IEEE/CSC & ESAS SUPERCONDUCTIVITY NEWS FORUM (global edition), April 2015.
Tutorial presentation given at KRYO 2014, Berlin, September 21-23, 2014.

In-vivo biomedical applications of magnetic nanoparticles

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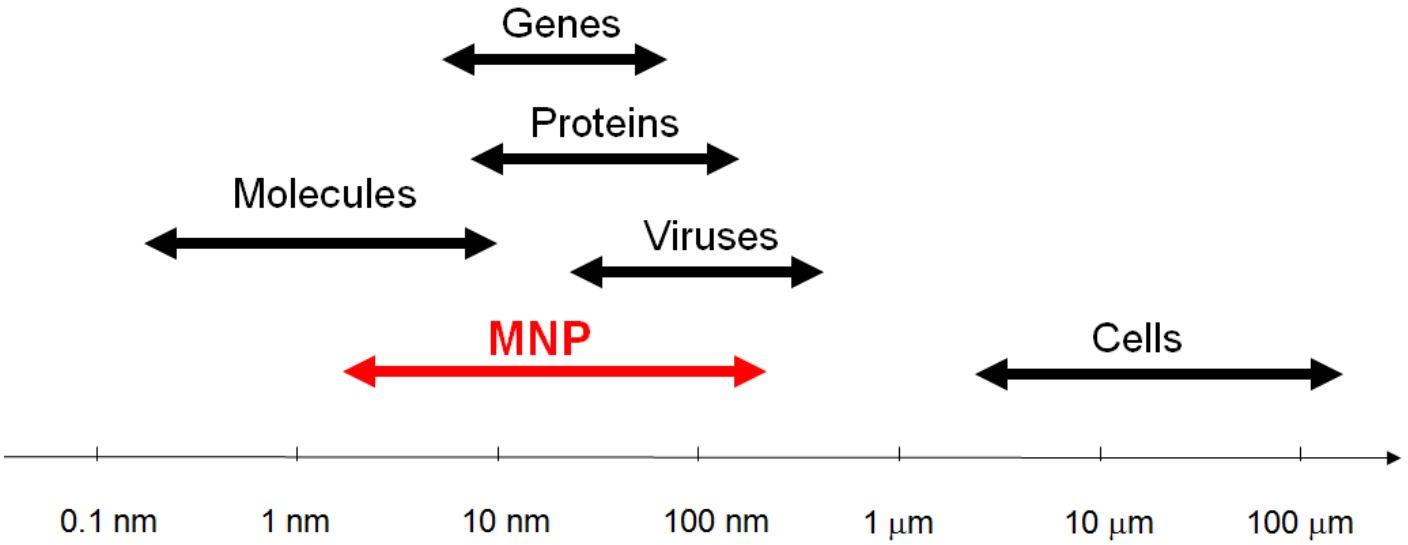
PTB Physikalisch-Technische Bundesanstalt

Outline

- Magnetic nanoparticles (MNP) in biomedicine
- Biomedical applications of MNP
- Characterization, quantification and imaging of MNP at PTB
- Summary

Why MNP?

Magnetic nanoparticles (MNP) have dimensions between molecules and biologic structures ...



.... and above all they are magnetic

What are MNP?

MNP:

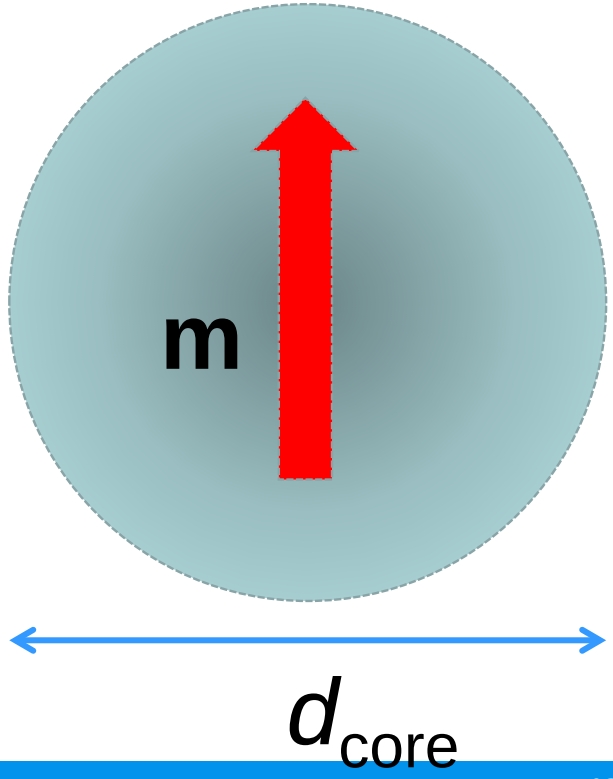
size: diameter d_{core}=1 nm ...100 nm

structure: iron-oxide

magnetic moment **m**=10^3...10^6 μ_B

anisotropy K= 10^3 J/m^3

→ **magnetic effects**



μ_B=9.27·10^{-24} Am^2

What are MNP in biomedicine?

MNP in biomedicine:

size: diameter d_{core}=1 nm ...100 nm

structure: iron-oxide

magnetic moment **m**=10^3... 10^6 μ_B

anisotropy K= 10^3 J/m^3

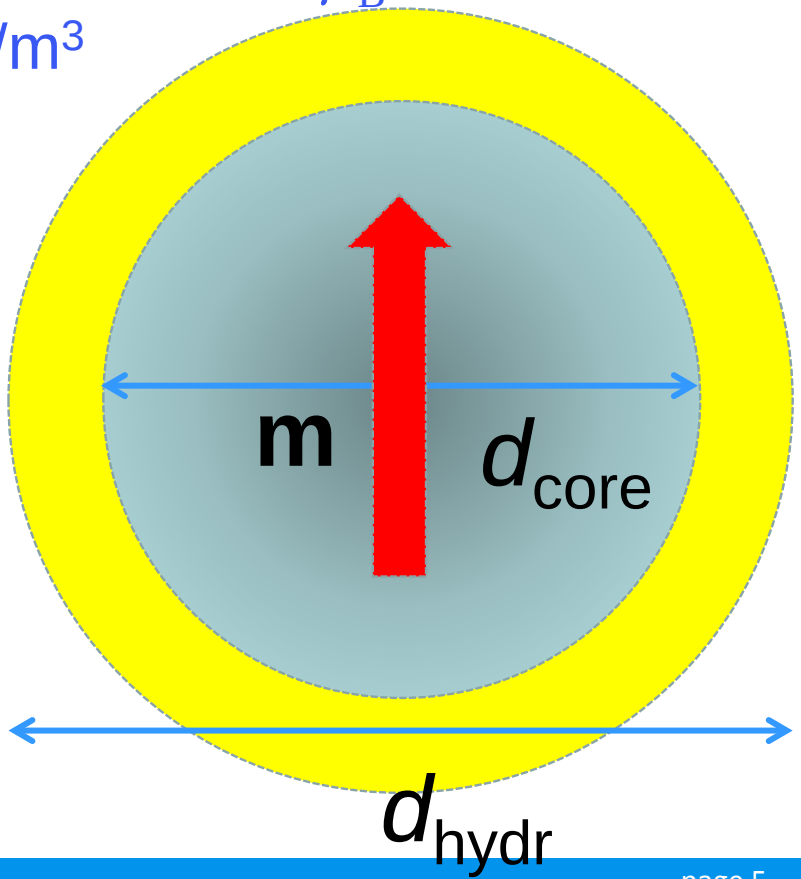
→ **magnetic effects**

coating: Dextran, Citric acid

→ prevent aggregation

→ biocompatible

→ functionalization



μ_B=9.27·10^{-24} Am^2

How do MNP work?

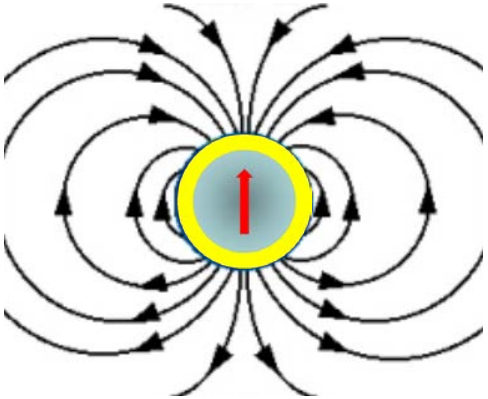
probe:

stray field of moment **m**

at proton sites → MRI contrast agent

directly → Magnetic Particle Imaging

→ Magnetorelaxometry

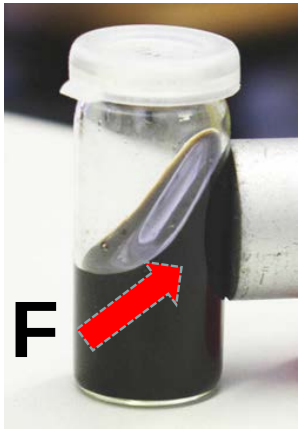


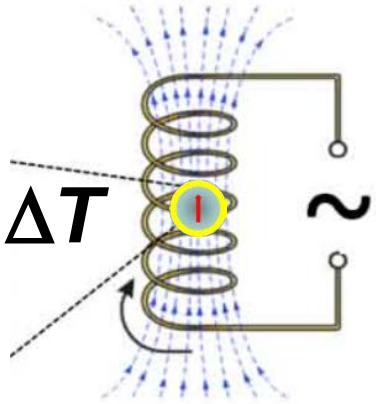
vehicle:

particles are directed by magnetic field gradients

→ magnetic drug targeting

→ magnetofection



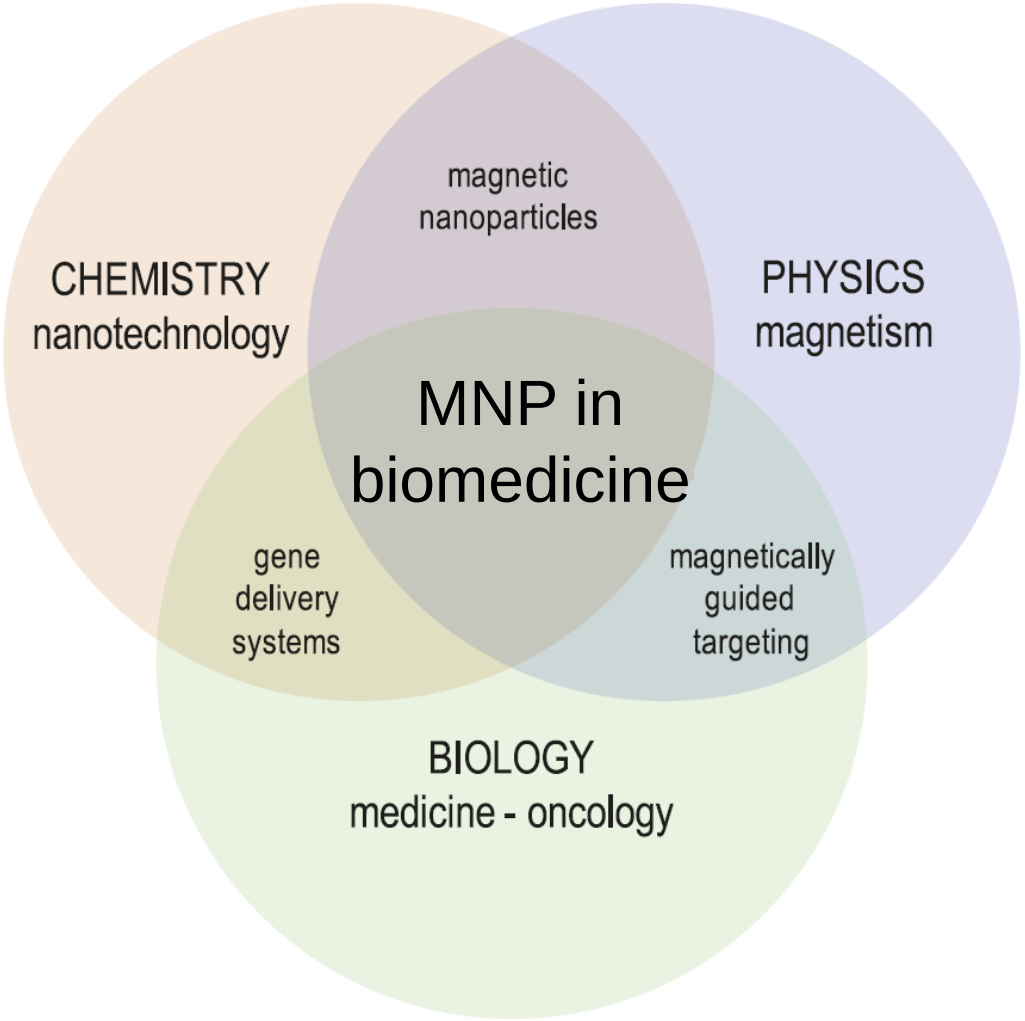


heat generator:

particles are heated up by AC magnetic fields

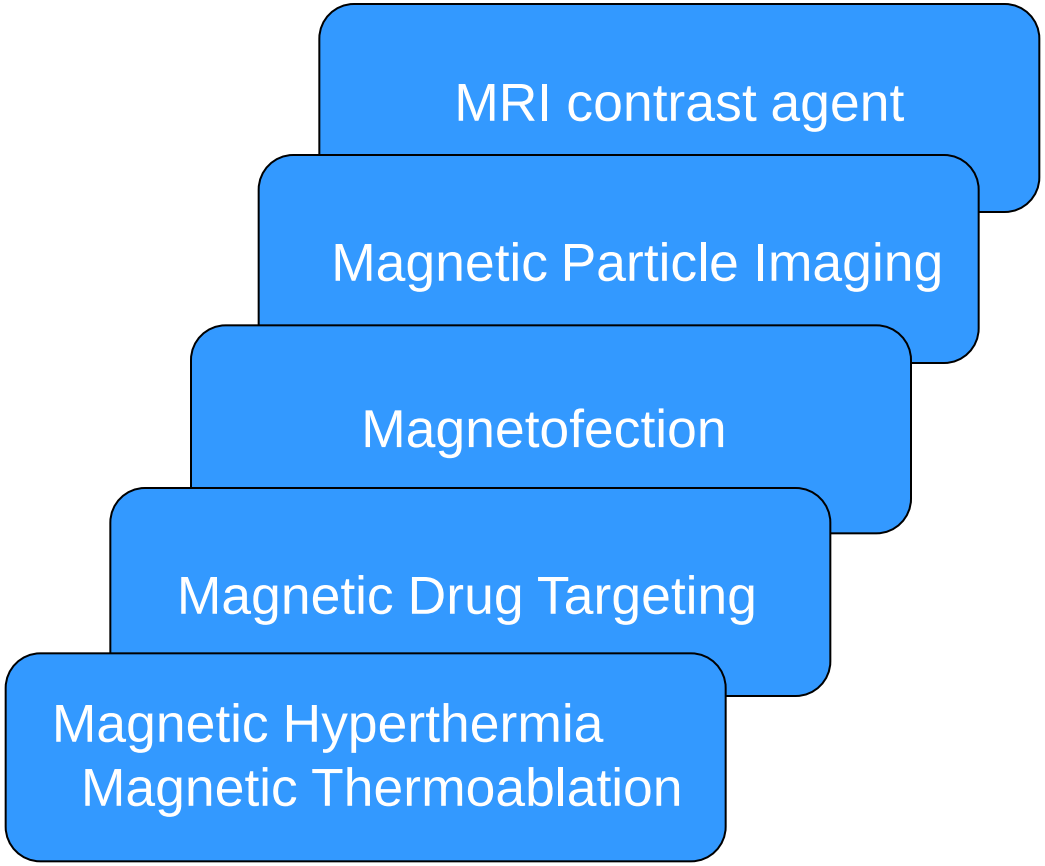
→ magnetic hyperthermia / thermoablation

MNP are physics, biology and chemistry

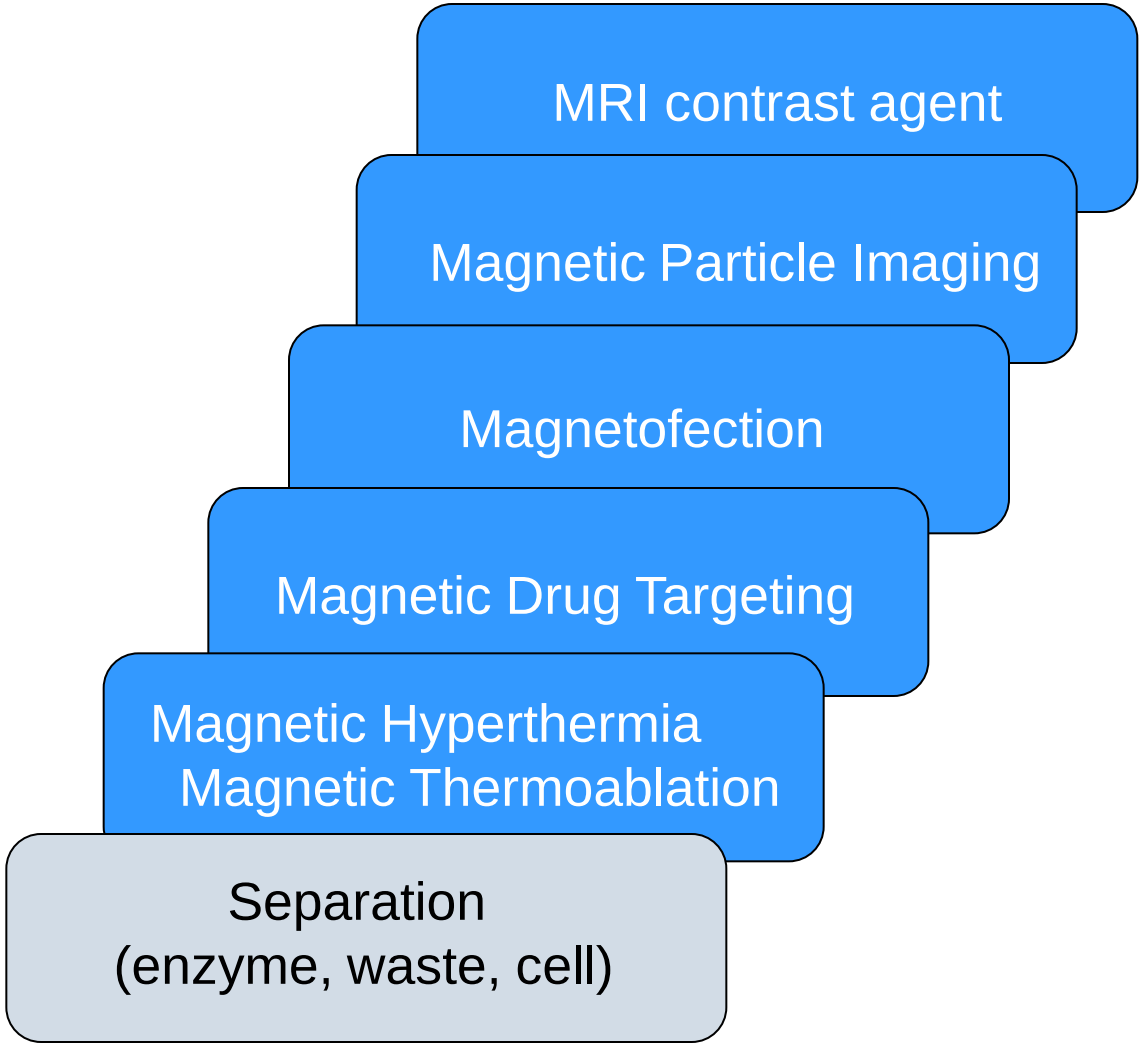


Each application requires ist own MNP!

Biomedical applications of MNP

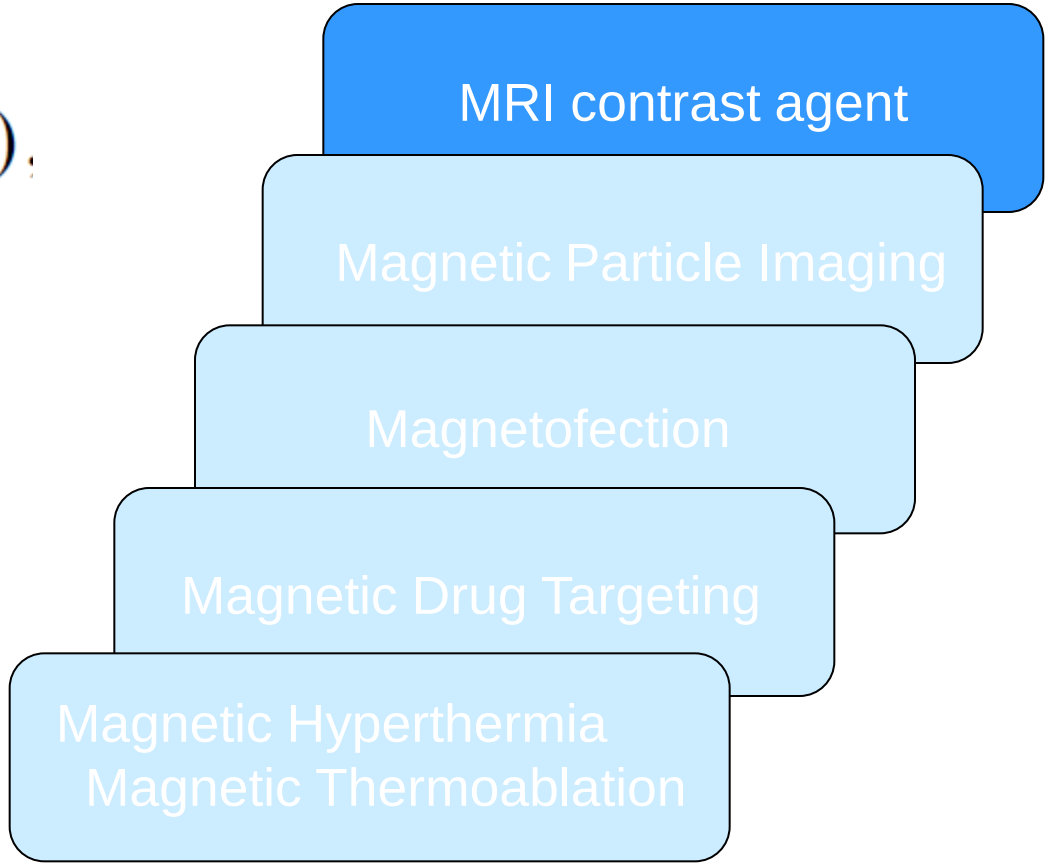


Biomedical applications of MNP



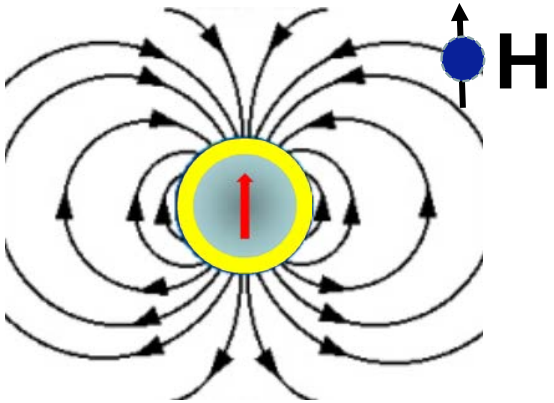
MNP as contrast agent

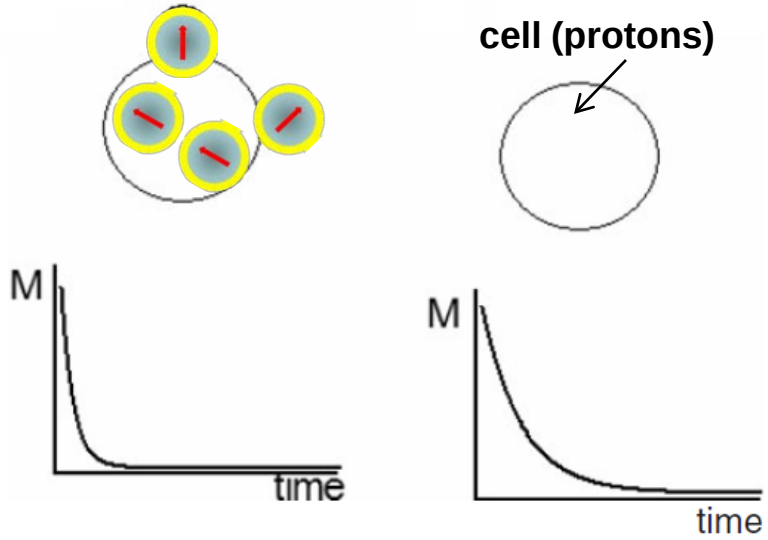
$$\boldsymbol{B} = \mu_0(\boldsymbol{H} + \boldsymbol{M}).$$



MNP as contrast agent

MNP change proton relaxivity (indirect probe)



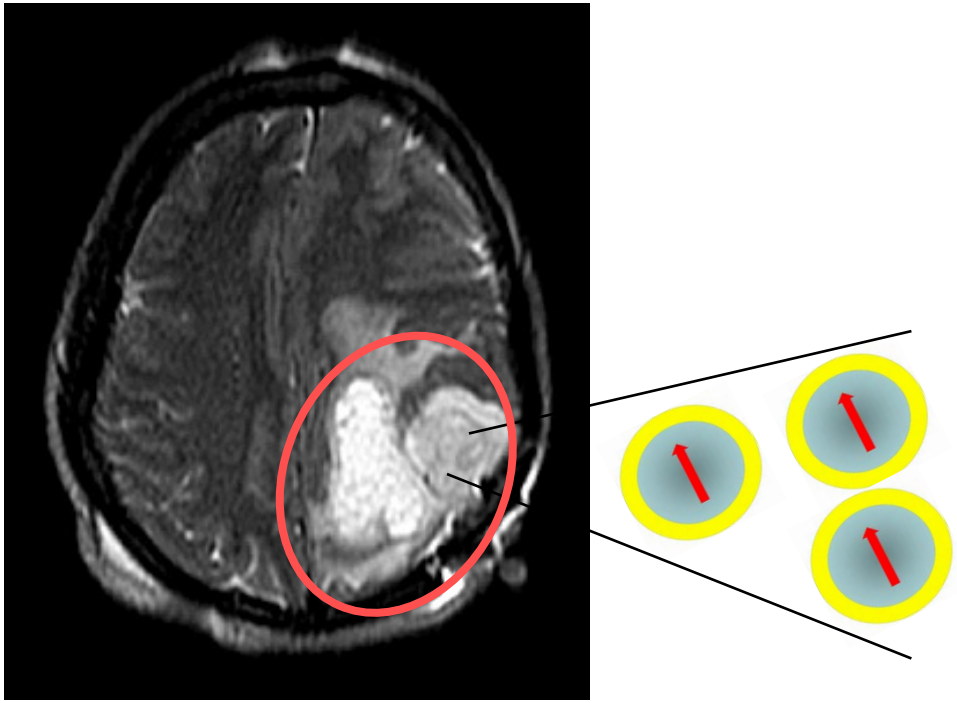


MNP shortens T2 relaxation time of proton

negative contrast

MNP in Biomedical Engineering

MNP change proton relaxivity (indirect probe)



Visualization of a glioblastoma using Resovist (d_{hyd}~60 nm)

MNP size:
iron oxide MNP
suited for imaging of
- liver, spleen
- lymph nodes
- tumor

Taupitz et al., Rofo. **175**:752-65 (2003)

What are MNP in biomedicine?

iron oxide nanoparticle formulations for clinical practice

Compound	Class	Core size (nm)	Hydr. size (nm)	Coating	Relaxivity	$T_{1/2}$	Indication	Trade name	Mode of administration
Ferristene (OMP)	SPIO	Crystals	3500	Sulfonated styrene-divinylbenzene copolymer	T_2* enhancer		Gastrointestinal	Abdoscan® (GE-Healthcare)	Oral
Ferumoxsil (AMI-121)	SPIO	Crystals	300	Siloxane	T_2* enhancer		Gastrointestinal	GastroMRK® (Advanced Magnetics); Lumirem (Guerbet)	Oral
Ferrixan (Ferucarbotran, SHU 555A)	SPIO	4	62	Dextran	R_1:12/R_2:188 (0.947 T) [112]	2.4–3.6 h	Liver	Resovist® (Schering); Cliavist™ (Medicadoc)	iv. bolus injection
Ferumoxide (AMI-25, SHU 555a)	SPIO	4.96	120–180	Dextran	R_1:11/R_2:120 (1.5 T) [113]	6 min	Liver	Feridex® (Advanced Magnetics); Endorem™ (Guerbet)	iv. slow infusion iv. bolus injection
SHU 555C	USPIO	5	<20	Dextran	R_1:11/R_2:38 (1.5 T) [114]	6 h	Angiography	Supravist™ (Schering)	iv. bolus injection
Ferumostran-10 (AMI-227, BMS-180549)	USPIO	5.85	20–40	Dextran	R_1:23/R_2:53 (0.47 T) [59]	24–36 h	Lymph node, liver and angiography	Combidex® (Advanced Magnetics); Sinerem® (Guerbet)	iv. slow infusion
Feruglose (PEG-feron, NC100150)	USPIO	5–7	20	PEGylated starch	R_1:20/R_2:35 (20 MHz) [115]	6 h	Lymph node, liver, perfusion and angiography	Clariscan™ (GE-Healthcare	iv. bolus injection
VSOP-C184	USPIO	4	2–20	Citrate	R_1:14/R_2:33 (1.5 T) [116]	0.6–1.3 h	Angiography (preclinical)	VSOP-C184 (Ferropharm GmbH)	iv. injection

but: Resovist withdrawn from market (for economical reasons)

SPIO: **S**uper**p**aramagnetic **I**ron **O**xides
USPIO: **U**ltrasmall **S**uper**p**aramagnetic **I**ron **O**xides
relaxivity: $R_1=1/T_1$, $R_2=1/T_2$ (normalized to MNP concentration, unit: $[mM^{-1}\cdot s^{-1}]$)

What are MNP in biomedicine?

iron oxide nanoparticle formulations for clinical practice

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but: Resovist withdrawn from market (for economical reasons)

at the moment no perfect MNP contrast agent surmounting Gd chelates

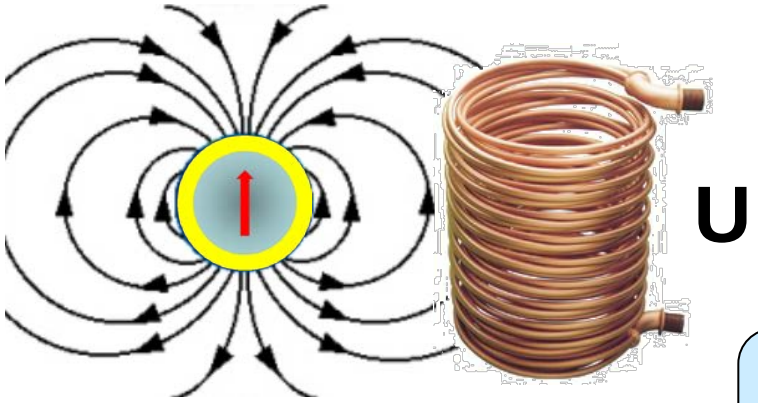
promising:

- MNP for cell tracking
- MNP to visualize imflammations (stroke)

PTB:
magnetic characterization
quantification of tissue samples

MNP in Biomedical Engineering

MNP as direct probes

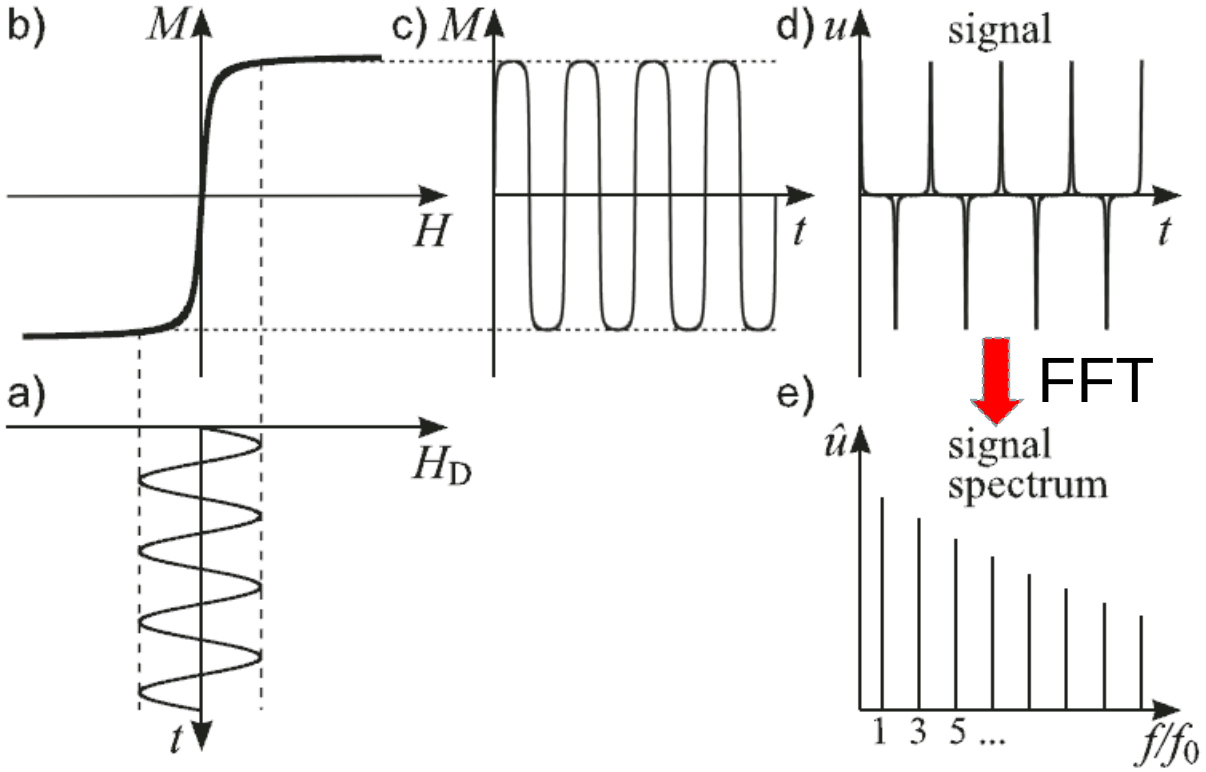


- MRI contrast agent
- Magnetic Particle Imaging
- Magnetofection
- Magnetic Drug Targeting
- Magnetic Hyperthermia
  Magnetic Thermoablation

Quantitative Imaging (MPI)

Magnetic Particle Imaging (MPI)

non-linear magnetic susceptibility



The drive field H_D creates an oscillatory non-linear magnetization response $M(t)$ in the MNP, which is detected as $u(t)$ by a coil. After Fourier transformation the signal spectrum $\hat{u}(f)$ is obtained.

B. Gleich and J. Weizenecker, Nature **435**:1214-17 (2005)

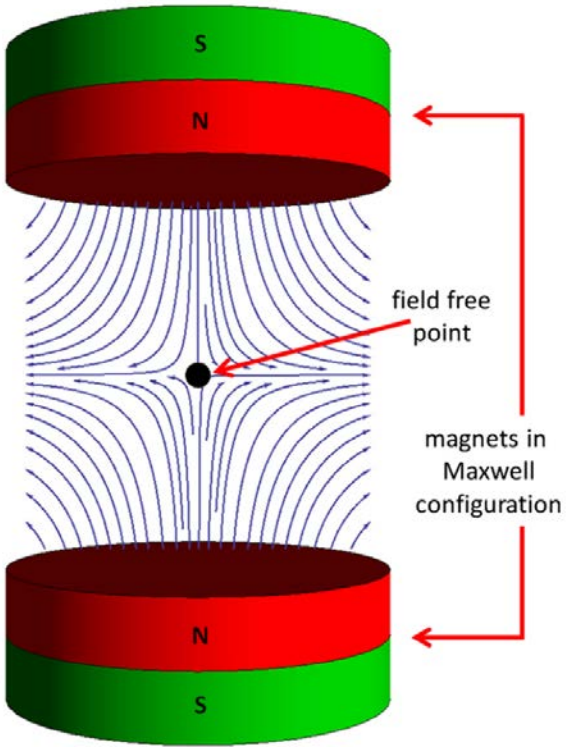
Quantitative Imaging (MPI)

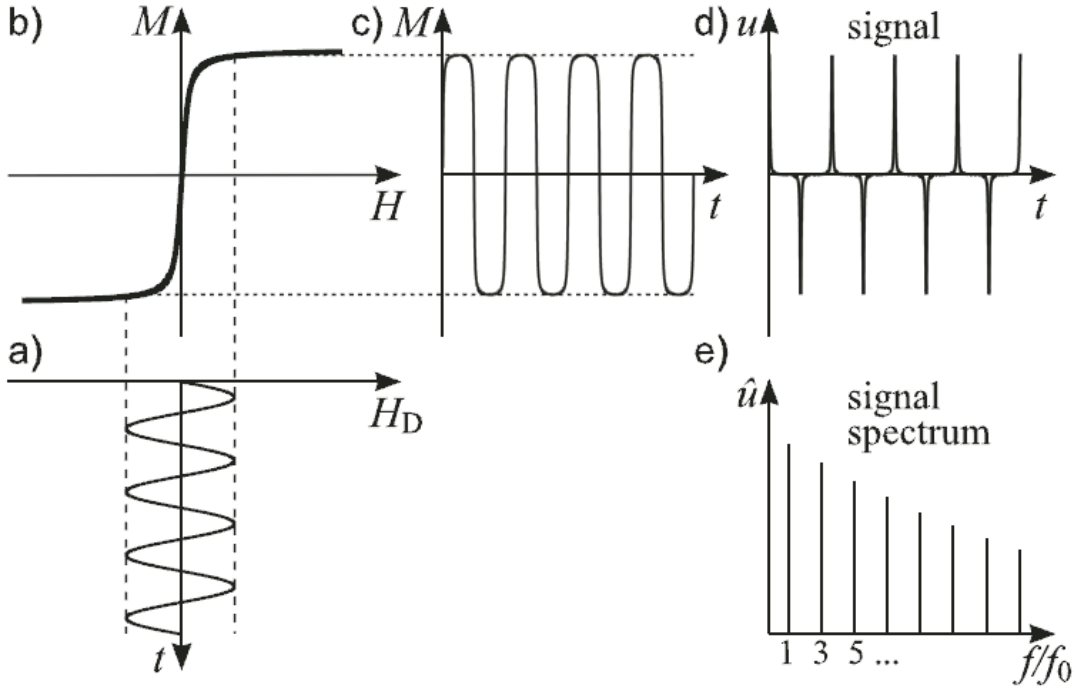
Magnetic Particle Imaging (MPI)

non-linear magnetic susceptibility

Outside the field free point the magnetization of the MNP is saturated and do not contribute to the MPI signal

Spatial encoding by the field free point

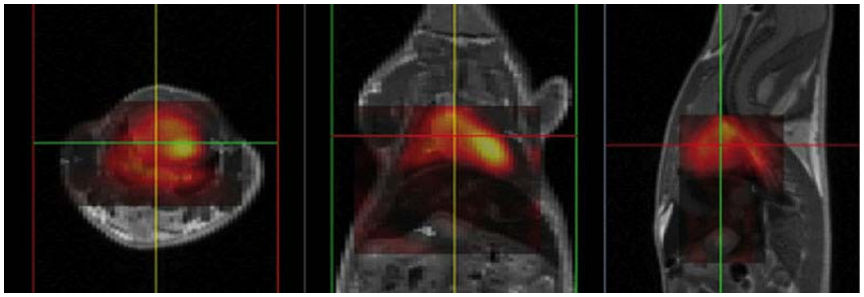




B. Gleich and J. Weizenecker, Nature **435**:1214-17 (2005)

MNP in Biomedical Engineering

MNP as direct probes



J. Weizenecker et. al., PMB **54**:L1-L10 (2009)

Blood flow in a mouse heart

- high sensitivity
- high specificity
- high spatial resolution (< mm)
- high temporal resolution (<20ms)
- quantitative (?)

Blood flow in a mouse using Resovist

- high temporal resolution
- high spatial resolution
- high sensitivity

only MNP visible
→combination with MRI/ CT

challenges:
upscaling of devices for humans
nerve stimulation

PTB:
magnetic characterization

Quantitative Imaging (MPI)

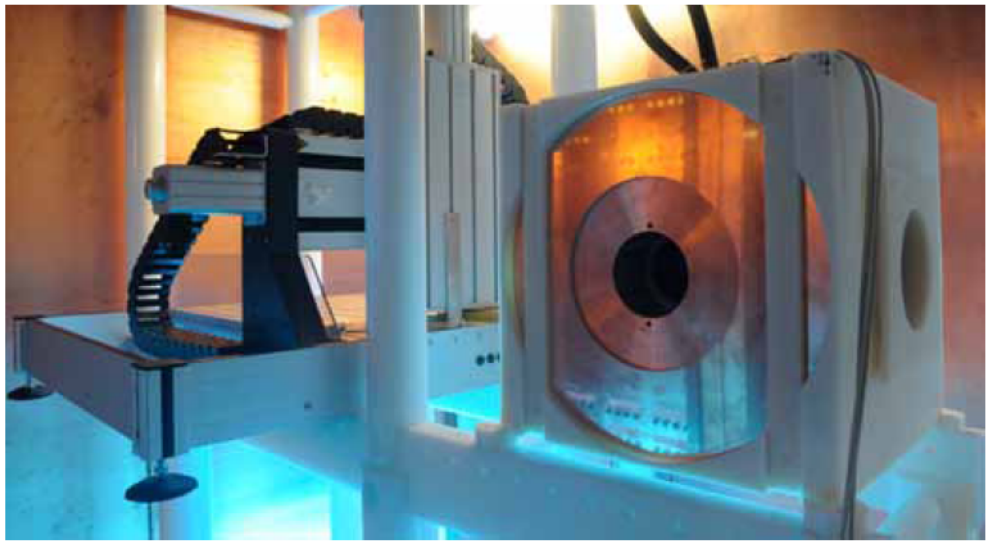
Magnetic Particle Imaging (MPI) –

2 MPI scanner funded by German research foundation

9/2014

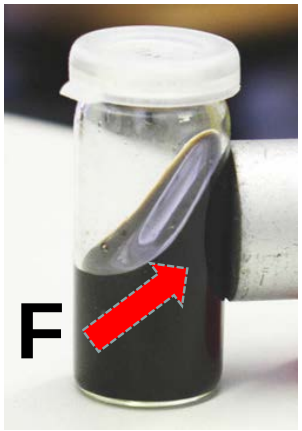
MPI-Scanner at Charité Virchow (Charité and PTB)

PTB:
Scanner maintenance
calibration phantoms
MPI signal generation



Prototype of a preclinical MPI scanner
(source: Philips Technologie GmbH Forschungslaboratorien, Hamburg, Dr. Jörn Borgert)

MNP in Biomedical Engineering



$$F_m = (m \cdot \nabla)B$$

- MRI contrast agent
- Magnetic Particle Imaging
- **Magnetofection**
- Magnetic Drug Targeting
- Magnetic Hyperthermia
  Magnetic Thermoablation

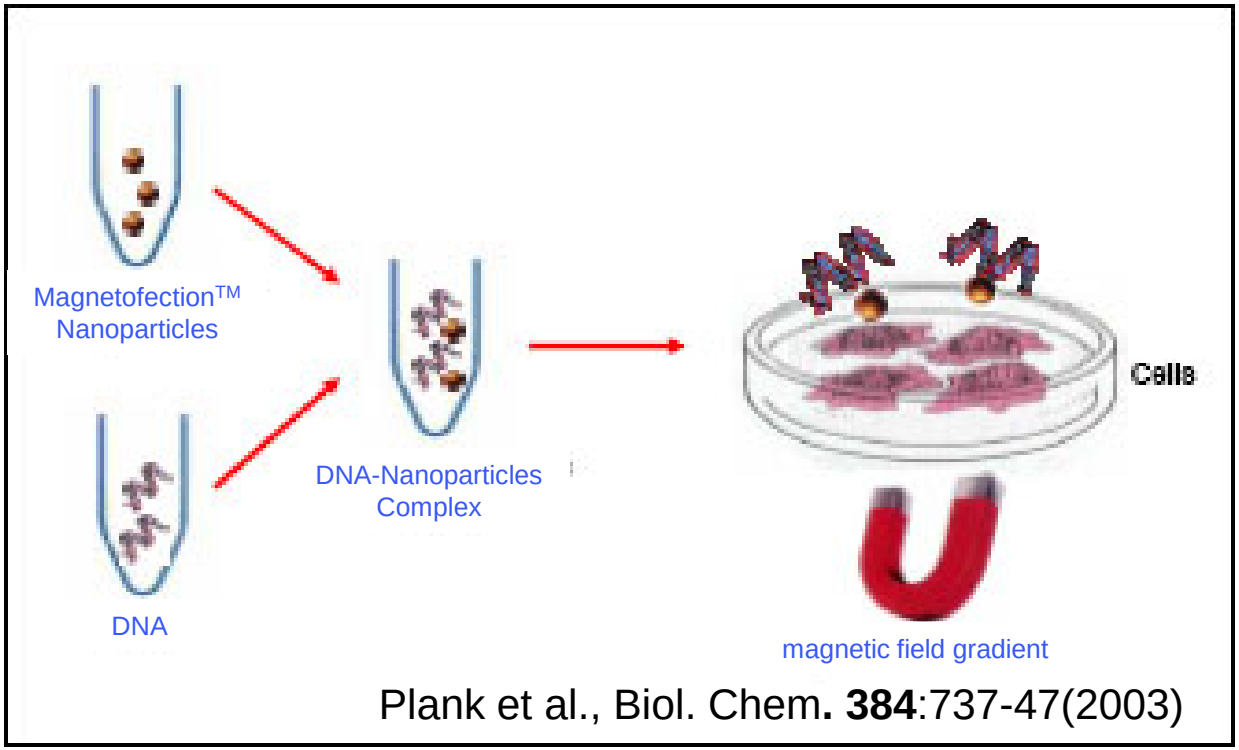
Magnetofection

Delivery of therapeutic genes into cells, tissues, and tumors

functionalized MNP coupled with nucleic acids

magnetic field facilitates introduction of nucleic acids into cells

Ch. Plank, München
S. Priij, Ljubljana



Plank et al., Biol. Chem. **384**:737-47(2003)

Magnetofection: Transfection method using magnetic field gradients to concentrate MNP containing nucleic acids into target cells

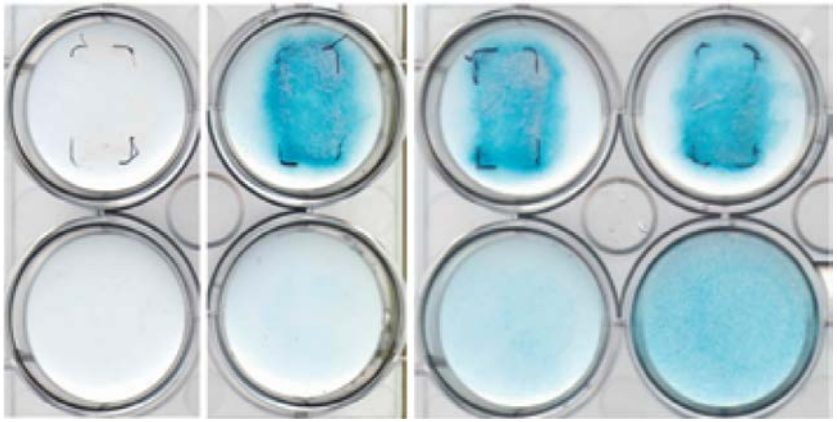
Magnetofection

Delivery of therapeutic genes into cells, tissues, and tumors

functionalized MNP coupled with nucleic acids

magnetic field facilitates introduction of nucleic acids into cells

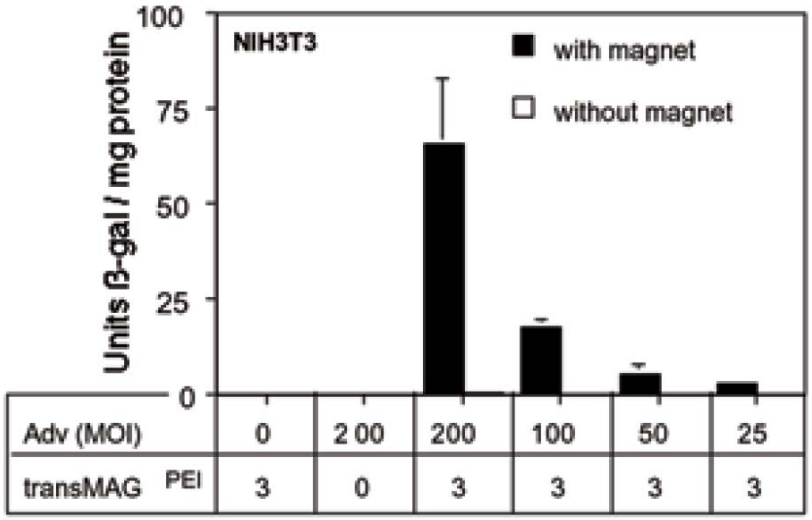
Adenoviral magnetofection (incubation for 30 min)



with Magnet

without magnet

0 µg 3 µg 6 µg 12 µg transMAG^{PEI}



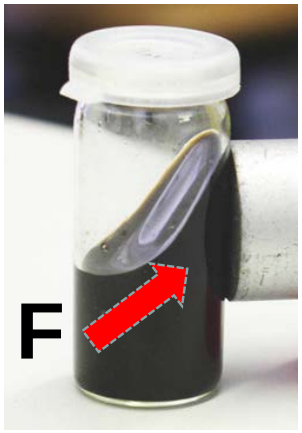
Scherer et al., Gene Therapy **9**:102-109 (2002)

- MNP to enhance efficiacy
- works well in-vitro, but in-vivo (efficiacy, cell viability)
- very sensitive to MNP coating (type, pH values,...)

challenge:
transfer to in-vivo modality

PTB:
Specific quantification of MNP uptake

Magnetic Drug Targeting / Delivery



$$F_m = (m \cdot \nabla) B$$

- MRI contrast agent
- Magnetic Particle Imaging
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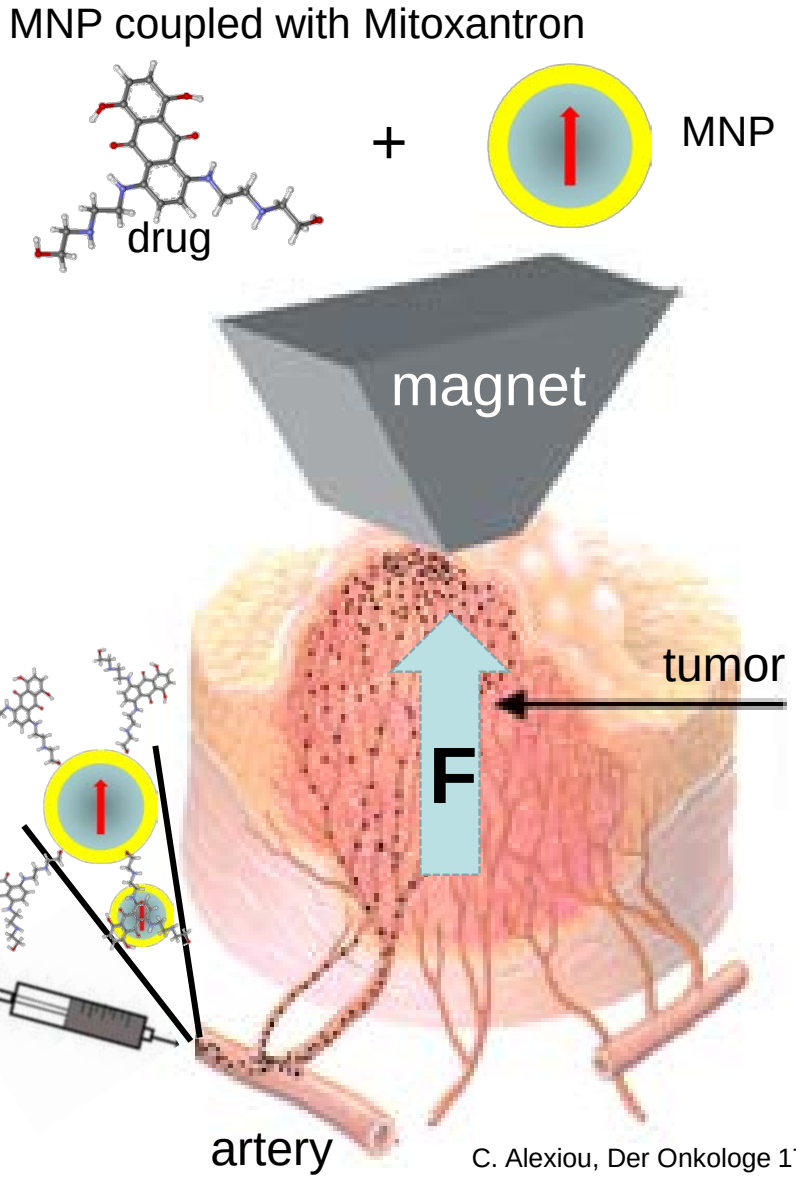
- **Magnetic Drug Targeting**
- Magnetic Hyperthermia
  Magnetic Thermoablation

Magnetic Drug Targeting / Delivery



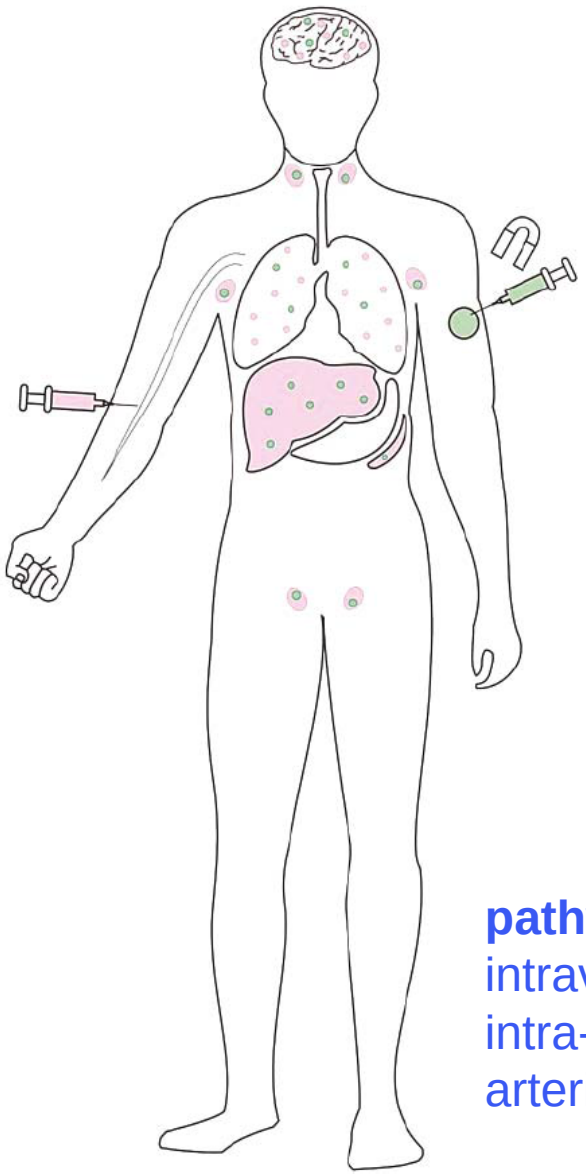
C. Alexiou, Der Onkologe 17:405 (2011)

magnetic drug targeting facility at university hospital Erlangen

A. Lübbe et al., Cancer Res. **56**:4686-93 (1996)

Ch. Alexiou, Erlangen, rabbit tumor model
B. Shapiro, Maryland, MEMS, flow systems

Magnetic Drug Targeting / Delivery

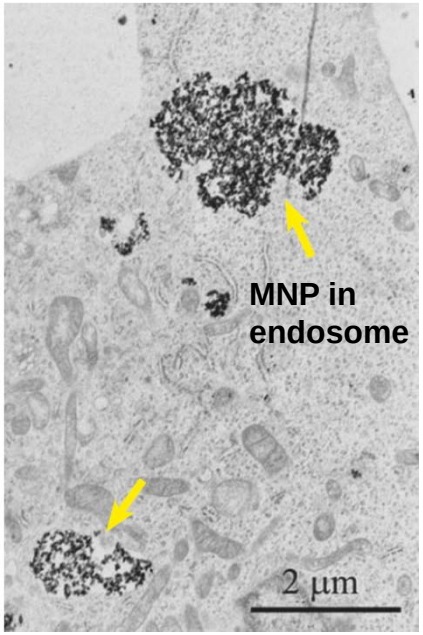


efficient internalization of MNP into cells/organs/tumor limited by
- cytotoxicity
- MNP aggregation
- short blood/plasma half-life

→ smaller MNP (d_{hydr}~10-20 nm) are better internalized than larger ones
→ MNP uptake higher by malignant cells than by normal cells

MNP clearance
d < 5…7 nm → renal
d > 5…7 nm → liver

pathways (MNP administration):
intravenous
intra-tumoral
arterial

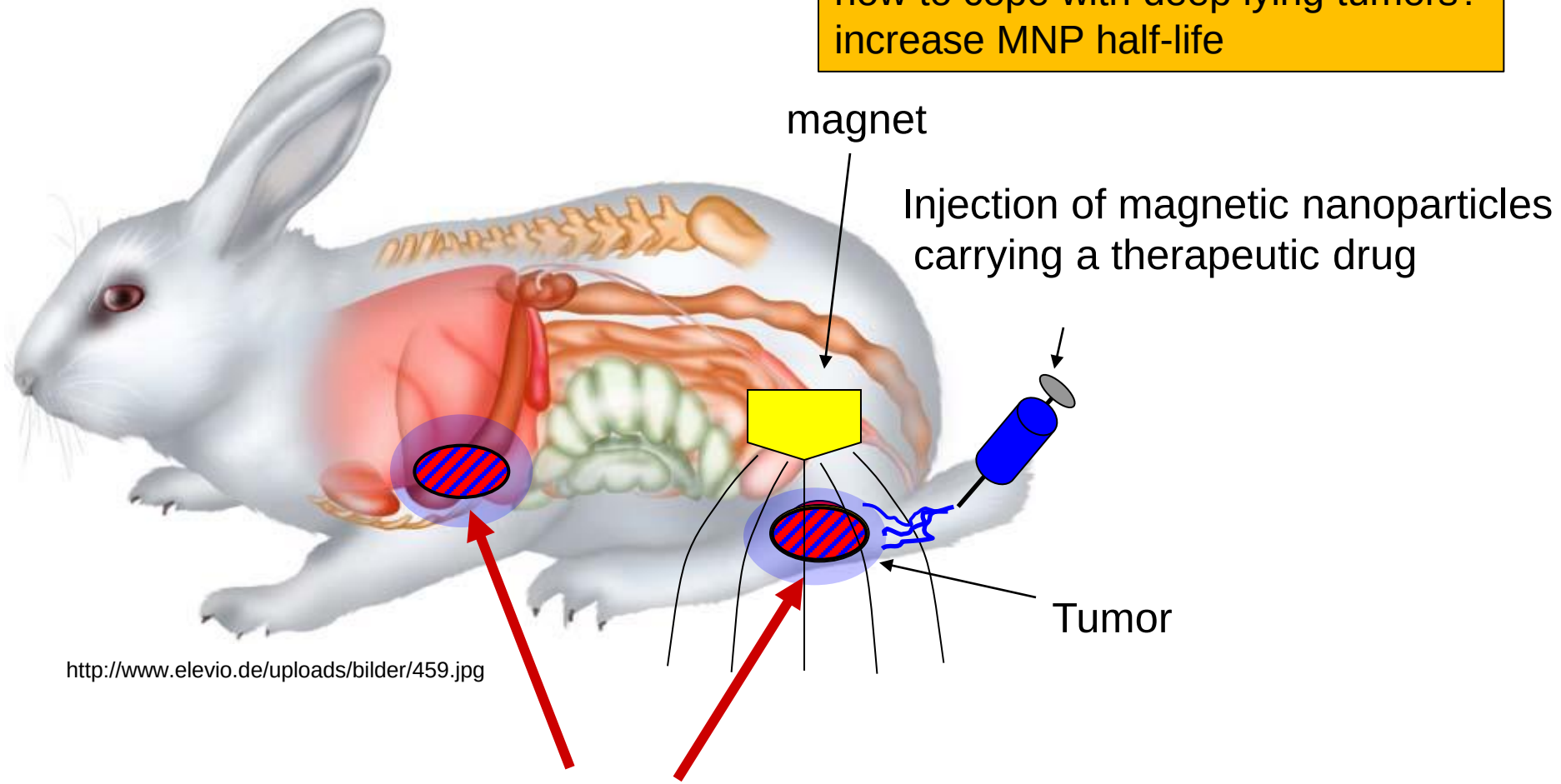


human melanoma
SK-MEL-28 cell
4 h after MNP incubaiton

S. Priij et al., Radiol Oncol **45**:1-16 (2011)

Magnetic Drug Targeting / Delivery

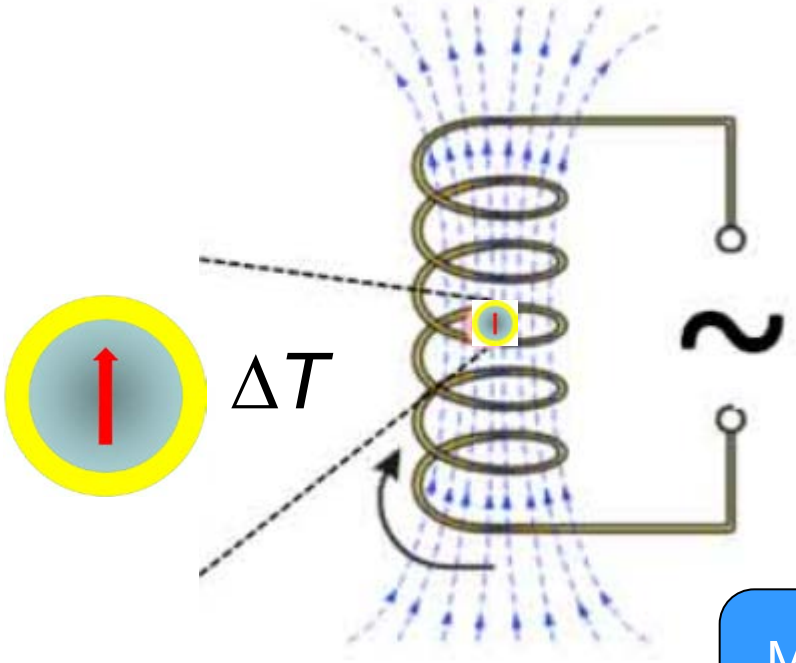
challenges:
how to cope with deep lying tumors?
increase MNP half-life



http://www.elevio.de/uploads/bilder/459.jpg

PTB: Biodistribution of MNP

Magnetic Hyperthermia/Thermoablation



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

- MRI contrast agent
- Magnetic Particle Imaging
- Magnetofection
- Magnetic Drug Targeting
- **Magnetic Hyperthermia**
  Magnetic Thermoablation

Magnetic Hyperthermia/Thermoablation

Specific heating of tumor/tissue by interaction of an rf-field with magnetic nanoparticles

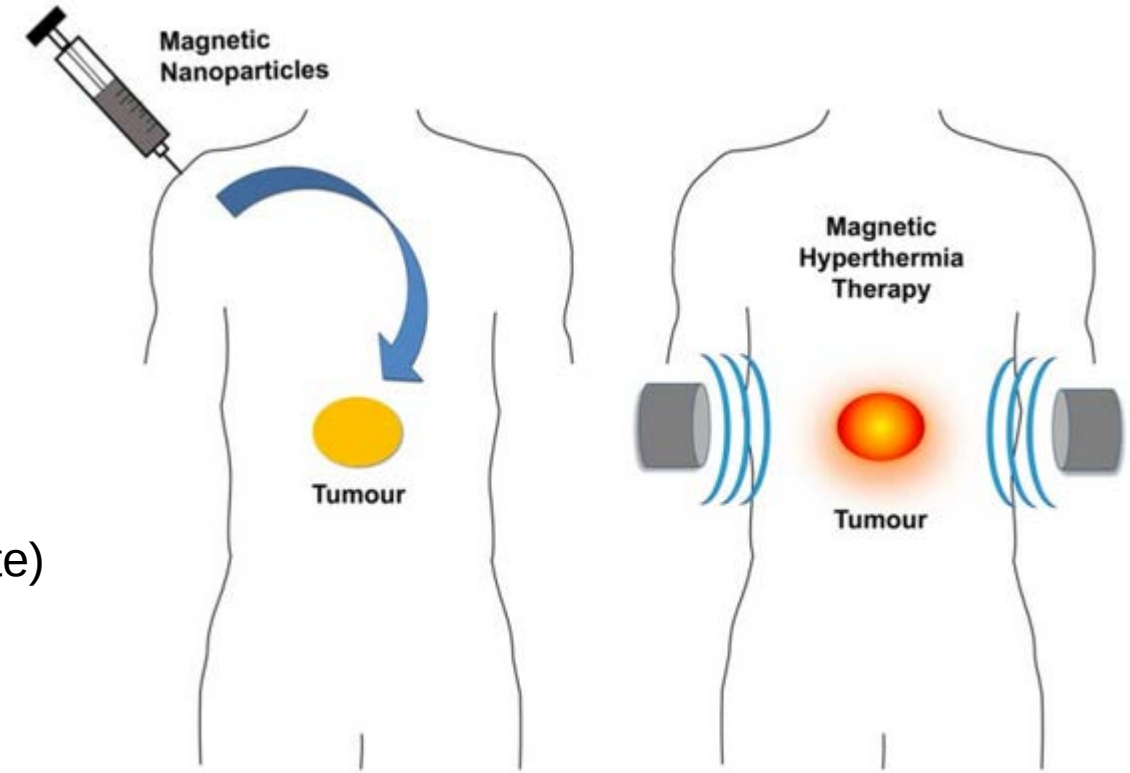
local modality

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

B_{AC}: 20 – 40 mT (15 – 30 kA/m)
f_{AC}: 100 - 400 kHz
←→ nerve stimulation

magnetic hyperthermia
T up to 44° C

magnetic thermoablation
T >> 44° C



A. Andrade in BME frontiers and challenges, ISBN 978-953-307-309-5, Chapter 8, (2011)

SAR (specific absorption rate)
~ 200 W/g

P_{SPM}=SAR · ρ

Magnetic Hyperthermia/Thermoablation

Specific heating of tumor/tissue by interaction of an rf-field with magnetic nanoparticles

B_{AC}: 20 – 40 mT (15 – 30 kA/m)
f_{AC}: 100 - 400 kHz

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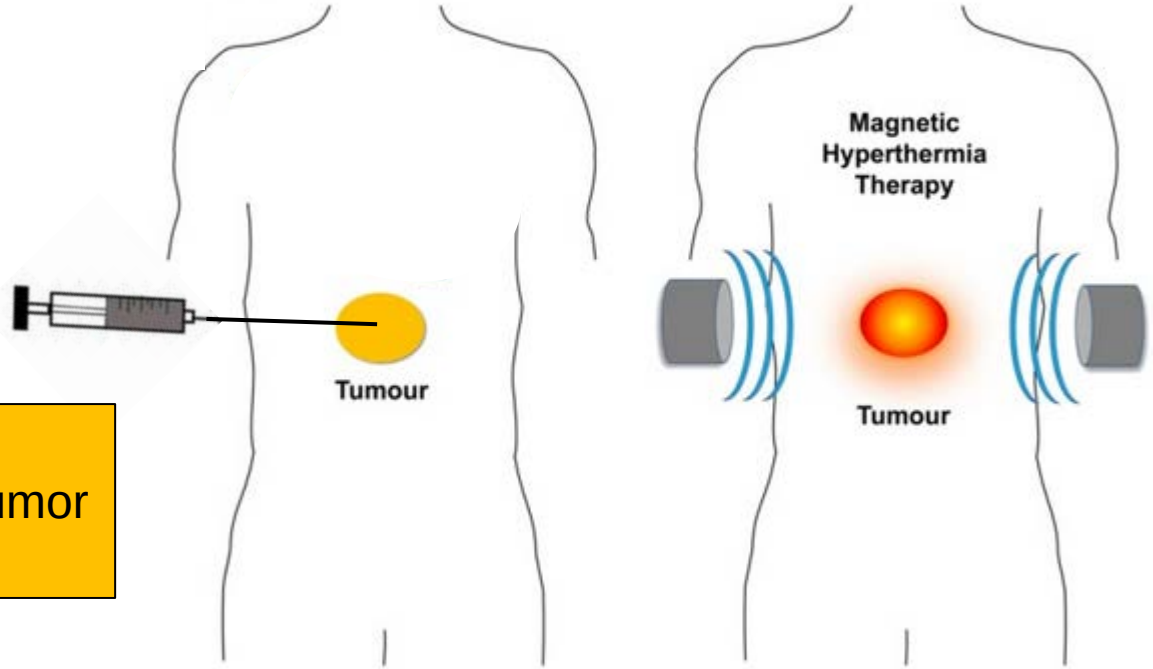
magnetic hyperthermia
T up to 44° C

magnetic thermoablation
T >> 44° C



challenges:
accumulation of MNP in tumor
intratumoral injection?

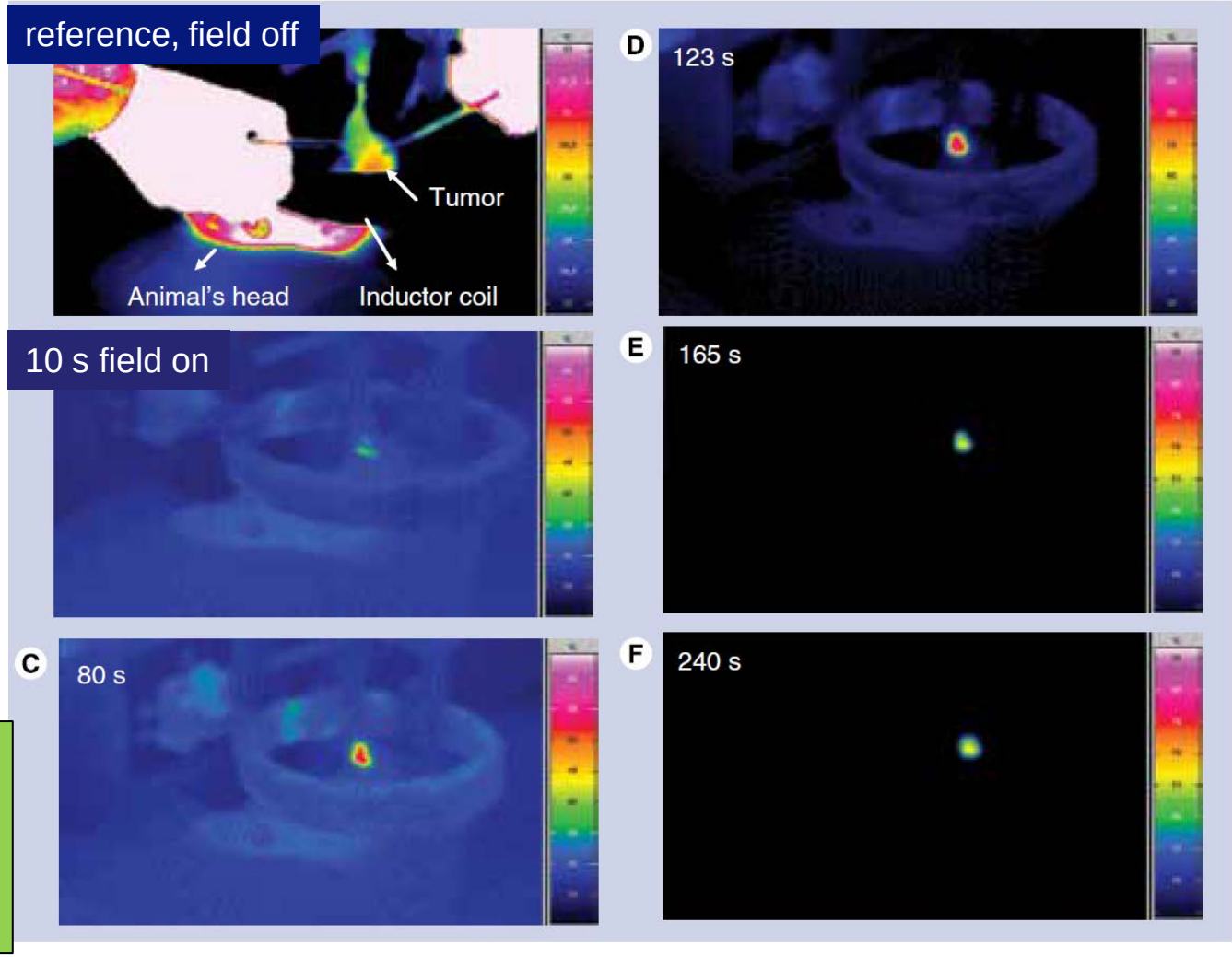
A. Andrade in BME frontiers and challenges, ISBN 978-953-307-309-5, Chapter 8, (2011)

Magnetic Hyperthermia/Thermoablation

preclinical studies (I. Hilger, Jena)

Specific heating of rat tumor by rf-heating with MNP

other sites
M Respaud ,Toulouse
F. Gazeau, Paris
C. Wilhelm, Paris



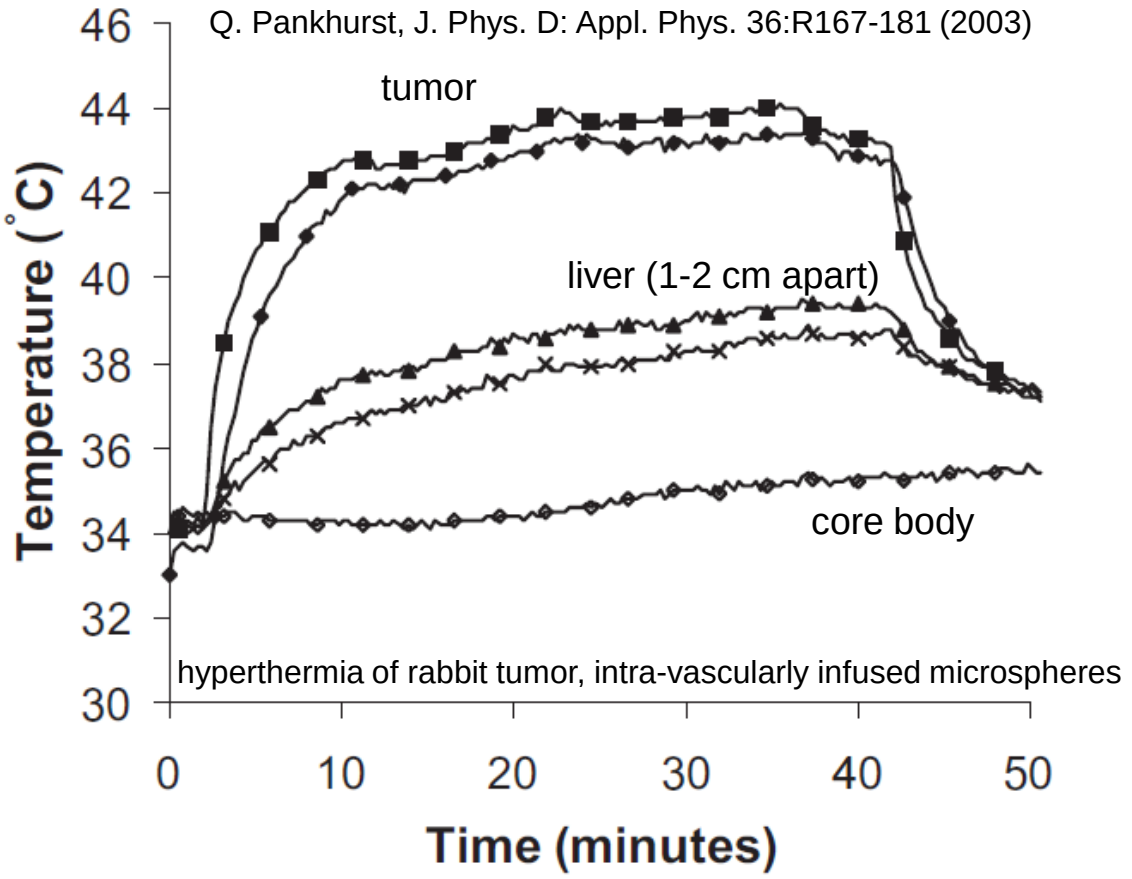
PTB:
Quantification of tumor uptake and biodistribution of MNP

Hilger et al., Nanomedicine **7**:1443-59 (2012)

Magnetic Hyperthermia/Thermoablation

Specific heating of rat tumor by rf-heating with MNP

Q. Pankhurst, J. Phys. D: Appl. Phys. 36:R167-181 (2003)



PTB:
Quantification of tumor uptake and biodistribution of MNP

challenges:
- intratumoral MNP injection
- determining the heat distribution

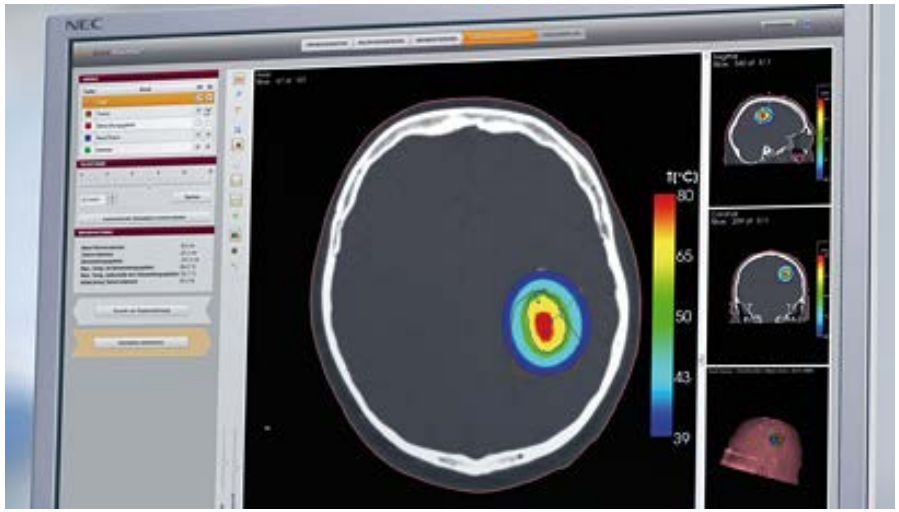
Magnetic Hyperthermia/Thermoablation

patient studies: mag*force*, A. Jordan

- glioblastoma (beyond treatment)
- prostate cancer

MNP: 15 nm iron oxide
with amino silane coating

magforce: NanoTherm™



magforce: NanoActivator™

at Charité, Münster, Kiel

Glioblastoma is the most common and most aggressive malignant primary brain tumor in humans

Magnetic Hyperthermia/Thermoablation

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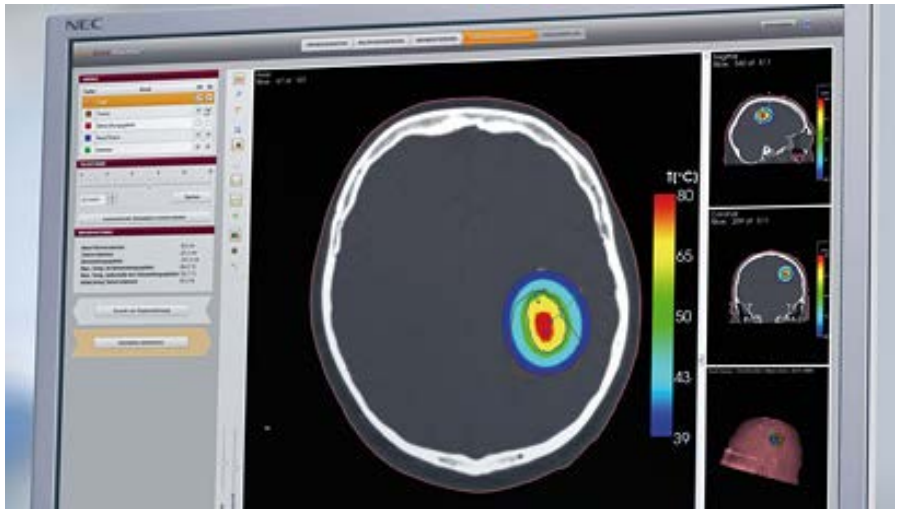


magforce: NanoActivator™

at Charité, Münster, Kiel

challenges:
- intratumoral MNP injection
- determining the heat distribution

How does PTB assist?

Characterization of MNP magnetism

Quantification of MNP in tissue, cell and blood samples

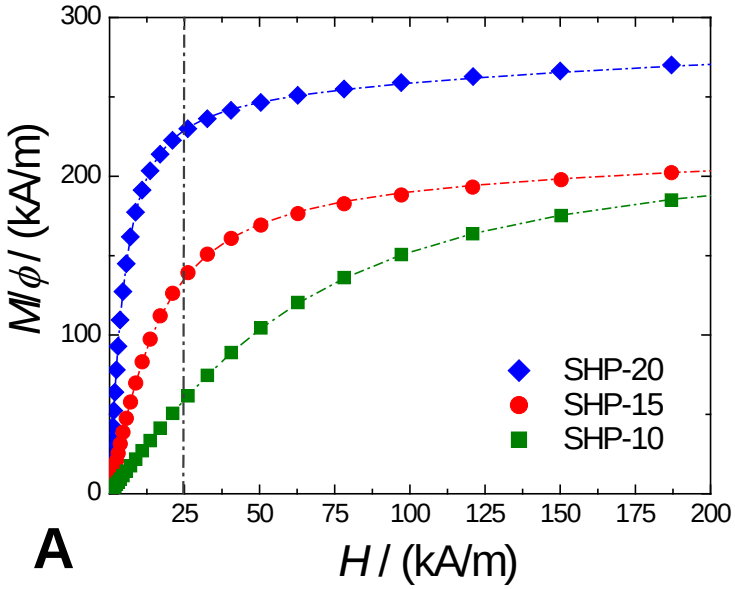
Imaging of MNP distributions

→ develop measurement procedures and devices

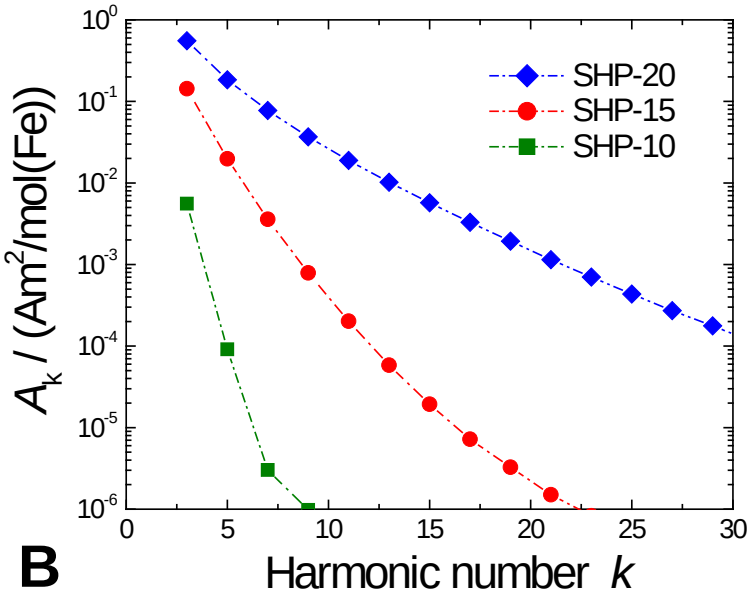
Characterization, quantification and imaging of MNP

Characterization of MNP

determine M_S, d_{core}, σ, K_{eff},…

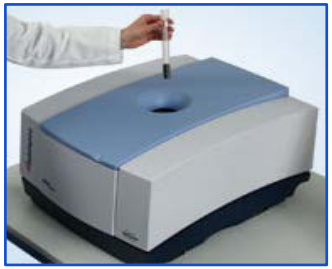


MPI-tracer **assessment**



SQUID- Magnetometry

Nuclear magnetic resonance (NMR)

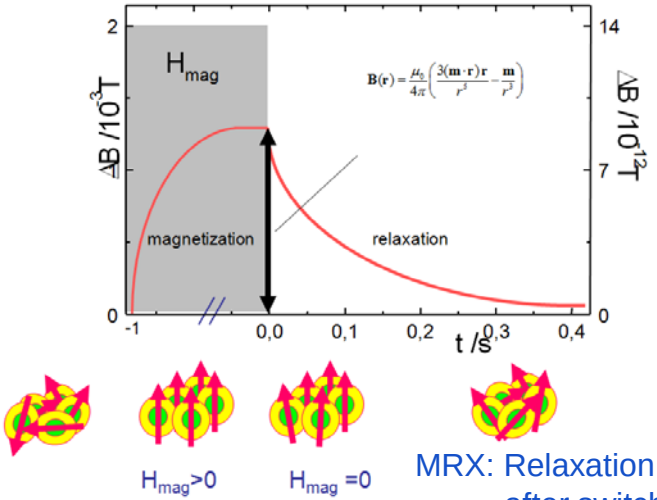


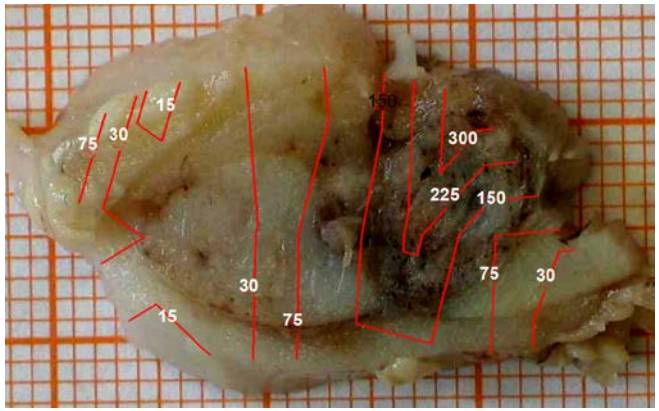
Assymetrical field flow field fractionation (A4F)

Magnetic Particle Spectroscopy (zero dimensional MPI)

Characterization, quantification and imaging of MNP

Magnetorelaxometry (MRX) to **quantify** MNP distribution in a tumor





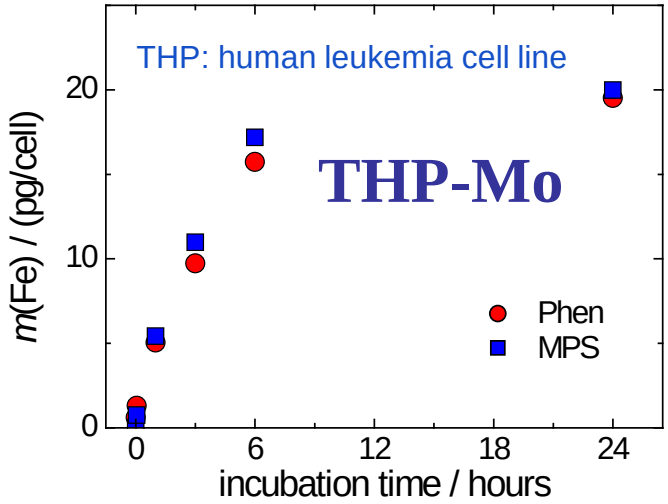
ng MNP / g tumor tissue

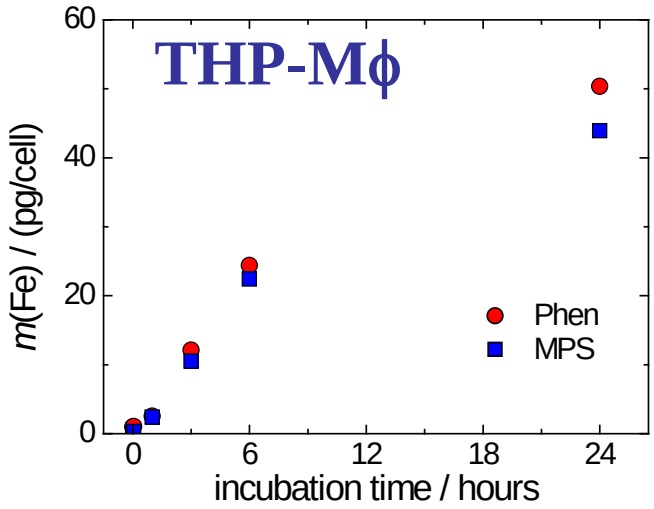
MRX measurement device

MRX: Relaxation of magnetic moments of MNP
after switching off of a moderate magnetic field (~1 mT)

MPS to **quantify** cellular uptake of MNP by THP-cells

MPS measurement device



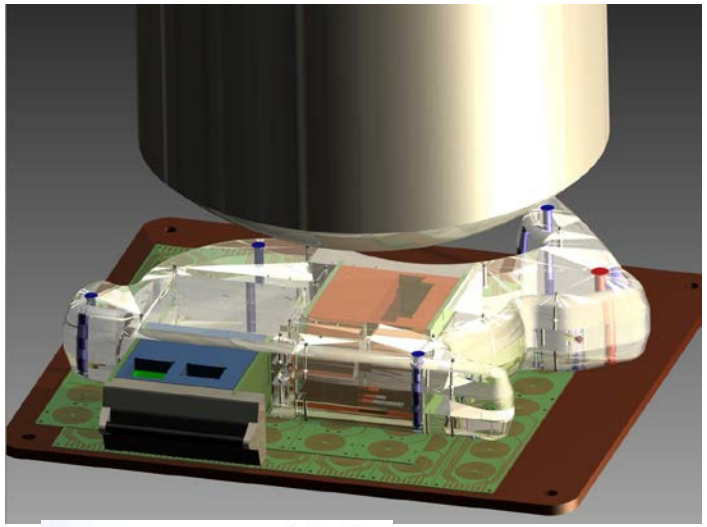


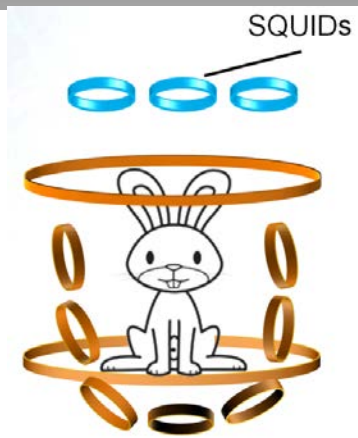
Characterization, quantification and imaging of MNP

PTB

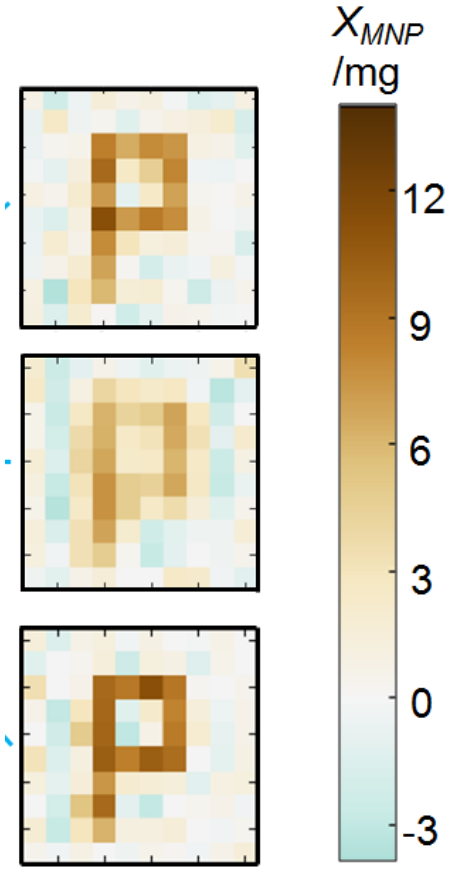
PTB 304 SQUID System

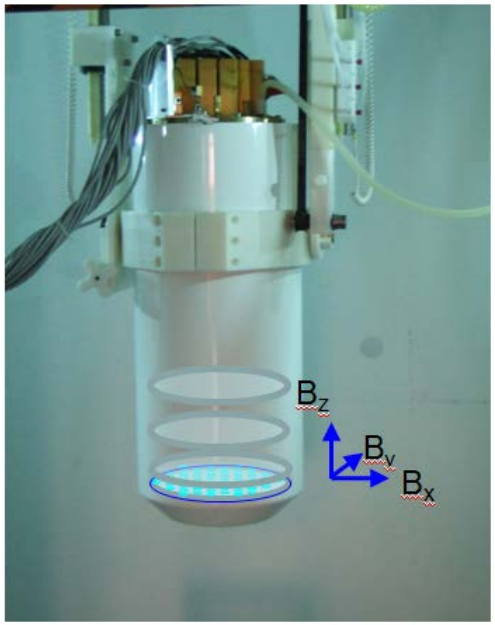
in-vivo imaging of MNP distributions by Magnetorelaxometry (MRX)



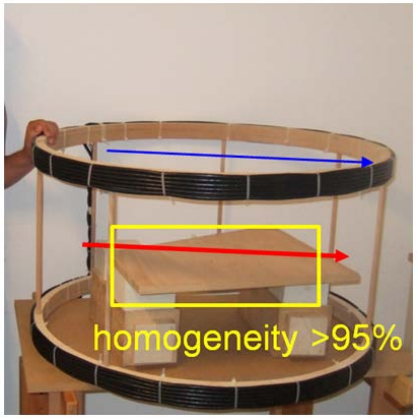


inhomogeneous MRX





homogeneous MRX



Summary

Biomedical applications of magnetic nanoparticles
are physically based on
- stray field of moment
- force in a magnetic field gradient
- heat production in AC field

Prominent applications are
MRI-contrast agent, MPI, Hyperthemia, Drug-Targeting,
Magnetofection

All these applications require knowledge of
- physical properties of MNP
- biodistribution

PTB develops measurement procedures
for imaging and quantification of MNP in tissue

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