

*As engineers of the molecular world,
chemists are making their mark in biology.*

by SARAH C.P. WILLIAMS illustration by MARIO HUGO

AT THIS VERY MOMENT,

your body is a living periodic table of elements. Chlorine atoms combine with hydrogen and churn through your stomach, breaking chemical bonds in the food you ate for lunch. Potassium pulses along your nerves, giving your fingers a sense of touch. Calcium makes up your bones and teeth; carbon is the backbone of your DNA; and oxygen seeps into your bloodstream with every breath you take.

If you are a chemist, you see the world in terms of these atoms. Not just humans, but plants, animals, bacteria, soil, computer chips, telephones, and light bulbs. Each is made of unique mixtures of the 118 elements posted on the wall of any high school chemistry classroom.

“Anything you see or touch or taste, it all comes down to these elements in different combinations,” says HHMI investigator Chris Chang.

Both Chang’s undergraduate degree and his Ph.D. are in chemistry. But now he studies the brain. His lab at the University of California, Berkeley, looks as much like a biology lab as a chemistry lab, with microscopes and mice and cell cultures. He’s one of a handful of HHMI scientists—and a growing number of scientists around the country—who are applying their background in chemistry to biological problems.

These chemists are driven by a fascination with the complexity of biology and a desire to work in a fast-moving field. But the way they approach problems is distinct from biologists—they break organisms down to their most minuscule atomic parts to study how they work. And they build those biological systems back up using new chemicals they create from scratch.

“Chemists are able to not only study things at this molecular scale, but we can also reorganize things and build them from the ground up,” says Chang. “It is this ability of chemists to create things that allows us to look at problems differently.” Like structural engineers who design buildings and genetic engineers who create new genes from scratch, chemists are engineers of the molecular world.

Biology-interested chemists face no shortage of biological questions to answer. Chemical approaches are solving problems in neuroscience, immunology, cell signaling, and cancer biology.

“There are chemists now that are indistinguishable from biologists at the cutting edge of biological discovery,” says Carolyn Bertozzi, another HHMI investigator whose research overlaps the two fields. “And then there are chemists who collaborate closely with biologists.”

As biologists and chemists learn to bridge the gap between their fields, with training programs and increased appreciation for what the other has to offer, they are realizing just how complementary their skills can be.

Brain Chemistry

Choosing where to apply his chemistry knowledge wasn’t hard for Chang. “There’s nothing more complex or beautiful in biology than the brain,” he says. Lucky for him, the brain is full of unique chemistry that’s ripe for investigation. When Chang was launching his research career, he discovered that the brain has at least 20 times more copper than most of the body, and no one could explain why. As a chemist, he saw an opportunity—copper is a chemical element, the simplest building block of an organism. By studying copper in the brain, Chang could fulfill his desire to explore neuroscience and put his background in chemistry to use.

Biologists, however, had no way to visualize where the copper was in the brain. They couldn’t track its movement or see where it was being integrated into larger molecules. So Chang created a new kind of copper—a copper atom attached to chemical probes that offer a way to watch copper’s path in the brain. He engineered the copper so that the probes could light up under a fluorescence microscope or potentially be visualized in an MRI of the brain.

In an April 2011 paper published in the *Proceedings of the National Academy of Sciences*, Chang’s team used the method to determine just how dynamic copper is in brain cells. They found that when a neuron receives a signal—in the form of calcium molecules—a wave of copper moves from one end of the neuron to the other.

“We showed that copper is not this static building block of brain cells like many believed. It’s a dynamic, mobile signaling molecule,” says Chang. “And this is the first time that someone

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CHRIS CHANG

can watch it flow through brain cells in real time.” Next, the group aims to understand what this wave of copper movement triggers.

Copper is far from the only dynamic chemical in the brain. Linda C. Hsieh-Wilson, an HHMI investigator at the California Institute of Technology, has used her combined knowledge of organic chemistry and neuroscience to discover how a set of molecules—glycosaminoglycans, or GAGs—influences neuron growth. GAGs are long strings of carbohydrates that attach to proteins and influence their behaviors.

Each of the dozens of types of GAGs has a different function. At a molecular level, their distinction lies in the sulfate clusters—groups of sulfur atoms—that decorate the carbohydrate strings. For biologists trying to study each molecule’s effect on the brain, the sulfate groups were frustratingly similar. There was no way to isolate only one type of GAG at a time. Moreover, biologists couldn’t use genetics to study the sulfate clusters because DNA doesn’t directly encode carbohydrates. And blocking the addition of all the sulfates at once caused such chaos that it was hard to tell what was what.

“And so here’s where my chemistry background became very important,” says Hsieh-Wilson. “We needed to be able to synthesize and study the different GAGs one at a time. So, we used organic chemistry to design and synthesize these very complex molecules from the ground up.”

Hsieh-Wilson’s group synthesized different GAG molecules and devised ways to block each one individually. Then, they

added the synthetic molecules to cells to study the effect of specific sulfate clusters. By experimenting with blocking and unblocking different combinations of GAGs, the researchers began to decipher how the position of the sulfates offered molecular instructions, telling the GAGs what functions to perform in the cell.

“What I think is cool about being an organic chemist is that you can create molecules that are entirely new, that no one has ever dreamed of, or molecules that only exist in minute amounts in Nature,” says Hsieh-Wilson. “And then you can use these molecules to discover something new and exciting about biology.”

Although Hsieh-Wilson still has lots more to discover about GAGs, she’s already found that the carbohydrates are involved in the growth and regeneration of nerve cells after injury. With this fundamental insight, she and her team are working to create a therapeutic approach to help treat spinal cord injuries.

Body Chemistry

Every organ in the human body functions through a constant interplay of chemicals. By modifying those chemicals—to block them, track them, or isolate them—chemists can add to the knowledge of how the body works.

Among the molecules constantly moving within cells is a large group of signaling molecules called protein kinases. There are more than 500 of them—and, like GAGs in the brain, they have widely varying functions but very similar chemical structures.



Stuart Schreiber and Linda Hsieh-Wilson create new molecules to test pathways and circuits and, if they’re lucky, discover exciting new things about biology.

To figure out which kinases do what, HHMI investigator Kevan Shokat developed a strategy similar to Hsieh-Wilson's approach to looking at GAGs.

Protein kinases work by binding ATP—a cellular source of energy—and then using it to add phosphates to proteins, a modification that changes the function of those proteins. Biologists know how to block kinases from binding to ATP, which shuts the enzymes down. But the action shuts down many different types of protein kinases in a cell at once.

“After six months of scrambling my brain on how I could tackle this problem through chemistry, I realized that I could chemically engineer the ATP pocket of one kinase at a time so that enzyme could be blocked specifically,” says Shokat, at the University of California, San Francisco. First, the genes for kinases are removed from a human cell grown in a lab dish. Then, the newly engineered kinases can be added.

His method paid off: labs using his technique have discovered the function of more than 70 kinases. His own lab is now focusing on the role of some of these kinases in cancer development.

“I call the whole thing ‘chemical genetics,’” says Shokat, “because neither chemistry nor genetics could have solved this problem on its own. You take the best of both worlds.”

The combination of chemistry and genetics is one that other scientists have joined forces to explore. HHMI investigator Gerald Crabtree, a developmental biologist at the Stanford University School of Medicine, frequently collaborates with Stuart Schreiber, a chemist and HHMI investigator at Harvard University and the Broad Institute. Crabtree studies how signals from other cells or the surrounding environment are transmitted into a cell, eventually leading to changes in gene expression. Schreiber, with his organic chemistry training, can build molecules that block these signals at any step along the way.

Their first collaboration, in the 1990s, showed how an immunosuppressant drug blocks immune cell functioning. Schreiber

altered different parts of the immunosuppressant at a time. After each chemical alteration, Crabtree tested whether the drug still blocked immune function.

“That collaboration allowed us to say which regions of the molecule were essential and to accurately order each of the steps of the pathway,” says Crabtree.

Despite being on opposite coasts of the country, the two continue to use small molecules designed by Schreiber to block chemical reactions within the cell. “Sometimes I’ll have a question about how a biological process works, and I’ll ask him how we can study this chemically,” says Crabtree. “Other times he’ll be interested in a particular molecule he’s made and approach me about studying what it does in the cell. Such molecules allow biologists to order and test biological pathways and circuits. They also provide verification for mathematical models of how things work, an essential aspect of modern biology.”

Schreiber is seeing more scientists embarking on this kind of collaboration. He says that now is a defining time in the intersection of chemistry and biology. He compares it, in fact, with the aftermath of Sputnik and the challenge by President Kennedy to send a spaceship to the moon.

“Kennedy didn’t propose that a group of very smart physicists come together to calculate the thrust required of a rocket to escape our atmosphere. He brought many types of scientists—physicists, engineers, mathematicians, even biologists—together. And he didn’t just have them calculate what would be needed to build a rocket. He had them actually do it. Fly a rocket to the moon.”

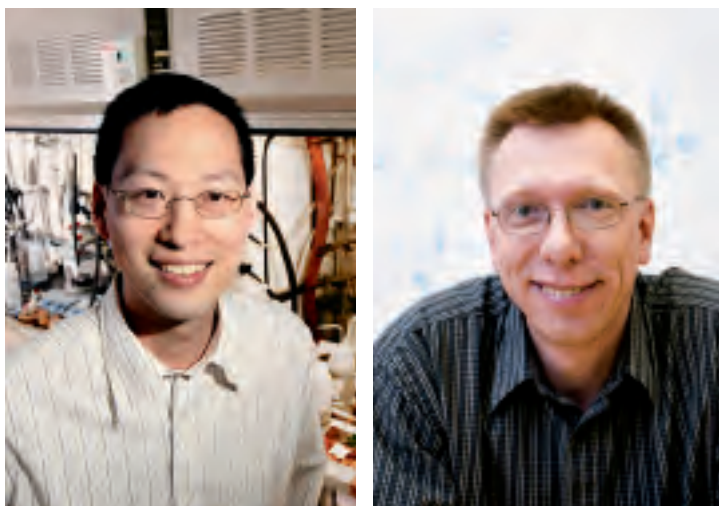
Biology without chemistry, Schreiber says, is like “hypothesizing without testing things.” Together, biologists and chemists might not be able to fly a rocket to the moon, but they can test biological hypotheses—and *do* things—using compounds created by chemists.

“The marriage of biology and chemistry has never been more important than today,” he says. “We are in a position to use small molecules to test emerging concepts in human disease in physiologically relevant settings.”

Learning from Biology

There are biological mysteries that chemistry can help solve, *and* there are also chemical phenomena that the biological world can help explain. The ultimate goal of the field of chemistry historically has been to be able to synthesize any molecule in the most efficient way possible. And Nature often is the best teacher when it comes to efficiency. The ways that cells produce chemicals—whether they’re hormones, defensive molecules, or signals between cells—have been culled by billions of years of evolution.

“Natural enzymes are generally really efficient and good at their jobs,” says Wilfred van der Donk, an HHMI investigator at the University of Illinois at Urbana-Champaign. Van der Donk, a chemist by



Chemists Chris Chang and Wilfred van der Donk say biologists and chemists have begun to understand what each can bring to the table to explore how the body works and to synthesize more efficient and cheaper drugs.

“The marriage of biology and chemistry has never been more important than today.” STUART SCHREIBER

training, takes apart reactions that occur in the natural world to learn how chemists can carry out the same reactions more efficiently in the lab.

Microbial cells naturally produce all sorts of antibiotics and antifungal chemicals, for example. His lab hopes to distinguish how cells do it and figure out which of these products have potential as human drugs. In a paper published July 19, 2011, in *Journal of the American Chemical Society*, van der Donk pieced apart how cells make one antibiotic that's currently in clinical development against cystic fibrosis. Understanding how the cell makes the chemical could help him design related molecules that also fight cystic fibrosis.

And then there's cellular chemistry that's like nothing chemists can do in the lab. He wants to understand that too.

“There are enzymes that do reactions where, as a chemist, you look at it and scratch your head and say ‘How can we do that?’”

Van der Donk cites one example that's already made a difference. Many enzymes—proteins that carry out chemical reactions—do their job by breaking a few bonds and creating a few others. Energy is transferred from bond to bond to rearrange a compound. This means that to build a large compound from raw elements—either inside a cell or by industrial chemists in a lab—many chemical reactions are often needed. Each reaction shifts a few bonds, gradually building the desired molecule.

But some enzymes in cells are more efficient, carrying out many bond rearrangements at once. Chemists have used these enzymes as inspiration to design enzymes for industry. “This can make drug synthesis, or material synthesis, more efficient and cheaper,” says van der Donk.

And sometimes it's not learning directly from cells but being inspired by a biological problem that drives chemistry forward. Schreiber calls it “next-generation synthesis.” It's the idea that chemists faced with a difficult biological problem sometimes have to create new chemical methods to solve it. Schreiber, for example, developed a way to generate compounds with the ability to modulate biological processes not otherwise possible. His method, called diversity-oriented synthesis, allows scientists to discover chemicals that target, for example, proteins that cause human disease.

“In the same way that next-generation sequencing is transforming genetics, next-generation synthesis is transforming molecular biology,” says Schreiber.

Learning to Cross Boundaries

While some chemists dive into postdocs or other training opportunities focused on biology to help round out their own lab's

work, others stay specialized in chemistry and collaborate with biologists. Neither path is easy. But with the right navigation, both routes can lead to success.

For those who want to collaborate, the key is understanding what each field has to offer. Carolyn Bertozzi, an HHMI investigator at University of California, Berkeley, believes that biologists and chemists have different motivations. Bertozzi, whose lab has used chemical methods to track sugars within cells, has mentored both biology and chemistry students (see Perspectives & Opinions, “Changed Expectations”).

“Biologists are very problem oriented,” she says. “They often get frustrated if they can't solve the problem they want to solve. But chemists like developing new technologies, even if it doesn't get to the heart of a problem. It's still a success if it works.” As a mentor, Bertozzi tries to help biology students see that their work can be successful as long as it leads to a discovery. For chemistry students, she pushes them to take greater responsibility when tackling an applied problem. “I want them to think about what biological questions cannot be answered using current methods and to focus their creative energies on technologies that really address that need,” she says.

These days, even a chemistry student who wants to stay focused on chemistry often works in a biology lab to get a feel for how to work with biologists, according to Schreiber. “You'll join a project where next to you, elbow to elbow, may be a developmental biologist trying to differentiate a cell, and on the other side is a computer scientist trying to convert data to knowledge,” he adds.

This won't necessarily teach chemists everything about developmental biology, or everything about computer science, but it will teach them how to work with those scientists. “The chemist simply needs to know what those fields are capable of achieving,” says Schreiber, “and how it connects back to their own skill set and discipline.”

Crabtree's biology lab frequently hosts chemistry postdocs. “Occasionally these students do actual chemical synthesis,” says Crabtree. “But mostly they're there to learn biology. And I always hope they come away with an appreciation for what happens when you bring together the tremendous power of genetics with the tremendous power of chemistry.”

Biologists too, are gaining an appreciation for how chemistry can help them, says Crabtree. “When you begin with a biological process that you want to understand,” he says. “One of the first questions you can now ask is, ‘Is there a chemical that prevents this process?’ And if not, ‘Can it be synthesized?’” Such a question

(continued on page 48)

CONTINUED FROM PAGE 17
(LIVING CHEMISTRY)

can launch career-changing collaborations, as Crabtree and Schreiber have learned.

“The important thing,” says van der Donk, “is that biologists and chemists are

really talking to one another more than we used to. As a result, biologists understand better what chemists can bring to the table. And chemists understand better the questions that biologists really care about.” This, he says, has led to a bigger impact of chem-

ists on biological problems. And they’ve only just begun. ■

FOR MORE INFORMATION: See other articles on researchers applying chemistry to biological questions throughout this issue, in print, online, and on the iPad.

CONTINUED FROM PAGE 23
(CALLING ALL TEACHERS)

were suspects, she added, and each suspect used a characteristic brand of pen. The students figured out how to use paper chromatography to distinguish the inks in Bic, RoseArt, and other pens. Most were able to finger the guilty suspect. “I wanted them to understand the concepts more deeply than they would if they had just been given the instructions,” Gurick says.

Getting in Practice

Stony Brook’s curriculum, like all good teaching programs, also requires preservice teachers to spend plenty of time in schools, watching and teaching. Before they’re allowed to student-teach in the third and final semester of their master’s course, preservice teachers at Stony Brook must spend

100 hours each observing teachers—in middle schools and high schools, in ordinary and high-need districts, and teaching different subjects. Many preservice teachers also help teach in the university’s unique biotechnology, chemistry, physics, and earth science teaching laboratories. Science teachers from 80 percent of Long Island’s school districts bring their students for half-day laboratories.

Establishing strong ties with local schools can pay off for much smaller teacher-training programs. At Trinity University, aspiring science teachers do a year-long internship at one of three “professional development schools”—elementary, middle, or high school—in San Antonio, where they are mentored by an experienced teacher. In exchange, the university appoints these mentors as clinical faculty for a year, complete with library and other privileges, and Trinity

faculty lead professional development initiatives for the teachers at each school.

Back in Kalamazoo, Lauren Miller will do her student teaching next spring, and next summer she’ll teach eighth graders the unit she develops on sex hormones and obesity. Beyond that, she plans to teach family consumer science, which includes personal nutrition, reproductive health, and parenting, to high schoolers. She’ll take her newfound enthusiasm for science with her. “Science is asking questions—you ask one question and you’ve got 10 more after that,” Miller says. “I want to take that to my students and get them excited about science.” ■

FOR MORE INFORMATION: To learn about new science and math standards and to see a comparison of preservice programs, visit www.hhmi.org/bulletin/nov2011.

CONTINUED FROM PAGE 29
(HAVE MICROSCOPE, WILL TRAVEL)

Planchon, now an associate professor at Delaware State University, plans to develop similar microscopes to look at live multicellular organisms and continue working closely with biologists. Ultimately, Betzig’s group would like to merge the Bessel sheet’s

capabilities with the super-resolution of PALM, a project that the Galbraiths—frequent collaborators at Janelia Farm who brought their own custom-built PALM with them to Woods Hole this summer—are urging forward.

The long days at MBL will transition into long days back at Janelia Farm, as the

Betzig team continues to improve the Bessel sheet. Because what they really learned at Woods Hole, Gao says, is how urgently biologists await those improvements. ■

WEB EXTRA: Hear Eric Betzig talk about the microscope and see how it dazzled Woods Hole students and faculty in an audio slideshow. Go to www.hhmi.org/bulletin/nov2011.

CONTINUED FROM PAGE 33
(STAR SEARCH)

of background information concerning both wild and captive mouse lemurs with new genetic and genomic data is very exciting.”

At Stanford, Krasnow and his group are pushing forward with mouse lemur research, starting with seeking out addi-

tional samples and setting up collaborations with Malagasy scientists and other lemur biologists around the world. They think that learning about the genetics and physiology of mouse lemurs could help preserve the endangered animals.

“For decades Madagascar has been seen as a hotspot for biodiversity, and rightly so,”

Richard says. “But it is welcome to see that recognition translating into a broader scientific interest in mouse lemurs—primates found nowhere else in the world.” ■

WEB EXTRA: Travel with Mark Krasnow and his team as they explore the rainforests of Madagascar. See the slideshow at www.hhmi.org/bulletin/nov2011.



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