

GOING FROM MEN TO WOMEN BIOMEDICAL RESEARCH BLOG

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Edited by Alisa Zapp Machalek

Contributing Writers

Elia Ben-Ari
Sarah Fecht
Alli Hanley
Alisa Zapp Machalek
Chelsea Toledo

Production Manager

Susan Athey

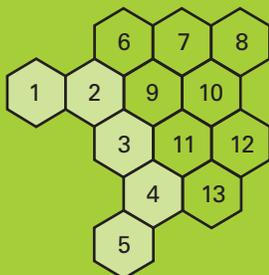
Online Editor

Jilliene Drayton

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Up Close With

Emily Scott

BIOCHEMIST

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

FAVORITE PASTIME

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- **“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 FRANCE, 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.



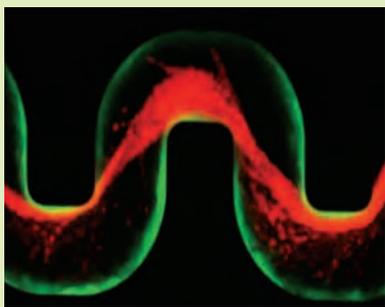
ANABEARSOLEY CHRISTENSEN, LAMAR UNIVERSITY

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.

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.

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.

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.

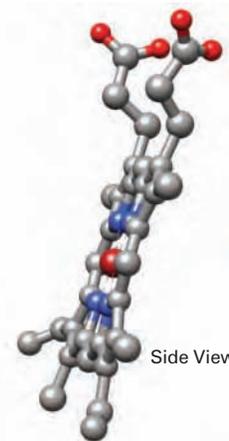
Researchers at Princeton University (including Bonnie Bassler; see “Bugging the Bugs” in the October 2004 issue of Findings) discovered how biofilms block such tubular devices. They created a time-lapse movie of the process (see <http://publications.nigms.nih.gov/multimedia/biofilm.html>) by recording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

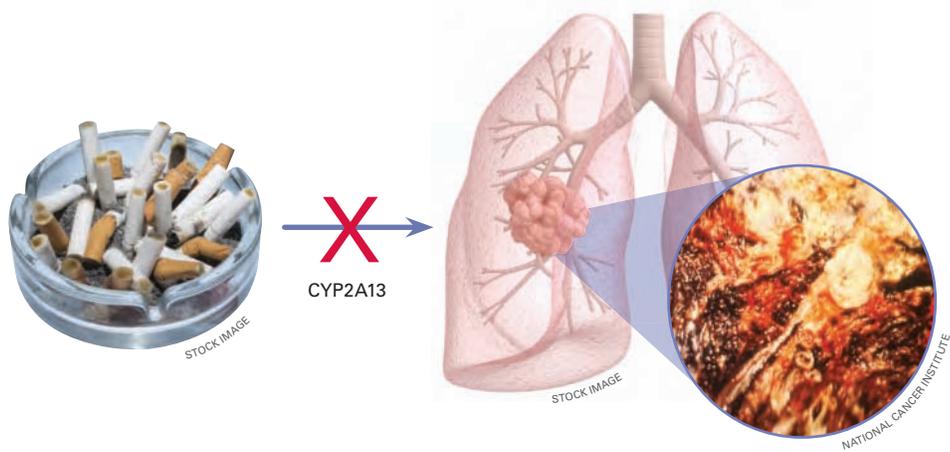
Blood’s color depends on the protein it uses to carry oxygen



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."

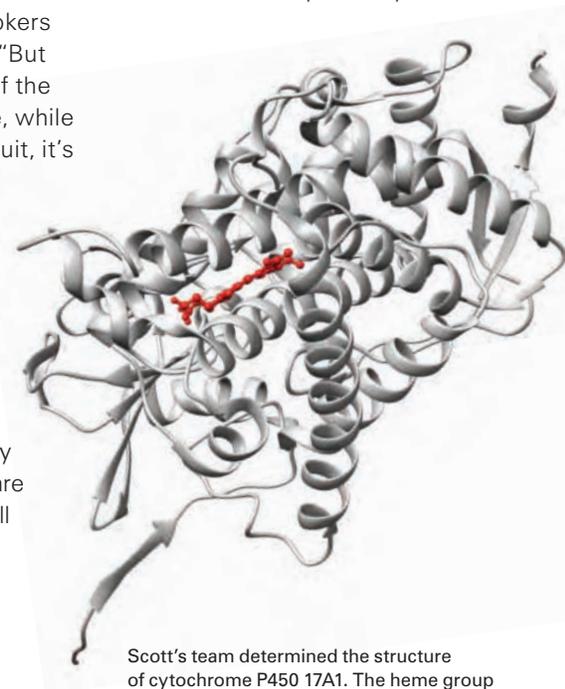
According to the Centers for Disease Control and Prevention, 20 percent of American adults still haven't kicked the habit. Scott believes that research advancements like hers might reduce the cancer risk faced by smokers, decreasing health care costs and improving the overall health of society.

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.

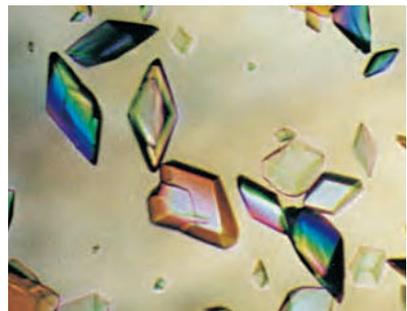
To target prostate cancer, Scott and her team aim to block only the lyase reaction, preventing the formation of androgens but leaving the glucocorticoid pathway intact.

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.



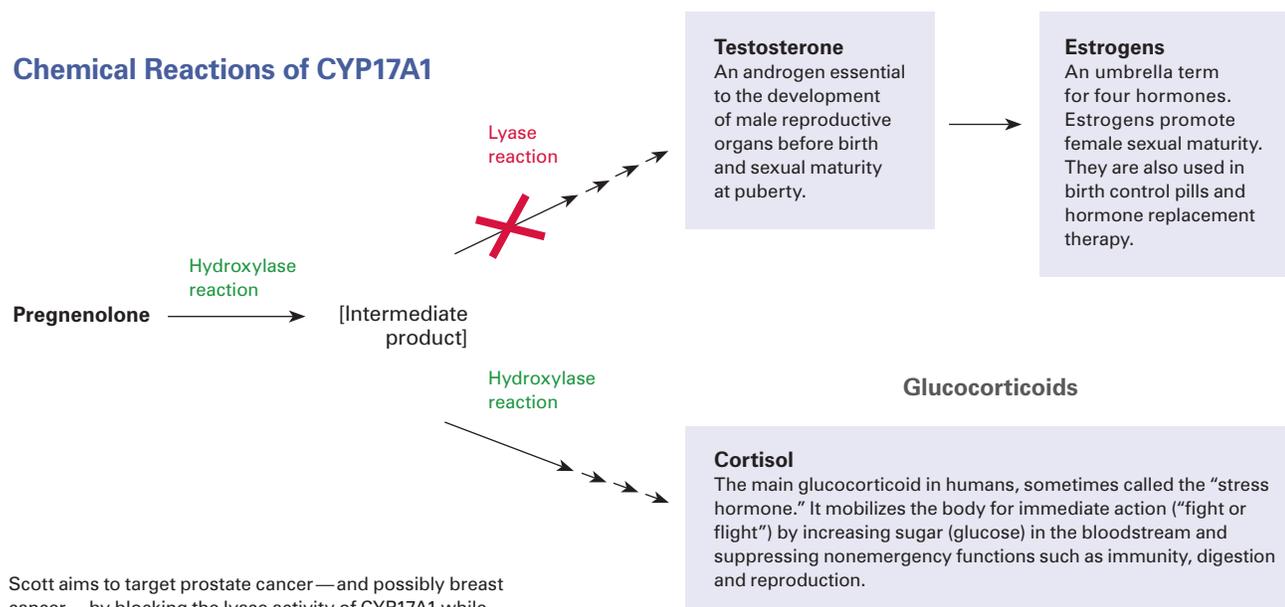
ALEX MCHEERSON, UNIVERSITY OF CALIFORNIA, IRVINE

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.

myself doing it.



Emily Scott (top right) poses with some of those on her research team, including Natasha DeVore (top middle) and Fernando Estrada (far left).

And she emphasizes that biomedical science is a team sport: “Every single person in the lab is a critical and devoted part of the research team—they really ‘get’ the excitement of what we are doing and how lucky we are to be able to do this research.”

To anyone considering a career in scientific research, she says:

“Science is all around us every day—from the foods in the grocery store to the medicines we take and the air we breathe. Find out about research that interests you. And if you find yourself drawn to exploring and discovering new biochemistry that can improve human health, then scientific research needs you!” ● ● ●

FIND MORE @

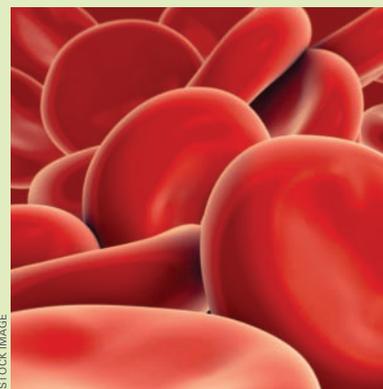
Learn how CYP450 proteins influence whether medications work properly at <http://1.usa.gov/18lAwuO>

Read about an NMR researcher at <http://1.usa.gov/1bB6rIn> and an X-ray crystallographer at <http://1.usa.gov/1bB6uxD>

Learn more about X-ray crystallography and NMR in chapters 2 and 3 of “The Structures of Life” at <http://publications.nigms.nih.gov/structlife>



Scott's research is funded by the National Institutes of Health through grants R01GM076343 and R01GM102505.



STOCK IMAGE

Researchers discover the molecular basis of a rare blood type, Vel-negative.

Mysterious, Rare Blood Type Explained

What's your blood type: A, B, AB or O? Rh positive or negative? In addition to these familiar blood groups, there are more than 30 others, with names like Colton, Kidd, Diego and Duffy. Each defines a specific molecular variation on the surface of red blood cells. New blood types are usually discovered in—and named after—someone whose body launches a life-threatening immune attack against donated blood.

One rare blood type, Vel-negative, was first noticed in 1952, but its molecular basis remained mysterious until this year. Bryan Ballif of the University of Vermont, along with scientists in France, discovered that people with Vel-negative blood have a genetic variation that results in the absence of a tiny, previously unknown protein called SMIM1 on their red blood cells.

About 1 in 2,500 people in North America and Europe are Vel-negative. If these people need blood transfusions, they may require Vel-negative blood to avoid potentially fatal complications. The scientists developed two genetic tests that will quickly detect Vel-negative blood, so those who have it can be cared for properly.

—Alisa Zapp Machalek

Just Found Just Found

How Porcupines and Geckos Inspire Medical Materials

By Alisa Zapp Machalek

Velcro® was inspired by the grappling hooks of burrs.

Supersonic jets have structures that work like the nostrils of peregrine falcons in a speed dive. Full-body swimsuits, now banned from the Olympics, lend athletes a smooth, streamlined shape like fish.

Nature's designs are also giving researchers ideas for new technologies that could help wounds heal, make injections less painful and provide new materials for a variety of purposes.

Quill Skills

The quills of the North American porcupine feature needlelike tips armed with layers of 700 to 800 microscopic barbs. As curious dogs and would-be predators discover, the backward-facing barbs make it agonizing to remove the spines from flesh.

To scientists, the flesh-grabbing abilities of quills point to myriad applications. Take, for instance, the work of Jeffrey Karp of Harvard University, Brigham and Women's Hospital and the Massachusetts Institute of Technology (MIT) and his Harvard/MIT colleague Robert Langer. These researchers created disks of medical tape impregnated with microscopic



Porcupine quills have given researchers new ideas on how to design needles that deliver less painful injections.

barbs. They are testing the patches as tools to repair hernias or close surgical wounds. The disks might have advantages over the meshes and staples currently used.

The same researchers recently examined porcupine quills from a completely different perspective. What intrigued them most was not how difficult the quills are to remove, but how readily the shafts penetrate skin. Barbed quills slip into flesh even more easily than ones with no barbs—or than hypodermic needles of the same diameter.

The scientists discovered, to their surprise, that a quill's puncture power comes from its barbed tip. Barbs seem to work like the points on a serrated knife, concentrating pressure onto small areas to aid penetration. Because they require significantly less force to puncture skin, barbed shafts don't hurt as much when they enter flesh as their smooth-tipped counterparts do.

To the researchers, barbed quills are a starting point for designing needles that deliver less painful injections. To get around the prickly—and potentially painful—problem of withdrawing barb-tipped needles, the scientists suggest creating synthetic barbs that soften or degrade after penetration, or placing barbs only on areas of the needle where they would aid entry but not hinder exit.

Gecko Grip

Geckos can skitter up walls and walk along ceilings because their feet are covered with a dense mat of fingerlike projections. Each projection, a few thousandths of an inch long and many times thinner than a human hair, ends in a tuft of hundreds of nanoscale fibers called spatulae. The tip of each spatula broadens and flattens into a rounded triangle, rather like



KELLY AR AUTUMN, LEWIS & CLARK COLLEGE

Geckos use nanoscale structures on their feet to accomplish gravity-defying feats like hanging upside down from polished glass.

a kitchen spatula. Together, the nanoscale spatulae vastly increase the contact area between a gecko’s foot and a surface.

With lizard feet in mind, Karp and Langer created a biocompatible medical adhesive that features a pattern of nanoscale pillars to maximize contact area. The material can stick to a variety of tissue surfaces, including those that are irregular and change shape.

Unfortunately, the material isn’t sticky enough to create an airtight, waterproof seal, so it can’t be used by itself on internal organs. In contrast, existing medical-grade glue can seal wounds tightly and quickly, but it can also cause tissue irritation.

The scientists combined the two products to create an ideal solution: a gecko-inspired tape coated with a thin layer of glue. The new tape conforms closely to surfaces, the glue seals any small gaps, and the entire product is nonirritating to tissues. These features could make it suitable for applications like repairing blood vessels or sealing up holes in the digestive tract.

Silky Stickiness

Every part of a spiderweb is strong and elastic, but only some strands are sticky. These features inspired scientists to design a medical adhesive that is more gentle on delicate skin.

Spider silk is strong (five times stronger than steel by weight), stretchy and lightweight. Some silk is sticky to catch prey, and some is not to let the spider scurry along it.

Karp, Langer and their postdoctoral associate Bryan Laulicht sought to create another new medical product with similar properties—a pliable, peel-off adhesive that doesn’t damage the underlying surface when removed. This sort of tape would be especially valuable for keeping tubes or sensors in place on those with delicate skin, including newborn infants and elderly people.

For reference, the scientists initially turned to traditional medical tape, which, like household masking tape, is made by spreading a sticky adhesive onto a thin backing material. But instead of spraying the backing with adhesive right away, the researchers

first applied a silicon-based film. Then, with another nod to the nanoscale pattern on gecko feet, they used a laser to etch a microscopic grid pattern onto the film. Finally, they added the sticky layer.

Along the grid lines, where the laser burned away the film, the backing touches the adhesive and the product acts just like normal sticky tape. In areas untouched by the laser, the backing floats on the silicon film and lifts off easily, leaving behind a layer of adhesive that either wears off naturally or can be rolled off with light finger pressure.

In essence, the resulting product has some sticky and nonsticky areas, just like a spiderweb. It goes on easily, adheres well and, best of all, comes off gently, even when pulled rapidly in an emergency situation.

Karp isn’t surprised that studying the natural world can reveal solutions to medical challenges. “I strongly believe that evolution is truly the best problem solver,” he said, adding that we still have much to learn from nature. ●



STOCK IMAGE

Spiderwebs inspired scientists to design a gentle, peel-off medical adhesive.

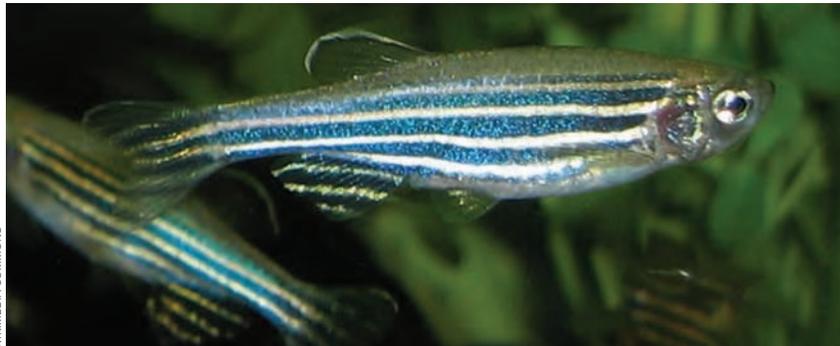
Learning About Human Biology From a Fish

By Chelsea Toledo

To learn details about how we develop before birth and how our biological systems work, some researchers have turned to a seemingly unlikely source: a fish.

That's because zebrafish — blue-and-white-striped fish that grow to be about 1.5 inches long — share similarities with us. For starters, we're both vertebrates, or animals with backbones. We also share similar genes. One crucial — and useful — difference between us and them is that zebrafish eggs and larvae grow outside of their mothers and are completely see-through, allowing researchers to watch what happens inside.

Zebrafish are earning their stripes as a model organism, giving scientists the opportunity to watch biological processes in action and apply the findings to human health.



As a model organism, the zebrafish provides insight into the way we develop before birth and how our systems operate.

How Blood Vessels Form

Vertebrates have closed circulatory systems that help deliver blood — and the oxygen it carries — to organs and tissues. By studying the molecular players behind blood vessel growth in zebrafish embryos, scientists at the Scripps Research Institute in La Jolla, Calif., have honed in on how the systems form.

The researchers focused on an enzyme called SerRS, which usually helps translate genetic material into proteins and also turns out to play an essential role in vascular development. Often, to understand a molecule's role in biology, basic researchers analyze what happens when the molecule is absent or doesn't function normally. So to see how SerRS facilitates blood vessel development, the scientists examined zebrafish that had abnormal versions of the enzyme. Their work sheds light on the role of SerRS in the development of closed circulatory systems — both in growing embryos and in evolutionary history.



NATIONAL CENTER FOR MICROSCOPY AND IMAGING RESEARCH

Watching zebrafish embryos grow allows scientists to understand how our blood vessels develop and how their closed structure evolved.

How Mysterious Molecules Help Mold Brains and Heads

Zebrafish are also offering insight into little-understood types of RNA and their role in brain development.

Only some types of RNA carry out the instructions for making proteins. Researchers are learning that other RNAs have important jobs, too.



NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Without certain lincRNAs, this normal zebrafish embryo would have an irregularly shaped head.

One type, called long intervening noncoding RNAs (lincRNAs), is involved in gene regulation. Little is known about how these RNAs function.

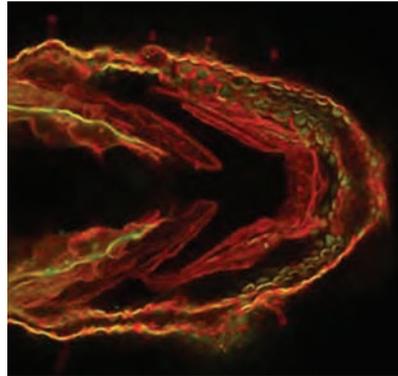
Focusing on two lincRNAs from zebrafish that have parallels in humans, researchers at the Whitehead Institute for Biomedical Research in Cambridge, Mass., have finally begun to shed light on these RNAs. When they disrupted the RNAs' function in zebrafish embryos, the scientists observed visible defects in the animals' brain and head development. Then, when the researchers inserted normal versions of the RNAs from human cells, the fish grew normal noggins. This finding suggests that the human lincRNAs have the same function as zebrafish lincRNAs, and it opens the door to studying other lincRNAs.

How Sugars Shape Embryonic Growth

Scientists have learned that glycans — or sugar molecules on the surfaces of cells — play key roles in a variety of important reactions in the body, especially during embryonic development. However, researchers' knowledge of glycan activity has been limited by the fact that they're difficult to view in action, even in a transparent zebrafish embryo.

One issue is that click chemistry — a widely used technique that allows researchers to label and image molecules by attaching fluorescent molecules to them as tags — employs copper, which can be toxic to live cells and restricts click chemistry to test-tube experiments.

Researchers at the Lawrence Berkeley National Laboratory in Berkeley, Calif., have modified the original technique to make click chemistry possible in living organisms, with zebrafish being the first.



Copper-free click chemistry allowed researchers to illuminate glycans inside the jaw of this zebrafish embryo.

CAROLYN BERTOZZI, UNIVERSITY OF CALIFORNIA, BERKELEY/
LAWRENCE BERKELEY NATIONAL LABORATORY

They have developed a slower, copper-free version as well as a copper-based one that masks the metal's toxicity but not its ability to speed up the click chemistry reaction.

Being able to tag glycans in living zebrafish embryos allows researchers to learn about the important roles the sugar molecules play in early development.

How Wounds Heal and Tumors Grow

Zebrafish remain see-through and stripe-less for the first few weeks after hatching, so their larval forms are also useful in research. For instance, University of Wisconsin-Madison researchers have used

the larvae to observe the immune response, particularly when white blood cells are drawn to the site of an injury or infection.

Wounds and tumors generate high levels of hydrogen peroxide, which signal certain types of white blood cells to travel to the area and trigger inflammation. While this response can be helpful for fighting infections, it can sometimes prolong wound healing and make tumors grow more.

To better understand these outcomes, the scientists monitored white blood cells called neutrophils as they moved toward wounds in zebrafish tails. The investigators determined that the release of hydrogen peroxide modified a protein called Lyn, which then guided neutrophils down a specific path to the wound. By blocking Lyn, they might be able to control immune cells so they go only to the site of infection, not a wound or tumor.

These and other findings demonstrate that this small fish is a big friend to scientists — offering important insights into how some of our own biological systems develop and function, potentially leading to new developments that improve our health. ●



Transparent zebrafish larvae allow scientists to observe processes in the body.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE

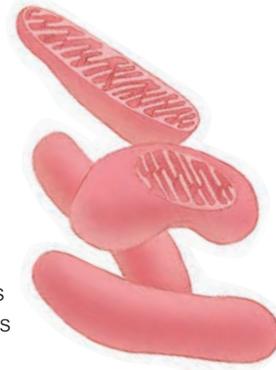
Mitochondrial Mix-Up

By Sarah Fecht

The mitochondria inside our cells use the food we eat and the oxygen we breathe to provide energy. It's vital to our survival, and yet sometimes this process goes awry. Every year, about 4,000 children in the United States are born with an inherited mitochondrial disorder—that is, their cells can't provide energy properly. The resulting byproducts may damage organs and cause developmental delays, seizures and even blindness.

Biologist Heather Fiumera of Binghamton University in NY, thinks that some of those health problems may lie in the fact that mitochondrial function requires the cooperation of two different genomes.

Every human inherits two genomes: one in the cell's nucleus, which is a mix of mom's and dad's DNA, and a different one in the mitochondria, which contains a replica of mom's mitochondrial DNA.



"It may be that some combinations of mitochondrial and nuclear genomes work together

more efficiently than others," Fiumera says. "While mutations in either genome may affect mitochondrial function, they don't explain the whole story. You might inherit a mitochondrial genome that helps you become a world-class marathon runner, but your brother"—who would have the exact same mitochondrial genome as you—"might not be as successful, even with the same training."

Similarly, a mitochondrial mutation may cause a severe metabolic disorder in one sibling but mild symptoms in another because of how the mitochondrial mutation interacts with their different nuclear DNAs.

The reason that mitochondrial DNA and nuclear DNA have such unpredictable interactions might be because the genomes originated from two different organisms. Scientists believe that a mitochondrion has its own DNA because it was once a free-living bacterium that was engulfed by another cell.

But instead of becoming dinner, the mitochondrion was co-opted to provide energy for its predator. The two cells managed to work together and, over time, became dependent upon one another.



JONATHAN COHEN, BINGHAMTON UNIVERSITY

Fiumera is working to untangle the interactions of mitochondrial and nuclear DNA.

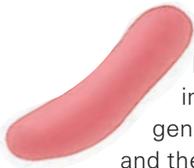


Understanding genetics in yeast may lead to new treatments for human metabolic disorders.



Mitochondria are the only cellular structures besides the nucleus that contain genetic material.

JUDITH STOFFER



Mitochondria have inserted some of their genes into the nucleus, and the nucleus uses protein messengers to control how much energy the mitochondrion produces and how it does its job. It may be that the two genomes are still co-evolving and learning the best ways to live together peacefully.

Fiumera studies these interactions in yeast, a single-celled fungus that is commonly used as a model organism in biomedical research. Using powerful genetic tools developed for studying genetics in yeast, Fiumera is able to mix and match mitochondrial and nuclear genomes. Her goal is to discover whether certain combinations of the two genomes produce yeast that is especially hardy, able to thrive even when starved, heated or poisoned.

So far, Fiumera has examined only a handful of different combinations and has already found that mitochondrial-nuclear interactions are responsible for as much as 20 percent of the differences in growth rates between yeast cells. She now plans to buy laboratory equipment that will allow her to scale up the research, measuring growth rates in about 200 samples at once. She predicts that her team will collect more than 10,000 growth rates in just the initial phase of the project.

Fiumera then plans to map the genes involved in determining how effective each combination is. Eventually, she'd like to see whether yeast cell populations in the wild skew toward certain beneficial mitochondrial-nuclear combinations in the same way that plants and animals genetically adapt to their environments.

But Fiumera won't be doing all of this work alone.

"This project is a marriage between yeast genetics and population biology, and it is enhanced by my actual marriage to a population geneticist," she jokes, referring to her husband, Binghamton biologist Anthony Fiumera, who is collaborating on the project. Binghamton computer scientist Kenneth Chiu is lending his expertise to help the biologists parse through huge data sets.

Since energy is so vital to a cell's functioning, mitochondrial genes and machinery tend to be highly similar in organisms as far-flung as yeast and humans. That allows Fiumera to hope that one day her research will be used to devise treatments for people who are suffering from debilitating metabolic disorders.

"You have to understand the mechanism behind a problem," she says, "before you can fix the problem." ●

Adapted with permission from Binghamton University Magazine.

Spotlighting the Ballet of Mitosis

By Alli Hanley

Like a pair of dancers

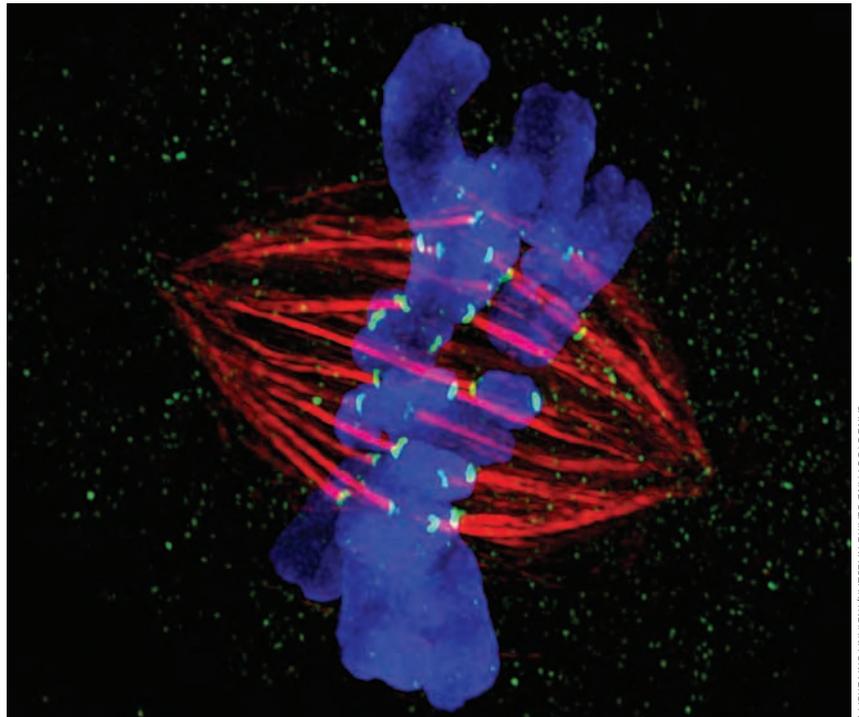
sheathed in blue, two chromosomes take the cell's center stage in this scene from the elegant—and usually perfectly performed—process of mitosis.

Mitosis divides a single cell into two new cells, which is essential for cellular growth, reproduction and repair. During this delicate production, supporting dancers called spindle fibers, shown in red, ensnare the chromosomes, grasping them with the aid of harness-like structures called kinetochores, shown in green.

Each chromosome is then gracefully escorted in opposing directions by the spindle fibers. This splits the duplicated genetic material in two for each of the new cells.

Indiana University researcher Jane Stout captured the stunning scene using a powerful OMX light microscope. Prior to the development of the OMX microscope, scientists had the “cheap seats”—the best imaging tools could only depict the performers of mitosis as a bright, nebulous mass enclosed in a harried arrangement of overlapping lines.

The new microscope is like a ticket for orchestra seating. It uses a combination of four separate digital cameras and different colored lasers to take snapshots as frequently as every 10 milliseconds, producing three-dimensional images with extremely high resolution. These capabilities illuminate the locations of proteins involved in complex biological processes, including mitosis.



JANE STOUT AND CLAIRE WALCZAK, INDIANA UNIVERSITY

A powerful light microscope captures this scene from the process of mitosis.

The increased detail will help scientists better understand what happens when the performance doesn't go as planned. Errors in mitosis can lead to unregulated cell division, as seen in many types of cancer.

The vivid images produced by the state-of-the-art system prompted the Indiana University scientists to dub it the “OMG microscope.”

Judges of the 2012 GE Healthcare Life Sciences Cell Imaging Competition were equally amazed. Stout's image was awarded first place in the high- and super-resolution microscopy category. As part of the prize, the image was shown in high definition on an electronic billboard at 42nd Street and 7th Avenue in New York City's Times Square on Saturday, April 20, and Sunday, April 21, 2013. ●

FIND MORE



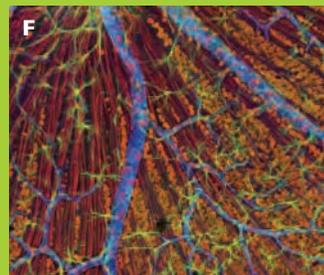
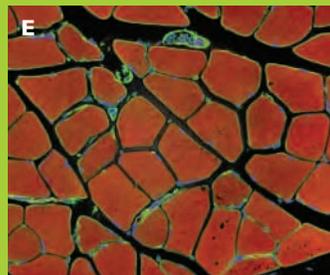
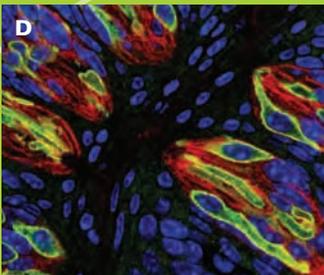
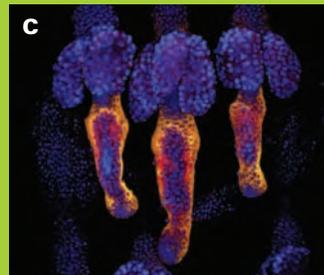
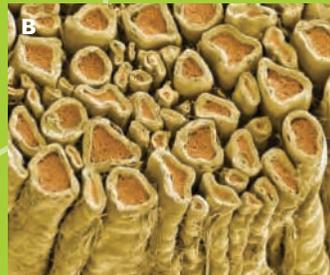
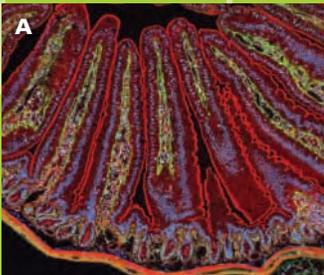
For more articles about how basic biomedical research lays the foundation for medical advances, see <http://publications.nigms.nih.gov/insidelifescience>



EXPLORE IT MATCH IT FIND IT

Where in the Body?

Each of these images shows a body part magnified with a microscope (the magnifications and microscope types vary). See if you can match each image with its description. Answers are upside down at the bottom of the page.



IMAGES A, B, E, F: NATIONAL CENTER FOR MICROSCOPY AND IMAGING RESEARCH, UNIVERSITY OF CALIFORNIA, SAN DIEGO; IMAGE C: HERMANN STELLER, THE ROCKEFELLER UNIVERSITY; IMAGE D: AKI TARUNO, PERELMAN SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

- _____ 1. Taste buds on the tongue. Cells within taste buds allow us to perceive five basic tastes: sweet, sour, salty, bitter and savory.
- _____ 2. Retina in the eye. The retina's pattern of the blood vessels is unique in each person and is used for identification in some high-security settings.
- _____ 3. Nerve fibers (axons). When insulated with fatty sheaths called myelin, axons can carry electrical impulses that travel more than 250 miles per hour.
- _____ 4. Small intestine. The main jobs of this organ are to digest and absorb nutrients from food.
- _____ 5. Skeletal muscle. There are more than 600 skeletal muscles in your body (not including the cardiac muscle—your heart—or all the smooth muscles in your internal organs).
- _____ 6. Hair follicles. Hair is produced by stem cells in the skin and grows out of structures called follicles.

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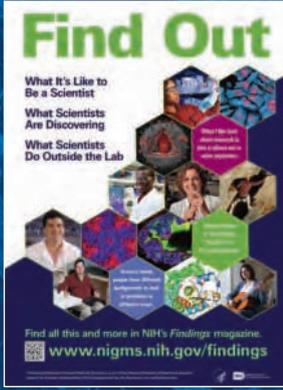
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