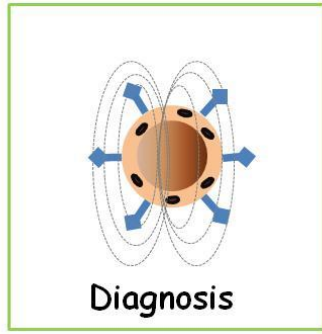
Enhanced efficiency  
Less side-effects

Criteria:

Stability

Bio/hemocompatibility

Multifunctionality



**Magnetic hyperthermia** (therapy)

**Targeted drug delivery** (therapy)

**MRI** (diagnostics)

**Radiolabeling** (therapy/ diagnostics)



# Design of magnetic nanostructures

**SYNTHESIS**

Control on composition, size, shape, yield, etc.

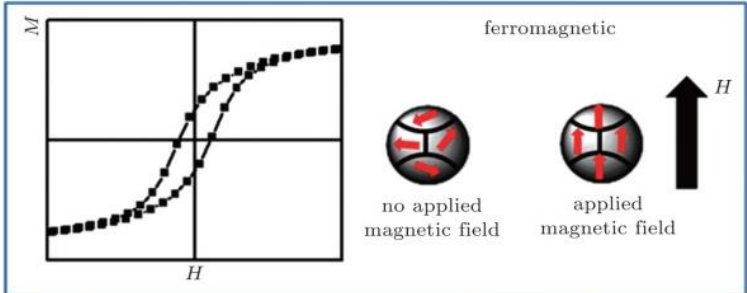
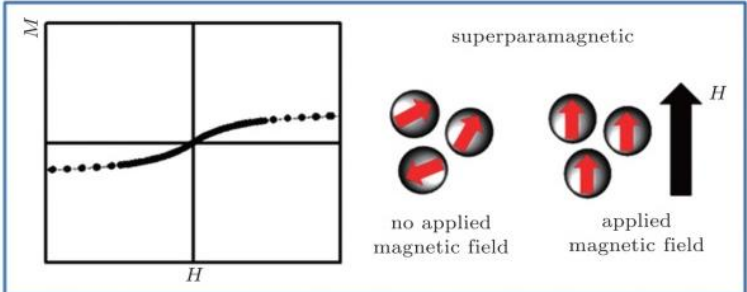
**STRUCTURE**

**MAGNETIC PROPERTIES**

- Composition
- Size**
- Size distribution
- Shape**

**!! MNP'S ANISOTROPY**

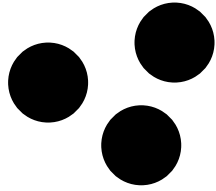
**!! MAGNETIC PROPERTIES**



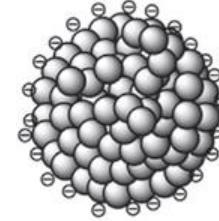
# Design of magnetic nanostructures for biomedicine TS.VI.D.5

**Magnetic core** - spinel ferrites ( $\text{Fe}_3\text{O}_4$ ,  $\text{Co}_x\text{Fe}_{2-x}\text{O}_4$ ,  $\text{Ni}_x\text{Fe}_{2-x}\text{O}_4$ , etc.)

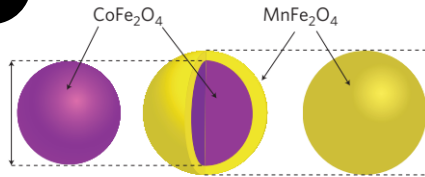
Single particles



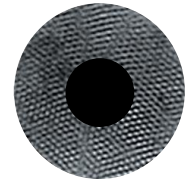
Nanoclusters



Core-shell nanomagnets



Nanocomposites



Lee, J.-H et al. Nat. Nanotechnol. 2011.

## Mesoporous silica nanostructures

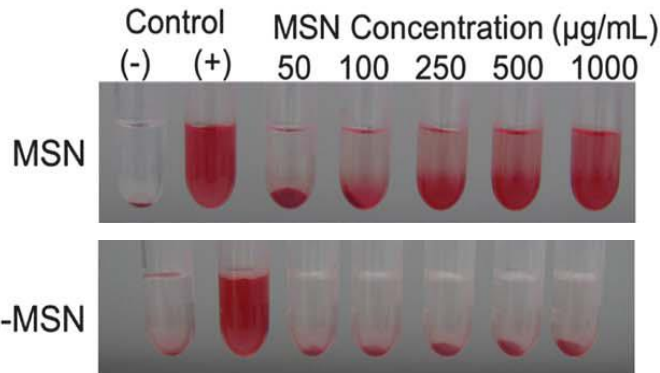
Specific surface area  $>1000 \text{ m}^2/\text{g}$  - functionalization, drug delivery

Size: 100-200 nm (preferred accumulation in tumour cells)

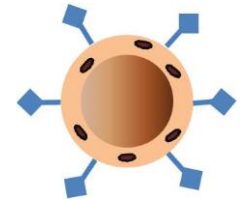
**Smart drug release**: changing biological, physical or chemical conditions (pH, T, etc.)

**Coating MNPs** by biocompatible compounds (citrate, polymers, silica, BSA)

**PEG: polyethylene-glycol/PEO: polyethylene oxide**

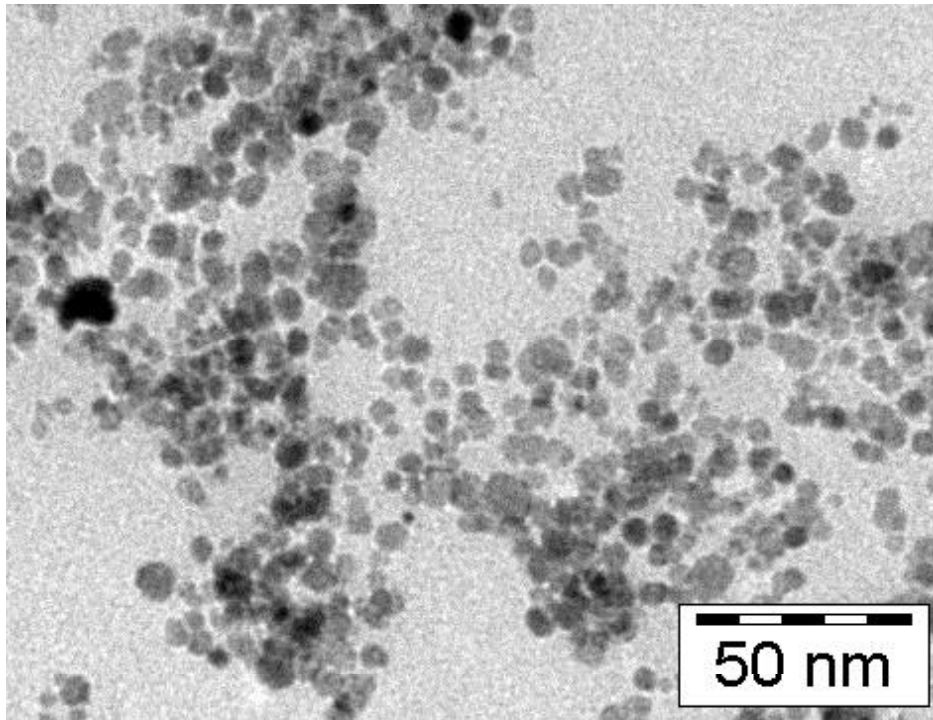


human serum albumine (HSA),  
gamma globulines ( $\gamma$ -Gs)

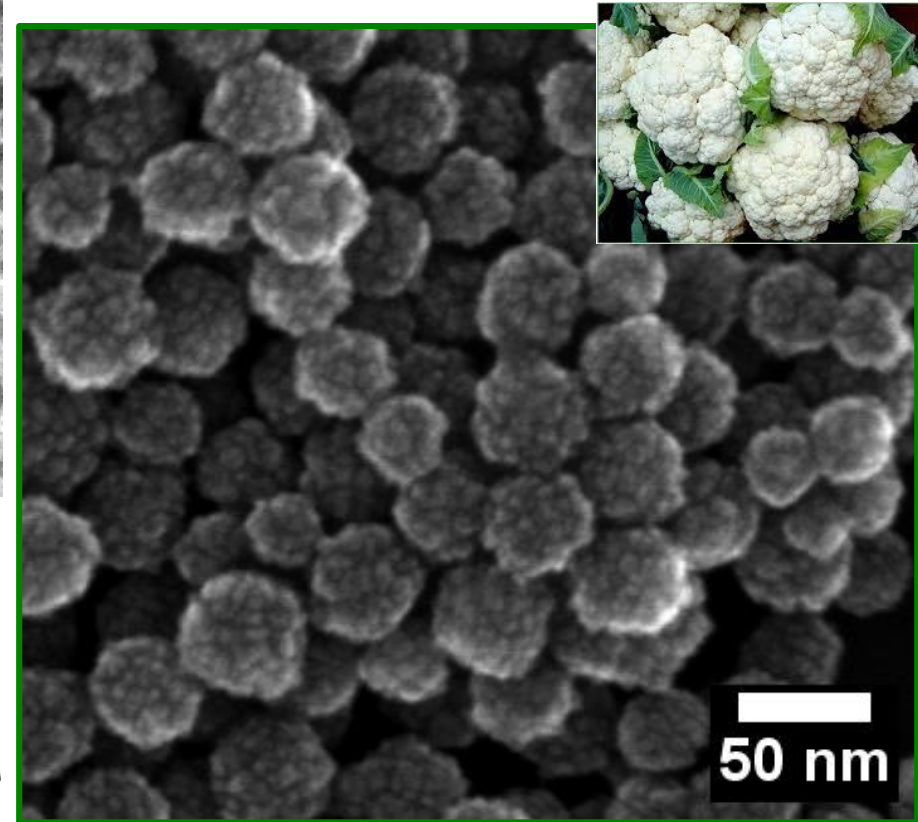


Non-specific protein adsorption is negligible

„recently cooked samples“



$\text{Fe}_3\text{O}_4$  particles - coprecipitation



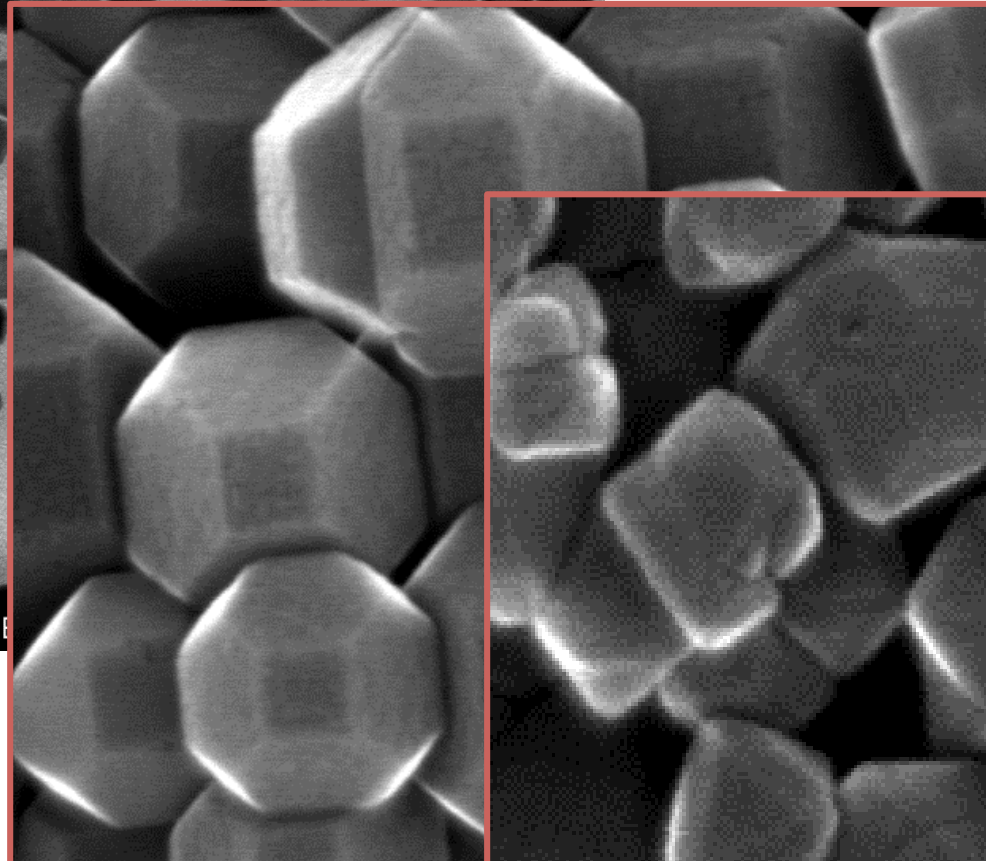
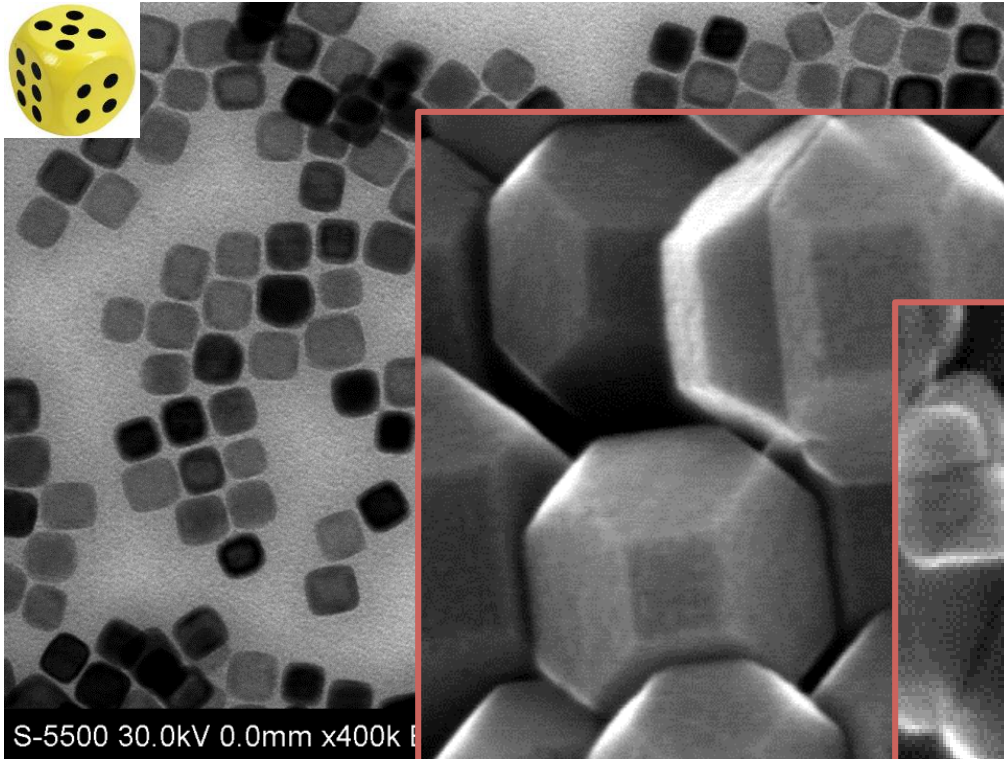
nanocube-aggregated cauliflower-like  $\text{NiFe}_2\text{O}_4$  particles - thermal decomposition

# Magnetic nanoparticles

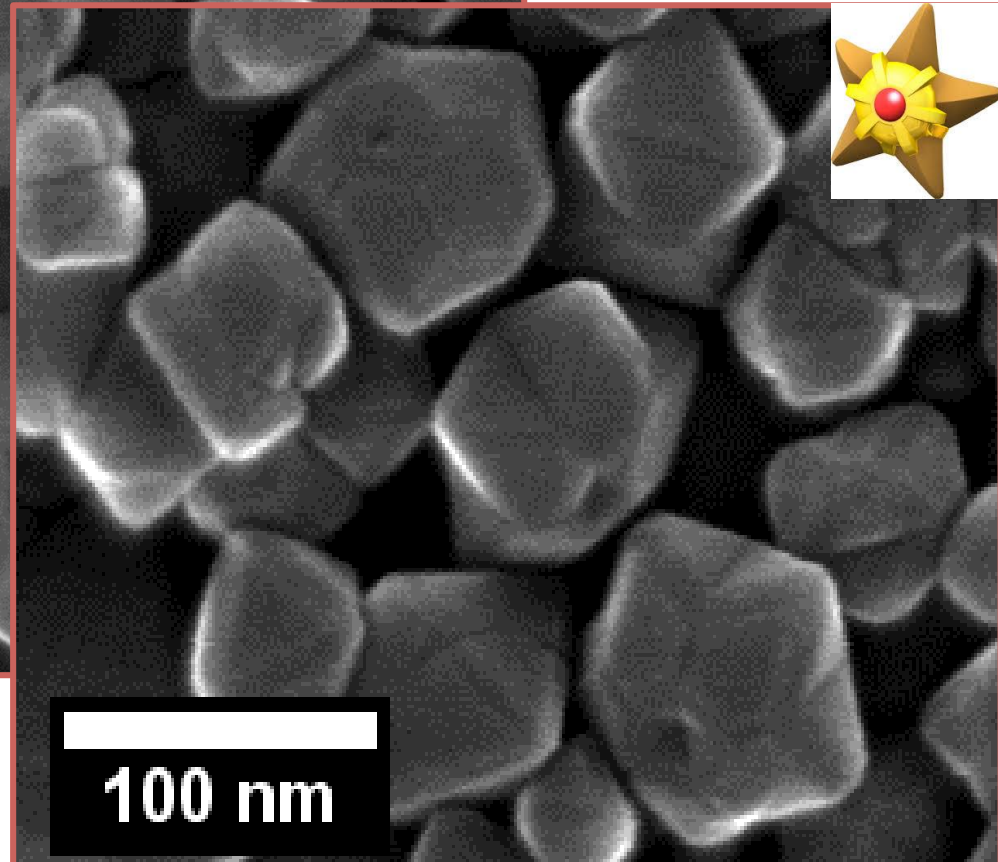
TS.VI.D.5

Cubic  $\text{Fe}_3\text{O}_4$  particles

„recently cooked samples“



$\text{Fe}_3\text{O}_4$  decahedras

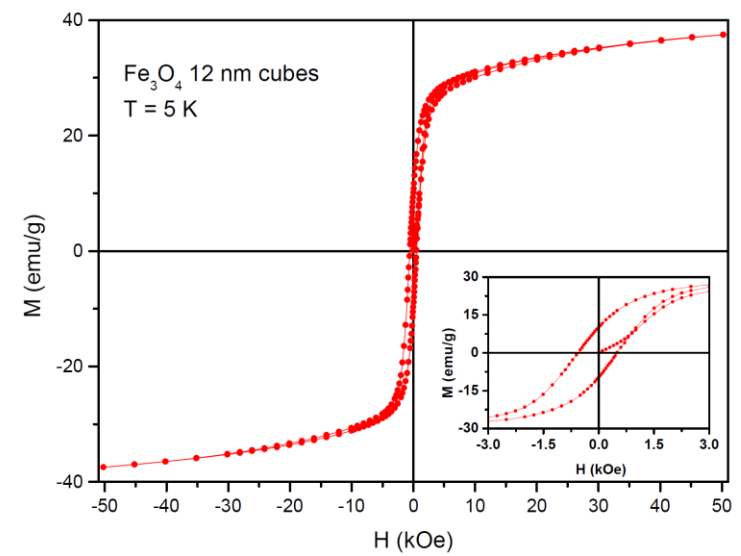
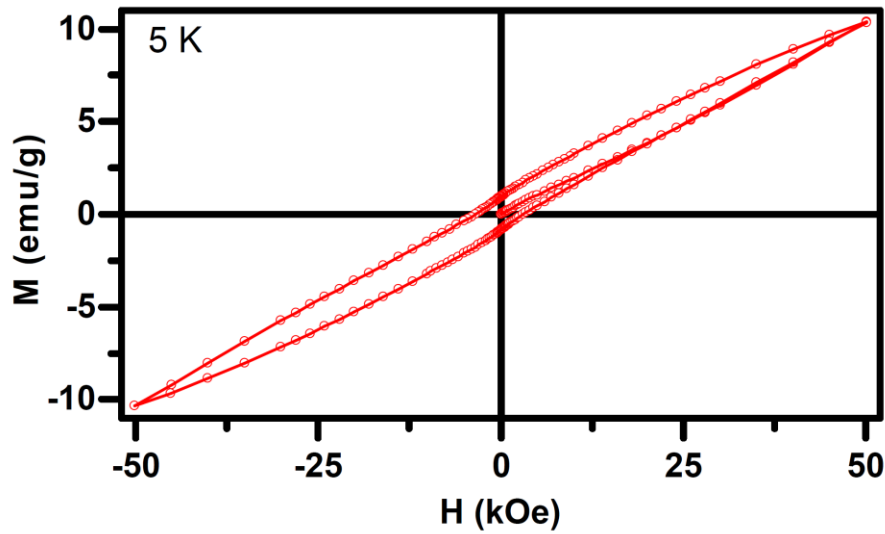
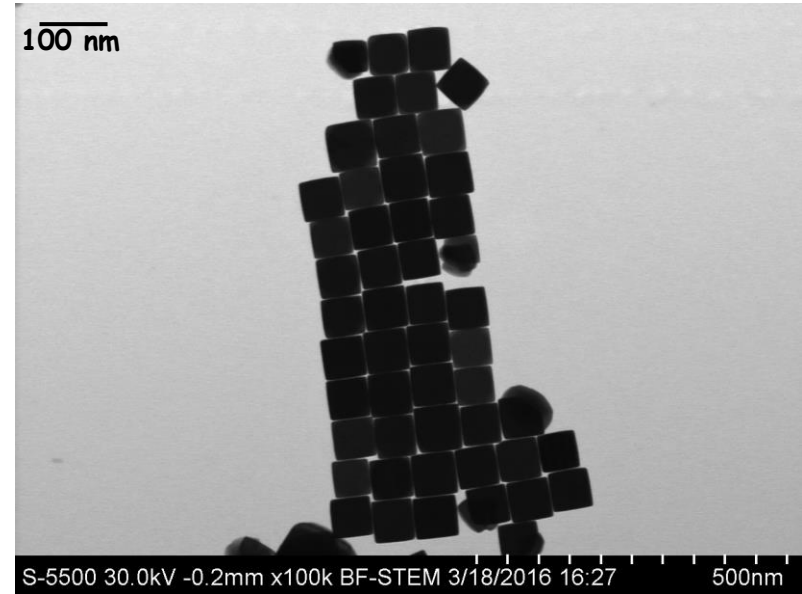
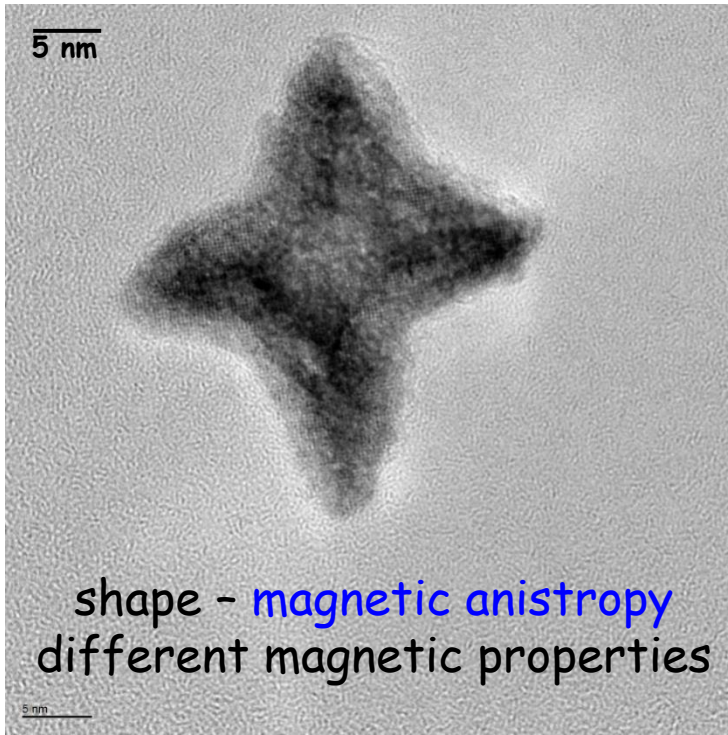


Truncated  $\text{Fe}_3\text{O}_4$  octahedras

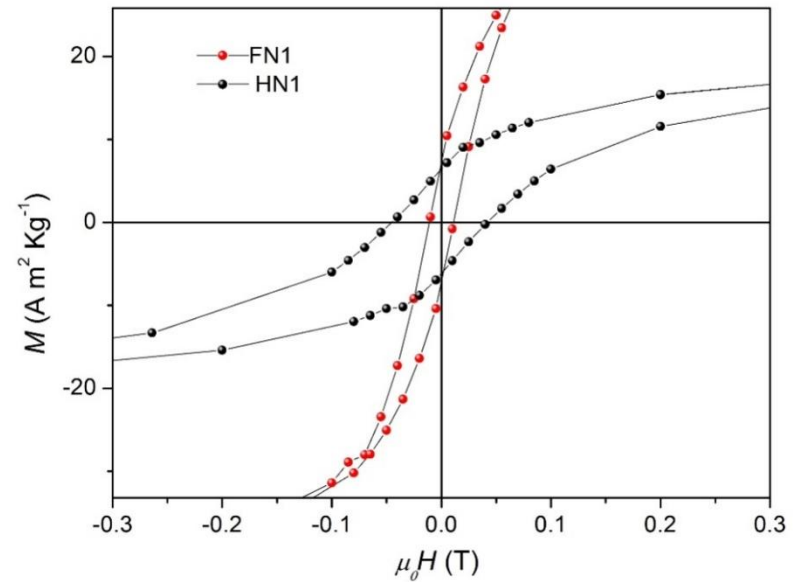
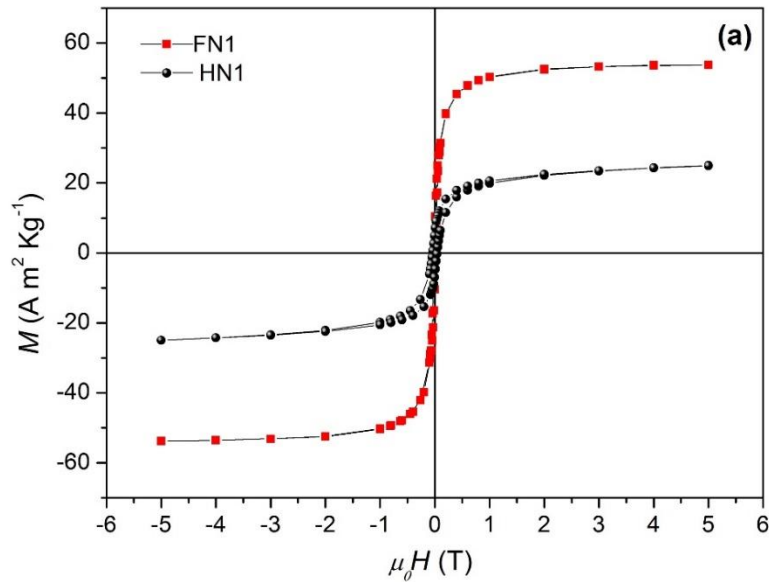
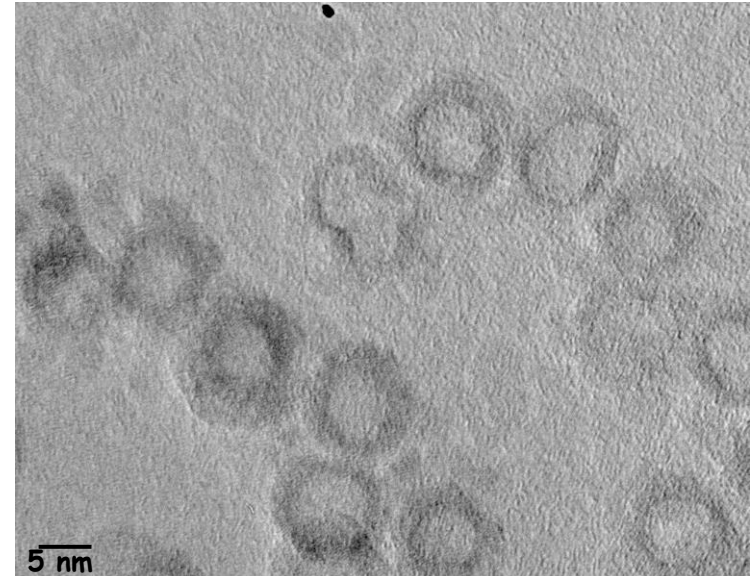
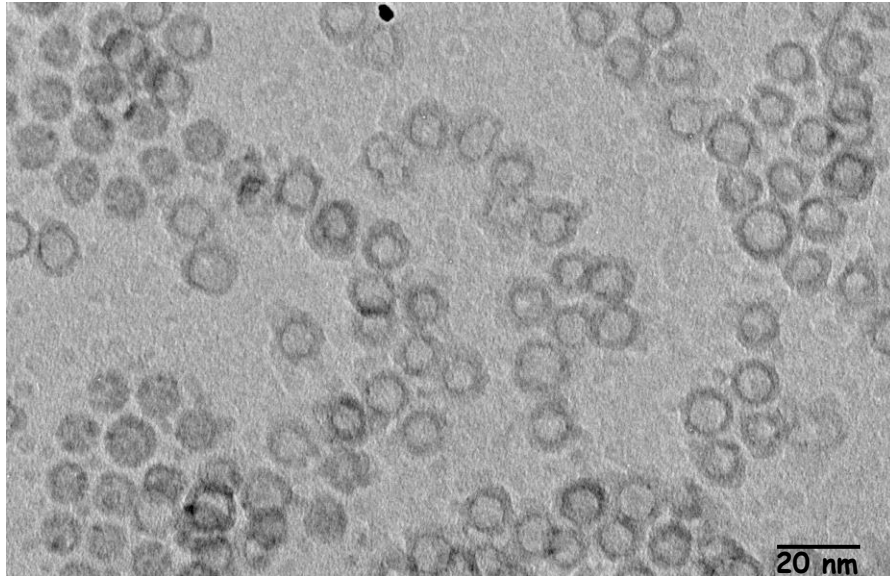


# Magnetic anisotropy - playing with shape

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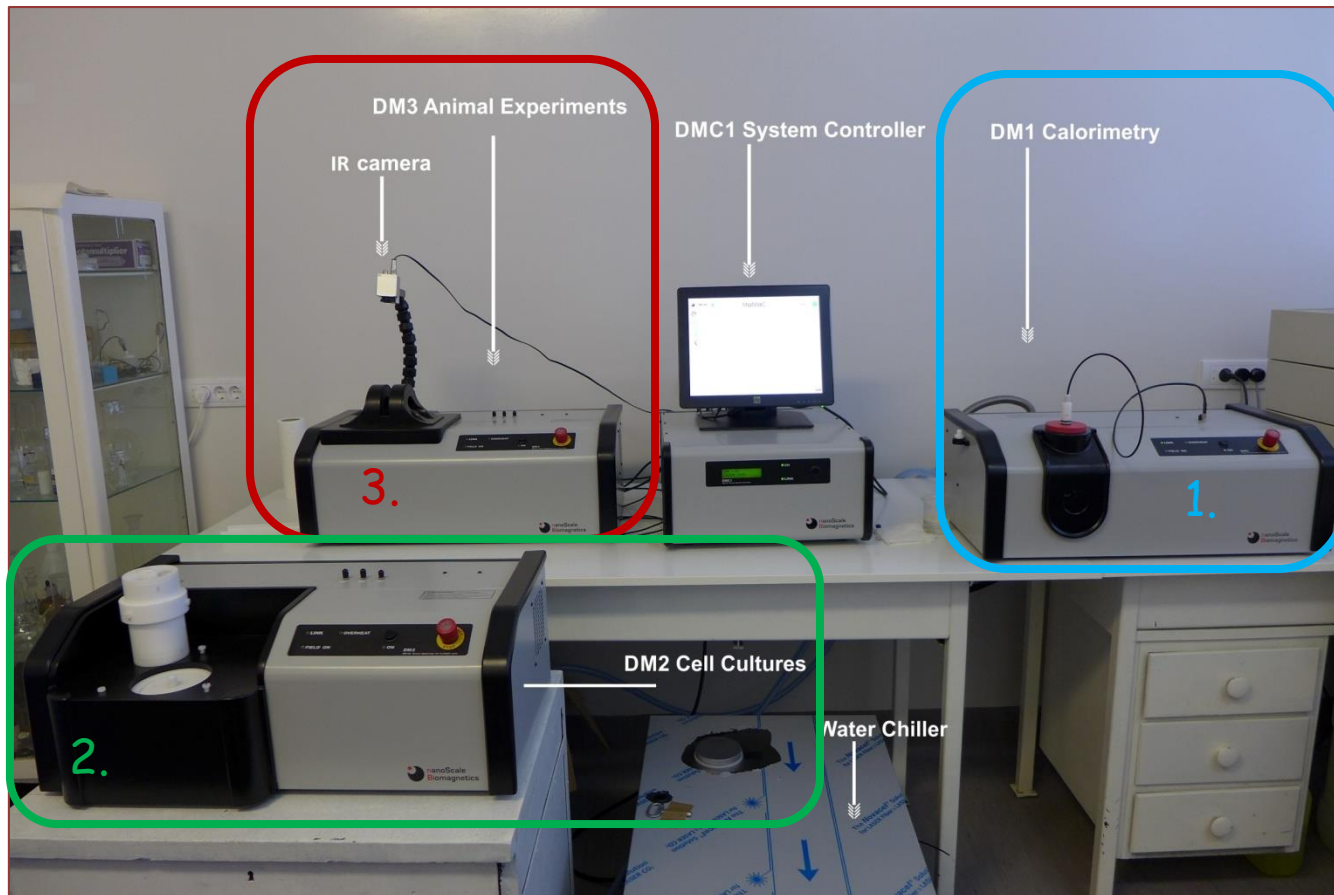


G. Muscas, R. Mathieu G. Singh, D. Peddis, in preparation



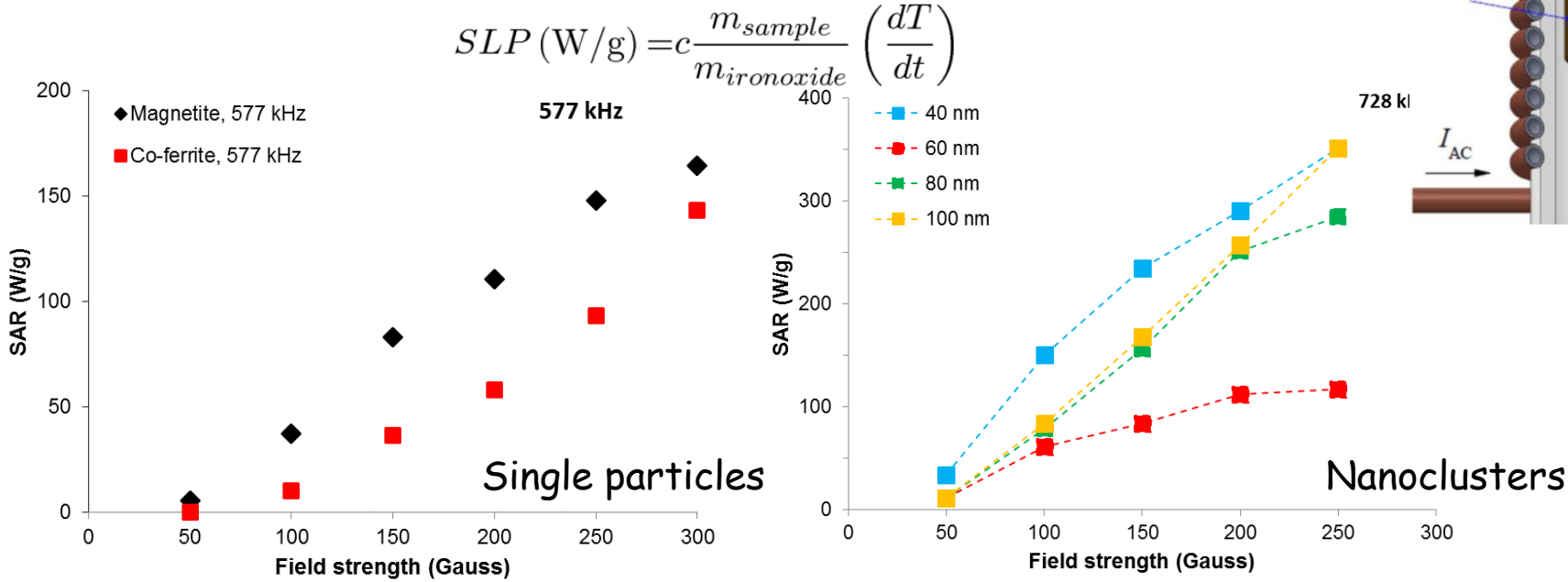
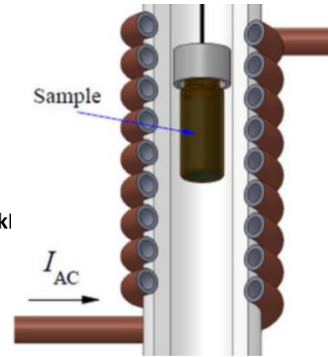
- The tumour cells are sensitive to heat
- Magnetic nanoparticles produce heat in alternating magnetic field -  
**Magnetic hyperthermia (min. 30 min, 42 °C)**
- Calorimetric measurements: DM100 (nB nanoScale Biomagnetics, Spain)
- Applicators: *physico-chemical*, *in vitro* and *in vivo* experiments

**DM1 - ferrofluids**    **DM2 - cell cultures**    **DM3 - small animals** (mouse, rat)



# Biomedical application - magnetic hyperthermia

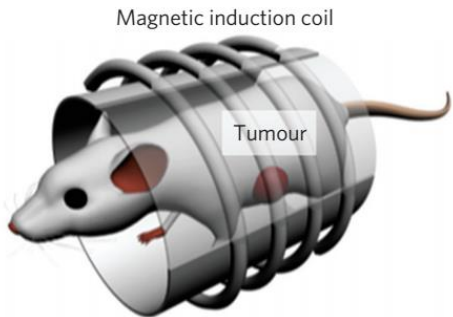
Ferrofluids - DM1 and DM2 applicators, *non-adiabatic conditions*  
 Field strength 50-300 Gauss, frequency: 82-808 kHz



*No uniform measurement protocol and evaluation method, home-made devices*

⇒ *difficult to compare results (various test conditions)*

**RADIOMAG COST TD1402 action** - interlaboratory measurements



**Brezovich criteria** - max. dose:  $4,85 \cdot 10^8 \text{ Am}^{-1}\text{s}^{-1}$

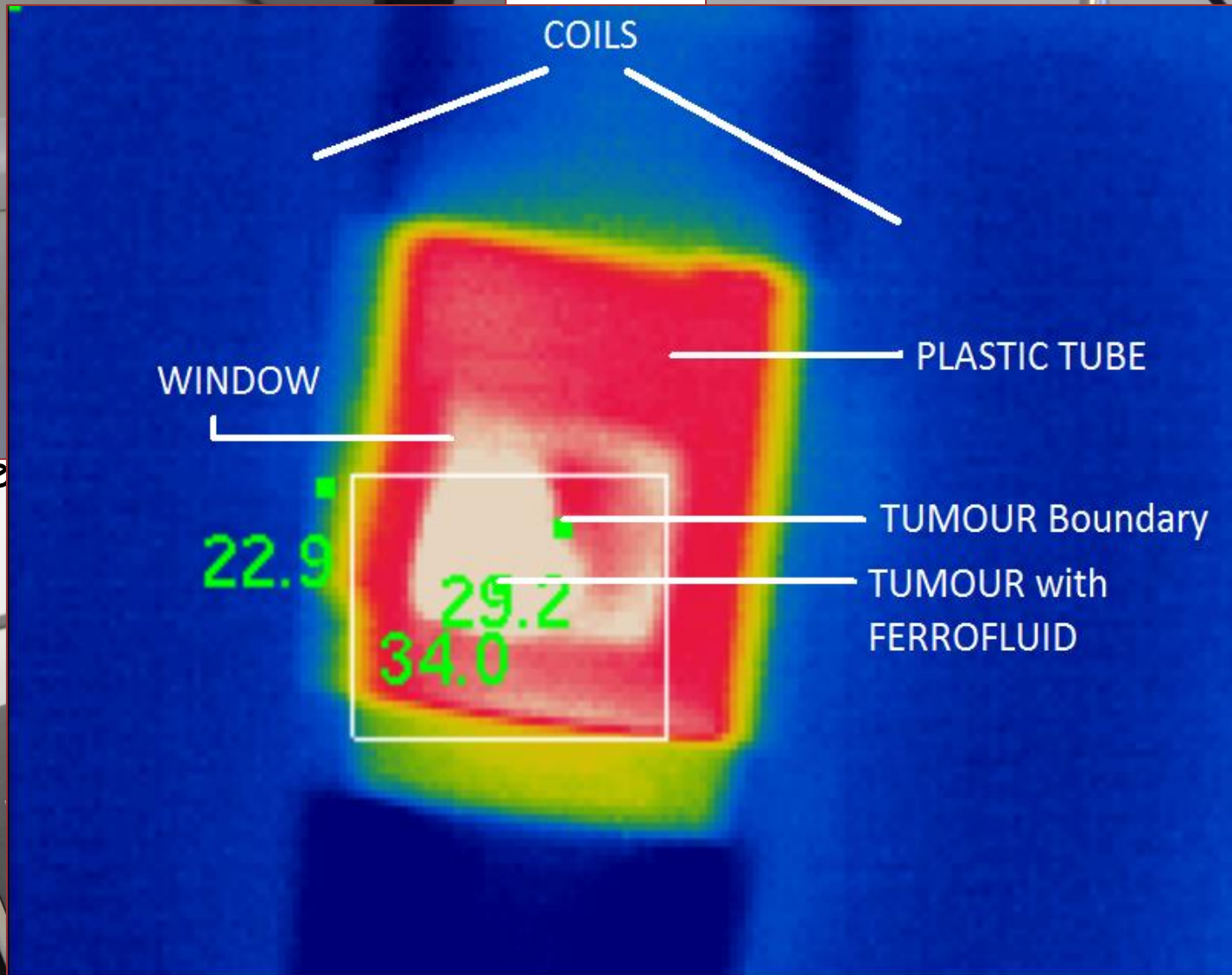
( $5 \cdot 10^9 \text{ Am}^{-1}\text{s}^{-1}$  Hergt et al.)     $110 \text{ kHz} \sim 20 \text{ kAm}^{-1}$  (250 Gauss)

*higher frequencies can induce irreversible changes in cells*

lower frequencies are preferred

magnetic field can be increased up to larger values

## DM3 - *in vivo* experiments + IR camera



Difference

MOUSE

# Biomedical application - radiolabeling

TS.VI.D.5

Vinča INN: radiochemical centre in the Western Balkan Region:

research, production and quality control - radiopharmaceuticals

Radiotracer technique - one of the most efficient way to monitor the MNPs *in vitro* and *in vivo* and to apply them for radiotherapy

$^{99m}\text{Tc}$	$\beta$	~6 h	Diagnostics
$^{131}\text{I}$	$\beta + \gamma$	8 d	Therapy and diagnostics
$^{90}\text{Y}$	$\gamma$	~2,7 d	Therapy

Used in 80% of nuclear medicine treatments

Thyroid diseases, neuroblastoma cancer(non-Hodgkin limphoma and liver~) treatment



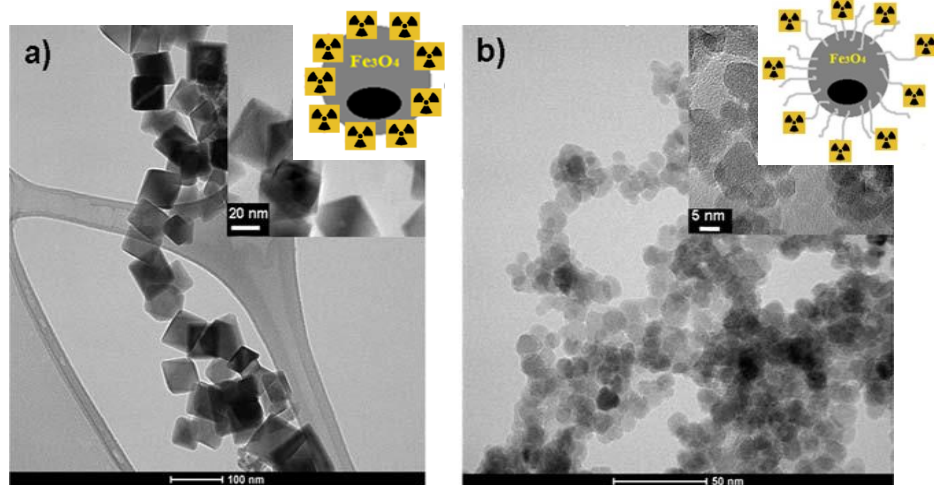
Laboratory for radioisotopes



$^{99}\text{Mo}/^{99m}\text{Tc}$  source

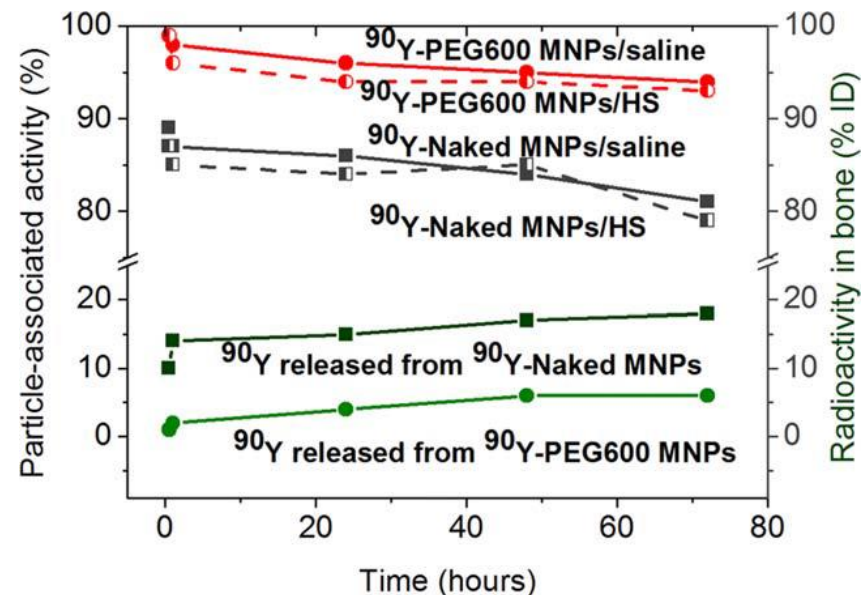


$^{131}\text{I}$ -capsules for diagnosis and treatment of thyroid tumours



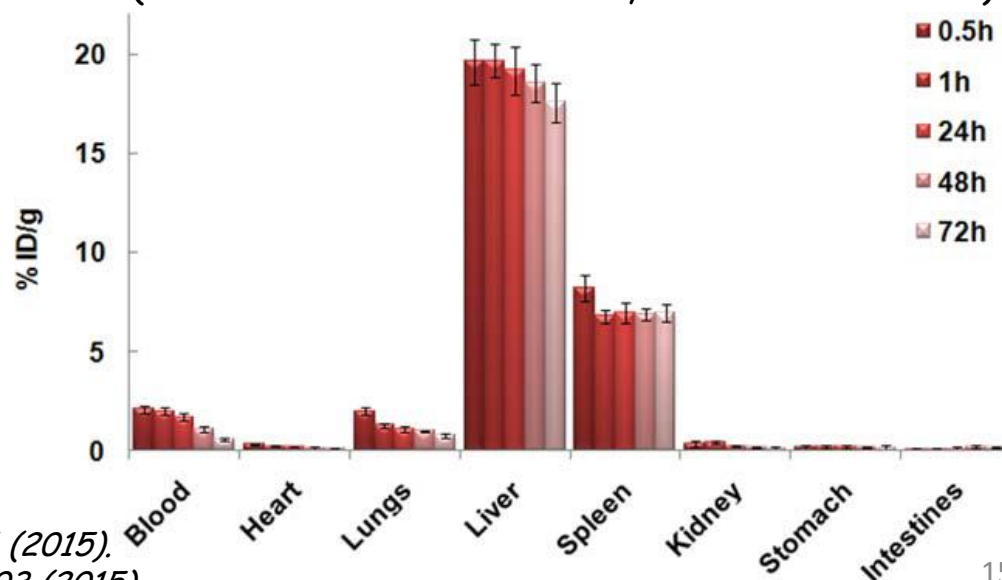
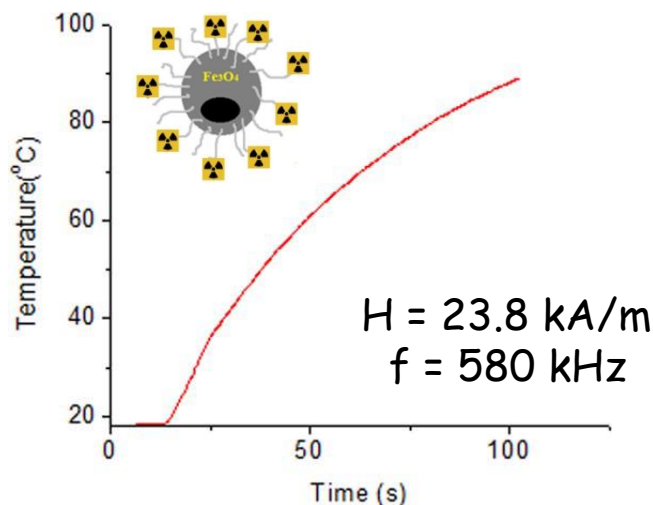
(a)  $Fe_3O_4$

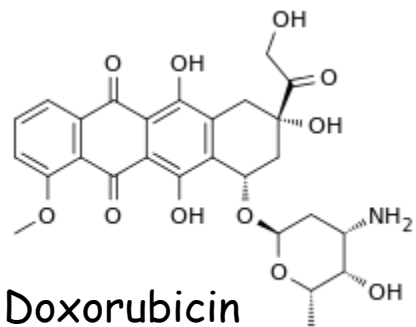
(b)  $Fe_3O_4$  -PEG600



## $^{90}Y$ - $Fe_3O_4$ -PEG600 MNP

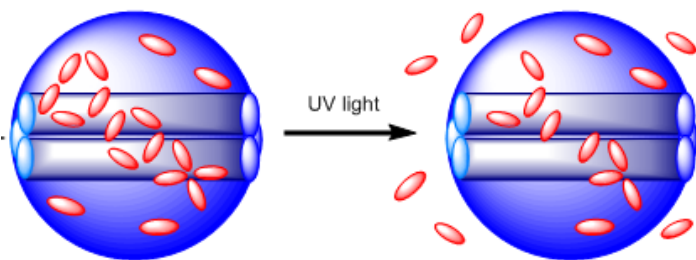
(intravenous administration, normal Wistar rats)



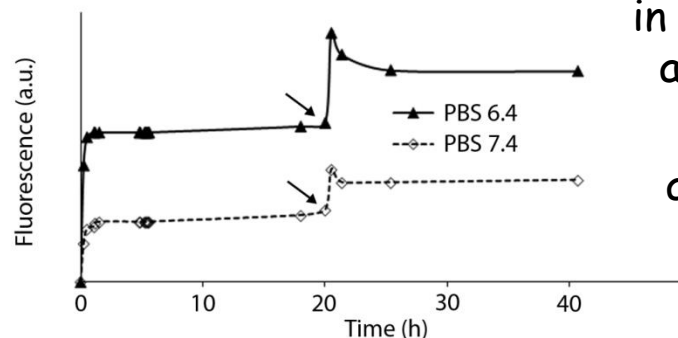
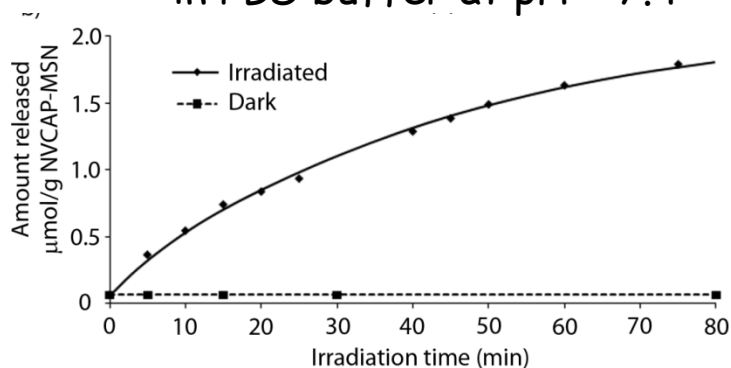


binding/release monitoring by HPLC or fluorescence

Mesoporous silica nanostructures  
Light or pH-controlled drug release

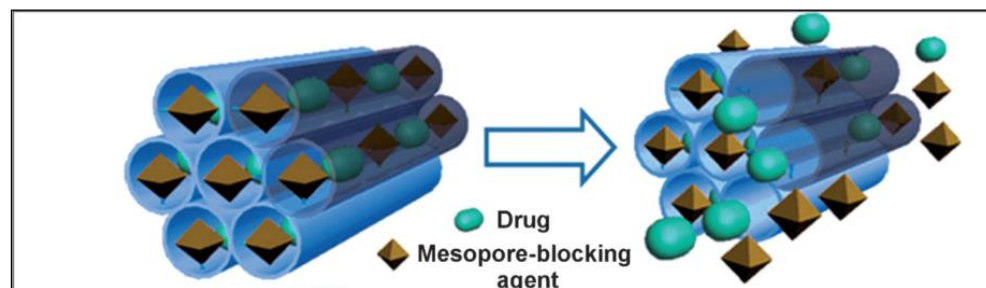


in PBS buffer at pH = 7.4



in PBS buffer at pH = 6.4

at pH = 7.4







Thank you for your attention!

Questions, remarks?

