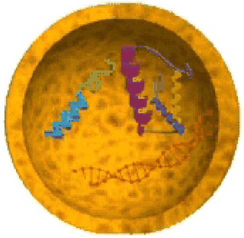


Block copolymer self-assembly: a powerful tool for the design of new smart biomimetic nano-carriers

Sébastien Lecommandoux

Laboratoire de Chimie des Polymères Organiques,
CNRS - ENSCPB – University of Bordeaux 1
Pessac, France

NanoSpain 2008, 14-18 April, Braga-Portugal

Outline

1. Block copolymers and Nanomedecine

2. Macromolecular design and synthesis

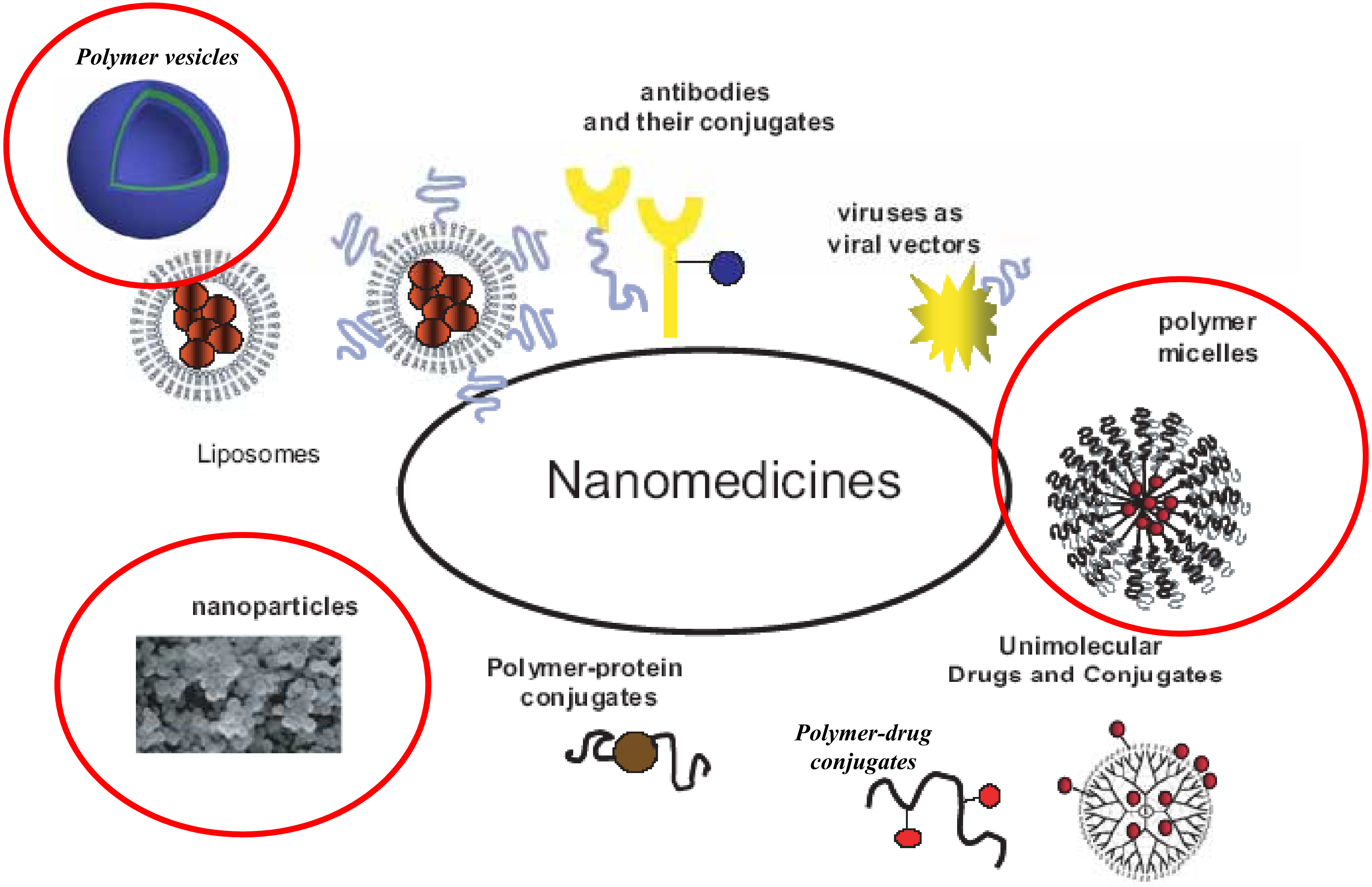
3. Micelles and vesicles

4. Stimuli-responsive self-assemblies (pH and T)

5. Hybrid nanostructures: magnetic micelles and vesicles

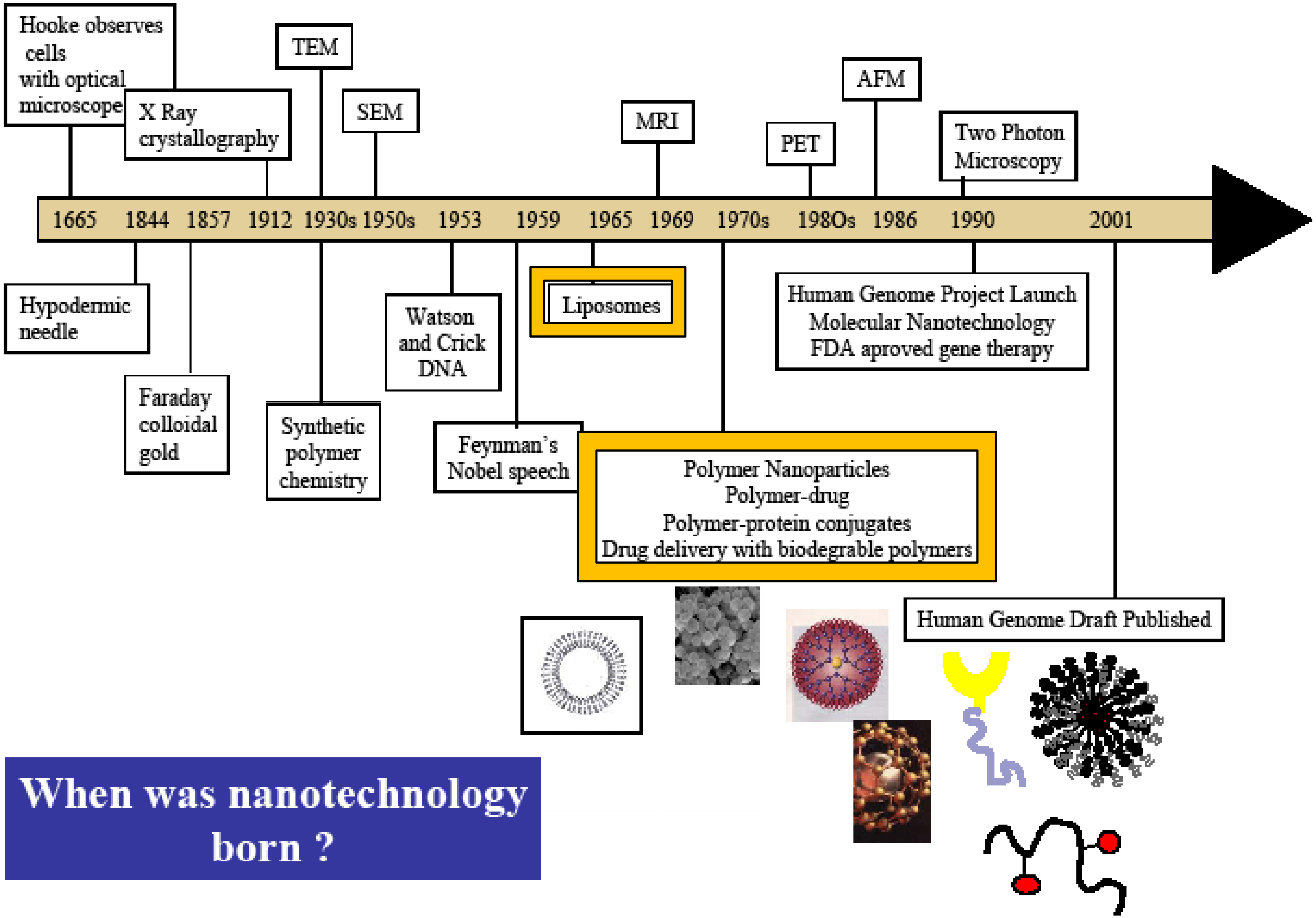
… on polypeptide-based rod-coil copolymers

Nanotechnology and medicine : Nanomedicine



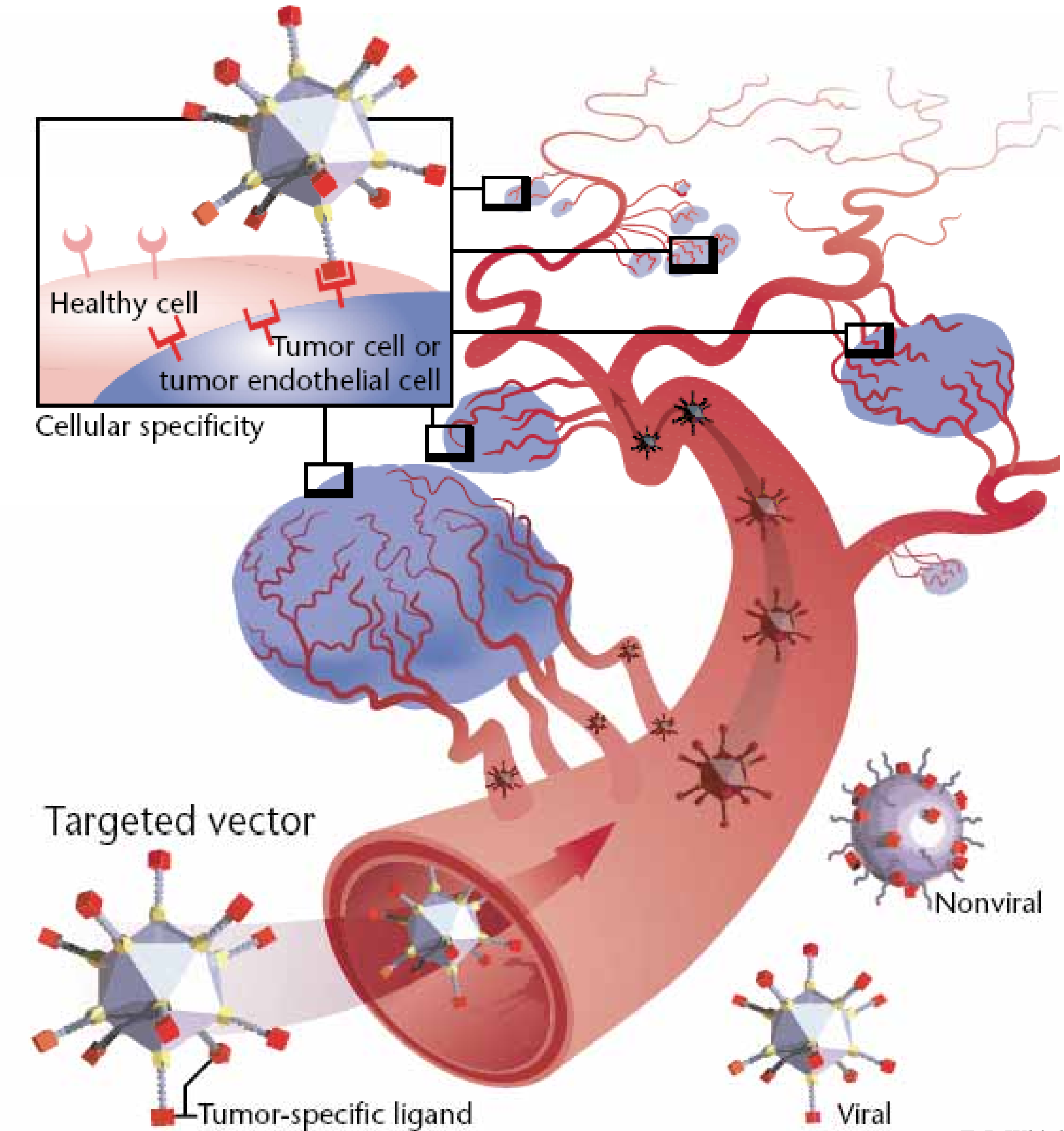
Duncan, R., Nanotoday (2005).

When was nanotechnology born ?



When was nanotechnology born ?

Nanotechnology and Drug Delivery Systems (DDS)



T.J. Whickham Nature Medicine 2003, 9, 135

Required properties of an "ideal" vector for drug and biomolecules

- ***Characteristic sizes***

  Nano-capsules or nano-objects (10-200nm)

- ***Stability***

  Blood circulation, encapsulation, functionalization…

- ***Furtivity to blood proteins (stealth)***

  Design of hydrophilic and inert surfaces (PEG,...)

- ***Targeting properties***

  Surface functionality of nanovectors

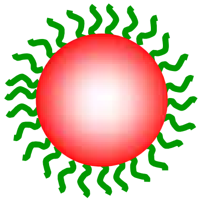
- ***Stimuli-responsive behavior***

  Development of smart systems

Block Copolymers and Surfactant Self-Assembly

$$R_B \approx a N_B^{2/3}\left(\frac{\gamma a^2}{T}\right)^{1/3}$$

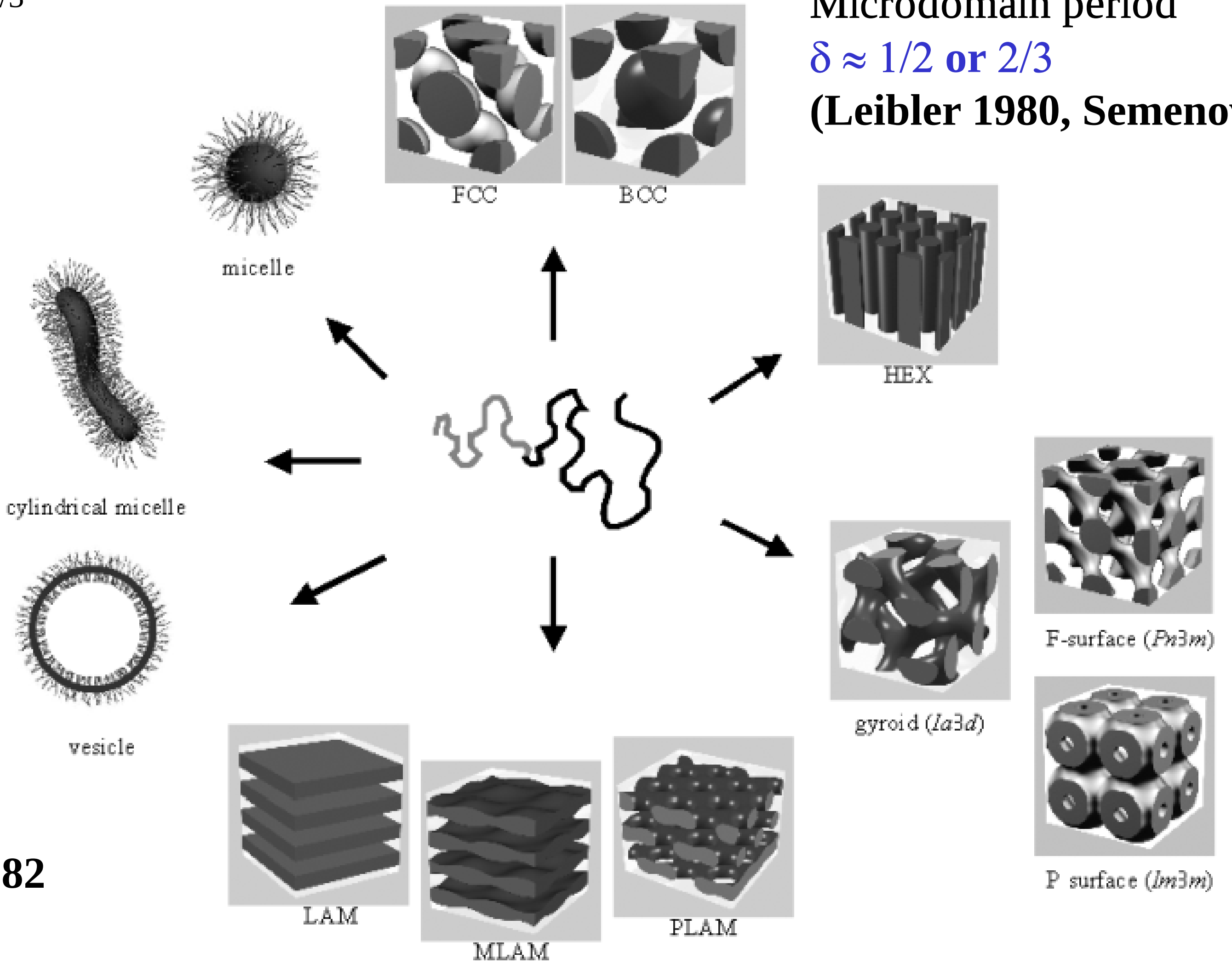
De Gennes 1978



Microdomain period $d \sim N^{\delta}$

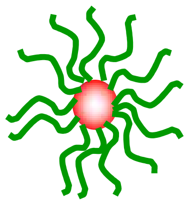
$\delta \approx 1/2$ **or** $2/3$

(Leibler 1980, Semenov 1985)

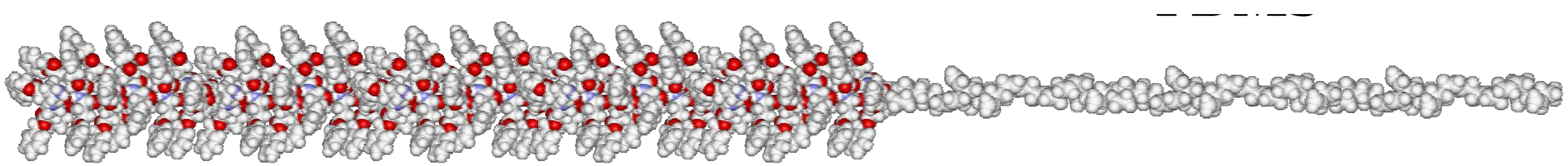


$$R \approx a N_A^{3/5} p^{1/5}$$

Daoud, Cotton 1982



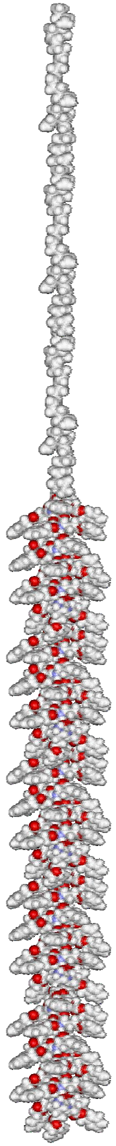
Rational design and synthesis



Design and synthesis of the targeted molecules

Polystyrene)
Poly(butadiene)
Poly(isoprene)
Poly(ε-caprolactone)
Poly(L-lactide)
PEO, PEO-PPO
PDMAEMA, PDMS
polysaccharides

Polypeptide block
Poly(L-glutamic acid)
Poly(L-lysine)
polysaccharides



Reversible secondary structure transitions induced by T, pH, ions…

Lecommandoux et col. , *Macromolecules* **2000**, *33*, 7819 / *Macromolecules* **2001**, *34*, 9100 / *Macromolecules* **2003**, *36*, 1118
Adv. Mater. **2001**, 13, 1217/ *Faraday Discussion* **2004**, *128*, 179.

Our macromolecular chemistry toolbox

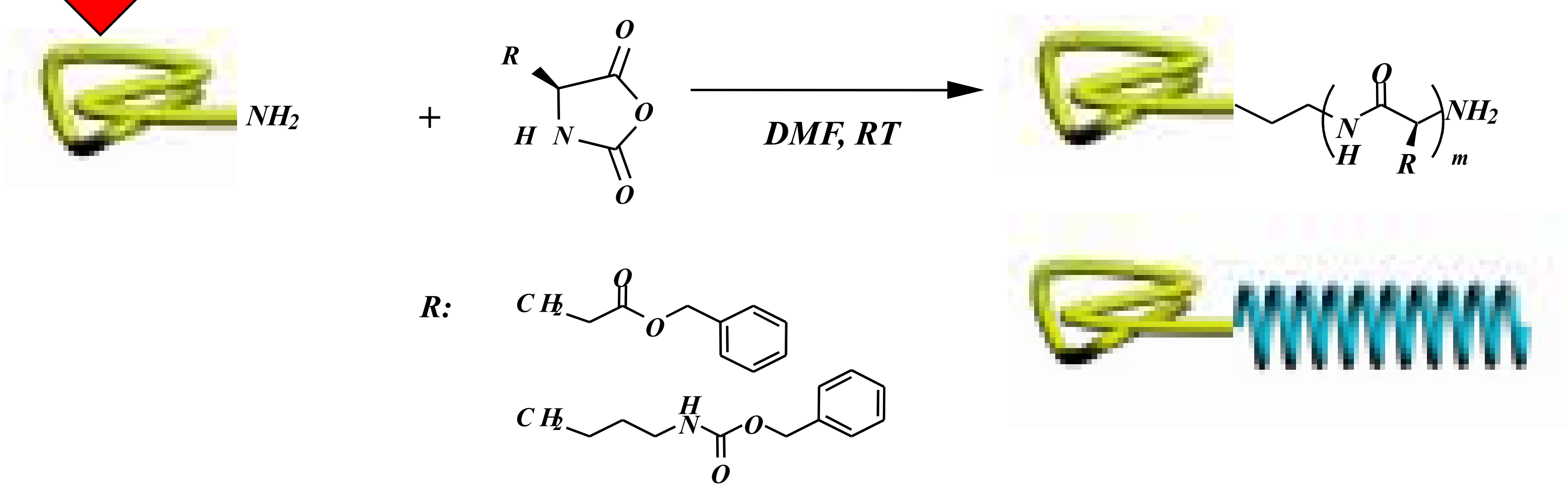
Polypeptide-based Rod-Coil : macroinitiator strategy

Anionic Polymerization (styrene, butadiene, isoprene)

Controlled Radical Polymerization (styrene)

Ring Opening Polymerization (lactide, ε-caprolactone, trimethylene carbonate peptides)

NCA- Ring Opening Polymerization

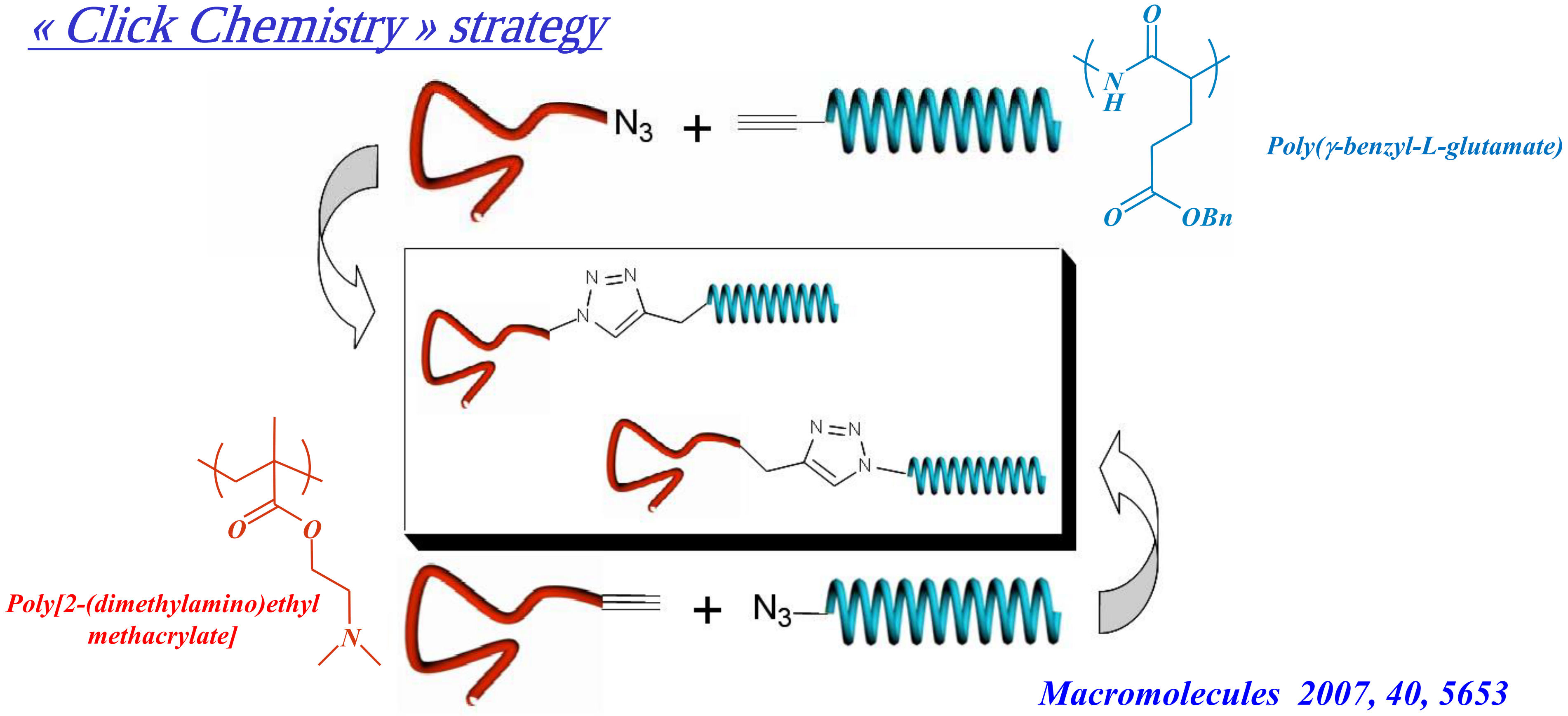


H. Leuchs, Ber. Dtsch. Chem. Ges. 1906, 39, 857

Macromolecules 2000, 33, 7819 / Macromolecules 2001, 34, 9100 / Macromolecules 2003, 36, 1118 / Adv. Mater. 2001, 13, 1217/ Faraday Discussion 2004, 128, 179.

Our macromolecular chemistry toolbox

« Click Chemistry » strategy



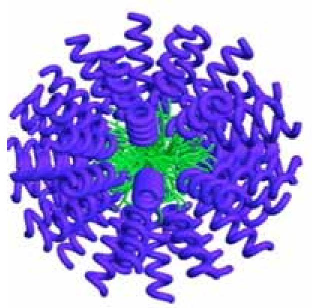
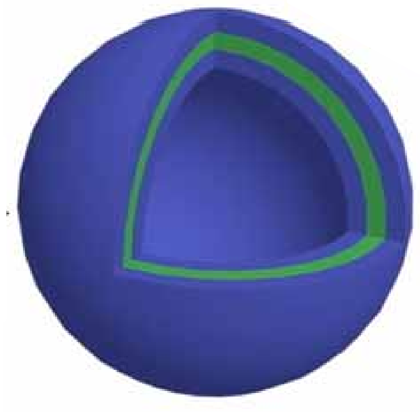
Macromolecules 2007, 40, 5653
Macromol. Rapid Comm. 2008

Polysaccharide-based copolymers

Chemical modification of common polysaccharides : chitosan, dextran, hyaluronan, alginate …

Patent in progress

Solution self-assembly of polypeptide-based block copolymers

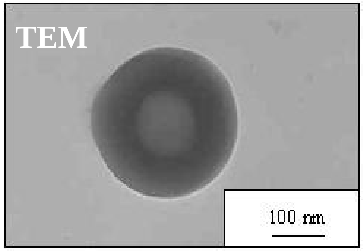
 

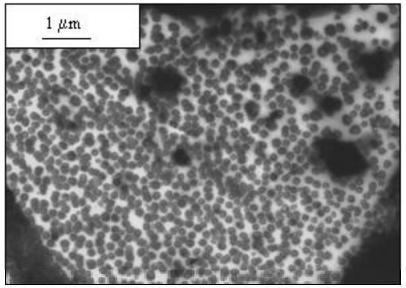
Solution Self-Assembly of amphiphilic block copolymers

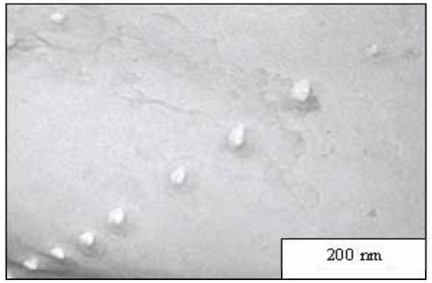
Example: PB_{48}-b-PGA_X series

Organic solvent (THF, CH_2Cl_2)

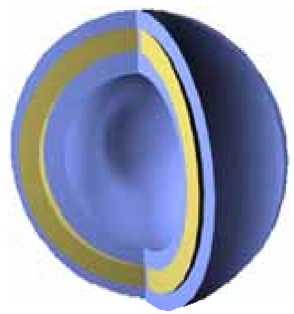
Water

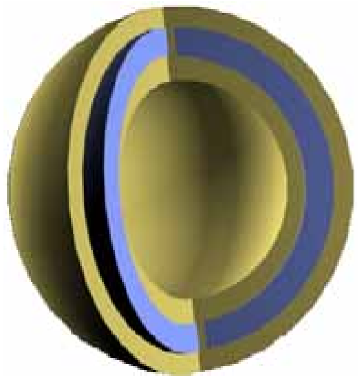


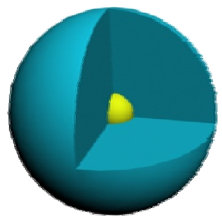


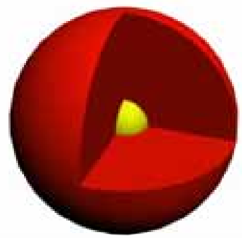


reverse vesicle









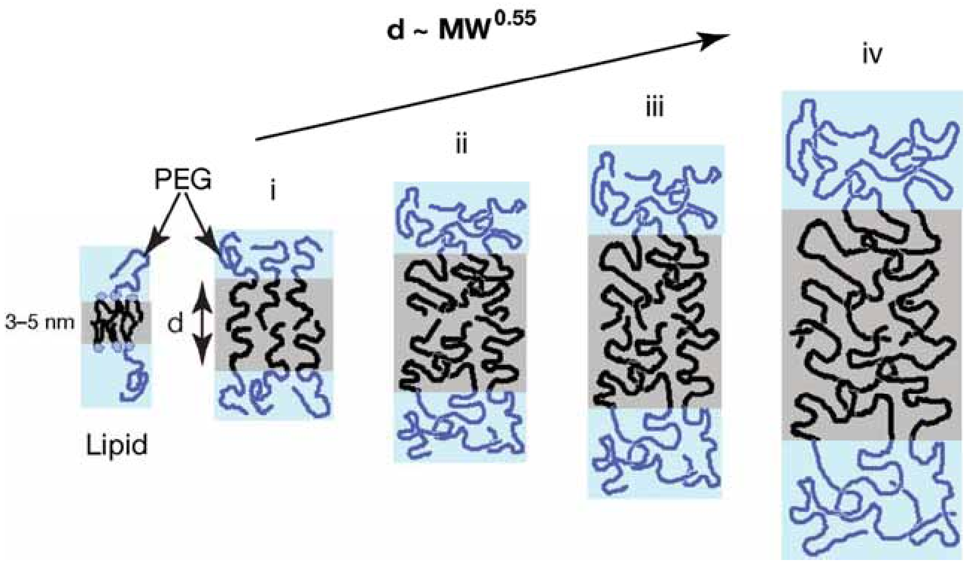
Spherical micelles 20-80 nm

Vesicle 100-400 nm

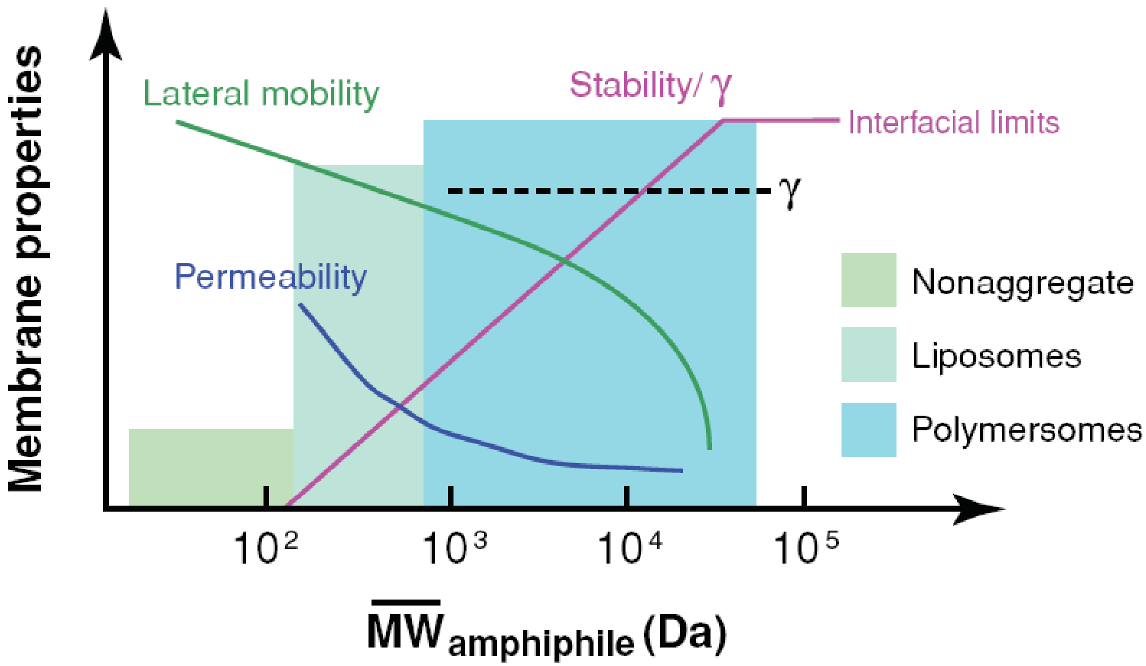
20 | 56 | 114 | 145 | X

Angewandte 2002, Eur. Phys. J. 2003, Langmuir 2005

Block copolymer vesicles or polymersomes



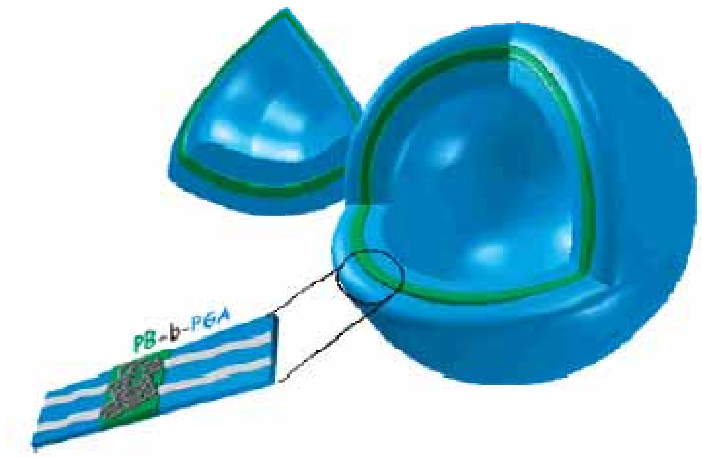
Schematic scaling of polymersome membrane thickness with copolymer molecular weight (MW).

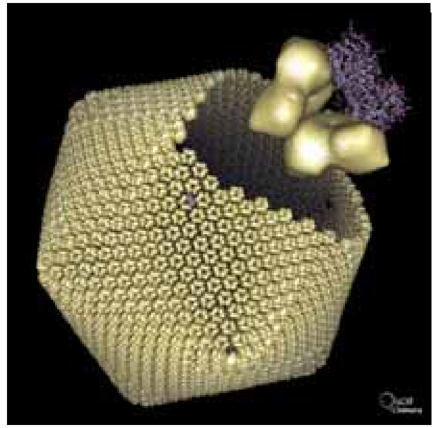


Schematic plot of typical physical properties of vesicles versus molecular weight of amphiphilic constituents (amphiphilic constituents consist of a series of amphiphiles with various molecular weights)

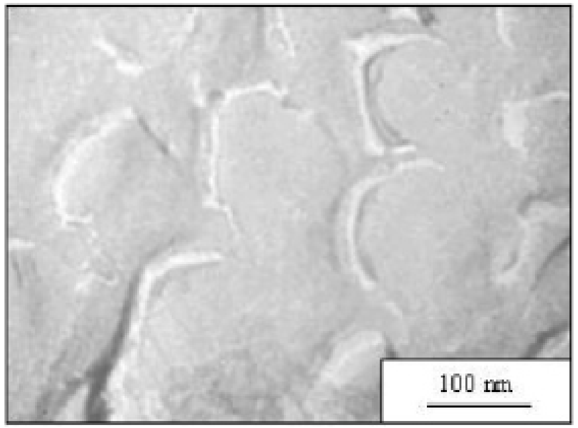
Discher and col. Macromolecules 2002

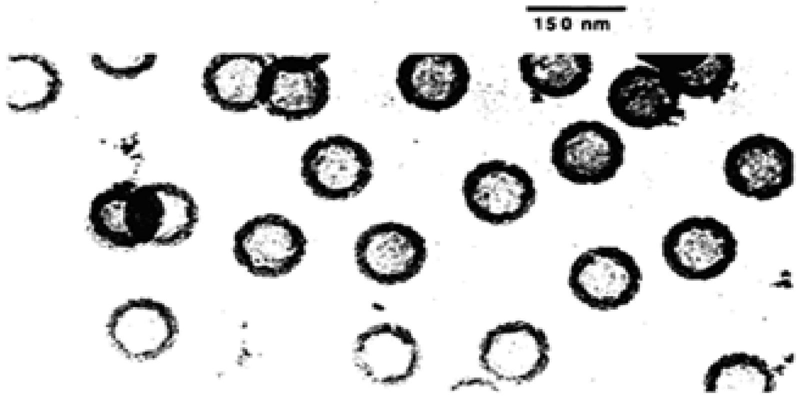
BC Vesicle, a synthetic model of a viral capsid





Paramecium bursaria chlorella virus





Herpes Simplex Virus Capsid

- Self-assembly of block copolymers with same range of molecular weight as proteins used in virus
- Size range (100-200nm) comparable to viral capsids
- Stability, membrane thickness and permeability very similar

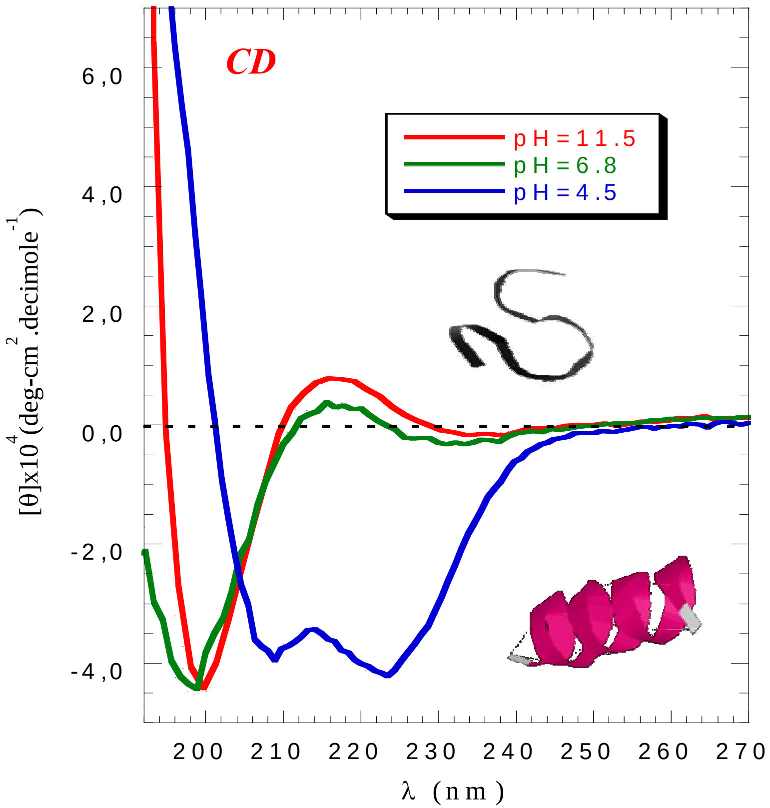
Stimuli-responsive BC MicellesVesicles

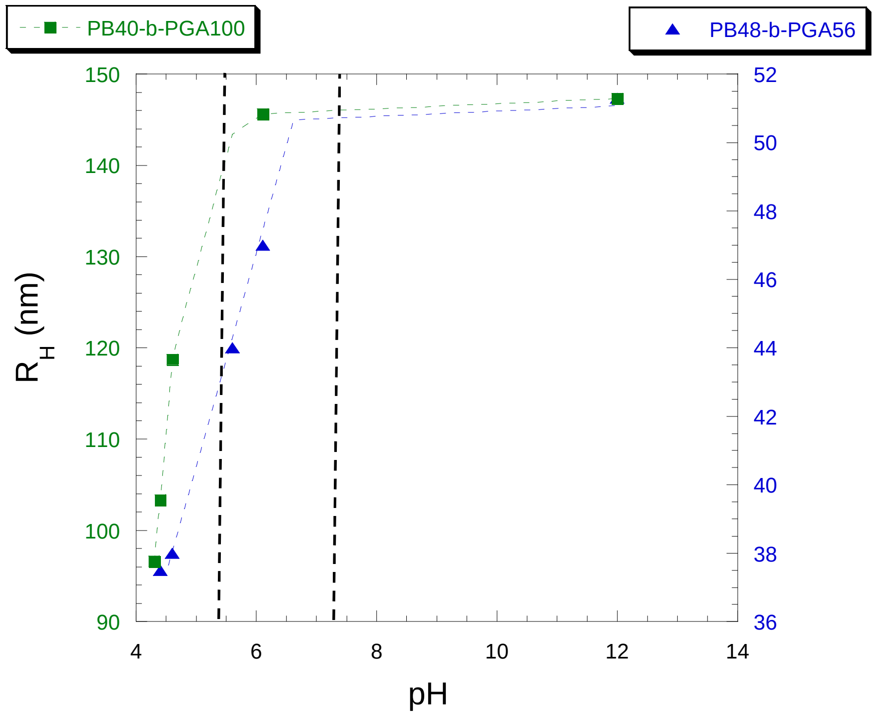
- *pH*
- *T*
- *Magnetic field*

pH-responsive nanoparticles

Polypeptide-based Rod-Coil : pH Responsive Vesicles

PB_{48}-b-PGA_{56}



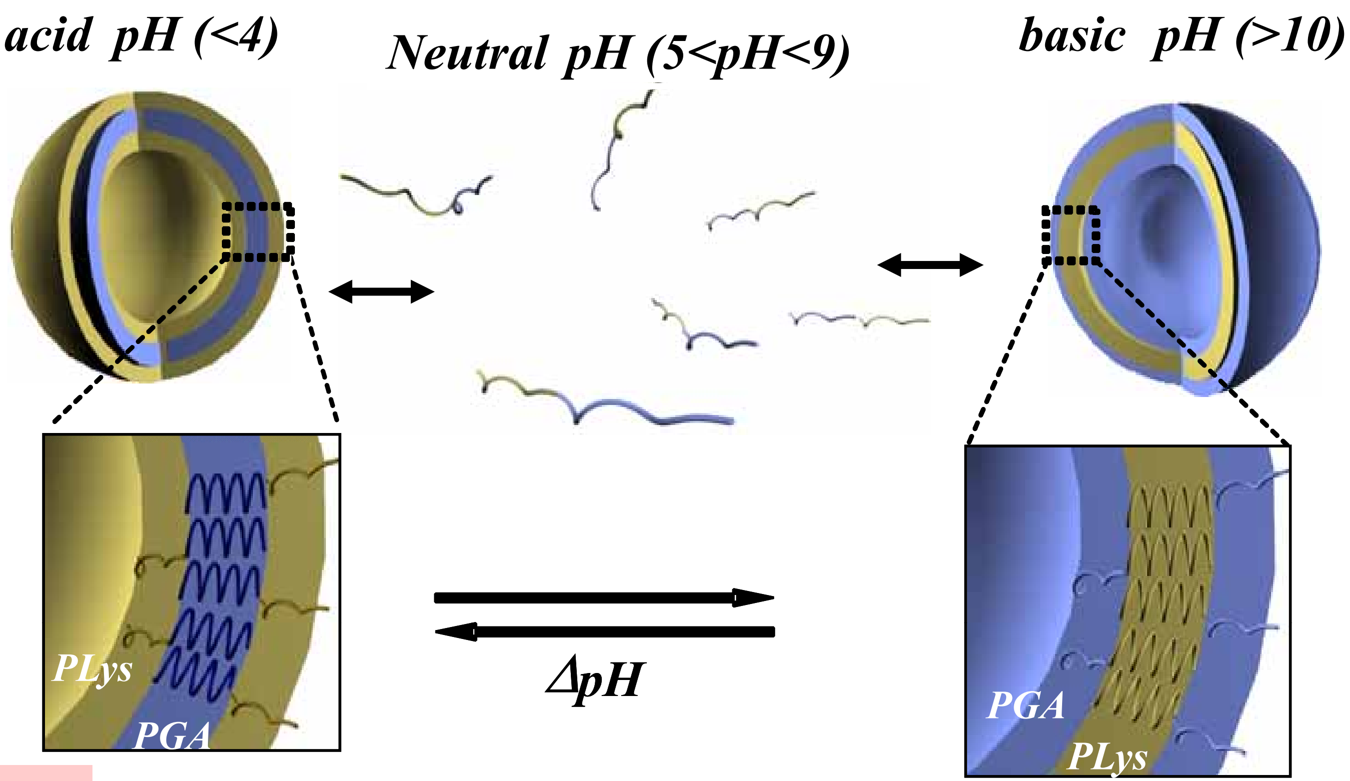


- ***Stimuli-responsive effect as a function of pH***
- ***Change in internal volume up to 300%***

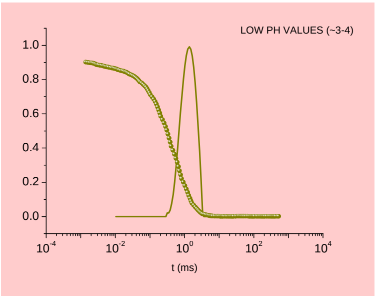
F. Chécot et al. Angewandte Chemie Int. Ed. 2002, 41, 1339
F. Chécot et al. Langmuir 2005, 21, 4308.
J. Babin et al. Faraday Discussion 2005, 128, 179

Diblock copolypeptides PGA-b-Plys : reversible pH assembly

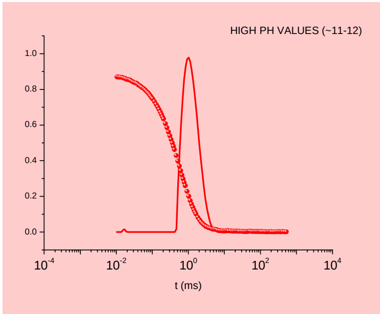
PGA_{15}-b-$PLys_{15}$



R_H=175nm



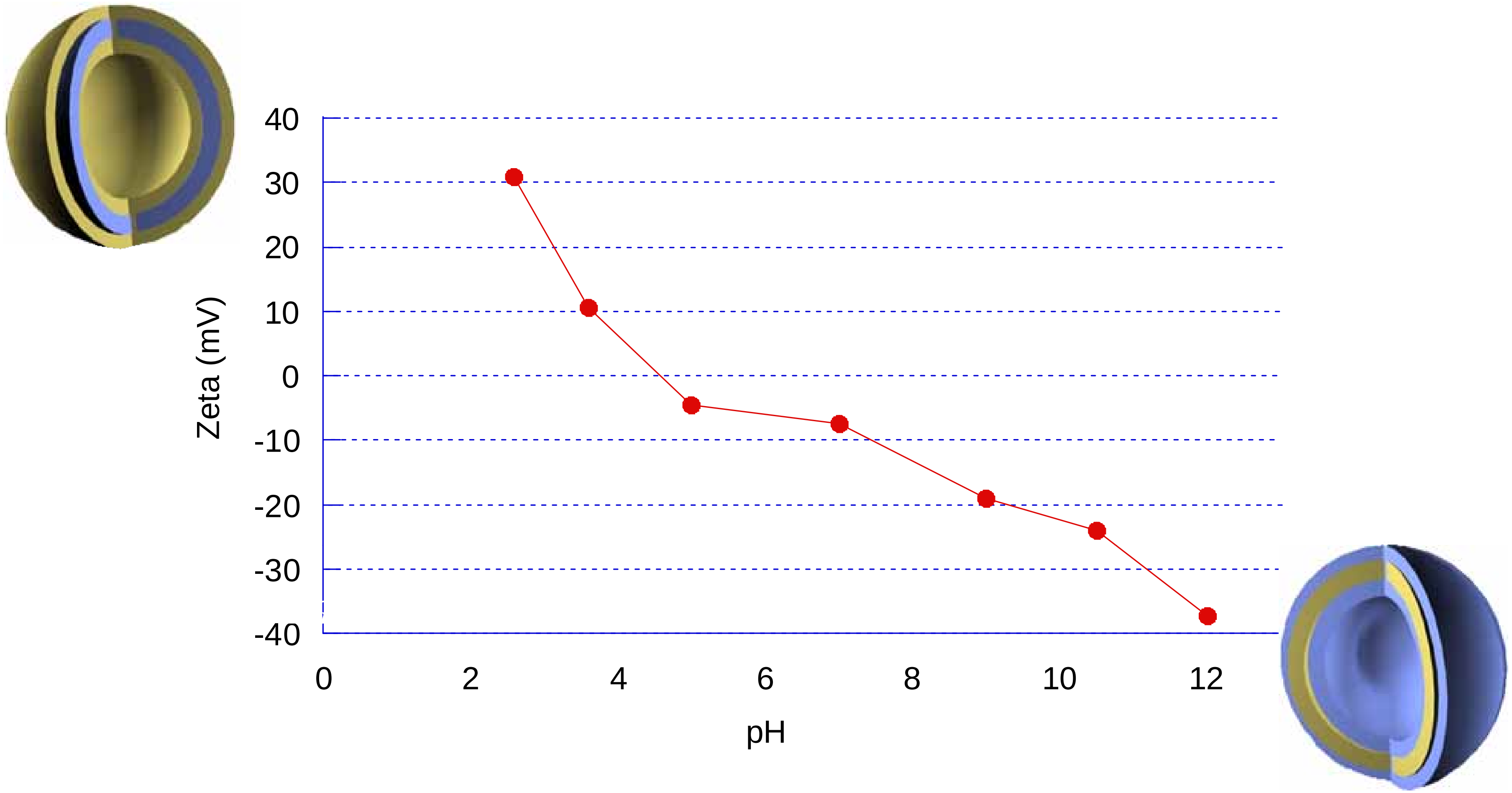
R_H=110nm



Schizophrenic vesicles!

JACS 2005, 127, 2026.

Diblock copolypeptides PGA-b-PLys

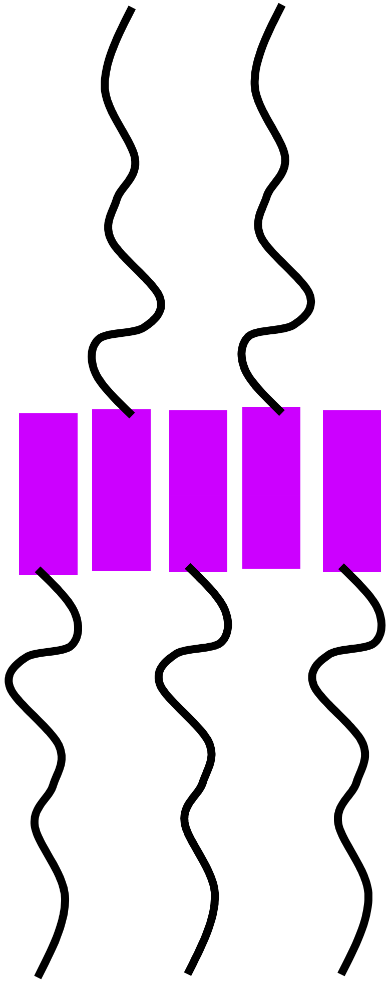


Schizophrenic vesicles!

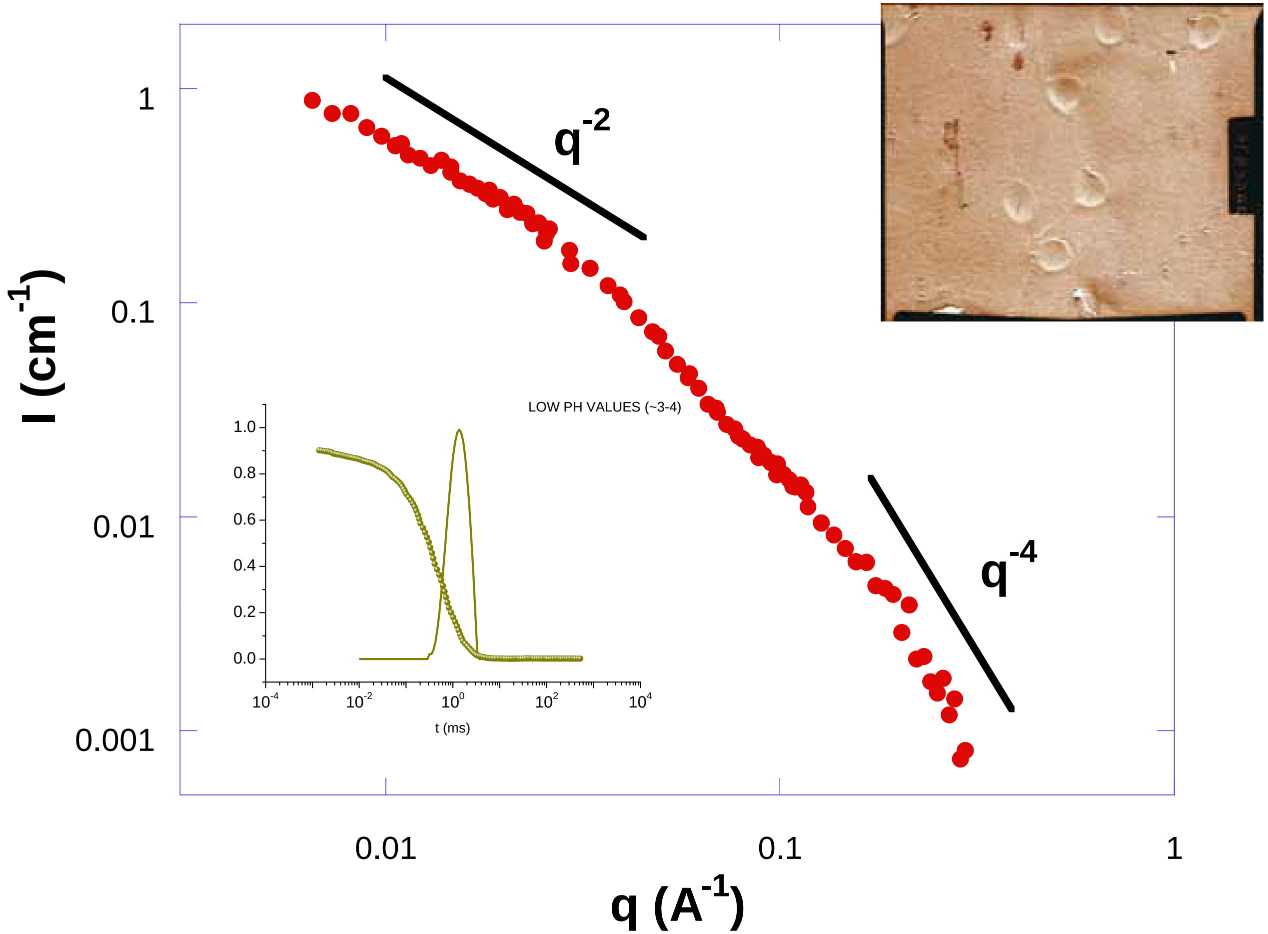
JACS 2005, 127, 2026.

Diblock copolypeptides PGA-b-PLys

Asymmetric** PGA_{62}-b-$PLys_{15}$ **, pH12



SANS, pH=12

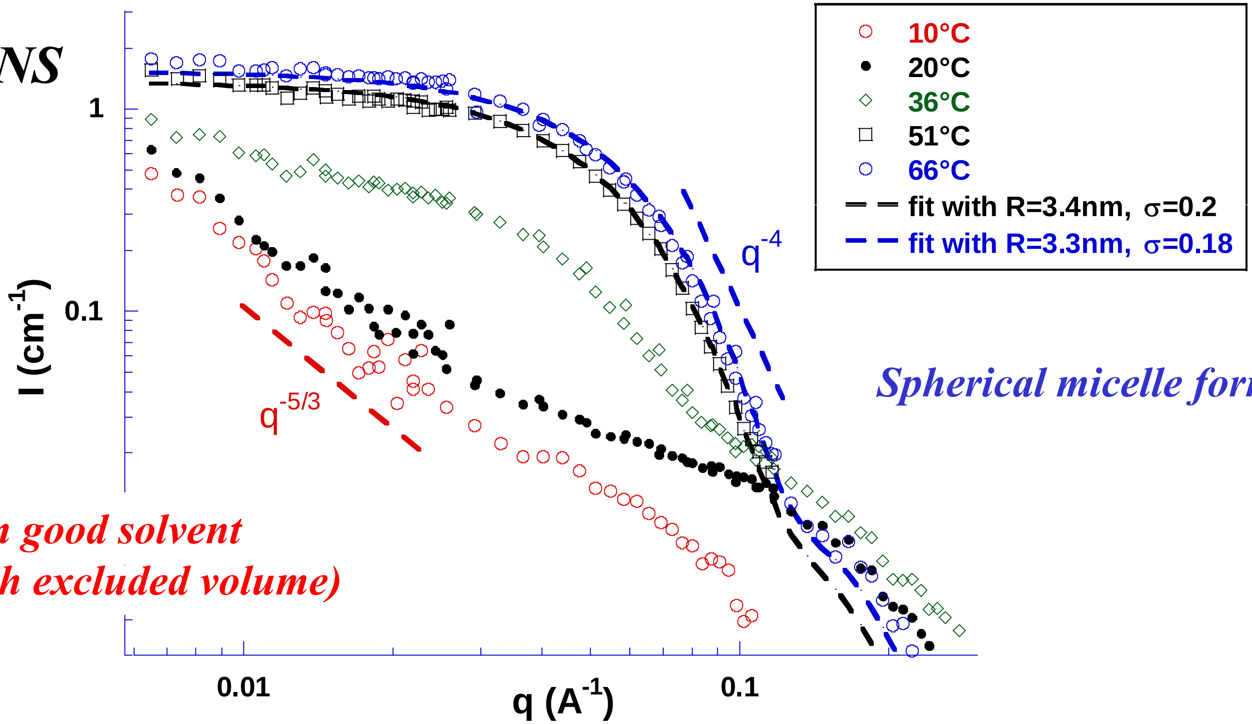


- rod-rod interaction → flat interface → vesicles !!!

Temperature-responsive nanoparticles

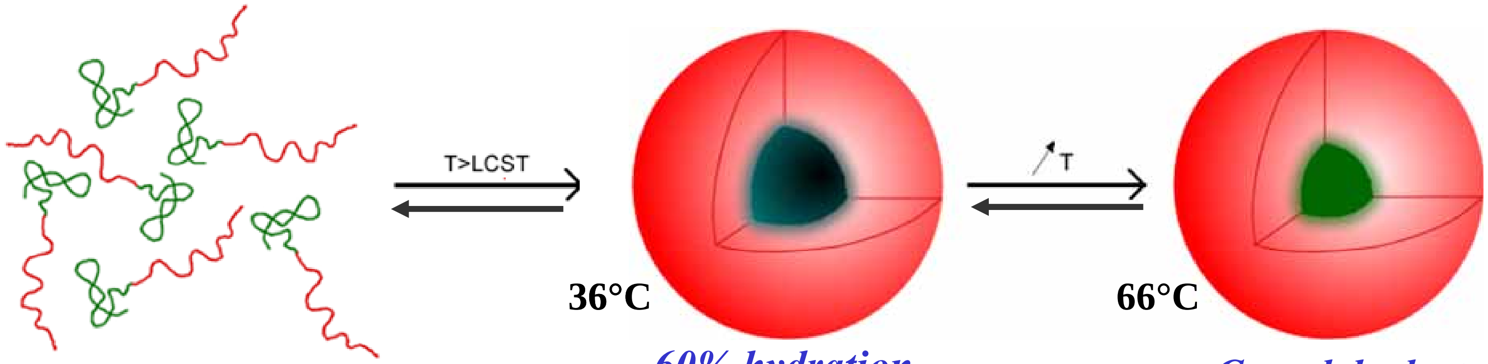
T-responsive mesoglobular micelles $(POE\text{-}r\text{-}PPO)_{40}\text{-}b\text{-}PGA_{30}$

SANS



Spherical micelle form factor

free chains in good solvent
(polymer chain with excluded volume)



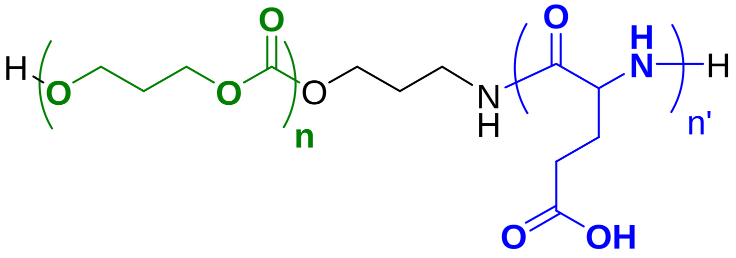
60% hydration

Core dehydrated

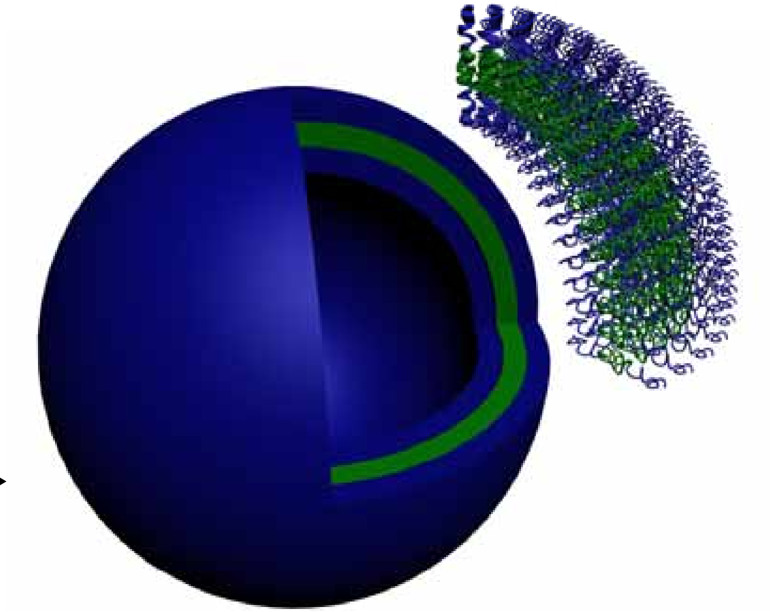
Core hydration controlled with temperature

Langmuir 2007,23,11526

Temperature Responsive PTMC-b-PGA BC Vesicles

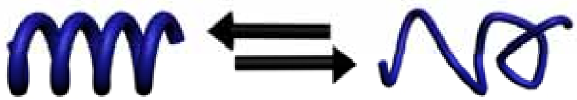


f_{philic} ~ 40%

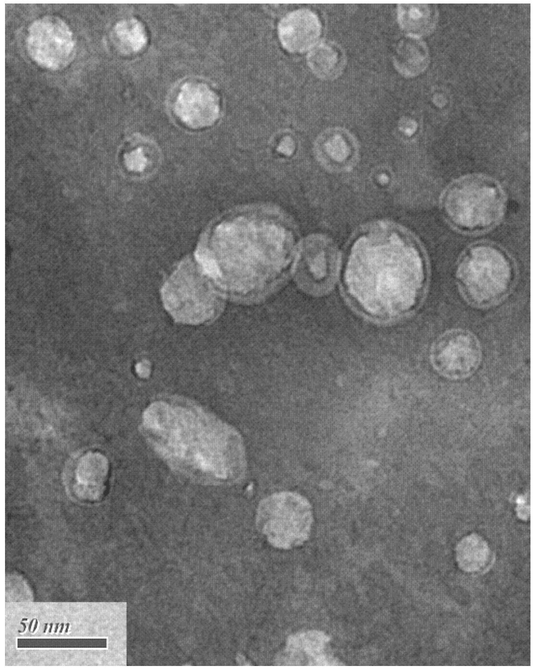


Biocompatible
Biodegradable
Bioresorbable

Biocompatible
pH responsive
Secondary structure

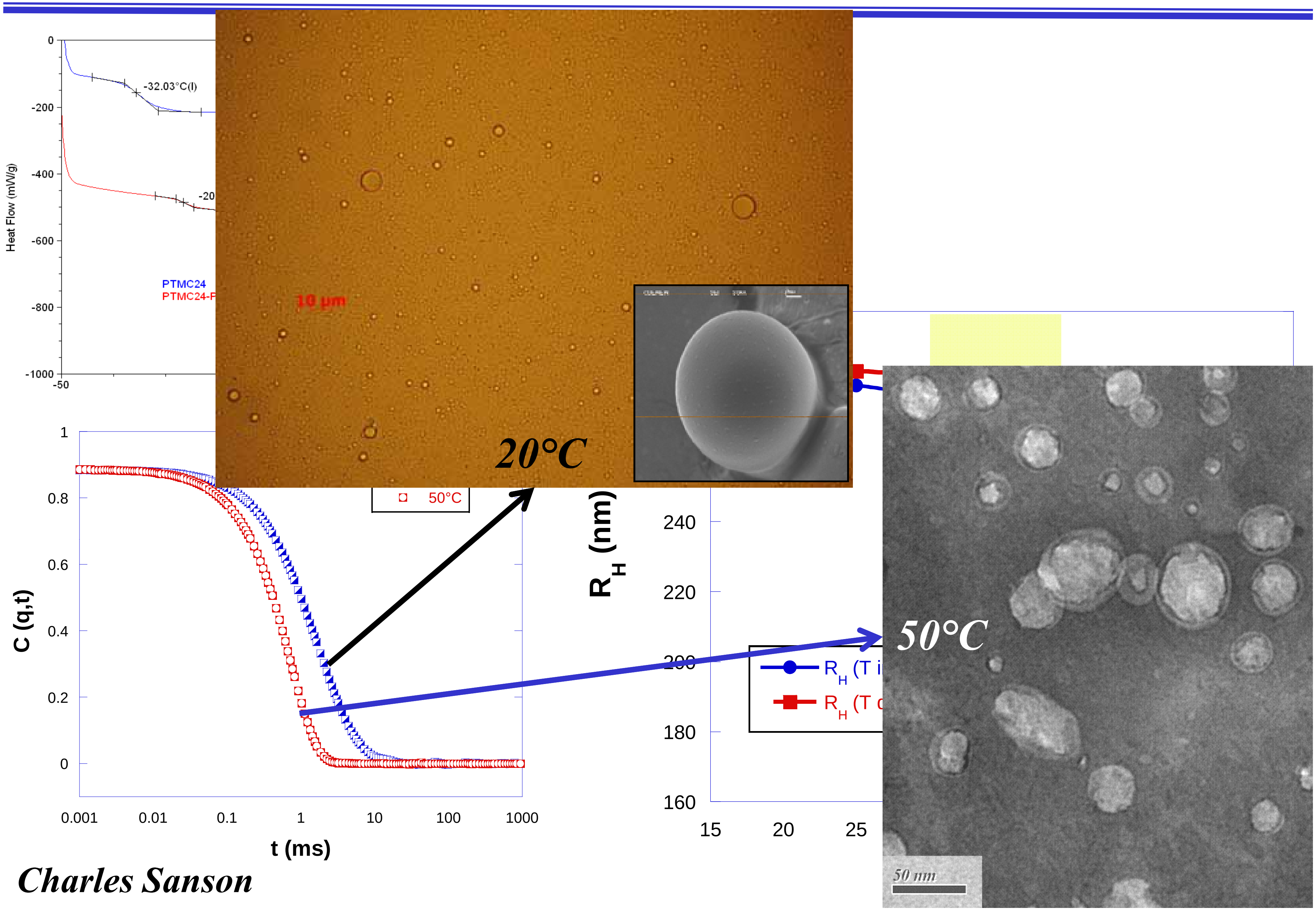


pH↑



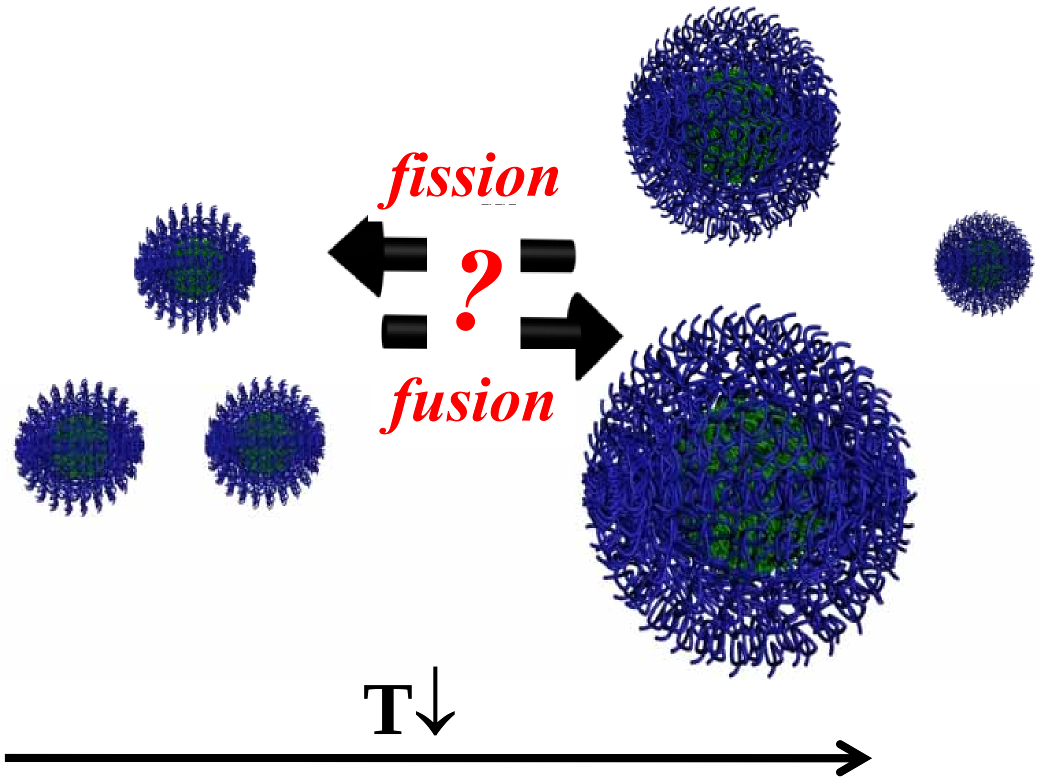
Charles Sanson

T-Responsive PTMC-b-PGA BC Vesicles : WHY???



Charles Sanson

T-Responsive PTMC-b-PGA BC Vesicles : Mechanism?



PTMC starts to « cristallize »

↑Interfacial tension

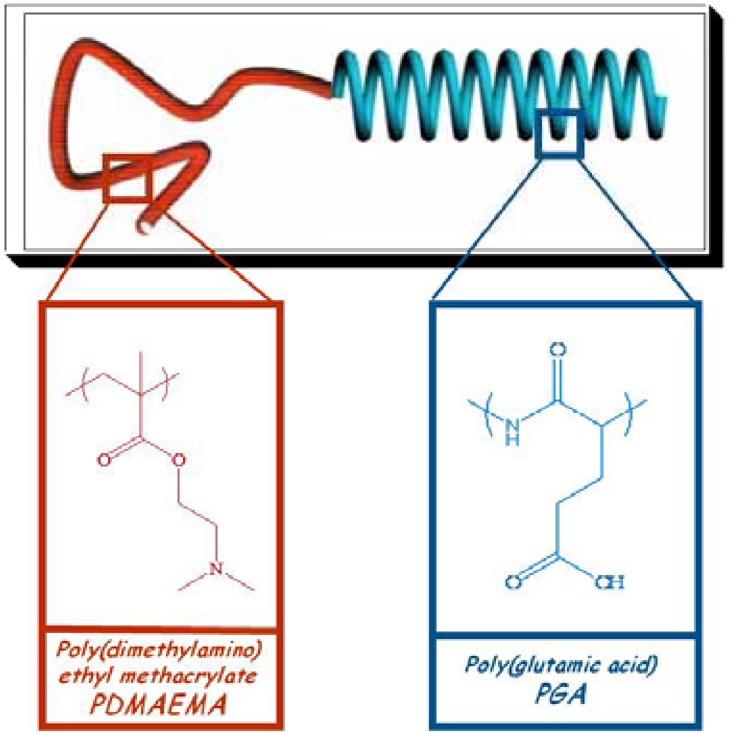
↑size

Free energy minimization

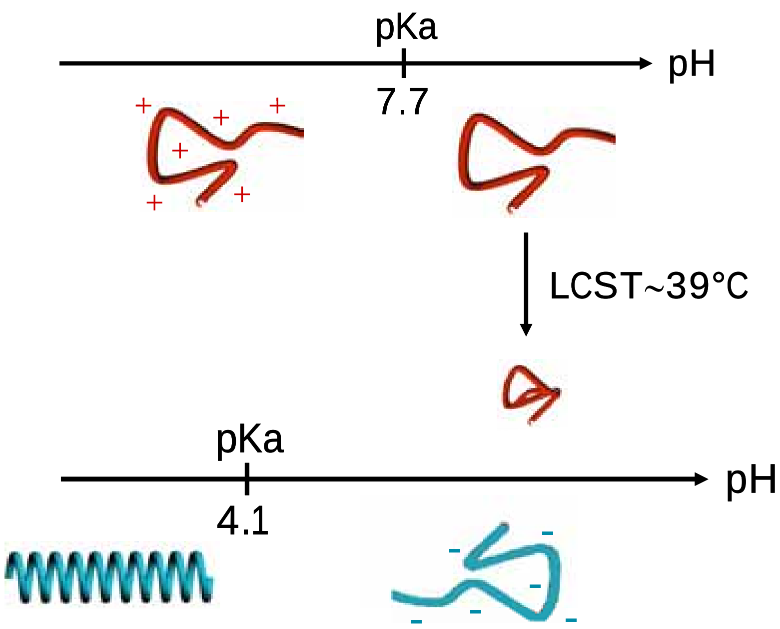
Charles Sanson

Multi-responsive nanoparticles

Multi-responsive block copolymer nanoparticles (T , pH, ions)

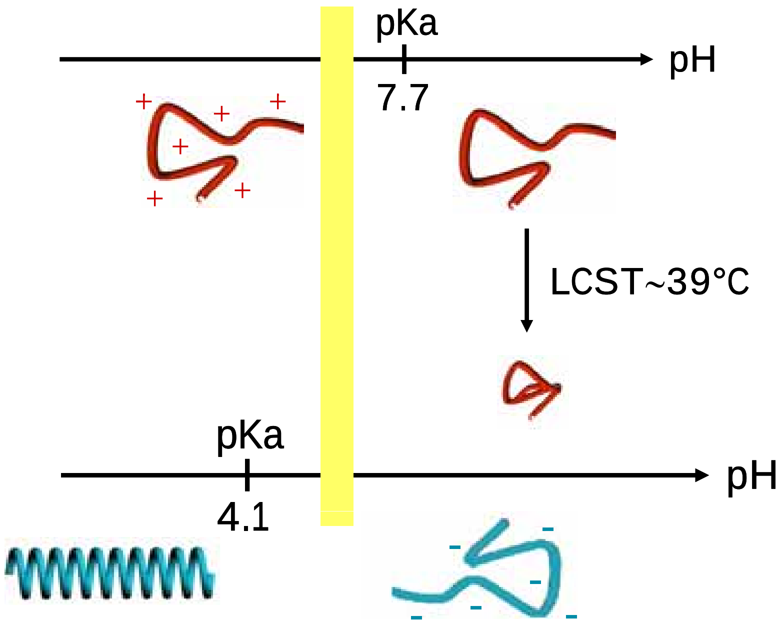


- ✓ ***Thermoresponsive LCST~39°C***
- ✓ ***pH-responsive pKa~7.7***
- ✓ ***DNA complexant***



- ✓ ***pH-responsive pKa~4.1***
- ✓ ***Change of secondary structure (α-helix to coil)***
- ✓ ***Biocompatible***

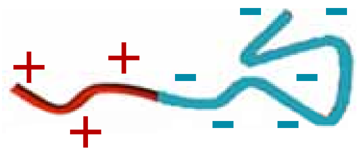
Willy Agut

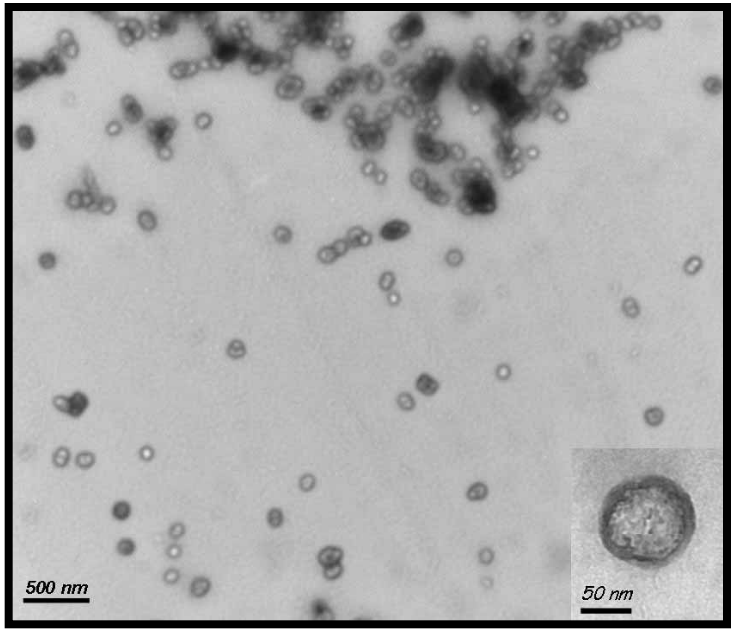


At this pH :

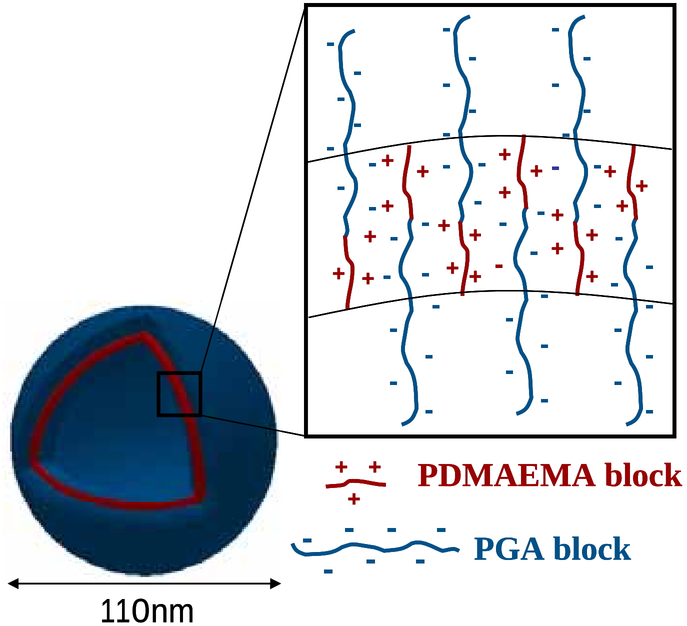
- ***PGA block is entirely charged***
- ***PDMAEMA block is partially ionized***

85-186 pH6.2

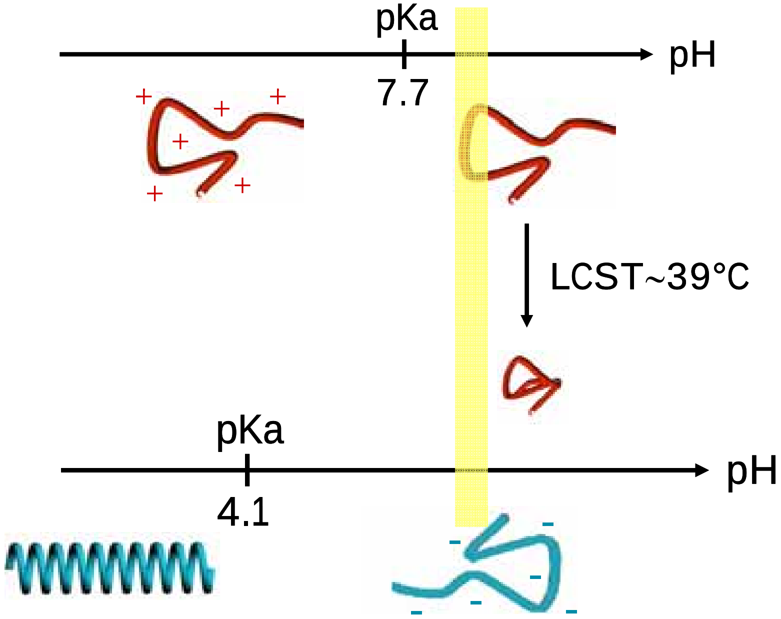


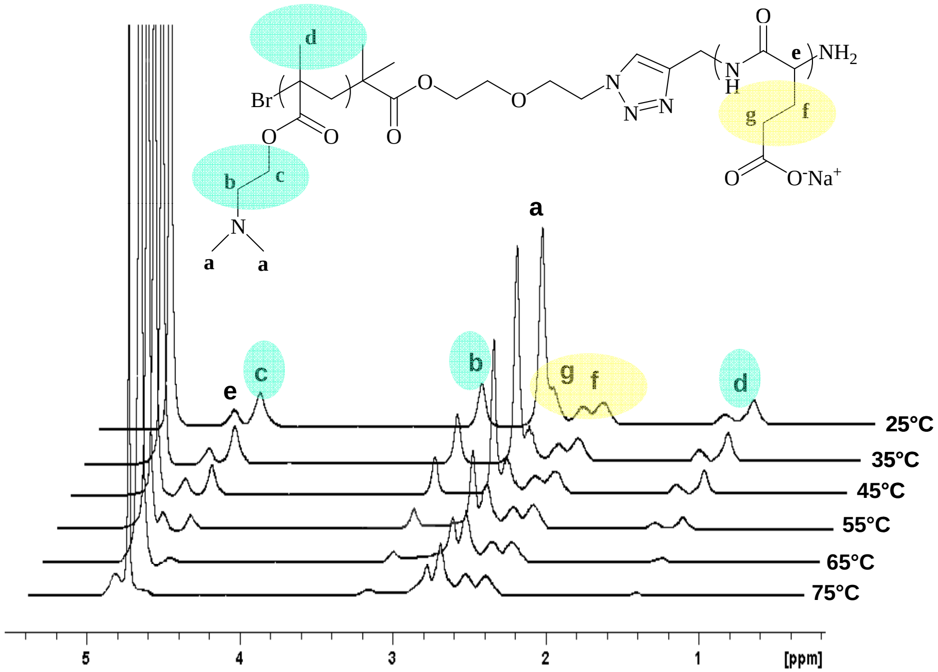


Willy Agut

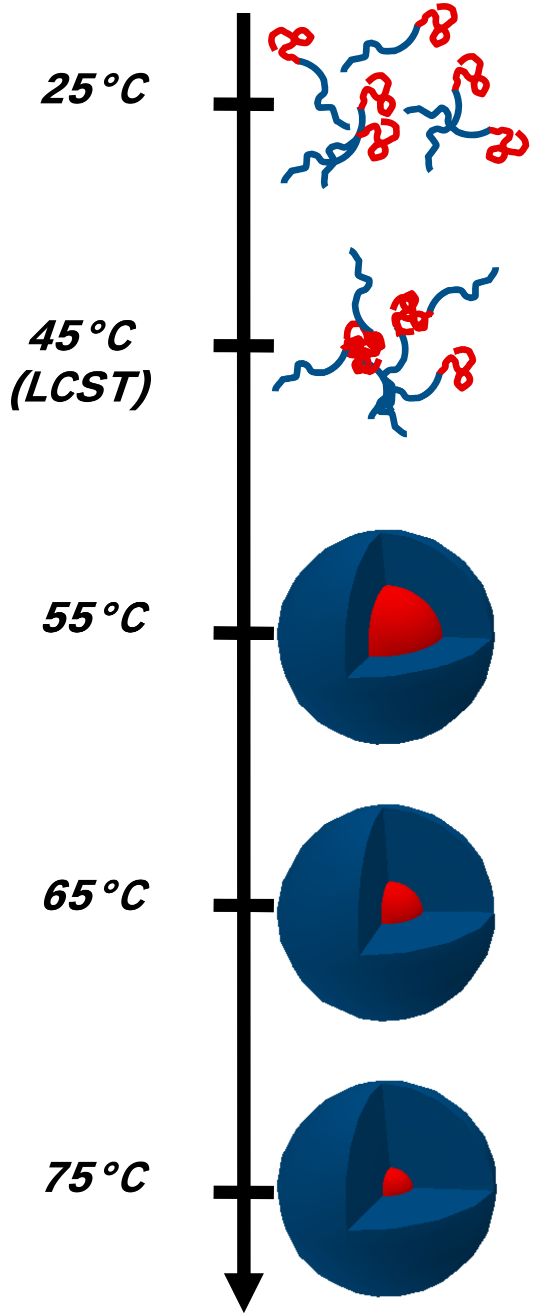


Schematic representation of an electrostatic vesicle





¹H NMR measurement

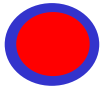


Langmuir 2007, 23, 11526

Willy Agut

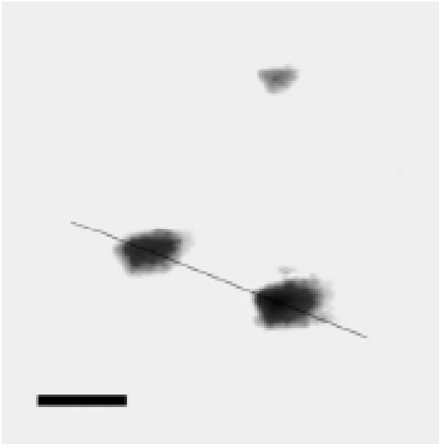
Magnetic-responsive nanoparticles

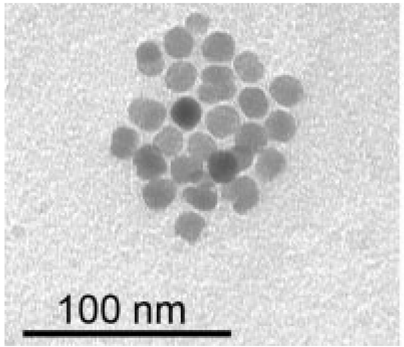
Magnetic micelles and complexes (γ-Fe_2O_3)



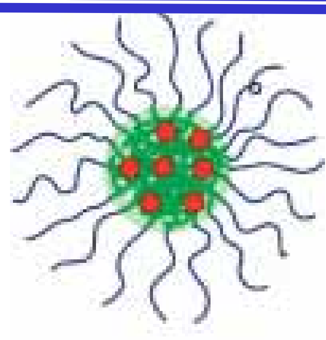
hydrophobically modified maghemite

+ amphiphilic $PBut_{48}$-b-PGA_{114}



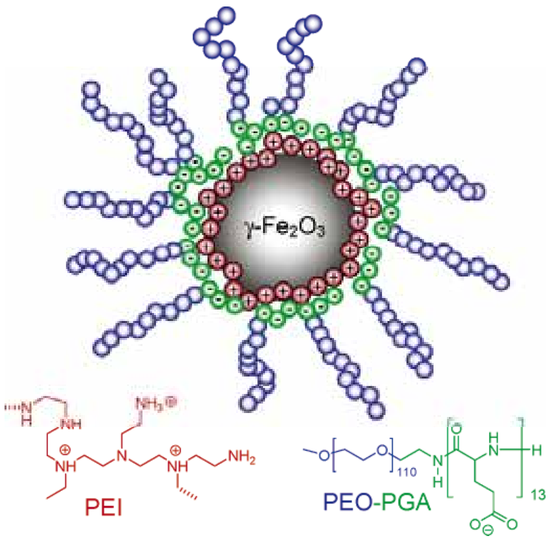


magnetic micelles



increase in the MRI contrast (x 10)

Gao et al. Adv. Mat. 2005
Lecommandoux Adv. Mat. 2005, Progress in Solid State Chem. 2006
J. Mag. Mag. Mat. 2006

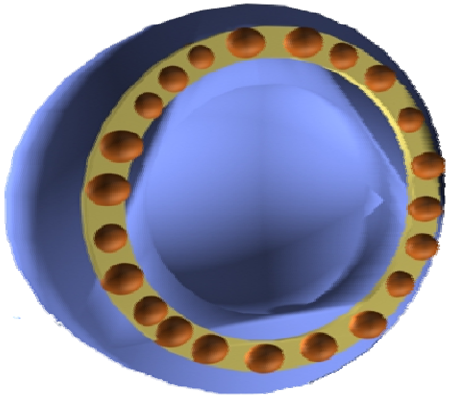


Electrostatic complexes

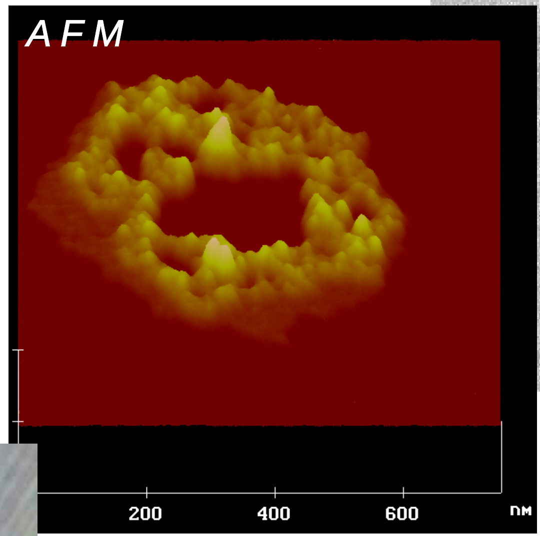
The branched poly(ethylene imine) (PEI) was used for the first layer (red), and poly(ethylene oxide)-b-poly(glutamic acid) (PEO-PGA) was used for the second layer (blue and green, respectively)

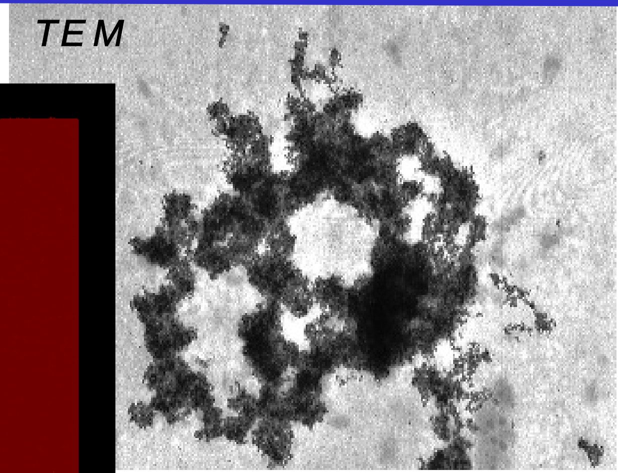
Möhwald, Langmuir 2006

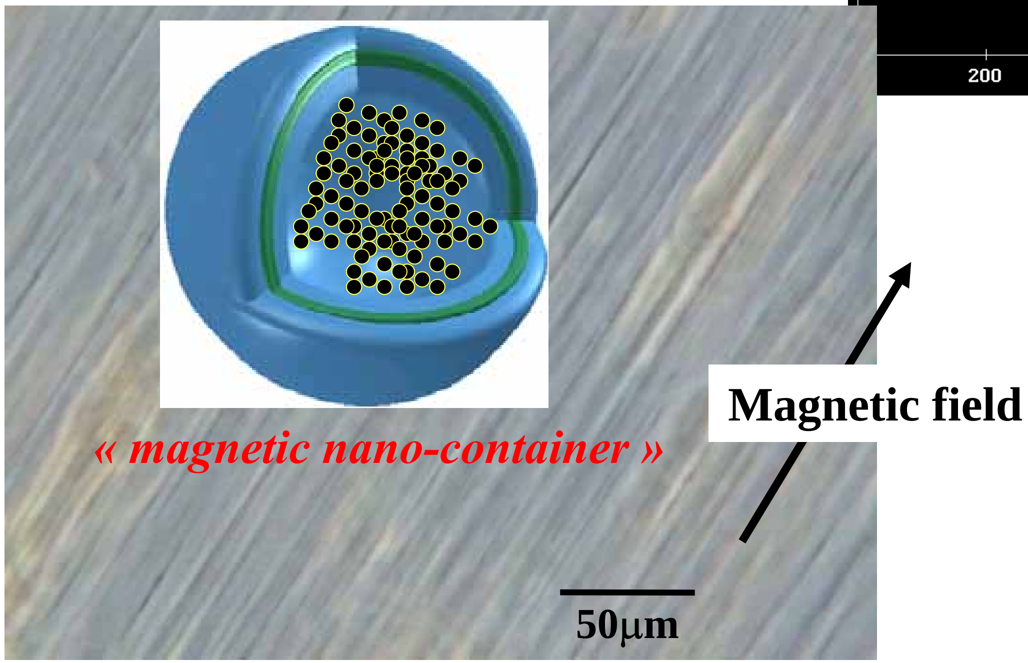
Magnetic vesicles : response to a magnetic field (1)



« fluid magnetic membrane »







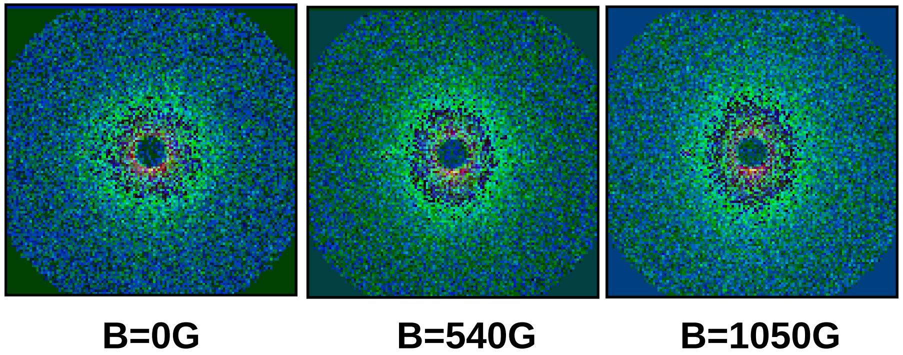
- Alignment of the magnetic baggies
- Easy redispersion
- Easy process

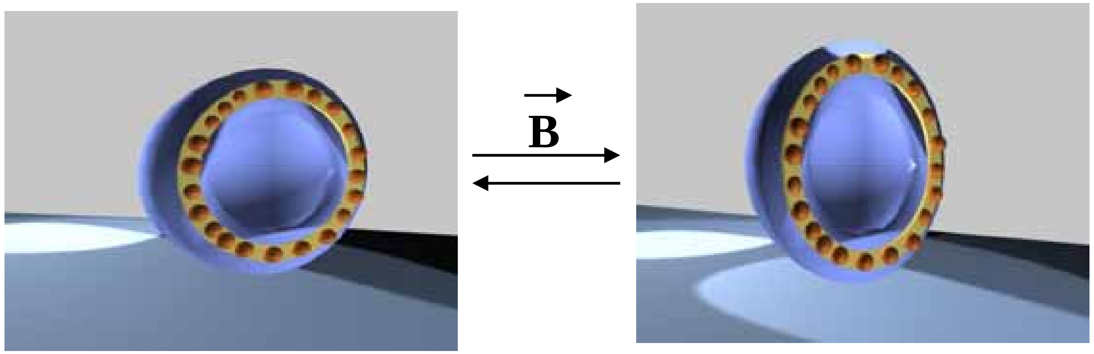
- Increase of contrast for MRI

Advanced Materials **2005**, *17*, 712 / ***J. Mag. Mag. Mat.*** **2006**, 300, 71

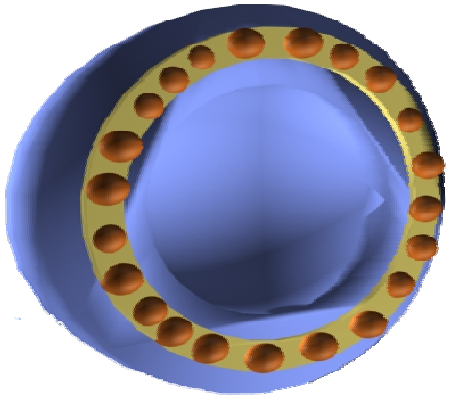
Magnetic vesicles : response to a magnetic field (2)

SANS





Scattering from the nanoparticles in the vesicle membrane



« fluid magnetic membrane »

Magnetically induced membrane deformation and permeability

Advanced Materials **2005**, *17*, 712

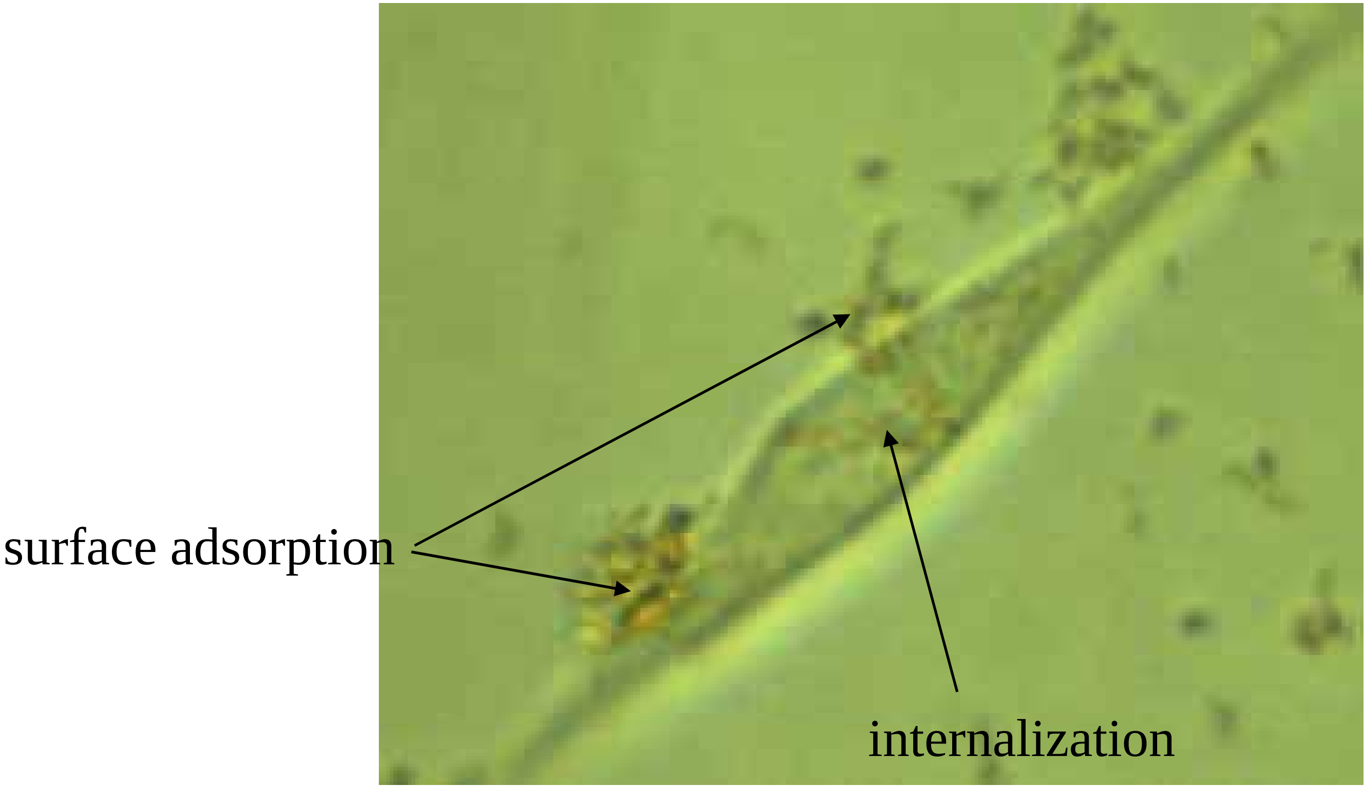
http://nano.cancer.gov/news_center/nanotech_news_2006-07-31b.asp

- diagnostic (MRI)
- multi-responsive release (pH, magnetic field, hypertermia)

"there are opportunities to design nanosized, bioresponsive systems able to diagnose and then deliver drugs (theranostics)" (Ruth Duncan, Nanotoday 2005), EU FP7

Magnetic vesicles : interactions with living cells

First in vitro experiments with HMEC5 , 2H exposition



- Cellular internalization

- No cytotoxicity

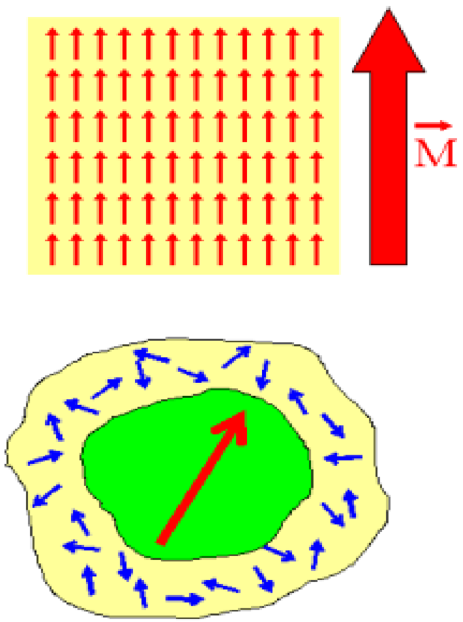
Collaboration K. Petry, U-Bordeaux 2

Magnetic nanoparticles and hyperthermia

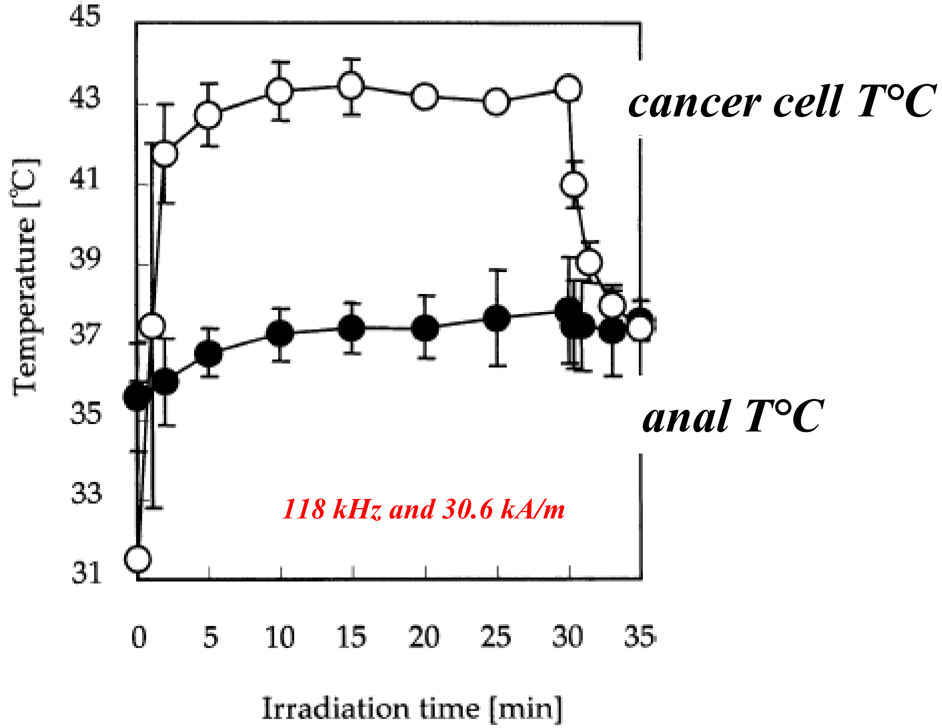
Hyperthermia** in its advanced state referred to as heat stroke, which occurs when **the body produces or absorbs more heat than it can dissipate

Hyperthermia can be created artificially by drugs or medical devices. In these instances it may be used to treat cancer and other conditions (local hyperthermia)

Different types of energy may be used to apply heat, including microwave, radiofrequency, and ultrasound... and magnetic hyperthermia!!



magnetite cationic liposomes (MCLs)

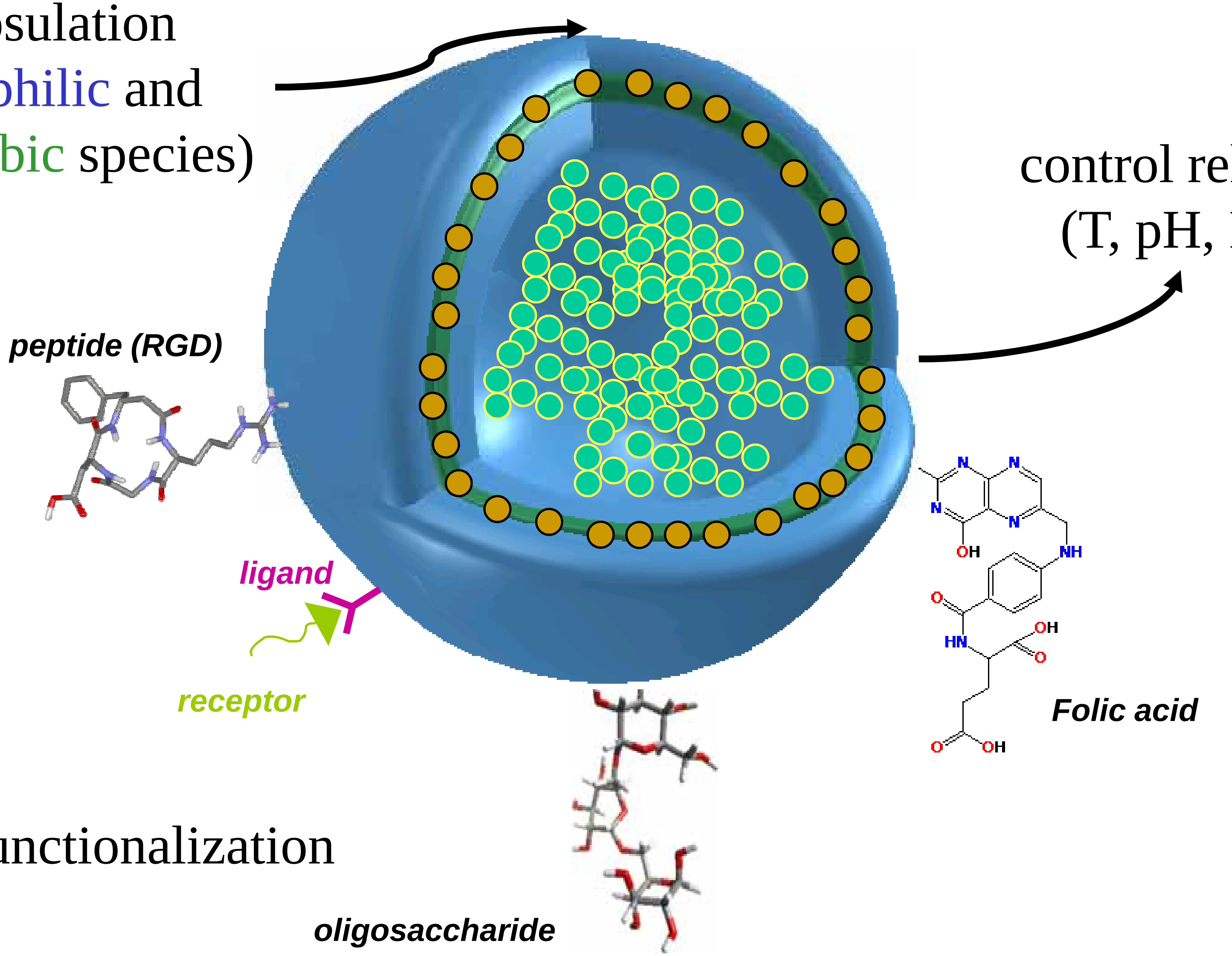


Cancer Immunol Immunother (2004) 53: 26–32

BC Vesicle: a versatile and multi-functional platform for drug-delivery and diagnosis

Encapsulation
(hydrophilic and
hydrophobic species)

control release
(T, pH, B)



Surface functionalization

Polymer Nano-Assemblies for Therapeutic Applications

- Sébastien Lecommandoux, Professor (Group Leader)
- Christophe Schatz, Assistant Professor
- Jean-François Le Meins, Assistant Professor
- 4 PhDs, 4 postdocs, 1 undergraduates

Synthesis and chemical modification of BIOCOMPATIBLE polymers and block copolymers

polypeptides, polyesters, polyethers, polysaccharides

Polymer self-assembly
- *nanoparticles*
- *micelles*
- *vesicles*

Physico-chemical characterization
- *microscopy (TEM , MEB, AFM, fluorescence)*
- *scattering methods (light, X-ray, neutrons)*

Drug loading
- *small drugs*
- *biomolecules*
- *magnetic particles*
- *fluorescent molecules*

Design of new POLYMER-BASED Drug Delivery Systems

http://recherche.enscpb.fr/lcpo/fr/pnata/index.html

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S. Louguet, K. Upadhyay
J. Mendez, I. Schmidt,
E. Castro
[F. Chécot, J. Babin]

Recombinant proteins

C. Rodriguez Cabello (Valladolid, spain)

Magnetic nanoparticles

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R. Perzynski
Etienne Duguet

Cryofracture & TEM

O. Mondain Monval

SANS & model

A. Brûlet
J. Oberdisse

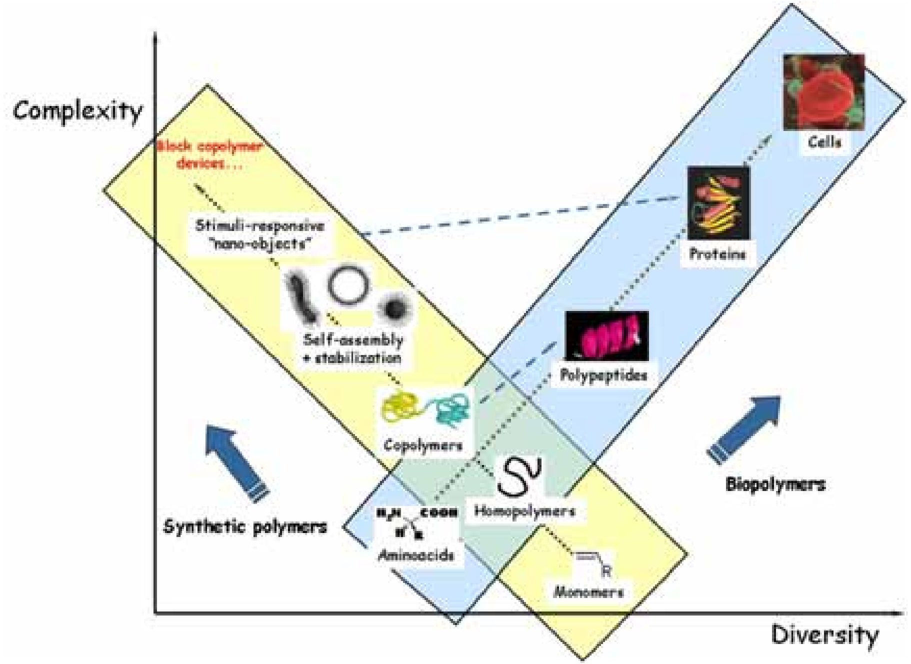
Peptide synthesis

H. A. Klok (EPFL, CH)

Gold nanoparticles

V. Mosquera, P.Taboada (Santiado de Compostela, Spain)

http://recherche.enscpb.fr/lcpo/fr/pnata/index.html



Solution Self-Assembly of Block Copolymers: Toward « Smart » nano-objects

***Prog. in Pol. Sci.* 2005, *30*, 691-724.**