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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
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.

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.”
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...
Shrews carry Lyme disease ticks, new research shows.

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.

continued from page 5

Many of today’s medicines come from natural products.

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.
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

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**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.
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.

—A.D.

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 in 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.

—END—

FIND MORE @

Watch a video of Erik Sorensen in his lab at http://www.nigms.nih.gov/findings.
McMurray fell in love with science in high school.

She realized that chemistry could help her understand the world.

When she’s not at the lab, you may find her:

...Listening to music at local jazz clubs

...Playing the piano at scientific meetings

...Sketching in charcoal

...Running on the treadmill
Tom makes a quick dinner for his wife and sons and then heads out the door. It’s the last Thursday of the month—his day to spend a few hours with friends.

They don’t bowl or play cards, or even munch on snacks. They sit in a circle and talk.

What brings them together is Huntington’s, a disease that’s ravaging the bodies and minds of their parents and partners.

An NCAA baseball cap hides Tom’s graying hair. His shadow of a beard and haggard face show that the last few weeks have been rough. Tom is the sole caretaker of his wife, Beth, who started showing symptoms a few years ago.

An incurable disorder passed from parent to child, Huntington’s targets the brain, triggering the death of cells vital to movement, speech, mood, and memory.

The disease has already stalled Beth’s mental and physical abilities. She can spend 2 hours signing her name on a greeting card or 20 minutes going down the stairs.

“She doesn’t get frustrated,” says Tom, who admits that he’s not always quite as patient.

Huntress of Huntington’s

Cynthia McMurray, 50, is also living with Huntington’s. For her, though, the connection is very different.

She doesn’t have the disease, but it’s a big part of her daily life. For the last 15 years, she has been doing research to learn how Huntington’s dismantles and destroys brain cells.

Huntington’s has been around for centuries, but we’re only beginning to know its secrets.

Records dating as far back as the Middle Ages have described people overtaken by a constant, uncontrollable, dancelike motion that makes them writhe, twist, and turn. People with this condition were said to have chorea—the Greek word for dance.

But this behavior brought on by Huntington’s hasn’t always been linked to the disease.
Missing Pieces
Researchers around the world are tackling different pieces of the Huntington’s puzzle. McMurray is looking for the molecular process that causes the Huntington’s gene glitch.

That process is called partial gene amplification. It means that certain parts of a gene are repeated over and over (see drawing, page 15).

The DNA in our genes is tightly packaged into organizational structures called chromosomes. As you probably already know, DNA is made of chemical building blocks that form the rungs of the DNA double-helix ladder.

Huntington’s has been around for centuries, but we’re only beginning to know its secrets.

In fact, experts suspect that some of the women persecuted as witches in Massachusetts during the late 1600s actually had Huntington’s, which caused their so-called “possessed” behaviors.

Many people with the disorder have been misdiagnosed. Doctors mistook the erratic moods and movements of folksinger Woody Guthrie, famous for his song “This Land Is Your Land,” for alcoholism and schizophrenia.

In 1952 and at the age of 40, Guthrie was properly diagnosed with Huntington’s. His mother and two children also had the disease.

Even though only 1 in 10,000 Americans is living with Huntington’s, each of their siblings and children has a strong risk for developing the disease.

Believe it or not, we all carry the gene involved in Huntington’s—just one of some 20,000 genes that make up the human genome.

But only those of us with a slight glitch in that gene go on to get Huntington’s. The genetic defect is heritable, and children of parents with the disease gene have a 50-50 chance of developing it, too.

And Huntington’s doesn’t discriminate: It affects men and women equally and crosses all ethnic and racial boundaries.

If you have the Huntington’s disease gene, you’d probably start to notice symptoms in your 30s, 40s, or 50s.

It might not be obvious at first. You might seem uncharacteristically irritable, depressed, clumsy, or forgetful. As the disease progresses, so does the severity of symptoms.

Although each person’s experience with Huntington’s is as unique as a thumbprint, many say that the disease can leave them feeling unbalanced and disoriented. Some report it’s like being blindfolded, spun around, and then asked to walk a straight line.

Some lose the ability to follow conversations, perform simple tasks like counting backward from 10, or even swallow food without choking.

They could, as many do, live like this for decades.

To date, there is no cure or treatment to slow the progression of Huntington’s. At best, people in the full swing of symptoms rely on an assortment of medicines to help them think more clearly, steady their stride, improve their mood, and, overall, enhance their quality of life.

Ask Cynthia McMurray about the biology of Huntington’s disease at http://www.nigms.nih.gov/findings. Send in your question by October 31, 2008, and in December we’ll post McMurray’s responses to 5 to 10 reader questions.
only beginning to know its secrets.

These bases are adenine (A), cytosine (C), guanine (G), and thymine (T). The order, or sequence, of the bases codes the specific biological instructions contained in a gene.

So, for example, attached or free earlobes are known to be inherited. Imagine that the sequence ATCGTT might say “attached earlobes,” while ATCGCT might say “hanging earlobes.”

In the early 1990s, when McMurray started her molecular biology lab at the Mayo Clinic in Rochester, Minnesota, she planned to study DNA structure. She was particularly fascinated by how gene segments get amplified, especially the repeating trio of bases C, A, and G.

Researchers have known since 1992 that CAG repeats in particular are common to several brain diseases, including Huntington’s.

People with Huntington’s have between 37 and 80 CAG repeats, while those not at risk have only a few dozen. For those at risk, more repeats typically mean symptoms will appear earlier in life and be more severe.

Looking back on her research, McMurray says, “It seems clear to me now that if we could stop the expansion of CAG in DNA, we could delay the onset of the disease.”

McMurray’s interest in Huntington’s was piqued in 1993 when scientists announced a breakthrough on the disease front: A team had located the Huntington’s gene at the tip of chromosome 4. The chromosomes in a single cell pack about 6 feet of DNA, so narrowing down the gene to a short region was a major accomplishment.

Patients and caregivers of loved ones with Huntington’s listened with great hope for new treatments and even a cure. McMurray started to think about how the disease could help her understand how genes produce repeats.

“Studying disease is a way to see how things work,” explains McMurray. “It’s a window that lets story continues on page 14
What’s Your Genetic Destiny?

Kind of like gazing into a crystal ball, could gene testing be a way to see your future health?

Today, you can be tested for nearly 1,500 different disorders. Starting with a sample of hair, saliva, or skin, lab researchers can scan your DNA for gene abnormalities linked to certain diseases.

The results may tell you if you are at risk for developing breast cancer, iron overload, or the brain disease called Huntington’s (see “Living With Huntington’s,” page 10).

Would you change your lifestyle? Undergo preventive treatment? Maybe you’d decide to do nothing. Faced with the choice, many people considering genetic testing seek advice from a genetic counselor.

But not everyone wants this information. Knowing you’ll develop a disease—or at least have that chance—could be devastating. If there’s no cure or effective treatment for the condition, you may feel helpless in facing the years ahead. With the possibility of passing on an errant gene, you may decide not to have children.

If your boss knew you’d develop a chronic disease in 2010, would she still give you a promotion? Would your insurance company deny you coverage? Many people think a person’s genetic information might lead to discrimination.

Looking ahead at these serious issues, legislators introduced a bill in 1995 that would protect genetic information from misuse. In 2008, the Genetic Information Nondiscrimination Act, or GINA, was signed into law.—E.C.
then to repeat themselves. The body tries to remove the structures, but for some reason fails. So the CAG repeats stay and continue to stretch.

“Our hypothesis is that the oxidative damage initiates the expansion process,” says McMurray.

Her recent experiments in mice with the Huntington’s disease gene show that normal DNA repair machinery can snip out the extra triplet repeats for a while but loses ground as oxidative damage increases with age. This may explain why symptoms typically appear in mid-life and appear earlier when there are more repeats to remove.

But McMurray suspects there’s more to this story.

She has also found that cholesterol accumulates in the brains of mice with Huntington’s. Cholesterol often gets a bad rap, but this waxy substance is critical for brain cells to work properly and stay structurally intact.

In the case of Huntington’s, cholesterol doesn’t get delivered to the right locations. McMurray likens the situation to a cholesterol “traffic jam.” Clearing the jam, she found, reversed the motor decline typically seen in mice with Huntington’s.

McMurray noticed that the cholesterol congestion also appeared to affect the mitochondria, which churn out the free radicals causing DNA damage. She’s currently running experiments to see if the cholesterol buildup might contribute to cellular stress and trigger more CAG repeats.

**Merger Views**

From the perspective of people who are living with Huntington’s disease, research has not advanced fast enough, but from the scientific perspective, progress has actually been impressive.

“It’s really difficult to find the genesis of a disease,” says McMurray. “But I think there’s huge hope for the future.”

Since scientists identified the Huntington’s gene in 1993, researchers worldwide have published more than 5,000 findings related to the disease. Among them is a genetic test to determine if someone at risk carries the disease gene (see “What’s Your Genetic Destiny?” page 14).

The scientific advances continue to drive McMurray toward a better understanding of Huntington’s and the underlying molecular process that causes it.

“Getting excited about results [of my experiments] and thinking about the implications is what I love the most,” says McMurray.

Each morning after a few cups of coffee, a blast of Aretha Franklin, and a quick workout, McMurray hits the lab and stays there for about 12 hours.

You can judge her progress by the papers on her desk. The taller the piles, the busier she is. When she finishes a project, she straightens up to make room for her next big idea.

McMurray also spends a chunk of her workday interacting with people who have Huntington’s and their caregivers. As a basic researcher working at the Mayo Clinic, which treats people with a range of complex diseases, McMurray is motivated by both scientific curiosity and a desire to help people.

She routinely answers calls from people with Huntington’s or others interested in learning more about the disease. Some even want to donate tissue samples for research. To update the community about research advances, she speaks to local support groups.

“The amount of courage and hope and love that exists in these families,” she says, “is just unbelievable.”

McMurray says these interactions help the Huntington’s disease community story continues on page 16.
Fix for a Broken Heart?

Embryonic stem cells have the potential to become any of the body’s 206 cell types. Scientists are working hard to get these “blank slate” cells to grow into replacement cells for different body organs.

The task has proven to be difficult, but researchers are slowly making progress. In one recent advance, cell biologist Gordon Keller of the McEwen Centre for Regenerative Medicine in Toronto, Ontario, Canada, transformed human embryonic stem cells into immature heart cells.

Keller perfected a concoction of nutrients and proteins that, when added to the embryonic stem cells, forced them to become immature heart cells. He then showed that the young heart cells could grow into all three types of cells that make up a functional, beating heart.

With more research, scientists may be able to coax the immature heart cells into forming new heart tissue, a complex blend of the three cell types. The work will also help researchers understand heart disease and test new medicines to treat it. —A.D.
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