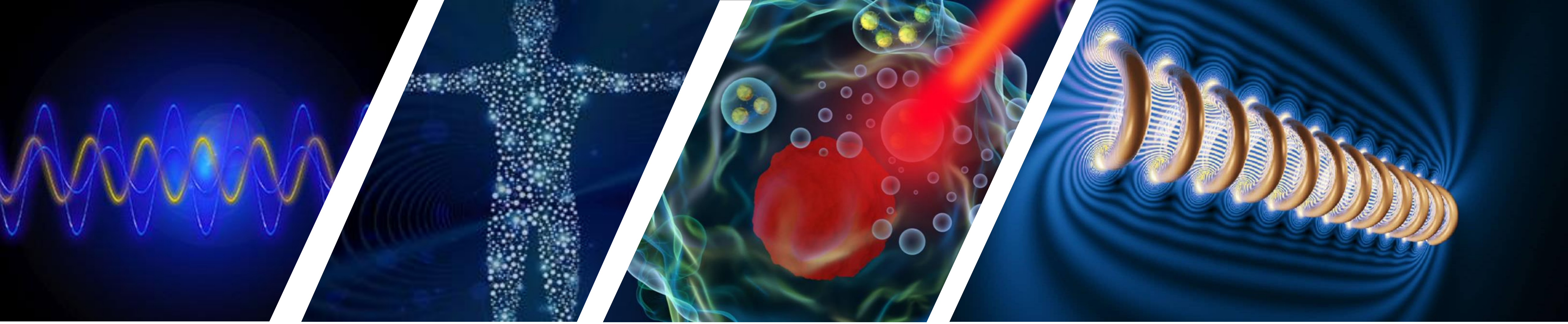

12th International Conference on Magnetic and Superconducting Materials (MSM22)

University of Duisburg-Essen, Germany, 28 August – 02 September 2022

Magnetically driven therapies:

Toxicity, Risks and Side-effects

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Magnetic Nanostructure Characterization Technology & Applications

http://magnacharta.physics.auth.gr

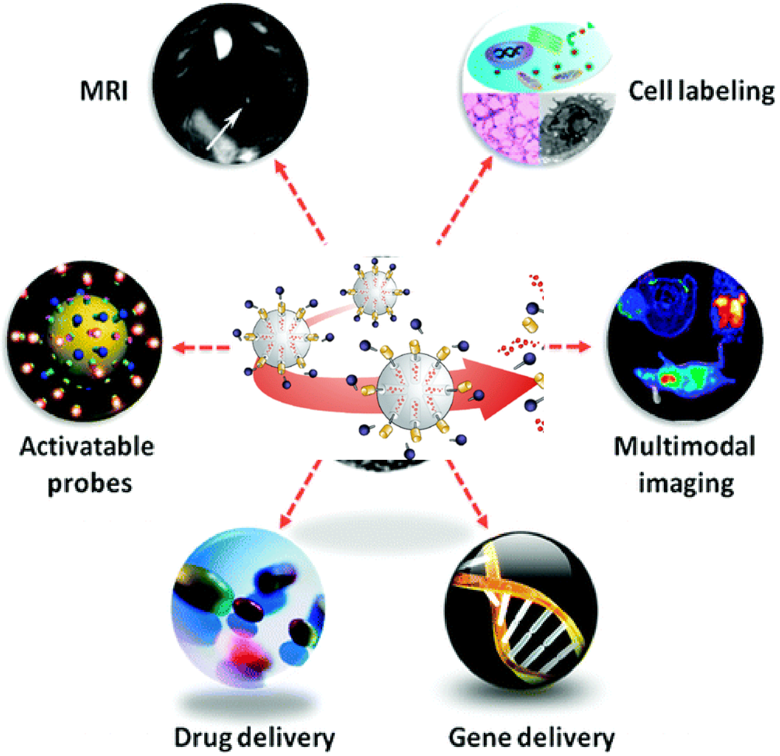
Issues to consider

Magnetically driven therapies: Toxicity, Risks and Side-effects

Magnetically Driven Therapies

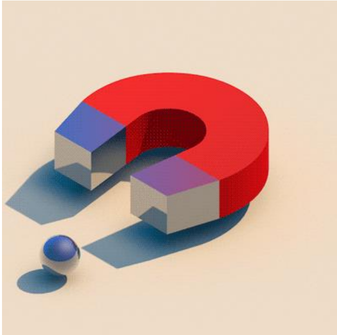
Magnetic field driven treatments involve the delivery of an energy form to the tissues, resulting in a physiological change or stimulation, which can in turn be used to generate specific effects.

Magnetic nanoparticles (MNPs) entered also in the play of magnetically driven treatments, particularly, in modern theranostics, as multifunctional carriers delivering specific ‘cargo’ under the guidance of an external magnetic field.

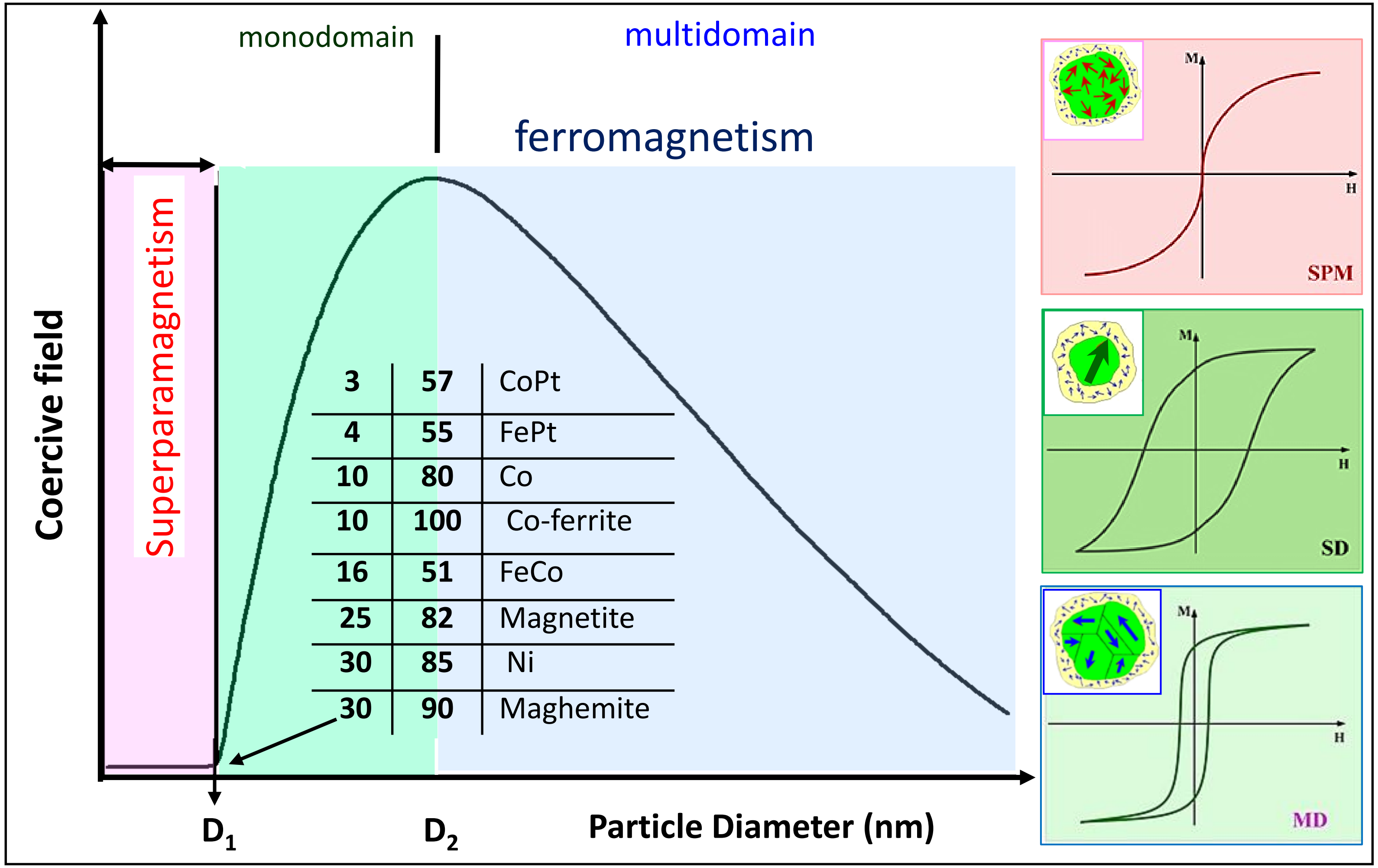


On the one side…

Magnetism is a phenomenon mediated by magnetic fields. The most familiar effects occur in ferromagnetic materials, which are strongly attracted by magnetic fields.



Maximize Particle - Field Interaction



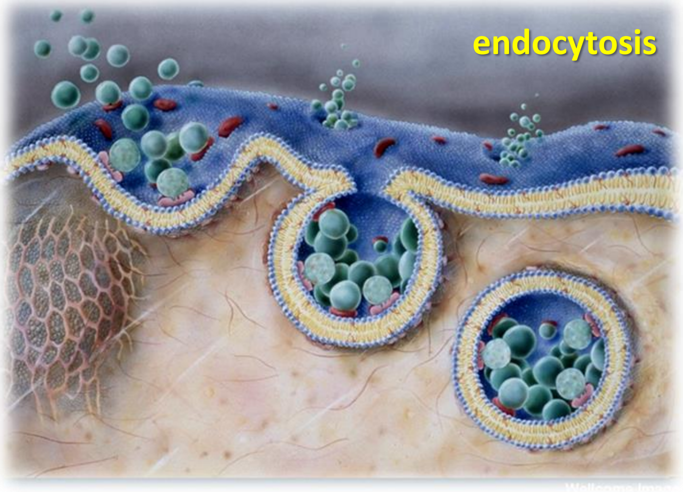
$$P_{SPM} = \mu_0 \pi f \chi'' H^2$$

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

Biochimica et Biophysica Acta 1861 (2017) 1642–1651,

On the other side…

- Nanoparticle formulations should be able to overcome major biological barriers to reach their targets.
- Intravenous injection of nanomaterials introduces new concerns such as dosage, distribution and circulation times as in pharmaceuticals.
- Possible changes in magnetic behavior upon injection and interactions with cells such as specific binding and endocytosis.
- Nanoparticle agglomerations or regions of high concentration with inter-particle interactions lead to altered magnetic properties.



- Do the specific magnetic fields with respect to amplitude & frequency pass harmlessly within human body?

Problem 1: Toxicity

Magnetically driven therapies: Toxicity, Risks and Side-effects

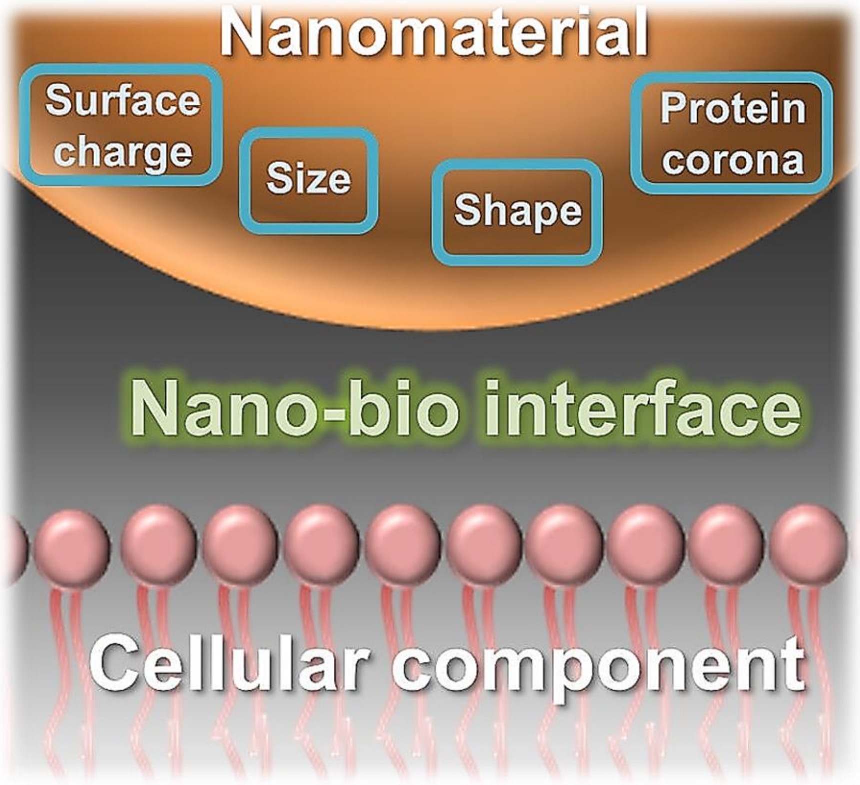
Nano-sized particles & Toxicity

- The toxicity of particles depends on materials and morphological parameters including **composition**, **degradation**, **oxidation**, **size**, **shape**, **surface area** and **structure**.

- 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.

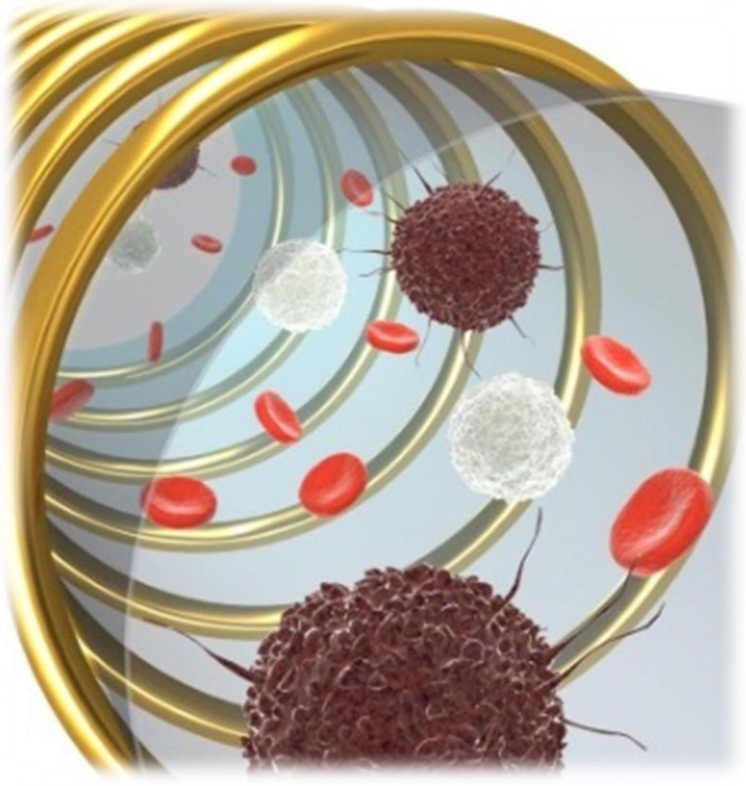
Nano-sized particles & Distribution

- Nanoparticles due to their multivalency and multifunctionality, pose challenge for understanding their pharmacokinetics because different components will have different features that affect their **distribution, clearance** and **catabolism.**



- The overall size of the nanoparticles (hydrodynamic size), surface charge and functionalization play a large role in their distribution and circulation time; however, these parameters may change upon interaction with in-vivo constituents.

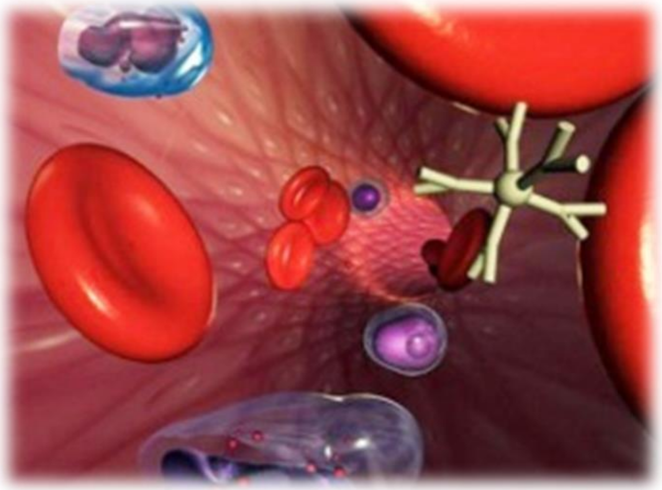
Nano-sized particles & Circulation



- **D > 100 nm**: larger-sized nanoparticles eliminated fast from the bloodstream
- **100 nm > D > 30 nm**: easily uptaken into endocytotic vesicles
- **D < 30 nm**: remain in blood circulation for long intervals

Nano-sized materials & Accumulation

- Nanoparticles have a large surface to volume ratio and tend to absorb plasma-proteins (**opsonization**), which are easily recognized by macrophages making them vulnerable to rapid clearance before reaching their target.



Accumulation

Rapid kidney clearance and reticular endothelial system (RES)

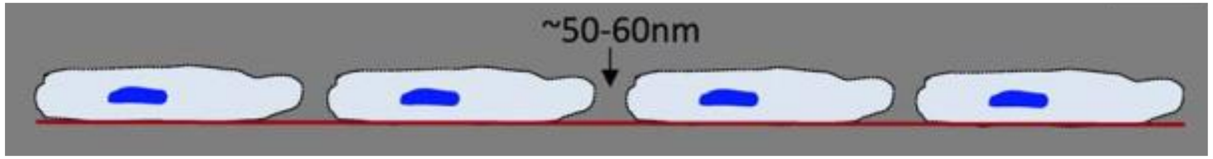
Fast opsonization and subsequent macrophage phagocytosis

Slow accumulation through the leaky vasculature in a variety of lesions

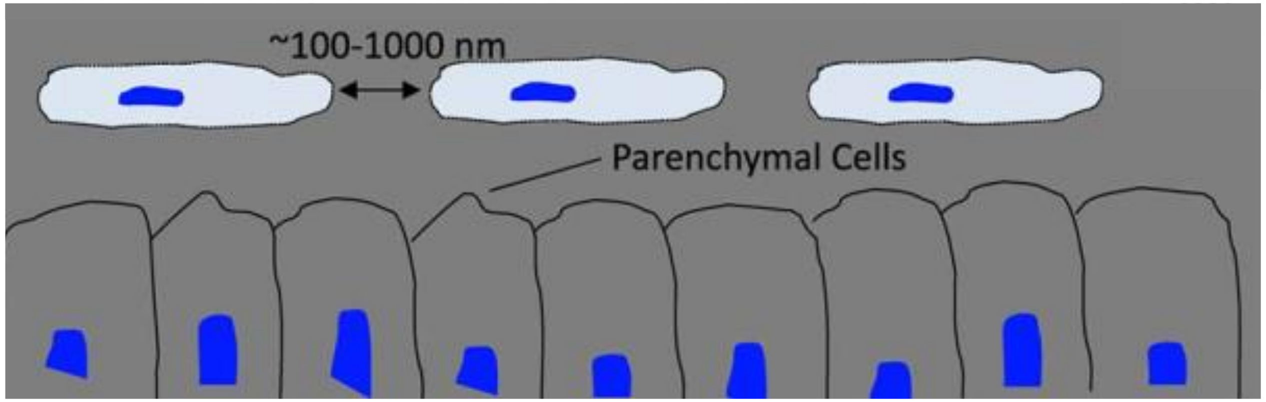
Metallic Iron upon metabolism – oxidative stress through harmful reactive oxygen species

Nano-sized materials & Clearance

- Fenestrated and Sinusoidal Capillaries are part of the filtration system where the kidneys remove objects below a certain size (~50 nm) and the liver/spleen prevent objects bigger than a certain size (~200 nm) from circulation, thus setting both an upper and lower bound.



Fenestrated capillaries include kidney, intestine and some endrocrine and exocrine glands.

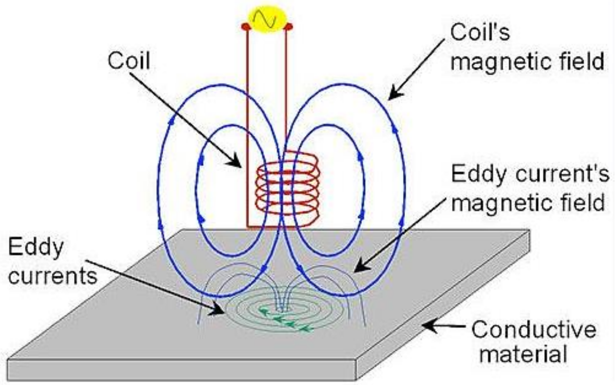


Sinusoidal Capillaries include liver, spleen and bone marrow.

Problem 2: Risks & Side effects

Magnetically driven therapies: Toxicity, Risks and Side-effects

Risks from magnetic fields



AMF generator system produces not only a magnetic field, but also an electric field. The electric field penetrates normal tissue and induces eddy currents, which result in unwanted heating of normal tissues.

Problems due to Eddy currents

1. Unwanted increase in temperature in healthy tissues
2. magnetic stimulation
3. muscle contraction
4. nervous stimulation
5. magnetophosphines
6. cardiac arrhythmias
7. patient discomfort

Criterion for safe use of magnetic fields

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

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 $\mathbf{H \cdot f < 4.85 \times 10^8 Am^{-1} s^{-1}}$ is safe and tolerable

First commercially developed equipment (Gneveckow et al 2004)

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

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

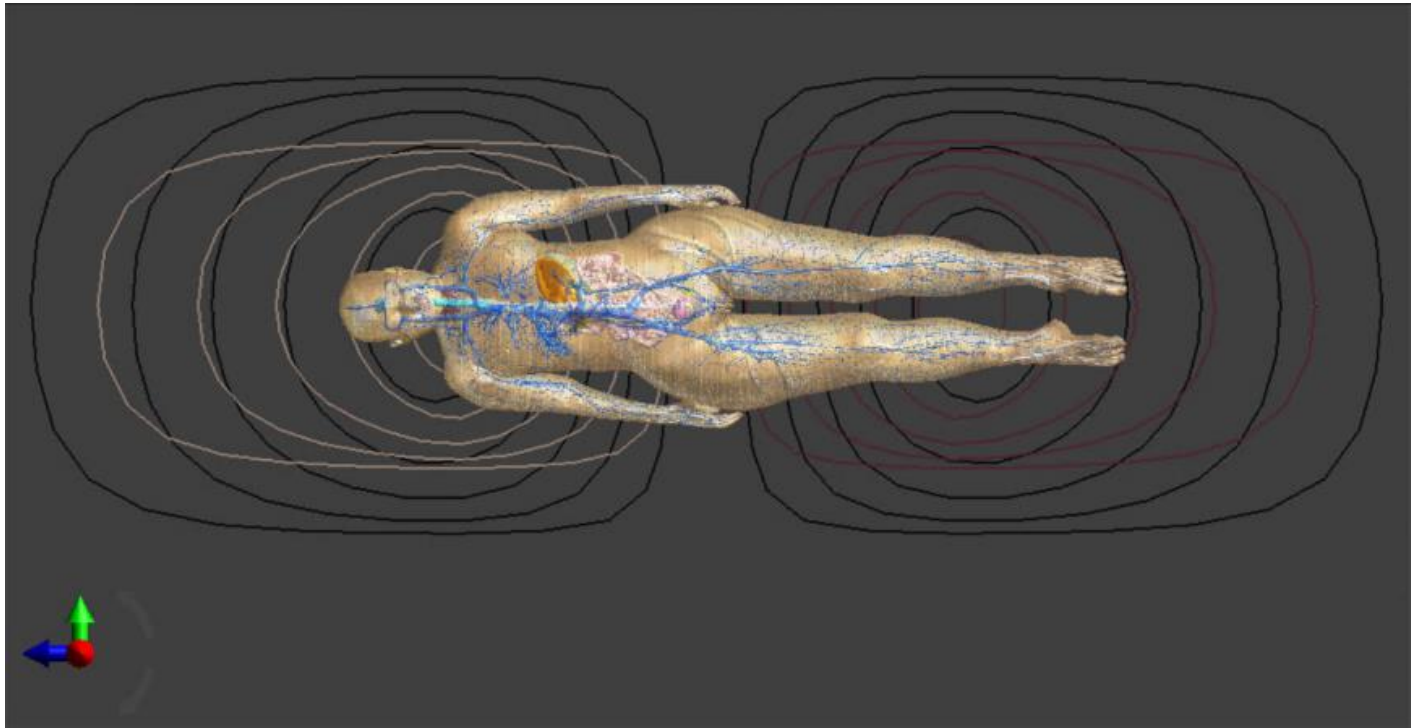
MRI Setup

Typically, magnetic fields in clinical MRI range between 1.5 and 3.0 T, while research MRI scanners beyond 10 T have also been reported.

A typical clinical MRI device consists of a magnetic field setup (major magnet, shim coils and gradient coils) and a signal processing section (radiofrequency [RF] transmitter and receiver, computer to acquire data).

Side effects

- Sim4LifeC software is used for MRI simulation components & conditions
- import the model of a human body (Yoon Sun 26 years old, 1.52 m height, 54.6 kg weight and 23.6 kg/m^2 BMI).
- model contains each tissue, bone, muscle, vain and other organs with realistic values on properties such as thermal and dielectric ones.



Continuous lines around the human body represent the gradient field lines

Nanomedicine, 2021, 16: 11

Side effects of magnetic fields

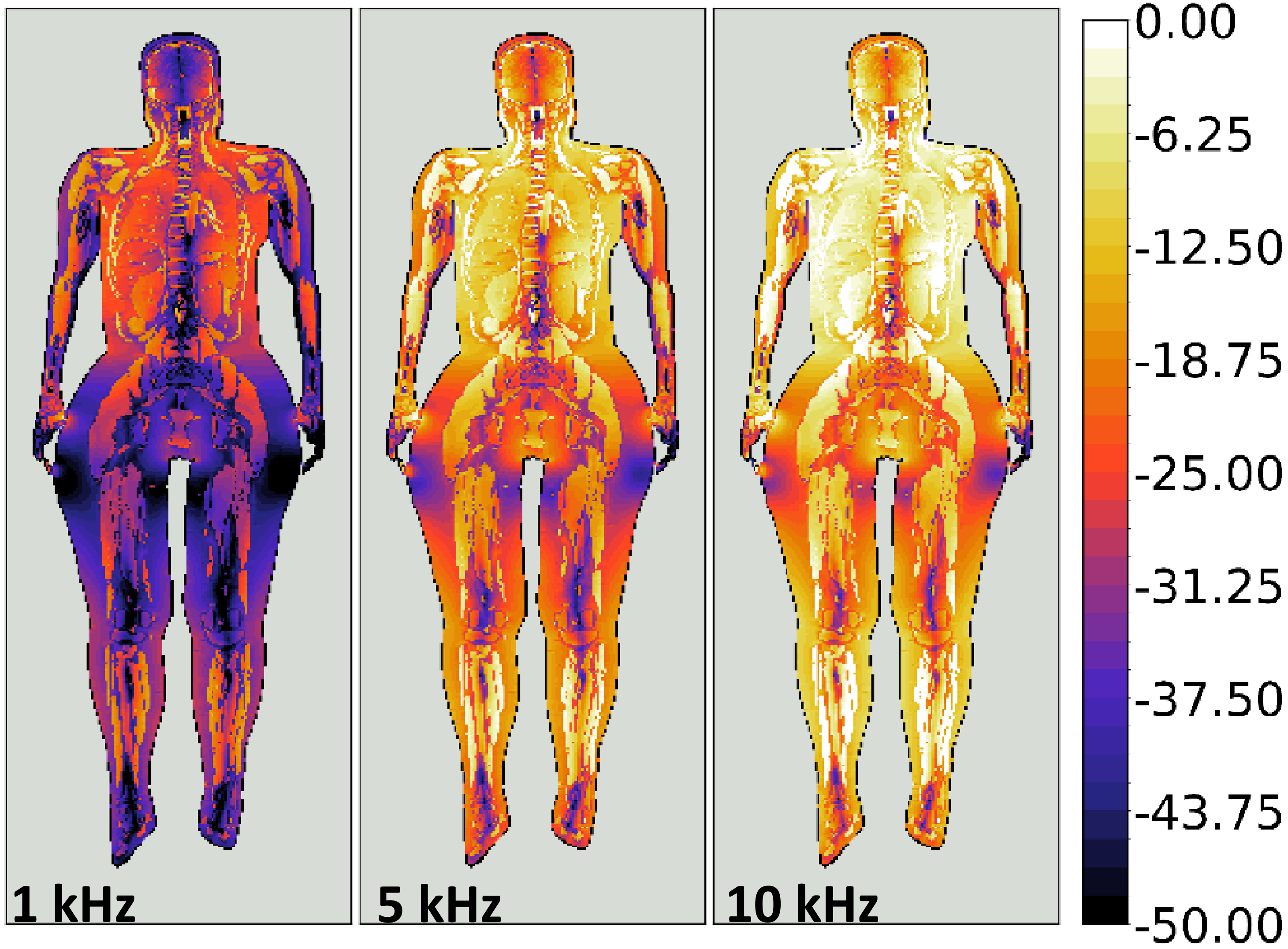


Illustration of the intensity of eddy currents in human body

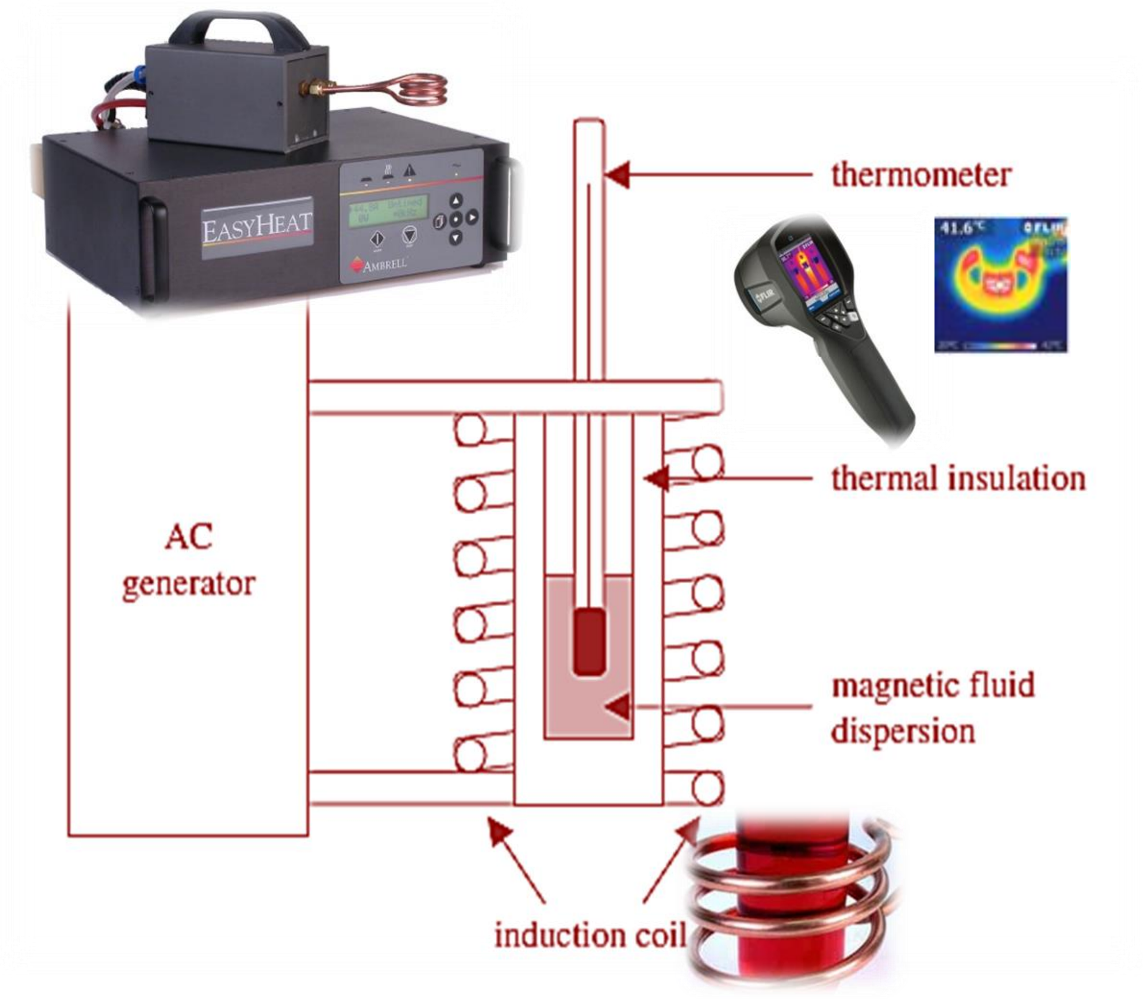
Color bar in a logarithmic scale corresponds to the intensity of eddy currents measured in A/m^2

Nanomedicine, 2021, 16: 11

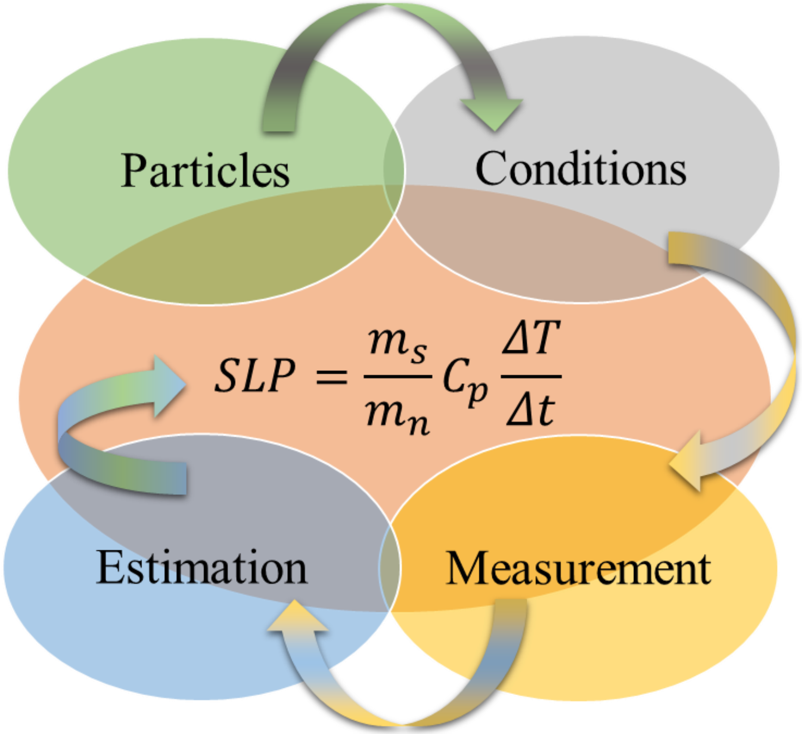
Magnetic Particle Hyperthermia

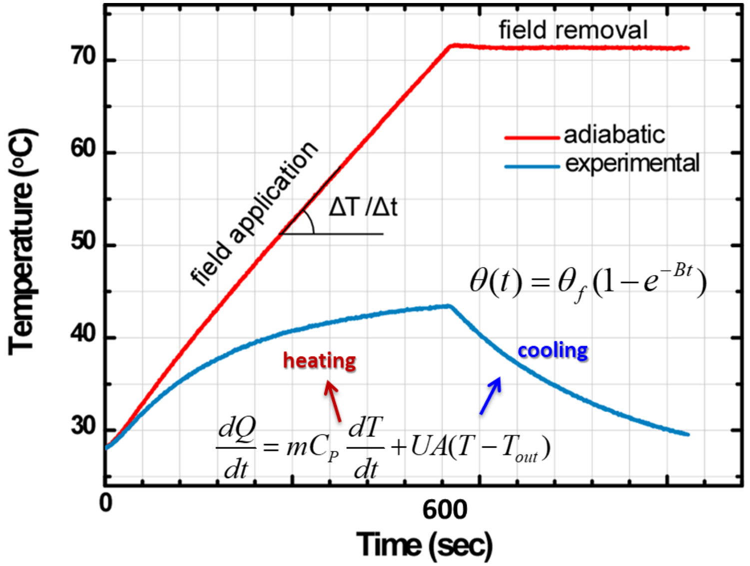
Frequency: 100-1000 kHz

Magnetic Filed Intensity Amplitude: 10-100 kA/m



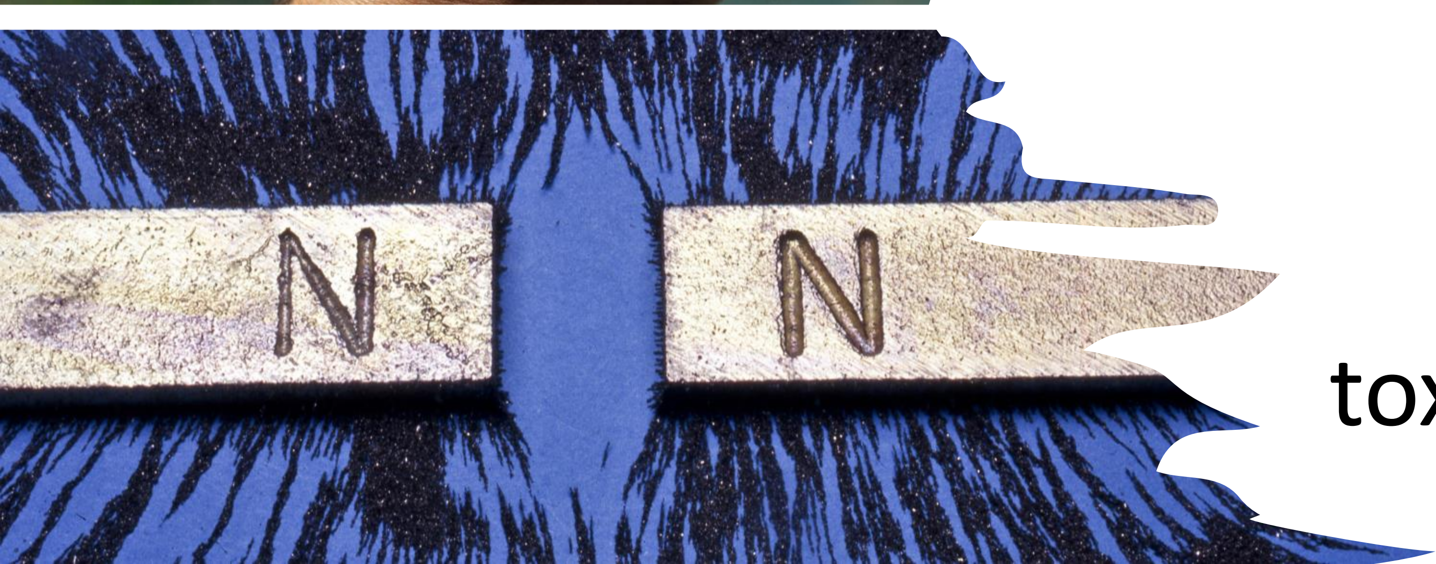
J. Phys. D: Appl. Phys. 2021 52 255001





How to solve the 2 problems?

Magnetically driven therapies: Toxicity, Risks and Side-effects



To minimize

toxicity, risks & side effects

Focus of MNPs

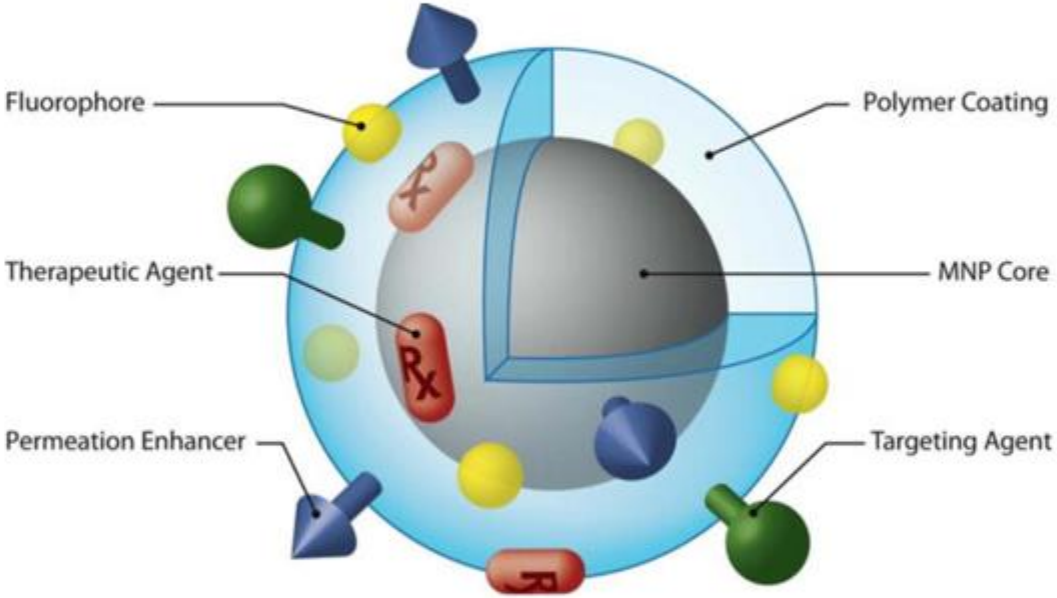
Stronger magnetic response to minimize size & dosage

Direct instead of intravenous injection

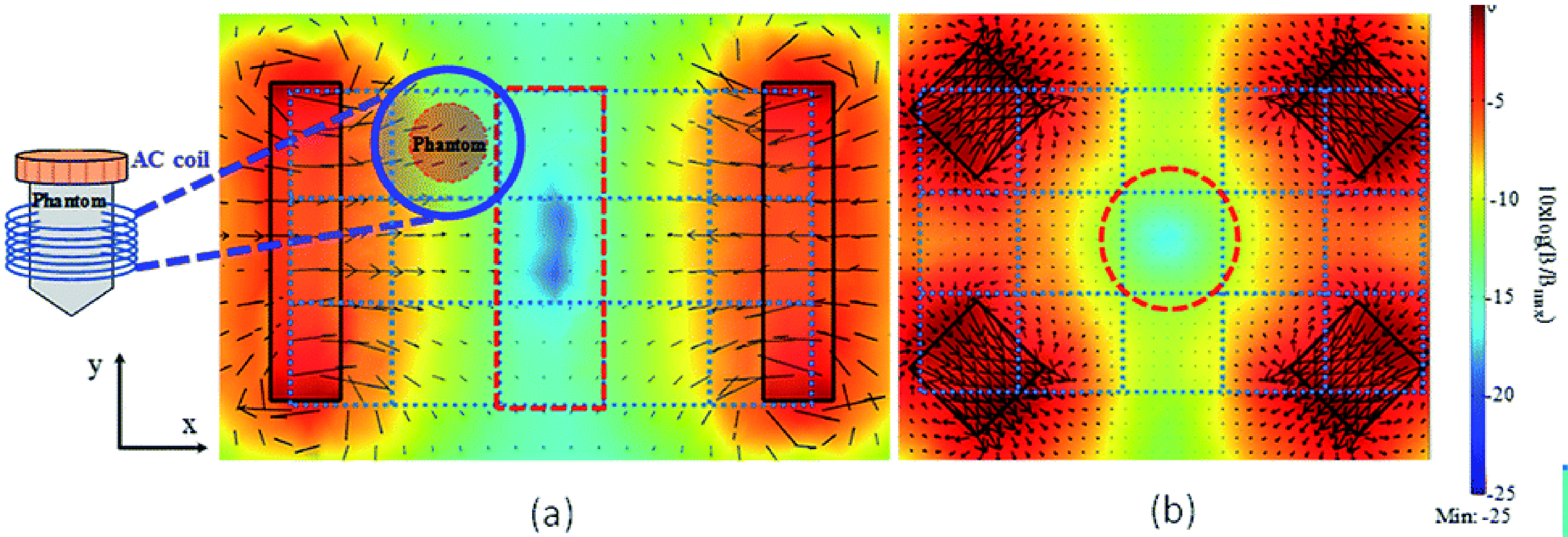
Functionalization to

selectively target malignant sites and

sustain hostile environment



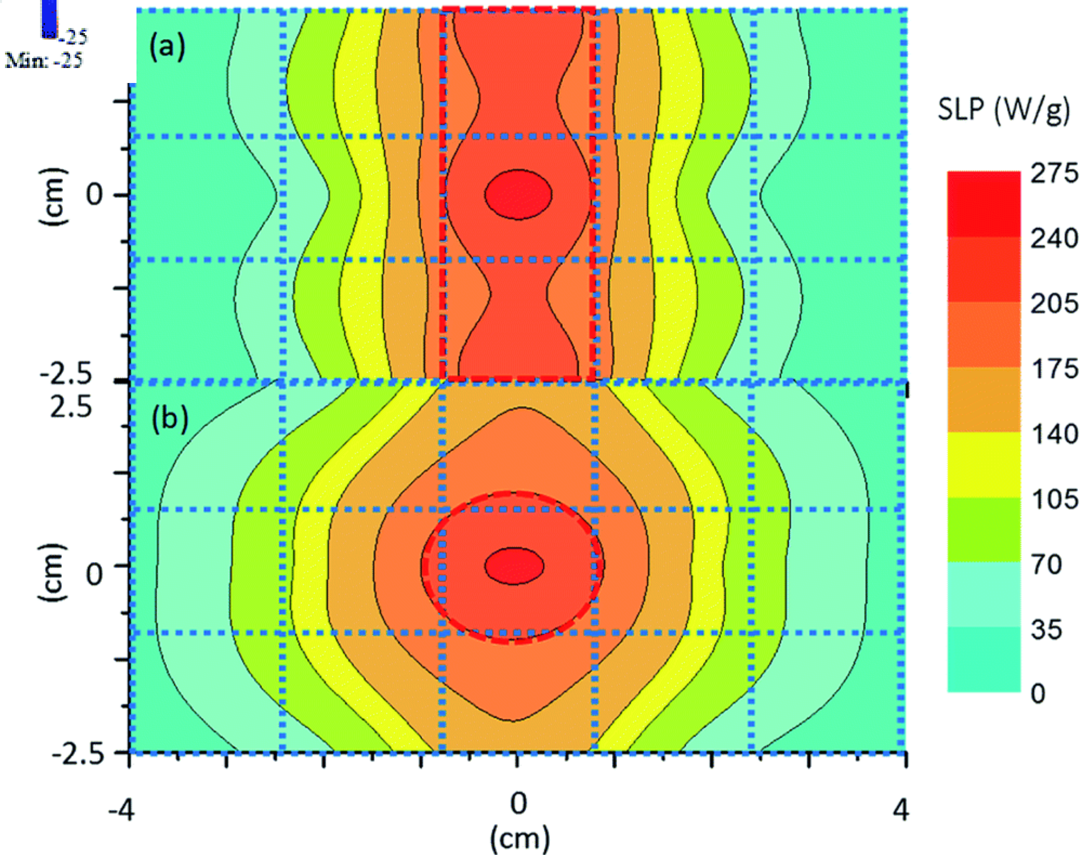
Field Focus



minimization

of heat side-impact on

surrounding healthy tissues

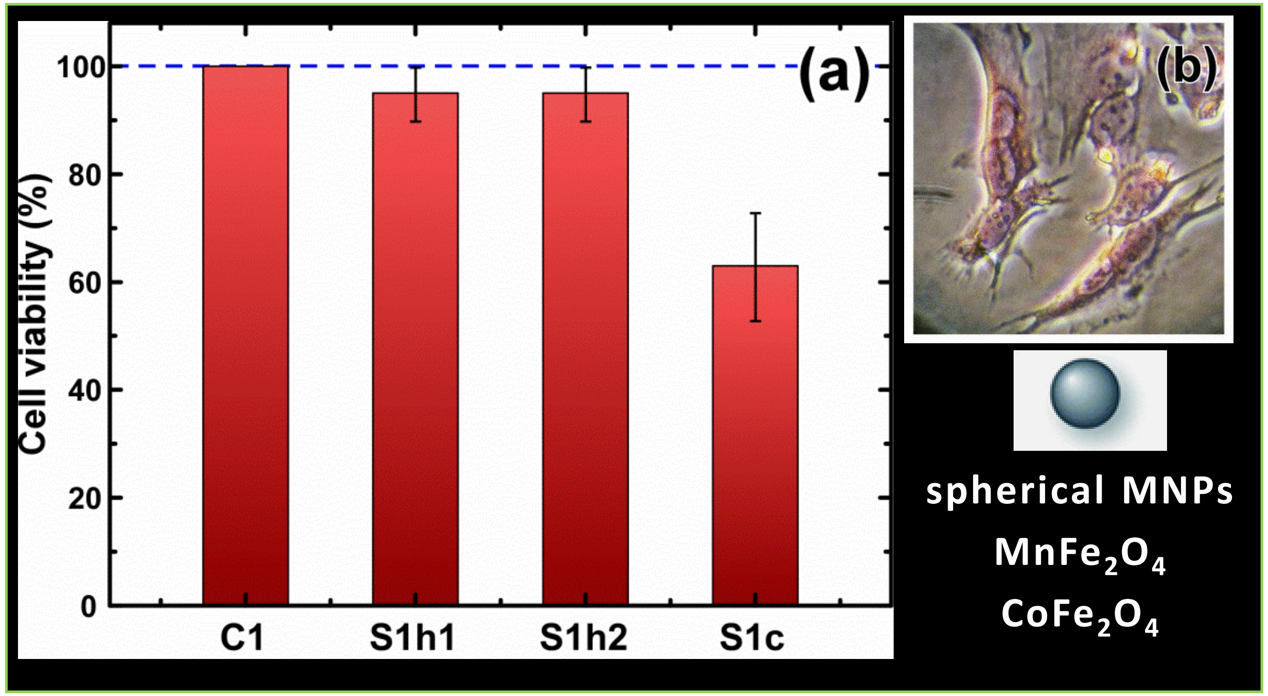


MPH much more effective

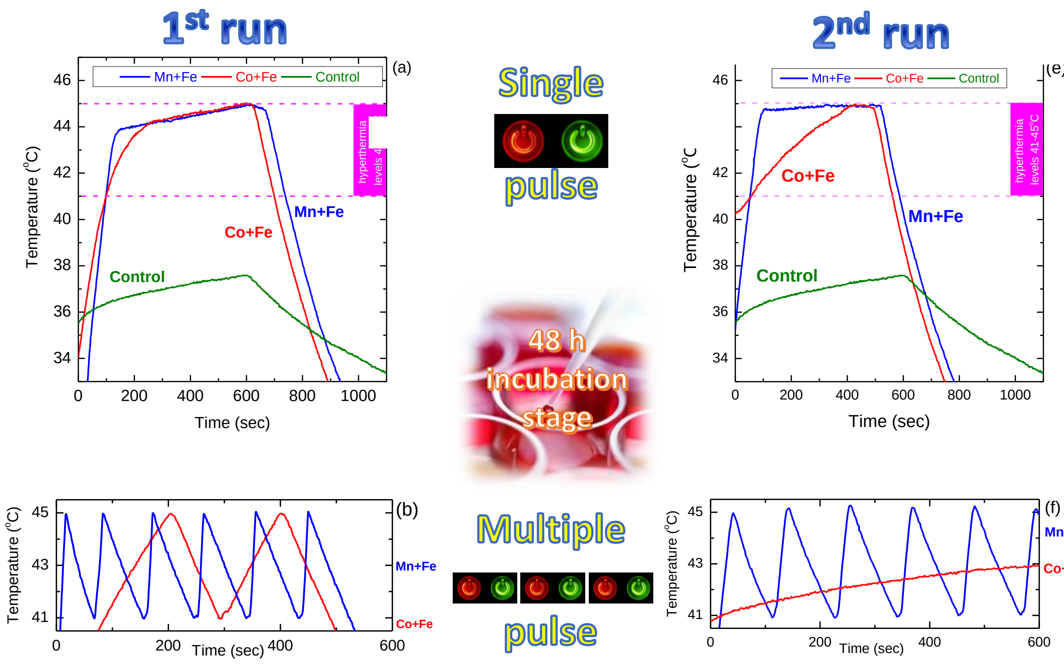
- better focusing capabilities
- tunable heat localization

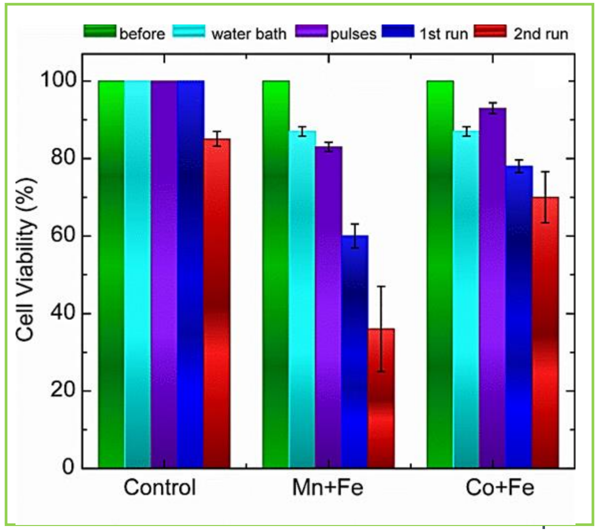
Nanoscale Adv., 2020,2, 408-416

Field Pulses



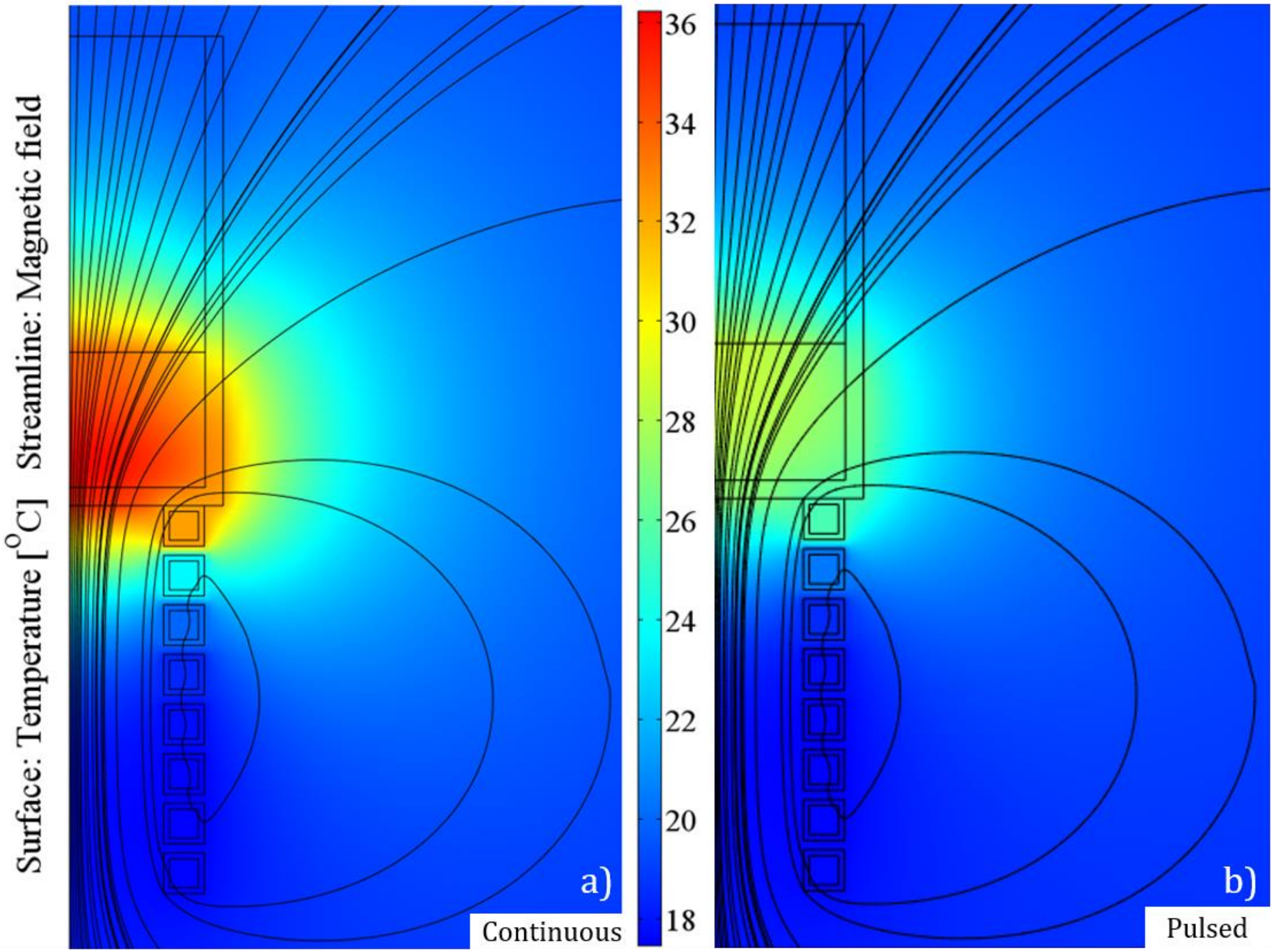
Comparative viability for the three cell lines : S1h1: primary bone marrow-derived osteoblasts, S1h2: 3T3-L1 fibroblast-like preadipocytes, C1 and S1c: Saos-2 osteoblasts control and sample (b), (c) Optical microscope images (36x) of Saos-2 osteoblast cell line control sample and MNPs after Prussian blue staining.

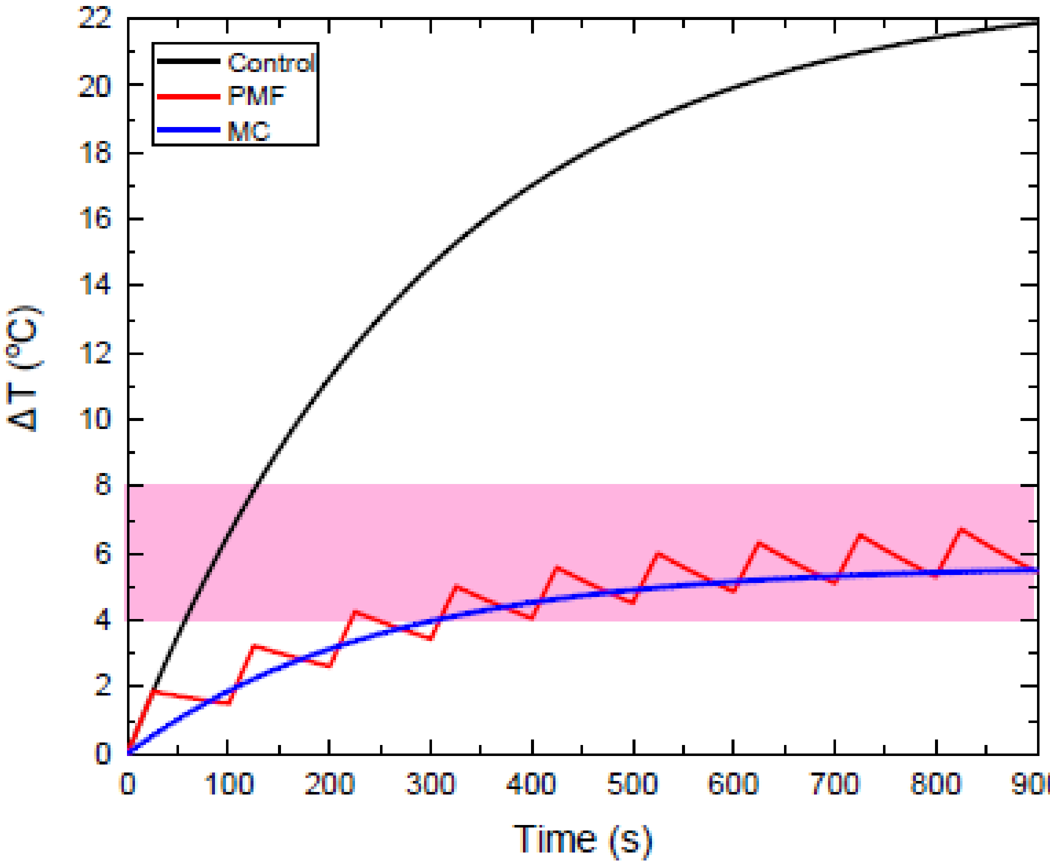




J. Mater. Chem. B, 2014, 2, 8390.
Int J Hyperthermia, 2017, 32(7):778-85.

Field Pulses

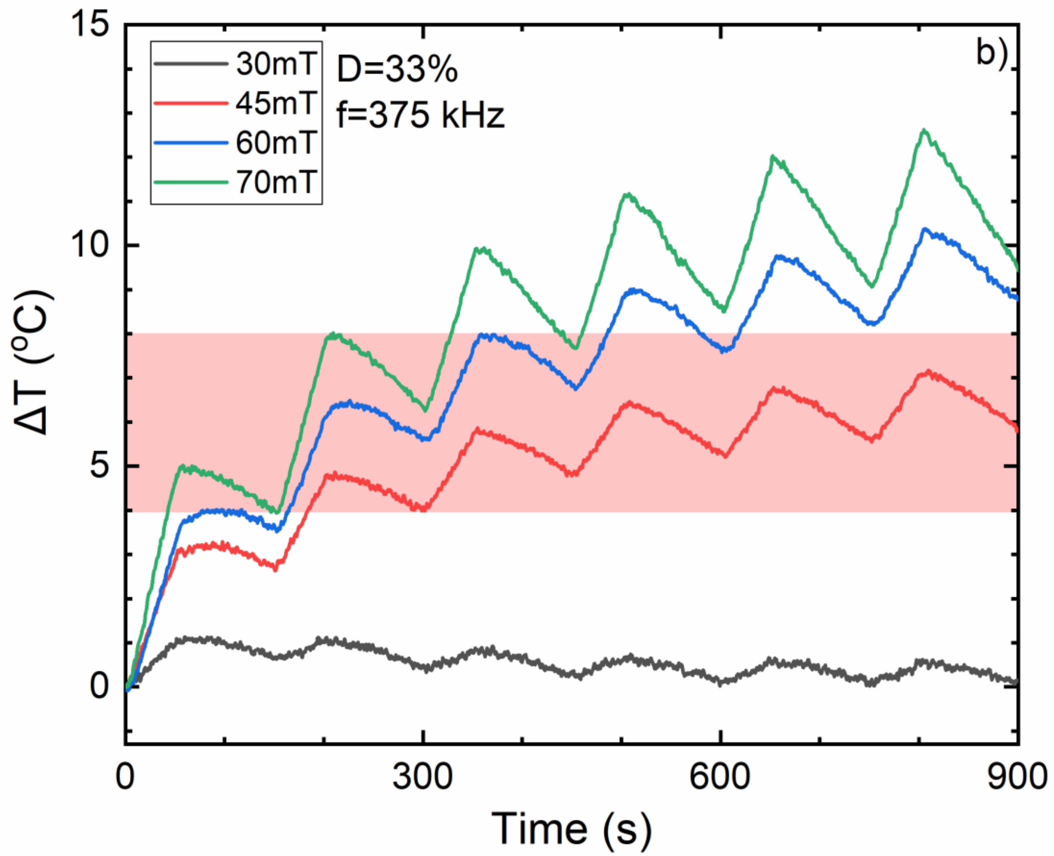


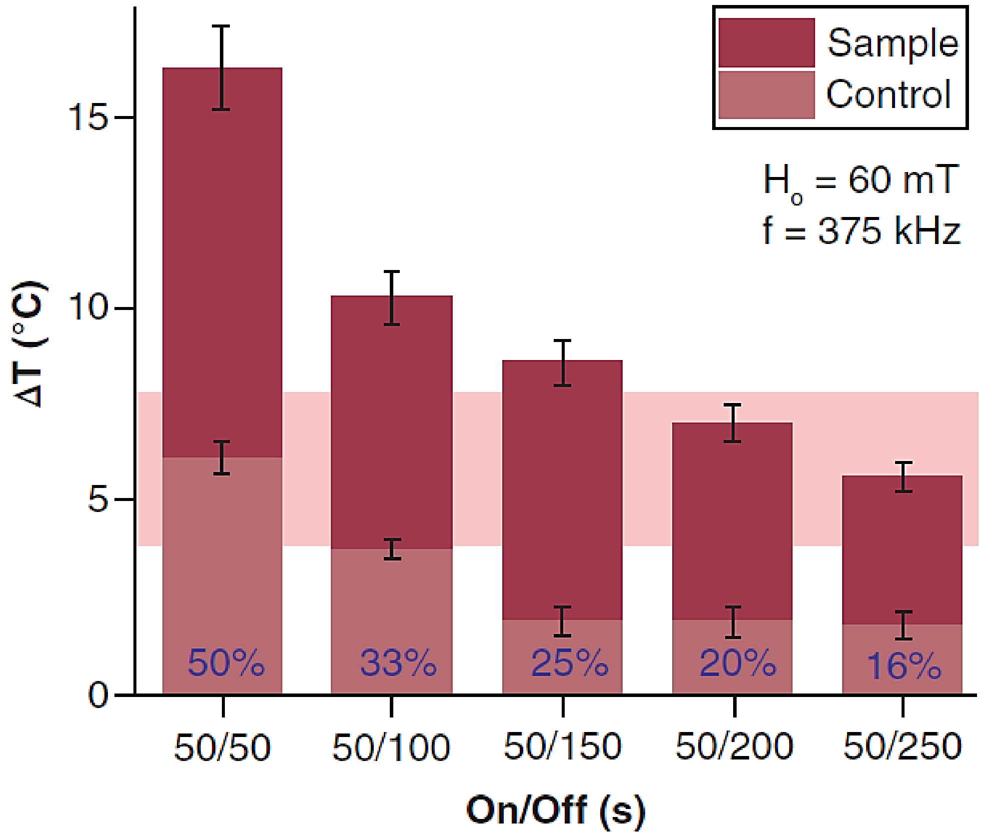


Nanomaterials 2022, 12, 554
Int J Hyperthermia 2021;38(1):511-522
Nanomedicine, 2021, 16: 11

Field Pulses

$$\text{Duty Cycle} = \frac{\text{Field ON time (s)}}{\text{Field ON time (s)} + \text{Field OFF time (s)}} \times 100\%$$





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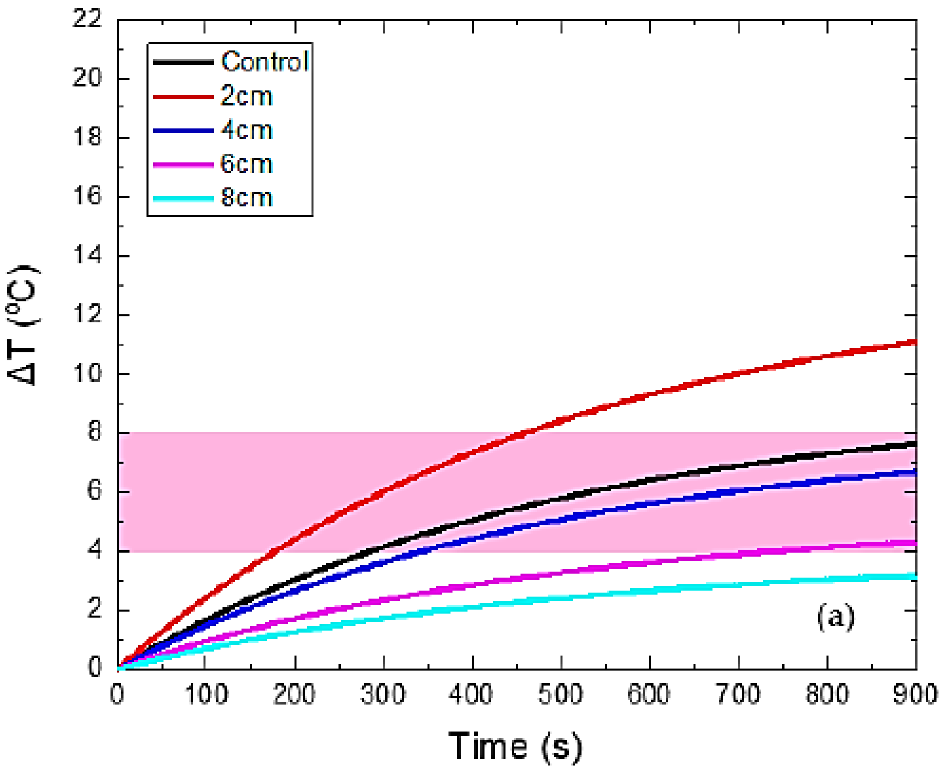
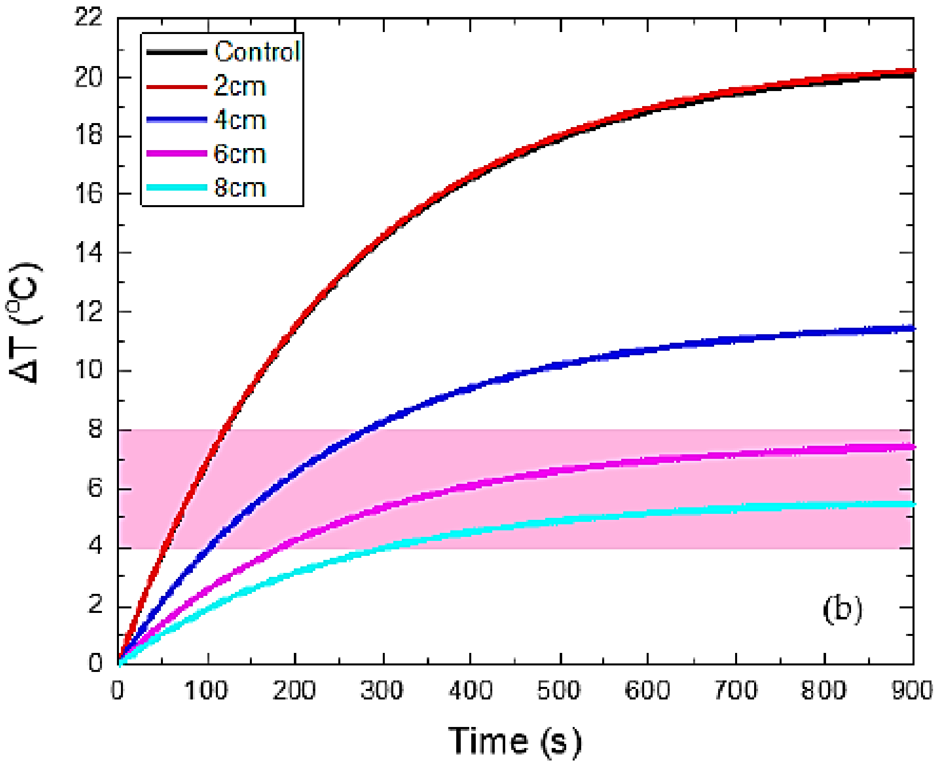
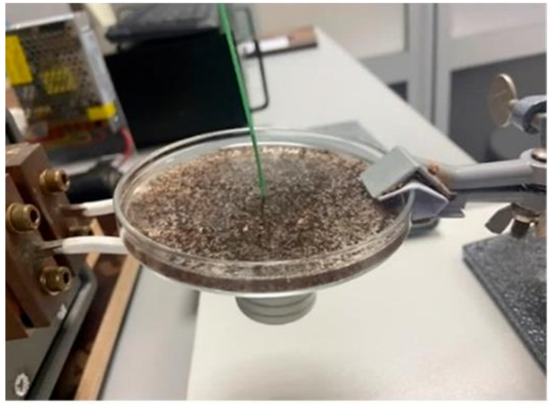
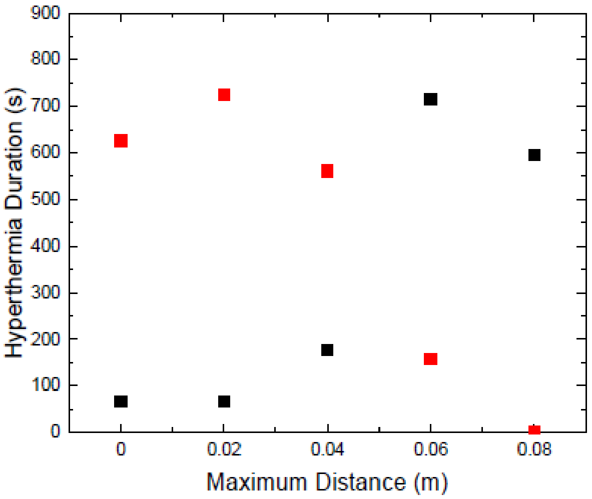
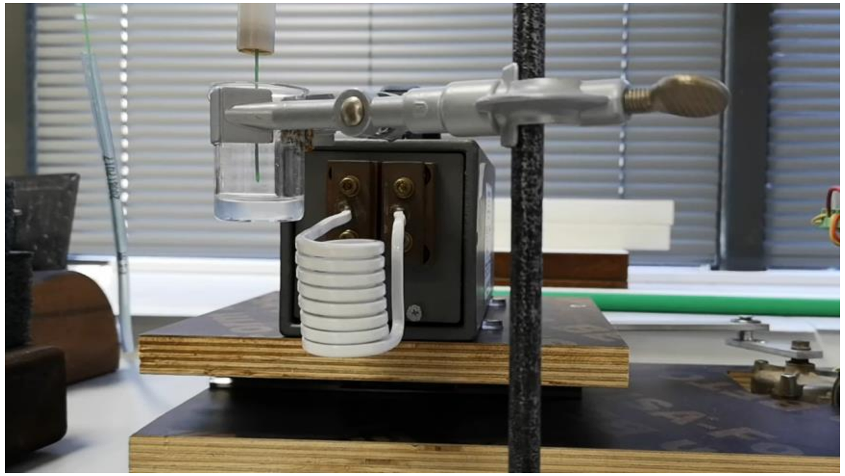
Field movement











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Take home message

Localization of MNPs+ magnetic field

to minimize

toxicity, risks & side effects

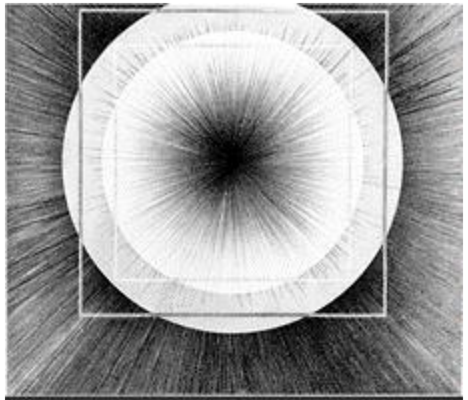
Acknowledgements

Magna Charta

Magnetic Nanostructure Characterization

Technology & Applications

http://magnacharta.physics.auth.gr



MaNaCa
Magnetic Nanohybrids for Cancer Therapy

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