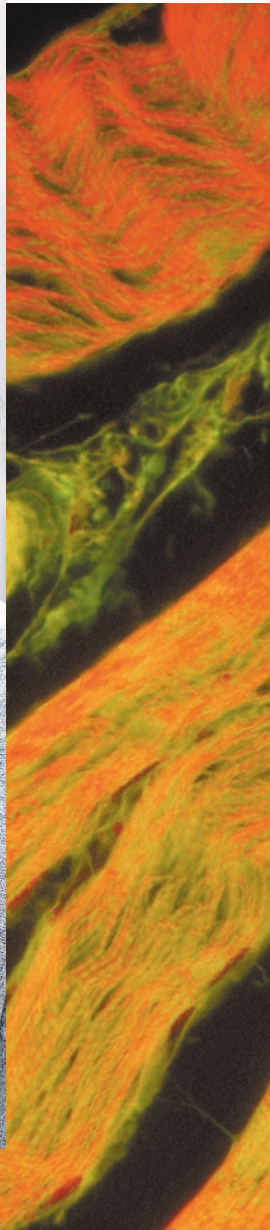


# FINDINGS



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**On the Cover**

Photo of Baldomero Olivera: *Kerry Matz*

Photo of Elaine Bearer: *John Forasté*

**G**etting together. More than ever, that's what science is all about.

If you think being a scientist means being lonely, you're wrong! Researchers spend most of their days working with other people. Biomedical scientists at colleges and universities spend up to half of their time teaching some area of biology or chemistry to undergraduate and graduate students. And scientists continually work with students to help turn neat ideas into testable research projects and to sort through the results of an experiment.

But biomedical researchers also do a lot of talking to other scientists, and not just biologists. As biology research broadens to include new fields like computer science, physics, and engineering, thinking together about how to attack a problem in an unconventional way can be the most fertile ground for discovery.

In assembling the materials for this issue of *Findings*, the importance of cooperation between scientists became undeniably apparent. Upon asking researchers to review the words about their work, these hard-working women and men insisted on giving credit wherever possible to their students and coworkers—all the people who sit at the benches in their labs and do experiments day in and out. There's never enough space to list every person who helped an experiment get done, but realize that science is indeed a group effort. Our health is all the better for it.



Alison Davis

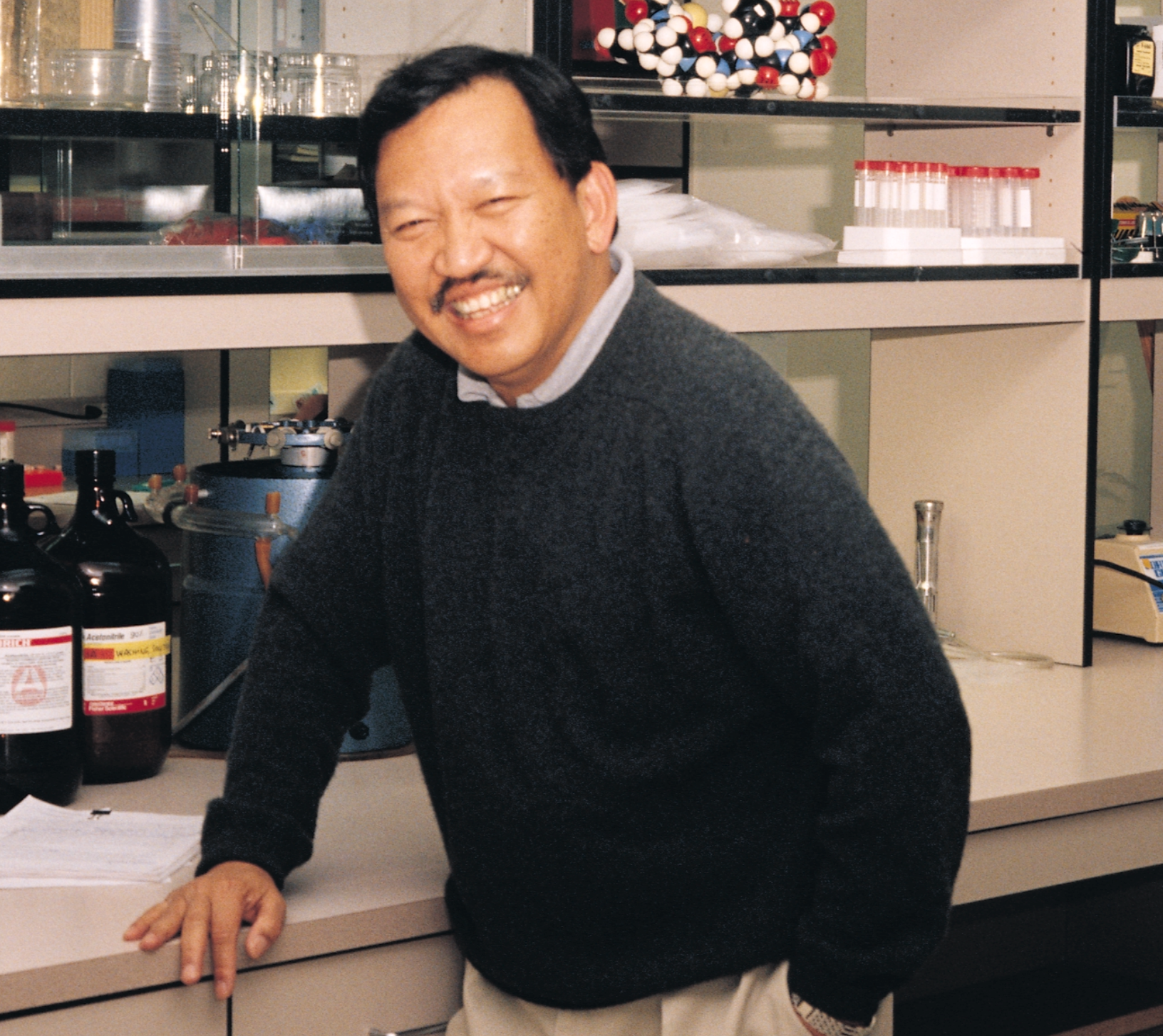
Editor

davisa@nigms.nih.gov

<http://www.nigms.nih.gov/findings/>



# Secrets of the K



# Painkiller Snails

Kerry Matz

**By Alisa Zapp Machalek**

It started out as a short-term project—a hobby, almost—to fulfill childhood curiosity about a beautiful, but deadly, sea snail. Now, the research may lead to relief for thousands who suffer from intractable pain, epilepsy, or neurodegenerative disorders.

The source of this medicinal boon, amazingly, is a poisonous venom. Found in marine cone snails, this venom contains a cocktail of nerve toxins unmatched in nature—or, as scientists learned, in chemistry labs. But that’s getting ahead of the story.

Back in the late 1960s, Baldomero Olivera needed a research project that was cheap and didn’t require fancy machines. Known as “Toto” by all his friends, Olivera had left his native Philippines to pursue scientific training. (The nickname was coined decades ago by one of his young cousins who couldn’t pronounce the “y” in “totoy,” the Filipino nickname for “little boy.”)

After earning a Ph.D. in biochemistry at the California Institute of Technology and working as a postdoctoral researcher at Stanford University, Olivera returned home flush with knowledge of the latest techniques in molecular biology. But his lab in Manila lacked the requisite funds and equipment to carry out these studies.

“I really wanted to continue my postdoc work,” Olivera confesses. “But it just wasn’t possible.” He describes this research as “working with” DNA ligase, an enzyme that seals together two pieces of DNA. Actually, he *discovered* this important enzyme, which now plays a key role in recombinant DNA technology.

In his fledgling lab, he chose instead a project inspired by his boyhood days of collecting sea shells. He remembered one shell in particular, that of the cone snail species *Conus geographus* (*C. geographus*), an animal so lethal that one sting kills an adult within hours. *C. geographus* also used to be called the “cigarette snail,” because when stung, its victims were said to have enough time to smoke a cigarette, but little else, before they died.

“My initial goal was to purify whatever caused human fatalities from *C. geographus*,” Olivera says. “It had local advantages and required little equipment.”

Olivera’s boyhood fascination with cone snails led him to discover that the snail venoms contain exquisitely specific and powerful nerve toxins. Today, research on the venoms spills out from dozens of laboratories worldwide and is the centerpiece of three pharmaceutical companies.

**Olivera’s boyhood fascination with cone snails led him to the discovery of a powerful painkiller.**

Kerry Matz

Baldomero (“Toto”) Olivera (left) is a biochemist at the University of Utah in Salt Lake City.

Olivera studies the venom of marine cone snails, which may be used to treat pain.

## Shake, Scratch, and Roll

Olivera began his experiments years ago by injecting *C. geographus* venom into the abdomens of mice. Immediately, the mice were paralyzed—just as are the fish that swim too close to a hungry snail. To find the secret paralyzing ingredient in snail venom, Olivera and his research team chemically divided the venom into a series of different fractions and injected them one by one into mice.

The researchers discovered, to their surprise, that the venom contains not one, but many different nerve toxins. And the toxins turned out to be peptides—small, protein-like molecules. Olivera set out to uncover how the toxins do their deadly work. He and his coworkers soon learned that a sting from *C. geographus* is equivalent to eating a lethal dose of badly prepared Japanese puffer fish while a cobra is biting you.

That's interesting, Olivera reasoned, but if the peptides merely mimicked the actions of other known toxins, they weren't unique enough to hold his interest. Yearning for the thrill of discovery, Olivera returned to doing molecular biology and nearly abandoned the cone snail research.

In 1972, he moved back to the United States and ended up at the University of Utah. Two or three years later, a 19-year-old undergraduate student named Craig Clark injected life into the nearly forgotten project, forever changing the course of Olivera's research.

"Craig got the brilliant idea of injecting components of the venom directly into the central nervous systems [instead of into the abdomens] of mice," explains Olivera. The results stunned them all.

Depending on which peptide the researchers injected, the mice would shake, sleep, scratch, convulse, or become sluggish. One of the peptides even caused different reactions depending on the age of the mouse—it put newborn mice to sleep, but whipped adult mice into a hyperactive frenzy. To a neuroscientist like Olivera, this was like discovering a sunken treasure ship. What were the peptides doing? How did they work? Could he find which ingredient caused the weird behaviors? Could it be harnessed as a medicine? What was once dismissed as blasé became a bounty ripe for discovery.

*Conus geographus* ("geography cone") gets its name from map-like markings on its shell. It is one of the few snails that can kill a human.



Now, 30 years later, the project has taken over Olivera's lab ("I gave up doing molecular biology about 10 years ago," he says). He even co-founded a company called Cognetix, Inc. in Salt Lake City, Utah, to tap the pharmaceutical potential of cone snail toxins, which he calls "conotoxins."

## "It Gets Pretty Interesting in There"

Olivera is not only interested in how snail toxins work, he is also intrigued with snail behavior. "Knowing how the snails actually use their venom is really useful," he explains. "It helps us make sense of what different toxins are doing."

Olivera keeps cone snails and fish in eight large aquarium tanks in his laboratory. "It gets pretty interesting in there," he chuckles. Once, he saw a *C. geographus* levitating in the middle of a tank and lowering itself like a spider down a thread. On another occasion, he saw a group of small, aggressive snails abandon their meal upon the arrival of a larger species of snail, leading Olivera to believe that the snails may use their venom to deter competition, as well as to kill prey.

And then there was the time that surface-swimming fish were mysteriously disappearing from the tank at night. Eventually, he witnessed a snail "extending its mouth like the barrel of a gun, clearly aiming at a fish." Then the fish started acting strangely. It was moving its fins, but not getting anywhere—as if it was swimming in place. The snail must have released some chemical that made the fish stay in place, Olivera concluded.

“This was an extraordinary insight, because it shows us there’s a substance [in the venom] that doesn’t have to be injected—it must be absorbed by the gills,” he says.

Now, in addition to injecting the toxins, Olivera will also squirt them into the aquarium and watch for unusual fish behaviors. This experiment never would have occurred to him if he hadn’t been observing live snails in action, he says.

### Pinpoint Accuracy

To really understand how the venoms work, Olivera’s group isolates and characterizes individual toxins in the deadly potions. The scientists discovered that each toxin hones in on just one type of molecule. In many cases, these molecules are “channel” proteins that control the flow of electrically charged particles such as calcium, sodium, and potassium into and out of cells. By blocking these channels, the toxins shut down messages between the brain and muscles, causing paralysis or electrical shock in a snail’s prey.

Olivera discovered that the peptide that puts newborn mice to sleep locks onto a corner of one type of brain protein. That’s about as specific as you can get. In fact, these peptides are so accurate in pinpointing their targets that they are now used by neuroscientists to identify and study specific brain proteins.

It’s like identifying one child from a crowd of kids who all have the same color hair, eyes, and skin, says Olivera. “If you were a parent of one of those kids, you’d have no trouble in picking your child out from the group,” he says. “In a sense, that’s what the toxins do.”

Such specificity is irresistible to designers of new medicines. It holds the tantalizing promise of leading to a highly effective medication with very few side effects. For example, most “calcium channel blockers,” which are medications used to treat high blood pressure, plug up calcium channels throughout the body, not just in the heart, where the drugs are needed. Conotoxins, on the other hand, seem to block only the calcium channels found in nerves, and not those in heart or other tissues. In this way, conotoxins could act as “smart” drugs that exert their effects only where they’re needed, without spilling over to other bodily systems and potentially causing unwanted side effects.

Already, pharmaceutical companies are tapping the potential of dozens of cone snail peptides to treat disorders including pain, epilepsy, cardiovascular disease, and various neurological disorders. In addition to Cognetix, two other companies focus their business around the toxins—Elan Corporation, plc, in Dublin, Ireland, and Xenome Ltd. in Brisbane, Australia.

The clinical applications of *Conus* toxins are inspired by the snail’s own biology. Paralyzing peptides might be used as anesthetics. “Sleepy” or “sluggish” peptides could be used as anti-epilepsy medications to tame nerve cells that fire out of control during seizures.

Olivera’s long-term goal is to use the peptides to treat even more elusive conditions such as Alzheimer’s, Parkinson’s, schizophrenia, and depression. “I’d like to make a contribution [to the treatment of] mental illness and neurodegenerative diseases,” he says.

Cone snails have strikingly beautiful shells.



## A Poison for Pain

One *Conus* peptide is already well on its journey to becoming a useful drug. Olivera originally called it omega-conotoxin MVIIA. Elan, which hopes to market the molecule, calls it by the generic name ziconotide. The peptide blocks calcium channels in one area of the spinal cord, preventing certain pain signals from reaching the brain. By testing the molecule in animals, scientists discovered that it is 1,000 times more powerful than morphine in treating certain types of pain. Even more exciting, it alleviates one type of pain, called neuropathic pain, for which morphine is inadequate.

Finally, it appears that ziconotide is free of morphine's fatal flaw—the development of tolerance. When people are given morphine for long periods of time, their bodies grow to “tolerate” the drug, requiring them to take more and more of it to provide pain relief. Ziconotide causes no such trouble. It appears to retain its potency without causing tolerance, even after prolonged use.

The peptide was tested initially on people with terminal cancer or AIDS. These trials were so successful that they were expanded to include other patients with severe, untreatable pain. Now the molecule is in phase III clinical trials—the last set required before requesting approval by the Food and Drug Administration (FDA).

Ziconotide is a rare—and possibly unique—example of a molecule used unaltered from a creature's chemistry. Usually, pharmaceutical chemists try to improve upon



natural compounds by designing molecules with the same action, but with better pharmaceutical qualities, such as how well the molecules are absorbed by the body. In the case of ziconotide, after hundreds of attempts

to design a “better” drug, the scientists returned to the original conotoxin.

Perhaps the most endearing part of the story is that the molecule was discovered not by a professional scientist, but by a young student, Michael McIntosh, just a few days after he graduated from high school. McIntosh went on to earn an M.D. and now, more than 20 years later, still works with cone snails and collaborates with Olivera. He is a research psychiatrist in the Department of Psychiatry and Biology at the University of Utah and uses *Conus* peptides to uncover the biochemical basis of mental illness. He also oversees the research of undergraduates, many of whom purify new peptides from cone snail venoms.

Olivera won't profit from ziconotide's success, because he never patented the discovery. But for this one fish that got away, there remains a school left to catch.

One pharmaceutical researcher calls the field an “ocean of opportunity.” There are 500 different cone snails, and each produces on average 100 different toxins. That means 50,000 possible nerve toxins—and 50,000 starting points for new medicines.

Compared to this, current knowledge is just a ripple on the surface. “We probably know the [peptide] sequence of more than 1,000 toxins,”

Olivera has a large collection of ancient pottery found in the Philippines.

Olivera says. He estimates that his research group has chemically manufactured about 100 toxins, but clearly

understands the biochemical workings of only 10 to 20.

## Another Type of Treasure

In addition to his quest for future medicines from the cone snail venoms, Olivera is on a more literal treasure hunt. He collects ancient pottery. These pieces, originally from China and the Far East, were used as ritual burial vessels in the Philippines from the 10th to the 16th centuries.



Years ago, the pottery was so plentiful that children would play with pieces that washed up in the



floods. “You could choose what you wanted—it was a little bit like cone snails,” Olivera says.

He has accumulated an impressive collection of plates, bowls, and vessels, usually paying under \$20 for each. Some years ago, the pottery piqued the interest of wealthy collectors and prices skyrocketed.

“We don’t have any big, famous objects—just a lot of small, pretty ones,” Olivera says. For him, the fun part is buying pieces he likes, then learning more about them.

Olivera’s world seems filled with researching things new and collecting things old. In either pursuit, he has a remarkable knack for discovering hidden treasure. In a way, isn’t that what science is all about? ■



Kerry Matz

## Deadly Treasures

What are the most poisonous creatures you can think of? Cobras? Scorpions? Japanese puffer fish? Now mix all these together and add 100 or so other nerve toxins. It sounds like a black magic witch’s brew straight out of a fairy tale. Shockingly, it’s a potion actually found in nature—in the venom of marine cone snails.

These snails live in the coral reefs surrounding Australia, Indonesia, and the Philippines. They use their venoms to hunt worms, other snails, or fish—some larger than themselves.

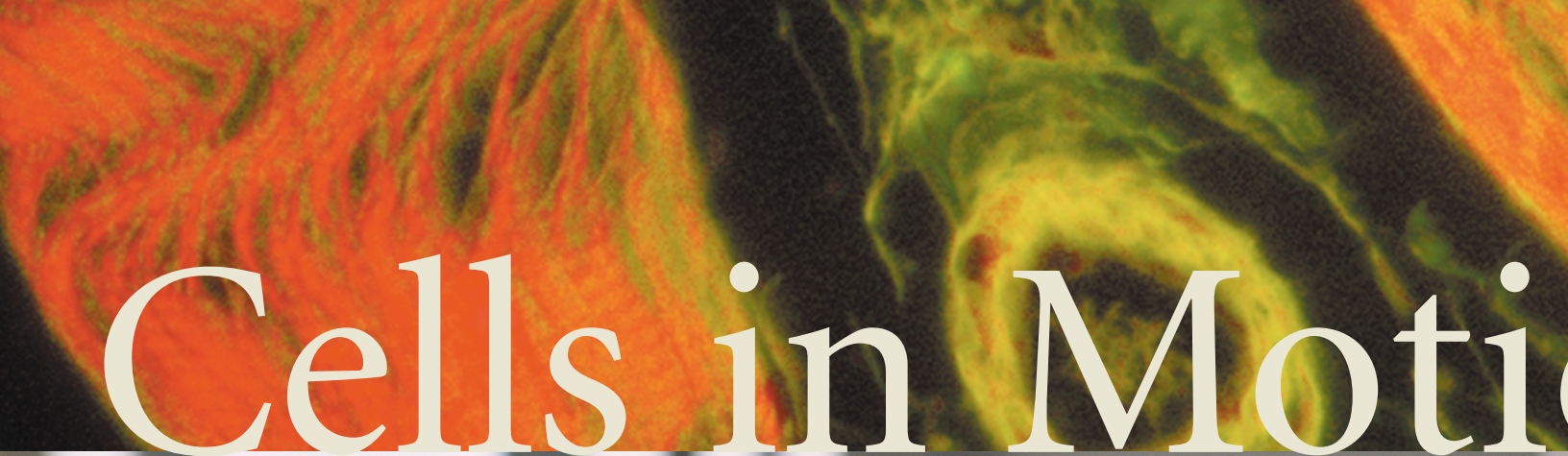
Each species of cone snail concocts its own unique venom containing dozens of nerve toxins. Some of these toxins instantly shock the prey, as does the sting of an electric eel or the poisons of scorpions and sea anemones. Others cause paralysis, like the venoms of cobras and puffer fish.

Cone snails use a variety of different hunting strategies. Some snails bury themselves in the sand and, when they smell a meal nearby, they extend a long, fleshy lure that attracts fish. Hidden in this wriggling, worm-like appendage is a sharp, barbed dart the snail uses to harpoon the prey and inject its venom. The snail then reels in the paralyzed fish and extends its mouth to engulf its catch.

Other snails open their mouths wide to capture entire schools of small fish. Then, at their leisure, the snails stab each of the unlucky swimmers with venom-filled darts. An hour or two later, the snails spit out all that remains of their meals—bones, scales, and the used harpoons.

In addition to their vast promise as a source of new drugs (see main story), cone snails are valued by collectors for their beautiful, intricately patterned shells. Some cone snail shells sell for thousands of dollars. According to one story, in 1796, a 2-inch-long shell fetched more at an auction than a painting by the famous Dutch artist Vermeer.—*A.Z.M.*

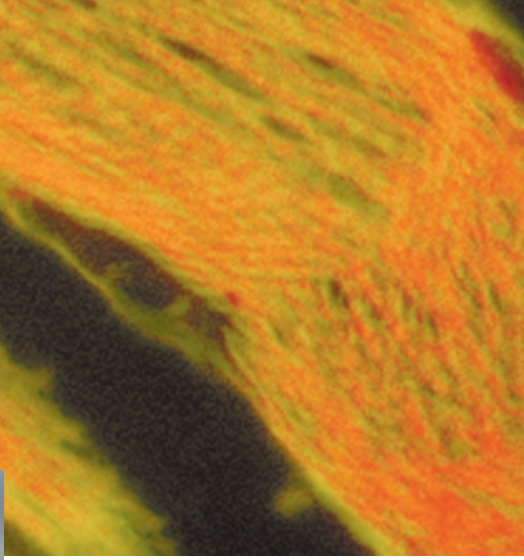




# Cells in Motion



on



Elaine Bearer

### By Alison Davis

**W**hen it comes to research, Elaine Bearer says one thing is for sure.

“You never know what you’ll find!”

To Bearer, the excitement of science is all about the adventure of discovery. Each experiment she carefully plans yields a new piece of information, and every discovery poses a new challenge. That’s not only in trying to understand what the new information means, she explains, but also in deciding what is the best experiment to do next.

Yet despite all the challenges and hard work, the Brown University pathologist cannot imagine doing anything else.

“Every day, I still get a thrill putting the key into the lock of my lab door,” admits Bearer, who is fascinated by how cells in the body move around and change their shape.

“When I open that door and enter my lab, I’m following my own imagination,” she says.

Once inside her lab, Bearer spends her time trying to unlock secrets about how changes in cell shape make the body tick, and how other changes in cell shape underlie disease. She began the quest as a graduate student at the University of California, San Francisco (UCSF) in the early 1980s.

### Turning to Science

Bearer arrived at science somewhat later than many students, having already established herself as a composer of music. She also has a faculty appointment in the Brown University music department.

Bearer still actively writes music, with recent performances in New York City and Boston. She earned a bachelor’s degree from the Manhattan School of Music in New York City and a master’s degree in music from New York University. She studied composition while playing French horn with the Pittsburgh Symphony.

But while Bearer has always loved to write music, she hated teaching it, and at age 25 she decided to pursue another, simultaneous career in medical research.

Bearer went to Stanford University as a student in the Human Biology program, where she became a teaching assistant to environmental scientist Donald Kennedy, who is now editor-in-chief of *Science* magazine. She went on to UCSF, where she was accepted into the Medical Scientist Training Program (MSTP), which is sponsored by the National Institute of

John Forasté

Elaine Bearer is a pathologist at Brown University in Providence, Rhode Island.

Bearer is fascinated by how cells in the body move around and change their shape.

*“When I open that door and enter my lab, I’m following my own imagination.”*

General Medical Sciences and leads students to earn a combined M.D.-Ph.D. degree. In 1983, Bearer was the very first UCSF graduate of the MSTP. The program's overarching goal is to train students to have the skills and knowledge to perform research and help translate findings to the clinic.

With Bearer, it worked. Her research on cell movement has uncovered important knowledge about how cell motion normally works, as well as about the errant cell movement that can provoke disease. Bearer credits much of her current scientific success to having lofty early ambitions.

"I was arrogant and naïve," she says more than two decades later, without apology. "I had big-picture aspirations. I wanted to understand everything there was to know about how cells change their shape."

Bearer uses squid, which have extremely thick and long nerve cell extensions, to study movement of the herpes virus.

After receiving her M.D. and Ph.D. degrees and completing a 1-year postdoctoral research fellowship in Switzerland, Bearer returned to UCSF to learn to become an anatomic pathologist, a type of physician who diagnoses disease based upon telltale alterations in tissue structure.

"Day after day, I looked through a microscope, searching for changes in cell shape," Bearer says. She yearned to take a more systematic approach, not just to diagnose disease by recognizing what unhealthy cells look like, but also to understand the roots of how and why cells get unhealthy in the first place.

"I had a more global idea about pathology," Bearer says, now recognizing the long-term gains of thinking that way



during her early training years. "Over time, I have achieved much more than I would have if I had set my sights lower," she says.

Bearer says that side-by-side training in doing basic research and practicing medicine gave her an eye for thinking about problems in very fundamental ways, while keeping a focus on the medical relevance of such problems.

## Moving Along

Take herpes, for example. Bearer has recently been investigating just how it is that the herpes simplex virus traverses nerve cells to do its dirty work of causing an infection.

Scientists have known for some time that the herpes virus hitches a ride into the body by entering a nerve ending in the mucous membrane of the lip, eye, or nose, then journeying along the long and winding nerve to its control center near the brain. Here, the virus takes hold and copies

itself. Bearer recently shed light on how this works by recreating the virus transport process in the giant axons of squid taken from local waters off the coast of nearby Massachusetts. Axons are spindly extensions of nerve cells that transmit electrical signals over great distances in the body.

Until Bearer completed these experiments, scientists did not have a model system in which they could study the individual viral proteins involved in transport along axons. This was partly because human nerve cells are small and finicky to grow in the lab, and human axons are too small to inject with test transport proteins. Squid axons are very thick and nearly 3 inches long—much, much longer and fatter than those in people.



Elaine Bearer

Elaine

Researchers had thought that herpes made its way toward the brain by successively infecting other cells along the way. Bearer and her coworkers at the Marine Biological Laboratory in Woods Hole, Massachusetts, injected the huge squid axons with a modified form of the human herpes virus. The researchers were amazed to measure its travel speed at 2.2 micrometers per second (1 micrometer is a thousandth of a millimeter). This speed can only be achieved, Bearer explains, by a single virus whipping down a nerve cell on a “track,” being driven by a protein “motor.”

The finding has plenty of practical importance, Bearer says. Understanding this movement process may allow scientists to send safe forms of herpes viruses with helpful genes attached into the nervous system, where the genes could treat certain neurological disorders. More fundamentally, the findings revealed how similar the nerve cell parts are between squid and humans.

“This kind of research is so powerful,” Bearer says, about the process of making connections by studying normal cellular and molecular events and linking them to diseases.

### Taking Shape

In addition to studying the movement of viruses along nerve cell tracks, Bearer investigates other kinds of cell motion, such as changes in cell shape. To this end, she has had a long-standing interest in platelets. In truth, platelets are not actually cells—they are rounded cell-like particles that are pinched off from the edges of cells in the bone marrow called megakaryocytes. As such, platelets do not contain all the usual components a cell has, like a nucleus. Nevertheless, these “mini-cells” are the parts of our blood that make a clot and keep us from bleeding excessively when we get a cut.

## Mountain Medicine



As a combined physician-scientist, Bearer is hooked on basic science but also committed to practicing medicine. At Brown, she teaches pathology (*“No medical student graduates from Brown Medical School without passing my course,” she states matter-of-factly*). In addition, Bearer directs an elective “clerkship” (clinical rotation for medical students) that serves the community of San Lucas Toliman, a poor Mayan population living in the highlands of Guatemala. The program, called the San Lucas Health Project, is sponsored by the Department of Community Health at Brown University, and involves doctors, nurses, dentists, and social workers from her local community of Providence, Rhode Island, in addition to medical students from Brown and all over the world. Nine years ago, Bearer began the clerkship program in part to satisfy her own need to supply medical care to needy populations. The project’s mission is multifaceted. In addition to providing direct med-

ical and dental care and educational support to local health care personnel in Guatemala, the Brown University team also gathers health-related data and provides financial and material support for instituting local programs to improve health, nutrition, and hygiene.

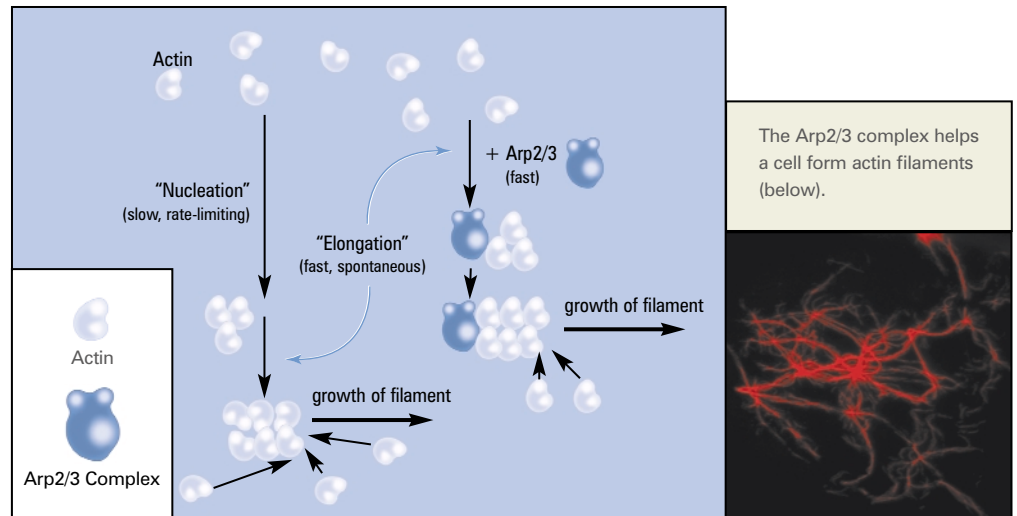
In recent years, Bearer has learned that AIDS has seriously impacted this Central American population, and since that time the group has set up HIV testing and counseling programs. Bearer is now trying to establish a research program there to learn more about the social relationships and family commitments that can play a big role in risk factors for AIDS and other sexually transmitted diseases.—A.D.

# Cells in Motion

According to Bearer, platelets are incredibly interesting to study when it comes to shape changes—they undergo dramatic maneuvers when the body sends a signal that it’s time to make a clot. When we cut ourselves, the wounded area of our skin sends messages that trigger platelets to snap into action, a process called activation. When platelets receive this activation signal, the normally smooth, disc-shaped cell particles stretch out, forming tendril-like “fingers” that grab onto tissue surfaces and other platelets. With their ragged edges, the activated platelets help to form a clot: a sticky, gel-like mass. The clot literally plugs up a wound and prevents blood loss. Activated platelets are also prompted to spill their contents, which include among other things a soup of clot-forming molecules. Despite intensive study, scientists do not know exactly how this happens.

In the lab, researchers like Bearer can trick platelets into activating themselves by spreading them onto a glass slide. Researchers know that the platelet activation process hinges on a cellular scaffolding protein called actin. All cells have actin molecules, and there are several different types of actin proteins. Actin is globe-shaped and can assemble itself into filaments that resemble a string of pop beads (see figure at top of page). In preparation for making a clot, a ring of actin filaments circling a platelet squeezes tightly, helping to dump clotting factors out of the platelet.

In smooth, unactivated platelets, actin proteins keep apart from each other. However, upon getting the activation signal, first two and then three actin molecules come together, forming a small group, or “nucleus.” After this initial step, other actin molecules follow suit, lining up alongside the nucleus and forming a long string. This filament-like assembly of actin forms the underlying structure for the foot-like extensions of the activated platelet cells that make clots.



For 15 years, Bearer has been searching for the molecular machine that causes actin molecules to come together, or “nucleate,” during the activation of platelets. She believes she has finally found it, and it is actually an assembly of several proteins, called a complex. This complex, found in many different creatures spanning evolutionary time, is named “Arp2/3.”

The Arp2/3 complex is a relatively recent discovery by scientists who study how cells move. Preparations of platelets like the ones in Bearer’s experiments have been used by other researchers to discover that the Arp2/3 complex is also the machine that helps certain disease-causing bacteria to move around inside cells. The complex works by bringing together actin proteins into a highly organized network at the rear of a bacterium. This network pushes these one-celled organisms forward.

Actin filaments also help cells move around in our bodies, for example, helping to propel white blood cells toward the site of an infection. The Arp2/3 complex allows them to shift direction rapidly in response to changes in their environment.

So why is understanding how the Arp2/3 complex works in platelets so important, you wonder? For starters, knowing what nucleates actin molecules during the activation of platelets means that scientists can look for ways to block that process. Take the logic one step further and you can imagine new treatments to control clotting. Clotting is a key process that’s essential to life, but clotting gone wrong can also cause serious health problems,

such as strokes and heart attacks, if a clot happens in the wrong place at the wrong time.

Platelets can't reach out and touch each other when the Arp2/3 complex is missing, Bearer explains, describing experiments she has done with platelets growing on glass coverslips.

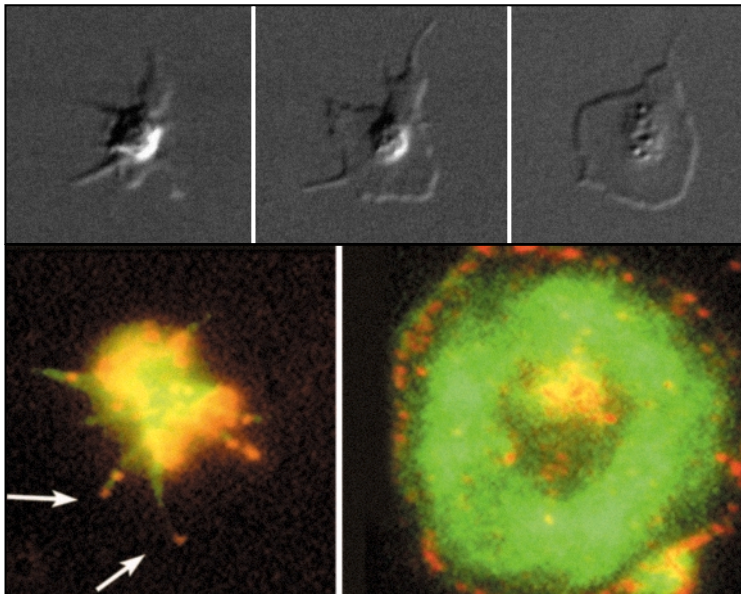
Bearer could not be more thrilled with the results. Just as with her herpes virus research, Bearer's work studying actin in platelets has both practical worth and fundamental value.

"There are definitely two sides of the coin," Bearer says. "These results help us understand cardiovascular disease and atherosclerosis, but they reveal a basic mechanism of action in cells."

### Practice Makes Perfect

Teaching, thinking of experiments, doing those experiments, and turning the results into scientific publications takes a lot of time, and Bearer also fits her musical life in between. How does she do it all?

The Arp2/3 complex (arrows, bottom) helps actin proteins get together as platelets stretch out during activation (top).



Elaine Bearer

"I have a lot of energy," Bearer concedes, adding that she doesn't watch television and reads the newspaper only twice a week, on Tuesdays and Sundays. She gets 9 hours of sleep every night and exercises every day, often riding 35 miles on her bike on a Sunday.

In Bearer's busy life, science and music co-exist, although she admits there is a certain "dynamic tension." She believes that for her, music and science work well together. Bearer's music emerges all the time, she says, sometimes in the middle of an experiment. She believes that her musical persona enriches the way she thinks about science, even helping her to write better scientific papers reporting her research data.

Don't for a second think it's easy, though, Bearer says. Years and years of diligence—musically and scientifically—have enabled her to do both music and science so well. In addition to rigorous scientific training, Bearer had strong musical influences early in life. One was Nadia Boulanger, the Parisian composer and mentor to a whole generation of 20th century composers, with whom Bearer studied when she was very young.

"Boulanger had a huge impact on my life," Bearer says, adding that the composer taught her to "think like Bach." Bearer learned how to listen to a complicated Bach fugue (a musical piece with multiple themes that appear and repeat in a complex pattern) and hear each musical "voice" independently, all at once.

It took a lot of work to acquire such a talent, Bearer says, but the work has paid off. "I can do an experiment and think music at the same time," she says.

Bearer juggles two careers, writing music and using pathology research as a window into understanding disease and normal cell behavior. She acknowledges the strong influence of superb scientific mentors, who guided her not only through her training years in California, but beyond.

"They really inspired me, and I still remember their terrific ideas," says Bearer.

One of those mentors, Donald Kennedy, remembers Bearer's spirit during her college days at Stanford.

"She was an outstanding student," Kennedy recalls, "but what I found remarkable was the way in which she could pursue serious interests in science and music at the same time. What is more remarkable still is that she has managed to continue both interests and develop them into an exceptionally rich, dual professional career." ■

## Cells' Sugar Coating Zaps Cancer

Heparin is an inexpensive “blood-thinning” drug that doctors use to stop blood from clotting. The medicine is widely prescribed to treat dozens of health conditions in which blood clotting can be especially dangerous, such as stroke and many heart disorders. Now, NIGMS grantee **Ram Sasisekharan** of the Massachusetts Institute of Technology in Cambridge has unearthed a brand-new potential use for heparin: treating cancer. Sasisekharan is a biochemist who studies the sugar molecules, or carbohydrates, that coat the surfaces of cells. To investigate the potential importance of a cell’s sugar “coat” in the development of cancer, he and his coworkers injected an enzyme called heparinase into mice with tumors. Heparinase is an enzyme that cuts up complex sugars, generating molecules of heparin. The researchers found that one particular heparinase treatment slowed the growth of skin, lung, and prostate tumors in the mice. Surprisingly, however, a chemical cousin of heparinase actually accelerated tumor growth in mice, indicating that slightly different forms of this family of molecules can have very different effects on cell growth and cancer. Heparin and molecules like it cloak the surfaces of nearly all the cells in our bodies, and Sasisekharan suspects that these sugary molecules interact with cancer-controlling proteins circulating in the blood and on the surfaces of other cells. If the findings can be repeated in people, heparin could be put to use quickly, since it is already an FDA-approved medicine and as such has been demonstrated to be safe for human use.

## Do the Math

Few would argue that the ability to accurately predict the course of disease outbreaks and other serious health problems affecting millions of people would be worthwhile. Two NIGMS grantees—**Simon Levin** and his group at Princeton University in New Jersey and **Martin Blaser** of New York University in New York City—have used entirely different approaches to mathematically model the behavior of infectious microorganisms that impact large populations of people. In the first case, Joshua Plotkin and Jonathan Dushoff, working with Levin, analyzed the gene sequences of flu strains from the last 16 years and discovered patterns that researchers may be able to use to predict which



particular strain of flu will emerge in the coming season. If accurate, such a prediction would be a helpful tool to avoid misery and save many lives by permitting the makers of the following year’s flu vaccine to better target the precise variants of flu likely to be the most prevalent. Levin and his coworkers delved into a computer database containing DNA sequences representing 560 samples of different flu viruses. The researchers discovered that the many strains separated naturally into a small number of distinct clusters, and they showed that clustering could be useful in predicting how the flu virus evolves over time. In the second case, infectious disease specialist Blaser teamed up with mathematician Glenn Webb of Vanderbilt University in Nashville to pursue a different line of research addressing another issue of widespread health concern. Blaser, who models the infectious behavior of the ulcer-causing bacterium *Helicobacter pylori*, applied his knowledge to produce a model of how the deadly bacterium *Bacillus anthracis* could be spread through the U.S. postal system. The researchers simulated the outbreak of mail-borne anthrax in the fall of 2001 and concluded that all the known cases of infection could be traced back to contamination through the mail from only six original envelopes. The researchers also concluded from their mathematical model that the rapid and widespread use of antibiotics probably averted many additional potentially deadly infections from this outbreak.

## The Side Effects of a Misspelling

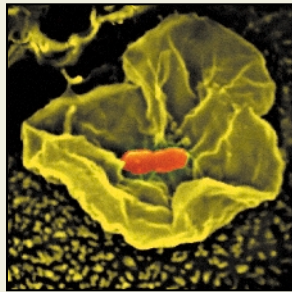
Many people are surprised to learn that medicines may only work properly in a percentage of those who take them. What’s more, whether or not people develop side effects—and if they do, which ones they’ll get—varies widely. While many factors such as diet, environment, and the amount of exercise a person gets can help account for this variability in drug response, a key determinant is genes. So-called pharmacogenetics research aims to unravel some of the biological reasons why people react so differently to medicines. In recent years, pharmacogenetics scientists have found many examples where a change in one or a few of the DNA “letters” that spell out genes can cause people to have different responses to medicines. For example, NIGMS grantee **Mark Ratain** of the University of Chicago has identified a group of cancer patients who have a bad reaction to a chemotherapy drug called irinotecan, which is used to treat a variety of solid tumors. Ratain and his research team have found that some patients have two extra letters in the gene that instructs the body to make a protein that metabolizes



irinotecan and other drugs. Because of this genetic difference, these people have much higher levels of irinotecan than most patients given the same dose. When administered this medicine, patients with extra letters in the gene experienced dramatic drops in their white blood cell counts, making these patients more likely to develop a potentially life-threatening infection. The same patients also experienced severe diarrhea, which can cause dangerous fluid loss in people who are already very sick. Ratain predicts that future genetic screening of patients may help avoid toxic side effects and help determine the precise dose of chemotherapy needed to treat their cancer.

### Natural Bacterial Shield Protects the Body

Your body may be better at protecting you from microbial invaders than you thought. Recently, NIGMS grantee **Charles Serhan** of Brigham and Women's Hospital in Boston, Massachusetts, made the surprising observation that naturally occurring molecules in the body that help fight inflammation also appear to protect tissue linings of the mouth, intestines, and airways from infection. While doing experiments to study the roles white blood cells normally play in controlling inflammation, Serhan and his coworker Sean Colgan unexpectedly discovered something new.



In the process of policing epithelial cells (the cells that line the organs of the body and skin), white blood cells shoot a chemical signal to the epithelial cells telling them to manufacture a microbe-killing substance, the research team found.

This chemical likely protects the cell from a potentially

dangerous infection by eliminating bacteria on contact. To verify the observation, the scientists infected epithelial cell cultures growing in plastic lab dishes with the bacterium *Salmonella typhimurium* and then added a chemical that provokes inflammation in the body. In earlier experiments, the researchers showed that in response to the inflammation-prompting substance, epithelial cells boost their production of a “molecular shield” component called BPI.

Serhan's research team found that as BPI levels in the cells increased, more and more *Salmonella* in the culture dishes died, whereas using a “dummy” chemical had no effect. The results are significant in describing a new defense mechanism in the body, but also, as Serhan states, in pointing to new strategies to thwart difficult-to-treat infections of the mouth, intestines, and esophagus.

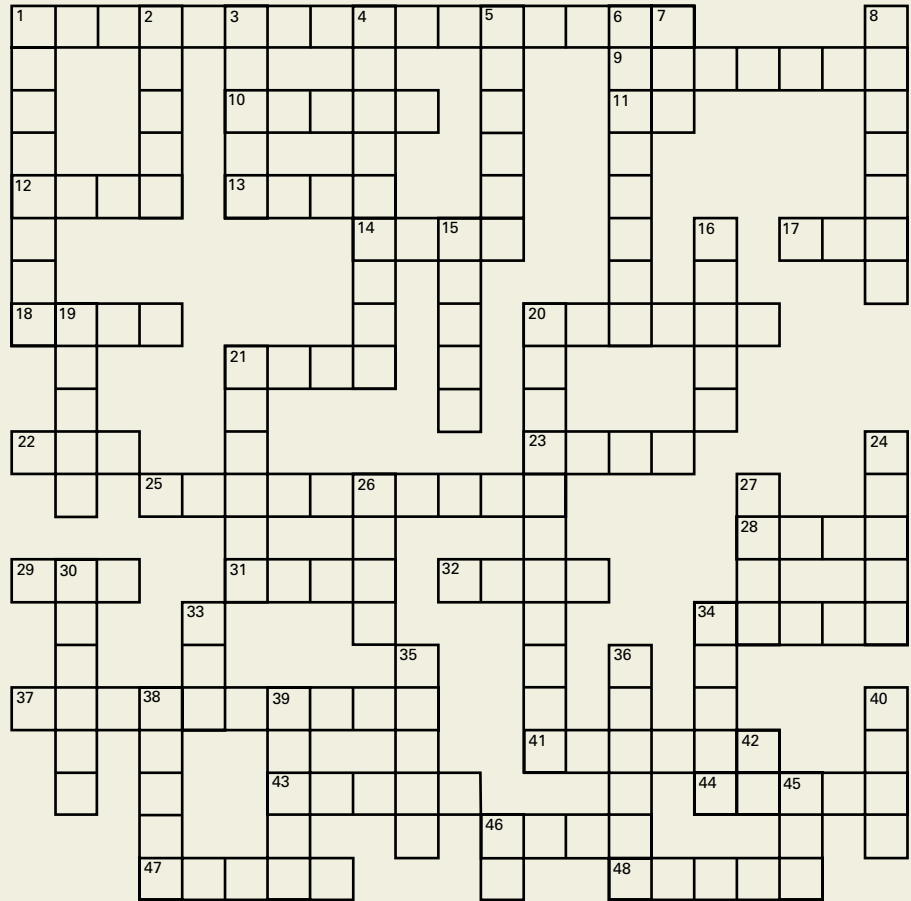
### Stop Cell Death, Help Treat Sepsis?

The body-wide infection called sepsis is the leading cause of death in critically ill patients nationwide, striking 750,000 people every year and killing over 210,000. Sepsis occurs when bacteria leak into the bloodstream, causing widespread damage all over the body. Blood pressure plunges dangerously low, the heart has difficulty pumping enough blood, and body temperature climbs or falls rapidly, in many cases causing multiple organs to fail. In recent years, researchers have come to realize that the gut,



or intestinal tract, plays an important role in sepsis. Scientists have found that after a severe infection or injury, cells in the intestinal lining die off. This form of cell death, called apoptosis, isn't always a bad thing—for example, nerve cells require apoptosis during development to form a healthy brain. However, researchers suspect that blocking apoptosis in the intestines of critically ill patients may help to prevent death from sepsis. NIGMS grantee **Craig Coopersmith** of Washington University in St. Louis, Missouri, reports experiments in mice that suggest this strategy may someday be effective in people. Coopersmith and his coworkers genetically engineered lab mice to produce large amounts in their intestines of a cell-death-blocking protein called bcl-2. The researchers exposed the experimental mice to the bacterium *Pseudomonas aeruginosa*, which can be deadly to people, and discovered that 40 percent of the mice escaped infection and survived, compared to only 4 percent of mice without bcl-2. The results suggest that stopping intestinal cell death may someday be an effective treatment for sepsis.

# The Last Word



## ACROSS

1. how genes affect drug responses
9. researcher Toto
10. testing period
11. belonging to me
12. odd opposite
13. what someone calls you
14. tailed lab animals
17. contagious sickness
18. factual
20. of the sea
21. soda
22. not he
23. companion of his
25. cell viewer
28. deadly snail type
29. bashful
31. snorkeling spot
32. cell's sugar layer
34. original source of ziconotide
37. organ liner
41. deadly infection
43. cunning
44. "I agree"
46. not sweet
47. south opposite
48. form

## DOWN

1. bleeding stopper
2. spring bird
3. cellular scaffolding molecule
4. Central American country
5. pathologist Bearer
6. Elaine Bearer's other job
7. done in secret
8. cell channel opener
15. hue
16. snake's protective fluid
19. left opposite
20. disease outbreak predicting tool
21. source of a tumor
24. home for 34 ACROSS
26. not hard
27. desktop symbol
30. nerve-traveling virus
33. cheer
34. sea animal with big axons
35. grin
36. salty condiments
38. poisonous substance
39. lamp
40. it can cause a stroke
42. Spanish yes
45. foot digit
46. because

Puzzle answers can be found at  
<http://www.nigms.nih.gov/findings/>

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