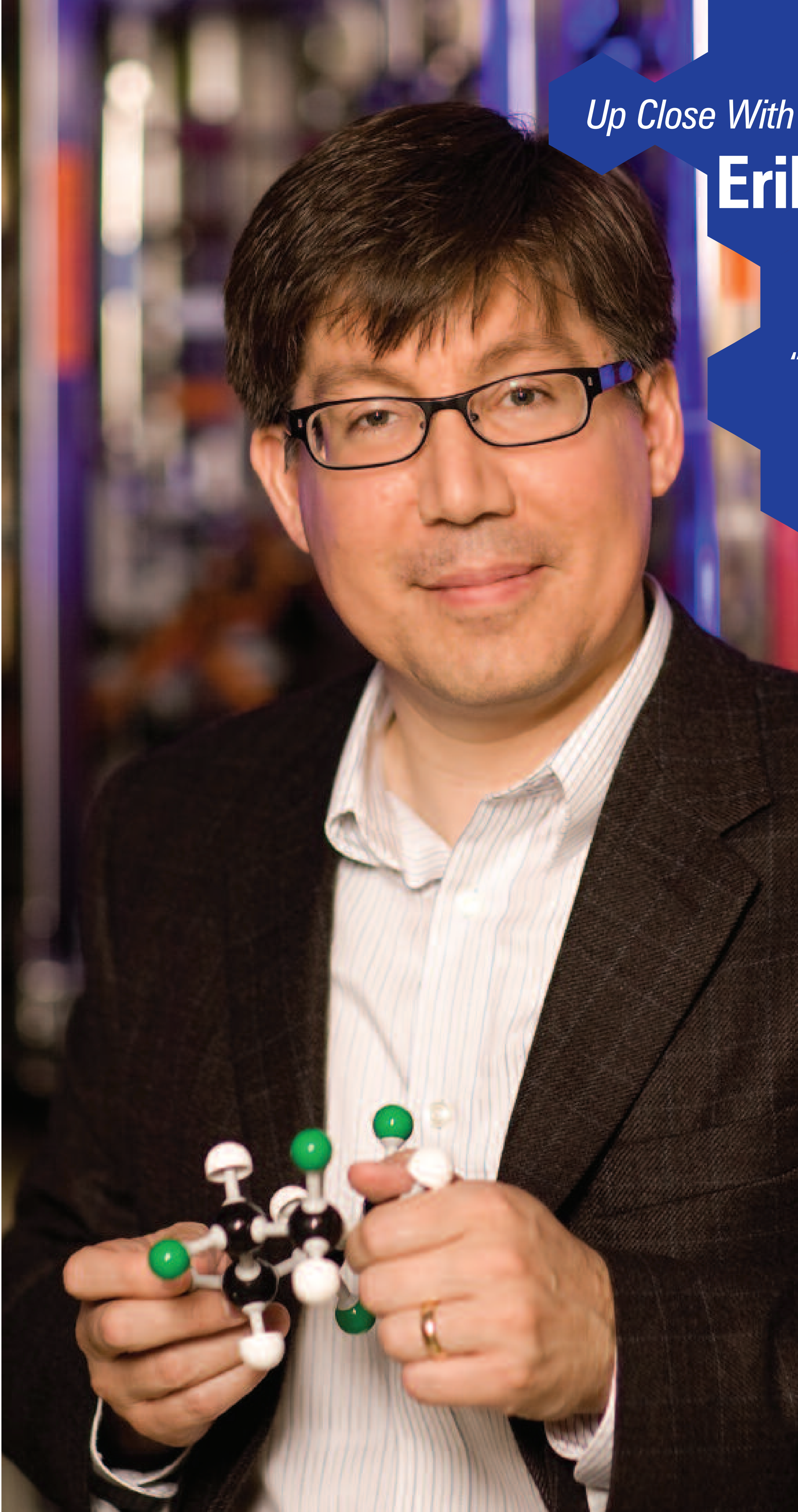


Up Close With

Erik Sorensen

SYNTHETIC CHEMIST

“I’m enraptured by the world of reactivity … and how to control it.”

FAVORITE ROCK BAND

Rush for their great drummer

HIDDEN TALENT

Counting to 10 in Onondaga, an Iroquois Indian language

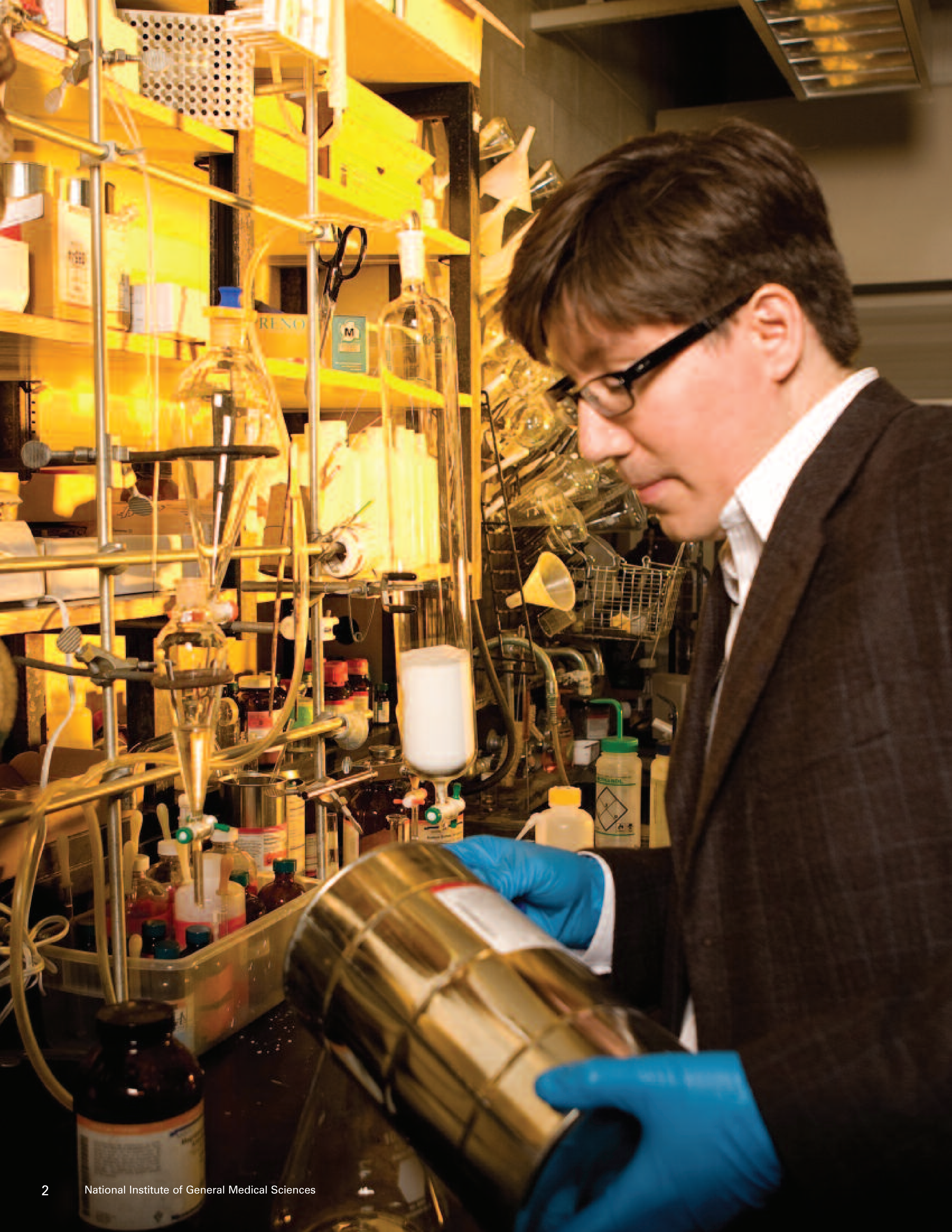
FAVORITE SPORTS TEAM

Syracuse lacrosse men’s and women’s

FAVORITE PASTIMES

Running, drumming, hanging out with his chemist wife and young daughter

BR AN W LSON



BRIAN WILSON

Mimicking Mother Nature

BY ALISA ZAPP MACHALEK

A tree whose bark cures cancer. A flower with the power to ease pain. A fungus that stamps out diseases that were once fatal.

Sound like medieval concoctions or potions from children's fantasy novels?

Nope. All of these are real medicines, taken by millions of people worldwide.

These natural products, or slight variations of them, account for a large percentage of today's medicines. They come from plants, animals, fungi, and bacteria from every corner of the globe.

And scientists believe that more natural products with useful properties are just waiting to be discovered.

After finding a substance with interesting biological properties, researchers try to make it in a lab so they can study it better. This challenging task is embraced by chemists like Erik Sorensen, 41, of Princeton University in New Jersey.

"The trick is to get molecules to dance to your tune," says Sorensen. He does that by knowing atoms and molecules so well that he can predict and guide their behavior.

The poisonous foxglove plant is harvested to produce digoxin, a drug used to treat heart failure.

Rhythm and Speed

Unlike some researchers, Sorensen doesn't come from a scientific family.

He never did experiments in his basement. He didn't even really like chemistry until college. His path to science was different.

Sorensen's parents divorced when he was a toddler. After that, he and his mother, an Onondaga, one of the Iroquois nations, spent several years on an Indian reservation in upstate New York.

There, Sorensen often helped his grandparents, who worked 7 days a week at Babcock's Inn, the restaurant they owned.

During high school, Sorensen's main interest was drumming. "Loud and fast," he clarifies.

"If I was 15 percent better as a drummer," Sorensen muses, "I would have gone into music. To this day, I love drumming."

"Running has taught me more about how to approach

Sorensen now jams on an electronic drum set with a powerful amplifier.

"If I wanted to, I could break windows!"

After ruling out a career as a musician, Sorensen decided on his next love: competitive running. As he sped through cross-country courses, willing his body to fly, he imagined himself as his childhood idol, Billy Mills.

In 1964, Mills, a Sioux Indian, won an Olympic gold medal in one of the longest and most grueling track events there is—the 10,000 meter race (6.2 miles). In the past 90 years, no other American has won any medal in this event.

Coast-to-Coast Chemistry

But just months before graduating from high school, Sorensen's aggressive, long-distance running caused a serious injury, ending his dreams of becoming a professional athlete.

It turned out to be the beginning of his scientific career.

"In college, the time I'd spent running I applied to schoolwork," Sorensen says. "I became fond of learning. That hadn't happened to me in high school."

Sorensen discovered synthetic chemistry, an area of science in which chemists make, or synthesize, molecules with a desired structure. Here, he really hit his stride.

"Whew! I became unreliable as a general student, because [synthetic] chemistry was all I wanted to do!" Sorensen remembers.

The three-dimensionality of chemistry was what captivated him.

"Each molecule has a unique shape—it's totally amazing," Sorensen says.

After graduating from college (the first in his immediate family to do so), Sorensen went on to graduate school at the University of California, San Diego. While there, he met fellow student Benjamin Cravatt, and the two quickly became close friends and collaborators.

Sorensen and Cravatt had a lot in common. In addition to being a graduate student, Cravatt shared Sorensen's passion for science and running. Together, they ran races, solved chemical problems, and discussed links between the two.

"Running has a lot in common with scientific research," says Cravatt. "Both depend on delayed gratification, and running has taught me more about how to approach science than anything I learned in class."

Sorensen agrees. Both running and chemistry require drive, commitment, and persistence, even in the face of setbacks, he says. Making a molecule from scratch with no instruction manual can take weeks, months, or years.

But for Sorensen, the effort is totally worth it. His excitement about synthetic chemistry is obvious and infectious. Many of his students and those who have worked with Sorensen credit him with sparking their initial interest in chemistry.

Nowhere is his enthusiasm more visible than in the lecture hall.

"[Erik is] legendary," says Cravatt. "He's able to take even the most esoteric concepts and breathe life into them."

Nature Provides

Sorensen's scientific inspiration often comes from natural products that act as chemical weapons.

Admittedly, for most of us, the notion of chemical weapons conjures terror and disgust. But such weapons—both offensive and defensive—are actually all around us.

Snakes, spiders, and sea snails use venom to kill their prey. Poisonous dart frogs, monarch

Many of today's drugs started in nature. Poppy flowers gave us morphine…

CHRISTINE L. CASE

…and mold yielded penicillin.

science than anything I learned in class."

butterflies, and plants ranging from buttercups to hemlock trees protect themselves with poison. Bacteria and fungi use toxins to kill competing microorganisms.

Over millions of years, nature has devised and refined these chemicals to latch onto protein molecules in living organisms. All creatures from bacteria to baboons have similar sets of proteins, meaning that natural products interact with the same molecules in people as they do in other organisms.

For chemists, many applications of natural products are clear from the start. A substance that kills viruses, regardless of whether it comes from a bacterium, a plant, or an animal, has a chance of working as an antiviral drug in humans.

But natural products have also proven effective against not-so-obvious conditions like heart disease, depression, and epilepsy. Sometimes, a natural product will inspire medicines for two or more diseases.

For example, a portion of the antibiotic molecule penicillin lowers cholesterol. A chemical spinoff of artemisinin, a malaria drug, seems to quell cancer.

Sorensen's lab has synthesized a wide collection of nature's firearms, including molecules that kill bacteria and cancer cells, suppress the immune system, or even enhance memory in lab animals.

"Mother Nature does remarkable things with a limited set of building blocks," Sorensen says.

But, he explains, natural substances are often too big or chemically complicated to be absorbed or transported well in the human body.

Chemists have techniques unavailable to nature, Sorensen continues. With these tools—like cranking the temperature down to -70 degrees Celsius or carrying out a reaction in an oily solution rather than in water—they can create hundreds, even thousands of molecules whose structures are slight variations of a natural product.

"The goal is not just to build a natural product, but to create a family of molecules based on the architecture [of that natural product]," Sorensen explains.

One member of such a molecular family might have all the right properties to be a medicine. Those include working properly in the human body as well as not being too toxic to people or the environment.

How to Make a Molecule

The two dozen students and researchers in Sorensen's laboratory each focus on synthesizing at least one molecule at a time.

They start out knowing all the atoms in their molecule, how those atoms connect to each other, and how the atoms fit together in three-dimensional space. The scientists have access to thousands of simple starting ingredients sold in chemical supply catalogs. And, most importantly, they have deep knowledge of how chemicals react with each other.

Their job, then, is to choose a few starting materials and design a series of chemical reactions that will convince these materials to attach at the correct places, release unneeded parts, and correctly swap one atom

story continues on page 6

FIND MOR
Listen to Erik Soren … drums at http://www.nigms.nih.gov/findings.

Shrews carry Lyme disease ticks, new research shows.

Shrew-ed Science

What do deer, mice, and shrews have in common? Easy—they all live in the woods.

But these forest dwellers are alike in another way that isn't so cheery: They all spread Lyme disease.

Deer pick up ticks from mice that drop the teeny bugs onto leaves and sticks. Humans and pets get Lyme disease when bacteria-infected ticks attach to skin and eat a blood meal. Until now, scientists thought mice were the main source, or "reservoir," of the bacteria that cause Lyme disease.

Two varieties of shrews can now be held to blame, according to new findings from evolutionary geneticist **Daniel Dykhuizen** of Stony Brook University in New York.

Dykhuizen's student Dustin Brisson showed that in the Northeastern United States, mice carried only 25 percent of the ticks that carry Lyme disease. Shrews carried 55 percent of those ticks, while chipmunks and other small birds and rodents likely accounted for the rest.

The study results suggest that public health strategies targeted at interrupting tick transmission in shrews and chipmunks, in addition to mice, may help prevent Lyme disease in people. —*Alison Davis*

Bioprospecting: Finding a Balance

Want an interesting job?

How about collecting snake and scorpion venom? Scooping up sand from the bottom of the ocean? Plucking leaves and flowers in remote jungles?

What about consulting with tribal shamans and traditional herbal healers?

These are some of the ways scientists gather natural substances and information about them that might lead to new medicines, agricultural products, or other things people need and want.

Many of the most promising places to look are ecologically unique habitats like tropical forests and coral reefs. These areas are home to a rich diversity of species that produce countless natural products. The vast majority of these products have never been found or studied.

But should we tap these environments for our own good? Many of the areas richest in biodiversity are in some of the poorest parts of the world. If impoverished locals use their natural resources for income, these ecosystems could disappear.

While there are many competing interests to consider, greater awareness of the importance of protecting biodiversity promises to bring us closer to a solution that works for all life on Earth.—*A.Z.M.*

Many of today's

NATIONAL INSTITUTES OF HEALTH

continued from page 5

for another to form the molecule and shape they want.

To do this, the researchers pour or scoop the raw materials one by one into a glass flask in proportions and under conditions (temperature, humidity, pressure) that encourage specific reactions. And then they wait.

"Chemical synthesis to me is a beautiful form of hands-off building," Sorensen says, adding that while architects design buildings that will be created by people in a hands-on way, in chemistry, "the chemical reactions do the work."

To track progress, synthetic chemists use techniques like nuclear magnetic

FIND MORE @

Ask Erik Sorensen about synthetic chemistry at http://www.nigms.gov/findings. Send in your question by October 31, 2008, and in December we'll post Sorensen's responses to 5 to 10 reader questions.

medicines come from natural products.

Bark from the Pacific yew tree is the source of the cancer drug Taxol®.

resonance [see "Enzymes, Magnets, Action!," February 2003 *Findings*] and X-ray crystallography [see "The Humpty Dumpty Dilemma," March 2006 *Findings*] to check the structure of the gradually changing molecule each step of the way.

Chemical Surprises

Although chemists try their best to predict how chemicals are going to react, there are usually surprises. Sometimes, these discoveries reveal entirely new chemical reactions.

That's what happened recently to John Schneekloth, one of the researchers in Sorensen's lab.

Schneekloth was synthesizing mitragynine (pronounced mit-ra-GUY-neen), a substance found in the broad, dark green leaves of the kratom plant that grows in Southeast Asia. The molecule has painkilling properties similar to morphine, making it compelling as a possible new pain reliever.

During his work, Schneekloth unexpectedly discovered a single chemical reaction that simultaneously bonded a molecule together in three places.

Forming three chemical bonds in this single reaction is extraordinary, says Sorensen, because "in the past 180 years of organic chemistry, the vast majority of reactions created only one or two bonds."

Making three bonds at once is a bonanza for chemists, who strive to synthesize molecules using the fewest steps possible, he explains.

Schneekloth and Sorensen have sent a description of this new reaction to a chemistry journal. Once it's published, other scientists can use the reaction for their own projects.

For Sorensen, that's true success.

"We always hope that the [chemical] synthesis will force us to be innovative—to invent new ways for transforming matter," he says. "And we're always asking: If we work on this project, what will it do for chemistry?"

That constant push to innovate, to come up with new approaches, feeds an artistic desire.

"I'm strongly drawn to the creative dimension of chemical synthesis," Sorensen says. "It really relates closely to art."

It also means that the designs in his lab don't always turn out as planned.

"We tend to work with reactions that hinge on chancy steps," he says, adding that this keeps them on their toes, thinking of workarounds.

More, Please

Even if chemists can make a molecule from simple, raw ingredients, it's often not enough to launch a commercially available drug.

"Chemists are good at making very small amounts of complicated materials. But, in many cases, we aren't very good at making large amounts," Sorensen admits.

story continues on page 8

A natural component of garlic is heart-healthy.

Garlic: To Your Health!

Garlic-infused cuisines, such as those from the Mediterranean and Asia, have been linked to good health. Previous studies have shown that garlicky diets reduce cholesterol and lower blood pressure.

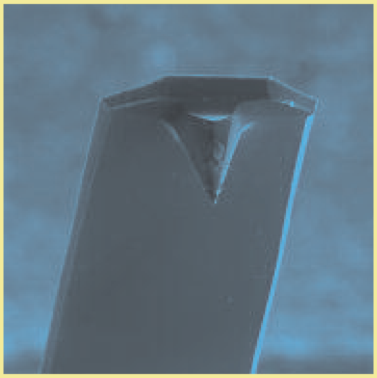
Researchers have suspected that allicin, a natural component of garlic released when the cloves are crushed, could be the pungent herb's "healthy" ingredient.

But allicin is an unstable molecule, breaking down very rapidly in body fluids. This has made it very hard to study and created doubt as to its health benefit.

Changing that view, physiologist **David Kraus** of the University of Alabama at Birmingham discovered that blood converts garlic-derived allicin into a powerful natural gas, hydrogen sulfide, which relaxes blood vessels.

Using a hydrogen sulfide sensor that Kraus invented, his team measured levels of the gas released from garlic juice-bathed blood cells in a glass chamber. They discovered that blood vessels relaxed in proportion to how much hydrogen sulfide appeared.

Kraus says that in addition to solving the allicin mystery, his method could find use in standardizing garlic dietary supplements. —*A.D.*



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The sharp tip of an atomic force microscope can feel "soft" cancer cells.

Feeling Cancer

Tumors start out in individual organs: the lungs, the bladder, bone, and so on. After gaining a foothold, cancer cells then travel, or metastasize, to other places in the body.

Cancer is much more difficult to treat after it has spread. Scientists want to know what gives metastatic cancer cells their ability to move around so nimbly.

To investigate further, nanotechnologist **James Gimzewski** of the University of California, Los Angeles, collected cancer cells from the chest fluid of people with lung, breast, and pancreatic tumors that had spread.

He then used a powerful microscope with a thin, sharp tip on a spring to gently poke individual cells and measure their stiffness. The results showed that metastatic cancer cells were "softer" than healthy ones, presumably so they can maneuver through tight spaces on their way to other spots in the body.

Gimzewski's discovery may offer a more precise way to detect cancer cells, since current methods rely mostly on appearance, which often cannot accurately distinguish between healthy and cancerous cells.—*A.D.*

Every molecule has its own shape.

continued from page 7

He learned this lesson personally when, as a graduate student in the mid-1990s, he helped devise a way to synthesize paclitaxel, the active ingredient in the lifesaving cancer drug Taxol®.

At the time, getting Taxol from its natural source, the bark of the Pacific yew tree, required harvesting vast numbers of the increasingly scarce trees, a prospect no one was very excited about.

Since Taxol was only available in limited quantities, demand for it was high. Cancer patients and their families learned of efforts to produce Taxol in the lab where Sorensen was working. Desperate for a cure, they called the scientists to beg for some of the precious substance.

Even now, after more than a decade of trying, chemists haven't come up with a very cost-effective way to make Taxol from scratch. Today's Taxol production starts with lab-grown plant cells or the needles of farm-raised or wild yew trees.

Scientists around the world continue to look to nature for chemical secrets that may help us fight many diseases. Some call this bioprospecting. Those who disapprove of the activity call it biopiracy (see "Bioprospecting: Finding a Balance," page 6).

Nonetheless, people and companies searching for new natural materials realize the importance of protecting threatened environments.

Governments and conservation groups are working to encourage sustainable practices like eco-friendly logging and harvesting a rainforest's renewable fruits and nuts.

Self-Made Molecule

One of Sorensen's recent research triumphs is making a molecule with Taxol-like effects against cancer. To indicate its structure and source, he named the molecule cyclostreptin.

It contains six chemical rings, each with a backbone of five or six carbon atoms. The "cyclo" in its name refers to these rings, which are fused together into a complicated arrangement.

The substance was isolated from *Streptomyces* bacteria, explaining the "streptin" in its name. It is one of the only molecules synthesized so far that can spontaneously fold itself into its final form under the right conditions.

This ability is the envy of every synthetic chemist. In one smooth movement, cyclostreptin coils into six connected rings and locks itself in place by forming four bonds.

Sorensen is now working with cancer researchers to learn more about cyclostreptin and its biological properties, including its potential to become a new chemotherapy drug. In tests on lab animals, cyclostreptin appears able to treat cancers that have become resistant to Taxol.

But even if cyclostreptin never makes it to pharmacy shelves, there are plenty more natural products with challenging structures and intriguing biological activities.

Where nature is hiding these medical treasures is anyone's guess. But what's clear is this: The creative handiwork of chemists like Sorensen is essential to making these molecules dance to our tune.

FIND MORE @

Watch a video of Erik Sorensen in his lab at http://www.nigms.nih.gov/findings.