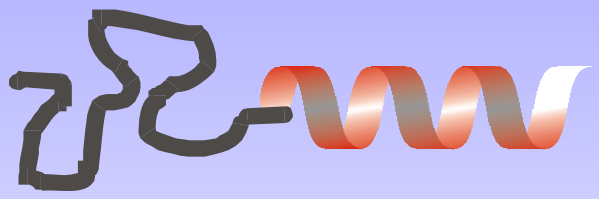
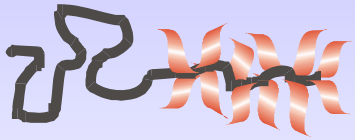
Part 2: Chimera-Surfactants:

hybrids between synthesis and biology



biology

synthetic chemistry



Biological fragments from:

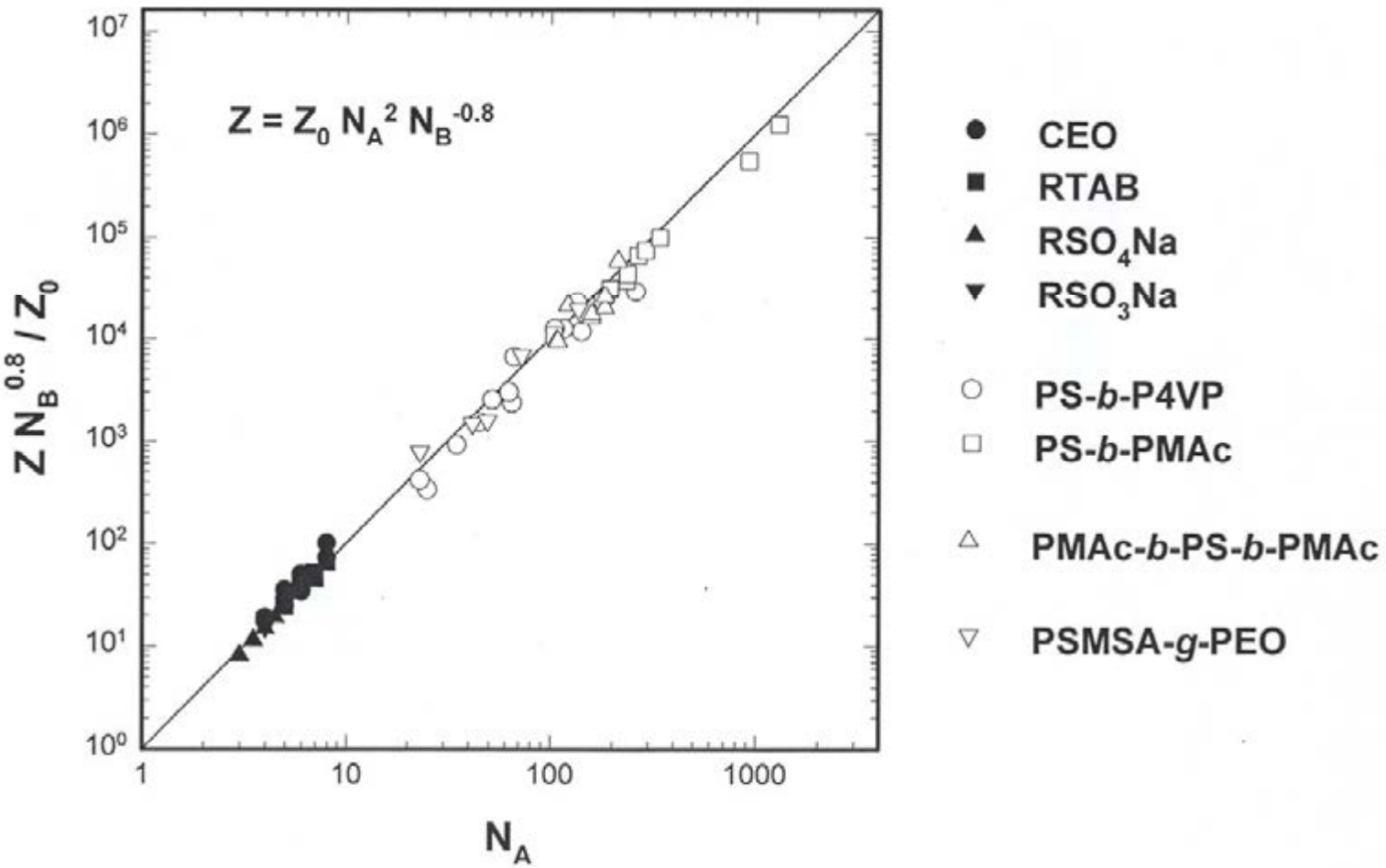
o peptide polymerization

o de novo peptides

o (biological fragments)

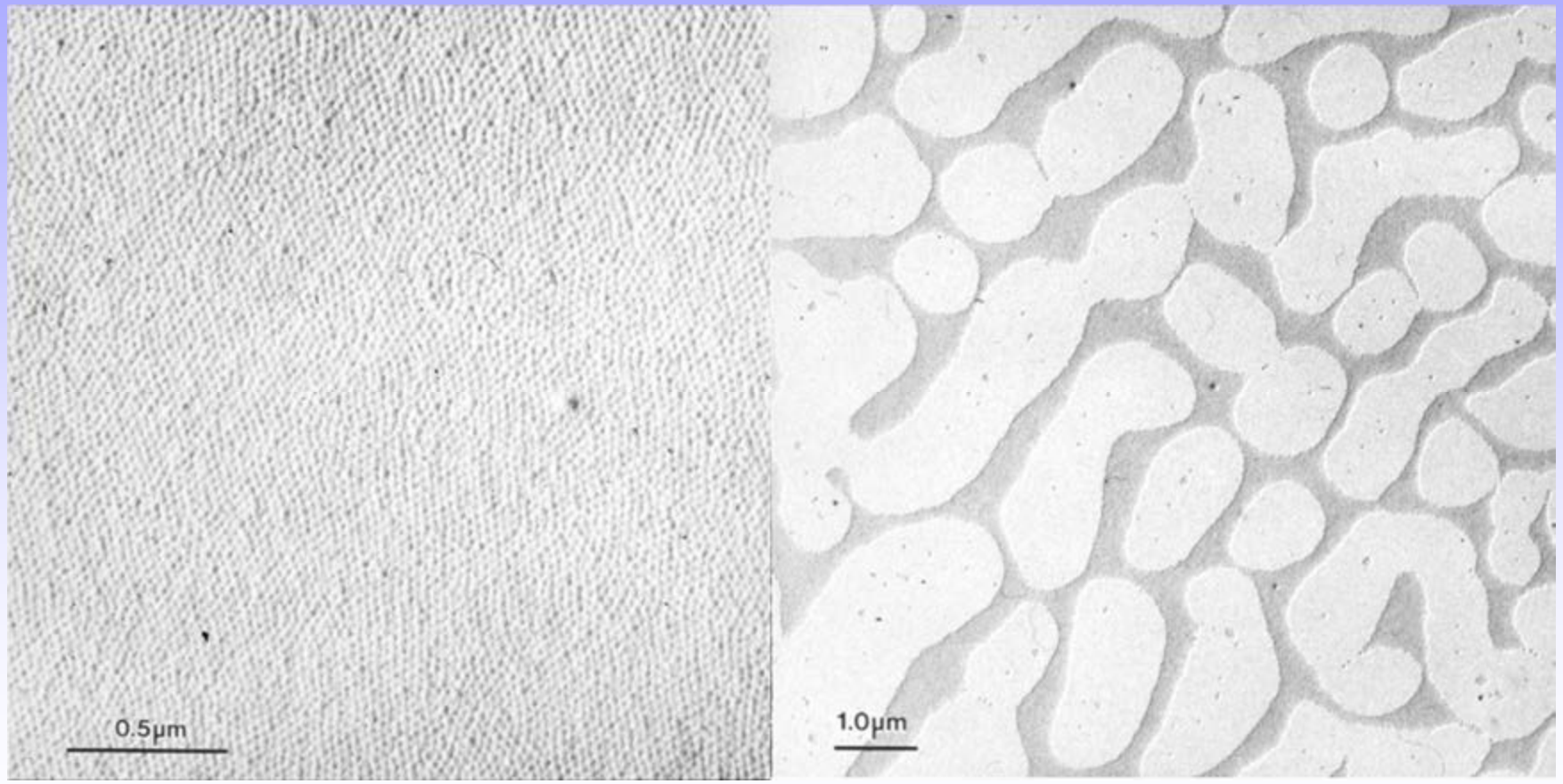
o (biotechnology)

Size can be rationally controlled

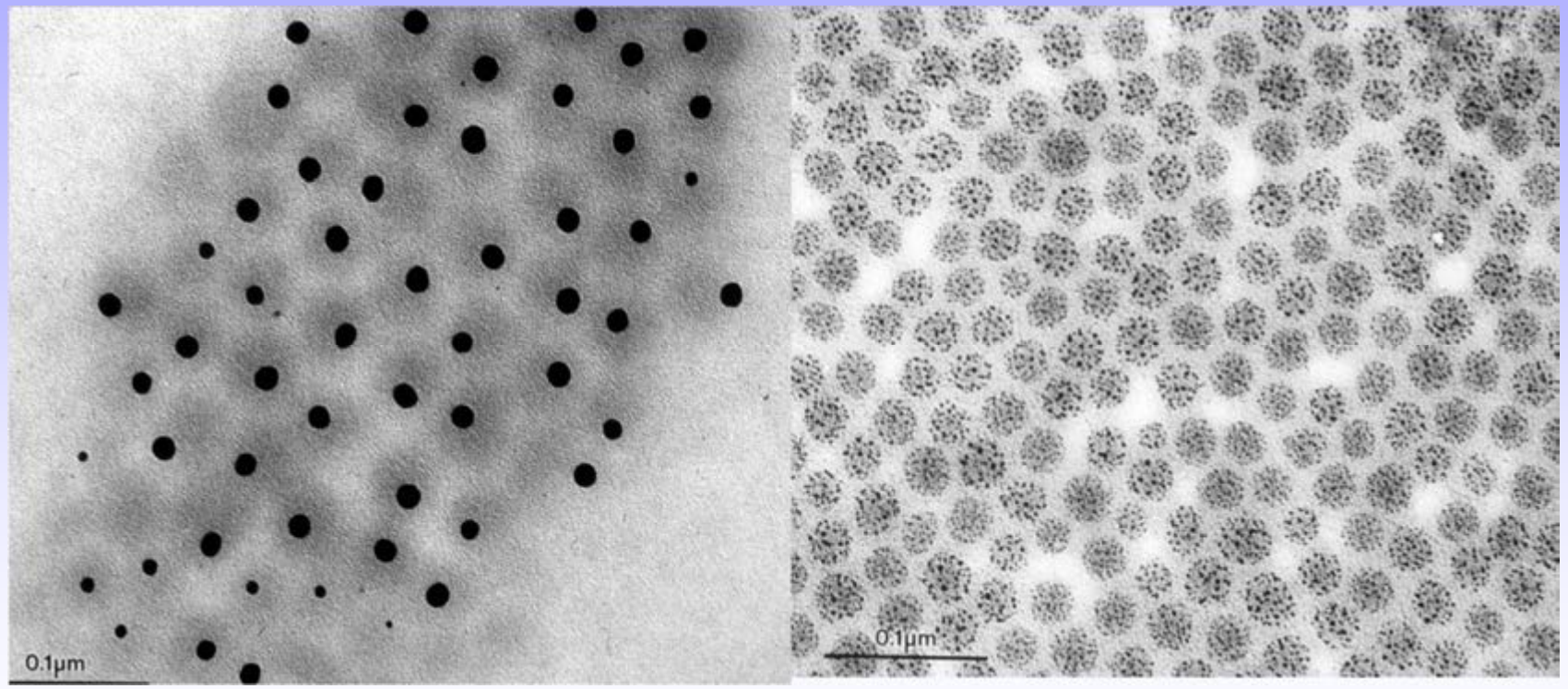


S. Förster S et al, J.Chem.Phys. **1996**, *104*, 9956-9970

Homogeneity of ABC micelles



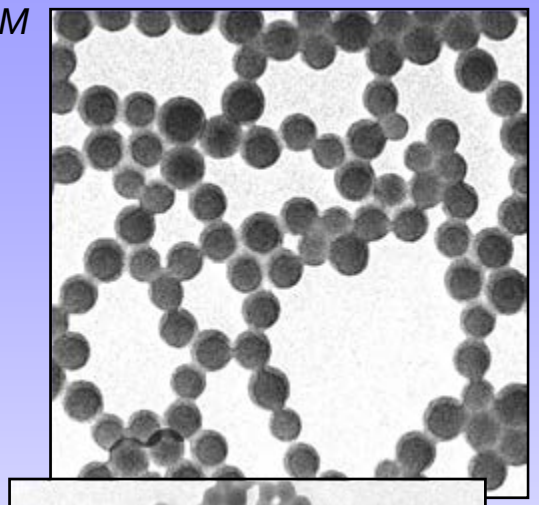
Use of polymer micelles as carriers

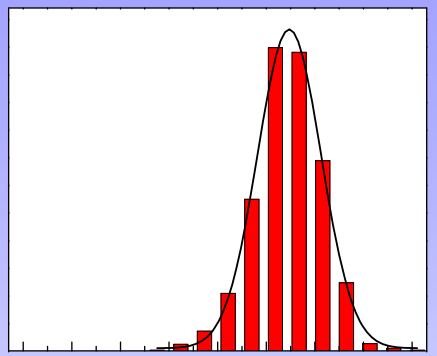


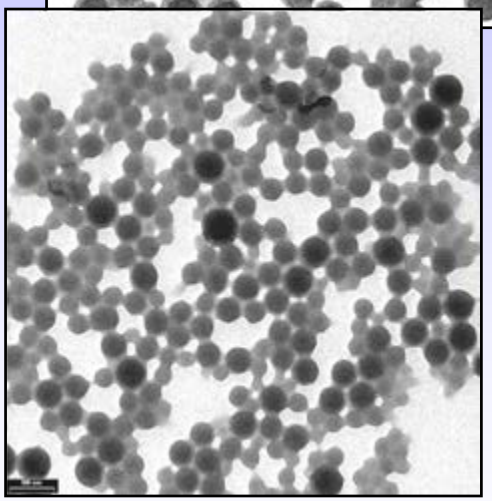
Au or Pt-loaded micelles

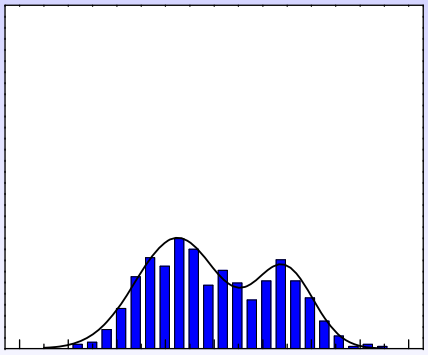
Chimera-stabilized Polymer Latexes

TEM

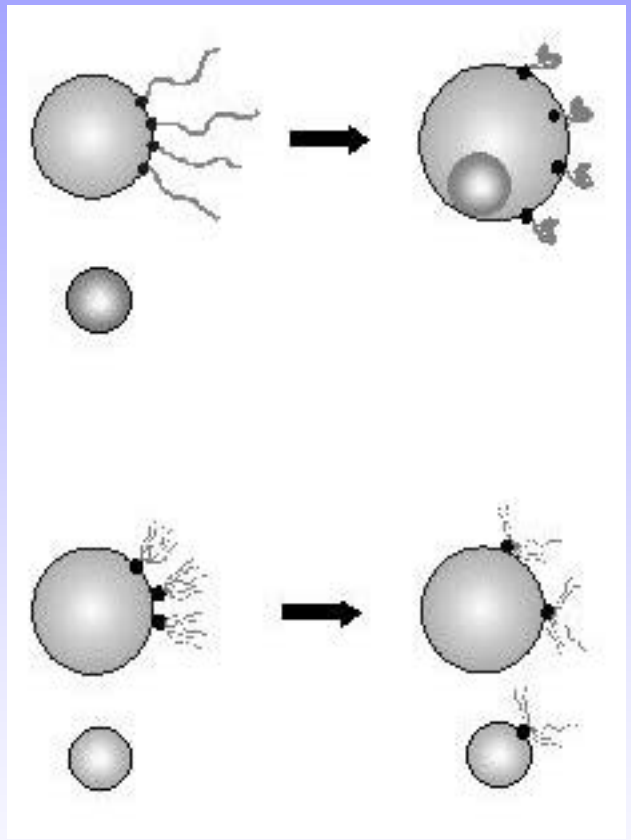








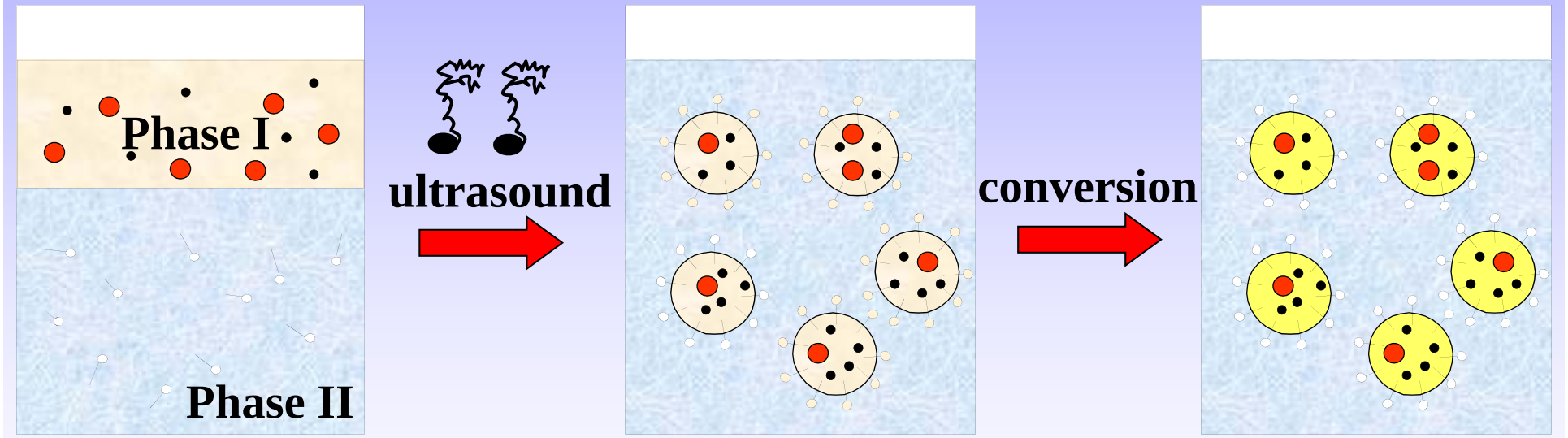
100 nm



H. Kukula, H. Schlaad, K. Tauer, *Macromolecules* **2002**, *35*, 2538.

Part 3: Nano- or Miniemulsions: Convenient synthesis of amorphous/ loaded nanoparticles

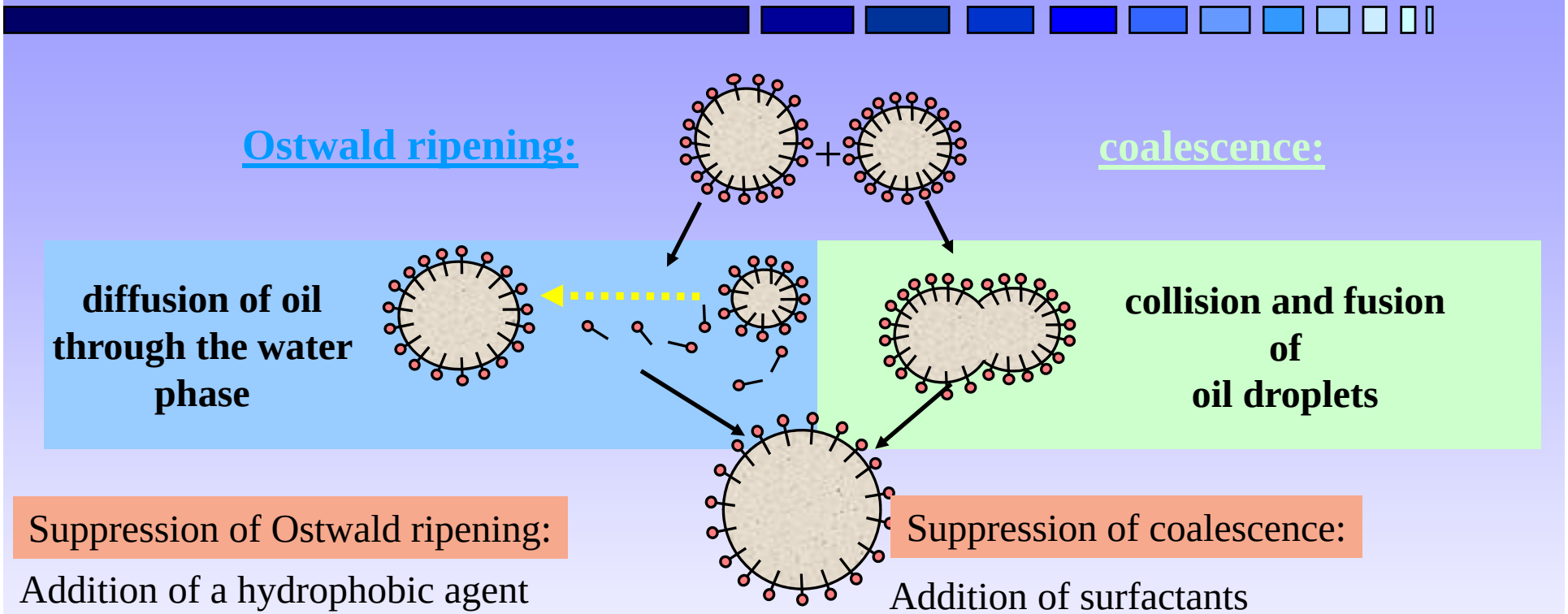
Miniemulsion process



stable nanodroplets
50-500 nm

1:1 copy
(nanoreactor)

Growth of droplets

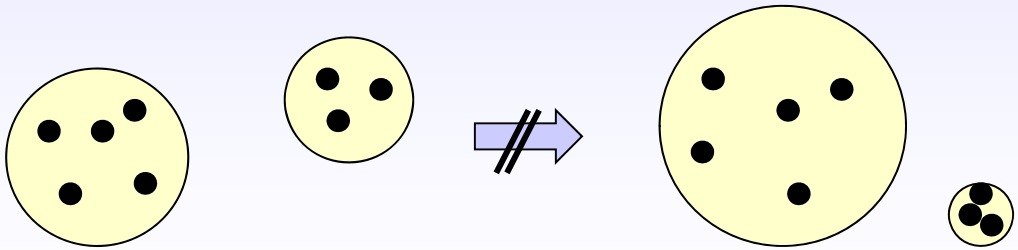


Suppression of Ostwald ripening:

Addition of a hydrophobic agent with very low water solubility:

Suppression of coalescence:

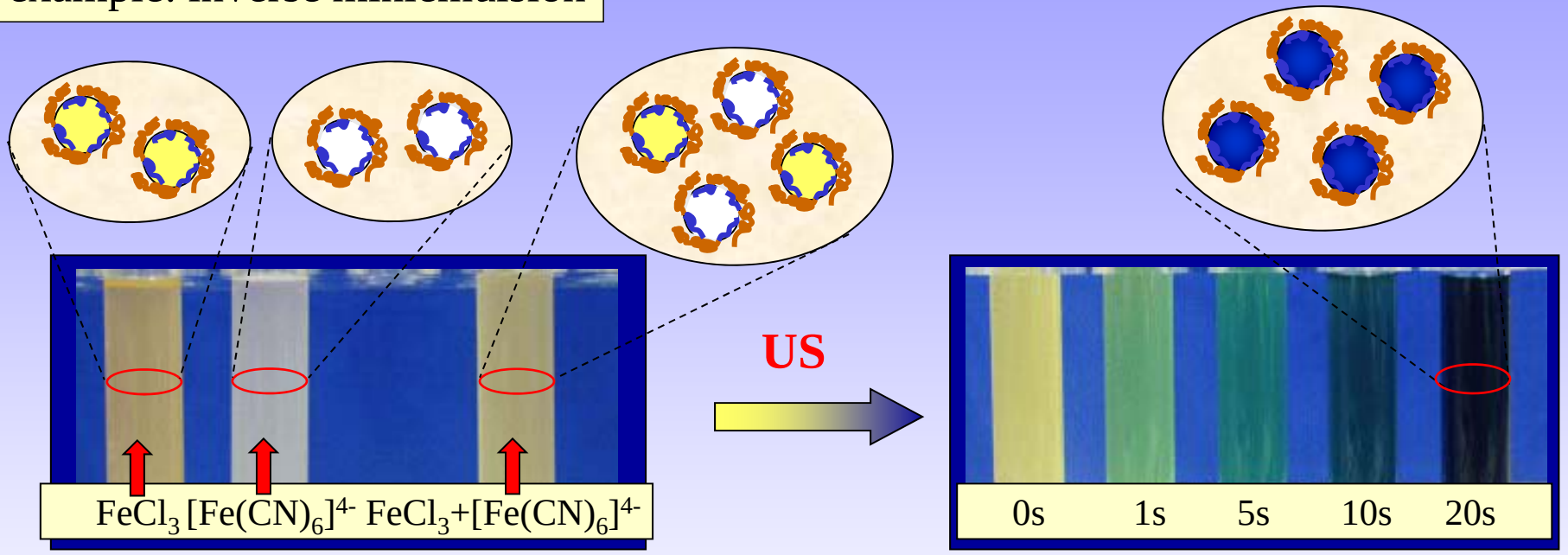
Addition of surfactants



Force: OSMOTIC pressure versus LAPLACE pressure

Stability of nanodroplets

example: inverse miniemulsion



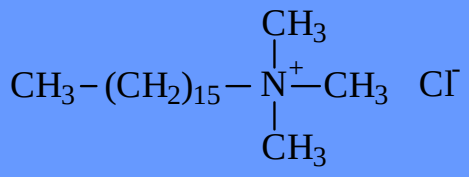
mixing of 2 miniemulsions

by ultrasound:
forced fusion and fisson

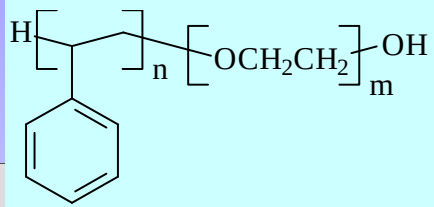
Surfactants for the formulation of miniemulsions

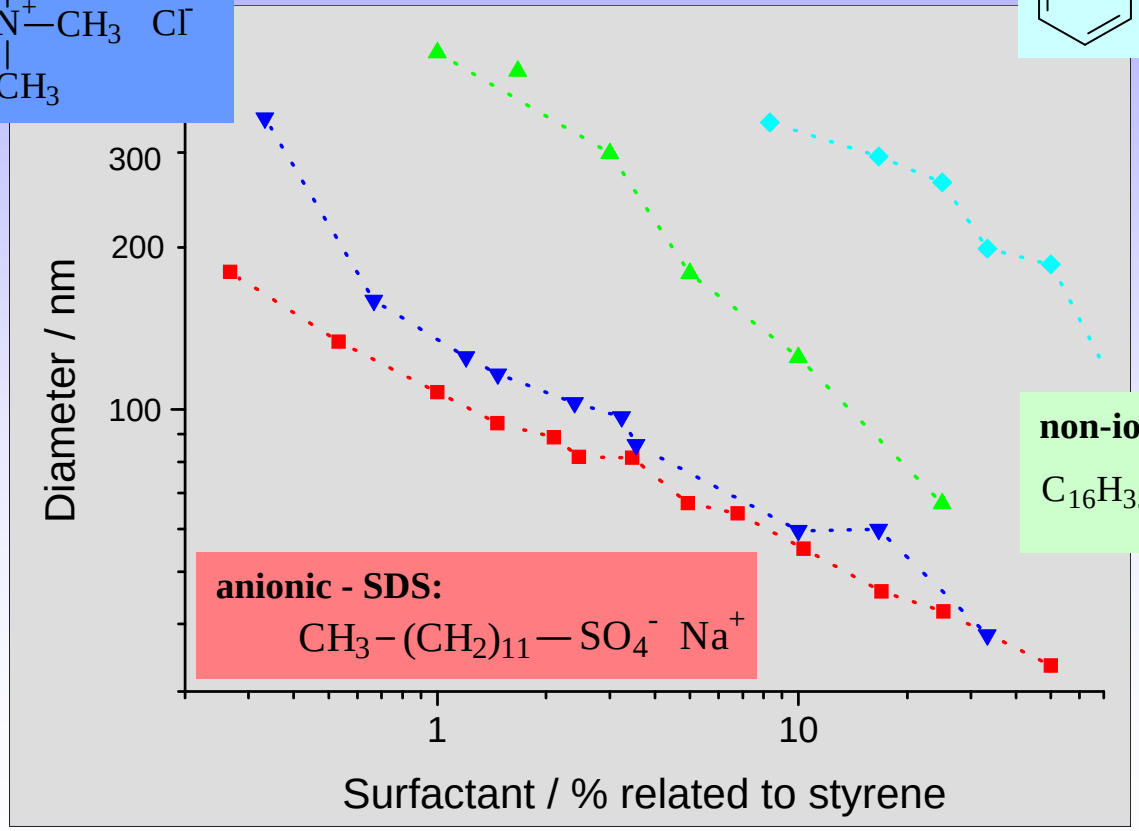
Particle size is governed by the type and amount of the surfactant

cationic - CTMA-Cl:



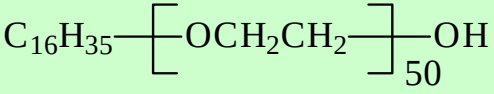
polymer - SE3030:





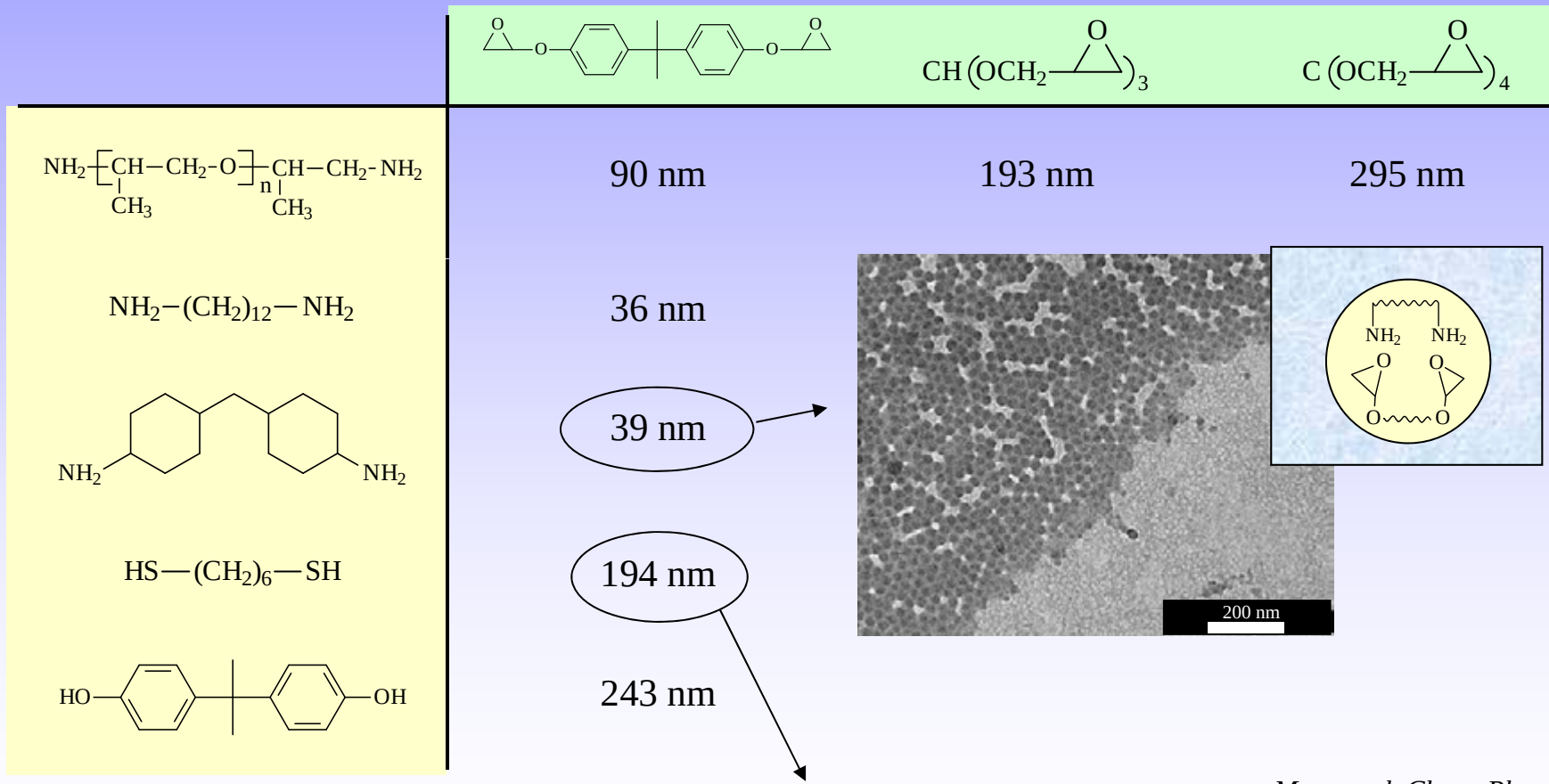
anionic - SDS:

non-ionic- Lutensol AT50:



miniemulsions: low coverage of the droplets by surfactant

New polymer reactions in dispersion: Polyaddition

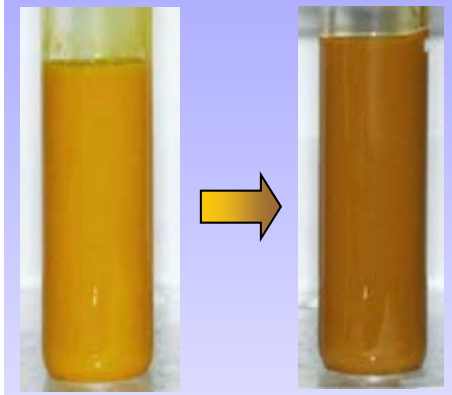


M_w = 20 000 g mol^{-1}

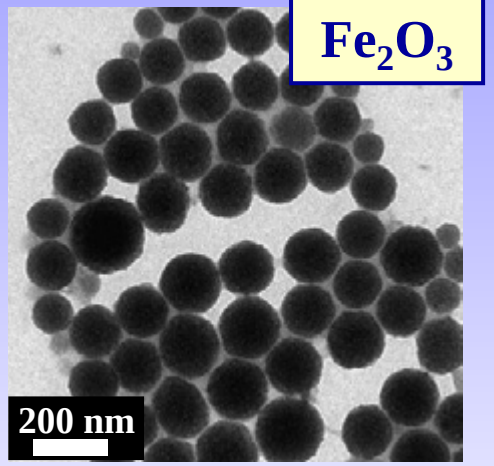
Macromol. Chem. Phys. **2000**, *201*, 1-5.

Reactions of miniemulsified salts to pigments and ferrofluids

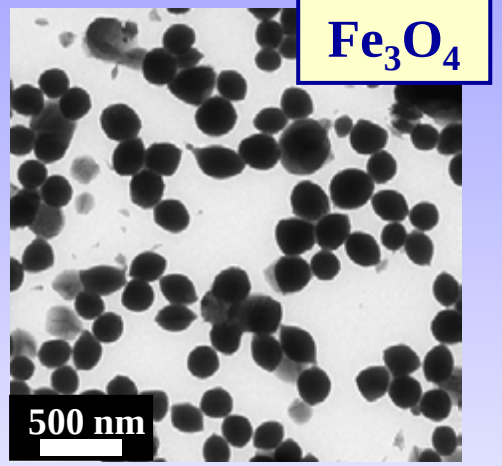
Fe_2O_3 from $FeCl_3$



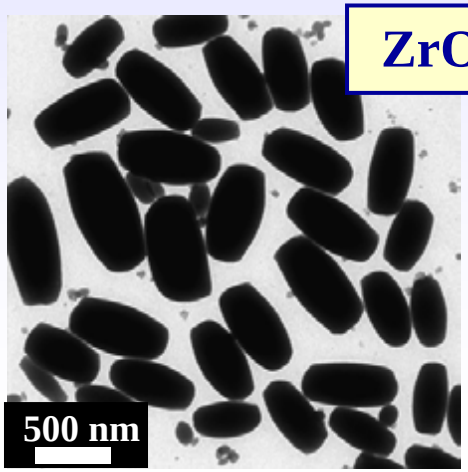
$FeCl_3$ Fe_2O_3



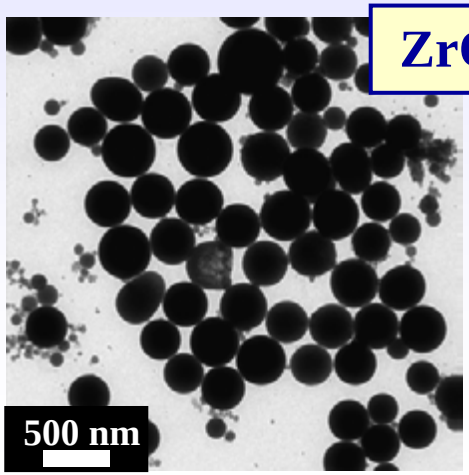
Fe_3O_4 from $FeCl_2/FeCl_3$



ZrO_2 from $ZrOCl_2$



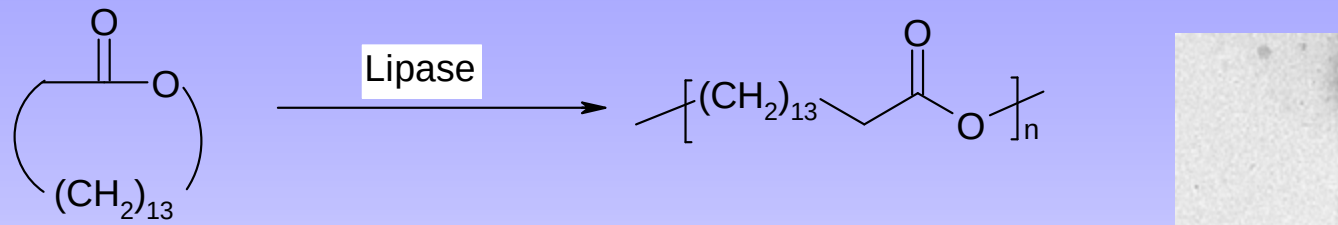
Base

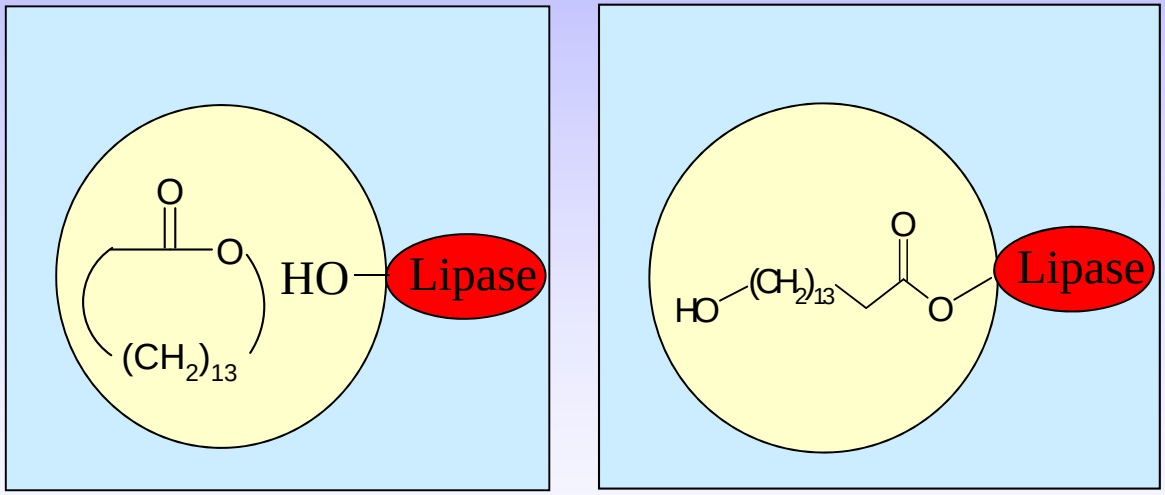


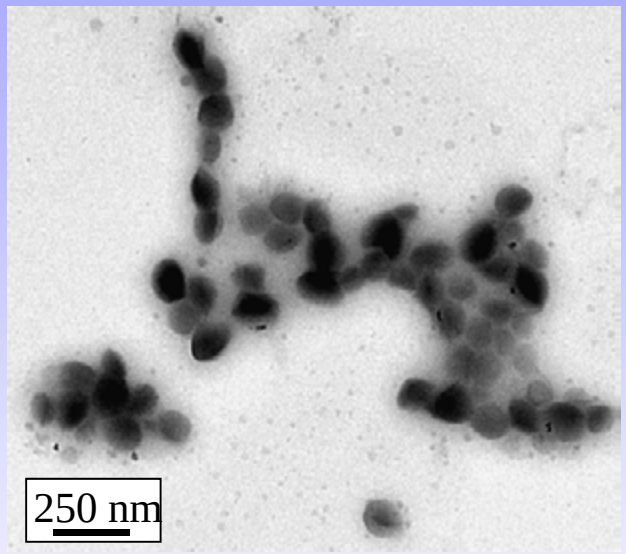
M. Willert, R. Rothe, K. Landfester, M. Antonietti, *Chem. Mater.* **2001**, *13*, 4681-4685.

Enzymatic Reactions in Miniemulsions

Simple access to polyesters, high value fat derivatives, biodegradable ABCs



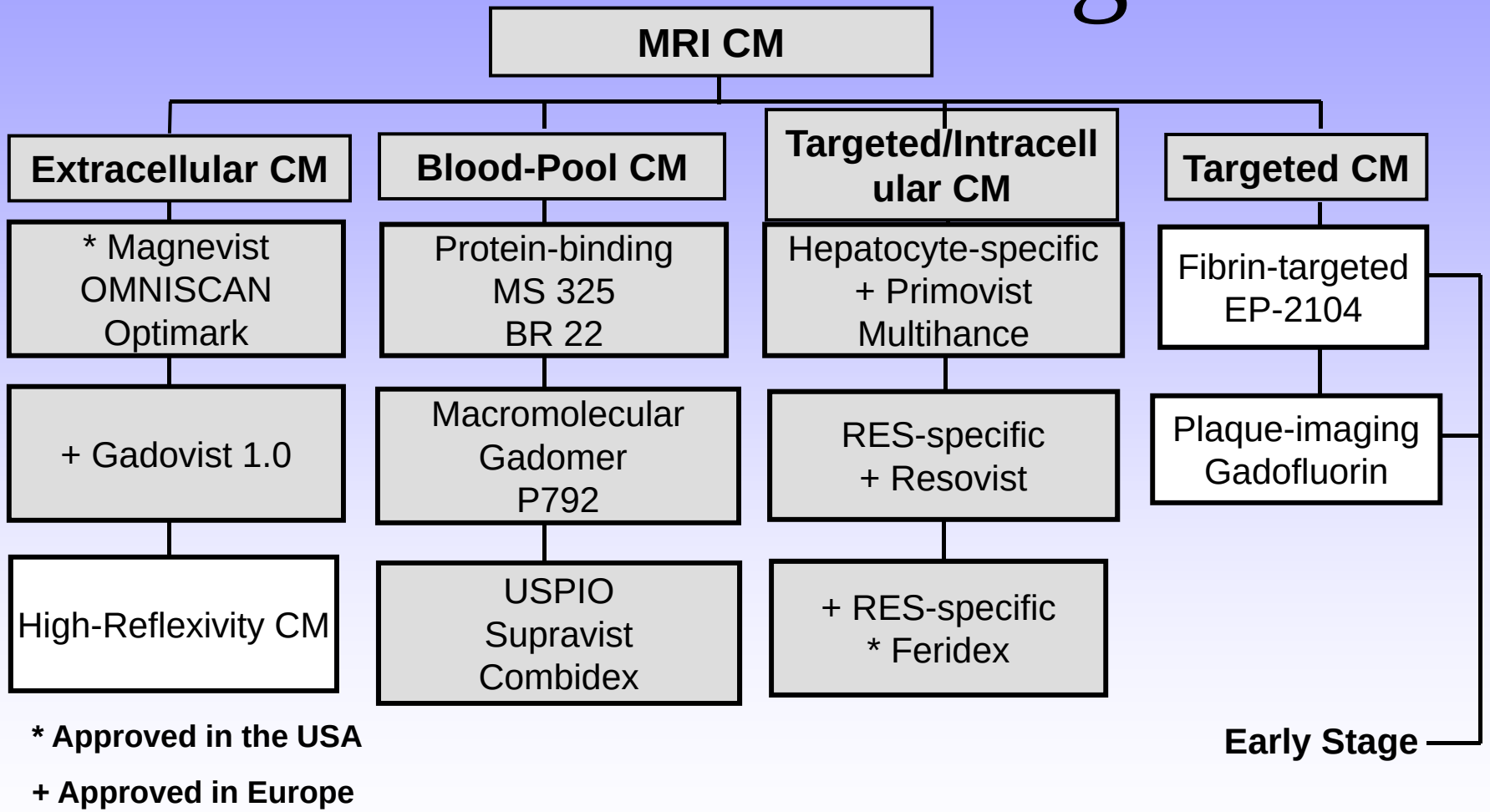




advantages:
- no solvent
- short reaction times < 30 min
- high conversions > 99.5 % (in org. solvent: < 80 %)

Some model cases in diagnostic/pharmaceutical applications

The MRI-Contrast Agents



*** Approved in the USA**

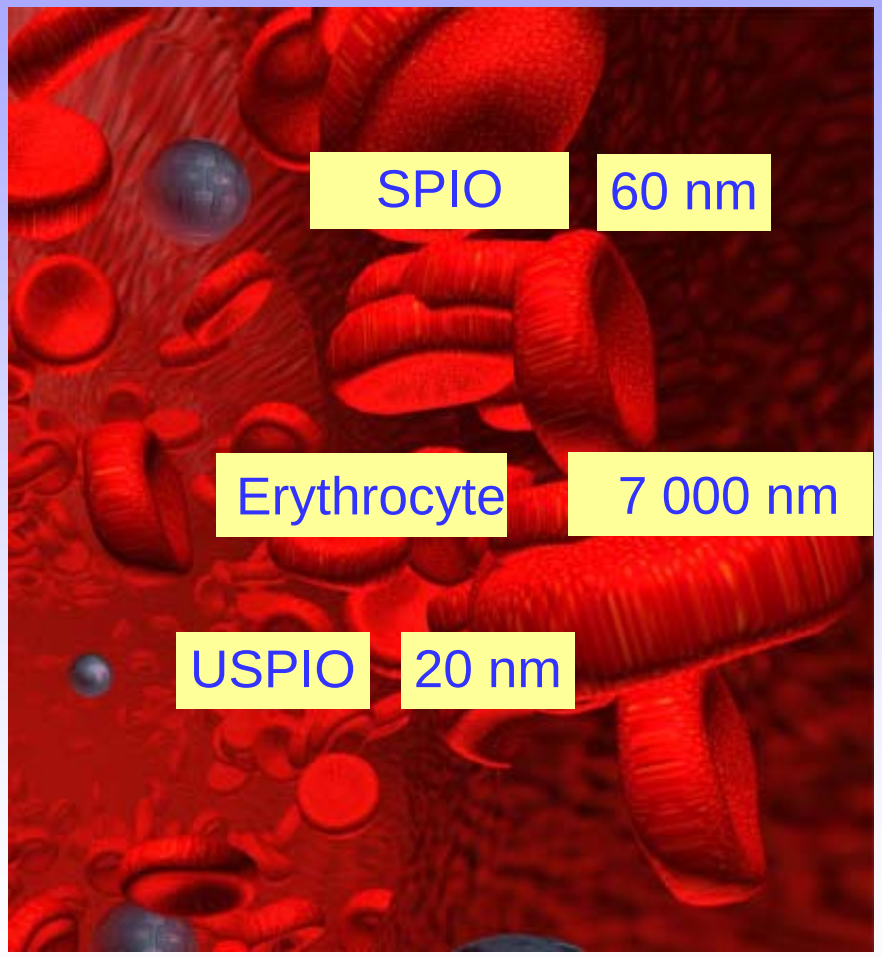
+ Approved in Europe

Gadolinium: first MR contrast agent

Magnevist was first MR contrast agent

>60 million injection experience

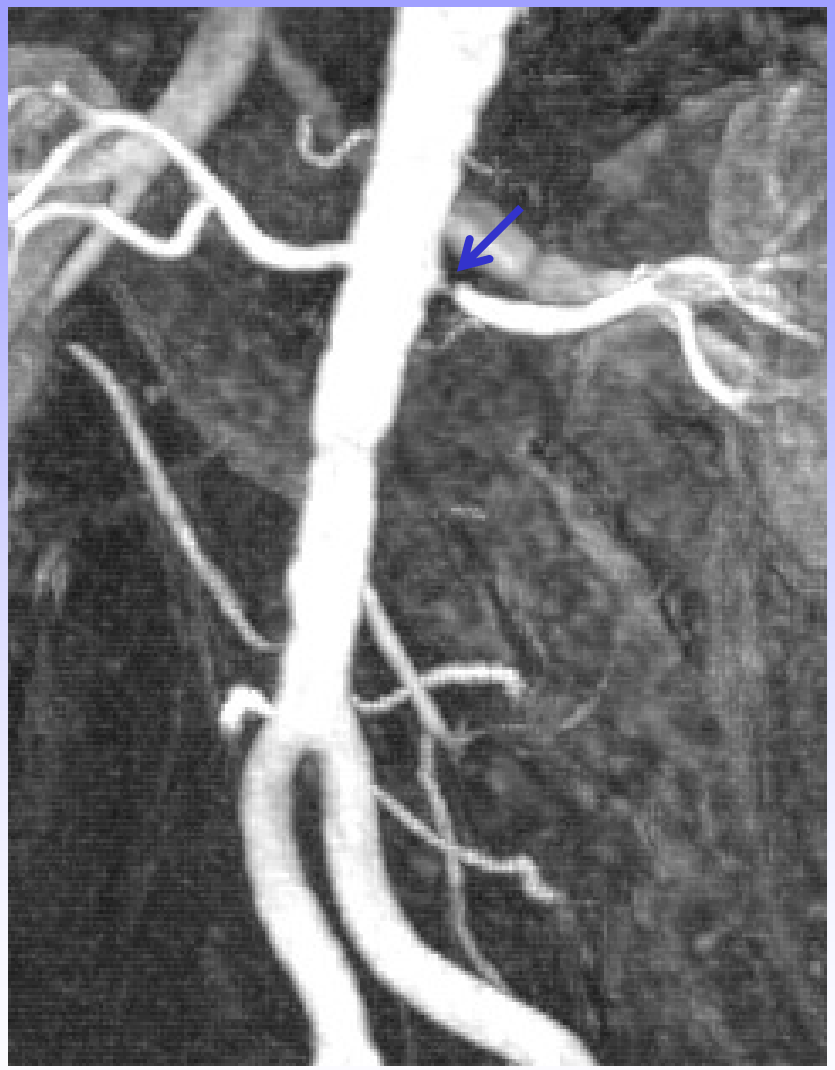
USPIO

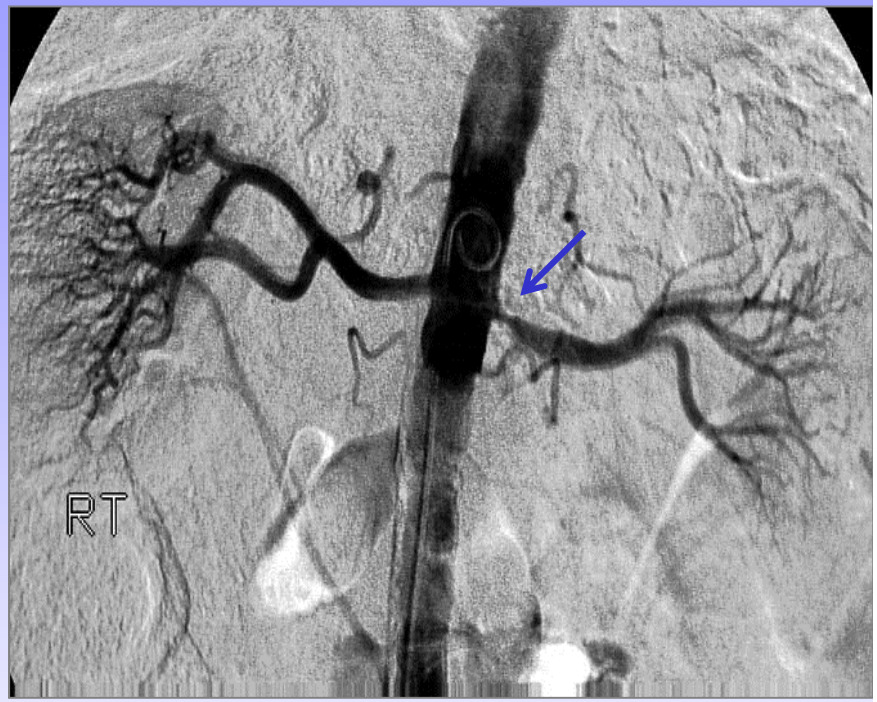


- **U** ltrasmall
- **S** uper-
- **P** aramagnetic
- **I** ron
- **O** xide particles,
  - coated with
  - carboxydextran

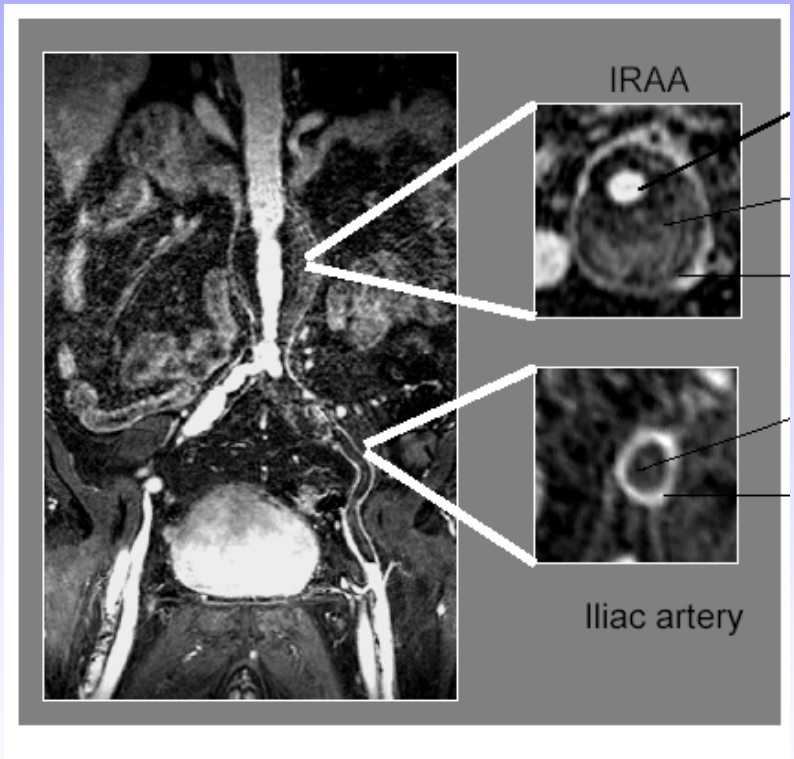
  - Optimized formulation
  - for T1 w-imaging (MRA)

MS-325 enhanced MRI





High resolution MRA: imaging of vessel wall



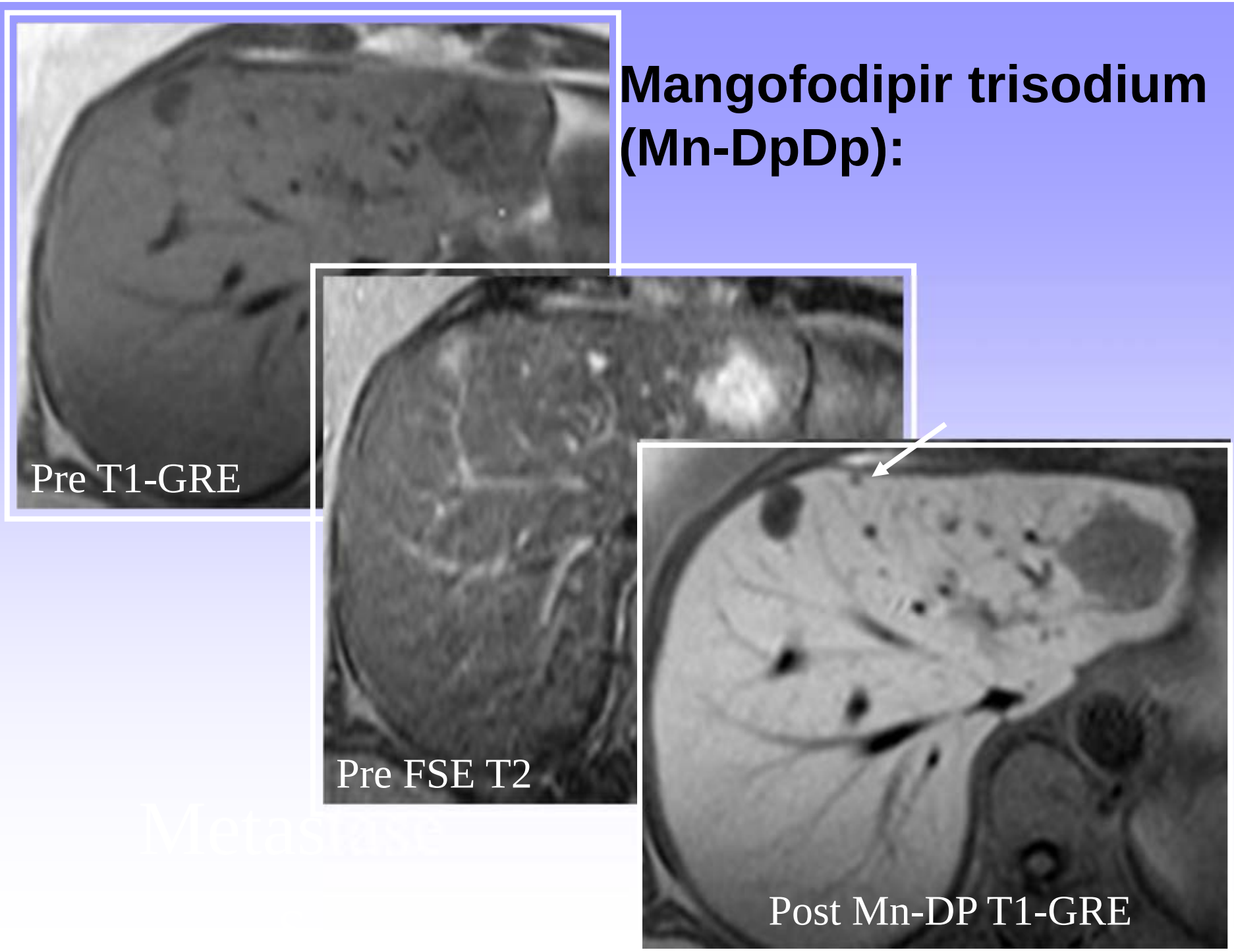
Liver-specific MRI-CM

•“Blackeners“

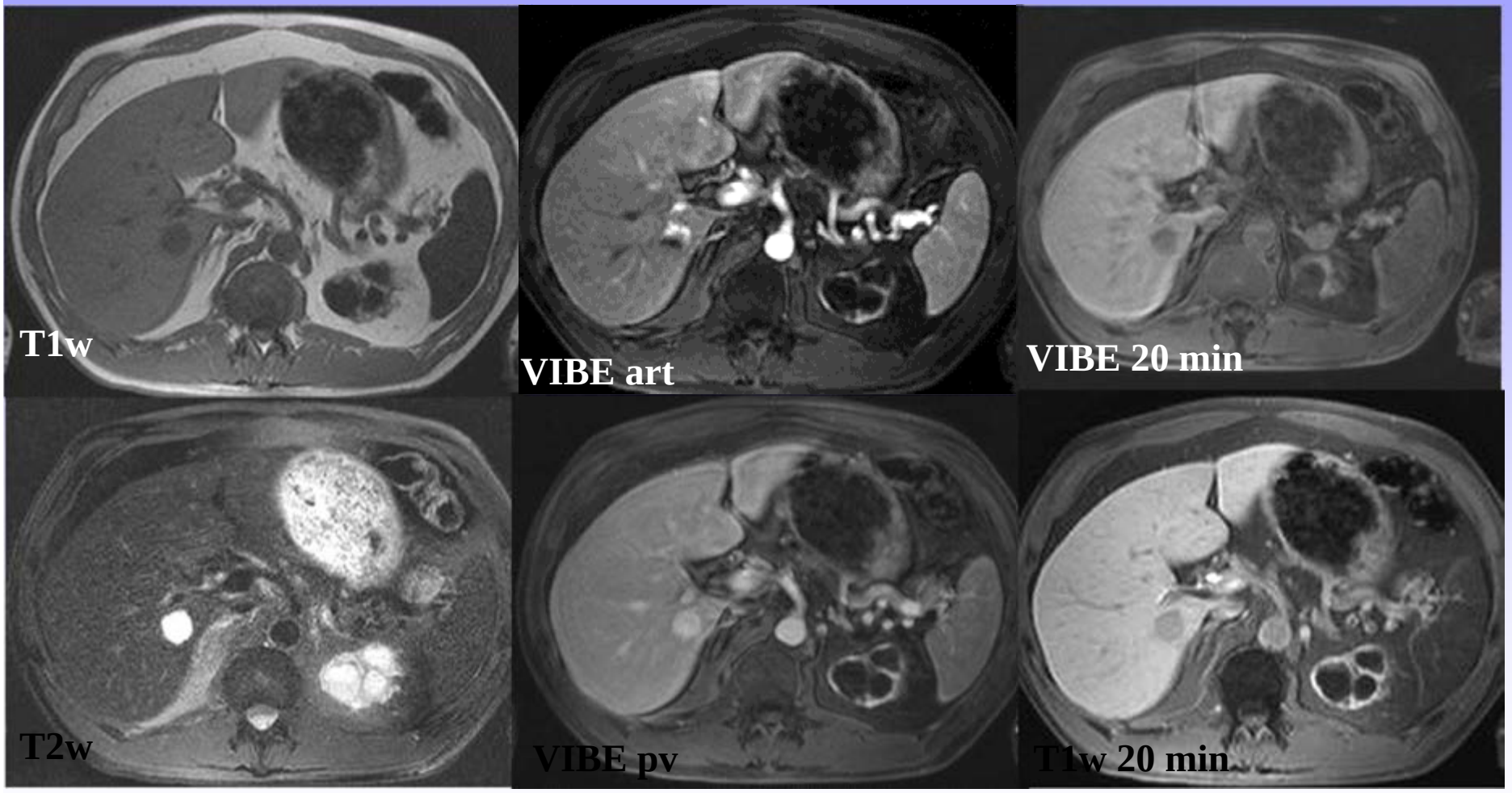
- Imaging with T2-Effect
- Feridex® **(SPIO)**
- Resovist® **(SHU 555 A)**

- “Whiteners“
- Imaging with T1-Effect
- Multihance® **(Gd-BOPTA)**
- Teslascan® **(Mn-DPDP)**
- Primovist ® ***(Gd-EOB-DTPA)***

Mangofodipir trisodium (Mn-DpDp):



Hemangioma with hepatocyte specific contrast agent (Gd-EOB-DTPA)



precontrast **dynamic** **hepatocyte phase**

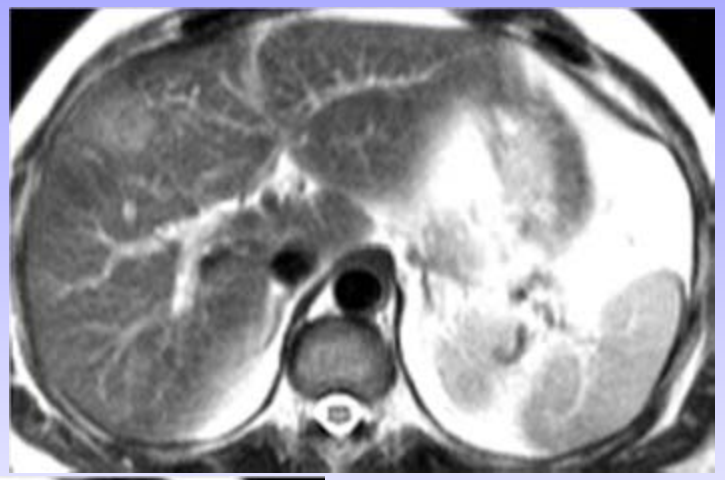
Courtesy of C. Czech, Munich, Germany

Resovist®

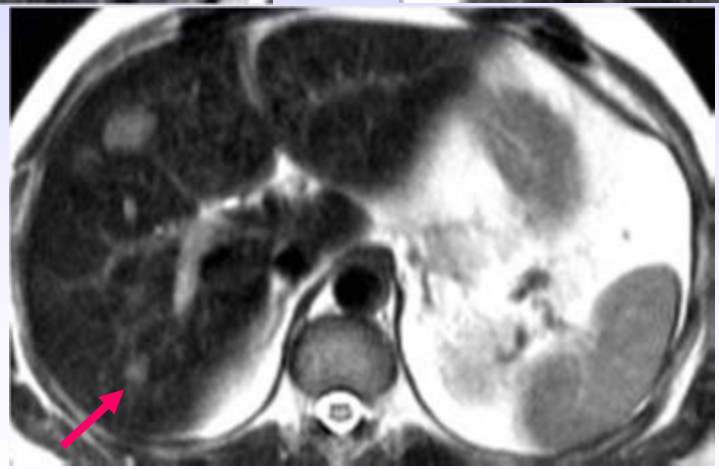
Lesion Detection

Pre T_1

Pre T_2



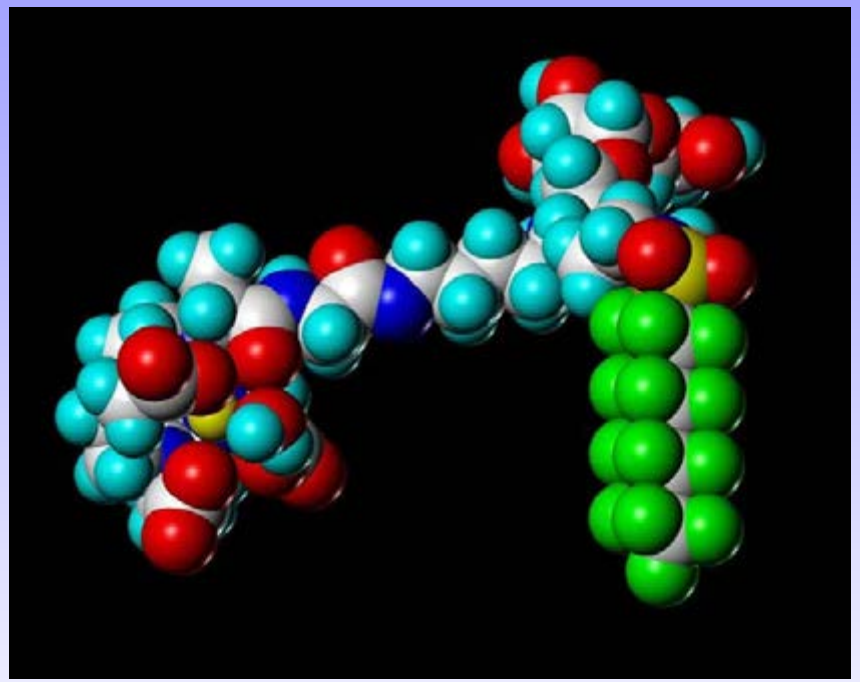
Post T_2



Metastases

Robinson, MD, Leeds, UK

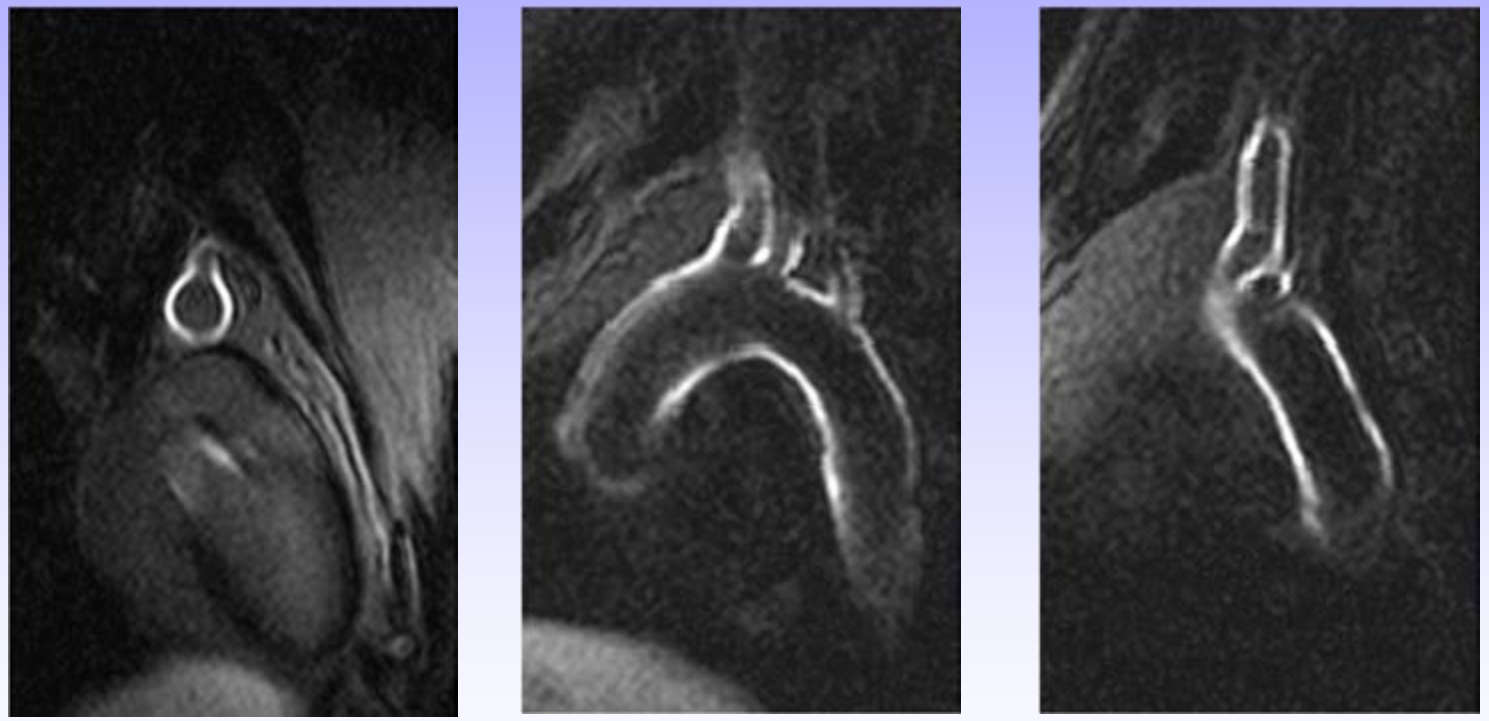
Plaque imaging: Gadofluorine M



- New water soluble, macrocyclic gadolinium chelates
- Micelle formation and longer half life, high relaxivity

Plaque Imaging Gadofluorine M
WHHL Rabbit

24 h post injection



IR turbo FLASH (300/4/120/20°)

The ‚Rabbit-story': Applications in Cancer Therapy

In cooperation with : Prof. Dr. Werner, Priv.Doz. Dr. A. Dünne,
Universität Marburg

Problem:

- Tumors in the head/neck region metastasize by way of the lymphatic system.

  Anticancer drugs injected into the blood system are not active.

  Tremendous reduction of life expectancy

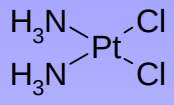
→

Idea:

- Using a chimera micelle as carrier tracer system for anticancer drug
- Direct injection of the tracer into the tumour ; lymphatic homing

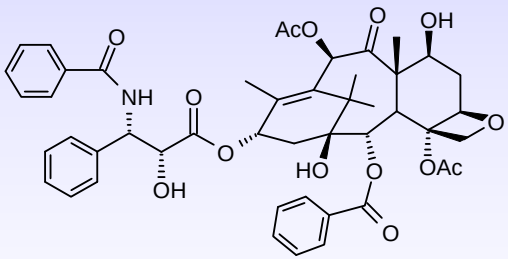
Anticancer Drugs

1. cis-Diaminedichloroplatinum(II) ‚cis-Platinum‘:



- Highly toxic
- Short circulation periods due to glomerular excretion

2. Taxol (Paclitaxel®):

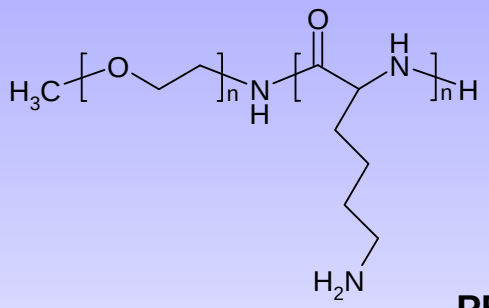


- highly toxic
- very low solubility in water

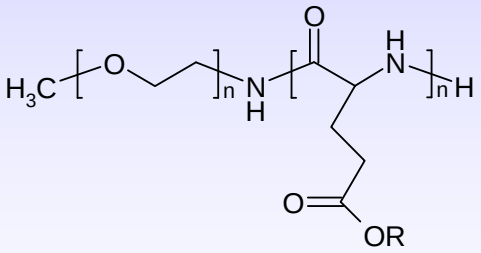
Tracer System: Chimera polymers

Demands:

- biocompatibility
- long circulation periods
- well defined, 20 nm in size



PEG-P(L-Lysin)



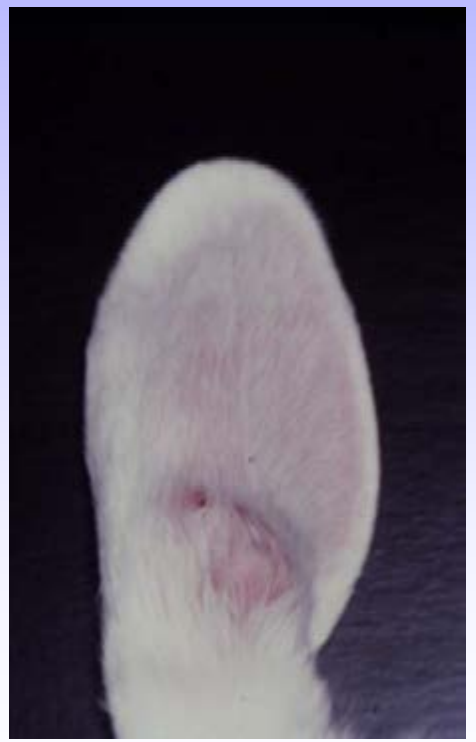
PEG-P(BLGlu), R=benzyl
PEG-P(L-Glu), R=H

The Model: New Zeeland white rabbit

- VX2-carcinoma which shows lymphatic metastasizing grows only in New Zeeland white rabbits (rats metastasize via blood vessels)

Experiments:

- Cancer cells of VX2-carcinoma are injected in the ears of the rabbits
- Growth of the tumor over several weeks
- First micro-metastases in lymph node after 8 days
- Therefore start of tracer injection after 8 days
- Tracer was injected 3 times over a period of 14-21 days

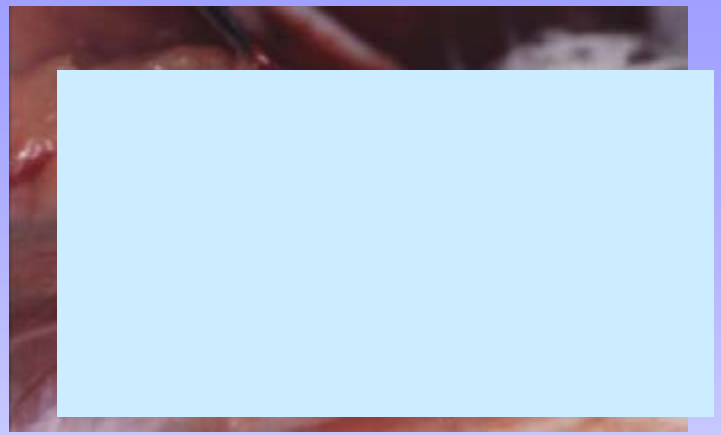


Tumor after 18 days

Results (1)

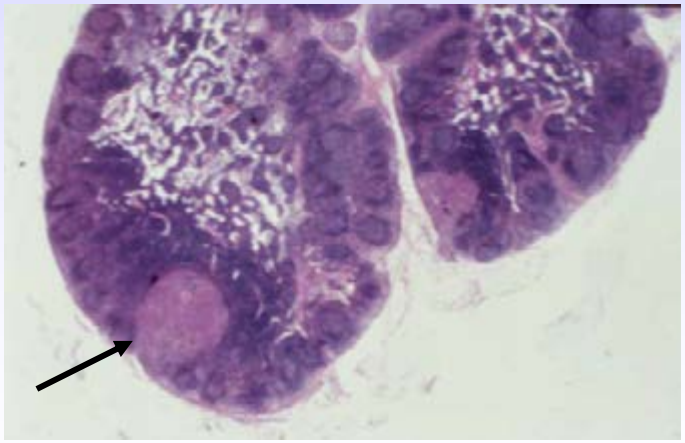
Control experiment,
rabbit without tracer after 21 days:

clear metastasizing in lymph nodes

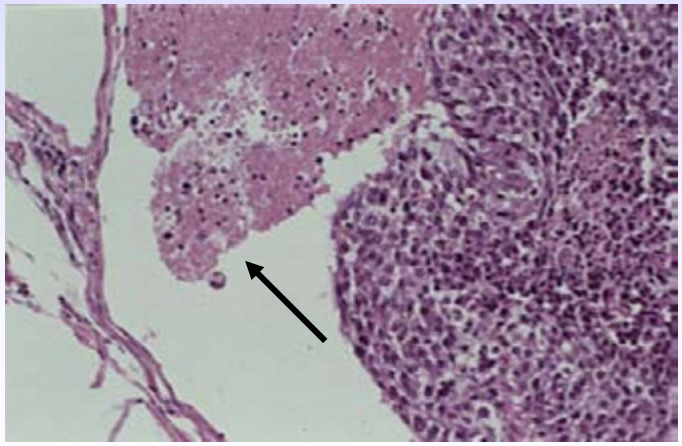


Metastasis in lymph node

Histological cuts:
(pink cells : metastases, purple cells: lymphatic cells)



Lymph node



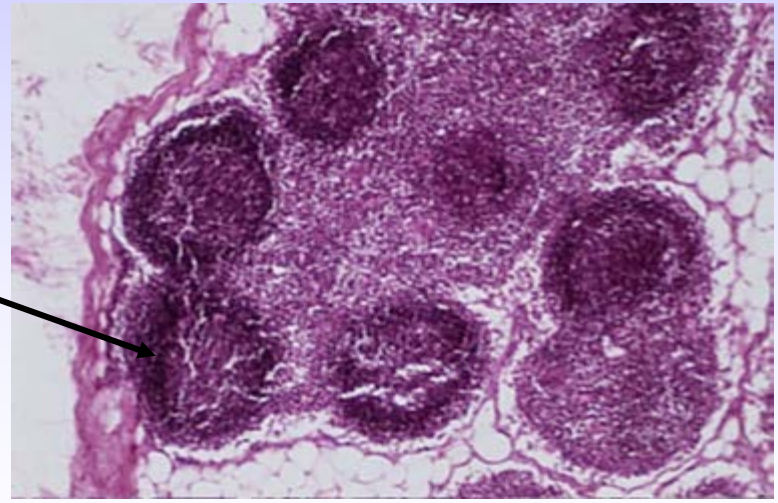
Lymphatic vessel

Results (2)

Animals with tracer application after 21 days:

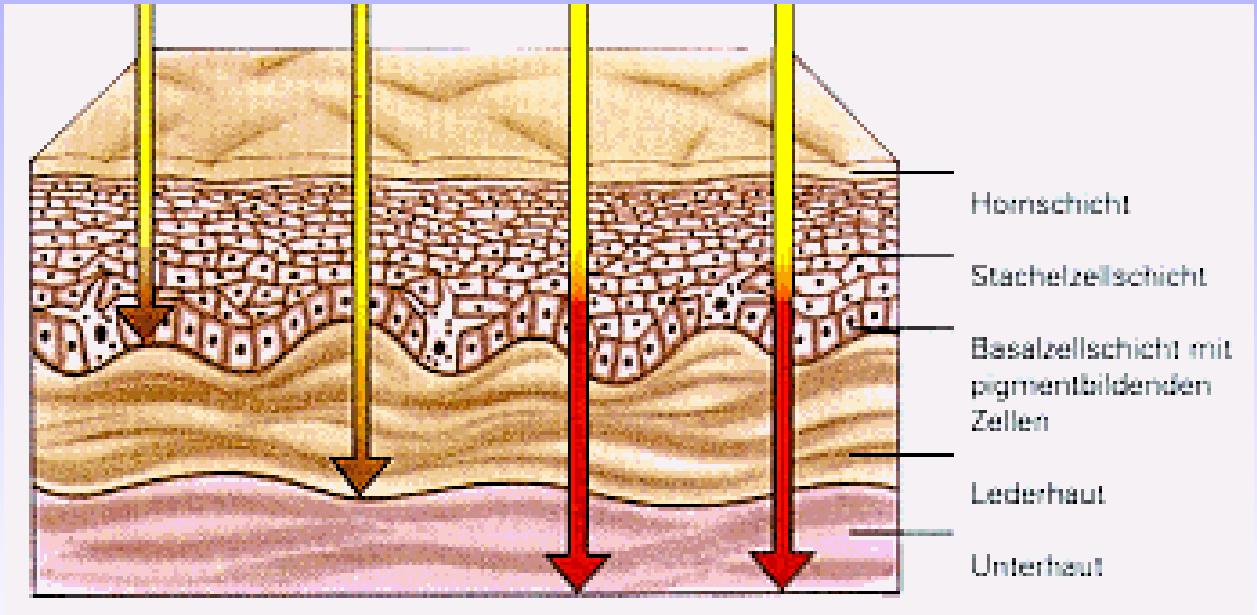
- no metastases in lymphatic system detectable
- normal morphology of lymph node, but a lot of secondary follicles (immuno answer of B-cells after antigene contact)

Histological cut of lymph node



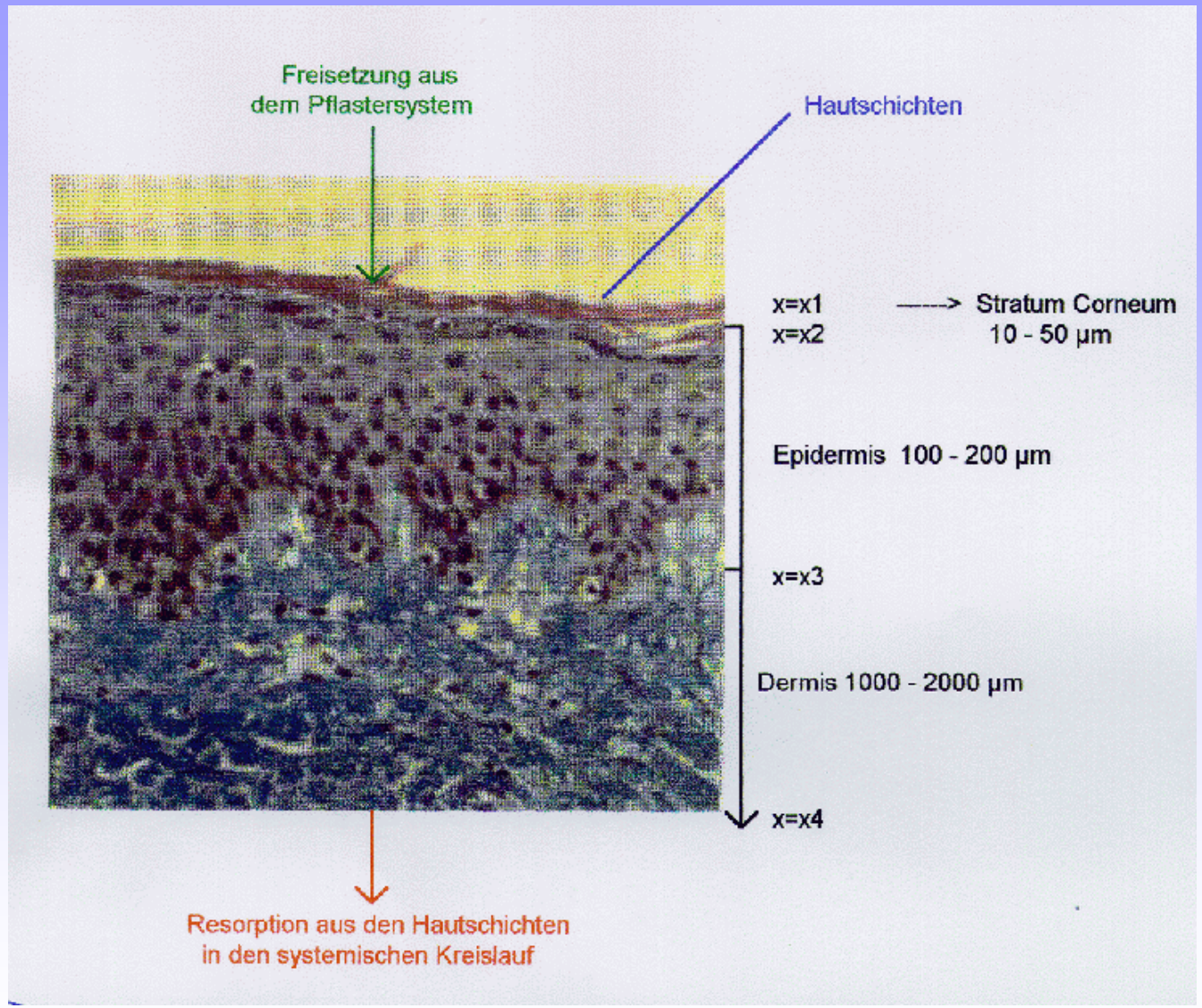
→ Chimera Surfactants have mediated transport and communication with biology

Das Problem: die Haut zu pflegen ist nicht leicht: Sie hat Schutzmechanismen !

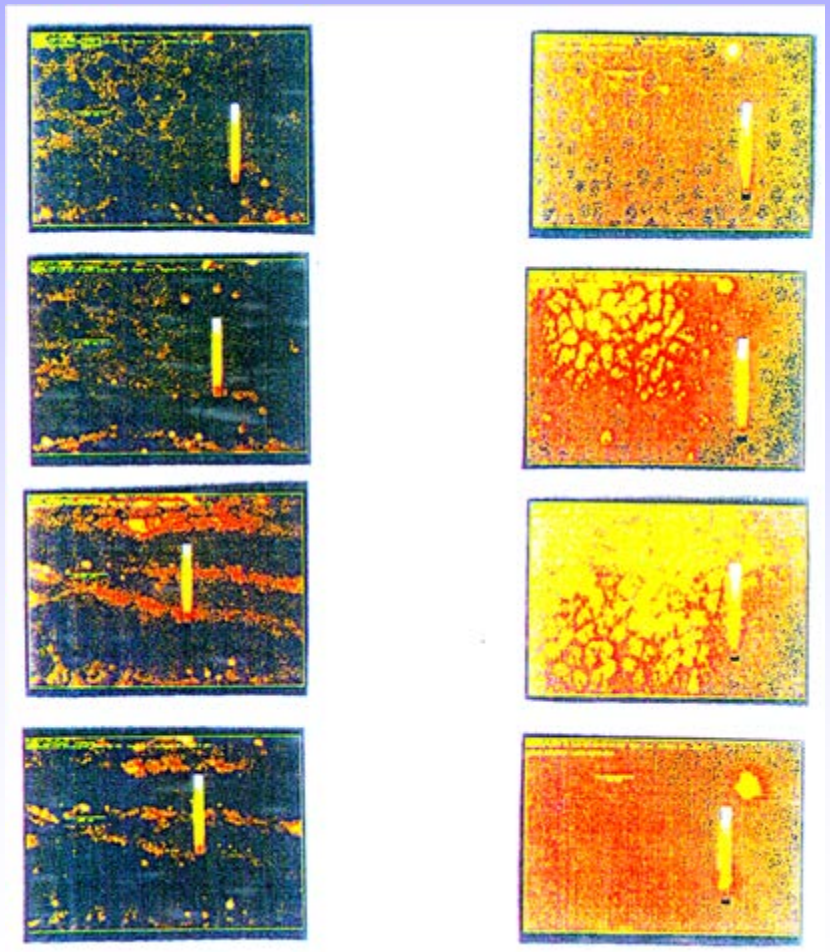


Fakt: 99+% der Kosmetika pflegen die Hornschicht und sind damit nicht nachhaltig wirksam.

Um Haut jung zu halten, muß die Basalschicht erreicht werden !


Freisetzung aus
dem Pflastersystem
Hautschichten
x=x1
x=x2
Stratum Corneum
10 - 50 µm
Epidermis 100 - 200 µm
x=x3
Dermis 1000 - 2000 µm
x=x4
Resorption aus den Hautschichten
in den systemischen Kreislauf

Lösung ??: kodierte Nanoteilchen
Schleichen sich durch das Porensystem der Haut



Konfocale Laserscanningmikroskopie mit Farbstoff statt Vitaminen (Pandora´s Box)

Links: Kontrollgruppe

Rechts: Probe mit 40 nm NPs

Future:

-„Follow and Fight“ systems

- multidetection assays

- higher tissue specifity