Magnetic nanoparticle hyperthermia

Robert Ivkov, Ph.D.
Johns Hopkins University

Selective Inductive Heating of Lymph Nodes *

R. K. Gilchrist, M.D., Richard Medal, B.S.,** William D. Shorey, M.D.,
Russell C. Hanselman, M.D., John C. Parrott, M.D.,
C. Bruce Taylor, M.D.

*From the Surgical Research Laboratories, Presbyterian-St. Luke's Hospital,
Chicago, Illinois*

Our work on the clearing of surgically removed specimens of carcinoma of the colon and rectum and especially the clearing of the retroperitoneal tissues of patients who died in the immediate postoperative period [1,2] convinced us that a new method was needed to destroy metastases in lymph nodes missed at operation. The outstanding facts of these studies made on patients in whom the surgeon thought that he had removed all demonstrable cancer were: 1) the pathologist was unable to demonstrate any metastases in retroperitoneal lymph nodes when an ordinary postmortem examination was performed, although all three of the patients examined in this manner had node metastases in the operative specimen: specimen (Fig. I). The four who had lymphatic metastases remaining in the retroperitoneal nodes also had involved nodes in the surgical specimen.

Drawings of these four postmortem preparations showed that all of the involved nodes were less than 1.5 cm. outside the operative field in three and even in the fourth the involved nodes would probably have been removed by present technics (Fig. II). The important point is that in these instances when such lesions could be found, the remaining *metastatic cancer involved only a small part of the node.*

Our studies [2] showed that cancer spreads through the lymph system by tumor embolism and the emboli are retained in the

Annals of Surgery, 1957

Nanoparticle hyperthermia – Key physical constraints

- **<u>Efficiency of heating</u>** – defines the potency
  - Normalized power (Watts/unit mass)
  - For hyperthermia, potency of heating defines minimum quantity that must be present to generate and sustain minimum effective thermal dose (~CEM43ºC ≅30 min in 90% of tumor, i.e. CEM43T90 = 30 min).

Nanoparticle hyperthermia – Key physical and chemical constraints

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- **Toxicity** – defines limit of tolerated dose that can be administered.
  - Physical properties and chemical constituents (*physicochemical* properties) of nanoparticles define interaction with biological systems (*physiochemical* properties).

Materials design cannot occur in a vacuum!

Requirements for magnetic nanoparticle hyperthermia

1. Particles must be localized specifically to target site(s) and deposit heat at tolerable AMF conditions
2. Device must produce consistent field to cover target which may include large regions of tissue
3. Methodology development – appropriate dose/schedule and dosimetry

Part 1: Physics and biology of heat

Why do we think magnetic hyperthermia will work?

Physics and biology of heat

- Internal energy is defined by the products of *intensive (Y),* and *extensive, (X),* variables

$$\Delta U = \sum Y_i \times \Delta X_i$$

$$\Delta U = T\Delta S + p\,\Delta V + \Phi\Delta e + (E \bullet \Delta P) + (H \bullet \Delta M) + \sum \mu_j\,\Delta N_j + \ldots$$

- First term is only term relating energy change to temperature.
- Temperature is related *to change of internal energy* through change of entropy!
- All others define other types of work performed through energy (heat) exchange.

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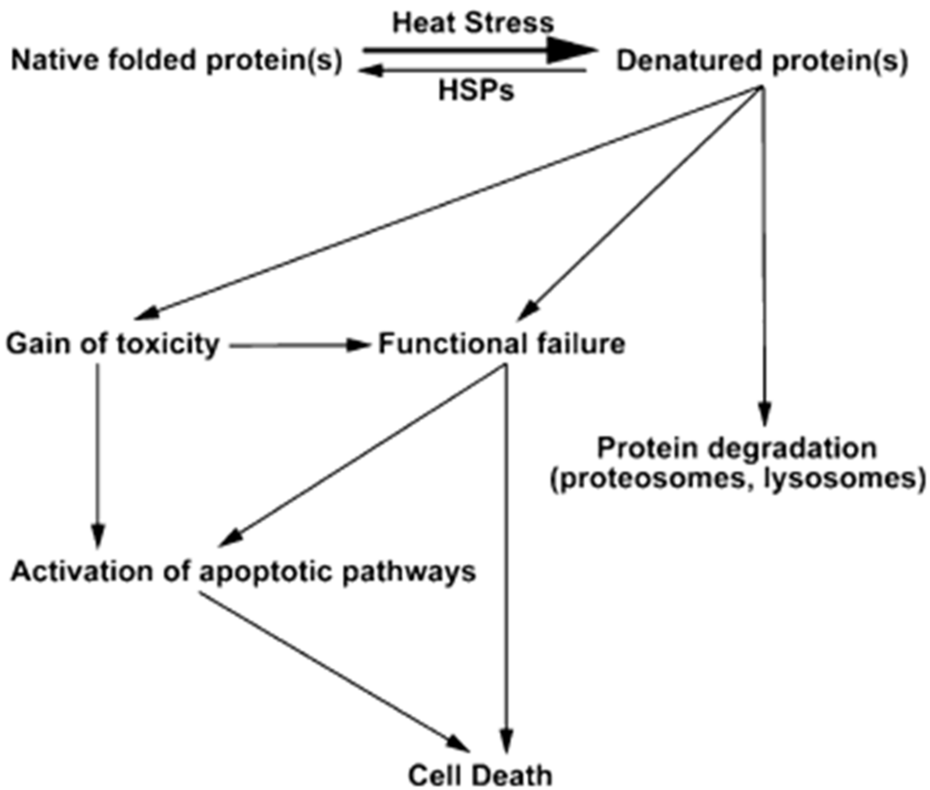
- **Cells tightly regulate balance of entropy and enthalpy at the molecular scale.**
- **Cells exist in dynamic ('metastable' or 'non-equilibrium') thermodynamic state balancing stochastic and 'deterministic' (e.g. repair) processes.**

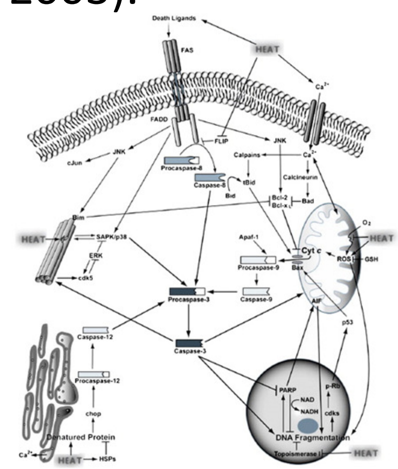
Biology of heat
Heat is a potent anti-cancer therapeutic

- Heat has multiple targets in cells
- Broadly affects cellular and physiologic processes
- Sensitizes cancer to radiation and chemotherapies
- Stimulates the immune system

Biology of heat



- Mild hyperthermia can promote protein misfolding and degradation by proteasomes, inhibiting DNA repair (Krawczyk et al. 2011, Horsman and Overgaard 2007, Storm et al. 1985, Dewhirst et al. *Int. J. Hyperthermia* 2003).



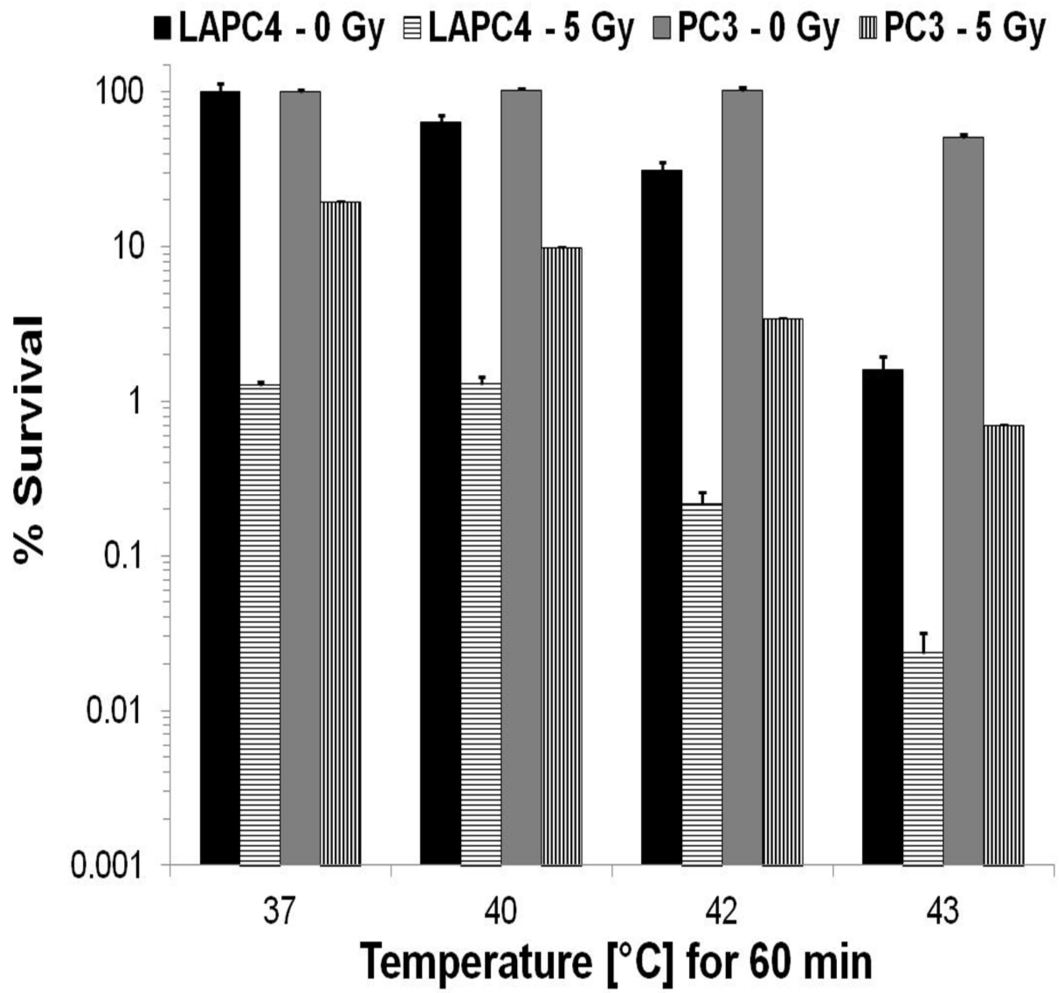
White M. G. et al.
Prog. Brain Res., 2007

In the biological sense, heat (even transient) causes stress, induces repair.

Cell death occurs via multiple potential pathways with failed repair.

Endpoint assays can typically measure only one metabolic process, or total death.

Hyperthermia enhances cytotoxicity of radiation therapy



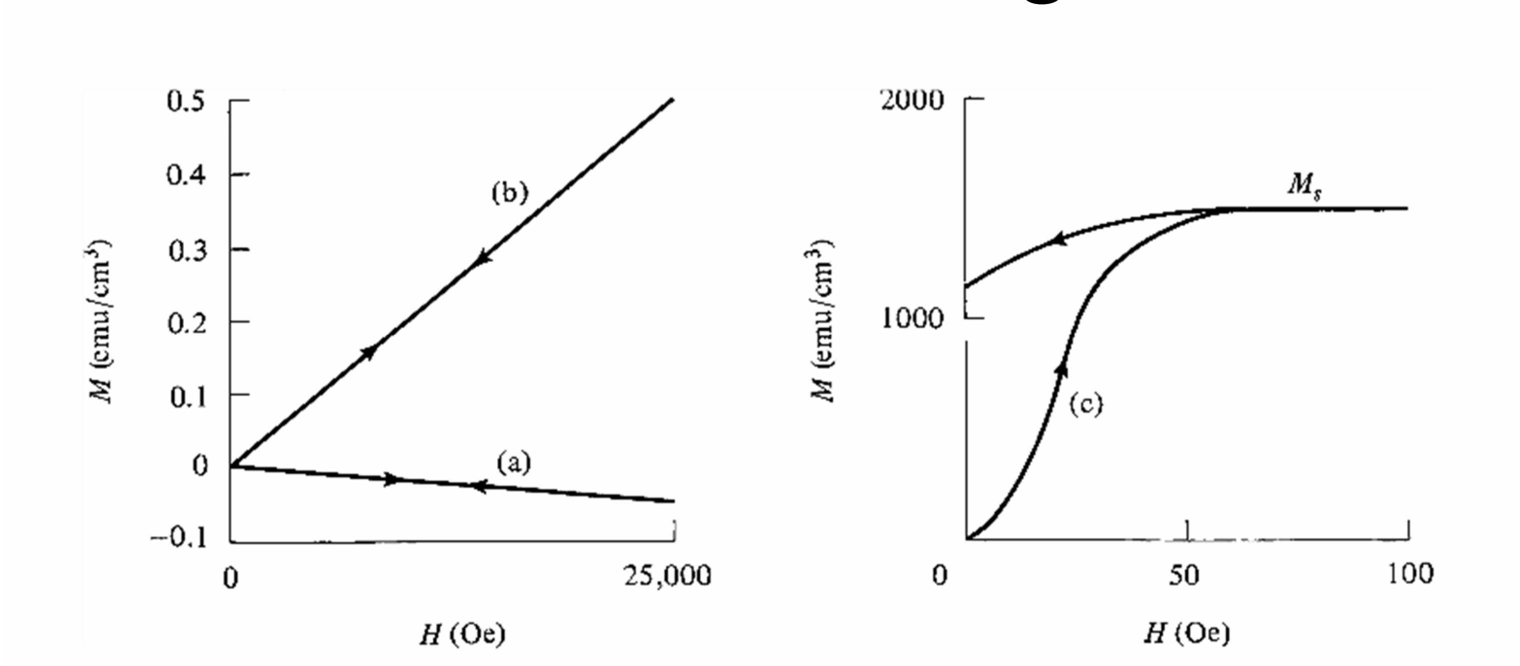
Attaluri, Kandala, et al., *International Journal of Hyperthermia,* 2015

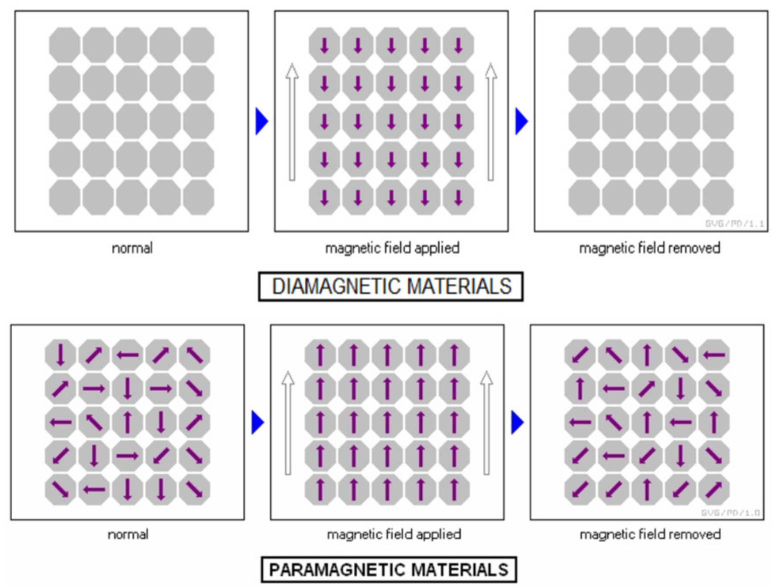
Controlled energy deposition creates challenges for heat therapy

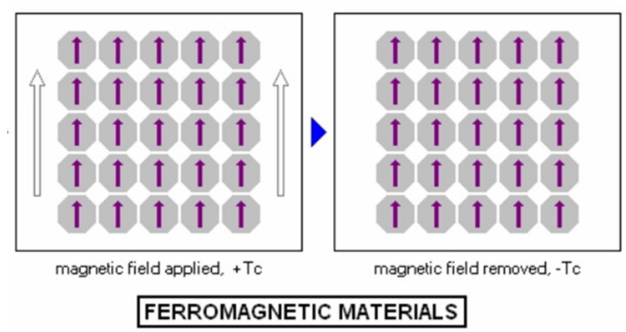
- Heat is mechanical, incoherent energy that acts on matter at atomic/molecular scale.
- Heat is indiscriminate – does not selectively damage cancer
- Thus, must control:
  - **Delivery** – target disease, spare adjacent tissue
  - **Distribution** – optimize (cyto)toxicity within target
  - **Dose** – ensure minimum effective dose throughout target

Part 2a: Magnetic hysteresis in fine particle magnetic materials

All materials are magnetic



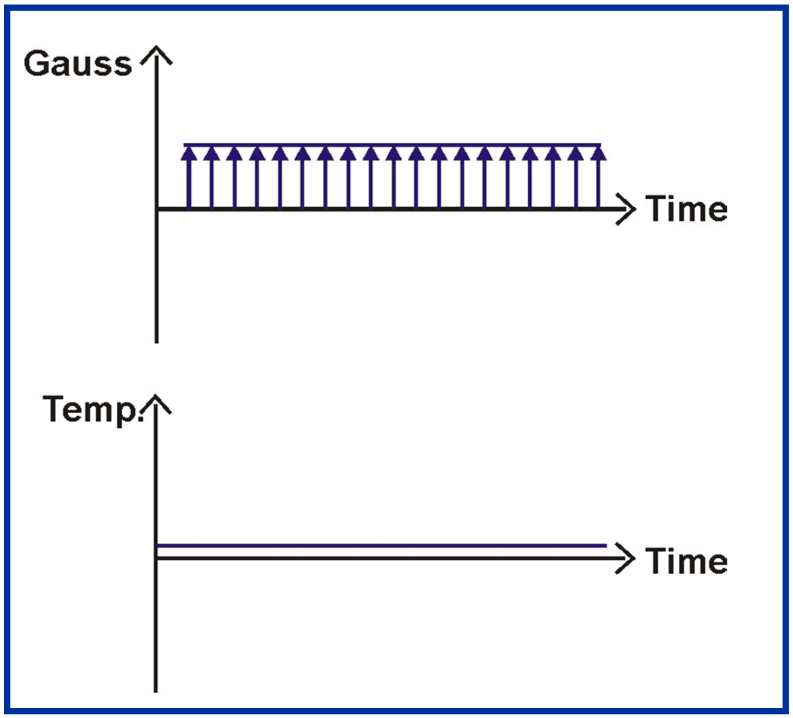




Hicthhiker's guide to magnetism, B. Moskowitz, UMN

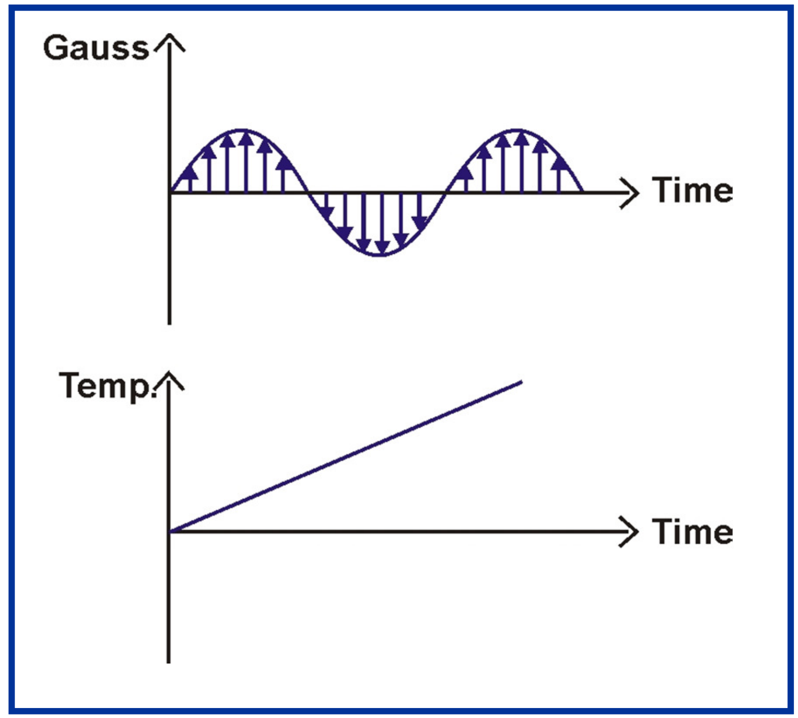
Magnetic fields exert effects on objects offering benefits for medical imaging and therapy

Static – time-invariant



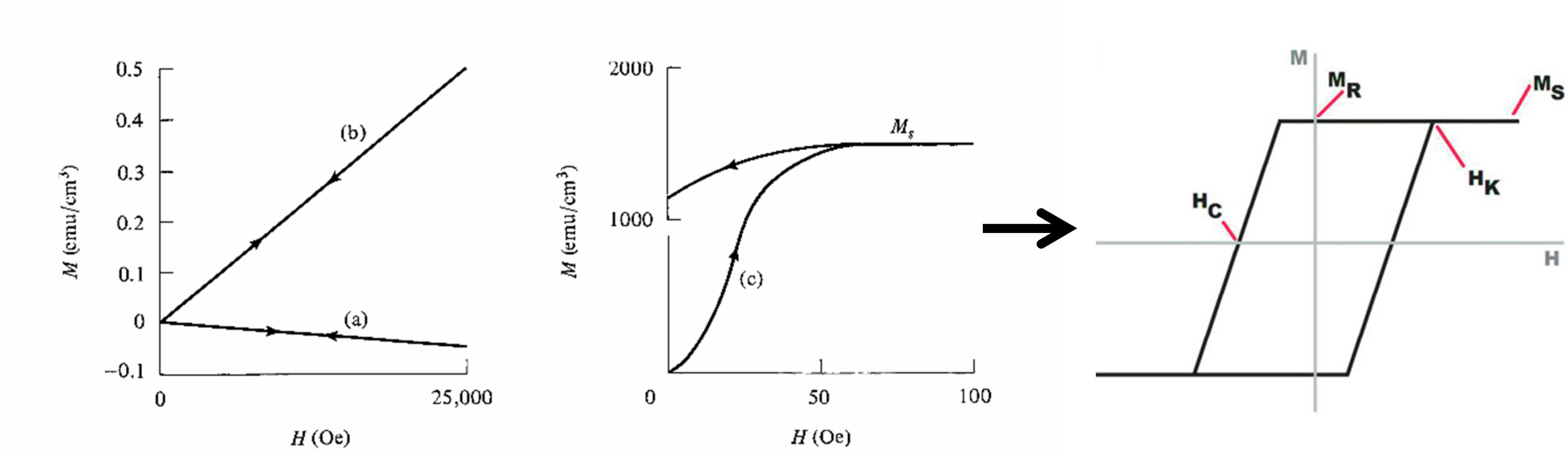
Very useful for imaging
Magnetic resonance imaging
(MRI)

Time-varying - alternating

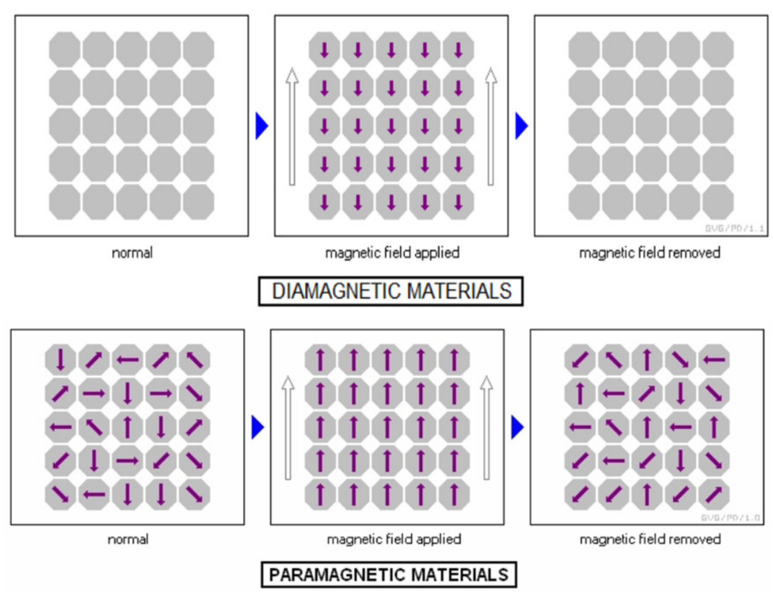


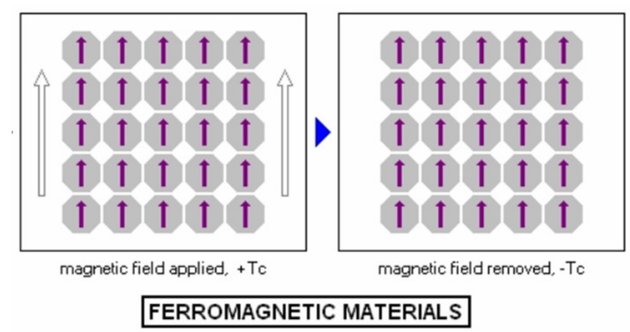
Useful for therapy
Heat or activating devices

All materials are magnetic



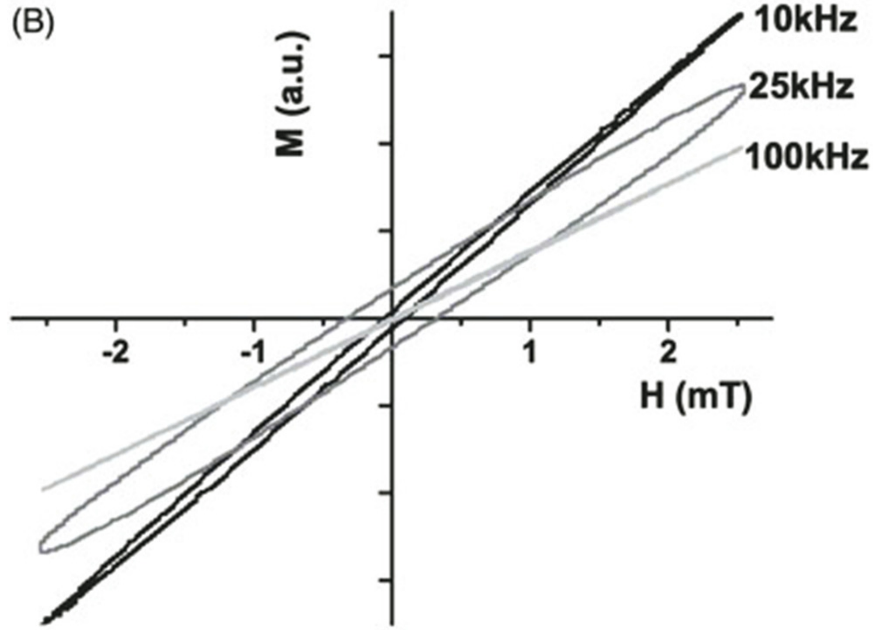
Dennis et al. *Int. J. Hyperthermia*, 2013





Hicthhiker’s guide to magnetism, B. Moskowitz, UMN

Time-scale of magnetization measurement affects the area of hysteresis loop



Dennis et al. *Int. J. Hyperthermia*, 2013

Physics of magnetic hysteresis heat

- Internal energy change of a system is equal to difference of heat and work

$$\Delta U = \Delta Q - \Delta W$$ <u>*First Law of Thermodynamics*</u>

- Internal energy is defined by the products of *intensive (Y),* and *extensive, (X),* variables

$$\Delta U = \sum Y_i \times \Delta X_i$$

$$\Delta U = T\Delta S + p\,\Delta V + \Phi\Delta e + (E\bullet\Delta P) + (H\bullet\Delta M) + \sum \mu_j \Delta N_j + \ldots$$

- For magnets, this is

$$dW = \vec{H} \cdot d\vec{M}$$ $\Delta U = 0$ and thus $Q = W$

$$W_{heat} = \oint \vec{H} \cdot d\vec{M}$$

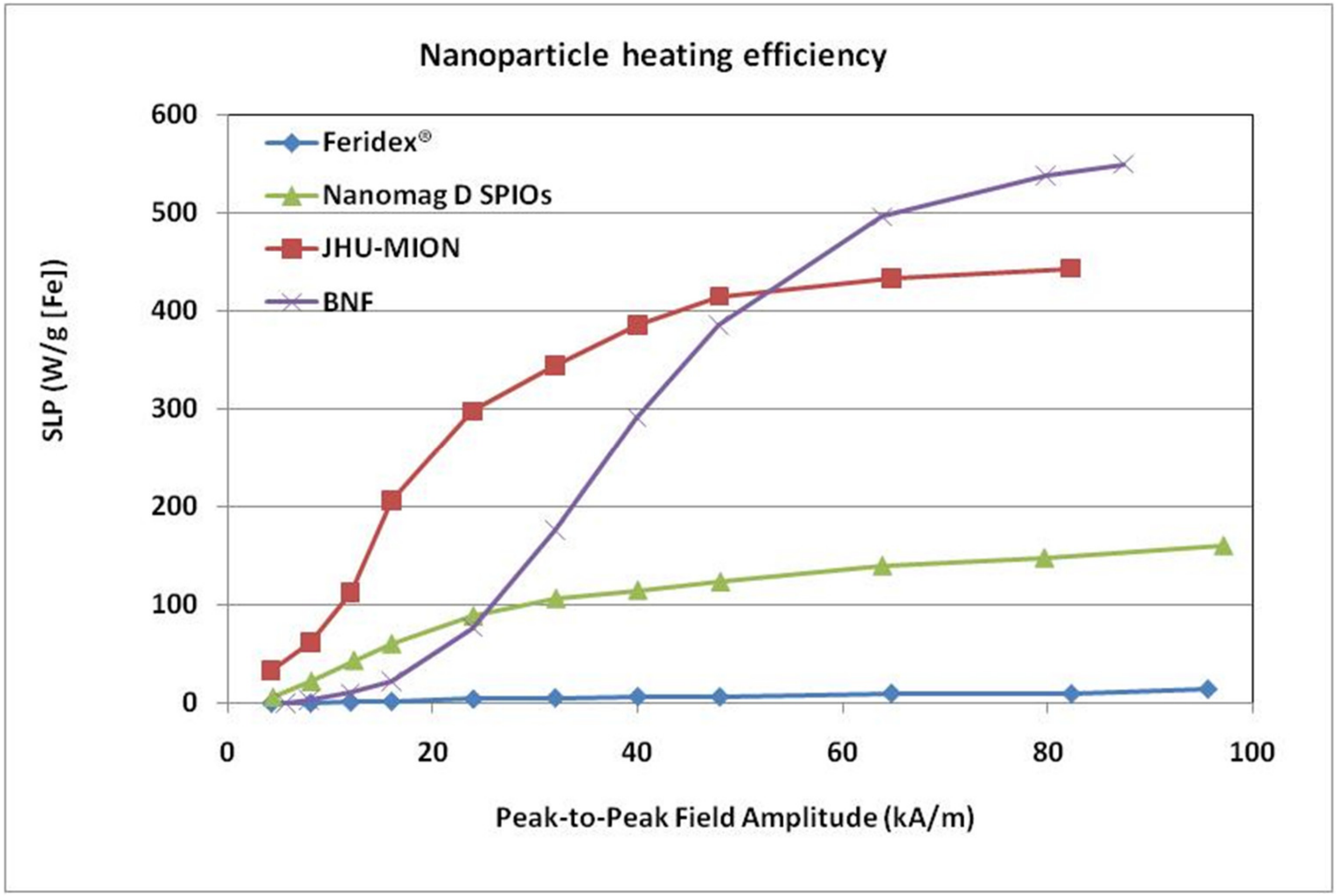
$$W_{heat}^{max} = 4 M_S \mu_0 H_k$$

Part 2b: Magnetic nanoparticles

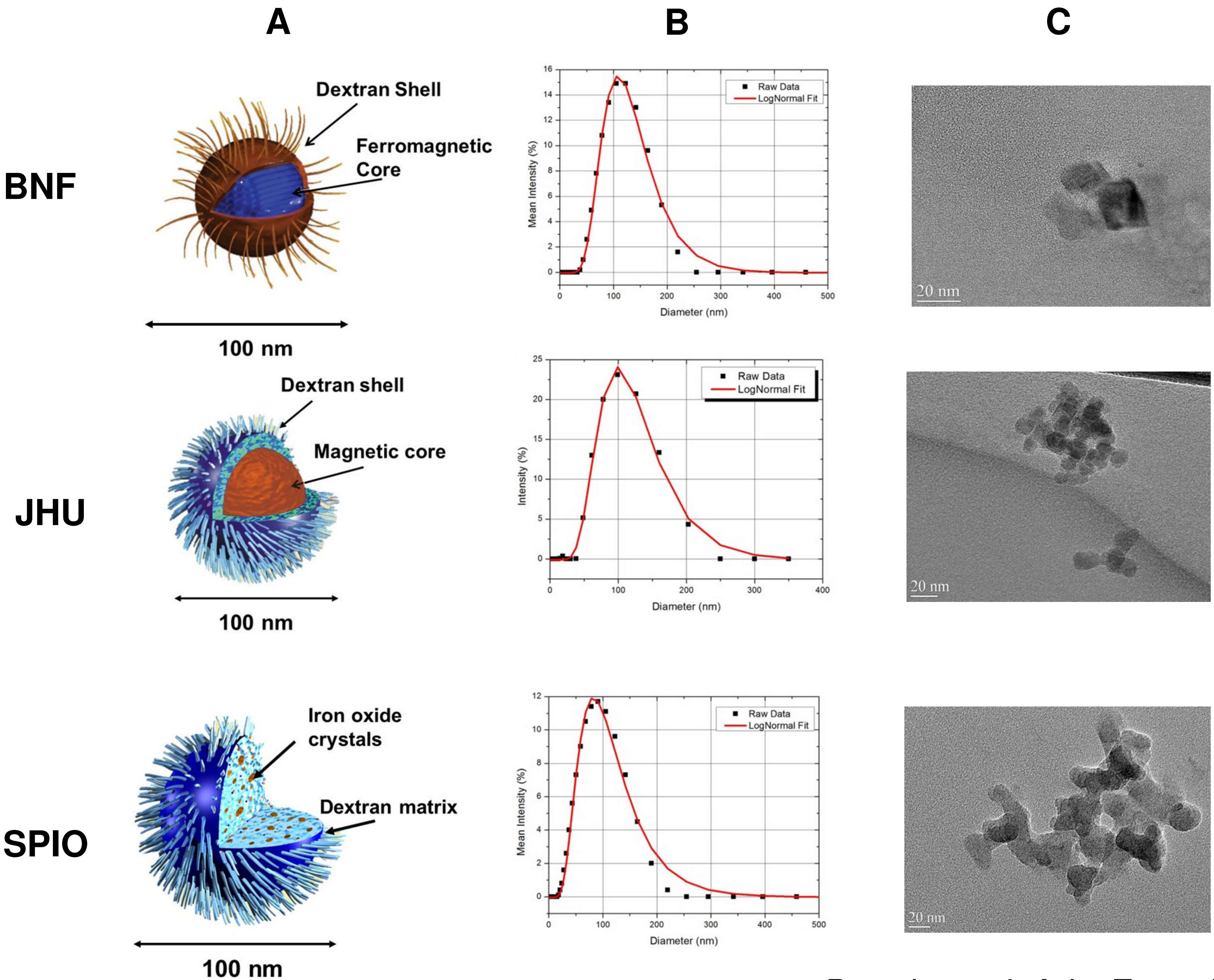
Synthesis of iron oxide magnetic nanoparticles

- Precipitation/Coprecipitation of iron oxides from iron salt(s)
  - $Fe^{2+}/Fe^{3+} + OH^- \longrightarrow Fe_3O_4 \longrightarrow \gamma Fe_2O_3$
  - Aqueous
  - Bulk (batch) process scalable
- Thermal decomposition
  - $Fe(acac)_3$, $Fe(CO)_5$, etc.
  - Non-aqueous (organic solvents) - biocompatibility
  - Scalability (?)
- Microemulsion
  - Reactants dissolved in 'microreactors'
  - Water-in-oil or oil-in-water dispersions create micro'vessels'
  - Scalability (?) and biocompatibility (?)

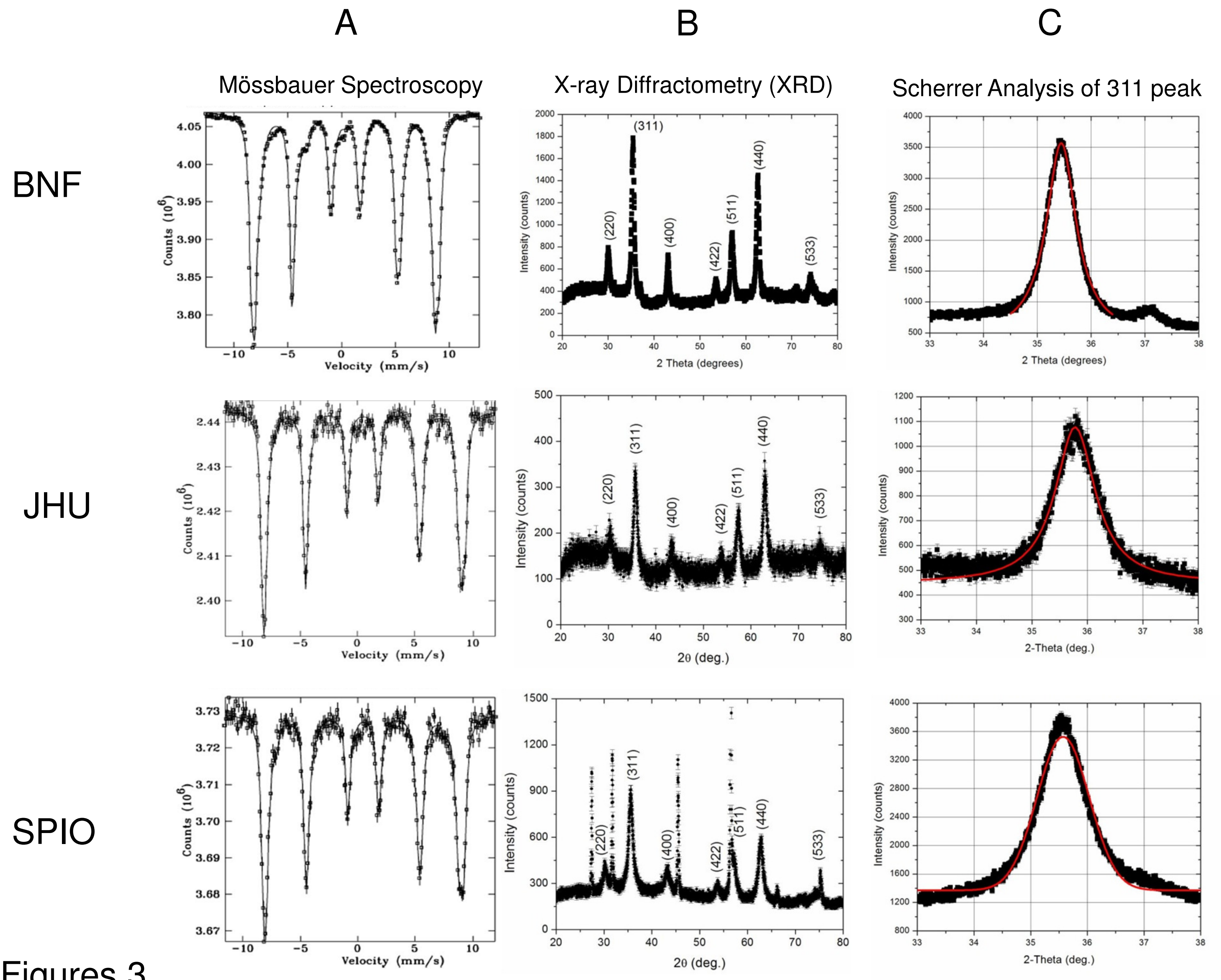
Magnetic nanoparticles exhibit complex response to AMFs



Bordelon, Ivkov, et al. *Journal of Applied Physics*, 2011
Hedayati, Ivkov, et al. *Proc. of SPIE,* 2013
Dennis, Ivkov, et al., *J. Appl. Physics* **103**, 07A319 (2008)
Dennis, Ivkov, et al., *J. Phys. D: Applied Physics* **41**, 134020 (2008)
Dennis, Ivkov, et al., *Nanotechnology*, **20**, 395103 (2009)
Krycka, Dennis, Ivkov, et al. *J. Applied Phys.,* **109,** 07B513 (2011)
Dennis, Ivkov, et al. *Adv. Func. Mat.,* **2015**

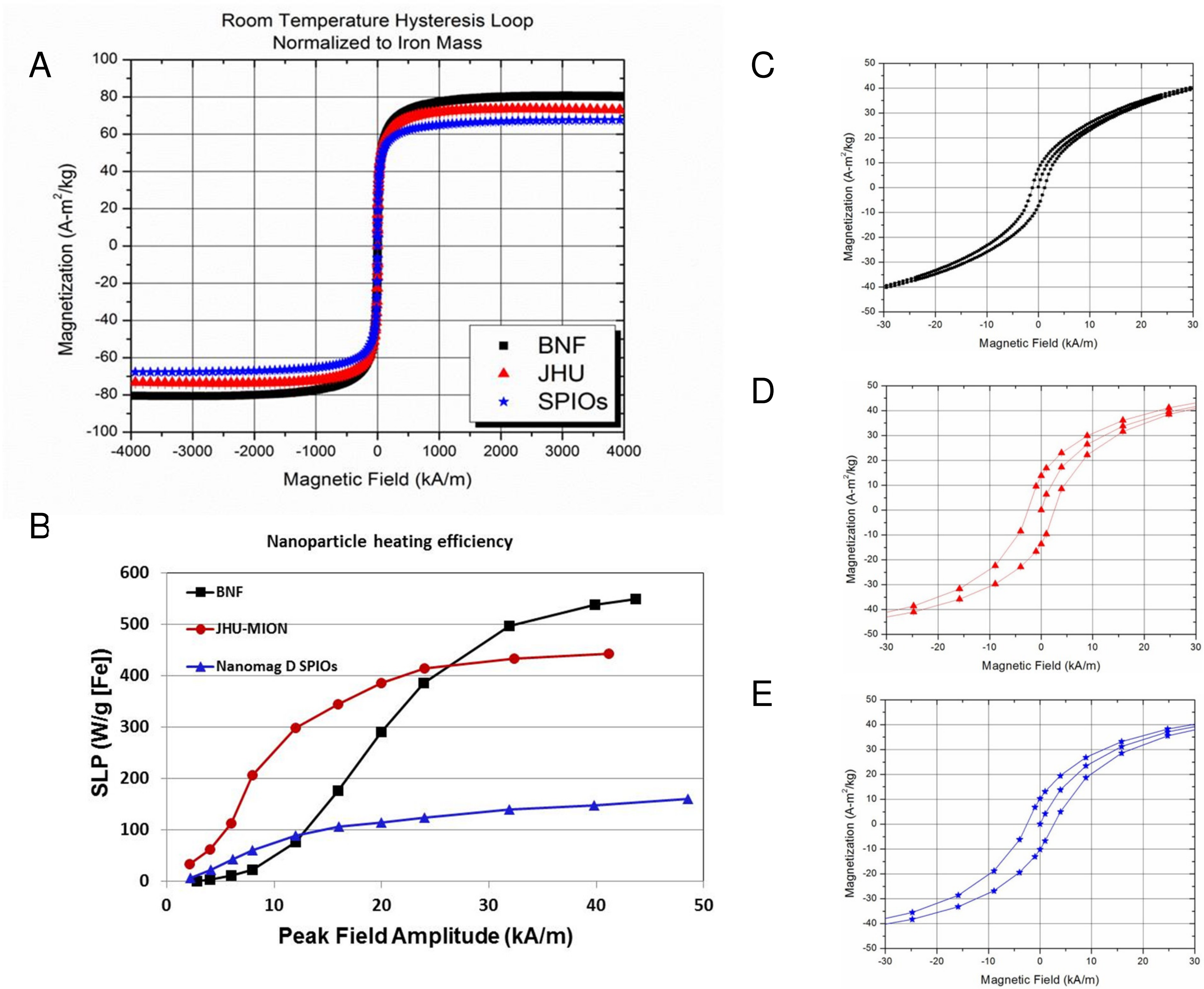


Dennis et al. Adv. Func. Mat. 2015



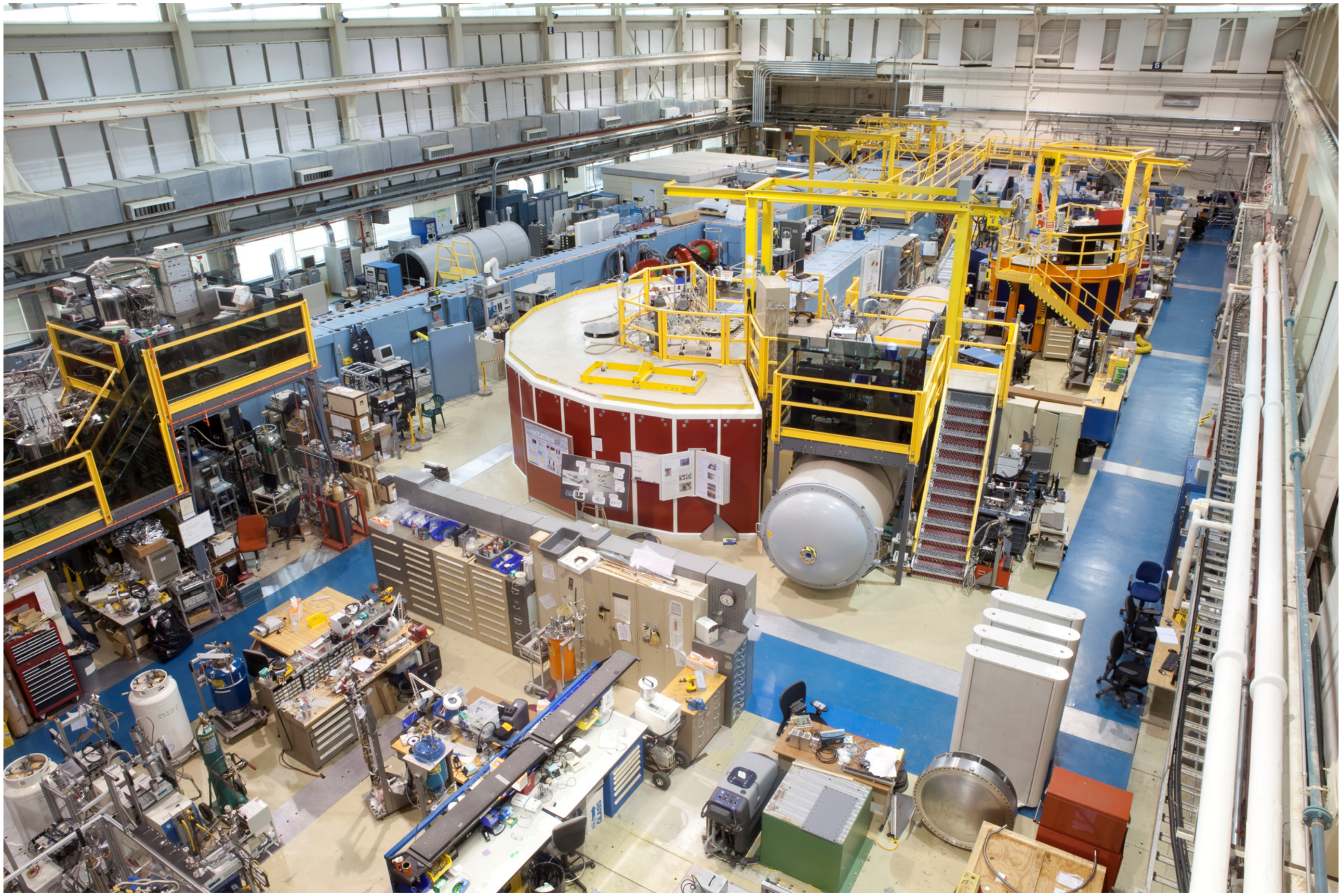
Figures 3

Dennis et al. Adv. Func. Mat. 2015

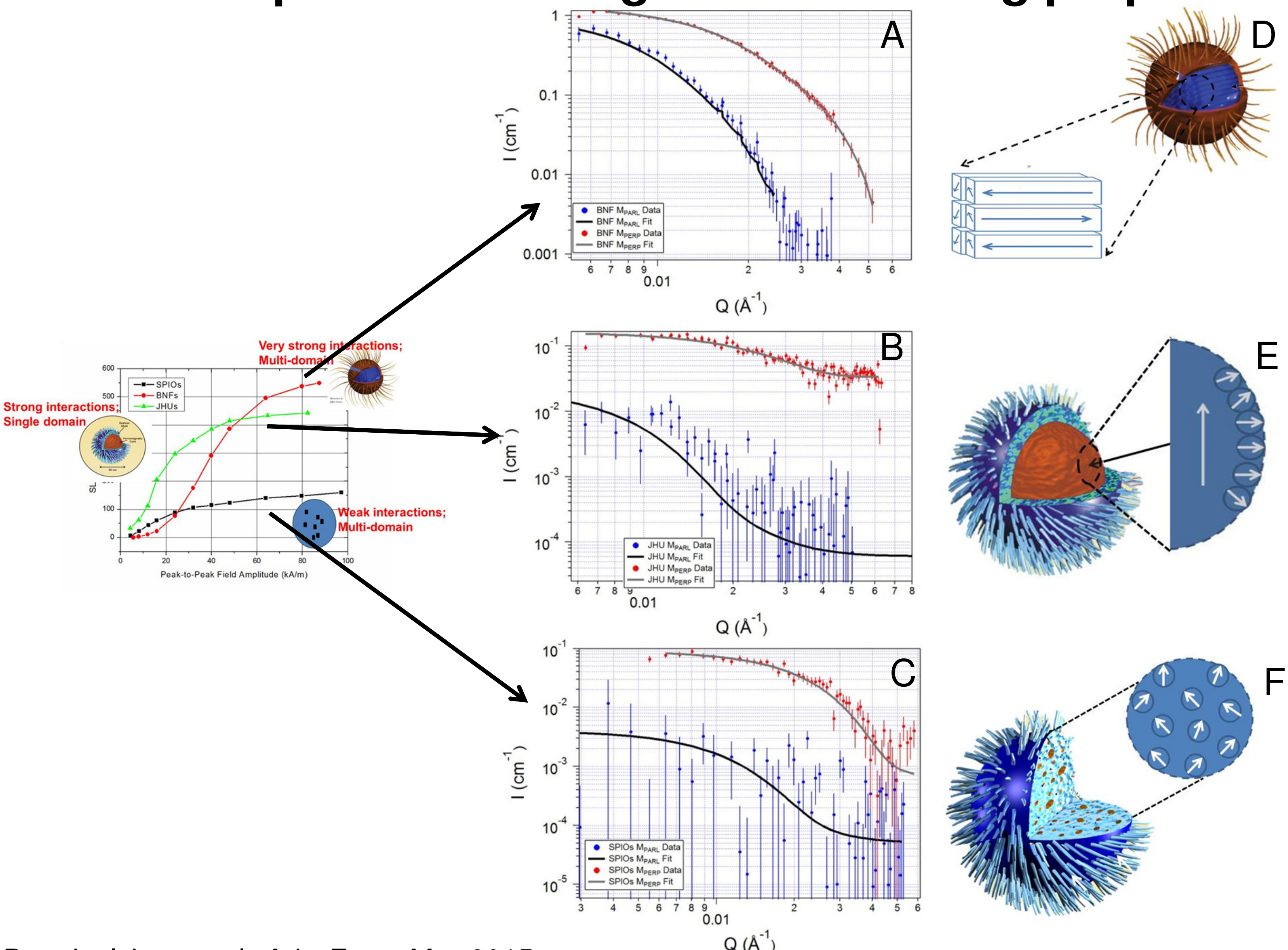


Dennis et al. Adv. Func. Mat. 2015

NIST CNR



Internal magnetic structure can be exploited to manufacture nanoparticles having desired heating properties



Dennis, Ivkov, et al. *Adv. Func. Mat.* 2015

Part 3: Magnetic nanoparticle hyperthermia for cancer therapy.

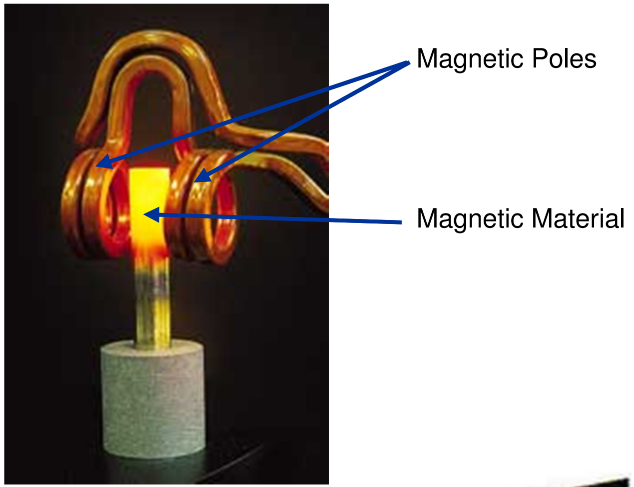
Device considerations

Forms of magnetic heating

Hysteresis Heating:

AMF causes magnetic materials to reverse their magnetic poles which produces heat.

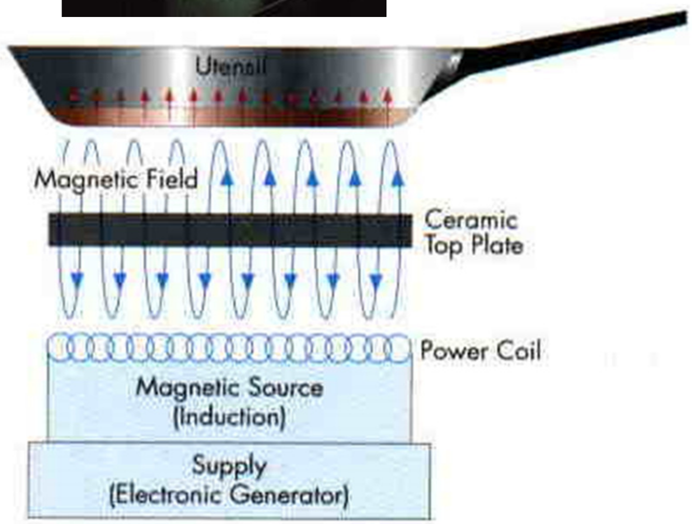
Magnetic nanoparticles heat by <u>hysteresis</u>.



Induction Heating:

AMF creates electric currents (called eddy currents).

Tissues heat by <u>induction</u> (eddy currents.)



Device requirements

AMF-tissue interaction produces heat from eddy currents produced by both magnetic (*H*- or *B*-) and electric (*E*-) fields

E-field

$$\mathrm{SAR} = \frac{\sigma \left|\vec{E}\right|^2}{\rho_m}$$

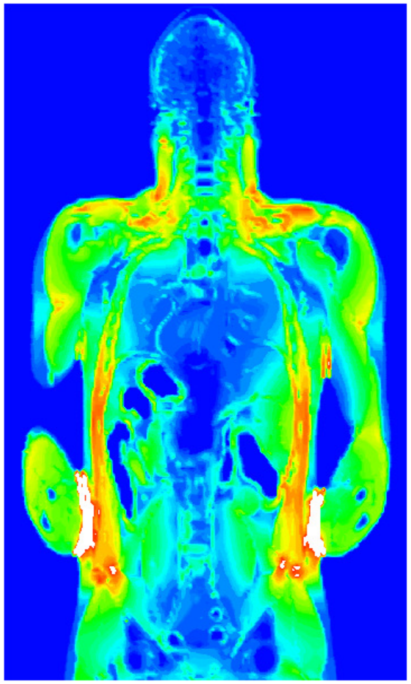
B-field

$$SAR \propto \sigma f^2 H^2 r^2$$

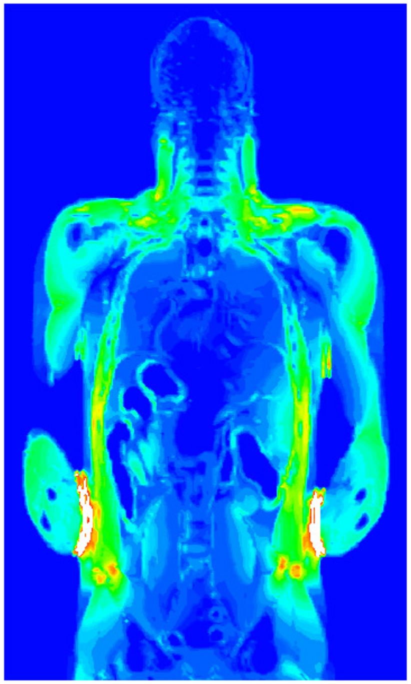
Goal – reduce total SAR without reducing particle heating

Tissue Heating Simulation

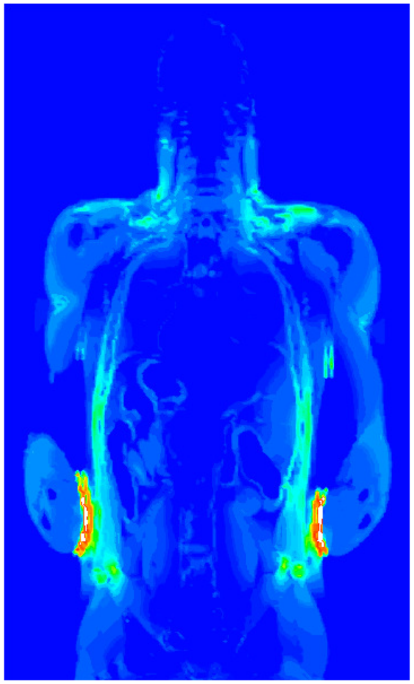
- Simulation of Direct Tissue Heating Using bipolar magnet in Humans
- Produced By Prof. Crozier, The University of Queensland (Australia), Utilizing Models Developed At U.S. Air Force Labs For Electromagnetic Radiation Effects on Humans (Brooks Airforce Base, Texas)



700 Oe, 150 kHz



400 Oe, 150 kHz

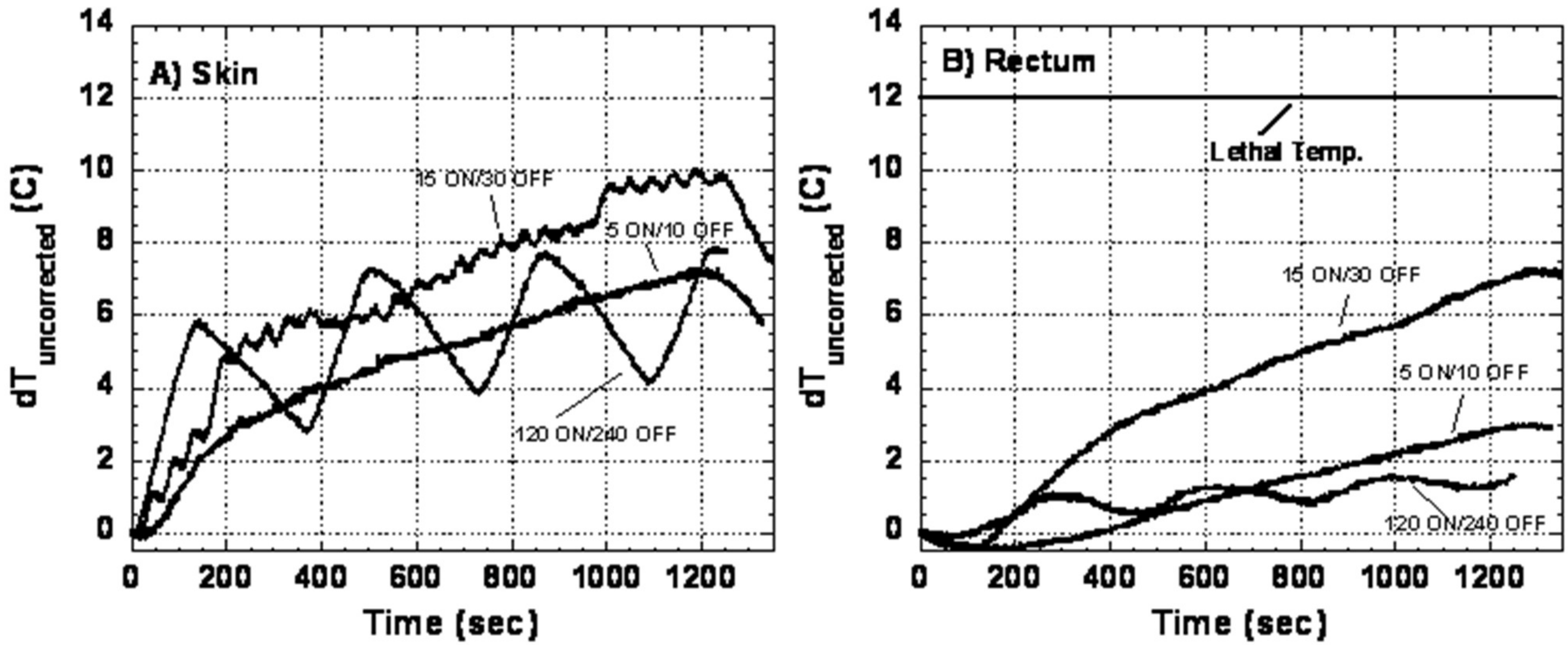


400 Oe, 75 kHz

- Simulations provide estimates of deposited power (SAR, W/kg tissue)
- To calculate temperature, we must employ appropriate heat transfer models

AMF-tissue interactions deposit heat

AMF interaction deposits energy to tissue, but response is complex due to active thermoregulation



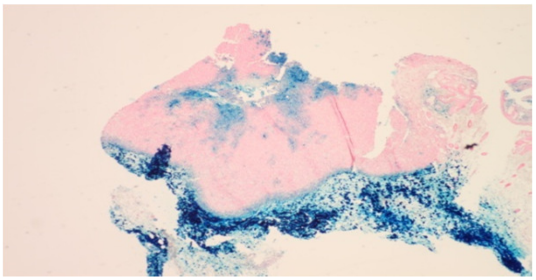
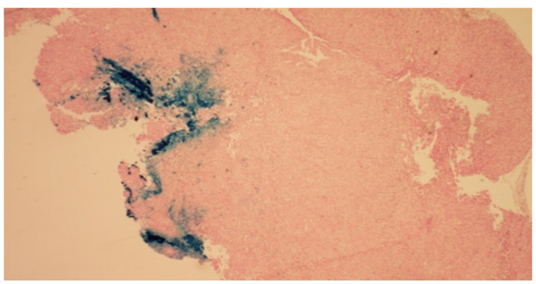
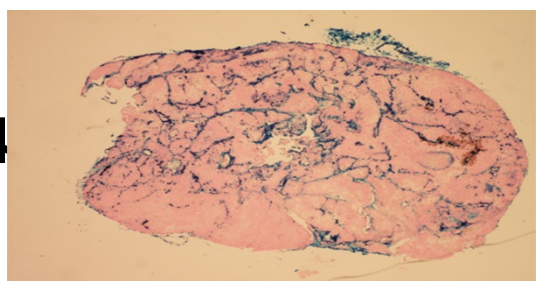
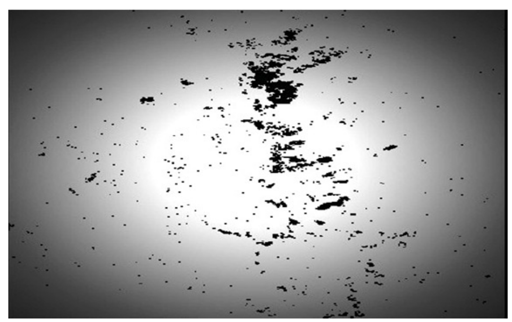
Conditions – 700 Oe @160 kHz, Duty cycle – 30%

Modelling must, therefore include the complexities of physiologic response to thermal stress

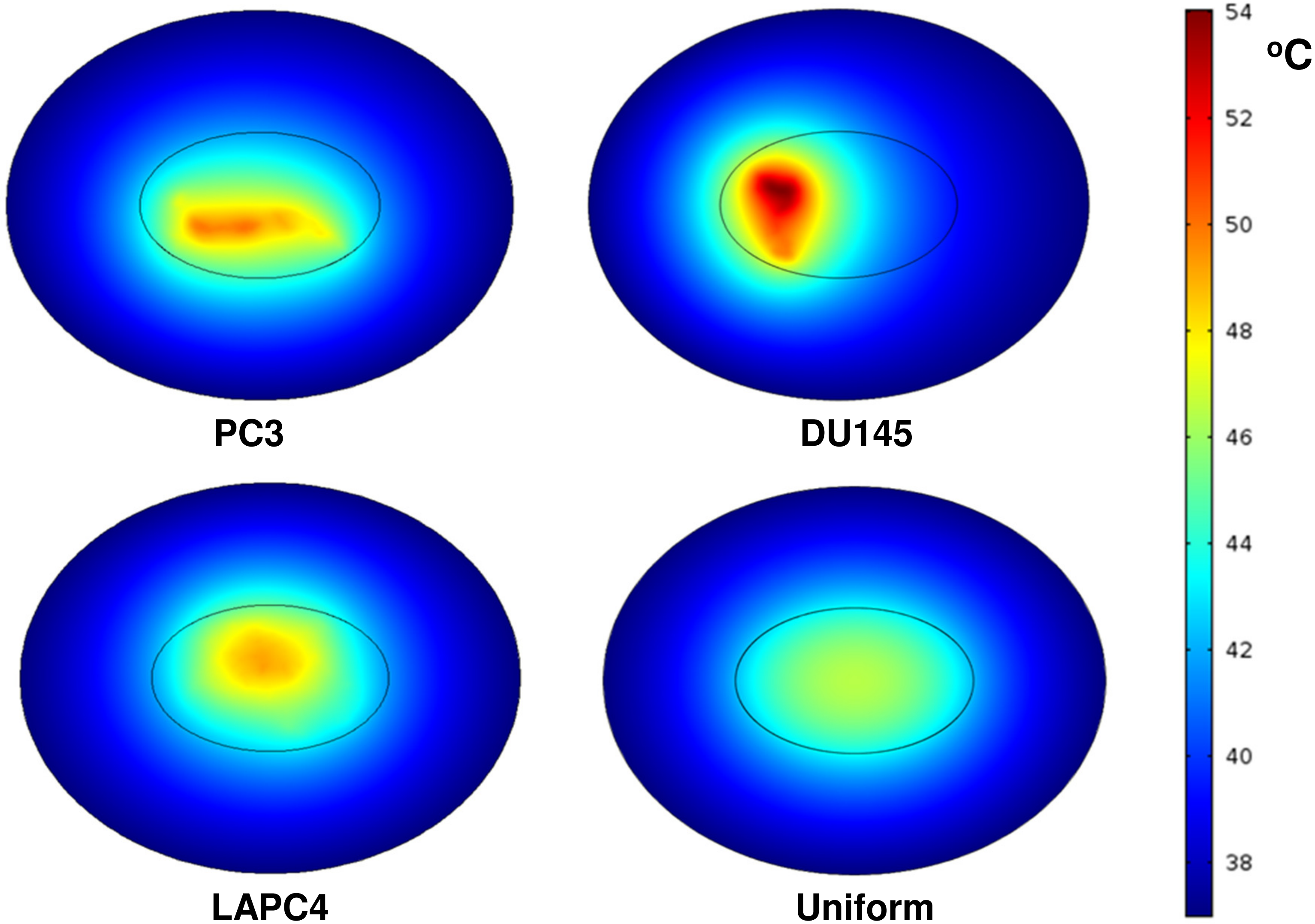
Ivkov et al., Clin. Cancer Res. 11, 7093s(2005)

Part 4: Tumor tissue heating with magnetic nanoparticles

Tumor structure determines nanoparticle distribution

	4X	Collagen-1	ICP-MS (µg Fe/mg tumor)
PC3			13.9 ± 4.7
DU145			12.4 ± 1.4
LAPC4			19.5 ± 2.0

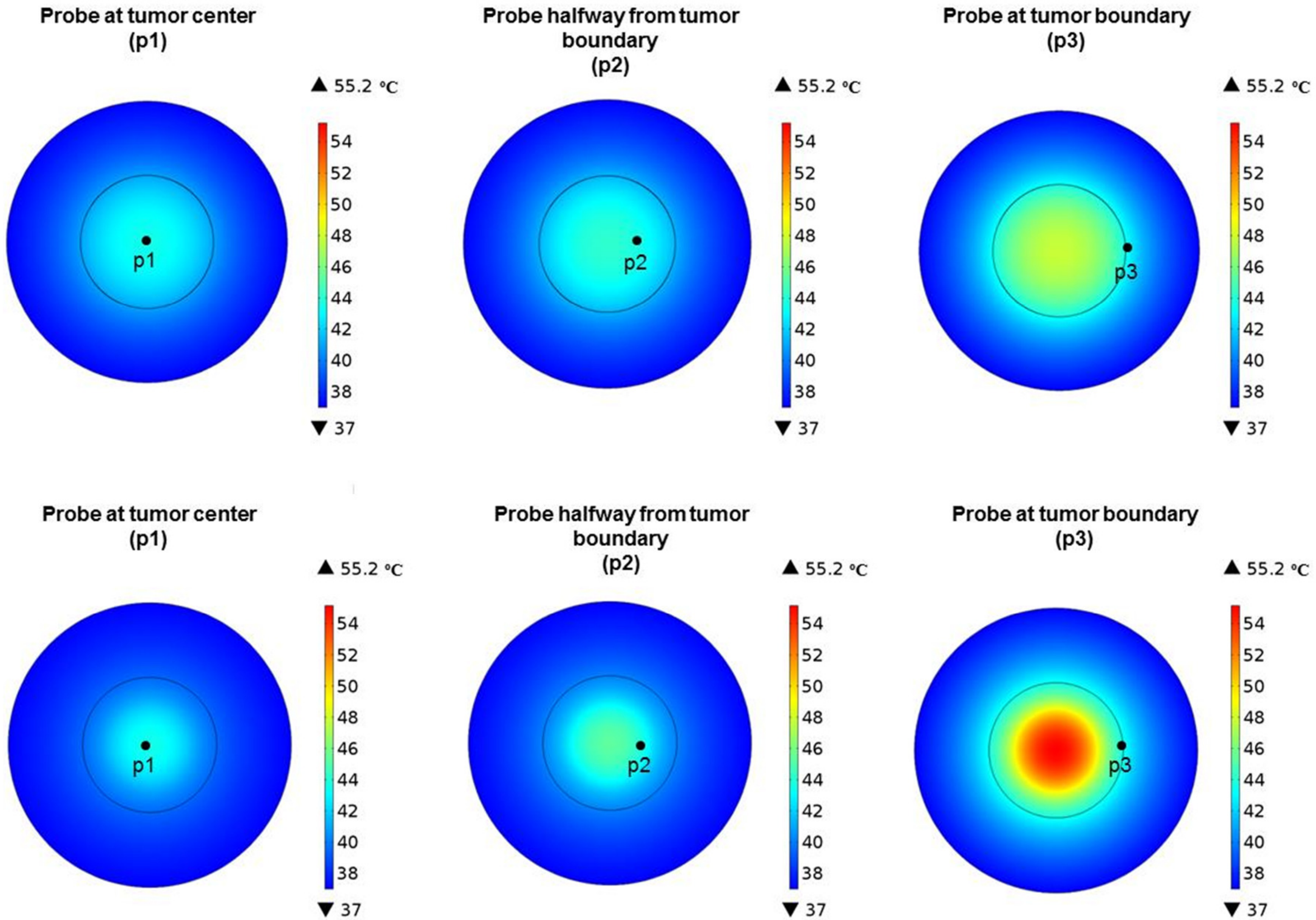
Temperature distributions with constant power



At $Q_p = 4.16 \times 10^5$ W/m^2 for 20 min

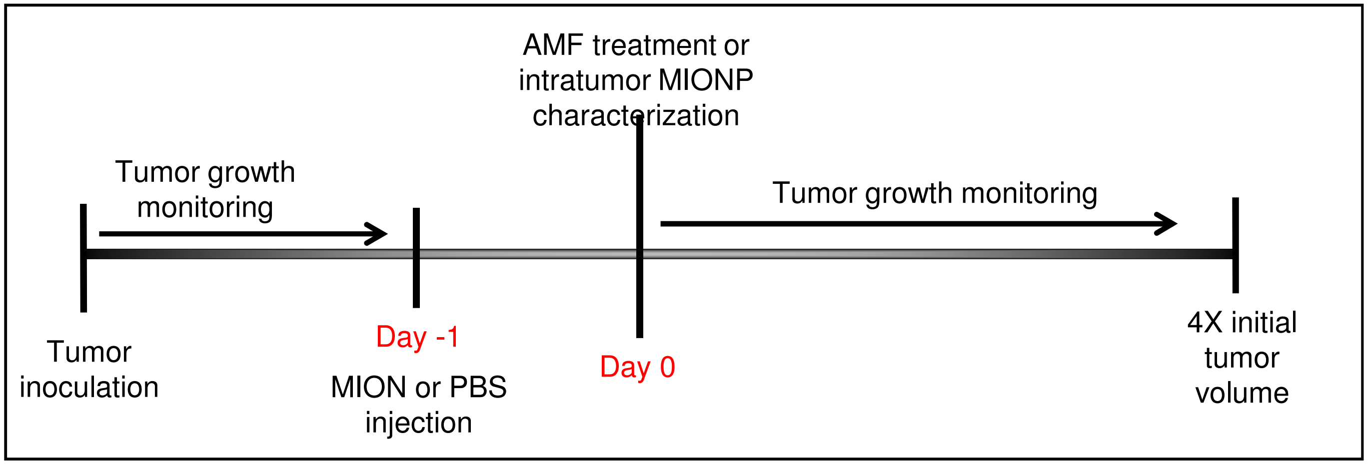
Attaluri, Kandala, et al., *International Journal of Hyperthermia* 2015

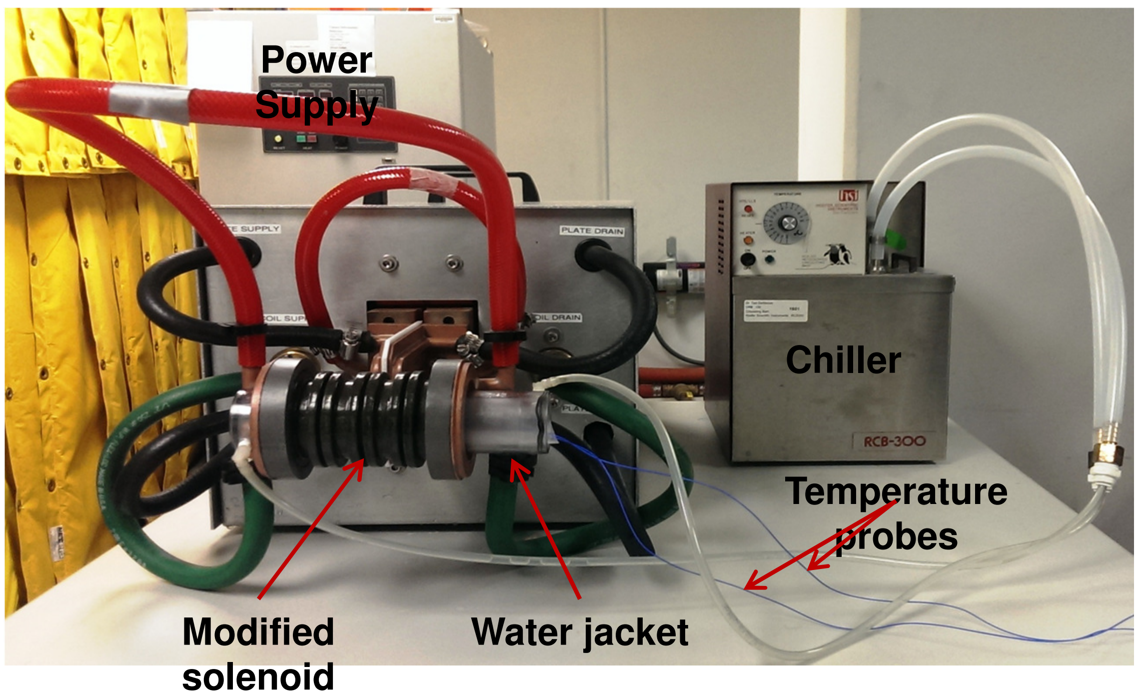
AMF power modulation with temperature feedback provides controlled thermal dose



Attaluri, Kandala, et al., *International Journal of Hyperthermia* 2015

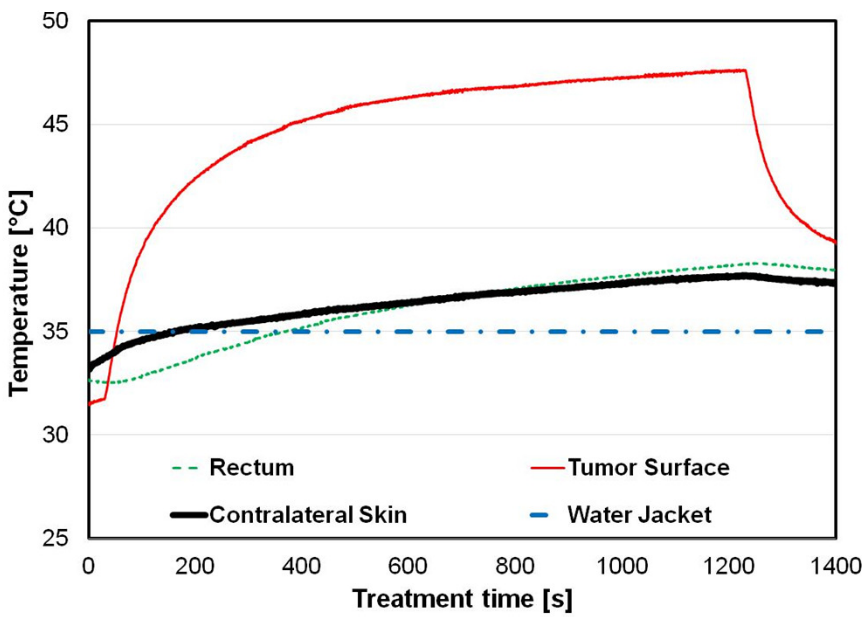
The experiment and equipment



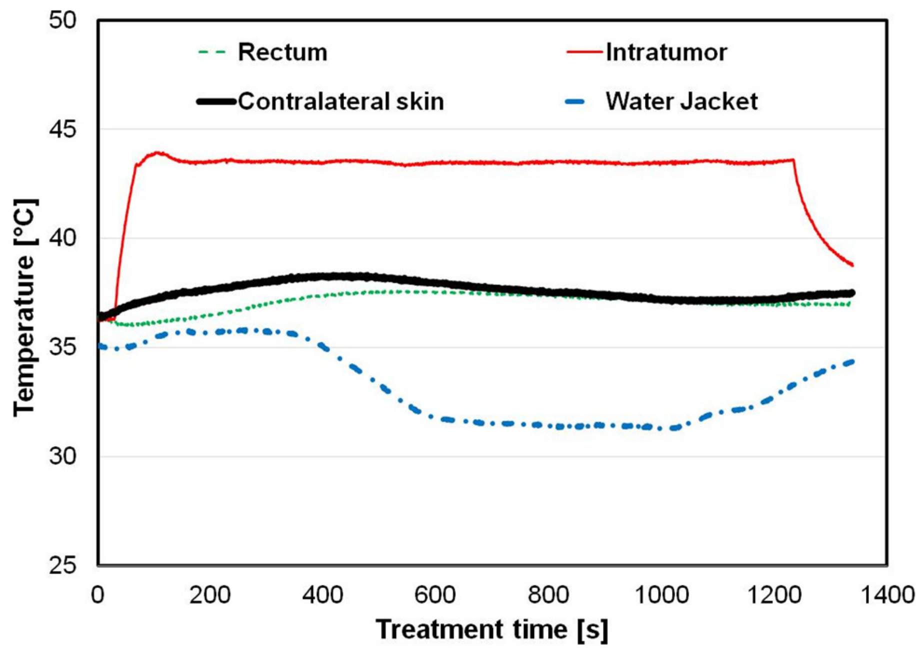


Attaluri, Kandala, et al., *International Journal of Hyperthermia,* 2015
Kumar, Attaluri, et al., *Int. J. Hyperthermia,* 2013

Nanoparticle energy deposition can be controlled by AMF



Constant AMF power
Variable thermal dose

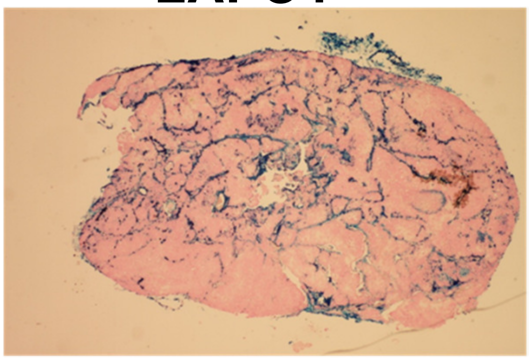


Variable AMF power
Constant thermal dose

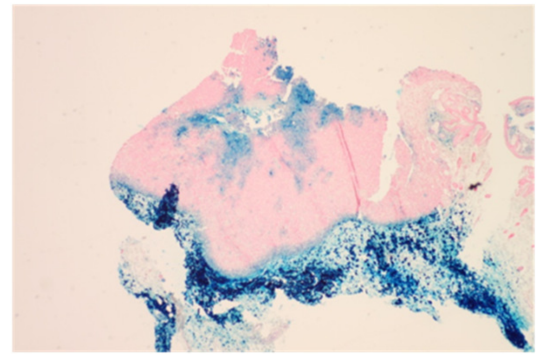
Attaluri, Kandala, et al., *International Journal of Hyperthermia,* 2015
Kumar, Attaluri, et al., *Int. J. Hyperthermia,* 2013

Effectiveness of nanoparticle heat therapy

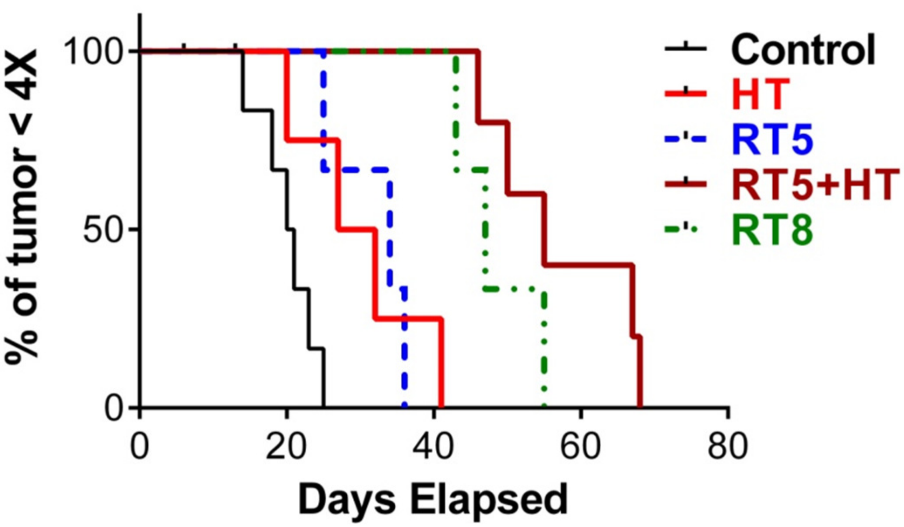
LAPC4



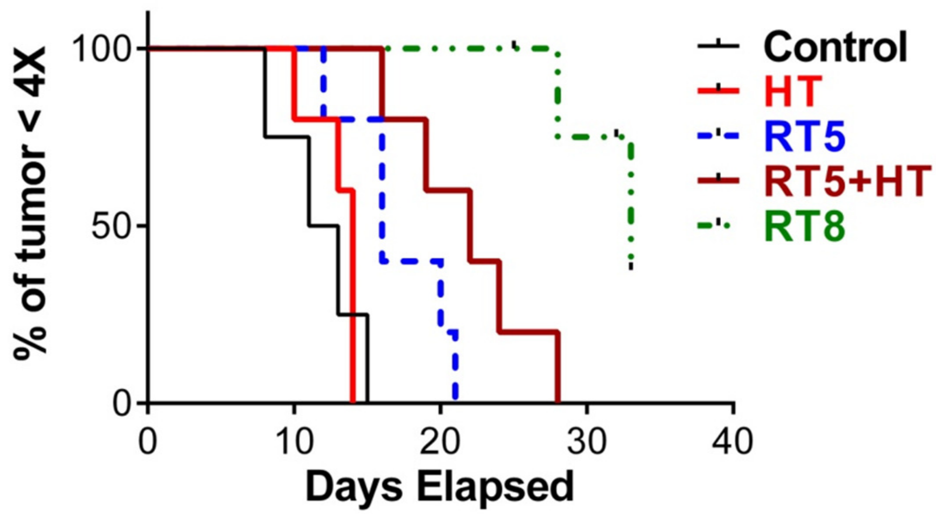
PC3



LAPC4

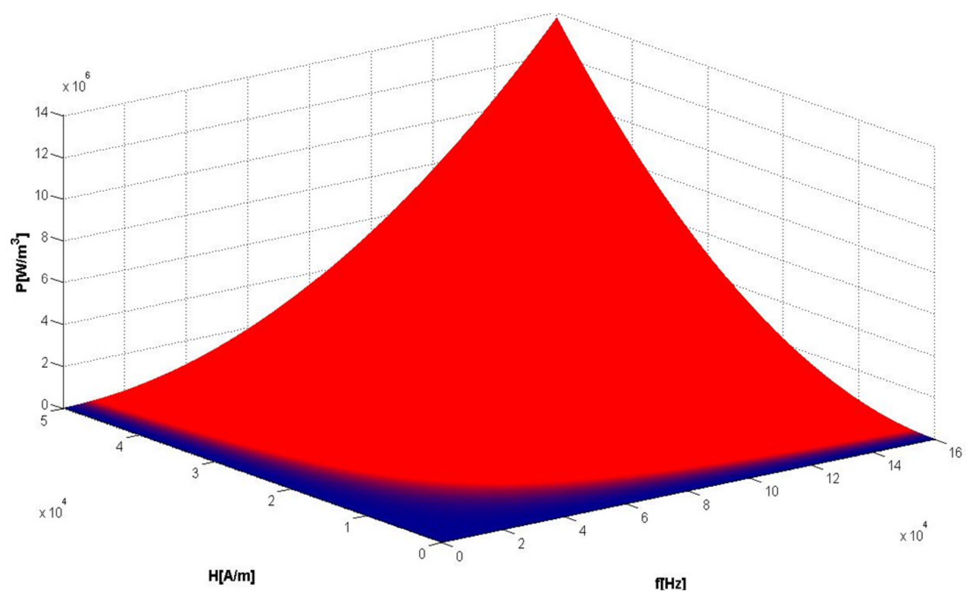


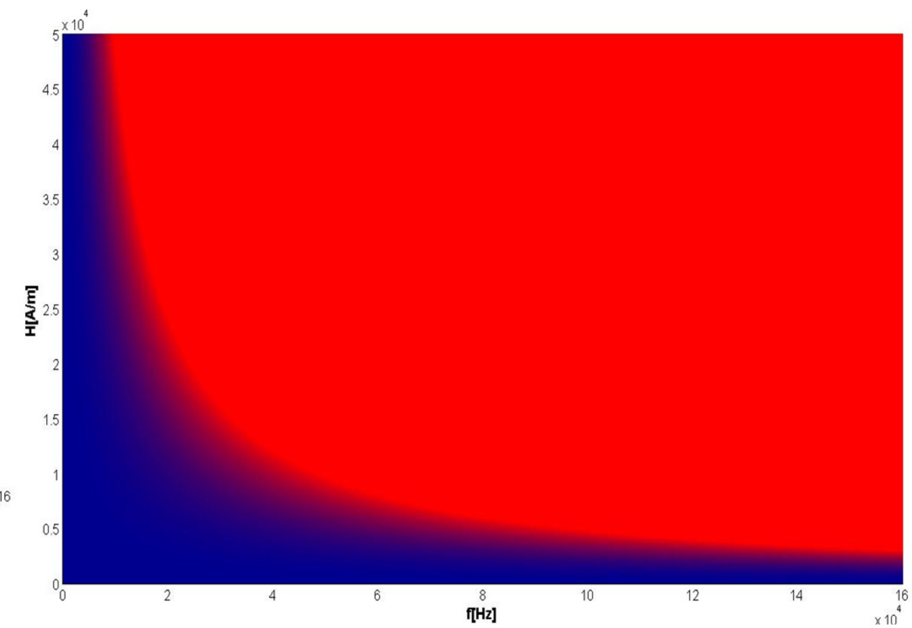
PC3



Attaluri, Kandala, et al., *International Journal of Hyperthermia* 2015

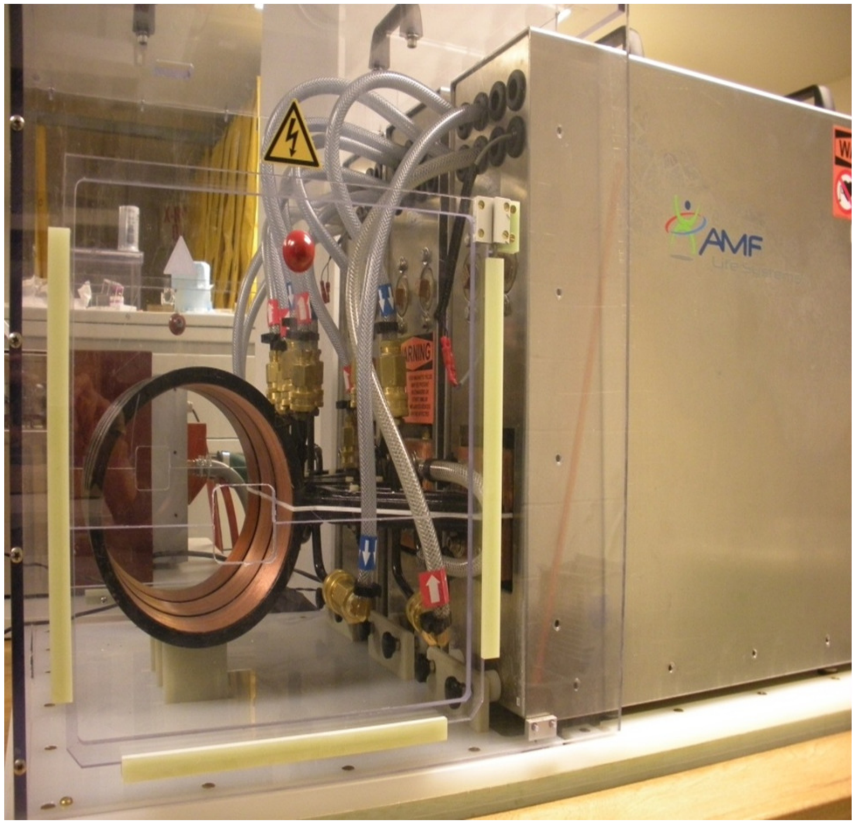
Scale up: Limitations of non-specific heating



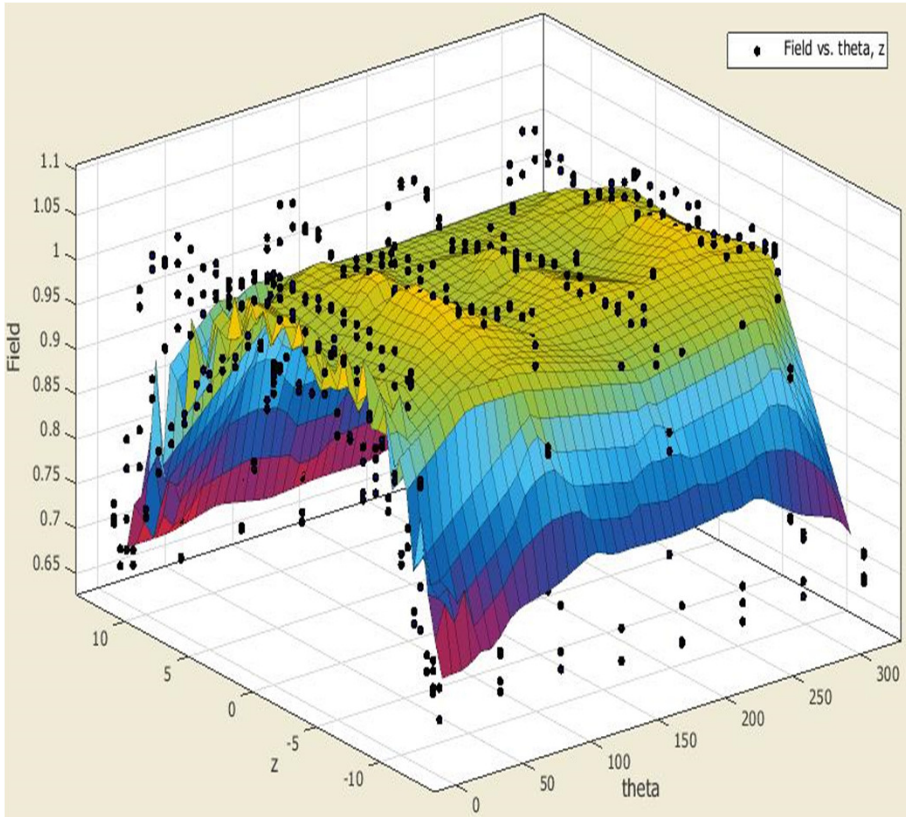


Scale up to large animals

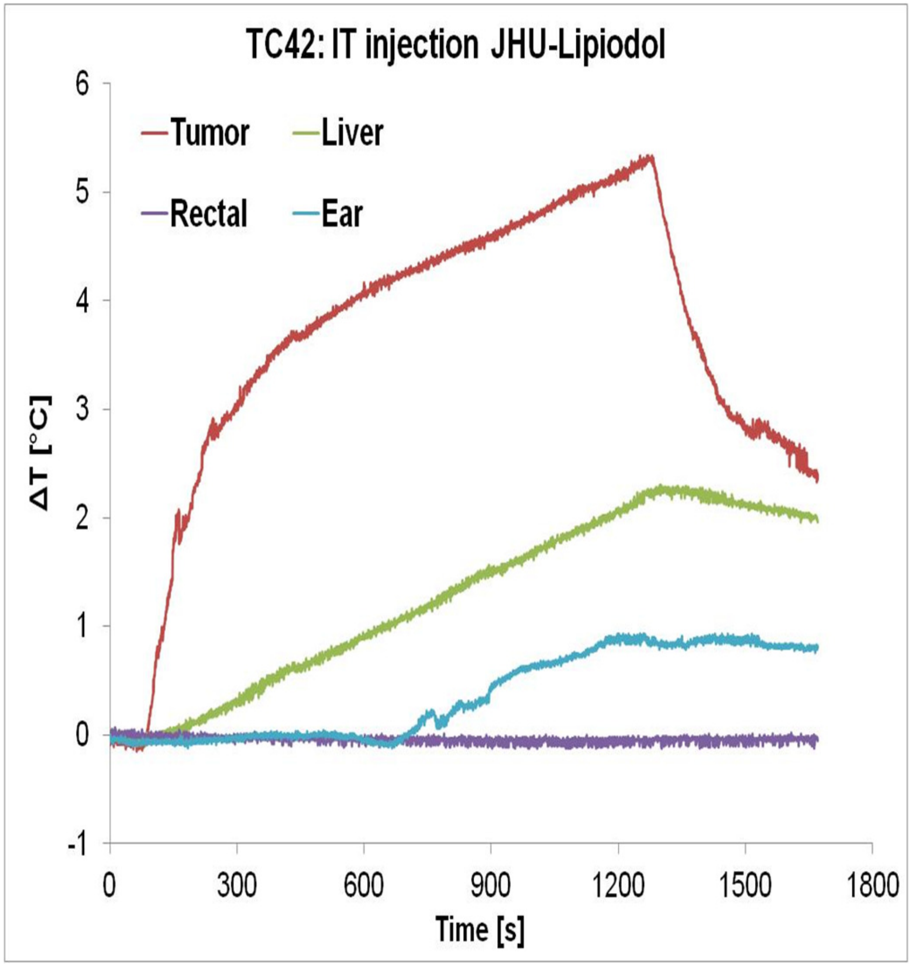
Picture of the preclinical 20 cm coil

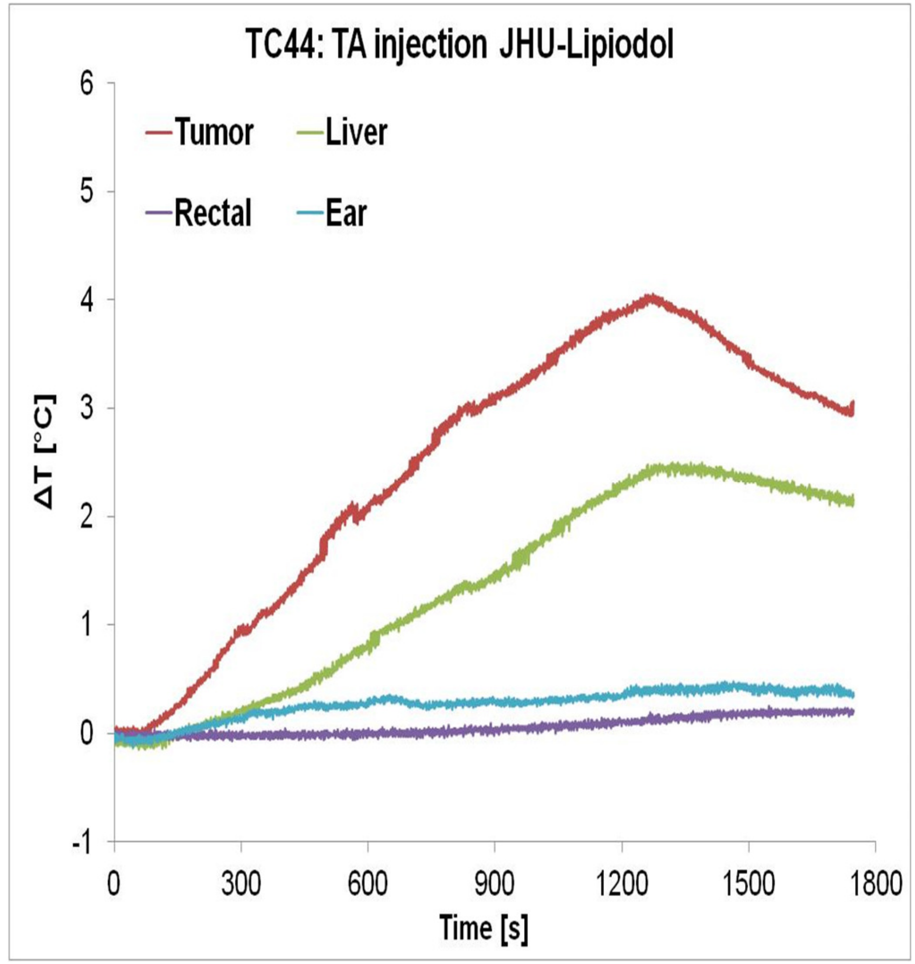


***H*-field map of 20-cm coil**



Rabbit liver VX2 tumors





Take-home message

- Heat transfer from nanoparticles in cells and tissues is indistinguishable from other forms of heating.
- Key advantages offered by nanoparticle heating arise from:
  - Internalization of the ‘fluidic’ heat source.
  - Loss power, or heat generation, can be adjusted with AMF amplitude.
  - Thermoregulatory response is plastic and dynamic.
- Therapeutic heating with magnetic nanoparticles demands consideration of nanoparticle, device, and tissue responses to achieve desired outcomes and avoid toxicity.

Resources

Hyperthermia and thermal therapy

- Basic Principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia, M.W. Dewhirst et al., *Int. J. Hyperthermia*, vol 19, pp 267-294 (2003).
- Hyperthermia, M.W. Dewhirst et al., Book chapter.

Magnetic nanoparticles (physics and characterization)

- Magnetic relaxation in fine particle systems, J.L. Dormann et al., *Advances in Chemical Physics*, vol XCVIII, pp 283-405 (1997).
- Physics of heat generation using magnetic nanoparticles for hyperthermia (review), C. Dennis et al., *International Journal of Hyperthermia,* 2013; 29; 715-729.
- Magnetic nanoparticle heating efficiency reveals magneto-structural differences when characterized with wide ranging and high amplitude alternating magnetic fields, D.E. Bordelon et al., *J Appl. Physics*, vol 109, 124904 (2011).

Magnetic nanoparticle hyperthermia

- *International Journal of Hyperthermia*, Volume 29 (2013).
- Ivkov et al. *Clin. Cancer Res.* 2005 (thermoregulatory response)

Heat delivery

- Direct heating - conduction through contact with heat source
- Indirect heating - deposition of coherent energy relaxing locally to incoherent energy
- Combination – energy susceptors activated by coherent energy
  - Thermal seeds
  - Magnetic nanoparticle suspensions (magnetic fluids)
  - Metallic or silica nanoshells (plasmon resonance)