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

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Outline

1. Block copolymers and Nanomedicine

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
Polymer vesicles

Liposomes

Nanomedicines

Polymer-drug conjugates

Antibodies and their conjugates

Viruses as viral vectors

Polymer micelles

Unimolecular Drugs and Conjugates

Duncan, R., Nanotoday (2005).
When was nanotechnology born?

R. Duncan, EPF, 3rd Summer School « Polymers for Biomedical Applications, 2005
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
\[ R_B \approx aN_B^{2/3} \left( \frac{\gamma a^2}{T} \right)^{1/3} \]

De Gennes 1978

\[ R \approx aN_A^{3/5} p^{1/5} \]

Daoud, Cotton 1982

Microdomain period \[ d \sim N^\delta \]
\[ \delta \approx 1/2 \text{ or } 2/3 \]
(Leibler 1980, Semenov 1985)
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

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

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

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

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Our macromolecular chemistry toolbox

«Click Chemistry» strategy

Poly(γ-benzyl-L-glutamate)

Poly[2-(dimethylamino)ethyl methacrylate]

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$_2$Cl$_2$)

Water

TEM

reverse vesicle

Vesicle 100-400 nm

Spherical micelles 20-80 nm

20  56  114  145

Block copolymer vesicles or polymersomes

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

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

Discher and col. Macromolecules 2002
BC Vesicle, a synthetic model of a viral 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 Micelles Vesicles
- pH
- T
- Magnetic field
pH-responsive nanoparticles
Polypeptide-based Rod-Coil: pH Responsive Vesicles

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

Diblock copolypeptides PGA-b-PLys: reversible pH assembly

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

- **Acid pH** ($<4$)
- **Neutral pH** ($5<pH<9$)
- **Basic pH** ($>10$)

$R_H=175\text{nm}$

$R_H=110\text{nm}$

Schizophrenic vesicles!

*JACS 2005, 127, 2026.*
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
**SANS**

1. **Spherical micelle form factor**

   - Free chains in good solvent (polymer chain with excluded volume)

   - SANS plots with temperature:
     - 10°C
     - 20°C
     - 36°C
     - 51°C
     - 66°C

   - Fits with $R=3.4nm$, $\sigma=0.2$
   - Fits with $R=3.3nm$, $\sigma=0.18$

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**Core hydration controlled with temperature**

- 36°C: 60% hydration
- 66°C: Core dehydrated

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*Langmuir 2007, 23, 11526*
Temperature Responsive PTMC-b-PGA BC Vesicles

Biocompatible  Biocompatible
Biodegradable  pH responsive
Bioresorbable  Secondary structure

Charles Sanson
**T-Responsive PTMC-b-PGA BC Vesicles: WHY???

Charles Sanson**
T-Responsive PTMC-b-PGA BC Vesicles: Mechanism?

- **Fission**
- **Fusion**

**PTMC starts to « crystallize »**

↑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

\[
\begin{align*}
\text{pKa} & \quad \text{pH} \\
7.7 & \quad 4.1
\end{align*}
\]

- 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

\[ \text{pKa} = 7.7 \]

\[ \text{pKa} = 4.1 \]

\[ \text{LCST} \approx 39^\circ C \]

85-186 pH 6.2

Schematic representation of an electrostatic vesicle
Magnetic-responsive nanoparticles
Magnetic micelles and complexes (γ-Fe₂O₃)

hydrophobically modified maghemite + amphiphilic \( \text{PBut}_{48}-\text{b-PGA}_{114} \)
magnetic micelles

increase in the MRI contrast (x 10)

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)

- Alignment of the magnetic baggies
- Easy redispersion
- Easy process
- Increase of contrast for MRI

Magnetic vesicles : response to a magnetic field (2)

Scattering from the nanoparticles in the vesicle membrane

Magnetically induced membrane deformation and permeability

Advanced Materials 2005, 17, 712

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

Encapsulation (hydrophilic and hydrophobic species)

Surface functionalization

Control release (T, pH, B)

Peptide (RGD)

Ligand

Receptor

Oligosaccharide

Folic acid
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

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

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

Design of new POLYMER-BASED Drug Delivery Systems

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