Magnetic nanoparticles in medicine:
future diagnostic and therapeutic applications

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Outline

Terminology

– Magnetic nanoparticles, ferrofluids

Diagnostic applications

– Magnetorelaxometry (MRX)

– Magneto-optical relaxation of ferrofluids (MORFF)

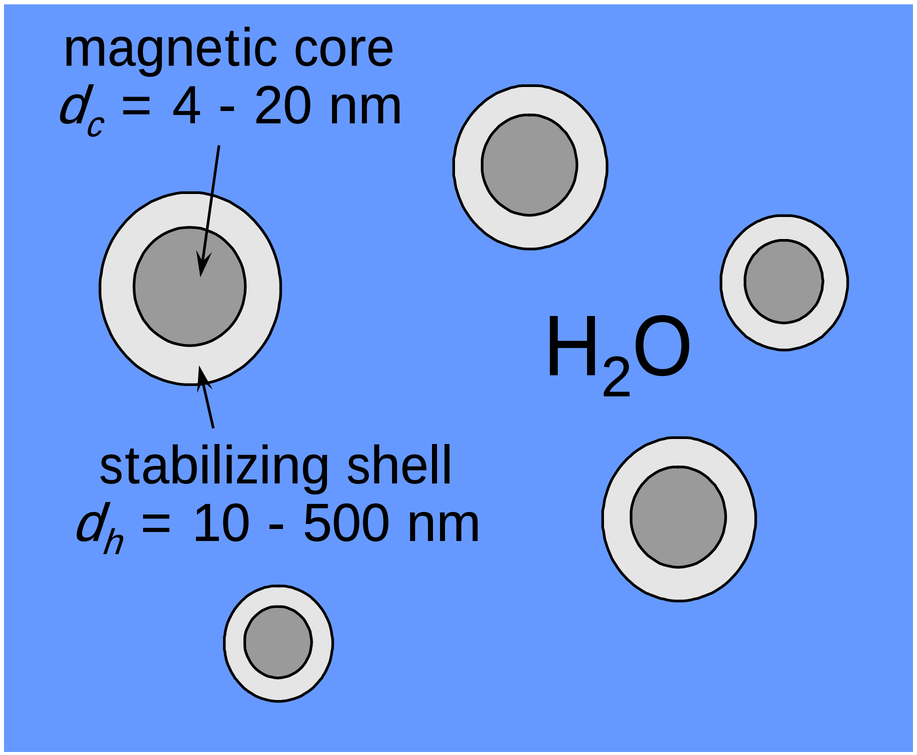
Therapeutic applications

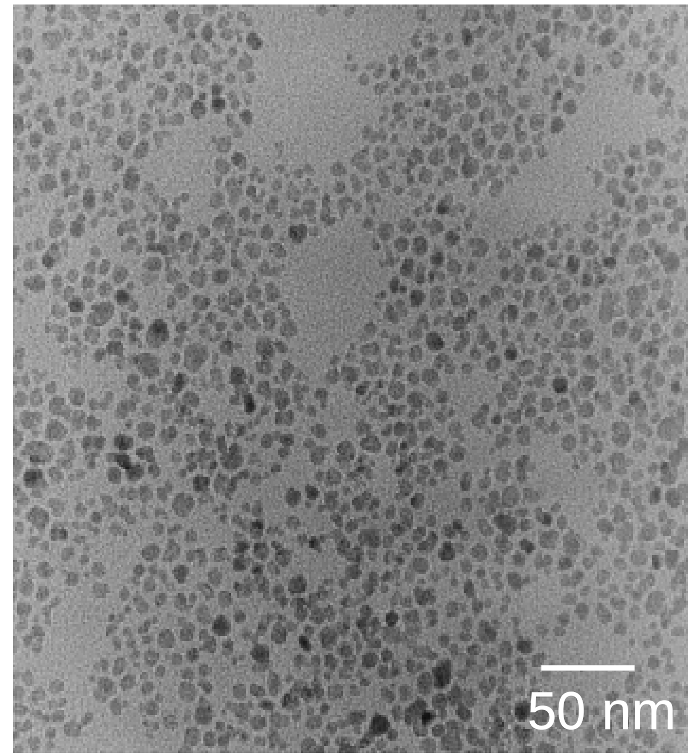
– Magnetic hyperthermia

– Magnetic drug targeting

Magnetic nanoparticles (MNP)

ferrofluid = colloidal dispersion of magnetic nanoparticles

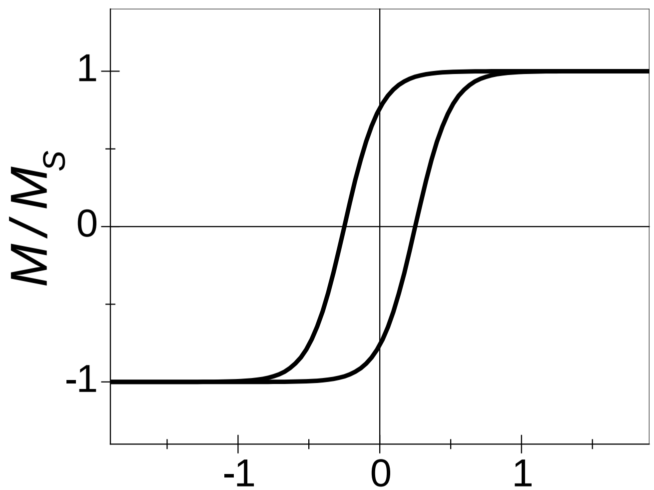




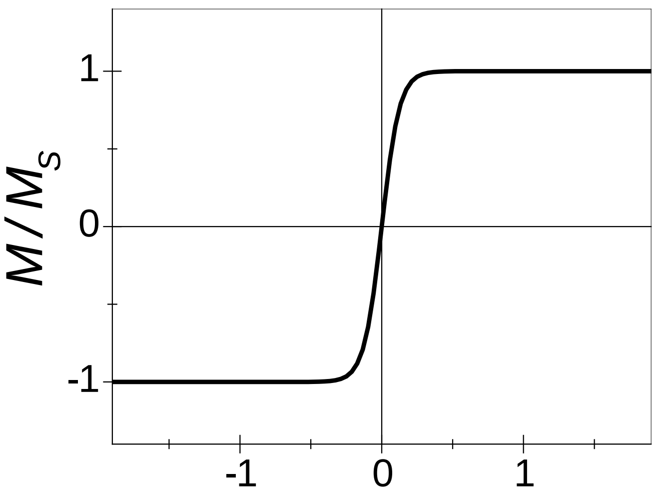
⇨ core: material, size, shape

⇨ shell: material, thickness

Superparamagnetism



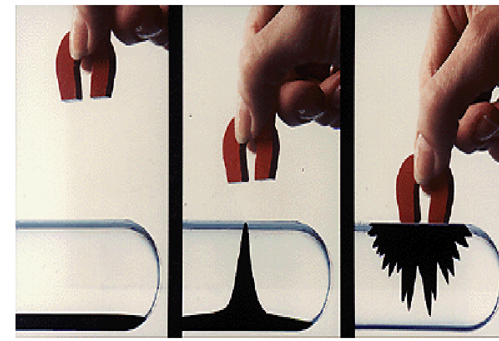
Ferro-/ Ferrimagnetism



Superparamagnetism

Application of ferrofluids

Engineering
- sealing, damping
- magnetic ink



Diagnostics

in vitro:
- magnetic separation (biomolecules, cells)
- magneto-optical relaxation immunoassay

in vivo:
- magnetic resonance imaging (MRI)
- magnetorelaxometry (MRX)

Therapy
- hyperthermia
- drug targeting (magnetic carriers)

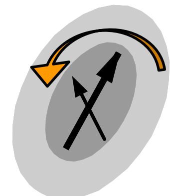
Why *magnetic* nanoparticles?

- Attractive forces in magnetic gradient fields
  - Use in separation technology
  - Magnetic drug targeting
- Susceptibility
  - Contrast agents in MRI (T2-shortening)
- Magnetic nanoparticle relaxation
  - Magnetorelaxometry
  - Magneto-optical relaxation
  - Heat generation, hyperthermia

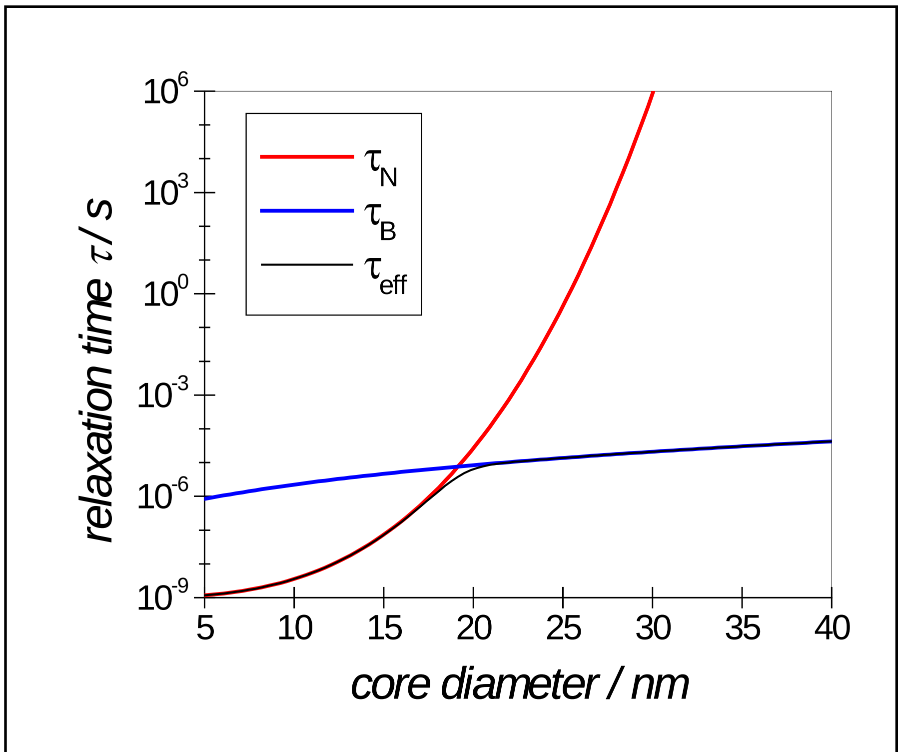
Relaxation

Néel

$$\tau_N = \tau_0 \exp\left(\frac{KV_{Kern}}{k_B T}\right)$$

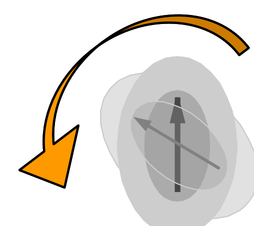


$$M(t) = M_0 \exp(-t/\tau)$$



Brown

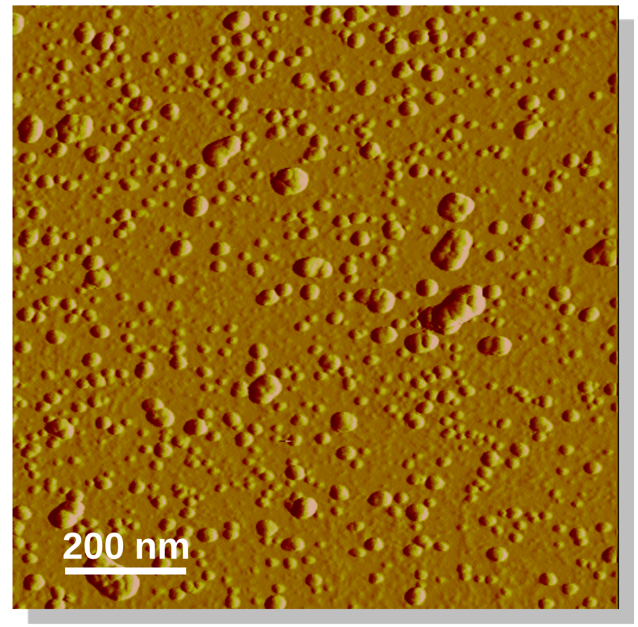
$$\tau_B = \frac{3\eta V_{hyd}}{k_B T}$$



d_{shell} = 4 nm, η = 1 mPa·s, T = 298 K, $\tau_0 = 10^{-9}$ s, K_{eff} = 10 kJ/m

Workhorse: DDM 128N (Meito Sangyo)

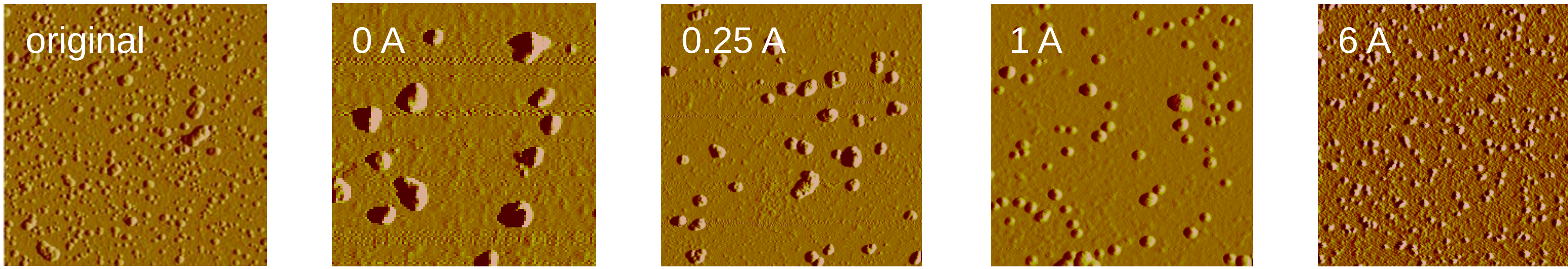
- core:
  - maghemite (γ-Fe_2O_3)
  - diameter 5-20 nm
  - partly aggregated
- shell:
  - carboxydextran (2.6 kDa)
  - thickness approx. 4 nm
- hydrodynamic diameter ≈10-100 nm (Ø 60 nm)
- biocompatible

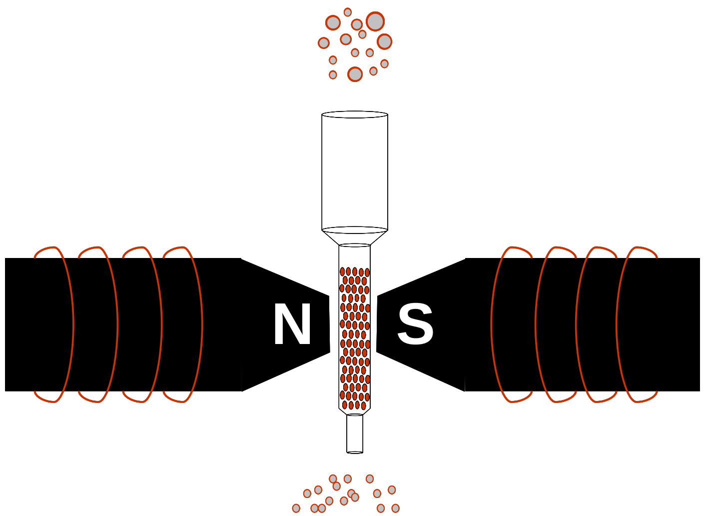


AFM amplitude image of DDM 128N on mica/PEI

Büscher et al. (2004) *Langmuir*

Magnetic fractionation



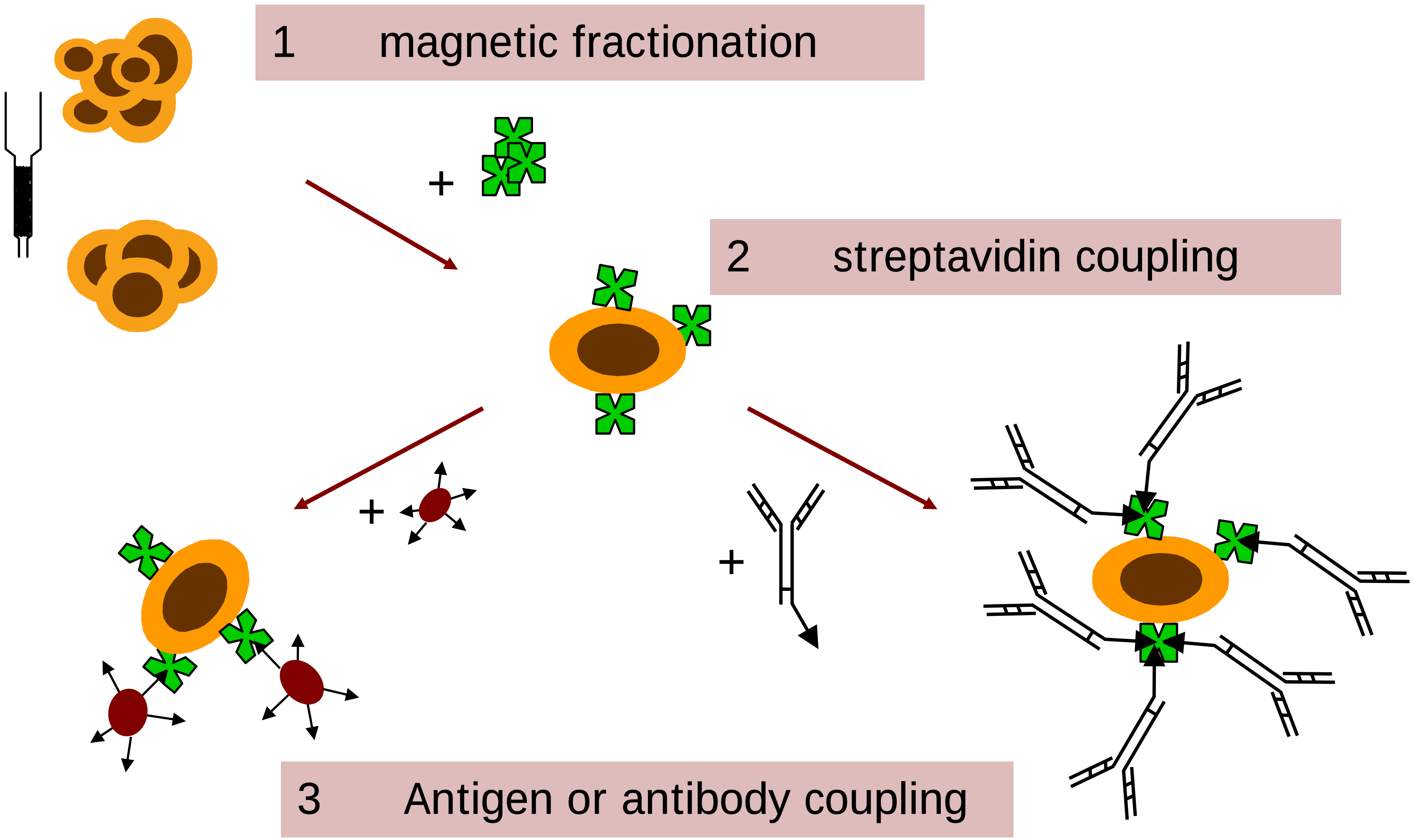


fraction	d_{AFM} (nm)	d_{PCS} (nm)
original	6.1	55.8
0 A	22.4	69.3
0.25 A	18.5	42.5
1 A	7.9	21.5
6 A	5.4	11.8

electromagnet with
magnetic separation column MACS® XS

Rheinländer et al. (2000) *Colloid Polym Sci*

Functionalization of magnetic probes



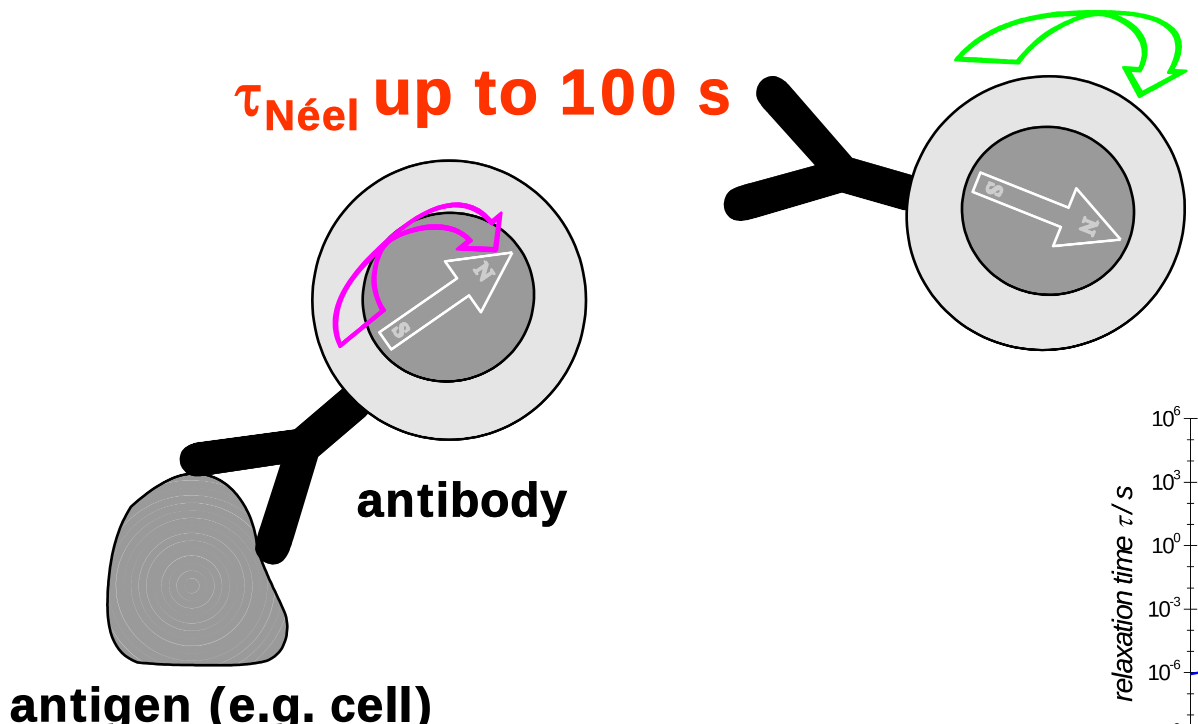
Diagnostic applications

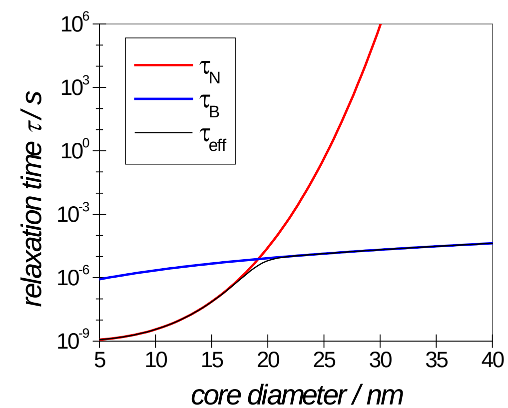
1. Magnetorelaxometry (MRX)

Magnetorelaxometry (MRX): Principle

Specific detection of magnetic relaxation signal of bound MNP.

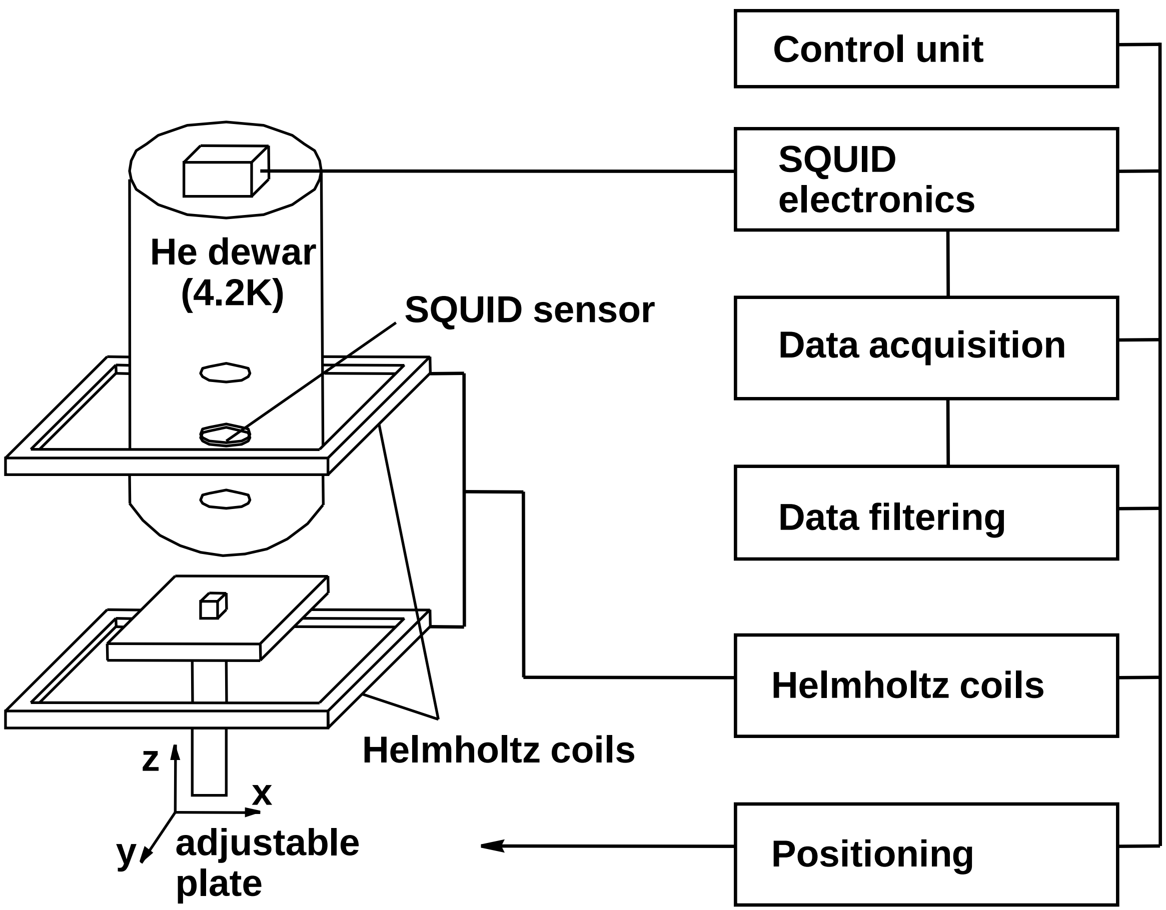
Precondition: $\tau_{Néel} > \tau_{Brown}$

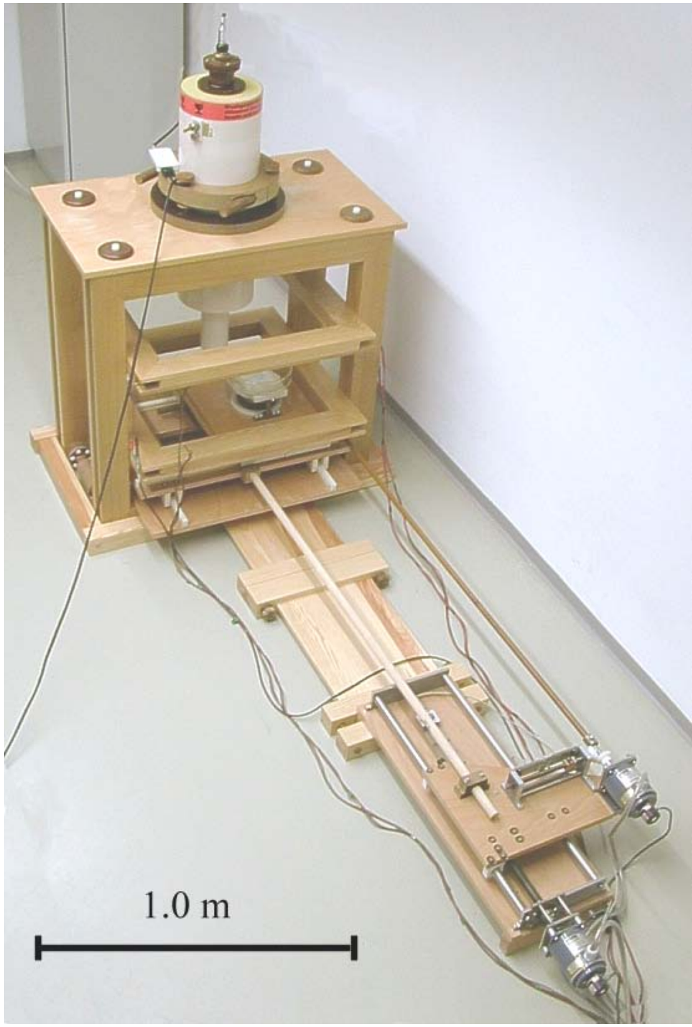




Weitschies et al. (1997) *Pharm Pharmacol Lett*

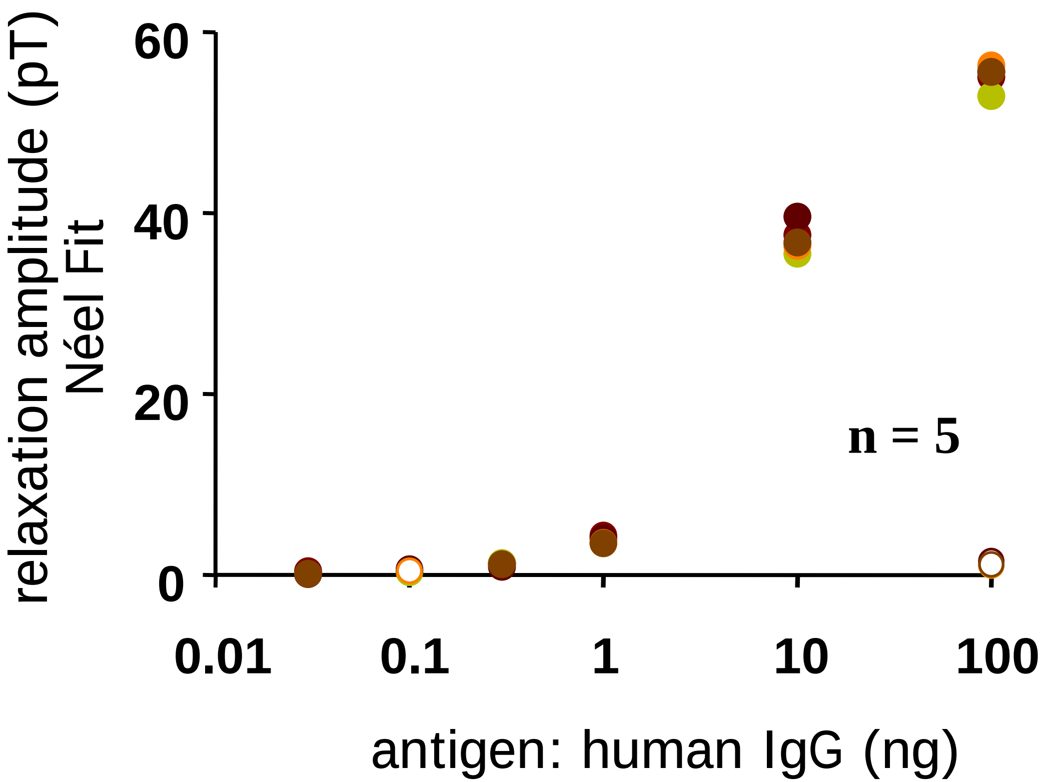
MRX: Measurement device

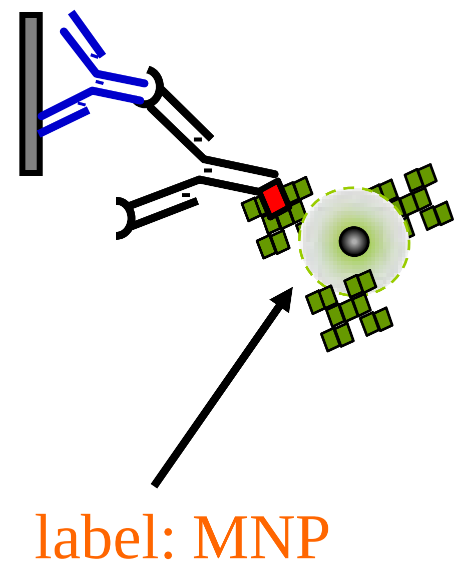




Warzemann et al. (1999) *Supercond Sci Technol*

MRX: Testing of specific probes



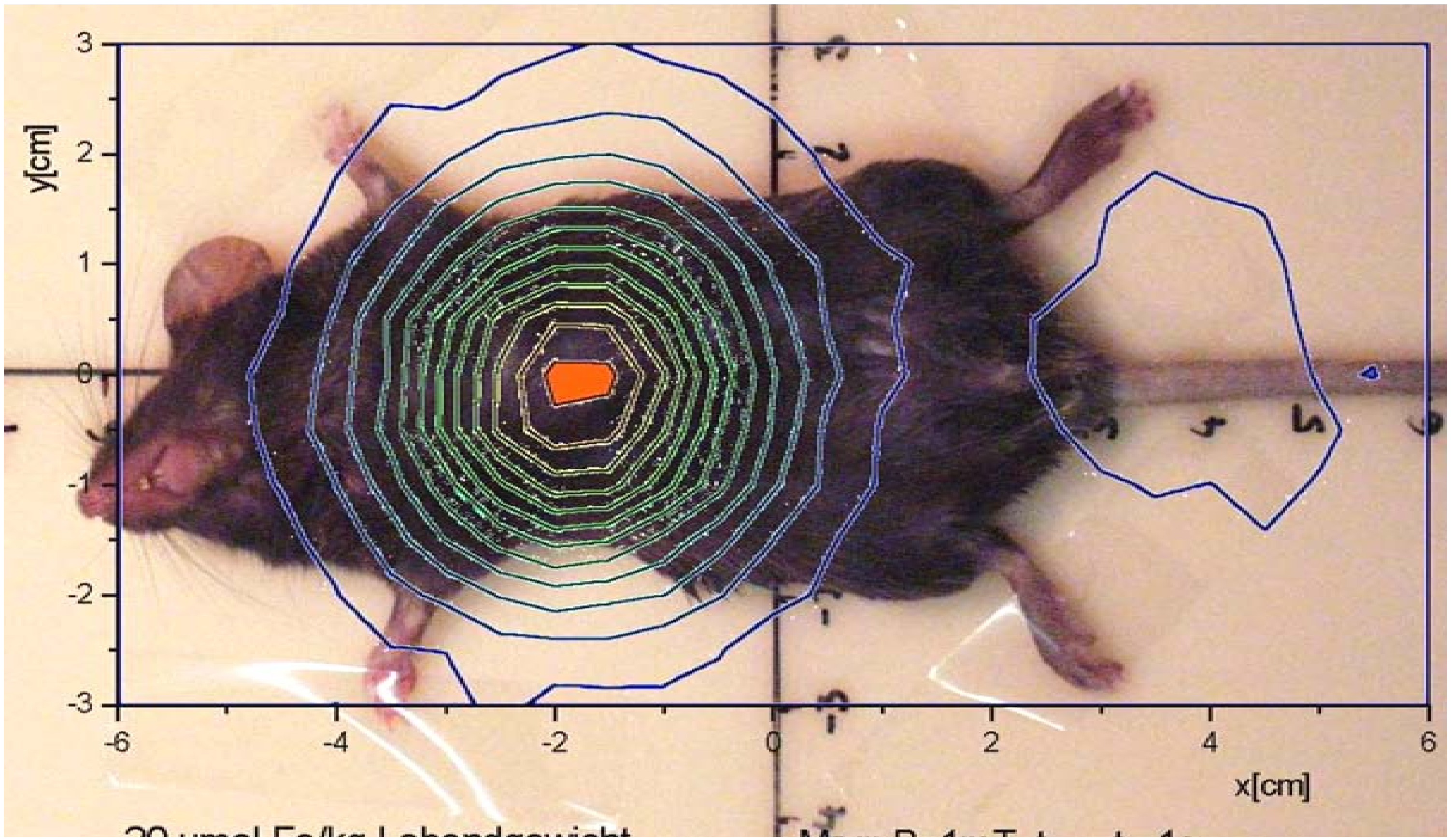


- ● specific antibody: anti-human-IgG-biotin
- ○ isotyp control: mouse-IgG-biotin

Lange et al. (2002) *J Magn Magn Mater*

MRX: Imaging

Magnetic fluid i.v.: 20 nmol Fe/g

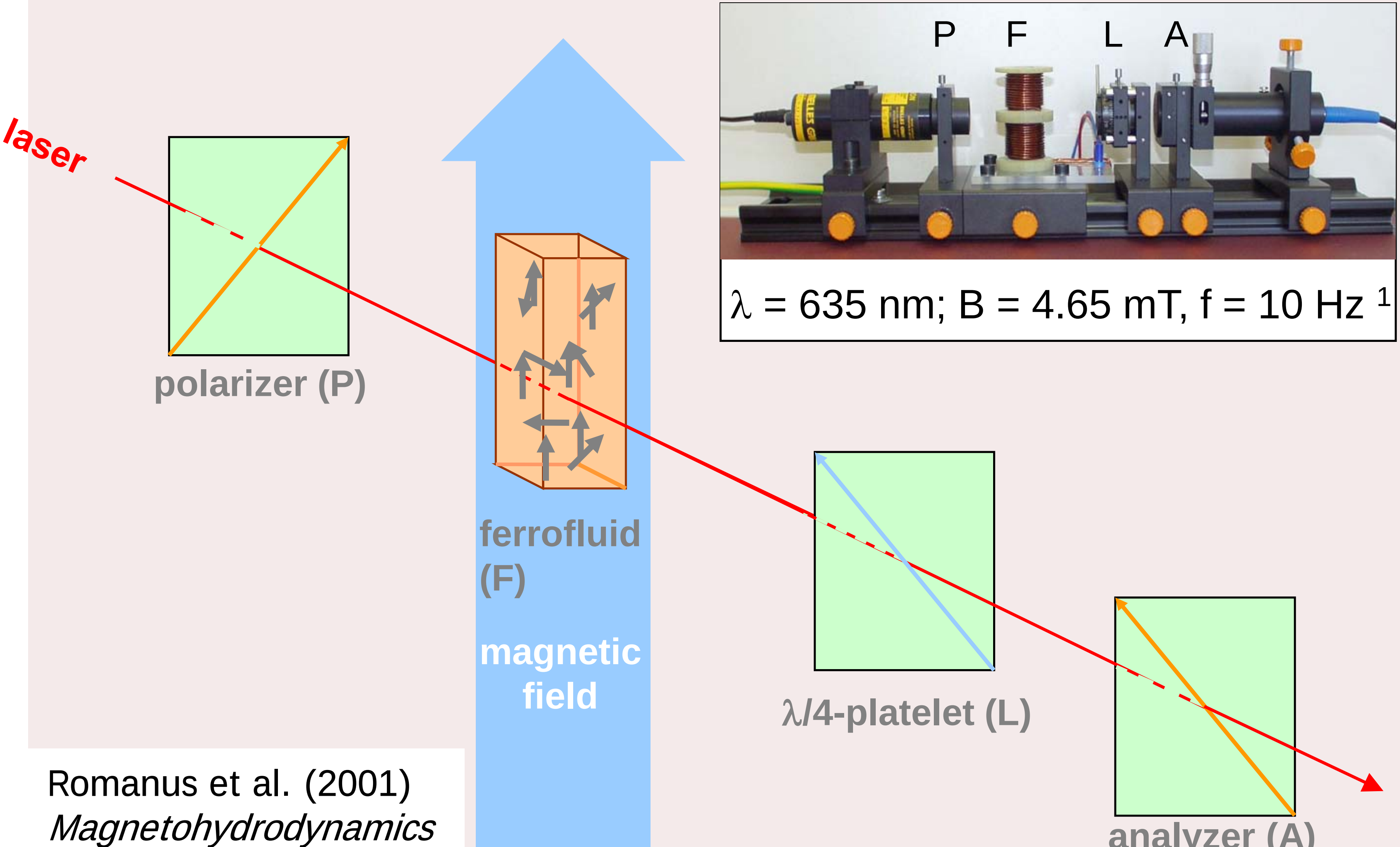


Romanus et al. (2002) *J Magn Magn Mater*

Diagnostic applications

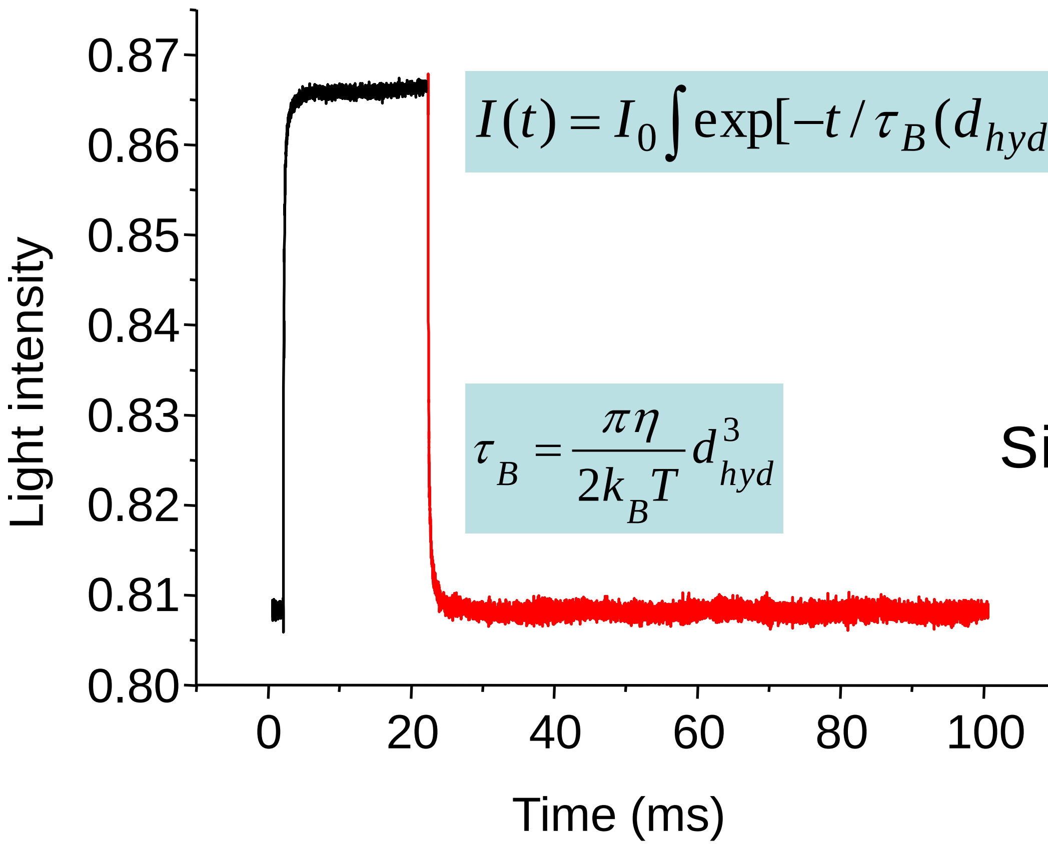
2. Magneto-optical relaxation (MORFF)

MORFF: Measurement setup



Romanus et al. (2001)
Magnetohydrodynamics

MORFF: Relaxation signal



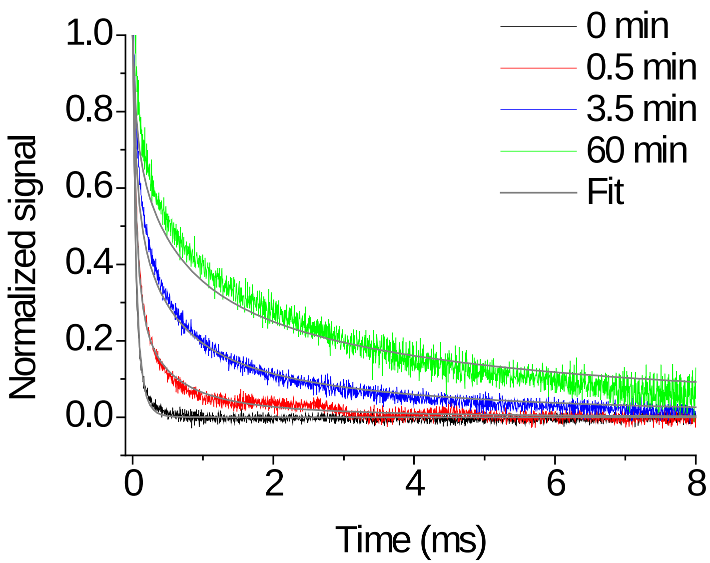
$$I(t) = I_0 \int \exp[-t/\tau_B(d_{hyd})] \cdot P(d_{hyd})\, \mathrm{d}d_{hyd}$$

$$\tau_B = \frac{\pi\eta}{2k_B T} d_{hyd}^3$$

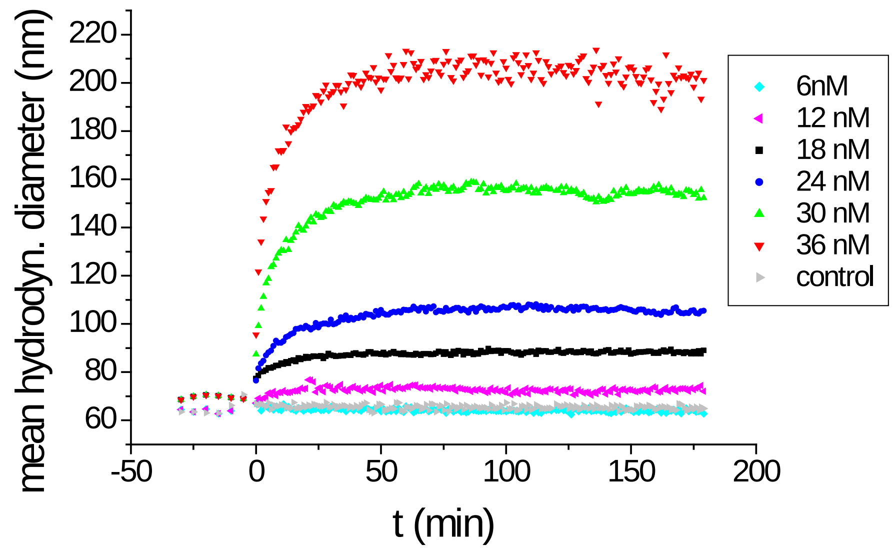
Size distribution

MORFF: Binding reaction

Incubation of 17 nM anti-human-Eotaxin-MNP with different amounts of human Eotaxin; control = 3 nM bovine serum albumin (BSA)



Relaxation curves after 0, 0.5, 3.5 and 60 min incubation with 36 nM Eotaxin



Change of mean aggregate size after incubation with varying amounts of Eotaxin

Aurich et al. (2007) *Anal Chem*

MORFF: Conclusion

Application for

- Characterization of particle size and size distribution
- Qualitative detection of biomolecular interactions
- Determination of kinetic properties in steady state

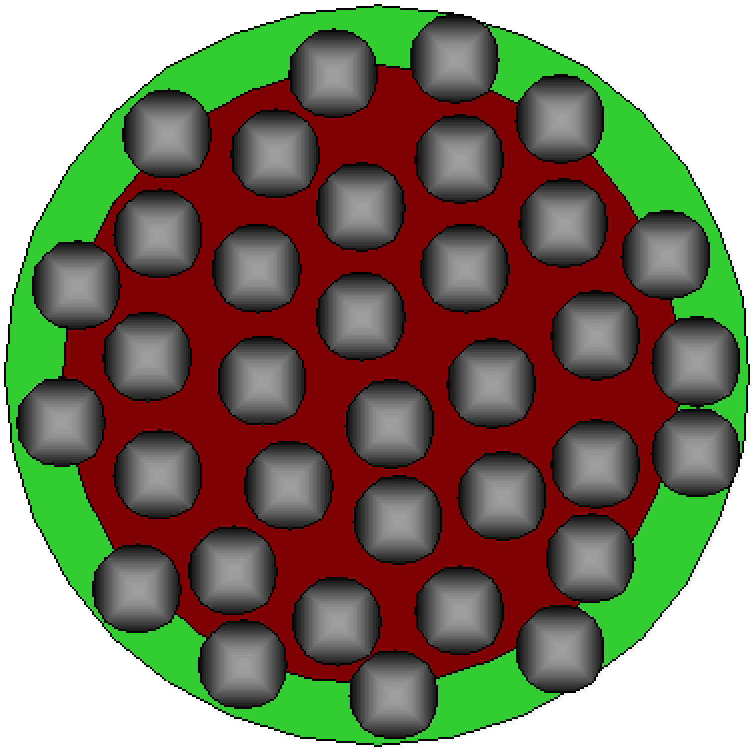
Outlook:

⇨ Improvement of sensitivity

Therapeutic applications

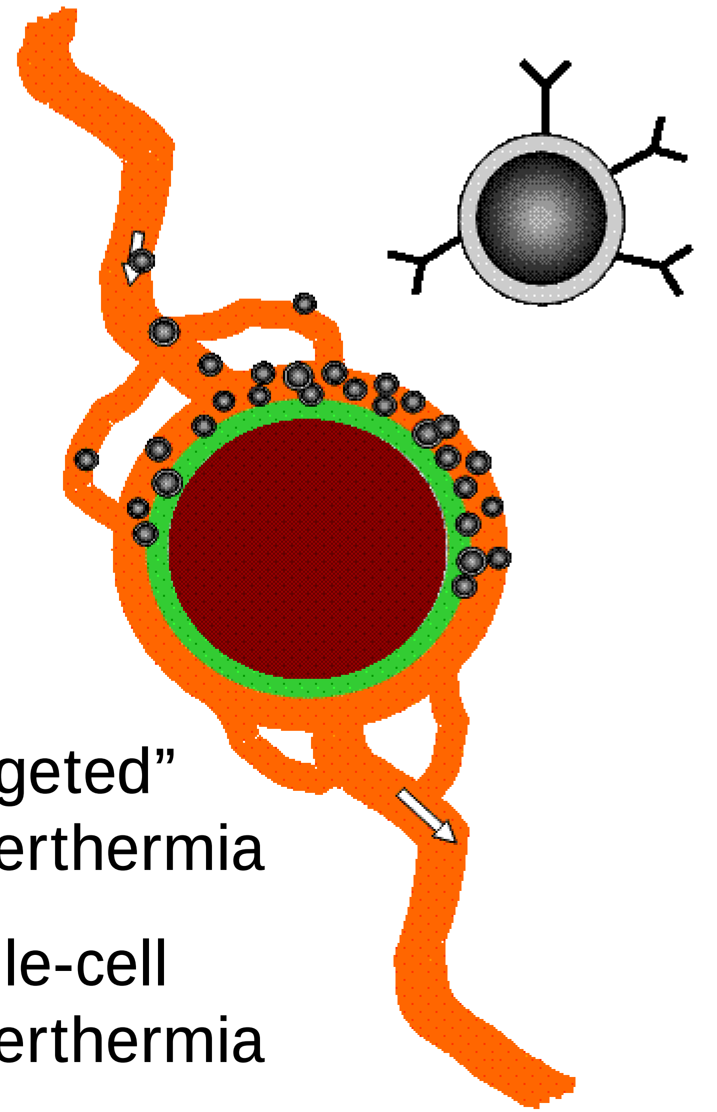
1. Magnetic hyperthermia

Hyperthermia: treatment modalities



direct-injection hyperthermia

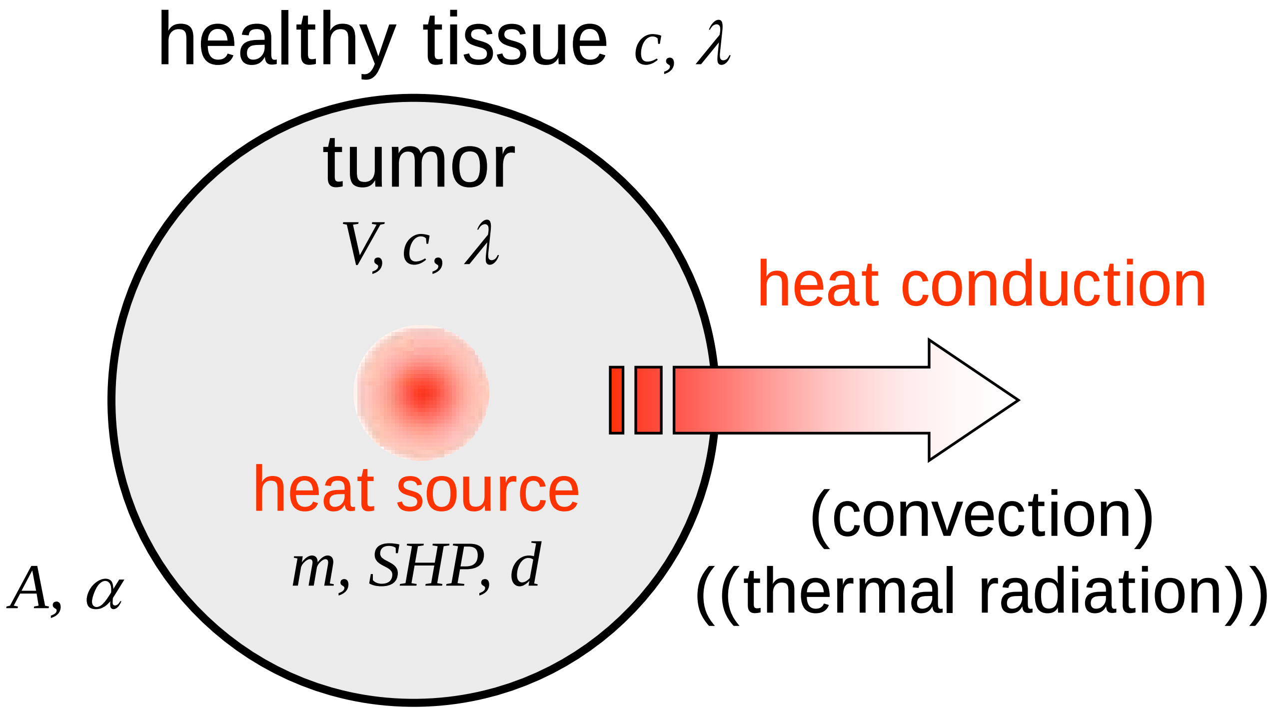
interstitial hyperthermia



“targeted” hyperthermia

single-cell hyperthermia

Heat distribution mechanisms



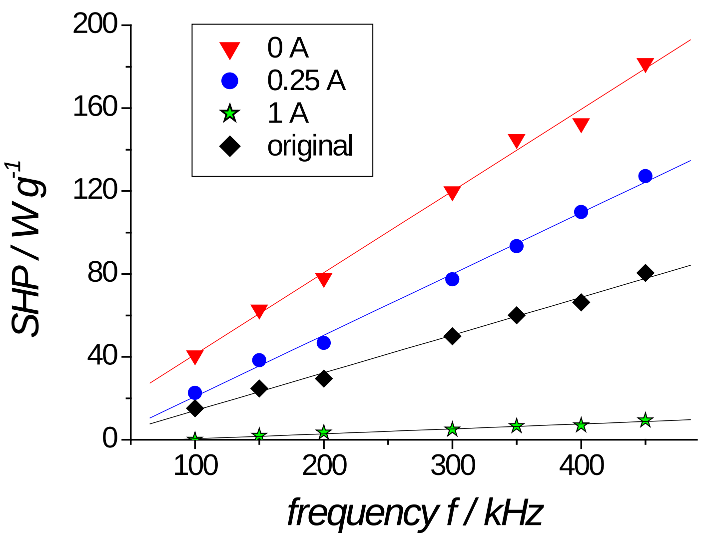
A – tumor surface area
α – heat-transmission coefficient
c – specific heat capacity
d – dimension

λ – thermal conductivity
m – mass
SHP – specific heating power
V – volume

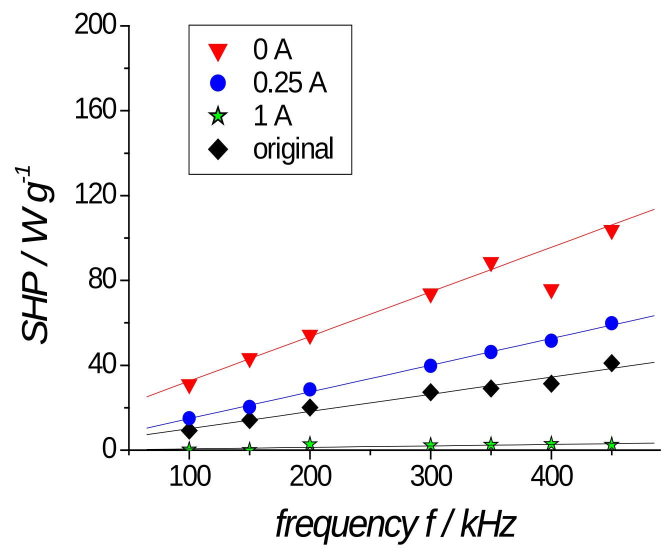
Frequency-dependent calorimetry

specific heating power *SHP* vs. frequency *f* @ 8 kA/m

particles suspended:
Brown & Néel



particles immobilized:
Néel only



⇨ linear dependency of SHP on frequency

⇨ reduction of SHP due to immobilization

Glöckl et al. (2006) *J Phys Condens Matter*

Hyperthermia - summary

- Heating power increases with:
  - particle core size
  - frequency
  - field amplitude
    - H^2 dependence with small particles
    - H^3 dependence with large particles
- Limitation *in vivo* (Brezovich)

$$H \cdot f \leq 5 \cdot 10^8 \frac{A}{m \cdot s}$$

- Large particles with maximum heating potential
  - superparamagnetism <> stable ferrimagnetism
  - hysteresis losses dominating at high amplitudes
- Higher heating power if particles are freely movable

Therapeutic applications

2. Magnetic drug targeting

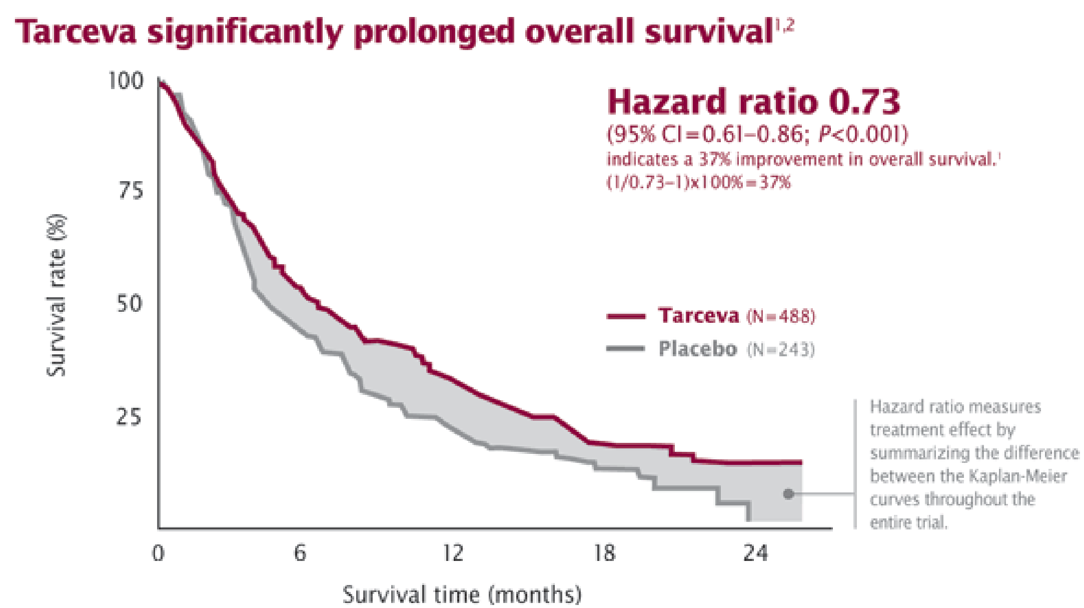
Non-small cell lung carcinoma (NSCLC)

- 3rd most common tumor disease in Germany
- in Germany more than 46.000 incidences per year
- poor 5-year survival prognosis
- in vitro effective drugs hardly show effect after systemic application

SATURN trial
(clinical phase III)

Median survival rate

- with Erlotinib 6.7 months
- with placebo 4.7 months



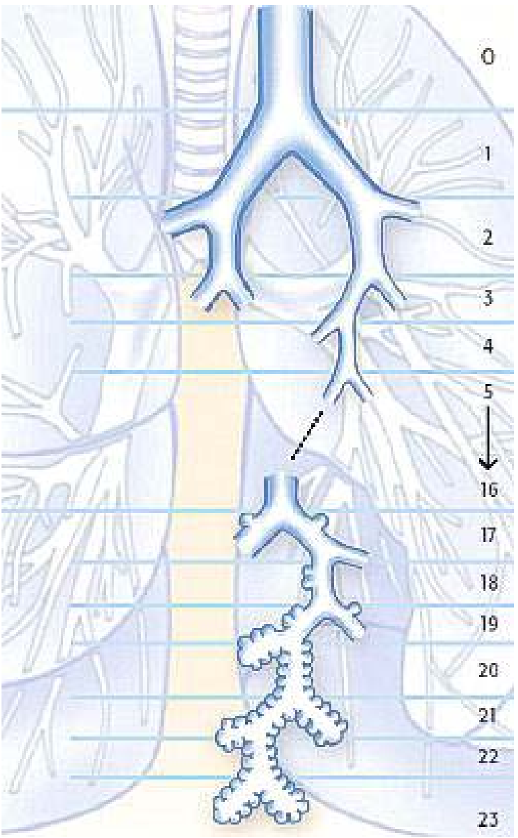
Non-small cell lung carcinoma (NSCLC)

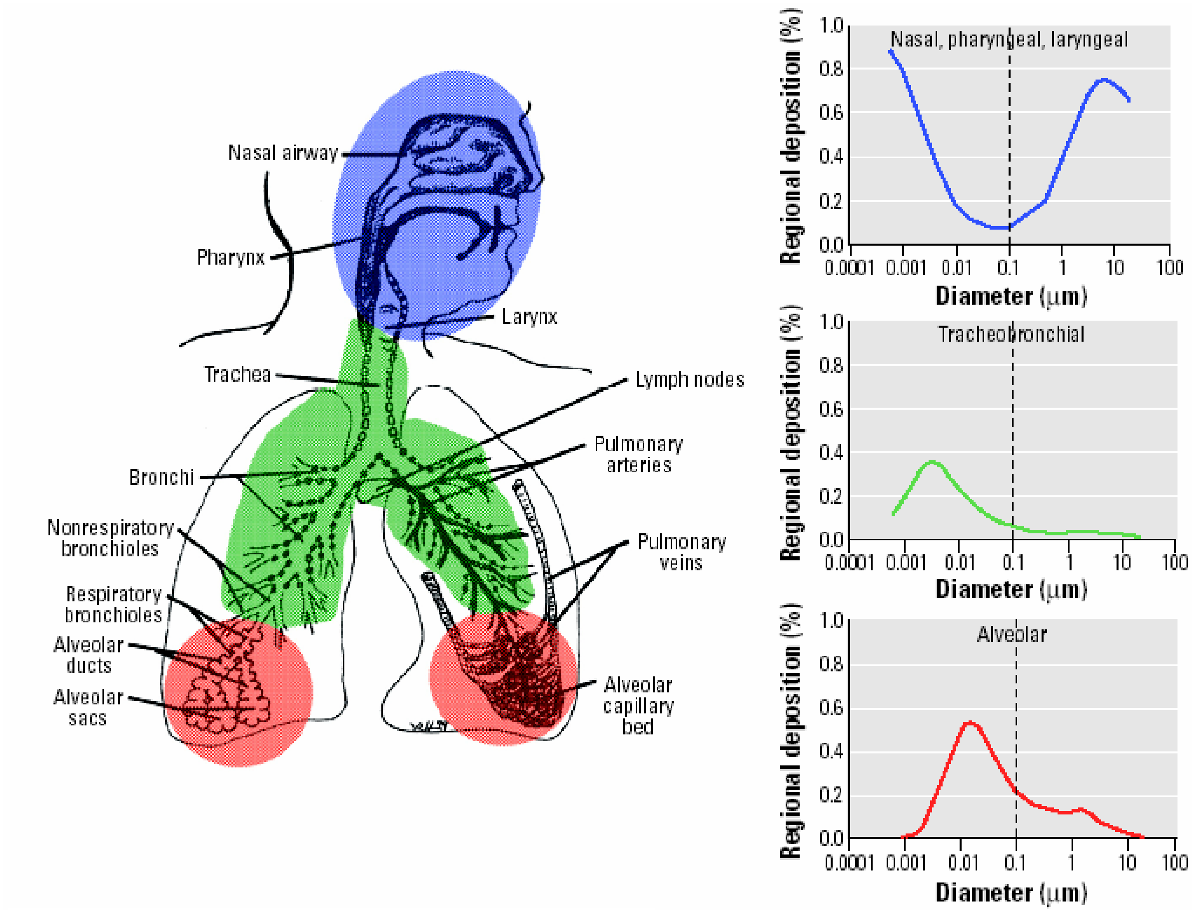
- 3rd most common tumor disease in Germany
- in Germany more than 46.000 incidences per year
- poor 5-year survival prognosis
- in vitro effective drugs hardly show effect after systemic application

Motivation:

- ➢ increase availability of drug in the tumor due to inhalation
- ➢ achieve effective drug doses in diseased lung regions by means of magnetic deposition
- ➢ reduce systemic exposure

Particle deposition

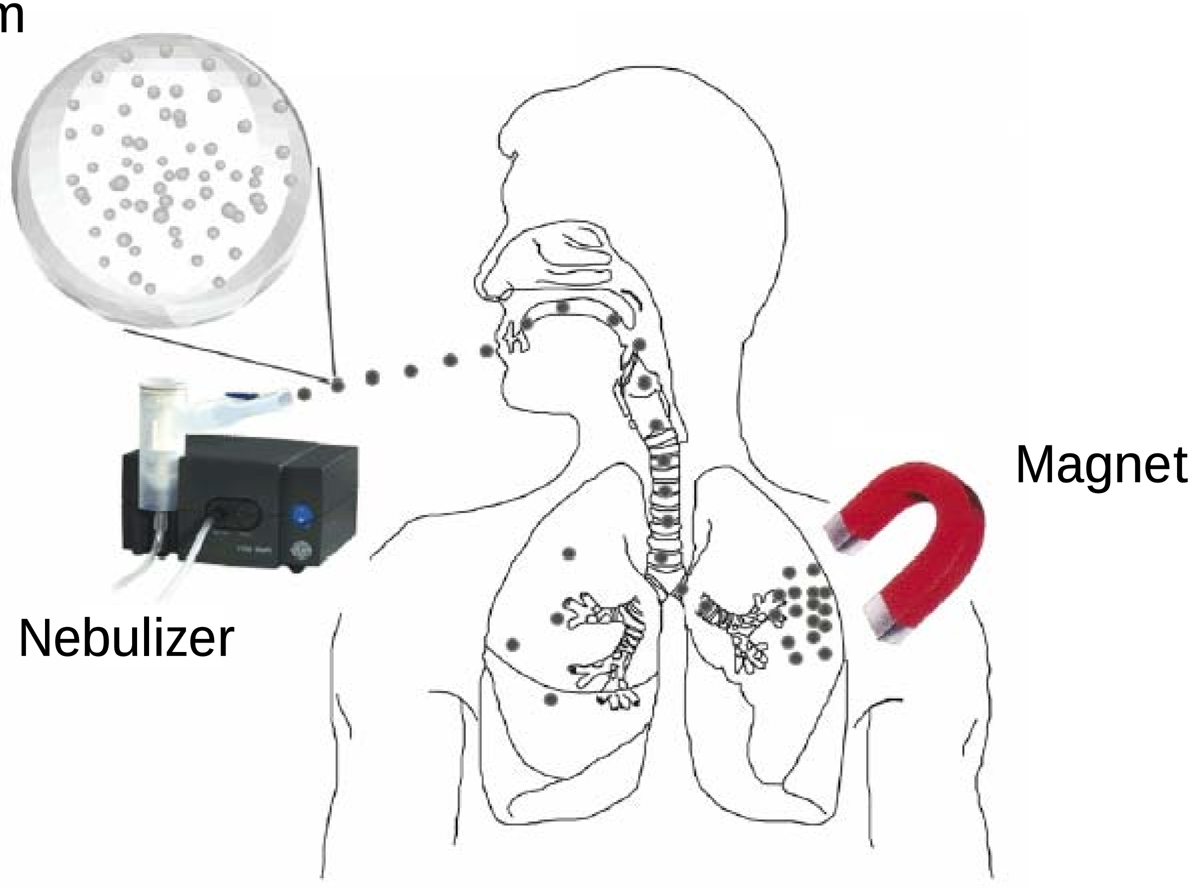




G. Oberdöster (2005), Environmental Health Perspectives

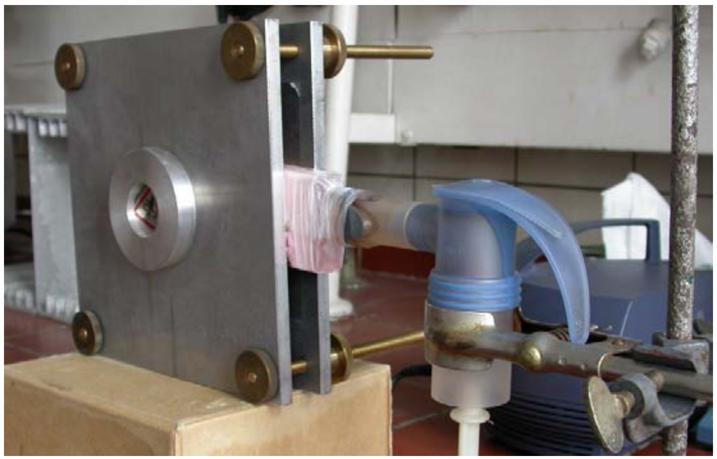
Concept

Aerosol droplets <1µm containing MNP and cytostatic drug



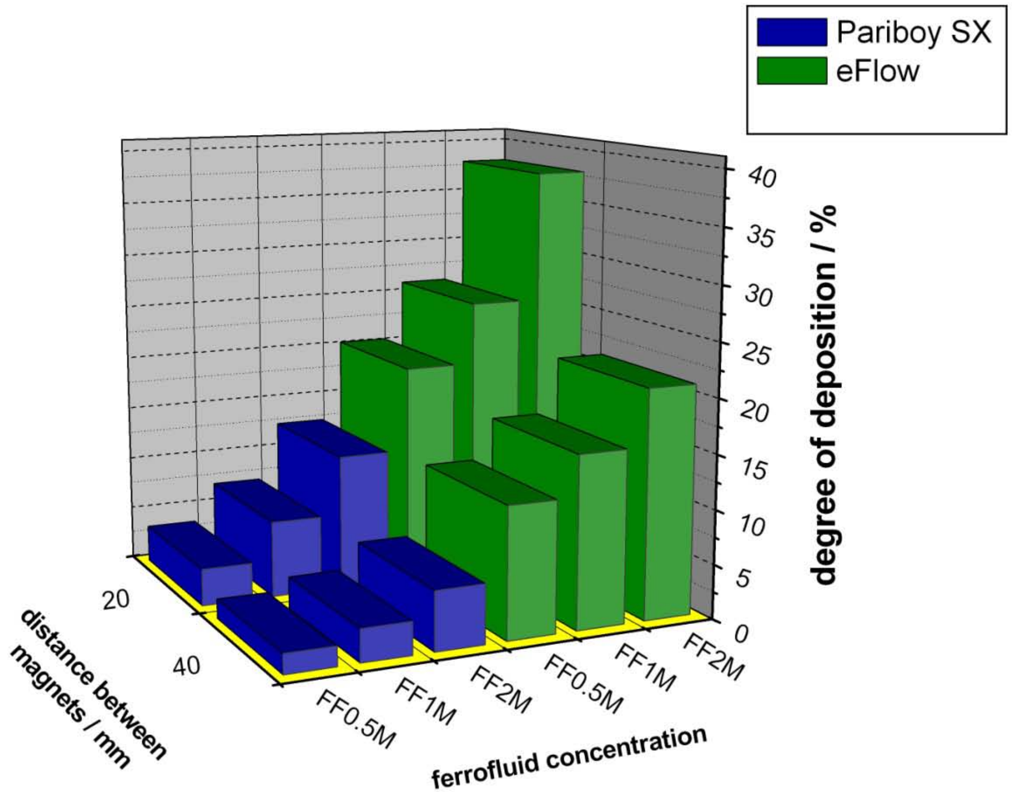
Targeted delivery of magnetic aerosol droplets. C. Plank (2008) ,Trends Biotech.

Magnetic deflection



Experimental Setup:

- square tube (5 x 2 cm) between two opposing circular disc magnets
- walls covered with paper
- ~ 50 mg iron sprayed into the tube
- iron content quantified by flame atomic absorption spectrometry



Degree of deposition after atomization of 0.5M, 1M and 2M ferrofluid with different nebulizer and at varying distances between the magnetic poles.

What are we looking for? *demand*

- control of size and shape
- REPRODUCIBILITY
- monodispersity ☺
- coating with access to chemical modification
- biocompatibility
- stability against aggregation *in vivo*

Thank you!

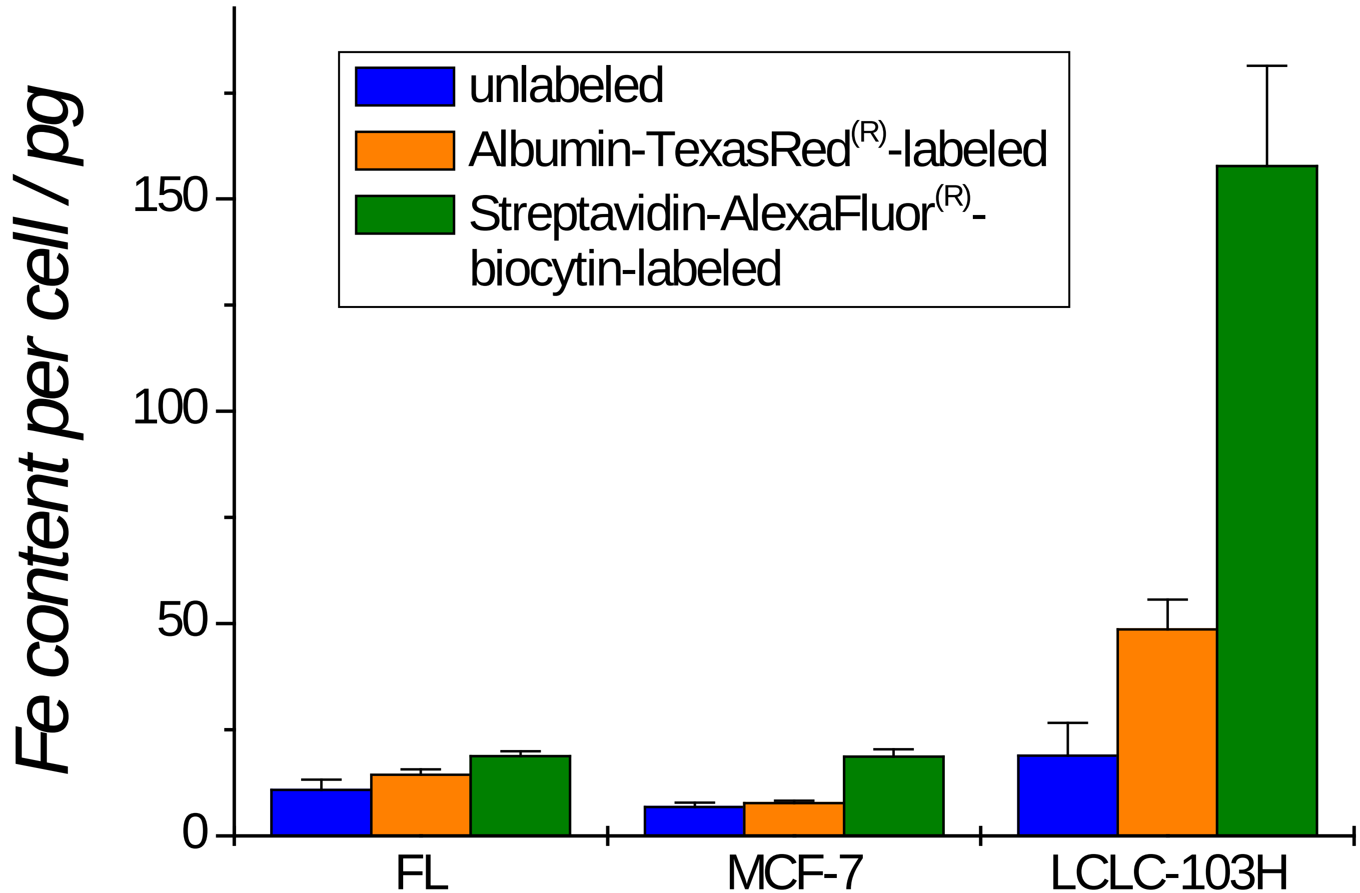
S. Nagel, K. Aurich, R. Baumann

C. A. Helm, M. Gopinadhan

E. Romanus, S. Prass, P. Weber, F. Schmidl

Deutsche Forschungsgemeinschaft

Cellular nanoparticle uptake *in vitro*

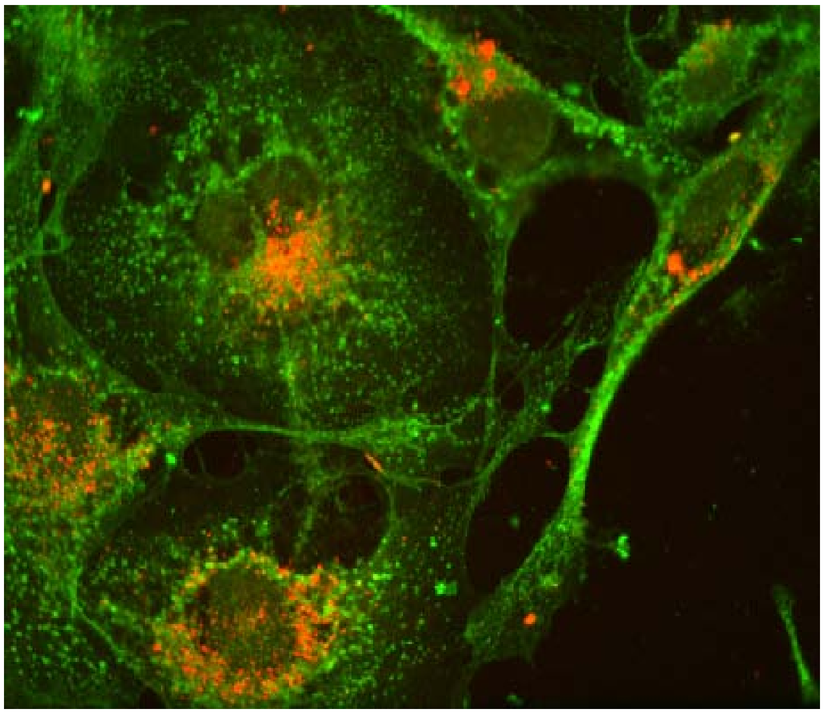


adherently growing cells incubated with 10 mM (Fe) MNP with different coatings for 30 min; Fe content determined by graphite furnace AAS

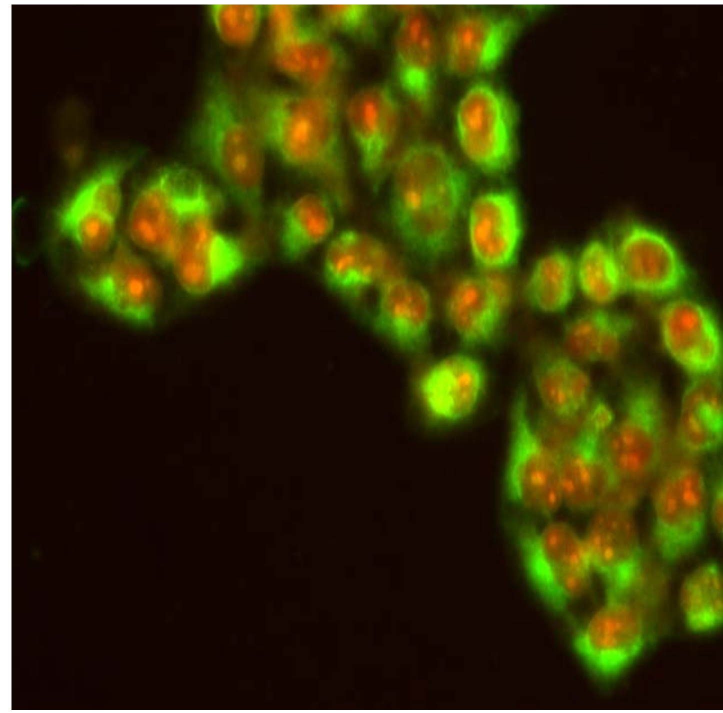
Intracellular localization

Confocal Laser Scanning Microscopy (CLSM)

red: Particle label; green: Oregon Green®-DHPE-counterstain



large cell lung carcinoma cells (LCLC-103H); red: Alexa Fluor®-biocytin-streptavidin-MNP



fibroblast-like cells (FL); red: Albumin-TexasRed®-labeled MNP

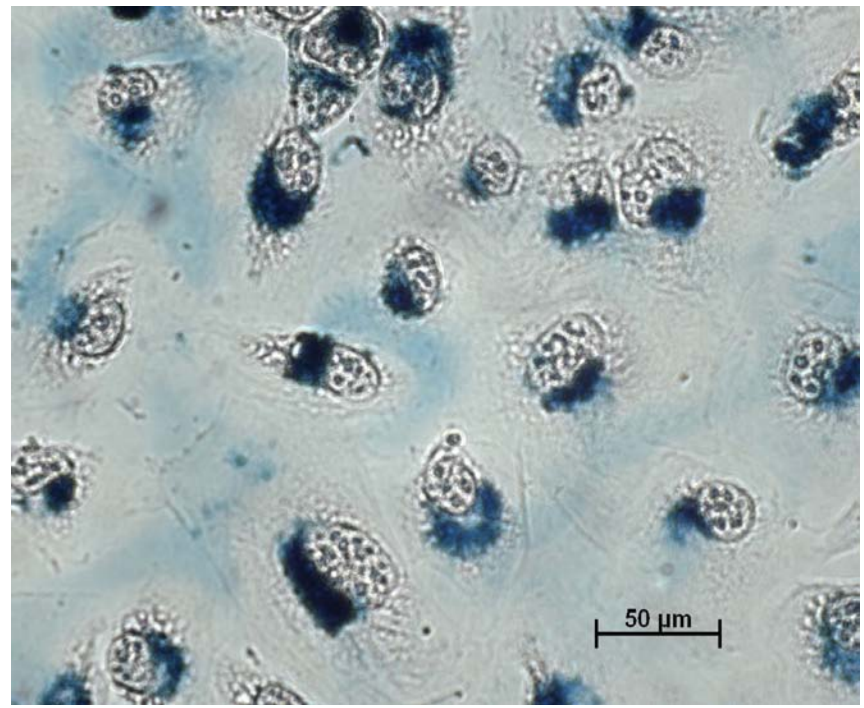
Histologische Eisenfärbung

$$4\,Fe^{3+} + 3\left[Fe^{II}(CN)_6\right]^{4-} \longrightarrow Fe^{III}\left[Fe^{III}Fe^{II}(CN)_6\right]_3$$

1.) Fixierung in HCHO
   - (1% in EtOH 96%, 30 min)

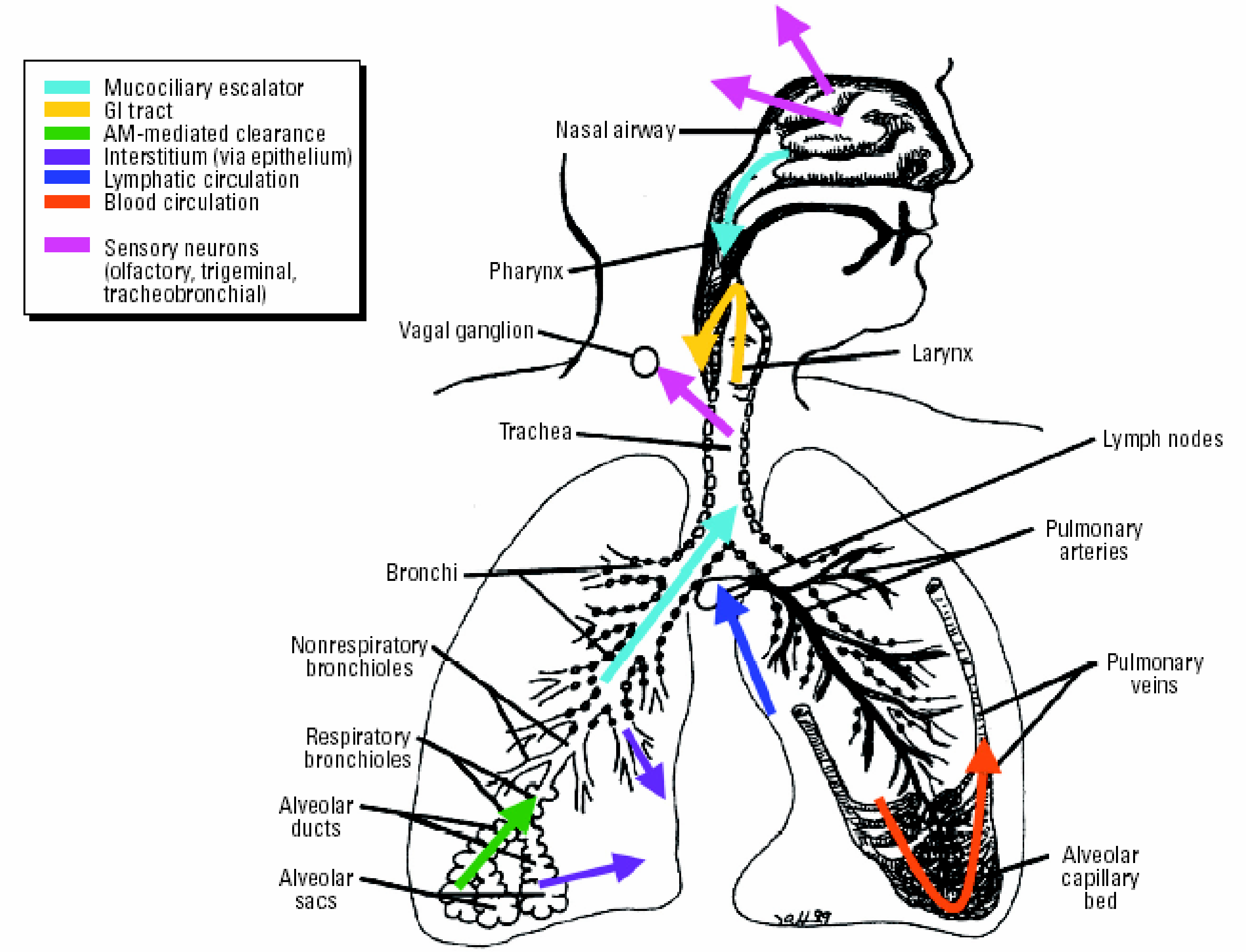
2.) Spülen mit PBS

3.) 20% HCl + 10% $K_4[Fe(CN)_6]$
   - (1:1-Mischung, 30 min)



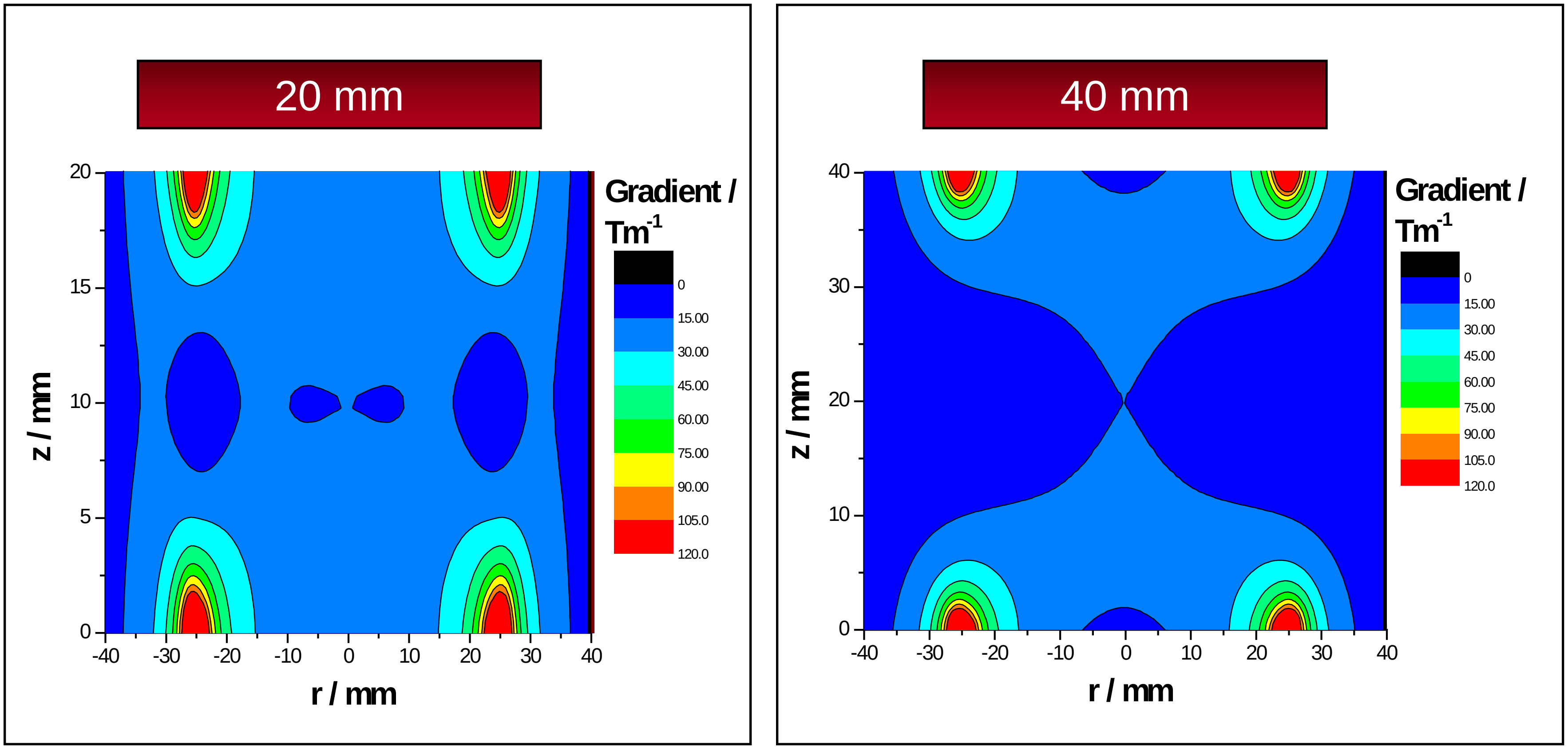
LCLC-Zellen 1 Tag nach Inkubation mit Nanopartikeln (0 A-Fraktion, 1 mM Fe)

Pulmonary clearance



G. Oberdöster (2005), Environmental Healt Perspectives

Magnetic fields



Gradient maps of two opposing circular disc magnets at a distance of 20 mm (left) and 40 mm (right).