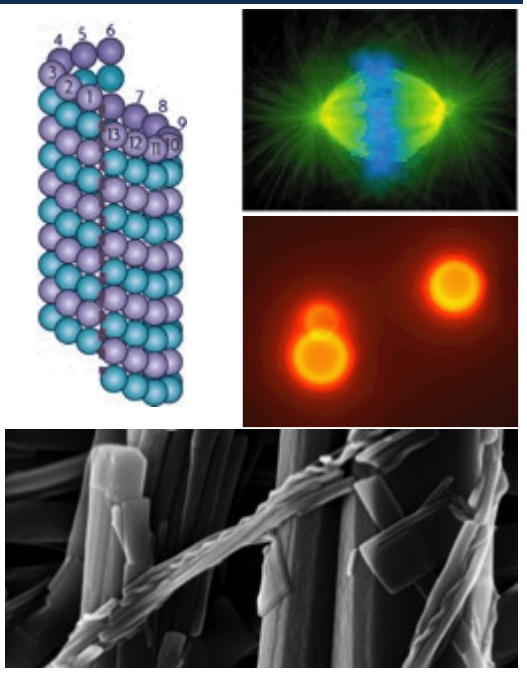

SAND2016-3260C

Molecular Biomimicry: Adapting Biological Form and Function in Synthetic Supramolecular Systems

Erik D. Spoerke, Ph.D.

Brad Jones, Jill Wheeler, Alina Martinez, Christina Ting, Ian Henderson, Mark Stevens and George Bachand

Sandia National Laboratories
Albuquerque, NM USA

Foundations of Nanoscience: Self-Assembled Architectures and Devices 2016 (FNANO16)
April 11-14, 2016
Snowbird, UT

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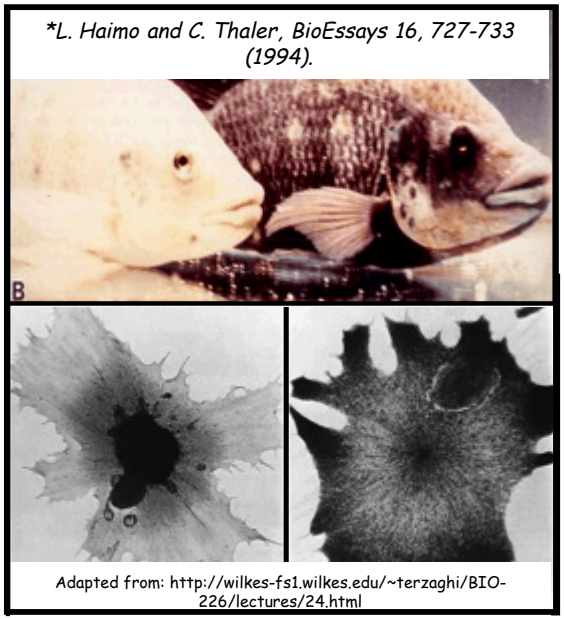
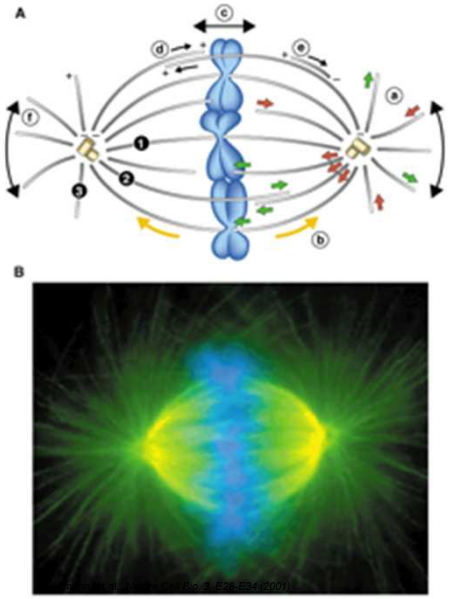
Microtubules (MTs) Impact a Huge Range of Biological Functions

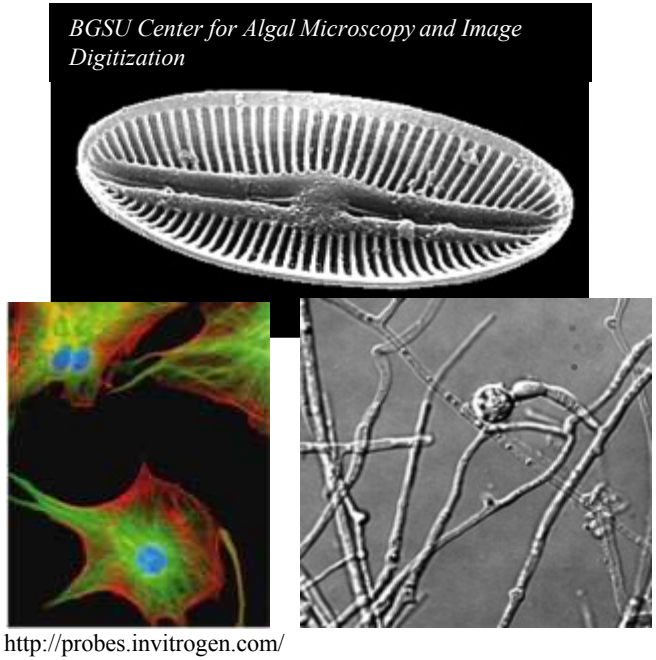
The remarkably diverse and highly scalable functions of microtubules are enabled by their dynamic, biologically programmable nanostructure and chemistry.



Adaptive reorganization of pigment granules in melanocytes



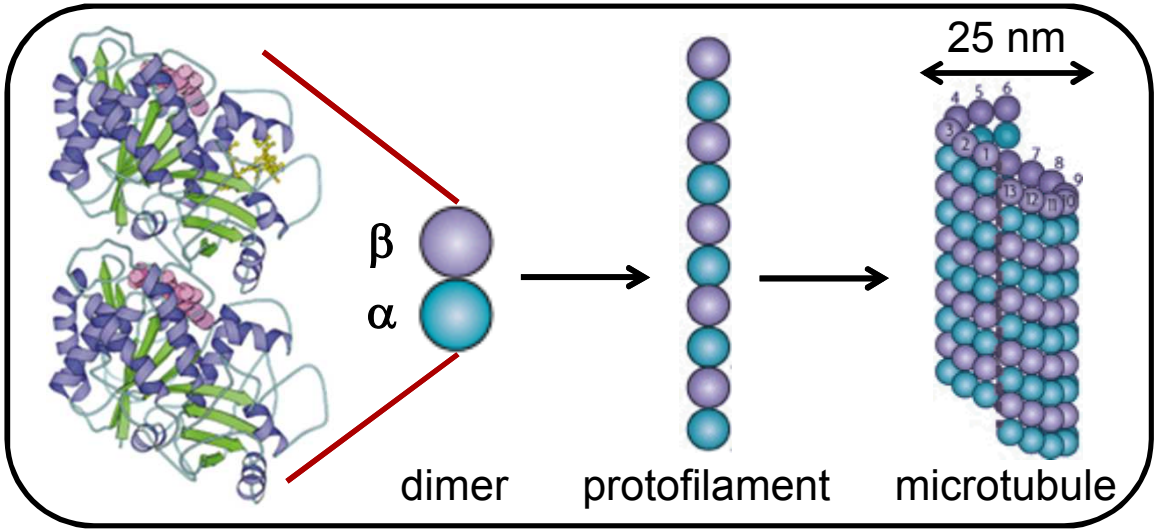
Chromosome positioning and separation during cell splitting



http://probes.invitrogen.com/

Trafficking of vesicles and macromolecule building blocks

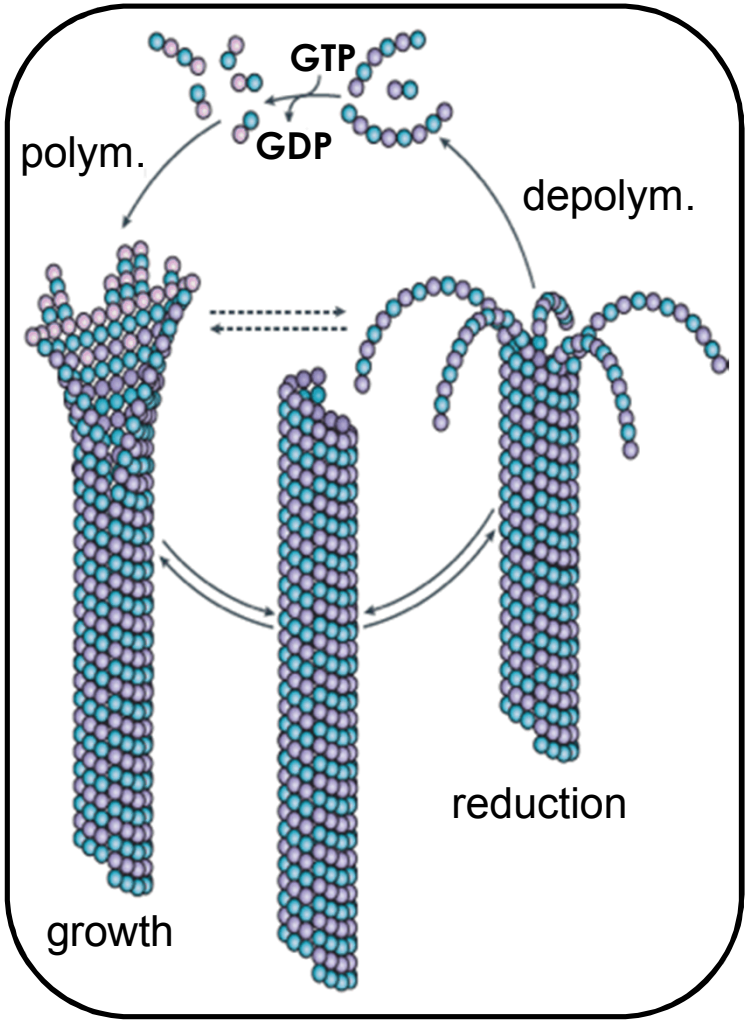
Microtubules: Dynamic Organized Protein Assemblies



Akhmanova, A.; Steinmetz, M.O. *Nat. Rev. Mol Cell. Bio*. **2008**, *9*, 309.
Nogales, E. *Annu. Rev. Biochem*. **2000**, *69*, 277.

Our Challenge:

Exploit/mimic concepts central to MT form and function in synthetic materials to enable novel new materials behaviors.



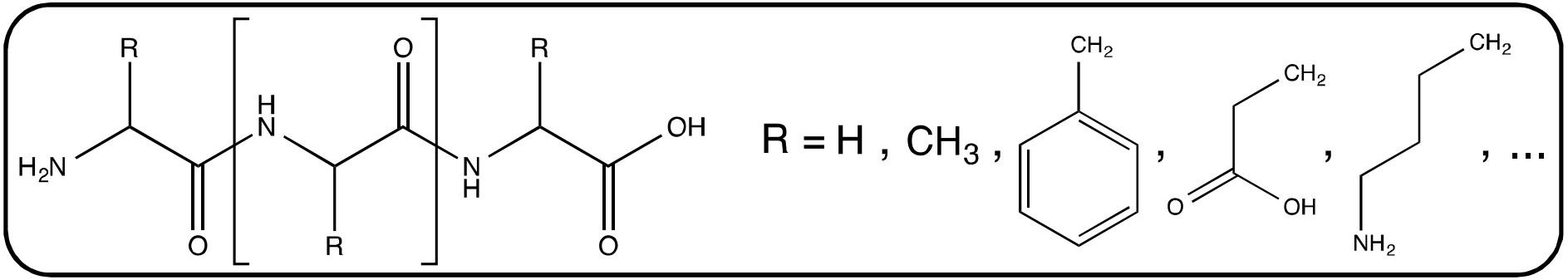
Akhmanova, A.; Steinmetz, M.O. *Nat. Rev. Mol. Cell. Bio*. **2008**, *9*, 309.

Key MT Characteristics

- 1-D nanostructure assembly
- Controllable dynamic assembly and disassembly
- **Multifunctional, *composite* building block structure**
- **Selective interactions with secondary molecules to control molecular behavior**

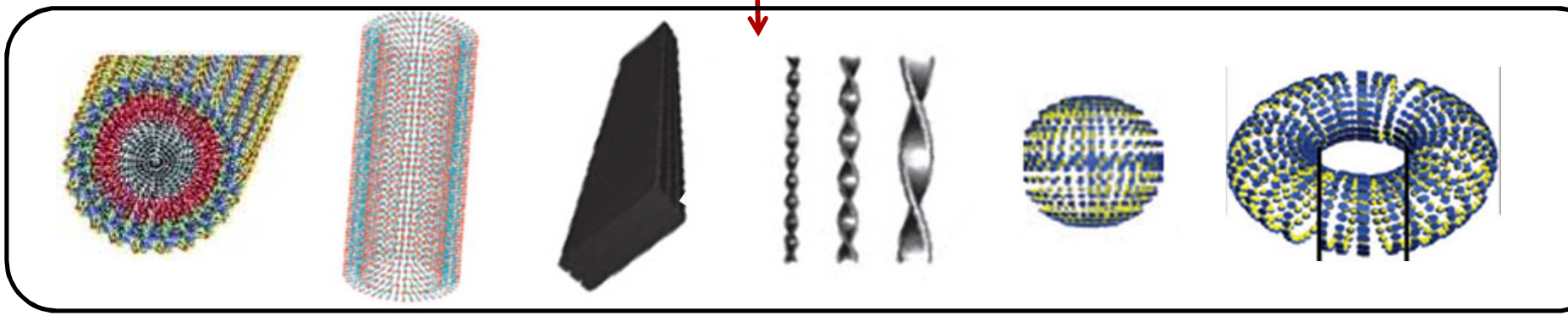
Peptides: Versatile Tools for Biomimetic Assembly

A complex balance of interactions drives spontaneous self-assembly



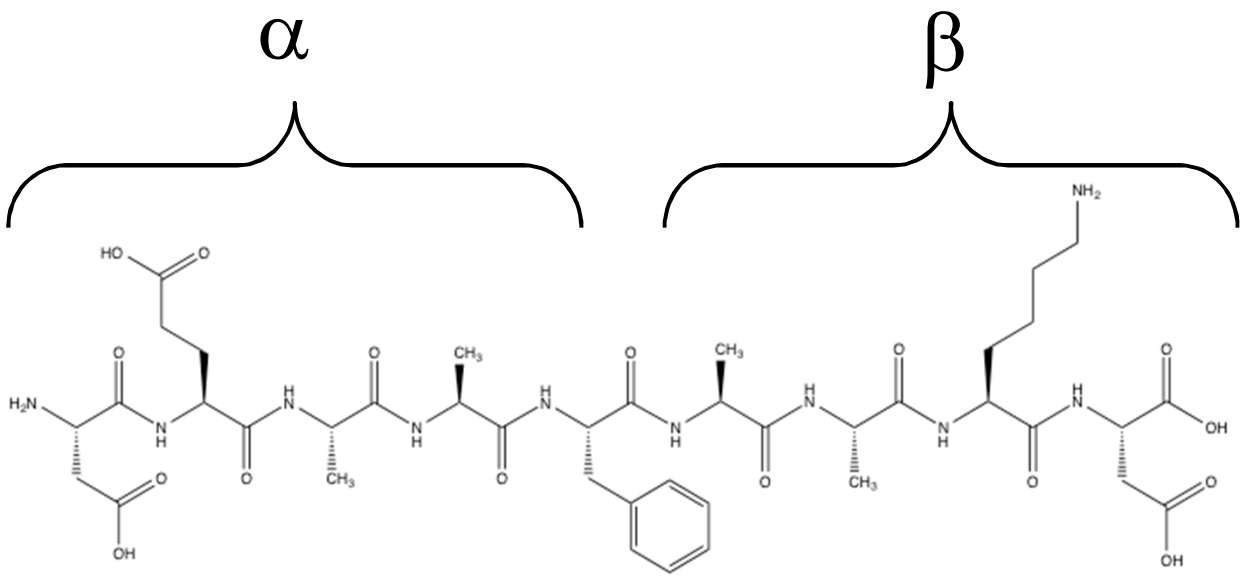
electrostatic interactions | hydrogen bonding | aromatic stacking | hydrophobic interactions

chemical environment



MT-Inspired Functional Block Peptides

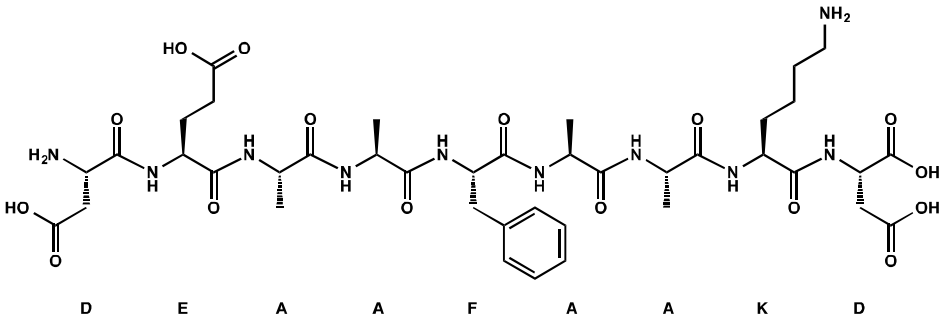
Inspiration: *MTs assemble from α/β tubulin dimers, through interactions with secondary biomolecules (e.g., GTP).*

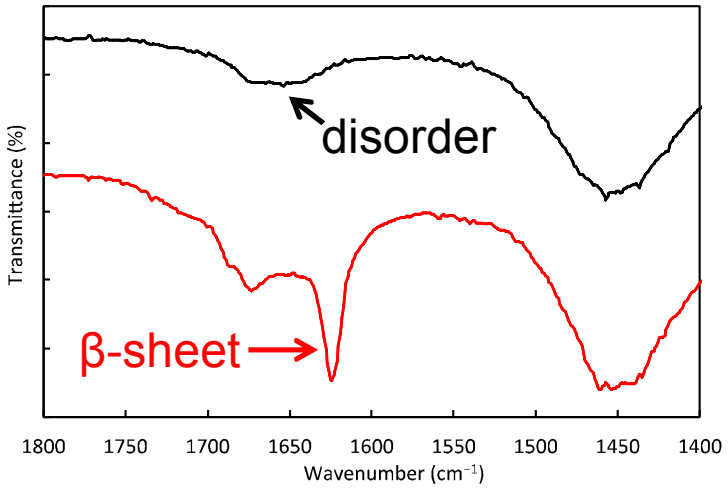


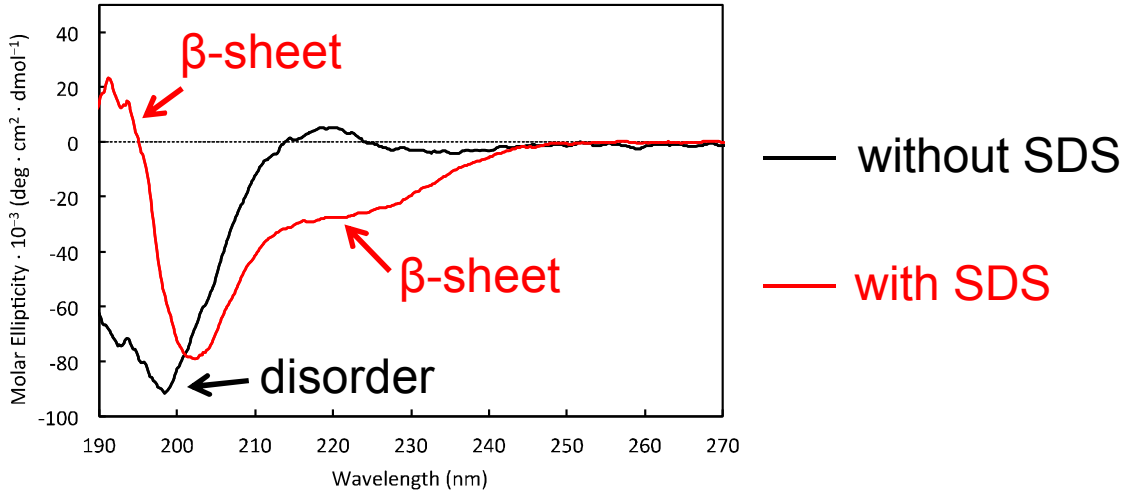
Technical Approach: *Create a peptide "dimer" with an enzymatically cleavable linkage, that assembles through interactions with secondary molecular interactions.*

Surfactant-Induced Secondary Structure

Small amounts of surfactant can induce ordered secondary structure and hydrogelation of otherwise unstructured peptides

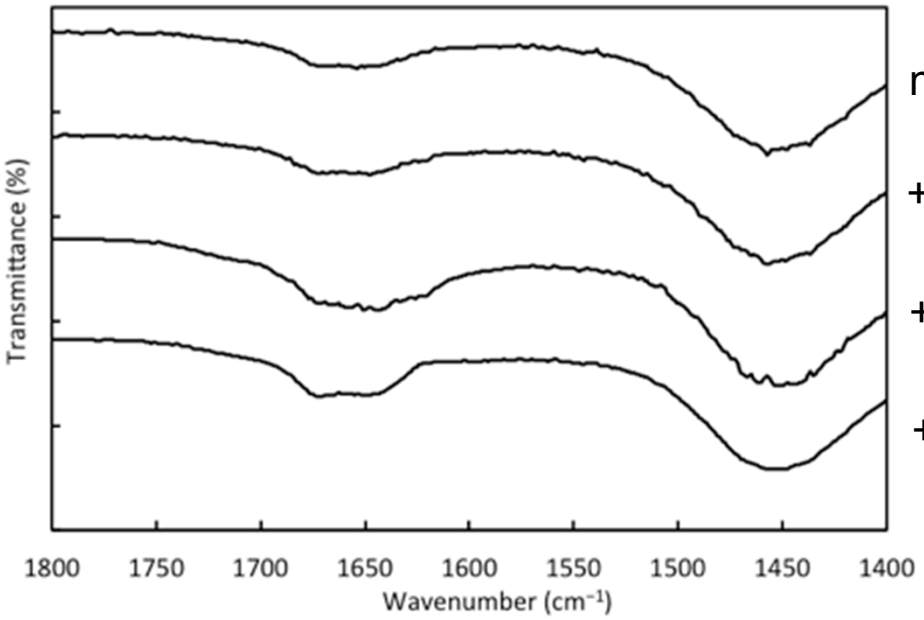






Mechanism of Assembly

Structure arises from cooperative self-assembly of peptide and electrostatically bound SDS



neat peptide

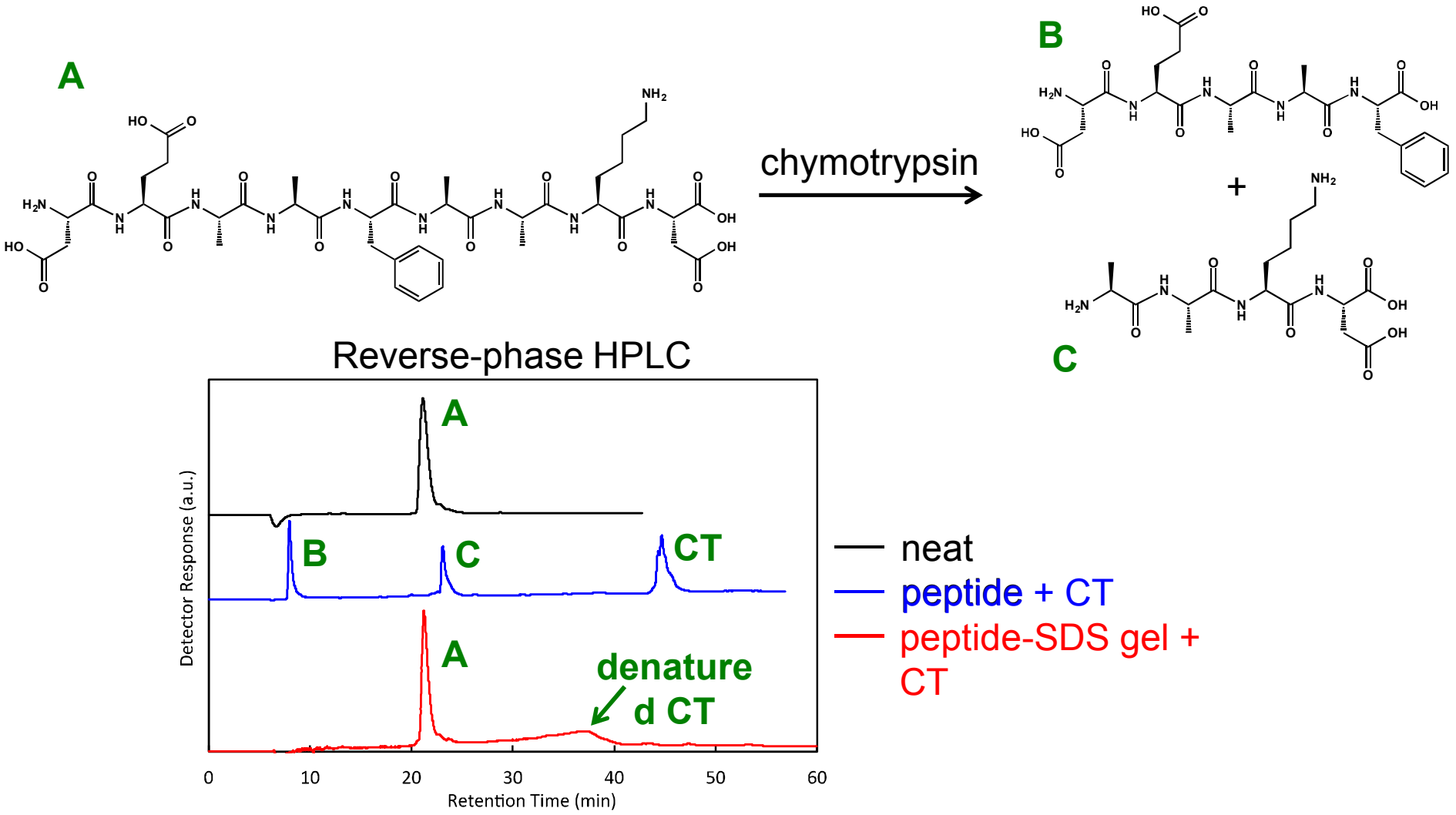
+ Triton X-100 → no micellar segregation

+ sodium sulfate → no charge screening

+ CTAB → electrostatic binding is involved

Enabled Function: Enzymatic Resistance

Peptide-surfactant hydrogels are stable to enzymatic degradation

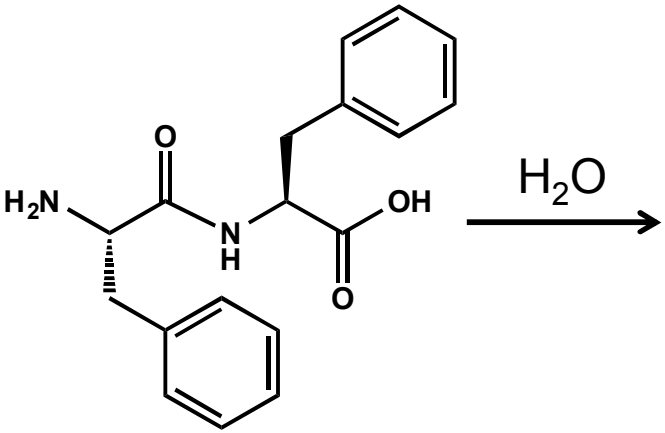


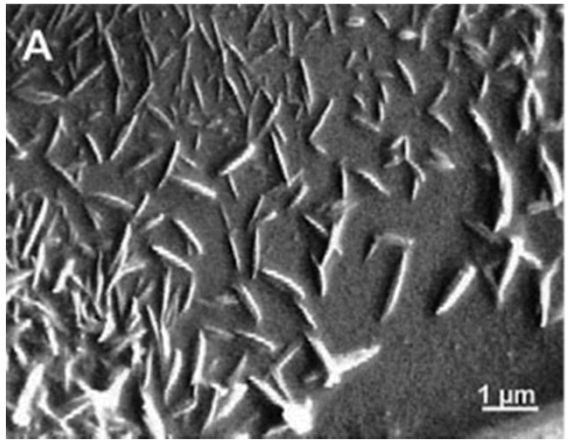
A Multifunctional Dipeptide?

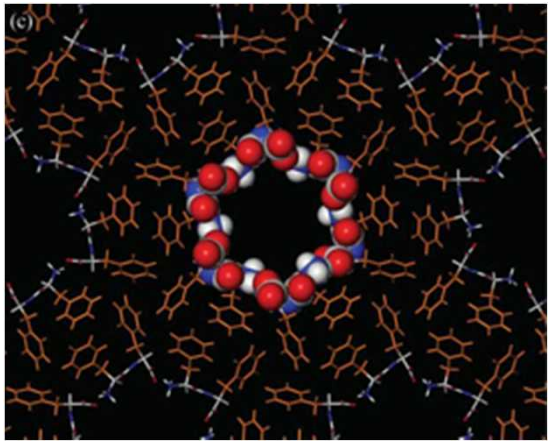
FF-Nanotube Formation

Diphenylalanine dipeptides will self-assemble into hierarchical nanotubes

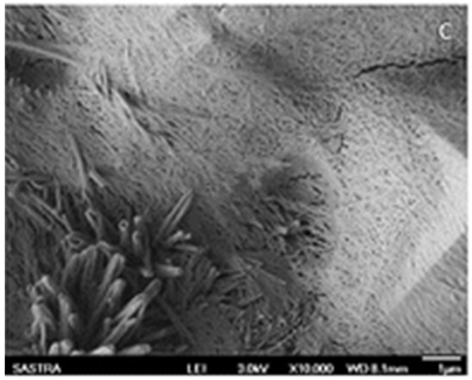
Nanotubes from di(phenylalanine)

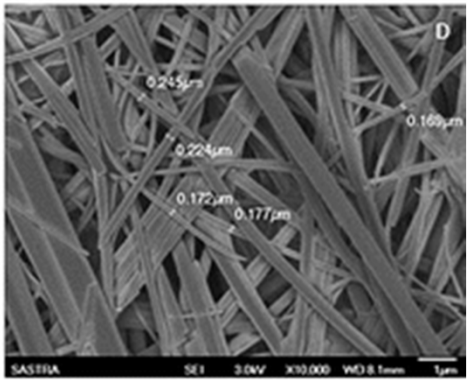






Reches, M.; Gazit, E. *Science* **2003**, *300*, 625-627; Görbitz, C.H. *Chem. Comm.* **2006**, 2332-2334.



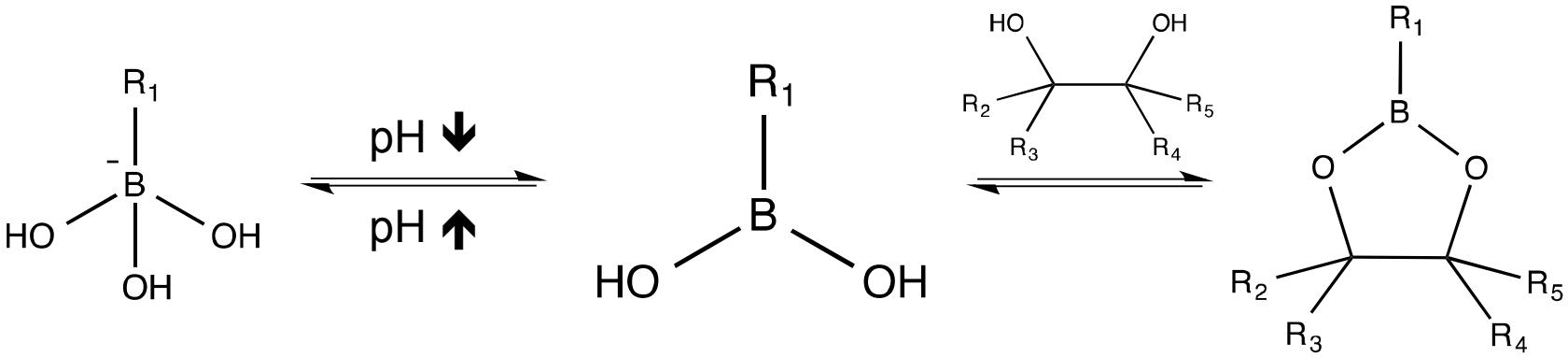


<u>Scientific Challenge:</u> *Can we modify this simple dimer building block for programmable self-assembly?*

P. Kumaraswamy, et al. *Soft Matter*, **2011**,*7*, 2744-2754.

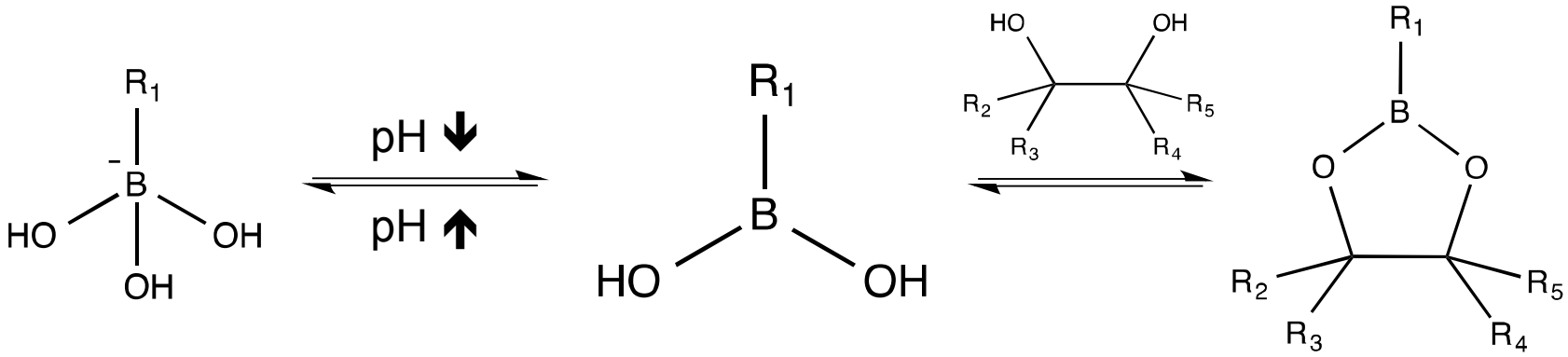
Boronic Acids

Boronic acids provide potential for pH- and polyol-responsive behavior

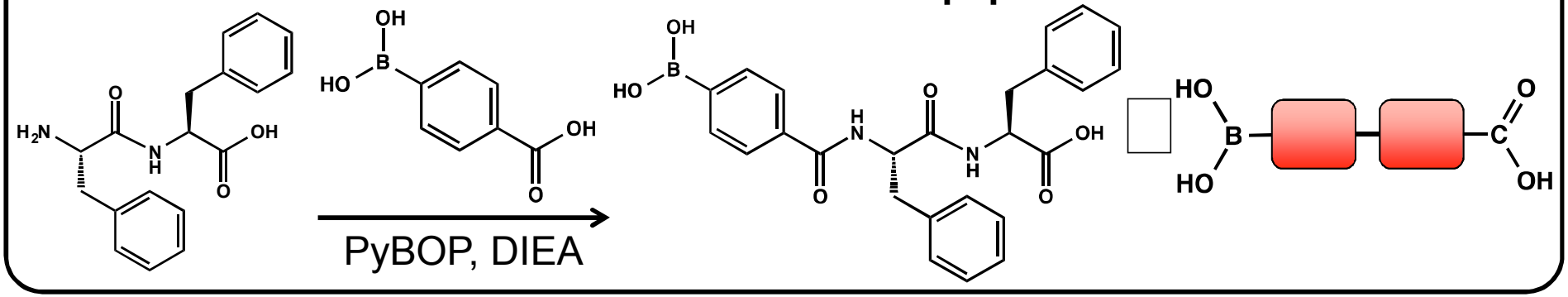


A Simple Boronic Acid Peptide

Boronic acids provide potential for pH- and polyol-responsive behavior



Our model boronic acid peptide

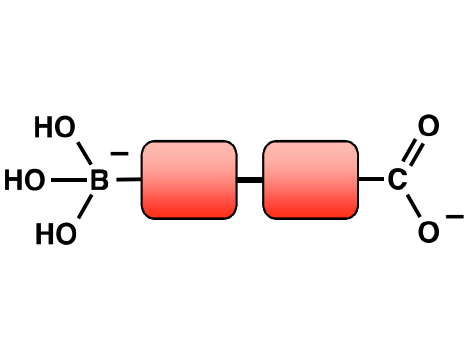


B.H. Jones, et al. *Tet. Lett.* (2015) **56** (42)**,** 5731-5734.

B.H. Jones, et al. *Chem. Comm.* (2015) **51,** 14532-14535.

pH- and Salt-Responsive Self-Assembly

Nanoribbon assemblies are reversibly formed by ΔpH or Δionic strength



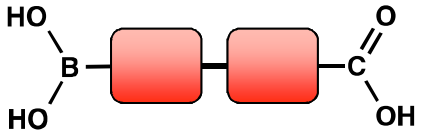
(a) + HCl, pH ≤ 5

(b) + NaCl

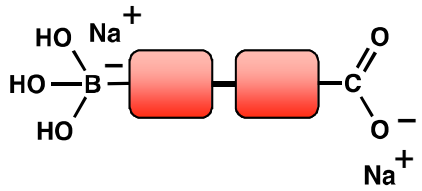
(a) + NH_4OH, pH ≥ 5

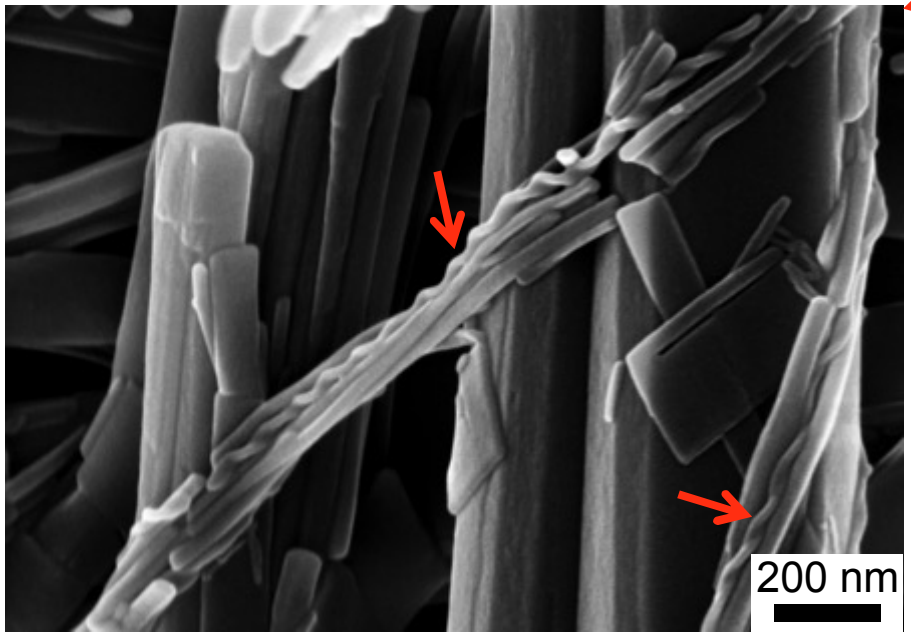
(b) + H_2O

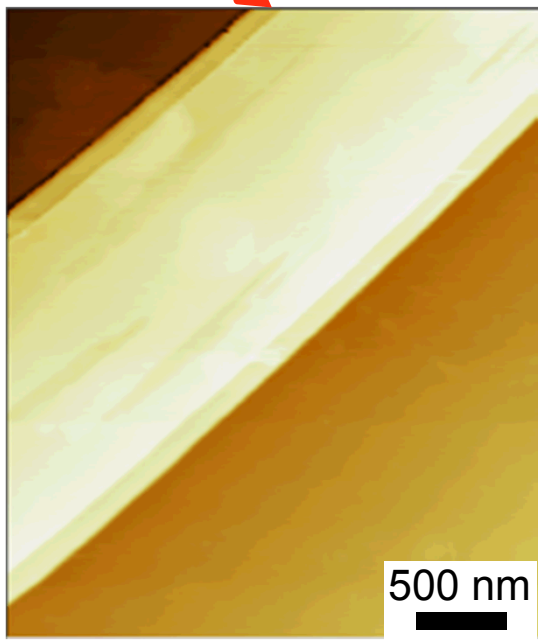
(a)



(b)



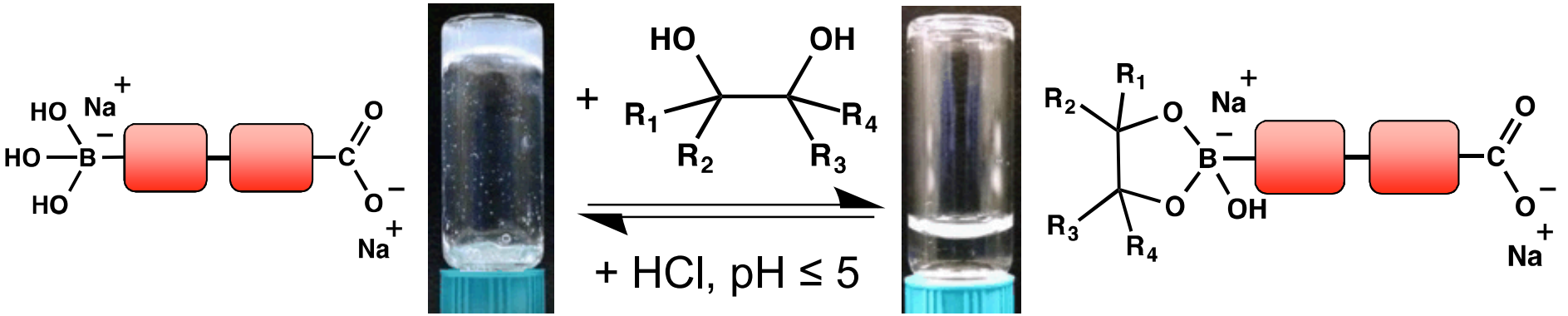


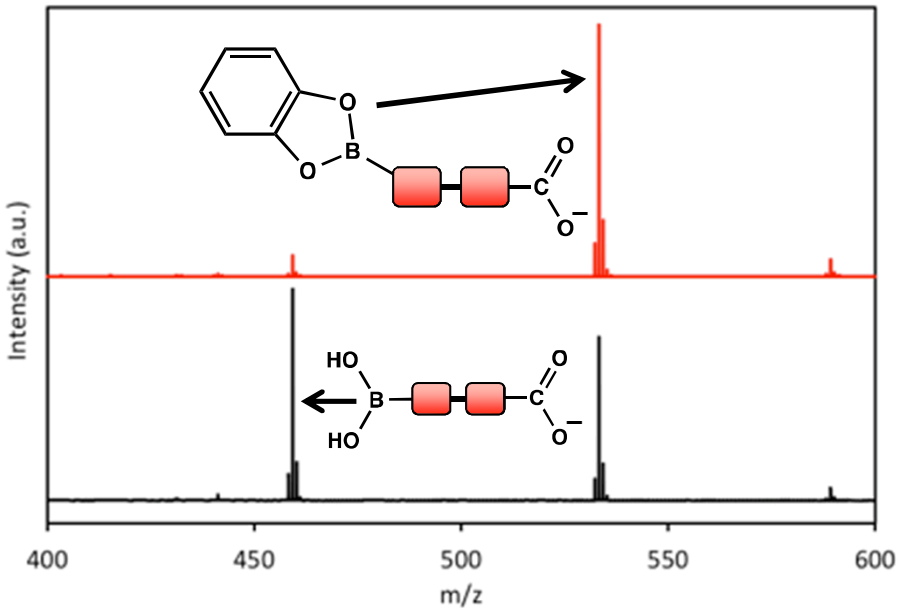


SEM courtesy of Bonnie McKenzie

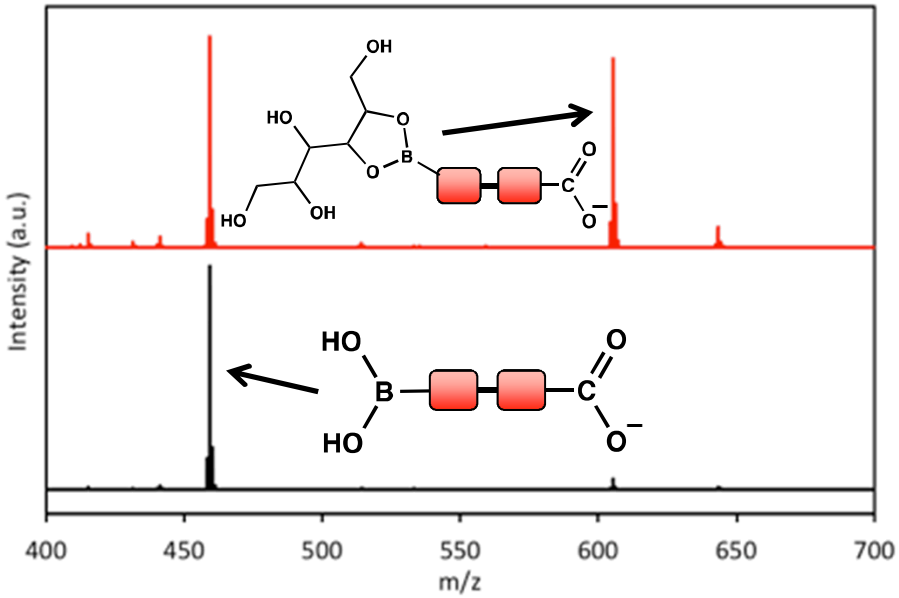
Saccharides/Polyols Induce Disassembly

Gel-sol transitions are triggered by addition of saccharides or polyols





[**catechol**]:[peptide] = 1:1 6:1



[**sorbitol**]:[peptide] = 1:1 6:1

MS courtesy of Lance Miller

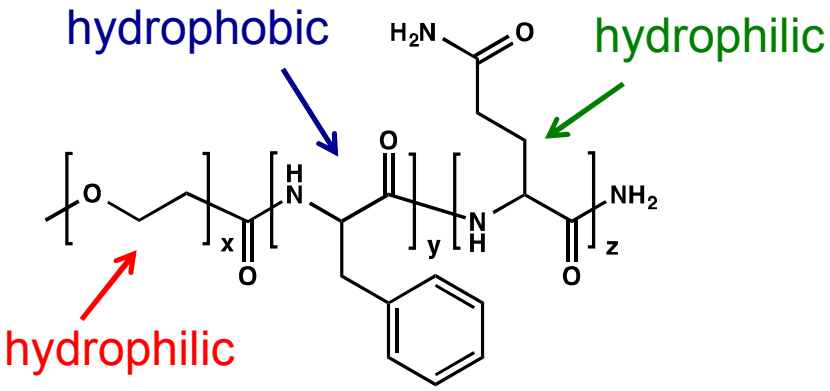
Simulation-Guided Peptide Assembly

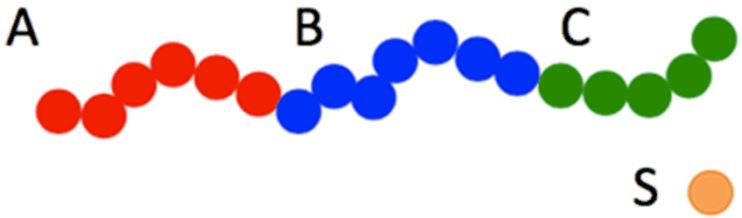
Can theory identify a multicomponent peptide building block capable of controlled assembly?

Can we synthesize a simulation-inspired peptide that assembles as predicted?

Simulation-Inspired Triblock Assemblies

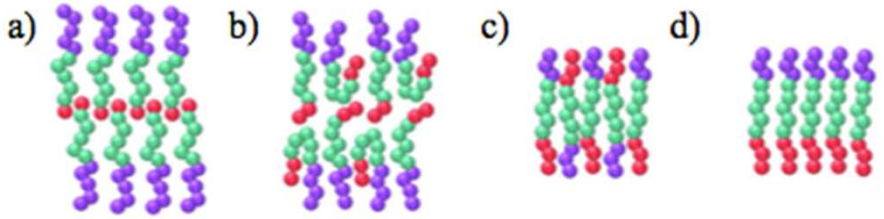
Self-Consistent Field Theory (SCFT) calculations guide molecular design of new blocky architecture





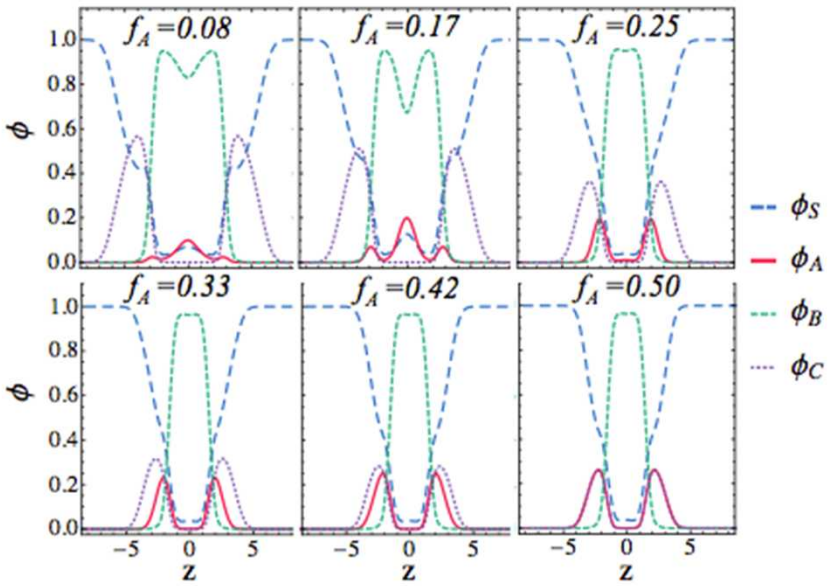
Molecular Knobs to turn:

- Block size (e.g., N_A, N_B, N_C)
- Relative block size (e.g., $f_A = N_A/(N_A+N_C)$)
- Block interaction parameters (χ_{AB}, χ_{AC}, χ_{BC}, χ_{AS}, χ_{BS}, χ_{CS})

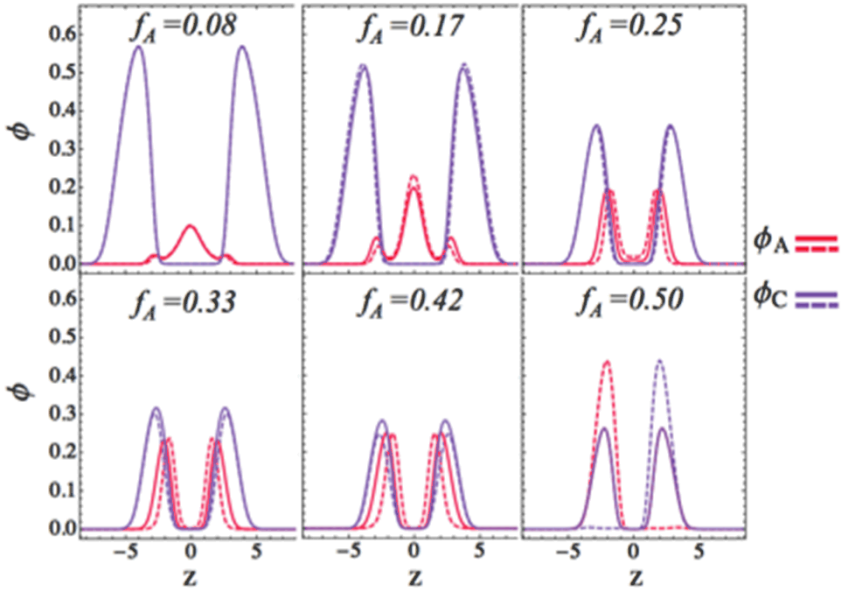


Schematic of SCFT sheet structures: a) bilayer; b) doubly mixed bilayer; c) mixed monolayer; and d) segregated monolayer

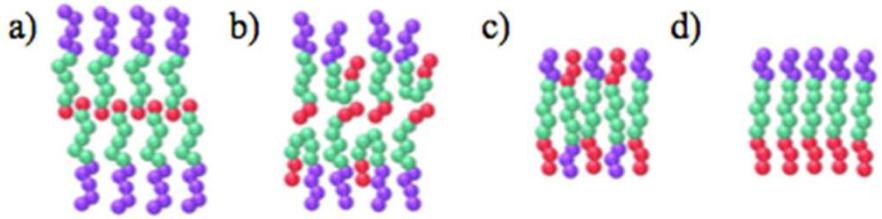
Predicting Molecular Orientation/Position



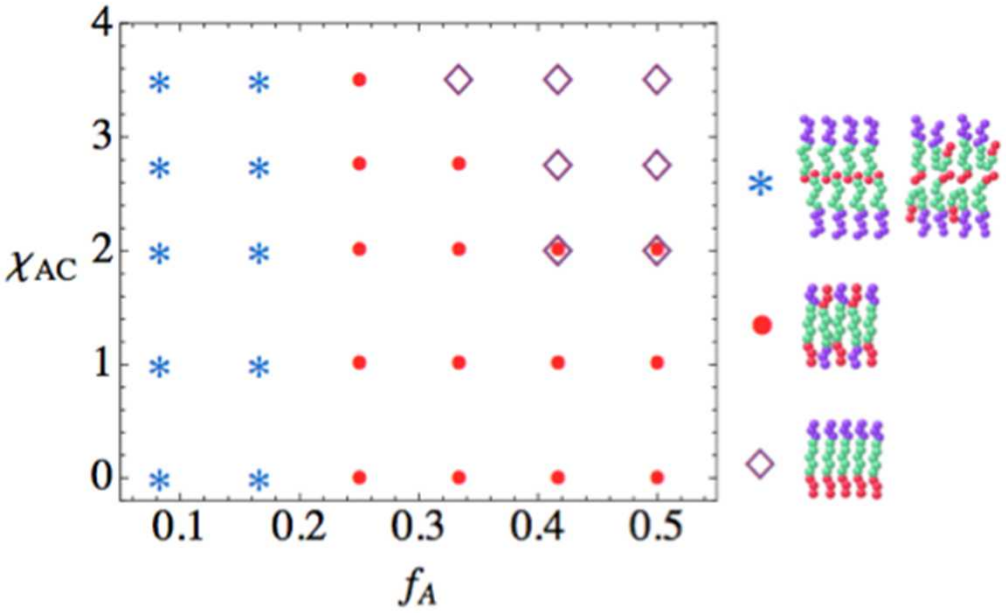
Volume fraction profiles in the direction z (nm) normal to the sheet for an ABC triblock with χ_{AC} = 0.



Comparison of volume fraction profiles in the direction z (nm) normal to the sheet for an ABC triblock with χ_{AC} = 0 (solid) and χ_{AC} = 3.5 (dashed).



Predicting Self-Assembled Morphology

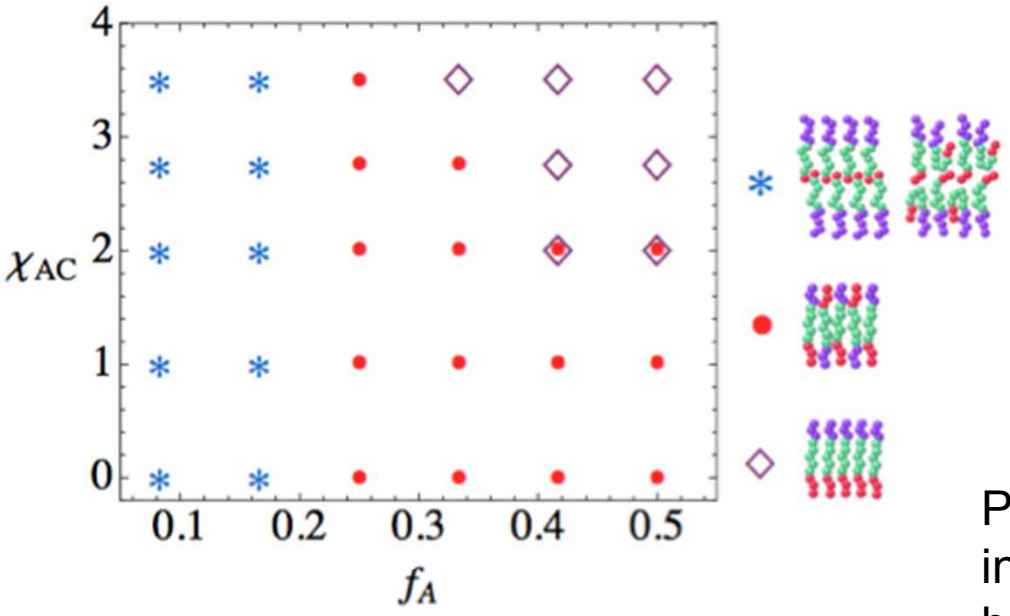


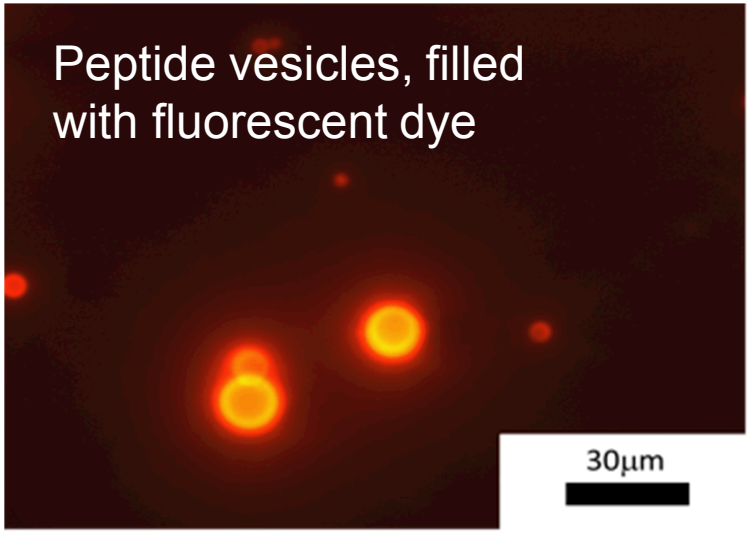
Volume fraction profiles inform predictive phase diagram of sheet morphology as a function of interaction asymmetry χ_{AC} and molecular asymmetry $f_{A.}$

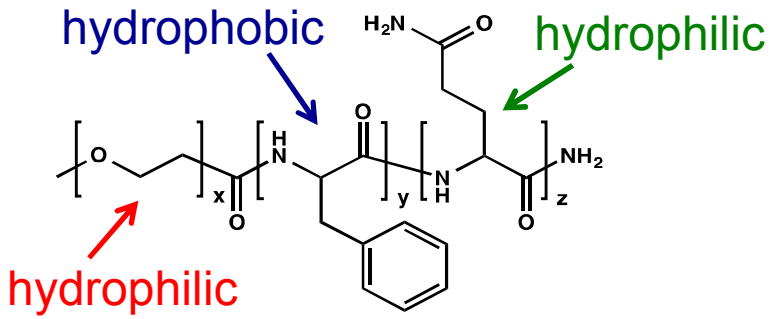
Asymmetric monolayers are likely most desirable for vesicle/tubule formation.

C.L. Ting, et al. *Soft Matter* (2016) DOI: 10.1039/C5SM01447F

Predicting Self-Assembled Morphology



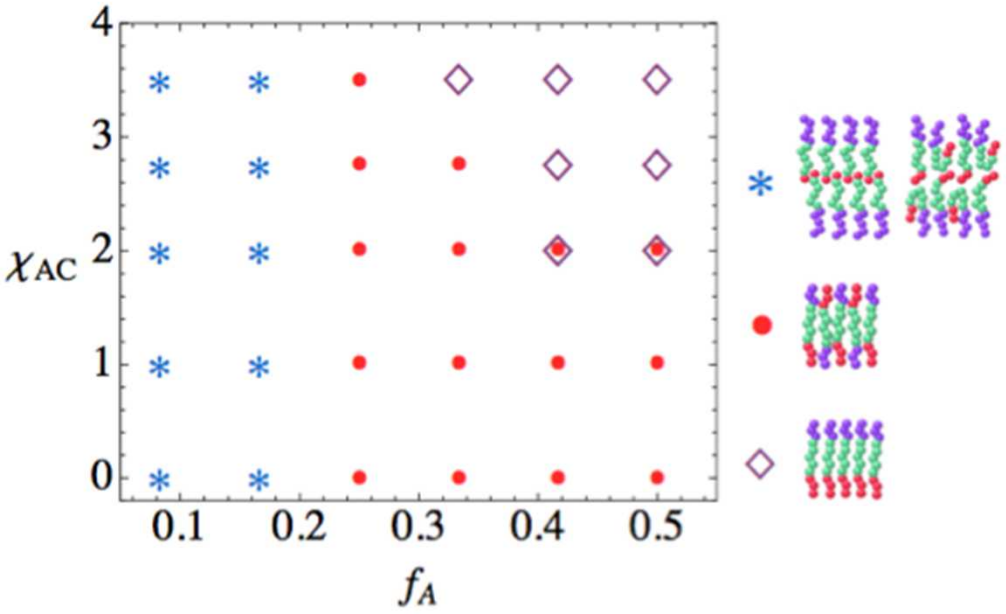


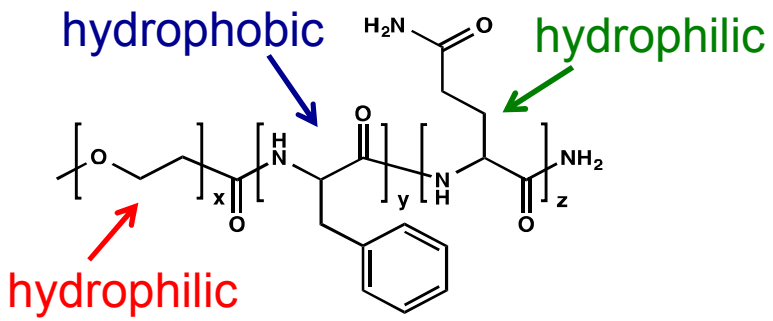


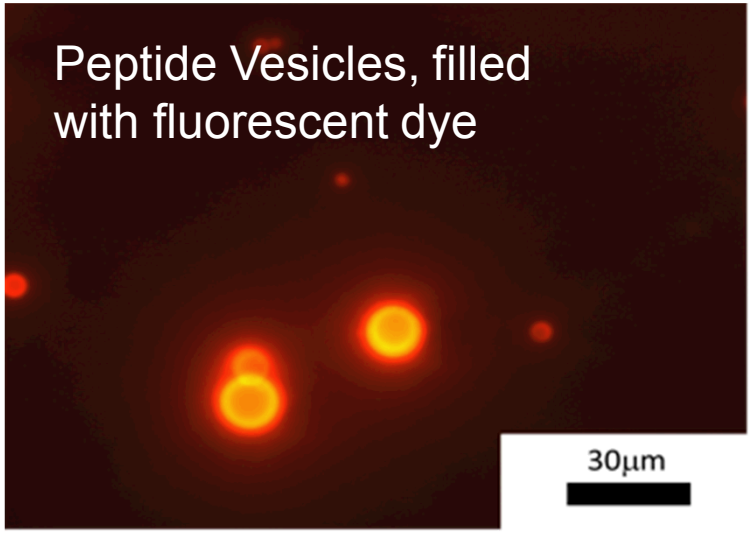
Peptides were designed to incorporate dissimilar hydrophilic blocks (polyglutamine and PEG) , flanking a hydrophobic core (polyphenylalanine).

Synthesized triblock peptides self-assemble in water to form hollow vesicles, consistent with predictions from SCFT.

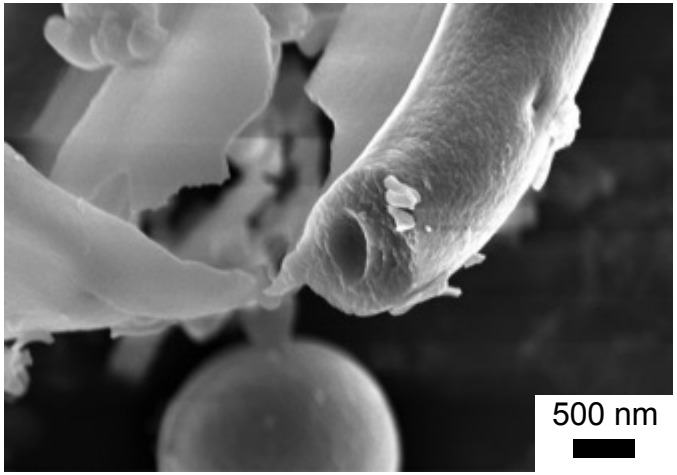
Predicting Self-Assembled Morphology







Nanotubes emerge with increased glutamine block size



Take Home Messages

Sandia National Laboratories

- ✓ MTs are complex supramolecular nanostructures, formed as dynamic assemblies through the aggregate interactions of ab tubulin dimers and secondary biomolecules.

- ✓ Designing synthetic peptides with key aspects of composite, multifunctional building blocks, enables dynamic assembly mediated by
  - pH
  - Ionic strength
  - Secondary molecular interactions
    - ✧ charged surfactants
    - ✧ diols/saccharides

- ✓ Computation can be used as a powerful tool in the design of composite molecular building blocks and understanding of supramolecular behavior.

Acknowledgements

Special Thanks to:

- Bonnie McKenzie (SNL) for Scanning Electron Microscopy
- Dr. Jon Ihlefeld for use of the Atomic Force Microscope
- Lance Miller for Mass Spectrometry

Thank you!

This work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering, Biomolecular Materials Program (KC0203010).

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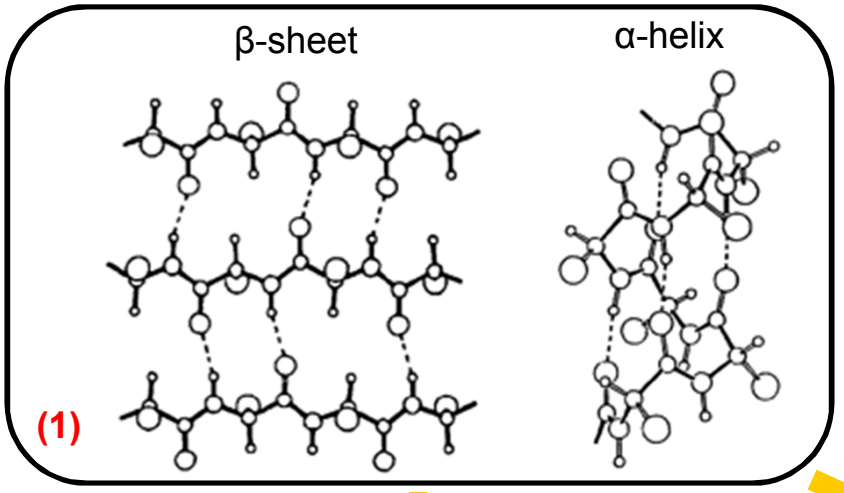
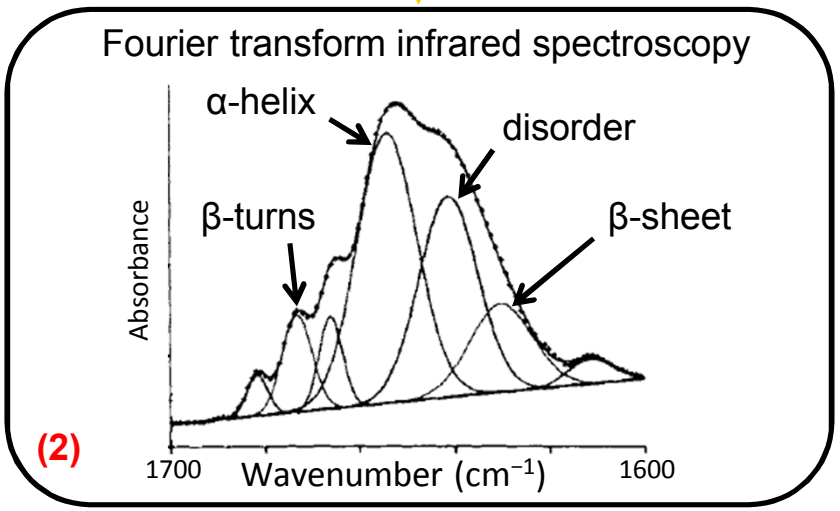
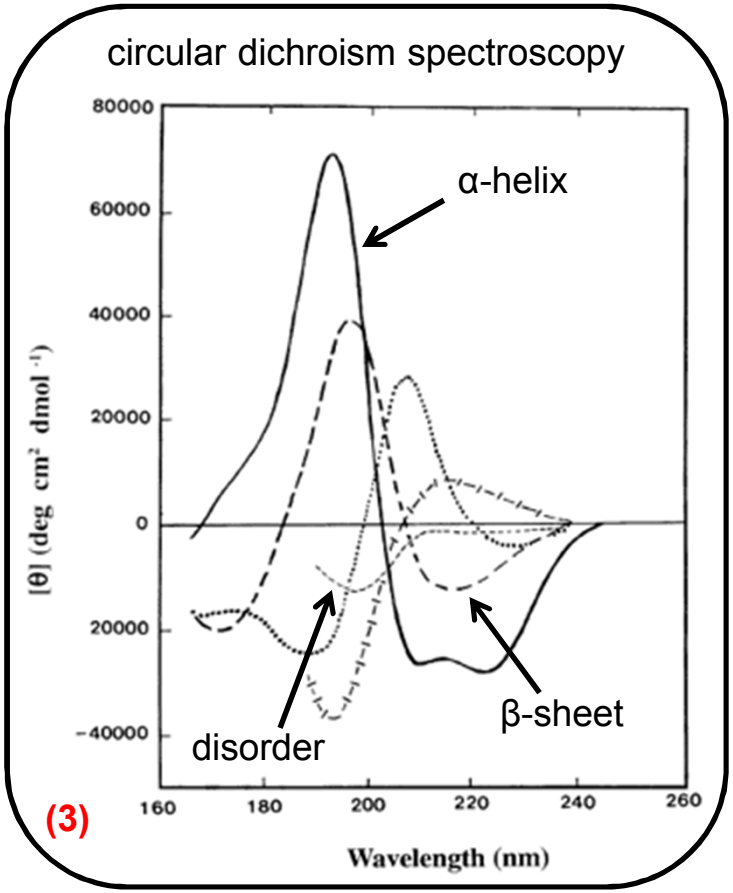
Backup Slides

Peptide Secondary Structure

Ordered peptide conformations exhibit unique spectroscopic signatures

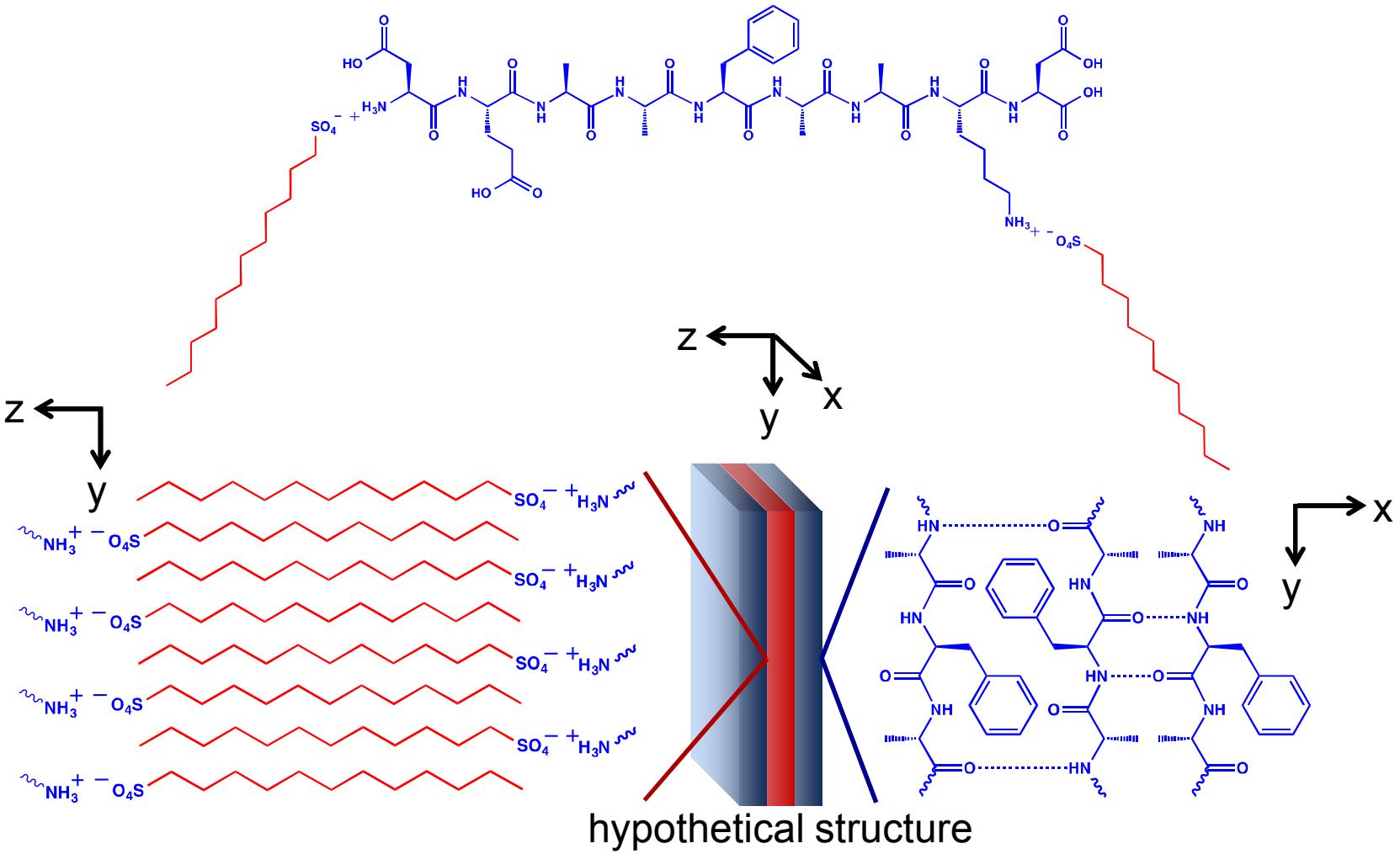






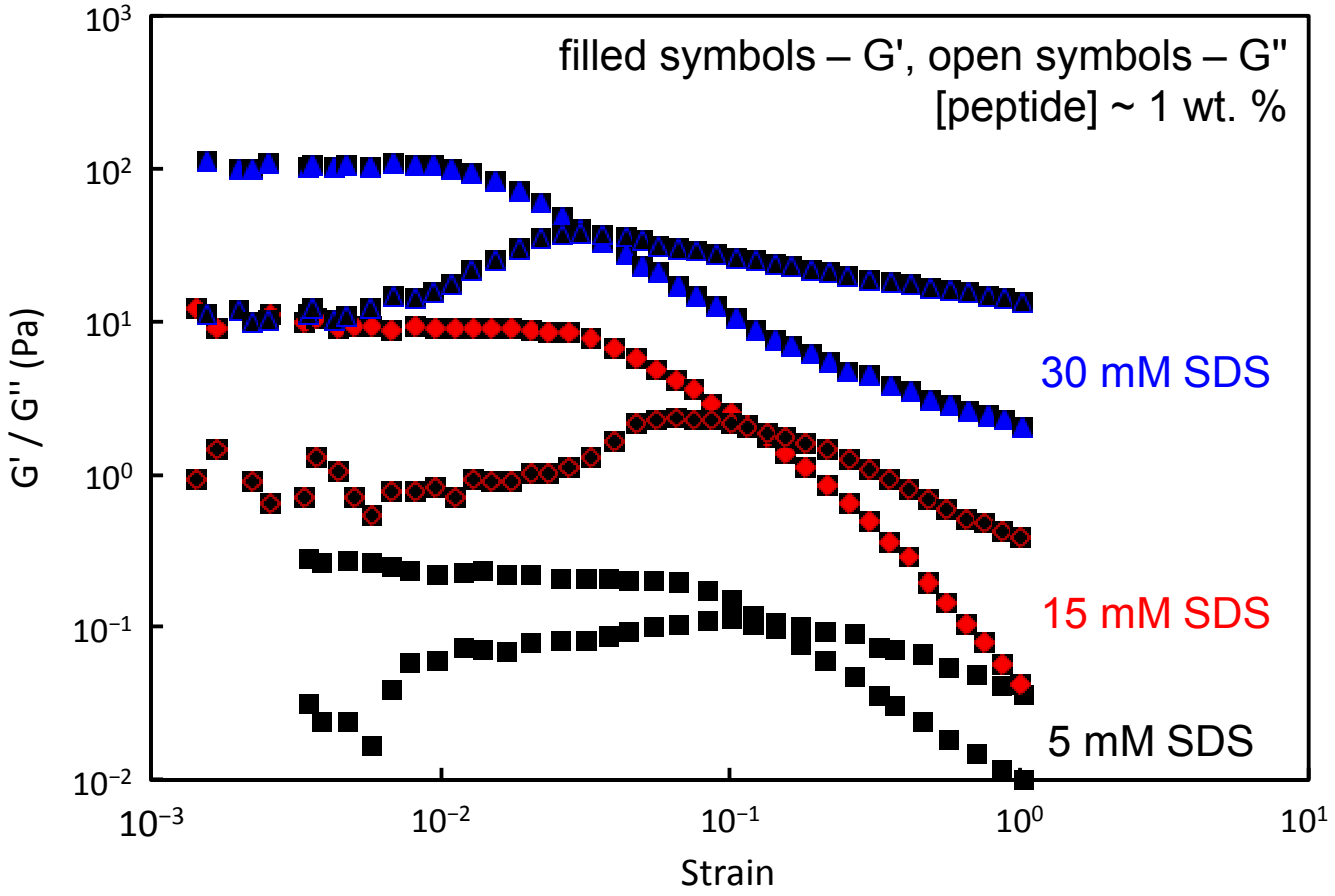
(1) Bandekar, J. *Biochim. Biophys. Acta* **1992**, *1120*, 123.
(2) Byler, D.M.; Susi, H. *Biopolymers* **1986**, *25*, 469.
(3) Kelly, S.M.; *et al. Biochim. Biophys. Acta* **2005**, *1751*, 119.

Proposed Structure of Assembled "Bola" Peptide



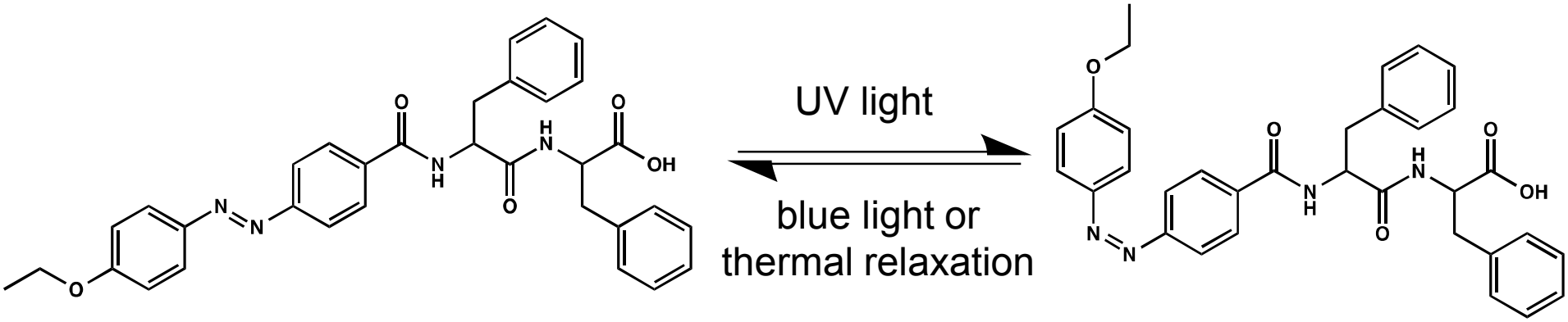
Gel Rheology

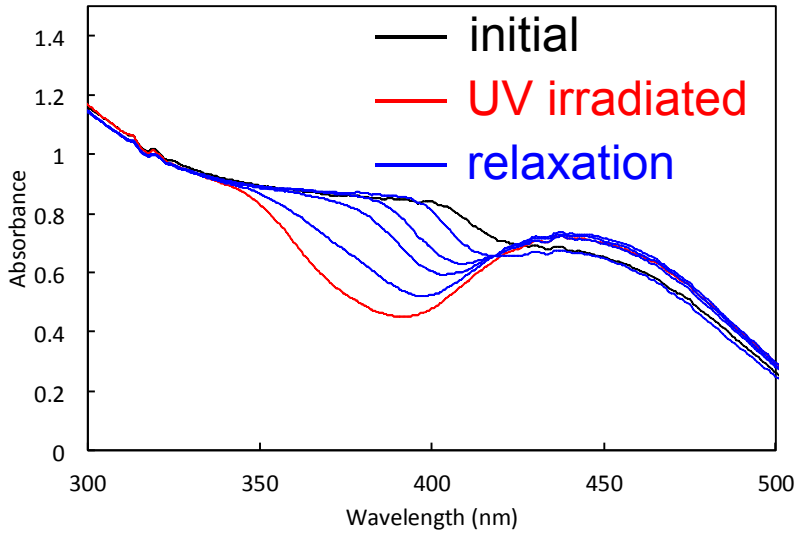
Peptide-surfactant hydrogels show solid-like behavior (G' > G") even at ultra-low loading of surfactant



Current Directions: Light-Responsive Assembly

Azobenzene functionality may allow control of peptide self-assembly through light-induced conformation changes





with Prof. Dominic McGrath and Edgardo Hernandez (U of AZ)