Active Assembly of Dynamic and Adaptable Materials: Artificial Microtubules

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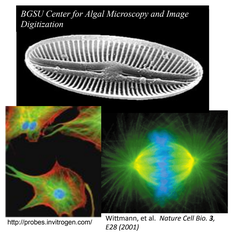
SAND2013-6802C

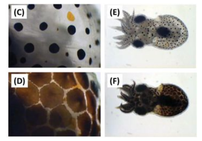
Project Description



http://probes.invitrogen.com/ Wittmann, et al. *Nature Cell Bio.* **3**, E28 (2001)

Programmatic Goal:

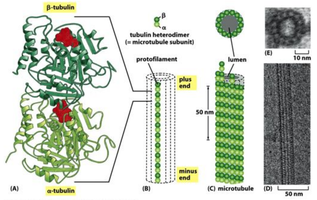
The objective of the *Artificial Microtubules* task is to combine theory and modeling with synthetic chemistry to study artificial, synthetic systems aimed at mimicking the complex structures and behaviors facilitated by energy consuming proteins such as tubulin and motor proteins.



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

Target Microtubule Characteristics:

- Self-assembly from nanoscale building blocks
- Biomolecular polarity (α−β asymmetry)
- Dynamic, programmable assembly
- Secondary structure formation
- 1-Dimensional nanostructures
- Motility and transport

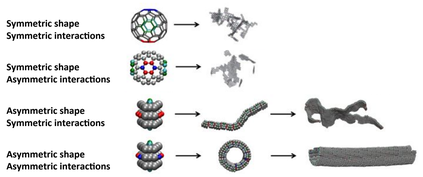


Research Results

Peptide Nanotube Assembly

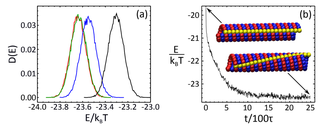
Erik Spoerke, Dara Van Gough, Jill Wheeler, Mark Stevens, Shengfeng Cheng, Christina Ting

Inspiration: *Molecular Dynamics (MD) simulations of self-assembling building blocks show us that asymmetries in molecular shape and intermolecular interactions preferentially lead to nanotube assembly.*

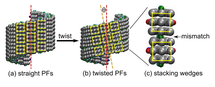


Cheng, *et al.*, *Soft Matter*, (2013) **8**, 5666-5678.

Monomers with chirality *m* self-assemble into tubules with pitch $p = m, m\pm1$. The range in *p* is due to a twist effect.

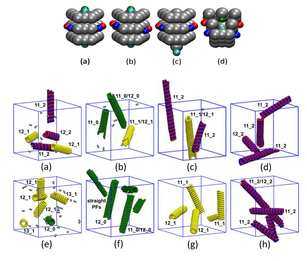


(a) The probability density of energy distribution per monomer, D(E), for equilibrated 13_*p* tubules with p = 0 (red), 1 (green), 2 (blue), and 3 (black). (b) A 13_2 tubule starting with straight protofilaments evolves into a lower-energy state with twisted protofilaments. Both (a) and (b) are for $A_s = 4.2$ and $A_a = 2.6$.



For $|m\text{-}p|>1$, twist requires rotation about the monomer vertical axis that causes misalignment of the attractive sites and yields higher pair energies.

Varying monomer interaction asymmetry reveals links between monomer chirality and tubule helicity.



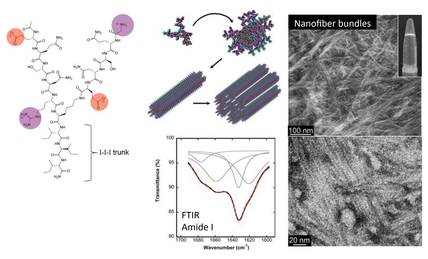
a) Chiral wedge monomer for non-helical tubules (p=0). b) Chiral wedge monomer with m=2 (for tubules with p = 2). c) Achiral wedge monomer with a lock-and-key configuration for the vertical binding site (sticking out the bottom surface). d) Chiral wedge monomer with m=2 and with a lock-and-key configuration for the vertical binding; top view shows vertical binding sites buried below the surface.

Simulations varying monomer structure and vertical/lateral interaction strengths shows that stronger vertical interactions reduce the range of chirality in the tubules. In addition, a lock-and-key mechanism, analogous to binding sites on tubulin dimers, makes $p \neq m$ unfavorable.

(a) S_0 at A_s=4.2 and A_a=2.6; (b) S_0 at A_s=3.0 and A_a=3.9; (c) S_1 at A_s=3.0 and A_a=3.9; (d) S_2 at A_s=3.0 and A_a=3.9; (e) VLK-S_0 at A_s=4.4 and A_a=4.2; (f) VLK-S_0 at A_s=3.0 and A_a=6.3; (g) VLK-S_1 at A_s=3.6 and A_a=5.4; (h)VLK-S_2 at A_s=3.0 and A_a=6.3.

Cheng and Stevens, 2013.

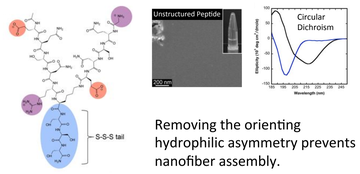
Synthetic Challenge: *Can we use molecular simulations to guide the study of critical variables affecting synthetic self-assembly?*



Van Gough, Wheeler, Spoerke, 2013

Manipulating peptide chemistry in this platform enables variation of:

Molecular size and shape *Electrostatic charge*
Amphiphilicity *Hydrogen Bonding*
Molecular Asymmetry

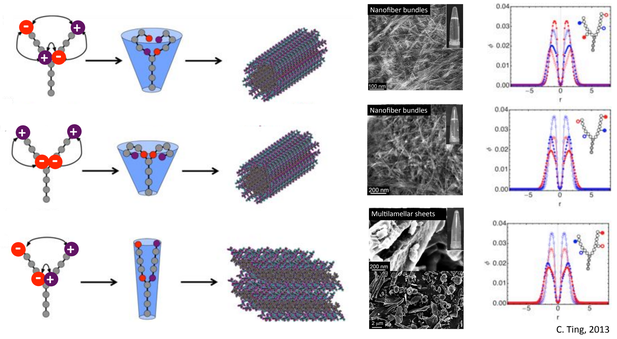


Removing the orienting hydrophilic asymmetry prevents nanofiber assembly.

Key Factors Affecting Nanofiber Assembly:

1) Shape asymmetry
2) Molecular orienting asymmetry
3) Charge balance and distribution
4) Combination of "Vertical" and "Lateral" interactions

Varying asymmetric electrostatic charge distribution influences self-assembled morphology.



C. Ting, 2013

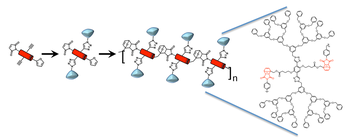
Thermally Reversible Dendrimeric Polymers

Dominic McGrath, Nate Polaske, Kiran Navath, Jim McElhanon, Leah Appelhans

Exploratory strategy: *Investigate polymerization of dendrimeric monomers to produce thermally programmable linear backbones, surrounded by dense functional peripheries.*

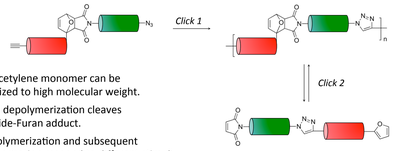
Combining "Click" and Diels-Alder Chemistries:

- Cu-catalyzed azide-alkyne "click" (CuAAC) chemistry is used to dendronize monomer building blocks.
- Thermally-reversible furan-maleimide Diels-Alder bonds form the polymer backbone.

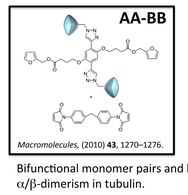


Synthetic alternatives:

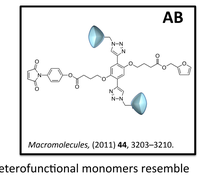
CuAAC Polymerization coupled with Diels-Alder Polymerization/Depolymerization of AB Monomers



- Azide/Acetylene monomer can be polymerized to high molecular weight.
- Thermal depolymerization cleaves Maleimide-Furan adduct.
- Initial polymerization and subsequent depolymerization respond to different stimuli.
- Modifying chemistry of linkers (green, red) allows for tuning of polymer functionality.

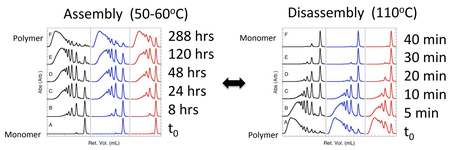


Macromolecules, (2010) **43**, 1270–1276.



Macromolecules, (2011) **44**, 3203–3210.

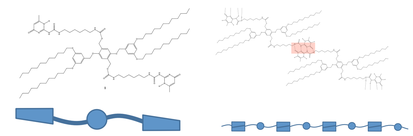
Bifunctional monomer pairs and heterofunctional monomers resemble α/β-dimerism in tubulin.



Both AA-BB and AB monomers show thermally-reversible polymerization by GPC for several generations of dendrons.

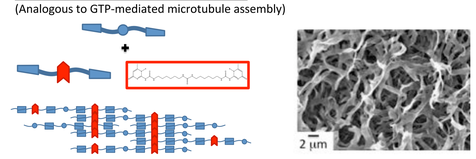
A hydrogen-bonding alternative:

Amphiphilic bifunctional ureidopyrimidonone (UP) Monomers



Molecularly-mediated assembly

(Analogous to GTP-mediated microtubule assembly)



Nanoribbon assembly in DMSO

Future Research

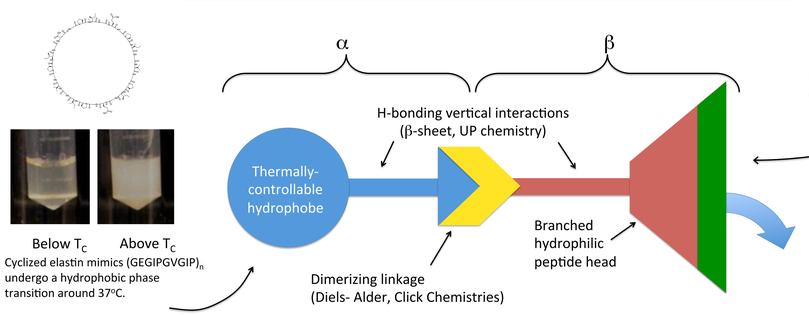
Advancing Development Chemistries:

- Expansion of peptide assemblies to include alternative thermal, optical, or enzymatic programmability.
- Tuning the stability of Diels-Alder chemistry to investigate stochastic assembly dynamics.
- Investigation of orthogonal assembly (vertical and lateral assembly).

Platform Integration: Developing capabilities will be integrated into a multifunctional platform to study:

- Advanced biomimetic assembly
- Biomolecular recognition
- Externally-triggered assembly
- Dynamic Instability
- Dimer-induced assembly
- Cooperative Molecular Assembly
- Motility

Modular Platform for Artificial Microtubule Development



Photoactive chemistry

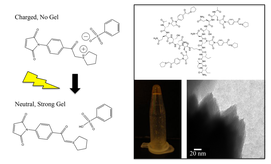


Photo-sensitive chemistries such as acyl-sulfonium moieties may be used program supramolecular function.

Enzyme phosphorylation chemistry

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

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