UNRAVELING THE MYSTERIES OF PROTEINS

Daniel Sem, Ph.D., wanted to put a heart in hard science — something that wasn't always easy when he worked in the profit-driven biotechnology industry.

"Whenever I would talk about tuberculosis, that would always make the venture capitalists cringe … because there's not enough money to be made," says Sem, who was founder and vice president for biophysics at Triad Therapeutics in San Diego. "They told me, 'Your motivation has to be in one place or the other. Are you trying to make money or are you trying to sort of save the world?' And my thinking was, 'Can't we try to do both?'"

Now Sem, an assistant professor of chemistry, can focus on the underdogs: diseases that don't get enough attention and the dangerous side effects of drugs and pollutants. His passion for applied research found a home in Marquette's Jesuit, service-oriented mission.

Sem's specialty is chemical proteomics, which is the study of how chemicals interact with proteins. You could have several thousand proteins in a cell, but only a few might interact with a certain chemical.

"I view it as a constant war that's going on between us and our environment," he says. "Chemicals can be drugs that are attacking certain proteins and having a desired effect, or they could be pollutants that are attacking and having an undesired effect. It's sort of the yin and the yang of chemicals."

At Marquette, Sem has state-of-the-art tools to study that war. He's the founding director of the Chemical Proteomics Facility, which recently received $1.2 million of new equipment funded in part by the National Institutes of Health and the National Science Foundation. The big gun is a powerful 600 MHz nuclear magnetic resonance spectrometer, which allows researchers to study the structure of proteins and their interactions with chemicals. A second new instrument, a 400 MHz spectrometer, has a robotic arm that can analyze hundreds of samples overnight.

Sem's recent work has included researching proteins in Mycobacterium tuberculosis that could be targets for new anti-TB drugs, studying estrogen receptors in zebrafish, and examining a troublesome enzyme that metabolizes nearly one-third of all drugs in humans.

To study a pollutant that is causing birth defects in aquatic wildlife, he designed a fluorescent molecule that binds to the estrogen receptor, which allows him to see what's happening inside developing fish. The binding site for zebrafish is nearly identical to that of humans, so zebrafish could be used to screen for human breast cancer therapeutics or to learn how pollutants are affecting the human body. Next, he'll use nuclear magnetic resonance instead of fluorescence.

"If we could turn this into an imaging probe, an MRI probe, then we could use it as a diagnostic for humans," Sem says.

Sem also developed chemical probes that assess the environment inside a cell.

"It turns out that a lot of diseases — Alzheimer's, arthritis, Parkinson's — all show an imbalance in the oxidation state of a cell," he says. "It's a way of measuring that things are wrong inside the cell."

"I view it as a constant war that's going on between us and our environment."

Sem was the first to create a fluorescent probe that could measure the oxidation state inside living cells, filling a crucial gap in what scientists understand about cell biology. The probe can also be used to see how drugs are working.

Sem is also researching the enzyme CYP2D6, which metabolizes 30 percent of drugs in the liver. In effect, that enzyme destroys a drug's effectiveness before it's even had a chance to work.

"We want to better predict what kind of chemicals bind to these proteins," Sem says. "Then there's the basic research question of trying to understand how one protein with just one little pocket can bind to hundreds of molecules. If it's like a lock and a key, how can one lock recognize several hundred keys? That's the mystery we're trying to solve."

Daniel Sem, Ph.D., is an assistant professor of chemistry and director of the Chemical Proteomics Facility at Marquette. He was the first to create a fluorescent probe that could measure the oxidation state inside living cells.

The lung: more than gas exchange

When most people think about their lungs, breathing — inhaling and exhaling — is likely the first thing that comes to mind. It's an important function, to be sure, says **Gary Krenz**, Ph.D., but the lungs accomplish much more than that.

Krenz, a professor of mathematics, statistics and computer science, researches various nonrespiratory functions of pulmonary circulation. For example, he studies what happens to blood as it passes through the lungs. "The lung is the only organ in the human body that receives all the blood from the heart," he explains. "The lungs modify the blood composition before it's passed to the rest of the body, and we're studying how and why that takes place."

Specifically, Krenz focuses his research on how chemicals are altered when they pass through this area of the body. "It's as if the lung protects the rest of the body by modifying certain chemicals," explains Krenz, who recently published in the *American Journal of Physiology – Lung Cellular and Molecular Physiology*, *American Journal of Physiology – Heart and Circulatory Physiology* and *Free Radical Biology & Medicine*.

Interestingly, Krenz is not a biologist or chemist by training — he's a mathematician — but he leverages biomathematical modeling to predict the properties of pulmonary circulation. "Our problems are initiated by cell biologists, anesthesiologists, biomedical engineers and others who want to know why the lung is behaving in certain ways," says Krenz. "In our hypertension studies, we examine the number of blood vessels, their sizes, and the combined impact on pulmonary pressures." Already, Krenz has broken new ground in understanding how the number of blood vessels increases and decreases due to external influences.

He splits his time between Marquette and a research lab in the Zablocki Veterans Affairs Medical Center, where pulmonary research is done on rats. Krenz lends his mathematical expertise to formulate models of how the lungs will react to treatments. The National Institutes of Health and Department of Veterans Affairs have supported his work with impressive research grants, paving the way for new discoveries in pulmonary physiology.

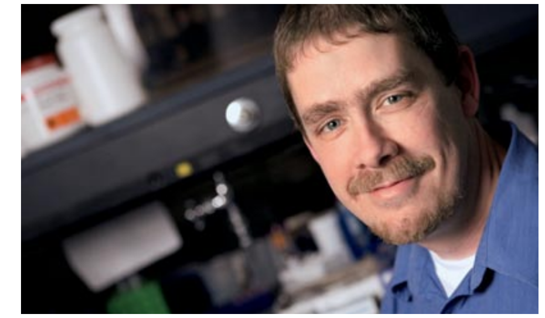
Cellular power

Just as any automobile depends upon its engine for movement, so human cells depend upon motor devices, cilia and flagella, for movement. It's the job of **Pinfen Yang**, Ph.D., to reveal how these two similar organelles "power" basic cell function and to understand why their defects result in a host of debilitating disorders — such as infertility, developmental disorder, cystic kidney and hydrocephaly.

Cilia and flagella are only visible with a microscope. But, according to Yang, they are "powerful biological machines" that oscillate with particular waveforms, just as people swim with different strokes using their arms and legs. A tightly regulated propulsive movement is required for cells in many organs to function normally. Only recently have biologists such as Yang tapped into the control mechanism of these similar organelles using green algae as a model organism.

"We did not appreciate the intricacy of these organelles until symptoms showed up because of various defective motilities, and we realized the machinery behind the movement was worth investigating," says Yang, an associate professor of biological sciences. "Now we know that diseases and disabilities could be due to defective motor machinery as well as the control mechanism."

When these motile organelles surrounding the chambers in the brain and spinal cord are defective, for example, headache or expansion of the cerebral ventricles develops. If biologists can restore normal motility, the disorders could potentially be reversed. Cells in other organs hold promise, as well. "This research will have a far-reaching impact if we can use our knowledge learned from green algae to repair or enhance the performance of cilia and flagella in patients," says Yang.



Healing the brain: the new frontier

For **David Baker**, Ph.D., glutamate isn't just another chemical in the brain. It's uncharted territory that could help neuroscientists better understand and treat schizophrenia and other disorders.

Baker, assistant professor of biomedical sciences, is researching a unique process in the brain that may be critical to treating brain disorders. His research is supported by the National Institute of Mental Health, National Institute on Drug Abuse, National Alliance for Research on Schizophrenia and Depression, and the Biomedical Technology Alliance.

While studying glutamate's role in addiction, Baker became intrigued by a mechanism, system xc-, that releases glutamate in a very unusual way.

"Essentially every neuroscientist assumes that neurotransmitters are released into very specialized gaps between nerve endings called the synapse. But system xc- appears to bathe the entire length of the nerve in glutamate," he explains.

Neuroscientists knew about this second pool of glutamate before, but they didn't know why it was important.

"The real discovery is that we are the first to show that glutamate released from system xc- is critical to how the brain functions," Baker says. "We have evidence that it's involved in addiction and schizophrenia. Other people believe it may be involved in Parkinson's Disease." Because glutamate is critical to most aspects of brain function, discovering a new pool may reveal a new treatment target for many neurological disorders.

The researchers initiated clinical trials for an existing drug that targets system xc-, and the results are promising. Baker also is collaborating with researchers from the University of Wisconsin–Milwaukee and the Medical College of Wisconsin to develop new and better drugs. Says Baker, "The new drugs will really be the test as to whether system xc- holds the key to the treatment of neurological disorders such as schizophrenia."

Marquette was one of the founding partners of the Biomedical Technology Alliance, which connects academic researchers with industry partners.

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