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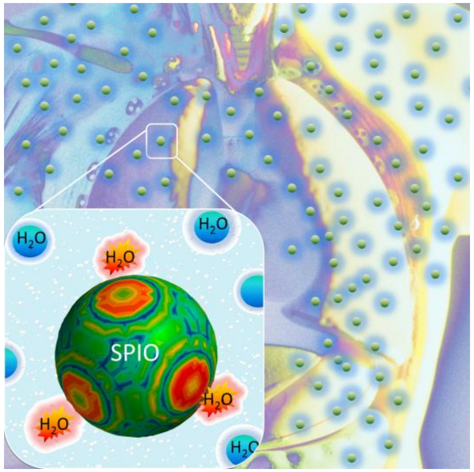
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Hydrophilic Superparamagnetic Iron Oxide Nanoparticles

What's Next in the MRI Contrast Agents Arena?



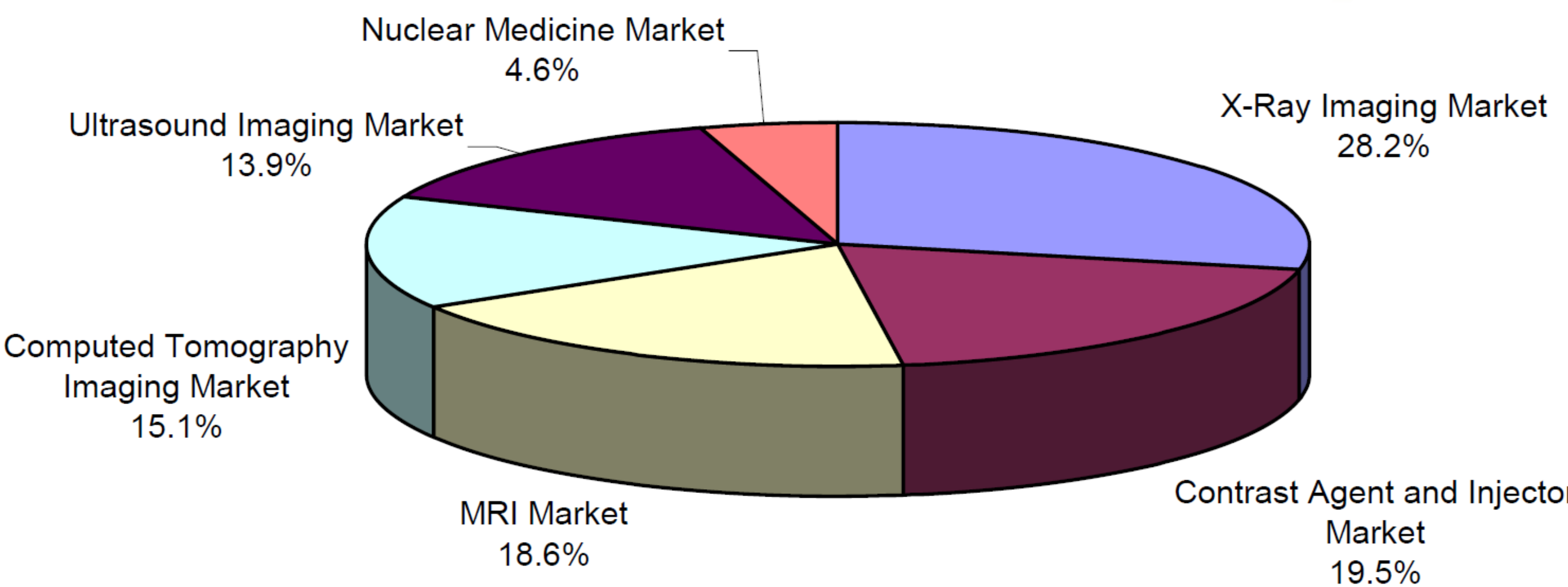
Giorgio Zoppellaro

The medical imaging market. Some facts

Averaged growing (EU/US) of 4.2% p.a. (since 2008)

$ 9.2 billion

€ 8.0 billion



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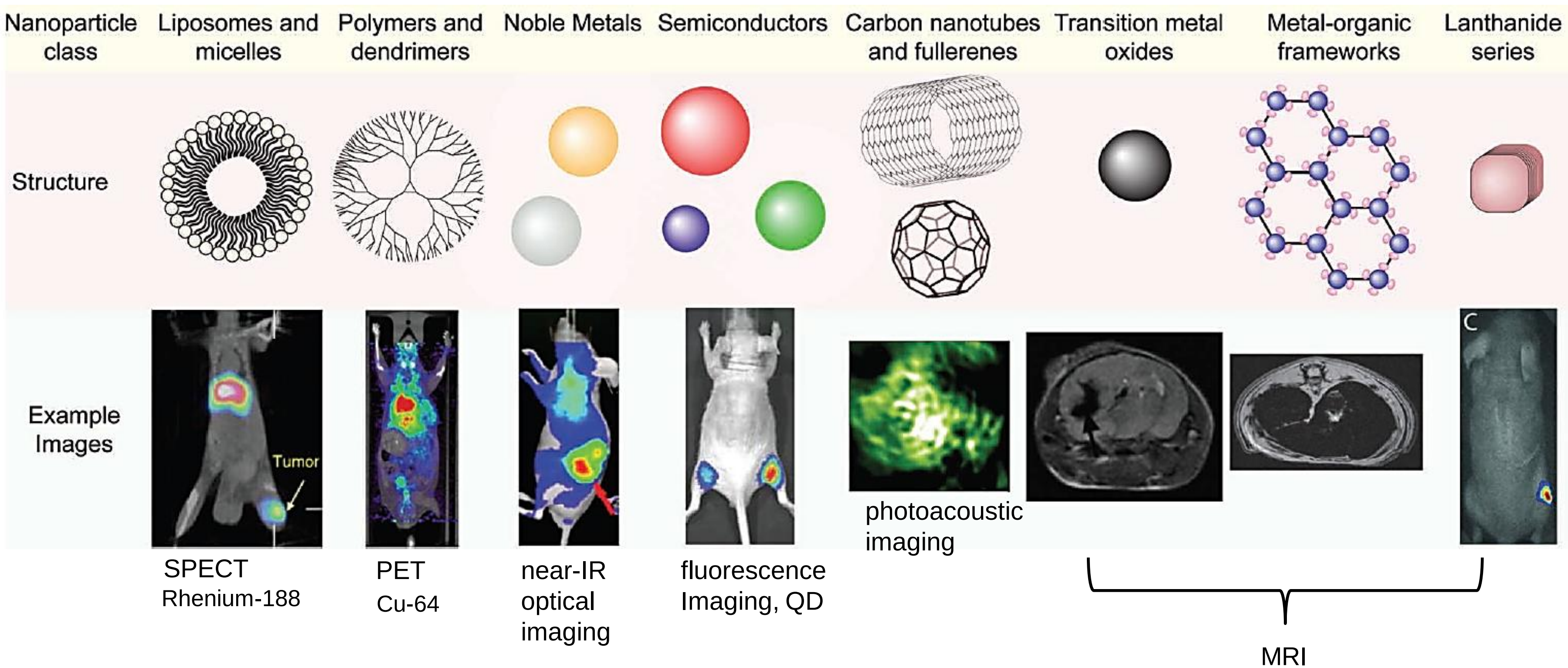

Typical nanomaterial formulations for imagine and therapy (e.g. cancer), their mechanism for imaging and associated representative images

Nuclear Medicine **X-Ray** **MRI** **Ultrasound** **Computed Tomography**

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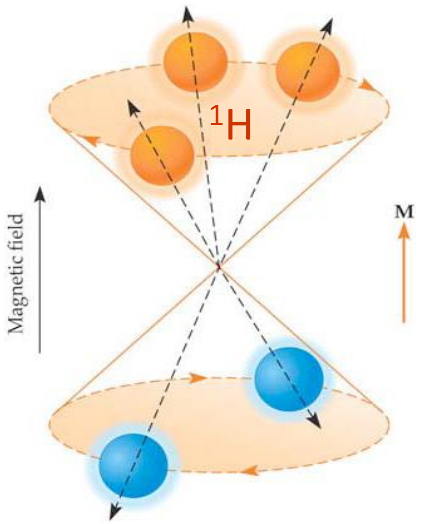
- ❖ Anatomical and functional imaging based on NMR principle
- ❖ Contrast developed due to local proton relaxivity

$$\mathbf{f = \gamma\ B_0}$$

f = Larmor frequency
γ = constant
B_o is magnetic field

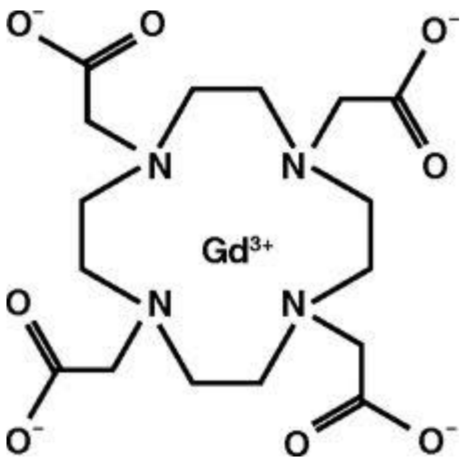


T_1 = spin-lattice relaxation ([C] / T_1 = r_1 = relaxivity)
T_2 = spin-spin relaxation ([C] / T_2 = r_2 = relaxivity)

T_1 MRI. FDA approved gadolinium-based contrast agents

Different types of gadolinium-containing contrast agents are available in different territories. For example, in the United States of America, Gd chelated contrast agents approved by the U.S. Food and Drug Administration (FDA) include:

gadodiamide (*Omniscan®*)
gadobenic acid (*Multihance®*)
gadopentetic acid (*Magnevist®*)
gadoteridol (*Prohance®*)
gadofosveset (*Vasovist®, Ablavar®*)
gadoversetamide (*OptiMARK®*)
gadoxetic acid (*Eovist®* in the USA,
Primovist® in other parts of the world)



T_2 iron oxide based MRI agents

Feridex I.V.® (also known as Endorem® and ferumoxides). This product was discontinued by AMAG Pharma in November 2008

Resovist® (also known as Cliavist®). This was approved for the European market in 2001, but production was abandoned in 2009

Sinerem® (also known as Combidex®). Guerbet withdrew the marketing authorization application for this product in 2007.

Lumirem® (also known as Gastromark®). Gastromark was approved by the FDA in 1996

Clariscan™ (also known as PEG-fero, Feruglose, and NC100150). Development was discontinued due to safety concerns

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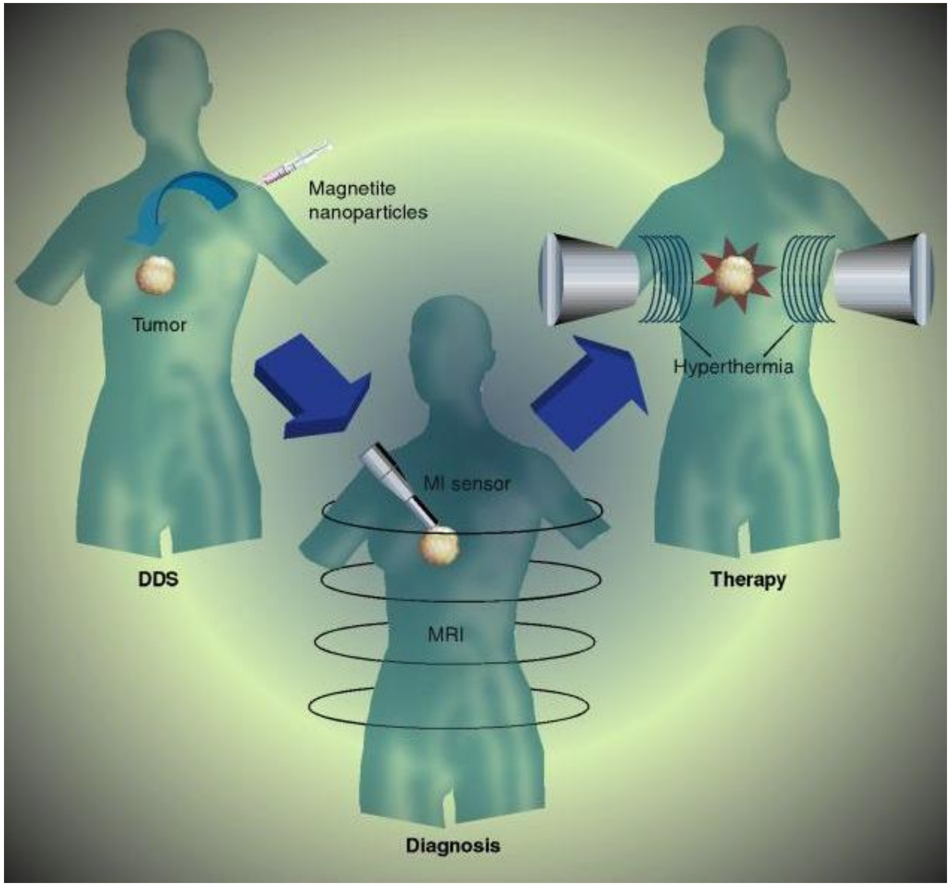
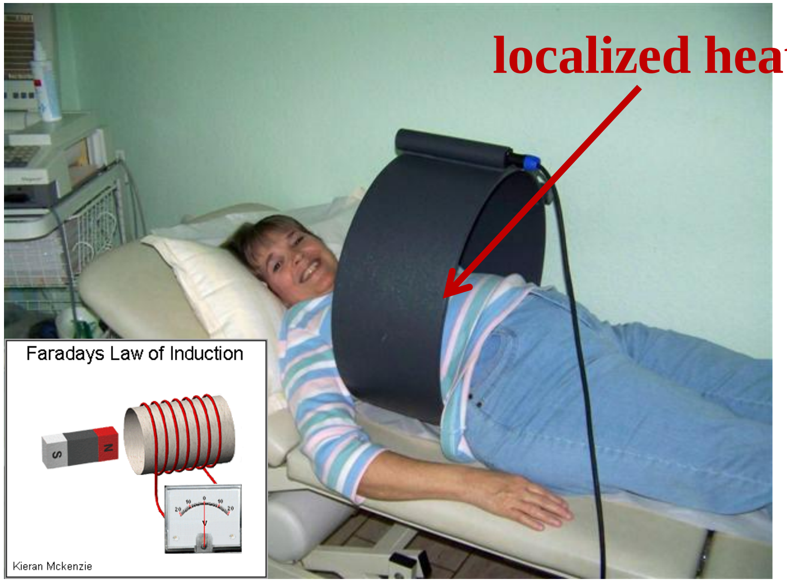
Theronestic Application (Therapeutic + diagnostic)



AC magnetic field induce localized heating (42-46°C) with SPIO

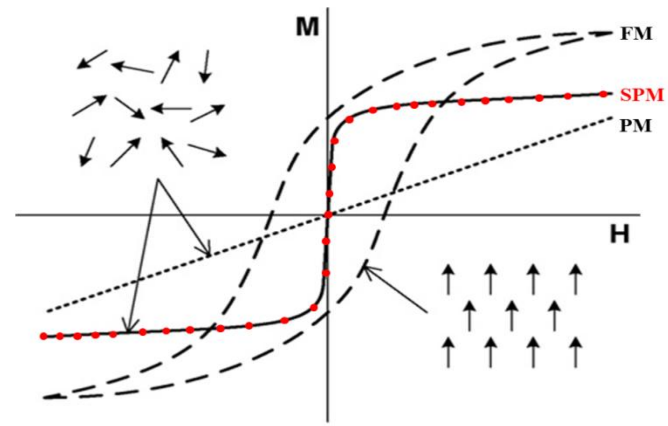


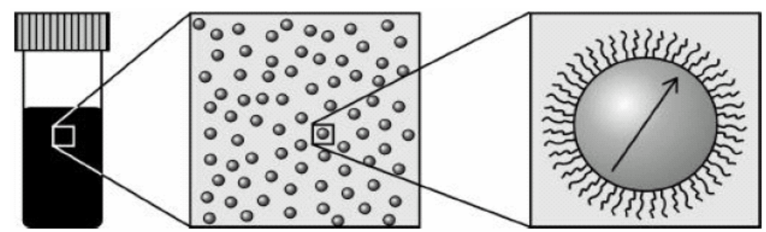
irreversible thermal damage of tumor

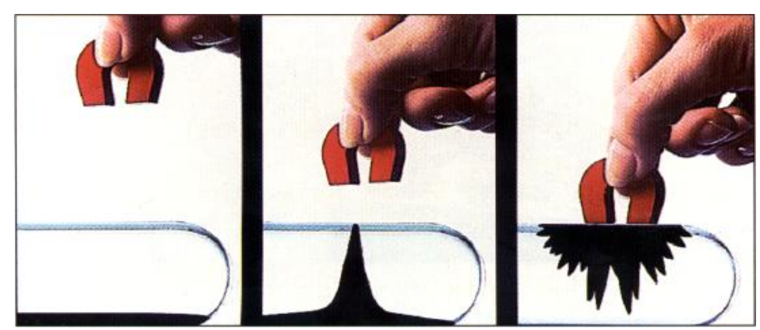
- ✓Viability of cancer cells significantly reduces over the normal cell
- ✓Destruction of cancer cell due to thermal shock induced toxicity

What is needed ?

- **Superparamagnetic**
- **Colloidal stability**
- **Controlled size & monodisperse**
- **High saturation magnetization (M_S)**
- **Biocompatibility & Non-toxicity**
- **Water soluble**
- **Tailored surface chemistry**





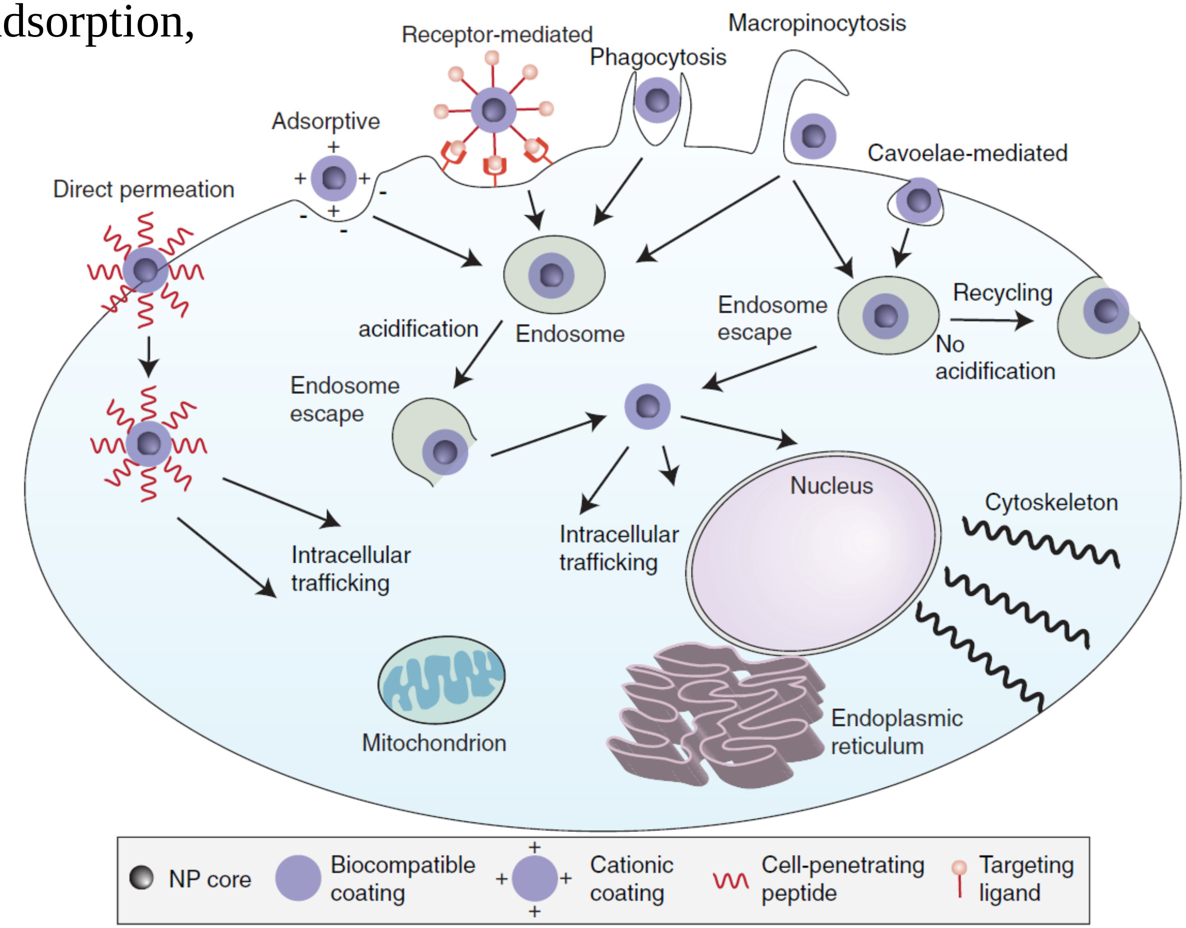


Tailored surface chemistry

The surface coating determine the adsorption,

distribution, metabolism

and excretion process



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Selection of Magnetic Nanoparticles

- **Ferromagnetic transition metal (Fe, Co and Ni)**

— unstable due to rapid oxidation
— unsuitable due to toxicity

- **Ferrimagnetic bimetallic oxide (M-Ferrites)**

— $MnO{\cdot}Fe_2O_3$, $CoO{\cdot}Fe_2O_3$ $NiO{\cdot}Fe_2O_3$
— unsuitable due to toxicity

- **Superparamagnetic iron oxide (γ-Fe_2O_3 , Fe_3O_4)**

— high chemical stability
— limited toxicity
— biodegradability
— environmentally safe

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Synthetic Procedures

❑ Physical (Top-down approach)

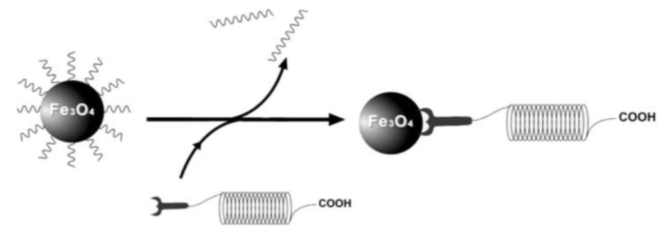
- Attrition or milling – **uncontrolled size and size distribution**
- Lithography – **low feature resolution or extremely high cost**

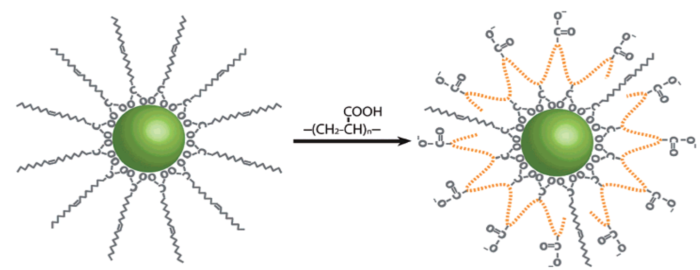
❑ Chemical (Bottom-up approach)

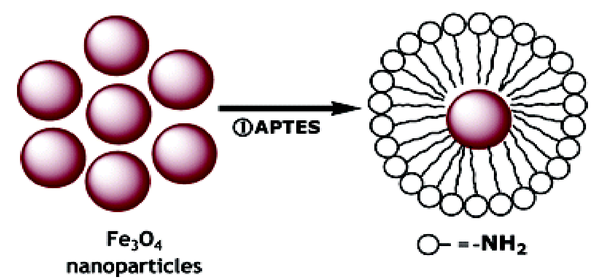
- Co-precipitation – **broad size distribution**
- Microemulsion – **surfactant impurity and low yield**
- Hydrothermal – **risk of high pressure**
- Thermal Decomposition – **controlled size and size distribution**

Problems in Functionalization

- Synthetically unfriendly
- Toxic solvents
- Risk of dissociation of the coating layers
- Risk of agglomeration
- Expensive methods
- Less yield



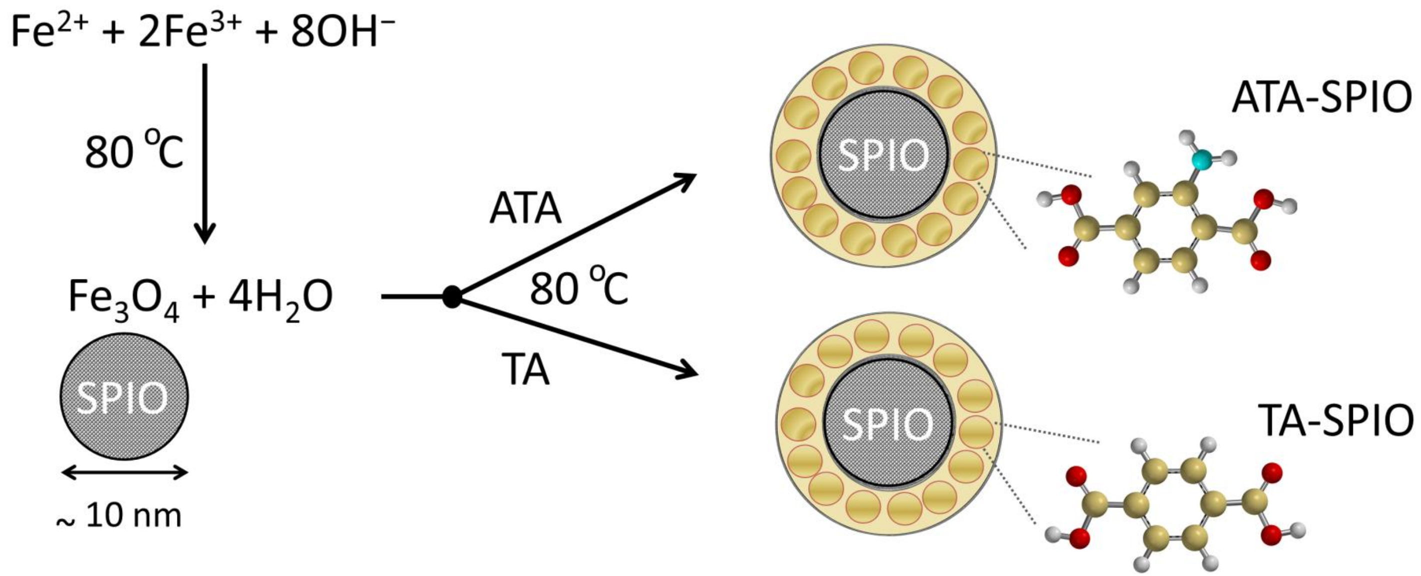




Challenges

✓One step synthesis of water stable SPIO
✓nanoparticles with high Ms by a facile, flexible and inexpensive method

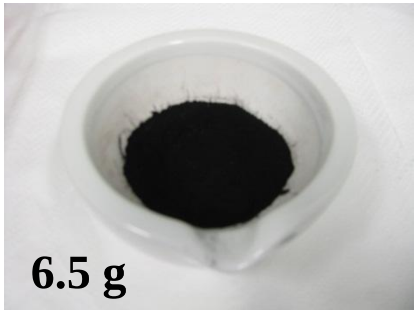
Our solution



- **Easy, inexpensive, large scale & faster synthesis**

$FeCl_3.6H_2O$ NH_4OH (29%)

$FeCl_2.4H_2O$ H_2O ATA or TA



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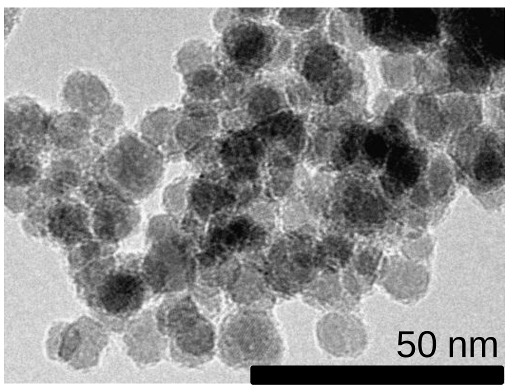
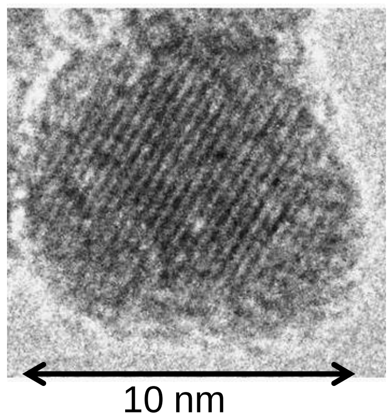
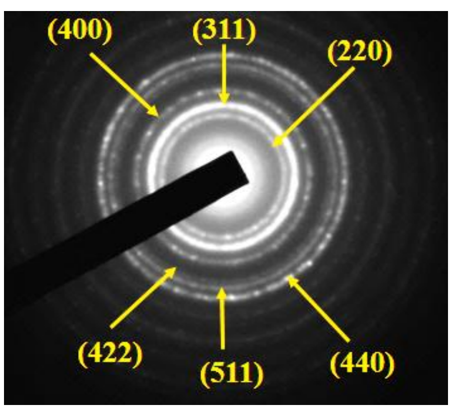
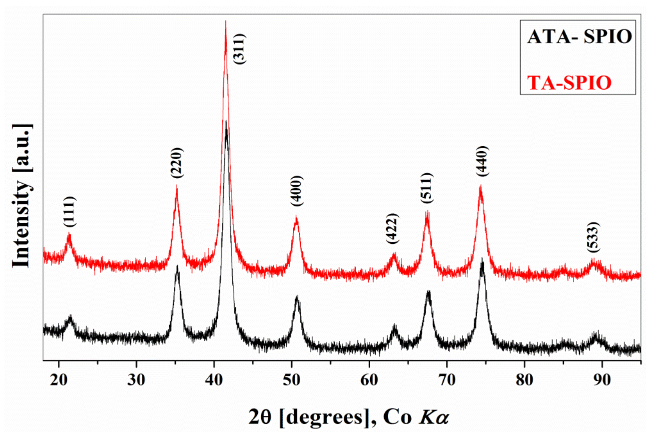
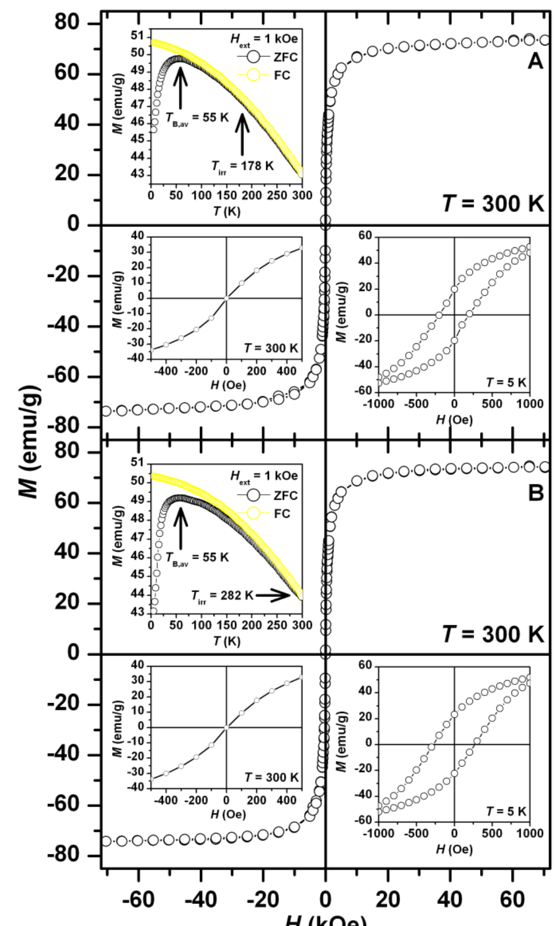
- **Good crystallinity. Small length (0.8 nm) of ATA or TA coating reduces diamagnetic content. The resulting SPIO systems exhibit good (~74 emu/g, RT) magnetization values**











ATA

TA

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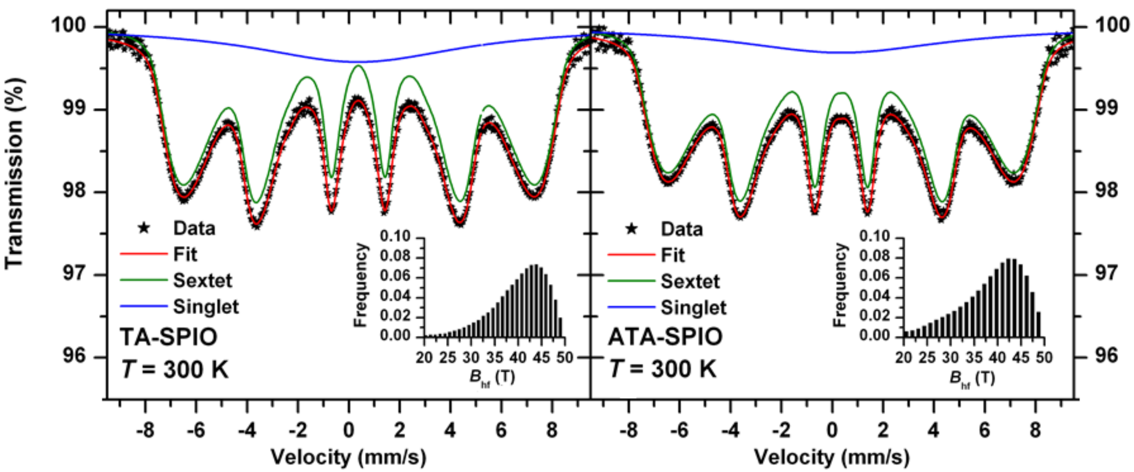
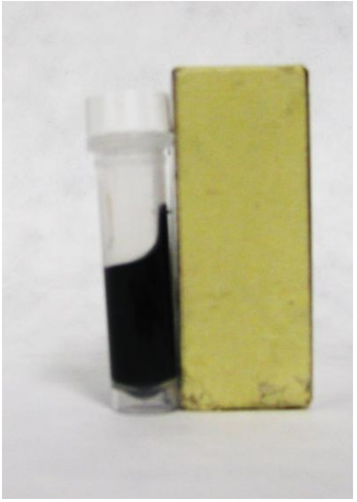
- **Non stoichiometric composition of SPIO**

Inner core (γ-Fe_2O_3), outer core Fe_3O_4

- **They maintain excellent ferrofluid properties for long time**

(after 4 for weeks)





Sample	T (K)	Component	δ ± 0.01 (mm/s)	ΔE_Q ± 0.01 (mm/s)	B_{hf} ± 0.3 (T)	RA ± 1 (%)	Assignment
ATA-SPIO	300	Sextet	0.36	0.02	38.8*	77	Blocked portion
		Singlet	0.36	--------------	-----------	23	Relaxating portion
TA-SPIO	300	Sextet	0.35	0.01	36.7*	82	Blocked portion
		Singlet	0.35	--------------	-----------	18	Relaxation portion

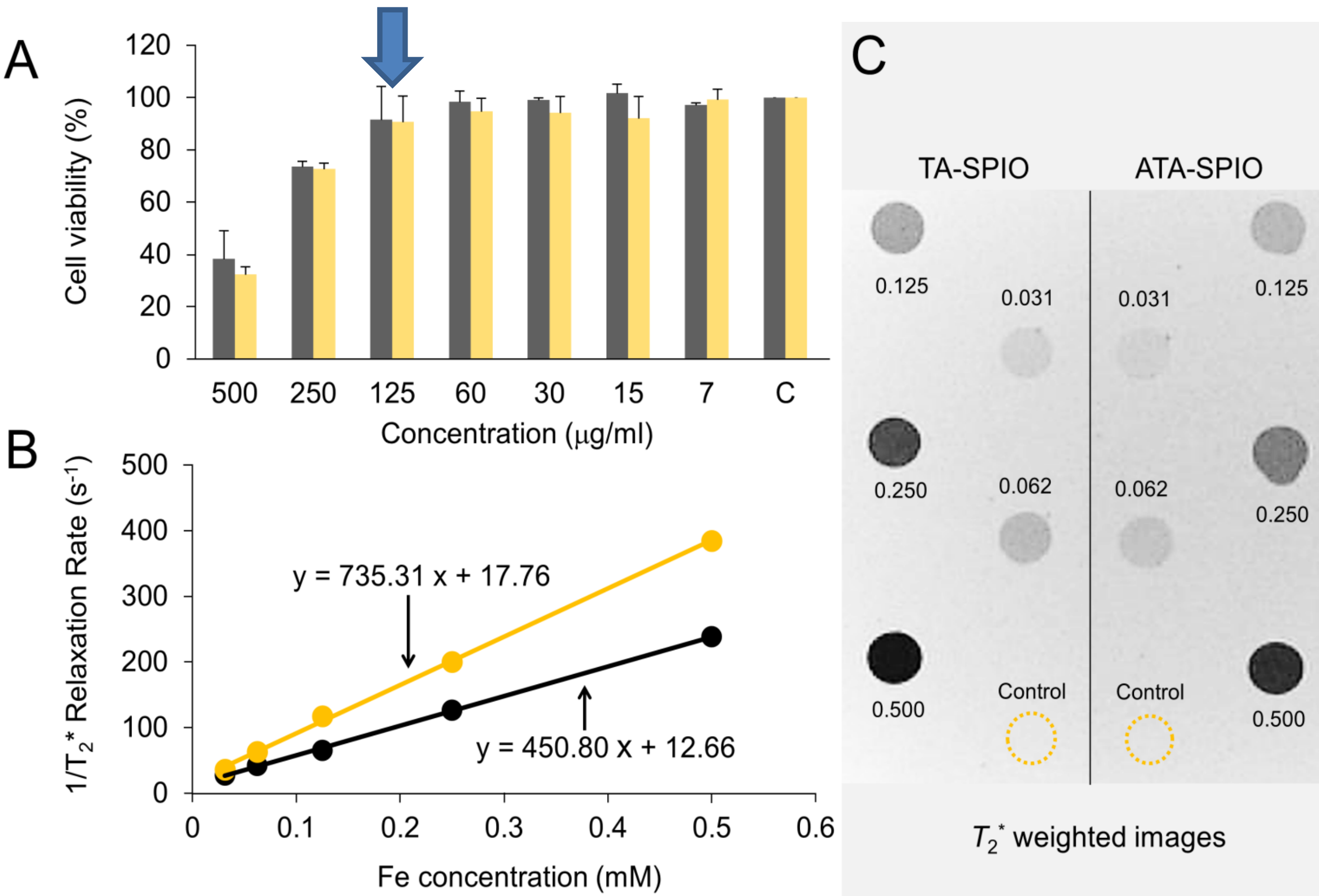
Zeta potential (mV, 298 K)

+ 17.5 for TA-SPIO
+ 8.39 for ATA-SPIO

Zeta –Average (nm, 298 K)

221 nm for TA-SPIO
283 nm for ATA-SPIO

SPIO highly biocompatible due to surface coatings, high relaxivities (r_2*) values



Cytotoxicity test and MRI contrast (T_2*) properties of TA/ATA− SPIO. (A) The cytotoxicity profile of ATA–SPIO (dark–grey bars) and TA–SPIO (yellow bars) NPs. The label C represents the control samples (no ATA/TA−SPIO added). (B) The transverse relaxation rates ($1/T_2$*) versus Fe concentration for ATA–SPIO (black circles) and TA−SPIO (yellow–circles) NPs with correspondent linear fittings. (C) Phantom experiments for TA–SPIO and ATA–SPIO NPs with Fe concentrations employed (mM) as those reported in panel (B).

Summary

- **SPIO nanoparticles have been engineered by one pot methodology, with a faster and economic procedure, and in large scale.**

- **Surface of the SPIOs are attached with ATA/TA coating which provide the water solubility, biocompatibility and free surface functional –COOH;NH_2/–COOH groups which could be further attached with biomolecules for *in vivo* targeting applications**

- **The small length ATA/TA coating provides better crystallinty and magnetization of SPIO nanoparticles (Ms = 74 emu/g at RT and Ms = 84 emu/g at 5K)**

- **The SPIO nanoparticles demonstrated higher MRI relaxivity (r_2^* = 450.8 & 735.3 $s^{-1}mM^{-1}$), thus they are promising nanocomponents as contrast agent in clinical MRI**

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The Group / Collaborations

G. Zoppellaro, L. Machala and R. Zboril	Design/Concepts
D. Maity	The Hard work and enthusiasm
V. Sedenkova, J. Tucek	The Mossbauer/SQUID souls and constant feedback
K. Safarova	The TEM/SEM pro and Master of kindness
K. Polakova, K. Tomankova	The supersonic bio-engines
C. Diwoky, R. Stollberger	The ultrafast MRI agents
K. Siskova	The IR/Raman ISI source of knowledge
J. Pechousek	The dedicated health keeper of our Mossbauer machines

And Colleagues

Dalibor Jancik	Jiri Frydrych	Jan Filip	Eleni Petala
Pavel Tucek	Cuda Jan	Jana Sevcikova	