## Molecular and Cellular Physiology at the Beckman Center: Deepening our Understanding of Life from Systems to Cells to Molecules

*By Krista Conger*

It was an unconventional location for a pair of neuroscientists. But Daniel Madison, PhD, and Richard Tsien, PhD, gamely set up shop in a building attached to the Stanford Museum of Art. It was late 1988 and their intended home-to-be, the Beckman Center for Molecular and Genetic Medicine, was still under construction.

"My 'office' was one of several pie-shaped spaces delineated by old cubicle dividers in the rotunda of a large dome, with its little cupola," Madison recalled. "It was pretty dark, and there was rarely anyone else around. I felt like I was in an ancient cloister. It was both a little cool and a little creepy."

Tsien and Madison had been recruited from Yale University as part of the then-newborn Beckman Center's audacious new effort to bring advances in basic science into clinical practice. The modern, light and airy building that would house the center would provide laboratory space and offices for an additional 20 faculty members in the Stanford School of Medicine and two new departments: Molecular and Developmental Biology and Molecular and Cellular Physiology.

The Beckman Center was ready for occupancy in February 1989 and Tsien and Madison eagerly moved into their new laboratories and offices on the building's first floor. Above them were floors dedicated to Howard Hughes Medical Institute investigators, the new Developmental Biology Department and the Genetics Department.

"It was an usual opportunity to populate a new department from scratch," said Tsien, who served as the department's first chairman, "and it was very exciting."

The researchers had no way of knowing that they had moved offices in the nick of geological time. In October of 1989, the Loma Prieta earthquake caused $250 million of damage across the university. The building that housed Tsien and Madison's former offices and laboratories was one of many architectural casualties destroyed beyond repair.

Not so the new building.

"The Beckman Center performed during the earthquake just as it had been designed, and the building itself was not significantly damaged," said Richard Lewis, PhD, a professor and former chair of the department.

Paul Berg, PhD, the Beckman Center's first director and co-recipient of the 1980 Nobel Prize in Chemistry for his work in recombinant DNA, later recalled for the Stanford News Service, "When we were allowed into the building hours later, the labs and offices on the fourth floor were a shambles; glassware had come off the shelves, floors were littered with liquids and broken glass, file cabinets and refrigerators had slid across the room. But the rooms were intact."

Ironically, the field of physiology was undergoing a similar upheaval at the time — one that Tsien struggled to balance as he began the recruitment process.

"Physiology has always been, fundamentally, the study of how things work," said Madison, an associate professor and associate chair of the department. "Traditionally the field had focused primarily on understanding organ systems like the kidney or heart, or tasks like digestion or respiration. But in the mid-1980s the focus had begun to shift more towards cellular and molecular biology as a way to learn how genes and proteins interact to help cells communicate with one another to carry out physiological processes."

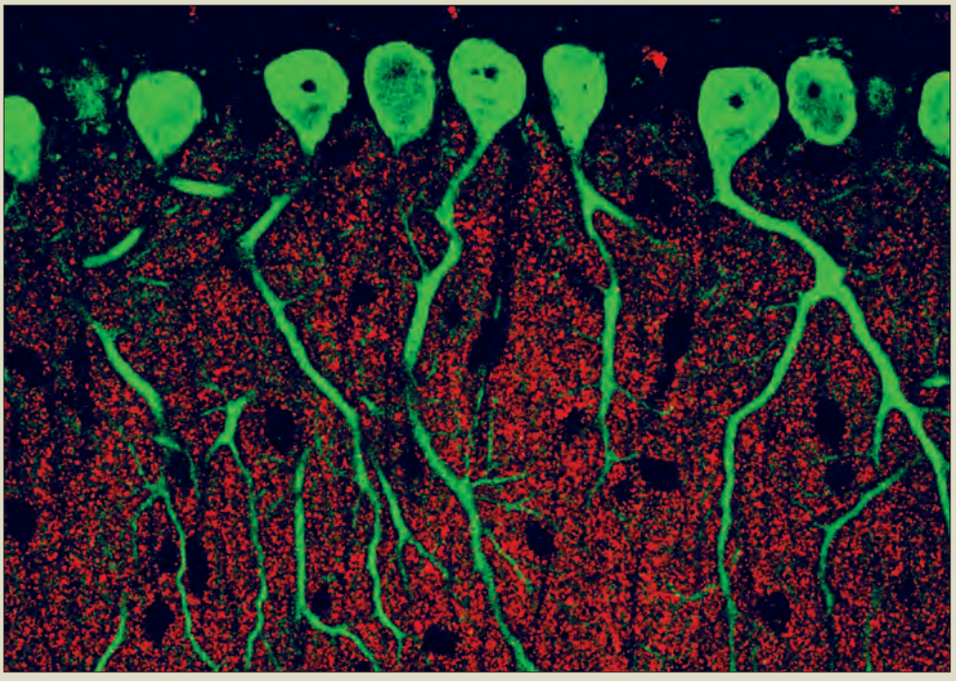
"Traditionally, the field of physiology had focused primarily on understanding organ systems," said Madison, "but in the mid-1980s the focus had begun to shift more towards cellular and molecular biology as a way to learn how genes and proteins interact to help cells communicate with one another to carry out physiological processes."

The shift was driven by new technologies and approaches that could hardly have been dreamed of as little as a decade earlier. Researchers had devised a way to measure the electrical currents triggering changes in activity in individual cells and begun to clone genes involved in ion channels spanning the cellular membrane. Advances in microscopy were enabling researchers to peer ever more deeply into the cellular soup and piece together protein structures and interactions that had previously been hidden, while voltage-sensitive dyes made visible the electrical changes across the cell membrane that precede functions as diverse as muscular contraction or nerve signaling.

Finally, proximity to the Stanford Positron Electron Accelerating Ring at SLAC, which generated the most intense X-rays in the world, made it feasible to study the three-dimensional structure of proteins responsible for sending and responding to signals inside and outside the cell.

The faculty members recruited by Tsien each had their own special research niche. But nearly all were united by a shared theme — an interest in how the nervous system functions at the molecular level. This focus was somewhat unusual for a physiology department.

"Historically, our department stood out from others nationally and internationally due to this focus on molecular neurobiology," said Axel Brunger, PhD, a professor and current chair of the department. "On the most basic level, many of our faculty members were and still are focused on signaling across cellular membranes. Some of our first colleagues studied ion channels, some focused on cell surface receptors and others on the process of membrane fusion that allows



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the targeted transport of signaling proteins within and without the cell. We've continued to maintain our strengths in this area, but our department has also evolved to become more diverse in its interests."

Using these emerging techniques, researchers in the department have over the past 25 years pieced together the molecular mechanisms of how nerve cells orchestrate the lightning-fast responses that allow us to recoil in pain, sense another's touch or codify information in the form of learning and memories. They've come to understand how cells develop and maintain the polarity and adhesion capabilities necessary for our muscles to contract and our hearts to beat. They are exploring how the size of our organs can change to meet varying physiological demands and they're investigating the role of a little known cellular antenna in cellular signaling and human health.

Discoveries made in the department are directly applicable to human health and diseases as diverse as neurological and neurodegenerative disorders, diabetes, obesity, heart disease and cancer.

Faculty members' achievements have been recognized with Nobel prizes in three separate categories — physics, chemistry, and physiology or medicine — the 2010 Kavli Prize in Neuroscience, the 2013 Albert Lasker Award for Basic Medical Research, multiple memberships in the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts & Sciences. Several are also Howard Hughes Medical Institute investigators and one was recently named an investigator for the Chan Zuckerberg Biohub initiative, the multi-billion dollar effort to "cure, prevent or manage all disease," within the coming decades.

Faculty members in the department participated in initiating Bio-X, the Stanford Neurosciences Institute, and the Beckman Center's Cell Science Imaging Facility, which provides state-of-the-art light and electron microscopy resources to researchers across the university. It's a remarkable legacy for a fledgling department, due in large part to the camaraderie and passion of the faculty members Tsien recruited.

"Neuroscience has blended with physiology in a more productive way at Stanford than in many other universities," said Tsien, who is now the director of the NYU Neuroscience Institute at New York University Medical Center. "I am really very proud of the department we built. Our team consisted primarily of newcomers to the university, and by and large we all had different backgrounds and skills. But we developed a warm sense of family and accomplished amazing things."

There wasn't as much earthquake damage on the ground floor of the building, but it still required cleanup. Plenty of time for the first members of the new team to think, discuss and prioritize what research questions to tackle.

"There was just an explosion of new molecular and cellular approaches that were beginning to take hold in the field of physiology," said Lewis. "And Dick Tsien did an extraordinary job of putting together a group of people who, although generally focused on neurobiology, also included enough breadth and depth in their techniques and interests to cover much of cellular physiology. Although we had different focuses in our research, we shared a common passion for using quantitative approaches and definitive experiments to generate the data we needed to say,

Discoveries made in the department are directly applicable to human health and diseases as diverse as neurological disorders, Alzheimer's, autism, diabetes, obesity, heart disease and cancer.

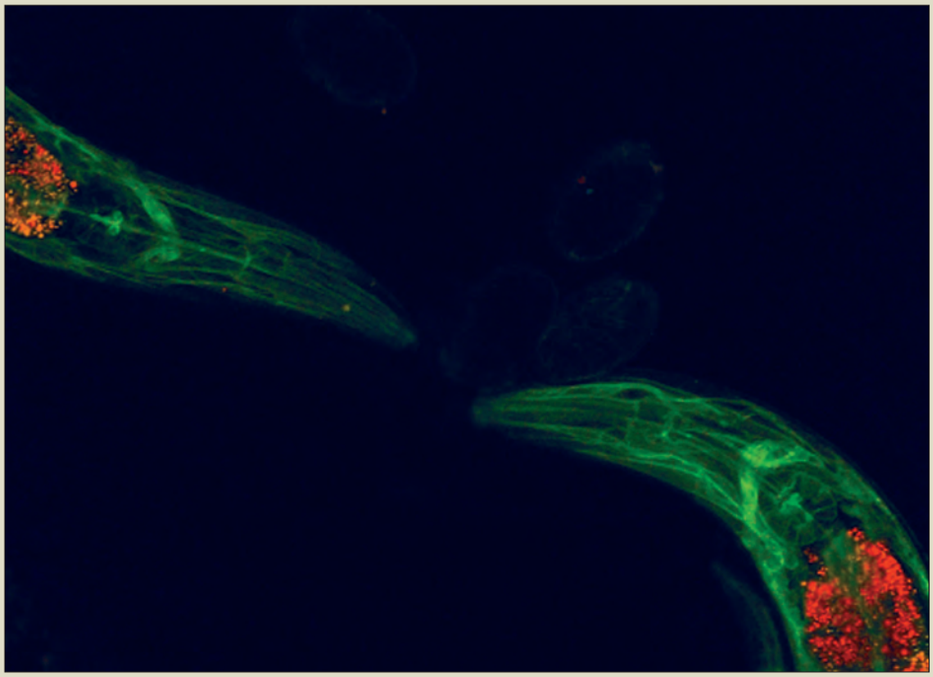
'Yes, ok. I really understand how this process works at the most basic, molecular level.'"

The word physiology was coined by the Greeks over 2500 years ago to describe a "philosophical inquiry into the nature of things." In 325 BC Aristotle proposed that every part of the body serves a purpose, and that that purpose can be deduced from a careful study of its structure. As centuries passed, the term "physiology" came to describe the scientific study of life and all its processes.

In the 1800s the French researcher Claude Bernard pioneered the idea that cells are life's functional unit that carry out their roles bathed in a soup of blood and other bodily fluids. An animal, be it mouse, fly, worm or human, requires its cells to interact and communicate with one another promptly and efficiently to keep its nerves firing and its digestive system humming. Any hiccups in the process could cause disaster.

But, of course, this all happens on a nearly infinitesimally small scale. Early eighteenth- and nineteenth-century researchers focused by necessity on broad concepts — examining the role of the pancreas in controlling blood sugar levels by removing the organ in animals, for example, or tracing the circuitous path taken by the blood as it leaves the heart, delivers oxygen to the body and returns again to be shuttled to the lungs. They lacked the experimental technology to do much more.

In 1847, German researcher Carl Ludwig invented the kymograph to measure blood pressure and muscle contractions, among other biological phenomena. And by the mid-1900s, physiologists had the technology and the knowledge necessary to begin to home in on



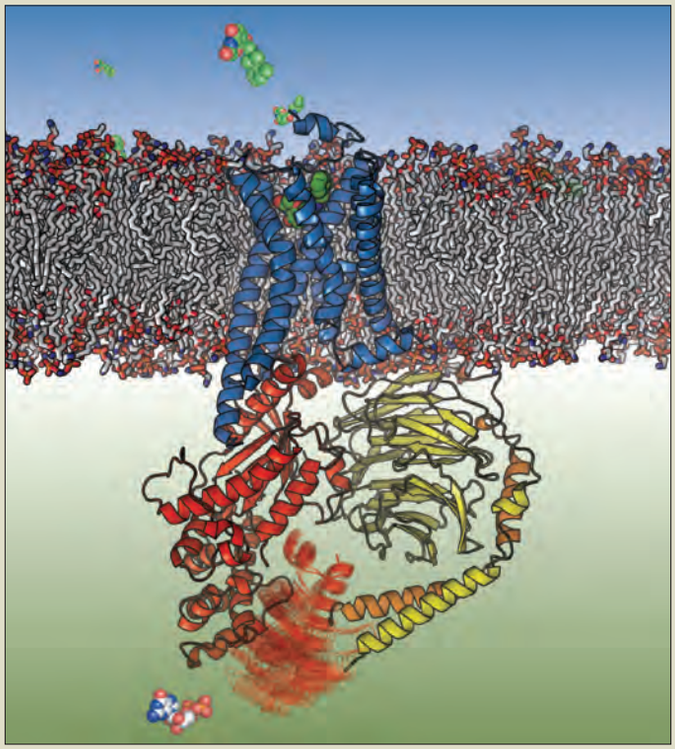
Faculty members' achievements have been recognized with three Nobel prizes, the Kavli Prize in Neuroscience, the Albert Lasker Award for Basic Medical Research, appointments to the Howard Hughes Medical Institute, memberships in the National Academy of Sciences, and many other honors.

smaller targets: identifying and learning, for example, how hormones — signaling molecules produced by glands like the pituitary delivered throughout the body via the circulatory system — enable long-distance communication between cells and organs. They'd also begun to identify neurotransmitters like serotonin that play critical roles in brain function.

In addition to identifying specific molecules, physiologists had begun to realize that cellular communication hinges on interactions on, in, around or through a protective, two-ply container of fatty molecules called lipids that encase the contents of the cell, keeping the outside out and the inside in. These cellular membranes are, by necessity, selectively permeable to allow cells to respond to changing external conditions. Signaling molecules must be allowed to exit and enter the cell, in many cases at extremely precise times and places.

In 1952, British physiologists Alan Hodgkin and Andrew Huxley proposed the concept of specific channels in the membrane of a nerve cell that could be opened or closed in response to external signals. These channels allowed the selective passage of charged ions like calcium, potassium or sodium, generating an electrical current that could power cellular functions. These ions form when salts such as sodium chloride, for example, dissociate in water to become a positively charged sodium ion and a negatively charged chloride ion.

Hodgkin and Huxley's 1952 mathematical model of how this current, called an action potential, travels in a wave along the length of a squid giant axon through the



Faculty members in the department also spawned the Stanford Neurosciences Institute, Bio-X and the Beckman Center's Cell Sciences Imaging Facility (CSIF), which provides state-of-the-art light and electron microscopy resources to researchers across the university.

sequential opening and closing of these channels earned them the Nobel Prize in Physiology or Medicine in 1963.

The subsequent confirmation in the 1970s of the existence of ion channels and the discovery in the 1980s of the genes encoding the proteins that form ion channels and receptors fundamentally changed how much of physiology was practiced and formed the basis for the new department at the Beckman Center.

"Our department began when the medical school thought it should close a gap in its educational lineup," said Tsien. "It had a department of physiology, but only one faculty member, Julian Davidson, PhD, who was studying reproductive physiology. So, James Spudich, PhD, was tasked with finding someone to head a new department, which would be more molecularly focused. He asked me for input, and I gave him so much advice that they finally just offered me the position."

At the time, Spudich, who was a professor of biochemistry, and Berg were lobbying for the inclusion of "Molecular and Cellular" in the department title to emphasize the break with the past and to fit in with the overall theme of the center, which was to serve as a bridge between developmental biology, physiology and medicine and recent advances in molecular biology.

"The term 'physiology' had a lot of baggage at the time," said Tsien. "It implied old-school organ studies, rather than the advanced molecular work in which many younger scientists were engaged. We wanted to capture the newness of the field, while distancing ourselves a bit from the older practice of physiology."

The new department struggled at first with finances. Although the medical school contributed $3 million to recruit the new faculty members, it was still difficult to make ends meet. Fortunately, the Howard Hughes Medical Institute agreed to fund two faculty members directly. Another HHMI position was available through the school's Department of Medicine. Finally, the New York-based Mathers Charitable Foundation also provided start-up funds.

"I'd never been chair of anything before," said Tsien, who was in his early 40s. "But I had my marching orders and I was ready for a challenge. I brought Daniel Madison, who had been a postdoc in my lab at Yale. And in short order we recruited Thomas Schwarz, PhD, from UCSF, Richard Lewis, PhD, from UC Irvine, and Stephen Smith, PhD, from Yale." The two additional HHMI positions went to Richard Aldrich, PhD, who moved from Stanford's Department of Neurobiology, and to Richard Scheller, PhD, who moved from Stanford's Department of Biological Sciences. Brian Kobilka, MD, from Duke University, assumed the third HHMI slot. James Nelson, PhD, was recruited shortly thereafter from Fox Chase Cancer Center in Philadelphia.

Tsien's route to neurobiology was circuitous. He had done his undergraduate work in electrical engineering at the Massachusetts Institute of Technology, but he had become interested in neuroscience when he received a Rhodes scholarship after graduation. He wrote to British physiologist Denis Noble at Oxford, who had reviewed Hodgkin's and Huxley's work on nerve signals in squid axons, and was accepted as a graduate student in Noble's lab. But when he arrived, Noble was studying the electrophysiology of the heart.

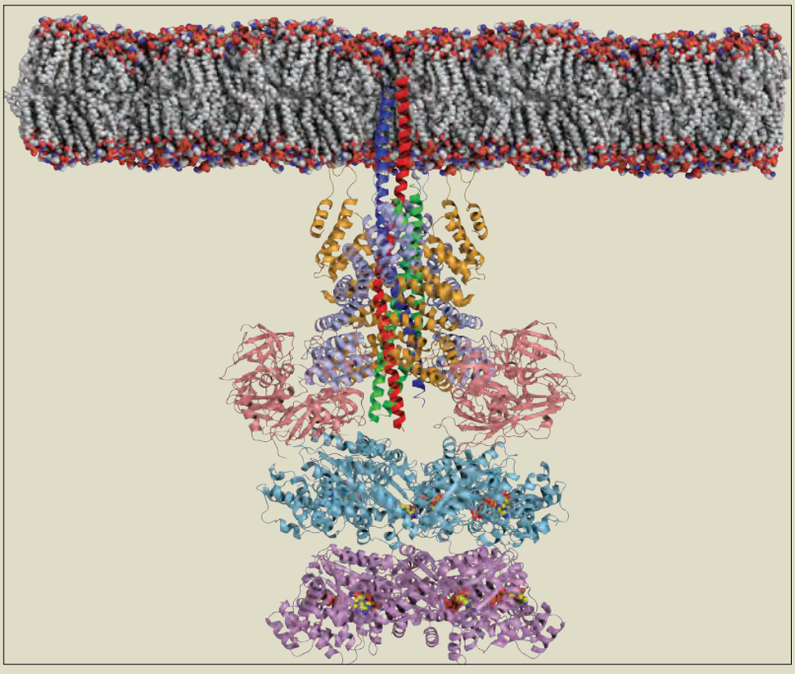
"So I had to choose, then, between working on the area that I thought I was going to work on, or joining

with Noble in trying to unravel the basis of the cardiac action potential. And, since I knew no biology, everything seemed interesting," recalled Tsien in an interview with an editor of the Journal of General Physiology in 2015.

Over the next several years, Tsien worked on identifying new types of calcium ion channels in heart muscle and learned how they control the heart's beating. But he never forgot his early interest in neuroscience and, about three years prior to his arrival at Stanford, he and Madison had begun to expand their studies into that area. Schwarz, Smith and Lewis were all also interested in learning how ion channels and protein interactions on the membrane drive the function of the nervous system.

"My nascent interest in neuroscience blossomed while I was at Stanford," said Tsien. Many of his first recruits were also interested in understanding in one way or another how nerve cells use ion channels and transmembrane receptors to communicate. "Eventually the Molecular and Cellular Physiology Department became about 60 to 70 percent focused on neuroscience, which has proved over the years to be an extremely interesting and productive field. It still forms part of the framework for folks in the department now."

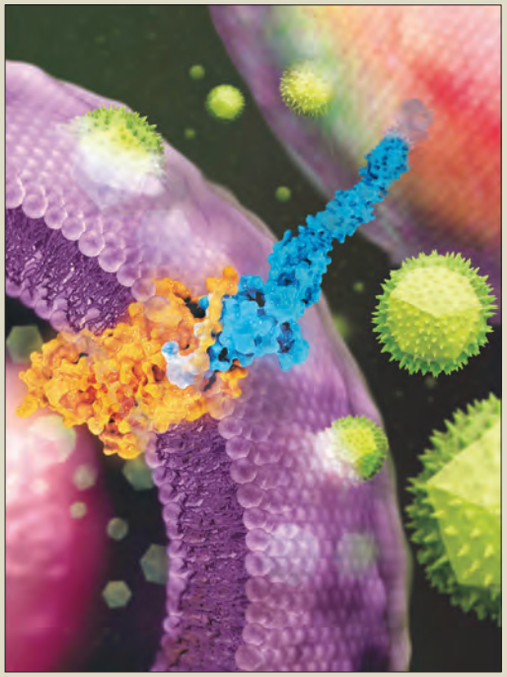
Imagine looking down from above on a very busy, very well-organized train station. From your bird's eye view, you can see people enter and exit the station via a variety of doors, elevators and escalators. Train

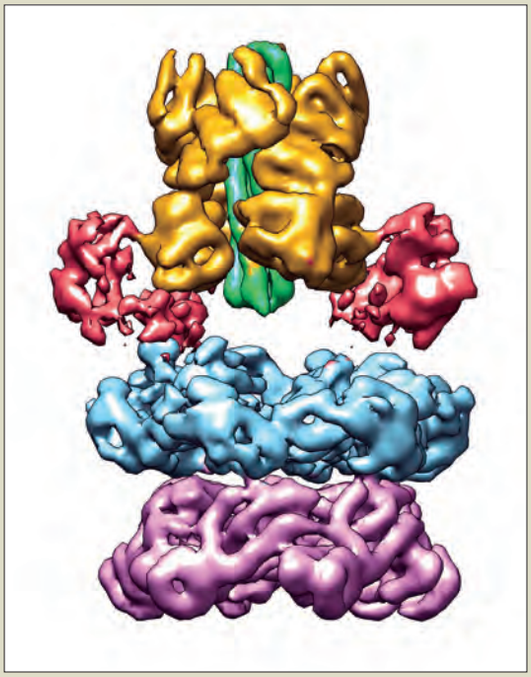


passengers board promptly to zip away through tunnels. In this scenario, the trains represent bubble-like vesicles that store signaling molecules within cells until triggered to deliver their payload to a neighboring cell. The entry and exit points from the station represent the specialized protein structures called ion channels or pumps that straddle the membrane of most cells.

There are hundreds of different types of ion channels. Many open and close based on voltage changes, when bound by specific signaling molecules, or in response to temperature or mechanical forces. Some require a combination of stimuli. Ion pumps actively transport the charged ion particles into or out of the cell, while ion channels permit the passive diffusion of ions across the cell membrane. Most ion channels are specific for just one type of ion, say, calcium, potassium or sodium, or restricted to allow the passage of only positive or only negative charges.

The ability to actively modulate the concentrations of positively and negatively charged ions within a cell means that all cells have the ability to maintain a voltage difference across the cell membrane — a concept known as membrane potential. Most commonly, the interior of a cell is slightly more negatively charged than the extracellular fluid around it. This, in effect, makes the cell membrane a kind of small battery. Opening the channels and allowing ions to flow across the cell membrane generates an electrical current that the cell can use as energy to drive many cellular processes.



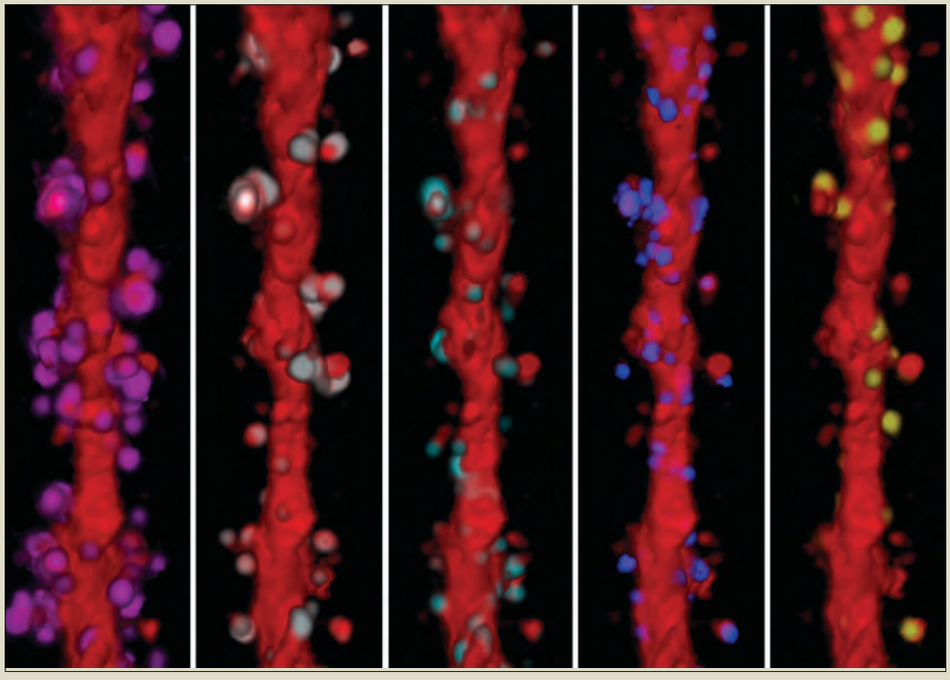


"The spirit of the department was focused on the synthesis of ideas from cell biology, biochemistry, molecular biology and more. Rather than just studying a gene, or a channel, we wanted to know how they all worked together. It was a systems philosophy, but focused on molecular and cellular systems rather than organs."

Muscle cells like those in the heart and nerve cells like those in our brain and spinal cord (as well as hormone secreting cells called endocrine cells found in glands like the pituitary) take things a step further. Known as "excitable cells," they can generate a wave of electrical current along their membranes called an action potential. In neurons, an action potential travels in one direction along the axon of a nerve until it reaches the space between two cells, known as a synapse. It then triggers a rapid release of signaling chemicals called neurotransmitters into the synapse, which launch themselves like chemical batons in a relay race across the gap to trigger a similar wave in the next neuron in line.

Tsien and Madison were interested in classifying the locations and types of calcium channels in the nerves that make up a part of the brain called the hippocampus, which plays a critical role in learning and memory. Madison was also interested in the role of a neurotransmitter called norepinephrine, which promotes vigilance and alertness in the brain and body. It also enhances memory formation.

"I was probably one of the more specialized in the department in those early days," he recalled. "But the spirit of the department was focused on the synthesis of ideas from cell biology, biochemistry, molecular biology and more. Rather than just studying a gene, or a channel, we wanted to know how they all worked together. It was still a systems type of philosophy, but one that focused on molecular and cellular systems rather than organs."



Understanding how ion channels and pumps work together is the key to unlocking the causes of diseases such as cystic fibrosis, long QT syndrome and perhaps even autism, Alzheimer's and cancer. And Madison and Tsien's research into how neurons adapt to repeated patterns of signaling activity through a phenomenon known as long-term potentiation, or LTP, provides a window into how we learn and how memories are formed.

Tsien and Madison were soon joined by Schwarz and Lewis. Schwarz had made a name for himself by helping to clone the first potassium channel gene, called the Shaker gene, in the fruit fly. Flies with a mutation in the gene move erratically and have a shorter lifespan than their peers. He went on to study a protein called synaptotagmin that helps the synaptic vesicle fuse quickly with the cell membrane and discharge its contents when signaled.

Lewis was studying how calcium channels in cells of the immune system are themselves regulated by calcium concentrations to create a kind of feedback loop that can generate characteristic signaling patterns such as sustained oscillations. These signals were known to be required for triggering the immune response, and are now known to occur in practically all cell types in the body.

"When I first arrived, the genes that encoded the calcium channel proteins were unknown. So we began by compiling a biophysical 'fingerprint' for the channel and its mode of regulation using electrophysiology, which helped us learn how calcium oscillations within the cell are generated, and in turn led us to study how oscillations can control gene expression," said Lewis. "Eventually the genes involved in channel formation and activation were identified, and we then turned to microscopy to visualize exactly how the channel is physically activated in a living cell."

Aldrich, who had been a Stanford graduate student in the Department of Biology studying large neurons from mollusks, had become keenly interested in understanding quantitatively how specific parts of ion channels act to control opening and closing of the ion-conductive pores. Aldrich became widely recognized for his biophysical dissection of potassium channel activation and inactivation, processes that are fundamental to how they carry out their cellular functions.

When Smith arrived, he was on the cusp of showing that cells called astrocytes, previously believed to be a kind of inert packing material between neurons in the brain could in fact actively communicate with neurons through the use of a neurotransmitter called glutamate. Glutamate was subsequently shown to play a key role in long-term potentiation and learning and memory.

In particular, Smith made a key discovery about a kind of protein on the membrane of nerve cells called an NMDA receptor. This receptor also serves as an ion channel. It responds to glutamate released by a neighboring cell by allowing positive ions like calcium, potassium or sodium to flow across the cell membrane. The number of ions permitted through the channel, and the direction in which they flow, is determined by the voltage difference across the membrane. The flow of calcium ions has been shown to be critical to synaptic plasticity and memory storage.

"Stephen had a big influence on my research over time," said Madison. "He developed a now widely used

technique called array tomography that allowed researchers to visualize the three-dimensional structure of a cubic millimeter of tissue through automated serial sectioning and antibody labeling to determine the precise location of proteins. He used this technique to learn many interesting things about the structure of neural circuits, and I later adapted it to investigate how individual neurons communicate."

Scheller was focused on the cellular and molecular basis of how synapses work—particularly at the level of the release of neurotransmitters into the extracellular space. His lab cloned the genes for proteins that controlled the release of neurotransmitters and began the process of understanding how cellular membranes fuse to release the neurotransmitters from the synaptic vesicle into the synapse itself.

Kobilka, in his turn, was investigating a class of proteins on the cellular membranes called G-protein-coupled receptors. These receptors are widely found on many types of cells and they modulate a cell's responses to external signaling molecules such as hormones and neurotransmitters. When the appropriate signaling molecule binds to the portion of the receptor outside the cell, the receptor undergoes a conformational change that allows it to activate and release a class of protein called a G-protein inside the cell. The G-protein is then free to activate many other cellular processes in a domino effect. The biological importance of these receptors is undeniable; about 40 percent of all drugs now approved for use in humans target G-protein-coupled receptors for conditions as diverse as schizophrenia and stomach ulcers.

"I wanted to understand more about the different physiological roles played by the various subtypes of these G-protein-coupled receptors," said Kobilka, a professor in the department. "I also wanted to understand how the receptors worked on a molecular level, and what they looked like in three dimensions. That last goal was by far the most technically challenging, and it took over 15 years to solve." In 2012, Kobilka shared the Nobel Prize for Chemistry for his research into the structure and function of G-protein-coupled receptors, in particular the beta-2 adrenergic receptor that binds to adrenaline, a hormone and neurotransmitter.

Finally, James Nelson, PhD, professor of molecular and cellular physiology and of biology, was researching how cells develop and maintain polarity, or the ability to discern their location in space and act appropriately in response to signals coming at them in three dimensions. As chair of the department from 1994 to 2001, he also shepherded it through critical transitions to its mature state.

As the years passed, the department has continued to recruit new faculty members and encourage productive collaborations among researchers within and outside the department and even the school of medicine.

William Weis, PhD, arrived from Yale in 1993 as a faculty member in the Department of Structural Biology. A former postdoctoral scholar in Brunger's laboratory at Yale, Weis was using X-ray crystallography to deduce the three-dimensional structures of proteins and understand how these proteins functioned within living cells. Among the proteins in which he was interested were the SNARE proteins that are essential to mediate the fusion of the synaptic vesicle with the cellular membrane to release neurotransmitters into the synapse. Weis is now the chair of the Department of Structural Biology.

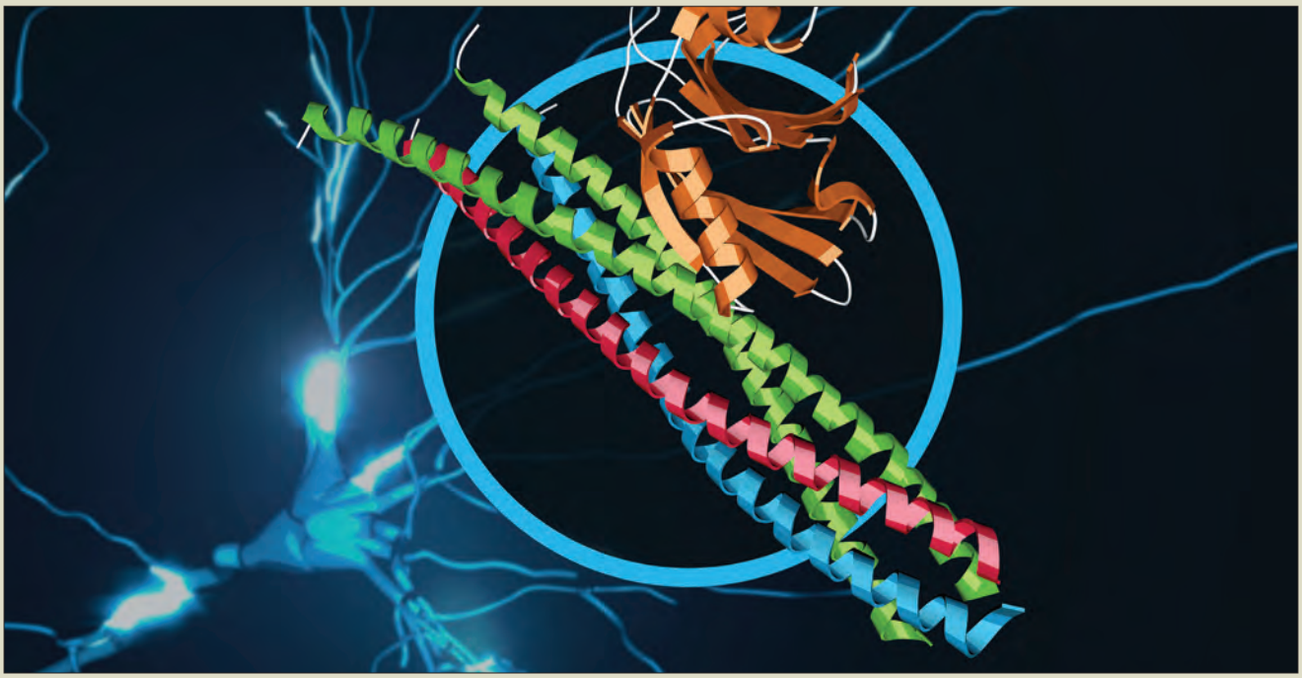
Weis's work paired nicely with other researchers in the department doing structural biology, such as Chris Garcia, PhD, and Brunger, who was studying the molecular mechanism of synaptic fusion.

"My lab studies the molecular mechanisms that triggers synaptic vesicles to fuse with the neuronal membrane within less than a second upon receiving an action potential," said Brunger. "In other biological contexts, membrane fusion generally occurs rather slowly. But evolution has fine-tuned the nervous system to accomplish this with exquisite speed and in precise reaction to changes in calcium concentration."

In 1998 Brunger and his lab determined the first crystal structure of the SNARE proteins in the vesicle and other proteins involved in the release of the vesicle into the synapse. More recently, they imaged how SNARE proteins link with synaptotagmin-1 to trigger the rapid fusion of the membranes and reconstituted the process with recombinantly expressed proteins and liposomes.

Thomas Südhof, a professor in the department who arrived in 2008, collaborates frequently with Brunger's lab. Südhof is also interested in vesicle transport, and in 2013 he shared the Nobel Prize in Physiology or Medicine for his role in parsing out how vesicles in nerve cells are primed to quickly release their contents when necessary.

"Axel's lab has enormous expertise in the analysis of structural atomic mechanisms," said Südhof. "From crystallography to determine a molecule's structure, to conducting functional assays at the single-molecule level. They complement our work beautifully."



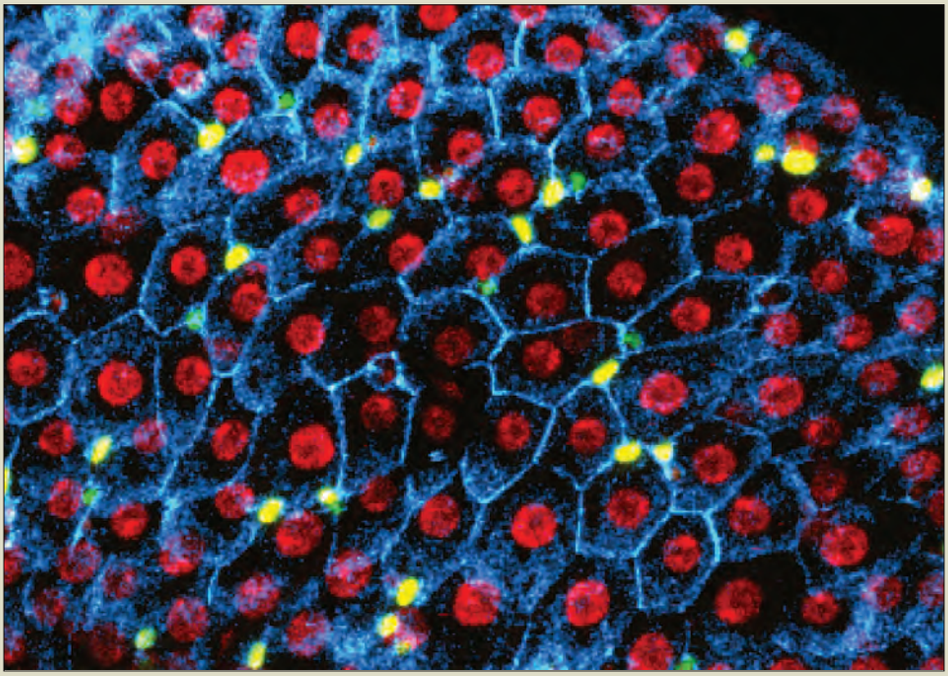
And Steven Chu, PhD, designed a device he coined "optical tweezers" that can trap atoms and enable precise measurements of molecular force. (Chu, who went on to become U.S. Secretary of Energy before returning to Stanford in 2013 as a professor in the molecular and cellular physiology and physics departments, received the 1997 Nobel Prize in Physics for the work.)

As the department matured, researchers moved on. Smith is now a senior investigator at the Allen Institute for Brain Science, while Scheller was recruited to Genentech in 2001 as Senior Vice President and Chief President of Research. He is currently Chief Science Officer & Head of Therapeutics at 23andMe. Schwarz is a professor of neurobiology at Harvard and Aldrich is the Karl Folkers Chair in Interdisciplinary Biomedical Research at the University of Texas.

But those early discoveries in neurobiology still echo in the research of current faculty members, such as that of Miriam Goodman, professor of molecular and cellular physiology, who arrived in 2002 from Columbia University. Goodman is studying the molecular physiology of touch sensation.

"At first, we wanted to know which ion channels are responsible for converting touch into signals that the brain can interpret," said Goodman. "Now we are working to understand how the energy in a touch activates those ion channels to generate signals that your brain interprets as a feeling."

Goodman relies heavily on the Cell Sciences Imaging Facility that sprung out of Stephen Smith's work. She uses the ability of the facility to freeze live biological samples from round worms so quickly that ice crystals,



"One of the aspects of the department that still appeals to me is that it was not really bound by the usual borders of disciplines," said Lewis. "We had a neuroscience focus, but it was open ended. We were free to follow our research in whatever direction it went."

which can destroy the tissue, don't have a chance to form. She collaborates heavily with Beth Pruitt, PhD, an associate professor of mechanical engineering.

"Together we've built devices I would have had no idea how to build and she wouldn't have known would be useful. I don't think that would have happened in another environment. It changed the kind of research I do in ways I couldn't have anticipated."

"My research spans thinking about how molecules work as proteins within cells and within animals," said Goodman. "This department provides an environment in which you can think about things across multiple layers of complexity. We want to do more than describe a physiological phenomenon; we want to also understand it. What makes it tick?"

Liang Feng, PhD, an assistant professor in the department recruited in 2012 agreed.

"While the research in the department today is very diverse, there are plenty of interactions and synergies," said Feng. "My research focuses on membrane transport proteins and enzymes, particularly how sugar is transported across the membrane. Sugar is a primary energy source and a basic building block in biological systems. This sugar transport process is very important in maintaining blood glucose homeostasis, so it's essential to explore." Feng has collaborated with Kobilka to learn a new crystallization technique to improve structural studies on proteins of interest. He has also collaborated with Ron Dror, an associate professor of computer science to capture the sugar transport process in action.

Other researchers include Maxence Nachury, PhD, an assistant professor studying the function of a cellular structure called the primary cilium that projects outward from the cell like an antennae. Coated with receptors, the cilium plays a little-explored role in cellular signaling, and defects in the cilium are associated with a variety of human diseases included obesity and kidney malformations. Nachury teamed up with Goodman to analyze an enzyme responsible for modifying the microtubules that provide structural support for cilia, demonstrating enzymatic function in test tubes, cells and animals.

Lucy O'Brien, PhD, an assistant professor, studies the gut of the fruit fly, which expands and contracts in size to meet nutritional demands, to understand how organs can be actively remodeled during adulthood in response to changing conditions, while the ion-channel-focused research of Merritt Maduke, PhD, an associate professor in the department, harkens back to the early days of the department.

Most recently, structural biologist Georgios Skiniotis, PhD, professor of molecular and cellular physiology and of structural biology, is joining the department from the University of Michigan. Skiniotis uses cryo-electron microscopy to study biological machines and molecular assemblies. His interests range from enzymatic complexes to cellular receptors to Zika virus, G-coupled receptors and ribosome function. In addition to these biological interests, he is also refining the application of cryo-EM to ever smaller molecular structures, enabling him to solve technically challenging problems.

"One of the aspects of the department that still appeals to me is that it was not really bound by the usual borders of disciplines," said Lewis. "We had a neuroscience focus, but it was open ended. We were

free to follow our research in whatever direction it went and not feel that we were straying outside the fold. After years of speaking to people in the halls and going to retreats, you start to absorb what others are working on and it's much easier and less intimidating to switch gears and follow up an interesting finding. It seems very natural."

Others agree.

"Science happens in the interaction between people, I believe," said Südhof. "It's not an activity carried out by an isolated individual."

"I learned many lessons at Stanford," said Tsien. "How to foster interactions, how to make sure people have a chance to do things they can take pride in and get credit for. I can't say how much I appreciate the confidence that Stanford put in us when they allowed us to build the department from the ground up. It was a wonderful time."

So wonderful, in fact, that Tsien is a bit wistful at times.

"I still keep my Stanford 'A' parking sticker in my file drawer here in New York, right next to my passport," he said. "I enjoy knowing that, at a moment's notice, I could appear on The Farm and have some people look at me as if I had never left."

**Photo credits:**

Page 7: Confocal image of mouse cerebellar slice immunostained with synaptic marker (vGluT1) and purkinje cell (Calbindin). By Lulu Chen. *Image courtesy of* Thomas Südhof.

Page 9: A color map of mechanical tension in the axons of a roundworm (*C. elegans*). The image was taken in the Cell Sciences Imaging Facility and shows the position and intensity of mechanical tension revealed by a molecular strain sensor; green colors indicate higher tension. For more information see Krieg M, Dunn A, Goodman MB, (2014). Mechanical Control of the Sense of Touch by b Spectrin. *Nat Cell Biol*. 16:224-233. By Michael Krieg. *Image courtesy of* Miriam Goodman.

Page 10: The beta 2 adrenergic receptor activating a G protein. By Xavier Deupi and Brian Kobilka. *Image courtesy of* Brian Kobilka.

Page 12: For more information see M. Zhao, S. Wu, Q. Zhou, S. Vivona, D. J. Cipriano, Y. Cheng, A. T. Brunger. Mechanistic Insights into the Recycling Machine of the SNARE Complex. Nature 518, 61-67 (2015). By Minglei Zhao and Axel T. Brunger. *Image courtesy of* Axel Brunger.

Page 13 (left): Viral GPCR engaging a chemokine ligand on an opposing cell. By Eric Smith and Christopher Garcia, adapted from Burg et al., Science 2015. *Image courtesy of* Christopher Garcia.

Page 13 (right): For more information see M. Zhao, S. Wu, Q. Zhou, S. Vivona, D. J. Cipriano, Y. Cheng, A. T. Brunger. Mechanistic Insights into the Recycling

Machine of the SNARE Complex. Nature 518, 61-67 (2015). By Minglei Zhao and Axel T. Brunger. *Image courtesy of* Axel Brunger.

Page 14: A segment of dendrite of a hippocampal CA3 pyramidal neuron, volume reconstructed by array tomography, immunostained for (L-R): Synatophysin, PSD95, and GluA1, GluA2 and GluA3 AMPA receptor subunits. By Dong Li and Krsitina Micheva. *Image courtesy of* Daniel V. Madison.

Page 17: Architecture of the synaptotagmin-SNARE machinery for neuronal exocytosis. For more information see Qiangjun Zhou, Ying Lai, Taulant Bacaj, Minglei Zhao, Artem Y. Lyubimov, Monarin Uervirojnangkoorn, Oliver B. Zeldin, Aaron S. Brewster, Nicholas K. Sauter, Aina E. Cohen, S. Michael Soltis, Roberto Alonso-Mori, Matthieu Chollet, Henrik T. Lemke, Richard A. Pfuetzner, Ucheor B. Choi, William I. Weis, Jiajie Diao, Thomas C Südhof and Axel T. Brunger, Nature 525, 62-67 (03 September 2015) doi:10.1038/nature14975. *Image courtesy of* Axel Brunger.

Page 18: Live confocal microscope image of the intestinal lining of *Drosophila*. Cells are outlined in blue. Stem cell nuclei are yellow and intestinal cell nuclei are red. By Judy Martin. *Image courtesy of* Lucy O'Brien.