SAND2015-7195C

U.S. DEPARTMENT OF ENERGY

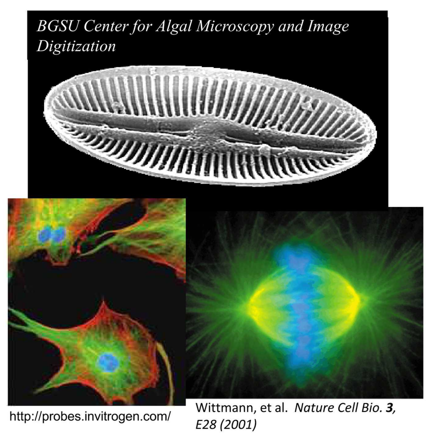
Active Assembly of Dynamic and Adaptable Materials: *Artificial Microtubules*

PI: George Bachand (gdbacha@sandia.gov) Task Lead: Erik Spoerke (edspoer@sandia.gov)

Co-PIs: Mark Stevens, Darryl Sasaki

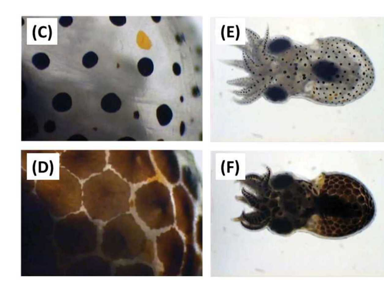
Sandia National Laboratories, Albuquerque, NM USA

Project Description

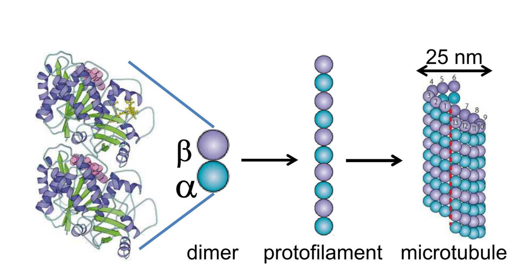


Programmatic Goal:

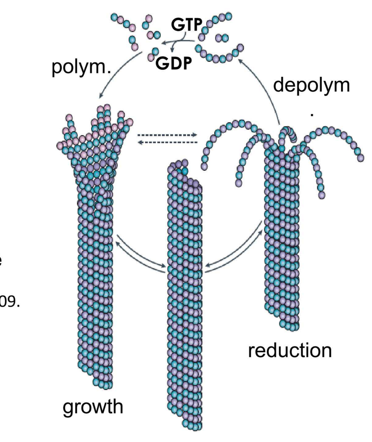
Within the scope of the *Artificial Microtbules* task, we aim to combine theory and experiment to explore synthetic molecular systems that mimic elements of form and function found in natural, energy consuming protein assemblies, such as microtubules (MTs).



E. Kreit, et al. Journal of the Royal Society, Interface / the Royal Society (2012)



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



Target Microtubule Characteristics:

- Self-assembly from nanoscale building blocks
- Cooperative $\alpha-\beta$ dimer asymmetry
- Dynamic, programmable assembly
- Cooperative molecular interactions
- Controlled nanostructure morphology
- Motility and transport

Recent Progress

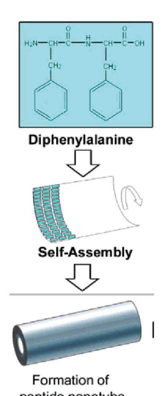
Modified Dipeptide Assembly

Brad Jones, Jill Wheeler, Alina Martinez, David Wheeler, Dominic McGrath, and Erik Spoerke

Inspiration: *Diphenylalanine dipeptides are known to self-assembly with crystalline order into tubules.*

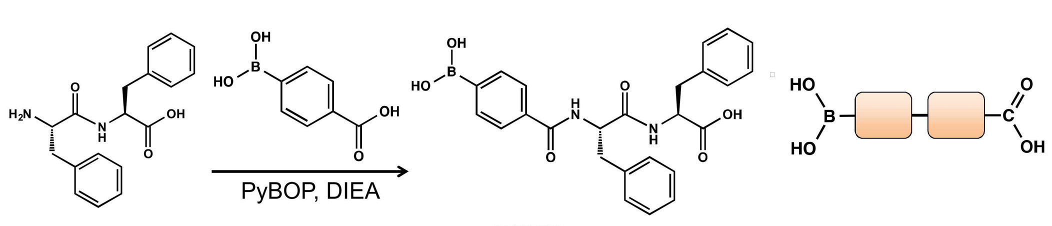
Scientific Challenge: *Can we modify this simple dimer building block for programmable self-assembly?*

Technical Approach: *Incorporate diol/polyol-reactive boronic acids into diphenylalanine chemistry.*



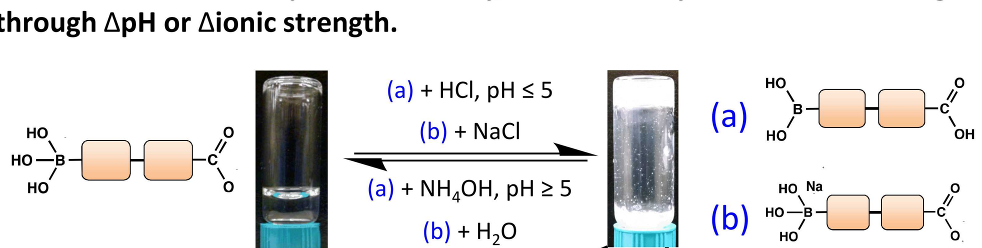
O. Carny, et al. *Nano Lett.* (2006) 5(6) 1594.

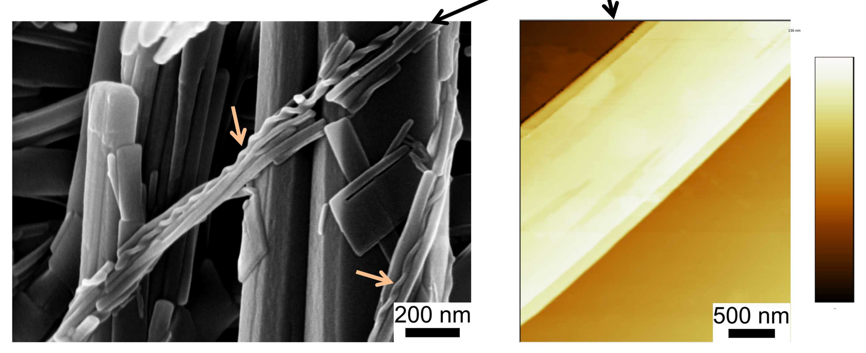
Model boronic acid diphenylalanine dipeptide: BFF



Jones, B.H., et al. *Chem. Comm.*, (2015) *In Revision.*
Jones, B.H. et al. *Tet. Lett.* (2015) In Review.

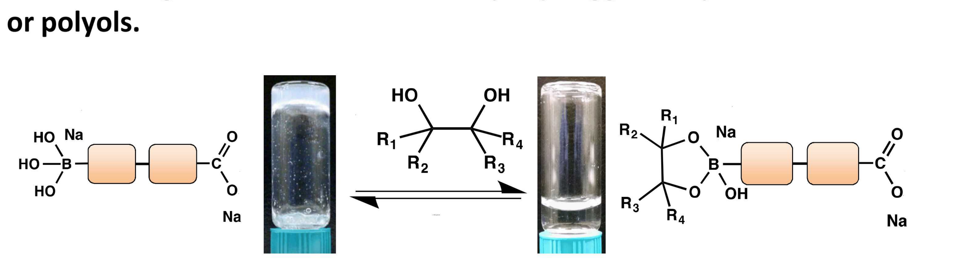
BFF shows increased aqueous solubility, and reversibly forms nanoribbon gels through ΔpH or Δionic strength.

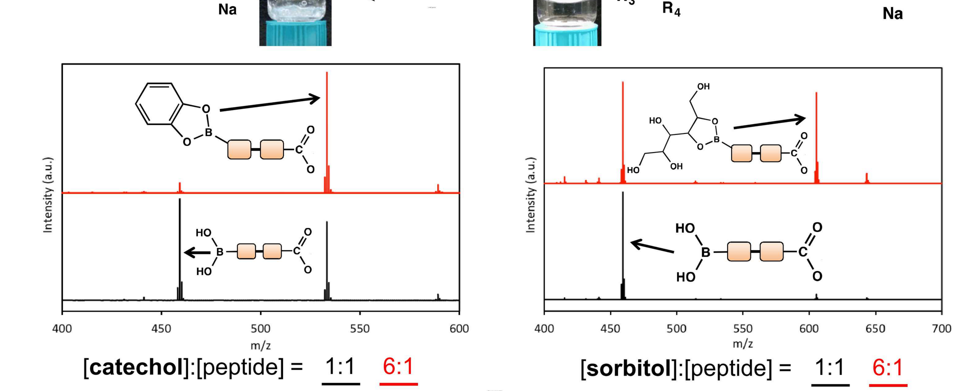




Scanning electron (left) and atomic force (right) microscopies reveal assembled BFF ribbon morphologies.

In addition, gel-sol transitions are uniquely triggered by addition of saccharides or polyols.





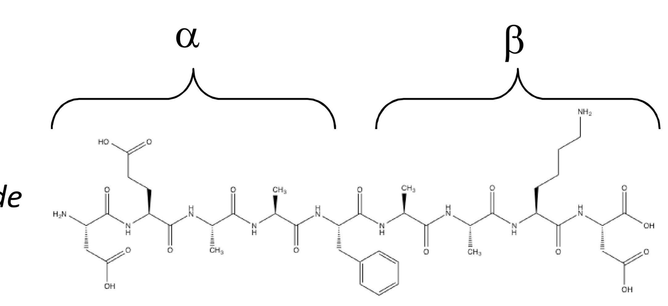
Mass spectrometry confirms boronate ester formation using catechol and sorbitol additives.

MT-Inspired Functional Block Peptides

Brad Jones, Jill Wheeler, Alina Martinez, and Erik Spoerke

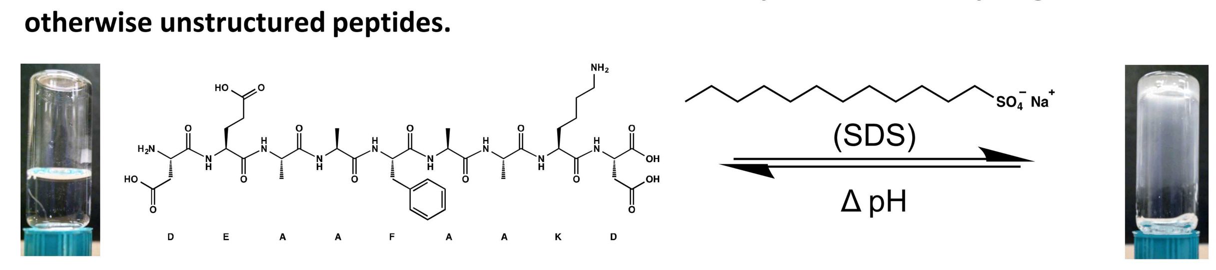
Inspiration: *MTs assemble from dimers, through interactions with secondary biomolecules (e.g., GTP).*

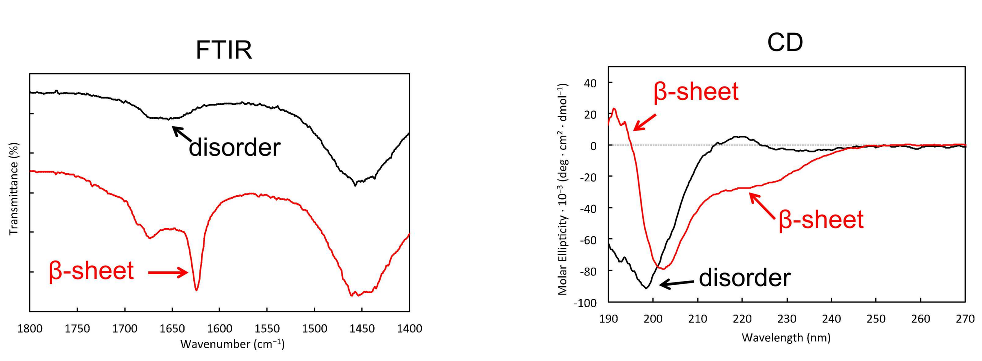
Scientific Challenge: *Can we create a peptide analog that follows this assembly motif?*



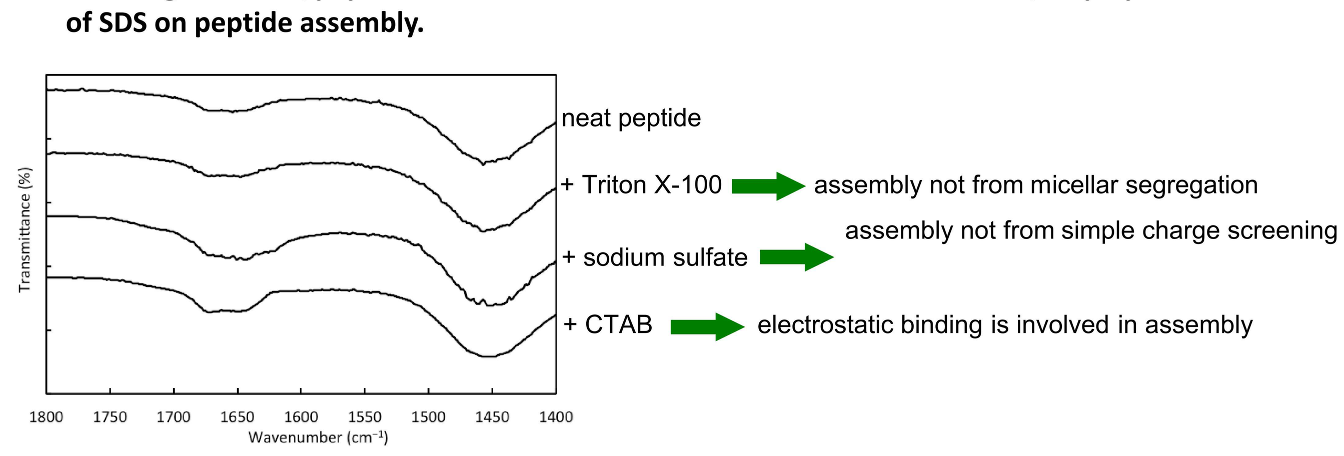
Technical Approach: *Create a "bola" peptide with an enzymatically cleavable linkage, that assembles through interactions with secondary molecular interactions.*

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

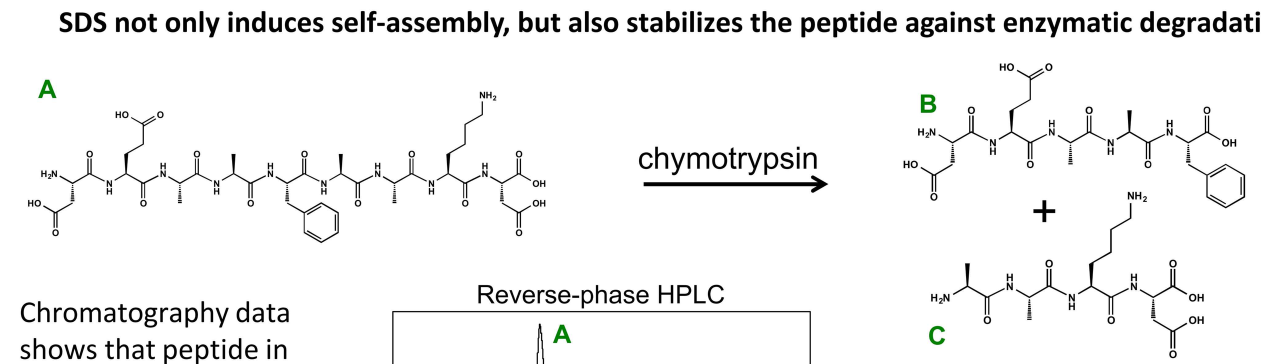




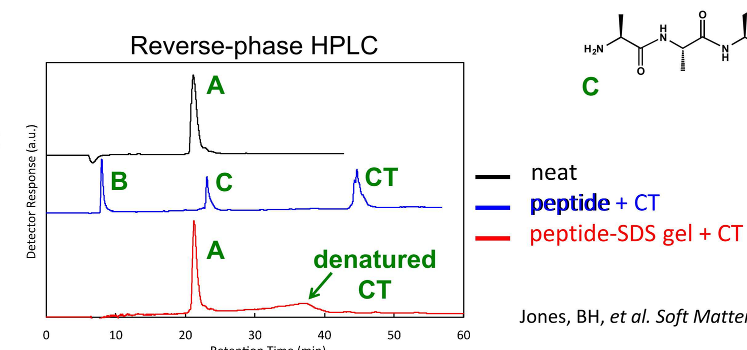
FTIR and Circular Dichroism (CD) spectroscopically confirm changes in peptide secondary structure resulting from SDS/peptide interactions and confirm combined electrostatic/amphiphilic influence of SDS on peptide assembly.



SDS not only induces self-assembly, but also stabilizes the peptide against enzymatic degradation.



Chromatography data shows that peptide in SDS/peptide gels does not cleave when exposed to chymotrypsin. Moreover, the chymotrypsin is evidently denatured by the SDS.

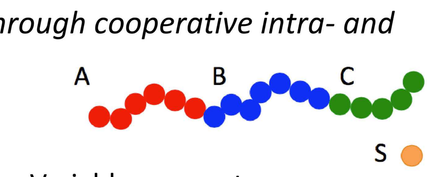


Jones, BH, *et al. Soft Matter* (2015) **11**(18), 3572-3580.

Simulation-Inspired Triblock Assemblies

Christina Ting, Brad Jones, Jill Wheeler, Amalie Frischknecht, Mark Stevens, and Erik Spoerke

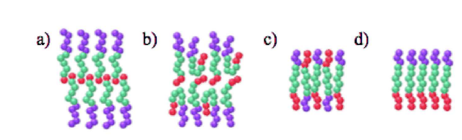
Inspiration: *Tubulin assembly is regulated through cooperative intra- and intermolecular interactions.*



Scientific Challenge: *Can we identify a multicomponent peptide building block capable of controlled assembly? Can we synthesize a simulation-inspired peptide that assembles as predicted?*

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

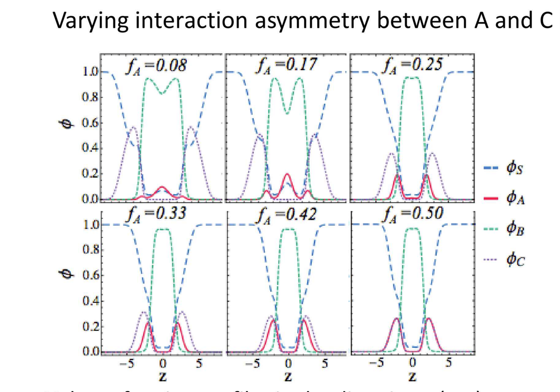
Technical Approach: *Combine self-consistent field theory (SCFT) and peptide chemistry to create a novel self-assembling triblock system.*



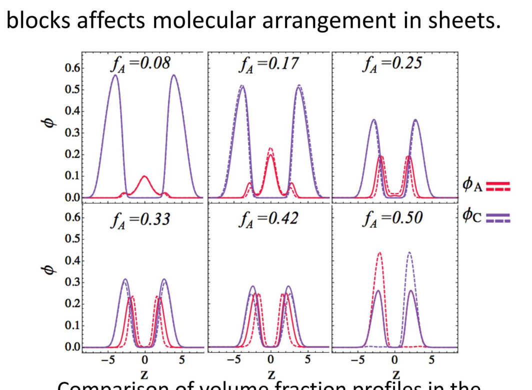
Schematic of SCFT sheet structures: a) bilayer; b) doubly mixed bilayer; c) mixed monolayer; and d) segregated monolayer

Volume fraction profiles identify ABC molecular arrangements and block associations in an assembled sheet morphology.

Varying interaction asymmetry between A and C blocks affects molecular arrangement in sheets.

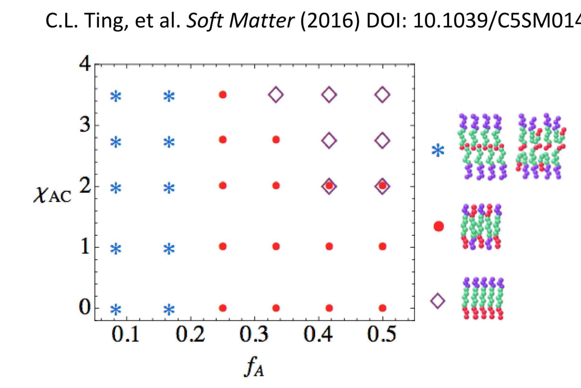


Volume fraction profiles in the direction z (nm) normal to the sheet for an ABC triblock with $\chi_{AC} = 0$.



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

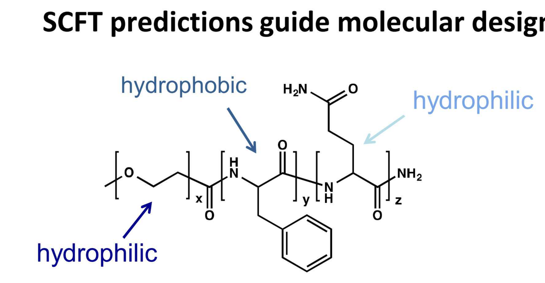
C.L. Ting, et al. *Soft Matter* (2016) DOI: 10.1039/C5SM01447F



Determined volume fraction profiles can be used to assemble a predictive phase diagram of sheet morphology as a function of interaction asymmetry χ_{AC} and molecular asymmetry f_A.

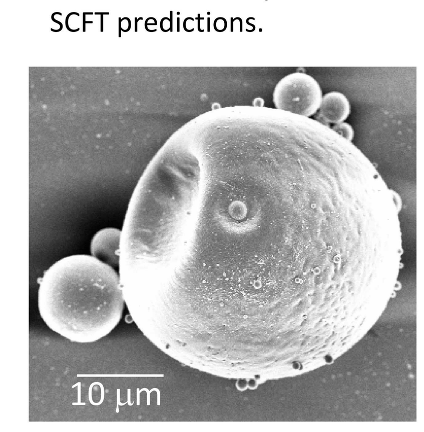
Asymmetric monolayers are likely most desirable for vesicle/tubule formation.

SCFT predictions guide molecular design of new triblock peptide.



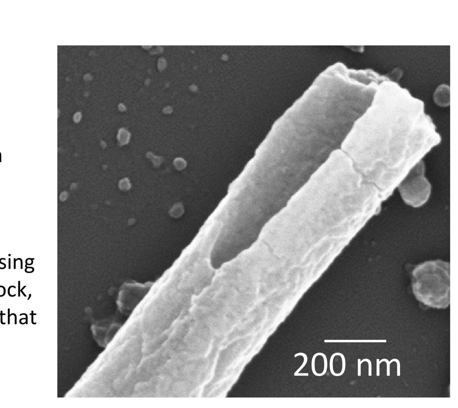
Peptide design incorporates dissimilar hydrophilic blocks (polyglutamine and PEG) , flanking a hydrophobic core (polyphenylalanine).

Triblock molecules were synthesized with block volume fractions approximating ratios predicted by SCFT to form asymmetric monolayers. Dissolved in polar organic solvents and precipitated/assembled in water, the simulation-inspired ABC triblock molecule forms spherical vesicles (below, left), consistent with expectation based on SCFT predictions.



The versatility of peptide chemistry allows systematic variation of triblock composition and interaction parameters.

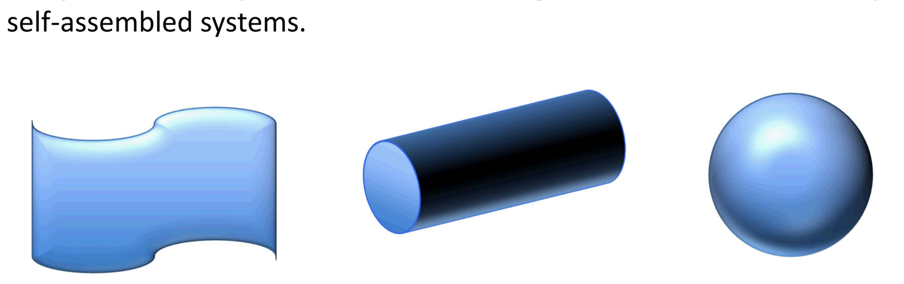
Initial variations in peptide composition, such as increasing the size of the glutamine block, result in a shift in assembly that produces tubular structures (right).



Future Plans

Looking forward, we plan to emphasize how developing alternative, bio-inspired synthetic systems can be used to manipulate the organization, transport, and function of biomolecular and synthetic nanomaterials.

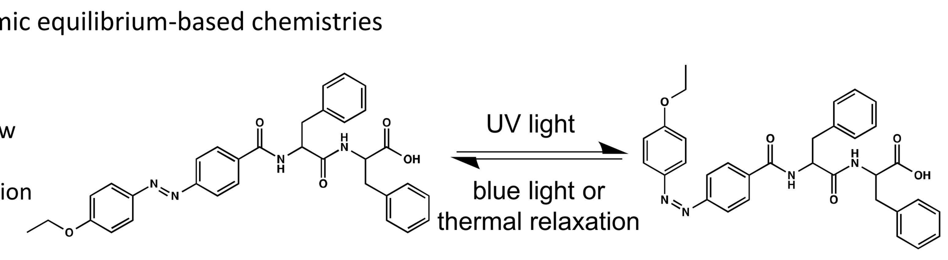
Employ versatile peptide chemistry, advanced characterization, and computation to improve our understanding of the drivers behind morphology in self-assembled systems.



Continue exploiting alternative approaches to regulate dynamic peptide assembly/disassembly, particularly through changes in molecular conformation, electrostatics, or cooperative bonding.

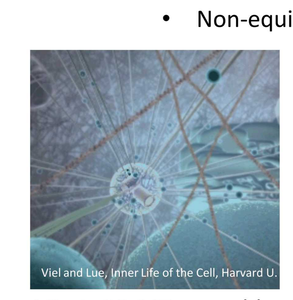
- Light
- Heat
- Secondary (Bio)molecules
- Stochastic, dynamic equilibrium-based chemistries

Azobenzene functionality (with Prof. Dominic McGrath) may allow control of peptide self-assembly through light-induced conformation changes



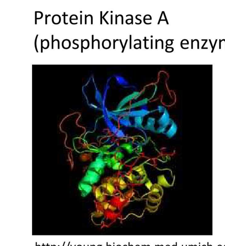
Explore secondary materials interactions with assembled peptides to drive organization into larger, multi-dimensional structures and to facilitate unique supramolecular functions

- Environmentally responsive, adaptive materials
- Non-equilibrium behaviors (e.g., alternative motility, triggered materials chemistry)



Mimic 3D MT assembly

Protein Kinase A (phosphorylating enzyme)

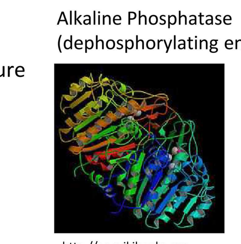


http://young.biochem.med.umich.edu

Controlled phosphorylation of peptides may be used to control peptide assembly or nanostructure interactions with secondary materials.

Candidate Phosphorylation peptides
- Protein kinase A (R-R-X-S-O)
- Casein Kinase II (S-X-X-E)

Alkaline Phosphatase (dephosphorylating enzyme)



http://en.wikibooks.org

National Nuclear Security Administration

We gratefully acknowledge support for this work from the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering, Biomolecular Materials Program (KC0203010).

Sandia National Laboratories is a multi-program laboratory operated by Sandia Corporation, a wholly owned subsidiary of Lockheed Martin Company, for the US Department of Energy's National Nuclear Security

Sandia National Laboratories is a multimission laboratory managed and operated by National Technology & Engineering Solutions of Sandia, LLC, a wholly owned subsidiary of Honeywell International Inc., for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA0003525.

Sandia National Laboratories