Inside Bioscience

(It's not a place for everyone)

Scientists are different than the rest of us. Driven by intense curiosity to find answers to life's most fundamental questions, they must cope with failed experiments, long hours, shrinking budgets and public ignorance. But most wouldn't trade their jobs for anything.
Why do they do it?

BY SALLY POBOJEWSKI

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Billy Tsai, Ph.D., is still fascinated by a question he's been trying to answer since he started graduate school 14 years ago: How do viruses and bacteria cross cell membranes to hijack the cellular components they use to infect a cell?

Tsai studies cholera toxins and polyomaviruses that can cause cancer. After years of research, he's discovered that these pathogens co-opt some of the cell's natural defense mechanisms to gain access and do their dirty work inside the cell. But the specific details of how they do this are still a mystery — one that Tsai is determined to solve.

"How did these toxins and viruses get so smart?" Tsai asks. "The cell has all kinds of protective barriers and defense mechanisms, but these guys know how to get in there and do their thing. I just don't understand how they do this."

An associate professor of cell and developmental biology, Tsai was born in Taiwan where his father was a physics professor. He's wanted to be a research scientist ever since he studied biology as an undergraduate at UCLA. After receiving a Ph.D. from Harvard University and completing postdoctoral research at Harvard Medical School, Tsai got his "first real job" in 2003 when he was hired as an assistant professor by the U-M Medical School's Department of Cell and Developmental Biology.

On September 1, 2008, Tsai was awarded tenure — the equivalent of winning the academic lottery. At age 37, with a wife and two young sons, he finally has job security.

Tsai collaborates with researchers at the U-M and Harvard University who believe his research findings could help them find new ways to treat cancer and infectious diseases. He says he'll be happy if other scientists find practical uses for what he's discovered. But he has a different motivation. "Honestly, for me, I just want to know how it works," he says.

It's a good thing Tsai's career in academia is working out, because he is the first to admit that he's not cut out for life in the serious, buttoned-down world of corporate research. "I treat this job as more of a fun thing than people do in the corporate world," says Tsai, sitting in his office in a T-shirt and a Michigan baseball cap. "If I have to wear a tie, it's all over for me."

It's sometimes hard to appreciate what drives scientists like Billy Tsai, who can spend a lifetime working in one narrow field of research. But there are about 1,500 people in the Medical School who know exactly how he feels. They are faculty members, postdoctoral fellows and graduate students who spend their days — and occasionally, their nights — working in the Medical School's basic science research laboratories.

Unlike applied or clinical research where there's an obvious connection to human health and disease, contributions made by research in the basic sciences are not as direct. The goal in basic research is not to develop a new drug or find better ways to treat a disease. The goal is to answer questions about the basic biology of life itself. Questions like: How do cells communicate? How does a single cell develop into a complex organism? How does the genome work? What causes disease?

Although their work is often misunderstood and not always valued by the general public, Medical School scientists emphasize that behind every medical advance we enjoy today, there was someone who was driven by pure intellectual curiosity to ask: "I wonder how that works?"

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HOW TO SUCCEED IN SCIENCE

Geoff Murphy, Ph.D., 47, an assistant professor of molecular and integrative physiology, loves it when a student walks into his office to report that the experiment didn't work.

"What do you mean it didn't work?" Murphy will respond. "Do you mean you didn't get the answer you expected, or did the equipment fail and everything's on fire? The latter would be the experiment didn't work. The former is yes, it worked. You got data, it just didn't turn out the way you thought it would."

One of the hard realities of science is that the experiment doesn't work most of the time. There's an endless list of things that can go wrong: The pipettes weren't calibrated correctly. The mice caught a virus and died. Cell cultures were incubated at the wrong temperature. Someone forgot to label the tissue samples.

It takes determination, dedication and dogged persistence to spend months completing a series of difficult experiments and then have to throw out the results and start all over.

"You have to be able to do the experiments, have them fail miserably, and not get mired down in that," Murphy says. "It's not easy and some people never achieve a level of comfort with it. Those people don't stay in science."

Because there are so many opportunities for error, the results of one experiment are never conclusive. Graduate students and research fellows in the lab repeat the experiment many times in many ways to make sure the data are valid. When results are published in a scientific journal, researchers describe the protocol, procedures and materials they used for each step of the study, so scientists at other labs can try to replicate the results. If they can't, they are not shy about letting people know — often in no uncertain terms. Every scientist has vivid memories of the first time he or she nervously presented research results at a meeting, only to be grilled afterwards with a barrage of pointed questions from the audience.

RED BLOOD CELLS: BOGDAN POP/ACTIV DESIGN/ISTOCKPHOTO

"A scientist by very nature is critical," says John Moran, Ph.D., 44, a professor of human genetics. "When something new comes up, it is always challenged. But you can't question your competitors unless you question yourself. You have to be your own worst critic."

The danger of falling in love with your hypothesis is very real in science. Competition is intense, the stakes are high and sometimes the hypothesis is just so intriguing, it's easy to overlook or dismiss small discrepancies in the data. Part of the training process in basic research is learning how to resist this temptation.

Among the stereotypes people have about scientists, one of the most common is of a brilliant, but eccentric, researcher with poor social skills who can't handle people. It's true that, as a group, scientists tend to be less extroverted than say, used car salesmen, but no one succeeds in science today by working alone. In fact, many U-M scientists say the opportunity to work with a diverse group of smart,

interesting — perhaps somewhat quirky — people is one of the attractions of the job.

Communication, networking and forming close working relationships are vital to success in science, because the opinions of colleagues can literally make or break a career.

"Peer review is what we live by," explains Michele Swanson, Ph.D., 48, a professor of microbiology and immunology. "We are judging each other all the time. So your reputation really matters. Do people in your community respect you?"

Peer review is fundamental to the business of science. It's based on the principle that scientists are in the best position to select the most significant research papers to be published and the most promising grant proposals to be funded. An invitation to review a journal manuscript or serve on a funding agency's study section is considered an honor. It means that others in your field value your work and respect your opinion.

But there's a dark side to peer review. The ability to get research funded and papers published can depend on the opinion of a few scientists in your specialty, some of whom could be direct competitors. Scientific merit is supposed to be the sole criteria for these decisions, but scientists wouldn't be human if they didn't occasionally have doubts about the fairness of the process.

"One of the critical roles of mentors is to introduce you to their peers, who will become your peers," says Chris Alteri, Ph.D., 33, a research fellow in microbiology and immunology, who is president of the U-M Postdoctoral Association. "It's a closed circle of people, so it's critical to get involved in that circle, because it's very difficult to get papers published or grants funded without them. To a large extent, they hold the academic careers of young scientists in their hands."

CHASING THE MONEY

Research costs money and, like everything else, it's getting more expensive every year.

In fiscal year 2007, research expenditures in the Medical School totaled $342.4 million. The majority of this money comes from the

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National Institutes of Health — the federal agency that has, since 1945, funded most of the biomedical research and postgraduate education taking place in U.S. universities.

Scientists compete for NIH funding by submitting a grant proposal — a 25-page, single-spaced document that describes the study they want to do, how they plan to do it, why they are the best person to do it and how much it will cost. Proposals are sent out for peer review and, several times each year, scientists convene at NIH headquarters in Bethesda, Maryland, to review and rate the grant proposals submitted in their respective fields. Proposals with the best scores are recommended to NIH administrators for funding.

The system works when there's a reasonable balance between the NIH budget and the number of investigators seeking funding. But during the last five years, the amount of NIH funding appropriated by Congress has remained essentially flat, when adjusted for inflation, while the number of scientists applying for funding has doubled. As a result, research investigators are spending less time doing science and more time trying to find the money to pay for it.

"I see too many of my colleagues just sitting in front of a computer writing, writing, writing," says Billy Tsai. "Instead of using their most productive years to do what they are really good at — doing experiments — they are chasing money. It's really a shame."

While the Medical School provides bridge funding for researchers who find themselves caught in the current funding squeeze, the money is limited and only meant to be a short-term solution.

The consequences of not getting funded or losing a grant are serious. External funding pays for everything in the lab from basic equipment to salaries. Without funding, labs can and do shut down, leaving postdoctoral fellows and graduate students scrambling to find other positions. Most universities require at least one, and sometimes two, NIH grants before a junior faculty member will be considered for tenure.

"There's a lot of stress and anxiety involved in the grant application process," says Christin Carter-Su, Ph.D., a professor of molecular and integrative physiology. "You have a whole lab dependent on you getting that money."

Even well-established scientists like Carter-Su put in 18-hour days preparing grant proposals that meet NIH's strict specifications and rigid deadlines. "Even after the grant is written, we encounter time-consuming difficulties compiling and submitting the proposal," she says. "There always seems to be some new technical problem or computer software glitch that has to be overcome at the last minute."

THE NEXT GENERATION

Scientists in the Medical School say one of the most satisfying parts of their work is training students and helping research fellows develop their own independent scientific careers. Scientists take their responsibility to train the next generation very seriously, and the bond between a mentor and a student or fellow can last a lifetime. But many of today's students have different ideas about what to do with a Ph.D. than their mentors did.

> "I went through four years of college, eight years of graduate school, four more years of a postdoc — so that's 16 years to get an assistant professorship, which was the first time I got benefits. My grandmother used to ask me, 'Are you out of school yet?' "

When Michele Swanson was a graduate student at Harvard in the late 1980s, for example, no one dared to even mention the possibility of a career outside academia. "There was a stigma attached to anything other than the life of a scholar," she says. "There are a lot more opportunities today, and students have more open minds about what they want to do."

Instead of following the traditional career path of doctorate degree to postdoctoral research fellow to assistant professor, more of today's Ph.D. graduates in the biomedical sciences are heading in different directions. Some go on to law school or business school, some become science writers or consultants and some pursue careers in the biotechnology or pharmaceutical industries.

Some of the interest in alternative careers is driven by the fact that there are many more Ph.D. graduates each year than new faculty positions available, which makes for intense hiring competition. But Swanson sees another factor behind the trend: Graduate students and postdocs see their mentors struggling to find research funding and spending long days in the laboratory. They aren't sure it's the kind of life they want for themselves, especially if they plan to start a family.

"This generation of students is more devoted to a balanced lifestyle," says Swanson, who had two babies while she was a graduate student at Harvard. While she admits she's in the minority, Swanson says she's "a bit of an activist" about dispelling the idea that the secret to success in science is the number of hours you spend in the lab.

"Putting in more hours does not guarantee more insight," she says.

Carter-Su agrees that today's students are more interested in balanced lifestyles. As a mother of two daughters, she knows how difficult it can be to manage work and family commitments, but points out that academics have more scheduling flexibility than other professionals. This makes it easier to handle the work-family balancing act.

She encourages promising students to put in the time and effort necessary to succeed in academic research. "I spend a lot of time telling many of my students and postdocs that they have what it takes, and I think they ought to go for it," she says.

"When I was in graduate school, I worked most nights and weekends," Carter-Su adds. "I didn't have a car; I walked to work. But it was OK, because I loved what I was doing. The time I invested was worth it, because to this day, the work is still extremely satisfying and I'm always learning new things."

WHY THEY DO IT

When Ming Lei solved the crystal structure of an enzyme involved in the development of cancer, he not only got a Ph.D. from Harvard, but also a job offer from Pfizer —where scientists had tried, but failed, to do the same thing.

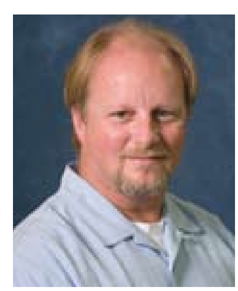
"I considered going directly into the pharmaceutical industry," says Lei, 36, an assistant professor of biological chemistry. "In a pharmaceutical company, of course, you make a lot of money. But for me, I'm unsatisfied in the sense I cannot explore a lot of unknowns. In a university, you can do whatever you want."

Geoff Murphy went to work for a biotechnology company after he finished graduate school, but found it wasn't a good fit. "They brought me into the company to study learning and memory," he says. "Within four months, they said 'This whole cognitive area isn't going to pan out money-wise, so you're now studying pain.' I didn't know anything about pain!

"The major disadvantage of doing research in corporate America is you don't have freedom over what you want to do," Murphy continues. "The big difference at a university

NAME: Christin Carter-Su
TITLE: Professor of molecular and integrative physiology
HOMETOWN: Newark, Delaware
DEGREES: Brown University (B.S. 1972), University of Rochester (M.S. 1974, Ph.D. 1978)
RESEARCH FOCUS: Growth hormone signaling pathways
QUOTE: "I like supervising the experiments, seeing data, strategizing and figuring it out. It's like a big puzzle. There's nothing like it, especially when you make that big discovery."

NAME: Geoff Murphy
TITLE: Assistant professor of molecular and integrative physiology
HOMETOWN: Alton, Illinois
DEGREES: University of California, Berkeley (B.A. 1990); University of California, Los Angeles (Ph.D. 1998)
RESEARCH FOCUS: How the brain learns and remembers
QUOTE: "My contributions will outlive me and my discoveries will outlast me. If I make a significant contribution that advances the field and people build on that, then I gain a bit of immortality."



is I can study anything I want, as long as I can find money to pay for it. To me, that's ideal. You have infinite degrees of freedom to do what you want."

If it comes to a trade-off between money and freedom, most scientists will choose freedom every time. It's not that money is unimportant. Scientists have mortgages and families to support like everyone else. And once they have tenure, most make a very comfortable living. But financial security comes later in life than it does for other professionals, because scientists spend their 20s and much of their 30s in training positions with minimal salaries.

"I went through four years of college, almost eight years of graduate school, four more years of a postdoc — so that's 16 years to get an assistant professorship, which was the first time I got benefits," says Moran. "My grandmother always used to ask me, 'Johnny, are you out of school yet?'"

In the end, however, U-M scientists say it's those rare moments of insight and discovery that make the long hours, funding hassles and hard work all worth it.

"You live for small moments of illumination," says Moran. "Every result, every experiment, every point of illumination shines the light in a new place."

To finally solve the puzzle after years of work, to hold the data in your hands and know something no one else in the world knows — that is the ultimate reward. [M]

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NAME: Michele Swanson
TITLE: Professor of microbiology and immunology
HOMETOWN: Barberton, Ohio
DEGREES: Yale University (B.S. 1982), Columbia University (M.S. 1986), Harvard University (Ph.D. 1991)
RESEARCH FOCUS: Interactions between white blood cells and *Legionella* bacteria
QUOTE: "What really attracted me to science was the opportunity to be surrounded by really smart people from all over the world who were passionate about what they were doing."

NAME: Billy Tsai
TITLE: Associate professor of cell and developmental biology
HOMETOWN: Alameda, California
DEGREES: University of California, Los Angeles (B.S. 1993, M.S. 1994); Harvard University (Ph.D. 1999)
RESEARCH FOCUS: How cholera toxin and polyomavirus get inside cells
QUOTE: "The relationship between student and mentor is important in science. It's my duty to give my students the same amount of time my mentor gave me."

DNA: DAVID MARCHAL/ISTOCKPHOTO