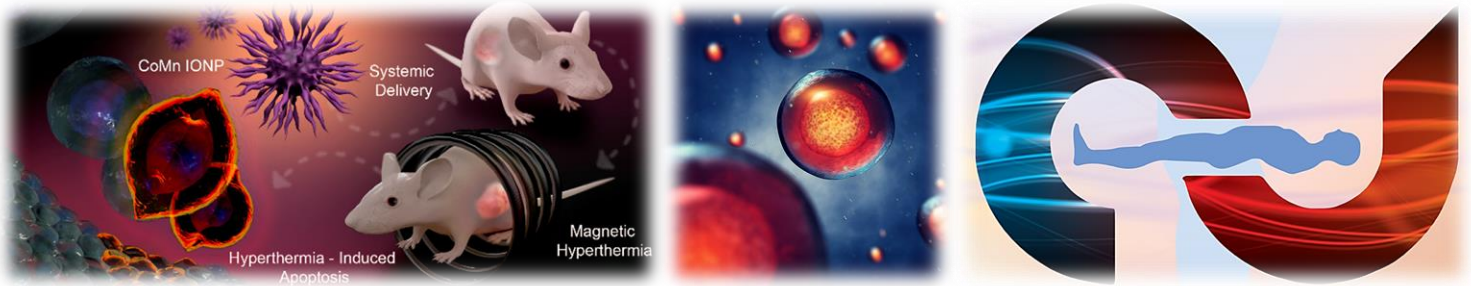
Magnetic Nanostructure Characterization

Magnetic Particle Hyperthermia:



Principles & Fundamentals

M. Angelakeris
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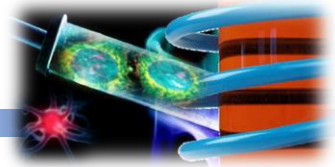
Magna Charta

Technology & Applications

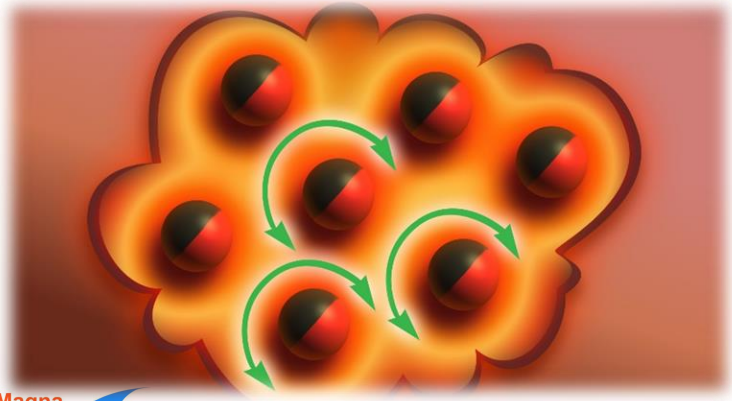
http://magnacharta.physics.auth.gr

Magnetic Particle Hyperthermia



Hyperthermia vs cancer:

- Many tumors thrive in a hypoxic environment in which the oxygenation of the tumor is much lower than in normal tissue.
- Because tumors cannot dissipate heat as quickly as healthy tissue, they can get hotter than that tissue if enough heat is applied.
- Hyperthermia at relatively low levels — as in the early clinical use of thermal medicine — ends up increasing the amount of blood flow and oxygenation of the tumor, making it more sensitive to radiation and chemotherapies.



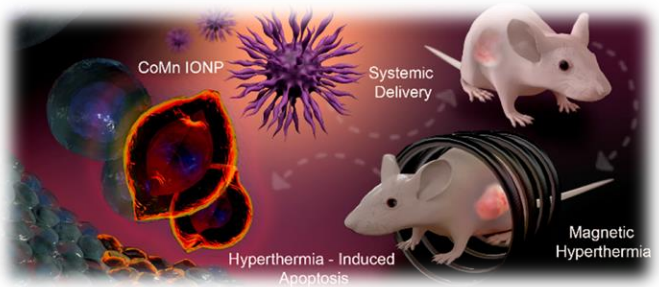
Magnetism + hyperthermia:

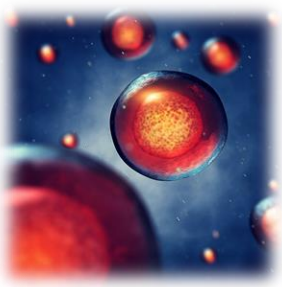
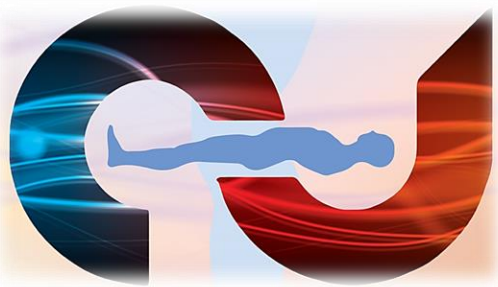
1957: Gilchrist and others proposed the use of magnetic materials in hyperthermia.

Today: MPH: Magnetic Particle Hyperthermia: The use of magnetic nanoparticles improves hyperthermia cancer treatment.

Introduction

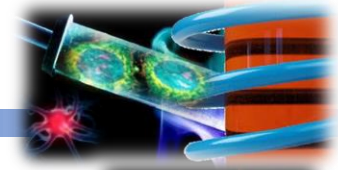
Magnetic Particle Hyperthermia:



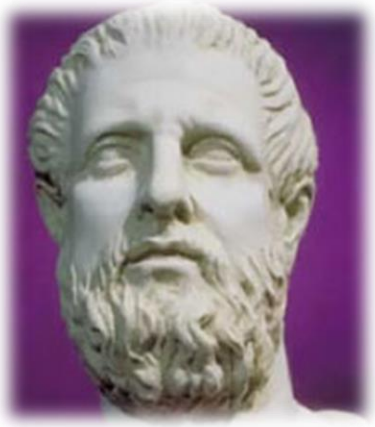



Principles & Fundamentals

Magnetic Particle Hyperthermia



500 BC: Hippocrates



*"What **medicine** cannot cure,*

__iron__ (the knife) cures;

*what **iron** cannot cure, __fire__ cures ;*

what fire does not cure, is to be considered incurable"

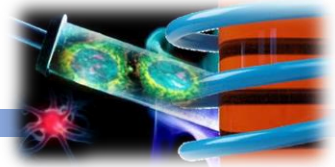
Hyperthermia is elevated body temperature due to failed thermoregulation that occurs when a body produces or absorbs more heat than it dissipates.

Hyperthermia differs from fever in that the body's temperature set point remains unchanged.

1891: A century ago, Dr. William Coley an innovative New York surgeon induced a fever in the body of a cancer patient to stimulate the immune response and cause cancer remission.

Coley's toxins: Bacteria used to treat patients with a variety of types of cancer up until the early 1950s. More than 1,000 patients over 40 years.

Magnetic Particle Hyperthermia



500 BC: Hippocrates

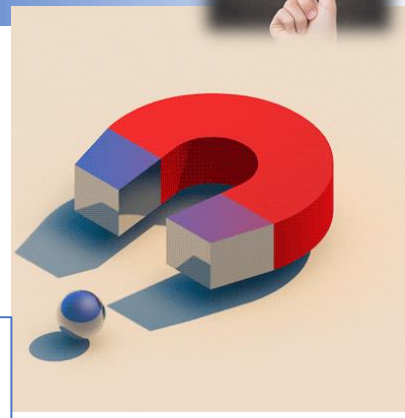
- **Whole body hyperthermia**: the systemic temperature has to be carefully controlled to ~41.8 ◦C by a heat bath.

- **Local hyperthermia**: the local temperature increase with respect to standard temperature of the human body is considered to be therapeutically useful over a relatively broad temperature range where different mechanisms of cell damaging occur with increasing temperature.
- **Local intracorporal heat generation by**: microwave radiation, capacitive or inductive coupling of radiofrequency fields, implanted electrodes, ultrasound, lasers.

- **Hyperthermia:** Treatments at temperatures of 41–45 ◦C for up to few hours—actually denoted as hyperthermia—need a combination with other assisting toxic agents (mostly irradiation or chemotherapy) for reliable damage of tumor cells.

- **Thermoablation:** aims for the thermal killing of all tumor cells by applying temperatures in excess of at least 50 ◦C in the tumor region for exposure times of at least few minutes.

Key idea



Magnetism is a class of physical phenomena that are mediated by magnetic fields. The most familiar effects occur in ferromagnetic materials, which are strongly attracted by magnetic fields.

Maximize Particle - Field Interaction

Magnetic Field

Magnetic Nanoparticle

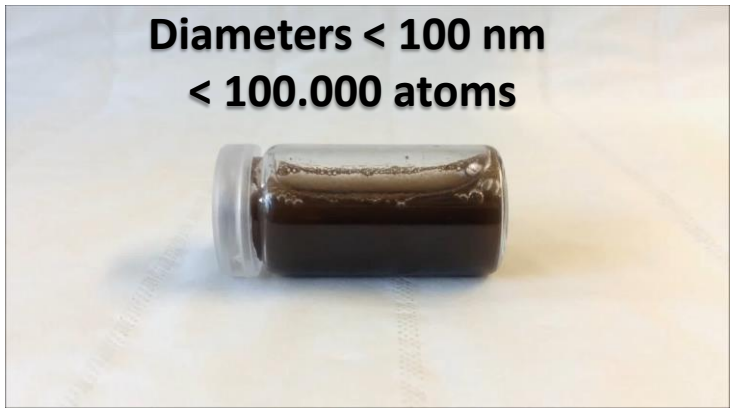
Maximum Effect Applicability

Biomedical Nanomagnetics

Nano

Size: They are only few tens of nanometer in size and therefore, easy passage into several regions is allowed. (cross blood-brain barrier).

Homogeneity: Moreover, MNPs provide much more efficient and homogenous treatment, compared to macroscopic implants.

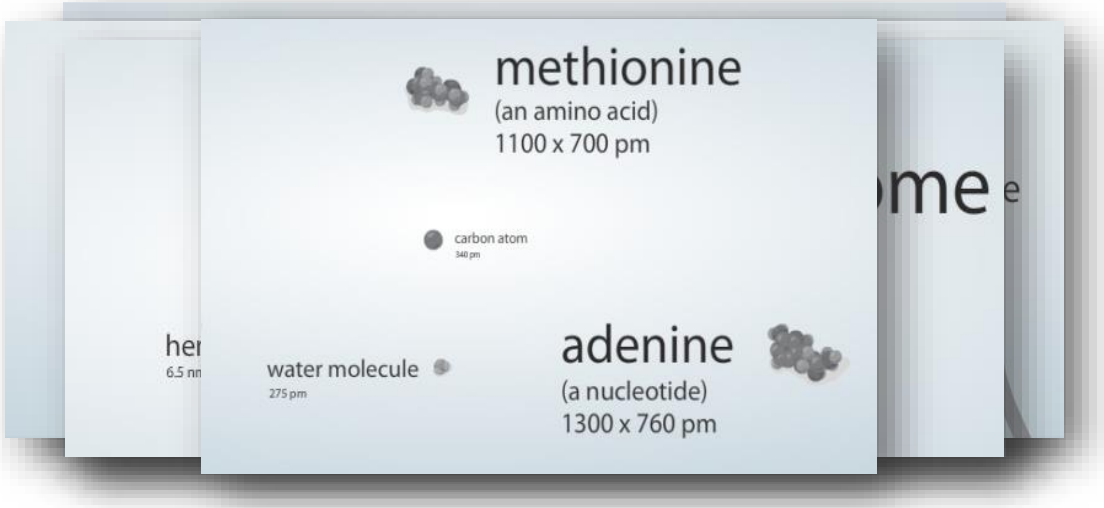


in vivo systems

magnetics

External: They can also be delivered at cellular level by external stimulation through magnetic field.

Less invasive: MNPs are less invasive, because with the frequencies and intensities of magnetic fields generally utilized, they can pass harmlessly through the body.

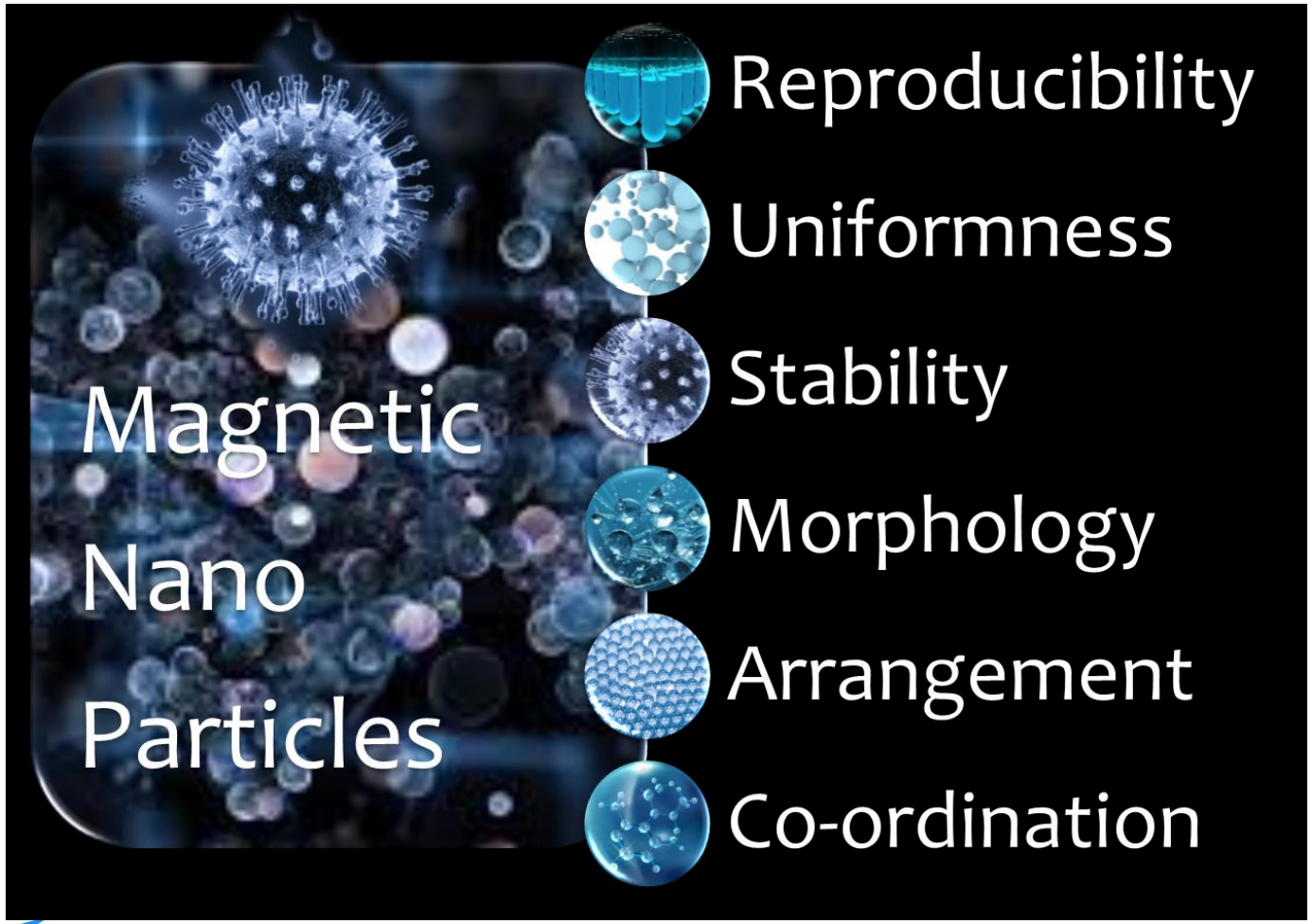


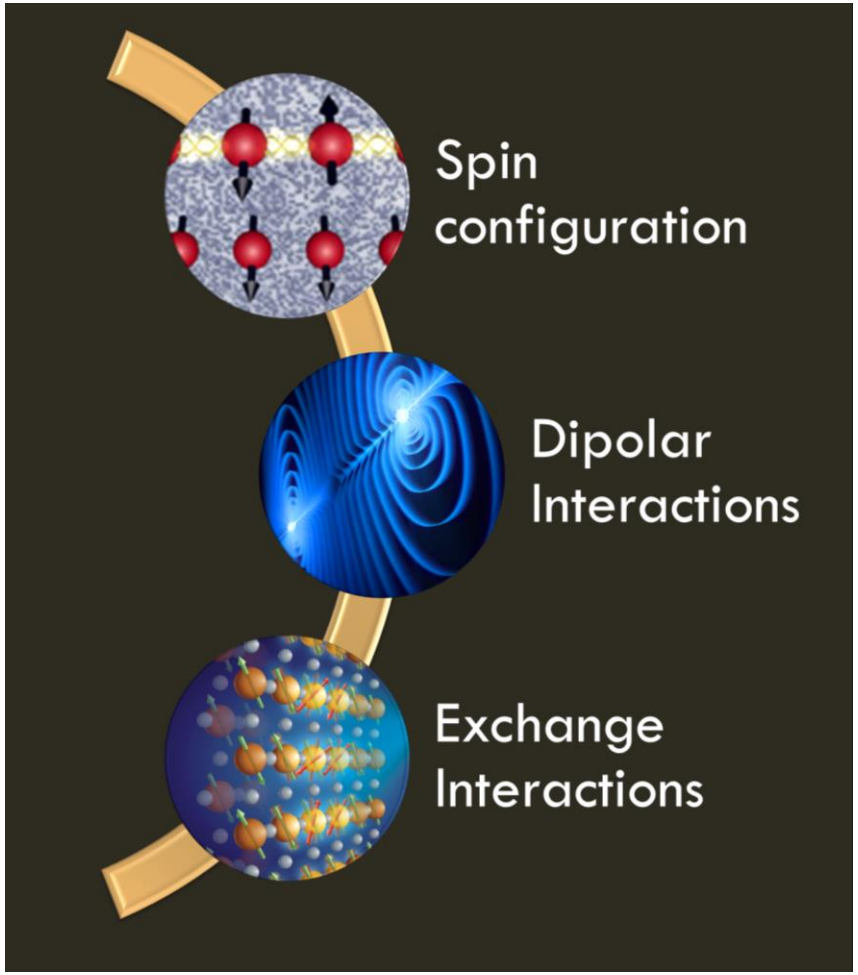
Cell: 10-100 μm, Virus: 20-450 nm,

Gene: 2nm wide, 10-100 nm long.

Magnetic Nanoparticles

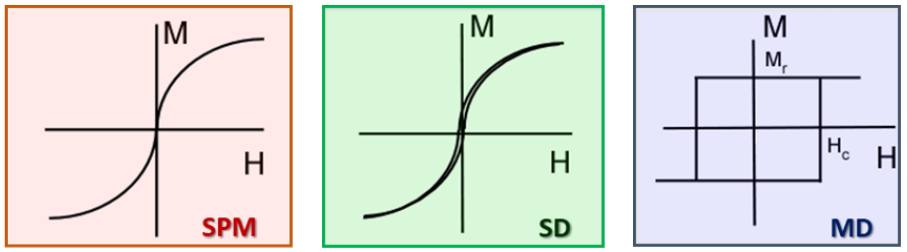
Spheres with diameter < 100 nm,
< 100.000 atoms

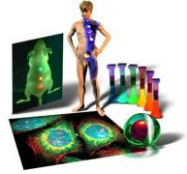




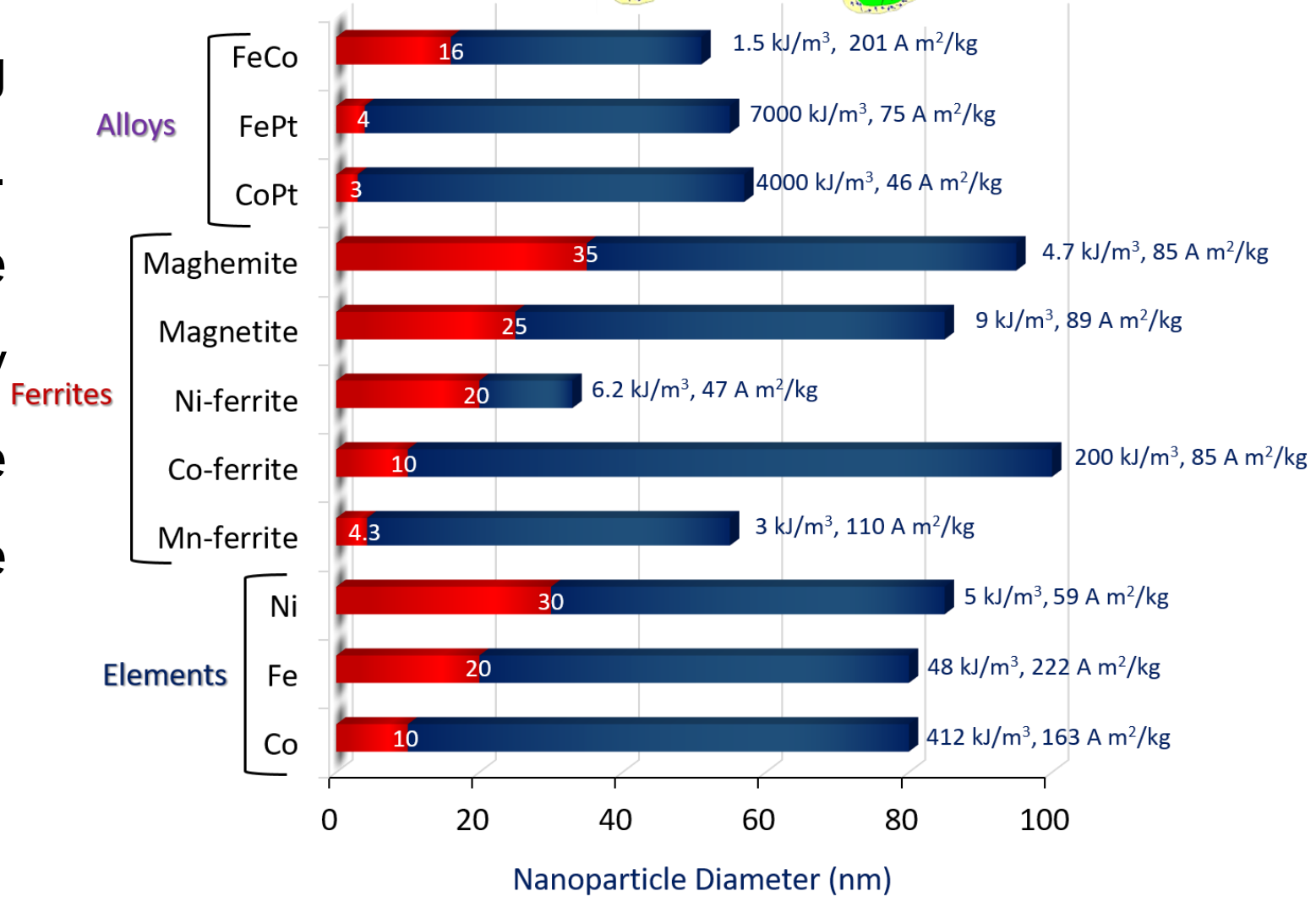
Magnetic nanoparticles: A multifunctional vehicle for modern theranostics, M. Angelakeris, Biochim Biophys Acta Gen Subj. 2017 Jun;1861(6):1642-1651

Nanomagnetic features



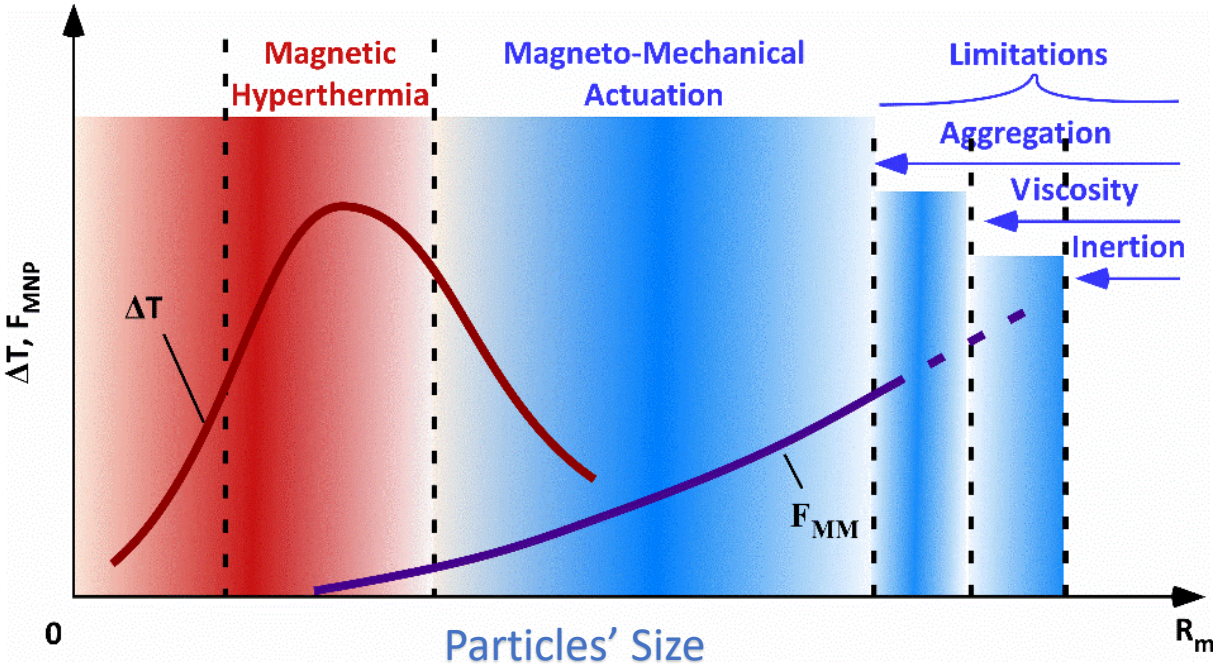


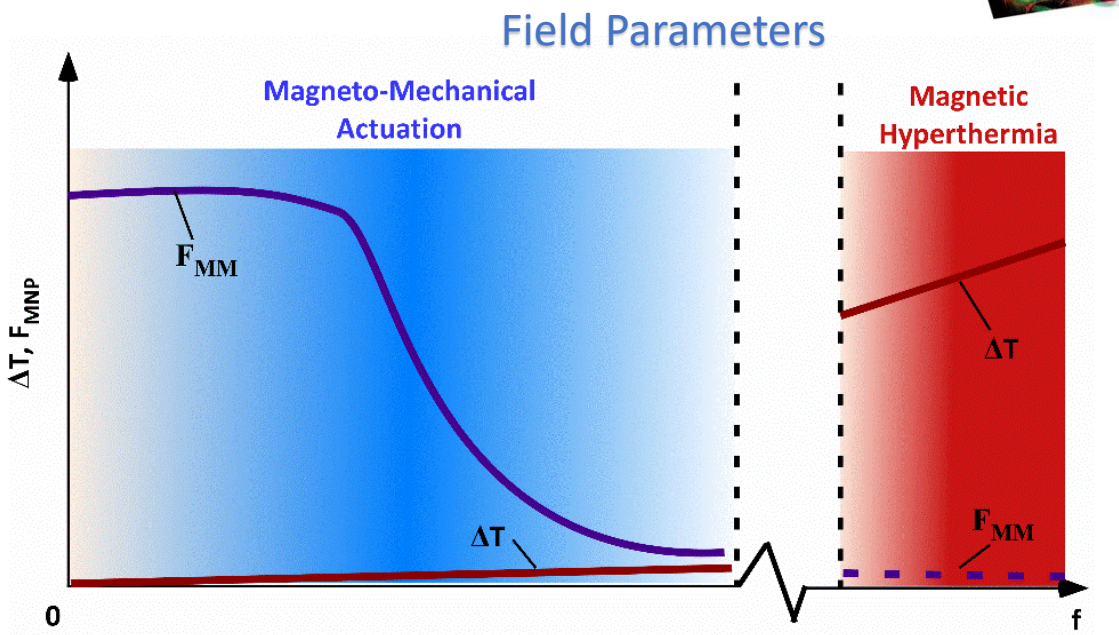
Nanomagnetic size effects: magnetic transitions occurring as MNPs grow in diameter. Main target is to fine-tune the interaction of MNPs, in a way that they respond to the external magnetic field more efficiently.

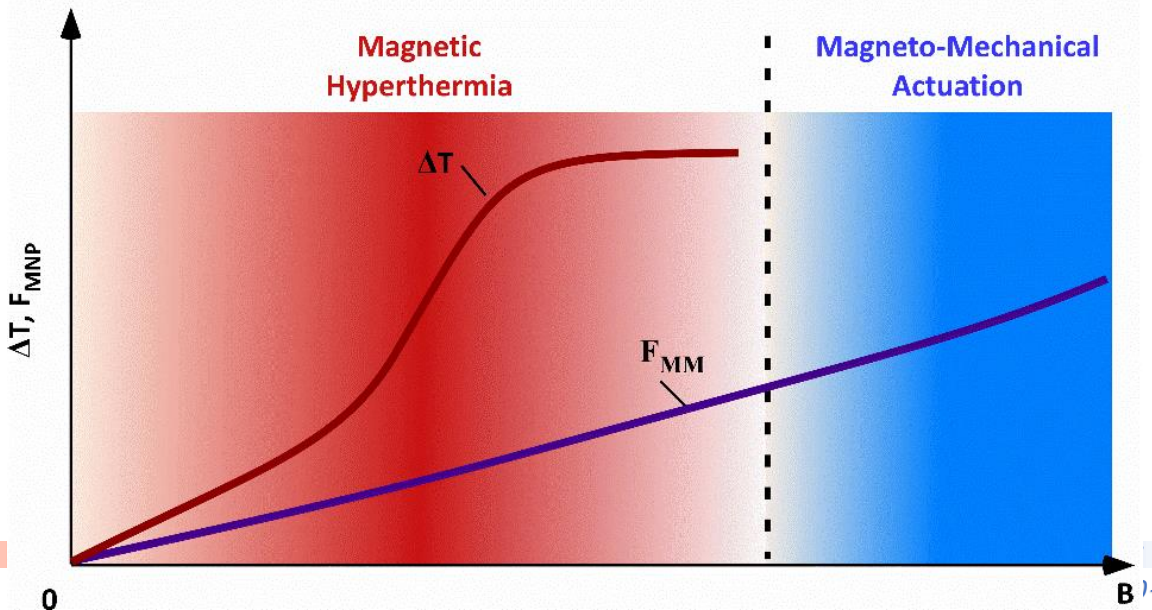


Particles & Fields

Optimal Conditions
for magnetic hyperthermia (ΔT)
and magnetic-mechanical (F_{MM}) application



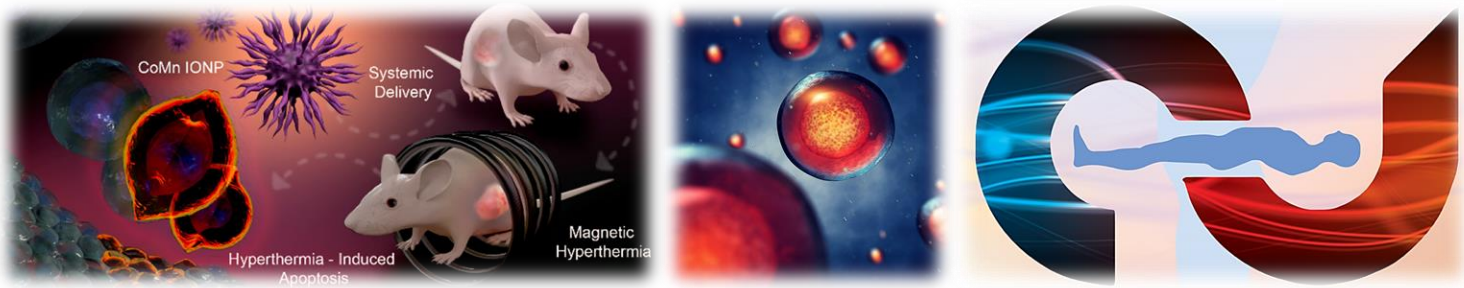




A. Makridis, PhD Thesis, Magnetic Nanostructures & Nanomagnetism for Modern Biomedical Applications, April 2019, School of Physics-AUTh

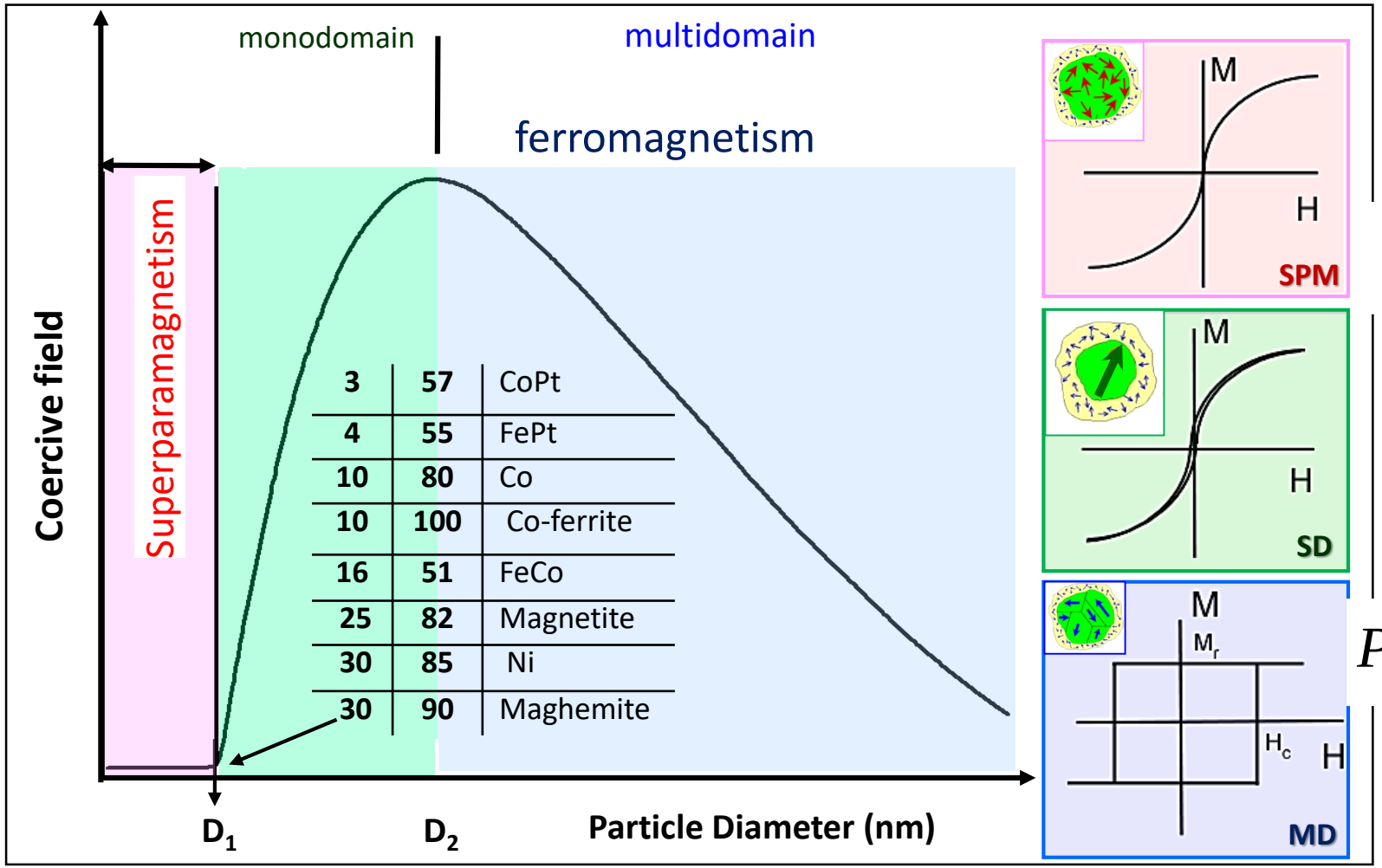
Principle of Operation

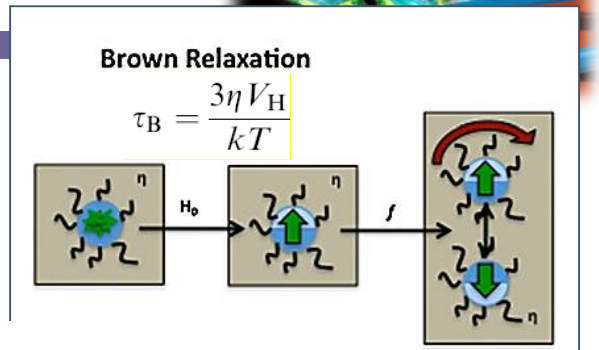
Magnetic Particle Hyperthermia:



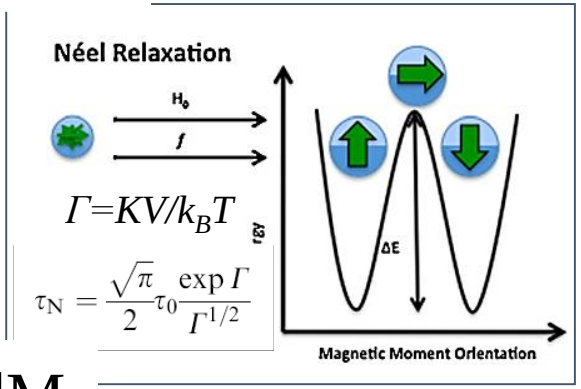
Principles & Fundamentals

Proof of Principle

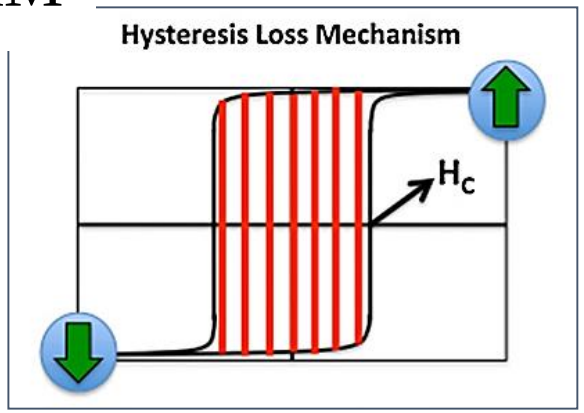




$$P_{SPM} = \mu_0 \pi f \chi'' H^2$$



$$P_{FM} = \mu_0 f \oint H dM$$



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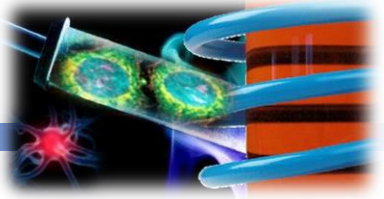
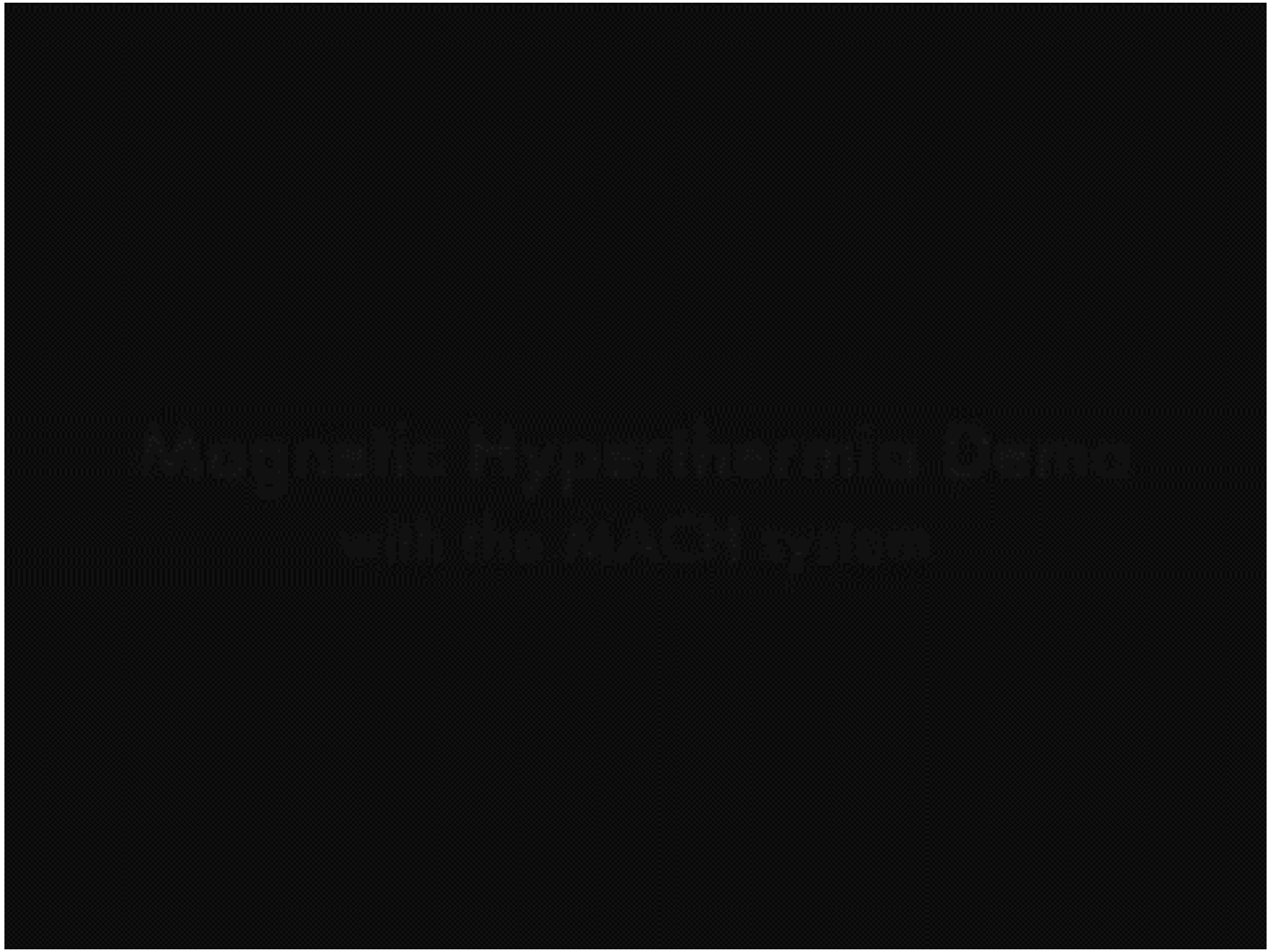
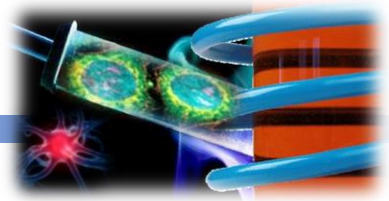
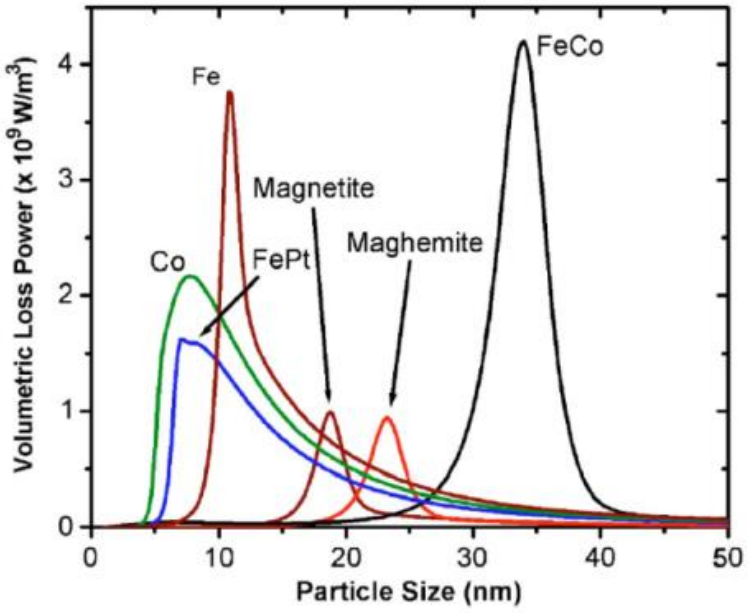
Proof of Principle

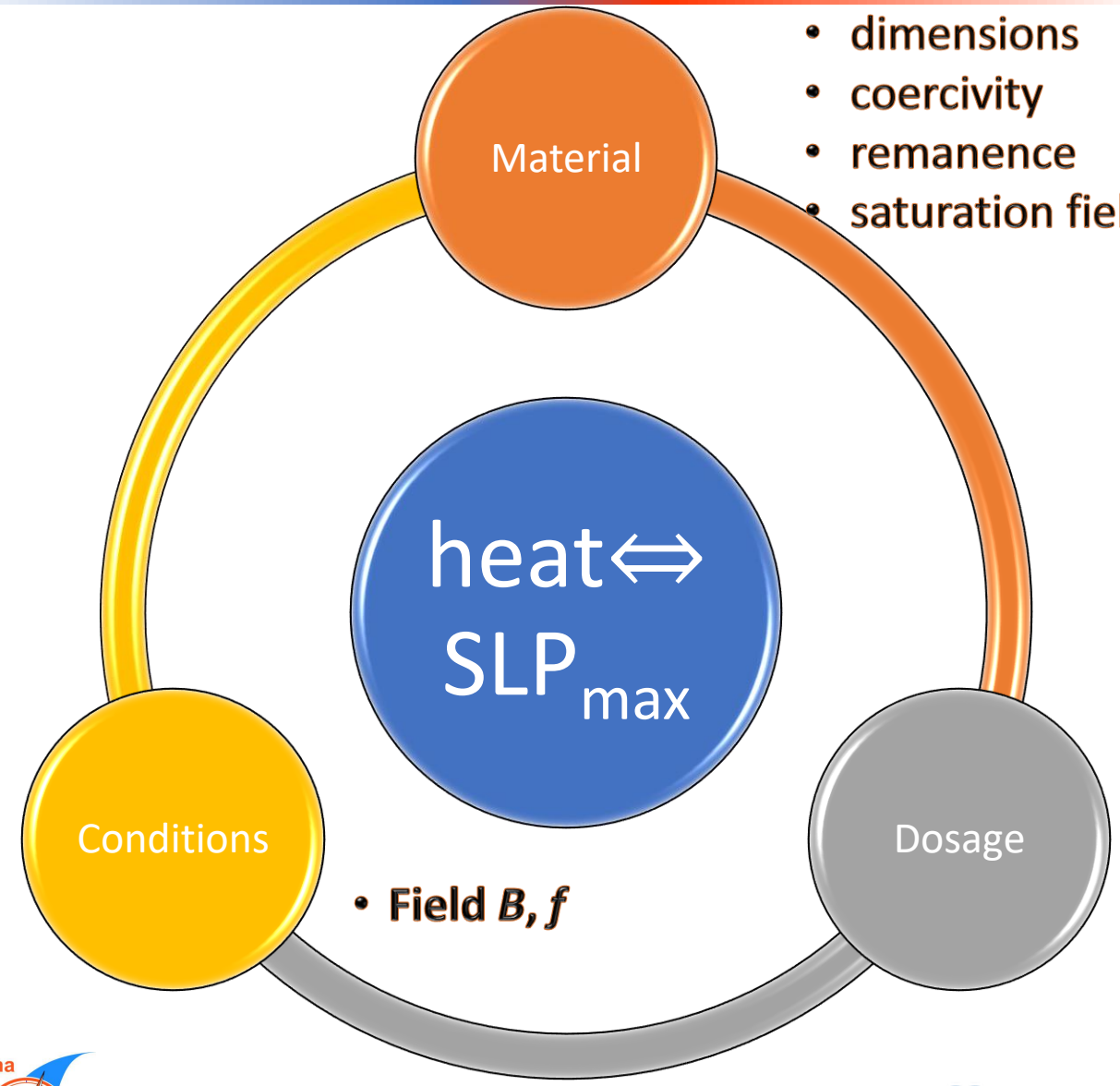




Magnetic Particle hyperthermia



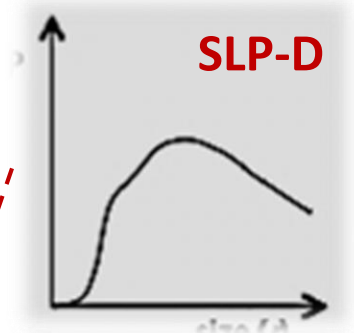


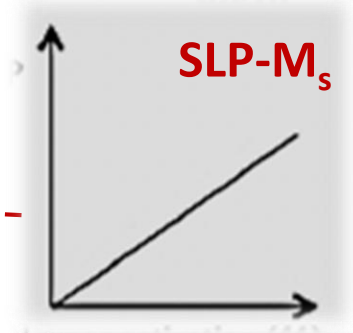


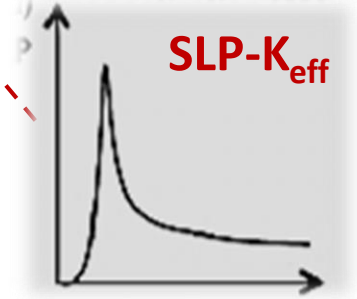
- dimensions
- coercivity
- remanence
- saturation field

- Field B, f

Theory predictions
$10 < D < 30$ nm
$60 < M_s < 100$ A m^2/kg
$5 < K_{eff} < 40$ KJ/m^3

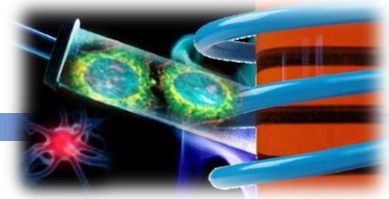




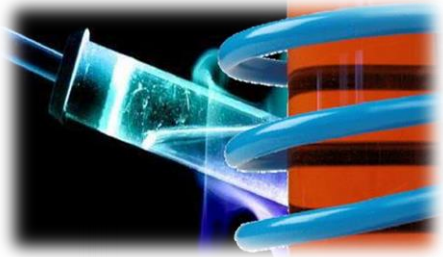


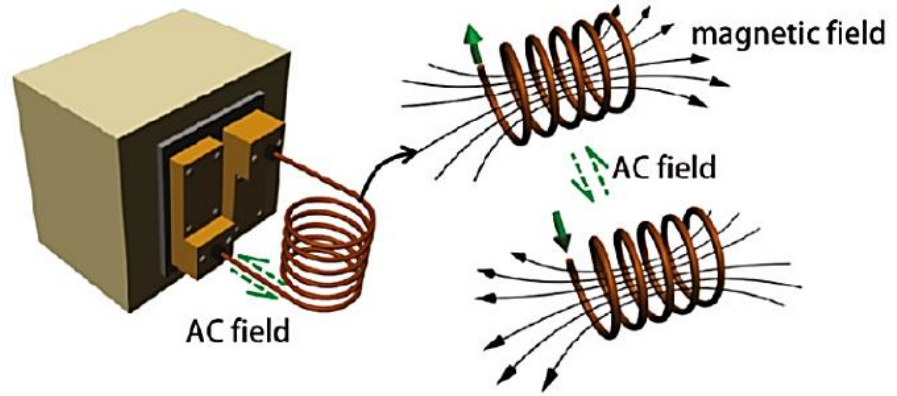
- **Colloidal Stability**
- **Concentration**
- **Toxicity**

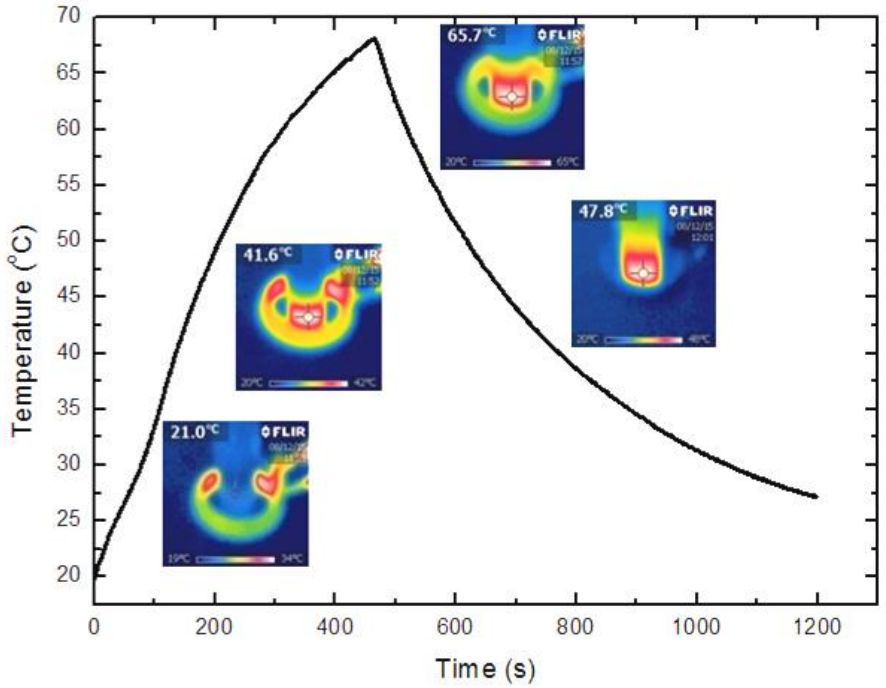
Experimental Sequence



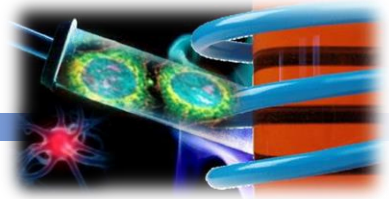
- Field Frequency: **100-1000 kHz**
- Field Amplitude: **10-100 kA/m**



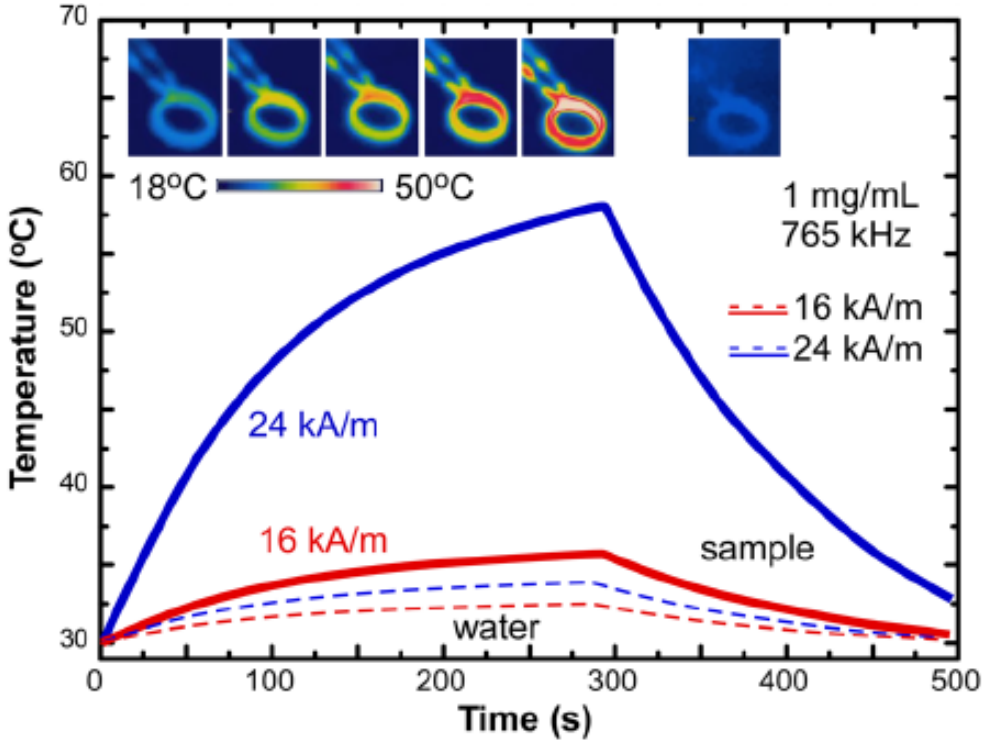




Evaluation



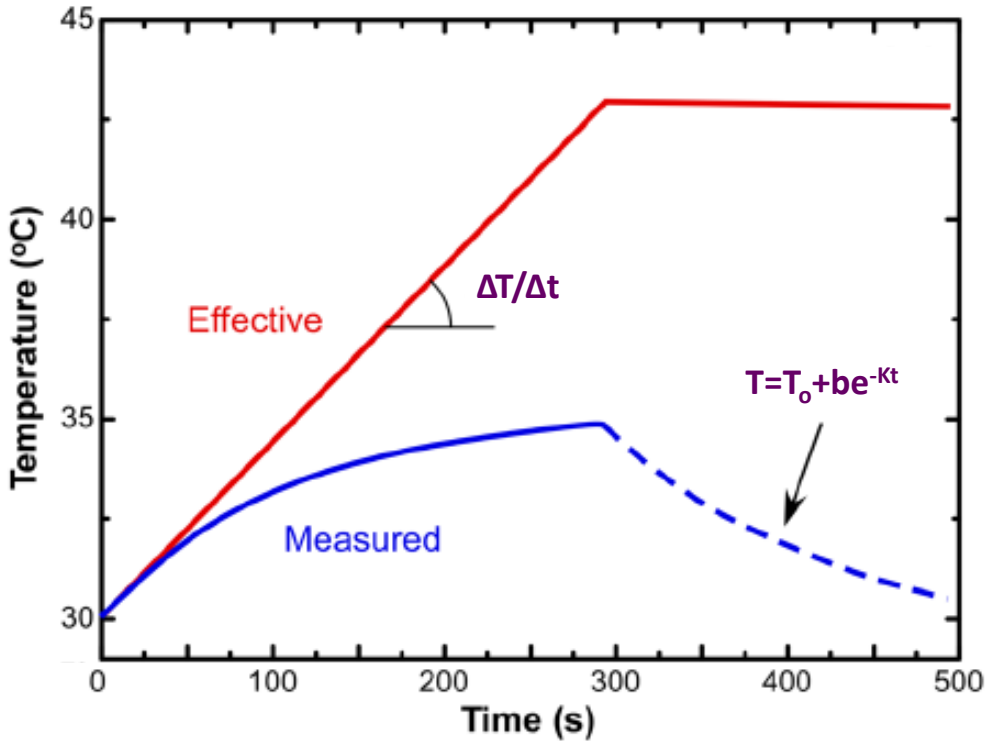
Obtained data corrected for heat losses



Coil heating effect

Environmental losses

Specific Loss Power (SLP) calculation



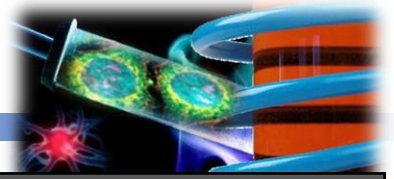
$$T(t) = T_f\left(1 - e^{-Bt}\right) \qquad \frac{dQ}{dt} = mC_P\frac{dT}{dt} + UA(T - T_{env})$$

$$\frac{dT'}{dt} = \frac{dT}{dt} + \frac{UA}{mC_P}(T - T_{env})$$

$$SLP \text{ or } SAR = \frac{W}{m_{magn}} = \frac{\Delta Q}{\Delta t \cdot m_{magn}} = c\frac{m_f}{m_{magn}}\frac{\Delta T}{\Delta t}$$

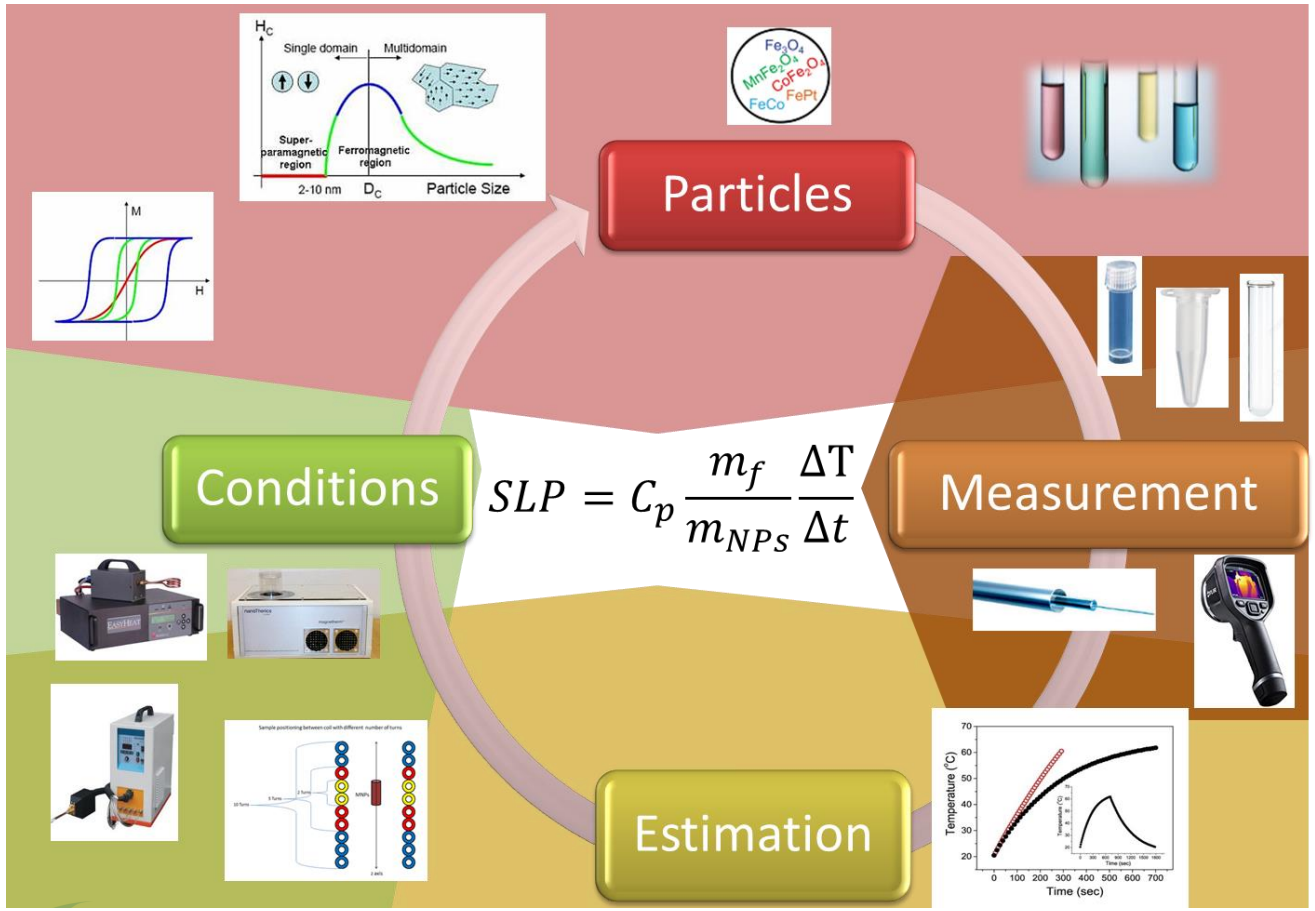
J. Magn. Magn. Mater. ***323*** *775-780 (2011).*
J. Appl. Phys. ***114****, 103904 (2013).*

Evaluation



$$SLP = f(d, V, m, C_p, \Delta T, \Delta t)$$

$$\delta SLP = \delta \mathrm{f} = \sqrt{\left(\frac{\partial f}{\partial d}\delta d\right)^2 + \left(\frac{\partial f}{\partial V}\delta V\right)^2 + \left(\frac{\partial f}{\partial m}\delta m\right)^2 + \left(\frac{\partial f}{\partial C_p}\delta C_p\right)^2 + \left(\frac{\partial f}{\partial \Delta T}\delta \Delta T\right)^2 + \left(\frac{\partial f}{\partial t}\delta \Delta t\right)^2}$$

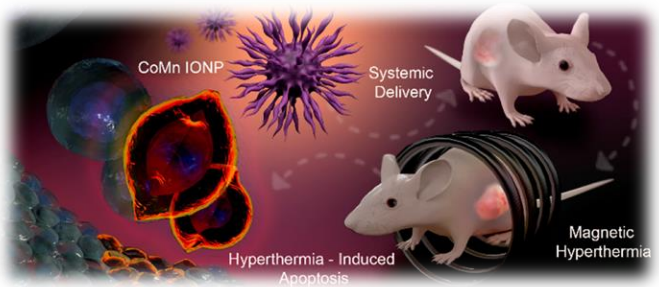


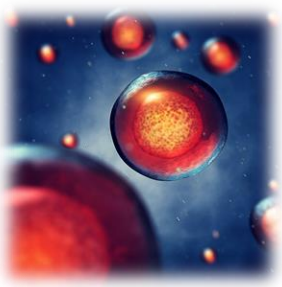
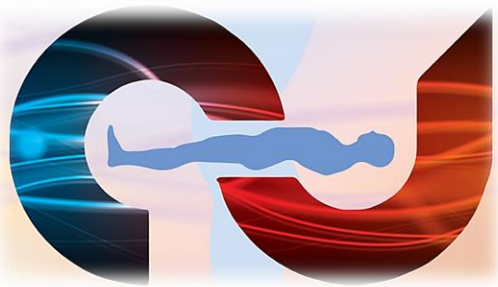
Source of uncertainty	SLP error (%)
Concentration (mg/mL)	<9%
Solution Volume (V)	<33% for 0.5-1 mL Stable for 1-3 mL
Magnetic field amplitude and frequency	Depends on MNP type SPM: <12% $SLP \sim H^2 \sim f^2/(1+f^2)$ FM: <18% $SLP \sim H^2 - H^3$
Magnetic field homogeneity	<2%
Positions of fibre probe	<6%
Vessel material	<40% between vessels
SLP estimation	< 30%

A standardisation protocol for accurate evaluation of specific loss power in magnetic hyperthermia
A Makridis et al. Journal of Physics D: Applied Physics, Volume 52, Number 25, 2019

Applicability

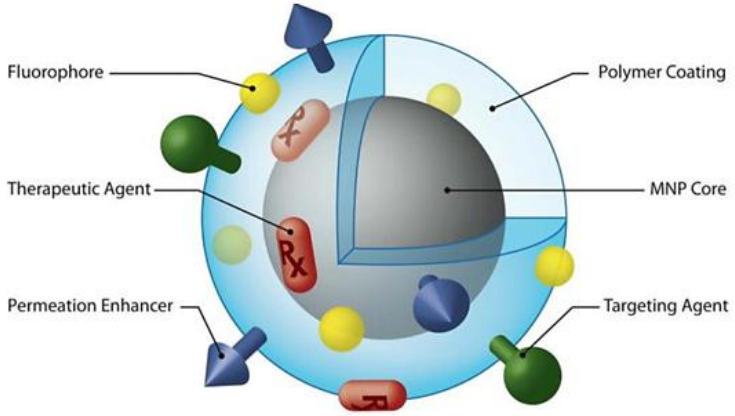
Magnetic Particle Hyperthermia:



Principles & Fundamentals

Particles & Fields → Biomedicine

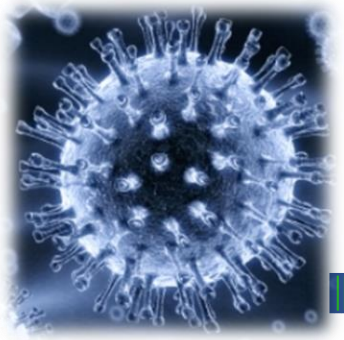


Optimizing the carrier in terms of:

- Material Choice
- Size
- Shape
- Magnetic profile
- Concentration
- Colloidal Stability

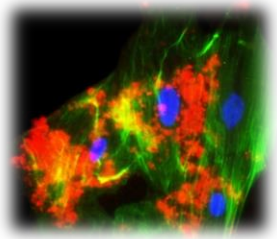
the conditions

- Frequency
- Field intensity



Colloidal Particles

Clinical Application



Optimizing the treatment in terms of:

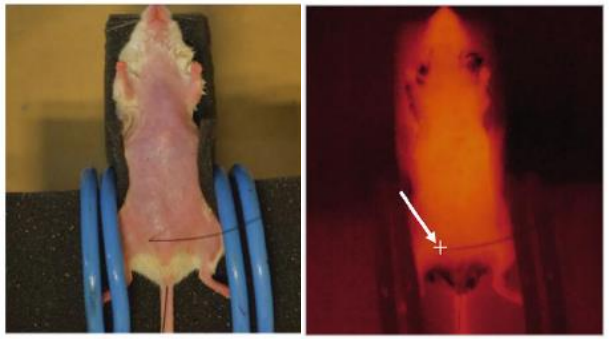
- biocompatibilty
- toxicity
- In-vivo efficiency

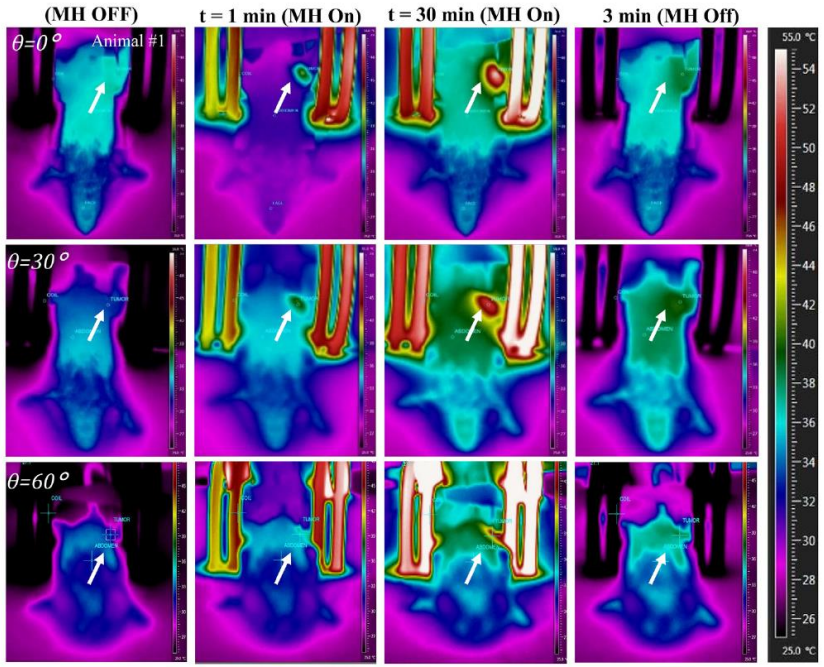
the side-effects

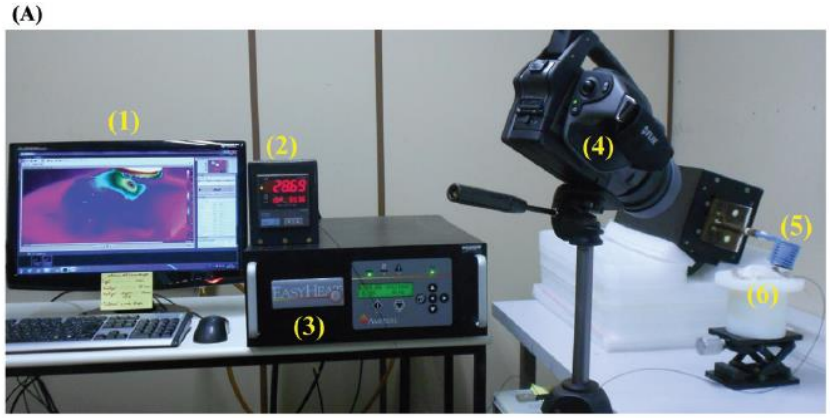
- Short-term
- Long-term
- extraction

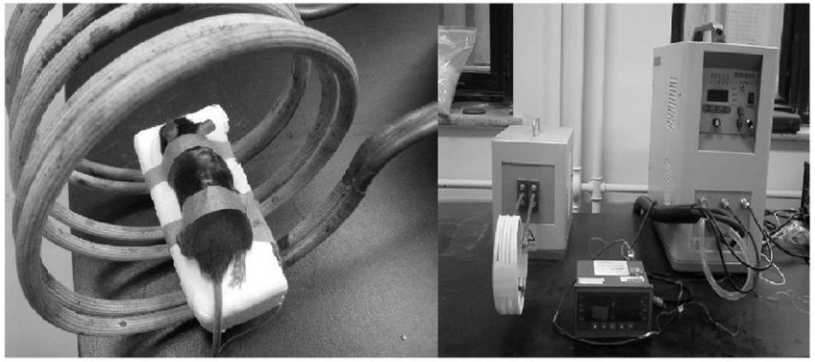
MPH: in vivo

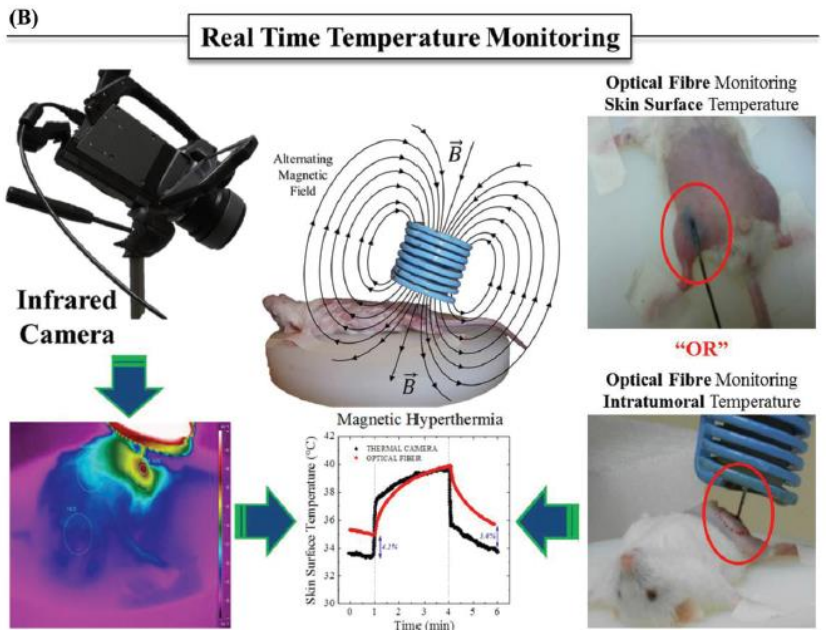
Versatile magnetic hyperthermia protocols

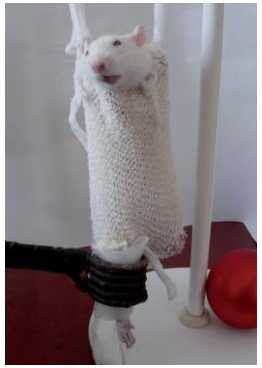


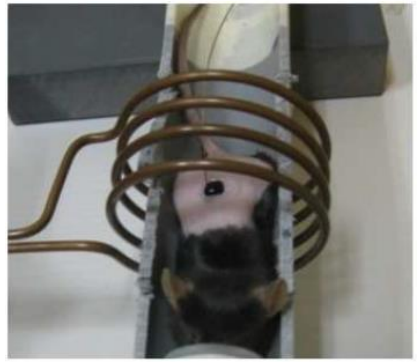


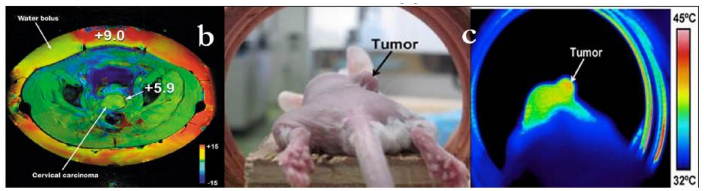






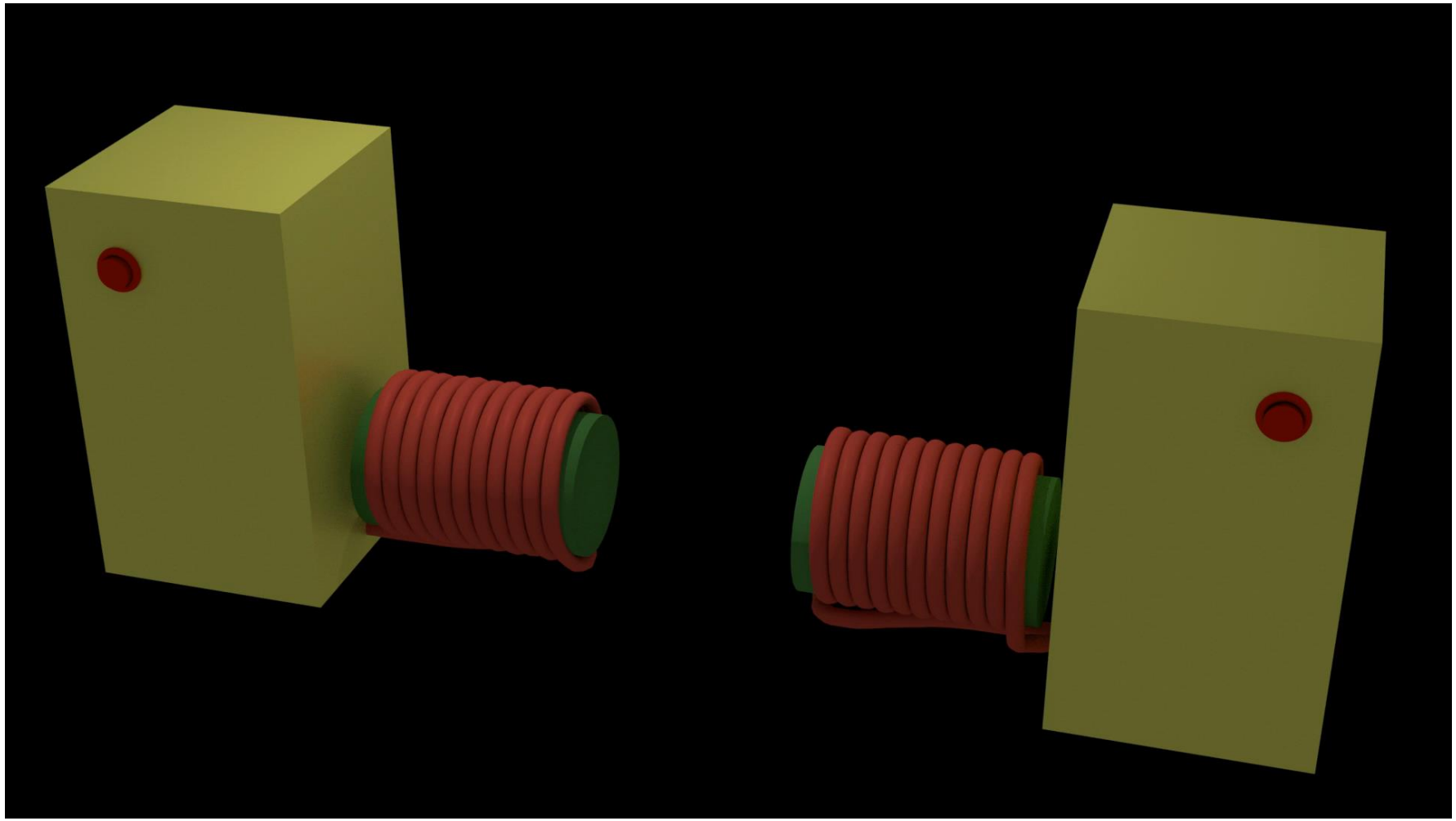






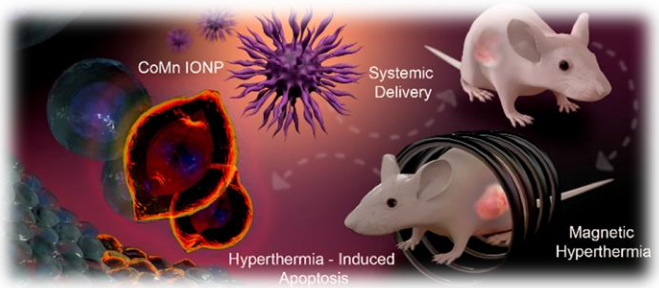
Rodrigues, Harley F., et al. "Precise determination of the heat delivery during in vivo magnetic nanoparticle hyperthermia with infrared thermography." *Physics in Medicine & Biology* 62.10 (2017): 4062.

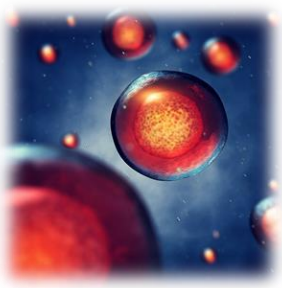
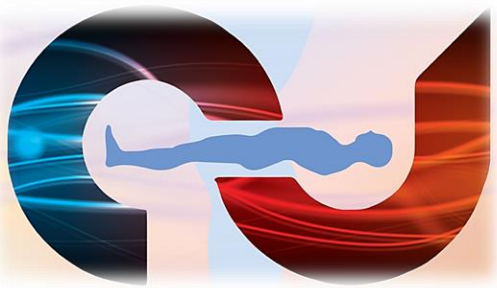
MPH in clinical practice



Constraints

Magnetic Particle Hyperthermia:



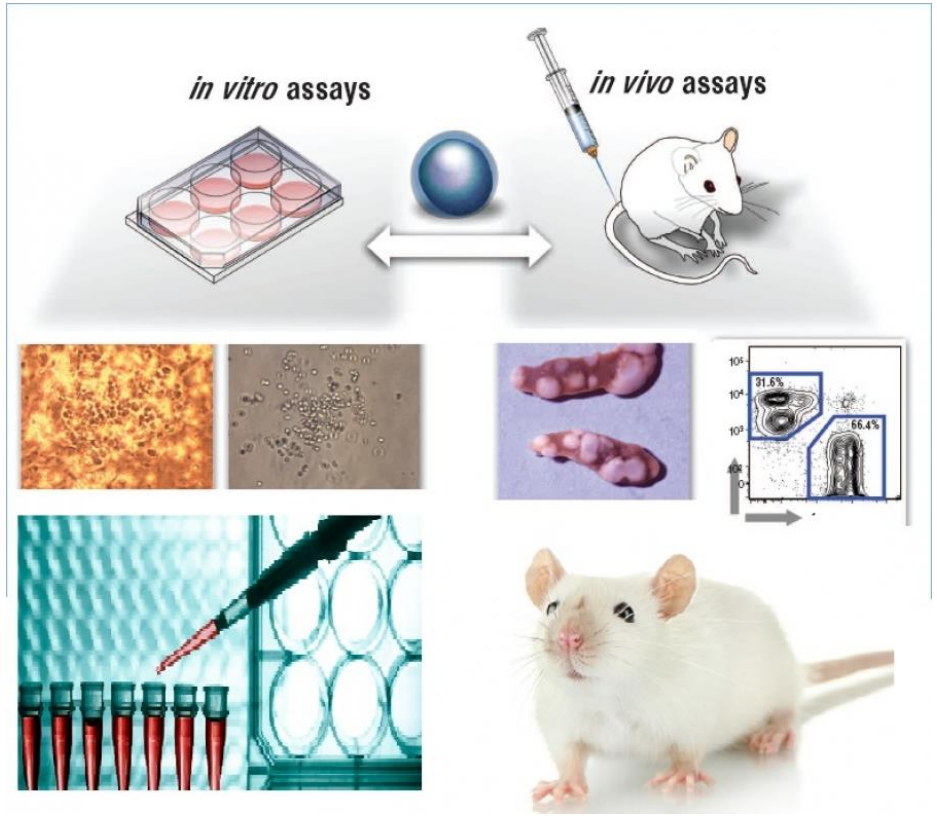
Principles & Fundamentals

Particles: Constraints

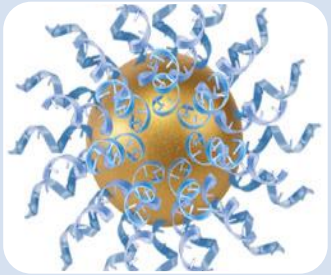
- The toxicity of magnetic particles depends on materials and morphological parameters including **composition**, **degradation**, **oxidation**, **size**, **shape**, **surface area** and **structure**.
- The surface coating and their morphology play an important role in determining nanoparticle toxicity.
- When compared to micron-sized particles, nano-sized particles can be generally more toxic because they have larger surface area (hence, more reactive), for a given mass, to interact with cell membranes and deliver toxicity.

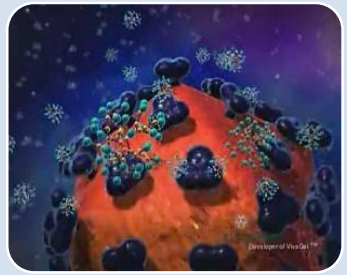
Particles: Constraints

In silico → *In vitro* → *Ex vivo* → *In vivo*



- Biocompatible surface
- Long blood half-life
- Minimal toxicity
- Colloidal stability over a wide pH range
- Evade or Allow uptake by RES
- Specific biomolecule Interactions





The 3Ds

Dose

Concentration

Dosology

Dimensions

Size

Surface Area

Aspect Ratio

Durability

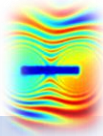
Chemictry

Crystal Structure

Surface Cover

Functionalization

Fields: Constraints



According to the induction law, the induced heating power is proportional to $(H \cdot f \cdot D)^2$

Atkinson et al developed a treatment system, based on eddy current heating of implantable metal thermoseeds.

Brezovich found for a loop diameter of ~ 30 cm that a 'test person has a sensation of warmth, but withstands the treatment for more than one hour without major discomfort

Exposure to fields where the product $H \cdot f < 4.85 \times 10^8 Am^{-1} s^{-1}$ *is safe and tolerable*

First commercially developed equipment (Gneveckow et al 2004)

reached a product of $1.8 \times 10^9 Am^{-1} s^{-1}$

but for smaller diameter of the body region and smaller time scale

Particle type dependent magnetic losses: SPM particles ~ H^2, ***FM particles ~*** H^3

Take home message