MISHA GRAVENOR

Leave and Learn

An interlude away from the lab was just what the doctor ordered for these accomplished researchers.

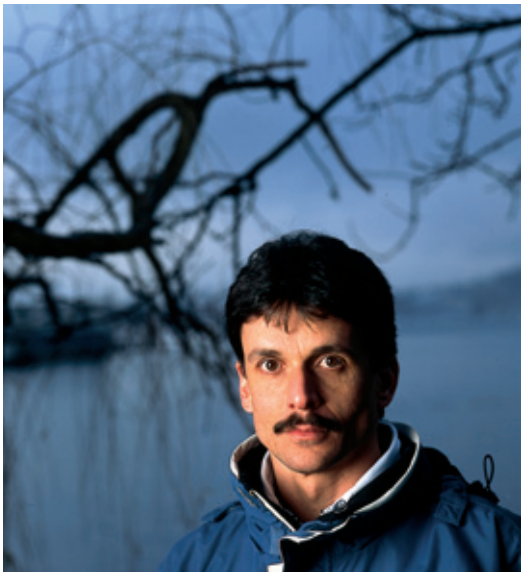
By Marlene Cimons

AFTER YEARS OF RUNNING HIS OWN LABORATORY, HHMI investigator William N. Zagotta went back to basics—he took time off to learn something altogether new in somebody else's lab.

Zagotta says he had reached a point where his research was stalled because he lacked certain technical skills. At the University of Washington School of Medicine in Seattle, Zagotta was studying the molecular mechanisms of ion channels, which he describes as "brain transistors," or proteins that produce electrical signals in the brain. But he needed to see the atomic structure of these molecules in three dimensions. He needed to learn the science and art of x-ray crystallography.

So he and his wife, Suzanne Black, packed up, took their dog, and drove cross-country to New York City in the fall of 2001 to spend 10 months learning the process from another HHMI investigator, Eric Gouaux, at Columbia University College of Physicians and Surgeons. Gouaux had specifically been applying the technology to ion channels.

"I had learned from trying to do x-ray crystallography on my own that I was never going to be able to do it without being in a lab where it is being done," Zagotta says. "You just can't read a book and do it. You really need to be there."



MISHA GRAVENOR

REX RYSTEDT

Both Pamela Bjorkman (left) and William Zagotta (above) traveled east to learn new techniques that helped them view cell structures in three dimensions.

PLACES TO GO, PEOPLE TO MEET

Never underestimate the restorative power of a break. "One of the great perks of this job is the sabbatical you can take every seven years," Zagotta says. "In effect, you get to be a grad student or postdoc for a whole year, and you can focus on your work in a way that you can't do most of the time," in large part because of administrative chores and seemingly endless meetings. The interlude allows seasoned researchers to get back to the bench, where their scientific careers began.

It could be a traditional sabbatical, like Zagotta's—typically one year off after seven on the job. Or it could be a "summer vacation" or a long weekend to learn a new technique. It could even be what some might regard as doing nothing at all: just taking time off from official duties. Regardless, it is a rare opportunity to generate new ideas in a climate free of the usual pressures.

HHMI investigator Pamela J. Bjorkman, who studies the structures of immune-system proteins at the California Institute of Technology, likes to talk about how she spent her 2002 summer. She visited the Laboratory for 3-Dimensional Electron Microscopy of Cells at the University of Colorado at Boulder, to learn electron microscopy from its director, J. Richard McIntosh.

Bjorkman went there with a feeling, much like Zagotta's, that she had reached an impasse in her work and needed to learn more to do more. She had been studying a molecule—called the neonatal Fc receptor, or FcRn—that transfers maternal antibodies to the fetus or newborn. "We wanted to see how the receptors and their cargo were actually arranged inside the intracellular vesicles," she says, and that required electron microscopy to be able to look inside cells—a tech-

nique that no one in her lab had the expertise to do.

So she went to Boulder to learn it. "The real fun of this," says Bjorkman, "was making three-dimensional reconstructions of the parts of the cell that I'd only seen before as two-dimensional pictures in a book. Looking at them was quite wonderful for me. You can rotate them and look at all angles. This taught me a lot of things about what goes on inside a cell."

Such experiences can be humbling. Accomplished researchers quickly realize that, despite their achievements, they are novices when it comes to acquiring the new skills. The toughest part for Bjorkman, for example, was trying to prepare the cells for microscopy, a process that involves high-pressure freezing of the samples. "It turned out to be quite tricky," she says. "You need to freeze them within milliseconds so you can capture these dynamic events without damaging them." And she did damage a few samples along the way, Bjorkman acknowledges. When that happens, "instead of the workings of the cell, you'll see ice crystals."

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Zagotta went through a similar struggle, though in his case, crystals were the aim—he had to turn his proteins into crystalline form so that an x-ray beam could obtain the desired information. It was hard work, but worth the effort, he says. With this technique, "people have been able to study the behavior of ion channels in incredible detail."

THOMAS BROENING

The effort of teaching new tricks to old dogs brings benefits to the hosts as well. While Bjorkman was learning the practicalities of doing structural biology, McIntosh says she enriched his lab. "Through visitors like Pamela, we are stimulated to think about scientific problems that are completely new to us," he says, adding that "Pamela's project also made technical demands on some of our standard methods." His staff had to manipulate conditions so that Bjorkman could work with the very small particles of gold she used to label her proteins.

Columbia's Gouaux agrees, stating that Zagotta taught his lab members about framing problems, designing experiments and analyzing data. "There is nothing better than having someone with unbridled enthusiasm and fantastic talent in your lab," Gouaux says. The New Yorker adds happily that his Seattle-based colleague got him re-addicted to caffeine. "I can now properly order an espresso beverage from my local barista."

ENHANCED CREATIVITY

Many scientists say that a major advantage of these kinds of sabbaticals is that they transcend the subject or technique being acquired. They can enhance the scientist's creativity in his or her own field, and at a fundamental level.

HHMI investigator Mark M. Davis and his wife, Yueh-hsiu Chien, both immunology faculty at Stanford University School of Medicine, say that this is what happened when they took a year off beginning in the fall of 2000 and spent it at Oxford University.

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They simply needed some space away from the academic bureaucracy, and some fresh influences.

"There are so many things that get in the way," Davis says. "The longer you've been at a place, the more jobs people find for you to do. The parking-lot committee can meet for hours. Meetings take forever, and accomplish precious little. You could work a whole week at these jobs, and not find time to do any science. On sabbatical, we suddenly had all this time that we'd never had before."

Living and working in a foreign country has other rewards as well. For example, "science is done differently in England," Davis maintains. "They can't do as many experiments as we can, so they have to put more thought into it. Ours is the only culture where we throw lavish sums of money into basic research."

SCOTT FERGUSON/FERGUSON AND KATZMAN PHOTOGRAPHY

Mark Davis (facing page) sought out and found refuge from long meetings. Randy Buckner (above) got so much out of his month in London that he's planning a full-fledged sabbatical next year.

This experience enabled him to review his own research priorities, and design new experiments, Davis says. He was never totally out of touch with his lab group—they communicated often by e-mail—and he did make five trips home during that year for some "face time." But most often, he just sat and thought. In doing so, "I thought up really good experiments," he says, and suggested them to members of his lab at Stanford. "Our lab has been incredibly productive since then. You really need that time to be creative, and you can run off that for years."

Results of one of those experiments, Davis notes, were published in the October 24, 2002, issue of *Nature*. "It was about how T cells recognize things," he explains. "What we were able to do was label the individual antigens as they sit on the surface of the cell that the T cell was looking at. We could tell, in real time, how many antigens the T cell was seeing and what it did about it."

Randy L. Buckner, an HHMI investigator at Washington University in St. Louis who studies memory and the brain, had a similar opportunity a few years ago, though for a shorter period, to "take a step back and look at the big picture." He took a month off and went to University College London—an experience that "was invaluable," he says, adding that it was actually a turning point in the direction of his research, when he shifted the focus of his studies of the brain to aging issues. It led to a paper in *Neuron* in 2002 delineating two distinct kinds of changes in brain function that occur with age. He says his group is now studying "whether these changes are responsible for the kinds of mild cognitive change we see often in aging or are the beginnings of Alzheimer's disease."

Having discovered the value of a month off, Buckner now hopes to take a real sabbatical next year to learn about genetics. "It's hard to learn a new field, and I want to take some time to talk to smart people and learn from those who do genetic work in aging," he says. "I'm starting to talk to leaders in that area to see what they suggest."

Buckner's new interest in genetics stems from an idea his lab group is starting to explore, that of genetic origins of brain changes. "We're very good at identifying those brain changes at the structural and functional level," he says. "What we don't know much about is, potentially, how to link those changes to genetic factors."

TRAVEL BROADENS

Once the visitor returns home, it isn't necessarily easy to continue applying the skills acquired elsewhere. For example, now that Zagotta is back in Seattle, he finds that one major piece of equipment he needs is not portable.

He and his colleagues can do the basic biochemistry and molecular biology of the initial experiments, but the laboratory doesn't have what it needs to take the final step and actually do the crystallography. Says Zagotta, "we need access to a synchrotron, the instrument that generates the x-rays. It generates very high energy and is roughly the size of a football field."

When he was in New York City, two synchrotrons were within driving distance. One was upstate in Ithaca, and the other—which he and his colleagues used—was at the closer Brookhaven National Laboratory on Long Island. But the Pacific Northwest doesn't have a synchrotron, so now things are more difficult for Zagotta—though not insurmountable. "The closest one is at Berkeley, which means instead of jumping in a car for two hours I have to jump in a plane for two hours," he says.

Such practical details do not diminish the fundamental value of their graduate-student-for-awhile sabbaticals, the researchers agree. Getting away is truly refreshing, rendering them more creative and productive upon their return.

Moreover, being in a new and different location carries its own benefits. Zagotta and his wife landed in New York City from Seattle fearing the worst—even under routine circumstances. They arrived there just a week after the September 11 attacks. Nevertheless, he says, their experience "was completely different from what we expected. New Yorkers have a reputation for being cold, but they were totally the opposite—incredibly welcoming—which was a real surprise to us."

At Oxford, Davis enrolled his teenage daughter, Sara, in an English school and enjoyed watching her attitude change from resistance to leaving home to embracing new friends and a new culture. And he especially savored his own downtime and temporary isolation from Stanford.

That respite was inadvertently aided by his assignment to a small office that had been used by a visiting Danish scientist. Its answering machine's outgoing message, in heavily accented English, "was enough to convince all those callers trying to reach us that they'd called the wrong number," Davis says. "We couldn't figure out how to change it, and that turned out to be a major plus." H