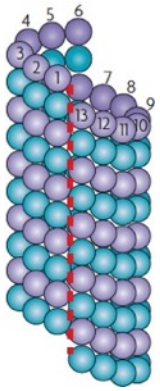
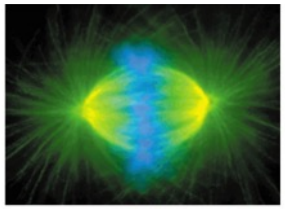
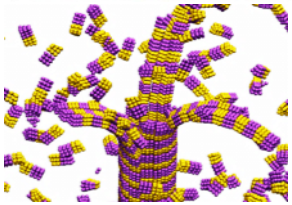
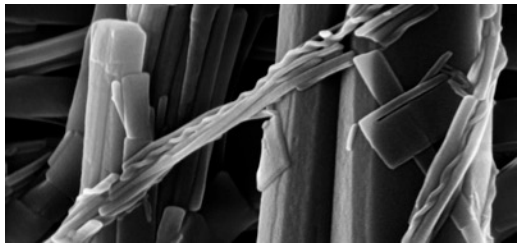

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Exceptional service in the national interest

Bio-Inspired Dynamic Supramolecular Assembly Controlled through Molecular Conformation

SAND2017-13061C

Erik D. Spoerke, Ph.D.

Brad H. Jones, Alina Martinez, Dominic McGrath (U. Az), Jonathan Bollinger, Mark Stevens, and George Bachand

Sandia National Laboratories
Albuquerque, NM

Materials Research Society
2017 Fall Meeting

November 26 - December 1, 2017
Boston, MA

U.S. DEPARTMENT OF ENERGY

NNSA National Nuclear Security Administration

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Inspiration: Microtubules (MTs) Impact a Huge Range of Biological Functions

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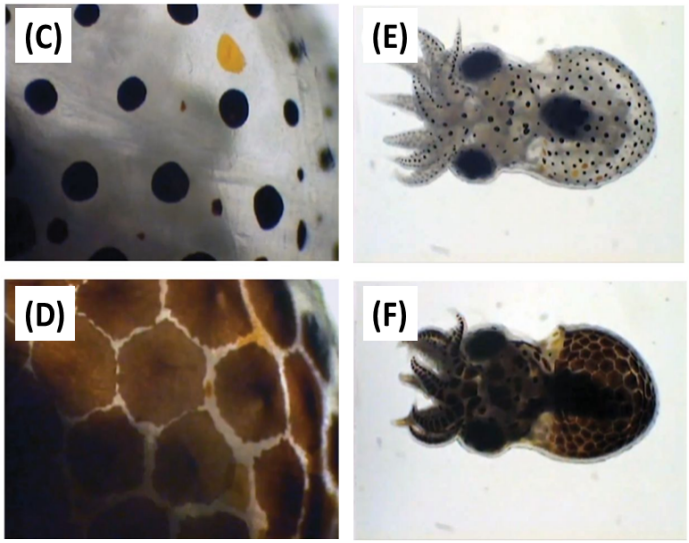
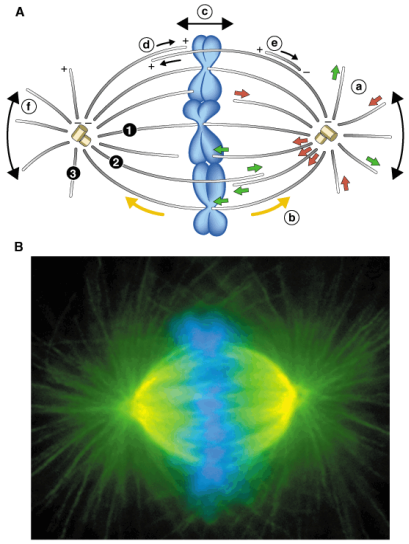
The dynamic, biologically programmable nanostructure and chemistry of MTs enable remarkable function.



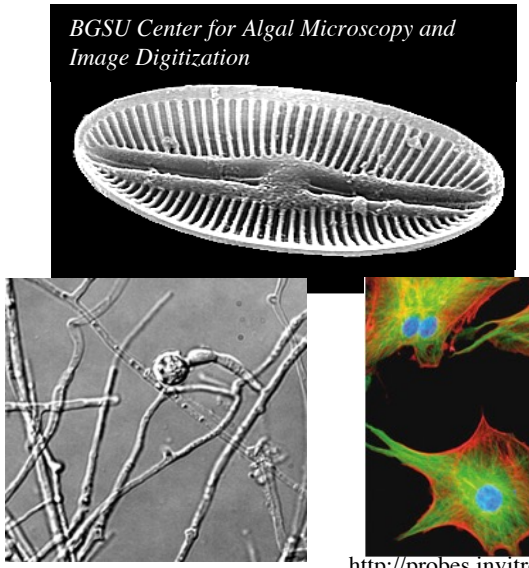
E. Kreit, *et al. J. R. Soc. Interface* (2012)

Adaptive reorganization of pigment granules in melanocytes



Wittmann, et al. *Nature Cell Bio.* ***3****, E28-E34 (2001)*

Chromosome positioning and separation during cell splitting

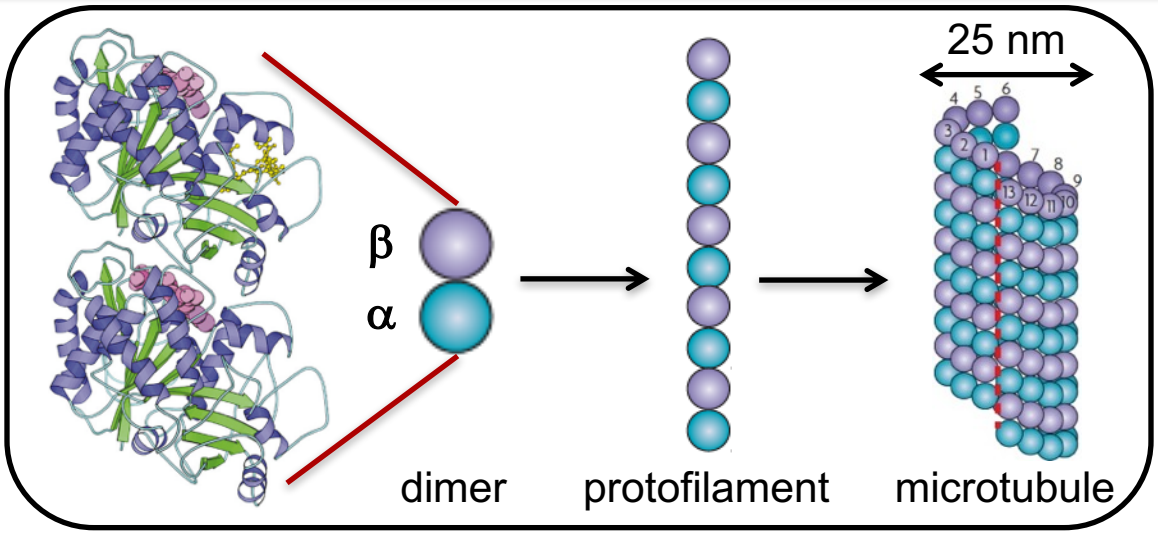


http://probes.invitrogen.com/

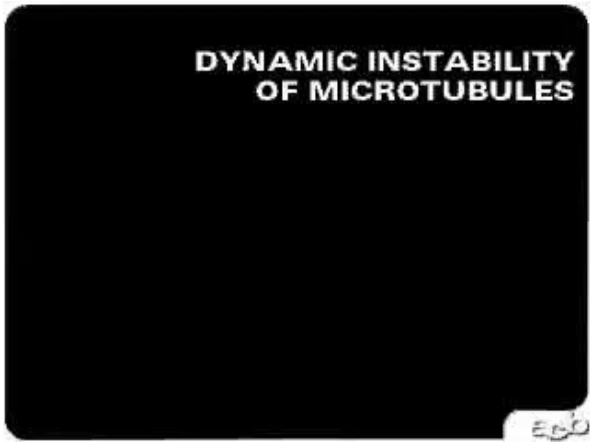
Trafficking of vesicles and macromolecule building blocks

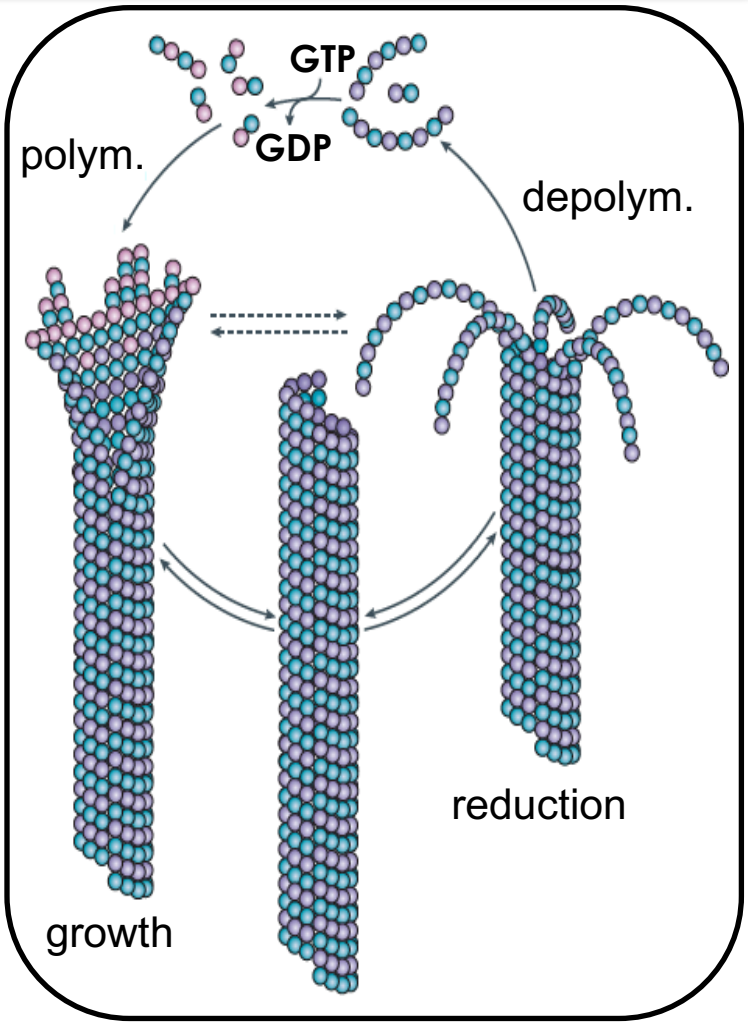
<u>Our Challenge</u>: *Exploit/mimic concepts central to MT form and function in synthetic materials to enable novel new materials behaviors.*

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.





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

Microtubules: Dynamic, Organized Protein Assemblies

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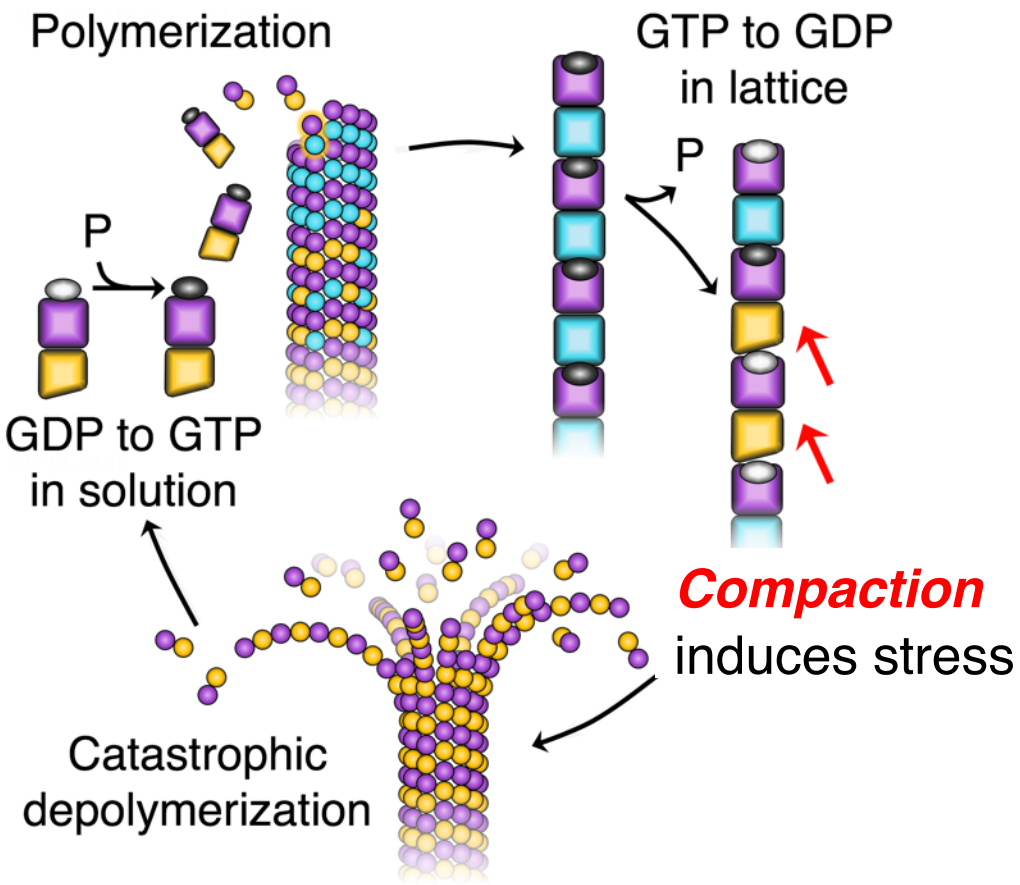
Inner Life of the Cell animation conception and scientific content by Alain Viel and Robert A. Lue. Animation by John Liebler/XVIVO.

MT Destabilization through Molecular Shape Change



Dephosphorylation of tubulin-bound GTP is hypothesized to induce molecular shape changes that destabilize the MT.

(J. Bollinger and M.J. Stevens (2017))

Using Molecular Dynamics to Simulate MT Behavior

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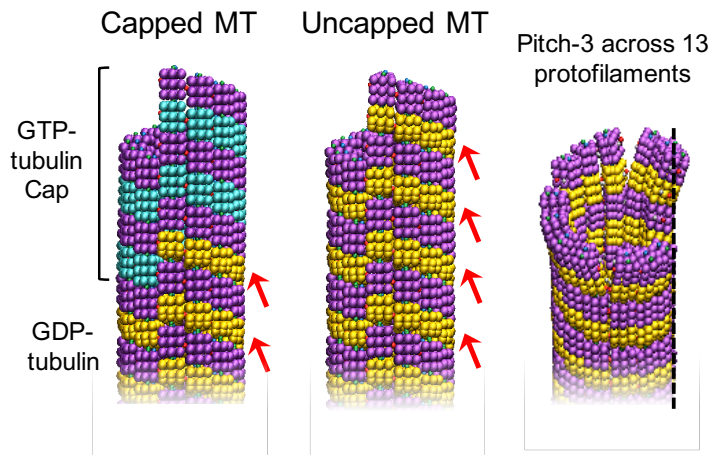
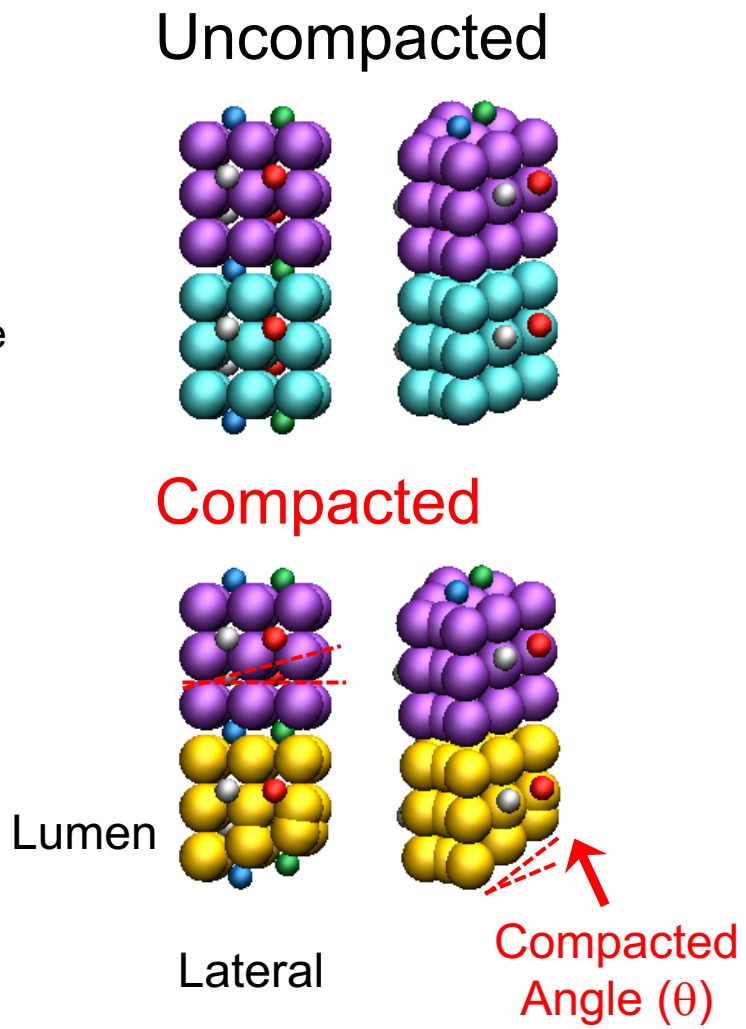
Technical Approach: Examine molecular dynamics (MD) simulations of MTs, built from a coarse-grained model of tubulin:

- Model α/β-tubulin as tubule-forming wedge-dimers with patchy attractions
- Angle $\theta=15^{o}$ mimics compaction of outer intermediate domain of a-subunit observed by cryo-EM and resembles "bent" tubulin
- Prebuild MTs with uncompacted/compacted dimers (optional cap)

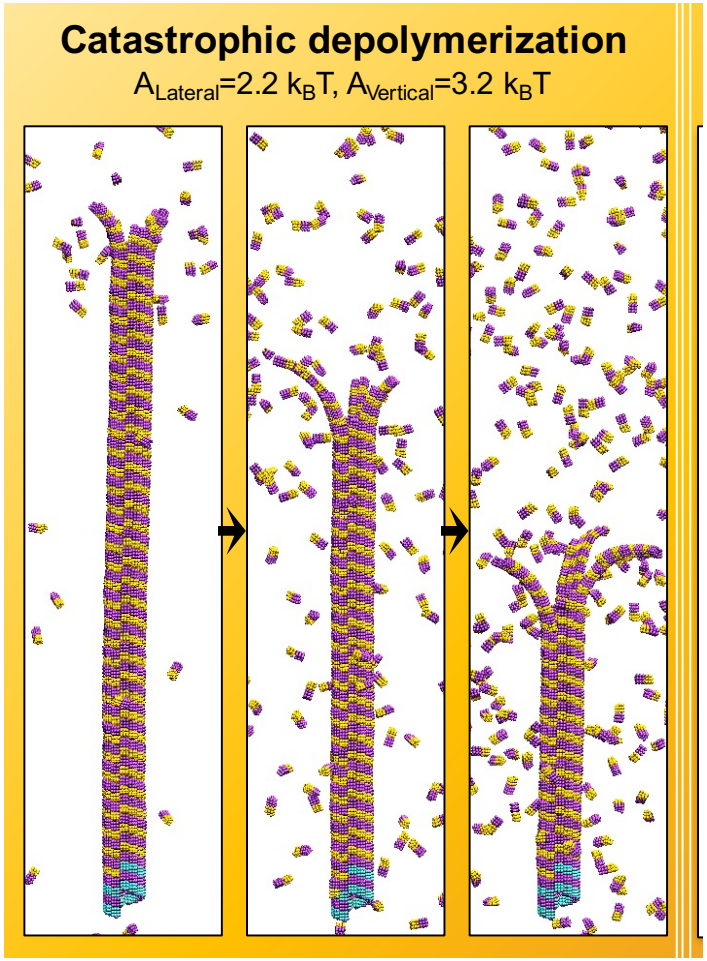




(J. Bollinger and M.J. Stevens (2017))

Strain-Inducted MT Depolymerization

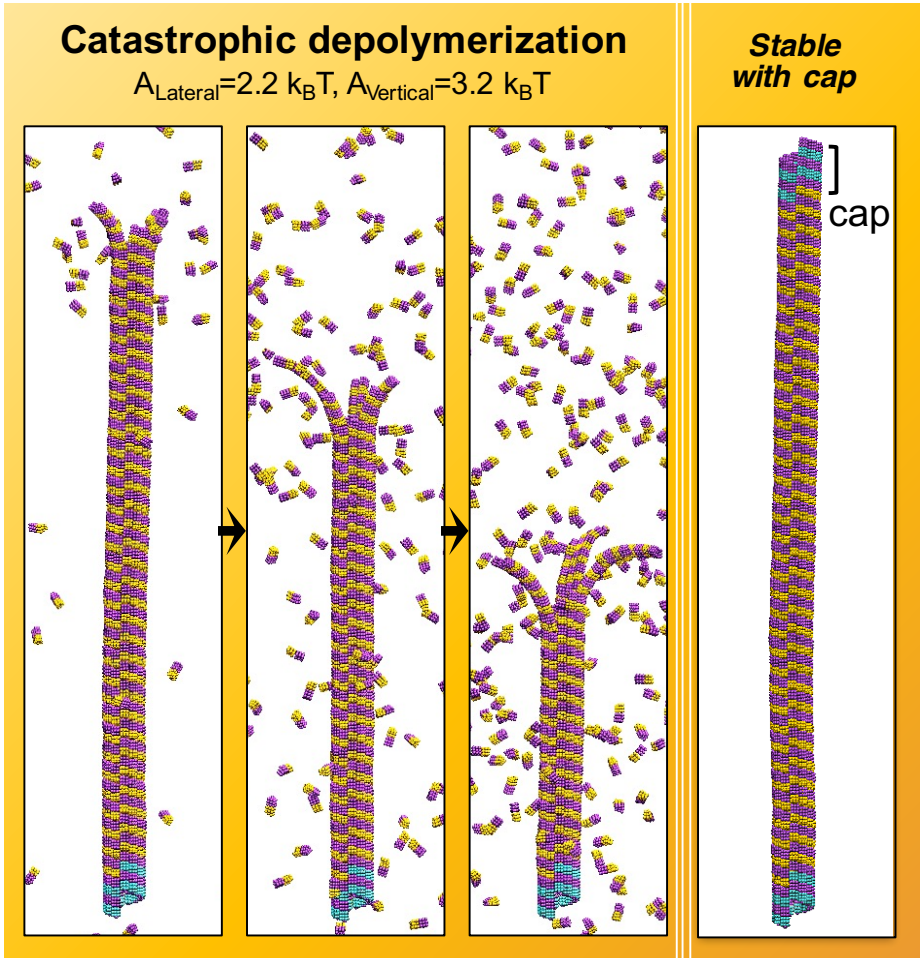
By incorporating compacted (strained) building blocks into simulated MTs, we can mimic elements of MT disassembly from GDP-strained tubulin.



(J. Bollinger and M.J. Stevens (2017))

A Stabilizing GTP Cap

The introduction of an unstrained “cap” simulates how GTP-tubulin caps can stabilize strained MTs!

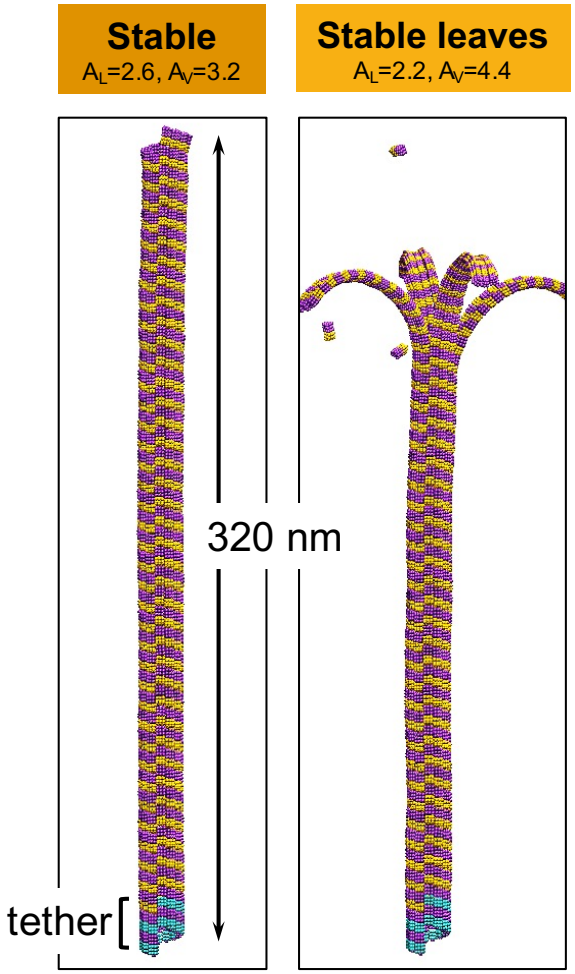


(J. Bollinger and M.J. Stevens (2017))

Balancing Stability and Strain

Strain-induced depolymerization can be overcome by stronger intermolecular interactions.

Controlling the balance of this dynamic instability means controlling balance between molecular attraction and strain-based destabilization of supramolecular nanostructures.



(J. Bollinger and M.J. Stevens (2017))

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Inspired by natural MTs and these simulated data, can we build a synthetic system to mimic this behavior?

Azobenzene derivative synthesized by Professor D. McGrath (U. Ariz.)

Peptides: Versatile Tools for Biomimetic Assembly

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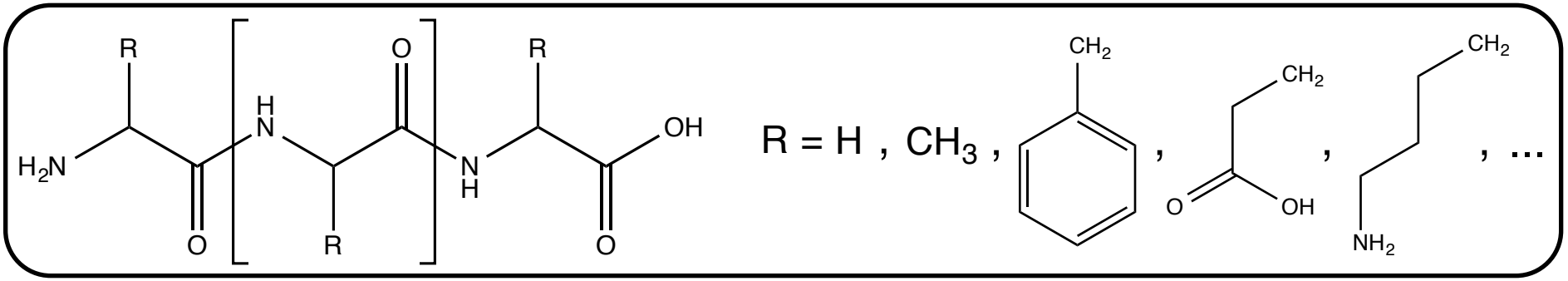
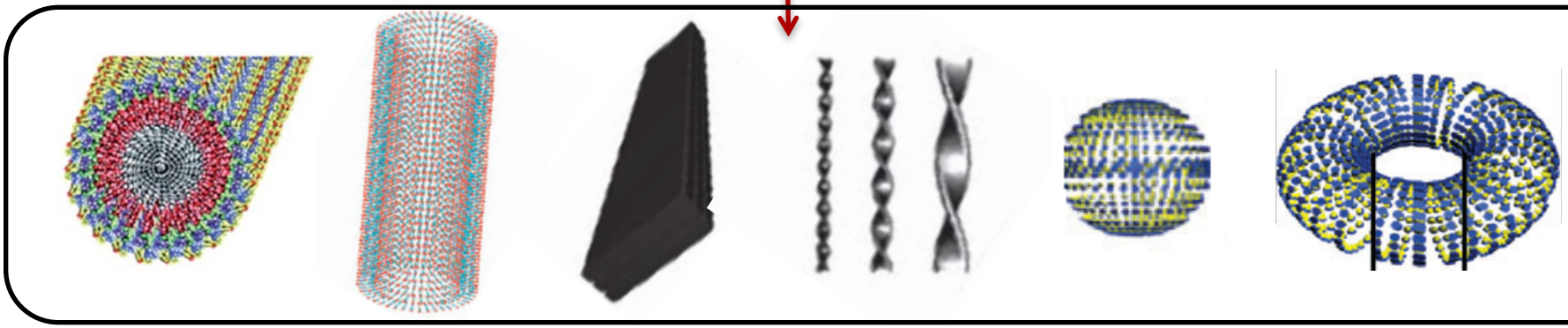
A complex balance of interactions drives spontaneous self-assembly



electrostatic interactions | hydrogen bonding | aromatic stacking | hydrophobic interactions

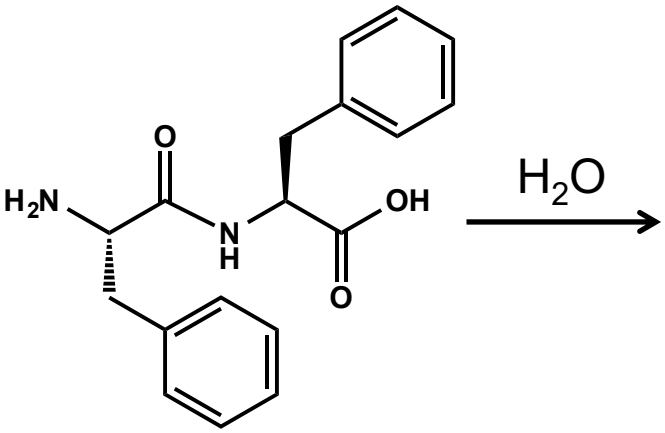
chemical environment

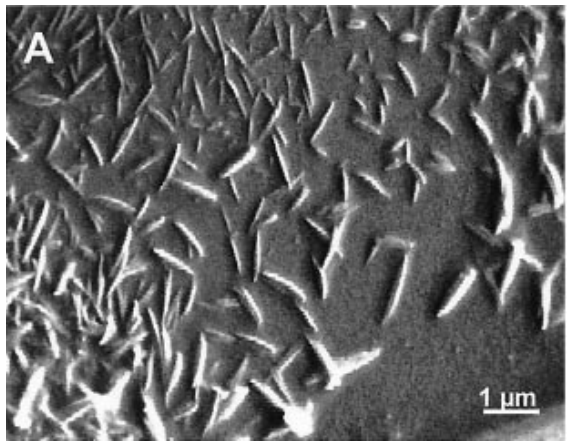


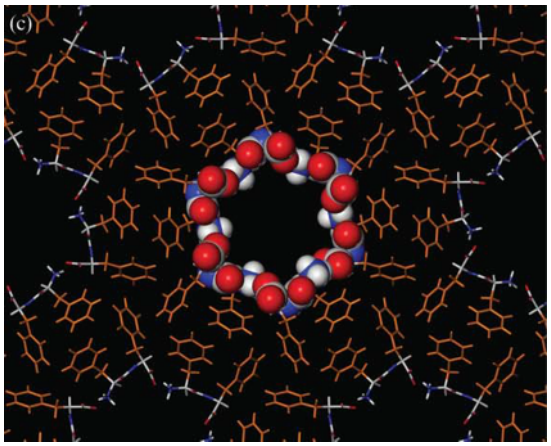
FF-Nanotube Formation

Di(phenylalanine) dipeptides will self-assemble into hierarchical nanotubes

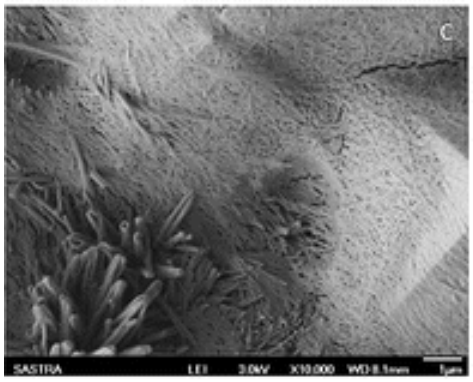
Nanotubes from di(phenylalanine)

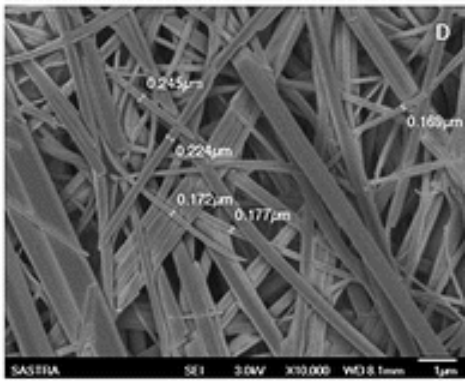






Reches, M.; Gazit, E. *Science* **2003**, *300*, 625-627; Görbitz, C.H. *Chem. Comm.* **2006**, 2332-2334.





<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.

A Conformationally-Switchable Peptide Building Block

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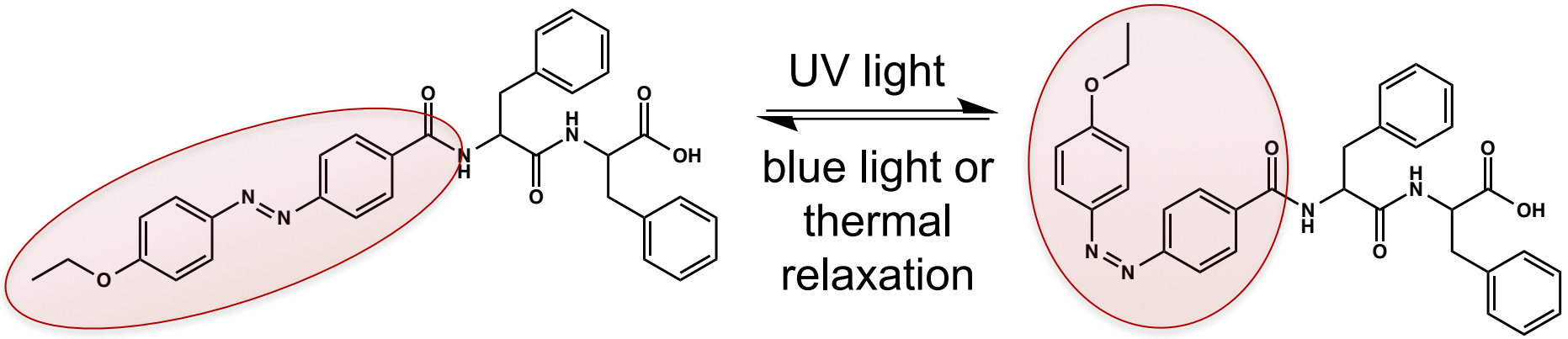
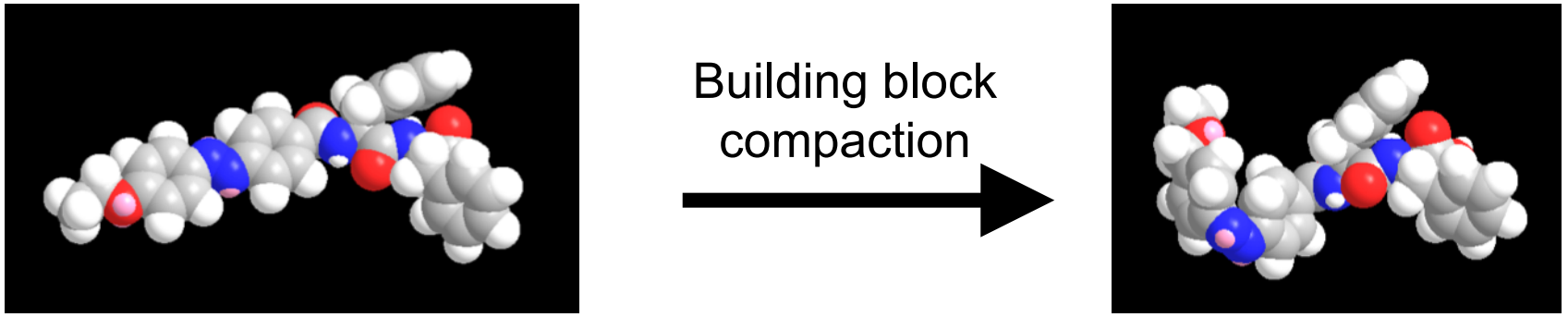
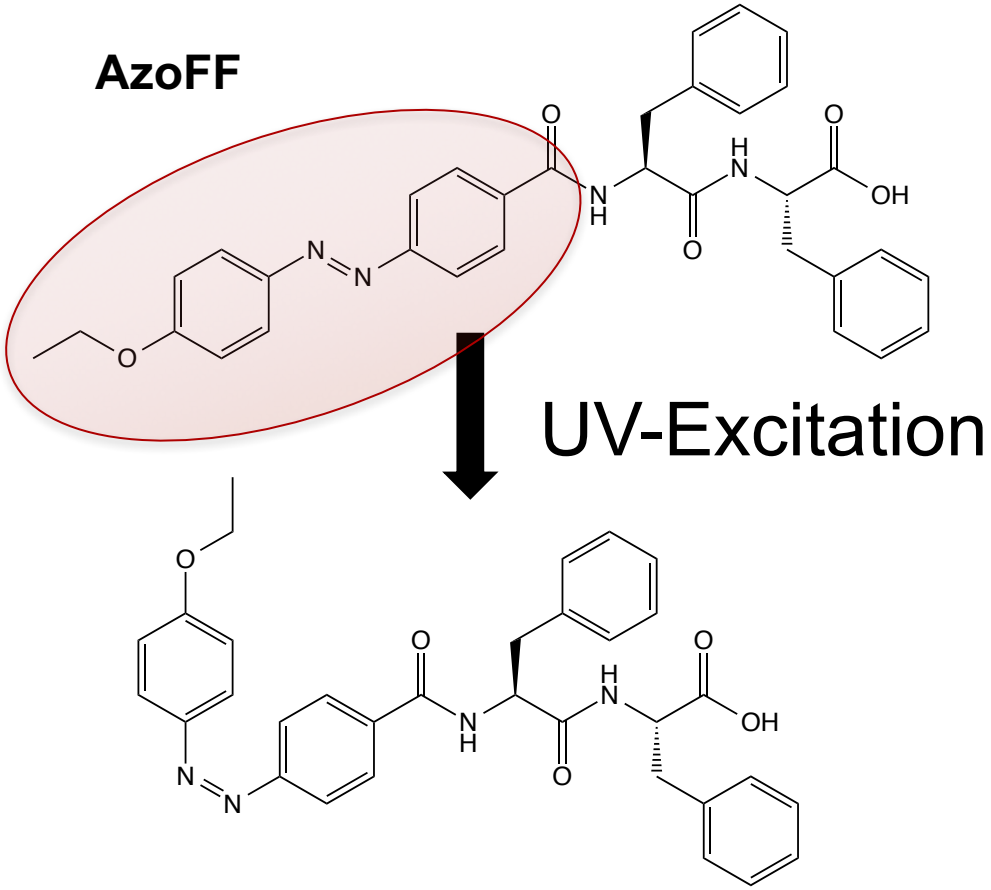
Technical Approach: Incorporate azobenzene derivatives into di(phenylalanine) dipeptides and utilize photoisomerization to induce shape changes and dynamic assembly.



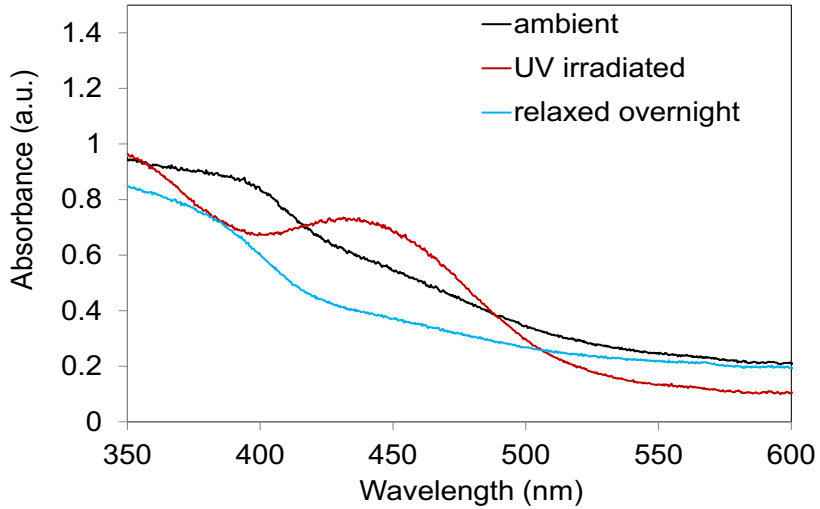


Azobenzene derivative synthesized by Professor D. McGrath (U. Ariz.)

Monitoring Molecular Conformation Change

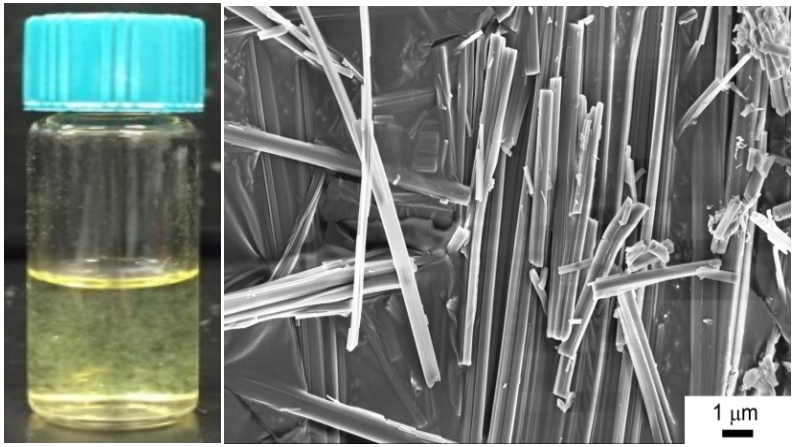


UV-Vis spectroscopy reveals reversible photoisomerization of AzoFF (0.2mg/mL).



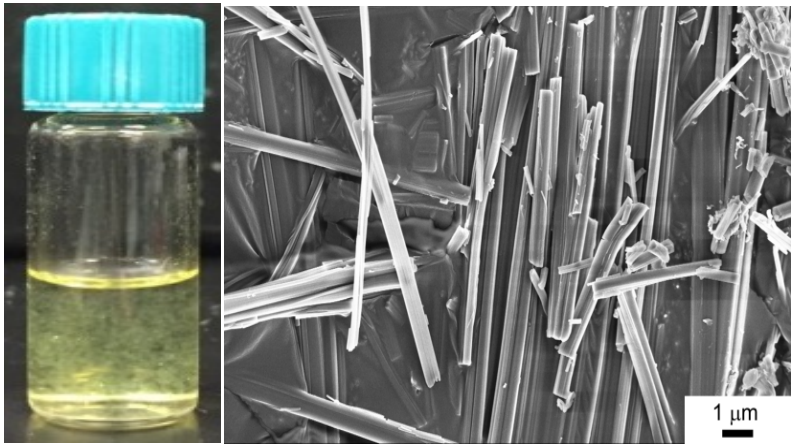
Azobenzene derivative synthesized by Professor D. McGrath (U. Ariz.)

Manipulating Molecular Conformation to Control Peptide Assembly

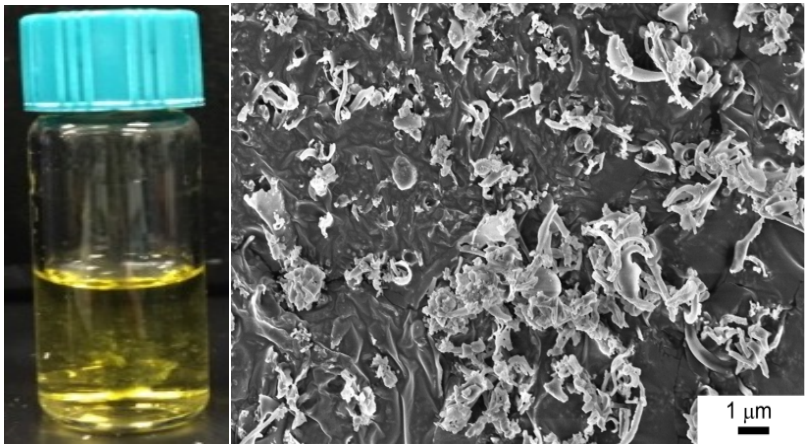


AzoFF dissolved in hexafluoroisopropanol (HFIP) and precipitated in water.

Manipulating Molecular Conformation to Control Peptide Assembly

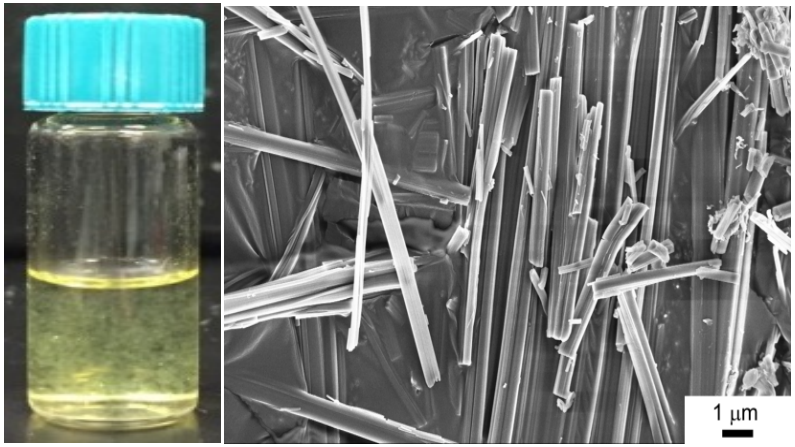


UV light on

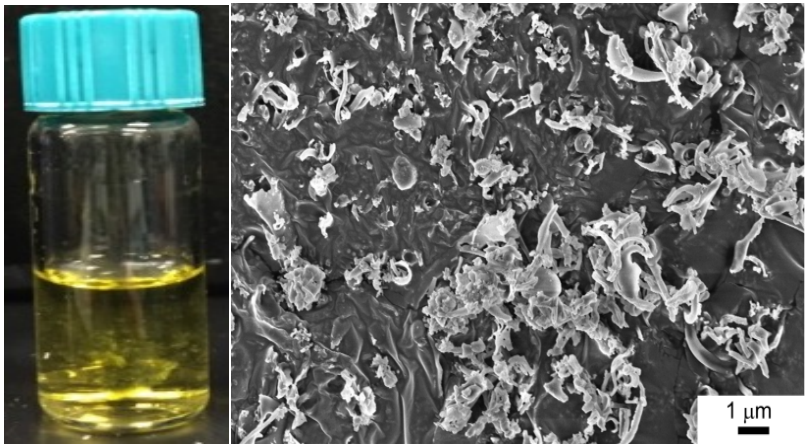


Illumination with UV light (~365 nm) drives *disassembly* of AzoFF.

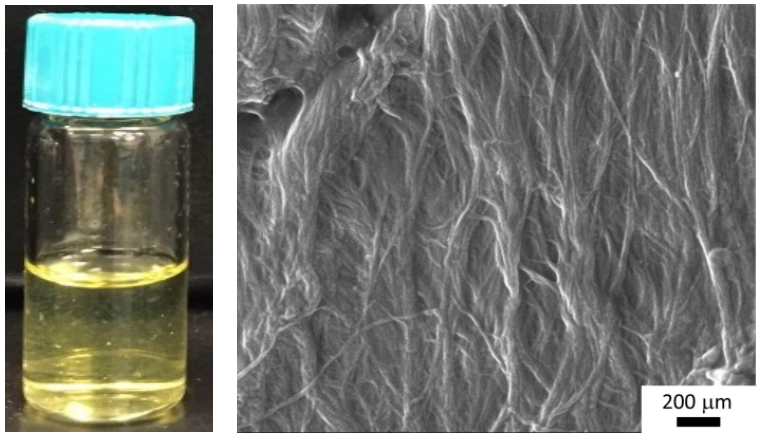
Manipulating Molecular Conformation to Control Peptide Assembly



UV light on



UV light off



Removal of UV-light allows relaxation of Azo functionality, facilitating "reformation" of (kinetically modified) AzoFF assemblies.

Manipulating Molecular Conformation to Control Peptide Assembly

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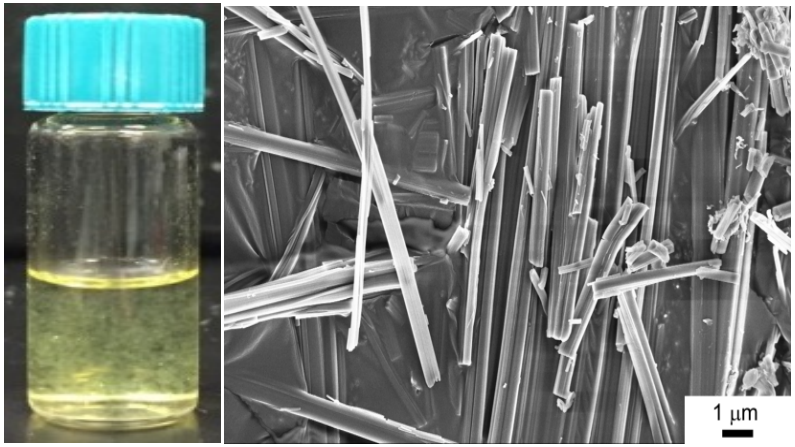
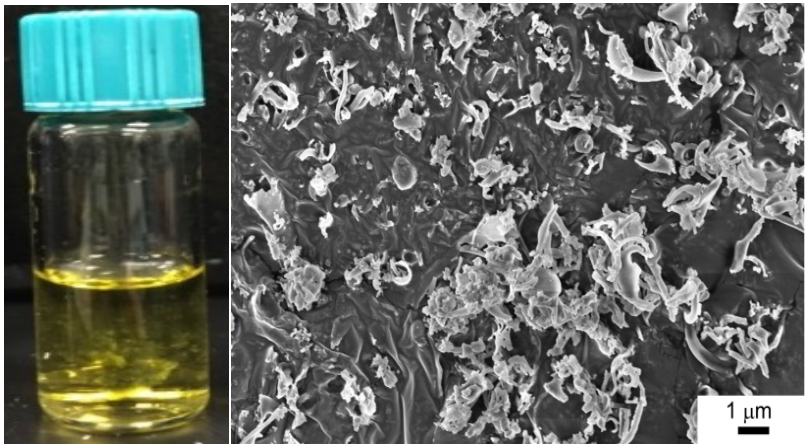
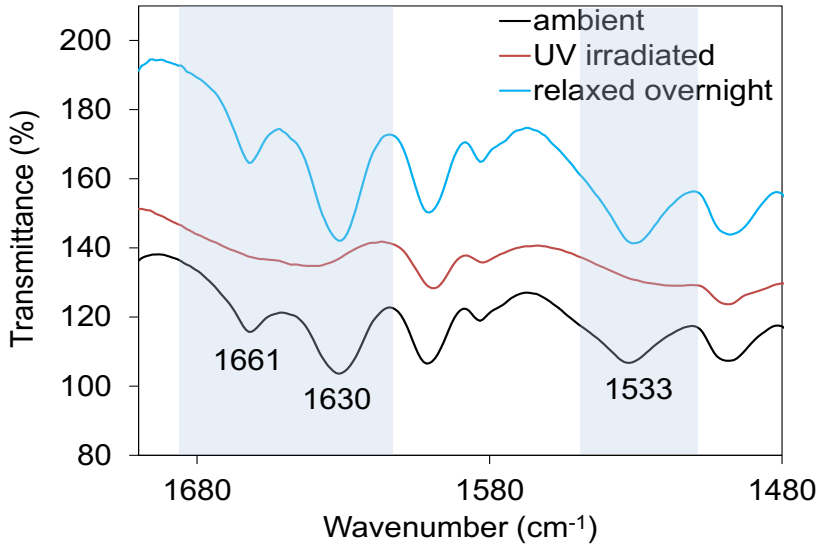


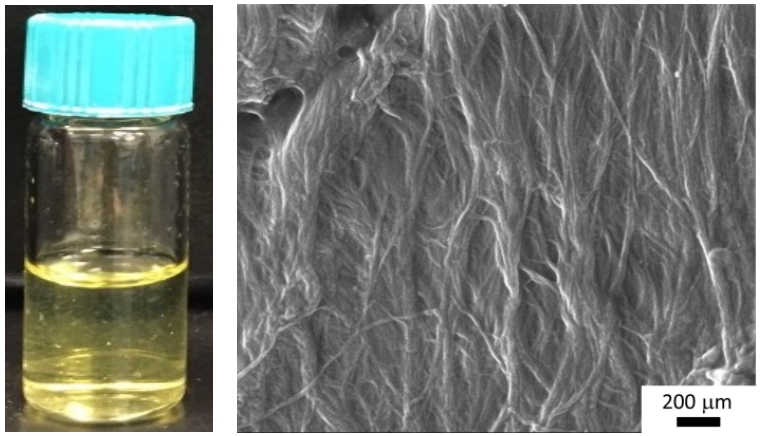
UV light on



FTIR reveals changes in secondary structure



UV light off



Take Home Messages

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- ✓ Microtubules are important biological examples of complex, dynamic supramolecular nanostructures that serve as inspiration for advanced, adaptive materials development.
- ✓ Biology shows that changes in molecular shape can be a powerful tool to control dynamic materials behavior.
- ✓ Molecular simulations can provide critical insights to guide synthetic materials development.
- ✓ Synthetic peptides can be modified with non-biological function to mimic biological behaviors.
  - *Changes in molecular shape change through photoisomerization can be used to control dynamic peptide assembly.*

By incorporating fundamental biomaterial assembly principles into synthetic systems we stand to enable a wide range of new complex, functional, dynamic materials.

Acknowledgements

Special Thanks to:

- Bonnie McKenzie (SNL) for Scanning Electron Microscopy
- Lance Miller (SNL) for Mass Spectrometry

Thank you!

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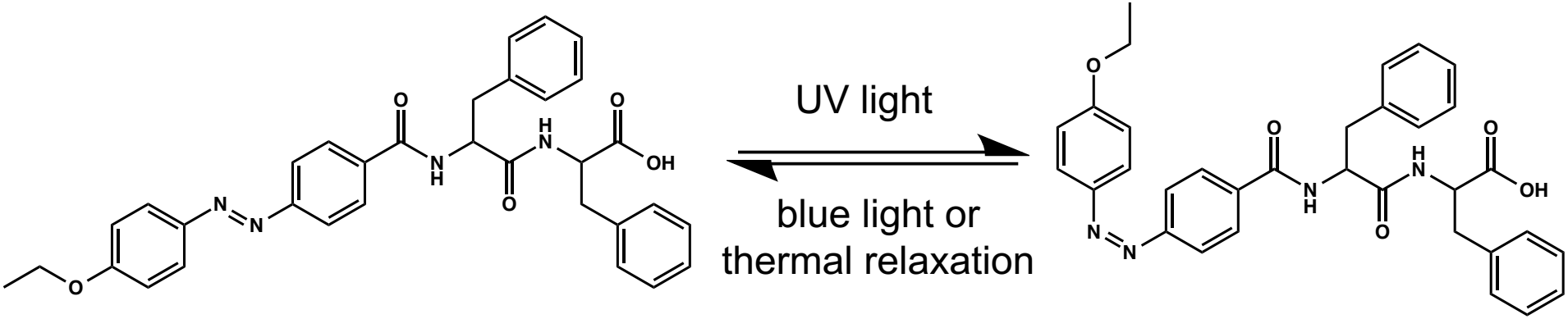
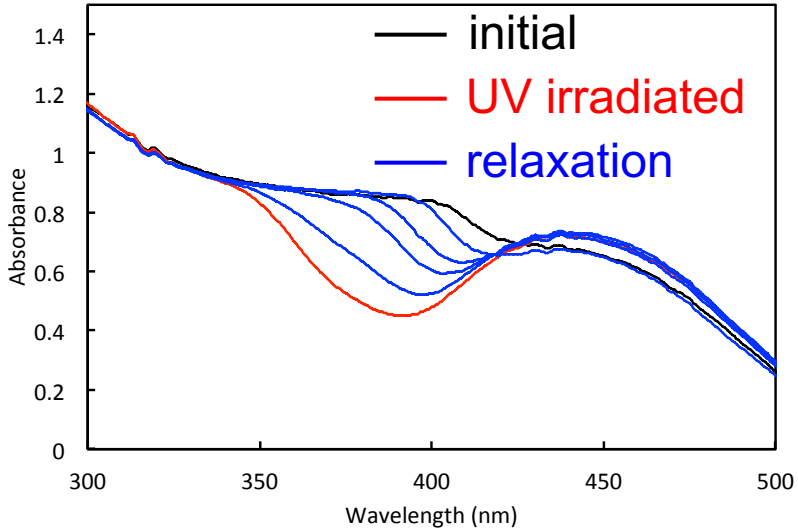
Backup Slides

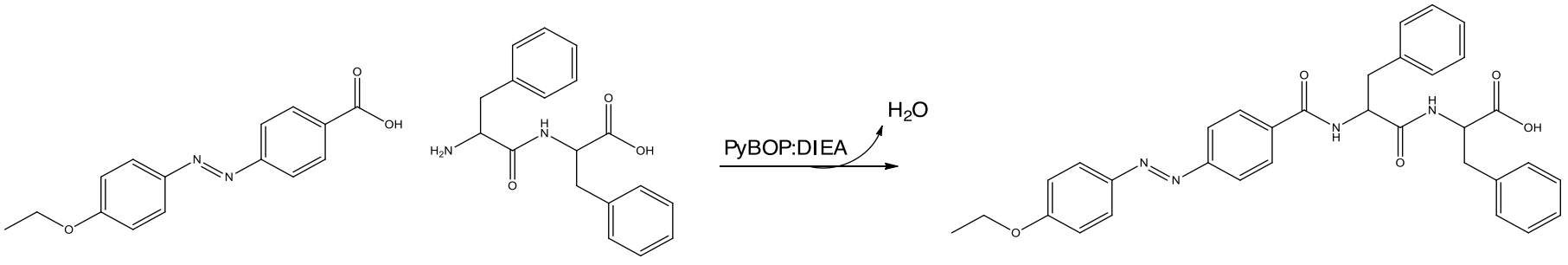
Current Directions: Light-Responsive Assembly

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





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


PyBOP:DIEA
H2O

Microtubules: Dynamic, Organized Protein Assemblies

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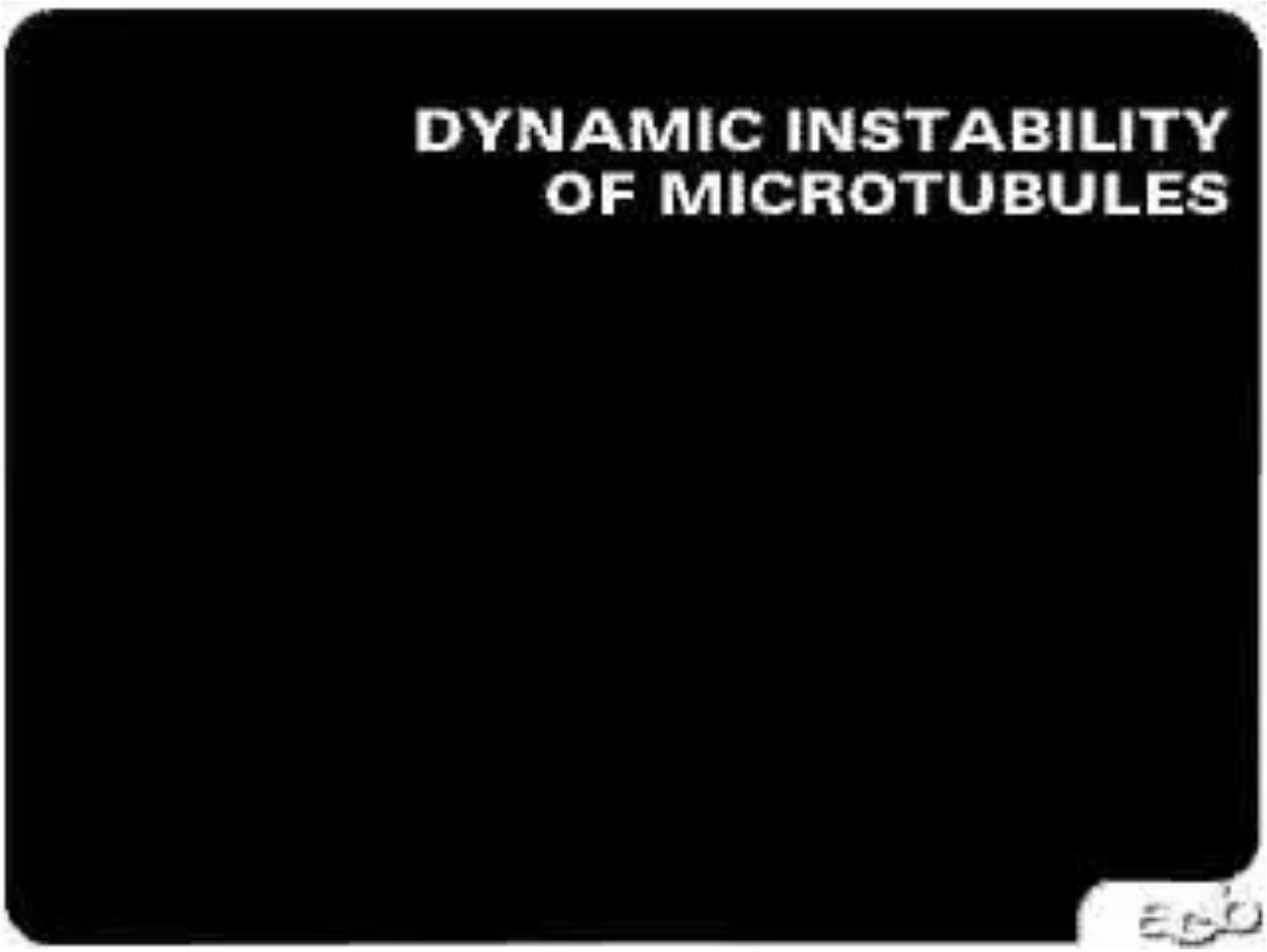

Video adapted from Essential Cell Biology (Alberts, et al., Garland Sci.,)