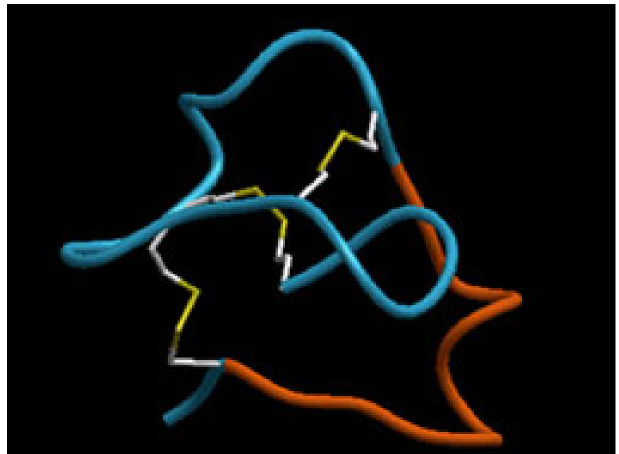
PEPTIDE POWER

PANEL SHOWCASES THERAPEUTIC POTENTIAL OF BIOENGINEERING

As recently as a couple of decades ago, biology struck many engineers as almost more of an art than a science, says Stanford Engineering Dean Jim Plummer. Unlike in physics, what was known in the field rarely could be quantified or modeled with equations. Experiments or simulations to test predictions therefore seemed too rare to provide a foundation for useful innovation.



A PROTEIN ENGINEERED IN JENNIFER COCHRAN'S LAB TO BIND TO TUMORS

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But at a panel discussion at the Clark Center Jan. 18 titled, "Engineering Therapies for Human Health," Plummer introduced two bioengineering faculty members who demonstrated just how much times have changed. Building on a newly rigorous understanding of the building blocks of life, each professor is custom engineering peptides, small snippets of proteins, to fight disease. In one case the peptides are meant to obliterate infections and protect damaged lungs, and in the other they have been conceived to diagnose and fight cancer.

"[Biology] is a new foundational science for engineering," Plummer said. "A lot of what you'll hear is about efforts to apply quantitative biology—understanding at the molecular level—to medical problems."

Pep-*toids*?

Bioengineering Associate Professor Annelise Barron is targeting deadly infections in the lungs and other places with artificial peptides she calls "peptoids."

Barron's peptoids are lab-synthesized mimics of naturally occurring antibacterial peptides, a class of molecules first discovered in frog skin in 1989 and since found in a wide variety of creatures ranging from bacteria to human beings. The peptides are like landmines in an organism, she said, in that they have the ability to destroy a wide range of invading pathogens.

While many researchers have tried to make drugs from the natural peptides, Barron said, they haven't been able to make the drugs cost-effective because natural peptides degrade very quickly in the bloodstream. Patients therefore have to take a lot of the drugs, must take them very often, and must inject them directly into their blood.

Barron's goal in making peptoids is to create molecules that have the same antimicrobial effect, but also greater durability and therefore lower cost and patient discomfort.

"We look at the biomolecules of interest, we quantitatively analyze their properties, we do a very careful study of the literature to understand what makes them work, and then we basically mimic them with something that is not natural but is much more useful for therapeutic applications," she said.

In studying natural peptides, Barron learned that they are positively charged, allowing them to attract negatively charged pathogens, and they include distinct "greasy" parts that somehow allow them to penetrate the membranes of the germ cells they attack.

With an underlying understanding of the chemistry required to synthesize these proteins, Barron's group created peptoids and, more importantly, tested them against various pathogens. One of the best peptoids, she says, has shown an efficacy comparable to a natural peptide-based drug that made it to advanced clinical trials. It has even worked well against bacteria that are showing resistance to traditional antibiotics.

One of the key applications Barron envisions for her group's peptoid research is the creation of a synthetic replacement for lung surfactant, which is a soapy coating for the lungs that reduces their innate surface tension enough to allow normal breathing to occur. When patients, such as premature babies or people who've spent a lot of time on ventilators, lack this naturally occurring surfactant, it is life-threatening. So far the only treatment has been to use the lung surfactant of cows, but that only works for babies and is very expensive.

In the next few months, Barron and student Nate Brown plan to begin animal testing of a peptoid that mimics a key protein in natural lung surfactant.

And, she added, "I'm going to the Netherlands in four weeks to meet with a group. We are trying to develop a surfactant that would treat acute anthrax inhalation and kill the anthrax before it can replicate."

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Choking off cancer

The ambition to improve human health is no less intense in the lab of bioengineering Assistant Professor Jennifer Cochran, who is focused on making peptides to not only enhance diagnostic imaging of cancer, but also to eventually deny tumors access to a sustaining blood supply.

The strategy is to create a peptide that will literally get in the way of the molecular mechanism that tumors employ to establish connections with nearby blood vessels. The tumors send out chemical requests that induce blood vessels to grow capillaries their way. The engineered peptide's role is to bind to and clog these channels so that the tumors and circulatory system never connect.

In the meantime, by making peptides that strongly attach to tumors, Cochran and her colleagues are also creating a way to "tag" tumors with attached probes that show up very brightly in diagnostic imaging systems. By precisely linking tumors to "contrast agents," Cochran's group hopes to develop a system that will allow tumors to be found early in their development, before they can spread.

Cochran's group has created engineered peptides through computational modeling, followed by an optimization process called "directed evolution." With this method, they harness a natural process of producing and replicating proteins but introduce small errors that result in a diversity of traits.

"We take peptides and make millions of different mutant versions of these molecules," she said. "Then we sort through them to find peptides that have the properties we are interested in."

In testing, the best peptides showed a high affinity for sticking to brain tumor cells. The researchers then coupled fluorescent or radioactive materials to the peptides and injected them into cancerous mice. After about half an hour, they began to see images of the mice with brightly glowing tumors.

"We are very excited by these results and we're hoping now to move towards clinical trials to use them in humans," Cochran said.

Time will tell whether those trials—or any of the research efforts discussed that evening—will be successful, but it already seems certain that engineers have the foundations and tools to build medicines to enhance human health.

soe.stanford.edu/research/profile_bio_leadingmatters.html
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