# Magnetic nanoparticles design for medical diagnosis and therapy

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***European Network of Excellence***
Functionalized Advanced Materials and Engineering of hybrids and ceramics

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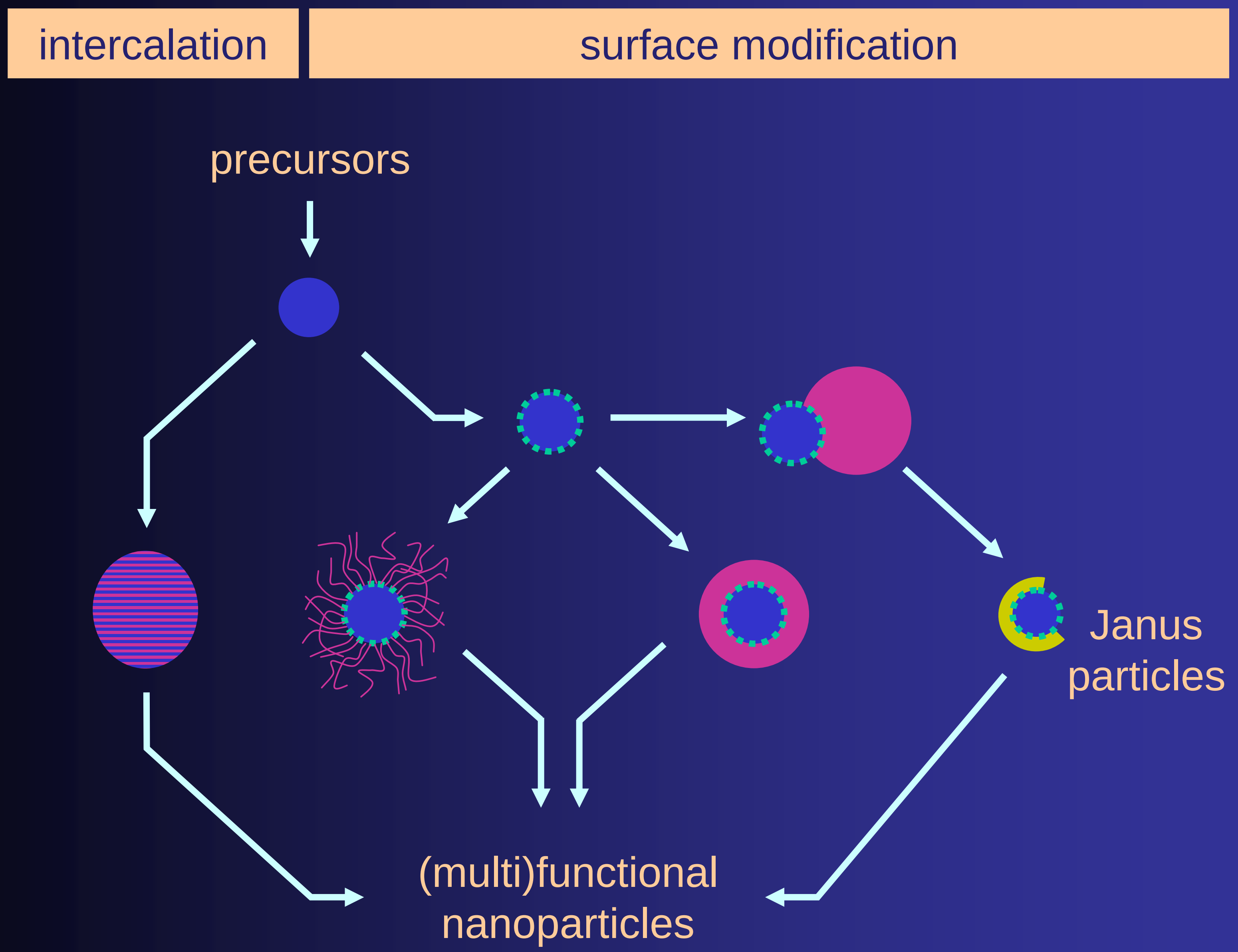
- intermetallics
- luminescent materials
- magnetic materials
- metal matrix composites
- molecular magnets
- ...

# Hybrid organic-inorganic nanomaterials



# Why are <u>magnetic</u> nanoparticles more and more relevant in biomedical applications ?

- penetrability of magnetic fields into human tissue
- absence of magnetic entity in living bodies

- tractable by a magnetic field gradient
  - *in vitro*: **separation** and **purification**
  - *in vivo*: **physical targeting** of drug
- able to alter $^{1}H$ relaxation
  - MRI contrast agent
- able to heat in AC magnetic field
  - mediator for local hyperthermia

Duguet and coll., *Nanomed.*, <u>1</u>, 157 (2006)

## Why are magnetic nanoparticles more and more relevant in biomedical applications ?

- small hydrodynamic diameter

- can "get close" to a biological entity of interest
  - cell (10 - 100 µm)
  - virus (20 - 450 nm)
  - protein (5 - 50 nm)
  - gene (2 nm wide and 10 - 100 nm long)

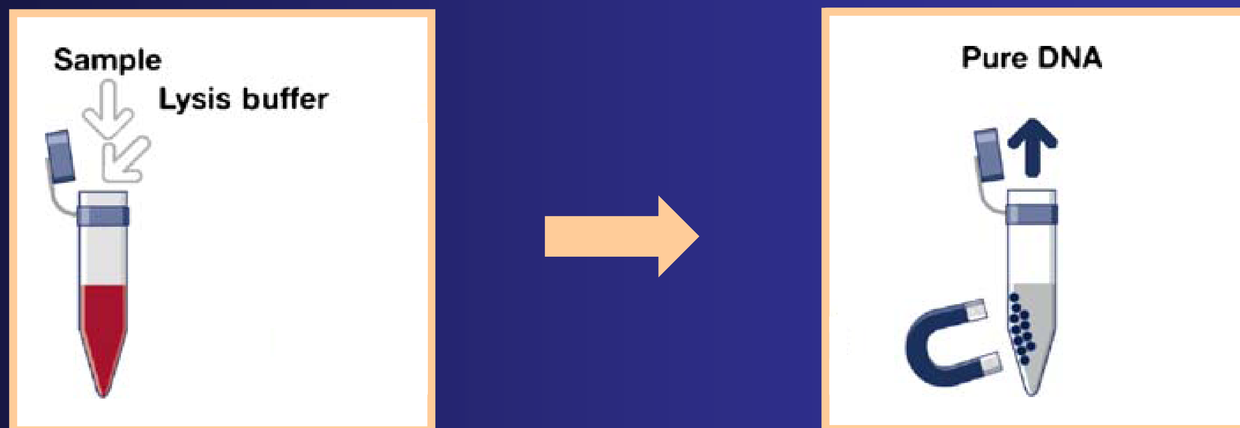
- able to circulate in the blood compartment
  - lung capillaries: 5 µm
  - stealthiness (*see* later)



Duguet and coll., *Nanomed.*, 1, 157 (2006)

# Biomolecules/cells sorting and purification

- **direct isolation** from crude sample materials (blood, tissue homogenates, cultivation media, water…)
- in combination with an appropriate buffer system
- ex: **nucleic acid purification**

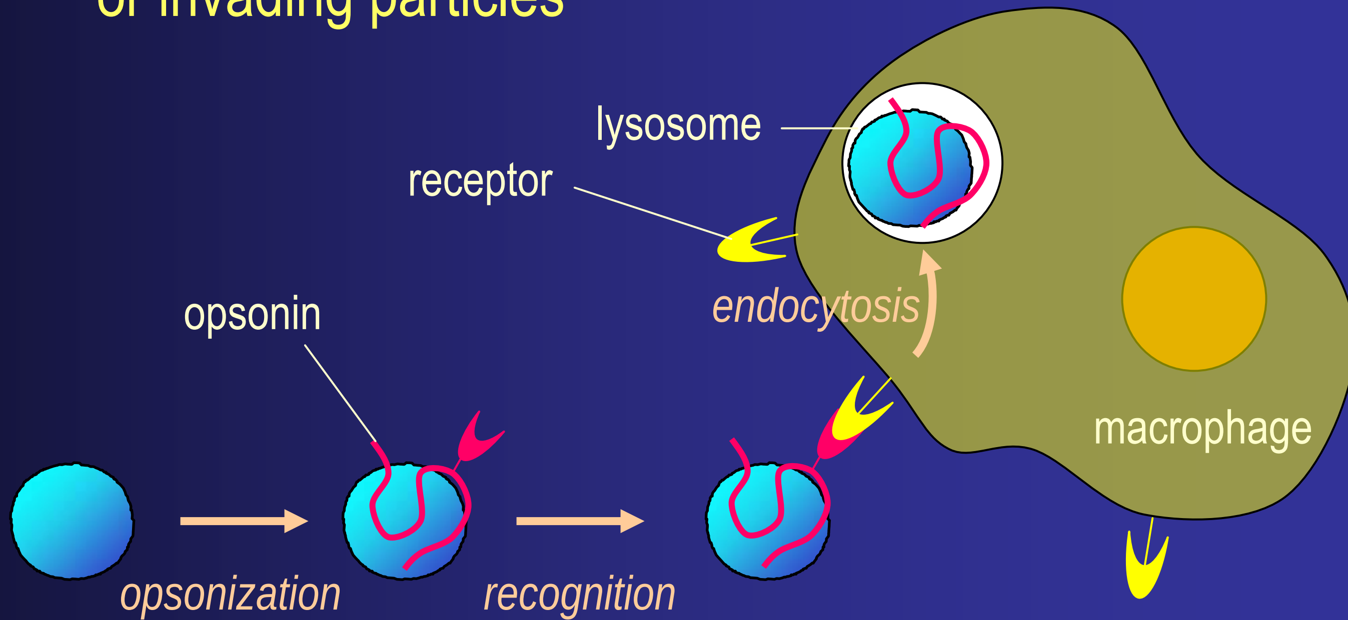



- **easy automation**
- commercial particle-based kits
- **superparamagnetic iron oxide** surface-functionalized or encapsulated in polymer or silica shell

Berensmeier, *Appl. Microbiol. Biotechnol.*, 73, 495 (2006)

# What happens to nanoparticles in the blood compartment ?

- the reticuloendothelial system RES
  - group of highly phagocytic mononuclear cells, known as monocytes, macrophages or Kupffer cells
  - able to recognize and clear altered or senescent cells, or invading particles




  - plasma half-lives : a few tens of minutes
  - final biodistribution : liver : 90 % ; spleen : 8 %…

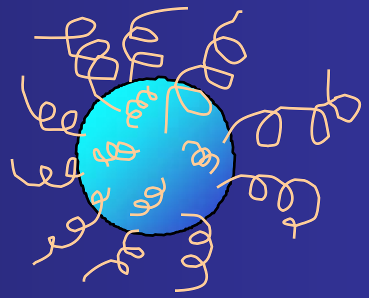
## design of long-circulating nanoparticles

Macrophage-evading particles (stealthy particles)

- **as small** as possible
- **hydrophilic and electrically neutral surface** (in physiological medium)

Corona of hydrophilic macromolecules

- **surface steric barrier** reducing opsonin adsorption
- **PEGylation** with poly(ethylene glycol)
- optimal molecular weight : **2 000 to 5 000 g/mol**

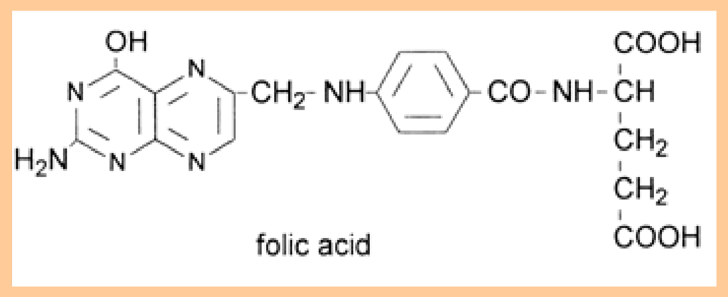
- stealthy particles may **accumulate in tumor tissues** because of the increased permeability of epithelium

## strategy for targeting tumor cells

### Active targeting strategy

- necessary surface coupling of specific ligands
- currently too complicated with antibodies

### Folate-mediation




- folate receptors overexpressed onto tumor cells



Couvreur and coll., *J. Pharm. Sci.*, 89, 1452 (2000)

# Magnetic nanoparticles as MRI contrast agent

- basic principles of MRI

Based on NMR signal of $^1H$

- water in tissues
- under the combined effect of a strong magnetic field (up to 3 T) and a transverse *rf*-sequence (5-100 MHz)
- two separate relaxation time constants :
  - $T_1$ : longitudinal relaxation or spin-lattice relaxation
  - $T_2$ : transversal relaxation or spin-spin relaxation

    → images are $T_1$ or $T_2$-weighted
- natural contrast due to $^1H$ densities, flow speeds…

## MRI contrast enhancement

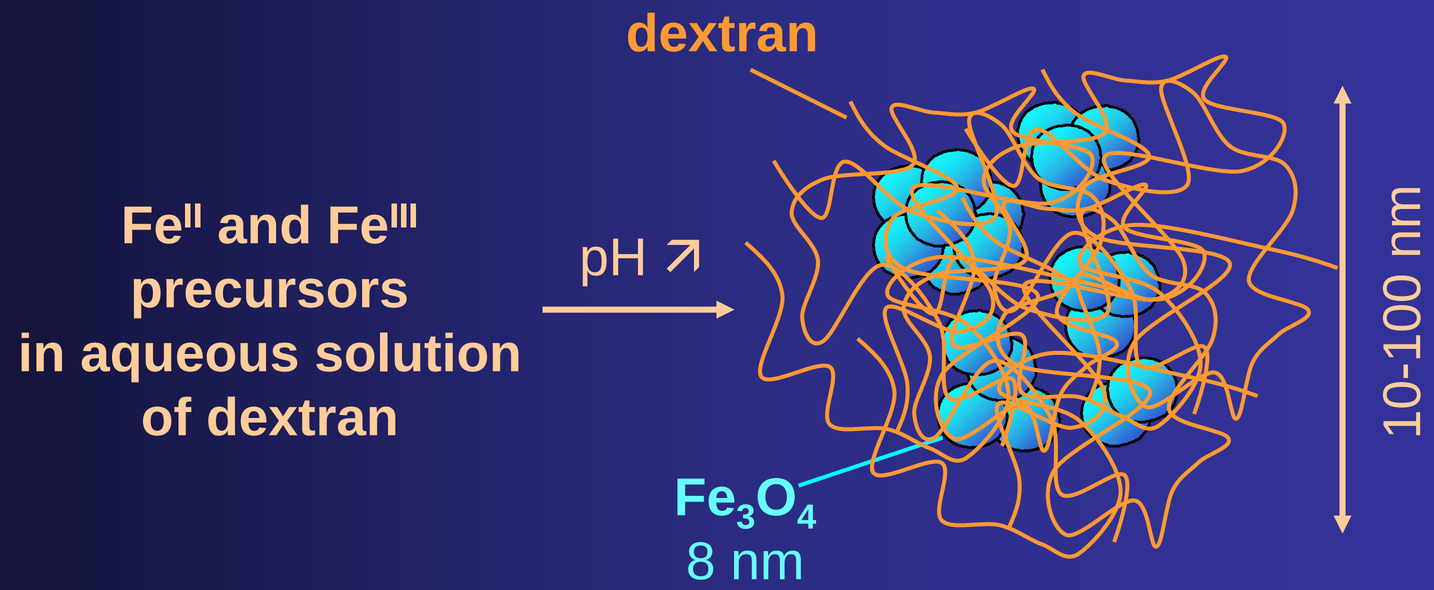
### Advantages of contrast agents

- for a **better delineation** of tissues
- **high spin paramagnetic metal** : Gd, Fe…
- **strong local effect** on relaxation times
- in general *i.v.* **injection** or **perfusion**

### Superparamagnetic nanoparticles ($T_2$ agents)

- 3 to 10-nm crystals of **magnetite/maghemite**
- create **large magnetic field heterogeneities**
- (Ultrasmall) SuperParamagnetic Iron Oxide : (U)SPIO
- some products in **clinical phase IV**
- clinical dose: *ca*. 1 mg Fe / kg of body

- synthesis and limits of commercial (U)SPIO
  - one-step alkaline co-precipitation method



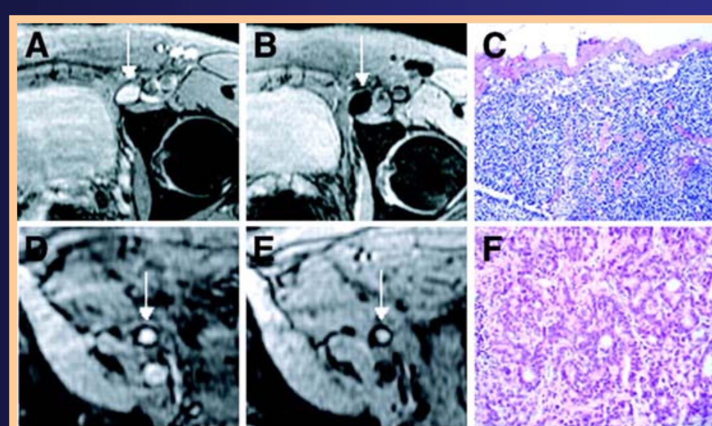

- dextran **limits particle growth** and ensures the **steric stabilization** and later the **stealthiness** of particles

but
- **laborious fractionation** for narrowing polydispersity
- **poor adhesion** between dextran and magnetite preventing any further chemical modification

- application to passive targeting
  - SPIO (50-100 nm) for **liver MR imaging**


Wallis and Gilbert, *J.R. Coll. Surg. Edinb.*, 44, 117 (1999)

  - **clearance rates** decrease with decreasing size :
    USPIO (17-20 nm) for **lymph nodes MR imaging**




Harisinghani *et al.*, *New Engl. J. Med.*, 348, 2491 (2003)

- current and future MRI developments

Molecular MR imaging
- from anatomical imaging to functional imaging
- for tumor, cardiovascular, inflammatory and degenerative diseases

Macrophage MR imaging

Stem cell MR tracking

Blood pool MR imaging

Magnetic core optimization ?
- not really

Surface functionalization
- covalent bonding
- ligand-labeling


Corot and coll., *Adv. Drug Delivery Rev.*, 58, 14 (2006)

# Magnetic nanoparticles as heat mediators

- medical benefits of heat

Thermoablation *vs.* hyperthermia

- tumor cells are more sensitive to heat than safe ones
- tumor growth stopped at 42°C
- thermoablation (T > 46°C): direct necrosis of cells
- hyperthermia: combined to radio- or chemotherapy

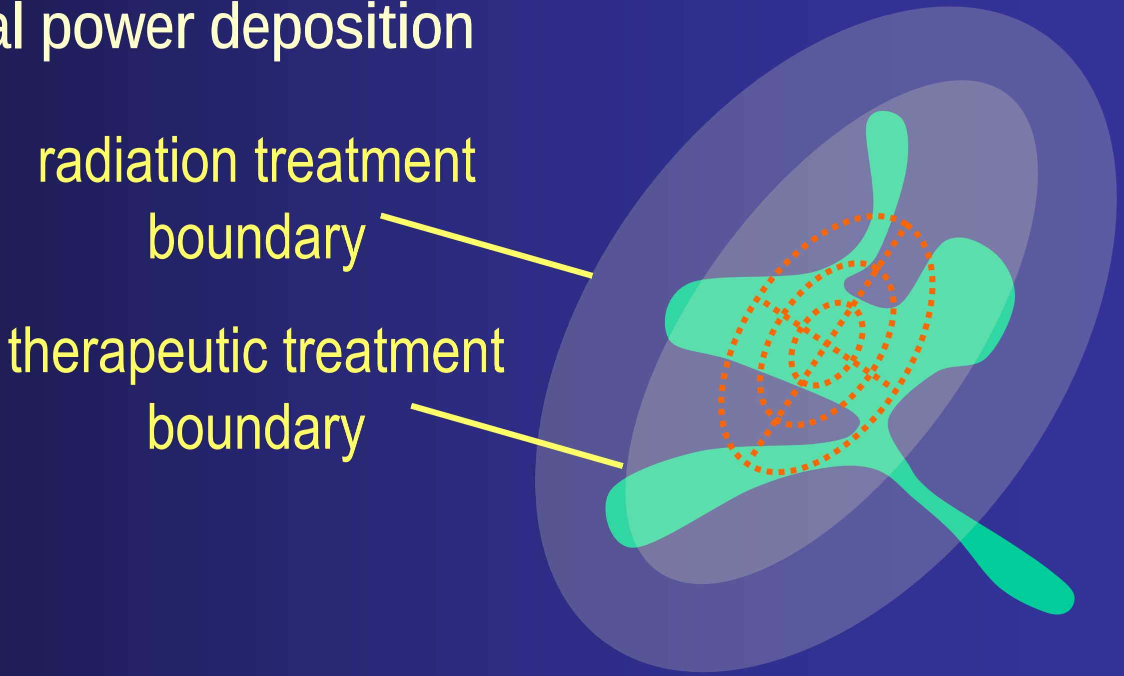
Current hyperthermia routes

- contact with a liquid externally heated
- inserted macroscopic sources: antenna, optic fibers…
- contactless applicators: microwaves, focused ultrasounds, *rf* or IR …

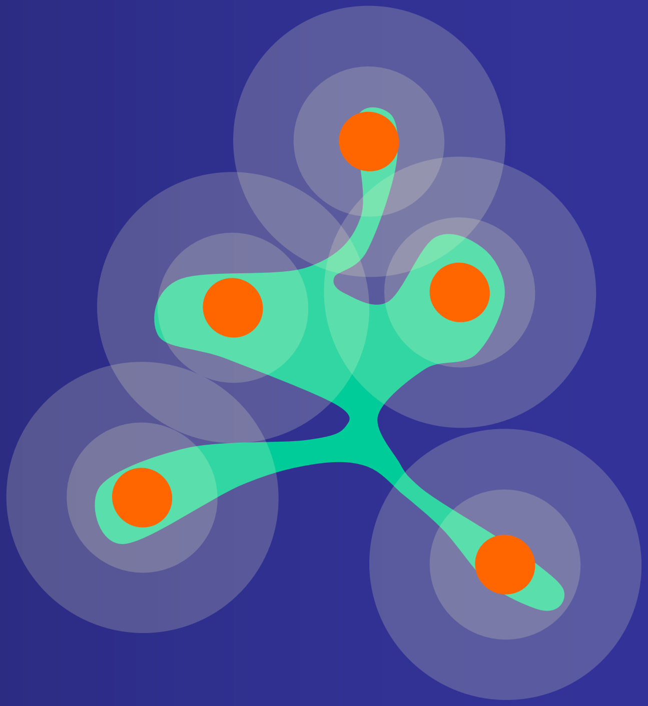
but
- stressful surgical intervention

and/or
- not applicable to profound or diffuse tumors
- temperature heterogeneities

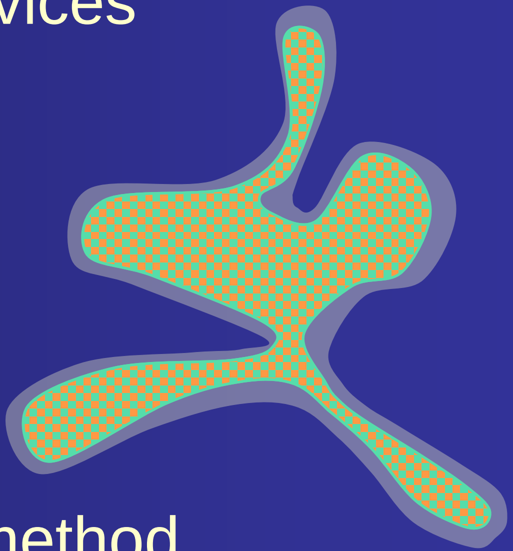
## External power deposition




## Inserted heating devices



- nanometer-size heating devices



- inductive radio-frequency method
  - magnetic materials may act as heat mediators

Physiological constraints

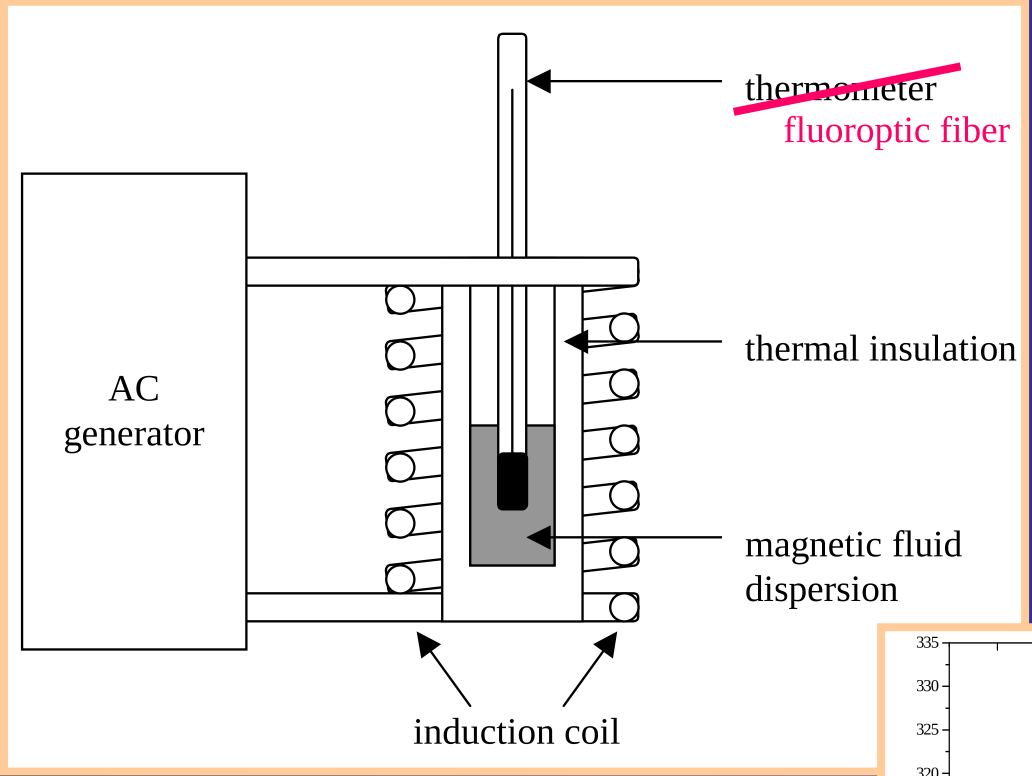
- 50 kHz < $\nu$ < 10 MHz
- ionic conductivity of tissues : 0,6 $\Omega^{-1}.m^{-1}$
- $H.\nu < 4.85\times10^{8}$ $A.m^{-1}.s^{-1}$ for one-hour treatment

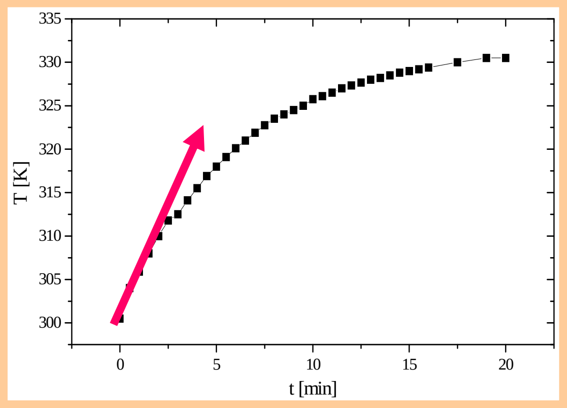
Three different mechanisms

- hysteresis losses (ferro- and ferrimagnetic particles)
- Néel relaxation losses (superparamagnetic particles)
- Brownian relaxation losses

## specific absorption rate (SAR)

- crucial for administered dose
- dependent on particles and AC magnetic field
- determined by calorimetry

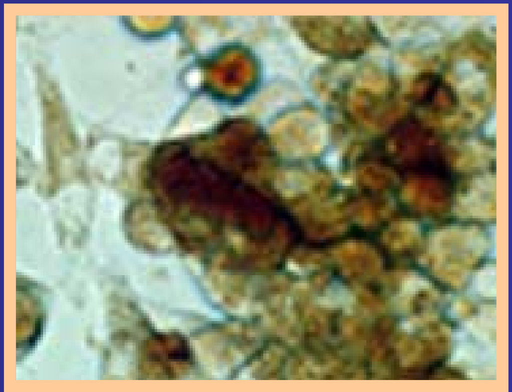



$$SAR = \frac{C_P}{x} \cdot \frac{dT}{dt} (W / g_{Fe})$$

## magnetic fluid hyperthermia

- aminated-magnetite nanoparticles
- directly **injected in tumor**
- **preferential nanoparticle uptake** by glioblastoma cells

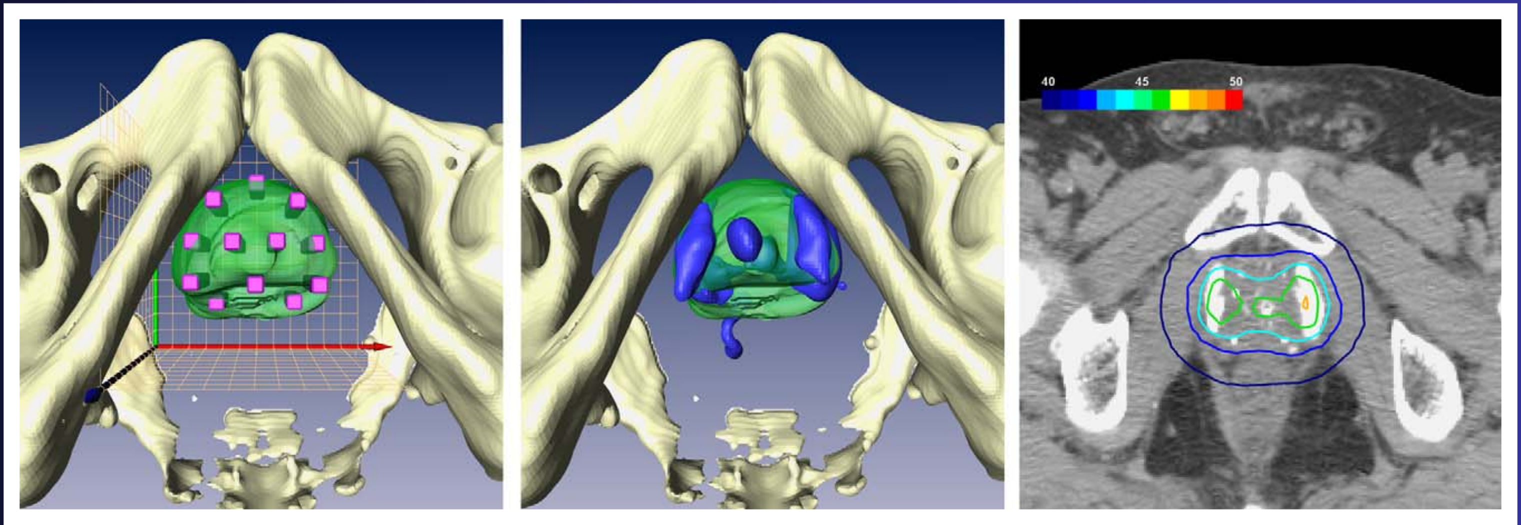


- H = 2-18 kA/m ; $\nu$ = 100 kHz
- combined with **radiotherapy**
- **clinical phase II** for glioblastoma multiform and prostate carcinoma

Jordan and coll. at Charité hospital, Berlin

■ magnetic fluid hyperthermia

but
- restricted to **solid and accessible tumors**
- **necessary calculations** of isothermic lines from computed tomography for deposit positions



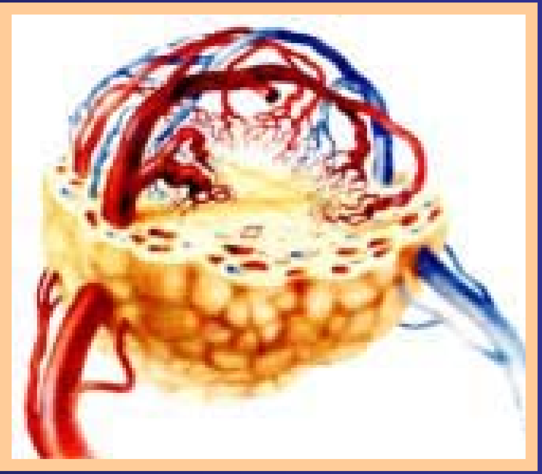

- **invasive thermometry** (up to 6 fluoroptic probes)

Johannsen and coll., *Eur. Urology*, 52, 1653 (2007)

## self-regulating hyperthermia mediators

Mediators and fuses ?

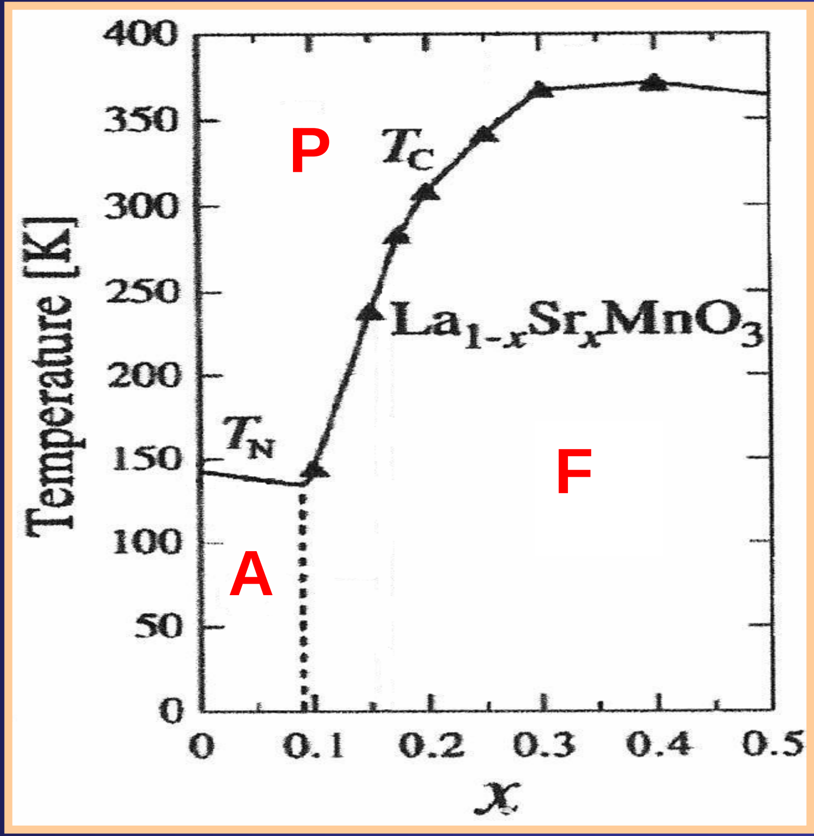
- stop to heat when therapeutic temperature is reached
- avoid overheating due to agglomerates
- achieve a uniform temperature distribution ?



- $T_C$-tuned ferromagnetic nanoparticles

## ■ self-regulating hyperthermia mediators

Manganese perovskite $La_{1-x}Sr_xMnO_3$



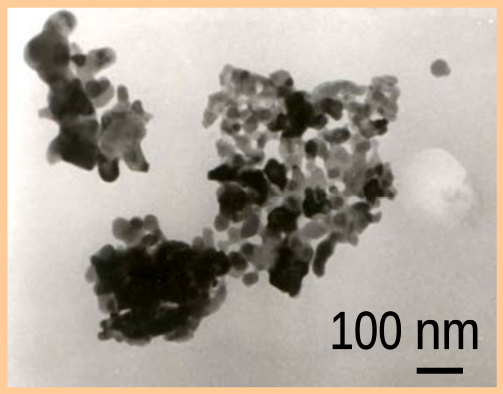

- is $T_{max}$ tunable thanks to the control of $T_C$ ?
- how to prepare nanocrystals ?

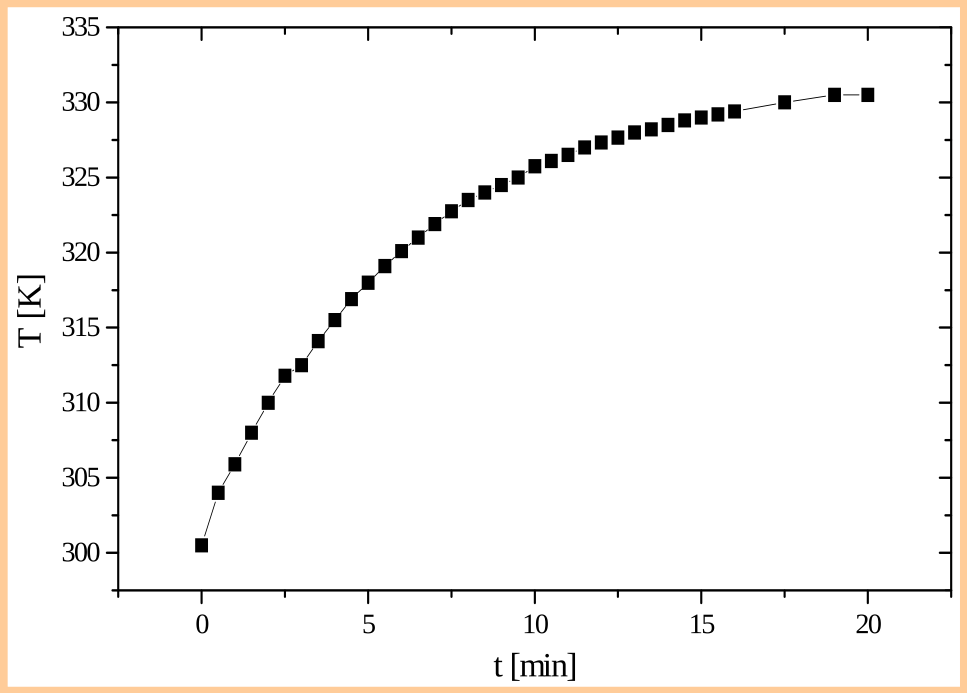
Y. Tokura et al., *J. Magn. Magn. Mater*., 200, 1(1999)

## sub-micron Tc-tuned particles

Manganese perovskite $La_{0.75}Sr_{0.25}MnO_3$

- citrate gel synthesis and annealing 550 to 900°C (3h)
- down to 20 nm (XRD)
- 52-nm particles : $T_C$ = 79°C



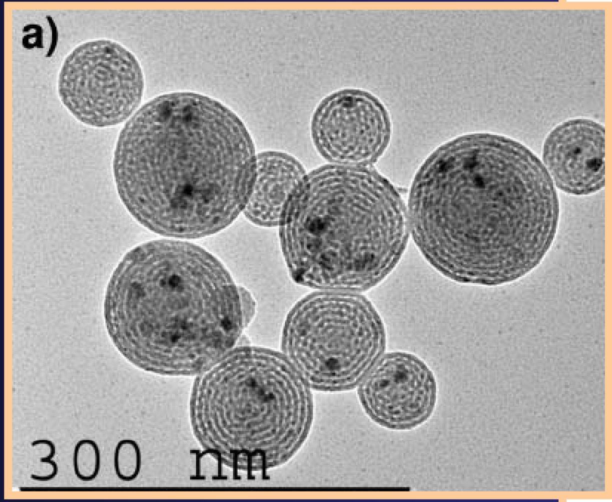

0.68 $g_{Mn}$/L
108 kHz
70 kA/m *i.e.* 88 mT

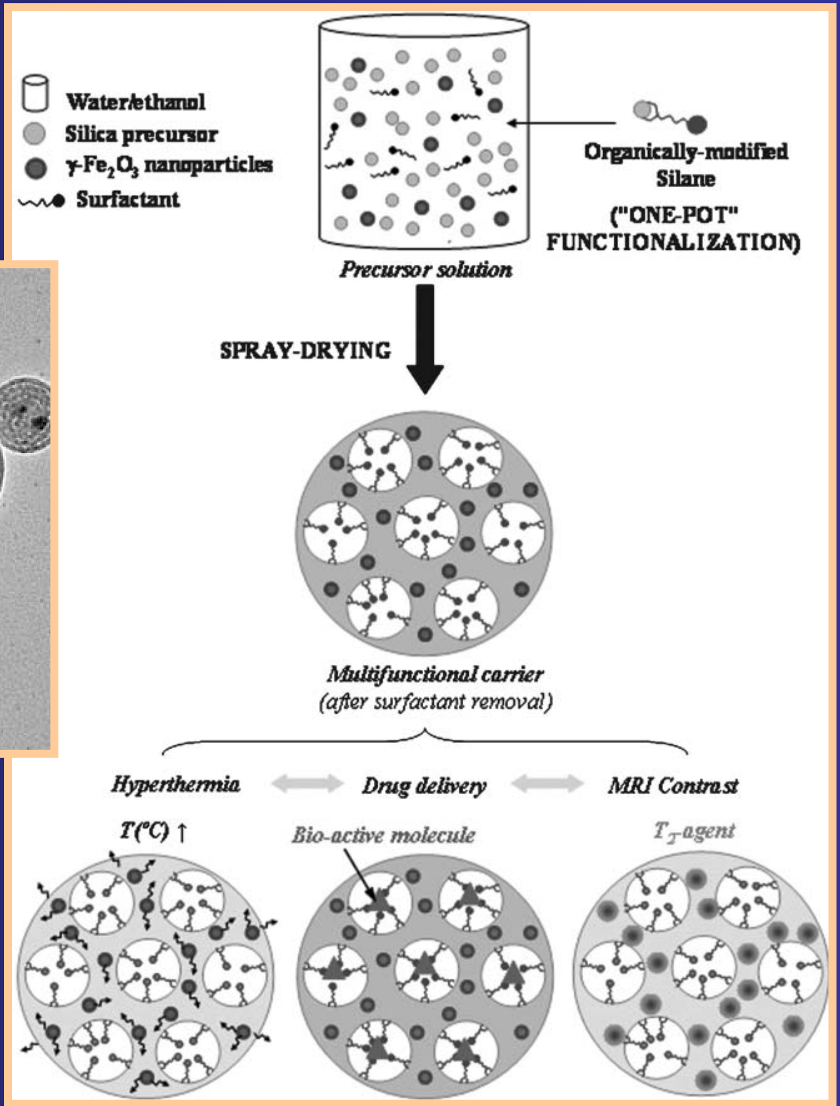
$SAR_{37°C}$ = 350 W/$g_{Mn}$
$T_{max}$ = 57 °C

Duguet, Pollert and coll., *J. Magn. Magn. Mater.*, 302, 315 (2006)

# Multifunctional platforms

- maghemite-filled mesoporous silica particles




Sanchez, Duguet and coll., *J. Mater. Chem.*, 17, 1563 (2007)

# Summary

- many important goals have been already reached
- the chemist part is still so essential
- fascinating challenges relative to the synthesis, the shaping and the control of bulk and surface properties

- " The drug development process is inevitably lengthy and breakthroughs more frequently a dream rather than reality " (R. Duncan, 1997)

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