Craig J. Hawker

Nanomanufacturing
Nanomanufacturing

Construction of materials using Molecular Scale Building Blocks

Block Copolymer Lithography

Magnetic 3-D coordination polymer

Self assembling systems

Nanoparticles – new strategies
Nanoparticles

* Spherical polymer particles – widely studied
  - tailored functionality
  - composite structures
  - core-shell materials

Amgen acquired Ilypsa for $420 million on July 18, 2007
* Future challenges
  - non-spherical systems
  - top-down and bottom up approaches
  - non-traditional building blocks

* Outcomes
  - Quantitative laws relating particle structure and function
  - High volume production methods
  - Ability to tailor placement of functional groups and incorporation of active entities
  - Can we design nanoparticles like small molecules
Top-down Approaches to Non-spherical Systems

- Embed polymer spheres (200 nm-10 mm) in poly(vinyl alcohol) film (PLGA, polyanhydride, albumin, ethyl cellulose)
- Liquefy polymer using heat or solvent
- Stretch film, solidify particles and dissolve film to collect particles

Prof. Samir Mitragotri - Chemical Engineering, UCSB
Top-down Approaches to Non-spherical Systems

- Simple strategy to Diverse shapes (1-, 2-, and 3-D particles)

- control of size and shape
  - 200 nm to 10 µm sphere
  - some degree of symmetry

Prof. Samir Mitragotri - Chemical Engineering, UCSB
Particle Replication in Non-wetting Templates

PRINT™ Particles

Cylindrical Series Characterization

- **200 nm AR = 1**
  - 6.77 mg
  - Zeta = + 41.64 ± 2.60 mV
  - Top Width = 134 ± 13 nm
  - Bottom Width = 159 ± 12 nm
  - Height = 479 ± 26 nm

- **150 nm AR = 3**
  - 4.05 mg
  - Zeta = + 34.78 ± 3.04 mV
  - Top Width = 75 ± 3 nm
  - Bottom Width = 118 ± 5 nm
  - Height = 277 ± 14 nm

- **100 nm AR = 3**
  - 1.86 mg
  - Zeta = + 40.55 ± 3.05 mV

Scale bar = 0.5 µm
Regio-selective Functionalization

Harvest
Characterization

• PEG-based particles (7 x 14 µm) containing covalently bound Rhodamine B (red) are fabricated in a PFPE mold. Primary amine groups are distributed throughout the particle matrix.

• Mold is placed in an aqueous solution containing fluorescein isothiocyanate and agitated for 1h, covalently binding fluorescein (green) dye regioselectively to exposed end of the particle.

• Particles are removed from solution, rinsed with water, harvested in a surgical adhesive, and isolated through dissolution of the adhesive.
Cross-disciplinary Research and Translation to Market

- Imprint Lithography
- Block Copolymer Lithography
Comparison: Lithography vs. Self Assembling Block Copolymers

Critical steps

1. Neutralization of surface
2. Vertical alignment of PMMA cylinders
3. Photochemical removal of PMMA cylinders

Expensive Photolithography
IBM's chip breakthrough comes from tiny holes. May 4, 2007

Chips with minuscule holes in them can run faster or use less energy, IBM said in announcing a novel way to create them — potentially one of the most significant advances in chip manufacturing in years.

To create these tiny holes, the computer company has harnessed a plastic-like material that spontaneously forms into a sieve-like structure. "To our knowledge, this is the first time anyone has used nanoscale self-assembled materials to build things that machines aren't capable of doing," said John Kelly, IBM's vice president of development.
Block Copolymer Lithography
Assembling a thin-film polymer template

Block Copolymer

** Critical to make cylinders ‘vertical’ not ‘horizontal’

** Use neutral layer
Random Copolymer

\[
\text{NO}_2 + \text{CHO} \xrightarrow{\text{Zn/HOAc}} \text{CHO}^+ \xrightarrow{\text{PhMgBr}} \text{PhNO}_2
\]

Routinely made on kg scale

Surface attachment

\[ \text{OH} \quad 58 \quad 42 \quad \text{OMe} \]

\[ \text{OH} \quad \text{Cl} \]

58% Sty
42% MMA

1. NaOAc
2. KOH
Effect of Surface Preparation

No surface preparation (native oxide / silicon)

NORMAL
PS-PMMA copolymer

PS-PMMA random copolymer - LFRP

* random copolymer neutralizes surface for proper diblock copolymer self-assembly
Air Gap Manufacturing

Size of holes is Critical < 20 nm

- Low Cost
- Compatible with Current Manufacturing
Future of Block Copolymer Lithography

Controlling self-assembly – asymmetrical structures
Directed Self Assembly

Directed pattern

Registration

1-3 nm

Imaging Layer

Substrate

Exposure

Spin Coat

Block Copolymer

Substrate

Bake

RI Etch

Substrate
Directed Self Assembly

**P(S-b-MMA) on Unpatterned Surface**

**P(S-b-MMA) on Patterned Surface**

Symmetric Poly(styrene-b-methylmethacrylate) $L_o \sim 48 \text{ nm}$

Assembly of non-regular device oriented structures such as 90° bends is facilitated by the localized **redistribution of homopolymer**.

Nanomanufacturing

Top-Down vs. Bottom-up strategies

Block Copolymer Lithography

Fabricated Nanostructures

Self assembling systems

Imprint Lithography
Nanoparticles

* Future challenges
  - non-spherical systems
  - top-down and **bottom up** approaches – *self-assembly*
  - non-traditional building blocks

* Outcomes
  - Quantitative laws relating particle structure and function
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Robust Nanostructures *via* a Bottom-up Approach, Involving Well-defined Block Copolymers

**Stabilization of self-assembled nanostructure**

Shell Crosslinked (SCK) Nanoparticle

Block Copolymer Micelle

Crosslinking Allows for Physical and Chemical Manipulation

(1) Morphology and shape

(2) Chemical modification

(3) Physical (re)shaping

(4) Core Excavation

Versatile Nanoscale Building Block
Self-assembly Process also Provides Opportunities to Manipulate Shape

ABC Triblock

Influence of assembly conditions

Functional Complex Morphologies

Non-classical, Hierarchical Micelles

Directed assembly of Au nanoparticles

Shape and Functionality Contribute to the Ultimate Utility of Nanostructured Materials

Spheres are internalized faster by cell permeation peptides - size

Cylinders are internalized faster via receptor-mediated endocytosis - multivalency

www.chem.purdue.edu/low/
Shrinking tumors with Taxol-loaded Filomicelles

Effectiveness increases with Length of Filomicelles

SHAPE MATTERS!

Human lung cancer A549 Xenograft

7 days Post-injection

A) Same doses

Effect of Shape on Performance

Dennis Discher - PENN
Nanomanufacturing

Self assembling systems

Synthetic Modification of Biological Materials

Block Copolymer Lithography

Magnetic 3-D coordination polymer

Nanoparticles – new strategies
- MS2 is one of the simplest viruses known
- Contains 3500 nucleotides of ssRNA (3 genes)
- Self assembles from 180 copies of a 13 kD coat protein
- Yields 30 mg of highly pure virus / L of broth
Installation of Functional Groups

- External modification allows installation of targeting groups
- Pores in capsid shell allow molecules to access interior
- Internal cargo attachment prevents degradation and minimizes influence on biodistribution

Cargo Attachment Strategy:

MRI

[18F]N
O
N

~100 GdIII complexes per capsid

PET

~40 Fluorine atoms per capsid

Photodynamic Therapy

~80 Eosin dyes per capsid
Light Harvesting with Modified Viral Rods

Donor
Oregon Green
$\varepsilon = 81,000 \text{ cm}^{-1}\text{M}^{-1}$

Acceptor
Alexa Fluor 588
$\varepsilon = 96,000 \text{ cm}^{-1}\text{M}^{-1}$

By optimizing chromophore composition, over 90% efficiency can be attained.
Integration of Electron Transfer Groups

- Porphyrin attachment site
- TMV protein monomer
- Self assembly
- Chromophore

- Light harvesting chromophore arrays
- Top views
- Integrated electron transfer component
- Semicconducting material with voltage bias

- H$_2$NO(ethylene)$_5$ porphyrin attachment
- Me$_3$N$_2$ porphyrin attachment

FRET
Conclusions

* Nanomanufacturing is rapidly growing and already has important commercial applications

* For either biomedical or microelectronic applications – must control structure – different structures give different performance

* Multi-disciplinary with a tight connection between synthesis, processing and theory

* Need better characterization tools
Materials Research Facilities Network – www.mrfn.org

* Provide access to advanced characterization tools for the wider materials community
* Cyber-infrastructure and education
* Support available

Members
UCSB, UMASS, Minnesota, Wisconsin, Southern Mississippi