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Tailoring biomolecular interactions of core-shell nanoparticles and their application to magnetoresponsive drug delivery vehicles

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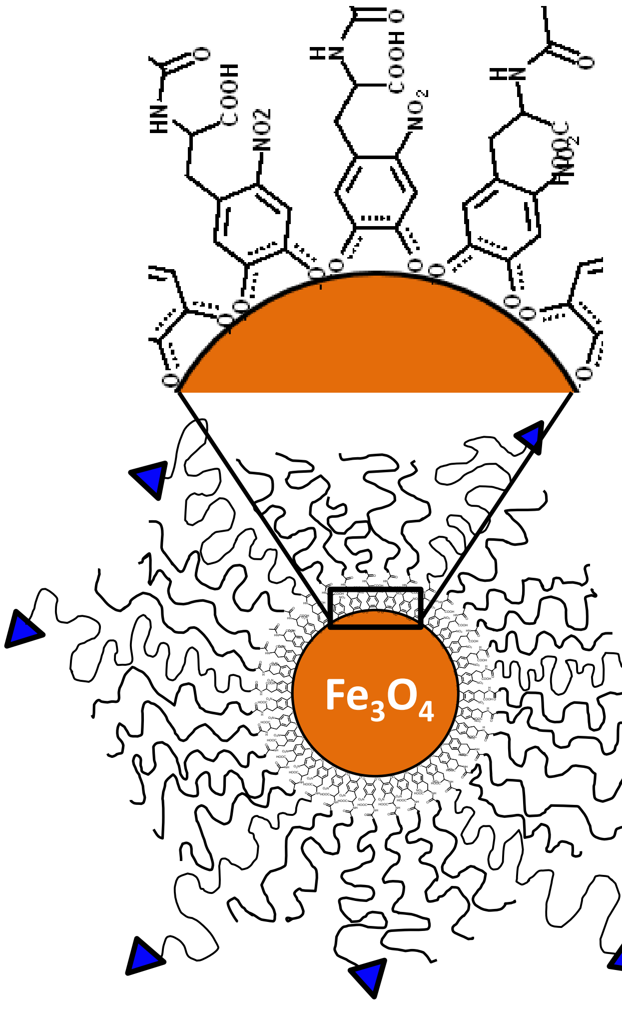
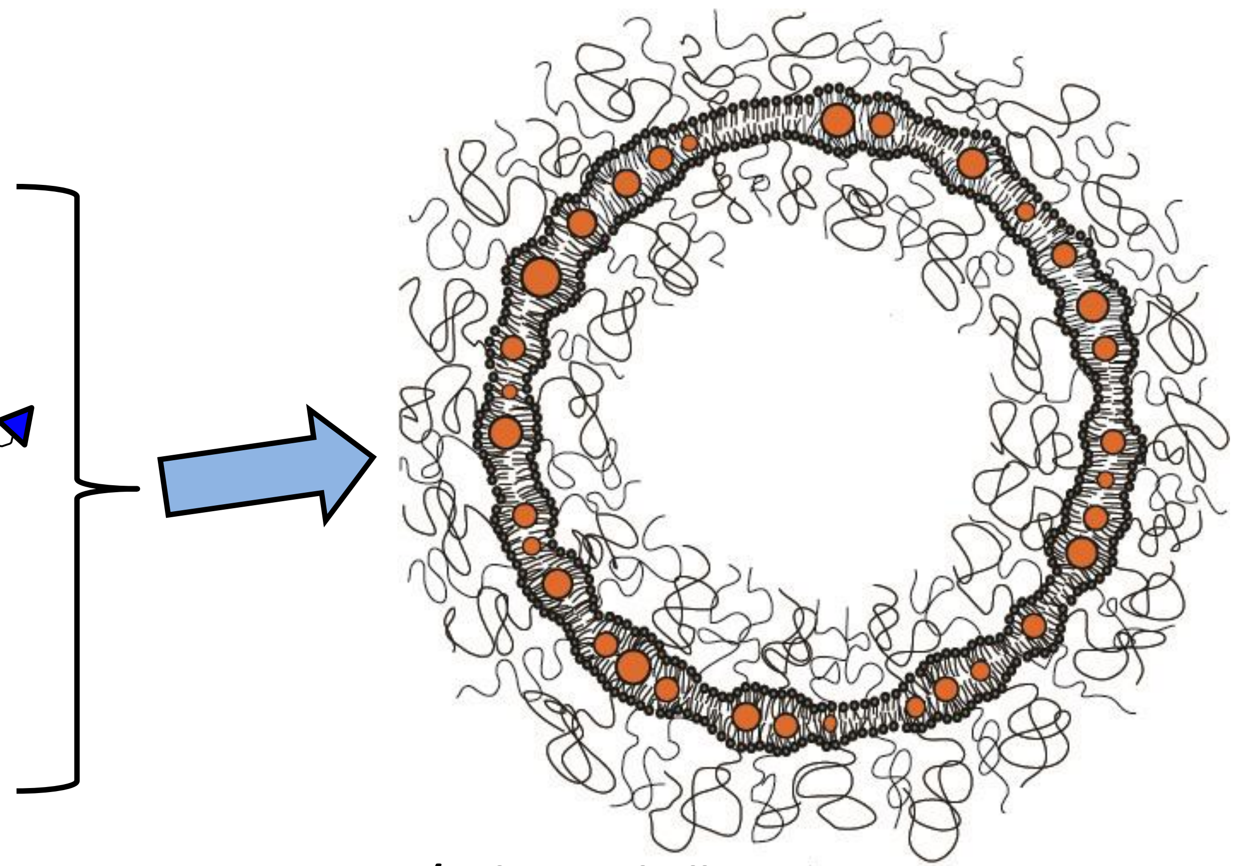
Austria

Outline

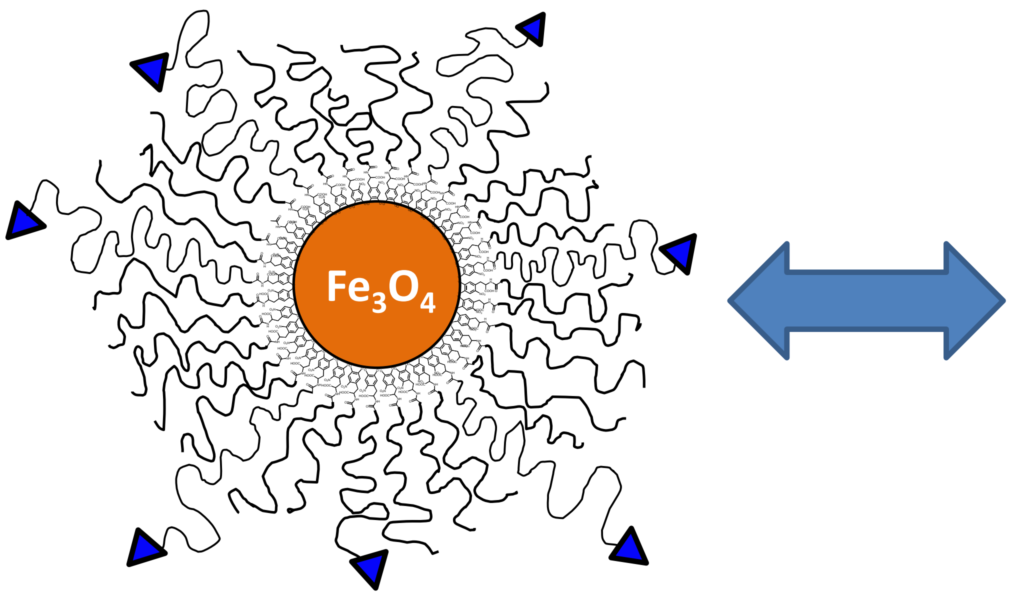


Superparamagnetic iron oxide / polymer brush core-shell NPs

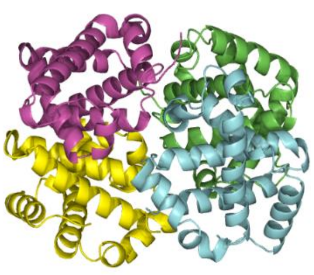


- **Monodisperse cores + homogeneous organic/polymer shell properties**
- **Self-assembly into membranous and responsive nanoscale vesicles**

Core-shell nanoparticle design and interactions



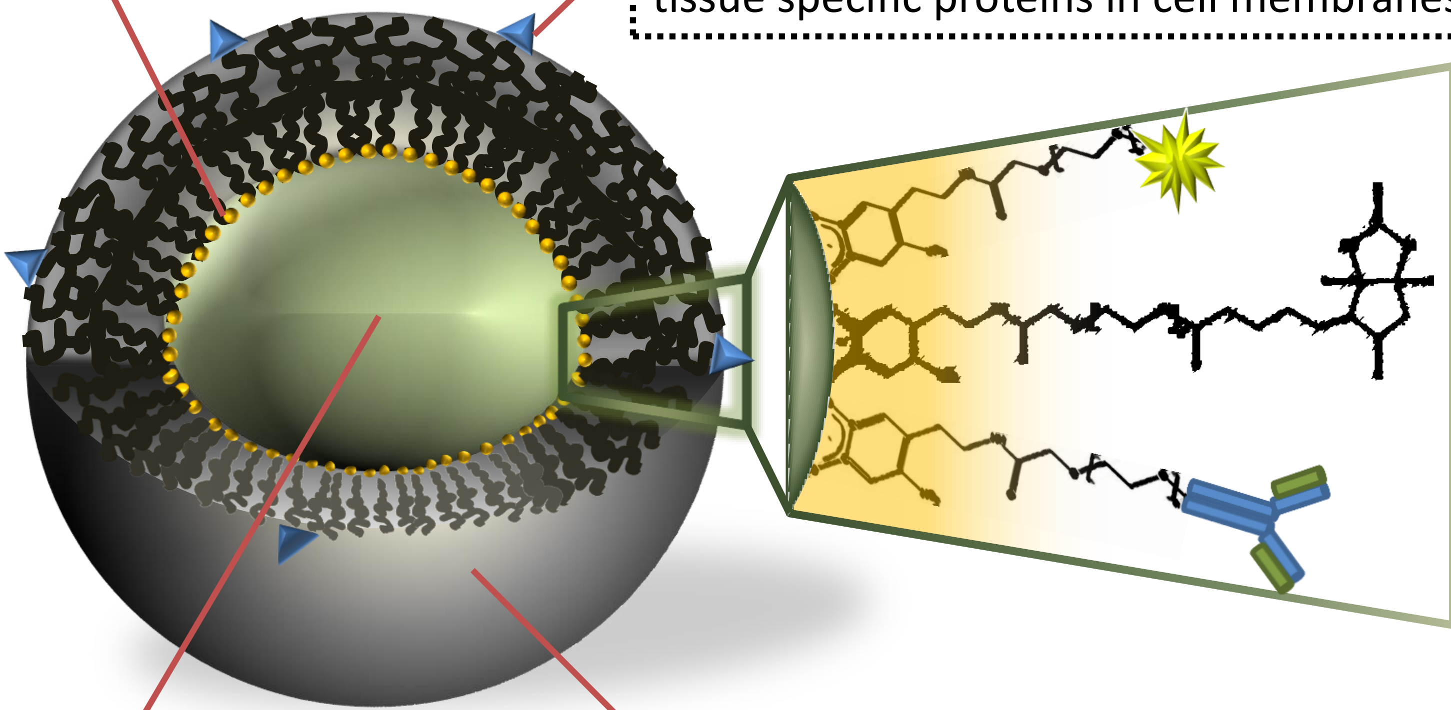
Application:
Biomedical imaging and biological targeting



Anatomy of core-shell nanoparticles

Anchor group:
Attaches shell to core.

Functional group:
Controls specific interactions, such as targeting of tissue specific proteins in cell membranes.

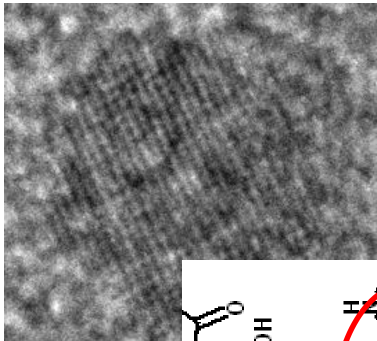


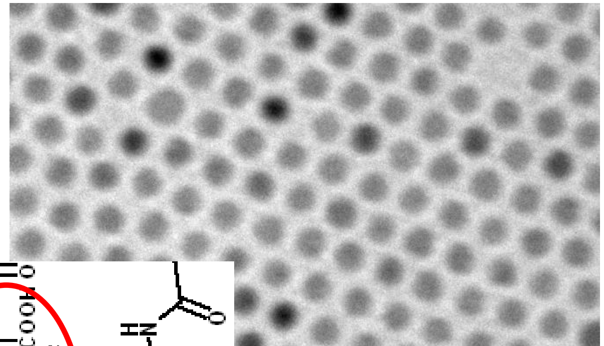
Core:
Desired functionality.
Works as antenna or container.

Shell:
Spacer/linker that defines the interaction of the NP with its environment; ideally it makes the core invisible until actuated.
Dense and end-grafted polymer brush

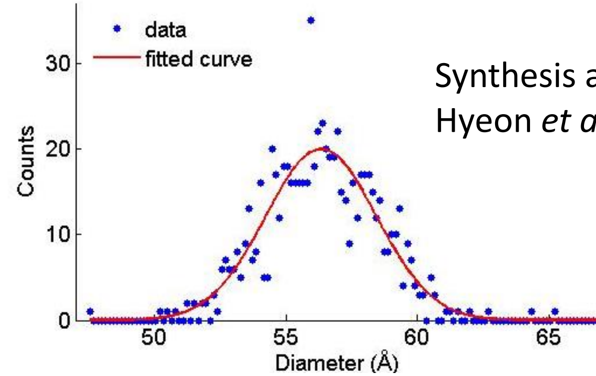
E. Amstad *et al.*, *Nanoscale* (2011)

Monodisperse superparamagnetic core-shell NP synthesis

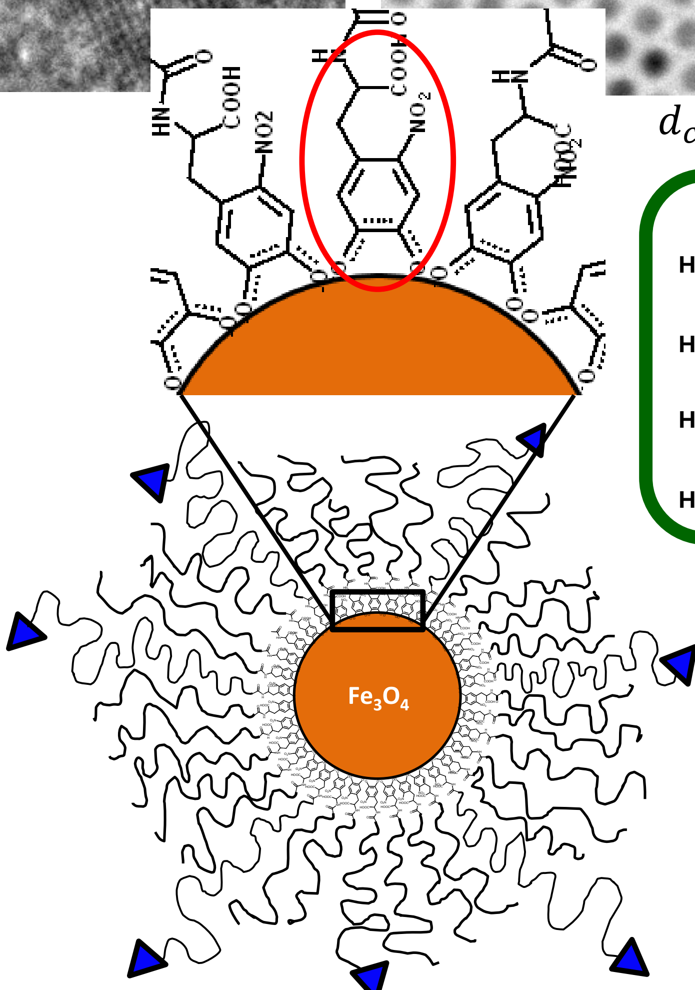




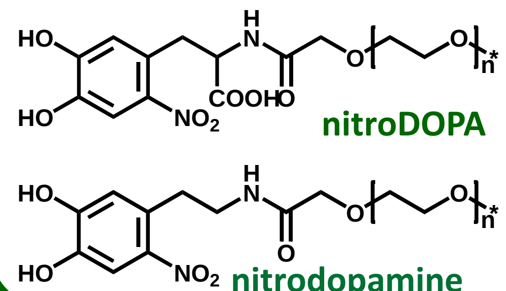
d_{core} = 8.3 nm



Synthesis adapted from Hyeon *et al. Nat Mater* **3**:891



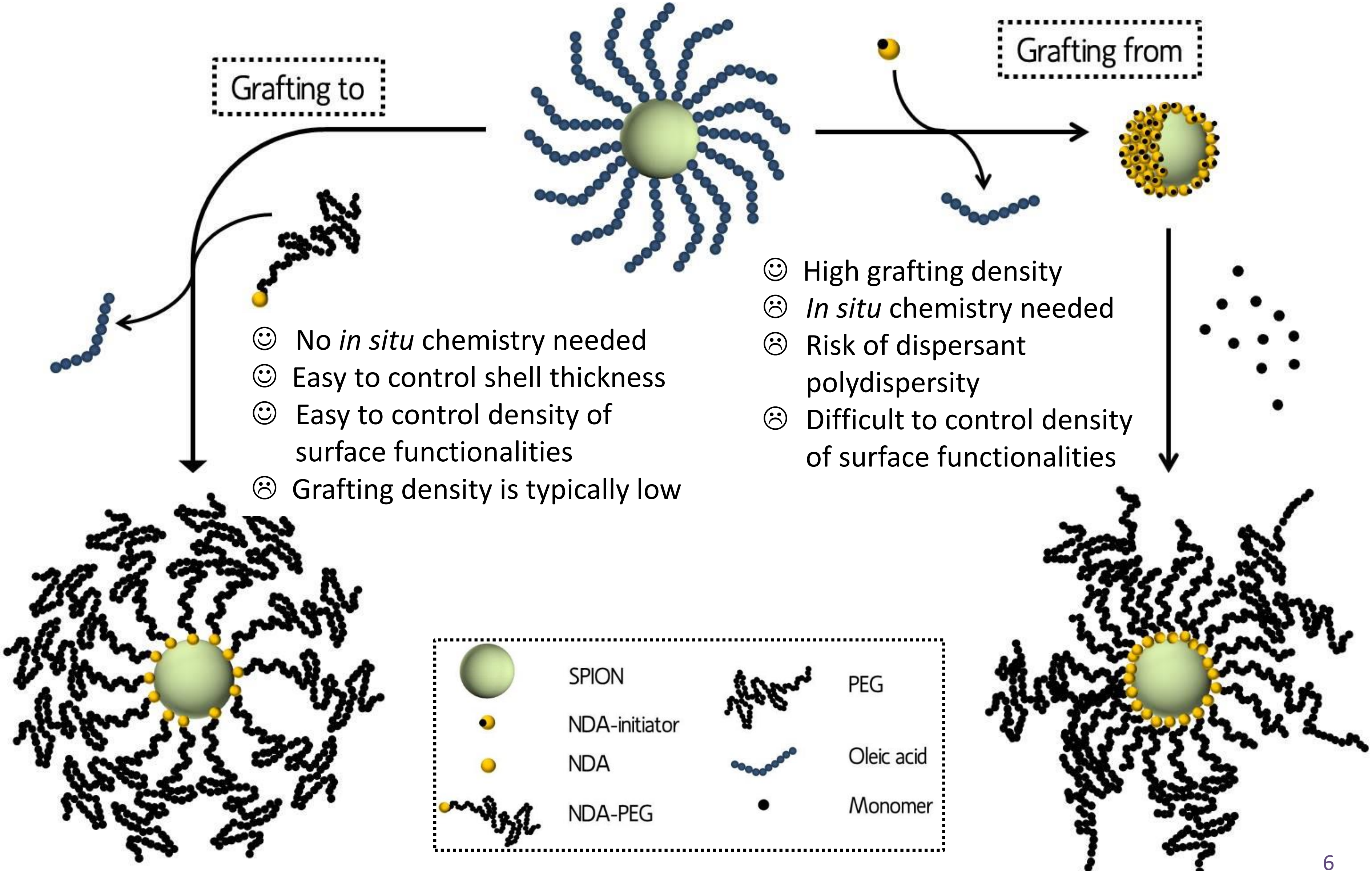
Good anchors



A. Lassenberger *et al.*, *Chem Mater* (2017)
A. Lassenberger *et al.*, *Langmuir* (2016)
E. Amstad *et al.*, *Small* (2009)
E. Amstad *et al.*, *Nano Lett* (2009)
E. Amstad *et al.*, *J Phys Chem C* (2011)
R. Zirbs *et al.*, *Nanoscale* (2015)
O. Bixner *et al.*, *Langmuir* (2015)
A. Lassenberger *et al.*, *ACS AMI* (2017)
B. Shirmardi *et al.*, *Nanoscale* (2017)

- Controlled superparamagnetic size **3.5-15/20 nm**
- ”Spherical”
- Monodisperse (**σ < 5%**)
- **Irreversible dispersant binding** (required)
- Controlled dispersant grafting density
- Free from excess dispersant

SPION stabilization with anchored dispersants



Grafting to

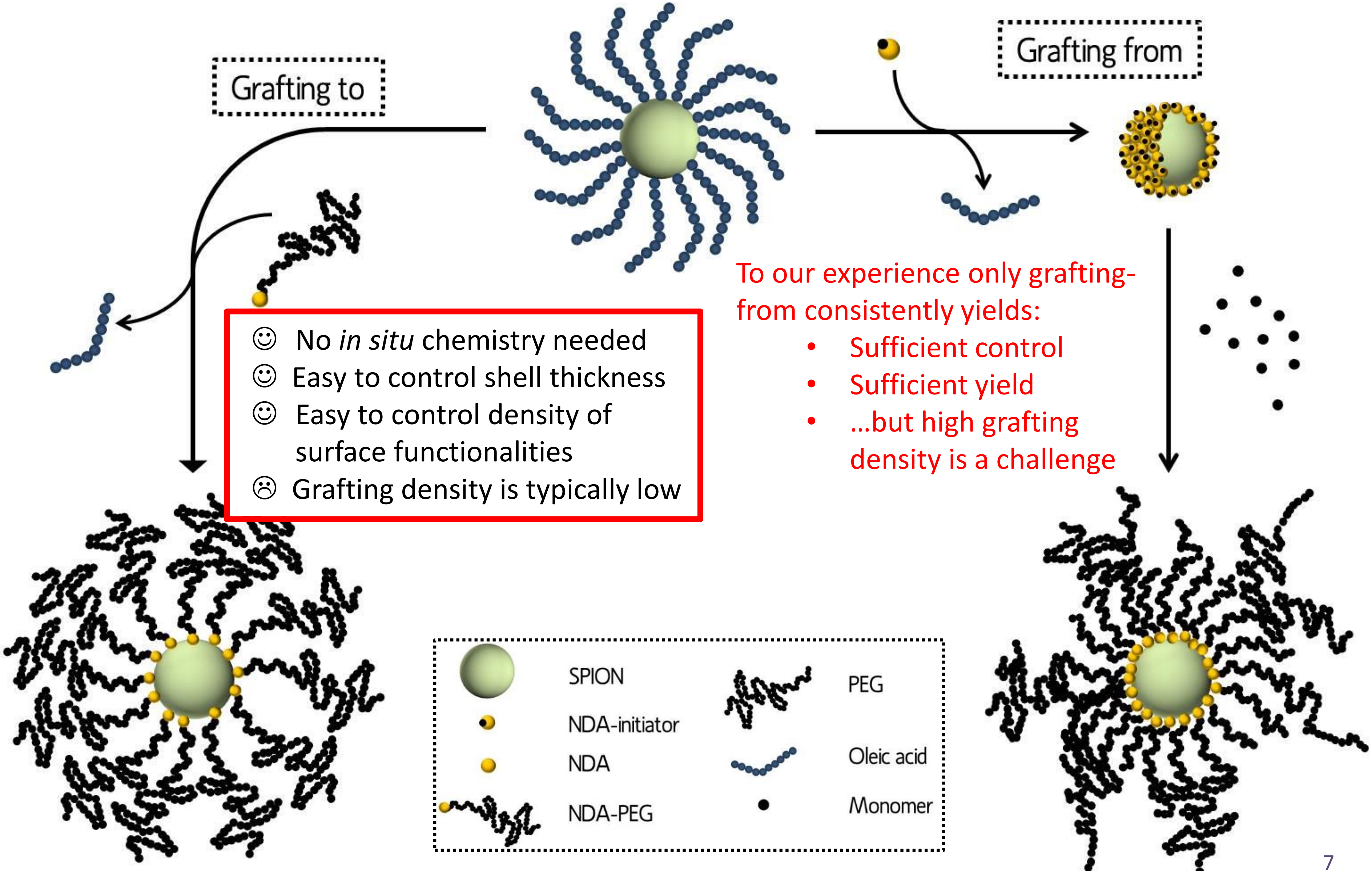
- ☺ No *in situ* chemistry needed
- ☺ Easy to control shell thickness
- ☺ Easy to control density of surface functionalities
- ☹ Grafting density is typically low

Grafting from

- ☺ High grafting density
- ☹ *In situ* chemistry needed
- ☹ Risk of dispersant polydispersity
- ☹ Difficult to control density of surface functionalities

E. Amstad *et al.*, *Nanoscale* (2011)

SPION stabilization with anchored dispersants



- ☺ No *in situ* chemistry needed
- ☺ Easy to control shell thickness
- ☺ Easy to control density of surface functionalities
- ☹ Grafting density is typically low

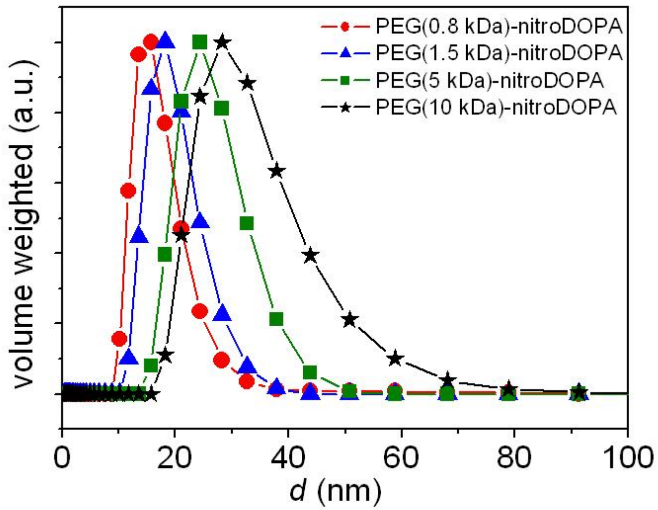
To our experience only grafting-from consistently yields:

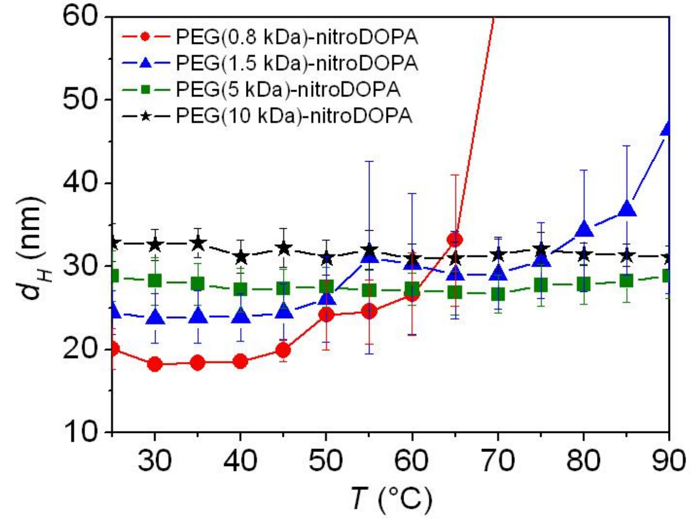
- Sufficient control
- Sufficient yield
- …but high grafting density is a challenge

E. Amstad *et al.*, *Nanoscale* (2011)

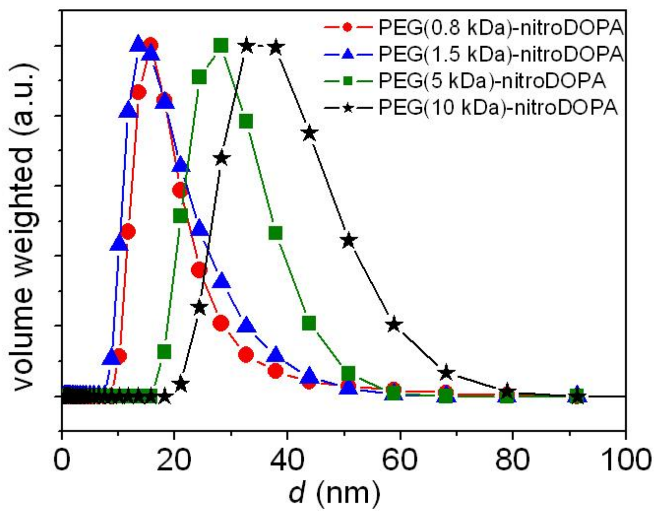
Control over shell thickness and NP stability

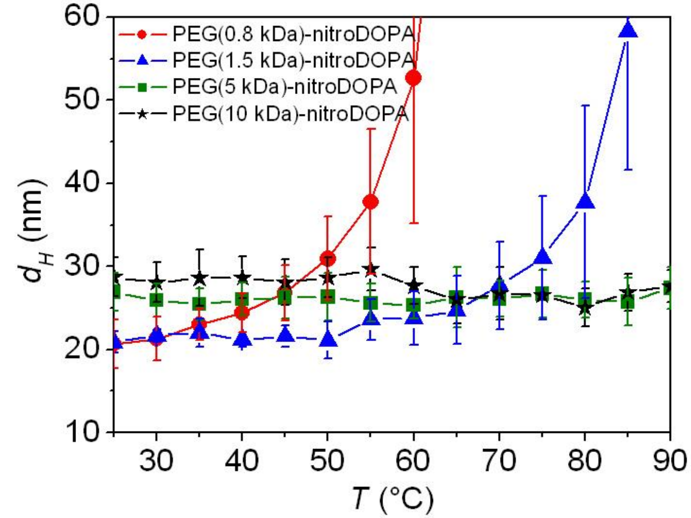
d_{core} = 10 nm





d_{core} = 5 nm

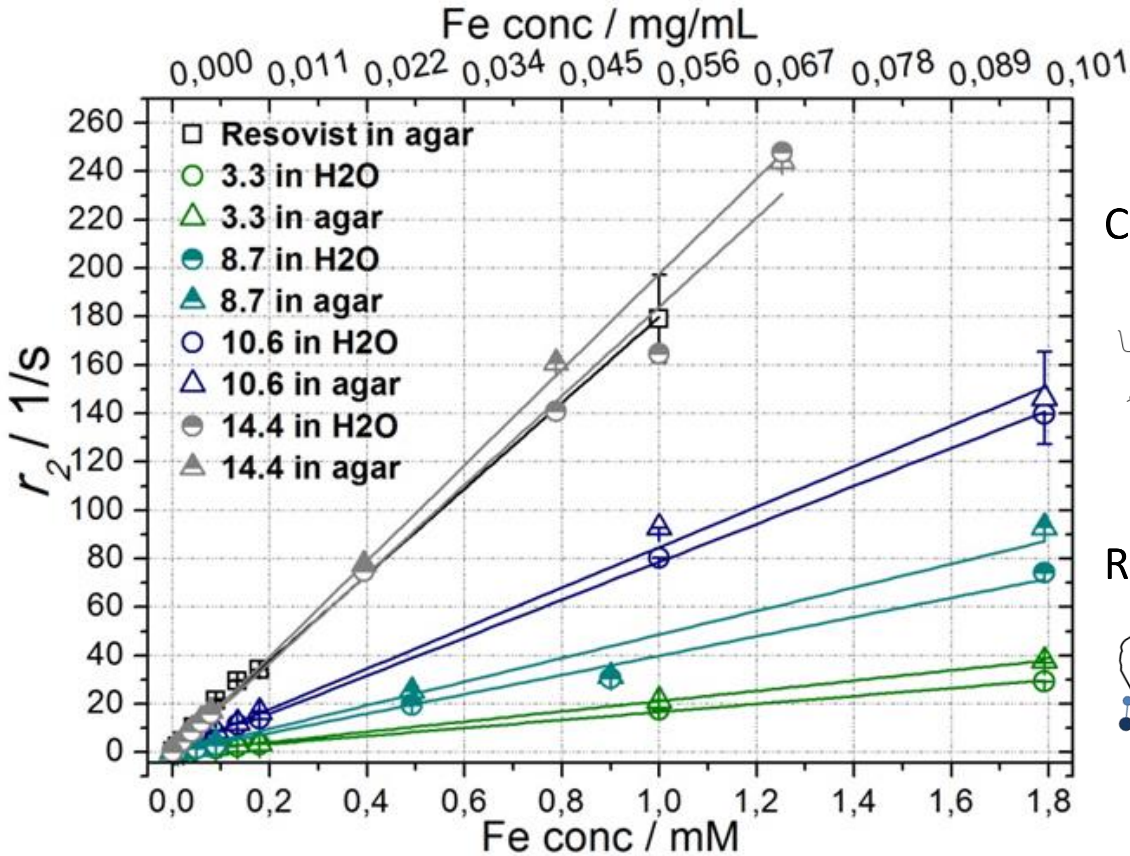


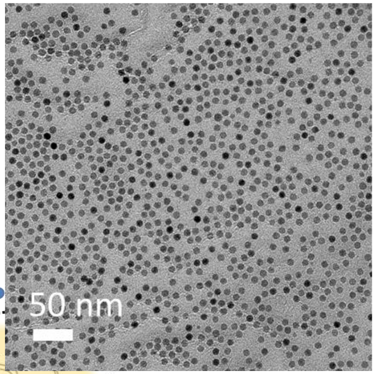


⇒ We can independently tune the core and shell size for monodisperse SPION

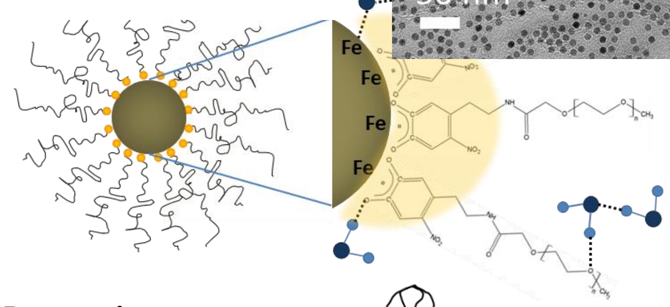
L. Isa *et al.*, *Chimia* (2010); A. Lassenberger *et al.*, *Langmuir* (2016); R. Zirbs *et al.*, *Nanoscale* (2015)

Properties as contrast agents

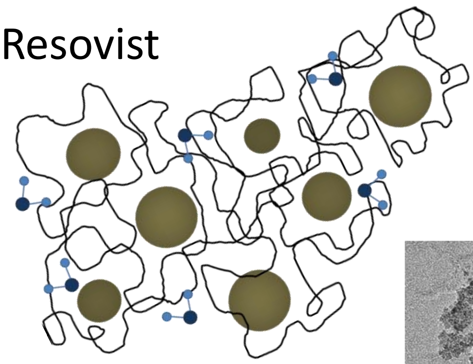


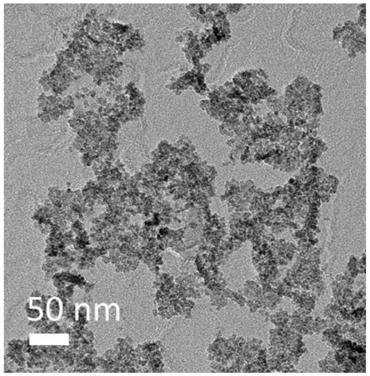


Core-shell SPION



Resovist



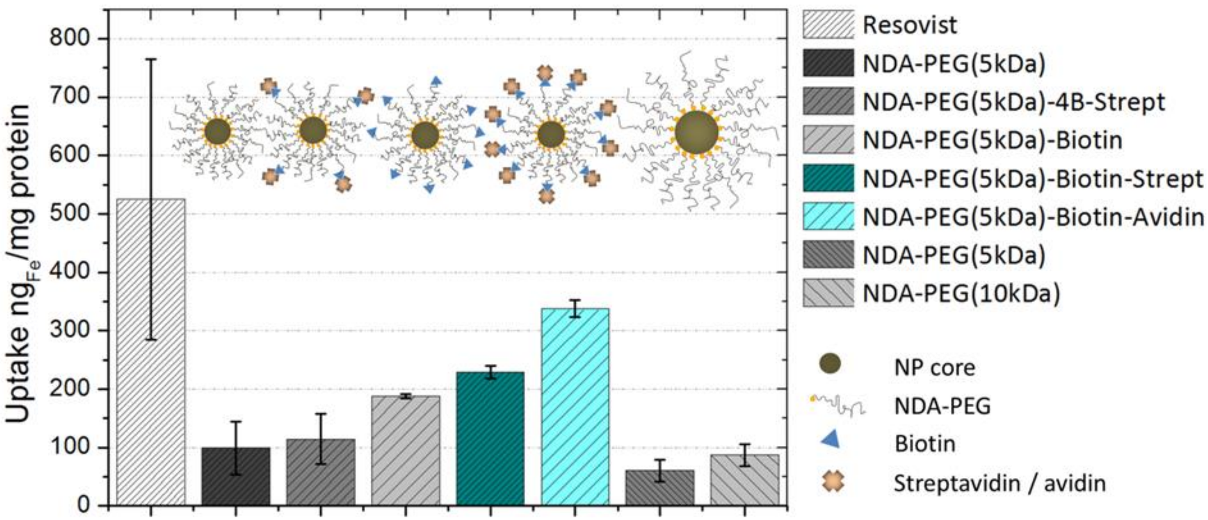


Comparison to clinical benchmark Resovist:

- Lower R_2 and somewhat lower R_2^*
- Defined architecture that enables development of targeting
- **Withstand aggregation in water** (also in the MRI magnetic field, 9.4 T)

A. Lassenberger *et al.*, *ACS Appl Mater Interf* (2017)

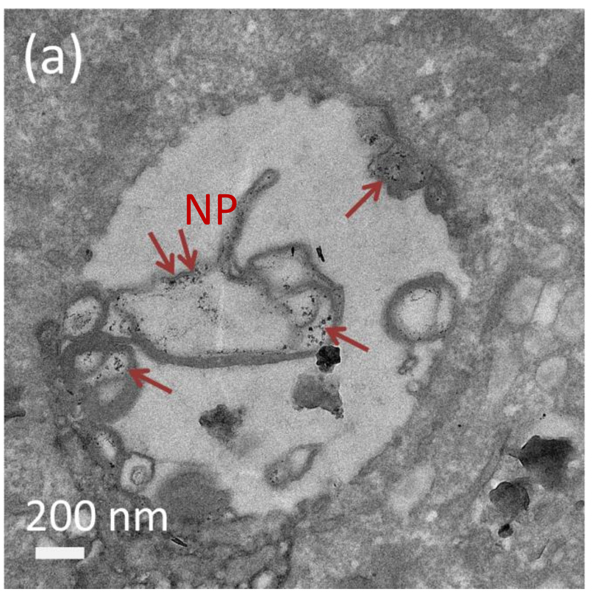
SPION cell uptake and cytotoxicity



- Negligible cell uptake even at extremely high exposure (**cell drinking only**)

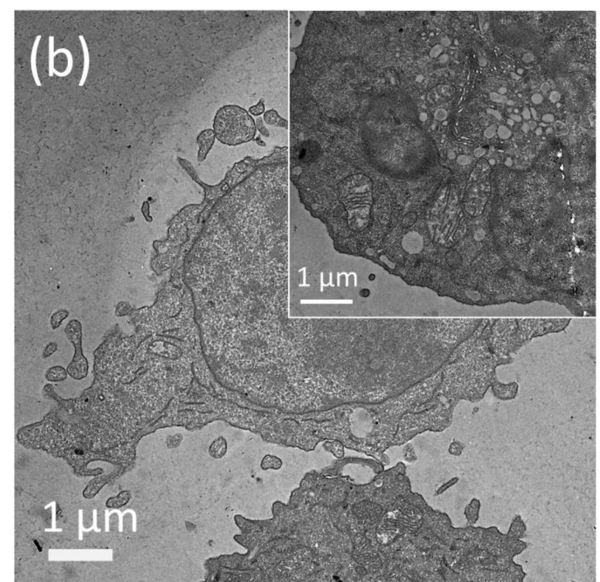
⇒ Macrophages (phagocytic cells) show even higher contrast in uptake between core-shell and coated SPION

Resovist (coated SPION)



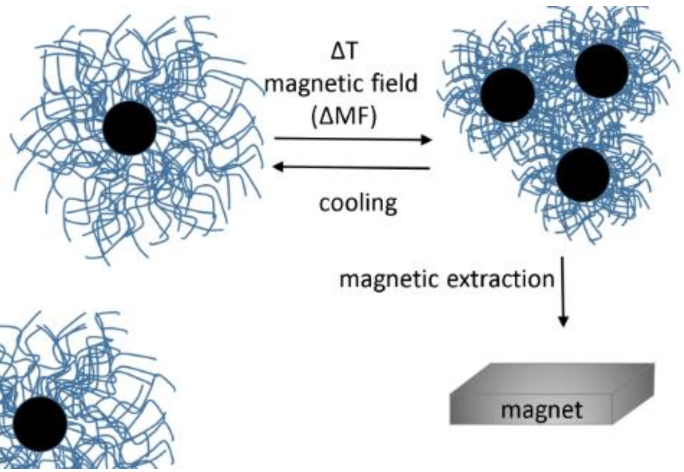
- Core-shell SPION can be functionalized to control recognition and cell uptake
- Dextran-enwrapped SPION but not PEGylated core-shell SPION are found in cells

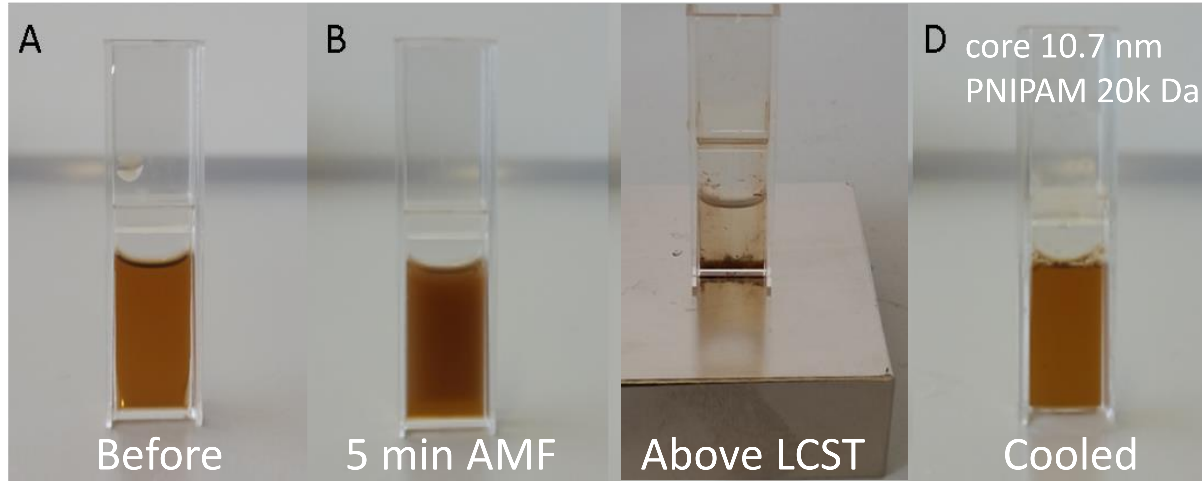
15-nm core-shell SPION



N. Noga *et. al.*, *ACS Biomater Sci Eng* (2017)
A. Lassenberger *et al.*, *ACS Appl Mater Interf* (2017)

Magnetothermal colloidal stability and extraction control





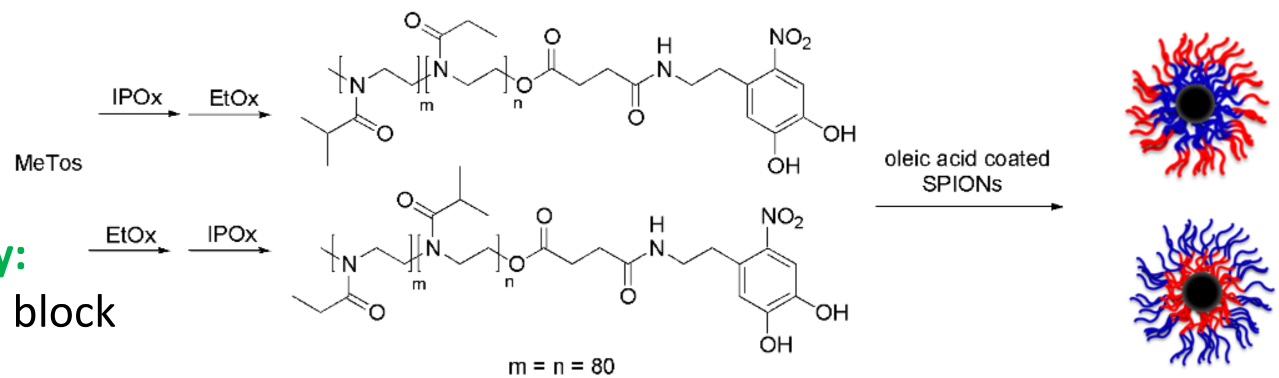
Dispersed | Aggregated | Precipitated | Redispersed

Heating by: alternating magnetic field through Néel relaxation of core

Shell compositions:
PNiPAm, PEtOx/PiPOx, polypeptoids

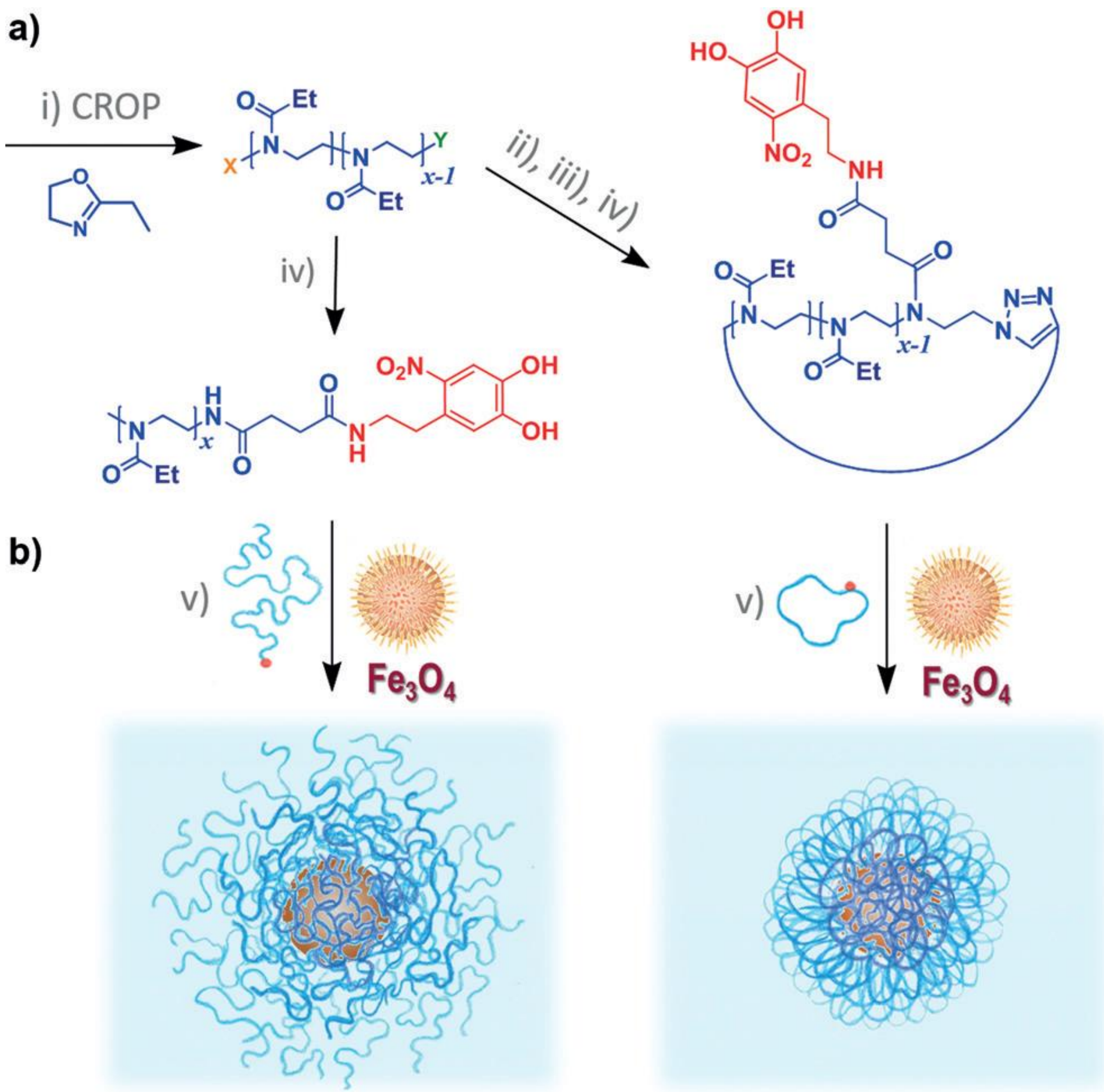
Shell morphology and topology:
Homo-, random-, gradient- and block copolymers; linear and cyclic

Polyoxazolines:



S. Kurzhals et al., Biomacromolecules (2018);
G. Morgese *et al.*, *Angew Chem* (2017); M. Schroffenegger *et al.*, Polymers (2018); N. Gal *et al.*, J Phys Chem (2018);
S. Kurzhals *et al.*, *ACS Appl Interf Mater* (2015); *Nanoscale* (2017); *Macromol Chem Phys* (2017); *J Coll Interf Sci* (2017)

Polymer brush topology – cyclic polymers

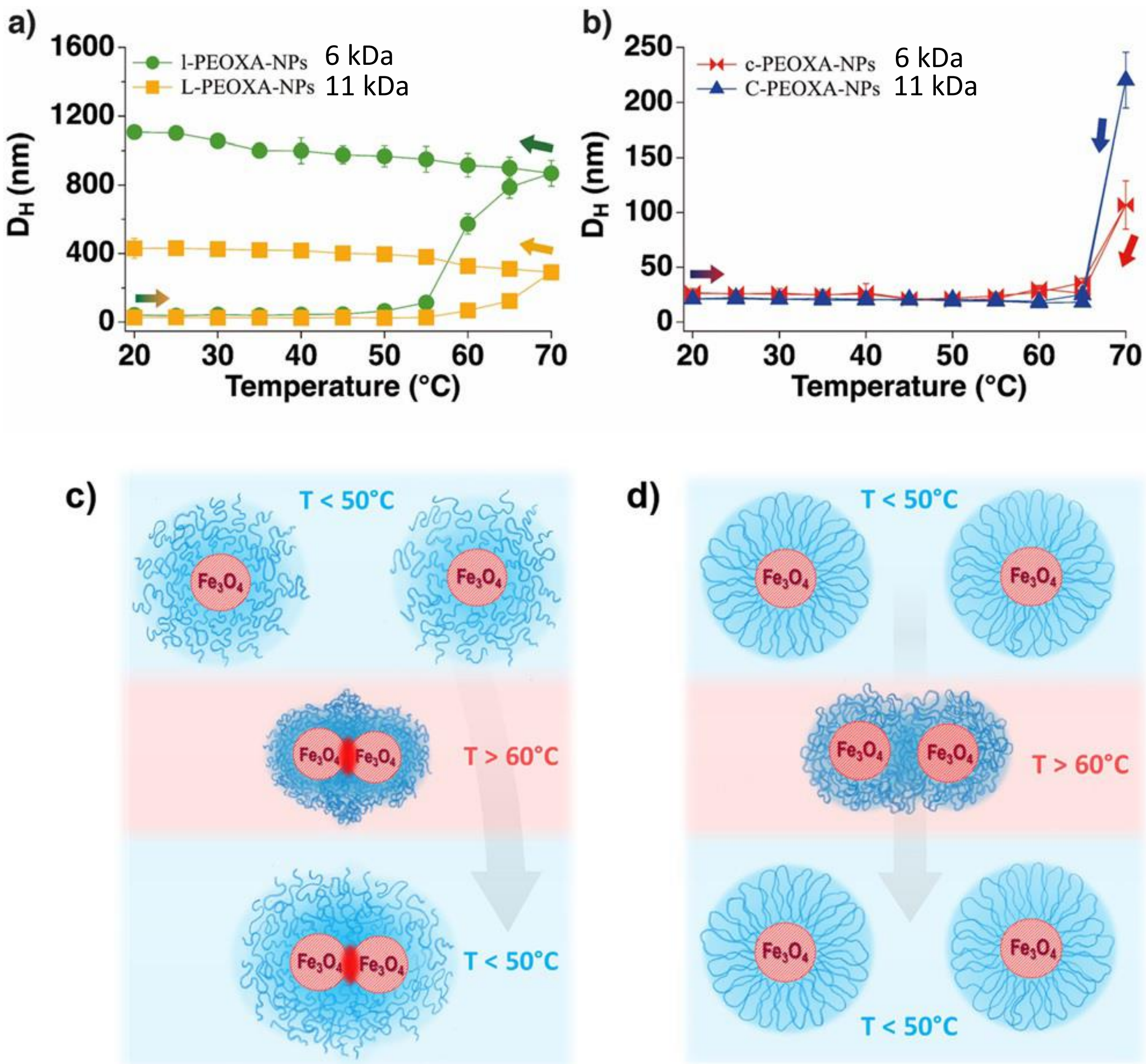


- Polymer topology influences brush morphology
- Grafted cyclic poly(2-ethyl-oxazoline) has shown higher protein resistance than linear on flat surfaces
- Grafted-to on monodisperse ion oxide nanoparticles

Collaboration:
Edmondo Benetti, ETH Zürich

G. Morgese *et al.*, *Angew Chem* (2017)

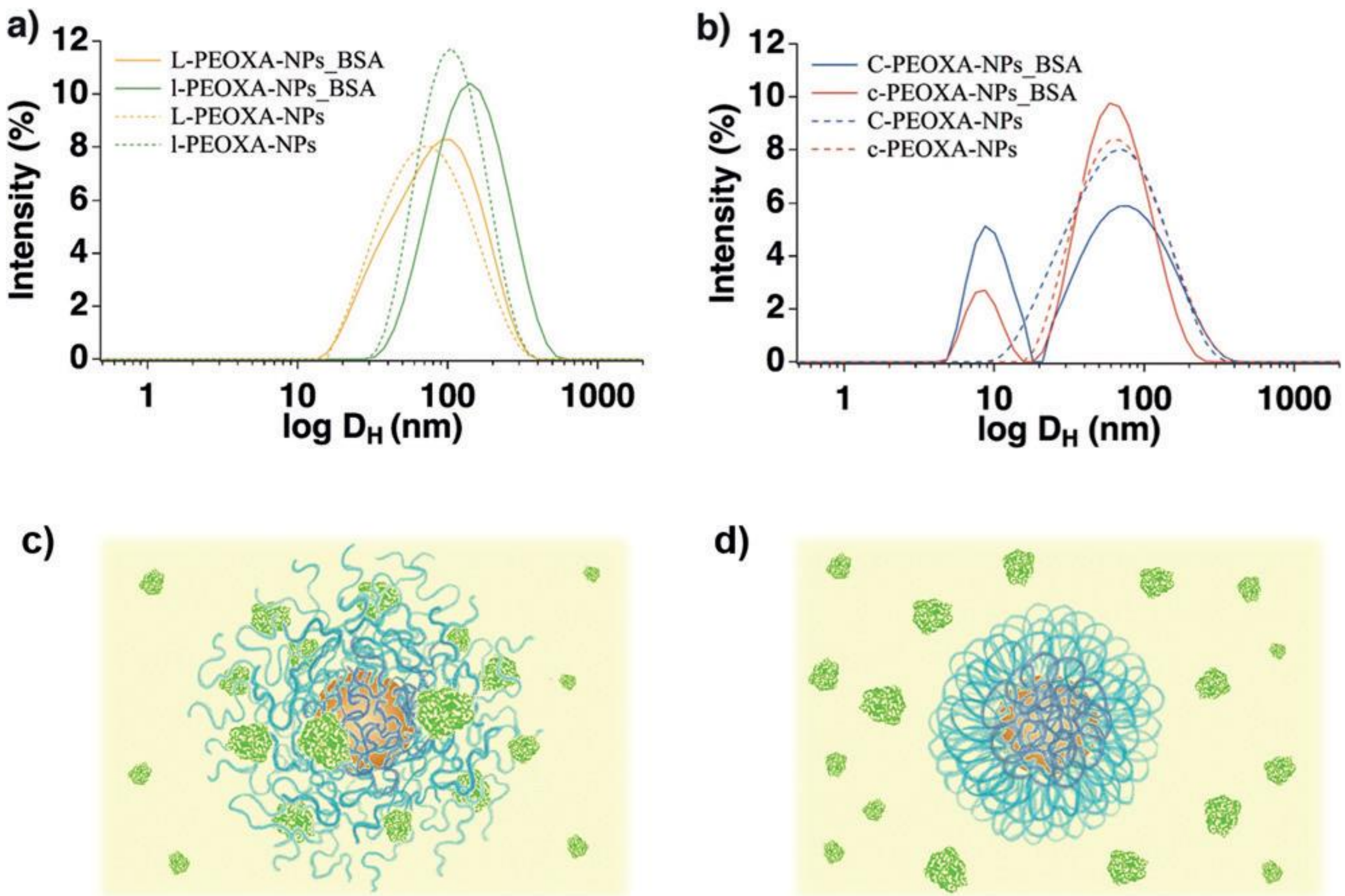
Polymer brush topology – cyclic polymers



- Linear PEtOx-grafted SPION aggregate irreversibly with temperature
- Cyclic PEtOx-grafted SPION prevents core-core aggregation and aggregation is reversible

G. Morgese *et al.*, *Angew Chem* (2017)

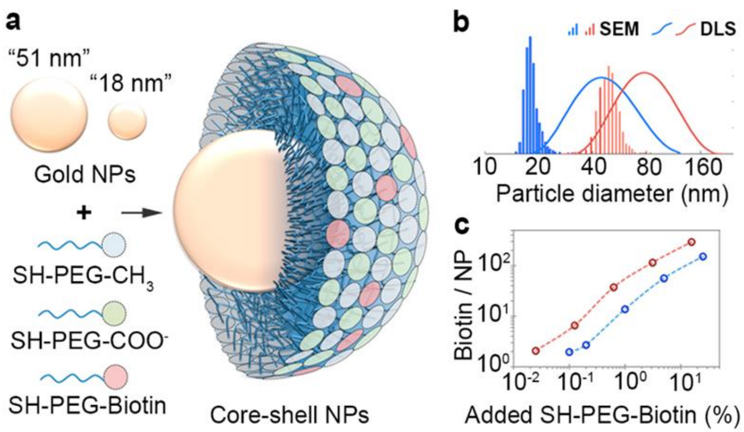
Polymer brush topology – cyclic polymers



- Linear PEtOx-grafted SPION show indications of protein adsorption in DLS and ITC
- Cyclic PEtOx-grafted SPION show little to no protein interaction

G. Morgese *et al.*, *Angew Chem* (2017)

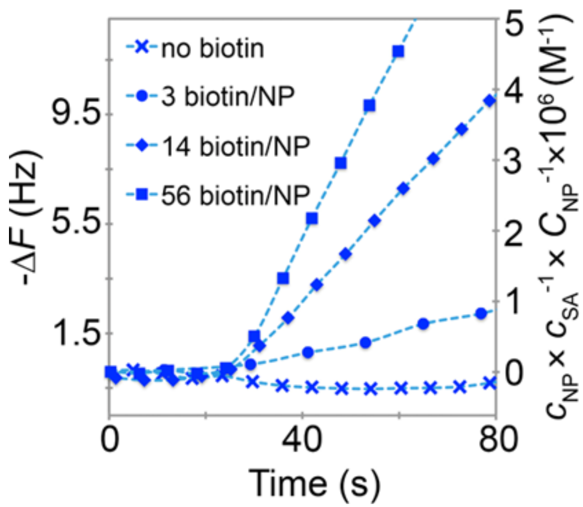
Size-dependent „specific“ binding



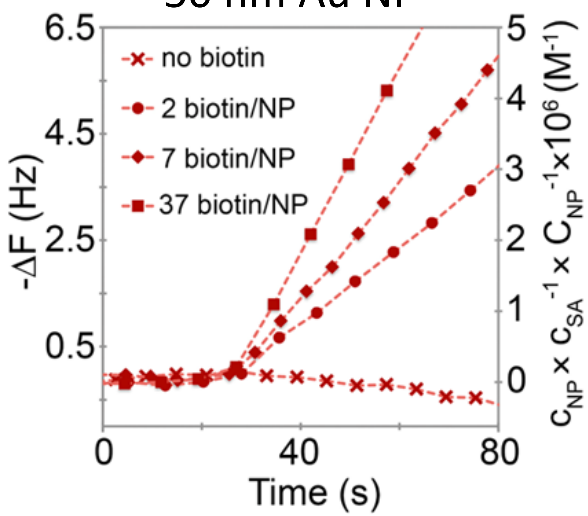
- PEGylated Au nanoparticles in the size range 15-60 nm
- Binding rate depends on number of binding ligands per particle
- **Large particles bind faster even at low ligand coverage**

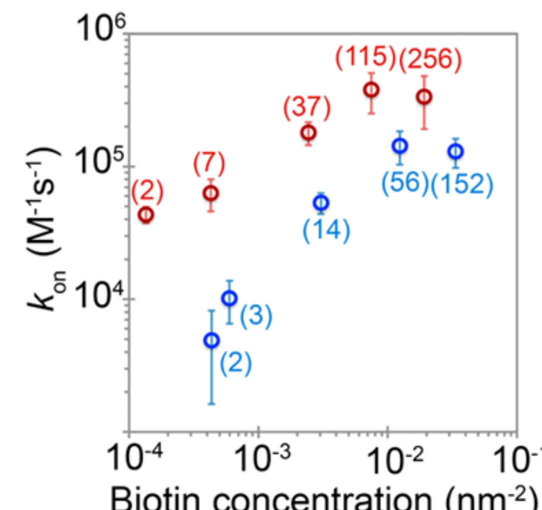
Why?

20 nm Au NP



50 nm Au NP



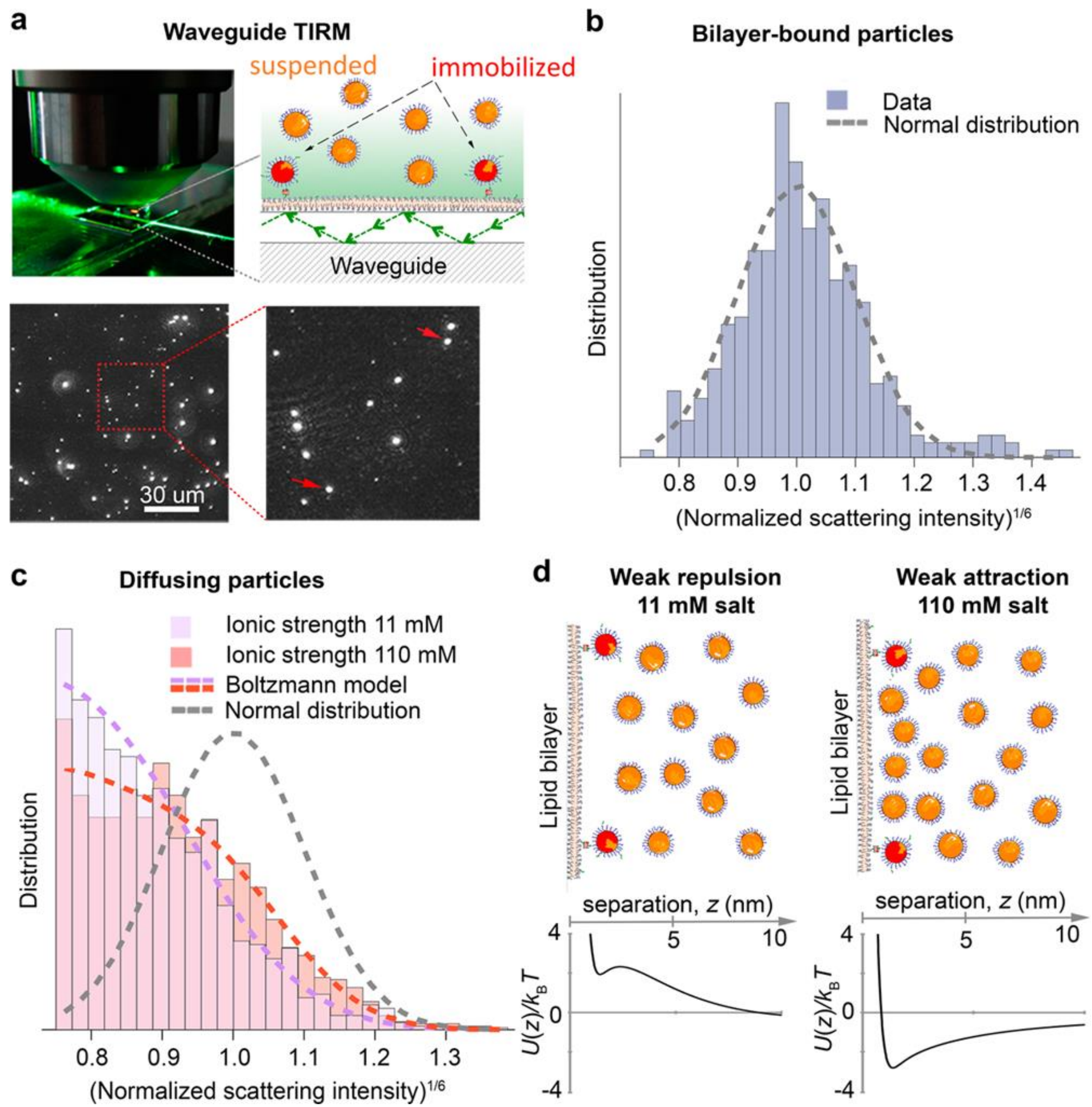


A. Lundgren *et al.*, *ACS Nano* (2016)

Size-dependent „specific“ binding

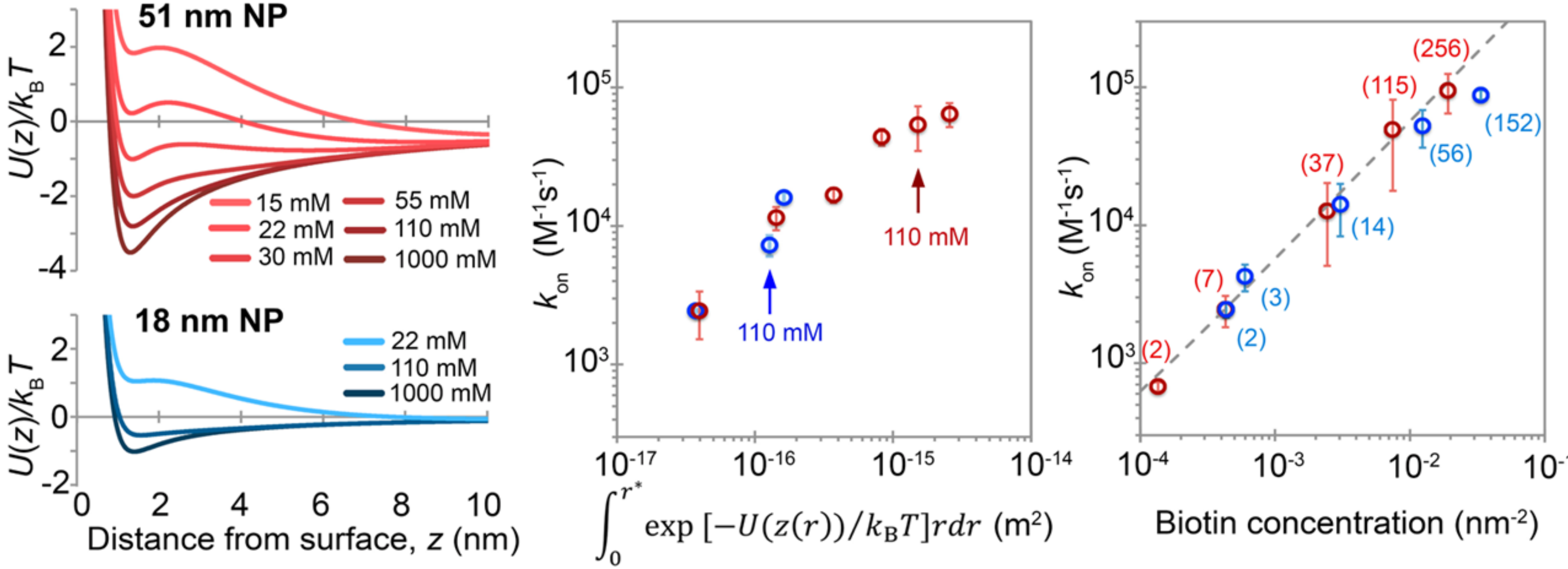
- The statistical distribution of nanoparticles close to a membrane surface can be measured by enhanced surface scattering from waveguide total internal reflection microscopy

- Colloidal interactions can be varied and the interaction potential between membrane and NP calculated



A. Lundgren *et al.*, *ACS Nano* (2016)

Size-dependent „specific“ binding



⇒ Large NPs experience stronger vdW attraction to the surface

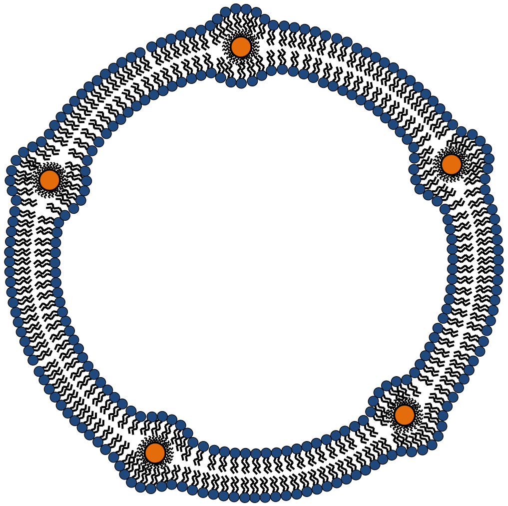
⇒ Large NPs reside on average longer at the membrane interface

⇒ Large particles demonstrate higher „effective affinity“ (avidity) for the same specific binding functionality

Valid for particle size and polarizability equivalent to viruses, exosomes and drug delivery nanoparticles when interacting with cells / cell uptake

A. Lundgren *et al.*, *ACS Nano* (2016)

Magnetically controlled drug delivery vesicles



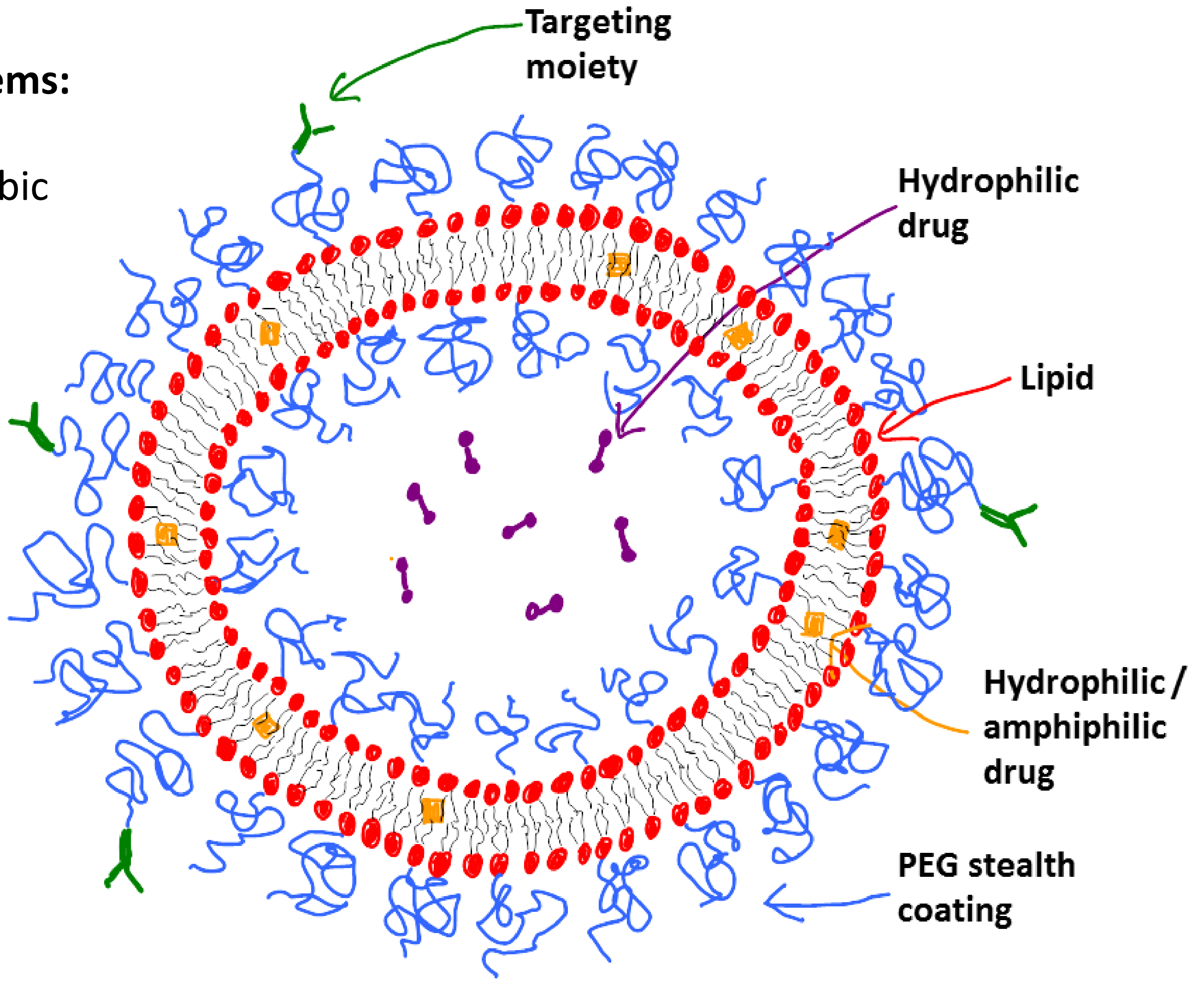
Application:
Transport and release of hydrophilic compounds (drugs)

Liposome drug delivery systems

Liposome drug delivery systems:

- High loading capacity
- Hydrophilic and hydrophobic drugs
- Biocompatible
- Stealth (with PEG-lipids incorporated)
- (Stable containers)
- Easy to functionalize with targeting moieties

Clinically approved (first "nanodrug" DOXIL®)



Liposome drug delivery release systems

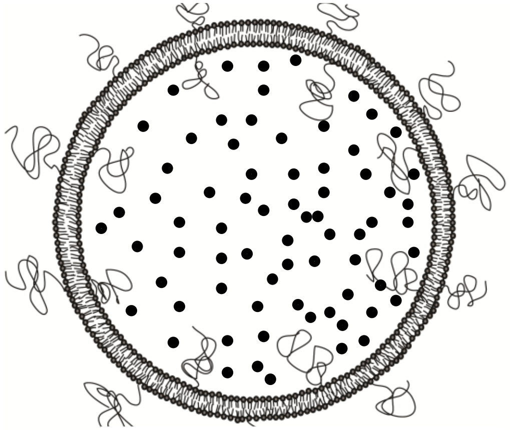
Major drawbacks:

- A stable stealth liposome is too stable to release drugs efficiently at the target location
- An unstable stealth liposome releases drugs while circulating

Thermosensitive liposomes are not a breakthrough system for triggered drug delivery

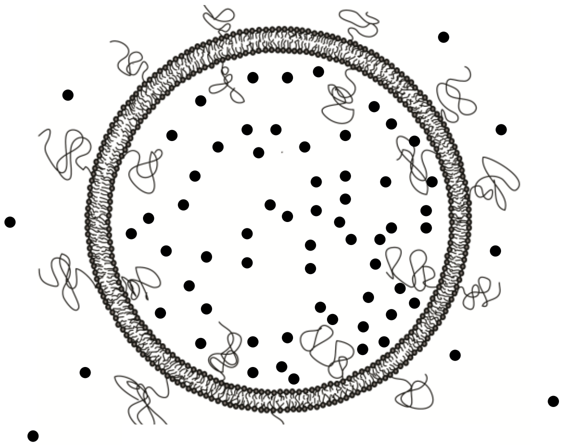
Inherent problem:

T_m > application temperature



inefficient release

T_m ≈ application temperature

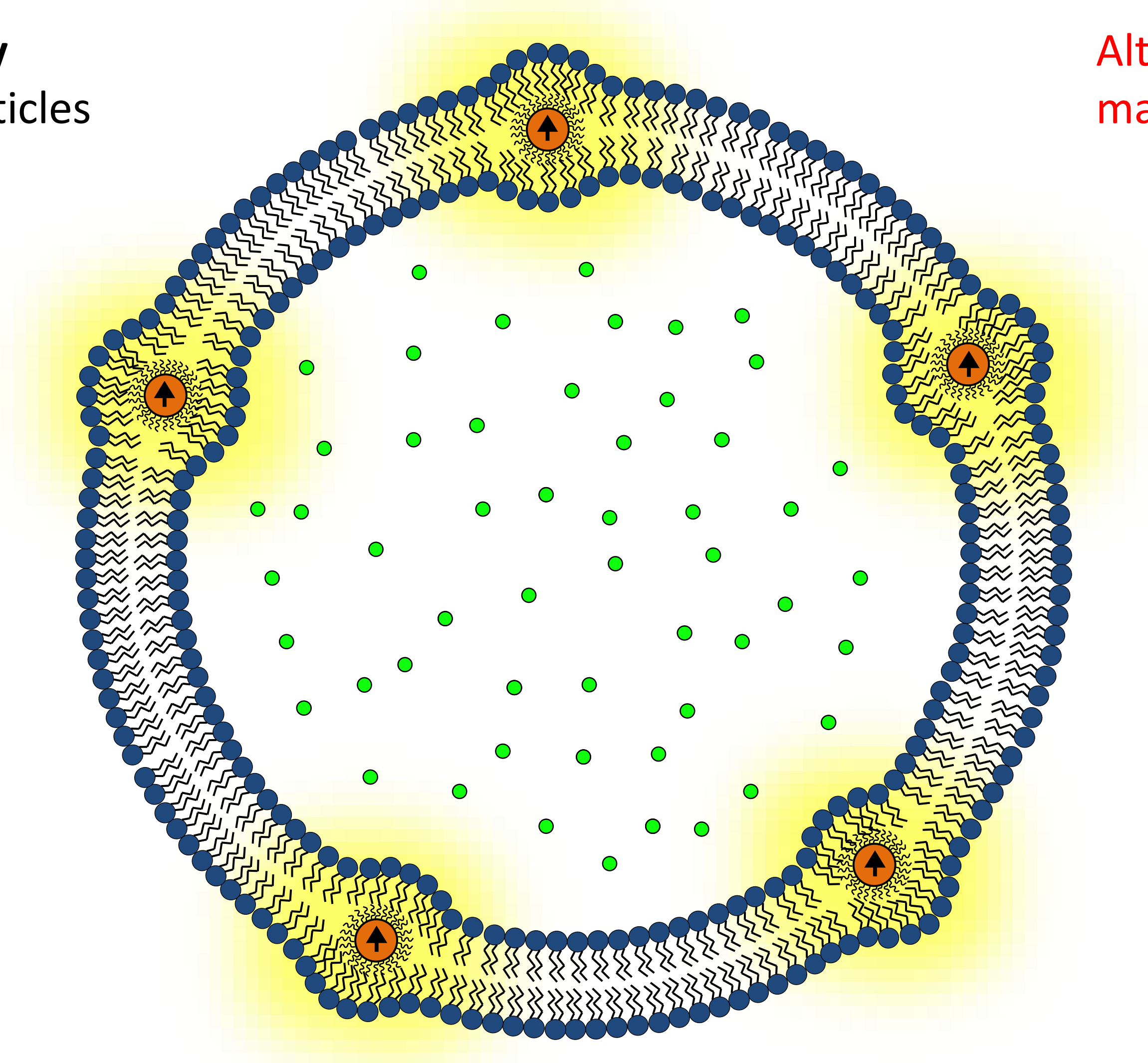


leaky liposomes

Magnetically triggered release from liposomes

Hydrophobically coated nanoparticles

Alternating magnetic field



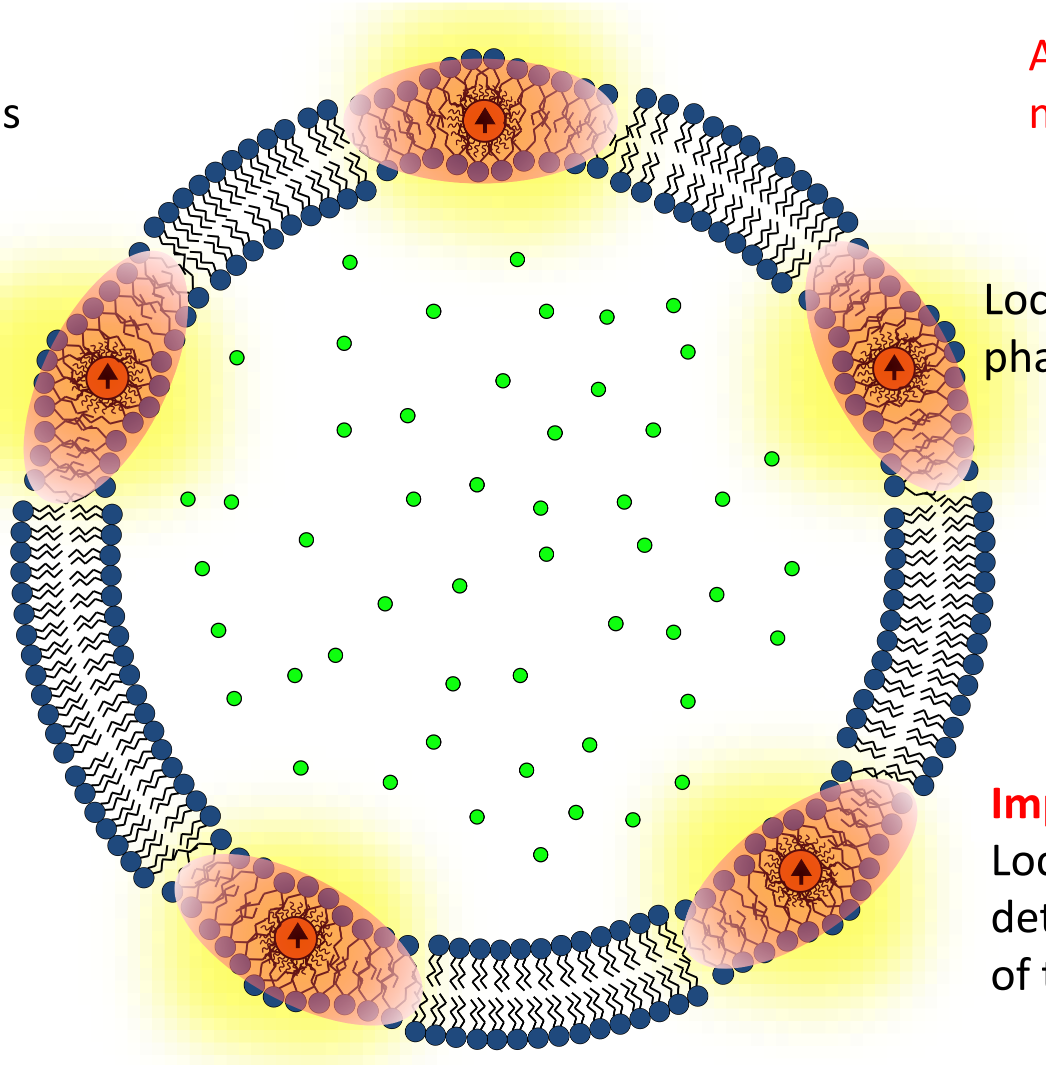
E. Amstad *et al.*, *Nanomedicine* (2011)
E. Reimhult, *New Biotechnol* (2015)

Magnetic heating of iron oxide NPs allows use of lipid compositions with T_m high above body T, e.g. DSPC ($T_m = 55°C$) or DPPC ($T_m = 41°C$).

Magnetically triggered release from liposomes

Hydrophobically coated nanoparticles

Alternating magnetic field



Local membrane phase transition

Important:
Local heating ⇒ No detrimental heating of the environment

E. Amstad *et al.*, *Nanomedicine* (2011)
E. Reimhult, *New Biotechnol* (2015)

Magnetic heating of iron oxide NPs allows use of lipid compositions with T_m high above body T, e.g. DSPC ($T_m = 55°C$) or DPPC ($T_m = 41°C$).

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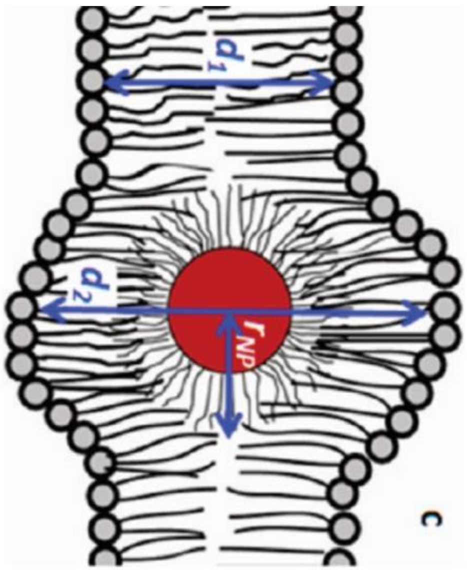
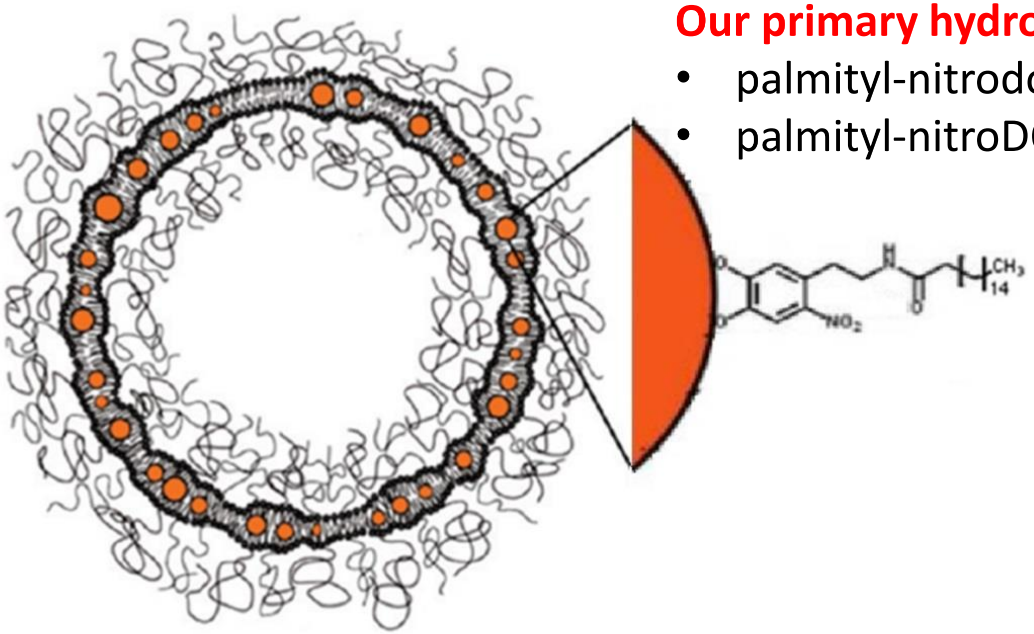
Monodisperse hydropbobic core-shell SPIONs in the membrane





Our primary hydrophobic ligands:

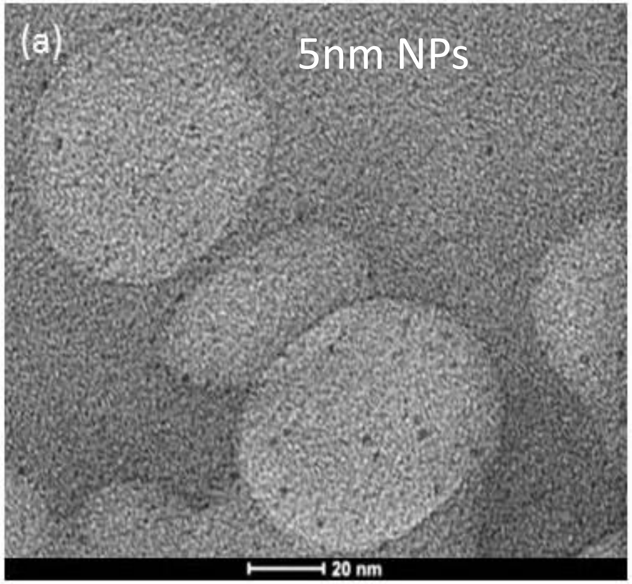
- palmityl-nitrodopamine (pNDA)
- palmityl-nitroDOPA (pNDOPA)

- There is limited space for nanoparticles within a lipid vesicle membrane
- The imposed membrane curvature yields an energy penalty
- The nanoparticle has to be hydrophobic with a stable coating to reside in the membrane
- **Complete replacement of excess oleic acid for stable ligand requires special methods**

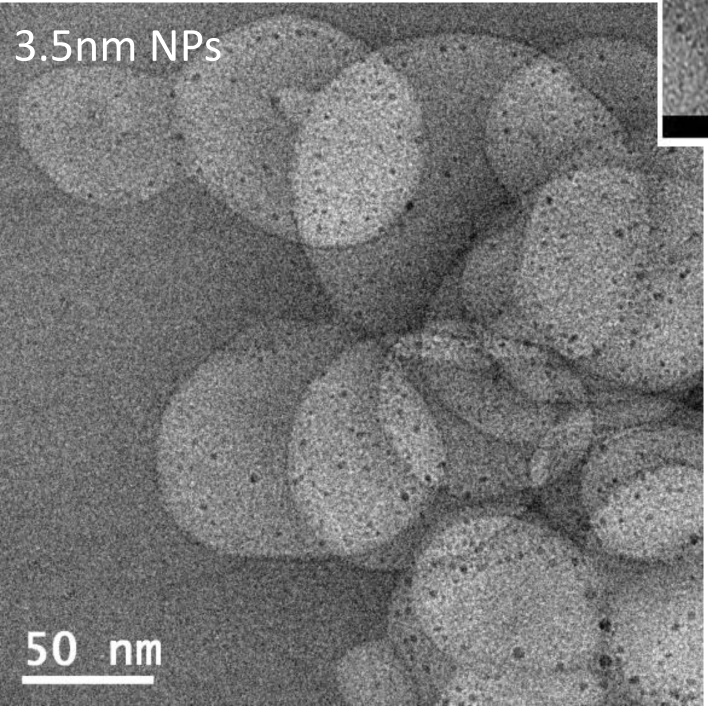
B. Shirmardi et al., *Nanoscale* (2017); O. Bixner et al., *Langmuir* (2015);
E. Reimhult, *New Biotechnol* (2015); E. Amstad et al., *Nano Lett* (2011)

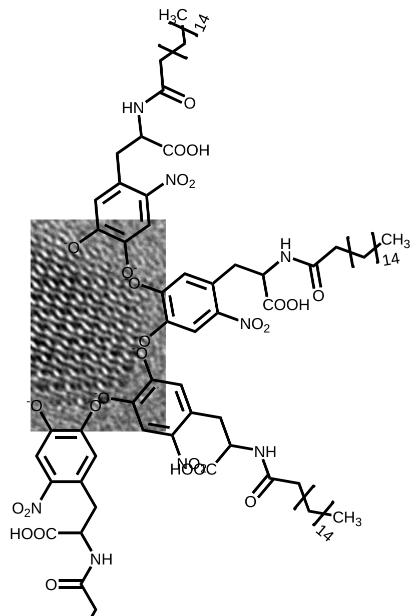
Nitrocatechol-palmityl coated particles incorporated in liposomes

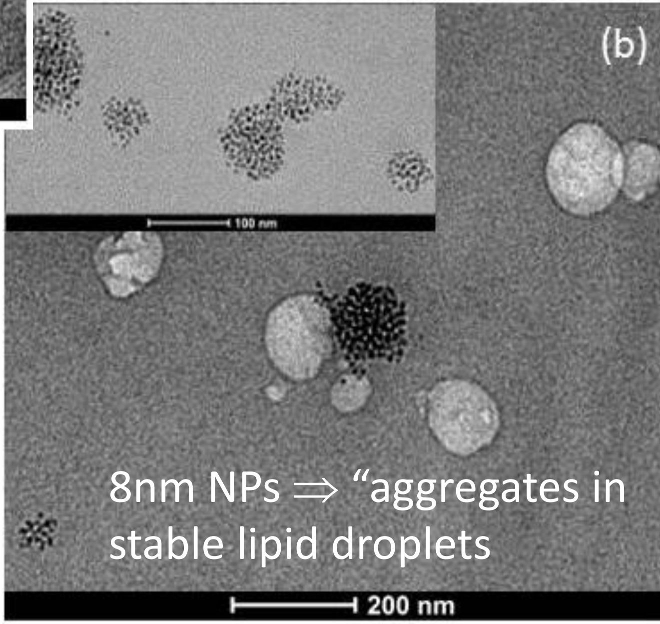
- Particles dispersed and colloidally stable within the membrane
- Particles ∅ **< 5.5nm** (estimated shell included) incorporated in membrane



- **Requires irreversibly grafted hydrophobic shell**
- >5 wt% only stable when ***all*** oleic acid is removed and replaced by P-NDA





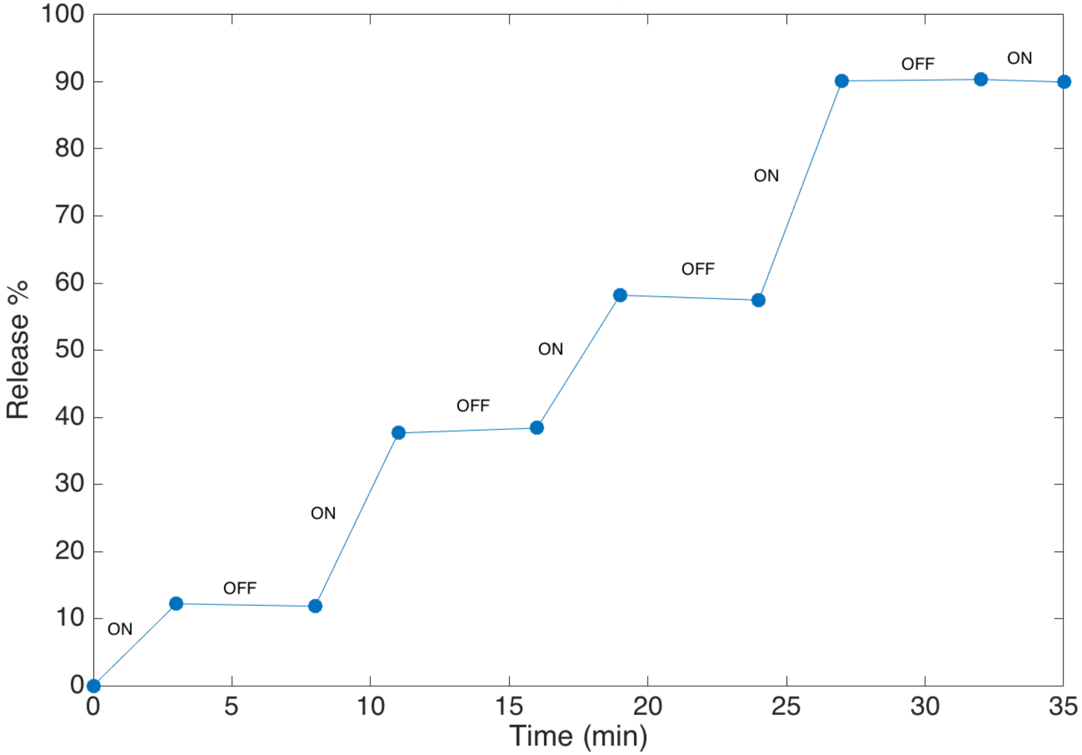


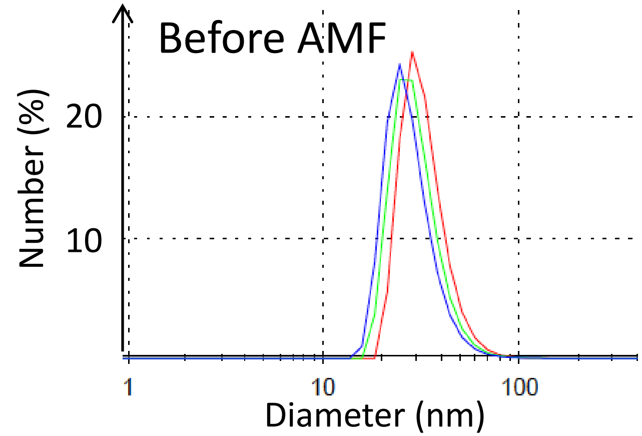
E. Amstad *et al.*, *Nano Lett* (2011)

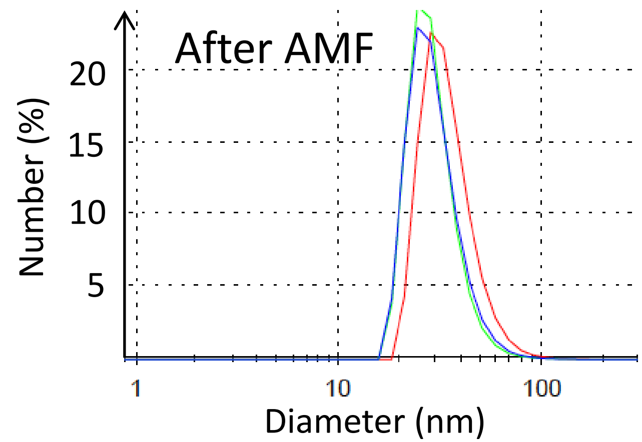
O. Bixner *et al.*, *J Coll Interf Sci* (2016)

Magnetically triggered release from liposomes

4 wt% 4-nm SPION in DPPC-PEG-liposomes loaded with calcein







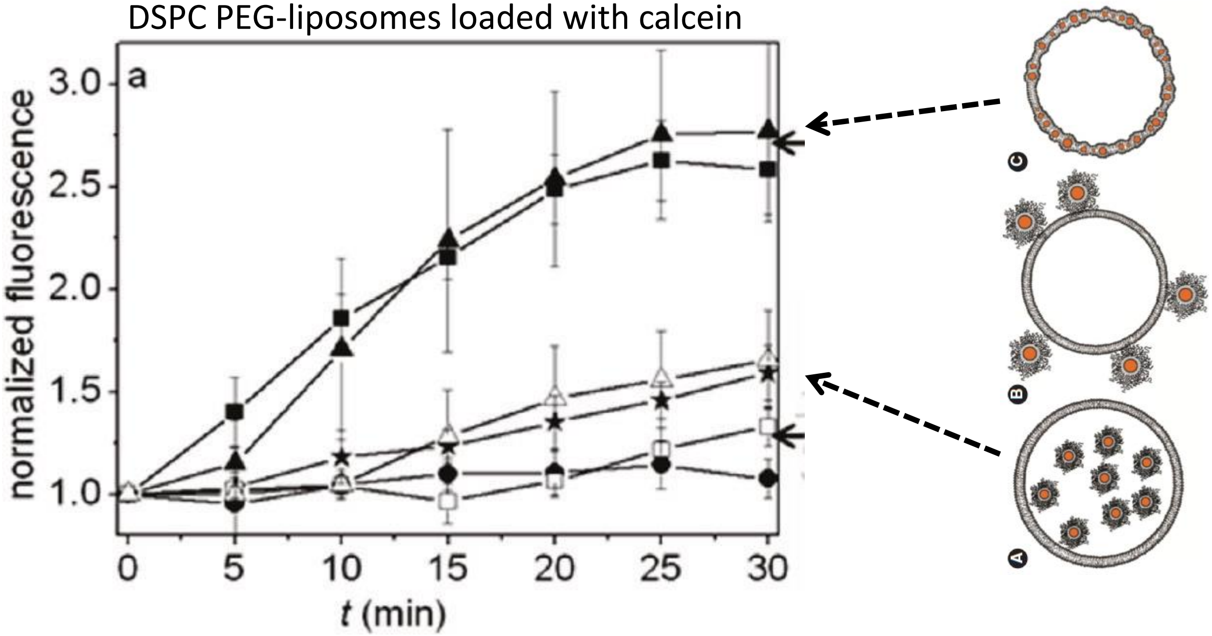
- Release only occurs when the alternating magnetic field is switched on
- AMF pulse length can be used to control release rate
- Vesicle size and integrity unperturbed

⇒ **enables pulsed release**

B. Shirmardi Shaghasemi *et al.*, *Sci Rep* (2017)

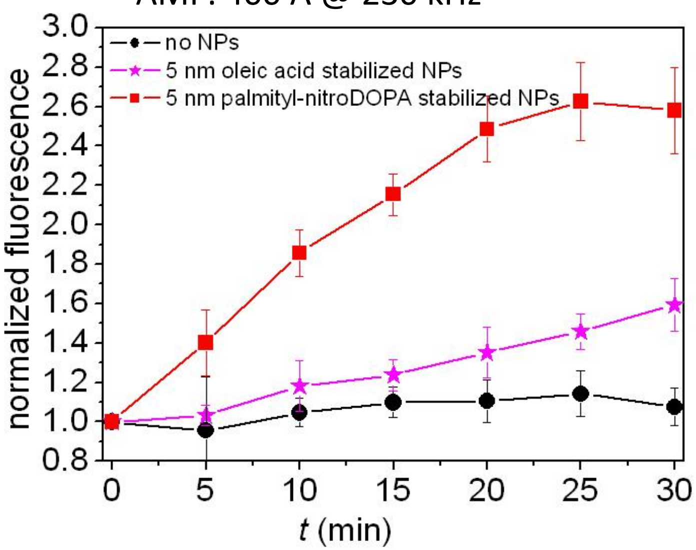
Magnetically triggered release from liposomes

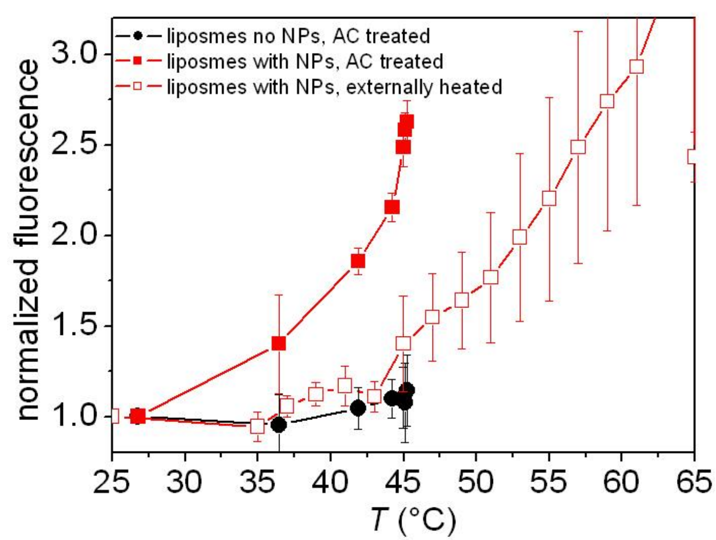
DSPC PEG-liposomes loaded with calcein

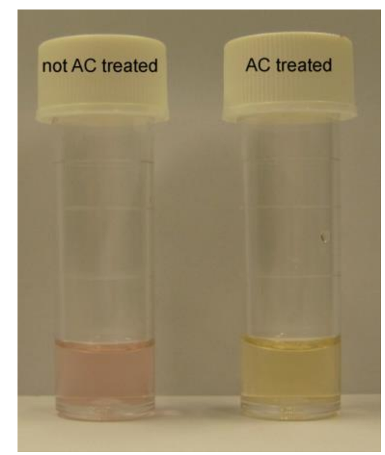


- Heat diffusion in water requires heating of SPION **in membrane**
- Release achieved **without heating the bulk**
- Only **well-stabilized SPION** allow for efficient release (no oleic acid present)

AMF: 400 A @ 230 kHz

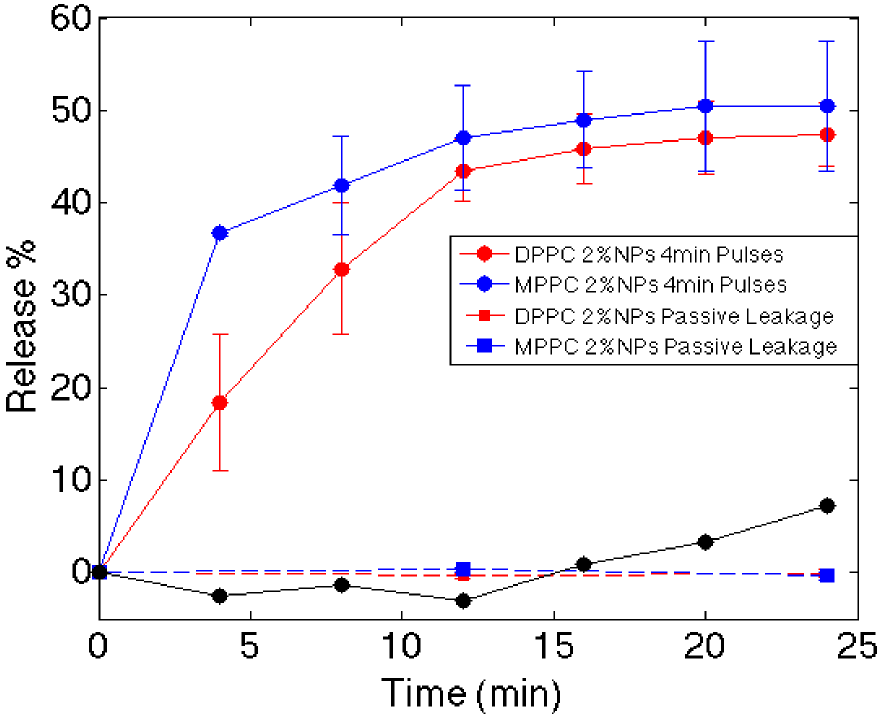


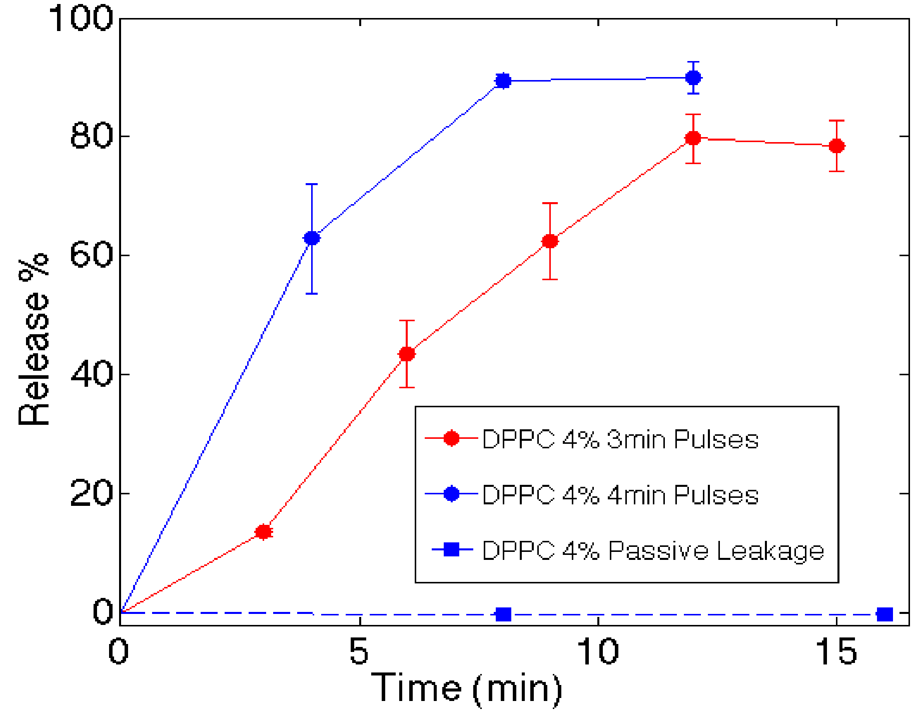




E. Amstad *et al.*, *Nano Lett* (2011)

Magnetically triggered release from liposomes



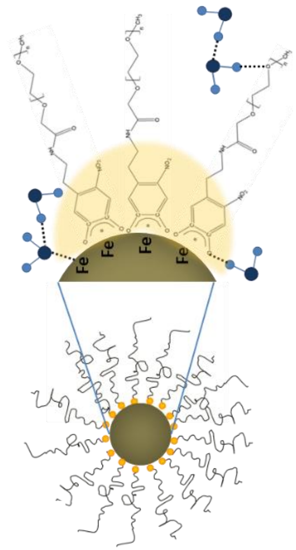


- The lipid membrane T_m determines the length of pulses needed to achieve a desired rate of release
- **Pulsed release rate can be controlled by:**
  - Lipid composition (T_m)
  - SPION loading wt%
  - Pulse length
  - Pulse frequency

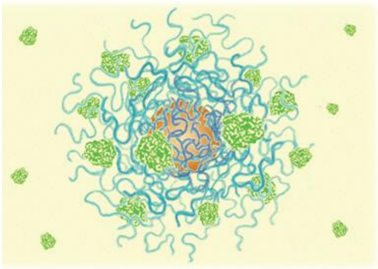
With **negligible passive release over > 1 week** (by removal of all OA and solvent impurities)

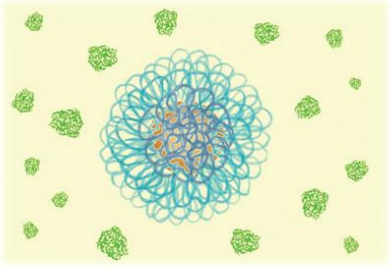
B. Shirmardi Shaghasemi *et al.*, *Sci Rep* (2017)

Summary

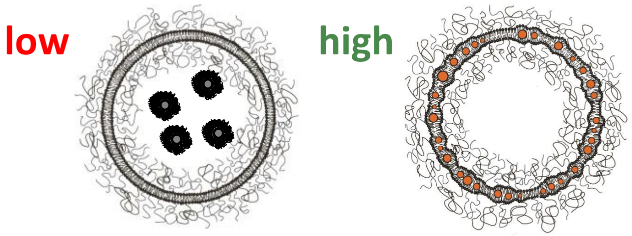


- Monodisperse superparamagnetic core-shell nanoparticle have been synthesized with high chemical and colloidal stability.
- Dispersant grafting is key to control NP stability and surface presentation of functionalities. Densely grafted shell morphologies and topologies are advantageous for biomedical applications.





- Stable, membrane-embedded NPs yield efficient triggered liposome drug release.



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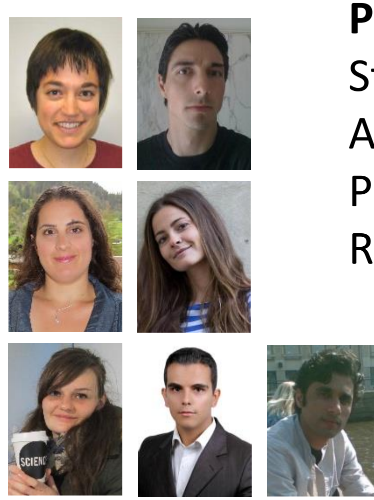

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Collaborators: Dr. Edmondo M. Benetti (ETHZ, CH), Prof. Thomas Helbich (Med Uni Wien, AT), Prof. Fredrik Höök (Chalmers, SE)

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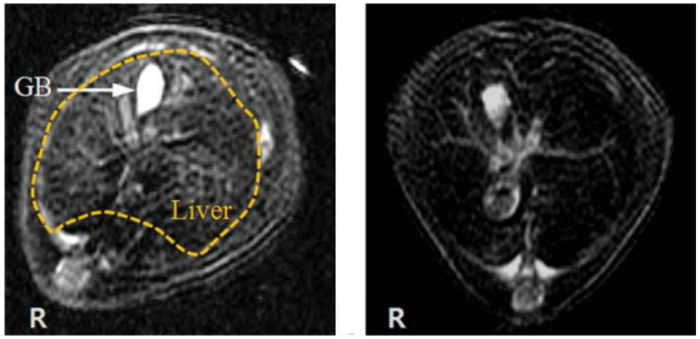
MARIE CURIE ACTIONS
ESRF

Applications of magnetic iron oxide nanoparticles

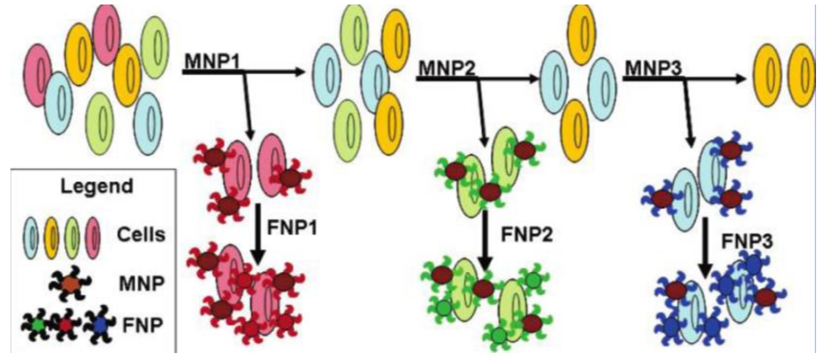
MR contrast agents



pre-contrast post-contrast

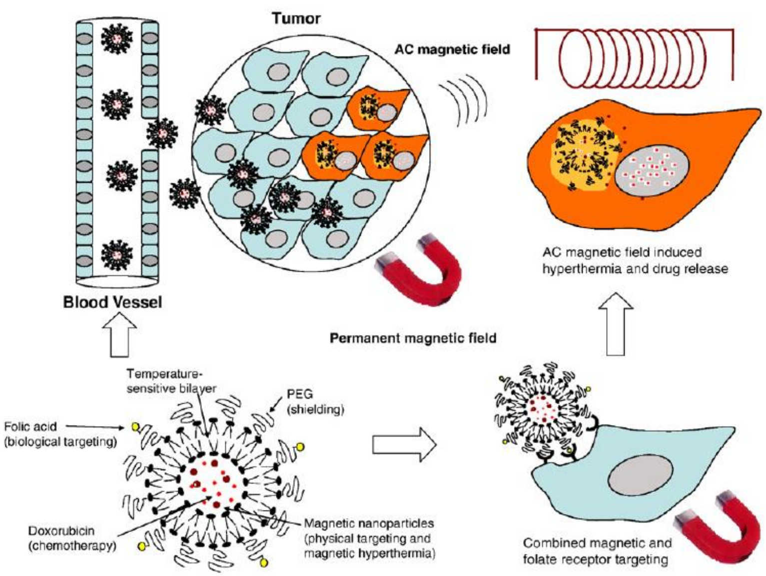
C. M. Lee, *et al., Magnet Reson Med* ***2009, 62, 1440.***

Separation



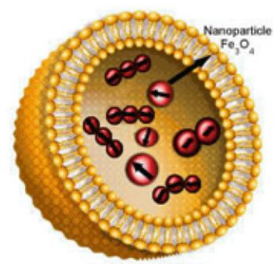
J. E. Smith, *et al., Analytical Chemistry* ***2007, 79, 3075***

Therapy: hyperthermia



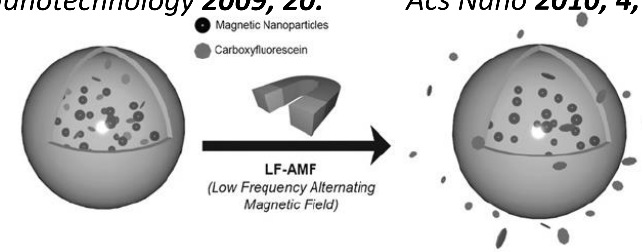
P. Pradhan *et al., Journal of Controlled Release* ***2010, 142, 108.***

Drug delivery



E. R. Cintra, *et al.*
Nanotechnology ***2009, 20.***

Y. J. Chen *et al.,*
Acs Nano ***2010, 4, 3215***

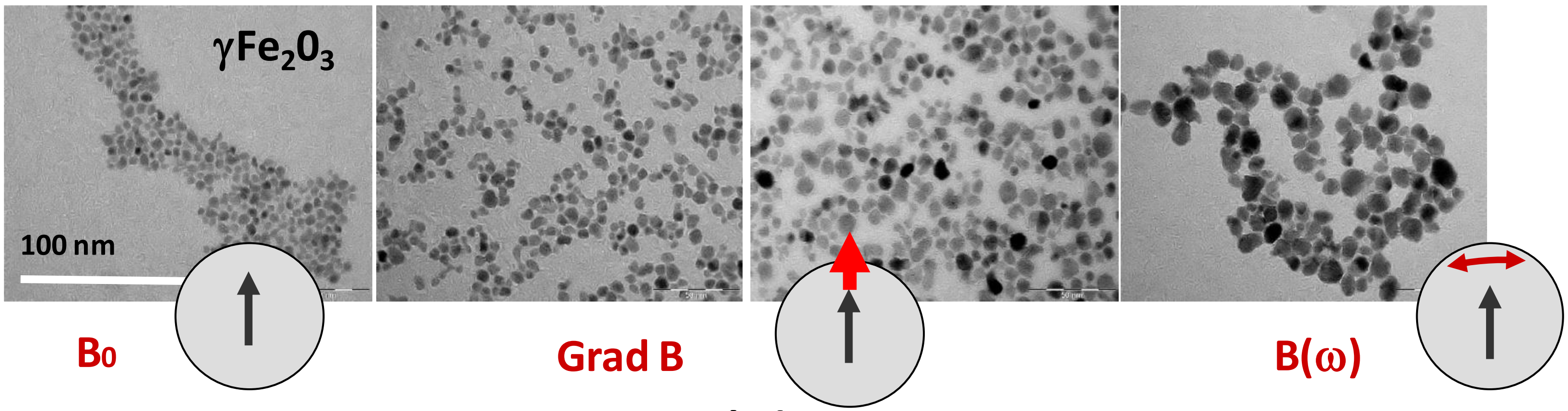


S. Nappini, *et al., Soft Matter* ***2010,*** *6, 154*

Why magnetic nanomaterials for biotech applications?

Magnetic fields penetrate tissue

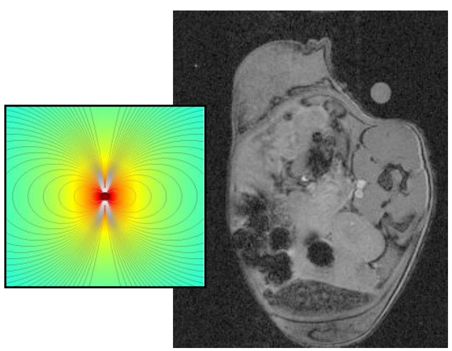
Superparamagnetic nanoparticles (∅ 3-15nm)



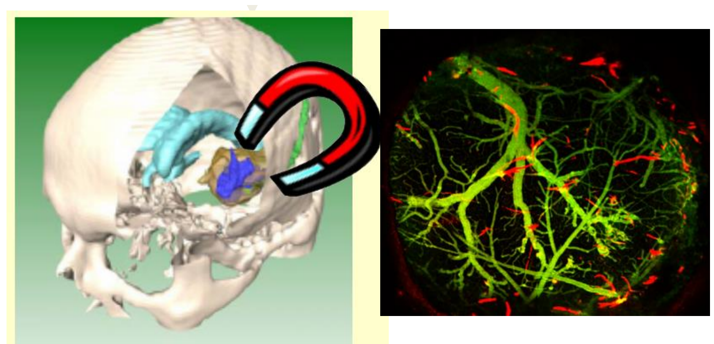
Magnetic moment

Magnetic gradient force

Oscillating magnetic field



Imaging / detection



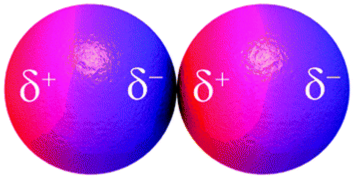
Targeting /manipulation

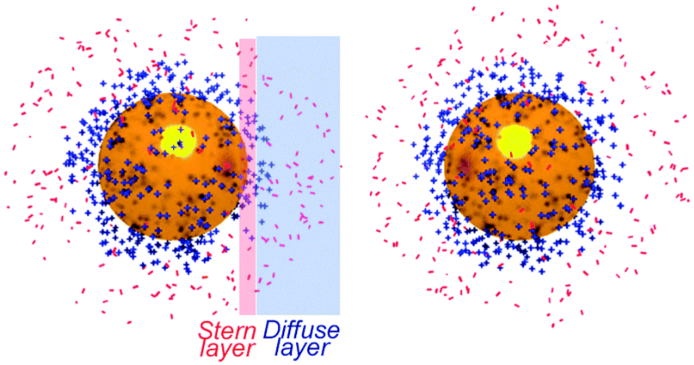
Hyperthermia treatment / actuation /release

Colloidal interactions: the fight to keep things nano

- **Dispersion forces: London-van der Waals forces**

  Very strongly attractive between all surfaces at short range.





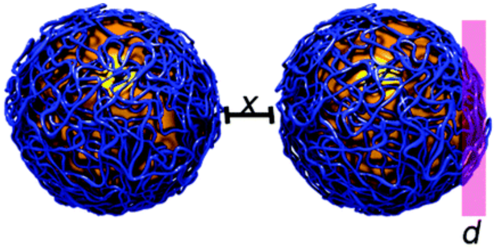
- **Double-layer (electrostatic) forces**

  Either attractive (opposite charge) or repulsive (same charge).

- **Entropic forces: hydrophobic and osmotic**

  Hydrophobic particles (less polar than water) aggregate in water.

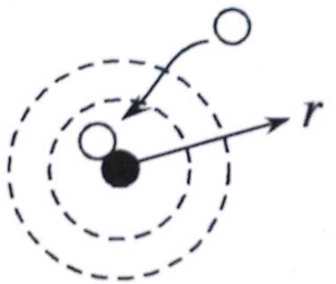
  Osmotic forces can be understood as a pressure difference caused by a difference in chemical potential (concentration of a polymer or other solute). Polymers cause strong (often) attractive and **repulsive (steric) interactions** between particles.



  Polymer bridging

Hard sphere aggregation under Brownian motion

The half-life of the dispersion is: $t_{1/2} = \frac{1}{k_r n_0} = \frac{3\mu}{4 k_B T n_0}$



How about the dependence on particle size?

$\Rightarrow$ There is **no dependence on particle radius** for a constant number concentration!

How about the dependence on particle size for a constant volume (material) fraction?

$$n_0 = \phi / \left(\frac{4\pi a^3}{3} \right) \quad \Rightarrow \quad t_{1/2} = \frac{3\mu}{4 k_B T \phi} \frac{4\pi a^3}{3} = \frac{\pi \mu a^3}{k_B T \phi}$$

For a given volume fraction the ***colloidal stability drops steeply with decreasing size***.

"Explains" why colloidal systems with nanoparticles are so hard to keep stable over long times, which includes biological fluids.

Hard sphere aggregation under Brownian motion

Table 7-3: Half-lives for perikinetic aggregation of spherical particles in water at 20°C.

(a) for various number concentrations of 1-μm diameter particles.

n_0 (#/cm^3)	ϕ (for $d = 1$ μm)	$t_{1/2}$
10^{11}	0.052	1.85 s
10^{9}	0.00052	3.09 min
10^{7}	0.0000052	5.14 hr

(b) for various particle diameters at a constant volume fraction of 0.05.

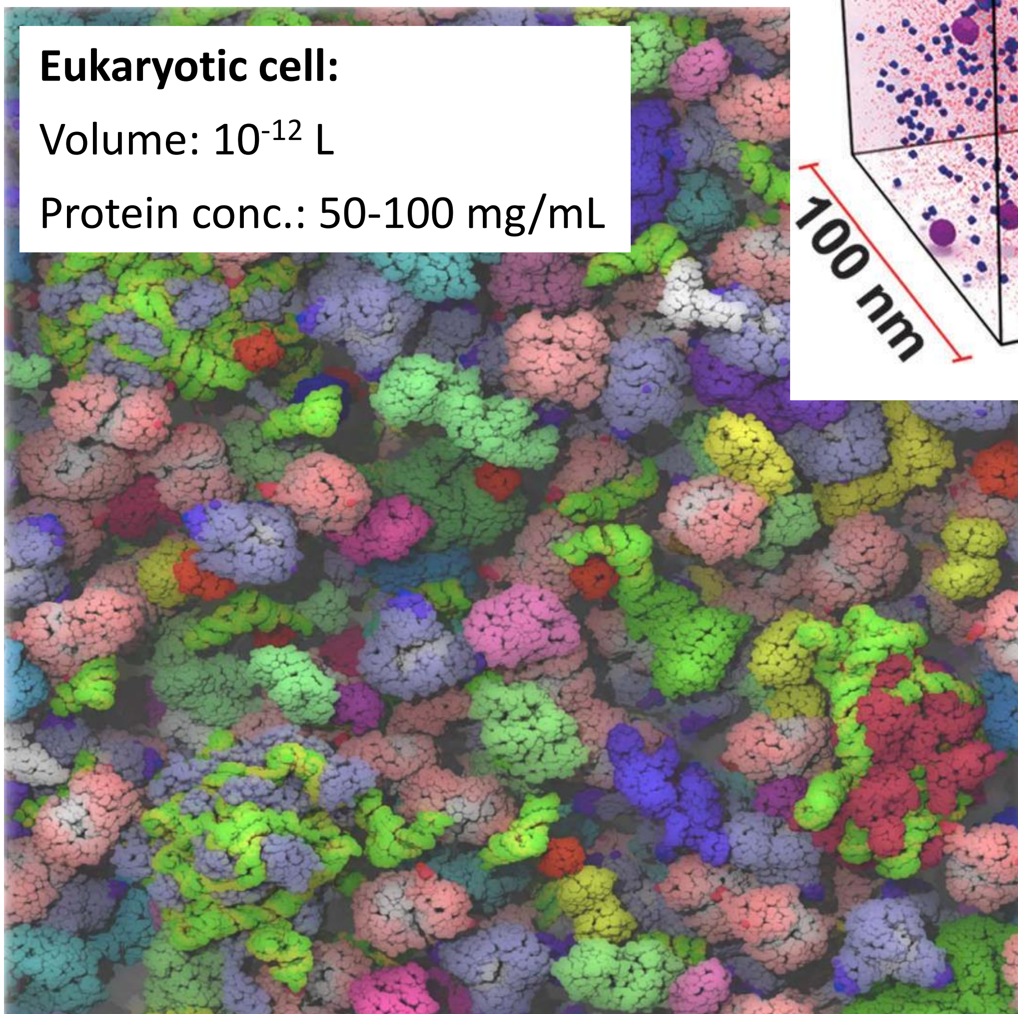
D	n_0	$t_{1/2}$
1 μm	9.55×10^{10}	2.16 s
100 nm	9.55×10^{13}	2.16 ms
10 nm	9.55×10^{16}	2.16 μs

Size of drug delivery vesicles → 100 nm

Size of proteins and NPs → 10 nm

Concentration of colloids in biology

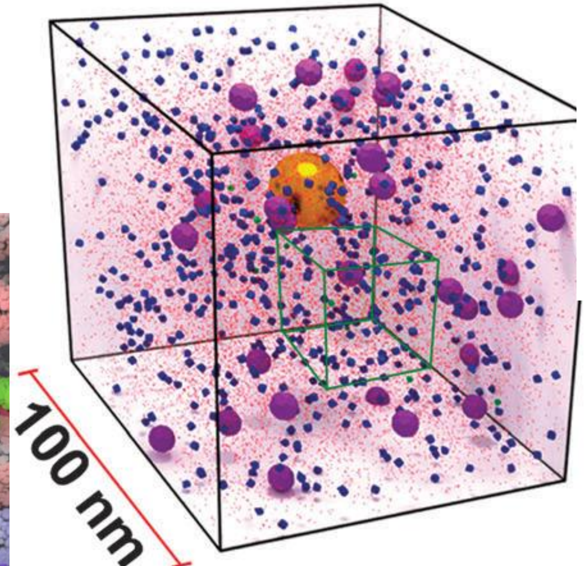
A simulation of the protein density inside a cell:



Eukaryotic cell:

Volume: 10^{-12} L

Protein conc.: 50-100 mg/mL



NP in 10% serum simulation:

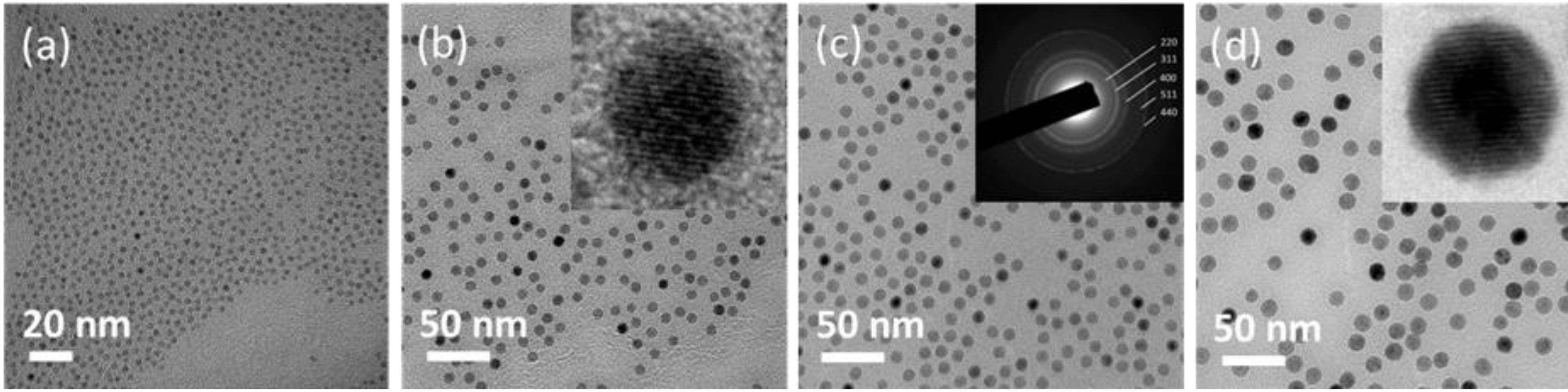
Volume: 10^{-18} L

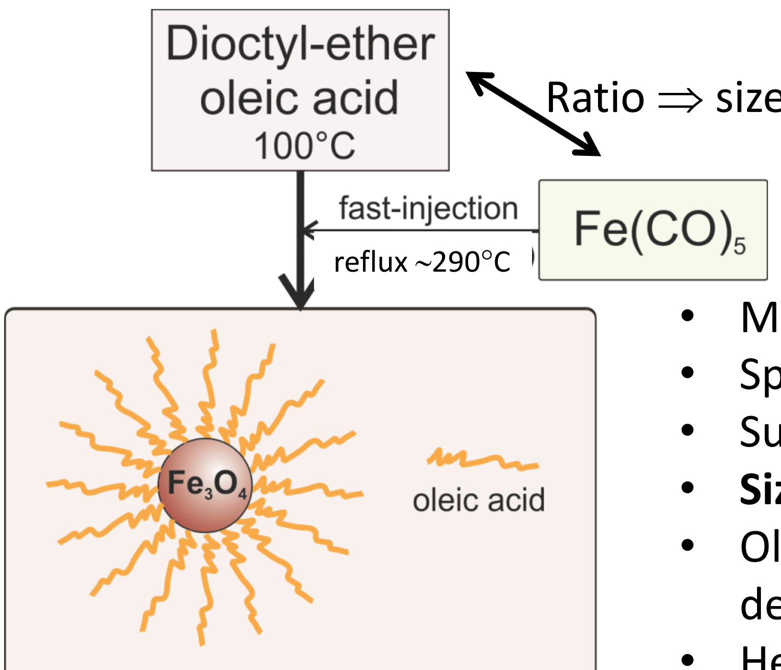
Protein conc.: 7.5 mg/mL

- ➢ Every surface is exposed to frequent molecular adsorption
- ➢ A protein is on average 10 nm from another surface (several volume-%)

⇒ Non-colloidally stable particles will aggregate rapidly

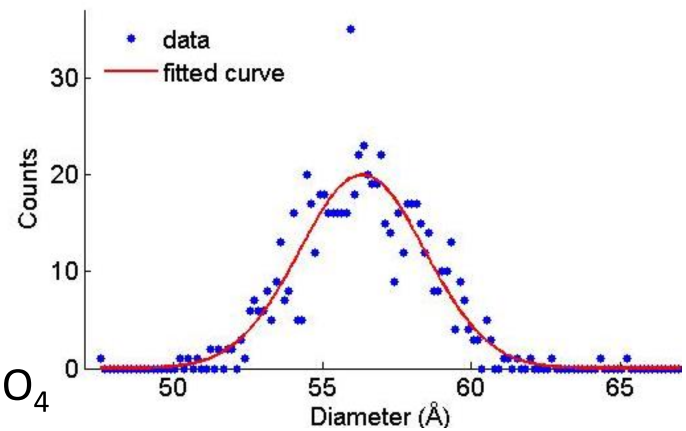
Core-shell NP synthesis: core





Adapted from Park *et al. Nat Mater* **3**:891

- Monodisperse ($\sigma < 5\%$)
- Spherical
- Superparamagnetic Fe_3O_4
- **Size range 3-15 nm**
- Oleic acid ratio determines size
- Heating ramp determines mono-dispersity

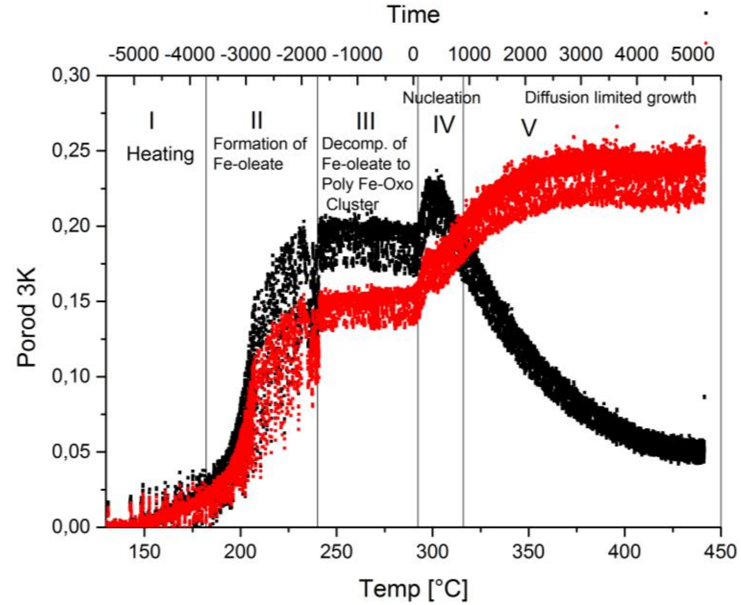


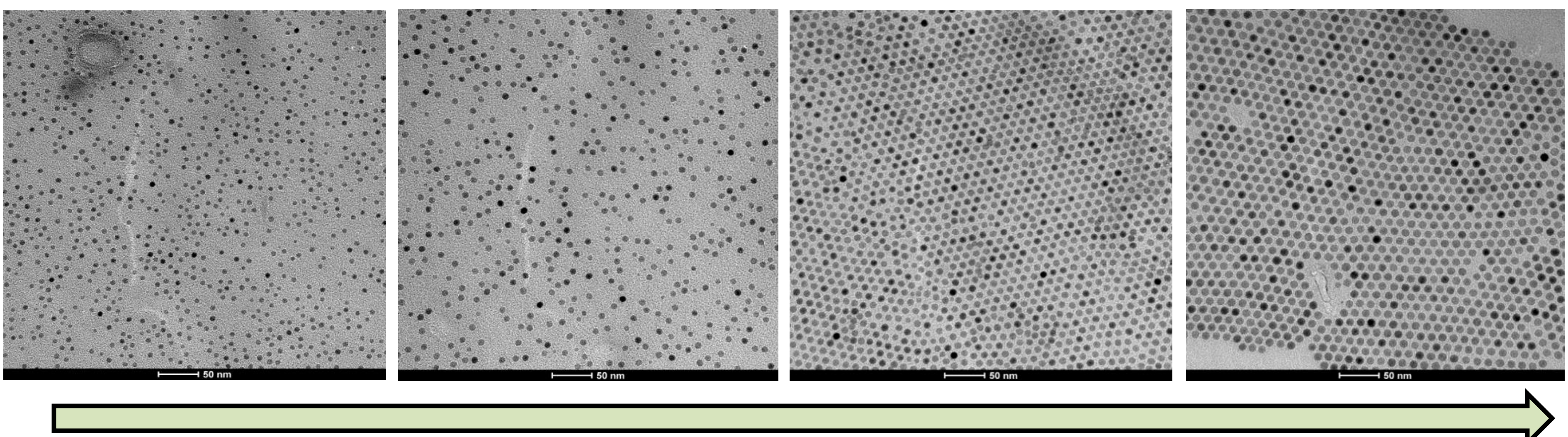
A. Lassenberger *et al.*, *in preparation*

Core-shell NP synthesis: core

- ✓ Controlled burst nucleation
- ✓ Followed by homogeneous growth

⇒ **Extremely monodisperse, size-controlled SPION**



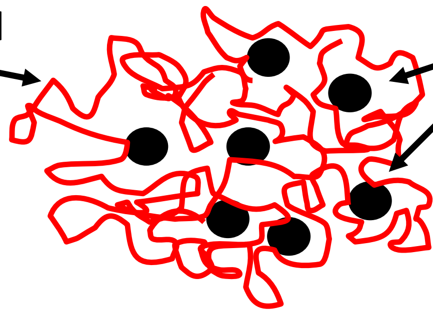


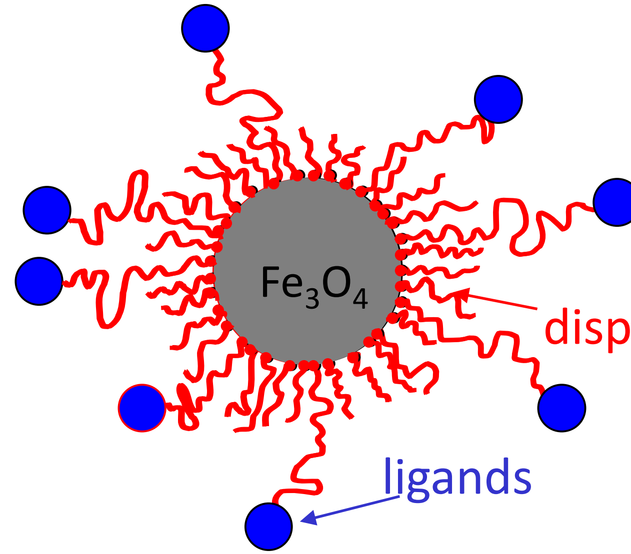
Growth time

T. Grünewald *et al.*, *in preparation*

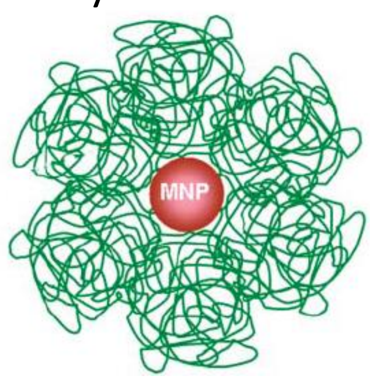
Stabilization of iron oxide nanoparticles

Resovist/Feridex
(clinical benchmark)





Crosslinked shell or multiple reversibly bound anchors



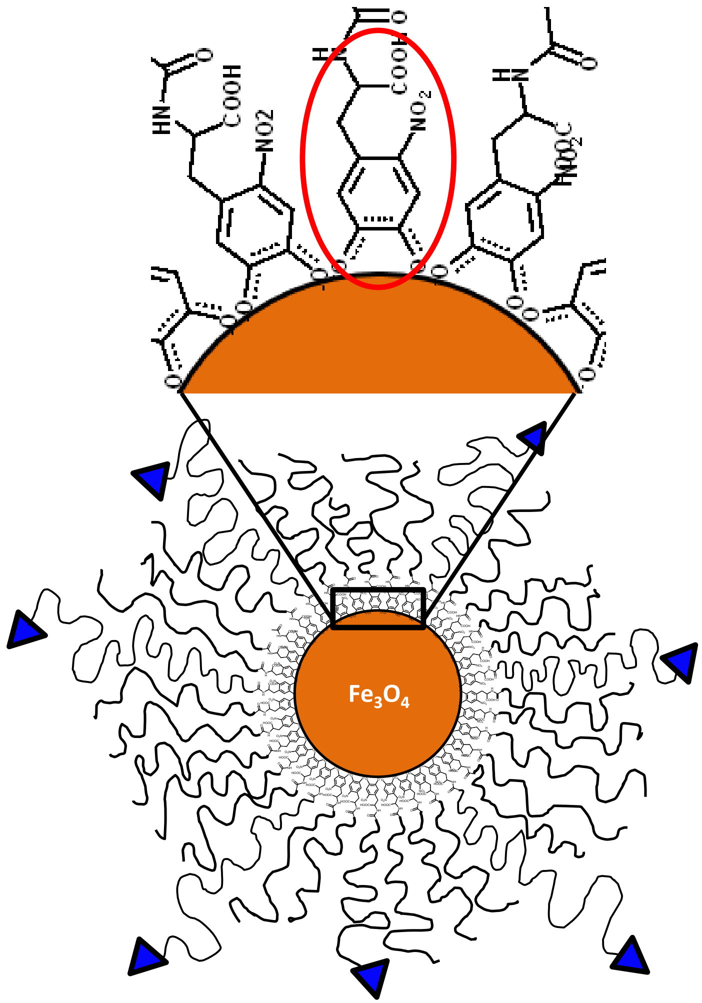
Weissleder et al. further development

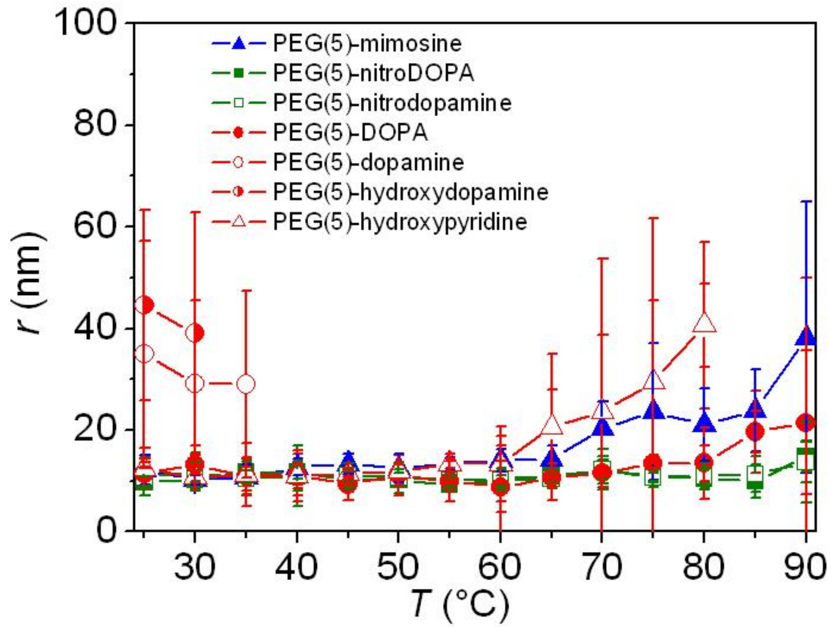
Core-shell nanoparticles enable:

- ⇒ Hierarchically tailored environmental interactions
- ⇒ Targeting
- ⇒ “Actuation” as well as “sensing”
- ⇒ Assembly to composite smart materials, e.g. for drug delivery or ultrafiltration
- ⇒ Reconfigurable “platforms” for multi-purpose use-

E. Amstad *et al.*, *Nanoscale* (2011)

Core-shell NP synthesis: anchoring of poly(ethylene glycol) shell

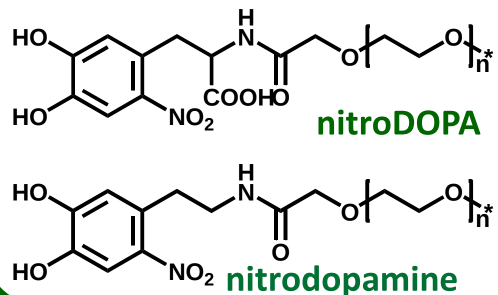




Grafted to bare Fe_3O_4

- Irreversible binding (**required**)
- Non-toxic and biocompatible
- “Not too strong”

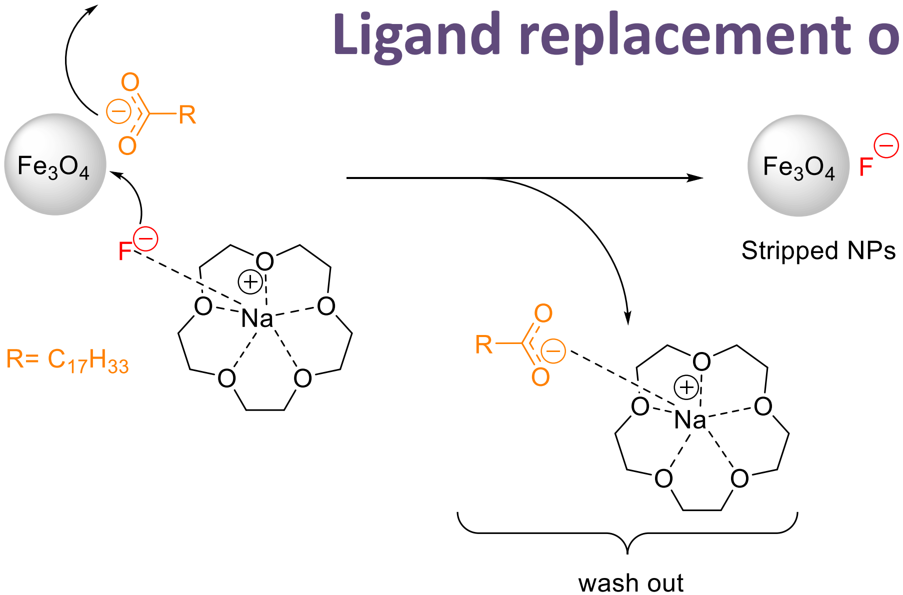
Good anchors



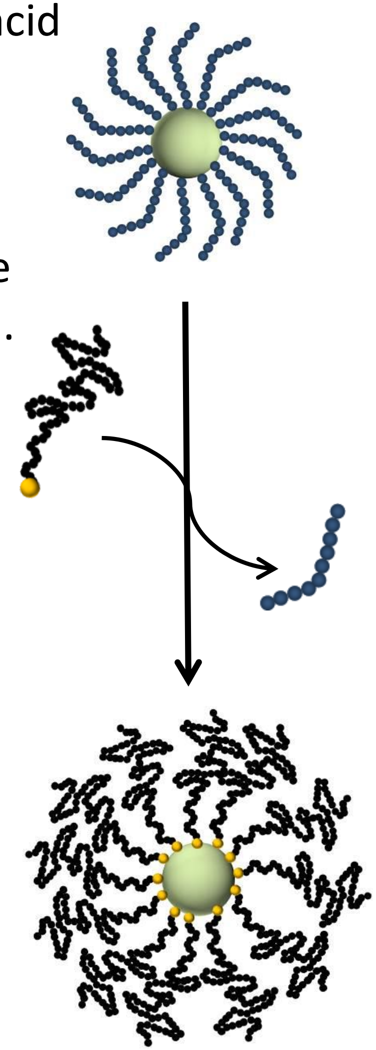
Optimize binding affinity, not maximize

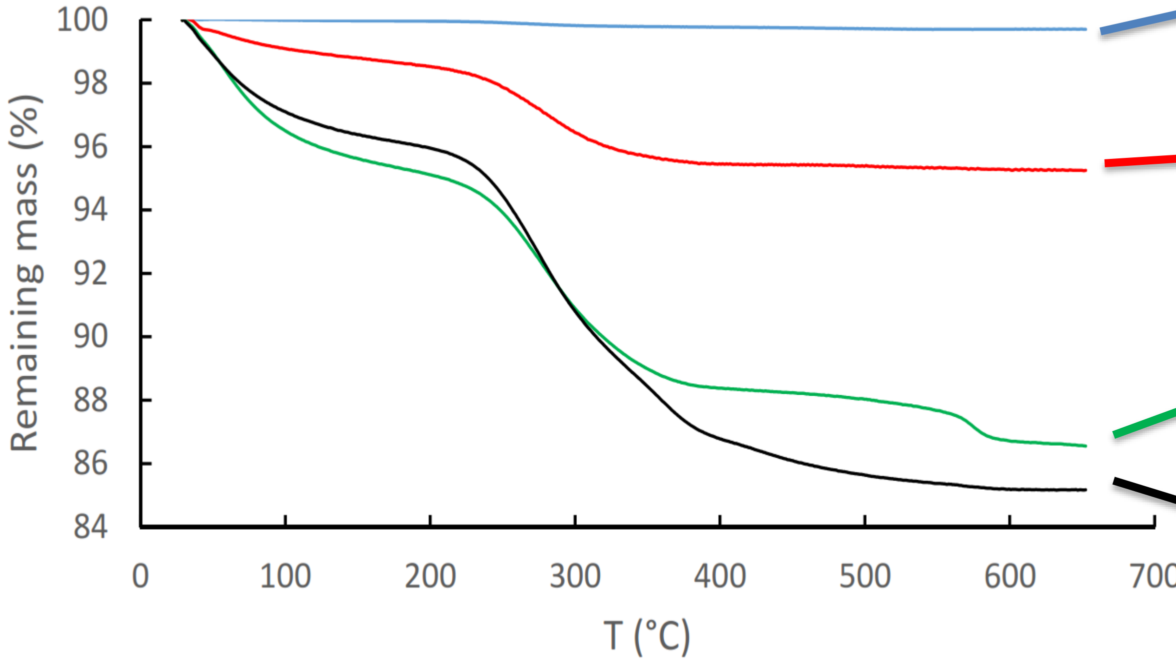
E. Amstad *et al.*, *Nano Lett* (2009); E. Amstad *et al.*, *J Phys Chem C* (2011);

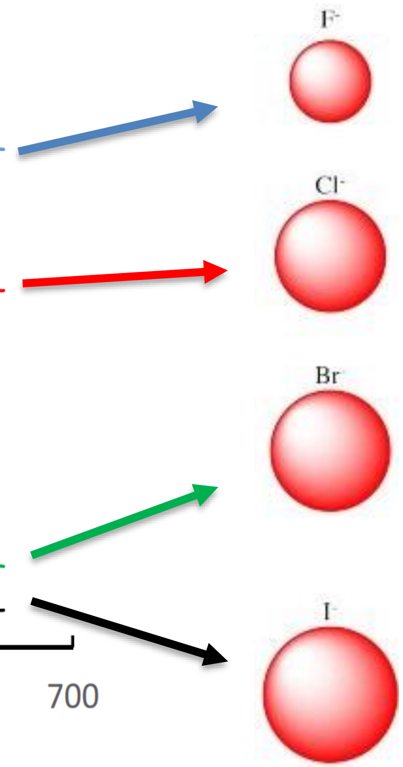
Ligand replacement on oleic acid coated SPION



- Strongly complexed oleic acid on as-synthesized NPs requires complete replacement
- Extensive incubation in the right solvent mixtures OR...



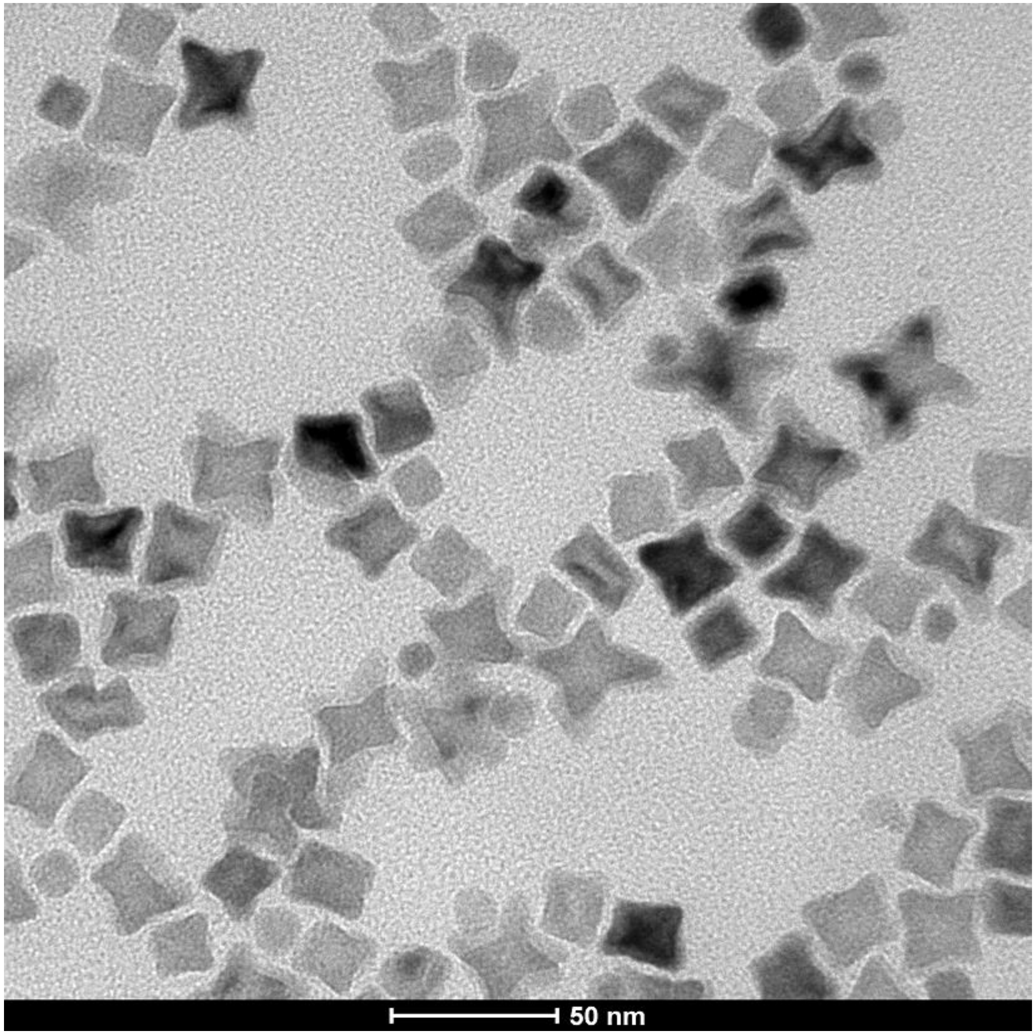




B. Shirmardi et al., *Nanoscale* (2017)

O. Bixner et al., *Langmuir* (2015)

Core-shell NP synthesis: “star” cores



- Superparamagnetic nanostars (octapods)
- formed by addition of surface active salts to inhibit growth of certain facets

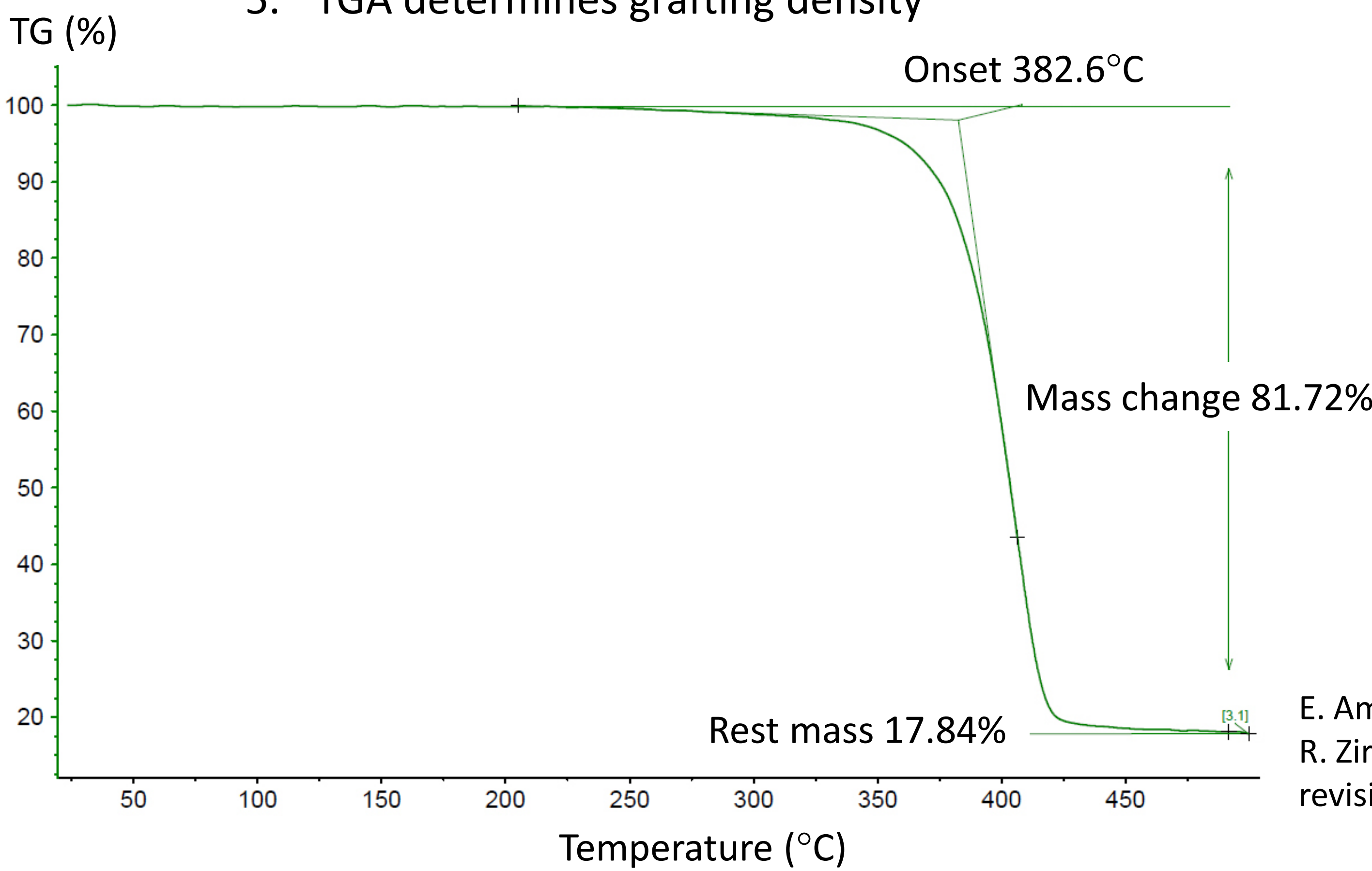
Benefits:

- Increased surface area
- Incrensed efficiency for theranostic radiation therapy

Shell grating density and stability

Determination of shell properties and colloidal stability:

1. Magnetically assisted precipitation and extraction
2. Column purification (multiple long passes through supradex and sephadex)
3. Freeze-drying
4. Heat cycled DLS
5. TGA determines grafting density



High grafting density required
$\geq$ 1 chain/nm^2

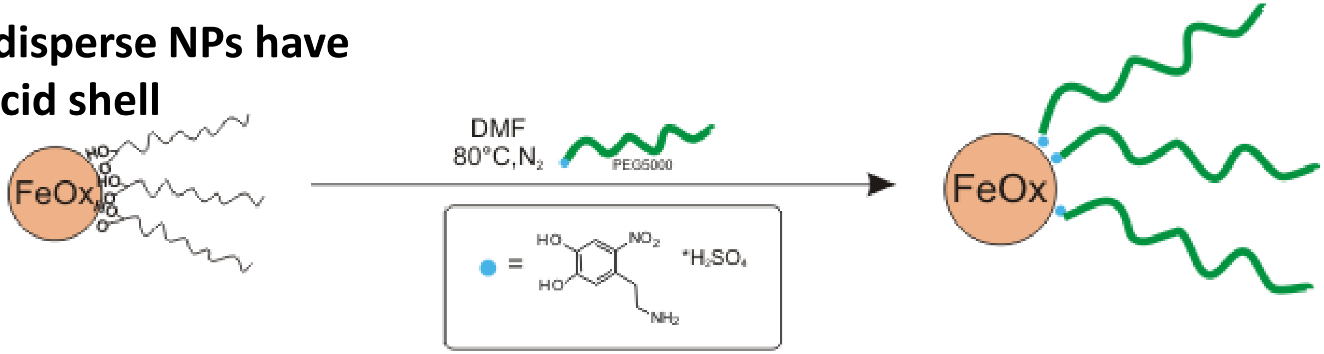
Mostly organic mass

High colloidal stability

E. Amstad *et al.*, *Nano Lett* (2011)
R. Zirbs *et al.*, Nanoscale in revision

Shell grafting by ligand replacement

Monodisperse NPs have oleic acid shell



Ligand replacement

d_{core} (nm)	MW(PEG) (kDa)	Grafting method	~chains/nm²
3-15	2-10	ligand replacement	0.7-1.2

Residual oleic (10-50% of surface covered) within the brush

Problems:

- R_G (coil size) too high
- Oleic acid affinity too high
- NDA anchor affinity too low (oxidation to Fe_2O_3)

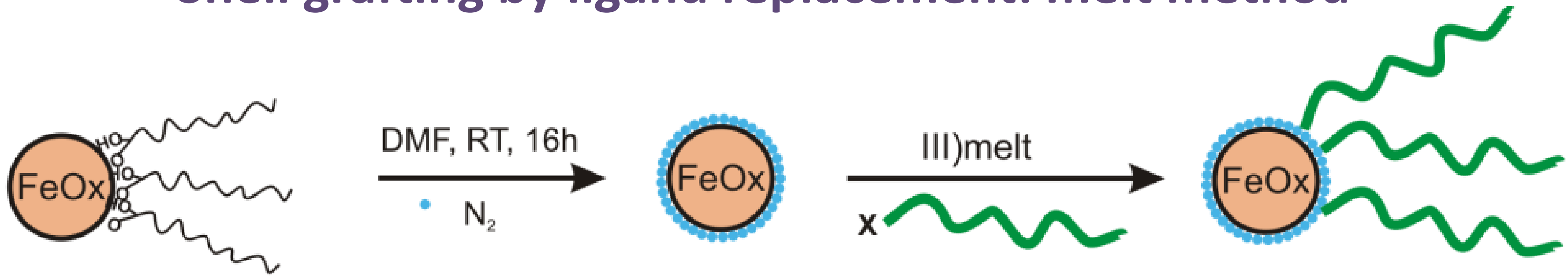
Cut-off for strong colloidal stability: ~1 chain/nm²

Grafting-to through ligand replacement often results in **no pass** for dextran size exclusion column purification (material lost)

$\Rightarrow$ ~1 chain/nm² required, which we have reached

R. Zirbs *et al.*, *Nanoscale* (2015)
A. Lassenberger *et al.*, *Langmuir* (2015)

Shell grafting by ligand replacement: melt method



Two-step grafting:

1) Dense nitrodopamine NP functionalization
2) optimized 'click' group, solvent and reaction conditions (near melt)

Polymer coupled to **stable anchors** under close to **maximum collapsed** (melt) conditions

d_{core} (nm)	MW(PEG) (kDa)	Grafting method	~chains/nm²
3-15	2-10	ligand replacement	0.7-1.1
3-10	**2-10**	**Two-step melt**	**2.0-3.5**

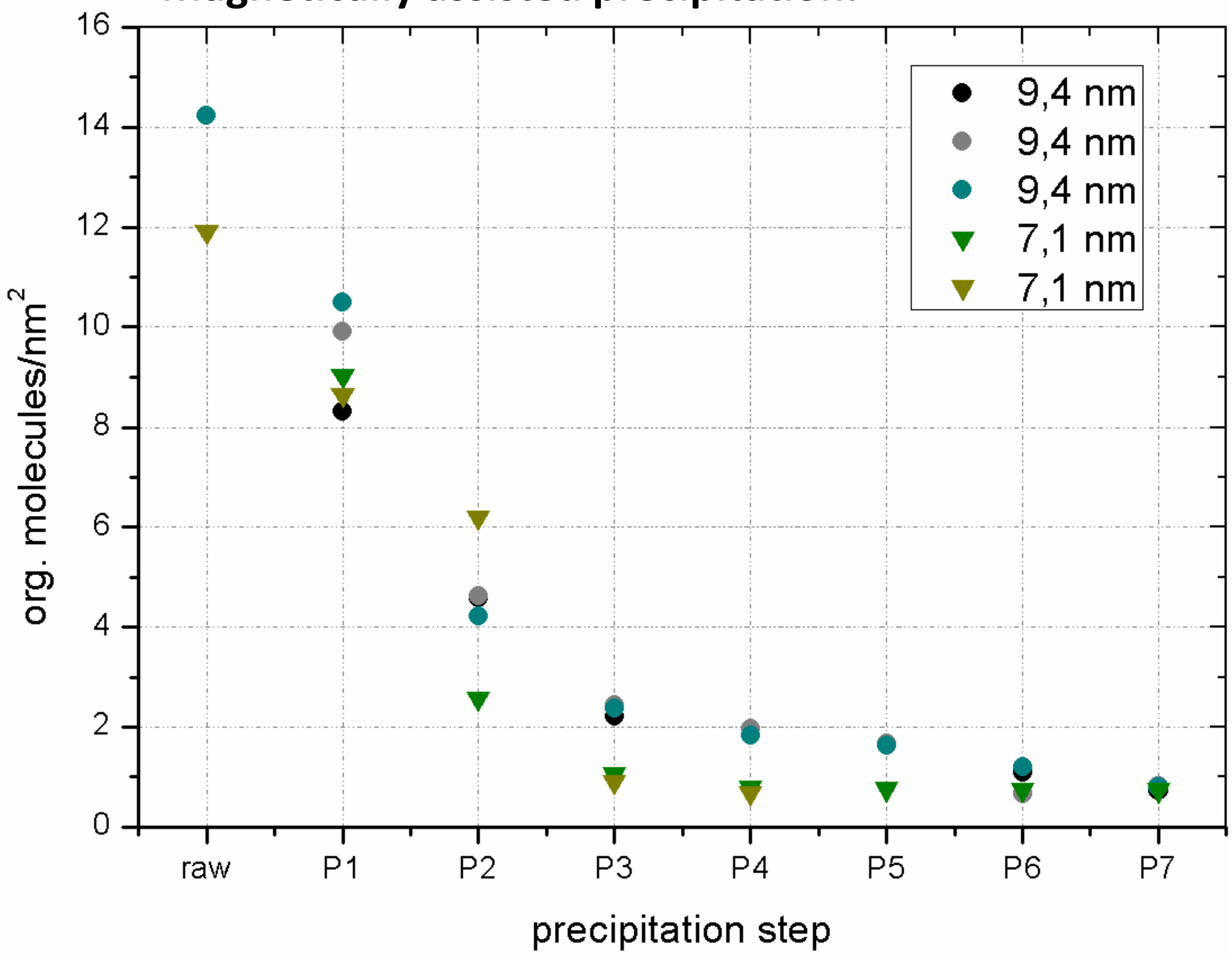
Record grafting-to density by >×5
Close to theoretical limit

Cut-off for strong colloidal stability: ~1 PEG(5-10kDa)/nm²

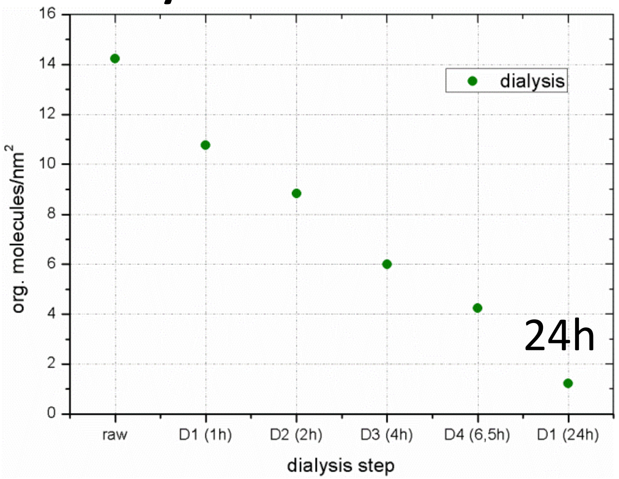
R. Zirbs *et al.*, *Nanoscale* (2015)
O. Bixner et al., *Langmuir* (2015)

Need for proper purification for proper characterization

Magnetically assisted precipitation:



Dialysis:



Challenges:

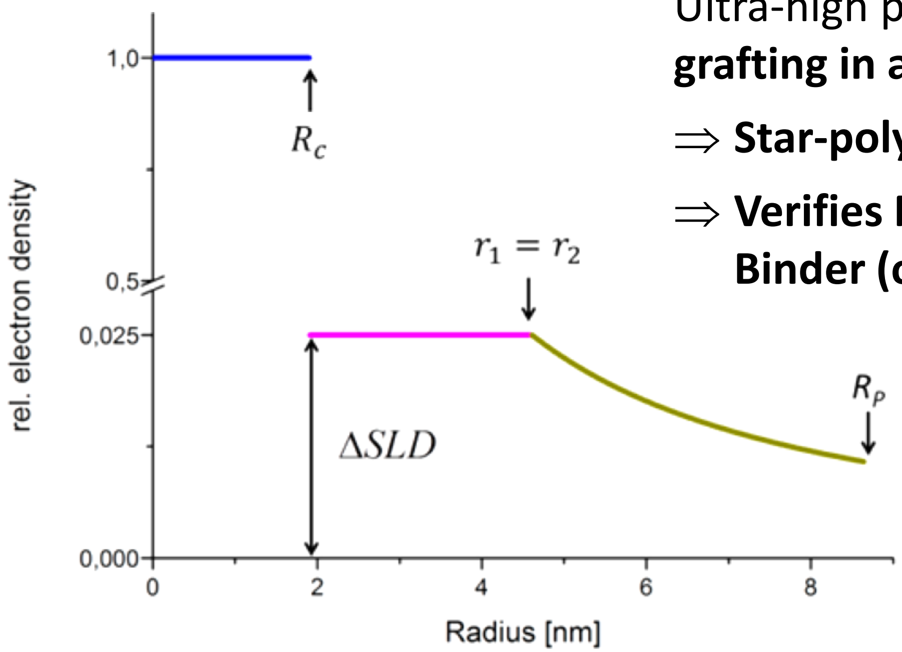
- Remove free polymer of *similar size* to the NP and with the *same chemical properties*
- Osmotic and mechanical *stress* during dialysis and column purification requires stable linking

⇒ Preferred method:

Multiple magnetically assisted precipitation

A. Lassenberger *et al.*, *Langmuir* (2015)

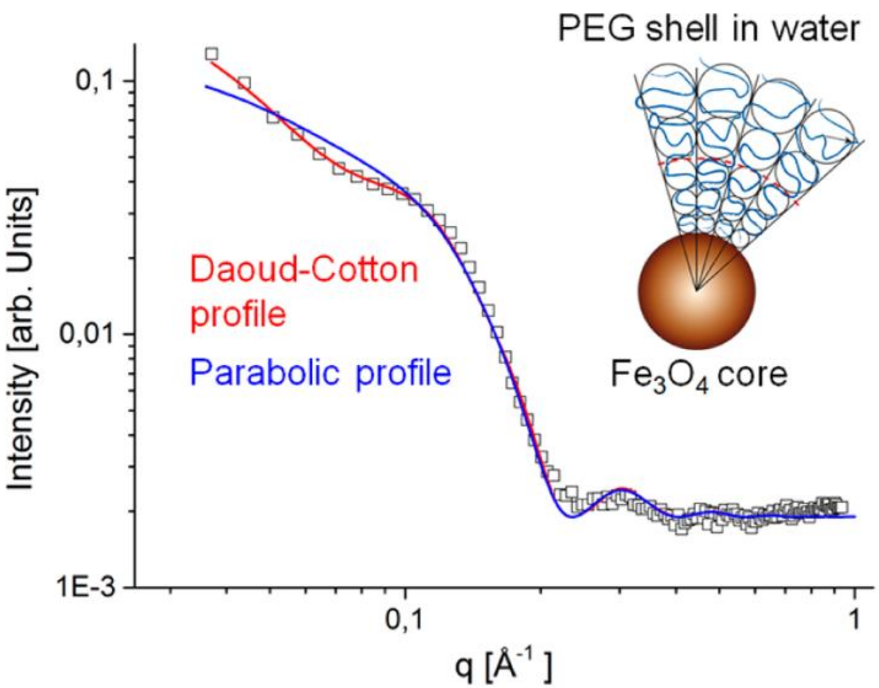
Shell profile for densely (melt-)grafted core-shell NPs



Ultra-high polymer grafting density achieved by **grafting in a melt**

⇒ **Star-polymer-like segment density profile**

⇒ **Verifies NP-simulations by Lo Verso and Binder (original theory Daoud-Cotton)**

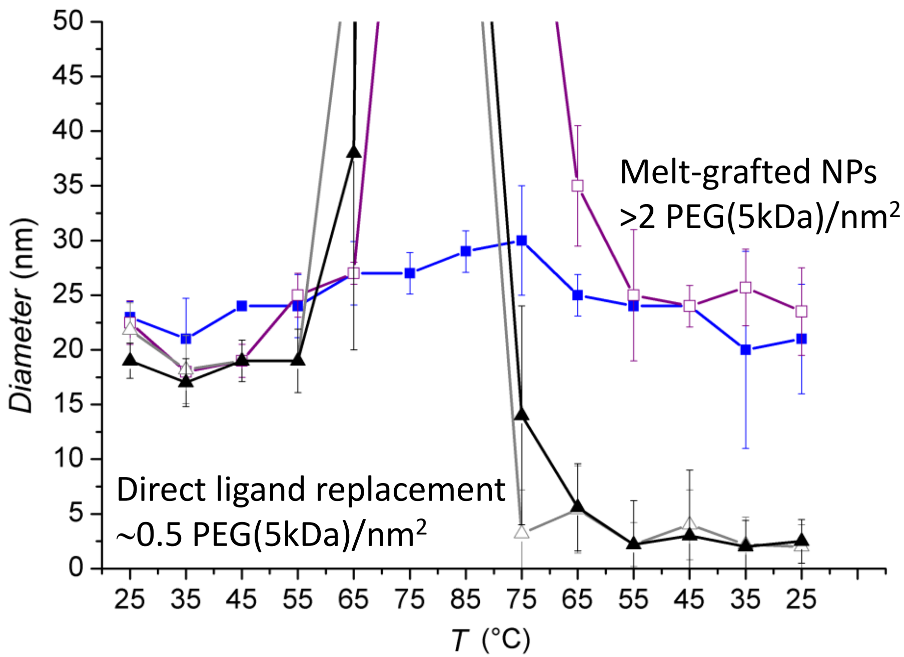


The high constant polymer segment density close to the core leads to unique colloidal stability and interfacial properties

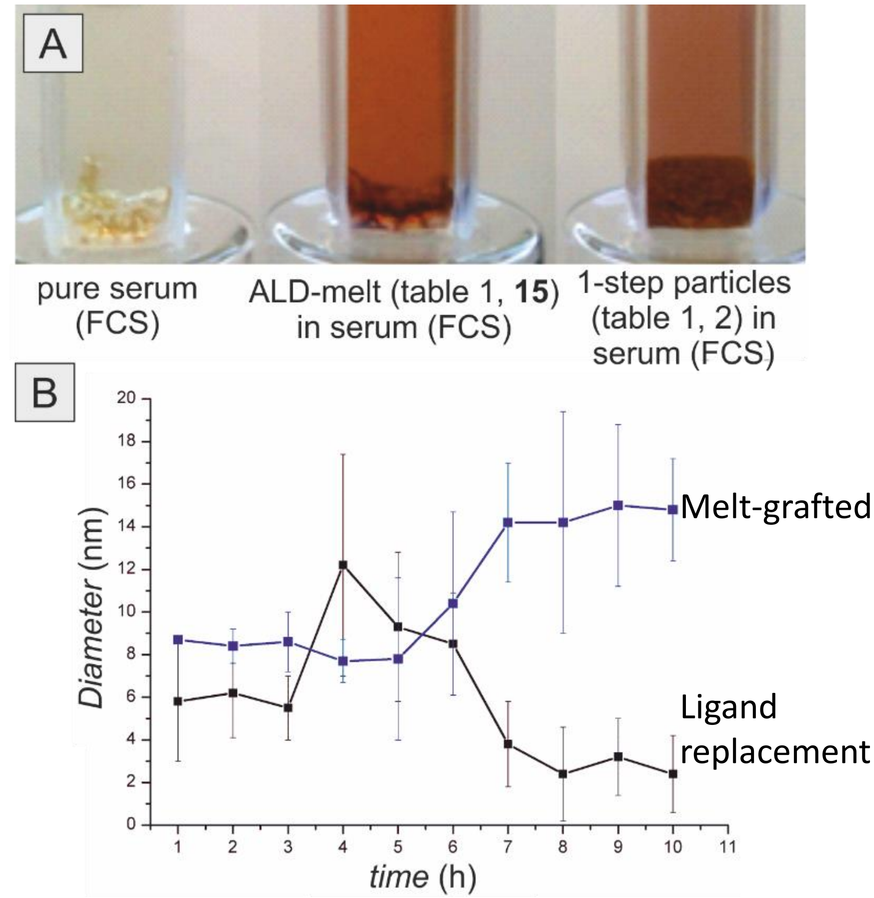
R. Zirbs *et al.*, *Nanoscale* (2015)
T. Grünewald *et al.*, *Chem Mater* (2015)

Collaboration with H. Lichtenegger (BOKU) / B. Capone (Uni Wien)
S. Prevost / T. Narayanan (ESRF ID02)

Colloidal stability for shell grafting by two-step melt-grafting



- Temperature-cycled DLS shows insufficient colloidal stability for direct ligand replacement
- Two-step melt-grafted nanoparticles show stability in both water and PBS
- **Grafting densities >1 polymer/nm^2 required**

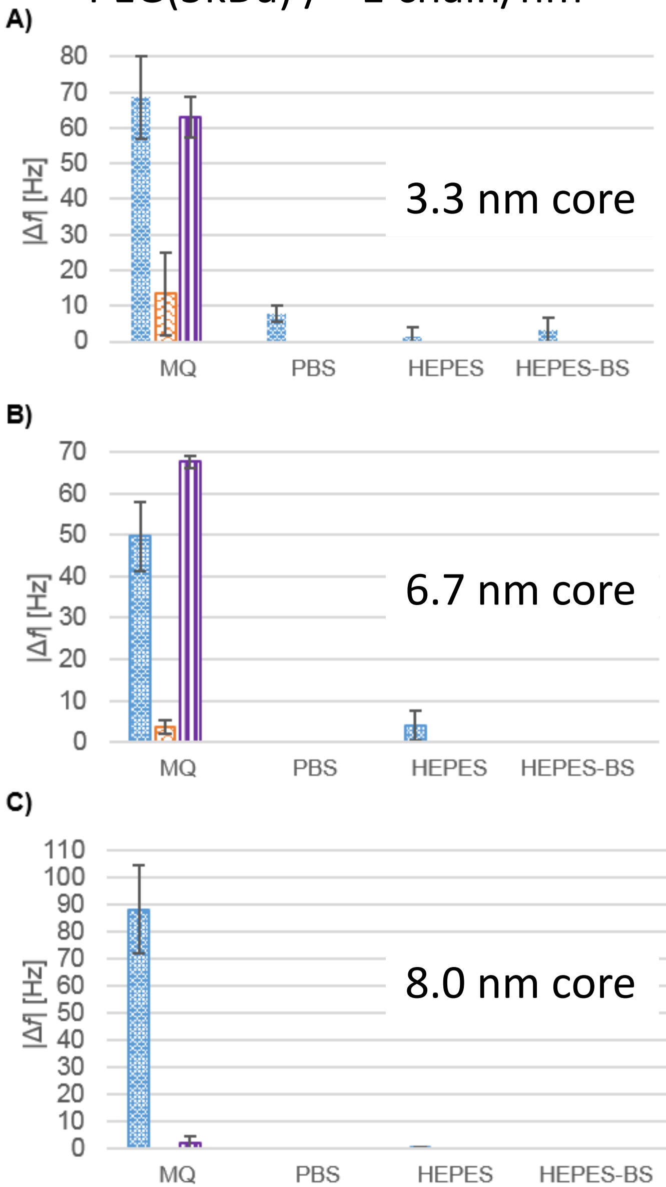


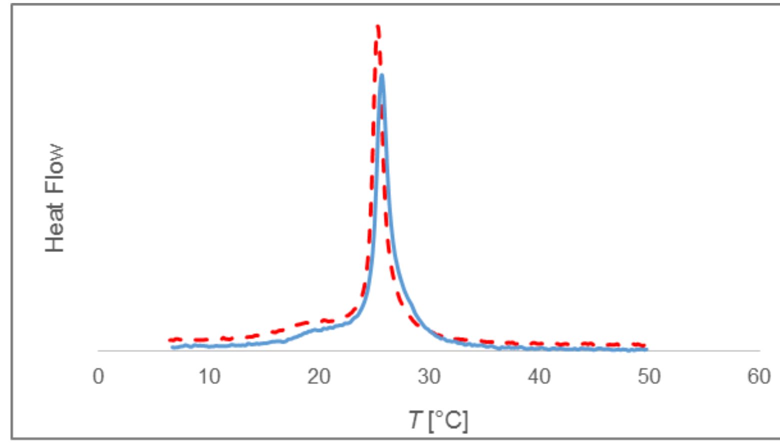
- Direct ligand replacement and melt-grafted particles show stability in serum
- Two-step melt-grafted NPs show stability upon T-induced denaturation of serum solution

R. Zirbs *et al.*, *Nanoscale* (2015)
A. Lassenberger *et al.*, *Langmuir* (2016)

Membrane interactions as function of size and medium

PEG(5kDa) / ~1 chain/nm^2



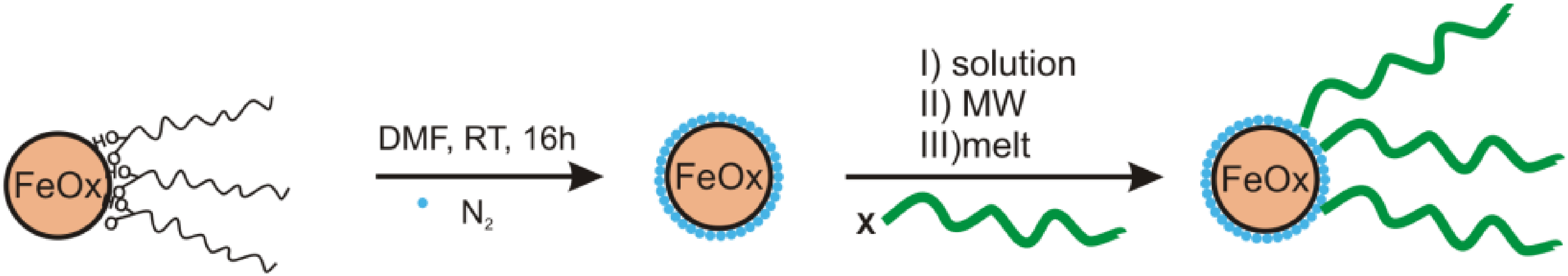


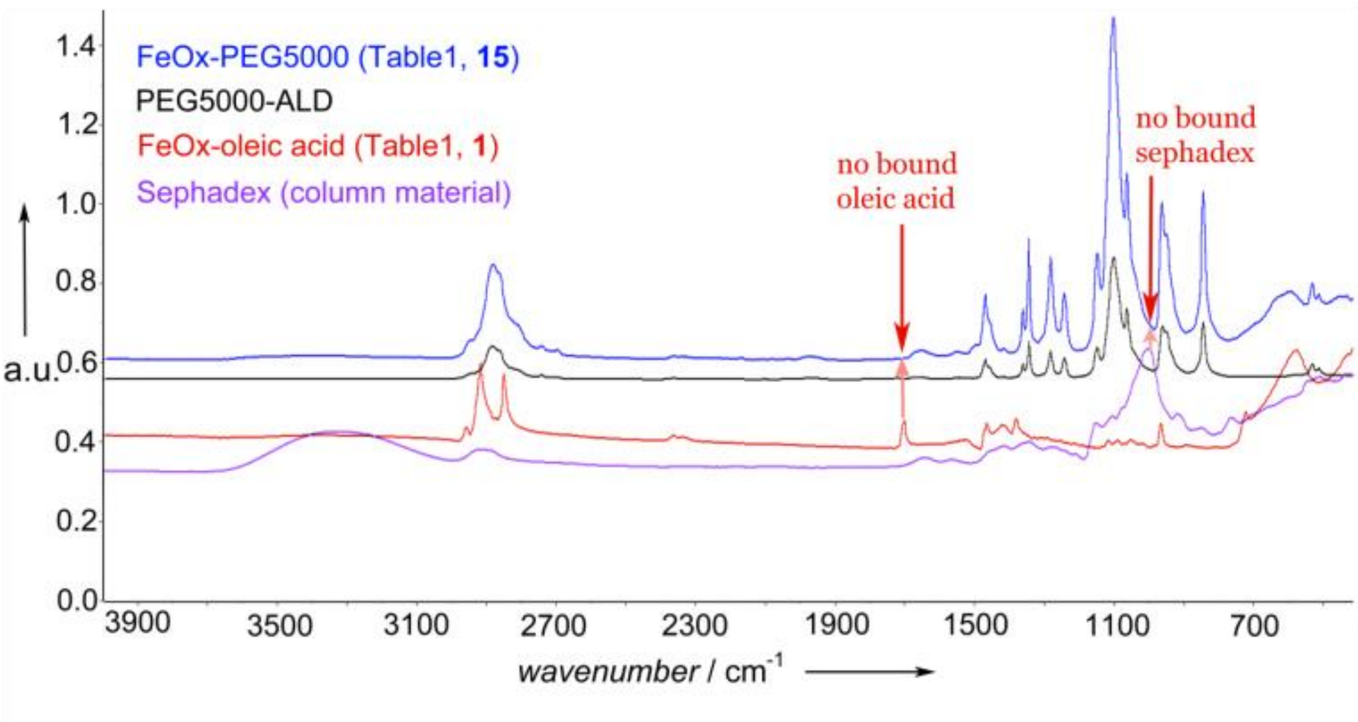
	main peak			pre peak		
	enthalpy [cal/mol]	T_m [°C]	$T_{1/2}$ [°C]	enthalpy [cal/mol]	T_m [°C]	$T_{1/2}$ [°C]
DMPC/DMPG	3540	25.24	0.995	673	20.57	4.33
DMPC/DMPG +PEG-SPION	3547	25.42	1.16	571	20.43	3.99

- DLVO-type interactions with membranes observed only:
  - ✓ for anionic membrane / interface
  - ✓ at low ionic strength
  - ✓ at low pH
- NPs with low curvature have weaker interaction at identical grafting density (⇒ denser brush)

N. Gal *et al.*, *ACS Biomater Sci & Eng* (2017)

Colloidal stability for shell grafting by two-step melt-grafting



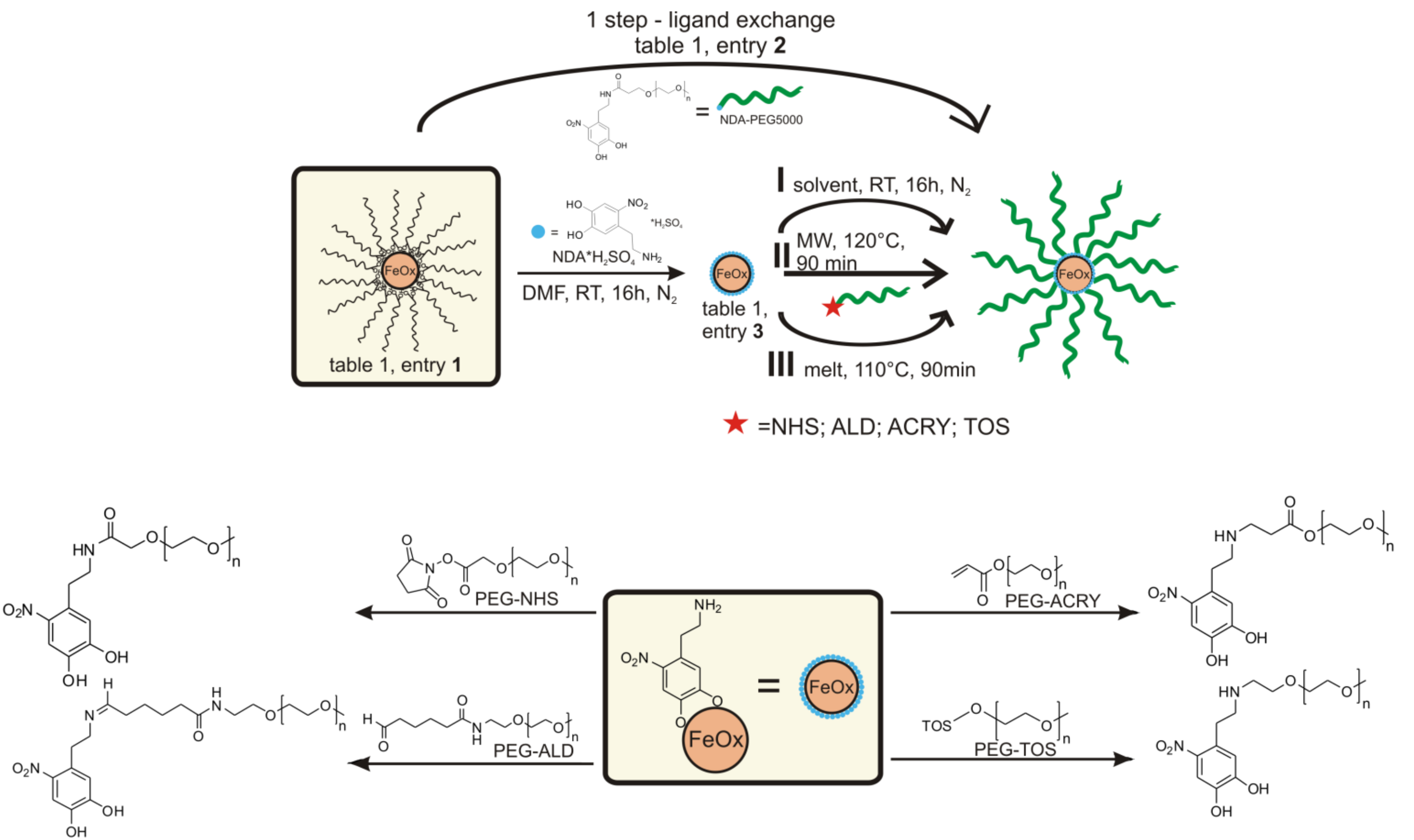


IR shows no trace of remaining oleic acid or other polymer contaminants…

…but some oleate complexes on the surface likely remain

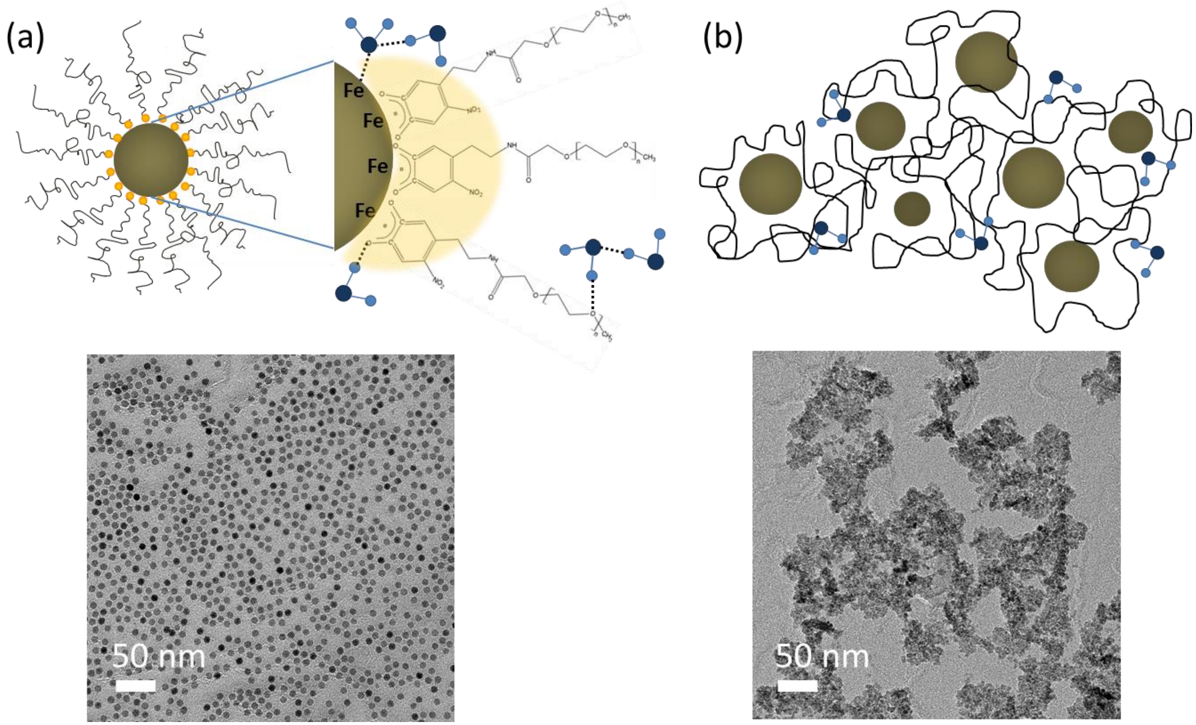
R. Zirbs *et al.*, *Nanoscale* (2015)

Colloidal stability for shell grafting by two-step melt-grafting



R. Zirbs *et al.*, *Nanoscale* (2015)

Properties as contrast agents

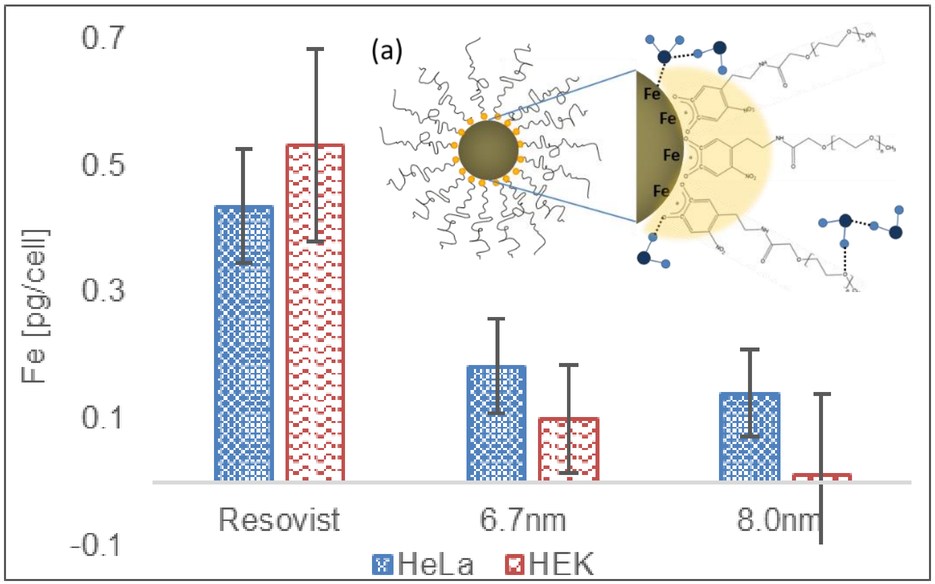


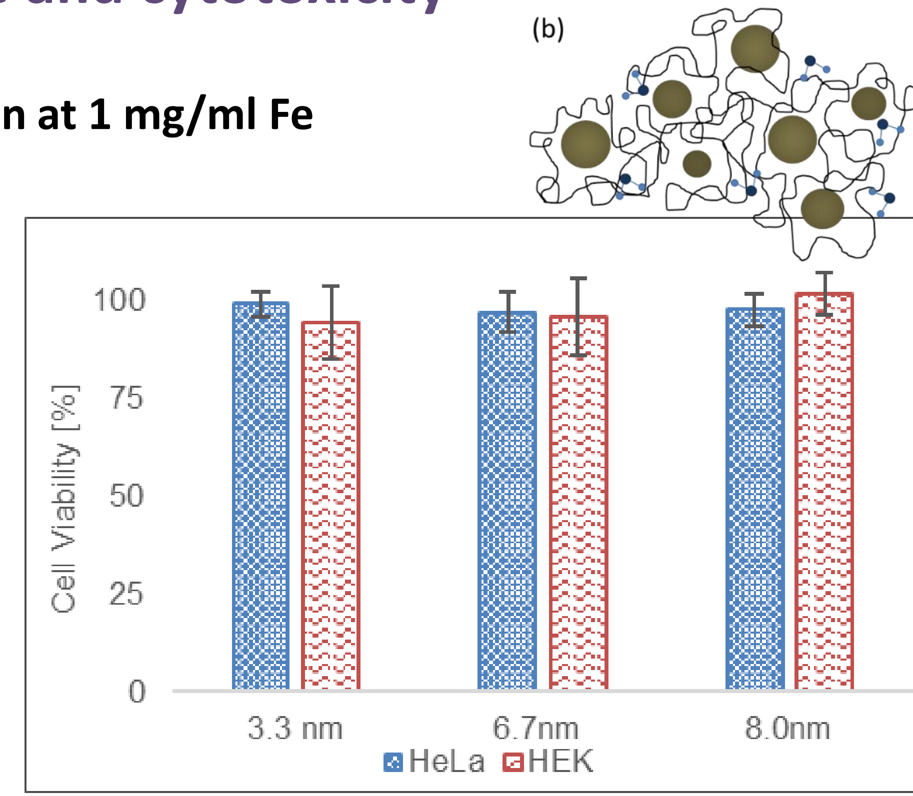
NP type	r_2 / $mM_{Fe}^{-1}s^{-1}$ in Milli-Q	r_2 / $mM_{Fe}^{-1}s^{-1}$ in agarose
Resovist	-	179 / 186[a]
Feridex	-	120[a]
Combidex	-	65[a]
PEGylated SPION, 3.3 nm	16.4	20.9
PEGylated SPION, 8.7 nm	39.6	48.1
PEGylated SPION, 10.6 nm	79.2	84.8
PEGylated SPION, 14.4 nm	183.9	198.1

A. Lassenberger *et al.*, *submitted*

SPION cell uptake and cytotoxicity

24h cell incubation at 1 mg/ml Fe





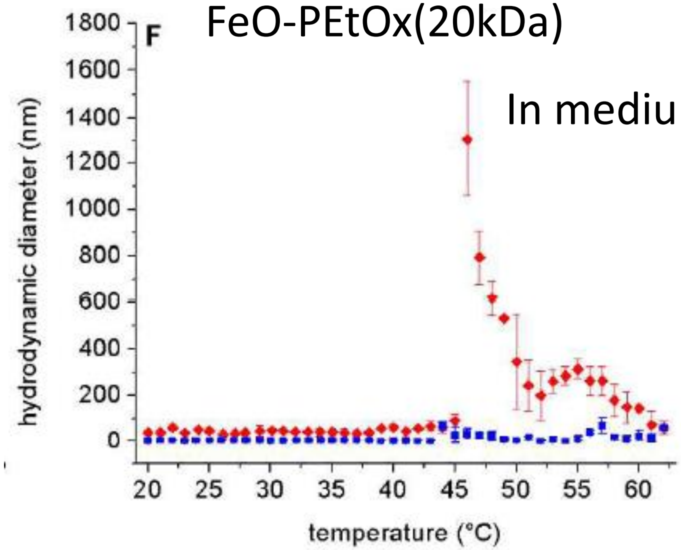
- Core-shell structure more effective than polymer coated
- Negligible cell uptake (stealth) even at extremely high exposure (cell drinking)
- Lowest for larger cores (lower curvature (trend, not statistically significant)

- Perfect cell viability
- Results correlate with measurements of biophysical interactions with protein and lipid membranes

N. Gal *et al.*, *in revision*

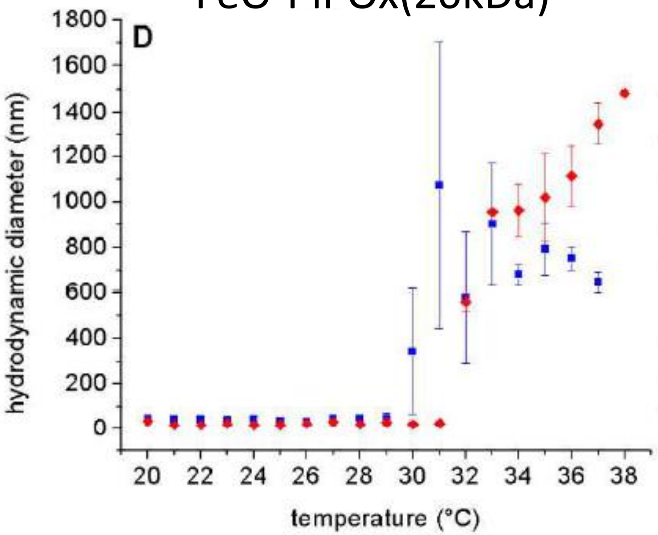
SPION cell uptake and cytotoxicity

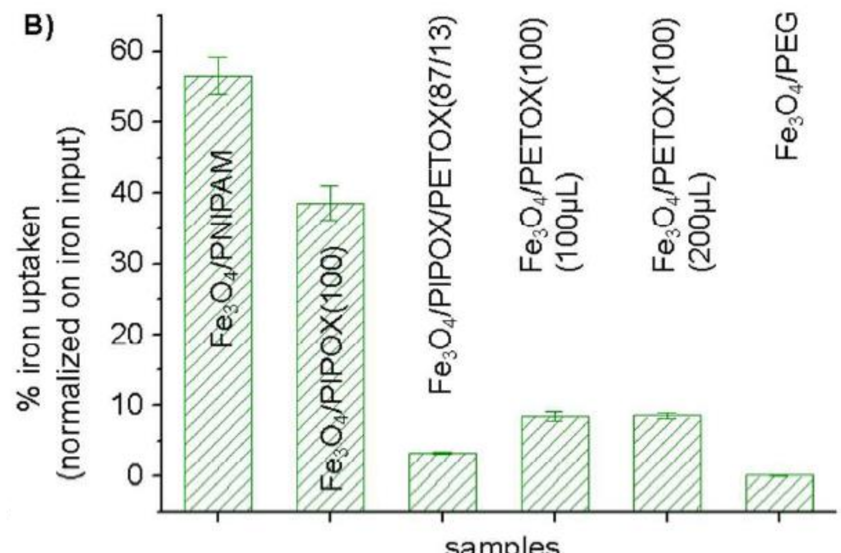
FeO-PEtOx(20kDa)



Densely grafted **polyoxazolines** above below their critical solution temperature seems to perform similarly well as PEG

FeO-PiPOx(20kDa)



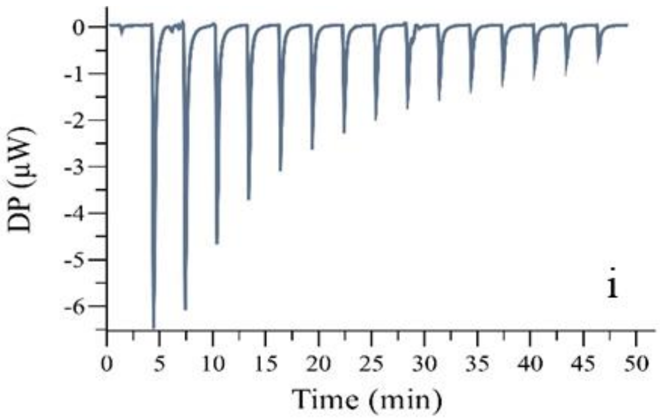


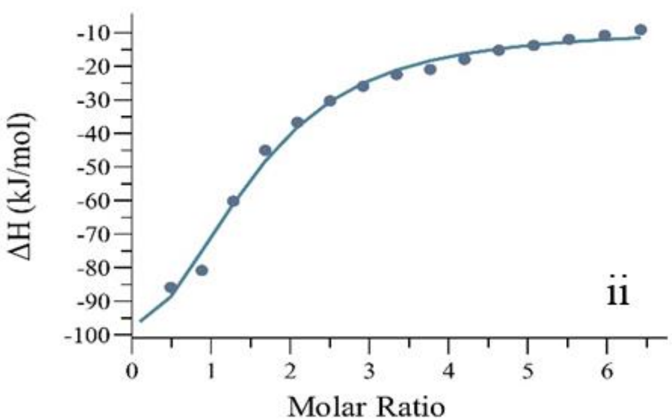
S. Kurzhals *et al.*, *Nanoscale* (2017)

...but serum proteins bind to core-shell brush nanoparticles

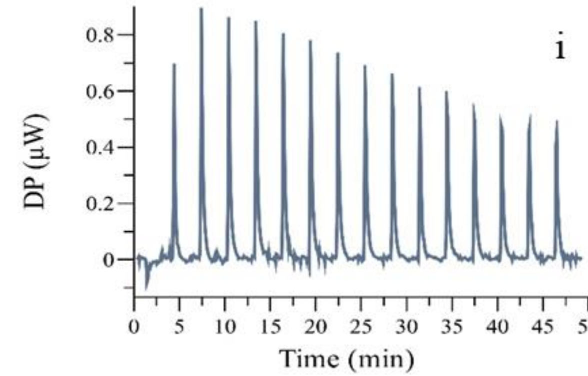
35 mg/ml BSA injected to:

3 mg/ml (16.5µM)
3.3 nm SPION in HEPES-BS





2.5mg/ml (4.1µM)
free PEG coils



- Several proteins bind per particle
- Interaction strength equivalent to ~1 H-bond
- **Independent of "stealth" polymer chemistry**

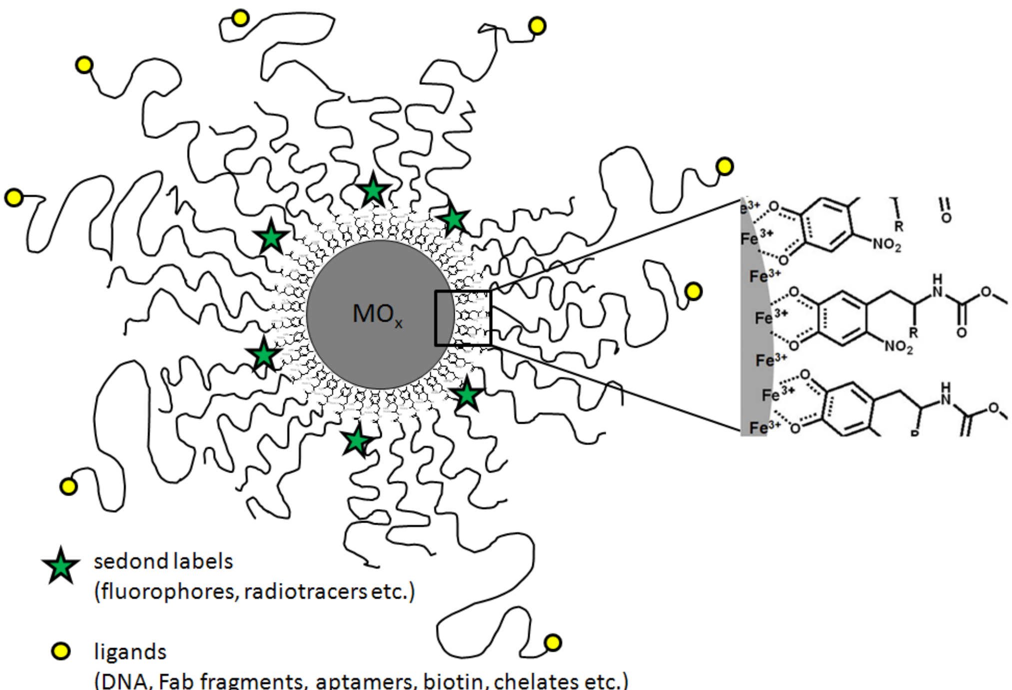
Sample	n [sites]	K_D [µM]	ΔH [kJ/mol]	ΔG [kJ/mol]	ΔS [kJ/mol/K]
PEG 3.3 nm	1.4±0.1	9.6±3.6	-126±24	-29	-0.33
PEG 6.7 nm	2.1±1.5	19.7±8.8	-340±290	-27	-1.03
PEG 8.0 nm	3.0±2.1	28.6±1.2	-340±320	-26	-1.04
PiPOx	9.9±2.1	21.7±4.5	-340±97	-27	-1.03
PEtOx	10.0±1.5	16.6±5.5	-210±55	-27	-0.62
PNiPAm	6.7±1.5	7.8±1.5	-340±90	-29	-1.03

Mystery: What is the respective role of the brush and of adsorbed albumin?

N. Gal *et al.*, *Submitted*

Multifunctional SPIONs for targeting and imaging

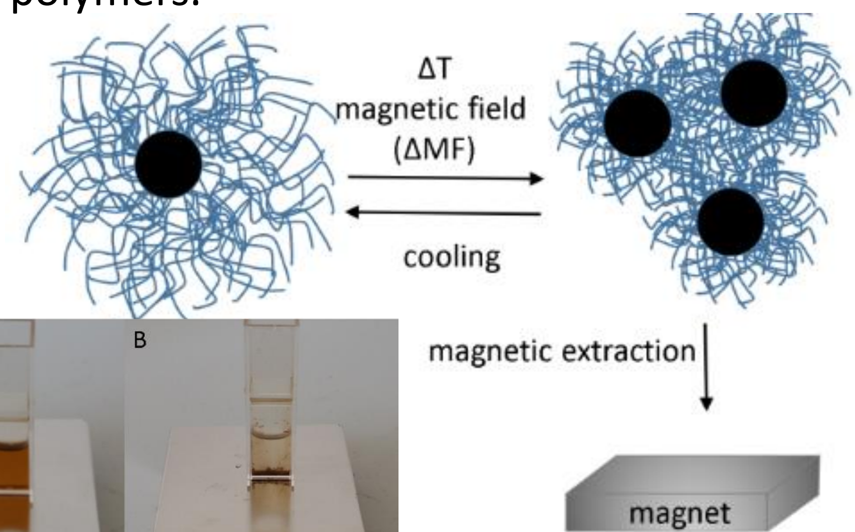
Controlling the shell architecture
⇒ **Number of functional groups in the shell and their avidity can be controlled**

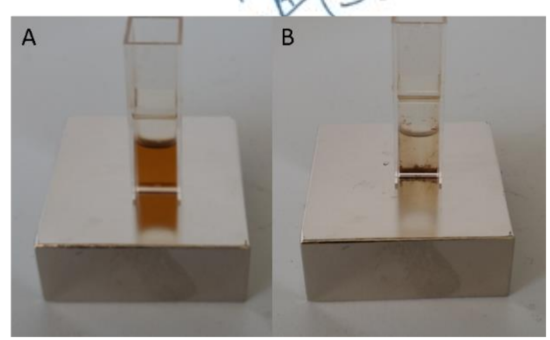


Shell can easily (and has been) exchanged for:

1. **Thermoresponsive**
2. **Structured (peptoids / block-copolymer)**
3. **Functionalized / crosslinkable**

polymers.

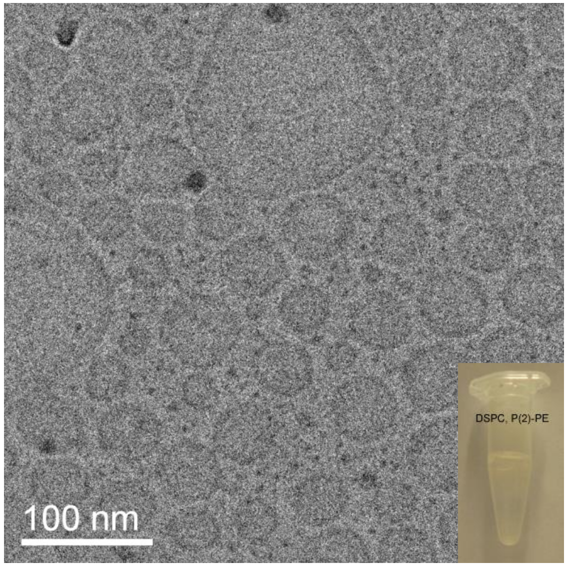




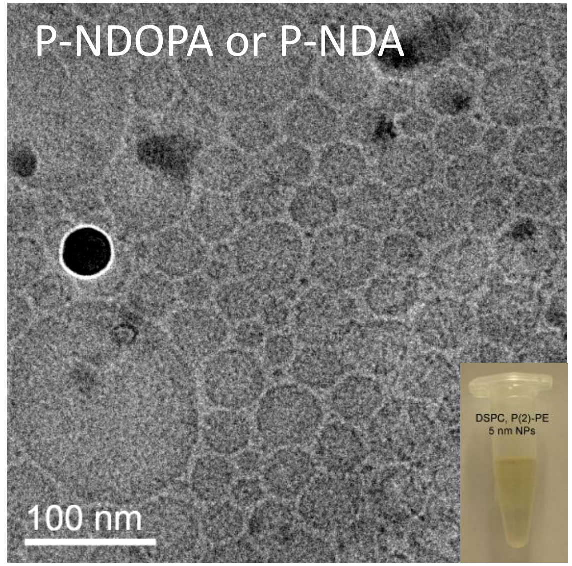
E. Amstad *et al.*, *Small* (2009);
E. Amstad *et al.*, *Nanoscale* (2011)
N. Noga *et. al.*, *ACS Biomater Sci Eng* (2017)
A. Lassenberger *et al.*, *ACS Appl Mater Interf* (2017)
A. Lundgren *et al.*, *ACS Nano* (2016)
S. Kurzhals *et al.*, *Biomacromolecules* (2018);
S. Kurzhals *et al.*, *ACS Appl Interf Mater* (2015); *Nanoscale* (2017); *Macromol Chem Phys* (2017); *J Coll Interf Sci* (2017)

Effect of nanoparticle stability on liposomes

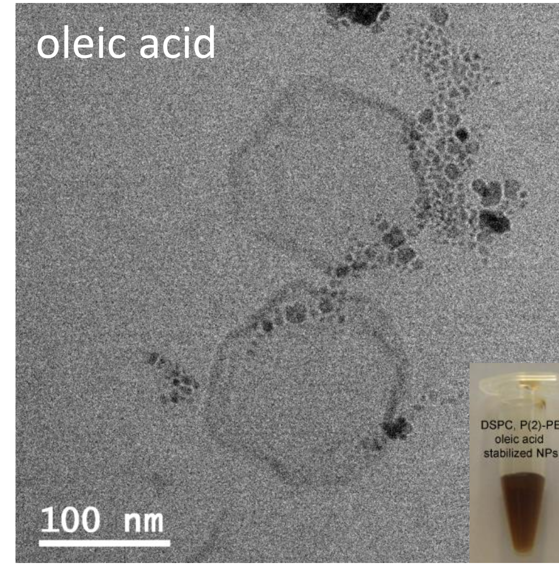
DSPC liposomes without NPs

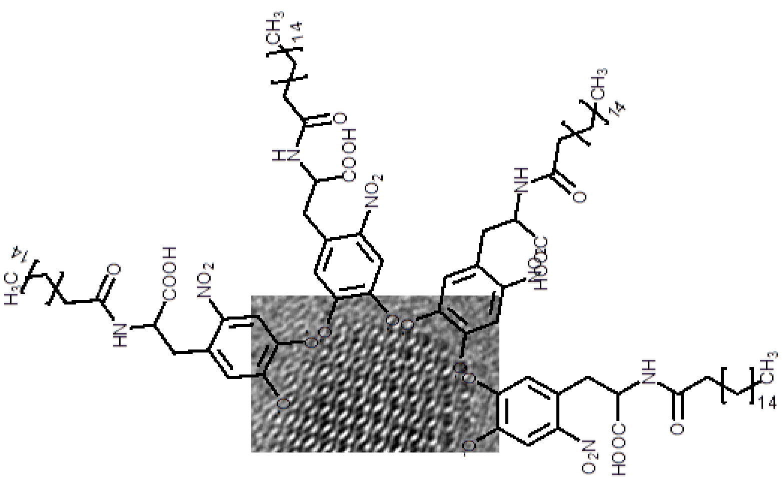


Individually stabilized NPs



Agglomerated NPs





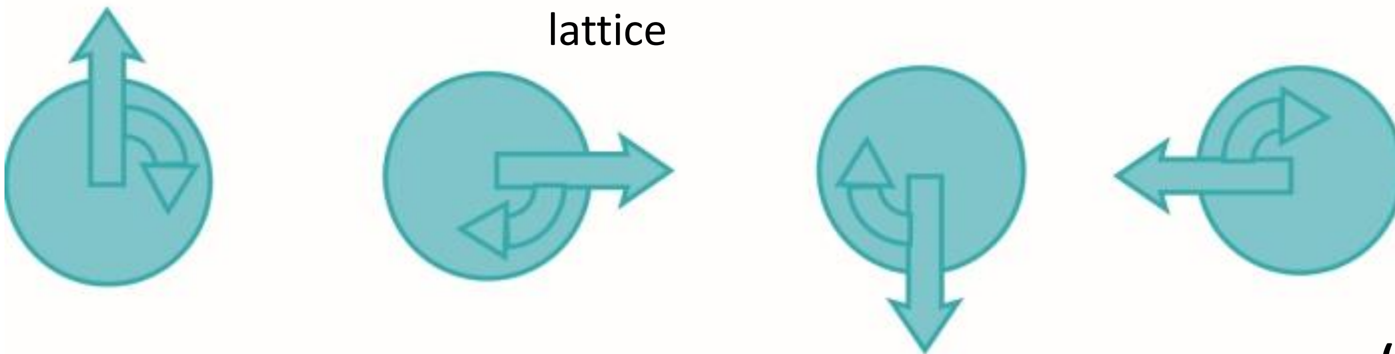
- Oleic acid coated NPs leads to aggregates, distorted and leaky liposomes
- Remaining oleic acid leads to lower vesicle stability
- Reminder: Complete removal of chemisorbed oleic acid requires two-step purification

E. Amstad *et al.*, *Nano Lett* (2011)
O. Bixner et al., *submitted*

Magnetic nanoparticle heating mechanisms

Néel relaxation

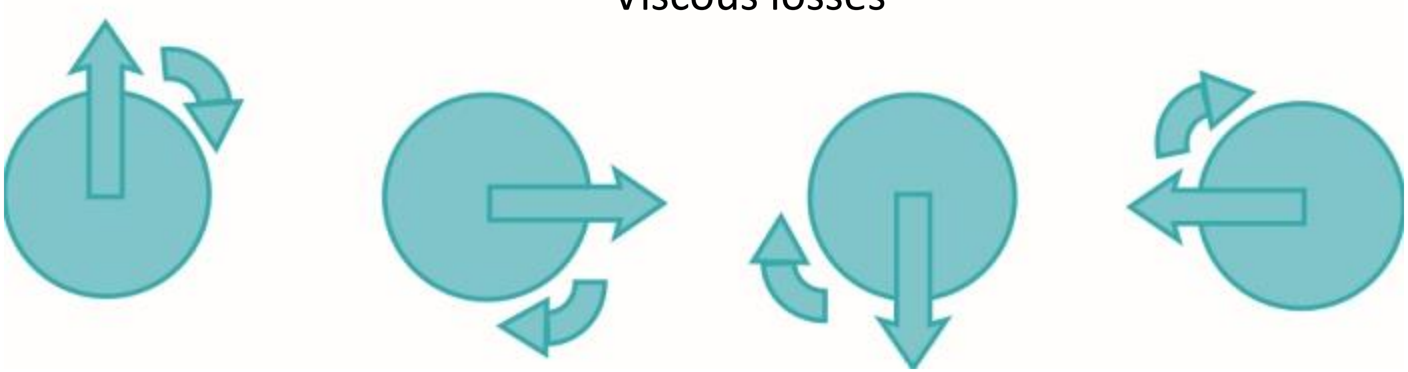
- Magnetic moment turns within the particle
- Smaller, superparamagnetic NPs / high frequencies
- Losses through anisotropy energy forcing alignment with crystal lattice



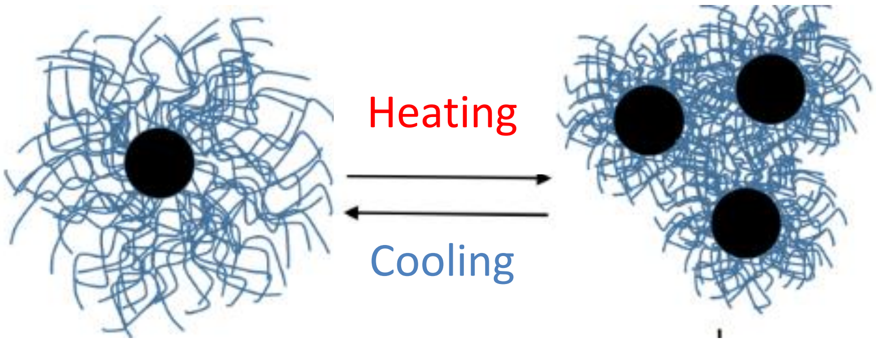
Brown relaxation

- The entire particle turns
- Larger particles / low frequencies
- Viscous losses

(Superpara)Magnetic nanoparticles can provide local heat for actuation



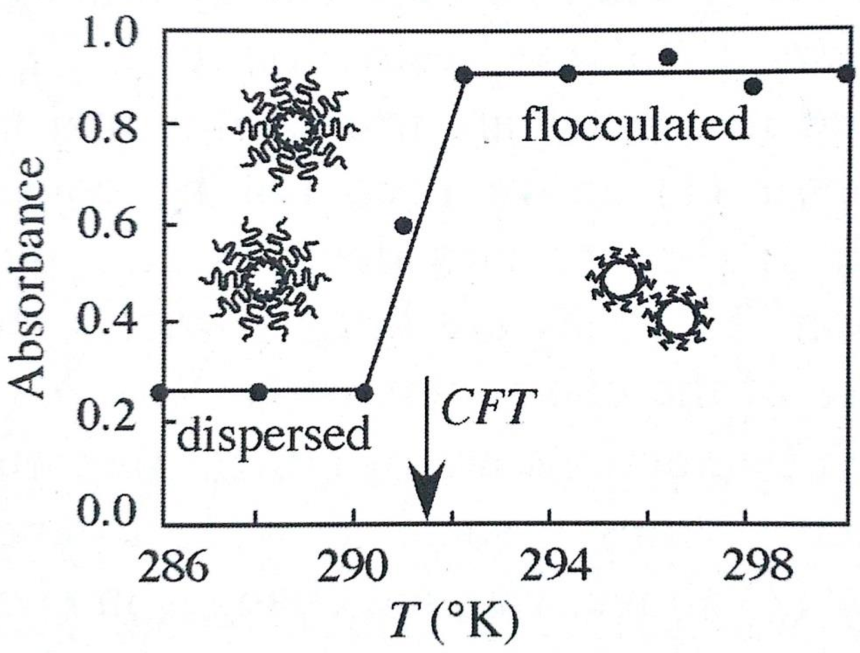
Responsive core-shell nanoparticle aggregation



Stability of polymer functionalized colloids

Catastrophic onset of aggregation as function of temperature:

CFT – Critical flocculation temperature



When polymers with a LCST are present in colloidal dispersions

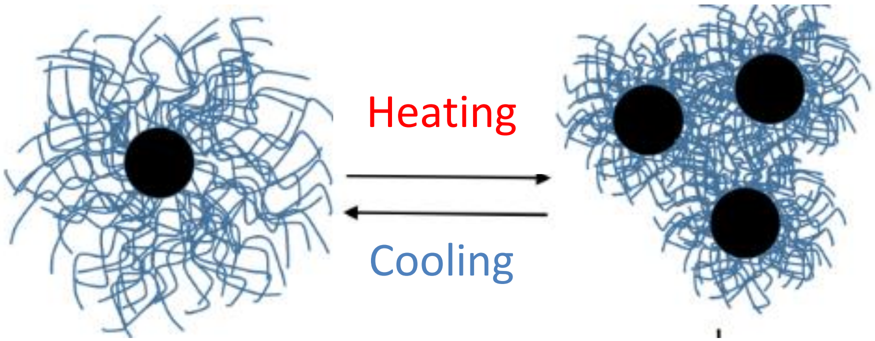
⇒ the colloids will aggregate at higher temperatures

In effect the colloid is taken from "lyophilic shell" to purely lyophobic by the solubility transition of the polymer

Temperature induced aggregation can be reversible

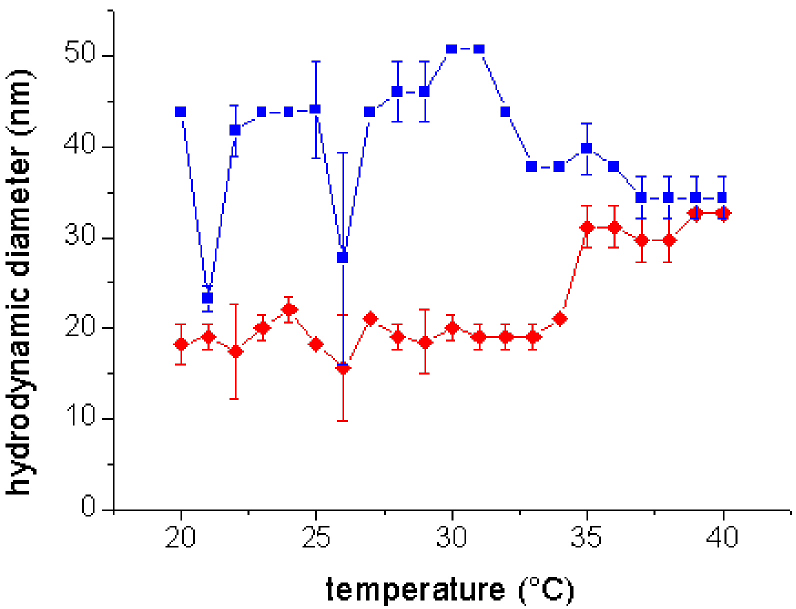
if the polymer layer is sufficiently high molecular weight and dense

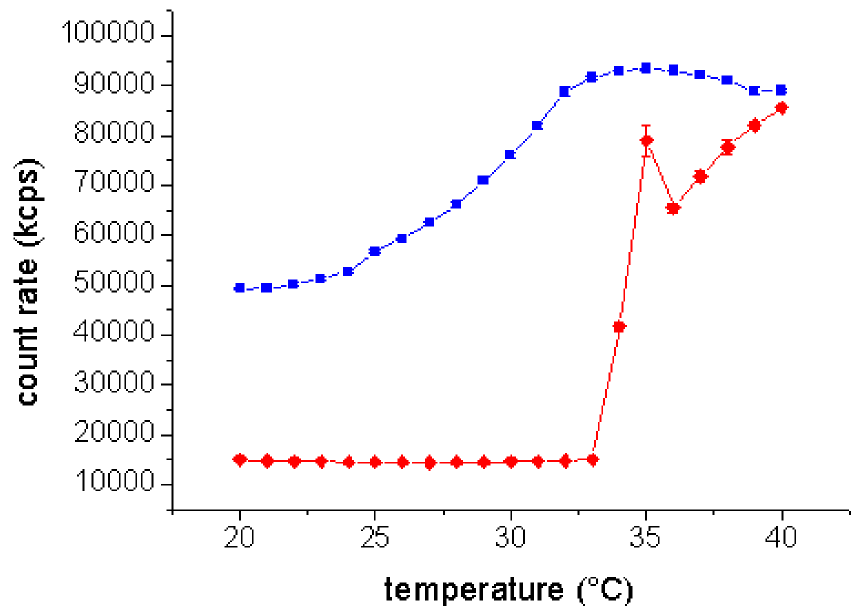
Thermoresponsive stable core-shell NPs



"Thin" 10kDa NDA-PNIPAM shell

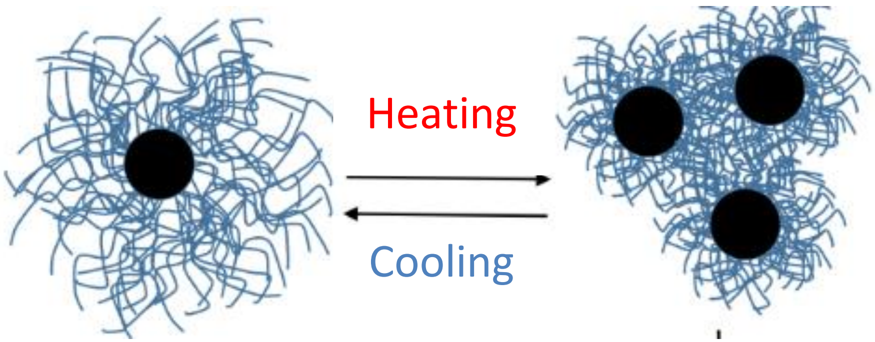
⇒ Hysteresis and slow reversibility of thermally induced aggregation
⇒ Small cluster size





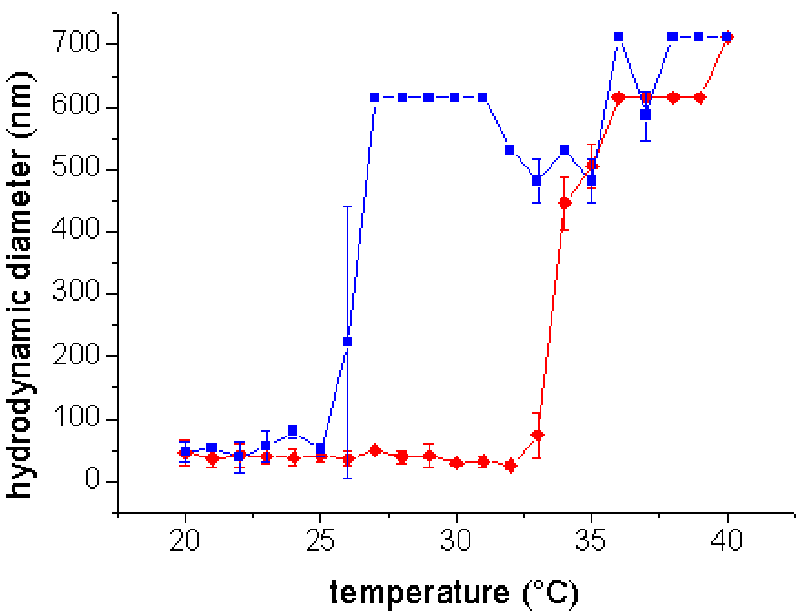
S. Kurzhals *et al.*, *ACS Appl Interf Mater* (2015)

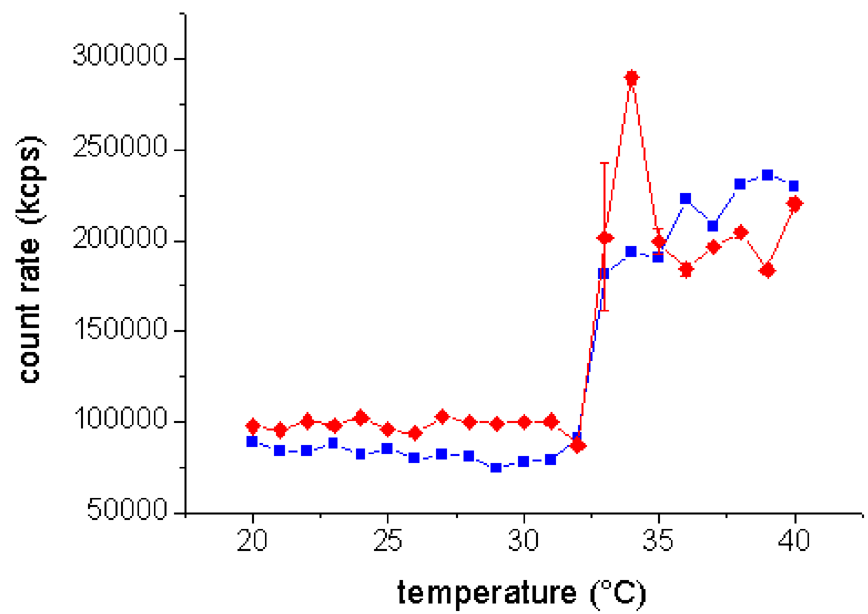
Thermoresponsive stable core-shell NPs



"Thick" 20kDa NDA-PNIPAM shell

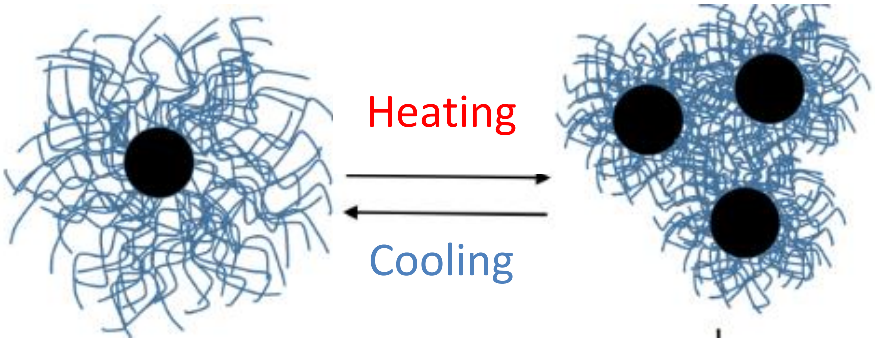
⇒ Fast and full reversibility of NP dispersion
⇒ Large cluster size





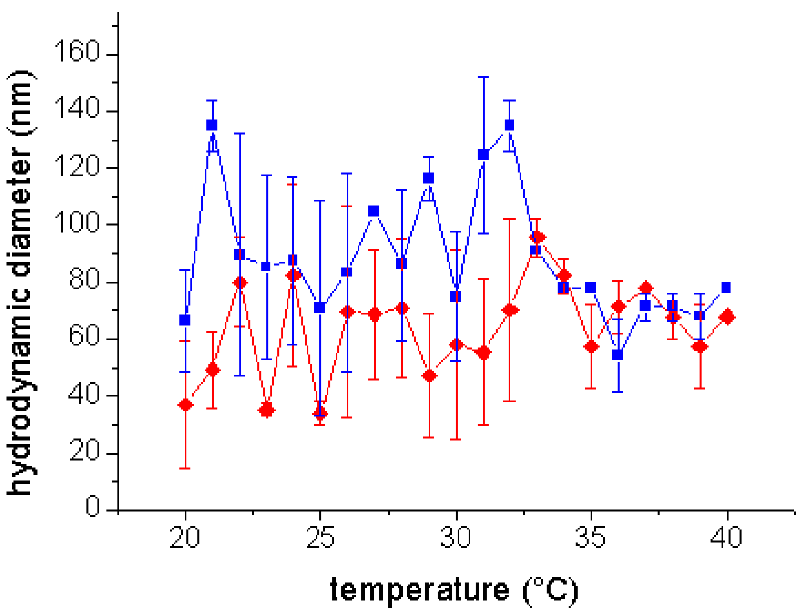
S. Kurzhals *et al.*, *ACS Appl Interf Mater* (2015)

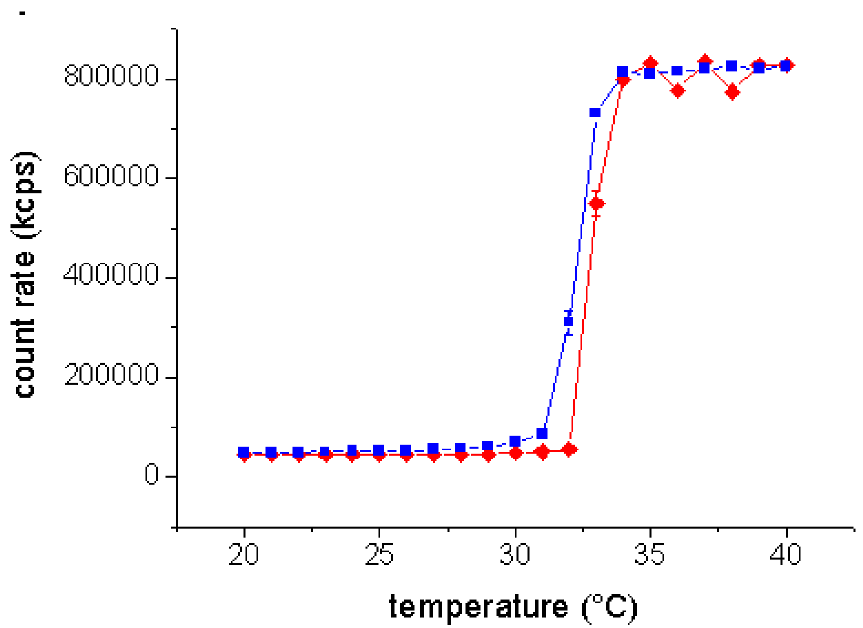
Thermoresponsive stable core-shell NPs



Grafting-from “very thick” 70kDa NDA-PNIPAM shell

⇒ Very large cluster size
⇒ Precipitation and reversibility





S. Kurzhals *et al.*, *ACS Appl Interf Mater* (2015)

The LCST transition broadens for shorter grafted polymers

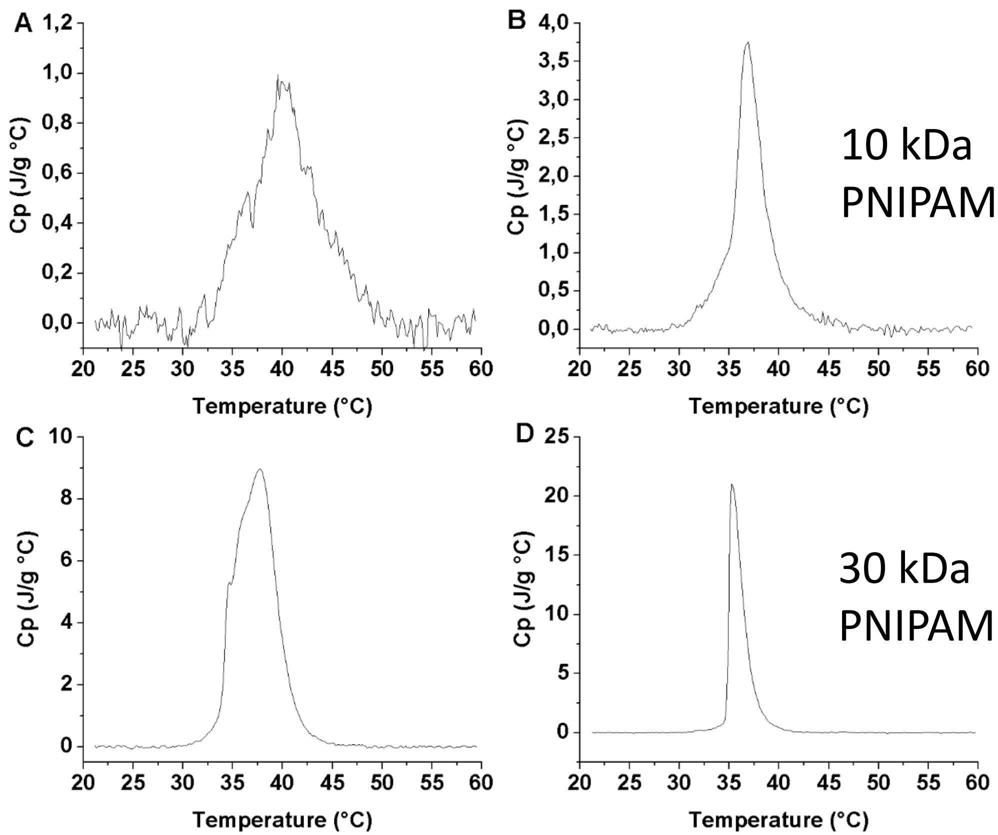
- **The local environment of the polymer matters for the LCST transition: grafting density, curvature, ...**

5 kDa PNIPAM

10 kDa PNIPAM

20 kDa PNIPAM

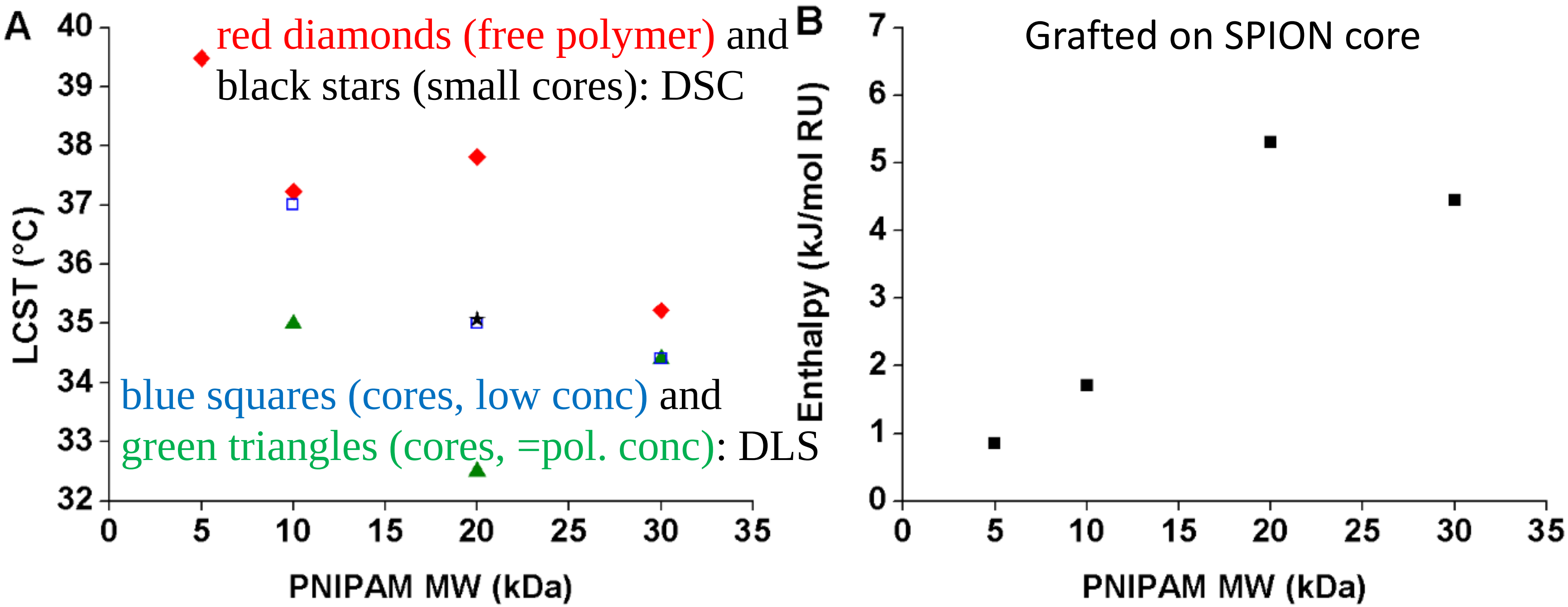
30 kDa PNIPAM



DSC thermograms for PNIPAM-brush grafted iron oxide nanoparticles 10-11 nm in diameter, at 1 mg mL^{-1}, 20-60 °C, 1 K min^{-1} heating rate; heat capacity in J g^{-1} $°C^{-1}$ of polymer.

S. Kurzhals *et al.*, *J Coll Interf Sci* (2017)

Solubility transition influenced by PNIPAM MW

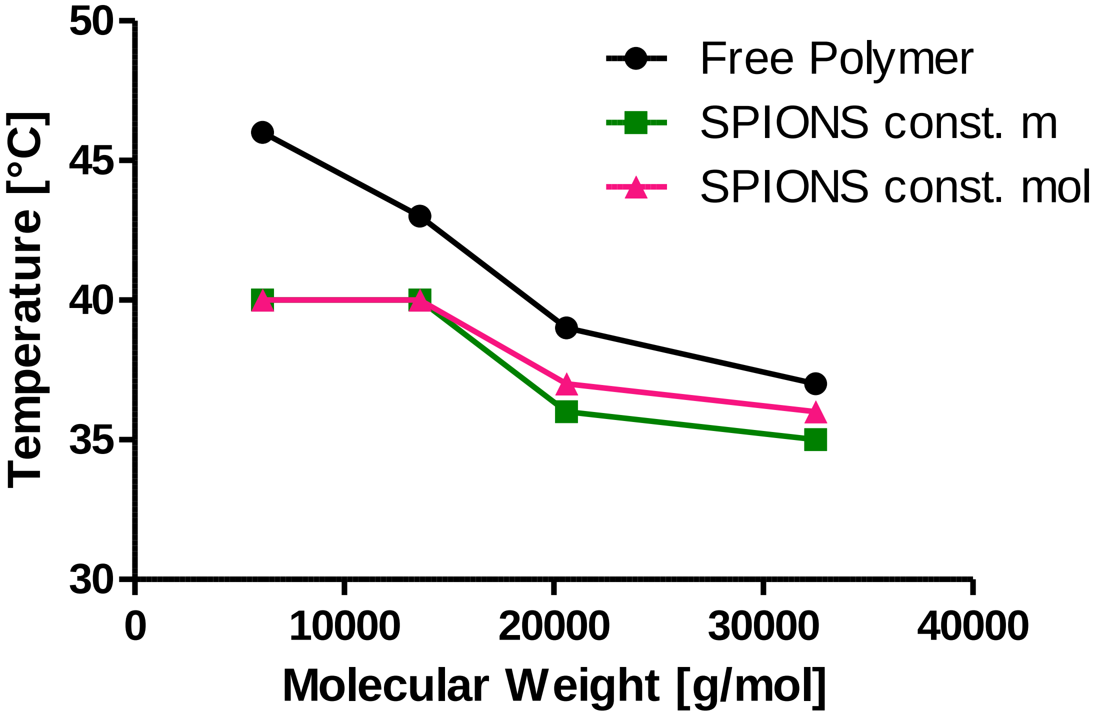


- LCST depends on PNIPAM MW
- LCST depends on method of measurement (polymer and colloidal transition are not the same since the particle interaction potential has to be added)
- Entropy of hydrated grafted brush influences enthalpy of LCST transition, leading to stronger MW dependence on core than for free polymer

S. Kurzhals *et al.*, *J Coll Interf Sci* (2017)

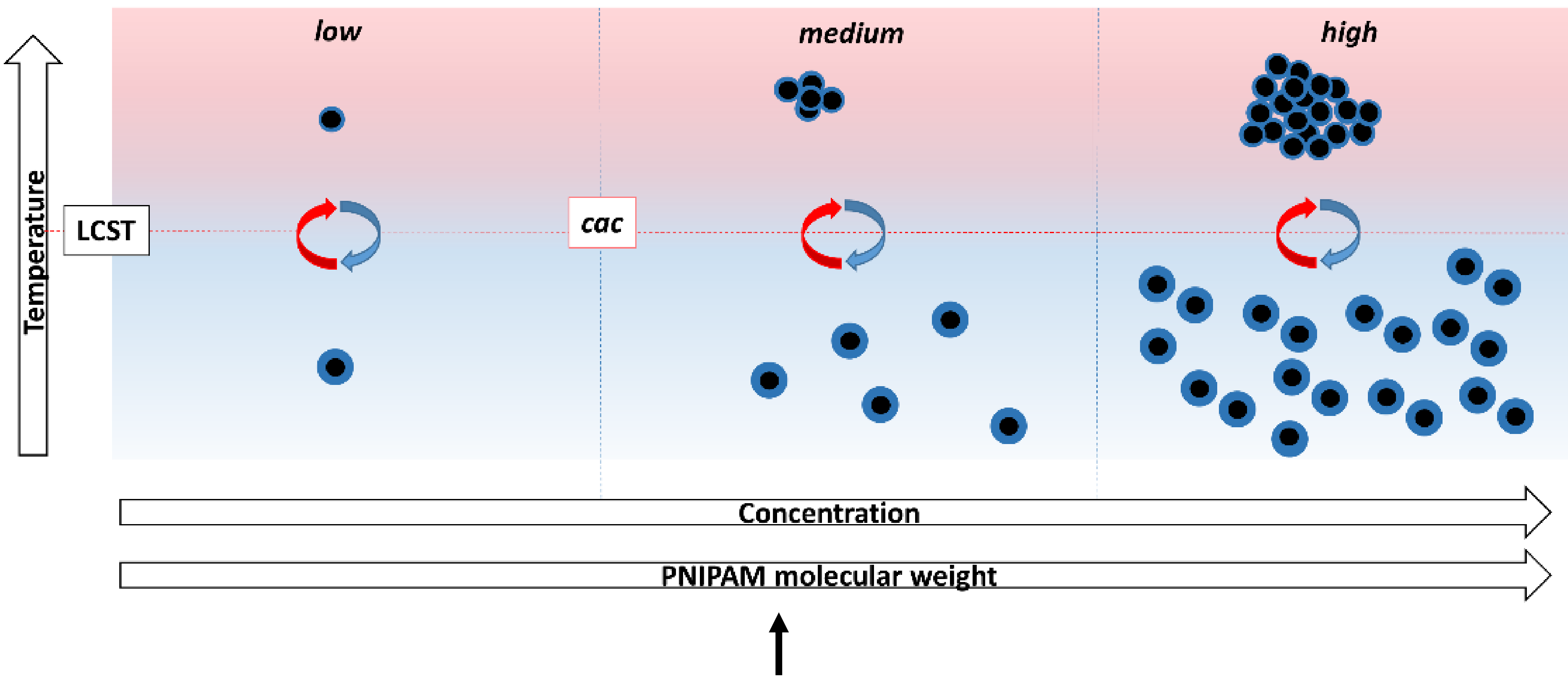
Poly(2-isopropyl-2-oxazoline) shows same trends as PNIPAM

Sample Name	Core D [nm]	target Mw [kg/mol]	Mw GPC [kg/mol]	PDI	TGA			D_H [nm]
					Weight loss [wt%]	Residue [wt%]	σ [M/nm²]	
FeOx-6	9.1±0.3	5.0	5.8	1.08	55.8	44.2	1.03	16.0±2.9
FeOx-14	9.1±0.3	15.0	13.6	1.05	70.0	30.0	0.81	17.2±2.2
FeOx-21	9.1±0.3	20.0	20.6	1.10	74.0	26.0	0.65	19.1±1.6
FeOx-33	9.1±0.3	30.0	32.5	1.15	86.7	13.3	0.95	20.2±2.4



- Other thermoresponsive grafted polymer shells show the same trends as PNIPAM

Summary: concentration and polymer MW influence aggregation

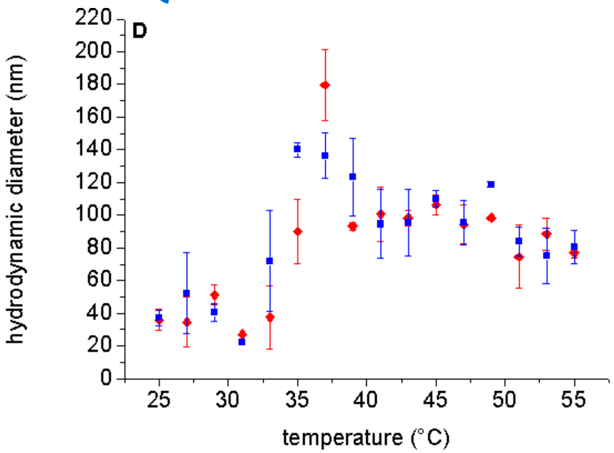


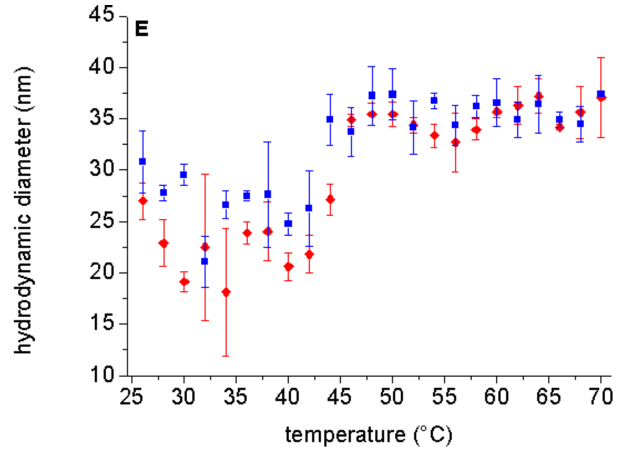
„Irreversible“
aggregation can occur

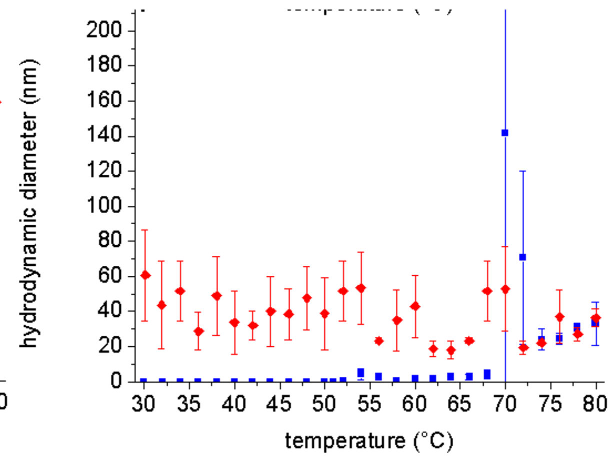
S. Kurzhals *et al.*, *J Coll Interf Sci* (2017)

Physiological conditions (ions) lower thermal colloidal stability

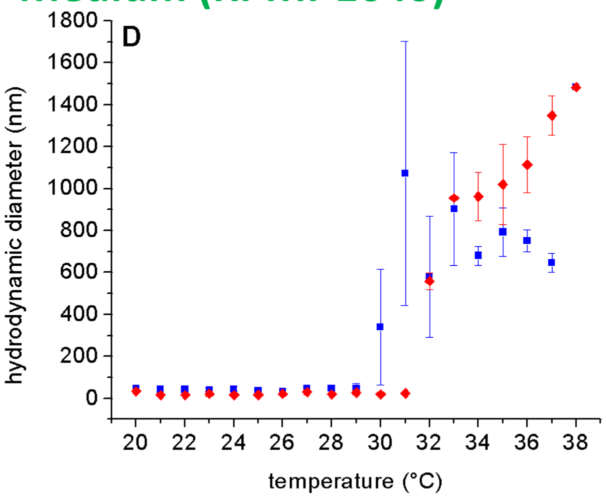
Milli-Q water

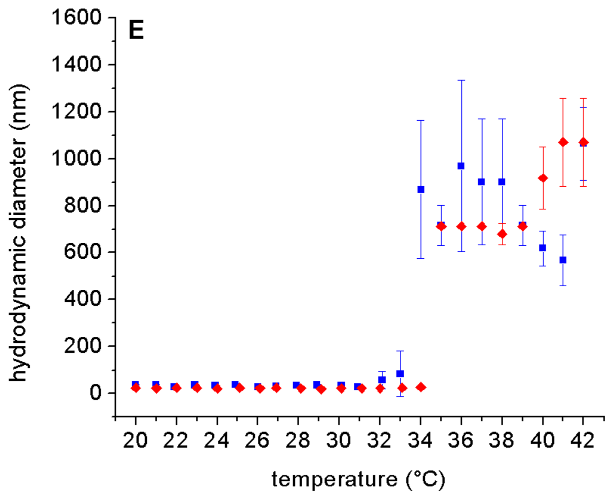


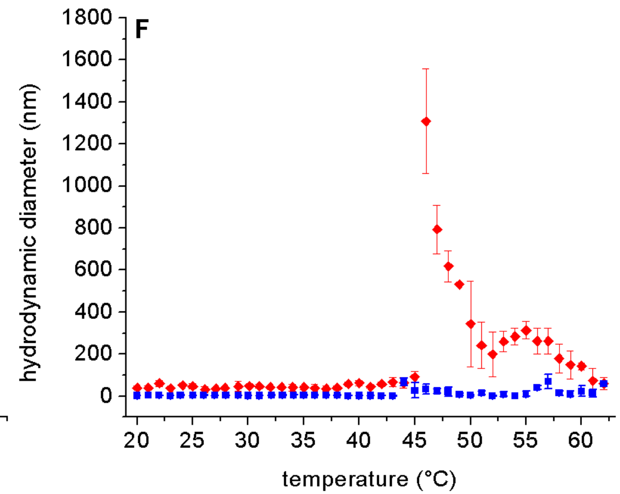




Medium (RPMI-1640)







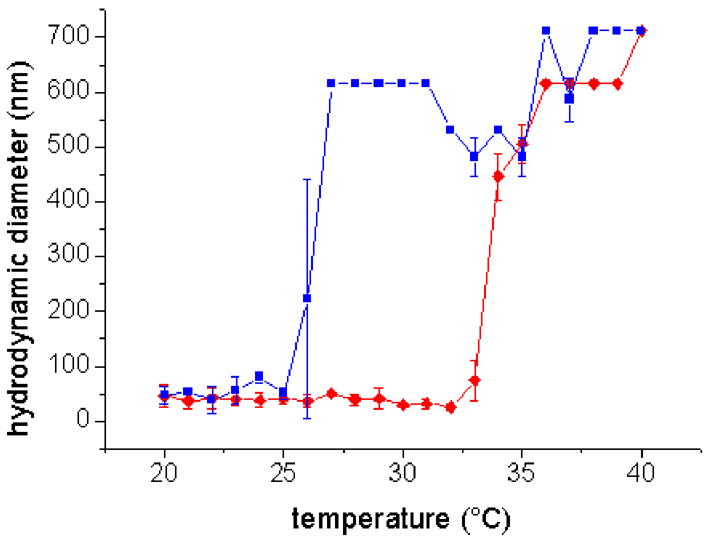
Fe_3O_4/PIPOX(100) **Fe_3O_4/PIPOX/PETOX(87/13)** **Fe_3O_4/PETOX(100)**

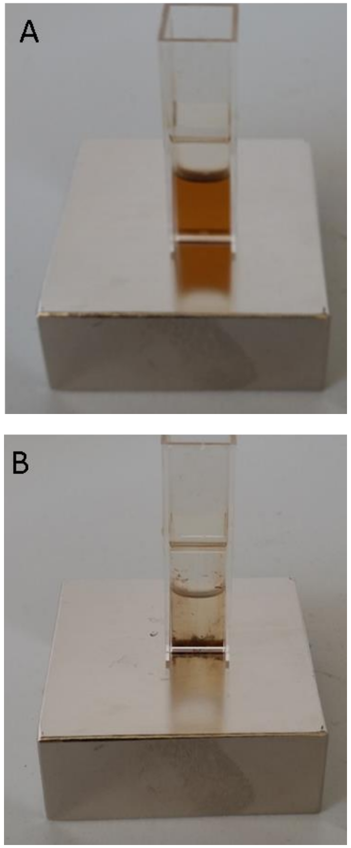
- **Dominated by effect of chaotropes/cosmotropes on water hydrigen bonding**

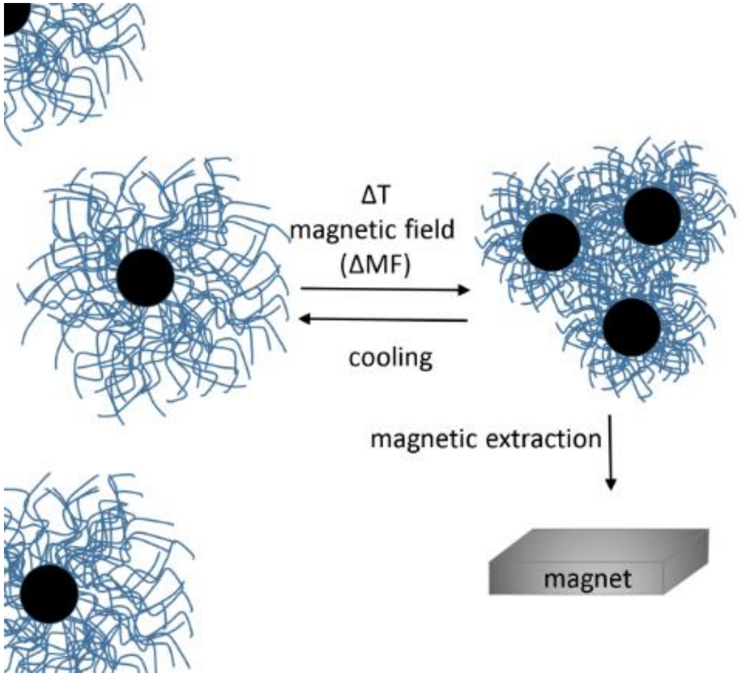
Control over shell thickness and NP stability + responsiveness

- For stability in protein solutions and media:
  ~1 PEG(5kDa)/nm^2
- For stability under thermal actuation:
  ~1 PEG(5kDa)/nm^2
- Special assembly and structural properties:
  >2 PEG(5kDa)/nm^2

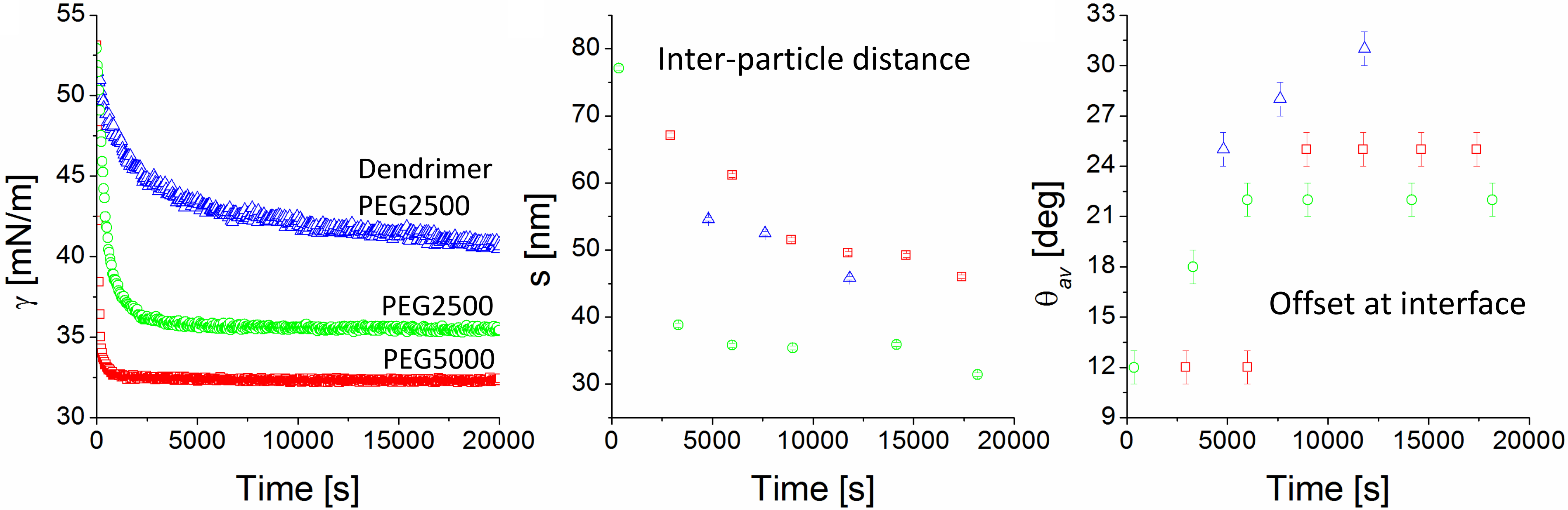
Example: magnetically heating of PNIPAM-grafted superparamagnetic particles for magnetic extraction







Core-shell nanoparticles at liquid-liquid interfaces – X-ray reflectivity



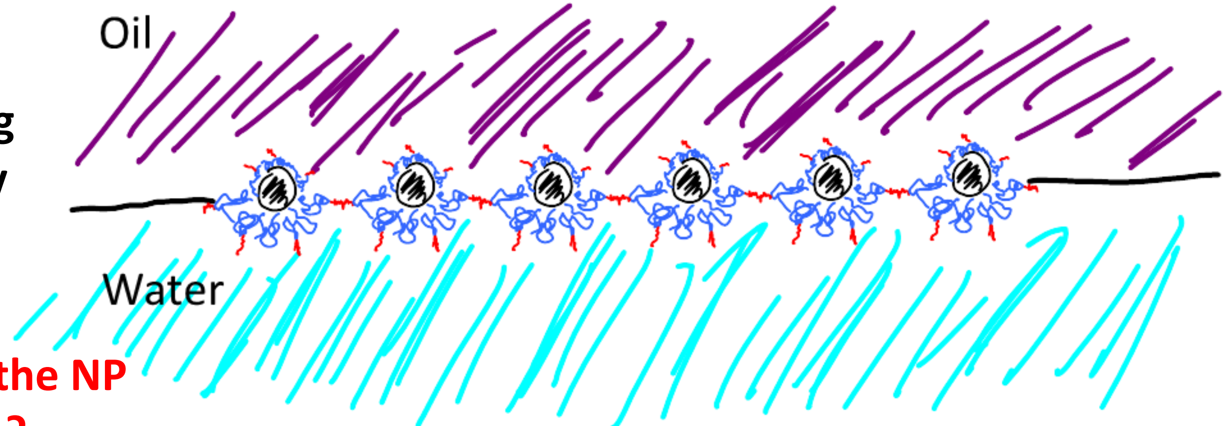
Results:

1. Thicker shell (higher MW) ⇒ Faster and saturated adsorption (higher trapping energy)
2. Higher MW linear shell ⇒ Larger particle spacing
3. Linear shell ⇒ Transition in the contact angle at high coverage ⇒ collective effect due to crowding

L. Isa *et al.*, *Soft Matter* (2013)

Core-shell nanoparticles at liquid-liquid interfaces

Small, non-neutrally wetting particles are not irreversibly trapped at the interface

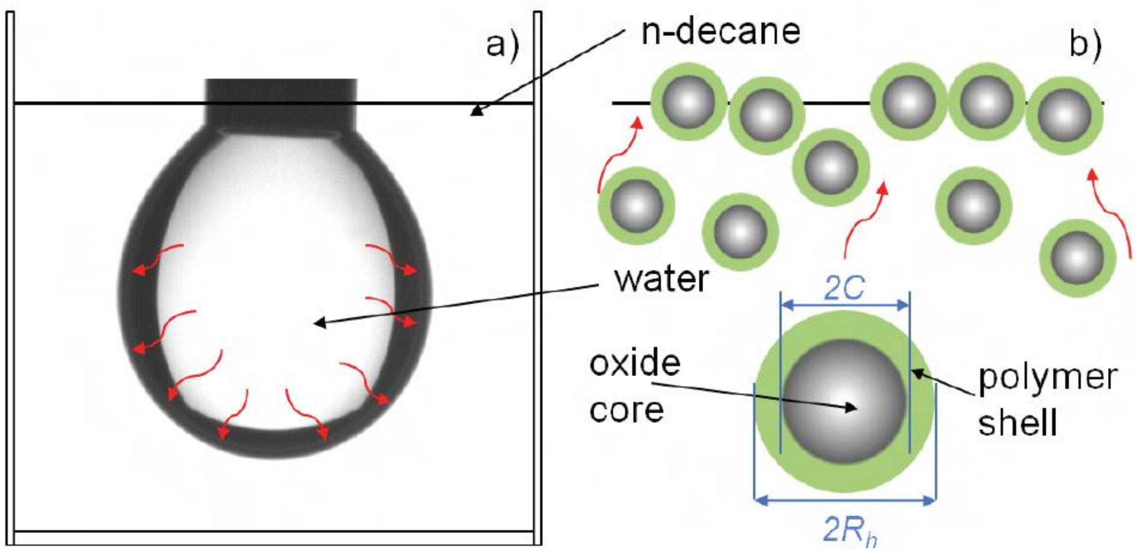


Does the polymer shell modify the NP trapping energy at the interface?

Does the polymer shell control the inter-particle spacing?

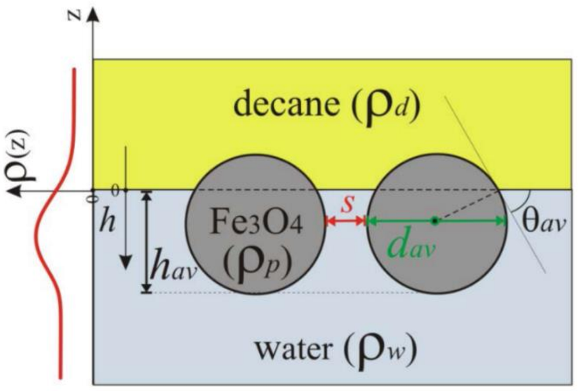
Measurement of adsorption binding kinetics at oil-water drop and planar interfaces

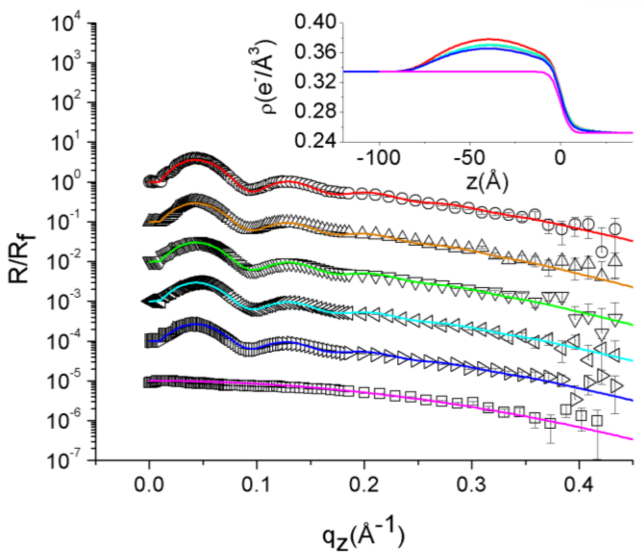
- Pendant drop:
  - interfacial tension
- X-ray reflectometry and grazing angle scattering:
  - NP position and distribution
- Transmission electron microscopy

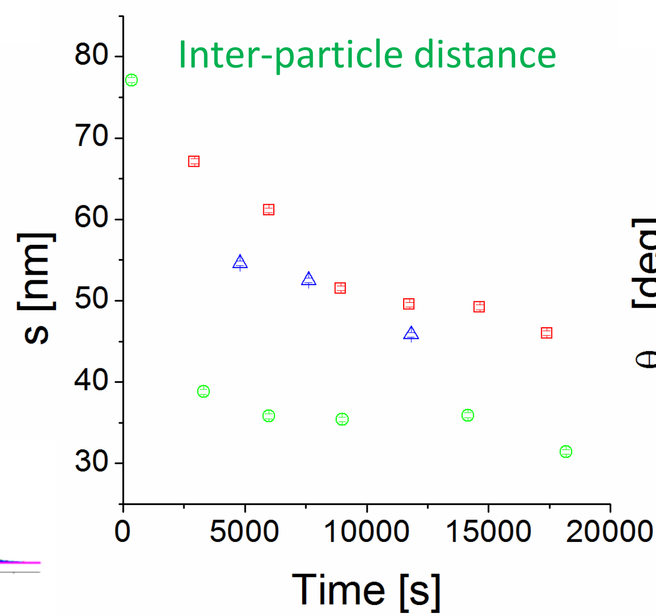


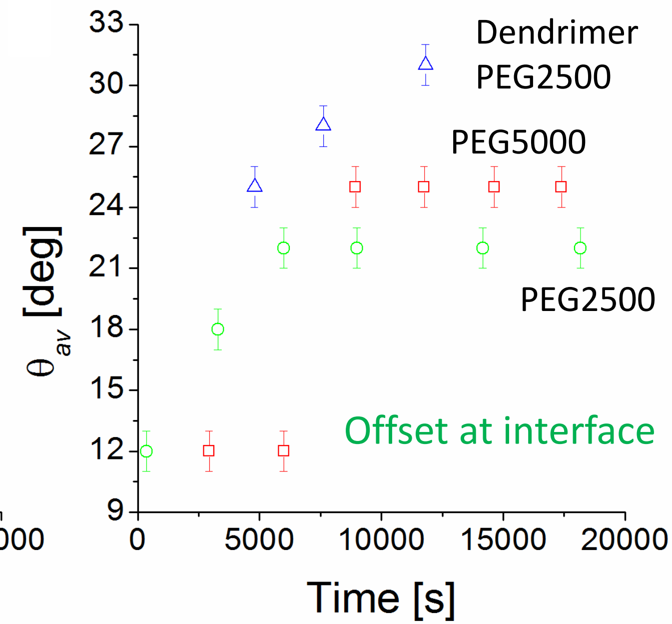
L. Isa *et al.*, *Soft Matter* (2011, 2013); L. Isa *et al.*, *Chimia* (2010); L. Isa *et al.*, *Nat Comm* (2011)

Core-shell nanoparticles at liquid-liquid interfaces – X-ray reflectivity









Collaboration with Dr. D. Pontoni (ESRF)

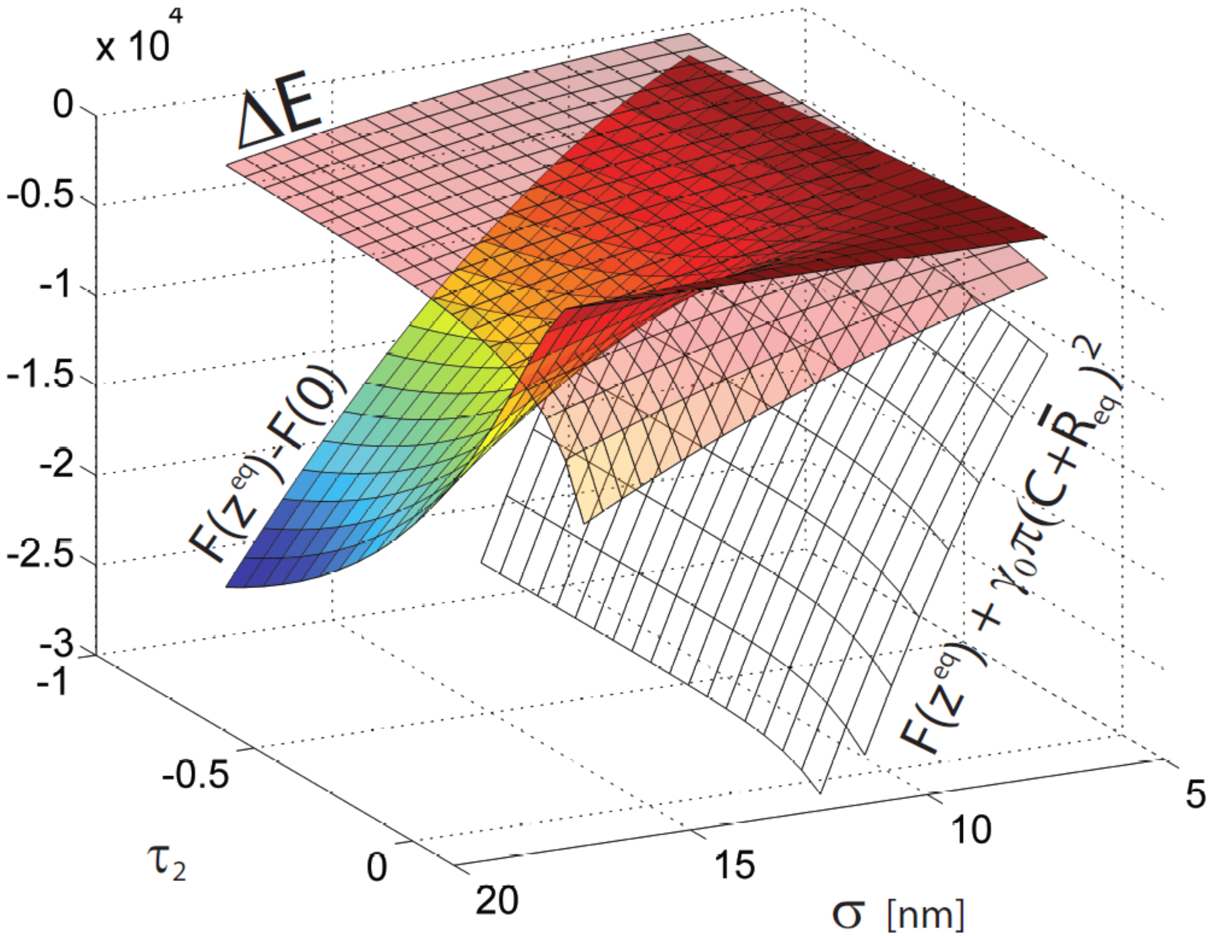
Results:

1. z-position of the core ⇒ strongly partitioned to water
2. Thicker shell (higher MW) ⇒ Faster and saturated adsorption (higher trapping energy)
3. Higher MW linear shell ⇒ Larger particle spacing
4. Linear shell ⇒ Transition in the contact angle at high coverage ⇒ collective effect due to crowding or polydispersity

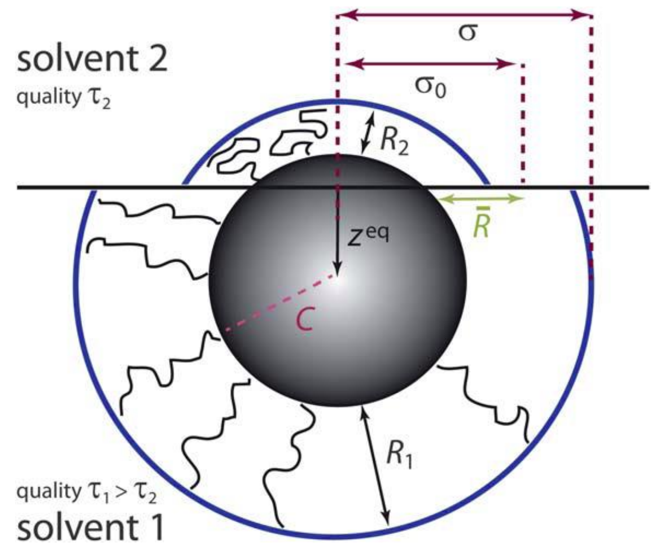
L. Isa *et al.*, *Soft Matter* (2013)

Core-shell nanoparticles at liquid-liquid interfaces – modeling

Deformation of Flory-type polymer at liquid interfaces



„Induced Janus particle“



For increasing size the trapping energy increases at the interface relative the equivalent hard sphere particle due to deformation of polymer

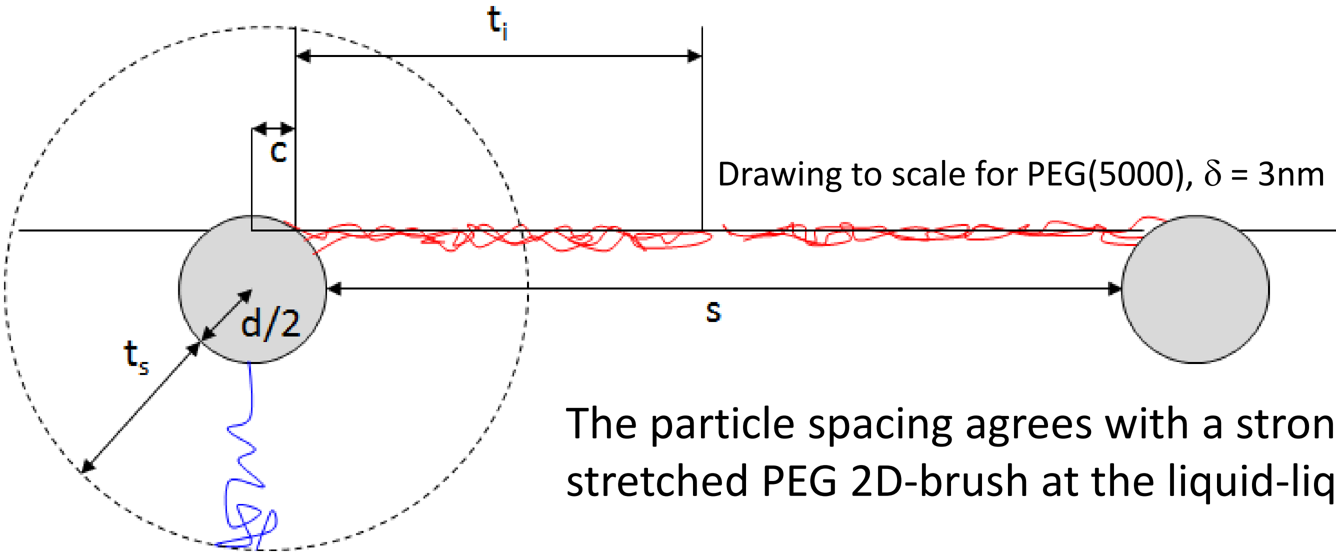
Collaboration with Prof. M. Kröger, ETH Zürich

L. Isa *et al.*, *Soft Matter* (2013)

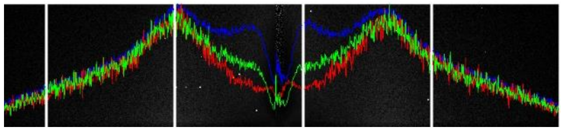
Chain stretching at the interface

Assuming polymer extension in 2D along the surface from an interfacial layer of thickness δ

NP batch	c [nm]	δ [nm]	t_i [nm]	δ [nm]	t_i [nm]	s [nm]
PEG5000	1.78	2	20.6	3	22.9	46.0
PEG2500	1.57	2	12.1	3	13.5	31.4



Drawing to scale for PEG(5000), δ = 3nm



GISAXS peak evolution confirms distance evolution

The particle spacing agrees with a strongly stretched PEG 2D-brush at the liquid-liquid interface

Collaboration with O. Konovalov / D. Pontoni (ESRF ID10)

L. Isa *et al.*, Soft Matter (2013); P.D.J. van Oostrum, in preparation

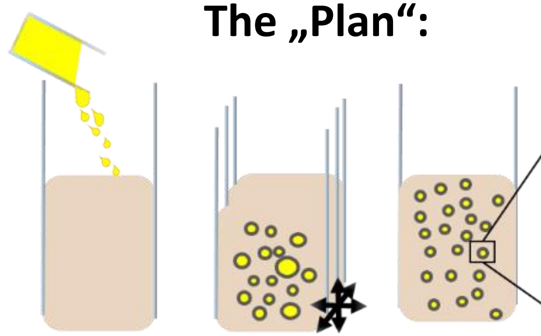
Core-shell nanoparticle assembly at oil-water interfaces

Oil

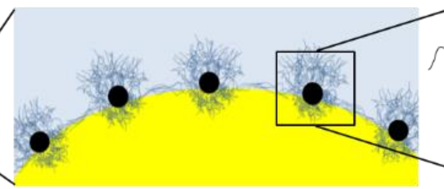
Application:
Transport and release of hydrophobic compounds (drugs)

Core-shell nanoparticles to stabilize nanodroplets

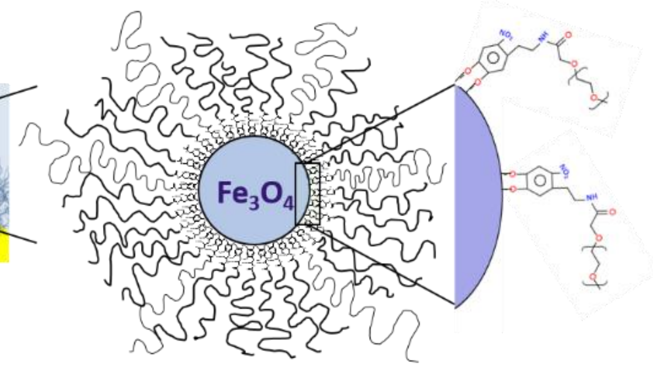
The „Plan“:



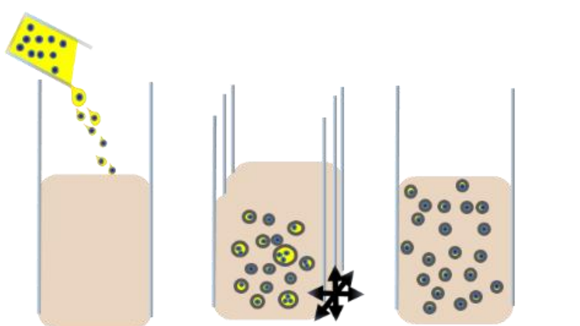
Mixing and gentle shaking of oil and nanoparticle solution; uniform long-term thermodynamical stable droplets form;



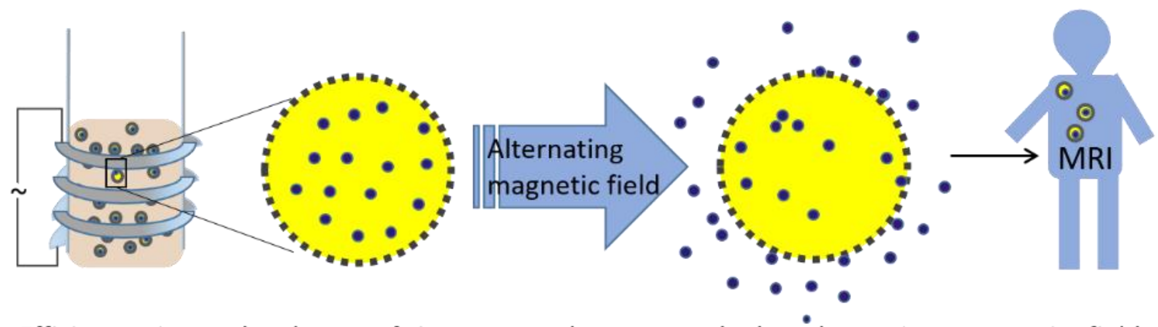
biocompatible materials: superparamagnetic magnetite core shell NPs (SPION); fatty acid providing low interfacial tension interface



hydrophilic monodisperse (σ < 5%) SPION; thermoresponsive crosslinkable polymer brush with nitrodopamine anchor promoting irreversible binding



Oil is loaded with hydrophobic compounds and mixed with nanoparticle solution



Efficient triggered release of incorporated compounds by alternating magnetic field promoting local morphological and interfacial changes of oil droplet; use as anti-cancer drug delivery vehicle and imaging agent

⇒ 100 nm-sized oil droplets are required for applications. Aren’t they highly unstable?

NP membrane capsules – core-shell NP nano-Pickering emulsions

From planar liquid interfaces

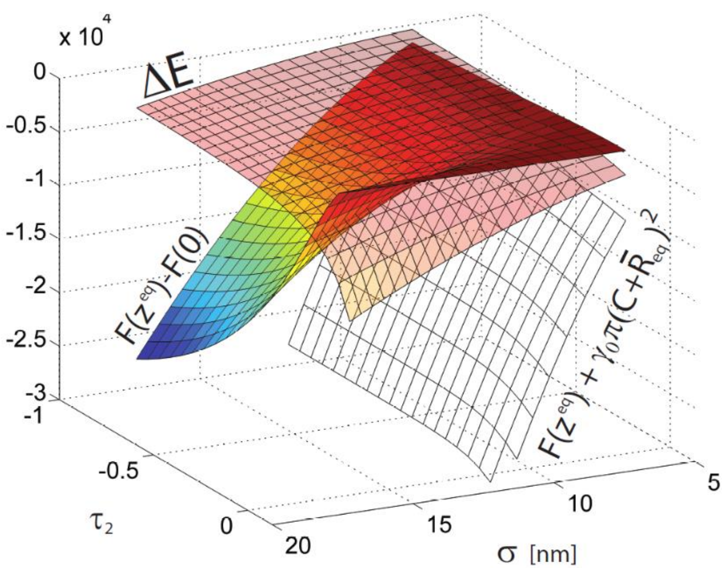
to

Nanoscopic droplets

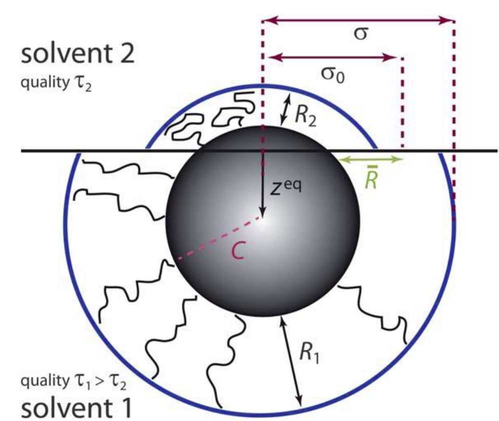
PEG or PEtOx/PiPOx shell
Fe_3O_4 core

Goal: effective and stable encapsulation of hydrophobic compounds in nanoscale containers

Problem: Pickering emulsions are stable for **micron-size** droplets and particles, but that is **too large** for biomedical applications



Solution(?): Hydrophilic **inorganic core – polymer shell nanoparticles** have sufficient adsorption energy at the interface to **allow Pickering-type stabilization**



L. Isa *et al.*, *Soft Matter* (2011); *Soft Matter* (2013); *Chimia* (2010); L. Isa *et al.*, *Nat Comm* (2011)

NP membrane capsules – core-shell NP nano-Pickering emulsions

From planar liquid interfaces

PEG or PEtOx/PiPOx shell
Fe_3O_4 core

to

Nanoscopic droplets

Goal: effective and stable encapsulation of hydrophobic compounds in nanoscale containers

With decane or fluorinated oils

Nanodroplets have to be formed to be stabilized

Summary of standard methods tried:

- **Shear emulsification** $\Rightarrow$ polydisperse and large droplets
- **Sonication** $\Rightarrow$ polydisperse; tip-particle contamination
- **Extrusion** $\Rightarrow$ right size; monodisperse; but time-consuming and low throughput; high materials loss
- **Droplet fluidics** $\Rightarrow$ requires optimization

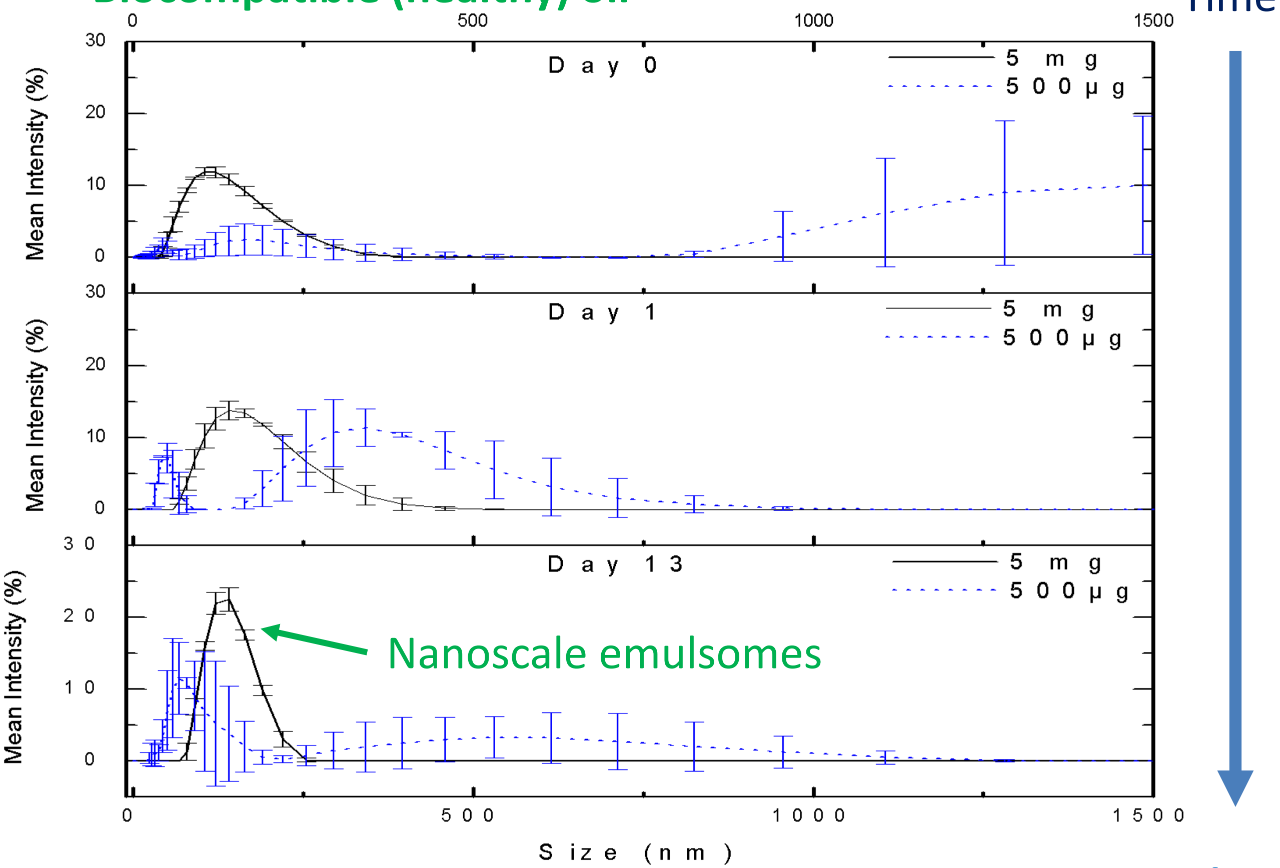
Pickering stability over days observed only for densely grafted NPs, but polydispersity leads to ripening

Core-shell NP thermodynamically stabilized emulsions

Pickering emulsions with low surface tension oils are more easily stabilized by nanoparticles

Emulsion of Nonanoic acid + PEG(5kDa)-Fe_3O_4(5nm) in water

Biocompatible (healthy) oil



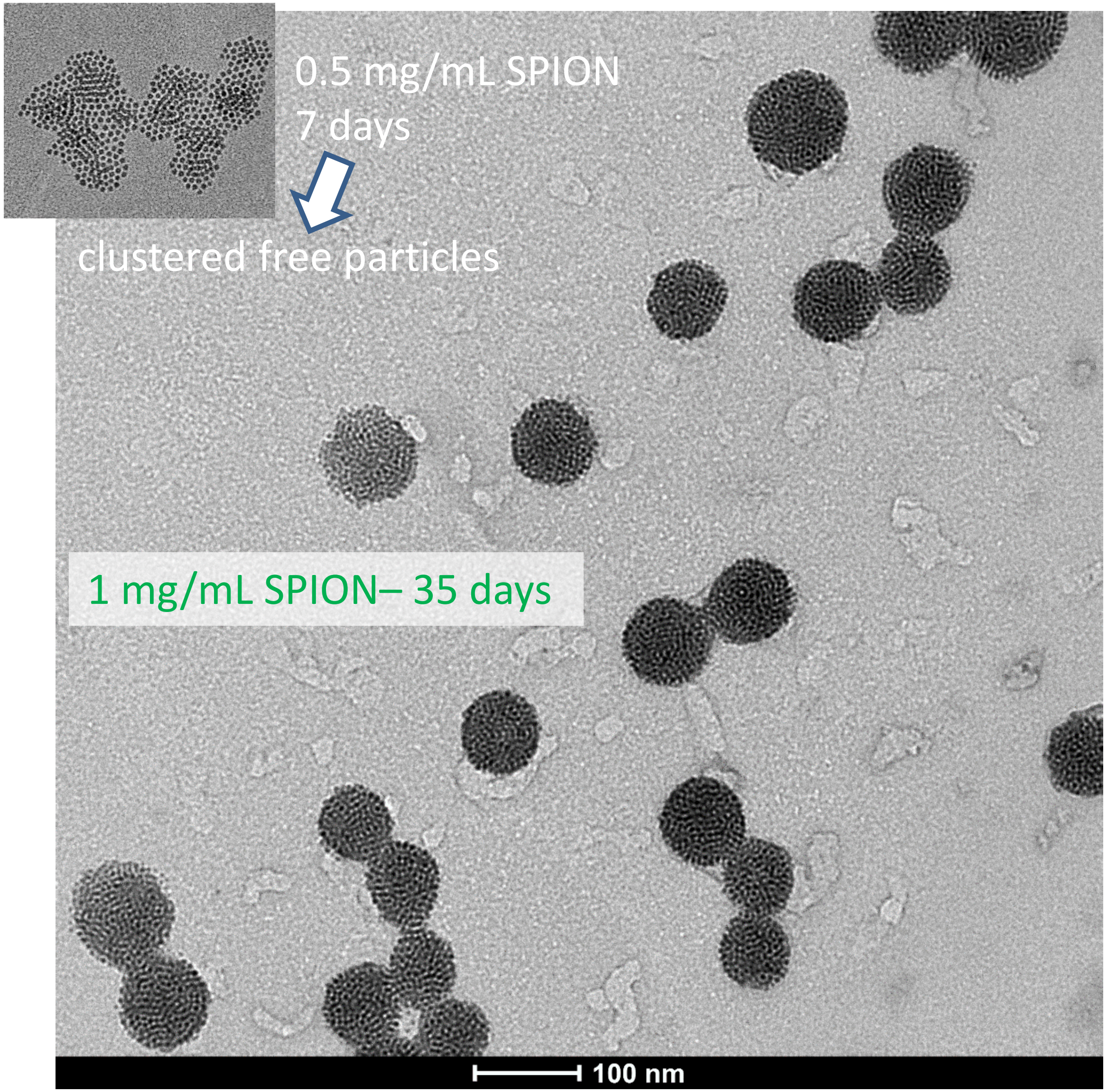
Fatty acid

- Mix and gentle shake
- Self-focusing of size (thermodynamically favored?!)
- Wait a few hours to a few days
- Reproduced for a range of fatty acids: heptanoic-decanoic acid

Inspired by Philipse, Kegel *et al. Phys Rev Lett* (2007)

I. Vonderhaid *et al., in preparation*

Core-shell NP thermodynamically stabilized emulsions



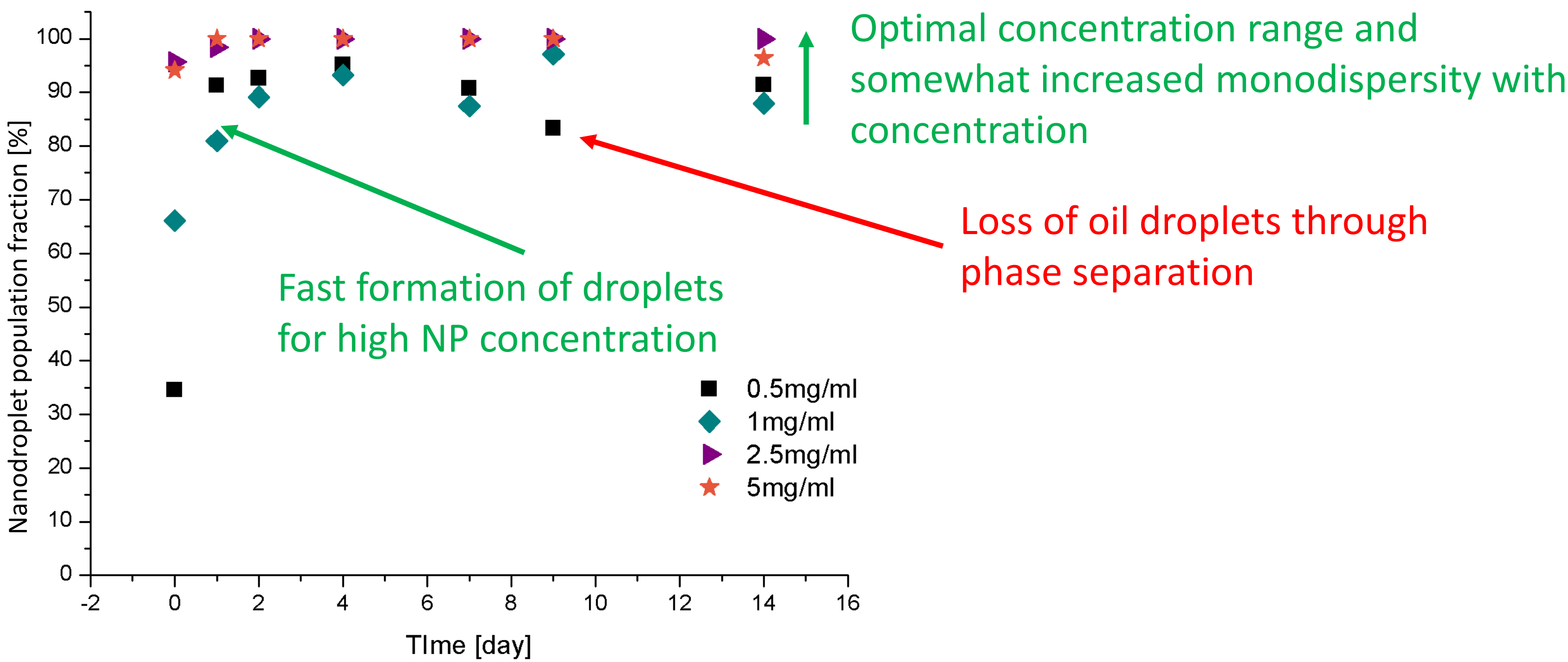
Fatty acid

Decanoic acid gelled at room temperature for separation and preparation of TEM sample

- **Dense membranes of SPION imaged on decanoic acid droplets**
- **Seem to be monolayer membranes**

I. Vonderhaid *et al.*, *in preparation*

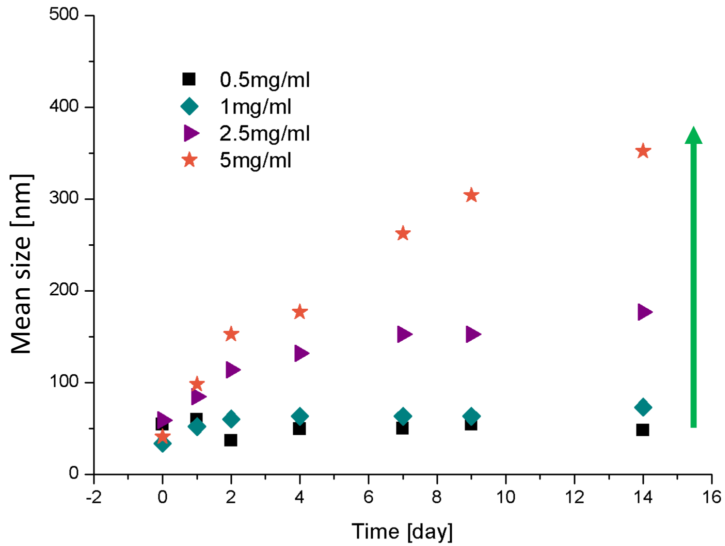
Core-shell NP thermodynamically stabilized emulsions: decanoic acid



- A threshold concentration of core-shell NP is required for spontaneous emulsification
  - (~1 mg/mL SPION; 10 µL/mL nonaoic acid in water)
- Kinetics of resizing depends on NP concentration (higher concentrations emulsify faster)

I. Vonderhaid *et al.*, *in preparation*

Core-shell NP thermodynamically stabilized emulsions: decanoic acid

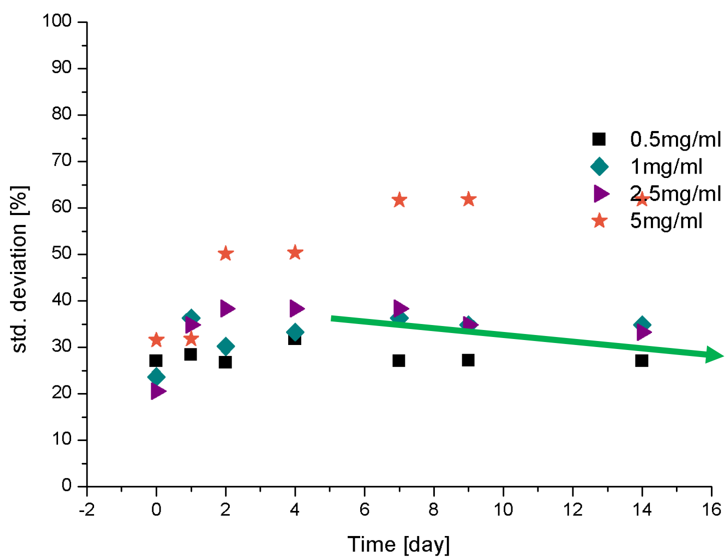


Increased size(?) with increased NP concentration

- Stable size reached within a few days
- Size and composition suitable for drug encapsulation and delivery

$\Rightarrow$ Under investigation

- No cytotoxicity but high uptake
- Triggered (magnetothermal) release using thermoresponsive core-shell SPION (not yet working)

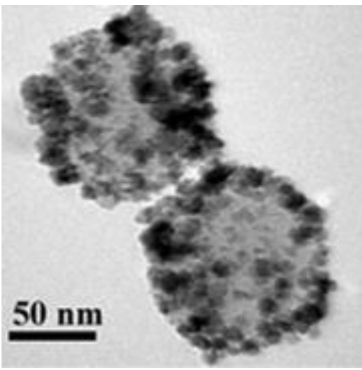


Support for size focusing from decreasing width of distribution

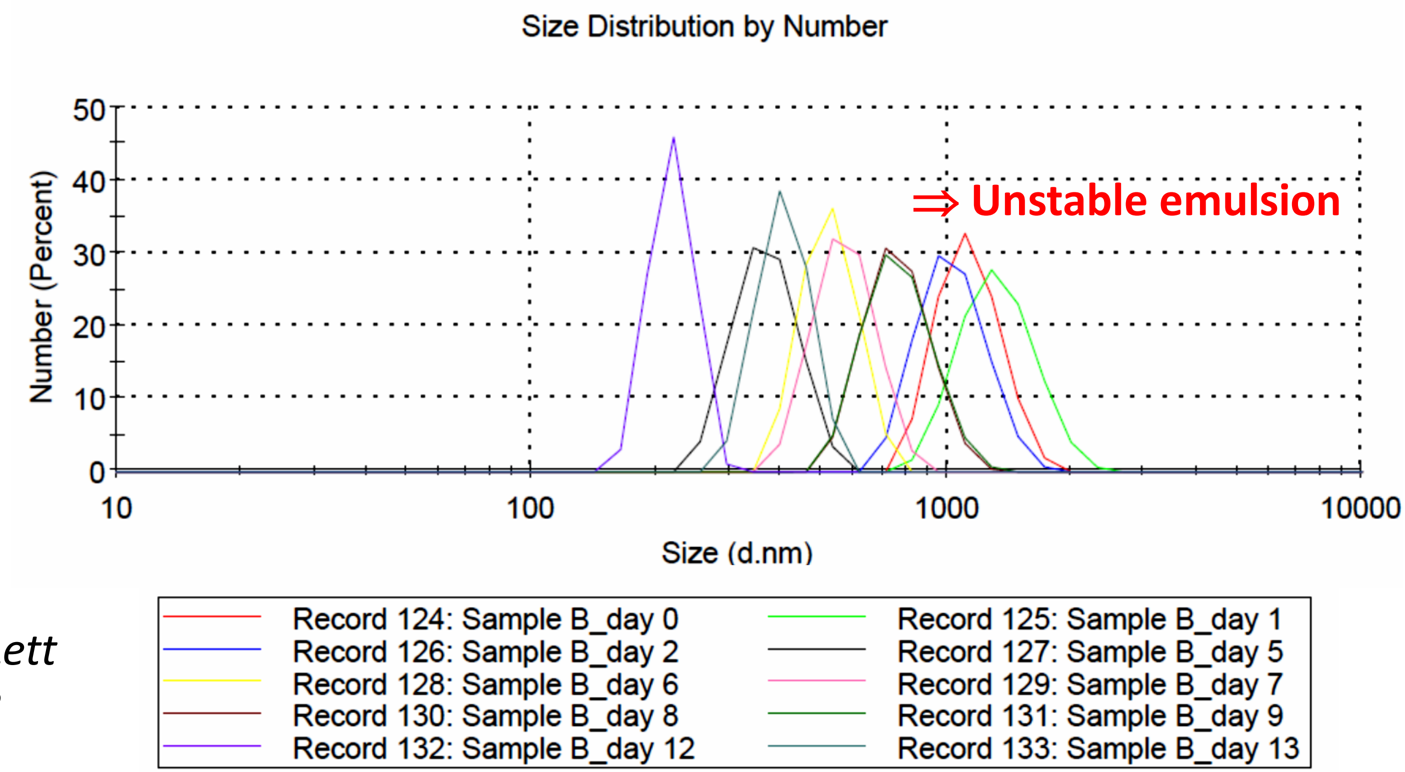
I. Vonderhaid *et al.*, *in preparation*

Core-shell NP thermodynamically stabilized emulsions

Emulsion of TPM + TMAH in water



Proposed by Philipse, Kegel *et al. Phys Rev Lett* (2007); *J Phys Chem B* (2010)



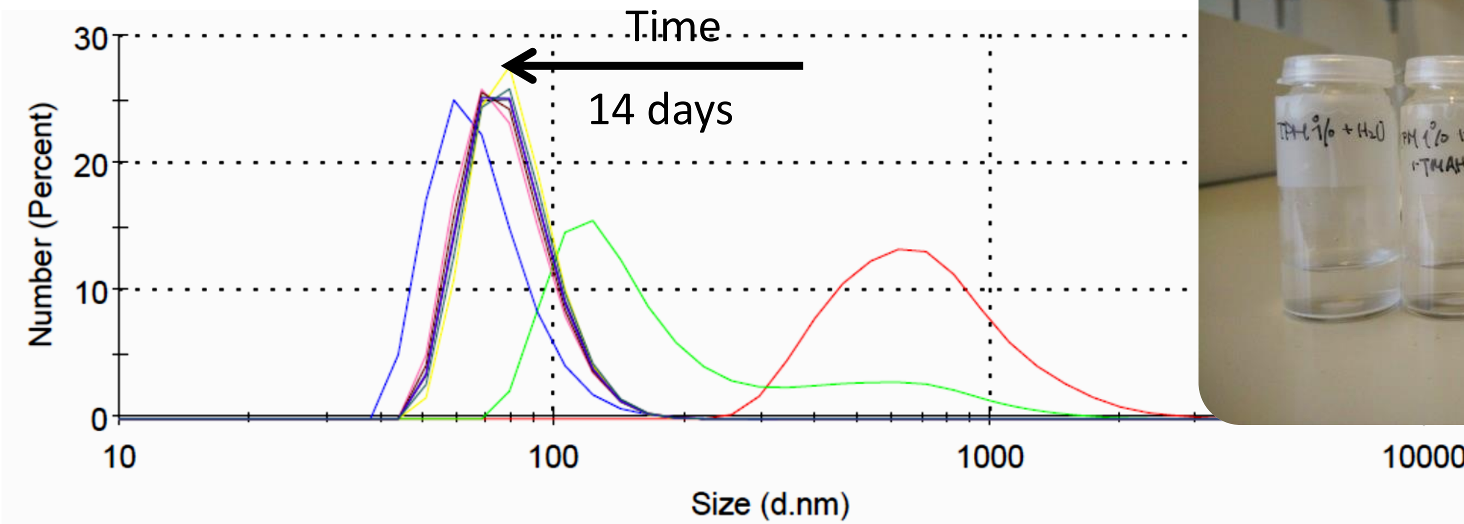
Low-surface tension emulsions can be thermodynamically stabilized using nanoparticles

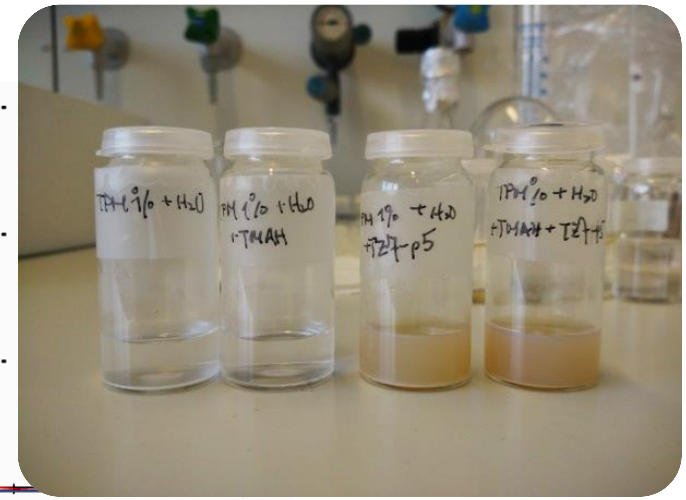
⇒ Driven by osmotic bending due to redistribution of interfacial counterions and preferred oil-wettability of NPs

⇒ Ripening to a preferred droplet size is given by NP-to-oil ratio

Core-shell NP thermodynamically stabilized emulsions

Emulsion of TPM + TMAH + PEG(5)-Fe_3O_4(5nm) in water





⇒ **Close-packed NPs with strong wetting can cause preferred curvature (droplet size) strongly, stretched-shell (core-shell) NPs could behave similarly (analogous to P. Kralchevsky et al.)**

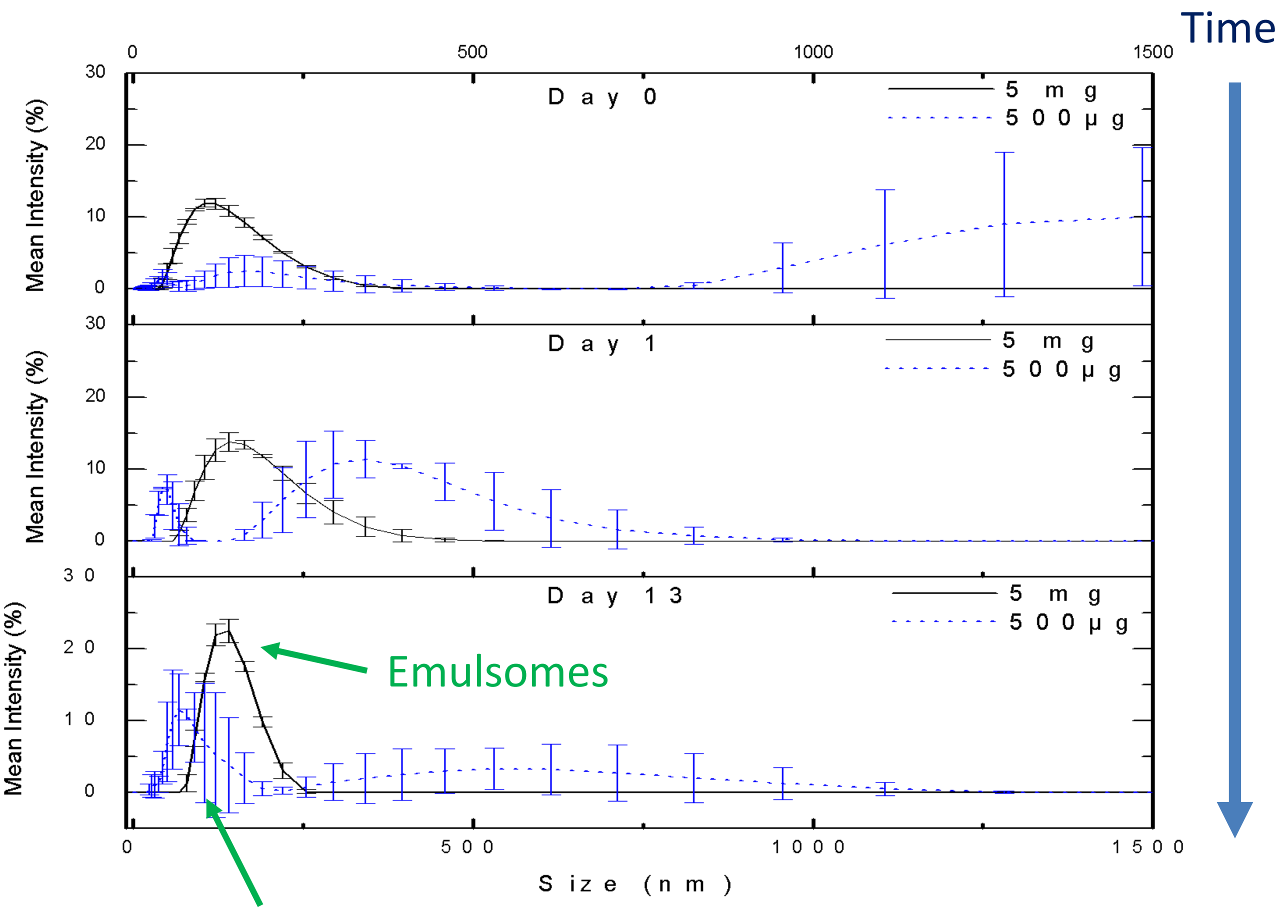
⇒ **Preliminary result: stable emulsions are formed spontaneously for *hydrophilic core-shell* NPs**

This oil is toxic ... but all we need is a low surface tension oil with some water solubility?

Core-shell NP thermodynamically stabilized emulsions

Emulsion of Nonanoic acid + PEG(5)-Fe_3O_4(5nm) in water

Biocompatible (healthy) oil



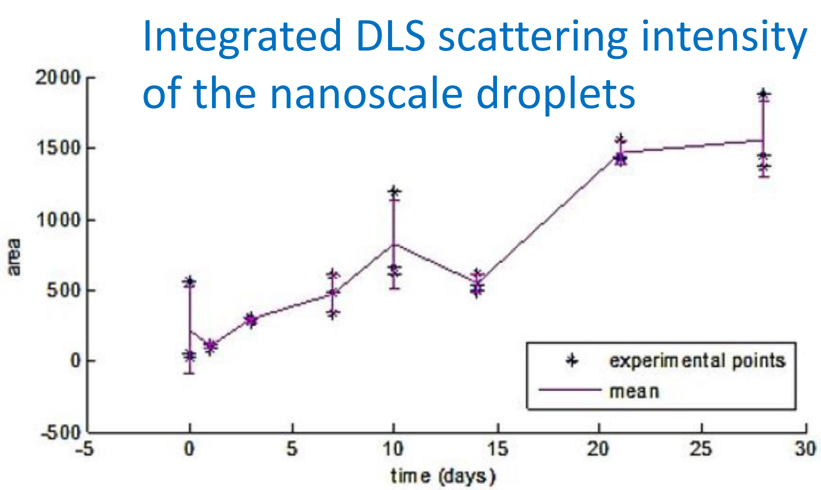
Nanoparticle peak
convoluted with droplets

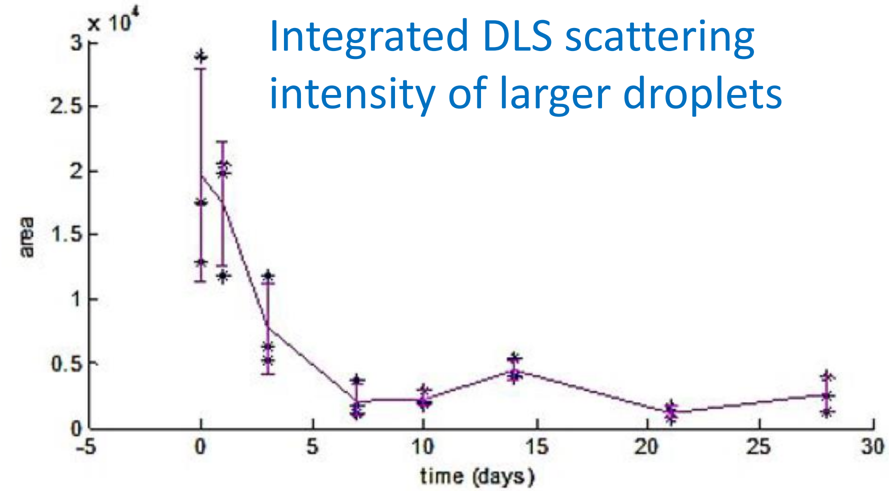
Fatty
acid

- Mix and easy shake
- Self-focusing of size (thermodynamically favored?!)
- Wait a few hours to a few days
- Reproduced for a range of fatty acids: heptanoic-decanoic acid

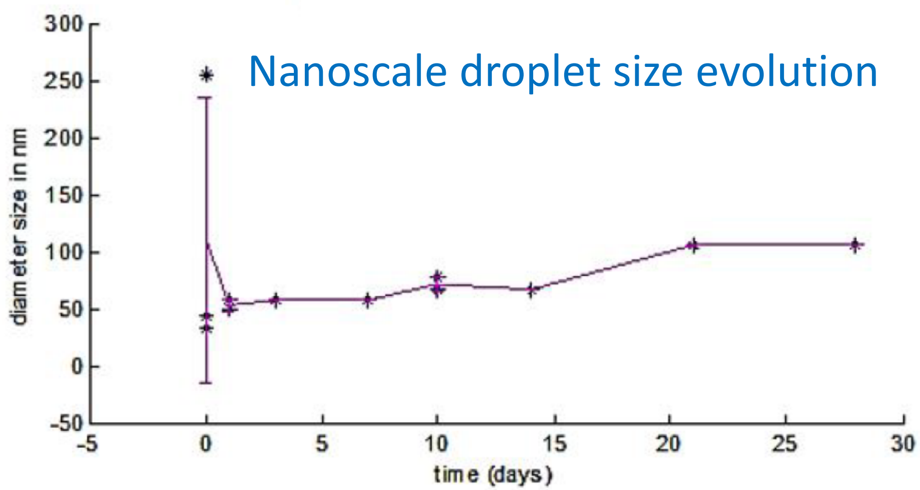
I. Vonderhaid *et al.*, *in preparation*

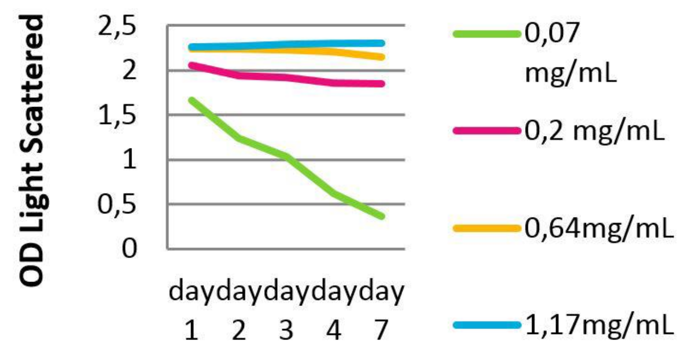
Core-shell NP thermodynamically stabilized emulsions: nonanoic acid





170 µg/mL core-shell NPs, 10 µL/mL nonanoic acid in water

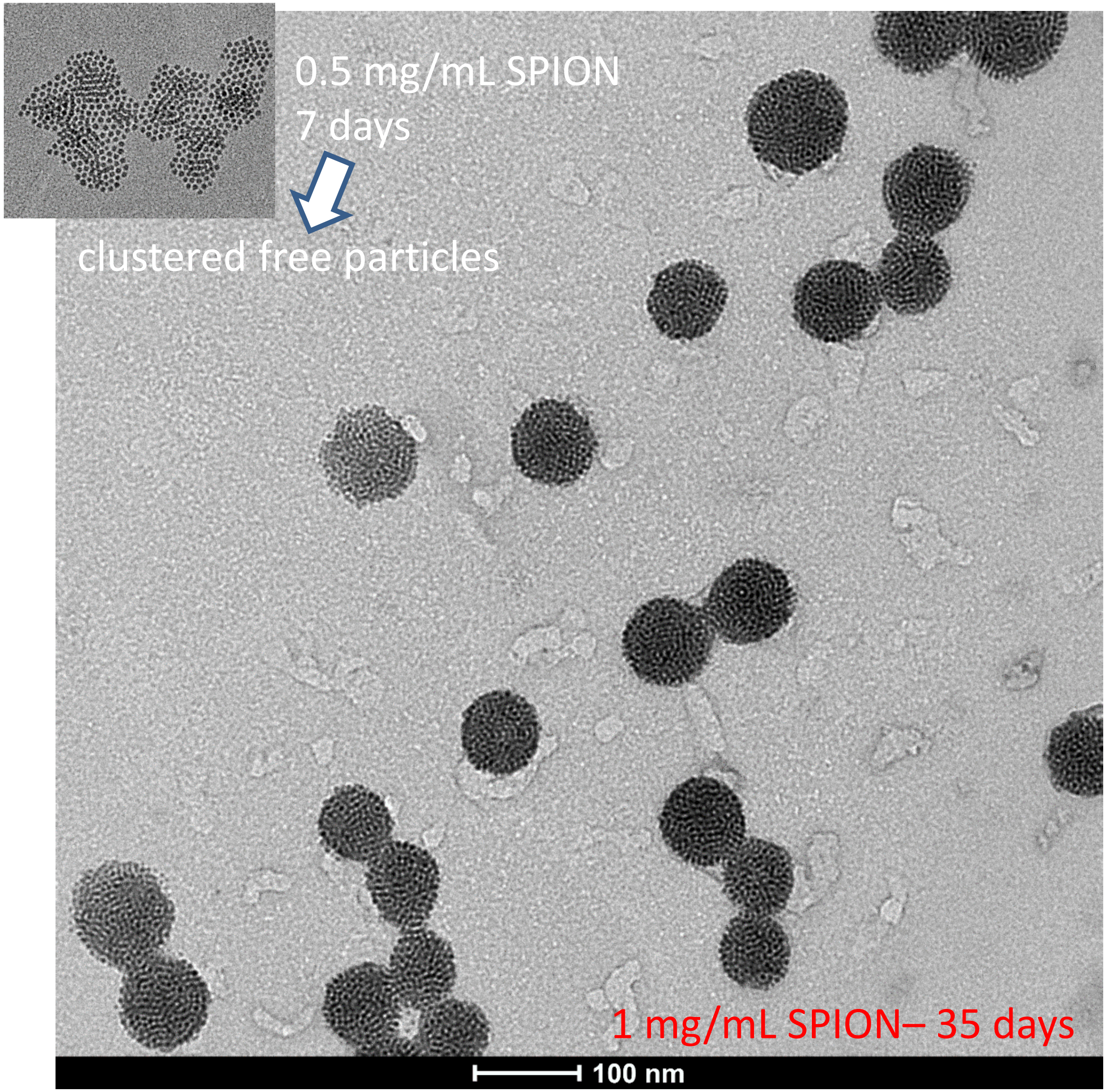




~100 nm oil droplets spontaneously formed over a week with decreased polydispersity

I. Vonderhaid / M. Ligier *et al.*, *in preparation*

Core-shell NP thermodynamically stabilized emulsions



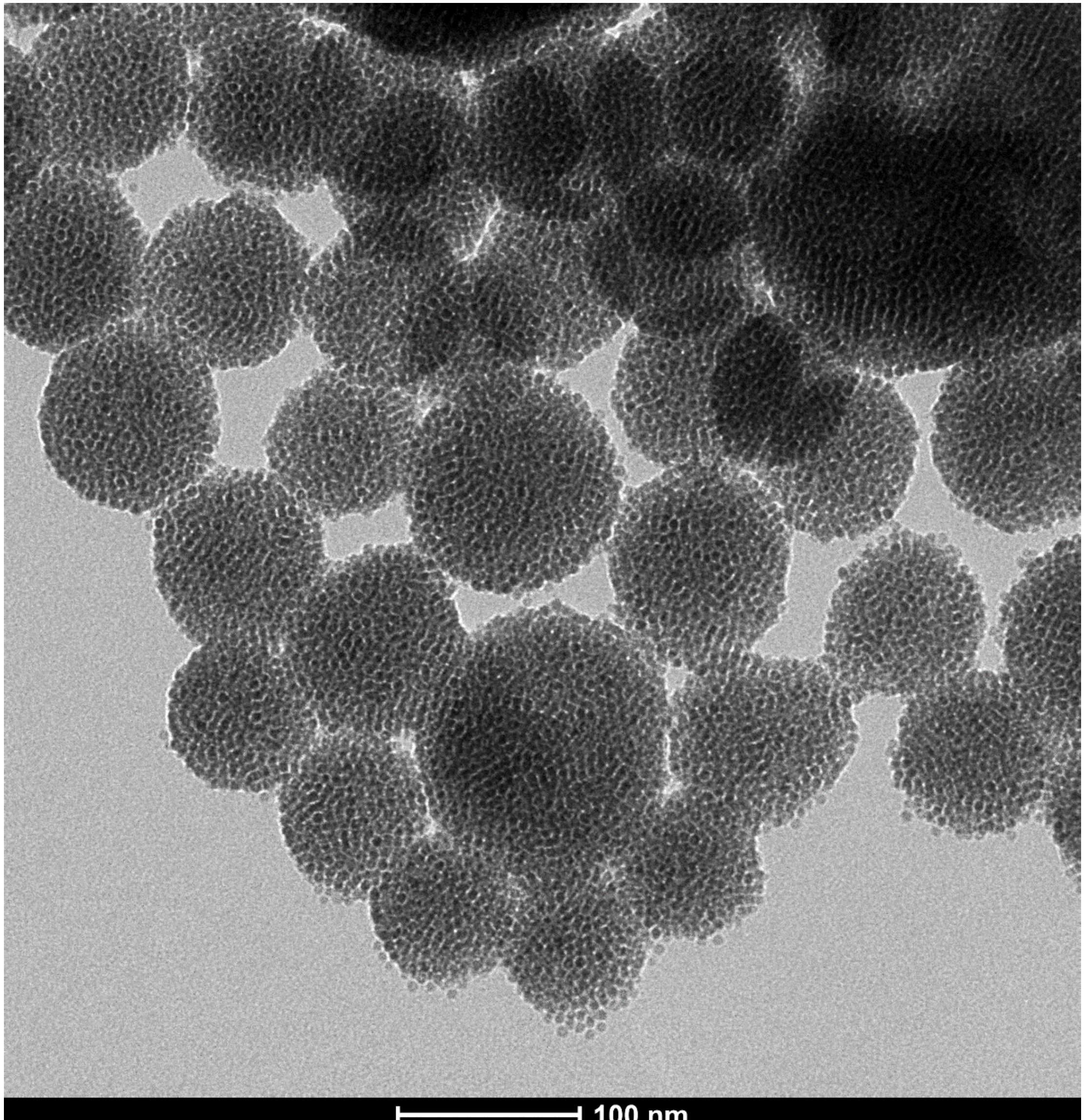
Fatty acid

Decanoic acid gelled at room temperature for separation and preparation of TEM sample

- **Dense membranes of SPION imaged on decanoic acid droplets**
- **Seemingly monolayer membranes**
- **Release and cell studies missing**

I. Vonderhaid *et al.*, *in preparation*

Core-shell NP thermodynamically stabilized emulsions



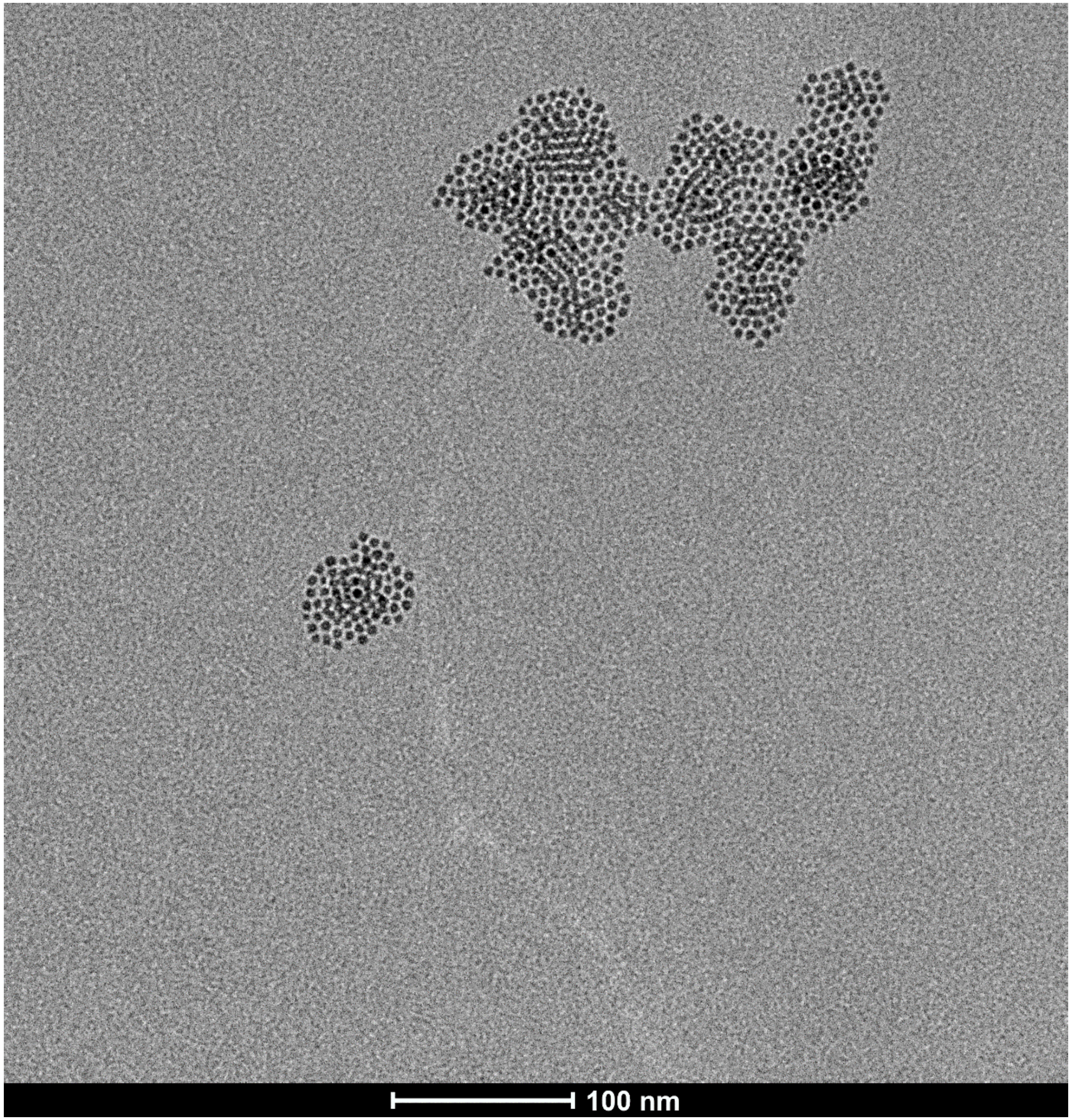
- 2.5 mg/mL SPION
- 7 days
- Centrifuged sample

SPION stabilized droplets:

- Possibly size increase with SPION concentration
- Monodisperse
- A monolayer nanoparticle coating seems supported

I. Vonderhaid *et al.*, *in preparation*

Core-shell NP thermodynamically stabilized emulsions



- 0.5 mg/mL SPION
- 7 days
- Centrifuged sample

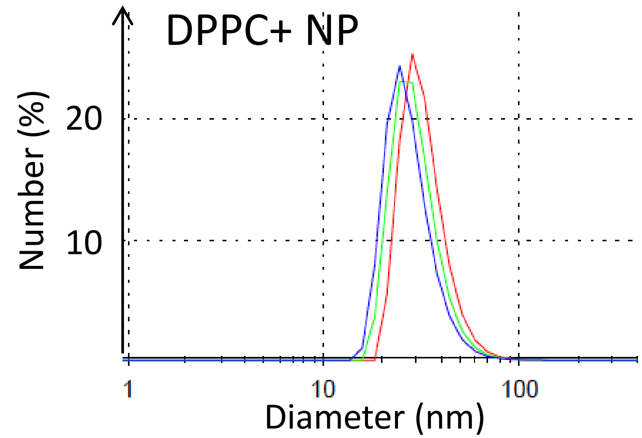
Droplets are not found, but clustered free particles

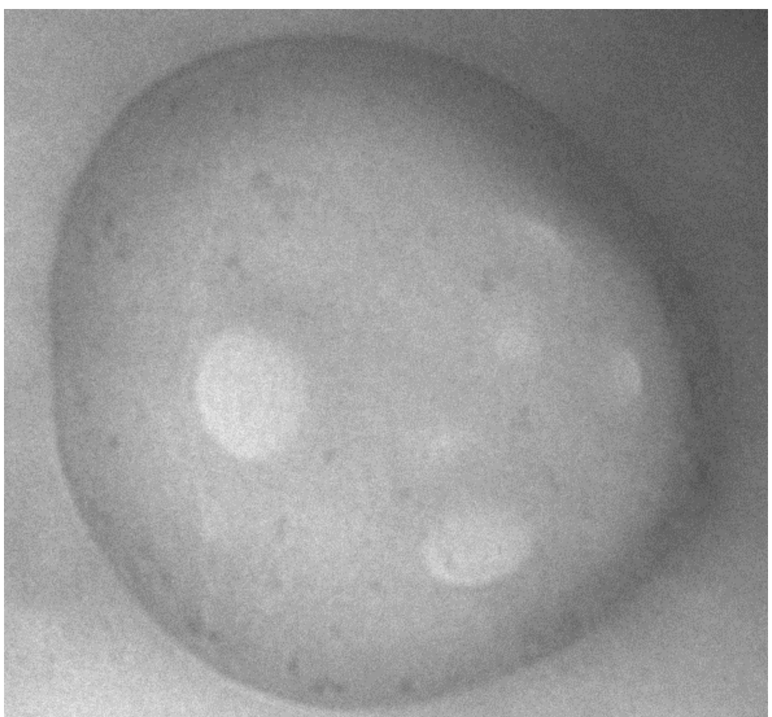
TEM data suports DLS analysis

I. Vonderhaid *et al.*, *in preparation*

Liposome NP-loading by THF solvent injection and sonication

- **Most efficient loading technique**
- Reduces vesicle size to 30-40 nm
- Sonication can keep NP fractions in unilamellar vesicles >10 wt% for saturated lipids (high T_m)
- >100 NPs per ~100 nm vesicle
- Liposome stability reduced >5 wt%



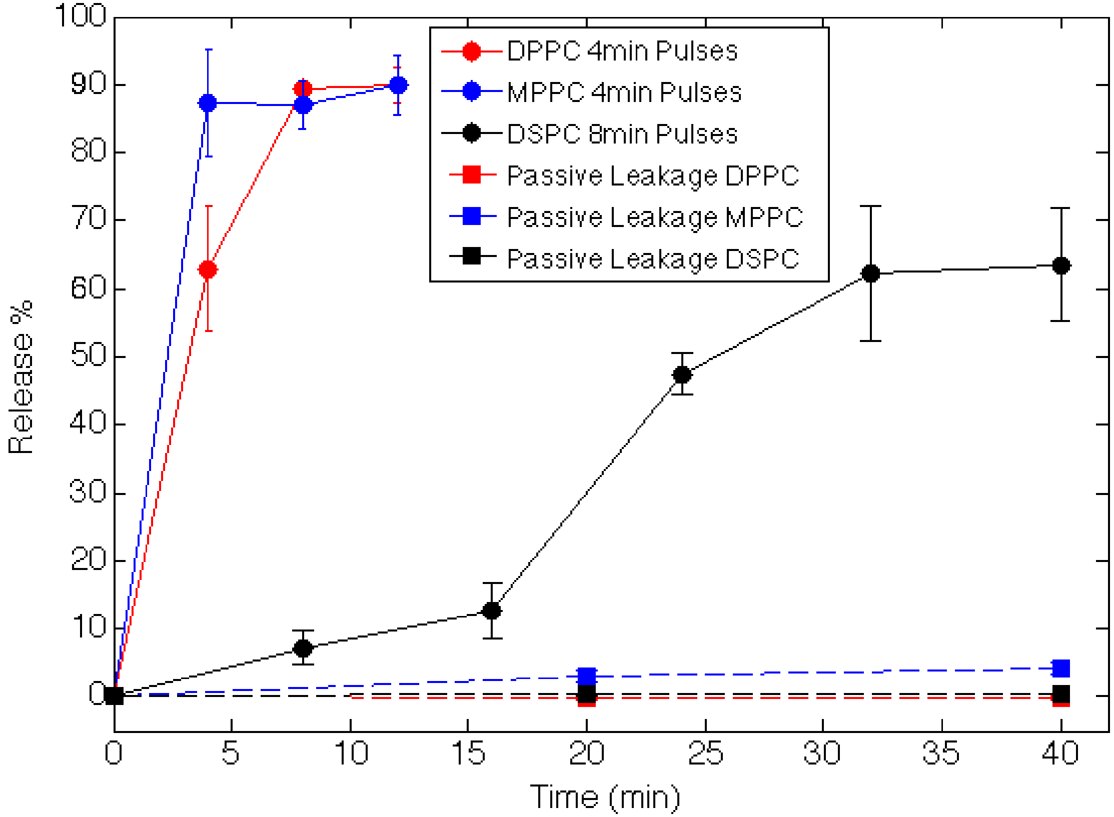


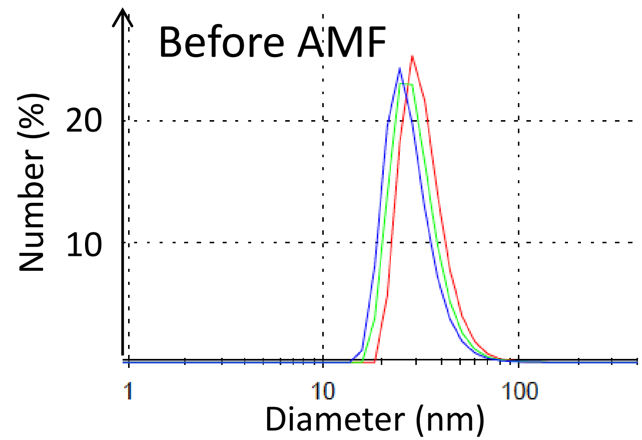
5wt% 10wt% 20wt%

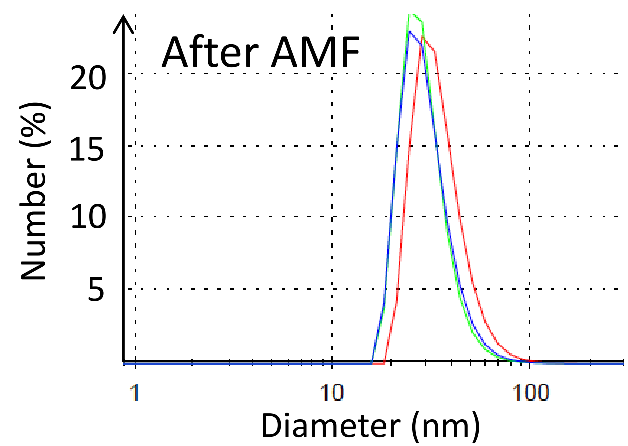
O. Bixner *et al.*, *J Coll Interf Sci* (2016)
B. Shirmardi Shaghasemi *et al.*, *Sci Rep* (2017)

Magnetically triggered release from liposomes

4wt% nanoparticle loading



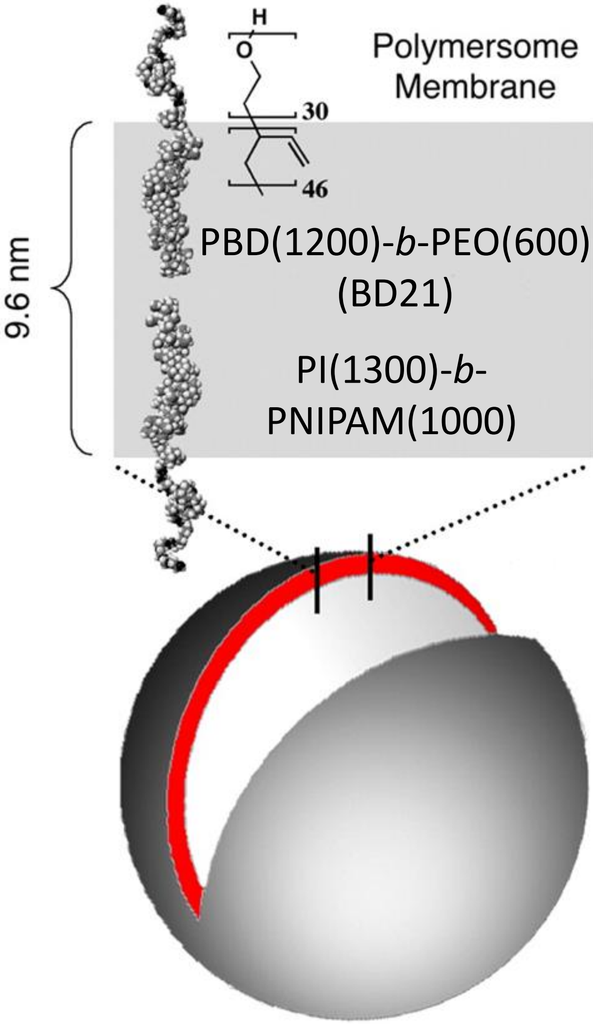




- Different lipid compositions can be used to tune the T_m
- The T_m determines the length of pulses needed to achieve the same rate of release
- Vesicle size unperturbed ⇒ **enables pulsed release**

B. Shirmardi-Shaghasemi *et al.*, *submitted*

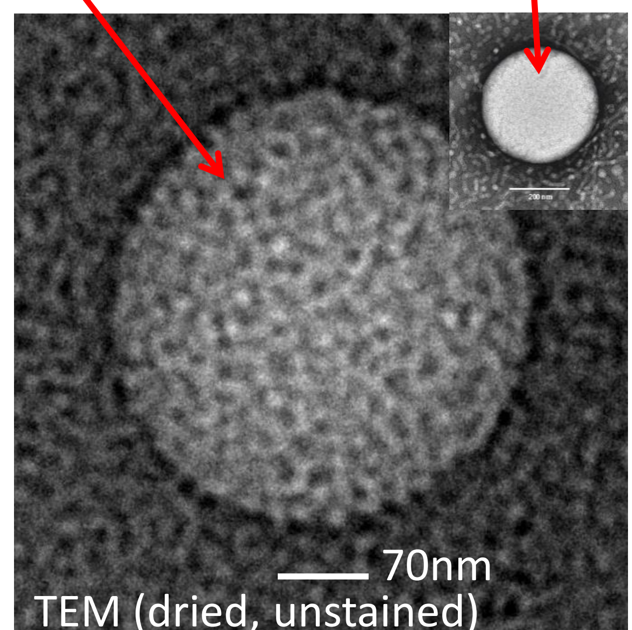
Magnetically controlled polymersomes



Easy modification of properties:

- Hydrophobic core 6-12 nm
- Fluorescence labeling
- Controlled charge and other targeting
- **Bulk quantities** of polymers

Polymersome with NP   Polymersome w/o NP

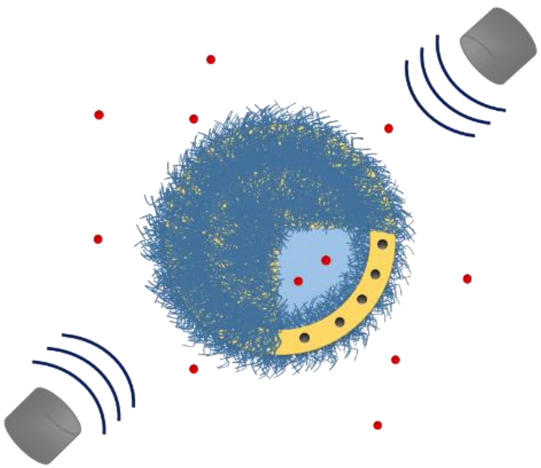


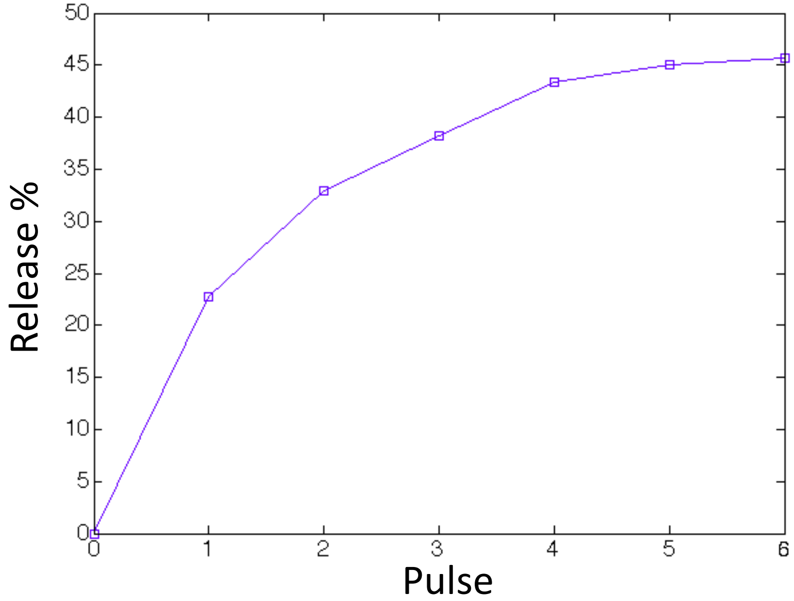
Pioneering work on mangetoliposomes by Lecommandoux and coworkers

O. Bixner *et al.*, *J Coll Interf Sci* (2016); Materials (2016)

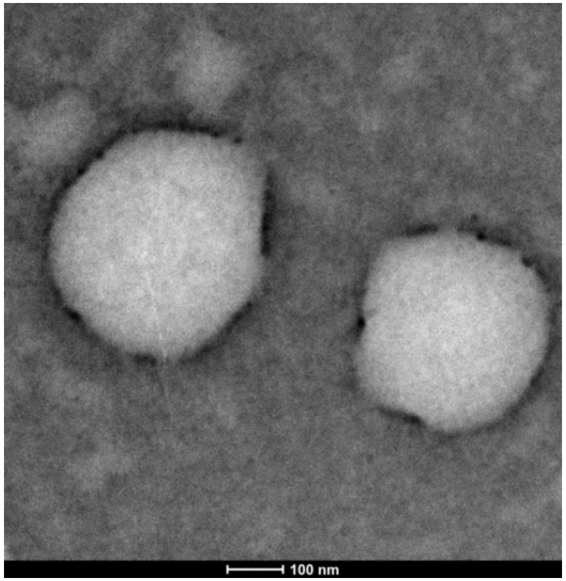
Thermoresponsive NP-polymersomes

Extruded PI(1300)-*b*-PNIPAM(1000) polymersomes





- 10 min pulses
- Passive release: 10% over 3h
- **Release due to increase in bulk temperature**
- Release mechanism not clear



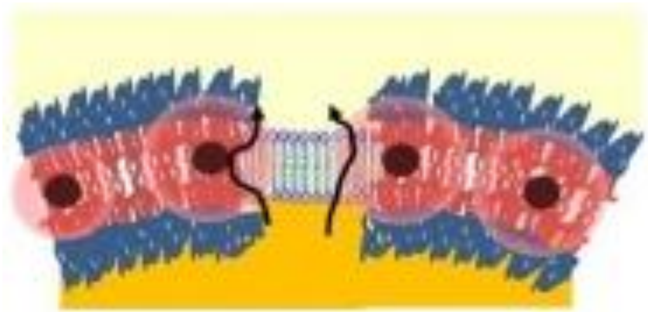
- A defined release mechanism as for lipids required
- …more work needed.

O. Bixner *et al.*, *Materials* (2016)

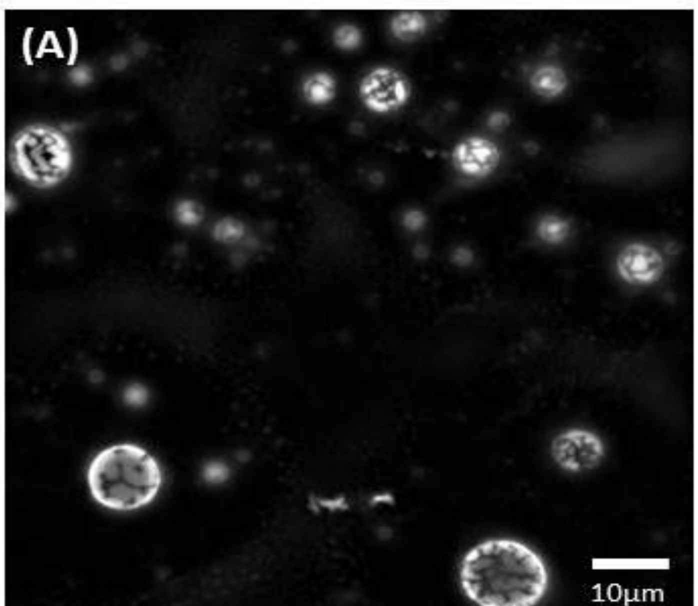
Thermoresponsive NP-lipopolymersomes

Including a minory component of saturated lipid can create phase separated lipid „windows“ for release from stable polymersomes

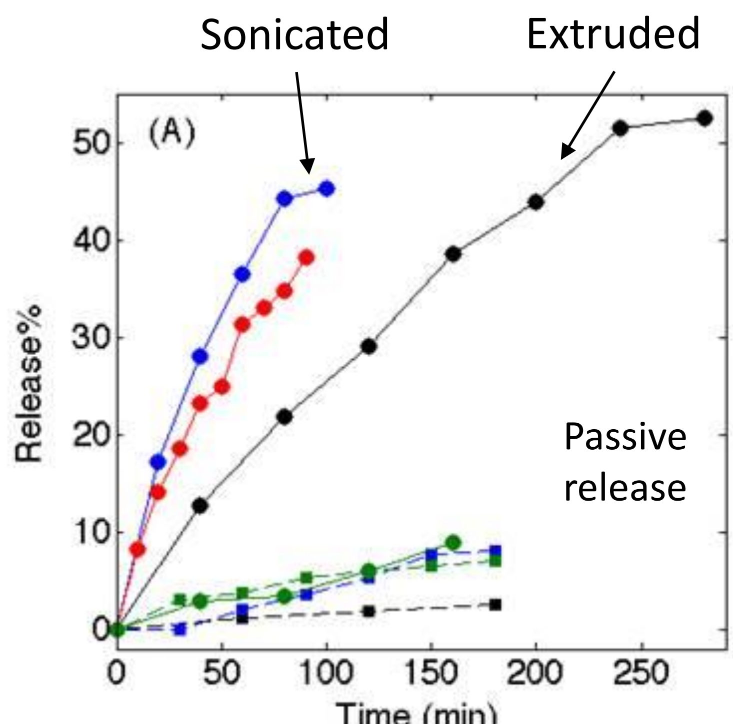
⇒ Similar release kinetics as liposomes, but mechanical stability of polymersomes



PBD(1200)-*b*-PEO(600) GUVs blended with 30% w/w DPPC



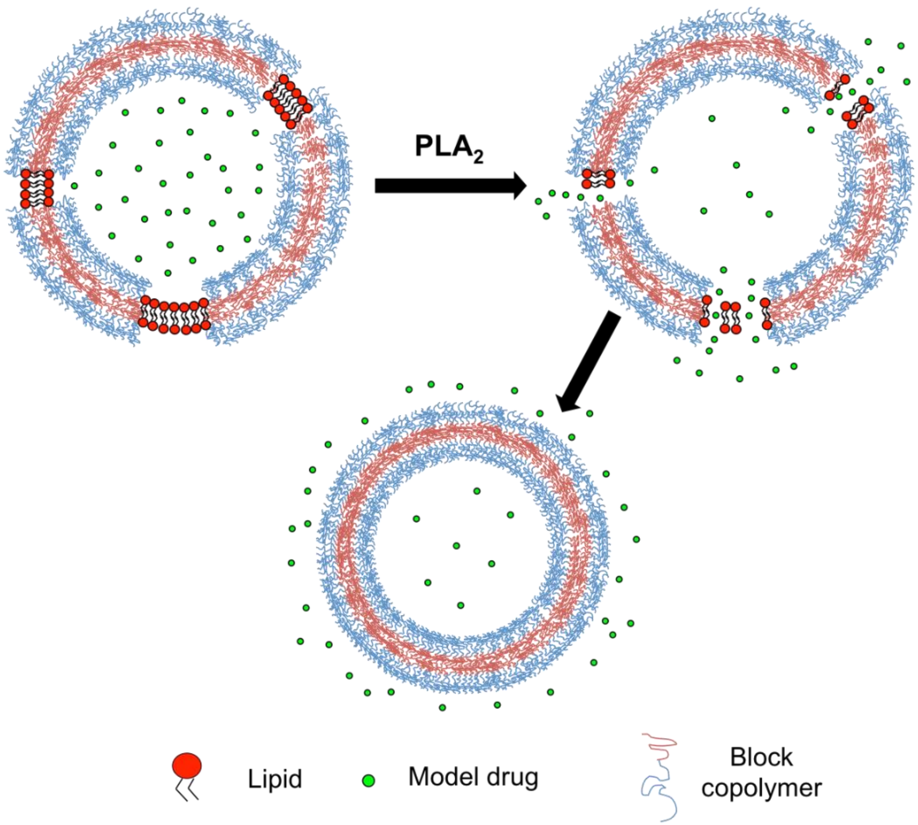
Lipopolymerosomes



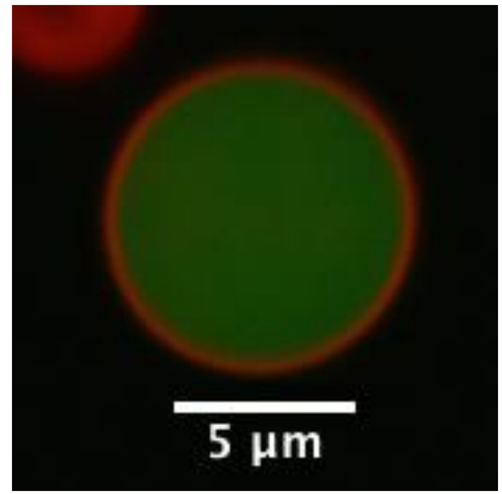
O. Bixner *et al.*, *ChemNanoMat* (2017)

Lipopolymersomes – combining block copolymers and lipids

Creating lipid „windows“ in block copolymer vesicles

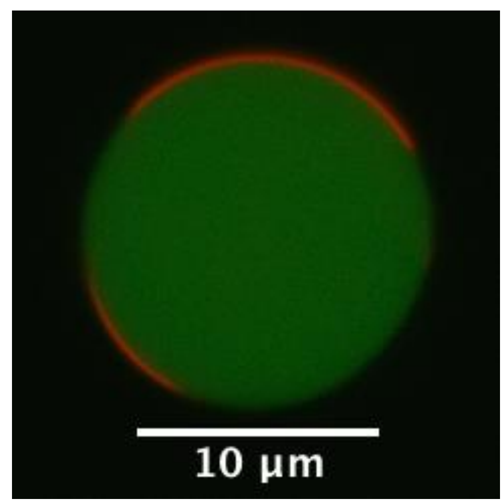


PBD(1200 Da)-*b*-PEO(1000 Da)



30% POPC (liquid phase)

Homogeneous mixing



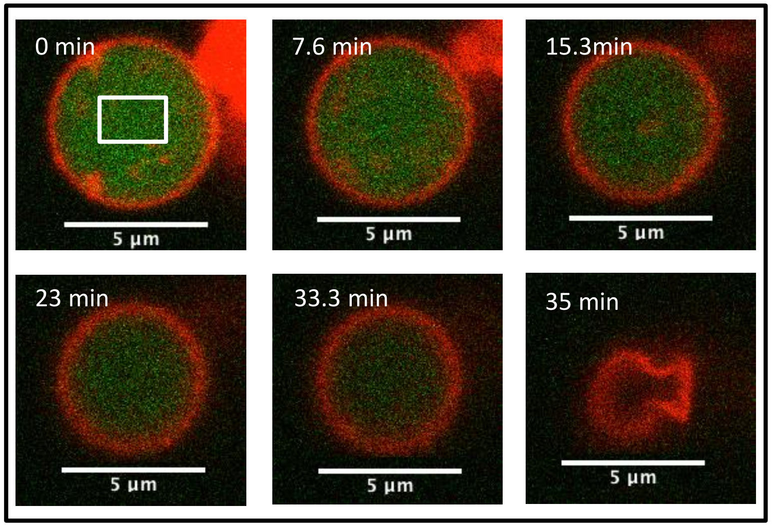
30% DPPC (gel phase)

Phase separated

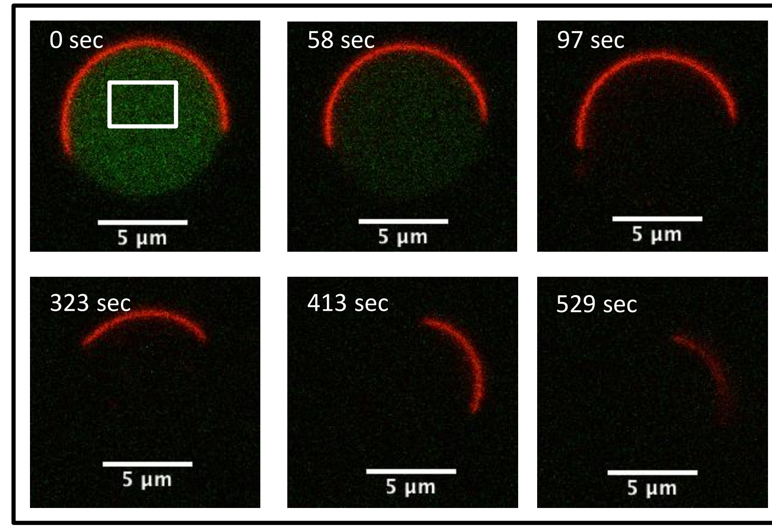
M. Virk *et al.*, *Langmuir* (2018)

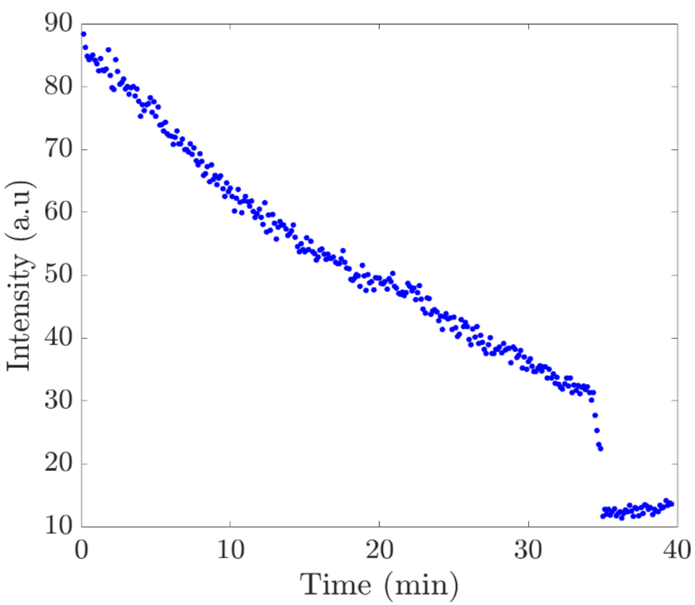
Lipopolymersomes – combining block copolymers and lipids

Liquid phase - homogeneous



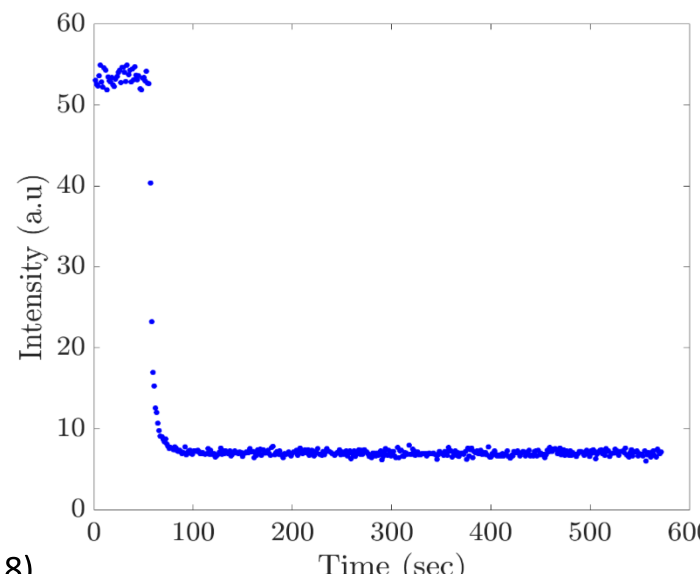
Gel phase – phase separated





- Enzymatically triggered release is slow for homogeneously dispersed lipids
- Lipid windows yield fast release

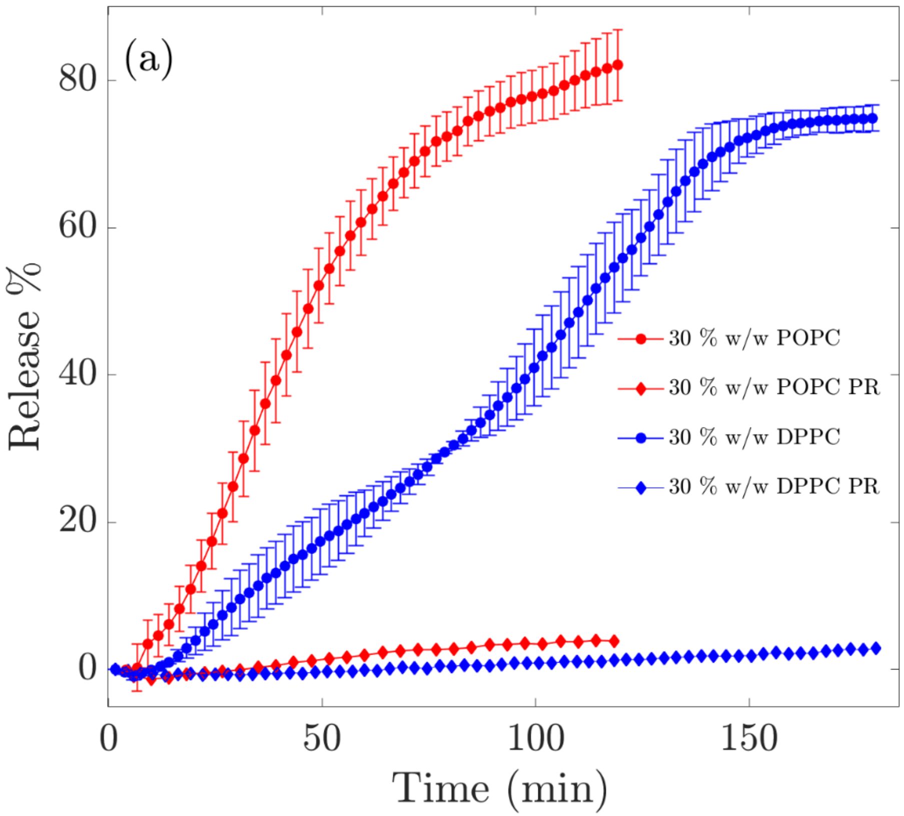
M. Virk *et al.*, *Langmuir* (2018)

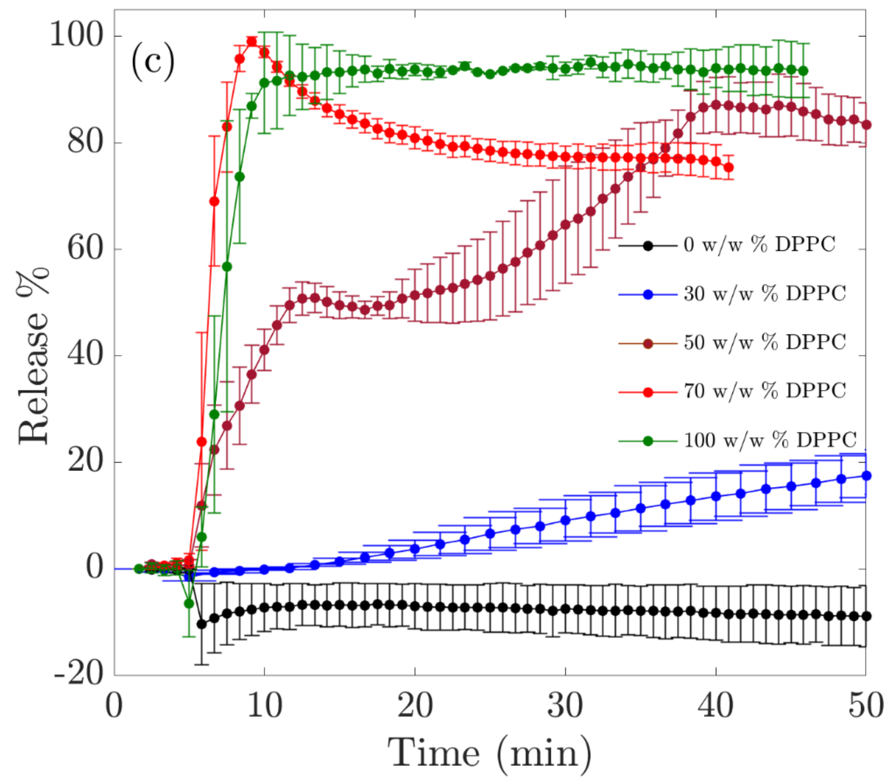


Enzymatically triggered release from nanoscale lipopolymersomes

- **Release faster for lipids above T_m**

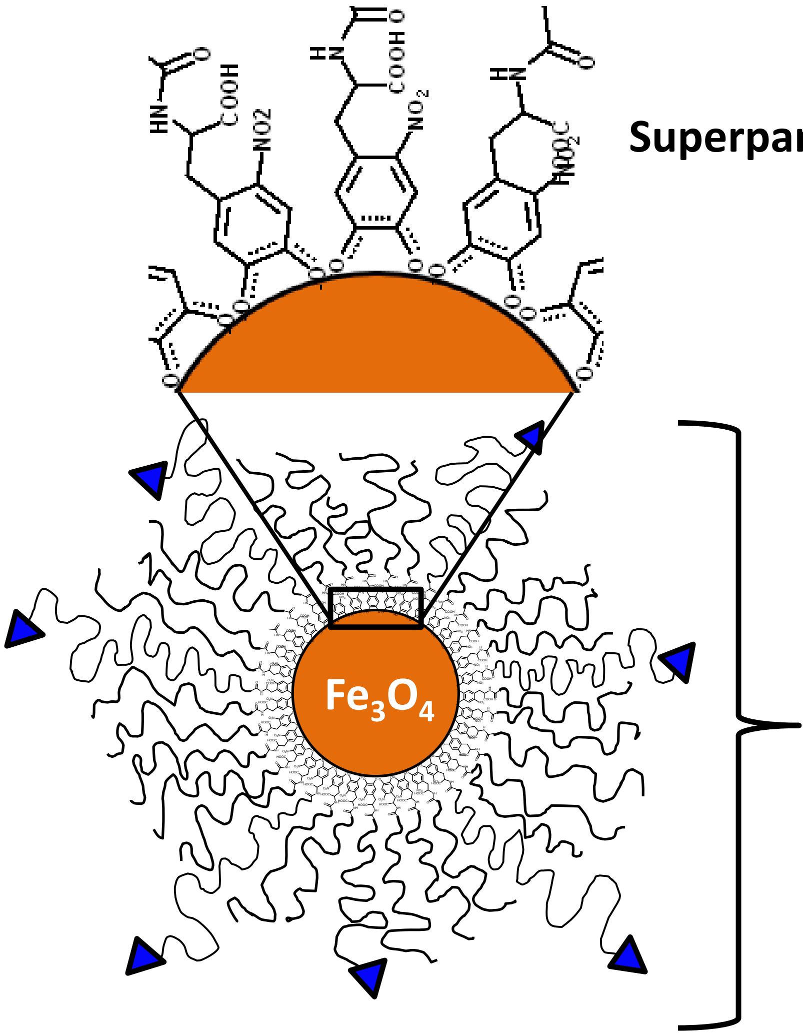
- Release rate is proportional to lipid fraction
- Potentially bimodal vesicle distribution in terms of composition



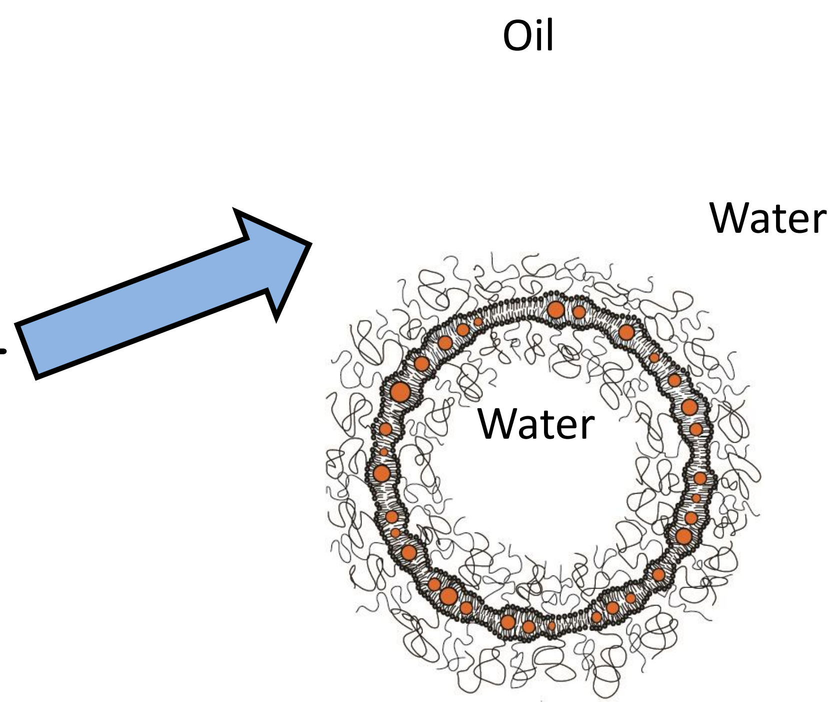


M. Virk *et al.*, *Langmuir* (2018)

Outline



Superparamagnetic iron oxide / PEG core-shell NPs



- **Monodisperse cores + homogeneous organic/polymer shell properties**
- **Self-assembly into membranous and responsive nanoscale vesicles**