

Up Close With

Emily Scott

BIOCHEMIST

“In science, a lot of times you have to start over and take a new approach.”

FAVORITE PASTIME

Scuba diving

FAVORITE TV SHOW

“Law & Order”

FAVORITE BOOK GENRE

True-life survival stories, like

- **“The Hot Zone: A Terrifying True Story”**
- **“Adrift: Seventy-six Days Lost at Sea”**
- **“Endurance: Shackleton’s Incredible Voyage”**
- **Anything about the 2006 Everest climbing season**

EARLY MORNING ROUTINE

Weightlifting

CHUCK FRANCIS, UNIVERSITY OF KANSAS



Hooked on Heme

Examining Enzymes and Cancer's Causes

BY CHELSEA TOLEDO

It started with a starfish. Or rather, a close relative of the starfish called a brittle star.

With an air tank strapped to her back, college student Emily Scott dove to the bottom of the Gulf of Mexico to examine life in the Dead Zone. Excess nutrients from soil runoff had fueled an explosion of algae in the area, depleting life-giving oxygen and killing or exiling most marine life. The bottom waters had once teemed with red snapper, croaker and shrimp. But to Scott and other members of the marine biology research team, the region appeared virtually devoid of life. Then, from out of the mud, appeared the long, undulating arms of a brittle star.

As Scott learned, that particular species of brittle star, *Hemipholis elongata*, survived the oxygen-starved bottom waters because it has something many other marine creatures don't: a protein called hemoglobin. This same protein makes our blood red (some organisms have blue, violet or green blood — see "Blood's Rainbow," page 5). More importantly, hemoglobin carries oxygen throughout our bodies.

Key to hemoglobin's oxygen-carrying skill is a small molecular disk called a heme (pronounced HEEM). At the center of heme is an iron ion that binds oxygen. When nestled inside certain proteins, heme gives the larger molecules special chemical properties.

Once she saw what it meant to brittle stars, Scott was hooked on heme and the proteins that contain it. She moved from studying marine biology to biochemistry, then toxicology, and finally medicinal chemistry. Her career path may seem circuitous, but with the possible exception of the break she took from college to operate a forklift for a salmon company in Alaska, all her moves have been motivated by a common theme — heme.

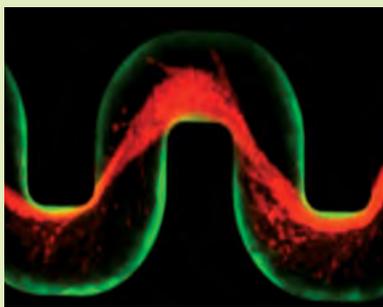


ANA BEARDSLEY CHRISTENSEN, LAMAR UNIVERSITY

Unlike many similar creatures, this type of brittle star, *Hemipholis elongata*, has hemoglobin, which colors its tube feet red and allows it to live in low-oxygen waters.



CHUCK FRANCE, UNIVERSITY OF KANSAS



KNUT DRESCHER, PRINCETON UNIVERSITY

This image from a time-lapse movie shows biofilm growth and streamer formation over a period of about 56 hours.

How Bacterial Slime Clogs the Works

Given a suitable surface, water and nutrients, bacteria will likely put down stakes and form communities called biofilms. These sticky, slimy microbial metropolises wreak havoc when they clog implanted medical devices like stents and catheters.

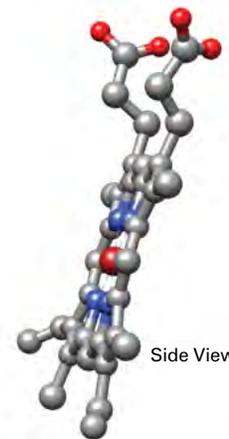
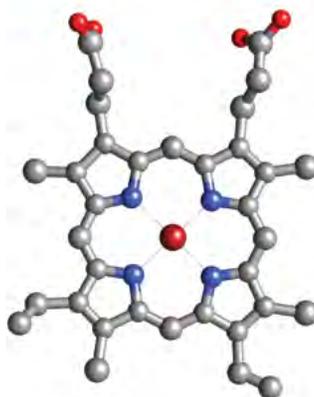
Researchers at Princeton University (including Bonnie Bassler; see “Bugging the Bugs” in the October 2004 issue of Findings) discovered how biofilms block such tubular devices. They created a time-lapse movie of the process (see <http://publications.nigms.nih.gov/multimedia/biofilm.html>) by recording fluorescently labeled bacteria through a microscope.

The scientists concluded that, after forming a layer on the inside of the tube (green), bacteria grow sticky streamers (red). The streamers tangle into a sievelike mesh that traps passing bacteria and debris, quickly blocking the tube completely. The researchers suspect that streamers are also the root cause of biofilms in industrial water filters, sewage facilities and natural settings like rivers and soil. If they could stop streamers from forming, scientists might be able to slow or even prevent bacterial clogging in medical and industrial settings.

—Elia Ben-Ari



It's like trying to put together



Side View

Heme is a small, flat molecule with an iron ion (dark red) at its center.

RACHEL KRAMER GREEN, RCSB PROTEIN DATA BANK

Now a researcher at the University of Kansas in Lawrence, Scott studies a family of heme proteins called cytochromes P450, hoping that targeting them will help treat certain cancers.

“I’m fascinated by these proteins and figuring out how they work,” Scott says. “It’s like trying to put together a puzzle—a very addictive puzzle.”

Moved by Science

Early on, Scott didn’t know that she’d end up in a laboratory focused on stopping cancer. In fact, she didn’t know where she’d end up at all.

When she was a child, Scott’s family moved to a different place about every 4 years. She’s lived in Kentucky, Florida, Alaska and many places in between. She believes this transitory upbringing helped prepare her for a research career.

“When you move all the time, you learn not to be intimidated by new situations or always having to start over,” says Scott. “And in science, a lot of times you have to start over, try something different, take a new approach and not be intimidated when things don’t work.”

Scott performed her first experiment in the fifth grade. Her class fed one rat a healthy diet and another a junk food diet, and weighed them once a week. You can probably guess the results. She realized then that the scientific process allows researchers to draw clear conclusions, fostering her fascination with the field.

Her persistent curiosity—and a devoted teacher—nurtured Scott’s interest in biology, chemistry and physics and helped her stand out in her high school class in Cairo, Ill. In her senior year, Scott was valedictorian of her class and student president of the Illinois Junior Academy of Science.

On Dry Land

Scott went to college at Texas A&M University at Galveston to study marine biology. While doing fieldwork for her degree—including the scuba expedition in the Gulf—Scott first learned about heme proteins. She also realized that the unpredictable nature of aquatic events might frustrate her.

“I didn’t want to go offshore for years and collect data, then not be able to draw any conclusions

a very addictive puzzle.

because there was no El Niño event in year three and an oil spill in year 12 of long-term field studies,” she says. Instead, she pursued research with more clearly defined and controlled experimental conditions.

Continuing her inquiry into heme proteins on dry land, Scott investigated different types of hemoglobin and myoglobin during Ph.D. studies at Rice University in Houston, Texas.

Myoglobin, like hemoglobin, is found in most mammals. However, unlike circulating hemoglobin, myoglobin is located within muscle tissue, where it stores the oxygen delivered by hemoglobin.

While her love of heme proteins continued to thrive, Scott didn’t see an opportunity to make an impact studying hemoglobin and myoglobin, which have been investigated extensively since the 1950s.

So, after earning her Ph.D. and gaining postdoctoral research experience, Scott moved back to Galveston to focus on the cytochrome P450 group of heme proteins at the University of Texas Medical Branch. She continues to work on these proteins in Lawrence, Kan., which has been her home for 9 years—longer than any other place she’s lived.

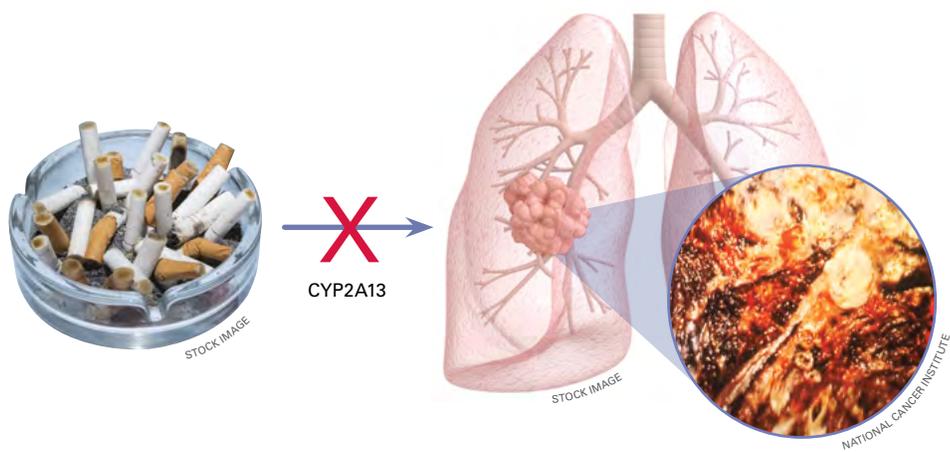
Blood’s Rainbow

Blood’s color depends on the protein it uses to carry oxygen

Hemoglobin 	Hemerythrin 	Hemocyanin 	Chlorocruorin 
<p>Most mammals, birds, reptiles, amphibians and fish have red blood. The color comes from an iron ion in heme within hemoglobin. Fair-skinned people appear to have blue blood in their veins, but it’s an optical illusion based on the properties of light.</p> 	<p>Peanut worms, duck leeches and bristleworms have violet blood. Hemerythrin needs two iron ions to capture an oxygen molecule (hemoglobin uses one). Also, despite its name, hemerythrin does not contain heme.</p> 	<p>Most spiders, crustaceans, snails, slugs, octopuses and squid have blue blood. It relies on copper, rather than iron, to carry oxygen. The blood of horseshoe crabs is used to test for bacterial contamination in injected medicines.</p> 	<p>Marine worms shaped like Christmas trees, feather dusters or lipstick tubes have green blood. They use chlorocruorin, which is similar to hemoglobin but with less oxygen-binding power. It floats freely in the bloodstream rather than existing within blood cells.</p> 



You are seeing vistas of biochemistry that no one on



Scott's team hopes to find a way to block the reaction of CYP2A13 with toxins in tobacco to reduce the incidence of lung cancer among smokers.

Smoking Out Lung Cancer

Cytochrome P450 proteins (CYP450s) are enzymes that facilitate many important reactions: They break down cholesterol, help process vitamins and play an important role in flushing foreign chemicals out of our systems. There are 57 of these enzymes in humans, identified by the abbreviation CYP (pronounced "sip") followed by specific numbers and letters.

Because they are embedded in membranes deep inside cells, CYP450 proteins have been elusive to see and study. But thanks to new technologies—and considerable dedication—Scott and her collaborators are making significant strides.

Many of these CYP450 enzymes chemically convert foreign substances into forms more easily removed from the body. In the process, however, one human lung enzyme called CYP2A13 converts a substance in tobacco called nicotine-derived nitrosamine ketone into two cancer-causing molecules. Scott and her research team aim to block this reaction. She envisions an inhaled medication that might help prevent lung cancer in people who can't quit smoking.

Scott's work comes none too soon. Lung cancer is the number one cause of cancer deaths in both men and women in the United States. According to the National Cancer Institute, 200,000 people in the U.S. are diagnosed with lung cancer and 150,000 die from it every year. Smoking leads to 80 to 90 percent of these cases.

"We already know how to reduce the risk of lung cancer in smokers—don't smoke!" says Scott. "But we also know that because of the addictive qualities of nicotine, while people try every method to quit, it's still very difficult to do so."

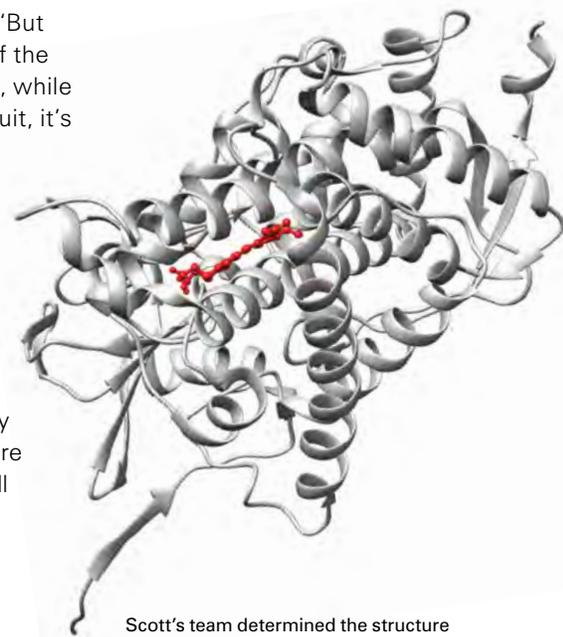
According to the Centers for Disease Control and Prevention, 20 percent of American adults still haven't kicked the habit. Scott believes that research advancements like hers might reduce the cancer risk faced by smokers, decreasing health care costs and improving the overall health of society.

Targeting Prostate and Breast Cancers

Scott and her colleagues also hope to target the second-leading causes of cancer deaths—prostate cancer in men and breast cancer in women. In the U.S., about 250,000 men are diagnosed annually with prostate cancer and 30,000 die from it every year. Breast cancer takes a similar toll on women: 230,000 new diagnoses and 40,000 deaths a year.

To treat prostate and breast cancers, Scott hopes that her team can create a drug targeting CYP17A1. This multitasking enzyme is essential to the body's production of steroid sex hormones such as androgens (including testosterone) and estrogens.

These hormones are essential for sexual development and health during our early and reproductive years. But in later life, androgens and estrogens can fuel the uncontrolled growth of prostate or breast cancer cells, respectively.



Scott's team determined the structure of cytochrome P450 17A1. The heme group is shown in red.

RACHEL KRAMER GREEN, RCSB PROTEIN DATA BANK

the planet has ever seen before.

Most enzymes specialize in one type of chemical reaction, but CYP17A1 can do two—a hydroxylase reaction and a lyase reaction.

For the hydroxylase reaction, CYP17A1 adds a hydroxyl group (one oxygen and one hydrogen) to a molecule called pregnenolone.

The resulting product can go down two different pathways.

One pathway leads to the creation of molecules called glucocorticoids, which play many important roles throughout the body. The other pathway—which involves CYP17A1's lyase reaction—leads to the creation of androgens and other sex hormones.

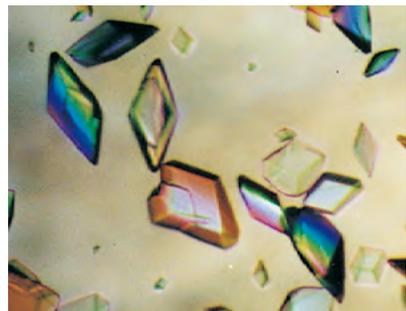
To target prostate cancer, Scott and her team aim to block only the lyase reaction, preventing the formation of androgens but leaving the glucocorticoid pathway intact.

Because androgens are the precursor to estrogens, blocking their formation in this way might also combat estrogen-sensitive breast cancer.

Protein Portraits

To understand how CYP450 enzymes work, Scott's lab uses a variety of techniques. Among them is X-ray crystallography, in which a very intense X-ray beam shines on a crystal that contains many copies of a protein packed tightly together. A detector picks up the pattern of light that emerges from the other side of the crystal. Researchers like Scott use these pictures to produce a three-dimensional image of the protein at the atomic level. This information can help inform scientists about how the protein functions and how to design drugs that selectively block its activity.

The tough part—growing crystals of sticky membrane proteins like CYP450s—takes a lot of hard work, a lot of discipline and a little luck, according to Scott. She encourages the researchers in her lab to be meticulous and to understand the detailed characteristics of the proteins to create the ideal conditions for crystallization.



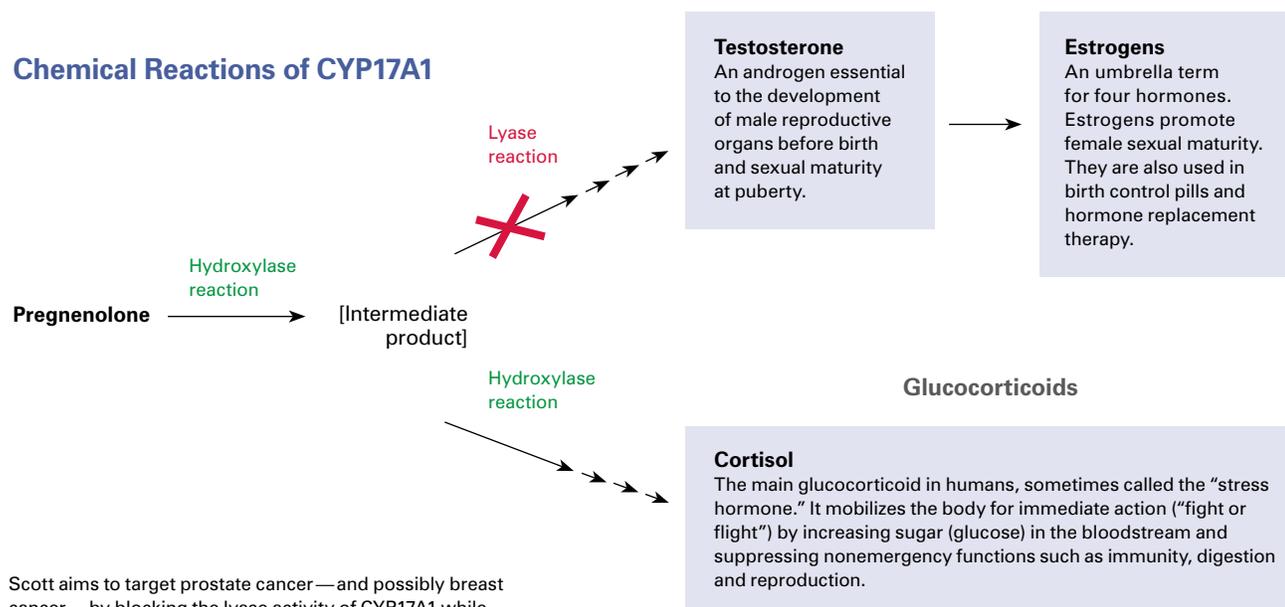
ALEX MICHERSON, UNIVERSITY OF CALIFORNIA, IRVINE

Growing crystals of proteins is the most critical—and the most difficult—part of X-ray crystallography.

"The person who knows the protein best has the best chance to grow its crystals," Scott says. "And the person who gets the crystals gets the protein structure."

"There's nothing like the day you get crystals of a new protein in the lab—except maybe when you see the resulting structure for the first time," she continues. "Then you know you are seeing vistas of how human biochemistry works that no one else on the planet has ever seen before."

Chemical Reactions of CYP17A1



Scott aims to target prostate cancer—and possibly breast cancer—by blocking the lyase activity of CYP17A1 while leaving its hydroxylase activity intact.



That's very cool research. I could see

Though crystallography is time-consuming and often frustrating, Scott relishes the entire process. Her enthusiasm for taking proteins from DNA sequence to 3-D protein structure isn't lost upon the researchers who have worked with her, including Natasha DeVore, who trained in Scott's lab for 6 years before accepting a position at Los Alamos National Lab in New Mexico. DeVore first interviewed to work in Scott's lab as a prospective graduate student.

"I had never heard of cytochrome P450 before, but after talking to her, I walked out thinking, 'Oh, that's very cool research; I could see myself doing it,'" DeVore says.

Another technique Scott's lab uses to study proteins is nuclear magnetic resonance spectroscopy (NMR)—and they are among the first to use it to spy on the inner workings of human CYP450s.

Using X-ray crystallography and NMR together provides a more complete picture of a protein's structure and reactive properties than either technique would on its own.

Postdoctoral researcher Fernando Estrada likens X-ray crystallography to taking a snapshot of a football game: It shows which players are on the field and where they're located. NMR, on the other hand, is like videotaping a few seconds of the game, allowing researchers to see the protein's internal movements and better understand how it interacts with other molecules.

An NMR machine is essentially a huge magnet. Only certain forms, or isotopes, of each chemical element have the right magnetic properties for NMR experiments. As the research team's NMR expert, Estrada devotes most of his time to preparing protein samples containing the right isotopes. He starts with bacteria that are genetically engineered to mass-produce a human CYP450 protein.

To coax the bacteria to make NMR-ready proteins, he feeds them with chemical building blocks that contain the correct isotopes. Once he isolates the human protein from all the bacterial proteins, he puts it into a narrow tube that will be inserted into a huge NMR machine.

"What's funny is that the machine is so big, but the sample tube is skinnier than a pencil," he says.



STOCK IMAGE

Although Scott no longer studies marine biology, she still enjoys scuba diving.

Contagious Curiosity

Scott's urge to uncover the unknown and her willingness to apply new techniques have inspired her students to do the same.

"One thing I've taken from her is that you can take a calculated risk as long as it's done carefully," Estrada says.

For her part, Scott credits her success—including several prestigious honors—to persistence, consistency, dedication and focus.

"I don't consider myself an exceptionally smart person, but I love my research and I work hard at the things I care about," she says.



BIO-NMR CORE FACILITY AT UNIVERSITY OF KANSAS

Scott and other researchers use this nuclear magnetic resonance machine to determine the structure of proteins.

