25 YEARS OF INNOVATION, DISCOVERY AND COLLABORATION

AT THE BECKMAN CENTER

By Krista Conger

In the early 1980s, molecular biology was exploding. Within the previous decade, scientists had learned how to sequence DNA and swap genes between organisms to coax bacteria to make human proteins. They'd devised ways to use the fluorescence-activated cell sorter to isolate subsets of immune cells and even sort human chromosomes. They'd discovered and sequenced oncogenes like src, and knew that these genes caused cancers by virtue of mutations in their DNA sequence. They'd identified evolutionarily conserved homeobox genes critical to the proper morphological development of many species.

But there was no structure in place to translate these advances to medicine to help human patients.

"We use the term 'bench-to-bedside' quite commonly now," says 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. "But at that time, only a few clinical faculty members had a PhD and most had no research experience. We'd seen earth-shattering discoveries in basic research, but these had had little impact on or connection to clinical progress."

"It became apparent that, in the future, we would need to focus on the molecular and genetic basis of disease, rather than just recognizing and treating symptoms," says Berg. "As a result, a group of us came together to promote the development of a major new endeavor in an area I dubbed molecular and genetic medicine."

Now, scientific concepts and breakthroughs from the center's laboratories are reaching the bedside of patients throughout the country and around the world. Beckman researchers have identified the molecular causes of skin, bladder and other cancers, they've identified and isolated human stem cells, and they've worked with chemists, engineers and physicists to design instruments to measure the molecular motors that go awry in heart failure or ALS. They've explored what happens at the boundary of a cell and how that affects how neurons communicate with one another or how a cell responds to a quick jolt of adrenaline.

They've also invented new ways to see deep inside a living cell, and to quantitate levels of gene expression in healthy and diseased tissues. They harnessed the power of the emerging field of bioinformatics to sequence genes and link genetic variation to human disease, and they developed sophisticated cell-sorting technology capable of analyzing protein signaling events in individual cells.

The push toward what's now known as translational medicine has led directly to the development of some of Stanford's most important research facilities, institutions and groups, including Bio-X, Stanford's Institute for Stem Cell Biology and Regenerative Medicine, and the Institute for Immunity, Transplantation and Infection.

"The Beckman Center has served as an incubator over the years for these tremendously exciting new thrusts in our scientific endeavors," says Lucy Shapiro, PhD, professor of developmental biology and the

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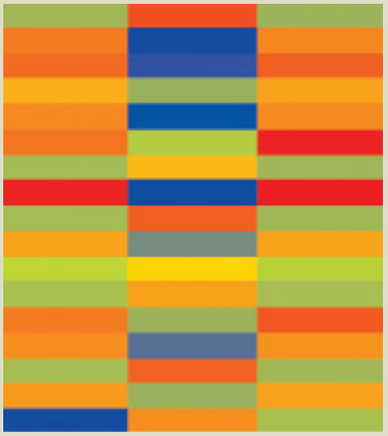
Center's current director. "We've taken rich advantage of Stanford's interdisciplinary nature — bringing together people working in chemistry, physics, engineering, computer science and biology — and just astonishing technical breakthroughs in functional genomics, biological imaging, and computational biology."

Along the way, Beckman faculty members have been repeatedly recognized for their scientific contributions with some of the most prestigious awards in science and medicine: The Albert Lasker Basic Medical Research Award, the National Medal of Science, and even a pair of Nobel Prizes.

The Beckman Center for Molecular and Genetic Medicine opened its doors in February, 1989. An impressive building, it was designed from the start with collaboration in mind.

"The building was designed in the shape of the letter Z," says Suzanne Pfeffer, professor and chair of the Department of Biochemistry who participated in the design process, "to minimize the distance between the two farthest points. The faculty members were very involved in trying to maximize interaction not just on a given floor, but also among all the floors of the building."

When complete, the entire existing department of Biochemistry would move into the building, as well as newly hired faculty members in two new departments — Molecular and Cellular Physiology and Molecular and Developmental Biology (subsequently shortened to Developmental Biology). A third proposed department, Molecular and Genetic Medicine, was adopted by the Howard Hughes Medical Institute as the Howard Hughes Medical Institute unit of Molecular and Genetic Medicine.



The repeated use of the word 'molecular' in the department and center names was deliberate — meant to emphasize the emerging bridge between developmental biology, physiology and medicine and recent advances in molecular biology. The influx of new people was a conscious decision by Berg to foster the creation of new, dynamic connections among researchers both old and new. It also allowed the department heads to craft a well-balanced, complementary team of researchers—an effort that continues to this day.

To make the dream a reality, however, it was necessary to find financial backers. When noted philanthropist and inventor of the pH meter, Arnold Beckman, indicated that he and his wife Mabel were interested in possibly supporting the effort, Berg and his colleagues prepared their pitch.

"We clearly emphasized what we felt was the most important point," says Berg. "We showed him we were doing great science, and explained that we wanted to see those advances translate into benefits in the clinic. He agreed to provide $12.5 million to create the Beckman Center."

Further support came in the form of an additional gift from the Howard Hughes Medical Institute via its incoming president and former director of the National Institutes of Health, Donald Fredrickson, MD.

"Donald foresaw that the training of people in both science and medicine was important," says Berg, "and he gave us an additional $12.5 million to begin design and construction of the building, as well as about $18 million to support 12 additional Howard Hughes Medical Investigators at the university."

With the blessing of university president Donald Kennedy, building construction — and the recruitment of new faculty members — was underway. When complete, the building would house about 45 faculty members, most new to Stanford. In addition to the four main groups, Stanford immunologists and geneticists Leonard and Leonore Herzenberg were invited to set up a cell-sorting facility in the ground floor of the building. (Leonard Herzenberg had developed the fluorescence-activated cell sorter in 1970, which was to prove transformative to the fields of immunology and stem cell biology.) An additional 75 to 100 faculty members from throughout the medical school and across campus were included in the nascent effort under the umbrella of the newly devised Program in Molecular and Genetic Medicine.

Berg recalls "At that time, with what I thought to be an incredibly impressive array of scientific talent, we were up and running."

Although the departments in the Beckman Center are unique, they're united by common themes: the belief that the study of fundamental molecular pathways — whether they be important for gene expression, anatomical development, cellular communication or movement and force — will lead to advances in human health; and the conviction that collaboration within and among departments and disciplines is a critical component of research.

"For example, our department strives to bring together people asking fundamental questions about the biological developmental process," says Shapiro. "These are very basic mechanisms that have evolved over millennia and are repeated again and again in

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organisms that are very different from one another. So we've hired very talented faculty members working in many different model systems."

Those model systems have evolved from the traditional workhorses of the fruit fly, nematodes and laboratory mice to encompass organisms as diverse as the zebrafish, the threespine stickleback fish, and even the single-celled Caulobacter, which Shapiro has utilized to map out how one cell can divide to give two cells of different fates — a fundamental mechanism for the generation of diversity in the living world. Her work in understanding the genetic circuitry of the bacteria, and how a linear type of information like DNA gives rise to a spatially organized, three-dimensional cell, has led to the development of novel antibacterial and antifungal drugs and garnered her the 2012 National Medal of Science.

It also helped to launch the field of systems biology, in which researchers study the integration of multiple genetic circuits and regulatory pathways to gain a broad understanding of the dynamic processes that make up a living cell.

"Our field has been completely transformed," says Pfeffer, of the evolution that has occurred during the past two decades. "Whereas we used to each study one type of molecule at a time, many of us now are studying whole protein pathways and systems. We're able to address more-complicated problems than ever before by using physical approaches that had not even been invented when the center was launched."

In the early 90s, for example, former biochemistry chair James Spudich collaborated with then-professor of physics and of molecular and cellular physiology Steven Chu, who had 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 in the physics and molecular and cellular physiology departments, shared the 1997 Nobel Prize in Physics for the work.)

Spudich used the technique to study the interaction between a single myosin molecule and a single actin filament and calculate the force conferred by each unit of the energy molecule ATP—a finding that helped earn him a Lasker Award in 2012 and has led to the development of several drugs in clinical trials for heart failure and other disorders. The collaboration between Spudich and Chu led them to launch Bio-X, an effort to expand and further the Beckman center model by bringing together researchers across campus with vastly different skills and expertise.

HHMI researcher and immunologist Mark Davis, who came to Stanford as a faculty member in 1983 and became a HHMI investigator in 1987, led a group that cloned the first T cell receptor gene while at the National Institutes of Health. In the mid-90s he used advances in imaging to show that a T cell can recognize just one molecule of antigen. He's since moved to using systems biology approaches to understand how humans respond to vaccines, and to understand the hallmarks of a healthy immune system. In 2004 Davis was appointed the director of the newly formed Stanford Institute for Immunity, Transplantation and Infection.

Davis also collaborated with professor of biochemistry and HHMI investigator Patrick Brown to design cellular,

or functional, microarrays in which living T cells are fixed to a solid support in a grid-like pattern for interrogation with peptides or antibodies. The technique grew from the development of DNA microarrays by Brown and Ronald Davis, a professor of biochemistry, in the mid-90s, which are now widely used to characterize changes in gene expression profiles in healthy and diseased cells under a variety of conditions. Microarrays have allowed researchers to predict cancer outcomes by subcategorizing groups of patients, and to identify organ transplant recipients who may be able to safely stop taking antirejection drugs. Ronald Davis is currently the director of the Stanford Genome Technology Center.

Many of the Beckman center's researchers focus on the study of cellular pathways known to be important in development or disease. Somewhat unexpectedly, many of these pathways are shared within and across very different species.

"One of the main themes discovered during the past 25 years is the astonishing extent to which pathways are conserved and reused in many organisms," says William Talbot, professor and chair of the Developmental Biology Department. "When the department was founded, the hope was that insights gained in studying model organisms would be relevant in humans. That's turned out to be true to a degree that is really remarkable."

For example, the Wnt protein, first identified in 1982 by professor of developmental biology and HHMI investigator Roel Nusse, governs a pathway that is highly conserved from fruit flies to mice to humans. Mutations in Wnt1 were originally identified as the cause of breast cancer in mice infected with the mouse mammary tumor virus. In Nusse's lab, Wnt proteins have since been shown play a role in human cancers, embryonic development and stem cell function.

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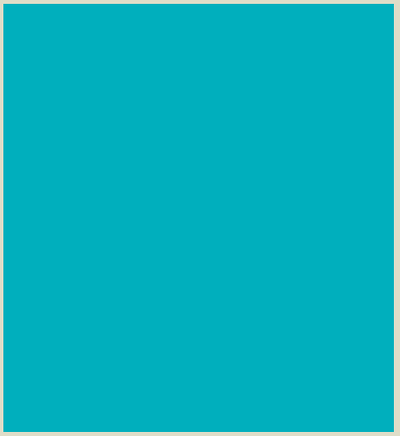
Another ancient developmental pathway, known as Hedgehog signaling, was discovered in fruit flies. Professor of biochemistry and developmental biology, and HHMI investigator Philip Beachy isolated the Hedgehog gene in 1992 and found corresponding genes in mammals. He showed that loss of Hedgehog function affects body formation in fruit flies and, in human embryos, can cause an often lethal brain malformation called holoprosencephaly, or cyclopia. The Beachy lab has also shown that the Hedgehog pathway plays an important role in the formation of cancer stem cells— self-renewing cells often resistant to conventional therapies that can repopulate a tumor after seemingly successful therapy. Beachy's research has implicated misregulation of the Hedgehog pathway in the development of bladder cancer and leukemias.

Professor of developmental biology, genetics, bioengineering and biology Matthew Scott, who came to Stanford in 1990, isolated the PTCH1 gene, which encodes the receptor for Hedgehog proteins, first from flies and then from mice and humans. Scott showed that excess activity of the Hedgehog pathway causes basal cell carcinoma—the most common human cancer— and medulloblastoma, the most common kind of childhood brain tumor.

Continuing research in the Beckman Center has led to many discoveries about how the Wnt and Hedgehog protein signals are produced, transferred, and interpreted. This kind of basic science investigation is leading to new opportunities for cancer therapies.

"These insights apply quite directly to many important problems in medicine," said Talbot. "We have people in different labs, studying different organisms, but attacking the same problems from different angles. This has given us an extremely detailed understanding of the types of basic processes that are disrupted in disease."



Studies in Talbot's laboratory of the zebrafish have given clues about how vertebrates myelinate their axons—a process critical to efficient signal conduction and nerve function. Another fish, the threespine stickleback, studied by professor of developmental biology and HHMI investigator David Kingsley, has yielded important information about how organisms, including humans, evolve and adapt to their environment, by, for example, changing their skin pigmentation.

"Twenty-five years ago, it was considered to be a very risky thing to move into zebrafish," said Talbot. "For zebrafish and many other organisms now used as model systems, it was not clear that whether they would be experimentally tractable or that they would lead to insights of broad relevance. Now it is absolutely clear that pursuit of diverse model organisms has accelerated the pace of discovery and advanced the understanding of basic processes."

"We've seen some just astonishing technical breakthroughs in functional genomics and biological imaging," say Shapiro. "Not only have the whole genomes of many organisms been sequenced, we're now able to begin to understand what those sequences are telling us and how they can lead to complex biological phenotypes. We're also now able to visualize individual molecules in living creatures. We can see what they are doing and where they are going."

Some of those molecules are responsible for critical physiological processes such as nerve signaling and environmental responses.

"Many of the faculty members in our department are particularly interested in understanding what happens at the boundary of a cell," says Miriam Goodman, an associate professor of molecular and cellular physiology and member of the department's executive committee. Goodman's lab studies the nematode Caenorhabditis elegans to learn how humans sense and feel the outside world. "How are the membrane proteins functioning to allow a cell to respond to its neighbors, and to its environment?" Goodman is also a deputy director of the Stanford Neurosciences Institute.

Thomas Südhof, professor of molecular and cellular physiology, explored these questions with his work on neurotransmitters. His research has elucidated how neurotransmitters are secreted across neural synapses by vesicles that fuse with the cell membrane. His fundamental discoveries of some of the key factors of the process of calcium-triggered synaptic vesicle fusion led to the 2013 Nobel Prize in Physiology or Medicine. Another professor in the department, Brian Kobilka, received the 2012 Nobel Prize in Chemistry for his work to understand how G-protein-coupled receptors translate signals from outside the cell across the cell membrane to regulate a plethora of physiological processes. His work is expected to lead to the development of better drugs for patients with many types of conditions.

"We're trying to understand these processes at a very fundamental, molecular and structural level," says professor and chair of molecular and cellular physiology, Axel Brunger.

Clearly, researchers are moving ever closer to understanding how healthy and diseased cells develop, communicate and move in their microscopic physical world. To peer ever-more deeply, they've turned increasingly to experts in many other disciplines such as computer science, engineering and physics.

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"My own lab has had a long-term collaboration with Beth Pruitt's laboratory in mechanical engineering," says Goodman. "As a result, we're designing mechanical devices that allow us to study how the sense of touch develops, for example. This has really allowed us to push our research forward."

"All of us in the biochemistry department have either a joint appointment or actively collaborate with someone in another department,"says Pfeffer.

Some of these collaborations give rise to new technologies or broadly useful tools. Many are wildly creative. For example, assistant professor of biochemistry, Rhiju Das, has designed an internet-based RNA-folding game available to the public in which players seek to design biologically active molecules for researchers to study.

"I see the Beckman Center as a place that is willing to push research boundaries and take the risks necessary to support important research ideas," says Goodman.

Gill Bejerano, an associate professor in developmental biology and of computer science, was formally trained as a computer scientist, for example. He's developed an internet-based tool called GREAT (for Genomic Regions Enrichment of Annotations Tool) to use information from deep DNA sequencing to identify far-flung areas of the genome that affect the control of gene expression.

"We have people in our department with extremely diverse expertise," says Talbot. "This interdisciplinary approach has spurred the technological advances from which we all benefit. Gil's contributions show the extent to which computational biology has advanced. We're increasingly dealing with big datasets and sophisticated computational analyses."

Physicist Harley McAdams, a professor of developmental biology, applies what he learned about electrical circuits as a former systems engineer at Bell Labs and Lockheed Martin to the analysis of the biochemical regulation of gene expression. Biophysicist and HHMI investigator Stephen Quake has pioneered, among other things, the fields of microfluidics, which allows entire experiments to be conducted on microchips for large-scale automation, and single-molecule biophysics.

One of the hottest topics of research, at least in the eyes of the public, is the study of stem cells and their potential to treat many human diseases. Irving Weissman, professor of developmental biology and former HHMI investigator, was the first to isolate the blood-forming, or hematopoietic, stem cell from mice in 1988 through the use of the fluorescence-activated cell sorter developed by Leonard Herzenberg. He's since isolated the human hematopoietic stem cell, human neuronal stem cell, and human leukemia stem cell. In 2002, Weissman was named the director of Stanford's newly formed Institute for Stem Cell Biology and Regenerative Medicine. Researchers at the institute have received more than $250 million from the California Institute for Regenerative Medicine to further their stem cell studies.

Institute-affiliated Program in Regenerative Medicine encompasses many other Beckman Center faculty, including professor of developmental biology and of genetics Margaret Fuller, who uses Drosophila gametogenesis, or sperm production, to study the

mechanisms governing stem cell self-renewal and differentiation. Another professor of developmental biology, Seung Kim, studies how insulin-producing beta cells in the pancreas develop with an eye to designing new diabetes therapies.

"After 25 years, the Beckman Center has proven to be one of the greatest research centers in the country, and even the world," says Berg. "It's a beacon in the world of molecular biology. Our original dream has come to fruition, and I, for one, am very proud of what has been accomplished."

Far from resting on their laurels, however, researchers at the center are always looking to the horizon, whether talking with colleagues about their next set of experiments, or thinking about new technological advances.

"Major advances in optical microscopy have enabled images of higher resolution than has ever previously been possible," says Brunger. "Now we'd like to achieve "super-resolution" imaging, on the order of tens of nanometers, and to do it in real time on living cells."

"I'm nearly 88 years old," says Berg. "I hope to see a lot more discoveries and the recognition of the center that comes with them. To me the future is as bright as ever."

"Ten years ago we thought we knew so much," says Shapiro. "Now we know that we knew very little, but we are seeing more and more windows of discovery in molecular and genetic medicine. It is an exciting time."