BE.342/442 Tuesday, December 6, 2005
Topic: Research in Biomaterials

Administrative
Take-home midterms will be returned on Thursday.
Evaluation forms will be filled out today.
The last 2 lectures will be dedicated to graduate student presentations.
Term papers (grads) or review articles (undergrads) are due December 23rd as a hard copy delivered to Prof. Zhang's office in person or by interdepartmental mail.

Research groups involved in biomaterials:
Google these people—they'll give you great ideas for research, and for your final projects!

Michael Hecht, Princeton University – graduated from MIT in 1985, and now works on combinatorial protein design, selection, and evolution.

> With over 10^{130} possible sequences for a protein of 100 residues, how can we select proteins for desired properties? Many large proteins form into a globular shape in solution, so that the hydrophobic groups can aggregate in the center. The middle position in the 3-nucleic-acid codons has high correlation to the amino acid identity (whereas the third position is usually involved in wobble). This allows a single mutation at the second position to change the encoded amino acid.
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> Michael Hecht designed alpha helices with amino acid sequences that follow a pattern in the primary structre: polar, nonpolar, p, p, n, n, p, p, n, p, p, n, n, p. This virtually guarantees self-assembly into a coiled-coil structure. Hecht incorporated 6 polar residues (Glu, Gln, Asp, Asn, Lys, or His) and 5 nonpolar residues (Met, Leu, Ile, Val, or Phe) and selected 50 of the $5x10^{41}$ possible proteins that display solubility, alpha-helical character, stability to unfolding, cooperative thermal denaturation, and high charge in enthalpy.
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> The protein design considered structure and function, including: globular folded structures, fibers (amyloid structures in nature, or biomaterials), and binding/activity. For example, proteins were selected for their ability to bind air, pattern on surfaces, etc.

Reza Ghadiri and Jeff Kelly, Scripps Research Institute (La Jolla, CA) – studies self-assembling peptide nanotubes as a novel class of antibacterial agents

> Ghadiri achieved supramolecular self-assembly of nanotubes directed by backbone-backbone hydrogen bonding, dictated by the chirality of the amino acid. Side chains of the amino acid are displayed on the nanotube surface, defining the chemical functionality of the outside of the tube. The diameter of the tube could also be tuned, but was generally in the range of a few angstroms, determining the sizes of ions (but not large molecules) that can pass through. (In Prof. Zhang's lab, self-assembled nanotubes have diameters of 20-50 nm.)
> *Nature* 1993, **366**, 324-327.

Stacking of the peptides into rings was observed.
Angew, Chem. Int. Ed. Engl. 1995, **34**, 93-95.

Molecular simulations show incorporation of the nanotubes into membranes.
Nature 1995, **369**, 301-304.
J. Am. Chem. Soc. 1998, **120**, 4417-4424.

This structure has potential to selectively incorporate into bacterial cell membranes and act as antibiotics, the same way fish toxins and insect venoms work by incorporating a hollow molecule into cell membrane, creating a lethal membrane channel. Due to increasing scarcity of effective antibiotics, the structures have been of great interest to pharmaceutical companies.

Darrin Pochan and Joe Schneidler, University of Delaware and UCLA: Artificial protein block copolymers

Block copolymers are common in nature, including silk and the byssal thread of bioadhesives. Pochan and Schneidler joined hydrophobic and hydrophilic chains, forming secondary structures that dictate self-assembly into a variety of structures. They used lysine (K) or glutamic acid (E) as hydrophilic residues, and leucine (L) or valine (V) as hydrophobic residues. The resulting secondary structures were:

K_xL_y -> alpha-helix
K_xV_y -> beta sheet
E_xL_y -> alpha-helix
$K_x(\text{rac-L})_y$, $K_x(LV)_y$ -> various structures

At 1 wt%, the peptides self-assembled into solid gels. Self-assembled tertiary/quaternary structures include bilayers/membranes, beta-hairpin polypeptides, and microspheres.

Amalia Aggeli and Neville Boden, University of Leeds, UK: Center for Molecular Self-organized Systems

Peptides self-assemble into a beta-sheet of specified length. The tapes of beta-sheets can stack, twist in ribbons, or stack and then twist in "thick" ribbons. The twisting strands form liquid crystals.
Aggeli et al., "Responsive gels formed by the spontaneous self-assembly of peptides into polymeric beta-sheet tapes." *Nature,* 20 March 1997.

Ehud Gazit and Meital Reches, Tel Aviv University, Israel: from amyloid structures to nanotechnology.

Peptides as short as tetrapeptides can self-assemble into fibrillar structures. Gazit and colleagues identified very short amyloidogenic motifs, and tried to identify the smallest

motif that could be used to recognize Alzheimer's. On the way, they found remarkable materials, including a dipeptide that can self-assemble into nanofibers.

This amazing property has financial implications as well: the shorter a synthetic peptide, the greater the chemical yield and the cheaper the material! (For example, the self-assembling molecules in Sam Stupp's work cost $10,000 per mg to synthesize, since the peptide has 5 very different parts! A dipeptide could be produced for just dollars a gram or even pound.)

The tubes can serve as casting molds for silver nanowires. The proteins can switch from a tube structure to a globular structure. Changing the R-groups can impart specific mechanical or electrical properties. Dipeptides of phenylalanine form conjugated tubes, and similar dipeptides with the linking $–CH_2-$ group removed form spherical shapes. Reches &Gazit (2002) *Nano Letters.*

Rein Ulijn, Department of Materials, University of Manchester, UK: Nanofiber scaffolds self-assembled from F-moc di-aromatic peptides

Dipeptide scaffolds with F-moc (two six-membered conjugated rings with one five-membered ring between them) groups self-assemble into gels containing nanotubes that vary in size and structure depending on composition, pH, concentration, etc. The proposed mechanism involves stacking of hydrophobic F-moc groups to form a core, followed by piling of the peptide portion to form a fibrous structure.

These simple dipeptide scaffolds are used to culture chondrocytes in 3D matrices.

Kaz Mihara, Tokyo Institute of Technology: Nanofiber self-assembly from designed peptides.

Controlled configurational changes in proteins can be a powerful tool in nanotechnology. The peptides designed by Mihara and colleagues can self-assemble into amyloid fibrils that undergo alpha-beta structural transitions. Such transitions are associated with prion diseases, so might inhibition of this transition be part of the solution for curing prion diseases?

Joanna Aizenberg, Bell Labs, Lucent Technologies
Sam Stupp and Philip Messersmith, Northwestern University
Kaz Mihira, University of Tokyo
Angie Belcher and Susan Lindquist, MIT
William DeGrado, University of Pennsylvania
David Tirrell, California University of Technology
Daniel Morse, Galen Stucky, Matthew Tirrell, and Tim Deming, UC Santa Barbara
Chris Dobson and Alan Windel, University of Cambridge, UK
Athene Donald and Mark Krebs, Cavendish Lab, University of Cambridge, UK
Susumu Yoshikawa, University of Tokyo
Tomi Sasaki, University of Washington
Dan Urry, University of Washington

Joel Schnur and Mark Spector, Navar Research Labs, DC
Heff Hubbell and Horst Vogel, EPFL-Lausanne, Switzerland
Marcus Texor and Peter Seeberger, ETH-Zürich, Switzerland
David Lynn, Georgia Institute of Technology
Lia Addadi and Steve Weiner, Weizmann Institute of Science, Israel
David Kaplan and Eddie Goldberg, Tufts University