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Findings

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Tracking Zinc in Brains and Bacteria in Guts

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
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Inside Science: Life in the Lab

Just Found: Quick Takes on Hot Science

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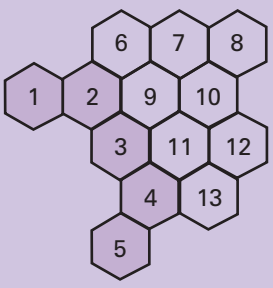

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Up Close With

Brian Bachmann

BIOSYNTHETIC CHEMIST

"It's possible to have it all. But you have to be willing to *do* it all."

CURRENT FAVORITE BANDS

LCD Soundsystem, Unkle, Antony and the Johnsons

ALTERNATE CAREERS

Philosopher and businessman

GOOD READING

Science fiction, especially Neal Stephenson, and biographies of early scientists

FIRST JOB

Burger King

UNUSUAL OFFICE OBJECT

"Captain Bachmann" hat for Talk Like a Pirate Day

STEVE GREEN/VANDERBILT UNIVERSITY


PETZL

JOHN RUSSELL / VANDERBILT UNIVERSITY

Drugs from Deep Down

BY STEPHANIE DUTCHEN

Two hundred feet below the spot where Tennessee, Alabama and Georgia meet, a group of mud-soaked explorers picks its way through cool, wet darkness.

The cavers are outfitted with knee pads and climbing gear and wear lights on their helmets like miners. They crawl through narrow stone passageways and carefully lower themselves into 200-foot pits.

Pale stalactites hang dripping from the cavern ceiling above them, while flowstone formations make it look like rock has bubbled up from the walls and floor. There's a distinctive, earthy smell in the air, like a damp basement.

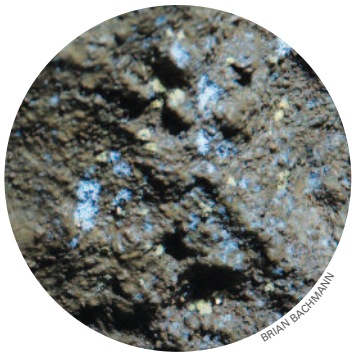
One of the men, Brian Bachmann, recognizes the scent. It's actinomycetes, a kind of bacteria people use to make antibiotics.

Colonies of the stuff—along with unknown species of bacteria, fungi and other mysterious substances—flourish as though the cave walls were Petri dishes in a lab.

Bachmann stops. He takes a piece of filter paper out of his backpack and wipes it gently along the rock before sliding it into a sterile tube, sealing it shut and putting it back in his bag.

He'll take 20 to 30 more samples like this during the expedition, collected from a variety of locations in the cave: a pool of water, a patch of soil, a stalagmite.

Bachmann, a biosynthetic chemist, is hoping that his samples will reveal sources of new medicines.



BRIAN BACHMANN

Cave walls teem with undiscovered life forms and the molecules they make.

The Glamorous Life of Secondary Metabolites

Bachmann analyzes his samples from his 12th floor laboratory at Vanderbilt University overlooking Nashville, Tennessee. He is interested not only in what molecules the samples contain, but also in how cave-dwelling creatures manufacture those molecules.

Bachmann ignores the molecules known as primary metabolites—DNA, amino acids, simple sugars and vitamins—that all organisms need to live.

His focus is on secondary metabolites, which endow organisms with abilities like communication and weaponry. These natural properties can be adapted for human use—to kill bacteria or reduce inflammation, for instance. Because of this, secondary metabolites, or chemically modified versions of them, have the potential to become invaluable drugs.

When we understand life's construction processes, we

All of the following are secondary metabolites: caffeine, penicillin, codeine, steroids, bacitracin (an antiseptic), artemisinin (for malaria) and atropine (for cardiac arrest). And that's just the tip of the metabolite iceberg. Between half and three-quarters of all drugs on the market today are based on secondary metabolites.

The search for new drug sources—either discovering organisms that make interesting metabolites or finding new uses for known metabolites—is what gets Bachmann excited about crawling around in the mud.

"I love science," he says, and has since childhood (see "A Born Chemist," page 6). "I brush my teeth with vigor every morning thinking about a problem, a puzzle, in chemical biology. You might think it's an obsession."

So far, his "obsession" has steered him into quests for better malaria drugs, cheaper HIV drugs, new technologies for drug discovery and half a dozen promising drug candidates.

It may sound like a motley collection of projects, but as Bachmann explains, "They're all unified by chemistry—the chemistry of how life makes molecules."

The long-term goal, he says, is to "know the design rules across all orders of life." He wants to understand life's construction processes so well that he can modify those processes to suit human needs.

"If we can teach *E. coli* to make ibuprofen or an AIDS drug—[or any other] compounds they don't make naturally—that will be the ultimate proof that we really understand," he says.

Do Drugs Grow in Caves?

Some chemists on the hunt for completely new drugs investigate natural products—particularly secondary metabolites. Rainforests rich in plant and animal life have yielded compounds that led to drugs such as the cancer fighter Taxol®.

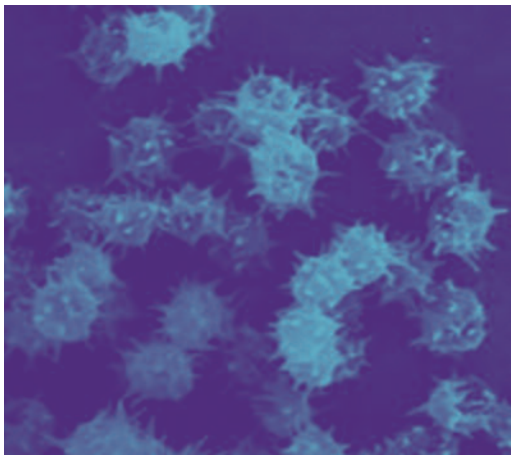
Other drugs and drug precursors, like a painkiller discovered in the venom of a cone snail, come from the ocean (see "Secrets of the Killer Snails" in the September 2002 issue of *Findings*).

"I have a lot of colleagues who go diving off coral reefs in Jamaica, Papua New Guinea and Indonesia. They work very hard, but they always come back tanned," laughs Bachmann. "I come back covered in mud, bruised, with a busted ankle."

Perhaps the unglamorous conditions in caves kept other people away, because Bachmann thinks he's one of the first to go spelunking in search of drug-making organisms. He suspects that the secluded, nutrient-poor environments underground create unique collections of microorganisms that constantly churn out metabolites to stay alive and out-compete their neighbors.

Bachmann wants to identify those metabolites and find out which ones could help treat human disease. To do that, he not only collects his filter paper swabs, he also sets out collection traps he hopes will entice microorganisms to come inside and grow. He comes back to collect the traps about a month later.

With each trip below ground, Bachmann learns more about which areas of a cave are most likely to have new and exciting microbes.



BRIAN BACHMANN

Microscopic, star-shaped spore capsules from a cave-dwelling bacterium.

"For instance, we've learned not to get samples from bat guano," he says. "That's the one place we've never found any kind of microorganisms we're interested in."

He also stays away from where humans have tread before, figuring that way he's more likely to find microorganisms no one else has discovered—and less likely to accidentally come back with microbes from some previous spelunker. Sometimes that involves convincing his caving partner to "Spiderman his way up a wall to get at some remote crevice."

In general, while collecting samples, he focuses on "being as creative as possible. We try to get as much diversity as we can."

And he's careful not to damage the caves or take more material than necessary. His team follows what he calls the caver's motto: "Take nothing

FIND MORE @

Read more about why chemists study natural products at http://publications.nigms.nih.gov/chemhealth/nature.htm

can modify them to suit human needs.

but pictures, leave nothing but footprints, kill nothing but time." After a trip, "there is more soil on our boots than in our sample tubes," he says.

In the 4 years he's been searching, Bachmann has plucked more than 20 compounds from cave organisms. About half of them are new to science.

"That's actually a very high success rate," he says, since a typical natural product discovery rate is more like 1 in 20. "It seems there is something special about caves."

How to Spot a Drug Candidate

When Bachmann brings his samples back to Vanderbilt, he tries to grow the most promising microorganisms in his lab.

It's not easy. The microbes are far from home and don't always survive in their new surroundings.

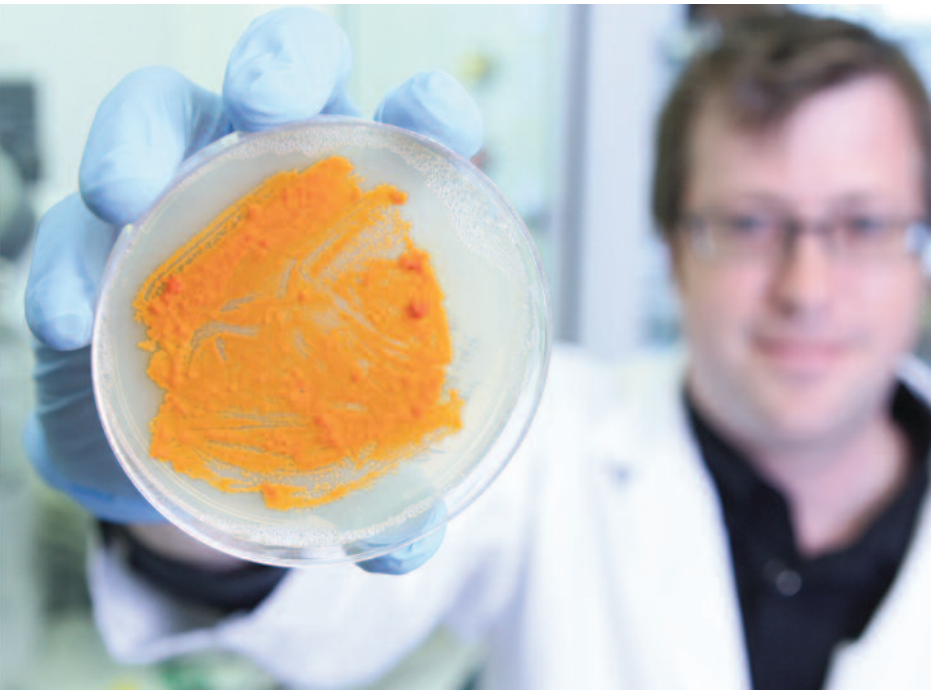
But if they make it, they sometimes do so with a vengeance. They've subsisted on meager rations all their lives, like college students living on instant noodles. When Bachmann puts them in dishes coated with nutrients, their metabolite production goes into overdrive.

"It's like they're at an all-you-can-eat buffet," says David Wright, a fellow chemist and one of Bachmann's collaborators at Vanderbilt. "They pump out all these potentially interesting compounds."

To find these compounds, Bachmann ferments the samples in a bacterial beer containing tens of thousands of compounds. Then he faces what he calls "the central question in natural product discovery: What's interesting in that broth, and how do you pull it out?"

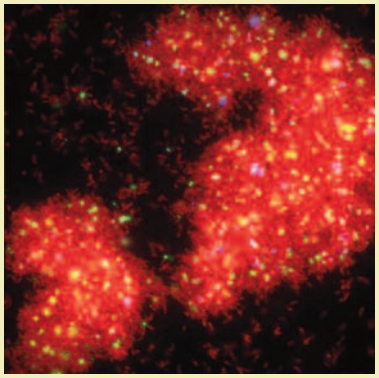
He could run a test on the whole brew to look for a single, specific ingredient—say, a cholesterol-lowering enzyme. But that risks

story continues on page 6



VANDERBILT UNIVERSITY

Bachmann gives his cave-collected creatures a new home on nutrient-rich laboratory dishes.



CÉCILE BERNE/ INDIANA UNIVERSITY

Close-up of a biofilm beginning to disperse.

Breaking Up Biofilms Is Hard to Do

Long before people started living in villages, bacteria figured out the advantages of community. When possible, most bacteria live together in what are known as biofilms. Like it did for early human populations, communal living protects bacteria from the hazards of the world—including antibiotics.

Biofilms form a tenacious slime that adheres to almost anything that tends to stay moist—hospital tubing, teeth, kitchen drains and oil pipelines. Although often harmless to humans, biofilms are responsible for many infections, including of the ear and urinary tract.

Now, researchers Jon Clardy, Roberto Kolter and Richard Losick at Harvard University in Cambridge, Massachusetts, think they have found a way to break up biofilms. The scientists are co-opting biochemical signals that biofilms use to disperse and spread to new locations when they run out of food or pile up too much waste. The signals are chemically simple and appear to act on a wide variety of bacterial species. If the substances can dissolve or prevent biofilms in real-world situations, their use could lead to advances in medicine, industry and even household cleaning products. —*Karin Jegalian*

A Born Chemist

You could say that Brian Bachmann was destined to be a chemist.

His parents met in an organic chemistry class in college.

A scientist, entrepreneur and inventor, Bachmann's father started a chemistry company in the basement of the family's Connecticut farmhouse.

Bachmann remembers that he loved working in the lab as much as other kids loved playing with toys. One Christmas Day when he was young, he set aside his newly opened presents and went into the lab with his father.

"It was something fun to do," he recalls. "And at the end of the day, we had a patentable invention."

He learned from his father about the scientific method—"knowing what's in your experiment, changing one thing at a time, having a hypothesis and testing it"—as well as the importance of thinking outside the box and deriving joy from science.

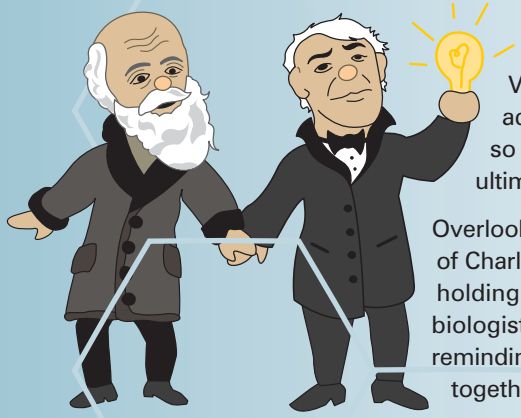
But like any teenager in the mood for rebellion, Bachmann decided he wasn't going to go into chemistry. In college, he took courses in physics, philosophy and English.

Then he took an elective in organic chemistry, and fell in love.

"It's such a beautiful system. You could come up with a theory on a piece of paper and test it the same day by mixing things in a flask, stirring and heating it and analyzing the results," he says.

A few years spent in industry taught Bachmann to look for practical applications, embrace useful technology and put together an interdisciplinary team.

Biochemists, synthetic chemists, microbiologists, molecular biologists, engineers and geneticists now work side by side in his lab to solve problems in innovative ways (see main story). The lab is set inside Vanderbilt's medical center and across the street from a hospital, so they never lose sight of their ultimate goal to help people.



Overlooking it all are magnetic puppets of Charles Darwin and Thomas Edison holding hands—the evolutionary biologist and the genius inventor, reminding Bachmann's team to work together.—*S.D.*

continued from page 5

overlooking other compounds like potential antidepressants or blood-clot busters.

Another technique is to add a strain of bacteria to the culture dish. If the added bacteria die, Bachmann surmises there's an antibiotic in the broth.

To isolate the antibiotic molecule, he must analyze each ingredient separately. Then it's rinse and repeat with a different bacterial strain.

It's a tedious process, and screening every broth ingredient for every possible biological activity isn't practical. So Bachmann has partnered up with academic and industry colleagues to develop technology that searches faster and smarter.

One method, developed by Vanderbilt chemist John McLean, is called ion mobility mass spectroscopy—a technical way of saying it flags molecules with funky shapes. Because many drugs have unusual shapes that allow them to do specific jobs in the human body, the spectrometer helps Bachmann pinpoint compounds that may have drug-like activity.

Another program in progress goes by the nickname NELI (short for Natural Extract Lead Identification System). In this case, "lead" (pronounced "leed") refers not to the heavy metal but to a molecule that might lead to a new drug.

Usually, natural products themselves don't end up on pharmacy shelves, but rather serve as drug leads. Scientists like Bachmann chemically tweak them to make them more effective, less toxic or otherwise better suited to the human body.

NELI lets Bachmann compare different growth conditions to find those that encourage an organism to produce interesting compounds.

to find truly new antibiotic drugs.

He and collaborator Wright use NELI to search for compounds that might treat malaria.

Medicine-Making Microbes

Beyond the search for new secondary metabolites, Bachmann is trying to unlock the secrets of how organisms make them in the first place.

Sometimes this involves analyzing the genome of a promising microbe and trying to predict what kinds of enzymes or compounds it makes. For example, he decoded the genetic "blueprints" for making anthramycin, a kind of natural chemical equivalent to Valium® that came from an organism found in a rotting compost heap.

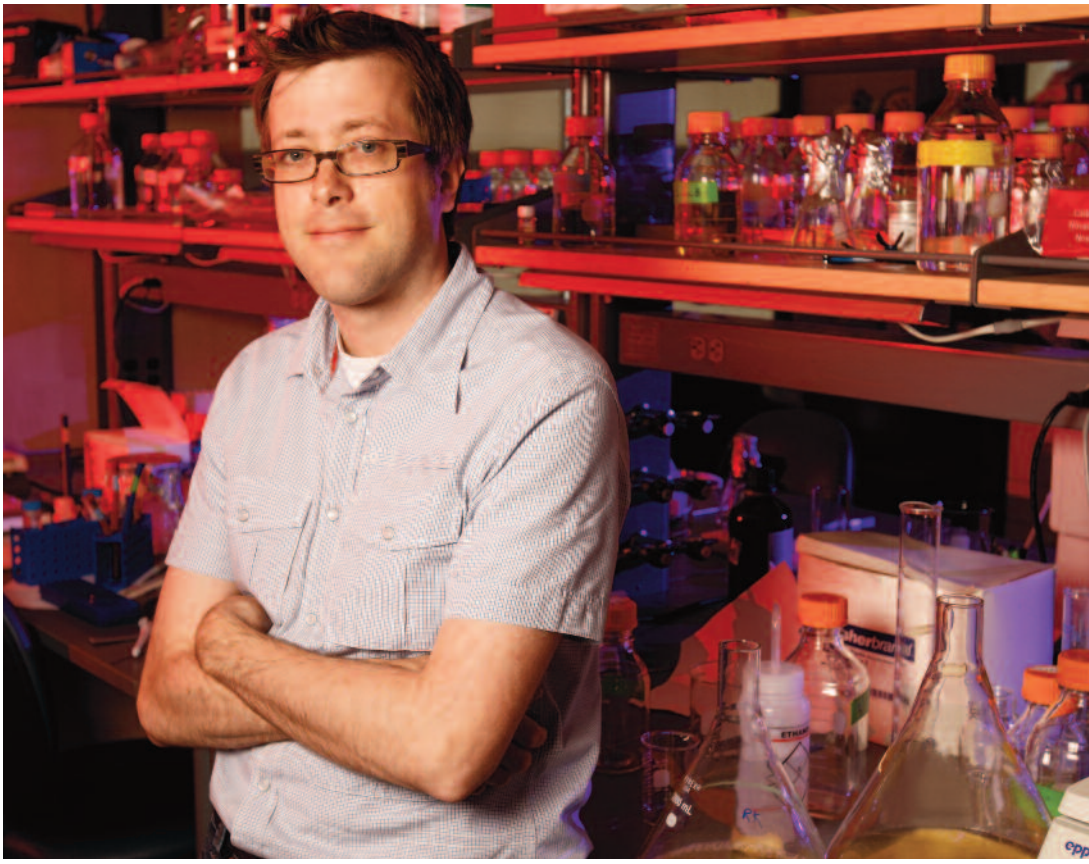
He uncovered the molecular structure of a compound called K-26 found in a soil sample next to a pond in Japan. K-26 contains a rare carbon-phosphorus bond and lowers blood pressure like a powerful ACE inhibitor. His work could provide insight into making a better blood pressure drug.

Bachmann is also working with Vanderbilt pharmacologist Tina Iverson to see if they can resuscitate a failed antibiotic called everninomycin.

It's critical to find new antibiotics because bacteria are becoming resistant to many existing treatments. Most new antibiotics "are really just modifications" of existing ones, says Iverson. She and Bachmann want to find truly new antibiotics.

Everninomycin could have been one, if it had worked better when it was tested in people.

Bachmann and Iverson believe that, by genetically "tweaking" the organism that makes everninomycin, they could coax it to produce a safer, more effective cousin—a potential new antibiotic.



JOHN RUSSELL/VANDERBILT UNIVERSITY

In his laboratory, Bachmann studies interesting cave creatures and the molecules they make. His research could lead to new medicines or other benefits.

Bachmann is also working with Iverson to genetically engineer *E. coli* bacteria to make affordable HIV drugs.

Drugs called nucleoside analogs make up about half our arsenal against tough viral infections like HIV and hepatitis. But manufacturing them is so expensive that people in developing countries can't afford them. If Bachmann and Iverson can co-opt *E. coli* into churning them out in large and cost-effective amounts, the drugs could fall to one-tenth of their current price.

"Right now, that's still a dream," says Bachmann. He compares the process to teaching organisms to make biofuel.

Still, if it takes years to pull off—or even if it never comes to fruition—the project is already contributing to basic science knowledge. And that knowledge has the potential to pay off in unforeseen ways.

In Search of Something New

In caves or at home, the search for the new extends throughout Bachmann's life.

He likes to use new power tools to fix up his family's 1940s-era home and dabbles in landscaping. He and his wife, Beth, an award-winning poet and English professor at Vanderbilt, experiment with new culinary techniques when they make

story continues on page 8

Studies in mice could help scientists treat vision problems in humans.

Cells for Sight

When it comes to cells involved in vision, rods and cones are considered top players. Together, these cells collect multicolored rays of light that the brain uses to create images of the vibrant world around us.

But biologists have now discovered that other, less well known eye cells also help with vision. A team led by Samer Hattar of Johns Hopkins University in Baltimore, Maryland, found that mice without rods and cones are not totally blind: They can exit a maze by recognizing a particular visual pattern.

How do mice that lack rods and cones see this—or any—pattern? According to Hattar's study, the mice use a type of cell called intrinsically photosensitive retinal ganglion cells (ipRGCs).

Scientists already knew that ipRGCs shrink pupils in bright light and influence waking and sleeping cycles, but they didn't realize that the cells also play a role in forming images.

Hattar's team found several kinds of ipRGCs, some of which project into a part of the brain involved in image perception. The unexpected discovery of ipRGCs' new role could lead to new approaches for treating vision problems. —*Kirstie Saltsman*

It's like walking on the moon.

continued from page 7

their own Indian food. When he gets bored with his current music, he pumps his nieces and nephews for new bands.

"Basically, if I can find something that sounds new, I get pretty excited," Bachmann says.

He has also been engrossed in what he fondly calls his new "synthetic biology experiment": his 3-year-old daughter, Ilyana.

"She's teaching me a lot. I'm learning fundamental things about what it's like to be human, and consciousness, and identity…."

He brings that same thrill of insight to his professional life.

"It's amazing that we are now potentially going to be able to understand much of what it means to be human, through chemistry," he says. "Sometimes my head reels with the magnitude of the understanding we're gaining about the molecular basis of who we are and what we could become."

A hobbyist philosopher, Bachmann embraces the big questions in science and in life. He wants to know: "Why does a soil organism make a compound that lowers human blood pressure? How does life manage these small miracles of chemical synthesis?"

"Brian's not afraid to grapple with really big questions," says collaborator Wright. "It makes me not afraid to ask my own big questions."

Whether he's pondering the meaning of life or examining the structure of a single molecule, Bachmann never loses his enthusiasm for the potential of synthetic chemistry.

"It's like walking on the moon. Oftentimes you look down at your feet and think, 'Nobody else has stepped here before.' That's a wonderful feeling, when you think you're the first person to have seen a new way to make a natural molecule, or use life's design rules to build a molecule, or see a molecule no one else has described."

With a lot of hard work and a little luck, Bachmann's ventures into unfamiliar territory—whether in caves or in the lab—will yield new knowledge and new drugs to help improve people's health around the world.

JEFF MILLER

Laura Kiessling

BRIAN WILSON

Erik Sorensen

SCOTT GALVIN

Lola Eniola-Adefeso

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Up Close With

Amy Palmer

BIOCHEMIST

"I never would have guessed I would become a scientist."

FAVORITE HOBBIES

Rock climbing and snowboarding

FAVORITE WEEKEND ACTIVITY

Cooking a giant breakfast for the family

FAVORITE BOOK

***The Power of One* by Bryce Courtenay**

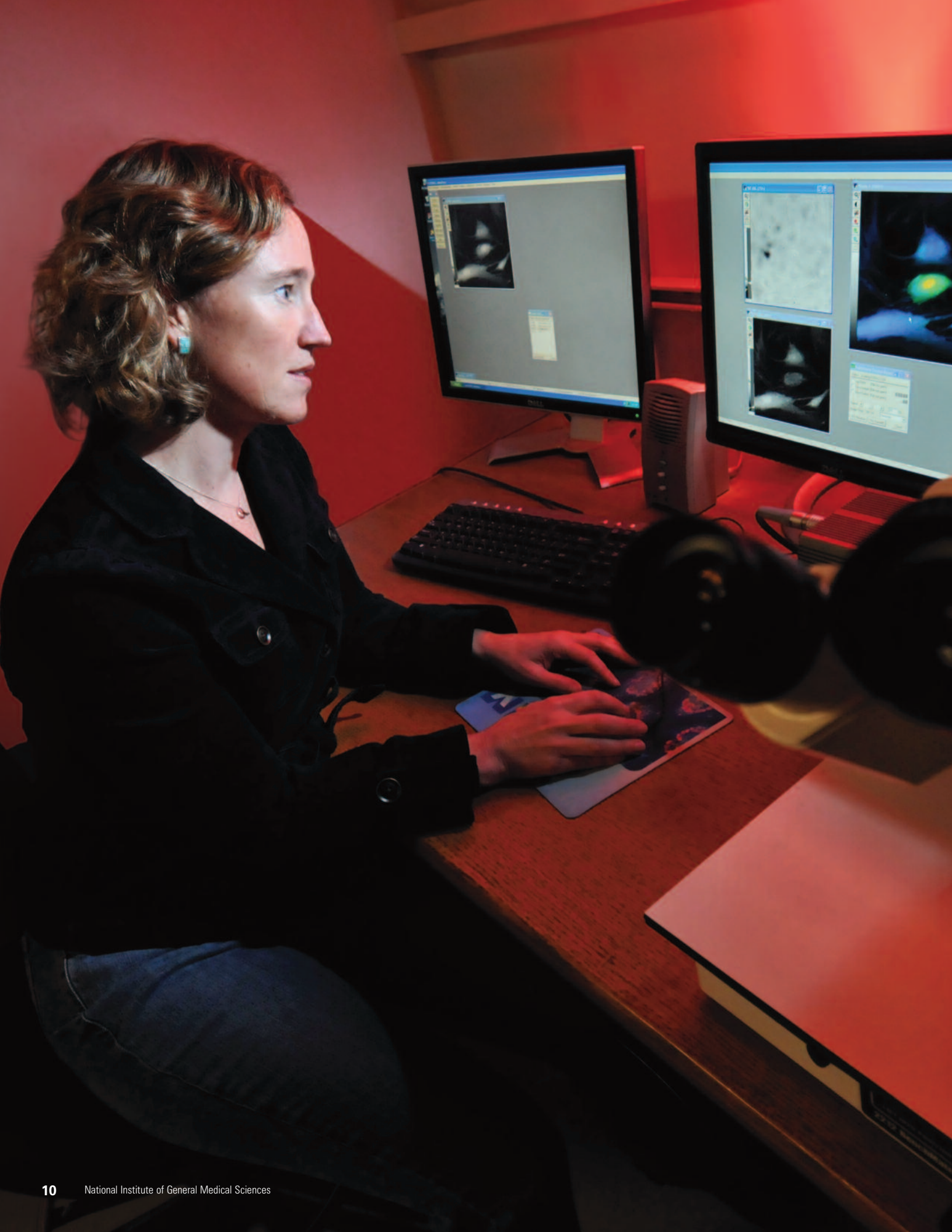
FAVORITE FOOD

Cilantro—just about everything tastes better with cilantro on it

HIDDEN TALENT

Knitting

CASEY A. CASS/ UNIVERSITY OF COLORADO AT BOULDER



CASEY A. CASS/UNIVERSITY OF COLORADO AT BOULDER

Mesmerized by Metals

BY JANELLE WEAVER

Some kids have chemistry sets when they're 5. Amy Palmer was not one of them. In her teens, she considered becoming a gymnastics coach or writer, and almost majored in Russian instead of chemistry.

"I always found the humanities more interesting," she says. "I never would have guessed I would become a scientist."

Palmer discovered her love for science in college. A professor offered her a rare opportunity to work in a well-regarded research lab investigating the health effects of toxic metal exposure. But to accept the position, she'd have to give up her spot in the Russian foreign study program in St. Petersburg.

She had faced a similar decision before, when a Dartmouth swim coach insisted that she, a competitive swimmer since kindergarten, decide between the swim team and the lab.

At both crossroads, she opted for research—an activity that attracted her because of her natural curiosity and drive for making discoveries.

"I didn't know why someone would let me work in their lab. I was not the perfect student," Palmer says. "But I gave it a shot, and [it was the] opportunity that defined the direction I took in my life."

Now a biochemist at the University of Colorado at Boulder, she uses creative chemistry to track the movement of metals and other molecules in living cells, especially when those molecules play a role in human diseases.

Beyond the hardware store: Metals like copper, zinc and iron are essential nutrients, needed in tiny amounts throughout our bodies.

Metal Overload

Throughout her research career, Palmer has focused on the role of metals in biology. Some metals, like iron, copper, calcium, zinc and magnesium, are essential for health (see "Metal Match," page 13).

Calcium ensures strong teeth and bones and is necessary for muscles to move, brains to send signals and hearts to beat.

Iron helps carry oxygen to tissues and is important for cells to produce energy, make DNA and grow. It's why our blood, when exposed to oxygen, is red.

But an excess of metals in our bodies can cause organ failure, nerve damage, cancer or even death. So, Palmer explains, there must be careful controls on how metals get where they need to go. That's where her research comes in.

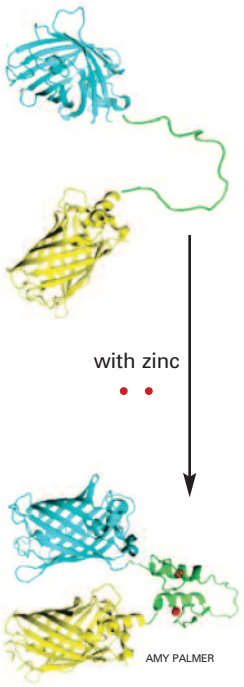
Her work has the potential to make an impact on people's health.

Zinc Zealot

Much of Palmer's work focuses on zinc, a metal used throughout our bodies to ensure proper immune responses and a healthy nervous system. Zinc also regulates the function of some genes, enables many proteins to carry out their vital roles and helps speed chemical reactions in our bodies. A zinc imbalance is linked to Alzheimer's disease, diabetes and prostate cancer.

When Palmer was doing research in college, it was impossible to track the movement of metals inside cells. Once she had a lab of her own in Colorado, she developed four fluorescent sensors to detect zinc in living cells.

These sensors allow Palmer—and other scientists—to see how cells use and store zinc. They can detect different levels of zinc in various parts of the cell and follow its flow during processes like nerve signaling, bacterial invasion and disease progression.



When zinc (red) binds to the floppy part (green) of Palmer's sensor molecule, it yanks together the two fluorescent proteins (blue and yellow).

"When she tackles a problem, she tackles it hard," says Tom Trainor, a chemistry professor at the University of Alaska Fairbanks whom Palmer met when they were both graduate students at Stanford University. "She's focused on getting whatever she sets her mind to."

Palmer made her zinc sensors using two fluorescent proteins, one that glows blue and the other that glows yellow. She linked these proteins together with a zinc-sensing segment, which swings around loosely like a slack rope.

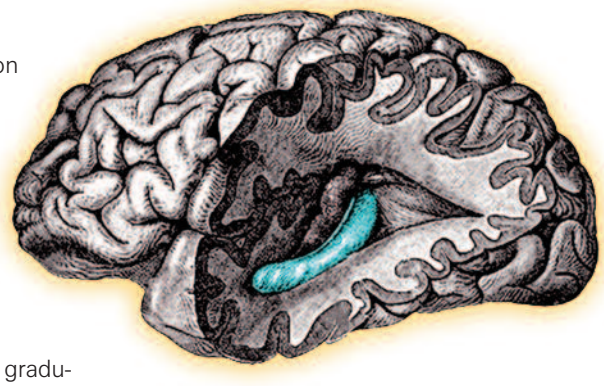
When this slack area binds to zinc, it constricts and yanks the two proteins together, causing the blue protein to transfer light energy to the yellow protein, which then glitters like ink from a yellow highlighter.

Palmer visualizes the yellow gleam by peering through a microscope specially designed to detect fluorescent molecules. She can track the levels and location of zinc for as long as she'd like.

Metals and Memory

In her latest experiments, Palmer has her microscope trained on cells from a part of the brain called the hippocampus, which helps mammals store memories.

The hippocampus is also the first area of the brain to be damaged by Alzheimer's disease, which robs patients of the ability to form new memories.



Tracking zinc in the brain region called the hippocampus (blue) might shed light on Alzheimer's disease.

By tracking the movement of zinc inside hippocampus cells, Palmer hopes to gain insights into what role the metal might play in forming memories and the progression of Alzheimer's disease.

She'd also like to determine which proteins, nerve signals and other factors influence the movement of zinc inside brain cells.

Ultimately, she hopes her work will have medical applications. She envisions a zinc-tracking technique that would enable early diagnosis of diseases like Alzheimer's and drugs that could control the level or location of zinc to prevent or treat such diseases.

Finally, she plans to expand beyond zinc and develop fluorescent sensors for other biologically important metals such as copper, which in high levels can cause liver damage, kidney failure, coma and death.

"Her work has the potential to make an impact on people's health, and that's a big deal to her," Trainor says.

story continues on page 14

FIND MORE @

To see the hippocampus inside a brain, check out the animation at http://en.wikipedia.org/wiki/File:Hippocampus.gif

Metal Match

Several metals are vital to life. By eating a balanced diet, you probably get enough of these essential nutrients. But if you lack one or more, you could experience symptoms ranging from tiredness and hair loss to severe brain damage.

Too much of certain metals can be equally disastrous (see main story).

See if you can match the metals with what they do in our bodies.

A: Iron
B: Manganese
C: Calcium
D: Magnesium
E: Zinc
F: Copper

☐ 1. The most abundant metal in our bodies (about 1 kg in the average person), stored in bones and teeth. Also critical for proper muscle and nerve function, hormone release and more. Found in dairy products, broccoli, figs and sardines.

☐ 2. Found in pennies, electrical wires and the Statue of Liberty's skin, this metal is also needed for firm skin, cartilage and ligaments, and to remove dangerous "free radical" molecules in the body. Rich sources include beef liver, lobster, shiitake mushrooms, chocolate and nuts.

☐ 3. The most widely used metal for making machinery, skyscrapers, cars and ships. It is also found in red blood cells, where it is responsible for carrying oxygen to our tissues. Abundant in red meat, beans and spinach.

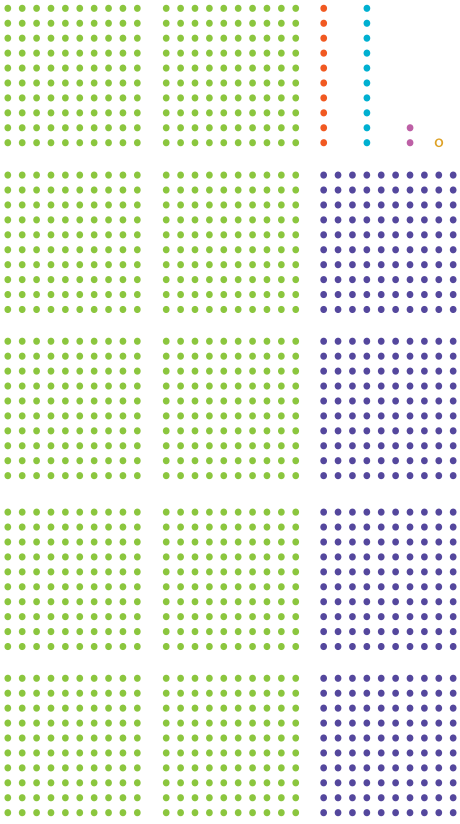
☐ 4. Used in batteries and to prevent rust on cars, fences and bridges, this metal is used throughout our bodies in many ways, including immune function, brain activity, and growth and development. To get lots of it, eat oysters, fortified cereal, baked beans or beef.

☐ 5. Used in flares and fireworks. Needed for healthy muscles, nerves, bones, a strong immune system and a steady heart rhythm. Abundant in whole grains, spinach and pumpkin seeds.

☐ 6. An essential additive in steel and used to make pink-colored glass, this metal is stored mainly in the liver and kidneys. It helps our bodies make DNA and RNA, break down food into energy and heal wounds. Good sources are oat bran and other whole grains, pineapple and chickpeas.

—Alisa Zapp Machalek

Recommended Daily Amounts (approx.)
Each dot represents 1 milligram (mg)



- Calcium, 1,000 mg
- Magnesium, 400 mg
- Iron, 10 mg
- Zinc, 10 mg
- Manganese, 2 mg
- Copper, 0.9 mg

Adapted from the U.S. Department of Agriculture's Dietary Reference Intake Tables, developed by the Institute of Medicine's Food and Nutrition Board.

Answers: 1. C 2. F 3. A 4. E 5. D 6. B

Sepsis is usually treated in a hospital intensive care unit, where IV antibiotics and fluids help fight infection and keep blood pressure from dropping too low.

Seeking the Causes of Sepsis

If you read about Kevin Tracey in the September 2010 issue of *Findings*, you know that sepsis, or body-wide inflammation, is a top killer that remains difficult to understand and treat.

Tracey discovered that the nervous system is involved in this immune response and that stimulating a particular nerve could protect animals—and possibly humans—against sepsis.

Other scientists are looking elsewhere.

Trauma surgeon Carl Hauser at Beth Israel Deaconess Medical Center in Boston focuses on mitochondria. These cellular power plants can spill into the bloodstream after an injury. Because they're biologically similar to bacteria, mitochondria can ignite a sepsis-like immune response.

At the Oklahoma Medical Research Foundation in Oklahoma City, cardiovascular biologist Charles Esmon points to histones, the spool-like structures that wind DNA into tidy shapes. Esmon found that histones can enter the bloodstream during an infection and cause sepsis. He also discovered that Xigris®, a drug used to treat sepsis, works by chopping up histones.

Because histones are also linked to multiple sclerosis, lupus and other diseases, finding ways to inactivate them could have benefits beyond fighting sepsis. —*Emily Carlson*

"I want to bring excitement and

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Salmonella Surge

Nudged by one of her students, Palmer is now using chemistry and imaging techniques to address another biological question: How does *Salmonella* attack cells?

Salmonella is a rod-shaped bacterium that causes severe diarrhea, fever and abdominal cramps. Every year, there are approximately 40,000 *Salmonella* infections reported in the United States. There have been outbreaks related to contamination of alfalfa sprouts, peanuts, salami and black pepper. Last year, there was a massive recall of eggs due to *Salmonella* poisonings across the country.

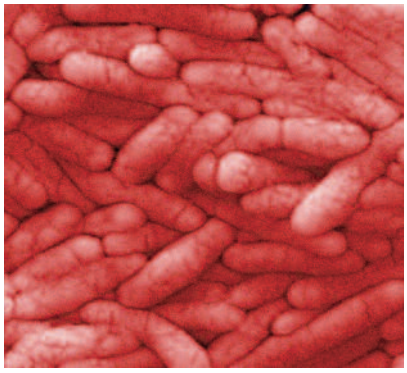
During an infection, *Salmonella* uses what looks like a miniature syringe to inject more than 60 proteins into cells in the infected person's intestinal lining. The cell's natural response is to engulf the bacterium. But rather than destroying *Salmonella*, this action just welcomes it in.

As *Salmonella* enters human or animal cells, a piece of the host cell's membrane engulfs the bacterium, forming a compartment called a vacuole. From this protected spot, the bacterium ejects another round of proteins that help it evade the host cell's defenses, prolonging the infection.

Seeing the Light

By using fluorescent sensors to track different *Salmonella* proteins, Palmer is figuring out how they enable the bacterium to infect and survive inside a host cell. She discovered that labeling proteins and tracking bacterial infection required a different technique than the one she used to track zinc.

She couldn't just attach her fluorescent proteins onto the *Salmonella* proteins, because the resulting complex was too big to get through *Salmonella's* narrow, syringe-like projection. So she split the problem in half—literally.



JANICE HANEY CARR / CDC

Rod-shaped *Salmonella* bacteria like those magnified here can invade the intestines, causing food poisoning.

She and her research team divided the barrel-like fluorescent proteins down the middle. They put the left half into the host cell and attached the right half to proteins in *Salmonella*.

Then they waited for the yellow glow. The fluorescent proteins only light up once the two halves unite within an infected cell. When the scientists see the light, they know that *Salmonella* has successfully infected the host cell. Then they track where the fluorescent proteins go and what they do.

Palmer tracked *Salmonella* proteins between 4 and 24 hours after infection. Her team found that some proteins home in on the vacuoles and create tubules that shoot out from them, like legs dangling from a spider. The tubules carry the vacuole around inside the cell and might help *Salmonella* spread from cell to cell.

Other *Salmonella* proteins wander over to the cell's "post offices"—compartments called Golgi bodies that package proteins, carbohydrates and fatty lipids for delivery to other parts of the cell. Palmer's team and other scientists suspect that *Salmonella* proteins may intercept these nutrient parcels and deliver them instead back to the bacteria.

innovation into the classroom."

Palmer is now working on ways to track multiple proteins simultaneously to see how they coordinate an attack. She is also collaborating with the U.S. Department of Agriculture to study how *Salmonella* invades pigs, cows and chickens. Eventually, her work may reveal how *Salmonella* maintains its niche in the cell, allowing infections to persist.

What Matters Most

When Palmer's not on campus, she's most likely spending time with her family—Alexis Templeton, a geology professor at CU-Boulder, and their two children, Ethan (5) and Ellie (3).

Palmer works hard to maintain a balance between her work and family life, says colleague and friend Deborah Wuttke, a biochemist at CU-Boulder. "She has an incredible ability to multitask and a strong commitment to both family and her professional life."

Though full of energy, Palmer recognizes that you can't excel at everything all at once. Her career and family are her top priorities.

So, at least for now, Palmer has less time for her hobbies, such as rock climbing. During graduate school, Palmer, Templeton and Trainor would spend weekends climbing in the mountains of California.

"It was one of my biggest passions," Palmer says.

"She was set on being a good climber and taking the lead," Trainor says. "She had a healthier perspective than most scientists in terms of balancing life inside and outside the lab."

The formula is simple for Palmer: "It's a matter of figuring out what matters the most and making compromises," she says. "If I have to choose between finishing a paper now and going to my son's preschool graduation, of course I'm going to the graduation."

Palmer is also grateful for the support of Templeton, who understands the lifestyle and stresses of academic life. She remembers how Templeton helped her address one particular challenge—knowing when to shut her door.

"I would leave it open all the time and never get any work done," she says.

Finally, Templeton gave her a crucial tip. "Now, if I close it most of the way, the students know not to bother me unless it's really important," Palmer says.

Opening the Door

Palmer's friendly and helpful nature makes it difficult for her to deliberately shut the door, even partway, on her students.

"I never had a professor like her," says Jose Miranda, one of Palmer's graduate students. "She always took the time to make sure everyone understood, and her door was always open. When I'm a professor, I'm also going to have an open-door policy."

Teaching is what initially attracted Palmer to an academic career. "I want to bring excitement and innovation into the classroom," she says.

To learn how, she obtained a master's degree in science education while working on her Ph.D. in biophysical chemistry at Stanford.

"I realized that not everyone learns the same way that I do, and I should adopt a lot of different strategies to reach the most students."

The dedication to teaching is a major factor that attracted her to CU-Boulder, which had initiated the Science Education Project under the direction of Nobel laureate Carl Wieman. The project works to improve science teaching by using research-validated classroom techniques and technology.

"It gave me the courage to try out different things in the classroom," Palmer says. She relates chemistry to daily life, intersperses lectures with discussions and encourages students to interact and ask questions.

story continues on page 16

AMY PALMER

Palmer and her partner, Alexis Templeton, take a break from academic life during their annual family vacation to Maine.

Research on an enzyme that repairs sun damage in plants and animals could reveal new ways to prevent and treat skin cancer in humans.

Sun Damage—More Than Skin Deep

Too much sun makes your skin wrinkled, burned and leathery. It also damages your DNA, increasing your risk for cancer. Plants and many animals have an enzyme called photolyase that can repair sun damage. Humans lack it.

Recent studies revealing the workings of photolyase provide a ray of hope for preventing or treating sun damage in people. The research was led by Dongping Zhong, a physicist and chemist at Ohio State University in Columbus.

The scientists first exposed a strand of DNA to ultraviolet (UV) light, causing the same kind of damage as the sun. Then they added photolyase. Using an ultrafast laser as a sort of high-tech flashbulb, they were able to see photolyase in action as it repaired the UV-damaged DNA.

Zhong's group discovered that photolyase sends an electron and a proton to repair the damaged genetic material. After this process, the electron and proton return to the enzyme—possibly to start over and heal other areas.

More research on photolyase might lead to new treatments for skin cancer and better sunscreen products.—*Jilliene Mitchell*

As a scientist, you create knowledge…

CASEY A. CASS / UNIVERSITY OF COLORADO AT BOULDER

Palmer's students soon realize that understanding natural phenomena can be pretty cool.

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One course she teaches is physical chemistry, or, as she calls it, "Chemistry for the Unwilling."

"Most students think they'll hate it," Palmer says. "My goal is to get them to realize that it's cool to understand something about the physical phenomena you see in the world."

According to Wuttke, Palmer is one of the most popular teachers in the rigorous course's history.

"She completely turned [the course] around by bringing in modern teaching tools. She holds her audience with rapt attention," Wuttke explains.

Palmer hopes that her teaching will have a tangible impact, moving some of the students, as she once was, from "unwilling" to "potentially interested" in a research career. For these students, the next step is to gain laboratory experience.

"Listening to lectures is not the same thing as being a scientist," Palmer says. "As a scientist, you create knowledge; you don't just learn what's been done before."

And Palmer hopes that students who experience research will become hooked, like she did.

"There's no one path or right answer, and every question leads to more questions," she says about a research career. "It's an incredible endeavor to be a part of."

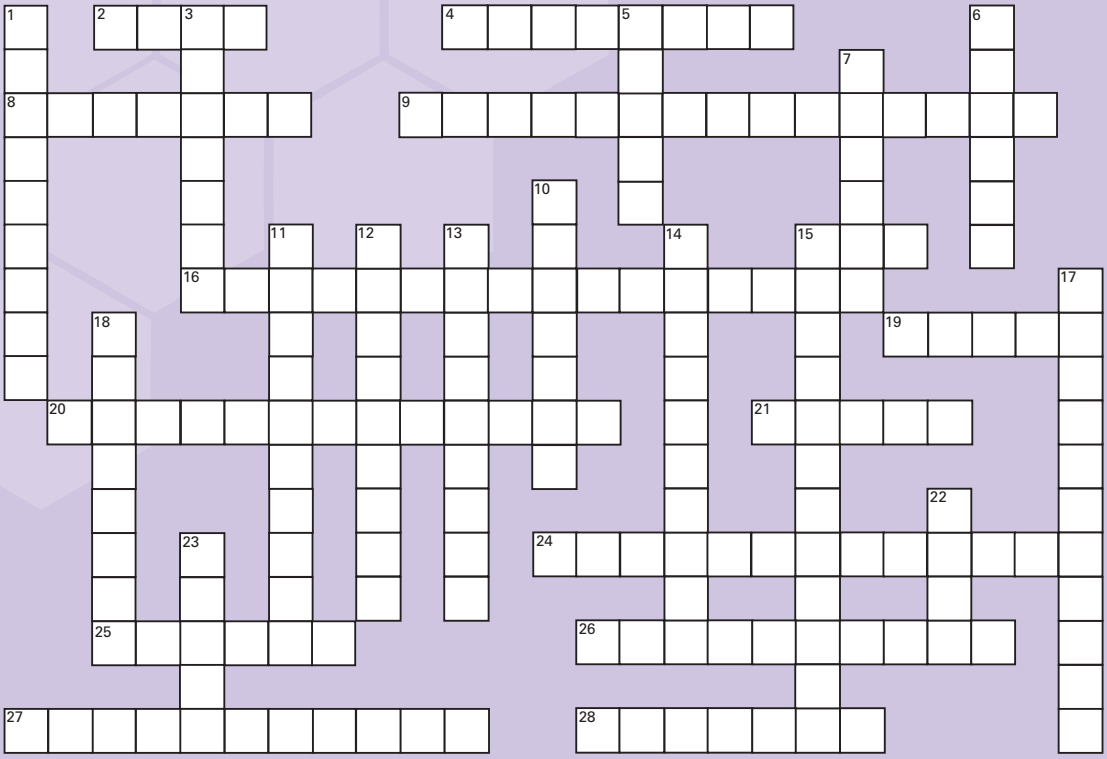
Hilary Godwin

MATTHEW GILSON

FIND MORE @

Read about a scientist who studies a metal that is toxic at virtually any level—lead—because it displaces healthy metals like zinc. Go to http://publications.nigms.nih.gov/findings/mar05/lead.html

EXPLORE IT **PUZZLE IT** FIND IT



ACROSS

2. Palmer tracks this metal in living cells
4. Studying metals in cells may lead to insights about Alzheimer's disease, _____cancer and diabetes
8. Bachmann and colleagues are searching for better drugs to treat this tropical disease
9. Compounds from the wild
15. The shape of the bacteria that Palmer studies
16. In addition to her Ph.D. in science, Palmer has a master's degree in _____
19. Nucleoside analogs can be used to treat these kinds of infections
20. The bacteria that Palmer studies cause _____
21. Scientists hope a genetically engineered version of this organism could make a cheaper HIV drug
24. Family of bacteria used to make many antibiotics
25. Ion mobility mass spectroscopy uncovers molecules with unusual _____
26. Everninomycin could lead to a new type of this medicine, with a lower chance of drug resistance
27. Brain structure involved in memory
28. Where both Bachmann and Palmer became interested in science

DOWN

1. Bachmann brews bacterial broths in order to pick out interesting _____to study
3. Zinc is important for our immune and _____ systems
5. To obtain samples of microorganisms from caves, Bachmann uses filter paper swabs and _____
6. Several _____ are essential nutrients, but can be toxic in large amounts
7. One of the two magnetic puppets in Bachmann's lab
10. Painkiller made from secondary metabolite
11. Palmer uses this to visualize sensor proteins
12. *Salmonella* bacteria attack this organ
13. Bachmann studies _____ metabolites
14. Nashville university where Bachmann works
15. The sport that was Palmer's passion in graduate school
17. Palmer uses _____ proteins to track metals within cells
18. *Salmonella* bacteria can inject more than 60 _____ into cells they infect
22. Software Bachmann uses to compare different growth conditions
23. A substance in caves that hasn't yielded useful organisms

SOLVE IT ONLINE An interactive version and answers can be found at http://www.nigms.nih.gov/findings.