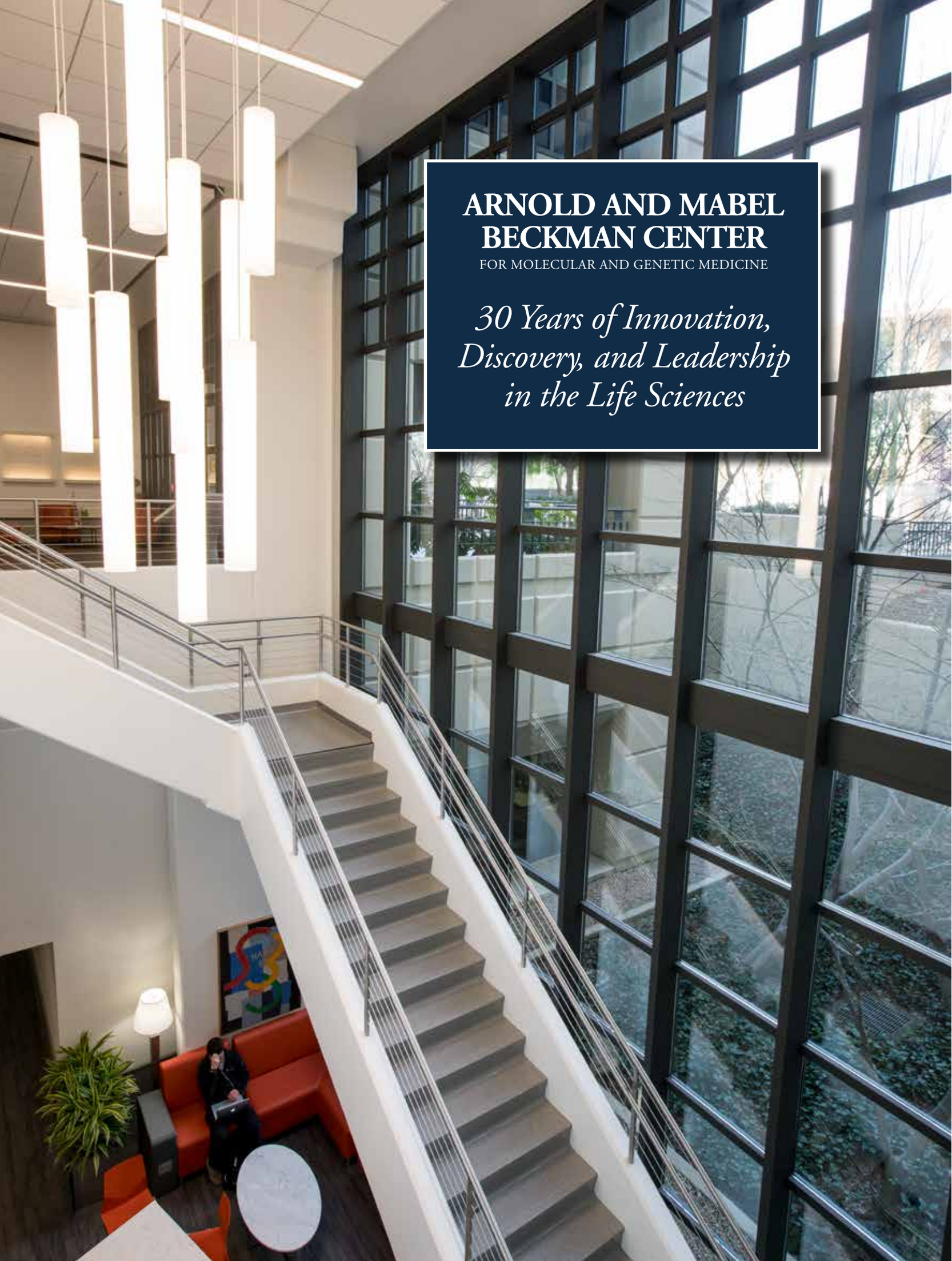

Stanford
Beckman Center
for Molecular and Genetic Medicine
30
Years
2019 ANNUAL REPORT



ARNOLD AND MABEL BECKMAN CENTER

FOR MOLECULAR AND GENETIC MEDICINE

30 Years of Innovation, Discovery, and Leadership in the Life Sciences

Message from the Director

Dear Friends and Trustees,

It has been 30 years since the Beckman Center for Molecular and Genetic Medicine at Stanford University School of Medicine opened its doors in 1989. The number of translational scientific discoveries and technological innovations derived from the center's research labs over the course of the past three decades has been remarkable. Equally remarkable have been the number of scientific awards and honors, including Nobel prizes, received by Beckman faculty and the number of young scientists mentored by Beckman faculty who have gone on to prominent positions in academia, bio-technology and related fields. This year we include several featured articles on these accomplishments. In the field of translational medicine, these discoveries range from the causes of skin, bladder and other cancers, to the identification of human stem cells, from the design of new antifungals and antibiotics to the molecular underpinnings of autism, and from opioids for pain without the side-effects of morphine to new approaches to vaccines. Beckman Center scientists have also developed innovative technologies that include DNA microarrays, novel optical probes to observe tiny subcellular structures, novel new molecules that bind to receptors on cell surfaces in more specific ways than those found in nature, computational tools to harness the power of bioinformatics to sequence genes and link genetic variation to human

disease, and video games that recruit citizen scientists to help determine how RNAs fold. In addition, contributing to these discoveries and innovations over the last 30 years have been a group of amazing women scientists at the Beckman Center, whose research is highlighted and celebrated in a special featured article.

This year's Beckman Symposium, "The Revolution in Diagnostics," focused on some of the latest developments in the field including single cell DNA sequencing, liquid biopsies for cancer and fetal DNA, implantable devices, state-of-the-art imaging technologies and other biomedical breakthroughs that are opening up whole new worlds of diagnostic possibility. This highly successful, well-attended symposium brought scientists from around the country and Stanford faculty together to explore the latest diagnostic advances. The event was co-hosted by Stephen Quake, DPhil, the Lee Otterson Professor in the School of Engineering, professor of bioengineering and of applied physics, and Lucy Shapiro, PhD, the Virginia and D.K. Ludwig Professor of Cancer Research, professor of developmental biology, and director of the Beckman Center.

The Beckman Center awarded five new Technology Development Grants this year from a truly outstanding applicant pool that included 62 faculty members representing 37 separate disciplines drawn from the Schools of Medicine, Engineering, and Humanities and Sciences. The grants support the exploration of novel research ideas that have enormous potential for developing new and improved instruments or devices, or the development of new methodologies to be used in biomedical research. Awards went to a team of researchers developing a next-generation imaging technology for human tissue atlases with the aim to deliver a powerful, practical and accessible tool that can revolutionize single-cell analysis in basic science and clinical medicine; a group whose goal is to target the influenza matrix layer through hyper-stabilization with the hope of developing a successful strategy for antiviral treatment; a set of researchers optimizing a new technology called CODEX (co-detection by antibody indexing) to reveal the cutaneous T cell lymphoma tumor microenvironment in response to immunotherapy; a computational group looking to build a scalable long-term DNA storage system allowing for random access to data; and a research group proposing to use optical tools to assess neuronal function in human stem cell-based disease models, with an emphasis on neuropsychiatric diseases, such as

autism and schizophrenia, which are difficult to study because there is limited access to human material.

This year, the Cell Sciences Imaging Facility (CSIF), one of the four Beckman Service Centers, in collaboration with Dr. Joanna Wysocka, the Lorry Lokey Professor in the School of Medicine, professor of developmental biology, and chemical and systems biology, and Howard Hughes Medical Institute investigator, received an HHMI grant totaling nearly $1 million, for the purchase of an Intelligent Imaging Innovations (3i) V2 Lattice Light Sheet Microscope (LLSM). The new microscope has the capacity to facilitate high spatio-temporal resolution live-cell imaging with minimal photo damage. This will allow the CSIF users to expand live-cell observation times, making them 50 to 100 times longer than current imaging techniques without compromising resolution. The ability to make observations over long time periods is particularly important for processes like chromosome transcription which takes place in bursts that in the past were impossible to capture because of photobleaching and toxicity.

Finally, the Beckman Center is in the process of organizing a special 30th anniversary symposium that will be held in early 2020. Stay tuned for more on this very exciting event.

As always, I want to thank each of you for all that the Foundation has done for the Stanford Beckman Center since its founding in 1989. We are grateful for your support and look forward to working together as we continue to innovate, discover, and lead technology development in medicine and the life sciences.

Sincerely,

LUCY SHAPIRO
Virginia and D.K. Ludwig Professor of Cancer Research
Director, Beckman Center for Molecular and Genetic Medicine

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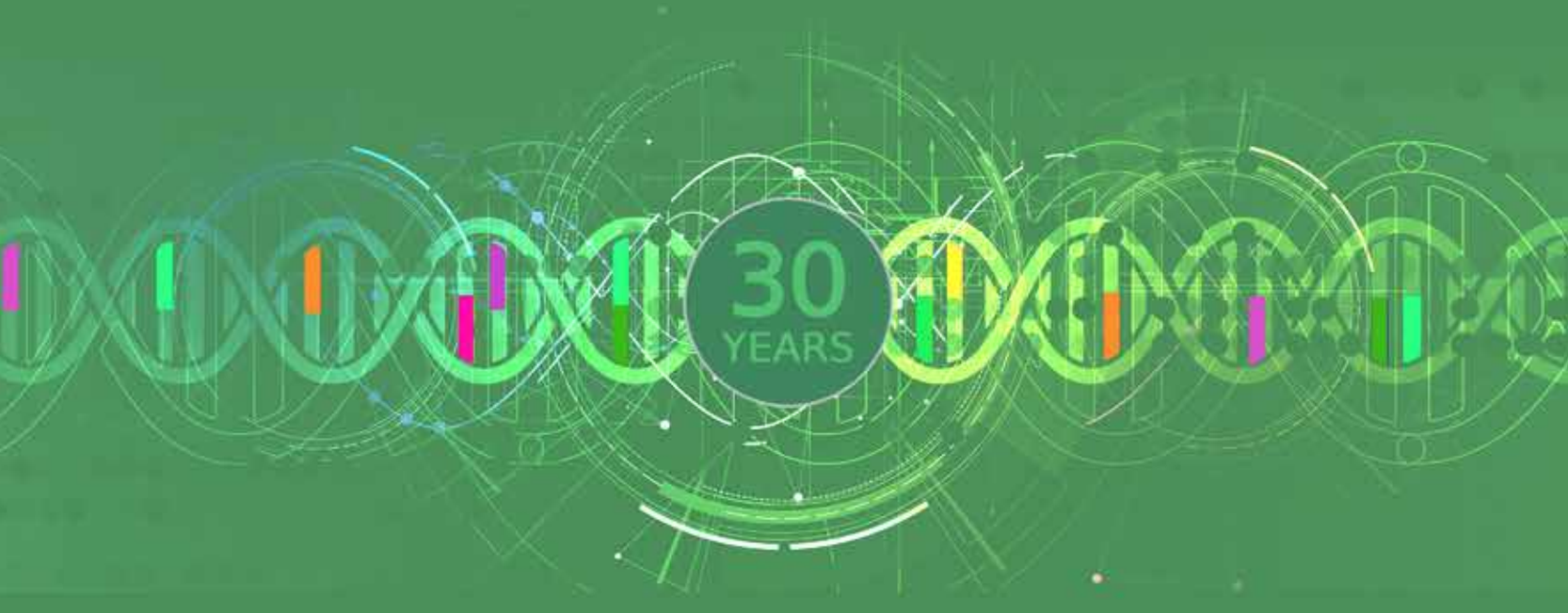


Translational Medicine

Beckman's Focus on Translational Medicine Yields Benefits for Patients

BY RUTHANN RICHTER

When biochemist Jim Spudich, PhD, began studying molecular motors three decades ago, he said it was unimaginable that he would find himself starting two companies. He saw himself as a pure bench scientist, immune from the "taint" of industry, as was the mindset back then.

"I had no idea – no thoughts whatsoever – that any of my work would translate into clinical issues," he said.

It was just his innate curiosity about these motors, which helped power movement, that led to some discoveries which Spudich realized could help patients with major heart and neurologic problems.

"It just seemed there should be some good drugs that needed to be developed for these terrible diseases and we wanted to make that happen," said Spudich, the Douglass M. and Nola Leishman Professor of Cardiovascular Medicine at Stanford.

That inherent curiosity has proven to be a powerful force among Beckman scientists, many of whom have moved fundamental findings into the clinic. They have done so with active encouragement from the Beckman Center, whose programs, facilities and collaborative environment all have created fertile ground for translational medicine.

Since the center's inception in 1989, Beckman scientists have devised new treatments for heart failure, amyotrophic lateral sclerosis, topical dermatitis and fungal disease. They're creating new opioids for pain without the side-effects of morphine. They've identified the molecular causes of skin, bladder and other cancers and probed the molecular underpinnings of autism. They have opened the way to new therapies for diabetes and are developing new approaches to vaccines to prevent infections that afflict millions worldwide.

In doing so, they've helped fulfill the goal of Beckman's founders 30 years ago, who envisioned it as a bridge between basic science and clinical medicine so lab discoveries would reach patients more rapidly.

The idea for the center emerged at a time when there was a revolution underway in the fields of genetic engineering, cell imaging and genomics, an explosion of new knowledge that could have implications for clinical medicine.

Beckman scientists have devised treatments for heart failure, amyotrophic lateral sclerosis, topical dermatitis and fungal disease. They have created new opioids for pain, identified the causes of skin, bladder and other cancers, and probed the underpinnings of autism. They have opened new therapies for diabetes and new approaches to vaccines.

"In the early 1970s, we saw major breakthroughs in recombinant DNA that enabled us to study the genetic system of humans. It was transforming biology in extraordinary ways, and in the 1980s corporate America began investing in new technologies," said Paul Berg, PhD, the Beckman Center's first director whose own research in recombinant DNA was key to the transformation and who was awarded the Nobel Prize in Chemistry in 1980. "But when we talked to the clinical people, most were unaware of that science. The whole field had a vocabulary few clinicians understood."

The goal was to create a new research hub, a rich community of people with backgrounds in science and medicine who could work together toward solutions in a highly collaborative environment, Berg said. It was a novel concept in academia at the time, but ultimately would become the model for other major, multidisciplinary research centers at Stanford, such as Bio-X, the Institute for Stem Cell Biology and Regenerative Medicine, Stanford ChEM-H, and the Parker Center for Cancer Immunotherapy.

Paul Berg, PhD
Professor of Biochemistry, Emeritus, and Founding Director of the Beckman Center

"It all really began here, not only in doing transformative interdisciplinary work but in transferring what we do in physics, biology, engineering, and other fields into applications for the betterment of humanity," said Lucy Shapiro, PhD, professor of developmental biology and current director of the center. "Making things accessible to society is part of Stanford. Certainly, the Beckman Center is front and center in doing that."

The four-story building itself was designed to promote as much interaction as possible. Shaped like the letter Z, it minimized distance between labs with easily accessible light-filled space near the elevator bank on each floor where scientists could congregate and hash out ideas. It provided shared conference and communal equipment space within a central core. Its basement was built to house sophisticated technologies – imaging facilities, a protein and nucleic acid facility, and cell-sorting technologies – that were open to everyone and that remain widely used today.

However, it was not just the facilities or the technologies, but the people – the recruitment of scientists with innovative and creative minds – that would make the building really hum.

"If you are able to bring the right people together, things will happen," said Roeland Nusse, PhD, a professor of developmental biology. "You see that in the Beckman Center over and over again."

His own work is a classic example of how he benefited from those around him. "I came here and had an interest in working with fruit flies. I came from the Netherlands where

there was no one working in fruit flies. Suddenly, I was in an environment where there were fruit fly labs left and right. That really influenced the work we were doing. For 20 years, I was a fruit fly lab."

His second-floor neighbor at Beckman happened to be Irving Weissman, MD, who was interested in stem cells. The two began to see a connection between the Wnt pathways Nusse was studying in fruit flies and the growth of stem cells. Nusse gravitated into the stem cell field and eventually built his own laboratory at the Stanford Institute for Stem Cell Biology and Regenerative Medicine, which Weissman directs.

Brian Kobilka, MD, professor of molecular and cellular physiology, is among those who have benefited from having ready access to colleagues who had expertise he could draw on.

"I was trained as an MD. I didn't have any formal graduate school training, so a lot of what I had to learn I learned from colleagues," Kobilka said. "For example, to purify receptor protein, I needed to make a special chemical reagent. I went across Campus Drive to chemistry and asked John Griffin, an assistant professor, how to do the simple chemistry to make the reagent." Those experiments ultimately enabled him to discern the structure of the G protein-coupled receptor, an achievement that won him the 2012 Nobel Prize in Chemistry.

Beckman also has provided financial incentives for people to work together. When Lucy Shapiro became the center's director in 2001, "One of my initiatives was to establish seed grants that would pair clinicians with faculty in engineering, chemistry, physics and other disciplines," she said.

"We brought people together who ordinarily don't talk to each other, and that has been extremely powerful," Shapiro said.

Immunologist Mark Davis, PhD, said, "One of the 'secrets' of Beckman is that it rewards a team approach, something that's not traditionally the case in academia. Nowadays, I rely on relationships with colleagues in bioinformatics, biocomputation, genetics, infectious disease and other disciplines."

"A team approach enriches everyone. You get people working on different aspects of the same problem. At the end of the day, you find out you know a lot more about it than you would have if you had been working by yourself," said Davis, professor of microbiology and immunology, and director of the Stanford Institute for Immunology, Transplantation and Infection. "So, I think that is part of the future of science. It's definitely part of the future of translation."

One of Beckman's early goals was to attract researchers who also had a footing in the world of medicine. Mark Krasnow, MD, PhD, was the ideal fit, a new medical school graduate who was committed to basic research.

When Krasnow established his lab in 1988, he was enthralled with the emerging technology of recombinant DNA, as it

"It all really began here at the Beckman Center, not only in doing transformative interdisciplinary work, but in transferring what we do in physics, biology, engineering, and other fields into applications for the betterment of humanity," said Lucy Shapiro, PhD, professor and director of the center.

When Lucy Shapiro became the center's director in 2001, one of her first initiatives was to establish seed grants that would pair clinicians with faculty in engineering, chemistry, physics and other disciplines. "We brought people together who ordinarily don't talk to each other, and that has been extremely powerful," Shapiro said.

provided a new way to study development. Scientists now had the tools to clone the genes that controlled the development process and from there they could identify the key proteins, molecules and mechanisms involved, he said.

He began in fruit flies, trying to understand the process of how organs are formed. His lab decided to focus on the lung and the respiratory process.

"At the time we couldn't imagine understanding the process in humans. It was too complicated, not feasible. But for *Drosophila*, the genes were being identified and the tools to isolate and analyze the genes were coming along. You could do precision biology at the cellular, genetic, molecular and biochemical level," Krasnow said. "And so, I learned how an animal builds an organ, how it maintains the organ and how that process goes awry in disease, and I learned how to do that in the best system available, which was *Drosophila*."

He then moved on to mice, whose respiratory system is bigger and more complicated, and more like the human system. Within a decade, he and his colleagues had made a comprehensive map of the developing mouse lung with its more than 5,000 branches. Probably the most detailed developmental map of any mammalian organ, he said.

In 2014, he achieved a breakthrough in working with bioengineer and physicist Steve Quake, PhD, who had developed a technique for expression-profiling individual cells. They used the technology to build a complete gene expression profile of the cells that build alveoli in mice, the tiny balloon-shaped air sacs involved in gas exchange that enable the animals to breathe.

"That was a watershed moment. Because now that technology could be used in any type of tissue," said Krasnow, now the Paul and Mildred Berg Professor in biochemistry. "Of course, we were thinking of human tissue, both normal and diseased."

He could hardly have imagined what would come next: his dear colleague and friend down the hall, Jim Spudich, showed up at his office with a startling revelation:

"He said, 'I'm going in tomorrow morning for surgery. I've got an early stage lung cancer,' which happened to be the exact kind of cancer we had been studying in mice, adenocarcinoma, which develops from one of the alveolar cells we had been studying in mice," Krasnow said.

In less than 24 hours, Krasnow mobilized his students, postdocs and colleagues from across the university to help collect and study Spudich's tissue, both the cancerous and the normal tissue taken from his lung during surgery.

The result, he said, "is one of the deepest, most extensive studies that's ever been done on any tissue or any disease." They have since built a molecular cell atlas

Mark Krasnow, MD, PhD
Professor of Biochemistry and
Howard Hughes Medical Institute Investigator

of the normal human lung and identified all of the normal lung cell types with molecular precision, including 15 new cell types that had not been recognized before. Their collection of data - 80,000 cells, each with 25,000 genes and half a million measures of gene expression in each cell - was so enormous that it could not be effectively managed in any computer on the Stanford campus, he said.

"Now we can understand diseases, like lung adenocarcinoma and many other lung diseases that are not well understood and begin thinking about what went wrong at the cellular and molecular level and how to fix it," Krasnow said.

Jim Spudich said being the subject of so much intense scrutiny was a curious experience. "It was a little weird to be the patient and the scientist, but I am able to step away from it all and just be the scientist," he said.

He recovered quickly from his lung cancer and was soon back in his lab, continuing his work of three decades on the molecular motors that power our muscle contractions and our heartbeats. These motors depend on two key molecules – the energy-dependent protein called myosin and a structural protein called actin, which provides the tracks along which myosin moves.

He said the workings of myosin, found in essentially all cells, depend on a very well-coordinated "city plan."

"The city plan in the cell depends on the cell type and also can vary within a cell type," he said. "If there is a cell that is dividing, it has to change its city plan. It may have a San Francisco city plan and suddenly it wants to divide into two daughter cells; it has to change so the tracks on which all these motors move disassemble and reassemble in a new way."

He and others have identified some 40 different myosin types that are found in various cell types in the body, and all of them contribute to our ability to carry out our myriad bodily functions. Myosin is also key to the workings of the heart, which is a sophisticated muscle.

"The major difference between the heart and skeletal muscle is you send brain signals to tell your skeletal muscles to move whereas the heart has a built-in pacemaker which is sending electrical signals all the time, and you don't have to think about it," he said. "But the molecular basis by which the contraction occurs is identical in skeletal muscle and the heart."

In 2012, Spudich received the Albert Lasker Basic Medical Research Award for his work, sharing the prize with colleagues Michael Sheetz, PhD, and Ronald Vale, PhD. Spudich said his research has been driven

by his natural curiosity, but that it became very apparent that it could be applied in the clinic in a number of ways. He ended up co-founding a company, called Cytokinetics, which has developed a small molecule that activates heart contractions and increases the heart's power output. Now in phase 3 clinical trials, the agent, taken as an oral tablet, binds to myosin in the heart to bolster cardiac function in patients with heart failure.

The flip side of heart failure is a condition known as hypertrophic cardiomyopathy in which the heart is hypercontractile and eventually becomes thickened and unable to pump effectively. "About one-third of cases of the disease arise from mutations in myosin that cause the heart to work overtime," Spudich said. "It's as if you are out for a run all the time with no rest," he said. In 2012, he founded a second company, MyoKardia, to test a drug that resets heart contractions back to normal.

"This MyoKardia small molecule also binds directly to the heart myosin, but does the opposite thing to the Cytokinetics agent. Instead of increasing the activity of the motor, this one binds to the motor and decreases its activity," he said.

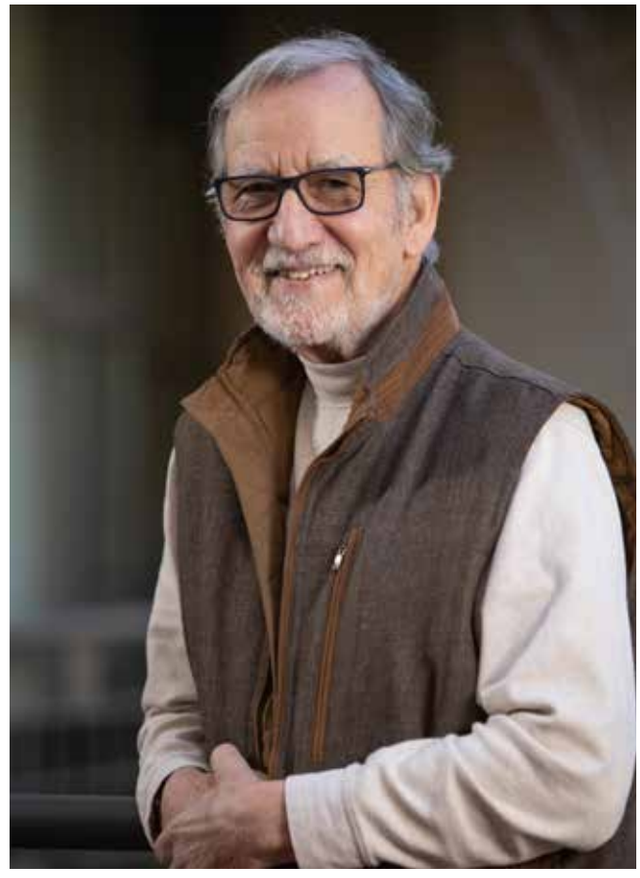
In addition to its heart failure drug, Cytokinetics has developed a molecule that activates skeletal muscle. This could benefit a variety of patients, including frail elderly and people with amyotrophic lateral sclerosis (ALS), which causes muscle atrophy. The agent is now in phase 2 clinical trials in ALS patients.

Like Spudich, Brian Kobilka, MD, is a committed basic scientist, but it was his early work as a clinician that inspired his interest in how certain cell receptors work. He was a resident at Barnes Jewish Hospital in St. Louis, doing clinical rounds in the intensive care unit. It was my favorite rotation because I could see the immediate impact of my interventions, he said.

"You get lab tests very quickly. People are instrumented so you can monitor their vital signs minute by minute," Kobilka said. "And many of the drugs we were giving patients work on a particular family of receptors. So, I started learning a bit about them."

This family of proteins, known as G protein-coupled receptors (GPCR), would become the single-minded focus of Kobilka's work for the next three decades. It's now recognized that they are essential to just about every biological process, including brain function, reproduction, sight and other sensory capabilities.

There are about 800 members of the receptor family that he studies, and some 40% of drugs now on the market target these GPCR's, including the antihistamine, Clarinex; Zyprexa, a schizophrenia drug; and Zantac, for treatment of stomach ulcers and acid reflux.



James Spudich, PhD
Professor of Biochemistry

"When I started in this field as a postdoc at Duke, I was probably aware of 10 members of this family," said Kobilka, professor of molecular and cellular physiology. "By the time I came to Stanford in 1990, other investigators were identifying new receptor subtypes that we didn't know existed. After the sequencing of the human genome, the remaining family members were identified. So, our appreciation of the size of the family has grown and with that, the appreciation of the number of potential drug targets has grown."

But when he started out, the receptors were largely a black box. In order to understand them, Kobilka knew it was important to know their structure, a challenge he doggedly pursued for 17 years. The first obstacle was obtaining enough protein to study the receptors, which are large, complex molecules. They are tightly embedded in the cell membrane, snaking in and out of the cell multiple times. On the exterior they bind to a specific signal, causing a cascade of events inside the cell that leads to a physiologic response, such as an increased heart rate or a change in blood glucose.

Ultimately, he and colleagues were able to make enough protein, but struggled to grow crystals that could be analyzed with X-rays. Through much experimentation, he finally succeeded in using the technique to visualize one of the receptors in three dimensions, frozen in the act of binding to its signaling molecule. It was a remarkable feat, winning him the Nobel Prize in Chemistry in 2012, which he shared with his colleagues.

A newer technology, cryo-electron microscopy, greatly facilitates the process of structure determination, enabling scientists to isolate protein structures and use these structures to screen large libraries of compounds computationally for possible drug applications, he said.

Brian Kobilka, MD
Professor of Molecular and Cellular Physiology

"Once you have a drug 'hit,' you can use the structures to help you improve the properties of other drugs," Kobilka said.

Through this process, my colleagues and I have identified an opiate compound that appears in preliminary animal studies to be very effective without some of the side-effects of current pain-killers, he said.

"We found that the compound is almost as efficacious at pain relief as morphine, but it has much less respiratory suppression," he said.

The compound has been patented and is now in pre-clinical testing at a company he co-founded, Epiodyne. He and his wife and colleague, Tong Sun Kobilka, MD, also founded a small biotechnology company, called Confometrx, in which they use structure-based approaches to drug discovery. They are now working with a

major pharmaceutical firm that is searching for new drugs to treat diabetes and metabolic disorders, he said.

Serendipity often plays a role in science, as Lucy Shapiro, PhD, well knows. She was prompted to form a company following a chance meeting on campus in the late 1990s with former university President Hennessy, PhD, then Dean of Engineering. He asked her what she was up to.

She told him she had found a way to disarm an enzyme that is essential to bacterial cell growth. It could be an ideal new target for antibiotics, desperately needed in an era in which antibiotic resistance has become a serious global problem.

"I remember him saying, 'Well, have you patented that?' It had never occurred to me," Shapiro recalled. "I went back and patented it. Then I said, 'Well, since it's patented, we should do something with it.'

Lucy Shapiro, PhD
Professor of Developmental Biology and Beckman Center Director

I called a friend who's a chemist at Penn State, Steve Benkovic, and said, 'We should do something to design new antibiotics and new antifungals.'"

And so Anacor Pharmaceuticals in Palo Alto was born in 2001.

The idea of a company had been unthinkable to Shapiro decades before when she'd decided to focus her research on a single-celled organism, *Caulobacter crescentus*. Her goal was to understand in minute detail how the various pieces of the cell worked together as an integrated system. Her lab found that rather than being an unorganized bag of free-floating proteins and DNA, bacterial cells are a highly organized factory, with each step of the cell cycle highly regulated in time and space. It would revolutionize the field of bacterial cell biology for which she was awarded the National Medal of Science in 2013.

After Anacor, Inc. came to life, Shapiro and Benkovic decided to do something "out of the box" in trying to develop new antibiotics and new antifungals. They built a library of new compounds based on boron at the active site rather than the usual carbon.

"Then I had all these various pathogens, bacteria and fungus, and tried a set of our novel, non-toxic boron-based compounds on inhibiting all of these different bugs," she said. "We got incredible activity. We did the crucial experiment, switching boron back to carbon, and we lost all activity. So, we had truly opened a new chemical space for drug development."

Based on this concept, Anacor developed its first product, a topical antifungal known by the trade name Kerydin, approved by the federal Food and Drug Administration in 2014.

Shapiro said the company began doing clinical trials with another boron-containing compound as a possible topical antibiotic

Inherent curiosity has proved to be a powerful force among Beckman scientists, many of whom have moved fundamental findings into the clinic.

for the bacterial infection, streptococcus. Strep can be a side-effect of the skin disease, eczema, particularly among kids, as they scratch the red, itchy rashes, which then become infected.

The clinical trials showed the compound wasn't great as an antibiotic, but it prompted calls from physicians who noticed it helped calm the inflammation of eczema, Shapiro said. It was serendipity at work again.

"We figured out the mechanism of action and discovered it was, in fact, a very safe anti-inflammatory drug with none of the side effects of steroidal topicals," Shapiro said. It was an exciting discovery – the basis for a new, nontoxic treatment for atopic dermatitis, a major worldwide problem. Anacor was bought by Pfizer in 2016 and the topical ointment is now being marketed under the trade name Eucrisa.

One day, Shapiro took a late-afternoon break to see the new documentary about Supreme Court Justice Ruth Bader Ginsberg at a Palo Alto theatre. "They had these trailers in the beginning. I looked up and there were these scratching babies with a big sign, Eucrisa. It was a Pfizer ad," she recalled, laughing. "I couldn't believe it."

Shapiro was recruited to Stanford to build the newly formed Department of Developmental Biology, housed at Beckman. Roeland Nusse, PhD, was among the department's early faculty, arriving in 1990.

A cancer researcher in the Netherlands, Nusse had been a postdoctoral fellow at UCSF when he and his mentor, Harold Varmus, MD, made a seminal discovery in 1982: using a mouse model of breast cancer, they found the gene for Wnt, a signaling protein involved in cancer development.

Nusse said he did not imagine then that Wnt proteins would ultimately have so many potential applications, as his work would show they were involved in many biological processes, including embryonic development, adult tissue repair and various forms of cancer. The research would win him the $3 million Breakthrough Prize in Life Sciences in 2017.

Early on, Nusse said he began to see the connection between the Wnt pathway and stem cell growth.

"If you have a tissue, you look at where the dividing cells are. It's always in a particular area where Wnt signaling is active," said

Roeland Nusse, PhD,
Professor of Developmental Biology and Howard Hughes Medical Institute Investigator

Immunologist Mark Davis, PhD, said one of the "secrets" of Beckman is that it rewards a team approach, something that's not traditionally the case in academia. "A team approach enriches everyone," said Davis. "This is part of the future of science. It's definitely part of the future of translation."

Nusse, the Virginia and Daniel K. Ludwig Professor in Cancer Research. "In fact, if you remove Wnt signaling from a tissue, the stem cells are not going to divide. If there is excessive Wnt in a tissue, the stem cells over-proliferate and that leads to cancer." That connection holds up in many different parts of the body, such as the colon and the liver, where Wnt appears to be a driving force behind the growth of cancers in these organs, he said.

The work has led to a worldwide effort to control cancer via the Wnt system. "There is a lot of knowledge being generated and hopefully in the future, it's going to lead to some form of therapy where you inhibit Wnt to prevent cancer or stop it from growing," Nusse said.

Conversely, because Wnt signaling helps spur growth, it might also be enhanced to restore tissues lost to degenerative diseases, like osteoporosis, he said.

"Wnt is basically a growth factor," he said. "It's a factor that makes cells divide, in particular stem cells. If you are able, say, to enhance it in a controlled way, you may be able to restore the growth of the tissue."

Recently, he's been exploring how adult stem cells in the liver may help the organ heal after injury. "Can we somehow cause liver cells to proliferate by helping Wnt or activating Wnt, to get the cells to divide? It all goes to this whole concept of regenerative medicine. Wnt is one major component in regeneration of tissues."

He has teamed up with Stanford colleagues Chris Garcia, PhD, a professor of molecular and cellular physiology and of structural biology, and Calvin Kuo, MD, PhD, a professor of medicine, to co-found a company, Surrozen, which is developing Wnt-like surrogates that could be used in the treatment of injury and disease.

If translational medicine means working with humans and human tissues then Mark Davis, PhD, epitomizes the field. He worked for decades studying immunology in mice and produced some seminal findings, including the identification of multiple T cell receptor genes, which are key to a successful immune response.

But over the years, he said he became disenchanted with the mouse model, as it rarely translated into people.

"I could see repeatedly that it was relatively easy to develop mouse models of disease and to cure mouse models of disease. But you'd take those things into humans with actual disease and it wouldn't work," said Davis, the Burt and Marion Avery Professor in Immunology.

So about 12 years ago, he began pushing the field in a whole new direction and focusing his lab on studies of humans.

Among his goals is to define what health means in people, from an immunological perspective. "We can measure all these things in the immune system, but we don't really know what is important," Davis said.

"What would be the immune equivalent of a cholesterol test?"

He secured funding to establish a Stanford center devoted to measuring thousands of variables in human blood samples in diverse groups of people. He and his colleagues began analyzing the samples using a variety of technologies pioneered at Stanford, including a single T cell technology he developed five years ago that enables scientists to better understand what T cells recognize that spur them into action. This newer technology will help in the development of more targeted interventions, especially for autoimmune conditions, in which patients now take broad-based therapies that inhibit their immune response and thereby harm their ability to respond to infection, he said.

Davis has focused some of his studies on twins, as it is an ideal way to look at immune variability in people who share the same genes. In one study, published in 2015, he analyzed 210 sets of twins, looking at 200 different immune variables.

"We found that 75% of the traits had no detectable genetic influence," Davis said. "It's about the environment. It's all about the diseases you've had and the vaccines you've gotten. It's an adaptive system." The findings were unexpected. "The results turned heads," he said.

Davis is particularly interested in using studies of immune function as a way to evaluate new vaccine candidates against the flu. He said the current vaccine – the same one used for the last 50 years – is a "dumb vaccine" with limited effectiveness, especially in older people.

He's developed a new model using human tonsils, which are, "basically big lymph nodes," he said, serving as the body's first line of defense against invading pathogens. A half million people have them removed

Mark Davis, PhD
Professor of Microbiology and Immunology and Howard Hughes Medical Institute Investigator

every year in the United States, providing an ample supply for study.

"You can culture tonsil cells and stimulate them with flu vaccine, and they make antibodies," he said. "So, I think this is going to be a big deal in terms of vaccine development. It will allow you to test hundreds of vaccine candidates in a way that normally would require enormous cost and time."

Some Beckman researchers are trying to find solutions to massive global problems – scourges like malaria and HIV – which impact millions of people.

Ellen Yeh, MD, PhD, is a malaria researcher who is focused on a somewhat obscure organelle of the malaria parasite known as the apicoplast. She said she was attracted

to studying the apicoplast because she was curious about its "weird biology," but also because it could be the key to new desperately needed medications for malaria.

"I was looking for an area of unmet medical need, and malaria historically has been a neglected and understudied disease," said Yeh, an assistant professor of biochemistry who came to Stanford in 2013. "I've always loved science and I wanted to learn new things, but I also knew the day-to-day life of a scientist can be hard. To get through the hard parts, you need another kind of motivation as well, so it's definitely an extra boost when the things you learn could translate in an area of real need."

Malaria is a mosquito-borne disease that impacts as many as 300 million people around the globe every year, particularly children, and is one of the top three infectious killers in the world. The disease is generally treated with a combination of drugs, such as chloroquine and the more recent, artemisinin-based compounds, but these are encountering resistance, Yeh said.

"It's a huge problem," said Yeh, who is a trained pathologist. "If artemisinin goes, there's no replacement."

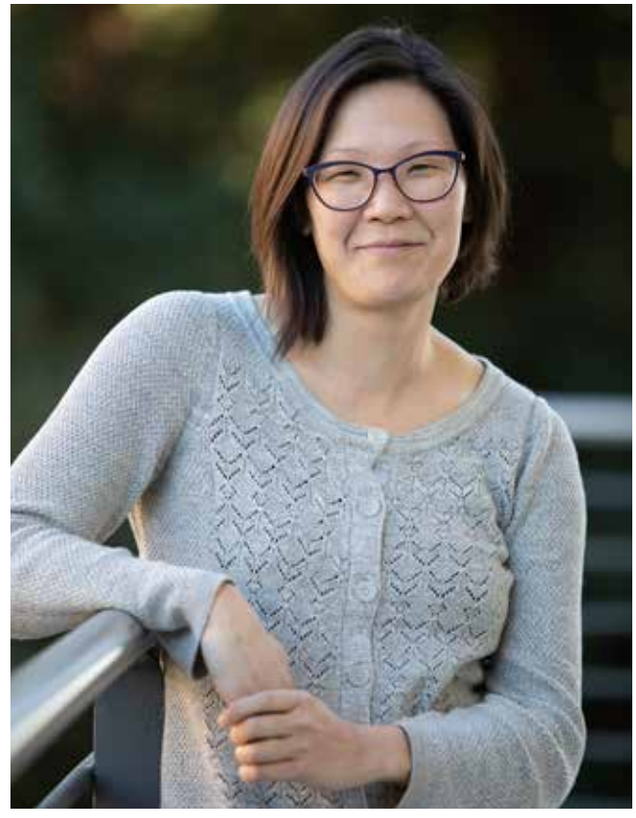
The apicoplast is an ancient plant-like plastid that is found in a number of different parasites, including the Plasmodium family of parasites that cause malaria. It's been found to be essential to the function of the parasite during human infection, particularly during the blood stage – the point when it enters the blood cells and causes the fever, fatigue, vomiting, headaches and other symptoms of the disease. Because of its key role in the disease, the apicoplast has emerged as a major target for antimalarial drugs.

Yeh's lab has been trying to pin down how exactly the organelle works. She discovered that the apicoplast really has only one function and that is to make isoprenoids. These diverse molecules are found in every cell and have varying jobs, but they have one thing in common: their basic building block is a metabolite known as isopentenyl pyrophosphate (IPP). Yeh's lab has found a drug that disrupts this isoprenoid pathway, thus, crippling the parasite.

"We screened it in malaria and found it stopped parasite growth by blocking a key step during isoprenoid synthesis," she said.

She is now working with the Japan-based Takeda Pharmaceutical Co., which has a collaboration with Stanford to help academic labs do pre-clinical drug development.

"Drug companies do a really good job of making drugs. But when it comes to malaria drugs, they don't have a commercial incentive," she said, as it largely affects poor populations. "So, this is a gap that academia can fill."



Ellen Yeh, MD, PhD
Assistant Professor of Biochemistry, of Pathology, and of Microbiology and Immunology

Her lab is pursuing other avenues for possible drug interventions, including methods to destroy the apicoplast outright. But that will require a much better understanding of the parasite at the molecular level, she said.

"We need to have more than one way to disrupt it because malaria drugs are not given in monotherapy. They are given in at least two compounds. And drug discovery has a high failure rate. So, you don't want to bank on one target. You want to be able to get at it in multiple ways and hope that one will be the winner."

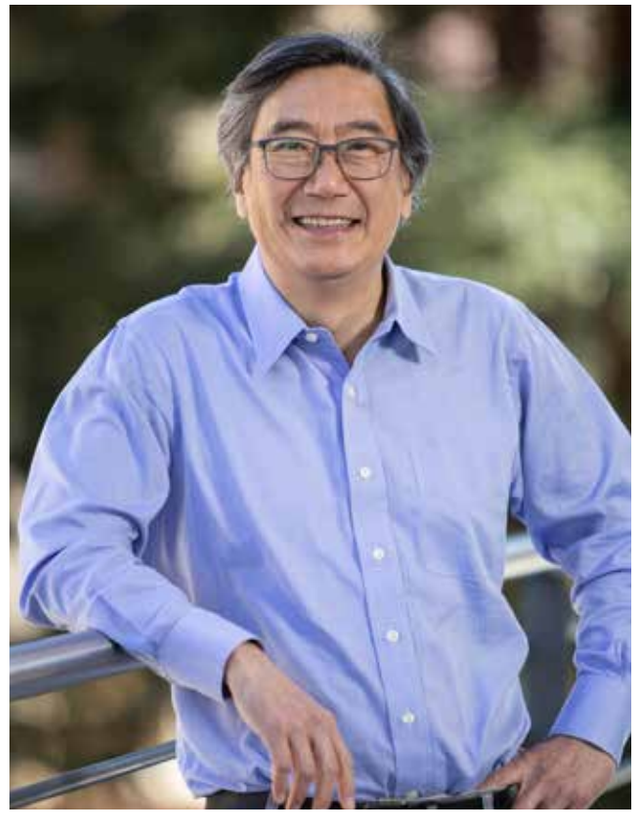
Peter S. Kim, PhD, has been focused on a global problem that has bedeviled the scientific community for three decades: the creation of an effective HIV vaccine.

Kim, who obtained his PhD in biochemistry at Stanford, served for 10 years as president of Merck Research Laboratories. In 2013, he returned to his Stanford roots and to basic research on HIV.

He said the development of an HIV vaccine has eluded scientists for a number of reasons. For one, the virus mutates so rapidly that when there are antibodies produced against it, it can quickly change its amino acid sequence to evade detection. It also targets and kills the very cells – CD4 T cells – that are key to fending it off. Moreover, the virus is highly variable with multiple subtypes, meaning an effective vaccine has to be broadly protective.

When he was at Merck, Kim oversaw the testing of a vaccine based on the idea of priming the immune system to generate specific cytotoxic T cells, supercharged killers that would recognize HIV-infected cells and destroy them. The approach worked well when tested in monkeys, but when it moved into the clinic, it failed miserably, he said.

"It was really devastating for the field," said



Peter Kim, PhD
Professor of Biochemistry

Kim, the Virginia & D.K. Ludwig Professor of Biochemistry. "It literally left the field back at square one."

His lab continues to pursue a novel approach toward an HIV vaccine that aims to inhibit the membrane-fusion process that is required for infection. When the virus's envelope protein, known as gp120/gp41, binds to the cell, the protein changes its shape, harpoons the cell and then snaps back on itself, forming a hairpin that brings the cell membrane and the viral membrane together. That leads to fusion and infection, Kim said.

The goal is to find a vaccine that binds to the pre-hairpin and stops it from snapping back; thus, preventing fusion, he said.

"The advantage of our approach is that we are targeting a highly-conserved region of the virus, so it should be harder for the virus to escape," Kim said. "The disadvantage

Beckman scientists have helped fulfill the goal of Beckman's founders 30 years ago who envisioned the center as a bridge between the basic sciences and clinical medicine.

is that we are targeting a transient intermediate, so it has to be there at the right place at the right time."

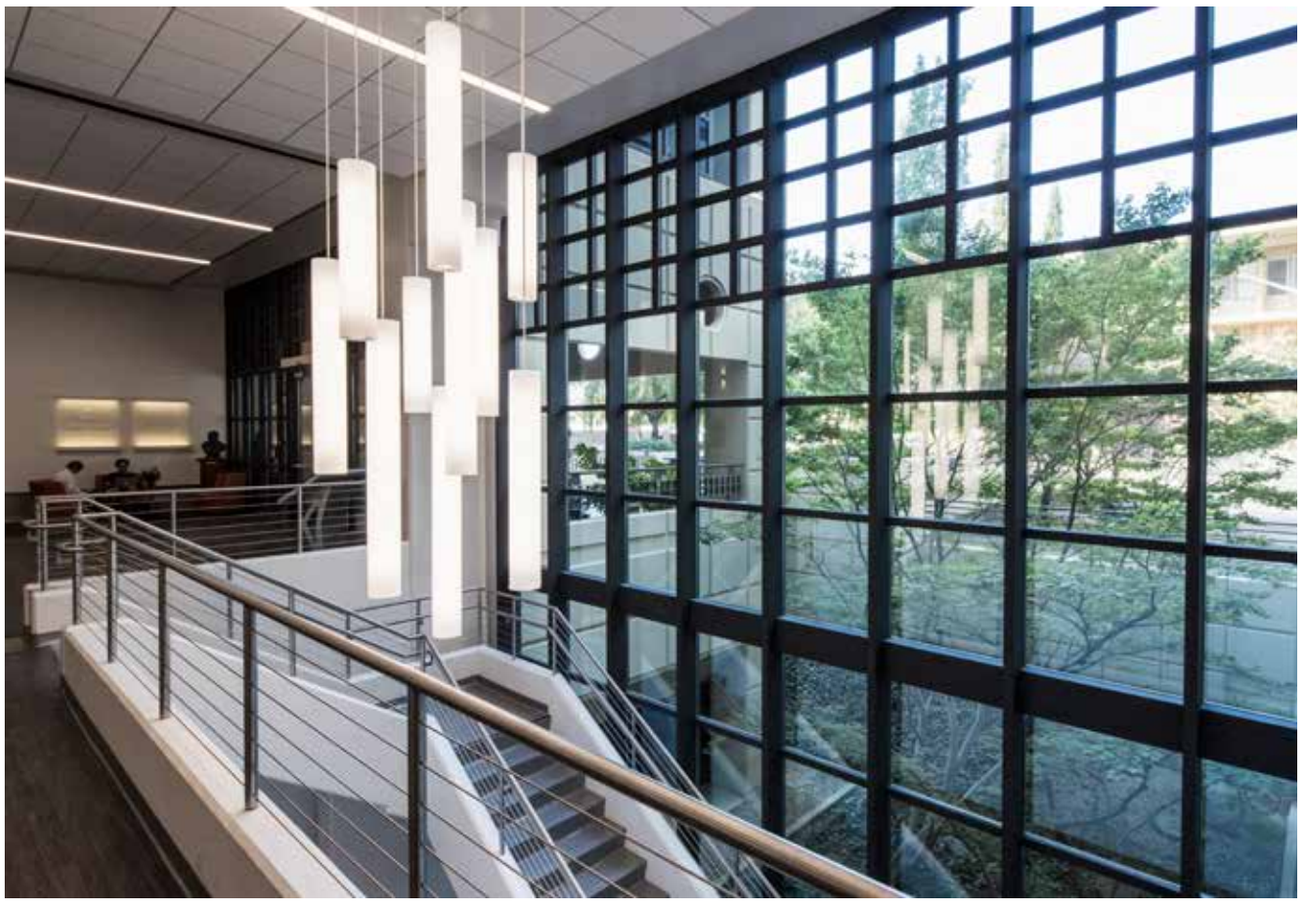
Nonetheless, a peptide that binds to the pre-hairpin already has been developed into an FDA-approved drug, called Fuzeon.

"The idea would be for a person to have antibodies like Fuzeon," Kim said. "The antibodies would be circulating in the body and if the virus enters the system, it would bind to the pre-hairpin intermediate and prevent infection."

Other viruses, such as influenza and the Ebola virus, appear to use the mechanism of the pre-hairpin intermediate to fuse to cells, meaning this approach has the potential for broad applications, he said.

Because of his experience in industry, Kim has a deep understanding of what's involved in the translational process. As a result, he's been tapped by the university to co-chair an initiative with radiology chair Sam Gambhir, MD, PhD, called the Innovative Medicines Accelerator (IMA), designed to move laboratory findings down the path to clinical applications.

"The intent of the IMA is to enable scientists, including all of those at Beckman, to push their discoveries further toward translation," he said. ■



Beckman Women Scientists

Women Scientists of the Beckman Center

BY ANNA AZVOLINSKY

"Science was an evolution of curiosity for me. My father was a chemist and in grade school, I spent time on the weekends in his lab, watching dry ice skate on water. In high school, I got into writing code with my friends. My high school was in Bethesda, Maryland, and a lab investigator came to our high school and asked if anyone likes to write code because he wanted students to come to his biophysics lab and write code for his research. My friend and I put our hands up to volunteer and after school, and in the summer, we worked in his lab. The lab needed a computer program to automatically analyze their data from a spectroscopy instrument. Today, the instrument would come with its own software, but that was not the case back then. The scientist gave us a scientific paper on how to implement a Fourier transformation and we had no idea what that meant, but we said, 'Ok, let's figure this out.' I loved solving puzzles and through that experience became fascinated by biology. The friend, Felasfa Wodajo, as it turns out, also came to Stanford. He worked as a computer programmer in Bill Newsome's laboratory before going to medical school and is now a musculosketal tumor surgeon."
–Miriam Goodman, Professor of Molecular and Cellular Physiology

"When I was seven, my dad took me out in the backyard with a yellow kitchen stepstool, a few jars and tubes: we put a jar full of water on each step and he taught me how to make a siphon. That was my formal introduction to physics. Later, in high school I loved how my physics course in Newtonian mechanics explained the things we see in our everyday world and decided to major in physics in college. After a year, I realized I wanted to do experimental rather than theoretical work, but right or wrong, I felt like there was always a big machine required between you and the questions. My sophomore year, I took an introductory biology course and asked one of the professors if I could work in his lab over the summer. He said yes and then went away on sabbatical. When left basically to my own devices in the lab, I discovered something, I realized that in biology, you could ask and answer questions with just your mind, your eyes, some test tubes and a water bath. I was hooked."
–Margaret "Minx" Fuller, Professor of Developmental Biology and Genetics

"I had lots of unscheduled afternoons growing up and would get lost in the natural world for hours and hours, roaming and exploring. It's the same free-roaming mental space as becoming lost, now, at the microscope for hours and hours. I would find dead animal carcasses, bring them home and preserve them in mason jars in the basement. In hindsight, my parents were so tolerant of it all. Not all kids would have been allowed to bring rotting carcasses into the basement and keep them there."
–Lucy O'Brien, Assistant Professor of Molecular and Cellular Physiology

"The single person that altered my life trajectory was my high school chemistry teacher who was an extremely inspirational woman and incredibly dedicated. She led a chemistry club where we spent afternoons, evenings, and weekends sitting in the back of our chemistry classroom, doing experiments and exercises. She prepared us for the chemistry Olympiad which I made twice to the international competition, representing Poland. This is how everything started for me. Those international competitions opened up my worldview. I saw that there was a bigger community of scientists around the world. Then I got to participate in a countrywide summer science camp in Poland that provided this amazing geek community for me where all of us, I think, saw that there were other strange kids like ourselves who liked science and that we were not alone. After that, I had little doubt that I would end up in science in some capacity although I couldn't even begin to imagine at the time that I would be a professor at Stanford University."
–Joanna Wysocka, Professor of Developmental Biology and of Chemical and Systems Biology

"I was always a good student, but it wasn't until college that I decided to focus on science. I majored in chemistry and in my senior year decided to take microbiology, where we learned about recombinant DNA and how to cut and paste genetic information. There was also a genetics course that I almost didn't take because I went to the University of Notre Dame where it was really cold, and I would have to walk across campus to the lab late at night to collect virgin fruit flies. But fortunately, I took the course and there, I learned that genetics was my natural language. There was also a sense I got that there was much in biology remaining to be discovered. Those genetics and microbiology classes made me realize that there were new tools available to help answer important questions in biology and that I wanted to do that."
–Anne Villeneuve, Professor of Developmental Biology and Genetics

All these different women had unique paths that led them into becoming experimental biologists and shaping them into being an integral part of a talented group of scientists that has been the backbone of the Beckman Center for Molecular and Genetic Medicine. One commonality that these women of science did share; however, was the desire to be part of what each one describes as the collegiate, collaborative, and inquisitive culture at the Beckman Center and Stanford University.

A Matter of Balance

As a young professor in the 1980s, Margaret Fuller's first job was at the University of Colorado at Boulder. There, she was assigned the task of teaching the section of an undergraduate developmental biology course on how blood stem cells differentiate to form every blood cell in the body. "The idea at the time was that there was a local stem cell niche, a microenvironment where the stem cells self-renew, but no one had proven that it existed," says Fuller. It was hard to study the niche when the first step commonly used in the field was to take the cells out of the body and sort them in preparation for transplantation. Thinking back to her days as a postdoc studying the genetics of cytoskeletal proteins during fruit fly spermatogenesis, Fuller realized that in the fruit fly, the adult stem cells that differentiate into sperm are known and that they could be studied within the body, in the context of their normal anatomy. The fruit fly could also be genetically manipulated, which means that this humble insect could be used to identify the factors necessary for both stem cell maintenance and the switch to differentiation.

And she did just that. Fuller began to use the fruit fly male germline to understand how adult stem cells are maintained and what governs their ability to differentiate, after she came to Stanford's Beckman Center in 1990. Then graduate student in the Fuller lab, Amy Kiger, now an associate professor at the University of California, San Diego, performed genetic screens to find mutants that affected the ability of the male germline stem cells to either maintain their 'stemness' or to initiate differentiation. Based on the structural arrangement of cells in the region of the fruit fly testis where the germline stem cells reside, Kiger surmised that communication between the stem cells and surrounding somatic cells might be crucial for the male germline to retain its ability to self-renew. Kiger, postdoctoral fellow Helen White-Cooper, and Fuller found that a key to the balance of maintaining the fruit fly's male germline stem cells is the activator

Margaret "Minx" Fuller, PhD
Professor of Developmental Biology and Genetics

of transcription (JAK-STAT) pathway in neighboring germline and somatic stem cells that is needed to preserve the two stem cell populations.

A few years later in 2003, Fuller and then postdoctoral fellow, Yukiko M. Yamashita, now professor at the University of Michigan, were looking for additional ways to ensure that balance is maintained between stem cell self-renewal and onset of differentiation in the cell lineage that leads to production of sperm. Yamashita had discovered that the germline stem cells go through an asymmetric cell division, in part, by relying on two intracellular factors, the centrosome and the Adenomatous Polyposis Coli (APC) tumor suppressor protein. The stem cell uses these two factors to align its mitotic spindle perpendicular to the niche, ensuring that one daughter cell maintains its attachment to and localization within the protective environment of the niche and so retains stem cell identity. The other daughter cell, meanwhile, is displaced away from the niche and begins its transition to differentiation. Then, Yamashito did what Fuller calls, "an amazing study." Yamashito labeled the mother and the daughter centrosomes—components of the cell that organize the spindle fibers that are necessary for cell division— that duplicate before a cell divides. Yamashito found that the older centrosome stays anchored near the niche while the younger centrosome migrates to the opposite side and goes off to the cell that will begin to differentiate. Thus, the stem cell retains the mother centrosome, a so-called, "centrosomal Eve," possibly through the life of the fly. The anchoring of the mother centrosome, likely to the protein complex that anchors the germline stem cell in the niche, may provide the mechanism that orients the spindle to make sure that each germline stem cell division has an asymmetric outcome, according to Fuller. This allows the germline stem cell lineage to persist throughout the fly's reproductive lifespan.

Anne Villeneuve, PhD
Professor of Developmental Biology and Genetics

"The best part about being a scientist is the hunt—the bringing together bits of disparate data together into a plausible model," says Fuller. For her, that hunt wouldn't be possible without the, "incredible students and postdocs at Stanford that have been part of her laboratory and that have been true partners in generating questions and ideas."

A Window into Meiosis

Anne Villeneuve came to Stanford in 1989 as an independent fellow after having just completed her graduate training at the Massachusetts Institute of Technology. "Instead of having a single mentor, I had multiple mentors including Lucy [Shapiro] and Minx [Fuller] who were both invested in my success," she says. Villeneuve's lab now studies the process of proper homologous chromosome segregation during meiosis in the nematode, *Caenorhabditis elegans*, but she came to the topic by serendipity.

During her second year at Stanford, Villeneuve was helping a graduate student friend apply for fellowships to study chromosome pairing during meiosis—the specialized cell division program that allows organisms with two sets of chromosomes to generate the sperm and ova reproductive cells that contain only one set of chromosomes. "As a graduate student studying *C. elegans*, I had learned about the interesting properties of chromosomal rearrangements and genetic recombination in nematode meiosis. As I talked to my friend, suddenly a light bulb went on in my head and I realized that I was getting more excited about these questions than what I was actually studying in the lab," she recalls. Villeneuve gave herself a deadline for progress on her original project after which she took a few days to formulate her plan for studying meiosis in the worm.

As a geneticist, she naturally started with a genetic screen—looking for mutants that had an increased frequency of embryos with aberrant chromosomal numbers due to errors in separation of chromosome pairs during meiosis. That initial screen and other screens resulted in mutants that led her lab to identify both chromosomal regions that facilitate homologous chromosome pairing and the protein machinery that is responsible for establishing and maintaining the pairings. Part of this machinery is the synaptonemal complex, a scaffold-like structure that assembles between homologous chromosome pairs during meiosis. Since that screen, Villeneuve's lab has investigated every aspect of meiosis, from chromosomal pairing, to assembly and function of the synaptonemal complex, to the DNA recombination process that creates crossovers between the chromosome pairs, and to the cell division processes that separate them.

More recent experiments in the lab has led them to a detailed and systems-level understanding of how the synaptonemal complex and recombination function together. Postdoctoral fellow Alex Woglar, developed methods to visualize parts of the process that had not been observed previously, revealing that the synaptonemal complex plays multiple roles in promoting and regulating recombination. In a related study, the lab also discovered that the synaptonemal complex morphs from a more dynamic and fluid state to a more stable one as the germ cells progress through meiosis and showed that this state transition is dependent on the DNA events of recombination. "What we are seeing is that there are multiple engineering principles at play in this system, including negative feedback, quality control and fail-safe mechanisms, that work in concert to yield a robust outcome," says Villeneuve.

Looking back, Villeneuve cannot forget that Lucy Shapiro took a chance on her. "She believed in me and that was really important," Villeneuve recalls. Another facet of her success comes from the Beckman Center's resources. Because her research relies heavily on visualizing the steps of meiosis in the optically transparent *C. elegans*, the Cell Sciences Imaging Facility has been integral to her lab's work. The microscopy tools have allowed Villeneuve's lab to continue to push the technology to see meiosis in ever greater detail, both using fixed preparations and also imaging of live worms to see

Villeneuve ascribes another facet of her success to Beckman Center resources. Because her research relies on visualizing the steps of meiosis, the Cell Sciences Imaging Facility has been integral to her lab's work.

the dynamic process of meiosis unfold over time. "The director of the facility, Jon [Mulholland] is not only terrific in the technical aspects of the microscopes, but takes a keen interest in the scientific questions and is constantly on the lookout for new technologies that can enable us to drive our science forward, which is special," she says. "The microscopy tools, over the years, have improved and they have allowed us to identify additional components of meiotic structures. It's a positive feedback loop where we are seeing a level of detail that we could never have seen before." And the aesthetic beauty of the images and movies that the lab generates, enabled by the Beckman Center, is not lost on Villeneuve. "The ability to look at the chromosomes and see what is happening through meiosis progression is one of the most amazing features of combining *C. elegans* with the latest microscope technology."

Gut Behavior

As a budding scientist, Lucy O'Brien had the untethered creativity and ability to endlessly explore. In graduate school, however, O'Brien was grounded with the realization that besides creativity and curiosity for the unknown that had driven her to do her own experiments, to be a successful biologist, she needed to incorporate strategy, planning and being able to fit in as part of a scientific team.

These characteristics of a scientist—taking cues from your environment, being able to adapt, and working as a team—it turns out, parallel those of cells within an organ. Organs are not locked into a single state, but rather can grow or shrink to meet changing physiological demands. This adaptation of adult organs to their environment is distinct, from the growth and maturation of organs during development and, O'Brien realized as a postdoctoral fellow, that the flexibility and adaptation of adult tissues is mostly unknown.

Lucy O'Brien, PhD
Assistant Professor of Molecular and Cellular Physiology

At the Beckman Center, O'Brien now uses the fruit fly midgut as a model system to uncover the rules that govern how adult tissues sense and respond to change. Why the midgut? "It is one of the simplest somatic tissues that undergoes continuous stem cell-based renewal," says O'Brien. The midgut is comprised of about 10,000 cells and about 2,000 stem cells and the numbers are even smaller for the midgut compartment that O'Brien studies—just about 2,000 cells and about 400 stem cells. In other words, it's knowable.

Recently, O'Brien's lab tackled the link between a cell dying within an organ and a new cell being made. In 2017, graduate student Jackson Liang, O'Brien and their colleagues found that it's the differentiated cells, rather than the stem cells that are, "leading the dance," as O'Brien puts it, of when a new differentiated cell is needed in the organ. The healthy somatic cells in the midgut inhibit the resident stem cells from dividing, but if a somatic cell dies, it releases a short-lived smoke signal of

sorts—a "puff" of EGF. This signal triggers the EGFR on the surface of the stem cells nearest the dying cell, prompting them to divide. "This mechanism, if we extrapolate it across an entire tissue or organ, could explain how tissues get to be the precise size that they are," says O'Brien. The team is now testing their model, to see if they can expand or shrink the reaches of the EGF signal and in turn, either grow or shrink the fly midgut.

O'Brien's lab also continues to push already leading-edge technology. "Many labs have tried and failed to live image the fruit fly midgut and I was not planning on tackling this right away in my lab." But, Judy Martin, a research technician in the lab, had seen a talk on how to cut a window in the fly brain and live image neuron recording. She told O'Brien that she wanted to see if the technique could be applied to the midgut. To both of their initial surprise, the test runs worked! Martin managed to keep the tiny fly alive, to make an incision in its back and image the still digesting creature. The live movie reel that emerged showed O'Brien and Martin that the midgut's stem cells move around much more so than the researchers had expected. "We knew that stem cells can respond and move to the site of an injury, but we found that the stem cells are actually moving around all the time. Martin, along with postdoctoral fellow XinXin Du, found that the stem cells are not randomly distributed but rather, space themselves to face away from each other, akin to the way people will space themselves out away from others in an elevator. "We think that the movement is helping to place the stem cells throughout the tissue so that if a somatic cell dies, there will be a stem cell nearby that will get that EGF signal and respond by making a new cell," says O'Brien.

O'Brien arrived on the Stanford campus six years ago. A big draw to the Beckman Center for O'Brien was the strong female leadership, including Lucy Shapiro. Since arriving on campus, "I've sensed the collective presence of strong, well-respected female faculty," she says, "which creates a positive environment at the Beckman Center and that has been wonderful for me as a young female faculty member."

Long-Distance Reach

Ending up at Stanford was a pleasant surprise for Wysocka who had never spent a significant amount of time on the west coast. "My interview at Stanford was one of the most intellectually stimulating ones that I went through," says Wysocka. "I got the impression that the people here consistently have the most out of the box thinking. Talking to the faculty, I found that they had creative ideas that made me think about biological problems in completely new ways." Wysocka, herself a creative thinker, fit right in. "I have not been disappointed with my decision."

By the end of her time as a graduate student, Joanna Wysocka became interested in chromatin and how it controls gene expression. As a postdoc, she discovered that the plant homeodomain (PHD) finger domain on chromatin remodeling proteins mediates an interaction with specific histone modifications. When she started her lab at Stanford, Wysocka used the opportunity to take a risk and do something new—to

"I've sensed the collective presence of strong, well-respected female faculty," said O'Brien, "which creates a positive environment at the Beckman Center and that has been wonderful for me as a young female faculty member."

take her expertise in chromatin to study gene regulation in developmental biology. Wysocka's lab studies gene regulation in human development and how it evolved and is distinct from that in primates. One big question is: how does the vast non-coding DNA—which makes up over 90% of the human genome—help orchestrate the turning on and off of combinations of genes needed at certain times and by certain cell types? In particular, Wysocka is studying DNA elements called enhancers that exert their effect on gene expression over long distances, and which are essential for genetic control during development in both time and space. The lab is using genomics and genetics, as well as live cell imaging to track the effects of enhancer DNA on various genes, most of which are nowhere near the genes they regulate. And her gamble to set up a system entirely new to her has paid off.

Wysocka and her colleagues recently developed a technique, using the CRISPR Cas9 enzyme to label enhancers and other gene regulatory elements in the genome

Joanna Wysocka, PhD
Professor of Developmental Biology, of Chemical and Systems Biology, and Howard Hughes Medical Institute Investigator

and watch their movement within the genome during stem cell differentiation. Their initial observations are that an uptick in the mobility of these DNA elements coincides with increased transcription of the genes under the control of these loci. To study human-specific gene regulation, Wysocka's lab mainly works with human cranial neural crest cells, what Wysocka calls, "the most fascinating cell type there is." In the embryo, these cells originate in the neural tube—the group of stem cells in the embryo that will become the brain and spinal cord—dissociates, and travels a long way to then become parts of the skull and face, forming an unusual number of cell types including neurons, bone, cartilage and connective tissues. She recognized the unique plasticity of these cells and wanted to understand how this relates to developmental plasticity. Tying in the DNA regulatory elements, Wysocka's lab is asking how different gene expression can lead to different cell types that originate from the cranial neural crest cells. The importance of this stem cell type is underscored by the numerous human birth defects—almost one-third of these are linked to malfunctions in the neural crest. Because the neural crest is not accessible in the forming embryo, Wysocka's lab painstakingly developed an *in vitro* model that mimics embryonic neural crest development. In 2015, then graduate student, Sara Prescott, and colleagues established that they could recapitulate parts of higher primate embryo development *in vitro* using induced pluripotent stem cells. Searching for enhancer DNA elements in the chimpanzee and human genomes, they found many differences, suggesting the evolution of these regulatory DNA loci from higher apes to humans.

Following on the human genome evolution thread, the lab is also exploring how transposable elements—which make up almost half of the human genome—have facilitated human evolution. "What

is not well appreciated is that the majority of these transposable elements invaded our ancestral genome after the primate lineage separated from other mammals. This means that we can think of them as a source of uniquely primate DNA sequences. We thought that this is fertile ground for exploring how new primate-specific and human specific regulatory mechanisms evolved," says Wysocka. Using their CRISPR DNA-labeling technique, the lab found that specific transposable elements found only in primates could act as enhancers that can control human embryonic genes over long DNA distances.

Immunology Tools

Leonore (Lee) Herzenberg came to Stanford University's Department of Genetics in 1959, as a research assistant to her husband, Leonard (Len) Herzenberg, who was starting his laboratory there. Lee worked alongside her husband in his lab, which grew into their joint laboratory that they ran together for more than 50 years, until Len passed away in 2013.

"I don't remember when I first felt that I was a scientist in my own right. Basically, I just grew into a scientist. I didn't know how to be anyone else," says Herzenberg. In 1981, she received an equivalent to a Doctor of Philosophy degree in immunology from the University Paris V Sorbonne, where Len was doing a sabbatical, and was promoted to professor of genetics at Stanford in 1989.

"At Stanford, I was accepted as a scientist," says Herzenberg. "I was able to essentially do almost all of the things that a faculty member could do. There were projects that Len led and I helped manage and projects that were mine, but that Len helped manage. We basically passed the baton back and forth, depending on whose ideas and whose thoughts made up more of the project at the time," she says. "To us, our science was simply what we lived and did." As a cell geneticist, Len recognized the need to automate the counting, characterization and sorting of rare cells within a population of cells, for example, from blood. He and Lee assembled a team of biologists and engineers to create the first fluorescence-based cell sorter, the Fluorescence Activated Cell Sorter (FACS). Now a broadly used tool in biology and medicine, modern flow cytometry instruments can identify and sort living cells by size and molecular content. In essence, flow cytometry instruments identify cells as they stream first past lasers that "light up" fluorescently labeled cells, then move past detectors that sense the amounts of fluorescent labels bound by each cell, and finally pass by stream-steering electrodes that sort cells expressing pre-selected combinations of fluorescent labels.

Leonore "Lee" A. Herzenberg, PhD
Professor of Genetics

While Len worked more with the engineers tasked with developing the FACS hardware technology for identification and sorting of desired cells, Lee focused on functional studies with FACS-sorted cells and on the development of the software tools used to analyze FACS data.

"Very early on, I learned to program computers. Leonard never did take to computers, but I found that programming was fun," says Herzenberg. "When the Beckman Center was built," she recalls, "there were arguments about whether to increase costs by building computer wires into the walls. It was a new idea, but ultimately, we won. In fact, as far as I know, Beckman Center was the first building on campus to have in-wall data transfer wires to connect the computers in the basement to data users on the upper floors. The building's designers thought we were crazy, but the labs thanked us for years thereafter."

Len and Lee Herzenberg were also involved early on in the development and distribution of fluorescent-labeled monoclonal antibodies for biomedical purposes. César Milstein in Cambridge, England, succeeded in fusing an antibody-producing tumor cell with a normal antibody-producing cell, creating an indefinitely surviving, antibody-producing cell line. This technology enabled long-term production and broad distribution fluorescent-labeled monoclonal antibodies, such as those now commercially available for FACS clinical and research studies. Len had foreseen this use of monoclonal antibodies and had arranged for a year-long sabbatical with Milstein. Len and Lee worked as a team in Cambridge, and then brought the technology back with them to Stanford. There was no simple name for these "hybridized" antibody-producing cell lines until, at a party celebrating New Year's Eve with Cesar Milstein in Cambridge, Lee suggested the name 'hybridoma' and the name stuck.

Herzenberg now still works on the basic questions that she and her husband asked when they set up their laboratory: what are the ways immune cells develop and how do they regulate gene expression? And she still loves working with her computer colleagues to develop and distribute software, including "CytoGenie" which provides new and easier ways to find subsets of cells within FACS data.

Unpacking Parkinson's

Suzanne Pfeffer joined Stanford University's faculty in 1986 and remembers well the planning and deliberations that went into building the Beckman Center. "There was a lot of discussion of how to design the building to maximize interaction between all researchers," Pfeffer recalls.

Part of the Beckman Center ever since, her lab studies how human cells transport receptors to the correct cellular compartments. "Very few labs study receptor trafficking and there are still many fundamental mysteries about this process," says Pfeffer. She takes full advantage of the Beckman Center, collaborating with Rajat Rohatgi's neighboring lab on signal transduction pathways and with Pehr Harbury's protein structure laboratory. Four years ago, she began an international collaboration with labs in the United Kingdom and Germany. Biochemists

Suzanne Pfeffer joined Stanford University's faculty in 1986. "There was a lot of discussion of how to design the Beckman Center, so that the faculty and students would interact well and collaborate," Pfeffer recalls.

Suzanne Pfeffer, PhD
Professor of Biochemistry

Dario Alessi of the University of Dundee and Matthias Mann of the Max Planck Institute told her that a protein they were working on, leucine rich repeat kinase 2 (LRRK2), which is mutated in some forms of inherited Parkinson's disease, chemically modifies several Rab GTPases, small proteins that Pfeffer's lab studies. Now, Pfeffer, Alessi and Mann are working together to figure out how LRRK2 affects these GTPases, which Pfeffer previously found, direct the shuttling of membrane proteins to their appropriate spot in the cell. In the patients who have LRRK2-mutated, inherited Parkinson's disease, the protein, a kinase, is constantly active and inappropriately modifies a subset of GTPases. "Studying how LRRK2 changes Rab protein function is giving us important clues into what may cause Parkinson's disease in patients with these mutations," says Pfeffer. Recently, the laboratories have made inroads into just how the action of pathogenic LRRK2 may trigger Parkinson's disease.

Parkinson's disease is associated with loss of dopamine-producing neurons in the brain. In a healthy brain, when this type of neuron is stressed, it sends a signal to another region of the brain that in turn, sends back protective factors so that dopamine neurons can continue to thrive. "We think that in LRRK2 mutant brains, a specific subset of cholinergic neurons loses their ability to receive these important stress signals and therefore fail to trigger neural protection for the dopamine neurons," Pfeffer explains. The neuroprotection might be necessary in the aging brain as part of the pathology of Parkinson's disease. Now, the teams are continuing their collaboration to provide additional evidence of how the disruption of cell signaling in the brain may lead to Parkinson's disease.

Says Pfeffer, "We started studying the basic roles of how these GTPases work in normal cells and now we are able to apply everything that we have learned to understand the molecular basis of a human disease that afflicts more than 1 million people in the U.S. alone. This is exactly what Paul Berg had in mind when he established the Beckman Center. Our success demonstrates the importance of studying fundamental cell biology and biochemistry because such knowledge has important consequences for our understanding the underlying cause of all diseases."

Ribosomes, Front and Center

Once Maria Barna discovered laboratory research as an undergraduate, she fell hard. "I became bitten by the science questions of the virology laboratory I worked in as an undergraduate and was very productive. I didn't want to leave the

Maria Barna, PhD
Assistant Professor of Developmental Biology and Genetics

lab. It became a lot of effort for me to even be able to walk home at night. I was so excited by what was happening, I couldn't wait to get back to it the next day," she says.

As a graduate student at the Sloan Kettering Institute in New York City, Barna was interested in tissue patterning and how cells in an embryo acquire complex forms and structures, such as an exquisite array of skeletal element of a precise shape and size. It was also a moment in which her former mentor, Lee Niswander, had started some of the first large scale mouse mutagenesis screens.

Foregoing a traditional postdoctoral fellowship, Barna became an independent researcher at the University of California, San Francisco through the Sandler Fellow program—intended for young scientists to pursue big and bold scientific questions. Inspired by her interest in tissue patterning and using mouse forward genetics to map unsuspecting gene products, she characterized a spontaneous mutant mouse that was first identified in the 1940s that had profound changes to its body plan so that the skeletal structures were jumbled up in the wrong spots—an extra set of ribs in the neck, for example, and nobody knew why. In 2011, she and her colleagues mapped the gene mutation, and discovered that it was a rather mundane one—in a so-called housekeeping gene encoding a core ribosome protein. A single cell can contain as many as 10 million ribosomes—the protein plus RNA machines in the cell responsible for decoding messenger RNAs to synthesizing proteins.

"I was obsessed with trying to understand how this seemingly boring ribosomal protein could be functioning to control the formation of the mammalian body plan," says Barna. "For decades, the thought was that although these are among life's most important machines, ribosomes are just backstage participants in gene regulation."

The prevalent view of ribosomes is that they are all the same and that although every crevice of a cell's cytoplasm is filled with them, that they are passive machines, picking up and reading any messenger RNA to translate them into proteins. Barna's research is turning that view on its head.

In 2017, Barna's lab analyzed 15 ribosomal proteins in mouse embryonic stem cells, and showed that ribosomes are heterogeneous, with distinct subpopulations of ribosomes in a single cell. To do the analysis, the team had to employ a new tool sensitive enough to pick up slight differences in ribosomal makeup. The technique, called selected reaction monitoring, uses mass spectrometry to sort molecules by their weight and allows the lab to identify different flavors of ribosomes.

The work so far suggests that distinct populations of ribosomes are dedicated to transcribing metabolic messenger RNAs, RNAs that function in cell signaling, and other categories. The results are adding an additional layer of the genetic code that has previously been hidden from view. "Our

"Stanford and the Beckman Center is probably the only place in the world where we can do this research," says Barna. "Everyone is extremely interactive."

results are hinting that there is regulation that is encoded in our genetic template that endows transcripts the ability to be translated by specific types of customized ribosome," says Barna.

The unexpected finding has spawned many new questions for Barna. Are there specific subcellular spaces dedicated to certain species of ribosomes? How is this ribosomal heterogeneity established? How did the distinct differences ribosomes evolve and what does that mean for species-specific differences in ribosome function? Does the presence of one ribosome species influence the characteristic of the proteome of a species?

Barna's latest data suggests that the way messenger RNAs get sorted to find their way to their appropriate ribosomal population is the way the RNA is folded. RNAs can form elaborate structures and the lab is now developing learning algorithms to try to detangle the RNA structure code. Like comparing a DNA or RNA sequence to a library of sequences to find a match, Barna's lab is trying to decode RNA secondary structure to find groups of RNAs with the same structure that might be translated by the same ribosomal population. "I think this is the missing link in that the instructions for these RNA structures are embedded in the transcripts and we just haven't seen them before," she says.

Barna's lab brings together many biology disciplines from biochemistry to developmental biology to informatics and uses a diverse set of model organisms to study the heterogeneity of ribosomes. "Stanford and the Beckman Center are probably the only places in the world where we can do this research. It's very easy to pick a direction by thinking creatively of what the problem is and finding expertise somewhere on campus. We can move our research quickly into directions whereas in other places this would be daunting. Everyone is extremely interactive. The students and postdocs drive the projects forward and start new ones which has been revolutionary for my science."

Old Disease, New Insights

One of the main research questions in Yueh-hsiu Chien's laboratory is the role that gamma delta (γδ) T cells play in host immune defense. These cells make up a relatively small proportion of T cells in the peripheral blood and express T cell receptors made up of gamma and delta chains rather than the more common alpha and beta chains of the T cell receptors found on $CD4^+$ helper and $CD8^+$ cytotoxic T cells. Research in Chien's lab has revealed several groundbreaking discoveries about these cells including that gamma delta T cells and alpha beta T cells are distinct in their antigen recognition and antigen-specific repertoire and also in activation requirements and effector-function development. These features allow gamma delta T cells to occupy unique niches both in space and time and initiate and regulate inflammatory responses.

Recently, the lab has begun to study the many components of the human immune system as a whole using a systems biology approach. Specifically, the lab is studying the immune system's response to a latent *Mycobacterium tuberculosis* (Mtb) infection. Tuberculosis is among the oldest and

most studied human diseases, affecting about one-fifth of the global population. Most infections with Mtb are clinically asymptomatic known as a latent infection. Fewer than 10% of the infected individuals eventually progress to an active tuberculosis disease state, which is the leading cause of death from infectious disease worldwide. Yet it's not known how the immune system of the vast majority of those infected people keeps the Mtb in check. And despite intense research efforts, how the immune system responds to a latent tuberculosis infection is not understood. Without this knowledge, the tried efforts to prevent a latent infection from advancing to active disease have so far not been successful.

"We are trying to understand how the immune system controls a latent tuberculosis infection," says Chien. Her lab has recently revealed some of the immune system changes that occur in those with

Yueh-hsiu Chien, PhD
Professor of Microbiology and Immunology

dormant Mtb by analyzing blood samples from a cohort of South African adolescents, some of who had a latent Mtb infection and some that were not infected. Rather than focusing on just certain aspect of the immune system, the team used high-dimensional mass cytometry to cast a wide net over the many types of immune cells and identified distinct host immune states that distinguish individuals with a latent Mtb infection from those control individuals without an infection. The work was a collaboration with Dr. Thomas Scriba of the South African Tuberculosis Vaccine Initiative and his colleagues. Their analysis revealed that a latent infection results in systemic inflammation along with significant reduction of the levels of naive B cells and impaired ability for T cells to respond to stimulation. This state of immune deviation was coupled with an enhanced antibody mediated cytotoxic response that is mediated mostly by immune cells known as natural killer cells, suggesting that a latent Mtb infection is associated with a major mechanism of protective immunity.

Collaborating with Stanford's Purvesh Khatri, an associate professor of biomedical informatics and immunology to analyze publicly available gene expression data sets, the researchers found increased levels of circulating natural killer cells as a common factor, irrespective of the age, genetic background and geographic location of the individuals. The natural killer cell levels in those with an active tuberculosis infection fell below the levels of those in uninfected individuals and returned to baseline levels of uninfected controls upon successful treatment. And, the peripheral natural killer cell levels at the time of a tuberculosis diagnosis was inversely associated with clinical parameters indicative of disease severity the team found.

"These analyses offer critical insights into the underlying pathophysiology in tuberculosis progression and the factors

that control and influence disease outcomes," says Chien. "The results will be useful for generating hypotheses that could lead to new intervention strategies to prevent the switch," she adds.

Science as Form of Rebellion

Lingyin Li, an assistant professor in the biochemistry department, joined the faculty at Stanford in 2015. Li grew up in Xi'an, China, an ancient capital city of China where many of the Chinese dynasties lived. Li was fascinated by her surrounding history and Chinese literature. But her attention quickly pivoted to chemistry and math when her sixth-grade math teacher said that literature and history are subjects for girls and math is for boys; she was set on proving him wrong. Following a PhD in chemical biology from the University of Wisconsin-Madison, Li focused her chemistry training on cancer immunology, including showing that certain metabolites of plants and fungi known as flavonoids could act as stimulators of an important immune pathway known as STING (stimulator of interferon genes). At the Beckman Center, Li is homing in on the chemical biology of innate immunity to understand how to use the naturally made defense molecules in the body to develop potential cancer, autoimmune disease and neurodegenerative disorder therapies.

Lingyin Li, PhD
Assistant Professor of Biochemistry

Full Circle

In a given living cell, there are magnitudes more types of RNA species than there are genes. Julia Salzman, assistant professor in the biochemistry and biomedical data science department is exploring why that is. Her lab uses both computational and molecular biological tools that allow the team to study RNA—and DNA —at the single nucleotide level in species that range from single-cell bacteria to humans. Her lab has developed statistical algorithms to precisely detect circular RNA. More recently, the lab has developed newer, more precise methods for detecting RNAs specifically expressed in cancer and other diseases, producing both new insights for gene function in cancer and new diagnostic tools for cancer genomics, including those that could be used in liquid biopsies to detect minute amounts of cancer cell-specific DNA in the blood.

Previously thought to be rare, Salzman's lab has found that circular RNA species are surprisingly abundant in human cells. Salzman and her colleagues sequenced the breadth of RNA species in both wild type and malignant human cells and found that these RNA circles are as abundant as their linear counterparts, suggesting that the circles are the rule rather than the exception in mammalian cells. The team scanned RNA molecules for those where the nucleic acid sequences were scrambled, that is, were in a different order compared to the corresponding DNA sequence of the gene. The lab has since been studying how these circular RNAs

Julia Salzman, PhD
Assistant Professor of Biochemistry and of Biomedical Data Science

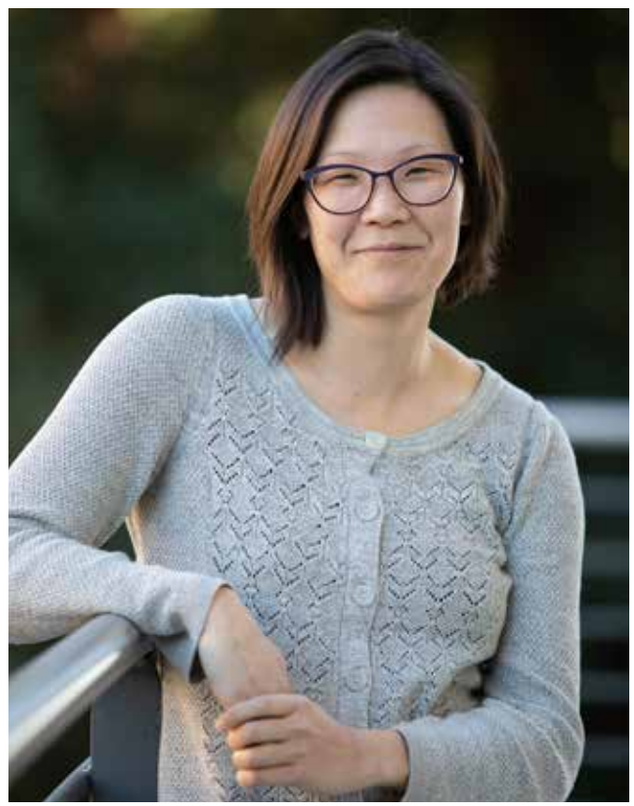
form *in vivo* and their biological functions. More recently, Salzman's lab found that circular DNA is not just a feature of mammalian cells, but are expressed across all eukaryotes tested, suggesting that the molecules are an evolutionary conserved part of gene expression.

Malaria's Achilles' Heel

Ellen Yeh, assistant professor in the Department of Biochemistry, first started working with *Plasmodium falciparum*, the parasite that causes malaria, as a postdoctoral fellow at the University of California, San Francisco (UCSF). Malaria is a major burden of infectious disease around the world, with more than 300 million cases per year and among the top three potentially lethal infectious diseases globally.

Yeh focused on the parasite's apicoplast, a unique and essential four-membrane organelle that was discovered in the 1990s. The organelle was acquired by parasites ancestral to *P. falciparum*: the ancient parasite got a two-for-one deal when it 'ate' an eukaryotic alga. That alga, it turned out, already possessed a plastid through the endosymbiosis of a free-living prokaryote, a cyanobacterium. Unlike plant plastids, the apicoplast had lost its ability to do photosynthesis and instead performed other essential functions in the parasite including protein synthesis. For Yeh and other researchers, the apicoplast was a good target for anti-malarial drugs. Because of its plant origins, some of the apicoplast processes and molecules might be unique to plants and targeting these would not harm human host cells. Yet, the function of the apicoplast during human infection had eluded researchers.

In 2011, at Joseph DeRisi's UCSF lab, Yeh showed that the essential role of the apicoplast during the human infection stage is to produce one metabolite, isopentenyl pyrophosphate (IPP), a precursor molecule to several molecules



Ellen Yeh, MD, PhD
Assistant Professor of Biochemistry, of Pathology, and of Microbiology and Immunology

essential for the parasite's ability to replicate in human red blood cells. At Yeh's own lab at Stanford, she used this finding as a starting point to identify multiple steps in this process that can be blocked by drugs and is working as part of the Stanford AIM with Takeda Pharmaceuticals to develop these into anti-malarial compounds. Yeh's lab is also not stopping at IPP; they are finding ways to disrupt the entire apicoplast irreversibly. The lab executed a mutagenesis screen to uncover essential genes required for making new apicoplasts and found several novel enzymes as promising drug targets.

Exciting Membranes

"I have always loved chemistry because it is tractable and because you can solve chemistry problems in a clear and quantitative way," says Merritt Maduke.

Yet, it was the biology questions that drew her into research. She has been using chemistry to pursue biological questions ever since. In graduate school, Maduke studied the physical and chemical basis of how proteins are imported from the nucleus into the mitochondrion, a membrane-enveloped organelle. She constructed artificial membranes without any protein receptors found intertwined within them and showed that the unique negative potential of the mitochondrial membrane can drive positively-charged helices-containing proteins right through the membrane to the inside of the mitochondria. The work demonstrated that a driving force, rather than energy-expending cargo-based import can be sufficient for charged peptides to traverse an organelle membrane.

Continuing the theme of applying biophysical and chemical properties to a biological system, Maduke focused on ion channels as a postdoctoral fellow in Christopher Miller's laboratory at Brandeis University in Boston. "I discovered that ion channels were, in 1995, a way to study a macromolecule at a single molecule level. We could look at an ion channel with ions opening and closing, and ions moving in and out very quickly. I found this to be completely fascinating," says Maduke. Potassium channels had recently been found in bacterial cells and Maduke wondered whether the one-celled organisms also contained chloride channels. She cloned what looked to be a chloride channel in *Escherichia coli*, purified the ion channel and added them to an artificial membrane. "It was amazing to see the first signal that told me this protein could shuttle chloride ions across this membrane. It seems so mundane now, but it was so exciting then," she says.

For Maduke, unlike the difficulty of choosing a graduate school and postdoctoral laboratory, choosing to come to Stanford University, as a faculty member

Merritt Maduke, PhD
Associate Professor of Molecular and Cellular Physiology

was an easy decision. “The students here are so fantastic. I love the naive curiosity they bring to our research questions and their innovative ideas.”

She also loves the collaborative spirit of Stanford and the Beckman Center. “I was walking to get coffee one day and Stanford’s William Newsome, a neurobiologist, approached with a question.” Newsome had read recently published papers that showed ultrasound could be used to activate neurons in the brain and wanted to understand the mechanism of how this happened. “‘I have no idea how this could be working but I know how I would approach the problem’, I told him.” Maduke told him that she would first want to pare down the question and ask what ultrasound does to an ion channel—the fundamental unit of excitability in the brain. The question turned into a collaboration among Maduke, Newsome, and other Stanford professors including Stephen Baccus, who studies the circuitry of the retina, and radiology researcher Kim Butts Pauly. Each lab tackles a different angle of the question. “It has been incredible to work with this team for the last 8 years within this still young field. We find results on the molecular and cellular level and then the other groups apply that to a whole organ and whole animal level,” says Maduke.

Their initial result was surprising. Using the synthetic lipid bilayer system that Maduke had developed, the lab showed that when ultrasound radiation is applied to membranes themselves, without any ion channels, the membrane responds with an electrical current, likely as a result of the ultrasound radiation pressure pushing on the membrane. The lab also demonstrated that a mechanically-activated, but not a sodium channel was activated with ultrasound stimulation. The lab is now testing these effects in native tissue—brain slices with neurons that have multiple types of ion and mechanically sensitive channels. “What we’re working towards is a unified theory to explain all of the effects of ultrasound at these different biological levels. Then, we can develop ultrasound better as an experiment and therapeutic tool,” she says.

The Hazards of Motion

The long, spindly sensory neurons in the skin have the endless task of helping us sense the world through touch. Yet, how petting a dog or sensing running water from the faucet on our hands is registered by these neurons mostly unknown. Added to this complexity is the need for these neurons to move and stretch along with the skin and remain intact. Miriam Goodman is striving to understand just how these neurons can take on these never-stopping stresses—using the nematode *Caenorhabditis elegans*, a 1-millimeter worm. Recently, a postdoctoral fellow in the lab, Michael Krieg, who is now a professor at the ICFO Institute of Photonic Sciences in Barcelona, Spain, uncovered mutants in cytoskeleton proteins that results in neurons that crinkle,

Miriam Goodman, PhD
Professor of Molecular and Cellular Physiology

Besides her scientific accomplishments, Goodman is shining a spotlight on the underrepresentation of women and minorities in science and on gender research.

fracture, and stretch, resulting in neurons that over time, are beyond repair. One of the mutated proteins was spectrin, which forms cylinder-shaped scaffolds on the inside of a cell's plasma membrane. The protein, according to Goodman, has been implicated in brain and heart function and is important for helping red blood cells keep their shape. When the spectrin mutation is combined with a mutation in tau—a protein found in the brain and that has been linked to Alzheimer's disease—the neurons, instead of crinkling, form tiny coils as a result of mechanical tension, twisting, and bending. To explain how these proteins are affecting the physical properties of the long sensory neurons in *C. elegans*, Goodman collaborated with a computer science lab in Munich, Germany to develop a computational model that could predict the shape defects based on modifications in physical properties. "In the mutants, instead of the neurons lying flat, you get these strange shapes because there is no longer a balance when the neurons are forced to move along with the tiny worm," she explains. Now, Goodman's lab is identifying additional proteins in the cytoskeleton that help the neurons keep their shape in the face of mechanical movement and stress.

To better study the forces that cells and cellular components experience as the worm moves, Goodman's lab is also collaborating with Jennifer Dionne's material sciences laboratory which is also at Stanford University, developing nanoparticles that can go inside the animal and measure these microscopic-scale forces, by emitting different forms of light that correspond to different mechanical forces.

One of Goodman's favorite features of the Beckman Center? The ability to try out what she calls her "crazy ideas." I've had lots of ideas where I want to try something new and need access to a piece of equipment I don't have in the lab. Every time I reach out to someone to use their equipment for a pilot study, no one has ever not responded, and no one has ever said no. Almost none of these crazy ideas have turned into anything, but the freedom to try without these other social barriers is really invaluable."

Besides her scientific accomplishments, Goodman is also shining a spotlight on the underrepresentation of women and minorities in science and on gender research. She spent a year as a faculty fellow at Stanford's Clayman Institute for Gender Research studying gender inequality in science. Building on that experience, Goodman, along with neurobiology professor Jennifer Raymond, started a social sciences journal for students and postdocs to discuss studies on the underrepresentation of women in different fields. "What surprised me most about the discussions, which I thought might be depressing, is how energized the students were by having these conversations! We had fantastic discussions on what the research says, what does that mean about how our brains work and what does that mean about how science works?" says Goodman.

Goodman's energy to create open dialog on gender inequality issues in science appears to have no bounds. Following on from the journal club, for the last three years, Goodman has been running a mini-course called 'Diversity and Inclusion in Science' for graduate students and

postdocs. Goodman says that students are now much more aware of gender inequality issues and that the course is enabling students to, "gather evidence so that they can make arguments based on evidence that some things need to change and for them to take action to improve conditions, diversity and inclusion."

A team of graduate students who took the course came up with a new mentorship program called Solidarity, Leadership, Inclusion, Diversity (SoLID), that provides an additional faculty mentor for graduate students on issues besides their research such as advocacy, diversity and inclusion, academic activism, mental health and wellness, balancing social justice work and lab productivity, stereotypes and imposter syndrome. "The students built this program entirely themselves, recruited faculty across our graduate programs who were open to holding office hours once a month. The germ of the idea was in my classroom and I am extremely proud of that and the students that built it," says Goodman.

Thinking in 3D

In 1967, Lucy Shapiro was a newly minted assistant professor in the department of molecular biology at the Albert Einstein College of Medicine in New York. The chair of the department, Bernard Horecker, told her that she could work on whatever she liked. "This was amazing," says Shapiro. "I realized that I was clearly going to spend the rest of my life doing whatever I chose and that it had to be something that I deemed important." Shapiro took three months to read, think and formulate a plan. "I sat down and wrote out what I wanted to do in some detail based on my view of the biochemistry of the cell," she says. At the time, researchers were either bursting open cells to get to their enzymes which they then characterized biochemically in the lab, separate from the intact cell. Or, researchers were using genetics and observing mutants to infer what happens inside of a cell. "I saw both approaches as beautiful, but limited. Everyone seemed to be studying cell regulation outside of the spatial parameters of the cell but how does the cell inherit the information that tells it where to place everything in the cell? To me, the cell had to be considered as a three-dimensional entity. I also wanted to understand how all of these events in the cell were coordinated. In essence, how is the cell an effective machine? I visualized the cell as an integrated system and my goal was to go all the way from the chromosomes to the proteins that are made in three-dimensional space, to do essentially what I called *in vivo* biochemistry," says Shapiro.

For such a complicated task, Shapiro needed a relatively simple model organism, and one that had polarity and an asymmetrical cell division in which the

Lucy Shapiro, PhD
Professor of Developmental Biology and Beckman Center Director

mother and daughter cells were distinct from one another. This type of asymmetric division, as Shapiro saw it, is an essential event that generates diversity in cells, organs and organisms. "My plan was to study this model organism by including the three-dimensional organization of the cell as a function of regulatory mechanisms that result in the integrated genetic circuitry that makes a living cell run," Shapiro says.

Although she had no microbiology experience, after a lot of reading, Shapiro settled on the *Caulobacter crescentus*, a stalked bacterium that had all of the characteristics she had been looking for. Although researchers had figured out how to synchronize *Caulobacter* populations, there was no genetics or biochemistry worked out for her seemingly simple one-celled organism. Her colleagues and former advisors attempted to dissuade her, but Shapiro stayed her course, and has been using *Caulobacter* ever since, to learn how the cell distributes organelles and molecules in a polar way and how the various processes of the cell, such as DNA replication function as part of the larger integrated and three-dimensional network of the cell.

In 1996, while looking for mutant *Caulobacter* cells that prevented the formation of flagellum, an appendage that allows the bacterium to swim, Shapiro's graduate student, Kim Quon, made a discovery that, 30 years prior, Shapiro had envisioned when she set her lab's researchers goals. Quon found CtrA, a master transcription factor that controls many of the genes necessary to coordinate *Caulobacter*'s cell cycle. "We had this big 'ah-ha' moment in the lab when we found the promoter sequence recognized by this transcription factor and that the chemoreceptor genes, flagellar genes, DNA replication genes and many others all had promoters that harbored this sequence for CtrA to bind to. We realized that this single transcription factor was controlling a whole array of genes that were dynamically controlled throughout the cell cycle," Shapiro explains.

Soon after moving to Stanford, graduate student Mike Laub (now a professor at the Massachusetts Institute of Technology) and Shapiro showed that the simple bacterial cell has a hard-wired genetic circuitry by which hundreds of genes are turned on and off as a function of cell cycle progression. The study was among the first evidence showing that bacterial cells have regulatory circuitry that functions in time and space to coordinate the multiple, complicated events that drive the cell cycle.

Still paving the way and identifying novelties about the living cell, Shapiro's lab, more recently, showed a new way that prokaryotic cells organize their functions using membranelles organelles made up of bimolecular condensates that concentrate signaling proteins at the cell poles providing directionality to their signaling output. Her lab has also developed tools to study the three-dimensional structures inside the cell, which is enabling the study of protein interactions inside living cells.

Shapiro moved her laboratory to Stanford University in 1989, becoming the founding chair of the Department of Developmental Biology. In 2001, she became the director of the Beckman Center for Molecular and Genetic Medicine. Shapiro has had a steady confidence that has served her well in her career. Shapiro, for whom mentoring is an extremely important part of her job, believes that it is her duty to instill confidence and self-assurance into her well-deserved science trainees and to help ensure their future success. ■

Technology Innovation

Three Decades of Technology Innovation at the Beckman Center

BY ASHLEY P. TAYLOR

Since the founding in 1989 of the Beckman Center for Molecular and Genetic Medicine, scientists and engineers have developed a wealth of technologies for learning about how life works at the levels of cells, molecules and genes. Scientists have figured out how to turn back the developmental clocks of ordinary, differentiated cells so that they can, like the cells in an embryo, differentiate into many different cell types. Scientists have sequenced the human genome, as well as the genomes of hundreds of other animals, not to mention those of plants, fungi and microorganisms. Now, whole-genome sequencing occurs on the level of individual patients. With the rise of the internet have come bioinformatics databases for analyzing genomic data. Beyond observing genomes, scientists have learned to edit them at precise locations using a technology called CRISPR. The list of recent developments in biotechnology could go on and on.

Many such groundbreaking technologies were developed at the Stanford Beckman Center. Ron Davis, PhD, professor of biochemistry and of genetics and director of the Stanford Genome Technology Center, and emeritus professor of biochemistry Patrick "Pat" Brown, MD, PhD, were instrumental in developing and first applying the microarray, which revolutionized molecular biology by allowing researchers to simultaneously examine the activity of thousands of genes. Also, in the 1990s, the Douglass M. and Nola Leishman Professor of Cardiovascular Disease and professor of biochemistry James "Jim" Spudich, PhD, developed a system for watching the interactions of purified muscle proteins and measuring the forces involved. In that effort, he collaborated with William R. Kenan, Jr., professor of physics and professor of molecular and cellular physiology, Steven "Steve" Chu, PhD. Chu is now developing novel optical probes to label tiny subcellular structures so that scientists can better observe them and thus learn more about how they work. Using protein engineering, professor of molecular and cellular physiology Chris Garcia, PhD, is developing new molecules, which he believes have great potential as drugs, that bind to receptors on the surfaces of cells and affect activity within. Associate professor of developmental biology, of computer science, of pediatrics and of biomedical data science Gill Bejerano, PhD, has developed computational tools to help researchers better understand the human

Patrick Brown, MD, PhD
Emeritus Professor of Biochemistry

genome and to aid clinicians in diagnosing genetic diseases. And associate professor of biochemistry and, by courtesy, of physics Rhiju Das, PhD, has developed online videogames that recruit citizen scientists to help figure out how RNAs fold, knowledge Das is using to design RNAs for diagnostics and therapeutics.

The Microarray: A Tool for Comparing Gene-Expression Patterns and More

The genesis story of the microarray begins in the early 1990s with two professors in the Department of Biochemistry, Ron Davis and Pat Brown, as well as Stephen Fodor, PhD, who was then working at a company called Affymax in Palo Alto. Today, all three scientists have won awards for their contributions to microarray technology, among other achievements. Affymetrix, the microarray company that Fodor founded in 1993 and which ThermoFisher Scientific acquired in 2016, became one of the major commercial suppliers of microarrays. But the technology that would later be called revolutionary was at first met with resistance. Brown's involvement, for example, started with a rejected grant application.

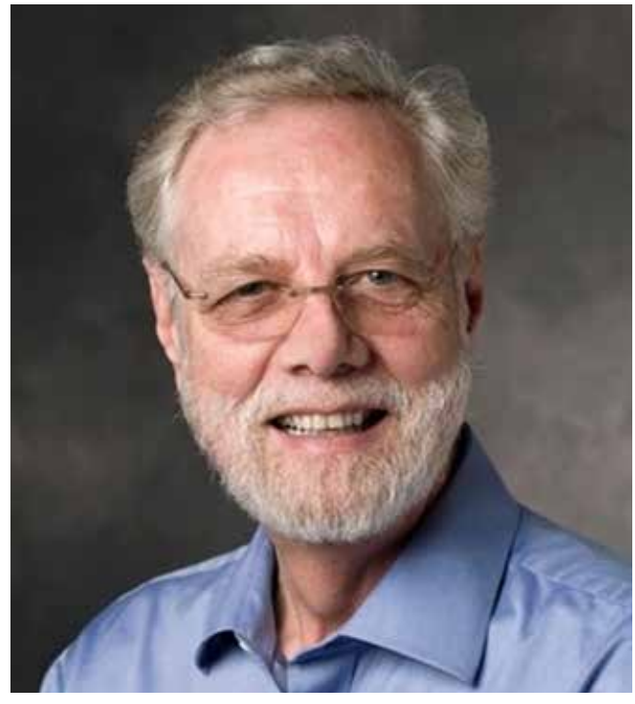
In 1992, Brown applied for federal funding to develop the microarray and for another unrelated project. The grant proposal was not well received. "It got the worst priority score I'd ever gotten or ever seen," says Brown. The National Institutes of Health (NIH) suggested Brown cut the microarray stuff and resubmit the proposal. Ignoring the NIH's advice, he developed the microarray anyway.

"What people didn't like about it was, it just seemed insanely ambitious, and they just didn't believe that it was practical, which they were wrong about," says Brown.

The DNA microarray, which is now a standard part of the molecular biology toolkit, is a way of comparing gene activity in two groups of cells. Specifically, what researchers compare on a microarray are the RNAs present in the two cell groups: both their identities—which genes they come from—and their quantities. Since RNAs are produced from genes and made into proteins, they can essentially serve as proxies for both gene and protein activity. What's exciting about microarrays is that they allow researchers to do this gene-expression comparison not just for one gene, but for thousands of genes, at the same time.

The classic image of a microarray is a grid of red and green dots. Each dot represents a gene, and the color of the dot indicates the relative expression of that gene in two different cell types. But this image represents a finished experiment.

The first step is to generate the microarray itself by attaching small segments of DNA to a substrate. Brown did this by building a robot that would drop tiny samples of DNA from tens, hundreds or thousands of genes onto a glass slide. Davis started out trying to print DNA spots on nylon, but as the nylon was unstable, he joined



Ron Davis, PhD
Professor of Biochemistry and of Genetics

Pat Brown and Ron Davis were instrumental in developing and first applying the microarray, which revolutionized molecular biology by allowing researchers to simultaneously examine the activity of thousands of genes.

Brown in working with arrays spotted on glass. Davis also collaborated with Fodor and others at Affymetrix on experiments in which the array DNA was synthesized directly onto the slide. Next, researchers isolate RNA from the two cell types they want to compare, convert it to fluorescently labeled DNA—red for one cell type, green for the other—and expose the microarray to the two labeled samples. Analyzing the fluorescence reveals the results: if a dot is mostly red or mostly green then the gene in question produces RNA at different levels—or is differentially expressed—between the two cell types. Differential gene expression could potentially explain how the two cell groups are phenotypically different, such as why one group is healthy and the other diseased.

Both Brown and Davis originally envisioned using microarrays for other purposes, but gene-expression analysis is the application for which microarrays are known. In their first paper published about microarray experiments, in 1995, Davis and Brown used Brown's spotted arrays and RNA samples from Davis' lab to compare the expression of 45 genes between the roots and leaves of the small flowering plant and model organism *Arabidopsis thaliana*. The paper illustrated how microarrays could be used and, in its conclusion, laid out the microarray's potential for studying gene expression in different human cell types and for detecting disease-associated gene-expression patterns that could be used for diagnosis. In myriad papers that followed, Davis, Brown and others used microarrays to do just that.

In 1996, Brown and Davis reported using spotted microarrays to analyze changes in gene expression that occurred in human T cells in response to two different experimental treatments: heat shock—exposing the cells to higher temperatures—and treatment with phorbol ester, which sets off a molecular signaling cascade. The first microarray experiment done on human tissue, this was, "groundbreaking," says Davis. The experiment was also significant because the genes on the array were of unknown function, and through this experiment, the researchers deduced something about what the differentially expressed genes did—that certain number of them were involved in responding to heat shock, for instance.

The following year, Brown and Davis published the results of the first ever genome-wide microarray experiment, which was in yeast. The experiment didn't include every gene in the yeast genome, but future experiments would. There are now microarrays that cover the entire human genome.

In 1998, Brown published a paper, which has now been cited more than 17,000 times, according to Google scholar, reporting that in general, genes with similar functions tend to be expressed together—that is, at the same time and under similar conditions. Knowing this could help scientists deduce the functions of uncharacterized genes, Brown and coauthors explained. Grouping genes with similar expression patterns and functions, which is called one cluster analysis, also just gave researchers a broad-strokes view of cellular activity—here are the genes involved in cell-division; another cluster are the genes involved in making proteins—that wasn't possible through examination of individual genes. "A very

large body of systematic data is worth way more than the sum of the parts," says Brown. "Because by having the systematic data, you can really see the underlying logic in a way that you can't just with occasional snapshots."

Microarrays can be used to study how a particular process, such as sporulation in yeast, or a regulatory molecule, such as a hormone, changes gene expression. They can also be repeated over time, comparing a sample undergoing some change, such as heat shock or progression through the cell cycle, to a control sample not undergoing that change. Brown, Davis or at times both researchers, did experiments to examine all of the above.

Starting in the late 1990s, Davis began to have doubts about the accuracy of spotted arrays. It was easy to make a mistake about which DNA sample you had put in each position, Davis says. For that reason, while Brown continued to use spotted arrays, Davis pursued experiments with Affymetrix arrays. One such project involved exploring the functions of each of the yeast genome's approximately 6,000 genes.

As reported in 2002, Davis led a consortium of researchers in creating a library of yeast strains, covering the entire yeast genome, in which one gene had been deleted and replaced with two different DNA sequences, called molecular barcodes, to identify the strain. In a typical experiment, Davis would grow the yeast strains under different conditions, such as heat shock, and see how well they coped with those conditions based on how well they grew. How well they grew could be determined by making fluorescently labeled copies of the barcode sequences and hybridizing them to the microarray, which had a spot for every pair of barcodes. To take the heat-shock example, if a particular microarray spot fluoresced less, Davis could infer that the strain had failed to grow well at high temperatures and that the deleted gene must be important for coping with heat shock. Because each strain had an identifying barcode, it was possible to mix together all 6,000 strains in one tube throughout the experiment—quite a feat.

"It would be a typical experiment that a person might do, but it would be done in the past one at a time and you'd have to do 6,000 such experiments. But this allowed you to do one experiment and read out the results for 6,000 genes," says Davis. Experiments using the deletion collection are ongoing.

This experiment illustrates what Davis sees as the overall importance of the microarray: it changed the way biologists approached their research. "Up until microarrays were developed, people were doing things one at a time," says Davis. They might examine the expression of one gene, realize they needed to do the same for another gene or two, and end up doing several experiments one after the next. Microarrays allow researchers to do thousands of experiments at the same time. "I think the biggest impact is teaching people that you could do things in parallel, as opposed to serially," Davis continues. DNA is not the only molecule scientists put on microarrays. There are arrays of proteins, of sugars, of antibodies. In all of these experiments, scientists are doing, in parallel, experiments they might otherwise have done one at a time. That approach to science paved the way for other large-scale experimental

Microarray technology also ushered in the era of precision medicine. "To do precision medicine you need lots of data on an individual, and you have to do it inexpensively or it won't be developed," says Davis.

Microarrays have become a standard way of determining which subtype of cancer a patient has and, accordingly, whether and how to treat it, says Brown.

efforts, such as automated DNA sequencing, Davis adds.

Much microarray work also has medical applications. Microarrays can help scientists doing basic research learn about gene-expression changes that occur in various diseases. They also, Davis says, ushered in the era of precision medicine or tailoring treatments to individual patients. "To do precision medicine you need lots of data on an individual and you have to do it inexpensively or it won't be developed," says Davis. Microarrays were the technology needed to gather those data.

A prime example of the use of microarrays for precision medicine is in the area of cancer diagnostics and treatment planning. Brown's lab, and others, characterized gene-expression patterns in different cancers and, in the process, learned that some cancers previously thought of as being monolithic groups had subtypes that were distinguished by their gene-expression patterns. "By recognizing those subtypes as distinct kinds of tumors, they could be treated differently," says Brown. Microarrays have become a standard way of determining which subtype of cancer a patient has and, accordingly, whether and how to treat it, says Brown.

Davis's work has also had precision-medicine applications. For example, in 2012, Davis contributed to a paper in which microarray analysis was used to identify five genes whose expression in patients' blood cells changed depending on whether or not a kidney transplant was rejected. Further, in a test group of blood samples from transplant patients, expression of these five genes could be used to diagnose transplant rejection.

Davis also collaborated on a project in which scientists identified gene-expression changes in the blood that could distinguish, 12 hours after a trauma, such as a car accident, between patients likely to have a smooth recovery and those likely to go into multiple-organ failure after a few days. As reported in January 2019, this work has led to development of a test that can predict, within 24 hours after a trauma, which patients will have organ dysfunction and other complications in order to better treat them.

The microarray technology developed in the 1990s is now being replaced by DNA sequencing, according to Davis, who says that sequencing is now a more efficient way to do many of the tests for which microarrays were previously employed. "But that's not surprising. That's what happens with technology," says Davis. "It exists for a while and it's replaced. But it had a big impact on the community."

And whether the experiments are done with microarrays, sequencing or other methods, the underlying concept, which originated with microarrays, of simultaneously screening for thousands of different molecules and using the information to learn about biology and human disease is of enduring value, says Davis.

The Dual-Beam Laser Trap: A Tool for Characterizing Molecular Motors

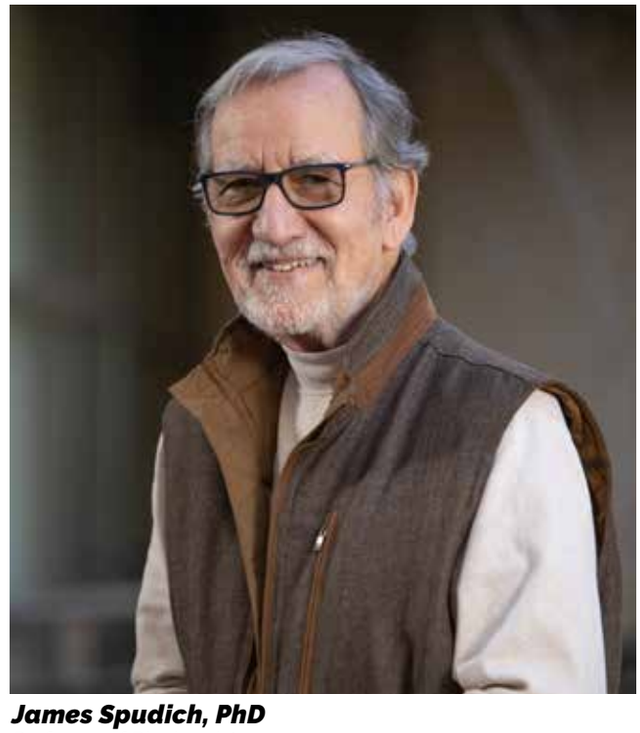
Around the same time that Brown and Davis were developing the microarray, Jim Spudich, then a professor of structural biology, was trying to understand how two essential muscle proteins, actin and myosin, interact to make muscles contract.

Scientists now know, from Spudich's work and that of others, that muscles contract when myosin molecules reach across and attach to actin filaments, pull the actin filaments back by 5 to 10 nanometers, then recock and repeat the cycle, like sailors pulling on a rope in a "heave ho" motion. Each cycle, which moves the actin filament by about one one-hundredth the width of a human hair, is powered by consumption of one molecule of the cellular fuel ATP. This results in muscle contraction because within the functional unit of the muscle, called the sarcomere, there are two sets of myosin molecules, both of which are pulling the actin filaments toward the sarcomere's center, shortening it. Evidence that actin and myosin interact this way was provided by a paper that Spudich and colleagues published in 1994. But in the 1980s, it was just a model.

In the '80s, Spudich and a graduate student, Stephen Kron, MD, PhD, now a professor of molecular genetics and cell biology at the University of Chicago, developed a method for watching purified actin and myosin proteins interact under the microscope. "When you added ATP, these actin filaments moved around on the surface in a directed fashion, being propelled along by something that these myosin molecules were doing to make the actin move," says Spudich. Spudich and Kron also showed that movement required just actin, myosin and ATP; no additional accessory sarcomeric proteins were needed. These experiments, "established that in fact, the model that actin moved along myosin, which was in all the textbooks, was correct," says Spudich.

But there were still open questions. Spudich's data suggested that myosin moved actin by 5 to 10 nanometers when it burned one ATP, but others had data suggesting that myosin moved actin by 100 nanometers or more at a time, which would not be consistent with the model favored by muscle investigators for actin-myosin interactions, that heave-ho motion, called the swinging cross bridge model. "And that's sort of where we were in the late 1980s," says Spudich. "It was clear that somebody was going to have to design a way to watch just one myosin molecule interact with a single actin filament and see how far it moved." That's exactly what, with help from a graduate student, a sabbatical visitor and fellow Stanford faculty member Steve Chu, he was able to do in the early '90s. Just as the endeavor to understand how actin and myosin interact depended on work that Spudich had done in the '80s, so it relied on work that Chu had done during that period, when he was a scientist at Bell Labs in New Jersey.

The idea of holding onto biomolecules grew out of the work that Chu did on how to hold onto atoms in a vacuum with light. The idea had been proposed by Chu's Bell Labs colleague Arthur Ashkin in 1978, but the optical forces that light could exert on atoms was far too feeble to hold onto fast-moving atoms. In 1984, Chu showed that a set of counterpropagating laser beams, which he called, "optical molasses," could be used to slow atoms from the speed of a supersonic



James Spudich, PhD
Professor of Biochemistry

The idea of holding onto biomolecules grew out of the work that Chu did on how to hold onto atoms in a vacuum with dual-beam lasers, for which he won the 1997 Nobel Prize in Physics.

jet plane to that of a scurrying cockroach. At those speeds, the atoms were cooled to less than 0.0001 degree above absolute zero, but once that cold, the atoms were easily trapped. For his laser cooling and atom-trapping work, Chu won the 1997 Nobel Prize in Physics.

The same physics applies to any size particle, but the optical forces are proportional to the volume of the particle. For a micron-sized particle, water at room temperature could substitute for the exotic optical molasses. In the same year atoms were trapped, Ashkin and Chu showed that the optical tweezers could be used to hold onto polystyrene spheres cooled by water. In the following year, Ashkin showed that optical tweezers could be used to trap bacteria and viruses. For the invention and demonstration of optical tweezers for biological applications, Ashkin received the 2018 Nobel Prize in Physics.

In the fall of 1987, Chu moved from Bell Labs to Stanford to join the Departments of Physics and Applied Physics. Biological molecules were too small to be held directly with optical tweezers at room temperature, but Chu reasoned that if a polystyrene sphere could be glued to an individual biomolecule, the laser trap could be used to directly manipulate molecules in aqueous solutions. In 1988, he began to search for someone to teach him enough biochemistry to glue the tiny plastic spheres to a single molecule of DNA and found Kron who was working in the laboratory of Spudich, observing actin filaments moving on a bed of myosin molecules in an optical microscope. While continuing to work full time on his PhD thesis with Spudich, Kron began to moonlight with Chu. By 1989, they showed for the first time that biomolecules could be directly manipulated with optical tweezers.

Independent of this work, Spudich's graduate student Jeffrey Finer, MD, PhD, had become interested in using laser traps to see if they could observe one myosin molecule interacting with a single actin filament. By then, Kron had graduated and ironically, it was Robert Simmons, PhD, a professor from King's College London on sabbatical in Spudich's lab, who pointed out that Chu was working nearby on the second floor of the physics building. In a modification of the laser trap apparatus used to hold onto DNA, Finer and Simmons glued a single bead to each actin filament and tugged on it with optical tweezers, watching under a microscope, as myosin molecules pulled in the other direction. "It's like you're pulling on one end of the rope and then the other person pulls on the other end of the rope to keep the rope stationary," says Chu. In this way, they determined that myosin was exerting a force in the range of 1 to 5 piconewtons—equivalent to 1 to 5 trillionths the force that your average apple exerts under the pull of Earth's gravity—on the actin filament, as they reported in a 1993 paper. Such a force is perhaps too tiny to conceptualize, but the combined forces of many myosin molecules pulling on many actin filaments drive the movements of cells, muscles and animals.

But the second floor of the physics building wasn't the ideal place to watch a single myosin molecule move an actin filament—too many vibrations. "It didn't have the stability we needed to see these 5 to 10 nanometer strokes and furthermore, we

"It was clear, in the late 1980s, that somebody was going to have to design a way to watch just one myosin molecule interact with a single actin filament and see how far it moved," said Spudich.

envisioned building a dual-beam laser system to trap an actin dumbbell that could be lowered onto a pedestal with a single myosin molecule on top," says Spudich.

It was around that time that Spudich, then chairman of Stanford's Department of Structural Biology, was recruited to join the Beckman Center, where Spudich found his ideal lab space for setting up a better microscope. This was a room in the Beckman Center basement: "a very quiet space with very little vibration, which was needed to do this very sensitive experiment. And they allowed me to use that room to build what we call the dual-beam laser trap for measuring one myosin molecule."

In the new setup, Finer and Simmons glued one bead to each end of the actin filament, creating what they call an actin dumbbell. They used two sets of optical tweezers, one at each end of the actin filament, to hold it above a glass slide covered in little bumps sparsely coated with purified myosin molecules. To do the experiment, Spudich says, they used the optical tweezers to lower the actin dumbbell onto the bumps in search of a myosin molecule resting on top. "Most of the bumps didn't have anything, so nothing happened. But if we found a bump that had a myosin molecule on it, then the myosin grabbed onto the actin and pulled on the actin filament. And we could see that because the dumbbell moved," says Spudich.

"What Jeff found was it did not move by a hundred nanometers or more; it moved by somewhere between 5 and 10 nanometers," says Spudich. Finer, Simmons and he had, in 1994, provided decisive evidence in favor of the swinging cross bridge model. The Spudich lab firmly established the model with further studies. In that same experiment, they reported the force generated by a single myosin molecule pulling on actin and using one molecule of ATP, and they found it to be 3 to 4 piconewtons—similar to the force measurement that Spudich, Chu, Finer and Simmons had made previously.

Now, Spudich is studying how problems with cardiac myosin result in hypertrophic cardiomyopathy, a disease in which the heart muscle gets too thick, and single molecule force measurements are essential for these studies. Indeed, since the early studies in the '90s, single molecule biology has exploded into a field of its own, and researchers everywhere are characterizing their favorite biological molecules at the single molecule level. By examining a cellular component one molecule at a time, one can truly ascertain how it works to perform its particular function in the cell, Spudich says. Hence, there are now hundreds of investigators meeting regularly at single molecule biology conferences around the world.

Rare-Earth Nanoprobes: Tools for Labeling and Visualizing Molecules

When Chu was collaborating with Spudich on laser trapping of biological molecules, his affiliation was with the physics and applied physics departments. But when, in 2013, he returned to Stanford from his time as President Obama's secretary of energy, he joined the Beckman Center's Department of Molecular and Cellular Physiology, while also retaining his affiliation with the Department of Physics. Recently,

Steven Chu, PhD
Professor of Molecular and Cellular Physiology and of Physics

he has been greatly improving rare-earth nanocrystals, a new class of fluorescent particles, as probes to label specific molecules and cellular structures. His goal is to be able to visualize proteins at work, in real time, at nanometer resolution—the resolution of molecules—but without the drawbacks of the current arsenal of optical probes.

"Fluorescent labels such as green fluorescent proteins (GFPs) and organic dyes have revolutionized molecular and cellular biology," says Chu, "but they fluoresce for about one second before they stop emitting light." This photo-instability makes it difficult to track individual molecules over time. Quantum dots are much more photostable, but are chemically toxic to cells, says Chu, adding that the wavelengths of light needed to excite quantum dots are phototoxic. In sum, using quantum dots for experiments can damage the cells under investigation.

Chu's rare-earth nanoprobes, while comparable in size with quantum dots, are much larger that fluorescent proteins or organic dyes. Their larger size (with diameters of greater than 10 nanometers) is a disadvantage, but they are completely photostable, and the infrared light used to excite the particles has no known phototoxicity. "Instead of looking for seconds with a limited number of photons, we can look for hours, weeks or months," says Chu.

By putting these nanoparticles into the vesicles that move neurotransmitters around in neurons, Chu can track vesicle movement with nanometer precision and millisecond time resolution in order to study fundamental questions in molecular transport and signaling, and to track movement of stem cells, cancer cells and immune cells.

Beyond basic research, such probes could help surgeons to achieve clean margins when removing tumors. Currently, surgeons find tumor edges by feel, Chu says. They then cut away some of what they presume to be healthy tissue around the tumor and send it off to be analyzed. Sometimes, unfortunately, they end up detecting cancer cells in that sample and have to operate again. Chu's very bright nanoparticles emit green light and when used to label cancer cells, could allow surgeons to see with their naked eyes a small number of remaining cancerous cells. While operating-room applications could take years to be approved by the Food and Drug Administration (FDA), they have a chance, since they are not chemically toxic, says Chu. Any particles not rinsed out during surgery will slowly dissolve over many months, Chu adds.

Synthekines' and Other Engineered Ligands for Tinkering with Cell Fate and Function

Chu's nanoparticle probes have to bind specifically to molecules of interest in the same way that molecular messages, such as growth factors, drugs and many hormones, bind to receptors on the outsides of cells and thereby affect what happens within. How these molecular messages,

called ligands, bind to their receptors is the domain of Chris Garcia. Using structural biology and protein engineering, Garcia is developing novel ligands that tweak this signaling system in ways that are helping him learn about biology—and could lead to the development of new drugs.

It's important to be able to target drugs to particular cell types and areas of the body, Garcia explains. You want a drug to have a specific function to solve a particular problem. For a while, it's been possible to design drugs that target what are called G protein-coupled receptors in this cell-specific way, Garcia says. In part for this reason, says Garcia, G protein-coupled receptors are the most common target for drug developers. They're also common in the clinic: more than 30% of drugs approved by the FDA target G protein-coupled receptors; these include treatments for allergies, hypertension and asthma. "But the class of receptors that I work on, which is an equally large class of receptors, nobody had really been thinking about the concepts for these receptors," says Garcia. Receptors in this class, which are called single-pass transmembrane receptors, and which include growth and cytokine receptors, "mediate a huge swath of human biology," Garcia says, yet he adds that there is virtually no drug development happening with these types of receptors.

People overlook this receptor class because, unlike the ligands that target G protein-coupled receptors, those that target cytokine and growth receptors tend to have effects in multiple cell types, a phenomenon called pleiotropy. "When you dose somebody with a cytokine, let's say, for example, interleukin-2 or gamma interferon or stem cell factor, you not only hit the cell that you want to activate, but you hit a bunch of other cells," says Garcia. Sometimes, this can result in toxicity. Sometimes, these multiple effects even cancel each other out. But using protein engineering, Garcia is creating versions of these receptors that can do all sorts of interesting and pharmacologically relevant things—without the pleiotropic effects.

"We have engineered tuned versions of these cytokines that basically gives them a whole new life as drugs; we have created a cytokine pharmacology. But even more than that, it opens up this incredibly important class of receptors for drug discovery again," says Garcia.

The process starts with atom-level three-dimensional crystal structures of the ligand and its receptor, which serve as "blueprints" for the Garcia group's ligand engineering efforts, much as a carpenter uses the blueprints of a house to guide remodeling. Garcia's lab has developed crystal structures—a notoriously difficult task—for many of the most therapeutically important classes of receptors bound to their ligands. The next step is to create a collection of ligands with structural variations near the receptor binding sites. Finally, Garcia and his group test all of the ligands to find the ones that bind receptors as intended and have the desired signaling output—for example stimulating, versus tamping down, the immune system.

K. Christopher Garcia, PhD
Professor of Molecular and Cellular Physiology, of Structural Biology, and Howard Hughes Medical Institute Investigator

For instance, the cytokine gamma interferon (IFNy), which Garcia calls, "a holy grail drug for immunotherapy," can bind to two different receptors: one that stimulates the immune system; another that has the opposite effect. Garcia engineered a version of gamma interferon in which only the first function remains. "We biased it towards immuno-stimulation," says Garcia.

Sometimes, Garcia's engineered ligands can alter cell fate. For example, when hematopoietic stem cells begin to differentiate, they can take one of two paths to become either lymphoid cells, such as T cells, or myeloid cells, such as red blood cells. One of Garcia's ligands stalls differentiation at a stage that appears to Garcia to be somewhere between the two cell fates. "It doesn't look like a stem cell or a myeloid progenitor. It's something intermediate," says Garcia. Another possibility, he adds, is that the novel ligand caused the stem cells to differentiate into a cell type that doesn't exist in nature all.

Creating receptors that don't exist in nature is, in fact, another area of Garcia's research. The receptors Garcia studies have two components, which the ligand draws together into what's called a dimer when it binds, like a Lego block that sticks to two others, bringing them together. Garcia is developing novel ligands that bring together naturally existing receptor components in combinations that do not naturally occur. These novel ligands, called synthekines (for synthetic cytokine), will likely have novel biological functions. "Synthekines induce new activities in natural cells by just taking advantage of different receptors that are expressed on the cell surface," says Garcia. "Looking beyond the menu of cytokines encoded in our genome to creating completely synthetic activities is going to be the future of cytokine drug discovery," Garcia believes.

By tinkering with naturally occurring ligands and by designing ligands that bring their receptors' Lego-like components together in new combinations, Garcia hopes to realize the potential of single-pass transmembrane receptors as drug targets.

Computational Tools for Decoding the Human Genome

Gill Bejerano wants to understand, in his words, "how the human genome does its `thing.'" To that end, since joining Beckman Center faculty in 2007, Bejerano has pursued three approaches to genomics research: comparative genomics, disease genomics and functional genomics. All three approaches help him correlate genotype, the DNA letters of the genome, to traits, including disease, which are referred to as phenotypes.

One approach, which Bejerano developed and dubbed Phenotree, correlates particular phenotypes and their emergence in or disappearance from different branches of the mammalian evolutionary tree with the appearance or disappearance of genetic changes in mammalian genomes in order to discover the genes and genomic regions that control phenotypes of interest. It's called a "comparative genomics" approach because it involves trying to learn more about the human genome by comparing it to the genomes of other species, Bejerano explains. Phenotree compares the genomes of humans, mice, dolphins, giraffes, monkeys and other mammals—over 100 species in total. The Phenotree approach

Using structural biology and protein engineering, Garcia is developing novel ligands that tweak the signaling system in ways that are helping him learn about biology and could lead to the development of new drugs.

continues to be refined and is available for any researcher to use.

One way that Phenotree identifies genes or groups of genes that control a given trait is by looking for genes that are absent or dysfunctional in species that have lost the trait. For example, Bejerano and colleagues tried using Phenotree to identify a gene that controls the ability to synthesize Vitamin C from food, an ability that is present in many mammals, but that has been lost in several branches of the mammalian evolutionary tree, such that multiple bat species, some primates, including humans, and guinea pigs cannot make Vitamin C. Bejerano explains the experimental approach, "We went across the genomes of all of these species and we asked, 'Can we find a gene that looks perfectly healthy in all the species that can synthesize Vitamin C, but looks like it's falling apart exactly in the species that cannot?'" Phenotree did just that and identified the gene, called GULO, that researchers already knew was essential for Vitamin C synthesis. This experiment told the researchers that their system was working. Since then, Bejerano's group has expanded their approach to answer a set of related questions, including, of course, those for which they do not already know the answers.

Correlating genotype and phenotype can also help diagnose human patients: "When you get the genomes, for example, of a few patients that have a mysterious disease and nobody knows where that disease starts in the genome, you can ask, 'Do these patients share anything that the healthy population of people that we've sequenced do not share?' And you often get very precise answers," says Bejerano. This is medical genomics. The Bejerano group has developed over a dozen computational components that together can greatly accelerate both patient diagnosis and disease-gene discovery. One such tool, which Bejerano created to compare human genomic data and phenotypes, is called Phrank.

Phrank relies on the increasing ease with which clinicians can sequence a patient's genome in order to diagnose diseases with a genetic basis. There are currently over 5,000 diseases that can be traced back to mutations in single genes, and researchers identify hundreds of new genes that can cause diseases every year. For a physician to go through the list of the hundred or so disease genes in which a patient has mutations can take many hours of a physician's valuable time. Phrank aims to save physician time by automating a portion of this process.

To use Phrank, a clinician takes the patient's sequencing results, makes a list of the disease genes that contain suspicious mutations, and gives that list to Phrank, along with a list of the patient's symptoms, or phenotypes, translated into codes Phrank can understand. The program then compares the patient's data to genotype-phenotype relationships in its database to generate a list of genes that could explain the patient's symptoms, ordered from most likely to least likely to be responsible. Phrank also generates a ranked list of genetic diseases that the patient might have.

According to a study published this past July, Phrank is better at ranking candidate

Gill Bejarano, PhD
Associate Professor of Developmental Biology, of Computer Science, of Pediatrics, and of Biomedical Data Science

The Bejerano group has developed over a dozen computational components that together can greatly accelerate both patient diagnosis and disease-gene discovery.

genes and diseases than two other tools that aim to produce similar results. In approximately one out of four cases, Phrank puts the gene responsible for the patient's disease at the top of the list; in over half of cases, the gene responsible for the disorder is one of the top five on the list. The same is true for the list of potential diseases.

In 2017, Bejerano put Phrank online for clinicians to use, free of charge, as part of the web portal AMELIE, which includes Phrank plus some other tools from the Bejerano lab. A special feature of AMELIE (which stands for Automatic Mendelian Literature Evaluation) is that it mines the scientific literature to find papers relevant to an individual patient's case. Its output is not only a list of candidate genes, but related scientific papers, also ranked and organized by gene. The code for Phrank alone has also been available for clinicians to download and incorporate into their own systems since July 2018.

Perhaps because of its accuracy, Phrank, via AMELIE, is very popular. AMELIE has received over 2,000 submissions of patient data per month for the last year, Bejerano says.

"We have evidence from the clinicians we talked to that we really are helping patients and their families by empowering the clinicians to very quickly find the causal gene in as many cases as they possibly can," says Bejerano.

A third tool, called GREAT correlates gene-regulatory datasets—such as those obtained by measuring transient marks on the histone molecules that pack our DNA—and phenotypes. Bejerano and his team first put GREAT, a functional genomics tool, online in 2010 and are continually improving it. Scientists can use GREAT to study how epigenomic modifications, such as histone marks, differ between healthy and diseased cells, for example, or to observe how epigenomic modifications change as cells differentiate during development. "[There are] many different questions you can ask both in the developmental context and in the disease context," Bejerano says of GREAT. "And that's why, I think, we have had over one million job submissions to this tool that we put out there. That's pretty cool for an academic lab."

Eterna: An Online Videogame for Designing RNA Molecules

Rhiju Das develops algorithms for designing RNA molecules. The goal is to be able to write sequences of RNA letters—A, U, C and G—that will fold up into particular structures and perform desired functions, many of which could be medically relevant. "There are numerous emerging therapeutics and vaccines, and diagnostics that are based on designer RNA molecules," says Das. But creating such molecules is easier said than done. "Some of these design problems are beyond the capabilities of our best computer simulations; they're beyond our best people, experts in RNA science, including folks who have won Nobel prizes for their discoveries in RNA. So, designing molecules that can fit at the heart of a new molecular therapy is a hard, hard problem," says Das.

Das and others have developed computer algorithms to predict how a given RNA sequence will fold and, conversely to write RNA sequences to form desired structures, but the algorithms are often wrong. To improve them, Das created an online videogame, called Eterna (http://

Rhiju Das develops algorithms for designing RNA molecules. The goal is to write sequences of RNA letters that will fold up into particular structures and perform desired functions.

eternagame.org), where the objective is to design RNA molecules with particular structures.

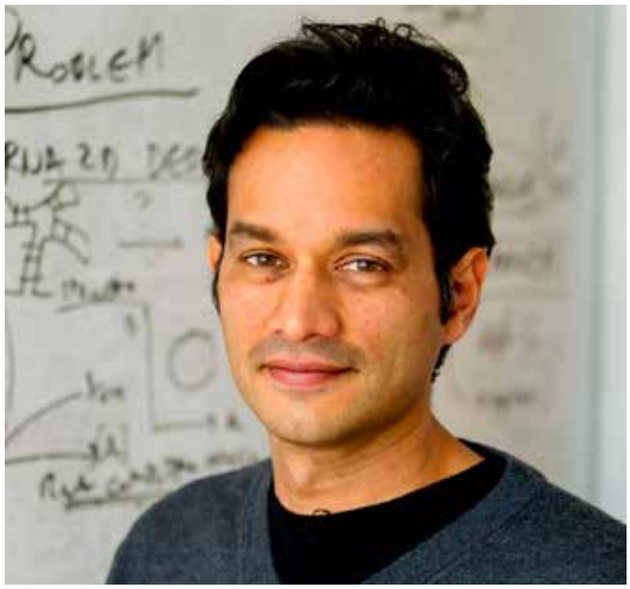
During early levels of the game, players' RNAs just fold up according to the algorithm of the day, but eventually, players get to a level called "lab," where researchers in Das's laboratory synthesize the RNA molecules players have designed and determine whether they fold as predicted. If not, the players learn that they need to change something about their RNA-design strategies and Das's laboratory learns that it needs to change its algorithms.

Eterna went online in 2011. Within a few months, tens of thousands of players were designing RNA molecules. "From this virtuous cycle of gameplay and experimental feedback, they became the best in the world at designing RNA molecules. Their efforts outperformed any algorithm that I or others in the RNA-folding field had prepared," says Das. The Das lab also started using artificial intelligence methods for developing their algorithms. With these methods, he says, "we do better than prior automated algorithms, but we are still having trouble doing as well as human players."

Now Das's group is using their algorithms—and working with Eterna players—to design two types of RNA molecules with medical applications. The first is a tuberculosis (TB) test to determine whether latent TB—present in one in four humans—has become active.

In 2016, another Beckman Center faculty member, Purvesh Khatri, PhD, associate professor of medicine and of biomedical data science and assistant professor at the Institute for Immunity, Transplantation and Infection, reported that he and his team had discovered three RNA molecules whose presence in the blood is indicative of an active TB infection. Soon thereafter, Khatri asked Das if he could develop a designer RNA molecule that could detect the three TB-associated RNAs and effect a color change on a piece of paper—something like a pregnancy test. At first, Das says, it sounded like a fairly easy problem to solve. Then Khatri told him that the RNA sensor on the test would have to detect not just the presence or absence of these three RNA molecules, but the ratios of their concentrations in the blood. The designer RNA would have to be a molecular calculator. That, Das thought, sounded impossible. But Das's team of Eterna developers and players themselves were more optimistic. "They said, 'Hey, if you could make an RNA that could fold up into two different structures depending on the concentrations of these input RNAs, then maybe you could make a molecular calculator and it might work,'" Das recalls.

Late in 2016, Das set up the OpenTB Challenge, which asked Eterna players to design such a molecule. He also worked with Beckman Center colleague Will Greenleaf, PhD, associate professor of genetics and, by courtesy, of applied physics, to design a specialized microscope that would allow them to test all of the candidate molecules that Eterna players submitted. Now, about two years and 30,000 candidate RNA molecules later, Das and Greenleaf have a few dozen molecules that perform as molecular calculators, folding one way when the ratio of the three RNAs is above a certain threshold, another way when that ratio is below the threshold. Last year, Das says, the Bill & Melinda



Rhiju Das, PhD
Associate Professor of Biochemistry

Gates Foundation heard about the OpenTB Challenge and Das had a meeting with Bill Gates. "Essentially, right after that meeting, the Gates Foundation cut us a check to then develop these OpenTB molecules designed by Eterna players and to try to translate these molecules into a point-of-care test," says Das. That's what the Das lab is working on now. The goal is that public health workers visiting communities in areas where tuberculosis is still a big problem could use such a test to quickly screen anyone who thought he or she might be infected with active TB. Anyone who tested positive could then visit a larger facility for a more thorough test and, if necessary, treatment.

Now Das and Eterna players are working on the OpenCRISPR Challenge in which the goal is to design RNA molecules that would improve the therapeutic potential of the gene-editing technology CRISPR, which depends on a so-called guide RNA to lead the gene-editing machinery to its target. "The problem is, when you put the CRISPR machines in and you get them going, you can't turn them off. It's kind of like giving someone an iPhone that only has an on button," says Das. But with the right guide RNA, which Das's lab and Eterna players are working to design, that could change. ■

Overview and Highlights

Overview and Highlights

BECKMAN CENTER OVERVIEW

The breakthroughs that took place in genetic engineering, cell imaging, and genomics in the late 1970s and '80s had a profound impact on the field of medicine, introducing new technologies and opening up new avenues for research in genetics and molecular biology. Recognizing the impact this new body of knowledge would have on improving the diagnosis, prevention, and treatment of disease, Nobel Laureate Dr. Paul Berg sought to establish a center at Stanford University that would integrate the basic, clinical, and applied sciences. The rapid advancements taking place in the fields of molecular biology and genetics might become more readily available to clinical scientists, and thus hasten the translation of scientific discovery into new medical technologies and clinical applications. With the inauguration of the Arnold and Mabel Beckman Center for Molecular and Genetic Medicine in 1989, Dr. Berg's vision became reality and Stanford ushered in a new era of rapid advancement in the field of molecular and genetic medicine.

Under the leadership of its current director, Lucy Shapiro, PhD, the Virginia and D.K. Ludwig Professor of Cancer Research in the Department of Developmental Biology, the Beckman Center continues to be at the vanguard of basic science, translational medicine and technological discovery. The Beckman Center, housing three academic departments and the Howard Hughes Medical Institute, has a world-class faculty of research scientists that includes 4 Nobel laureates, 27 members of the National Academy of Sciences, and 21 Howard Hughes Medical Investigators.

Serving as a model of interdisciplinary collaboration at Stanford University, the Beckman Center has given rise to such forward-thinking approaches as the BioX program and the Department of Bioengineering, a novel joint department that spans the Schools of Medicine and Engineering.

The Beckman Center plays a central role in the School of Medicine's strategic plan to integrate the basic, applied, and clinical sciences at all levels of education and research. With the completion of the Human Genome Project and the advent of novel imaging technologies, the Beckman Center continues to influence scientific research through its support of key alliances and innovative programs.

PROGRAMS AT A GLANCE

The Beckman Center established the Program in Molecular and Genetic Medicine (PMGM), a scientific cooperative governed by a 12-member advisory board from the Schools of Medicine, Engineering, and the Humanities and Sciences, to provide programmatic leadership in basic science research and education. This year the PMGM has elected to support an exciting array of innovative programs. They include:

Translational Research Program

- supports early-stage research for interdisciplinary technology development projects with a translational "bench-to-bedside" emphasis.

Faculty Recruitment Program

- helps to bring in world-class faculty in the basic sciences whose research goals are particularly well suited to the overall mission of the Beckman Center.

Seminars and Symposia

- funds numerous seminar series and symposia including the annual Beckman Symposium.

Research Technology Resources - underwrites state-of-the-art technology development at the Beckman Service Centers to facilitate scientific research and discovery.

Beckman Medical Scholars - helps to fund medical students engaged in basic science scholarly concentrations.

2018-2019 HIGHLIGHTS

The Beckman Center has enjoyed an exciting and productive year of scientific achievement. This year's highlights are as follows:

Dr. Paul Berg 2018 Commencement Speaker for the Stanford University School of Medicine

Paul Berg, PhD, the Robert W. and Vivian K. Cahill Professor of Cancer Research, Emeritus, and the founding director of the Beckman Center for Molecular and Genetic Medicine, gave the keynote address at the Stanford School of Medicine's 110th Commencement on June 16, 2018. A world-renowned biochemist, educator and advocate for scientific freedom, Berg shared the 1980 Nobel Prize in Chemistry for his work creating the first recombinant DNA molecule. During his talk to the Class of 2018, Berg emphasized the indispensable role of investigation and charged the graduates to, "aim high and keep learning, be skeptical of accepted certainty and stay fast in the belief that facts matter."

2018 (Fall) Beckman Symposium

This year's annual symposium took place on September 10, 2018. Titled, "The Revolution in Diagnostics," it attracted a large audience. Research presentations were made by some of the world's leading scientists on topics such as single cell DNA sequencing, liquid biopsies for cancer and fetal DNA, implantable devices, state-of-the-art imaging technologies and other technological breakthroughs that are opening up whole new worlds of diagnostic possibility. Speakers included Ash Alizadeh, MD, PhD (Stanford University), Euan Ashley, MD, PhD (Stanford University), Joseph DeRisi, PhD (UCSF), Sanjiv "Sam" Gambhir, MD, PhD (Stanford University), Kari Nadeau, MD, PhD (Stanford University), Stephen Oesterle, MD (New Enterprise Associates), and Stephen Quake, DPhil (Stanford University). Drs. Stephen Quake and Lucy Shapiro served as hosts. The symposium dinner was hosted by former Secretary of State George Shultz at his campus home.

New Technology Development Grants Awarded

The Beckman Center awarded five new interdisciplinary Technology Development Grants in the Biomedical Sciences. The grants will support the development of new and improved instruments or devices, or the development of new methodologies to be used in biomedical research. Each seed grant provides funding of $100,000 per year for a two-year period.

Applicants to the Technology Development Grant Program were encouraged to submit proposals that had a disease focus, involved collaboration between basic and physician scientists, and had a translational medicine (bench-to-bedside) emphasis.

Twenty-six outstanding grant applications were submitted from 62 faculty members representing 37 separate disciplines drawn from the Schools of Medicine, Engineering, and Humanities and Sciences. The selection committee was composed of Beckman Center Advisory Board members.

Beckman Faculty Member Finds Hidden DNA Sequences Tied to Schizophrenia, Bipolar Risk

Dr. David Kingsley, professor of developmental biology and a Howard Hughes Medical investigator, has discovered that a series of repeated DNA sequences unique to humans may be linked to the development of schizophrenia and bipolar disorder. The finding suggests that the rapid evolutionary changes that led to the extraordinary complexity of the human brain may have predisposed our species to psychiatric diseases not found in other animals.

Although the sequences exist within a small stretch of DNA

that has been previously linked to schizophrenia and bipolar disorder, they represent a kind of genomic stutter that is particularly difficult to detect using conventional sequencing methods.

"The human genome reference sequence shows only 10 repeats of this 30-nucleotide sequence, but we've found that individuals actually have from 100 to 1,000 repeats, and that the sequence itself can vary," said Kingsley. "In contract, chimpanzees and other primates have just one repeat of the sequence, indicating that the region has greatly expanded during human evolution. Some of the sequence variants now found in people are also closely associated with the development of schizophrenia and bipolar disorder."

The study also outlines a possible way to one day identify people at risk for, and ways to intervene in, these disorders.

For more information about Dr. Kingsley's research, see the MEDIA section of this report.

Beckman Faculty Member Finds That in Apoptosis, Cell Death Spreads Through Perpetuating Waves

Dr. James Ferrell, professor of biochemistry and of chemical and systems biology, and his research group, have found that inside a cell, death (apoptosis) often occurs like the wave at a baseball game. This kind of a rolling surge, spurred by the activity of one or a few things, is known as a trigger wave. Once cell death is initiated, by way of disease or something else, specific killer proteins in the cell, called caspases, activate. These proteins then float to other caspases and activate them; those follow suit until the entire cell is destroyed.

To see how death takes over a single cell, Ferrell and his group used Xenopus frog eggs. One egg is a single cell and as cells go, these are enormous, making them a prime candidate to observe how death spreads from one end of the cell to the other, which can be done with the naked eye.

By using a fluorescent technique linked to the activation of apoptosis, Ferrell could watch as the bright green glow moved its way down the tube at a constant speed, indicating that apoptosis was spreading via trigger waves, as opposed to some other more rudimentary mechanism, such as diffusion, which slows down as it moves.

Now, they're asking whether trigger waves might be responsible for how our innate immune response spreads from cell to cell.

For more information about Dr. Ferrell's research, see the MEDIA section of this report.

Beckman Faculty Member Discovers New Algorithm That Could Improve Diagnosis of Rare Diseases

Today, diagnosing rare genetic diseases requires a slow process of educated guesswork. Dr. Gill Bejerano, associate professor of developmental biology and of computer science, is working to speed it up.

Bejerano and his research group have developed an algorithm that automates the most labor-intensive part of genetic diagnosis: that of matching a patient's genetic sequence and symptoms to a disease described in the scientific literature. Without computer help, this match-up process takes 20-40 hours per patient. The algorithm developed by Bejerano's team cuts the time needed by 90%.

"The algorithm also holds potential for helping doctors identify new genetic diseases," Bejerano said. For example, if a patient's symptoms can't be matched to any known human diseases, the algorithm could check for clues in a broader knowledge base.

For more information about Dr. Bejerano's research, see the MEDIA section of this report.

Beckman Faculty Member Able to Predict Osteoporosis, Fracture Risk with Genetic Screen

A new genetic screen developed by Dr. Stuart Kim, emeritus professor of developmental biology, may predict a person's future risk of osteoporosis and bone fracture.

Specifically, the study, one of the largest of its kind, identified 899 regions in the human genome associated with low bone-mineral density, 613 of which have never before been identified.

People deemed to be at high risk – about 2% of those tested – were about 17 times more likely than others to develop osteoporosis and about twice as likely to experience a bone fracture in their lifetimes. In comparison, about 0.2% of women tested will have a cancer-associated mutation in the BRCA2 gene, which increases their risk of breast cancer to about six times that of a woman without a BRCA2 mutation.

Early identification of people with an increased genetic risk for osteoporosis could be an important way to prevent or reduce the incidence of bone fracture, which according to the National Osteoporosis Foundation affects 2 million people each year and accounts for $19 billion in annual health care costs.

"There are lots of ways to reduce the risk of a stress fracture," said Kim. "But currently there is no protocol to predict in one's 20s or 30s who is likely to be at higher risk, and who should pursue these interventions before any sign of bone weakening. A test like this could be an important clinical tool."

For more information about Dr. Kim's research, see the MEDIA section of this report.

Beckman Faculty Member Deploys Worms to Investigate How Neurological Drugs Work

There are drugs derived from plants to treat epilepsy, to prevent migraines and to halt manic episodes in people with bipolar disorder. But in many cases, no one knows exactly how those and other neurological drugs work – what chemical processes in the brain those drugs alter, or sometimes even what the active ingredients are.

Dr. Miriam Goodman, professor of molecular and cellular physiology, along with her collaborators, Sue Rhee, PhD, and Thomas Clandinin, PhD, propose to use a tiny roundworm called *Caenorhabditis elegans* as the perfect platform for studying these questions. *C. elegans* are much simpler than humans, but have a lot of genetic similarities.

The team will start with a large collection of *C. elegans* worms containing a range of genetic mutations and a plant called valerian, extracts of which are now used in drugs to treat epilepsy, and which have been used for thousands of years to treat mild anxiety.

When the team exposes their worms to valerian extracts, they'll watch to see which ones wiggle closer and which flee, as they sort themselves according to their genetically encoded responses. The researchers will then look to see which genes are responsible for that behavior.

The hope is to use these experiments not just to understand the genetic and neural pathways through which plant extracts and plant-derived drugs work, but also to discover new drugs.

For more information about Dr. Goodman's research, see the MEDIA section of this report.

Beckman Faculty Member Teams up with Colleagues to Fight Common Viral Infection in Kidney Transplant Recipients

Dr. Mark Davis, professor of microbiology and immunology and Howard Hughes Medical investigator, along with his colleagues, Olivia Martinez, PhD, and Stephan Busque, MD, have joined forces to learn how immune cells in some kidney transplant patients fight a common virus. The work could lead to a test to predict who is at risk for potentially deadly infections like cytomegalovirus (CMV), and possibly develop new treatments.

The researchers plan to examine special immune cells, called T cells, in two groups of transplant patients – one with CMV disease and one without. To find out why T cells aren't always successful in controlling viral infection, the team will analyze T cells in blood samples taken from one group of transplant recipients in whom the virus is under control, and another group in whom CMV

is reactivated. The researchers will sequence the proteins that dot the outside of T cells and recognize infections – there are billions of such sequences – in order to find combinations that are present in one group of patients, but not the other.

Results from the study will not only help develop better tools for identifying transplant patients at risk of CMV disease, but give researchers a better understanding of basic characteristics of viral immunity and vaccine design.

For more information about Dr. Davis's research, see the MEDIA section of this report.

Beckman Faculty Member Reveals the Molecular Mechanism Underlying Hypertrophic Cardiomyopathy

About 1 in every 500 people is born with hypertrophic cardiomyopathy, a genetic disease caused by any one of numerous mutations that, mysteriously, cause heart muscle to contract with too much force. Now, researchers led by Dr. James Spudich, professor of biochemistry, have discovered the mechanism behind this workaholic heart.

The protein myosin is a motor of sorts, whose dynamic action contributes to the overall contraction of a muscle. But it only works part-time, spending much of its existence in a posture akin to that of a sleeping flamingo, with its head tucked tightly into its torso. This is typical of normal heart function.

Spudich and his colleagues discovered that many mutations associated with hypertrophic cardiomyopathy, although they occur at different points along the myosin gene's sequence, often wind up affecting the amino acids on the same surface of the folded protein's outer edge, altering the myosin molecule in ways that coax it out of its sleeping flamingo posture.

The changed postural preference, in turn, keeps the myosin molecule from spending too much time snoozing on the job, collectively causing constant overdrive in the heart muscle's power output.

For more information about Dr. Spudich's research, see the MEDIA section of this report.

Beckman Faculty Member Uncovers Puzzle of a Mutated Gene Lurking Behind Many Parkinson's Cases

Genetic mutations affecting asingle gene play an outsized role in Parkinson's disease. The mutations are generally responsible for the mass die-off of a set of dopamine-secreting, or dopaminergic, nerve cells in the brain involved in physical movement.

The pathogenic variants of the gene, LRRK2, share a common tendency: they cause the protein it encodes to run in constant overdrive, upsetting the delicate balance of a healthy cell.

Dr. Suzanne Pfeffer, professor of biochemistry, and her colleagues, have previously reported that mutant LRRK2 renders some classes of nerve cells deficient in their ability to create an important subcellular structure called the primary cilium. In the new study, Pfeffer and her research team discovered that cells lacking primary cilia are unable to respond to a powerful chemical messenger known as sonic hedgehog. Secondly, the scientists learned, the types of cells that can't make a decent primary cilium when their LRRK2 protein is in overdrive include a set of cholinergic nerve cells. And these cholinergic cells have a close working relationship with the dopaminergic cells implicated in Parkinson's disease.

So, an LRRK2 protein in overdrive leads to no primary cilia, which leads to no response to the sonic hedgehog signal, which leads to no chemical help for the dopaminergic cells and, therefore, to their death.

Could the breakdown of that support system underlie the unrelenting loss of dopaminergic cells in Parkinson's? Pfeffer's lab is now studying that very question.

For more information about Dr. Pfeffer's research, see the MEDIA section of this report.

TECHNOLOGY RESOURCES HIGHLIGHTS

The Beckman Service Centers are continually undergoing key technological enhancements in order to better serve our research community. Beckman Foundation funds have been instrumental in this process, building the infrastructure and providing the financial leverage that has made the facilities competitive for both internal and external grant awards. These service centers operate on a fee-for-service basis.

The Cell Sciences Imaging Facility (CSIF)

Dr. Joanna Wysocka, the Lorry Lokey Professor in the School of Medicine, professor of developmental biology and chemical and systems biology, and Howard Hughes Medical Institute investigator, received an HHMI grant award in the amount of $972,126 for the purchase of an Intelligent Imaging Innovations (3i) V2 Lattice Light Sheet Microscope (LLSM), that facilitates high spatio-temporal resolution live-cell imaging with minimal photo damage. The instrument will be housed in the CSIF and available to researchers across the Stanford campus. The LLSM technology delivers much lower light dosage while achieving signal-to-noise ratios that are equal to or higher than other conventional live cell imaging modalities. It has the advantage of **1)** minimizing photobleaching of the fluorophores and thus lowers the requirement of extensive optimization of fluorophores used for labeling, and **2)** it greatly minimizes phototoxicity and thus extends typical imaging time by at least an order of magnitude with uncompromised frame rates. The School of Medicine's Dean's Office is contributing startup funding to staff the services provided on this new instrument. Installation is scheduled for summer 2019.

With financial support from the Beckman Center, the School of Medicine's Dean's Office and the Stanford Cancer Institute, the CSIF has purchased a CODEX, highly multiplexed imaging platform together with an epifluorescence microscope and analysis workstation. This combined instrument will allow automated, highly multiplexed, antibody localizations of potentially an unlimited number of proteins on tissue sections or tissue arrays, with cellular level of resolution. The CODEX instrument will provide greatly increased throughput and analysis of multiple cancer, neurological and other tissue specific markers which will allow phenotypic cluster analysis of different cell types within their spatial context. The facility will provide image analysis and pipeline development support, as well as, develop and validate antibody panels for research groups. The CSIF's CODEX service will start in early 2019.

In collaboration with the Otolaryngology Department at the Medical School, the CSIF has purchased a Leica ICE High Pressure Freezer (HPF) with the capacity to do optogenetic light and electrical stimulation. This new HPF will allow larger, thicker sample loading for ice-free vitreous ice freezing, the gold-standard for cell preservation, than previously available and will be used for advanced ultrastructural and immuno-EM localization studies in the EM lab. This new instrument was installed in December 2018.

Fluorescence Activated Cell Sorting (FACS) Facility

The FACS Facility has grown at a rapid pace and has continued to add instruments to provide the latest technologies and easy access for researchers. Using funds provided by the Beckman Foundation, the facility has added a spectral analyzer. This instrument measures fluorescence using the full emission spectra rather than each dye's peak spectra. Using this approach, this new instrumentation offers unique flexibility in the reagent combinations that can be used simultaneously. In its current iteration, the spectral cytometer enables 20+ colors excited by only 3 lasers. Two additional lasers are already slated for further upgrade of this instrument in 2019. ■

Expenditures

Expenditures

FOUNDATION FUNDS IN THE CONTEXT OF CENTER OPERATIONS

The Arnold and Mabel Beckman Center for Molecular and Genetic Medicine officially opened in 1989, with an initial gift from the Beckman Foundation of $12 million. Another $50 million of funding from private sources made it possible to complete the center on time and under budget. The center houses three academic departments—Molecular and Cellular Physiology, Developmental Biology, and Biochemistry—as well as, the Howard Hughes Medical Institute (HHMI) Unit in Molecular and Genetic Medicine, all dedicated to basic sciences research and the teaching and training of medical students, graduate students, and postdoctoral fellows.

The Beckman Center plays an important role by providing funding that would not otherwise be available for interdisciplinary research, for the translation of basic science discovery into new technologies, and for the provision of cutting-edge resources and services to the research community. The center's programs and initiatives serve to complement and enhance the research efforts of the resident departments, the PMGM faculty, and the broader research community of the university. Funds from the Beckman Foundation leverage our continued ability to obtain additional funding from federal sources. Without the Beckman Foundation support, many of our highly successful programs would simply not exist.

In recognition of the unique role the center plays with respect to the basic sciences, the Office of the Dean provides an annual operating budget to the Beckman Center to cover the costs of administering the programs funded by the center. In addition, the School of Medicine recently funded a complete overhaul of the Beckman Center building.

The Beckman Service Centers—Computational Services and Bioinformatics (CSBF), Cell Sciences Imaging Facility (CSIF), Fluorescence Activated Cell Sorting (FACS), and Protein and Nucleic Acid (PAN) facilities, used by scientists throughout the campus and managed by the Beckman Center, are expected to generate nearly $5.3 million in user fees this year, continuing a level of service that sets the standard at Stanford University. Service Centers operate at or close to break-even each year.

THE IMPORTANCE OF FOUNDATION FUNDS TO STANFORD'S MISSION AND GOALS

Service Centers

Major advances in new imaging, bioinformatics, and genomics technology are having a remarkable impact on our ability to translate basic research into medical applications. These new technologies are very expensive, and many investigators find themselves unable to purchase state-of-the-art instrumentation. We have created service centers that provide these instruments and technologies on a fee-for-service basis, underwritten and administered by the Beckman Center.

An important component of these service centers is technology development. The Beckman Center enables the design and implementation of leading-edge technologies that are then made available to the Beckman research labs, using Beckman funds to leverage scientific discovery.

Technology Development Grants

In order to help initiate innovative new translational research projects, the Beckman Center conducts a highly competitive program in which

pairs of investigators (one a basic scientist and the other a clinician scientist) propose risky, but high pay-off experiments in technology innovation. PMGM advisory committee members evaluate the proposals and the center provides $100,000 a year (for projects of two years duration) to the best proposals. This program has been highly successful and has leveraged a large multiple of funding from both federal and private sources for many of the seeded proposals.

Medical Scholars Program

To foster the training of medical students in translational research, the center provides a stipend to selected students doing research in top tier research labs with PMGM faculty. This is a competitive program, closely monitored by the Beckman Center.

Research Communication and Education

Communication among the biomedical and technology communities is, as Arnold Beckman firmly believed, the bedrock of doing innovative scientific exploration. Accordingly, the center supports the "Frontiers in Science" seminar series and the annual Beckman Symposium on a critical area in scientific innovation. These symposia attract students and faculty, as well as the lay community.

EXTERNAL REVIEW

The Stanford Beckman Center runs several programs providing support for outstanding technological and scientific advances. The center provides services in: 1- state-of-the-art imaging technologies, 2- protein and nucleic acid molecular analyses, 3- computer and bio-computational work, and 4- fluorescence activated cell sorter (FACS) technologies. All four service centers provide cutting-edge high-tech resources to scientists on a fee-for-service basis and the demand for these services as measured by the revenue generated, as well as the acknowledgment of the work done by these facilities in peer-reviewed journals are important measures of their overall success and value to the scientific community at Stanford.

Each of the service centers is under the oversight of two separate committees: an advisory committee of prominent users tailored to each service center, and a Cores Advisory Board that oversees and evaluates all service centers at the School of Medicine.

It is precisely because members of the advisory committee tailored to each service center are users that makes them so valuable. The role of both these advisory committees has several goals: one is to review revenues and expenses and determine which services should be continued or discontinued. Most importantly, the primary goals of the advisory committee tailored to each service center are to:

- Inform the service center directors about the research tools and methods that are most needed by users of the facility.
- Provide feedback to the director about the effectiveness of the services being provided.
- Assess the quality of those services.
- Assess the timeliness of the work being done by service center staff.
- Evaluate the level of training provided to graduate students, postdocs and other research staff.
- Assess the service center staff's input and advice related to sample preparation, experimental design and data analysis.

The second tier of review is the School of Medicine's Cores Advisory Board, which meets at least once a year, but also on an ad hoc basis, and is composed of faculty members from throughout the School of Medicine, often chairs of departments, appointed by the senior associate dean for research. The purpose of this board is to:

- Review and approve detailed business plans for proposed new service centers.
- Invite existing service center directors, in rotation, to present their budgets, revenues/expenses and list of users.
- Analyze overall subsidies required to operate each facility, including the cost to income ratios of each service being provided.
- Evaluate the overall demand for services in a given facility over time.
- Review the list of users for each facility and the dollar

volume of activity per user, in order to determine the scope of demand for those services.
- Assess the degree of duplication of services between service centers across the campus.
- Evaluate which high cost technologies should be subsidized.
- Determine the need for new services or new service centers.
- Evaluate whether or not certain services have outlived their usefulness, are readily available outside the university, or should be discontinued.

With respect to the Beckman service centers, the board's recommendations are summarized and relayed to the Beckman Center director for consideration. The evaluation of the service centers by the Cores Advisory Board provides important feedback that allows the Beckman Center director to consider changes (expansion or elimination) of services provided by the four service centers.

In addition to these review committees, the University's Department of Audit, Compliance, and Privacy conducts internal financial audits of the facilities, and the Office of Research Administration oversees compliance of the facilities with the university's cognizant agency, the Office of Naval Research.

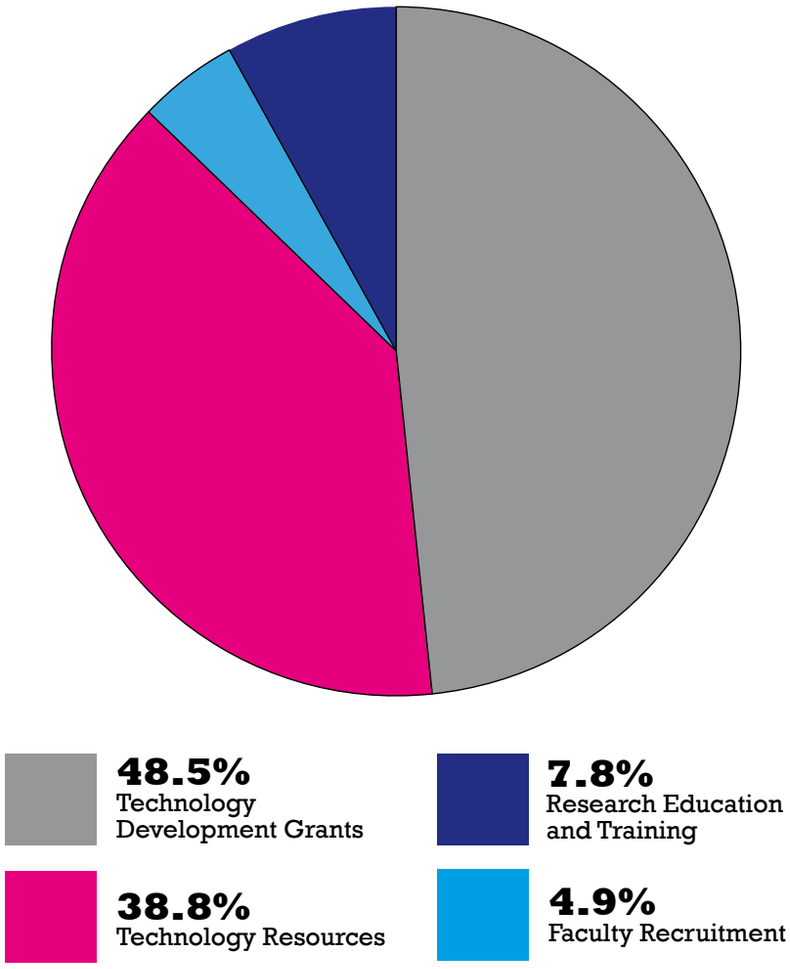
The Beckman Center established the Program in Molecular and Genetic Medicine (PMGM), a scientific cooperative governed by a 12-member advisory board from the Schools of Medicine, Engineering, and the Humanities and Sciences, to provide programmatic leadership in basic science research and education. Members of this PMGM Board review seed grant applications for highly innovative work in interdisciplinary technology development. The goal is to ensure that awards are made equitably and on the basis of outstanding merit. In addition, the PMGM Advisory Committee functions to advise the director on matters of faculty recruitment and the need for new or revised programming.

ENDOWMENT FUNDS

In lieu of endowment funding from the Beckman Foundation, the Stanford Beckman Center received an initial $12 million gift from the foundation to partially defray the cost of building construction and the center receives an annual gift to cover operational expenses.

FUND DISTRIBUTION

The Beckman Center receives an annual gift from the foundation that is distributed to its programs in medicine, faculty recruitment, research technology resources and development, and education. The accompanying pie chart shows how the Beckman funds were distributed during this fiscal year. ■



Programs

Programs

TECHNOLOGY DEVELOPMENT GRANTS

Advances in our knowledge of basic biology, together with a rapid increase in our understanding of molecular genetics, are providing unprecedented opportunities to develop new approaches to the diagnosis and treatment of human disease. As part of the Beckman Center's emphasis on translational medicine, the PMGM established the Interdisciplinary Translational Research Program (ITRP).

The primary goal of the ITRP seed grant program is to stimulate collaborations across multiple disciplines and forge a meaningful interface between the basic, applied, and clinical sciences so that laboratory research and discovery can be "translated" into new diagnostic and therapeutic applications. The program also seeks to engage trainees—medical students, graduate students, clinical fellows, and postdoctoral fellows—in groundbreaking collaborative research. Projects funded under this program represent innovation in a broad array of scientific disciplines, with teams composed of two or more researchers, including a combination of physician-investigators, basic scientists, applied scientists, and trainees.

In October 2018, the Beckman Center awarded five new Interdisciplinary Translational Research Program (ITRP) grants that were geared toward support for technology development in the biomedical sciences. Each Technology Development Grant provided funding of $100,000 per year for a two-year period.

Applicants were encouraged to submit proposals to support innovative applications for 1) the development of new and improved instruments or devices, or 2) the development of new methodologies, to be used in biomedical research. Preference was given to applications that had a disease focus, were truly innovative, and met the interdisciplinary, and translational criteria for the ITRP grant program. Part of the selection process for the Technology Development Grants was based on an assessment of the likelihood that the pilot research project would attract new or additional extramural funding.

The five grant recipients chosen in 2018 and a description of their research proposals are as follows:

A Next-Generation Imaging Technology for Human Tissue Atlases

Pehr A.B. Harbury, PhD
(Biochemistry)
Tushar Desai, MD, MPH
(Medicine–Pulmonary and Critical Care)

Pehr A.B. Harbury, PhD
Department of Biochemistry

Tushar Desai, MD, MPH
Department of Medicine (Pulmonary and Critical Care)

Recent advances in single cell analytical methods have made it possible to measure the unique molecular fingerprint of individual cells isolated from the human body. Classification of the molecular fingerprints has yielded comprehensive lists of the specialized cell types that make up each organ system. A current challenge is to map the three-dimensional organization of all the cell types, and the signals exchanged between them, within intact tissues. The desired molecular atlases will be critical for understanding how autonomous cellular programs process local input and output signals, through distributed decision making, control the development, maintenance and destruction of tissues.

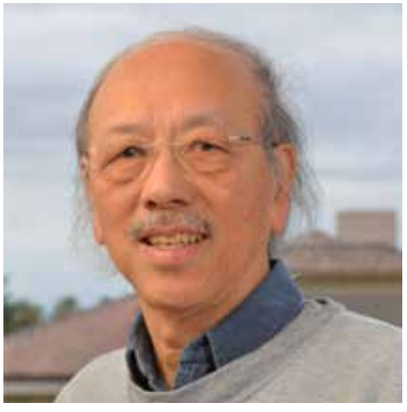
The tremendous potential of single-cell atlases; however, is confronted with an urgent need for more powerful tools. Although innovative *in situ* molecular mapping strategies are emerging, they are fundamentally and severely limited by their reliance on fluorescence microscopy for imaging, and on passive transport for delivery of imaging agents. Fluorescence microscopy suffers from low information throughput due to the small number of spectrally-resolvable data channels, and it often fails to detect low-abundance molecular features in human tissues, which fluoresce strongly. Beyond that, fluorescent imaging reagents do not penetrate many types of specimen by passive diffusion. This has particularly undermined mapping in large, anatomically-intact structures.

Here, the researchers propose to develop a next-generation genomic imaging technology that will potentiate the performance and utility of existing molecular mapping strategies in human tissues. Chemical probes and hardware for a new type of luminescence imaging will be created that detects 20-35 different 'color' channels and is 100-fold more sensitive than fluorescence microscopy in human tissues. The study will involve implementation of ultra-fast electrophoretic delivery and removal of luminescent imaging agents to and from samples mounted on a microscope stage, enabling rapid and fully automated mapping. The technology will be used to construct the first comprehensive three-dimensional atlas of a vertebrate lung. This work is the continuation of a fruitful collaboration between a physician-scientist and a molecular biochemist. The aim is to deliver a powerful, practical and accessible tool that can revolutionize single-cell analysis in basic science and clinical medicine. ■

Targeting the Influenza Matrix Layer Through Hyper-Stabilization

Karla Kirkegaard, PhD
(Genetics, and Microbiology and Immunology)
Wah Chiu, PhD
(Photon Science, Bioengineering, and Microbiology and Immunology)

Karla Kirkegaard, PhD
Departments of Genetics, and of Microbiology and Immunology



Wah Chiu, PhD
Departments of Photon Science, of Bioengineering, and of Microbiology and Immunology

Viral matrix layers and capsids are shells formed of many copies of a single protein that protects the genetic material of the virus. These shells first have to self-assemble to form a stable protein layer around the viral DNA or RNA. Then, they must disassemble to release the viral genetic material into the cell during an infection. To execute these diverse tasks, viral matrix and capsid proteins must change shape at critical times during infections. Thus, matrix and capsid proteins are crucial components of the viral infectious cycle and are often highly genetically conserved. Furthermore, due to their self-assembling character, compounds that target these viral shells have been shown to suppress the emergence of resistant viruses. However, due to challenges in assay development and difficulties in targeting protein-protein interactions, they have not been widely explored as antiviral targets.

Within influenza A virus, the viral matrix layer is formed by copies of the matrix protein M1. At the beginning of a viral infection, the virus gets trapped within a cellular compartment called an endosome. The acidic pH of the endosome triggers a rearrangement of the matrix layer, causing the release of the genetic material into the cell. Then, when new viral particles M1 self-assemble, they do so in the neutral pH of the cytoplasm to form a new matrix shell around the viral RNAs.

This proposal involves a novel strategy: to hyper-stabilize either the acidic- or neutral-pH conformation of M1, given that structural changes between these forms are necessary to complete the entire viral infectious cycle. A combination of cryo-electron microscopy, cryo-electron tomography, mass spectrometry and thermal unfolding will be used to characterize and target specific M1 conformations and interfaces involved in matrix layer formation.

The hypothesis is that targeting the matrix layer by hyper-stabilizing M1 conformations will be a successful strategy for antiviral treatment that can suppress the outgrow of resistant viruses and be applicable to other viruses that contain matrix and capsid layers. This research will encourage academic and industrial research to focus on oligomeric viral proteins as novel anti-viral targets that can prevent the emergence of drug resistance. ■

Developing FFPE-Optimized CODEX to Reveal the Cutaneous T Cell Lymphoma Tumor Microenvironment in Response to Immunotherapy

Garry Nolan, PhD
(Microbiology and Immunology)
Youn Kim, MD
(Dermatology)

Cutaneous T cell lymphoma (CTCL) is a malignant tumor of the skin for which treatment options are currently limited. Brentuximab is a new antibody-drug conjugate that targets CD30 and has shown remarkable success in treating Hodgkin and systemic anaplastic large-cell lymphomas. Recent clinical trials of brentuximab for therapy-refractory CTCL also showed unprecedented high rates of response, with up to 70% of patients achieving a sustained clinical response. In addition to high treatment costs, brentuximab has potentially devastating side effects in a subset of patients. Thus, it is critical to find predictive biomarkers that allow stratification of patients in probable responders and non-responders before therapy is initiated. The proposed study will adapt and optimize a new imaging technology called CODEX (CO-Detection by antibody indEXing) for use in formalin-fixed, paraffin-embedded (FFPE) tissue samples, which is the most common type of specimen used for clinical diagnostics and therapeutic prediction.

Specifically, CODEX will be used to image CTCL skin biopsies with 50+ protein markers simultaneously to determine the precise cellular and molecular mechanisms underlying brentuximab response, with a focus on tumor-infiltrating immune cells and their spatial interactions with tumor cells and other cell types in the CTCL microenvironment. Additionally, laser-capture microdissection, coupled with RNA-sequencing, will be used to obtain global gene expression information for tumor and immune cells. Combining these techniques will enable deep phenotyping of the CTCL tumor microenvironment and identification of biomarkers for brentuximab response. This proposal provides a new approach for examining FFPE tissue samples and will improve the understanding of how immunotherapy affects the tumor microenvironment in CTCL. As a novel diagnostic tool, FFPE-optimized CODEX will predict the therapeutic success for CTCL, with applications for many additional cancers. ■

Garry Nolan, PhD
Department of Microbiology and Immunology

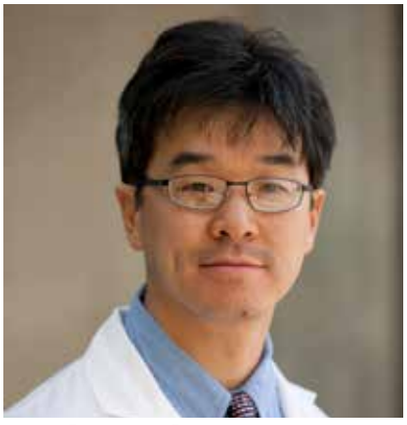
Youn Kim, MD
Department of Dermatology

Scalable Long-Term DNA Storage with Error Correction and Random-Access Retrieval

Tsachy Weissman, PhD
(Electrical Engineering)
Hanlee P. Ji, MD
(Medicine – Oncology)

Civilization's rapid accumulation of digitized information of all forms gives rise to the urgent challenge of maintaining it for future generations. This data includes notable accomplishments and history, administrative and experiential data, and even the environment's genetic makeup. Current media technologies lack the capacity required for the sheer volume of data being generated, and lack the persistence required to store data in the longer-term, ideally for millennia. If current technologies are continued, the cost has the potential to become insurmountable. In this context, the promise of DNA storage is staggering; DNA is extremely dense and extraordinarily stable, potentially allowing for the long-term storage of data on the scale of exabytes. Given the advantages of DNA's compression and chemical stability, this approach would potentially entail only a small fraction of the current cost. However, the current DNA storage systems fall short of this ideal due to high costs and lack of scalability. By combining efficient and robust molecular technologies with information theoretic schemes for storing information in DNA, the plan is to build a scalable long-term DNA storage system allowing for random access to data. ■

Tsachy Weissman, PhD
Department of Electrical Engineering

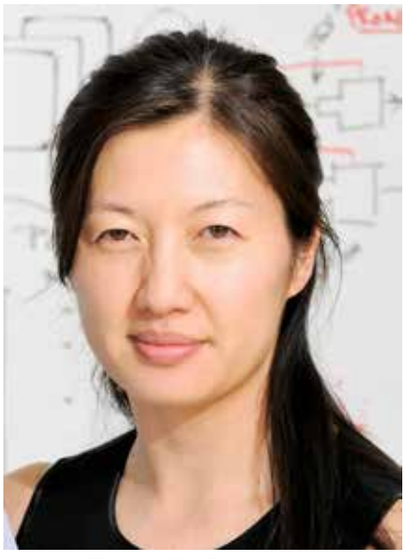


Hanlee P. Ji, MD
Department of Medicine (Oncology)

Optical Tool to Assess Neuronal Function in Human Stem Cell-Based Disease Models

Marius Wernig, MD, PhD
(Pathology)
Alice Ting, PhD
(Genetics and Biology)

Marius Wernig, MD, PhD
Department of Pathology (Stem Cell Institute)



Alice Ting, PhD
Departments of Genetics and of Biology

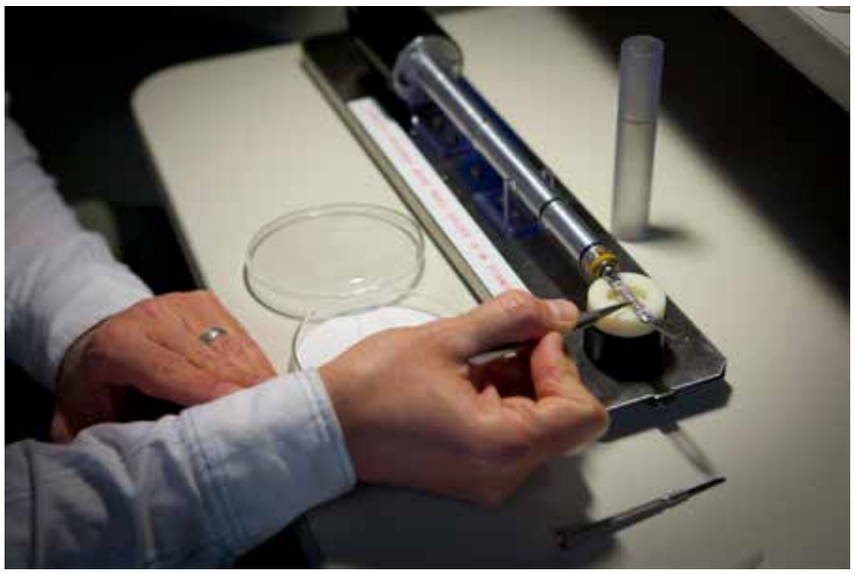
Neuropsychiatric diseases, such as autism and schizophrenia, are difficult to study because there is limited access to human material. These diseases are caused by many different variations of genetic factors and the disease symptoms are strongly influenced by the general genetic make-up of the patients. The function of single genes can be studied well in mouse models (given that the gene is conserved between mice and humans), but the effects of many different genetic variants and the complex human genetic background can only be modeled in human cells, ideally in patient-derived cells. Cell reprogramming and stem cell biology offers an attractive new approach to generate human neurons. Drs. Wernig, Ting and others have shown that skin and blood cells can be directly converted into neurons and pluripotent stem cells which can be converted into neurons in a second step. This technology allows in principle the generation of human neurons from a large number of patients.

However, one of the main obstacles to characterizing these derived human neurons is that current methods for proper functional synaptic assessment are labor-intensive and low-throughput, requiring several months per sample. This limitation represents a major bottleneck and largely prevents the implementation of the promising potential of human neuronal cell models. Since neuropsychiatric diseases will likely have functional rather than morphological phenotypes, it will be of utmost importance to develop new tools that allow functional characterization in a more high-throughput manner. This would allow implementation of "clinical trials in a dish," i.e. the functional characterization of large numbers of patient-derived neurons and screening for potential new therapeutic drugs.

To solve this problem, the proposal is to develop two new classes of optical tools to characterize human stem cell-derived neurons: a class of tools to measure overall neuronal activity and a class that specifically reports synaptic transmission. An optical readout for both has been chosen because imaging-based readouts are highly compatible with high-throughput screening and assessment. To detect overall neuronal activity a co-incidence detector of intracellular calcium and visible light will be developed. This detector induces the accumulation of a fluorescent protein depending on the amount of neuronal activity only when neurons are exposed to light. This will make it possible to tune the system to make it most sensitive for the level of activity in human stem cell-derived neurons. To report synaptic activity, a co-incidence detector of light will be developed with either synaptic glutamate or synaptic

GABA, the main excitatory neurotransmitter and inhibitory neurotransmitter, respectively, in the brain.

These novel tools will be applied to human neurons, benchmarked and validated using established electro-physiological methods. A further evaluation will be done to determine whether the new tools will be able to detect functional phenotypes in human neurons derived from Fragile X Syndrome patients.



SEMINARS AND SYMPOSIA

The Beckman Center has become a vital source of support for faculty leaders seeking to promote broad-based scientific interaction and training through speaking events. PMGM support for seminar series, conferences, and symposia enables departments to bring leading scientists to Stanford to share cutting-edge research and engage in dialogue with Stanford faculty, students, and postdoctoral investigators. The Beckman Center has provided funding for a variety of seminar series, conferences, and symposia, such as those listed below, that are primarily interdisciplinary in nature. Selected descriptions of these programs are:

Beckman Symposium

This year's annual symposium took place on September 10, 2018. Titled, "The Revolution in Diagnostics," it attracted a large audience in Berg Hall (Li Ka Shing Center), where the event was held. The event was also streamed live to Munzer Hall in the Beckman Center. Research presentations were made by some of the world's leading scientists on topics such as single cell DNA sequencing, liquid biopsies for cancer and fetal DNA, implantable devices, state-of-the-art imaging technologies and other biomedical breakthroughs that are opening up whole new worlds of diagnostic possibility. Speakers included Ash Alizadeh, MD, PhD (Stanford University), Euan Ashley, MD, PhD (Stanford University), Joseph DeRisi, PhD (UCSF), Sanjiv "Sam" Gambhir, MD, PhD (Stanford University), Kari Nadeau, MD, PhD (Stanford University), Stephen Oesterle, MD (New Enterprise Associates), and Stephen Quake, D.Phil. (Stanford University). Drs. Stephen Quake and Lucy Shapiro, the Virginia and D.K. Ludwig Professor of Cancer Research in the Department of Developmental Biology at Stanford University School of Medicine and director of the Beckman Center, acted as hosts.

Frontiers in Biological Research Series

Support for the Frontiers in Biological Research Seminar Series spans several basic science departments in the School of Medicine. The series is designed to present and discuss cutting-edge research involving interdisciplinary approaches to bioscience and biotechnology. Leading investigators from Stanford and throughout the world present a broad set of scientific and technical themes related to interdisciplinary approaches to important issues in bioengineering, medicine, and the chemical, physical, and biological sciences. The series also gives students the opportunity to meet informally with seminar speakers to discuss their research and future directions. Support for the Frontiers in Biological Research Seminar Series spans several basic science departments in the School of Medicine.

Frontiers in Integrative Microbial Biology Series

This seminar series focuses on the integration and interplay between physiological, ecological, evolutionary and geochemical processes that constitute, cause, and maintain microbial diversity.

Cancer and Tumor Biology Seminar Series

This series is held throughout the academic year and features guest lecturers from Stanford and peer institutions who discuss the molecular, genetic, cellular, and pathobiological aspects of cancer, as well as, the current state of clinical diagnosis and treatment of human cancers.

Regenerative Medicine Seminar Series

The Beckman Center, Bio-X and the Institute for Stem Cell Biology and Regenerative Medicine jointly sponsors these seminars that meet weekly on Thursdays throughout the academic year. The seminars bring students, post-docs, faculty, and trainees together from Bioengineering, Engineering, the Medical School and the Biological Sciences to hear about and discuss work in progress. It has been a tremendous help in making the Stanford research community aware of the broad range of research going on in regenerative medicine on campus.

FACULTY RECRUITMENT PROGRAM

The Faculty Recruitment Program helps persuade outstanding faculty candidates, whose research goals are particularly well suited to the overall mission of the Beckman Center, to join the Stanford faculty. Competition for the most outstanding researchers is keen and the innovative services and technologies provided by the Beckman Center offer a strong incentive to join the scientific community at Stanford. The Beckman Center is currently recruiting faculty for several departments.

The Beckman Center has become a vital source of support for faculty leaders seeking to promote broad-based scientific interaction and training.

BECKMAN CENTER MEDICAL SCHOLARS PROGRAM

The Beckman Center Medical Scholars Program was established in 1997 for the purpose of creating a source of funds to provide financial stipends to medical students doing translational biomedical research under the direction of a PMGM faculty member. This support is critical to the success of the work of the Beckman Center and is aligned with the center's goal of ensuring that the results of basic and applied sciences are made broadly available for clinical use and practical application.

The program targets medical students engaged in projects appropriate to the Beckman Center's mission, and selection is made through the Stanford Medical Scholars Program by the Medical Scholars Committee, which is composed of leading PMGM faculty members drawn from the basic and clinical sciences in the School of Medicine. Applications are reviewed on a quarterly basis. Student awardees are required to make an oral presentation of project results to an audience consisting of the faculty advisor and others, with expertise in the field and must also prepare a written summary of the project results. This year the Beckman Center is supporting the research of two Beckman Scholars:

To foster the training of medical students in translational research, the center supports a select group of medical students doing research in top tier research labs with PMGM faculty.

Razina Aziz-Bose

Academic Year: 2018-19
Year at Stanford Medical School: 3
Undergrad Education:
Amherst College; Neuroscience, BA
Hometown: Lexington, MA
Title of Medical Scholars Project: Role of the Nogo Receptor in Diffuse Intrinsic Pontine Glioma (DIPG) Invasion

Research Description

Diffuse intrinsic pontine glioma (DIPG) is a devastating childhood brain cancer, in part due to its characteristic aggressive infiltration into surrounding tissue that prevents the option of surgical resection. The lack of surgical options for DIPG contributes to the poor prognosis of the disease – the median survival of patients with DIPG is 10 months after diagnosis.

DIPG is thought to arise from early oligodendroglia lineage precursor cells (OPCs or pre-OPCs) and peaks in incidence during a specific developmental timepoint in mid-childhood, suggesting that the tumor may arise from dysregulated signaling cues in its environment. However, the microenvironmental signaling that regulates DIPG invasion and migration is currently not well understood.

An emerging principle is that signaling pathways classically involved in axon pathfinding during neural development are repurposed in malignancy to regulate cancer invasion. Early studies in adult glioblastoma indicate that inhibition of the Nogo receptor (NgR), important for axon pathfinding and neurite outgrowth, may modulate tumor cell migration *in vitro*. RNA sequencing studies of patient-derived DIPG samples demonstrate that NgR is highly expressed in pediatric DIPG tumors, although the functions of Nogo-NgR signaling have not been well characterized in cells of the oligodendroglia lineage or DIPG tumors specifically. To evaluate the role of NgR in DIPG migration, CRISPR technology was used to delete NgR from a patient-derived metastatic DIPG culture. This study will assess NgR-null tumor spread *in vitro*, with a 3D spheroid migration assay, and *in vivo*, utilizing a mouse xenograft model. The work has elucidated the importance of Nogo pathway signaling in diffuse intrinsic pontine glioma, which may be targeted therapeutically to limit tumor spread. ■

Heather Elizabeth desJardins-Park

Academic Year: 2018-19
Year at Stanford Medical School: 4
Undergrad Education:
Harvard College; Chemistry, AB
Hometown: Fulton, Maryland
Title of Medical Scholars Project:
Establishing the Molecular Basis of the Engrailed-1-Positive Fibroblast Scarring Phenotype

Research Description

Fibrosis causes an estimated 45% of all deaths in the U.S. The formation of nonfunctional, fibrotic scar tissue can result from tissue injury in any organ. Notably, in adult patients, any cutaneous injury involving the dermis – whether from burns, trauma, or other forms of damage – will result in some degree of scarring. Scarring represents a massive clinical and financial burden on our healthcare system, affecting over 250 million patients worldwide every year and translating to an over $20 billion consumer market in the U.S. alone. Despite this substantial burden of disease, no targeted molecular therapy for scarring has ever demonstrated consistent clinical benefit.

While scarring is the inevitable outcome of postnatal mammalian wound healing, mammalian fetuses are capable of scarless healing, wherein normal tissue is regenerated with no scar formation. In 2015, the Longaker lab reported that a specific lineage of fibroblasts, identified by embryonic expression of *Engrailed-1 (En1)*, is responsible for producing scars in the dorsal skin of mice. Interestingly, this "scarring fibroblast" lineage initially contributes to fetal scarless healing, then transitions into a scarring phenotype as development progresses. The aim of the current study is to determine the molecular basis for this scarless-to-scarring phenotypic transition.

Initial work employing reciprocal transplantation of fetal and postnatal En1-positive fibroblasts (EPFs) into a non-native cell niche has demonstrated that EPF healing phenotype (whether scarless or scarring) is cell intrinsic. Additionally, assessment of chromatin accessibility via ATAC-seq showed that the transition from scarless to scarring EPF phenotype is associated with a dramatic epigenetic shift, and specifically may involve epigenetic modulation of certain TGF-B pathway components. The hypothesis is that these signaling factors may regulate the development of the EPF scarring phenotype. Current work is focused on performing transcriptional and functional analysis of EPFs in order to further refine our understanding of which genes are critical for the EPF scarring response. Ultimately, this project aims to identify molecular "master regulators" of scarring which may represent novel therapeutic targets for scarring and other fibroses. ■

Technology Resources

Technology Resources

The Beckman Center's shared technology resources comprises of four highly specialized scientific facilities that serve departments and laboratories throughout Stanford University. In continuous operation since 1989, these core service centers are currently among the best well-operated and most successful service centers at Stanford and generate revenue in excess of $4.5 million annually from faculty, postdoctoral fellow, and graduate student users' campus-wide, as well as from the broader scientific community. This allows the service centers to operate at or close to break-even. The service facilities include:

- Cell Sciences Imaging Facility (CSIF)
- Protein and Nucleic Acid Facility (PAN)
- Fluorescence Activated Cell Sorting Facility (FACS)
- Computational Services and Bioinformatics Facility (CSBF)

The ability to keep these services available and viable is dependent on user fees that reimburse general operating costs, labor, and overhead. Rates are structured by the Beckman Center, with review and consultation by service

center managers. Rate-setting decisions are made annually, based on a review of needs for labor, equipment updates, and other unusual operating costs. Stanford University's Office of Research Administration audits the rate-setting process on an annual basis, certifying to the campus community and the university's cognizant federal agency that service center rates are reasonable and therefore appropriate to charge to sponsored project funds.

In order for the facilities to remain competitive within the academic community and to avail Beckman-affiliated scientists of the use of state-of-the-art scientific technologies, the Beckman Center provides funding as needed to underwrite new technologies employed by the service centers that cannot be recovered through fee structures. The goal is to keep the rates as low as possible in order to encourage the use of services housed in the Beckman Center. This year, the Beckman Center provided supplemental funds to all four service centers. Provided in this section are detailed descriptions of the four service center's operations, their importance to the Stanford research community, and how they used center funds.

Cell Sciences Imaging Facility

OVERVIEW

The Cell Sciences Imaging Facility (CSIF) provides high-resolution, state-of-the-art technologies for imaging and analyzing the molecular and structural organization of cells and tissue, as well as bioengineered materials. The facility offers sophisticated and demanding microscopy techniques (e.g. super-resolution, confocal, FLIM, FRET, FRAP, 2-photon live cell imaging, photo-activation and uncaging, array tomography, atomic-force measurements, immuno-electron microscopy, high-pressure freezing) to Stanford University and industry researchers. The CSIF is organized into three interdependent imaging labs: the Fluorescence Microscopy Core (FMC) which houses multi-photon, confocal, super-resolution, fluorescence lifetime and deconvolution microscopes and image analysis software; the Electron Microscopy Core (EMC), which houses high-resolution scanning and transmission electron microscopes and the Multiplexing and Array Tomography Core (M-ATC) that provides multiplexed marker imaging and tomography services.

Jon Mulholland
Director

The CSIF was founded in 1994 to address the Stanford biomedical research community's growing need for advanced light microscopy expertise, services and equipment. In 2002, in response to many researchers' need for state-of-the-art electron microscopy imaging services, the CSIF established its integrated electron microscopy core. Then, in 2008, with support from the Beckman Center and Stanford's BioX program, the CSIF's Array Tomography Core was created. In 2006, the CSIF joined the School of Medicine's successful effort to establish a NIH Cancer Center and is a member of the Stanford Cancer Institute supporting cancer research. More recently (2014), in a collaborative effort with Stanford's School of Engineering (SOE), the CSIF opened a satellite light microscopy facility in the SOE's Shriram Center. This new facility brings much needed biological imaging instrumentation and expertise to the departments of Bioengineering and Chemical Engineering. Additionally, the CSIF has added a new service of bioimage analysis; this service provides expertise in assembling individual methods into complete bioimage analysis/processing pipelines for specific projects using Python/SciPy. Shriram-CSIF manager, Cedric Espenel, PhD, is spearheading this new expanded service. Lastly, the CSIF is now (2019) adding highly multiplexed antibody marker fluorescence imaging to its array tomography core.

Today, the CSIF's mission remains the same as when it

was first established: to provide access and training in high-resolution, state-of-the-art imaging technologies. While these technologies have evolved substantially over the last 20 plus years, they remain essential, basic tools for studying molecular, sub-cellular and cellular biology and disease. A major element of the CSIF's commitment to its mission is the continuous and ongoing process of upgrading technologies, equipment, and expertise to remain at the forefront of cell sciences imaging.

EXPERTISE

A ten-member advisory committee provides leadership and direction for the CSIF. The committee is chaired by the Beckman Center director, Dr. Lucy Shapiro, and includes among its members, Beverly Mitchell, MD, professor of medicine, member and former director of the Stanford Cancer Institute; Tim Stearns, PhD, Chair of Biological Sciences and an expert in microscopy, as well as seven other researchers from Stanford's Beckman Center, Stanford Cancer Institute, School of Medicine, School of Engineering, and School of the Humanities and Sciences. The CSIF is staffed, in addition to its director, by 6 full-time and 2 part-time research professionals who have expertise and training in electron and light microscopy.

CSIF Group

Back Row, Left to Right: *Tom Flores, Jon Mulholland, Cedric Espenel, Marcin Walkiewicz, John Perrino.* ***Front Row, Left to Right:*** *Anum Khan, Ibanri Phanwar-Wood, Ruth Yamawaki, Kitty Lee*

DESCRIPTION OF SERVICES

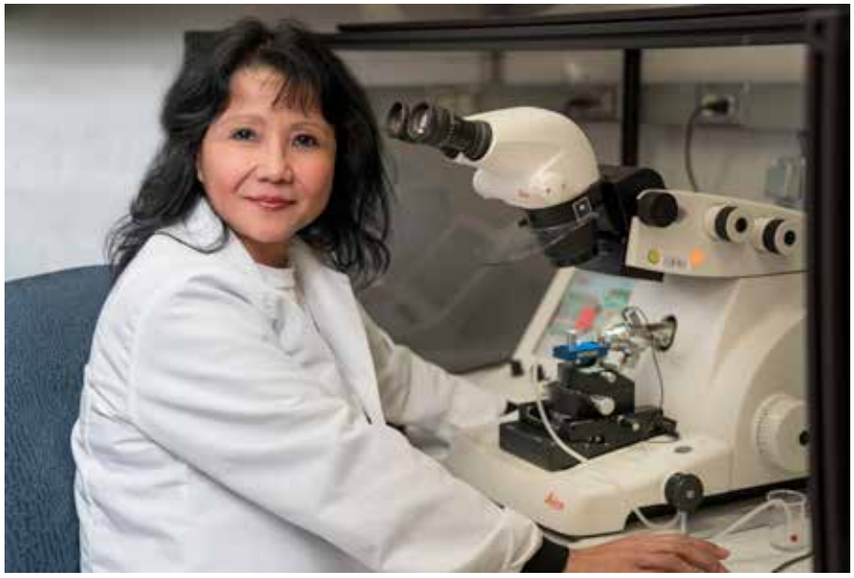
FMC: Fluorescence Microscopy Services

The CSIF's FMC provides training and consultation in the application of super-resolution (API OMX-SIM, STORM; Leica SP8-gSTED, Zeiss AiryScan), laser scanning confocal (Zeiss LSM880, LSM780, Leica SP8, Leica SP5), spinning disk confocal (Nikon-Yakogawa), deconvolution (API OMX Delta Vision), 2-photon (Zeiss LSM780, Leica SP5 - each with Spectra Physics DeepSee laser), fluorescence lifetime imaging (FLIM) light microscopy technologies and Bio-atomic force microscopy (Bio-AFM, Bruker Resolve BioScope). Two-photon, confocal and deconvolution technologies allow optical sectioning while eliminating out-of-focus fluorescence. This makes the precise 3D localization of fluorescently labeled proteins within the cell or tissue possible. Super resolution technologies allow researchers to exceed the diffraction-limited resolution limits of conventional light microscopy (<200nm). This allows researchers to image and resolve structures and cellular dynamics that were previously unresolvable with other optical technologies. FLIM allows researchers to measure changes in a molecule's or protein's fluorescence lifetime in addition to its fluorescence intensity. Bio-AFM enables innovative live cell experiments that provide high-resolution force measurements and mapping over the surface of soft materials, cells and other biological material. Using epifluorescence, brightfield and phase contrast optical imaging, these measurements can be directly correlated with macromolecules, proteins and subcellular structures as cells sense and respond to mechanical cues and

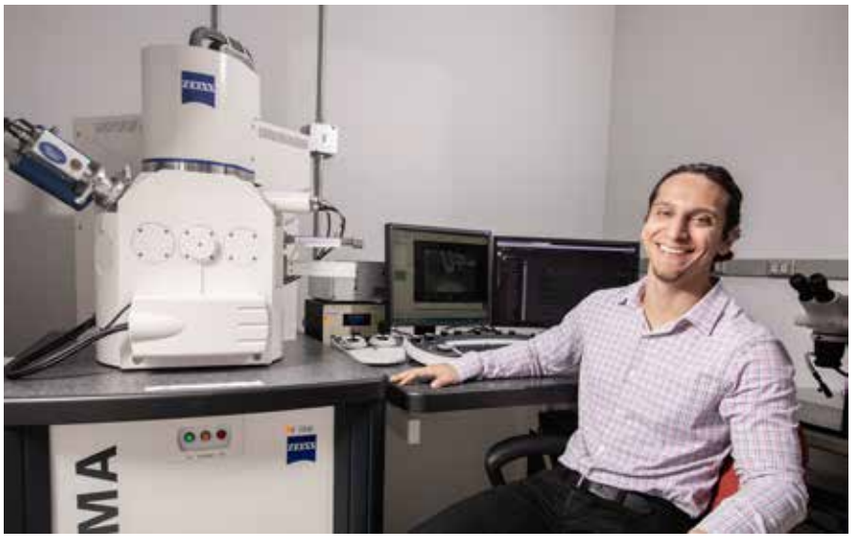
environmental changes. The CSIF also has capabilities for TIRF and super-fast, wide-field live cell imaging. Additionally, time-lapse software allows 3D localization of labeled protein over time; thus, providing 4D data sets. The CSIF provides advanced software resources for 3D, 4D interactive, volume imaging (Improvision Volocity, Bitplane Imaris) of data sets, as well as advanced deconvolution software packages (SoftWoRx and SVI Huygens).

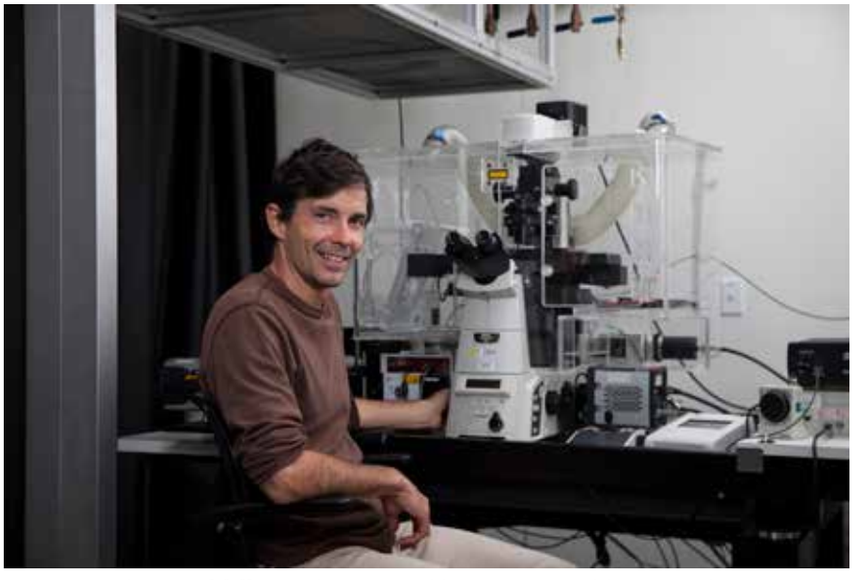
EMC: Electron Microscopy Services

The facility's EMC is a full-service lab that offers sample preparation, training and consultation for both transmission and scanning electron microscopy technologies. The Electron Microscopy Core houses a transmission electron microscope (JEOL 1400-TEM) equipped with high-resolution, cooled CCD cameras for digital acquisition of images. The CSIF's TEM can produce a resolution of 2 angstroms; thus, making it possible to image and study isolated macromolecules and subcellular structures. The TEMs are also fitted with a high-contrast, biological objective lens making it ideal for imaging thin, immuno-localized samples used for the determination of a protein's subcellular location. The facility is also equipped with a field emission scanning EM (FE-SEM, Zeiss Sigma) for high-resolution study of specimen structure and topology. Ancillary equipment includes 3 ultramicrotomes for cutting



Top: *Ibanri Phanwar-Wood,* ***Middle:*** *Anum Khan,* ***Bottom:*** *Marcin Walkiwicz*





Top: *Tom Flores,* ***Middle:*** *Ruth Yamawaki,* ***Bottom:*** *Cedric Espenel*

ultra-thin sample sections (less than 100nm) and a cryo-ultramicrotome for sectioning ultra-thin frozen sections, as well as all the necessary ancillary equipment for sample preparation and computers for image analysis. Additionally, the EMC houses a new state-of-the-art Leica ICE high-pressure freezing machine. High-pressure freezing is the gold standard for fixation of biological microscopy samples and in the numerous studies where it has been applied, high-pressure freezing has extended our understanding of the structural and molecular organization of cells and tissues.

M-ATC: Array Tomography Services

The facility's ATC provides complete multiplexing marker localization and array tomography (AT) services. AT imaging method was invented at the Beckman Center in the Department of Molecular and Cellular Physiology by neuroscientists, Stephen J. Smith and Kristina D. Micheva. Compared to previous microscopic methods for 3D imaging of fixed tissue, array tomography offers increased resolution (z resolution of 200 - 50nm), quantitative reliability, antibody multiplexing capacity and throughput and volume (automated image acquisition). Array tomography also complements live, whole animal or tissue explant imaging studies, providing higher resolution, 3D data with many more molecular markers that can extend the molecular interpretation

of *in vivo* dynamics. Array tomography permits easy acquisition of electron microscopic images in register with immunofluorescence. Array tomography; thus, promises an opportunity to explore the 3D molecular architectures of tissue at an unprecedented level of detail. This methodology is applied by many Stanford researchers and provides unprecedented insights into structural organization and protein location in tissue of numerous organisms and disease models. As described below, the CSIF has added highly multiplexed imaging services to the AT core; thus, giving it a new name M-ACT.

NEW DEVELOPMENTS

1) With financial support from the Beckman Center, the School of Medicine's Dean's Office and the Stanford Cancer Institute, the CSIF has purchased a CODEX, highly multiplexed imaging platform together with an epifluorescence microscope and analysis workstation. This combined instrument will allow automated, highly multiplexed, antibody localizations of potentially an unlimited number of proteins on tissue sections or tissue arrays, with cellular level of resolution. The CODEX instrument will provide greatly increased throughput and analysis of multiple cancer, neurological and other tissue specific markers which will allow phenotypic cluster analysis of different cell types within their spatial context. The facility will provide image analysis and pipeline development support, as well as develop and validate

Top: *Kitty Lee,* ***Bottom:*** *John Perrino*

antibody panels for research groups. The CSIF's CODEX service will start in early 2019.

2) By cost-sharing with the Otolaryngology Department in the medical school, the CSIF has purchased a Leica ICE High-Pressure Freezer (HPF) with the capacity to do optogenetic light and electrical stimulation. This new HPF will allow larger, thicker sample loading for ice-free vitreous ice freezing, the gold-standard for cell preservation than previously available, and will be used for advanced ultrastructural and immuno-EM localization studies in the EM lab. This new instrument was installed in December 2018.

3) Collaborating with the CSIF, Dr. Joanna Wysocka, professor of developmental biology, and of chemical and systems biology, has received approximately $1 million in funding for a lattice light sheet microscope. This microscope will be installed in the CSIF in summer 2019.

4) CSIF director, Jon Mulholland, along with Dr. Rich Lewis, assistant professor of molecular and cellular physiology, and Neuroscience Imaging Service Center director Andrew Olson, taught their now annual 8-week course in biological light microscopy. This course serves as a foundation for supporting the next generation of light microscopists.

Instrument Upgrades:

1) The Beckman Center's Leica SP8 confocal microscope has been upgraded with new scan head, Windows 10 workstation and Lightning Expert (including STED) software. This upgrade will allow the confocal to run Leica's newest software – Lightning – that includes real-time, improved resolution and deconvolution options. The new scan head will provide increased scanning in both linear and resonant mode. Together, the upgrade provides higher resolution, sensitivity and speed, and makes our 5-year old SP8 confocal microscope state-of-the-art again.

2) The facility's spinning Disk confocal microscope (Shriram Center) has been upgraded with a Photometrics Prime 95B sCMOS camera. This camera has a 95% quantum efficiency and is an excellent match for resolution and sensitivity for our CSU-X1 spinning disk. https://www.photometrics.com/products/datasheets/Prime95B-Datasheet.pdf

3) The CSIF has purchased a combined e-Bean carbon, metal evaporator/sputter coater/glow discharge Leica ACE600 unit. This unit will replace our 18-year old sputter coater and carbon evaporator with a single, easy to use tool. The e-Beam will allow very thin (typically 5-10nm), fine grain metal and carbon coating and films. This will make DNA and protein shadowing possible.

FUTURE DEVELOPMENT GOALS

1) Expanded support and services in 2019 will include a negative staining, imaging pipeline for imaging proteins and macromolecules, cryo-EM sample prep using our new ICE HPF, as well as development of the CODEX service.

2) Lastly, the CSIF is continuing to develop and provide correlative electron to light imaging, as well as large volume 3D and array tomography imaging. ■

Protein and Nucleic Acid Facility

OVERVIEW

The mission of the Protein and Nucleic Acid (PAN) Facility (http://pan.stanford.edu) is to be adaptable and responsive to the changing needs of biomedical research by providing the Stanford scientific community continued access to key research tools and applications in an efficient and cost-effective manner. The PAN Facility is committed to providing a diverse array of instrumentation and technical capabilities in molecular genetics and protein analytics with the goal of benefiting investigators in their biomedical research projects and helping them succeed in relevant grant applications.

The advancement and expansion of the PAN Facility's services, since its inception in 1989, is the result of a conscious team effort by the Beckman Administration and PAN Facility to expand services to support the increasing variety of Stanford research programs.

EXPERTISE

An eight-member advisory committee provides oversight, leadership and direction for the PAN Facility. The committee is chaired by the Beckman Center director, Dr. Lucy Shapiro, and includes among its members the PAN director, Dr. Michael Eckart, and seven other researchers drawn from Stanford's Beckman Center, Cancer Institute, School of Medicine, and School of Humanities and Sciences.

Michael Eckart, PhD
Director

The PAN Facility is staffed, in addition to its director, by six full-time experienced research professionals who have been trained in all the services provided by the facility and also offer expertise in specific service areas. The PAN Facility is currently organized into interdependent resources as listed below.

DESCRIPTION OF SERVICES

- Gene Expression Analysis
  - Microarrays
  - Real-time PCR
  - Pyrosequencing
  - Nucleic Acid QC
  - Single Cell Genomics
  - Next-Generation Sequencing (NGS)

- DNA Sequencing
- Oligonucleotide Synthesis
- Biomolecular Interaction Analysis (Surface Plasmon Resonance)
- Peptide Synthesis
- Mass Spectrometry

The core services enable and facilitate efficient and economical biomedical research by providing the user with technology without the necessity of major capital or staffing expense. With the organized and efficient infrastructure that shared resources such as the PAN Facility provide, researchers are able to investigate complex research questions. Beyond merely making facilities and services available, the PAN Facility also enables education, methods development, and new applications development, designed to meet the needs of Stanford's biomedical research community.

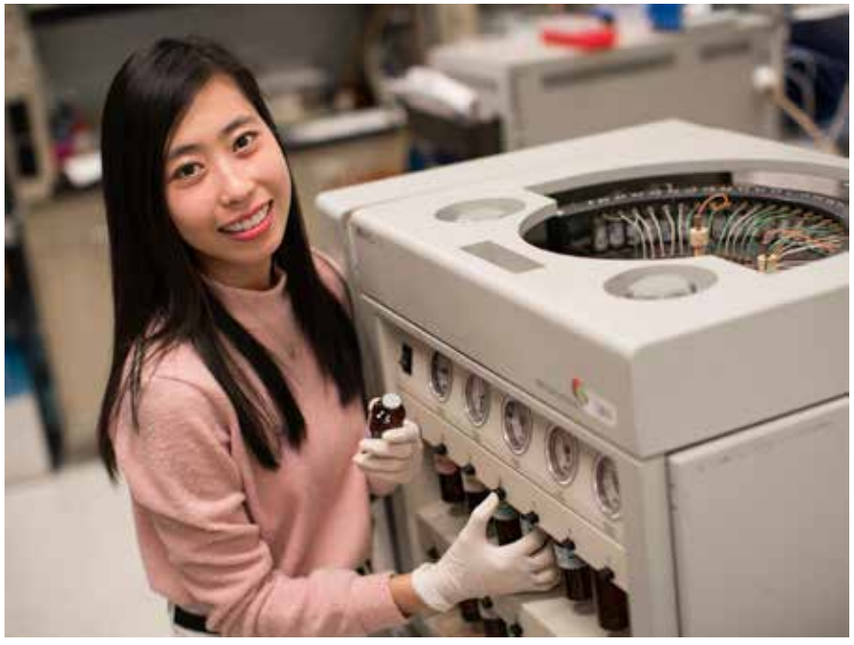
In order to leverage the full potential of the technologies, each of PAN's services is staffed and maintained by highly experienced, and dedicated scientists. They are not only specialists in their respective areas of expertise, but also cross-trained in the operation of multiple instruments and applications to provide the best possible comprehensive research support, including participating in training the next generation of scientists. The PAN Facility can provide as much assistance as needed, from the initial study design through all the procedures needed for an experiment to the final interpretation and analysis of data. Services include standard assays, as well as customized services. The PAN staff are always interested in developing new assays or adapting existing established assays to address a specific research question. Researchers are encouraged to interact closely with PAN staff to obtain maximum benefit of services. Development and implementation of new applications and technologies at Stanford are often achieved when a research group and the PAN Facility staff engage in a joint project whereby each contribute their individual strengths. The results of these efforts are often highlighted in publications to which PAN scientists have made contributions. The consultation provided by PAN staff is often as important as the data since biomedical researchers not trained in a specific technique or field can find it difficult to interpret specialized data without help from PAN scientists who update their skills through appropriate training courses.

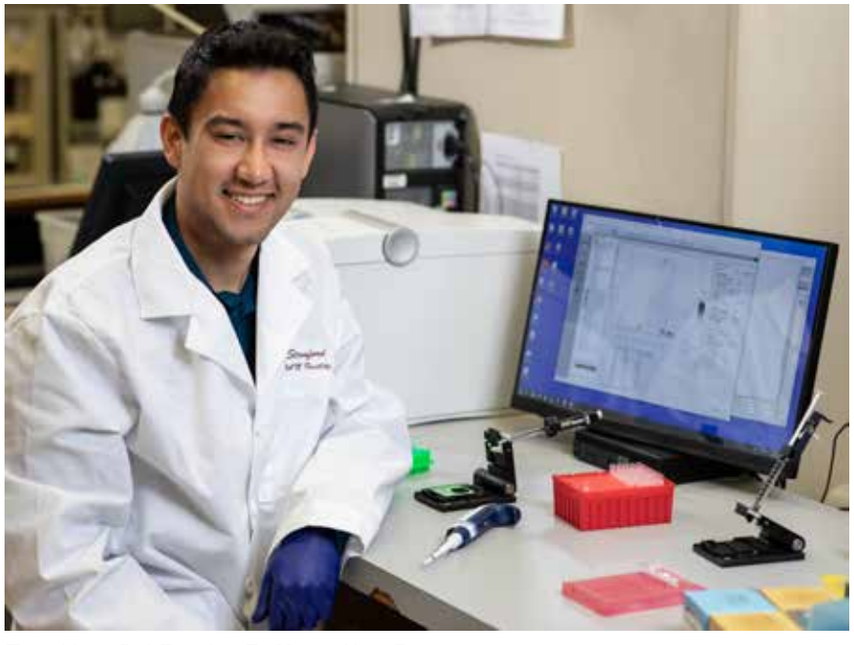
Protein and Nucleic Acid Facility

Back Row, Left to Right: *Ian Anderson, Jennifer Okamoto, Kyle Fukui, Michael Eckart,* ***Front Row, Left to Right:*** *Yen Tran, Nghi Cat Bao Le, Jessica Tran, Agustin Sanchez*

Single-cell genomics, the application of genomic technologies to understanding biology at the level of an individual cell rather than an entire population of cells, continues to be a fast-growing area of science. Elucidating the biological differences between individual cells at the molecular level in, for example, tumor tissue, stem cells, or rare subpopulations of immune cells can provide significant insight into how cells differentiate, how tissues regenerate, and how cells change in disease development. The Single Cell Genomics Laboratory aimed at advancing discoveries and the development of methods in single cell genomics was created by the Beckman Center together with a group of research programs in cancer, stem cell and immunology. PAN

provides a full range of services aimed at advancing discoveries and the development of methods in single cell genomics while fulfilling a critical need for SoM researchers to analyze genomes and transcriptomes in single cells. The Single Cell Genomics Laboratory encourages and enhances collaborations among single cell researchers in the different research areas. Single cell sequencing is performed in three major steps: cell isolation, whole genome/transcriptome library construction, and high-throughput sequencing. The successful, rapid isolation of single cells for genomic analysis is the essential prerequisite and critical step for obtaining meaningful results. This can be achieved by using, for example, fluorescence-activated cell sorting (FACS), by simple micromanipulation or by capture using microfluidic technology. The PAN single cell genomics resource features single cell captures microfluidic technology, the C1 Single Cell Auto Prep instrument (Fluidigm), that processes 96 or 800 single cells, and the ddSEQ Single-Cell Isolator instrument (BioRad) that performs rapid single-cell isolation using droplet partitioning technology. PAN also works closely with the Beckman Center FACS Facility (https://facs.stanford.edu) to perform high-throughput isolation of single cells from the biological system of interest. Cell acquisition is confirmed via an EVOS Cell Imaging System. Once isolated, the cells are automatically lysed, and nucleic acid template generated on the microfluidic chip. Subsequently,



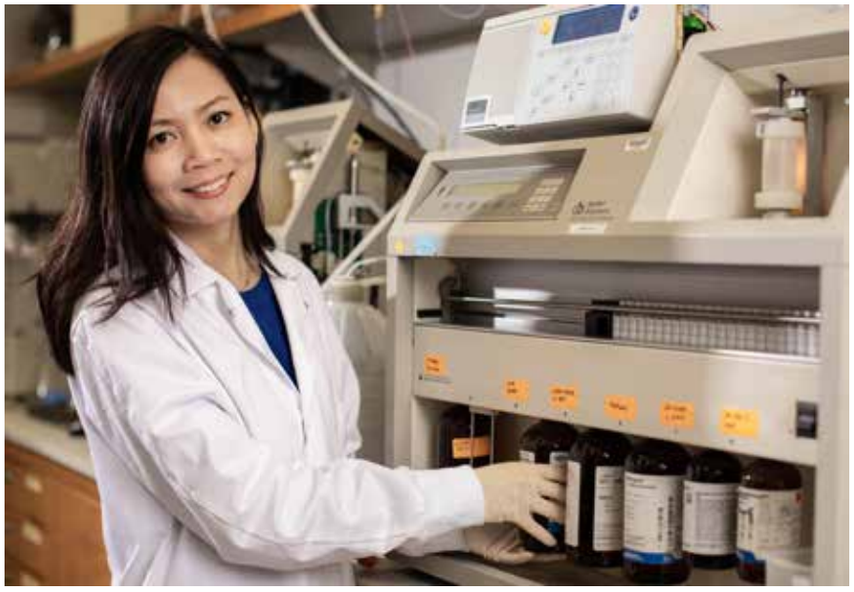


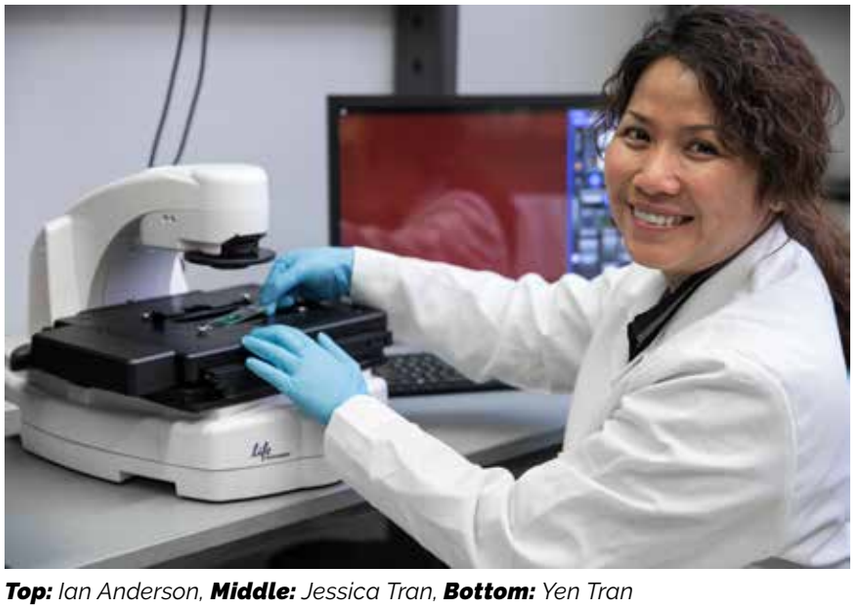
Top: *Nghi Cat Bao Le,* ***Bottom:*** *Kyle Fukui*

PAN processes the templates generated from individual cells for analysis by Next Generation Sequencing. The conversion to Next-Generation Sequencing libraries is accomplished using automated liquid handling instruments. The nanoliter Mosquito HTS liquid handler (TTP Labtech) makes it possible to significantly decrease library preparation costs and increase throughput. To QC different steps in all the workflows, a Fragment Analyzer instrument is used to perform nucleic acid QC.

Currently, single cells are collected from suspensions of dissociated tissue, in which spatial information has been lost. Spatial resolution of gene expression enables

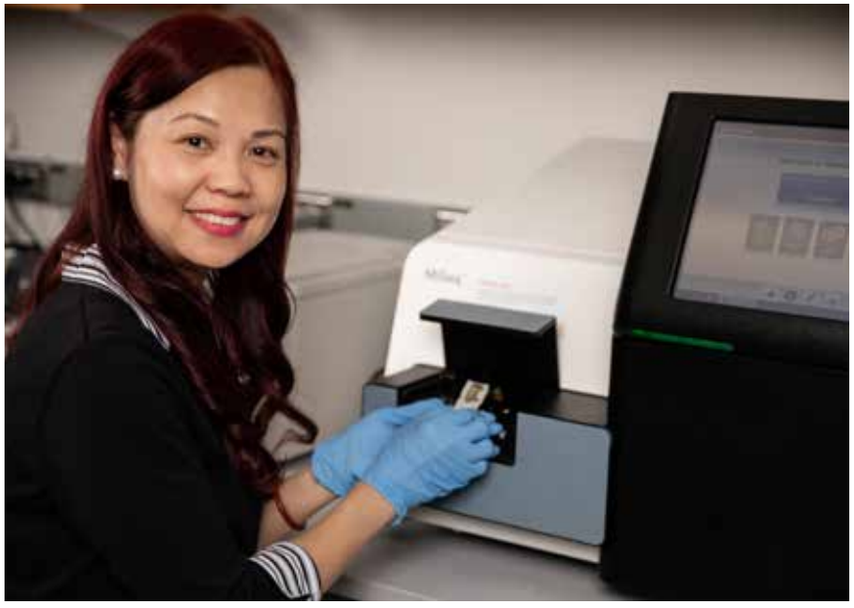
gene expression events to be pinpointed to a specific location in biological tissue. The ability to not only determine the gene expression within a cell, but how the cells are organized in relation to one another, offers invaluable insight into understanding not only disease states in oncology, neurology and immunology, but organism development, as well. Spatially resolved gene expression in tissue sections is traditionally analyzed using immunohistochemistry (IHC) or *in situ* hybridization (ISH) which aside from being laborious and challenging, are low throughput and nonquantitative technologies. To overcome these limitations the PAN Facility is implementing a recently developed technology termed "spatial transcriptomics." This technology combines traditional histology with high-throughput single cell RNA sequencing (scRNA-seq) whereby intact tissue sections are captured on an array containing spatially barcoded, complementary DNA primers for the capture of either full-transcriptome or transcript subsets. Subsequent RNA library generation for Next-Generation Sequencing of a single intact tissue sample utilizes the existing instrumentation in PAN's Single Cell Genomics laboratory. The Spatial Transcriptomics workflow bridges new microscopy techniques and RNA sequencing to generate complete transcriptome data from a single intact tissue sample. To accomplish this the PAN Facility is working with the Beckman Cell Sciences





Top: *Ian Anderson,* ***Middle:*** *Jessica Tran,* ***Bottom:*** *Yen Tran*

Imaging Facility (CSIF; https://microscopy.stanford.edu). The interaction of PAN with the different research programs and technologies in other shared resources (FACS & CSIF), in accordance with our mission, adapts and takes advantage of single-cell tools, protocols and technologies, including equipment acquisition, as they become available so that scientists and clinicians within the Stanford scientific community remain on the cutting edge of scientific research. It is anticipated that the advances made using PAN's scientific resources will enable researchers to obtain a deeper understanding of the underlying causes of diseases such as cancer and immune disorders, and the differentiation of stem cells which have the promise of developing diagnostics and therapeutics in the different areas.



Top: *Jennifer Okamoto,* ***Bottom:*** *Agustin Sanchez*

PAN continues to provide Affymetrix microarray technology for gene expression analysis. Besides a cost and time differential between the NGS and microarray platforms, with microarrays being less expensive and faster, the PAN Facility continues to provide both technologies in a manner that is most effective, most informative and carefully tailored to the scientific question, and the biological system that is being addressed by researchers. With the Next-Generation Affymetrix GeneChip Clariom microarrays a highly detailed view of the transcriptome is achieved that rapidly leads to actionable results. The comparison of array and RNA-Seq profiling technologies in terms of throughput and performance found that the Clariom arrays outperformed RNA-Seq in most all parameters when detecting exonic changes implicated in human disease and genetic disorders. A cost-free easy-to-use Transcriptome Analysis Console (TAC) software is available for Affymetrix microarray data analysis and visualization to allow easy interpretation of significant gene expression changes. Overall, PAN Facility scientists continue to work closely with stem cell and cancer researchers to develop both NGS and microarray methods for genomic profiling of single cells.

PAN's portfolio of technologies also encompasses those that are required for validation of genes and proteins identified in large scale genomic and proteomic studies. We believe that the need for validation technologies will continue to grow since

it is key to demonstrating how genetic or proteomic differences have an effect in a specific disease. Quantitative-PCR (Q-PCR) continues to be popular as a technique to validate array study data. The use of pyrosequencing using the Qiagen PyroMark Q24 instrument for real-time, sequence-based detection for quantification of sequence variants (SNPs/mutation detection) and epigenetic methylation has also increased. The validation of methylation events identified by microarray and high-throughput massively parallel sequencing technologies has been the main driver in pyrosequencing services. Other research phases involve the use of technologies such as peptide synthesis, mass spectrometry, and Surface Plasmon Resonance (SPR) to facilitate a more detailed and more comprehensive molecular study focusing on the complex of proteins expressed in a biological system, their structures, interactions, and post-translational modifications. SPR is a key technology in support of our efforts to meet the post-genomic biological challenge of understanding the complex networks of interacting genes, proteins, and small molecules that give rise to biological form and function. PAN's Biacore T200 instrument offers researchers the opportunity to work confidently at the limits of kinetic, molecular weight, and concentration ranges, bringing improvements in data quality to a wide range of new applications. Using the capabilities of the T200 instrument, PAN scientists have and will continue to work with investigators to perform Fragment-based Lead Discovery (FBLD) to discover small-molecule drug candidates for a variety of drug targets in different disease indications.

The coupling of the existing genomic and protein analysis tools within the PAN Facility significantly extends the understanding of many research questions and helps to further accelerate research programs. For example, by applying and combining a "multi-omics" (single-cell genomics, epigenomics, proteomics) approach researchers are discovering the variation that exists between genetically identical cells within a tissue in response to various physiological and pathophysiological stimuli.

The PAN Facility environment allows the Stanford research community to bridge the technical diversity gap and encourages collaborations that apply the different technologies to biomedical research. PAN Facility scientists reach out for new technical opportunities to broaden horizons by working closely with scientists from different disciplines in implementing scientific breakthroughs and associated methodologies in genomics and proteomics. This enables researchers to make connections between basic and clinical research that will benefit the field of translational medicine. PAN Facility scientists have made significant contributions to many different scientific programs in the form of publications in peer reviewed journals, patents, and presentations at scientific meetings.

FUTURE VISION

The PAN Facility will continue, in an ever-changing scientific environment, to focus on providing solutions to the scientific technological needs that confront researchers. In utilizing its existing strengths and expertise in the different areas, the PAN Facility will continue to support and lay the foundation for the research and discovery efforts of the Stanford scientific community. ■

Fluorescence Activated Cell Sorting Facility

OVERVIEW

Fluorescence Activated Cell Sorting (FACS), also known as flow cytometry, is a high-throughput technique for measuring, classifying, and sorting single cells. For this technology, biological cells are labeled with one to 20 or more fluorescent reagents, often antibodies detecting specific molecules inside cells or on their surfaces. These labeled cells are passed at a high rate in a stream through a sequence of laser beams, and the resulting fluorescence is measured on a per-cell basis. Quantitative evaluation of multiple reagents on each cell enables resolution and analysis of complex mixtures of cells types such as tumor and bone marrow cells. Cell sorters, an advanced subset of flow cytometers, can utilize the quantitative criteria provided by the fluorescent labels for selection, and physically isolate those subsets at a high rate for further studies. Particular strengths of FACS are the flexibility of the selection criteria (e.g., high for label A, but low for labels B and C) and the ability to isolate up to 6 specified live cell types at once. Besides the typical applications using mammalian cells, FACS is also valuable for work with yeast, bacteria, plankton, and other small particles.

Lisa Nichols, PhD
Director

A team led by the late Dr. Leonard Herzenberg of the Stanford Department of Genetics was one of the main developers of FACS instrumentation and techniques in the late 1960s and early 1970s, and throughout the subsequent years the Herzenberg laboratory continued to be a major source of innovation in the field. Dr. Herzenberg initiated the precursor to the FACS Facility in the mid-1980s and joined the Beckman Center when it opened. The FACS Facility, which was then part of the Herzenberg group, also moved to the Beckman Center at that time and was reorganized into a service center.

Since the opening of the Beckman Center in 1989, the FACS Facility has provided cell analysis and sorting capabilities to Beckman Center researchers, other Stanford research groups, and to the regional biotechnology community. The facility also acts as a hub for general FACS education and provides training for users who desire to become self-operators of the facility instruments. The FACS Facility director and staff members provide, as a group, over 100 years of flow cytometry knowledge and are available to assist users in designing experiments and in data analysis. Staff members maintain the facility's instruments and

support facility operations in addition to developing improved technology for advanced applications and instrumentation.

EXPERTISE

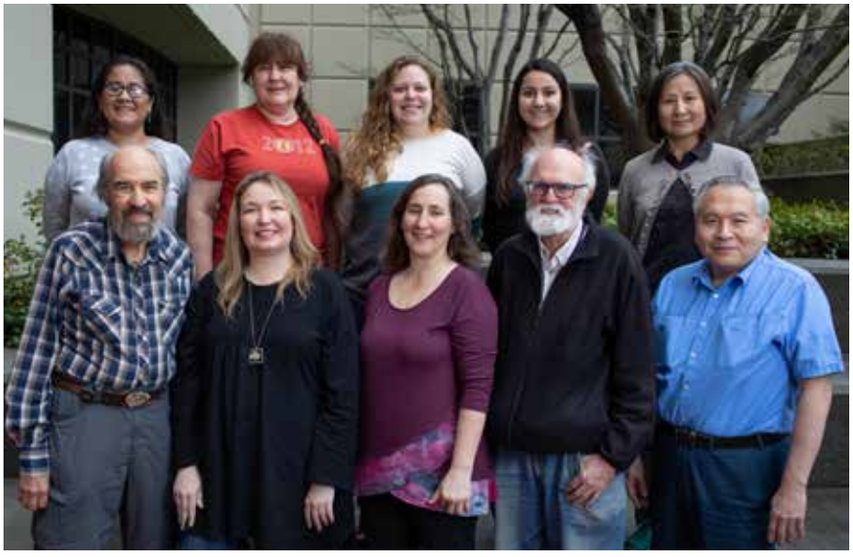
The FACS Facility is under the general oversight of a faculty advisory committee chaired by Dr. Garry Nolan, professor of microbiology and immunology, who did his graduate degree in the Herzenberg lab. Dr. Nolan's current research is ground breaking in its use of cell sorting technology to measure intracellular phosphorylation signaling networks in single cells. The facility director, Dr. Lisa Nichols, is a flow cytometry expert with over 15 years of experience, as well as a scientist with expertise in T cell immunology and cancer immunotherapy. The rest of the staff, with similar long histories in flow cytometry, contribute a level of expertise available at no other site to enable researchers to perform innovative and top-quality work using flow cytometry.

DESCRIPTION OF SERVICES

The services offered by the FACS Facility include the following:

Cell Analysis

Including both BSL-1 & BSL-2 samples, measurements more than 20 simultaneous fluorochromes, and support acquisition from either single sample tubes or automated from 96-well plates. Analyzers are also available to trained users 24/7. Currently, there are six analyzers available, each with different capabilities.



Fluorescence Activated Cell Sorting Facility
Back Row, Left to Right: *Bianca Gomez, Ometa Herman, Meredith Weglarz, Katayoon Atabakhsh, Cindy Jiang,* ***Front Row, Left to Right:*** *Dave Parks, Mary Rieck, Lisa Nichols, Tim Knaak, Tom Nozaki*

Cell Sorting

Including BSL-1 & BSL-2 samples, aseptic sorting, single cell sorting into 96-well and 384-well plates (cloning), and measurement and sorting using up to 18 simultaneous fluorochromes. Sorting is either operator supported during normal business hours or self-operated 24/7 upon completion of training. Ten sorters are available, each with different capabilities.

Mass Cytometry

Analysis of samples using Time of Flight (TOF) mass spectrometry measuring up to 100 different parameters with proteins conjugated to metal ions. Training and operator support are also available.

Instrument Training

Intensive instrument training is provided to users of the facility and is tailored to the user's needs and experimental goals.

Consulting

Staff expertise is available to aid researchers in experimental design and data analysis. An educational seminar series will continue this year with topics ranging from basic cytometry techniques to advanced or specialized cytometry applications.

Software Support

The facility manages a site license for FlowJo data analysis software (FlowJo, Inc., Ashland, OR). The FlowJo license provides Stanford researchers with a discount of approximately 60% off the cost of an individual license.

Data Management Services

Data collected in the facility is stored and archived in a secure, highly redundant system, and made available over the web.

This service is available to the entire Stanford community. The Institute for Stem Cell Biology and Regenerative Medicine and the Canary Center for Cancer Early Detection utilize this service for their flow cytometry data.

Federated Sites

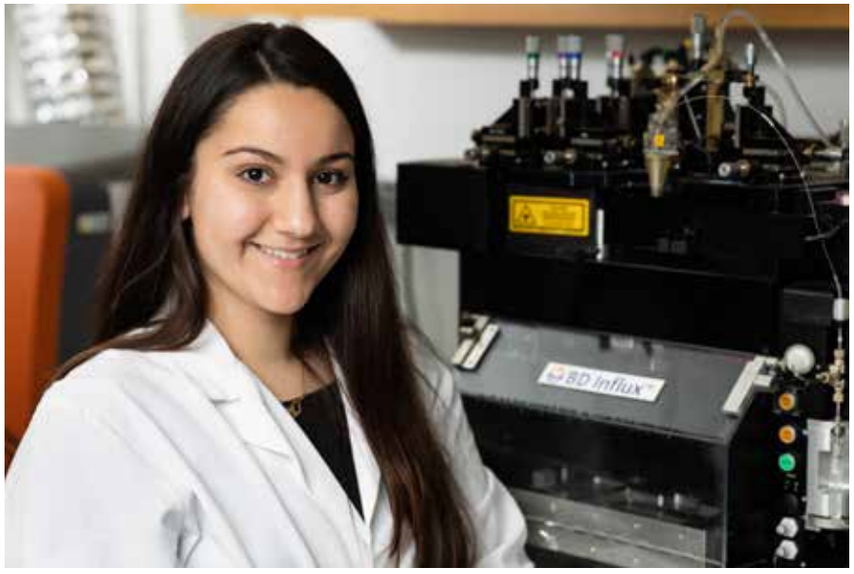
Some research laboratories, because of the nature of their work, need to have flow cytometry equipment on-site. The facility offers individualized contracts to provide management and technical consulting for these groups.

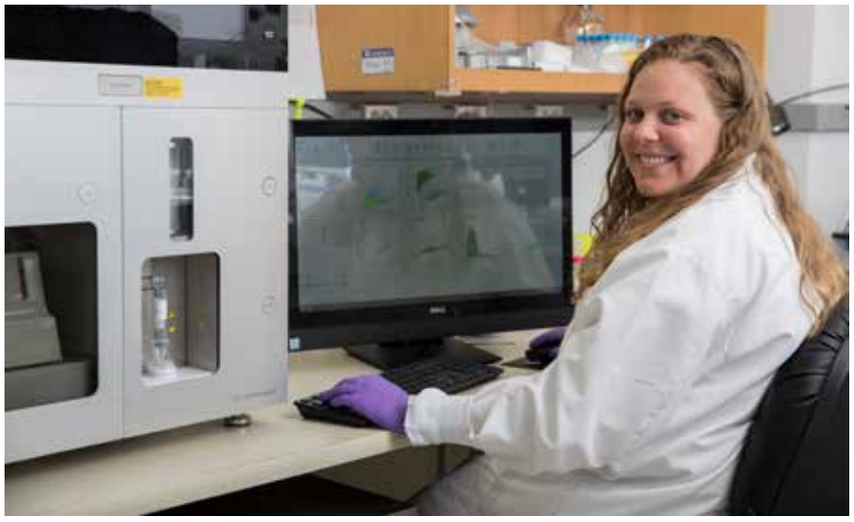
In 2018-2019, the facility provided services to 779 researchers from 290 different labs.

YEAR IN REVIEW

The FACS Facility has continued to enhance its user access and training to support the growing researcher needs for flow cytometry services.

To minimize wait times for instrument access, the facility has steadily increased the instrumentation available to users. In the past two years, the facility has purchased 2 bench-top "walk up" sorters, and the Parker Institute for Cancer Immunotherapy provided funds to purchase another Aria class sorter. As of late 2017, these instruments were fully integrated into the FACS Facility and significantly increased instrument availability for users on the main campus. The facility also maintains and staffs a satellite facility to support the research community at the

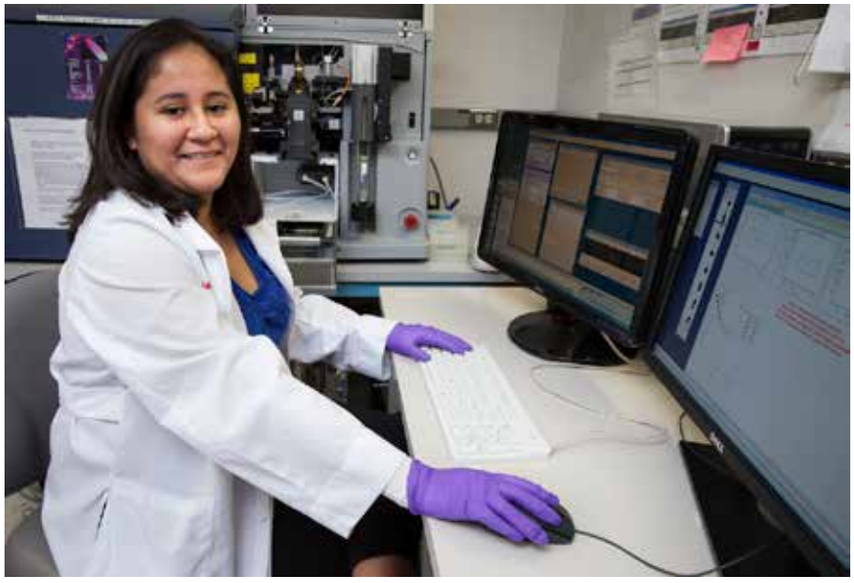


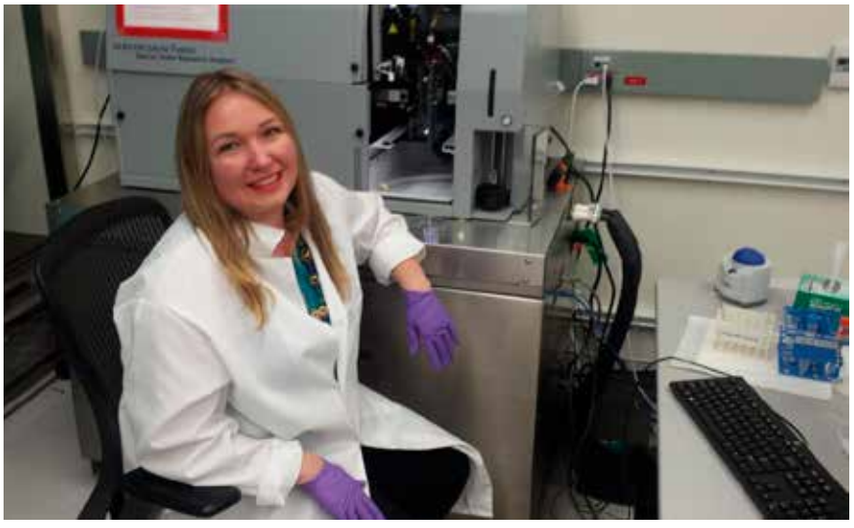


Top: *Katayoon Atabakhsh,* ***Middle:*** *Cindy Jiang,* ***Bottom:*** *Meredith Weglarz*

School of Medicine Technology and Innovation Park at Porter Drive. With the increased number of instruments, facility infrastructure has been completely updated to allow users more streamlined access to training sessions, as well as staff assistance with sorter operation. This satellite service center, established in mid-2017 at the 1651 Page Mill Research Building, supports one analyzer, and one Aria class sorter in space shared with the Human Immune Monitoring Center (HIMC).

Just as demand for FACS Facility sorting services has continued to grow, the need for analyzers (measurements without sorting) has also increased. Analyzer schedules are often filled with more than 12 hours per day of continuous operation. To help meet user needs, the Beckman Foundation generously provided funding for purchase of an additional high-end analytical instrument. The Cytek Aurora cytometer implements state-of-the-art technologies to provide high-quality cytometry data. It utilizes arrays of detectors with high-efficiency light collection for analysis of the emitted fluorescence photons, and it's also a "full-spectrum" or "spectral" cytometer. Traditional cytometers use narrow filters to collect the peak of the fluorescent labels' emission. In contrast, as a "spectral" cytometer the Aurora has an array of detectors/ filters evenly spaced across the spectrum of light emission to collect not only the peak, but the majority of photons emitted from each label on the cells. Altogether, this approach has





Top: *Ometa Herman,* ***Middle:*** *Bianca Gomez,* ***Bottom:*** *Mary Rieck*

provided a new instrument with excellent sensitivity allowing researchers to resolve more than 20 fluorescent labels simultaneously, even for low level signals.

Finally, to complement purchase of new instrumentation, funding from the Beckman Foundation had enabled upgrade of some of the older sorting and analytical instruments. In recent years, the number of stable fluorescent dye labels commercially available for researchers has grown exponentially, and with modest investment, such upgrades as laser additions, extend the useful lifetime of high-end equipment.

Altogether, with the opening of the satellite facility, and the additional instrumentation at the main campus site, the FACS Facility currently provides complete support and training for 10 sorters, 6 analyzers, and one CyTOF mass cytometer. Looking forward, primary goals will be to provide educational opportunities in flow cytometry, both at Stanford and in the surrounding research community. With excellent staffing levels, the Stanford Shared FACS Facility is positioned to provide users a wide-range of support. This includes access both to operator-supported instrument operation for sorting or analysis, or alternatively, access to our hands-on cytometry training. Currently, training for all instrumentation includes small group, as well as extensive one-on-one instruction geared towards individual experimental goals. The facility's ongoing

seminar series complements this focus on cytometry education with guest and in-house speakers providing short-talks and workshops on various topics including experimental design, advanced techniques, and data analysis.

SUMMARY

The FACS Facility provides critical support for a large and diverse group of researchers at the university. This includes access to state-of-the-art flow cytometry technology, secure data management, instrument training and operator support when needed, as well as consultation by FACS scientists on experimental design and data analysis. Although focused on the more basic research community, the facility can, and has supported clinical research, analyzing primary samples from patient populations, and provides BSL-2 analysis and sorting capability to accomplish this goal. The facility has built upon this successful record and continually updates both instrumentation and its infrastructure to promote accessibility and facilitate high-end research. Moreover, the Stanford Shared FACS Facility has been and will continue to be committed to introducing new technologies that further the discovery potential of its user base. ■

Computational Services and Bioinformatics Facility

OVERVIEW

Under the direction of Lee Kozar, the Computational Services and Bioinformatics Facility (CSBF) provides computer software support for more than 5,000 people in over 300 different research labs and 36 different departments at Stanford University. Both commercial and public domain software for sequence analysis, molecular modeling, and mathematical and statistical analysis are available from this facility. A full description of the facility and its services can be seen on the facility's website: https://csbf.stanford.edu.

EXPERTISE

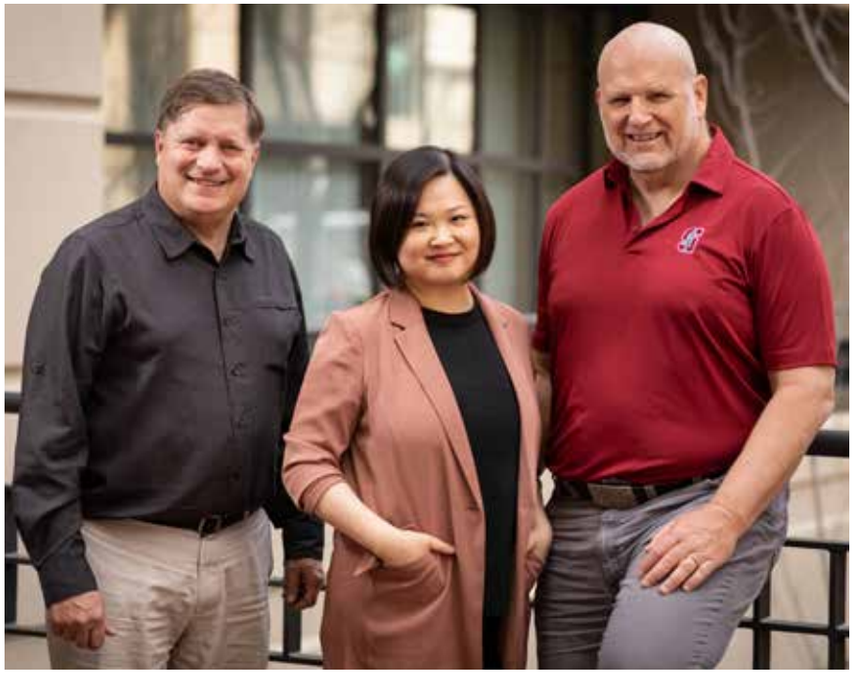
The CSBF staff members have many years of experience in providing computer support to biomedical researchers and have worked in the lab at some point in their careers. They are intimately familiar with the CSBF software and the needs of the scientific research community. The CSBF works closely with other core facilities within the Beckman Center to ensure that the CSBF has the necessary hardware and software for analyzing the wide variety of data that is generated by the different cores. Basically, the other service centers within the Beckman Center provide the instrumentation for generating the data, while the CSBF provides the computer hardware and software for analyzing the data flowing out of these facilities.

Lee Kozar
Director

DESCRIPTION OF SERVICES

The CSBF provides a variety of Macintosh, Windows and Linux software for scientific research and general administrative use. The CSBF obtains concurrent network licenses that work under the control of a software license manager. This allows the facility to purchase a limited number of copies of expensive software, but distribute the software widely within the Stanford network; thus, providing a substantial savings to the individual researcher. For example, one of CSBF's most popular software

packages costs over $20,000 per license per year, which makes it prohibitively expensive for many labs. Other software packages cost hundreds or even thousands of dollars per license. With a membership in the CSBF, researchers can gain access to these software products at a significantly lower cost. This gives even small labs access to the software tools that previously only large, well-funded labs could afford. The CSBF also shoulders the hidden cost of installing and managing the licenses and license servers, making a membership in the CSBF attractive even when labs can afford to purchase their own software.



Computational Services and Bioinformatics Facility
Left to Right: *Lee Kozar, Ling Xie, Alan Hebert*

While there are many public domain software packages available for doing scientific research, the CSBF has focused on providing access to commercial software because, in most cases, commercial scientific software has significant advantages over its public domain counterparts. Commercial software offers technical support, is usually easier to install and run, is updated more frequently, and is less prone to errors.

In addition to providing a full range of popular software programs like Microsoft and Adobe products, the facility offers software in the following categories:

- Sequence Analysis (DNAstar, SnapGene, MacVector, Sequencher, Geneious, CLCBio)
- Molecular Modeling (Tripos Sybyl, Spartan)
- Microarray Analysis (GeneSpring, Partek, iPathwayGuide)
- Genomics Analysis (Geneious Server, Golden Helix, Partek Flow, JMP Genomics)
- Mass Spectrometry (Mascot, PEAKS, ProteinMetrics)
- Database (MySQL, FileMaker, EndNote)
- Statistical & Mathematical Analysis (SPSS, Matlab, Mathematica, Systat, GraphPad)
- Graphics (Illustrator, Photoshop, BioRender)
- Microscope Imaging (Volocity, Imaris,Metamorph)
- Gel Electrophoresis Imaging (Nonlinear Dynamics)
- Electronic Lab Notebooks (LabArchives, Benchling)

These software packages are repackaged by the CSBF so they can be easily downloaded from the facility's website and installed, already configured for use within the Stanford network. Many of these software packages can be used from off-campus and special licensing arrangements can be made so that the software will still work even when not connected to a network. This means that Stanford researchers have access to the software they need no matter where they may be.

A full list of the software offered by the CSBF can be found on the facility's website: http://csbf.stanford.edu/software

Researchers may also request that specific titles be added to the software library. The CSBF is frequently able to negotiate a concurrent network license with the vendor so that the facility is able to purchase the license and make it available on the CSBF server.

The Beckman Center offers Technology Innovation Grants

to faculty members to fund the development of new core facility services that can be used for the benefit of all core facility users. In the past year, we have funded two proposals to bring new software into the core facility. Along with benefitting the individual lab that requested the grant, this software can be shared with other users of the CSBF software library.

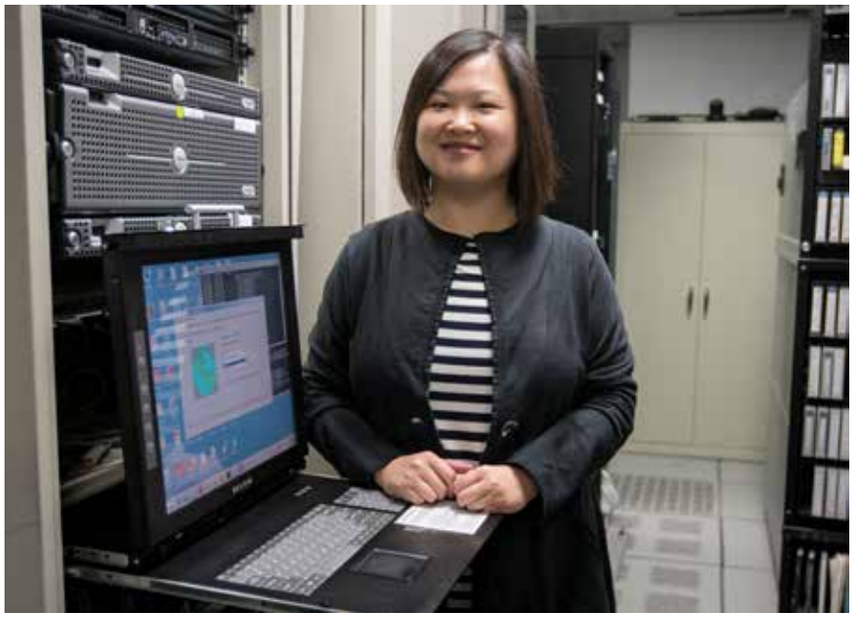
The quantity and quality of software available through the CSBF is unmatched by any other university. Most other bioinformatics service centers provide only open source, free software. While the CSBF also provides a wide variety of public domain software, we also attempt to obtain the very best commercial software for biomedical research. Very few other universities provide even one of the commercial packages that the CSBF makes available to Stanford researchers.

To access CSBF software, the first step is to obtain a CSBF membership. This can be done online from the following website: http://csbf.stanford.edu/membership.

The CSBF has two levels of membership:

A Level 1 membership gives everyone in a specific lab access to the bioinformatics computer facilities. This includes the large library of commonly used Mac, PC and UNIX software.

The Level 2 membership gives a specific lab access to all CSBF software including



Top: *Ling Xie,* ***Bottom:*** *Alan Hebert*

the more expensive software packages such as GeneSpring, iPathwayGuide, Imaris, Volocity, Partek and others.

It is also possible to join at Level 1 and upgrade to Level 2 at a later date with a prorated charge.

Information about the different levels of software are available at: http://csbf.stanford.edu/membership/Level1.html http://csbf.stanford.edu/membership/Level2.html

In the past year, over 300 different labs from 36 different departments have had memberships in the CSBF. On average, over 5,000 computers per month utilize this software library and at peak usage over 500 individual software licenses are checked out. The CSBF software library has become an indispensable asset to researchers in the Beckman Center, as well as to the broader research community at Stanford. Besides the software library, the CSBF provides a variety of other facilities for CSBF members.

The CSBF has a wide variety of different computer hardware platforms. The main server, CMGM, is a Sun V490 server running the Solaris operating system. This server has a wide variety of UNIX based sequence analysis software and also functions as the web server that is used for downloading the CSBF software library. This web server also hosts many lab and departmental websites. The CSBF also has a large Linux system that hosts proteomics and genomics software.

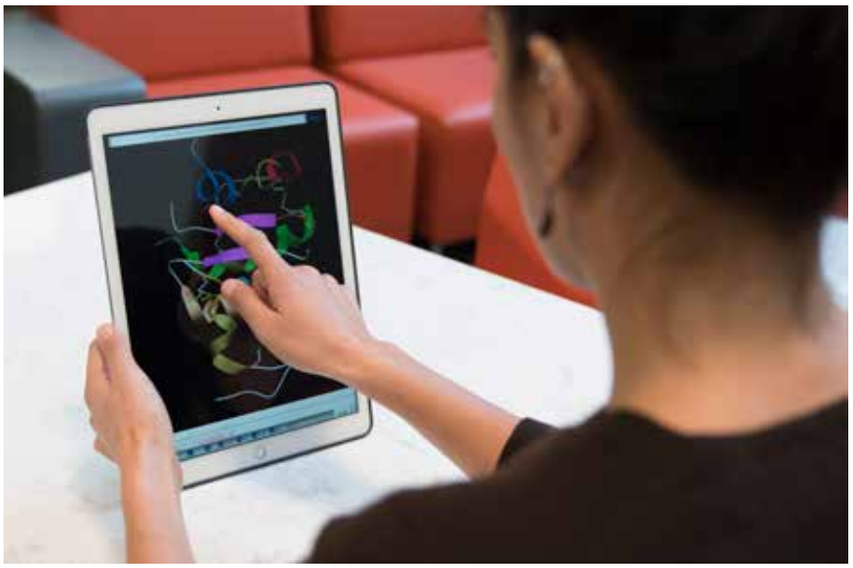
Lee Kozar
Director

The CSBF also offers desktop computer support for Beckman Center researchers. Services such as software installations, troubleshooting, data recovery and minor computer repairs are routinely provided through phone calls, email, online chat or personal visits. We recently installed a steriolithographic 3D printer which we use to create physical models of molecular structures or laboratory equipment. These models are useful to help visualize the structure of biological molecules. The CSBF has recently remodeled its main office area to provide a more comfortable work environment and area for consultation with users.

The CSBF houses most of its computer equipment in a dedicated server room in the Beckman Center, as well as the main Stanford server farm. This special room in the Beckman Center is controlled for temperature and humidity, along with a regulated power source to control any power spikes that may damage equipment. It has been earthquake retrofitted and is also protected by a Halon™ fire suppression system. The server room also houses computer equipment from other labs and service centers in the Beckman Center, providing a secure location to store important computer hardware and research data. The server room is equipped with a variety of environmental monitors and the CSBF staff is alerted by email or text message if there is a problem in the room.

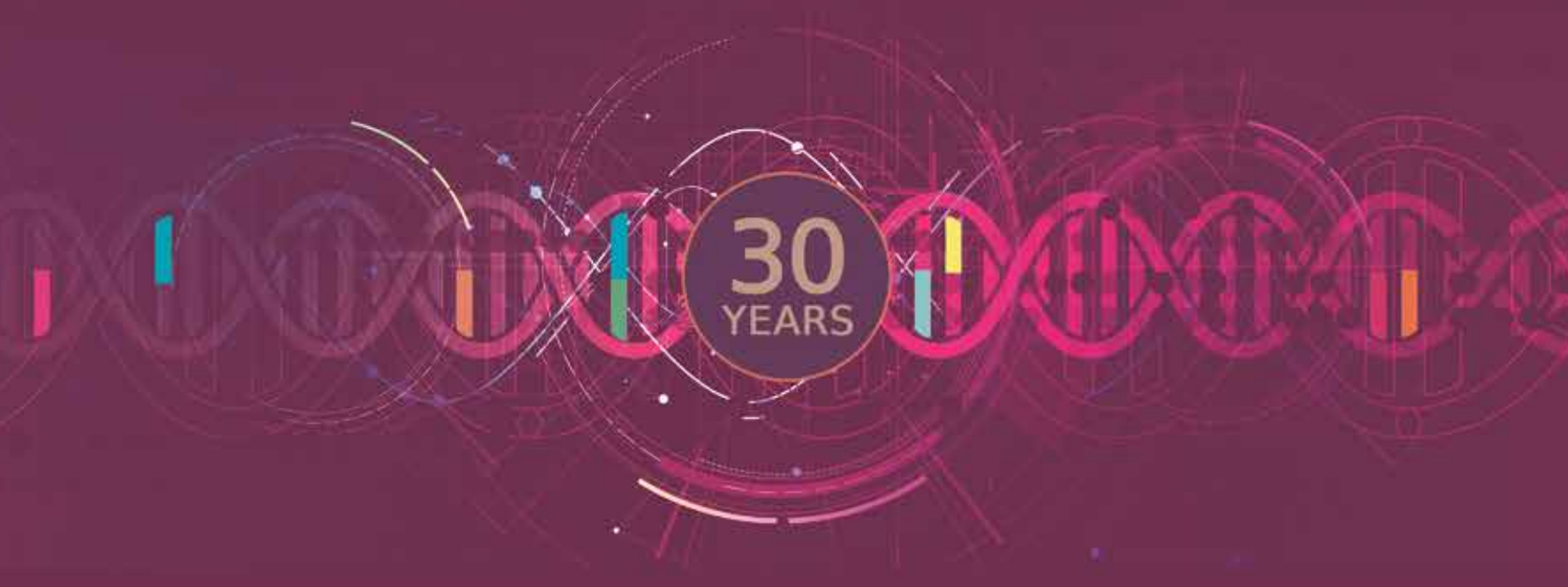
There is a significant amount of institutional knowledge in the CSBF that is critical to the functioning of this core facility. While it is important to back up the computer data, it is also important to back up the knowledge that each member

of the CSBF has acquired over time. To accomplish this, the CSBF has set up two Wiki sites: one public and one private. The public Wiki site has information that the users of the CSBF might need in order to better utilize the available software and hardware offerings. The private Wiki is only accessible by members of the CSBF and contains important information regarding policies, procedures, license codes, troubleshooting techniques and any other information that the CSBF team deems important to record. ■



Top: *Alan Hebert, Ling Xie,* ***Middle:*** *Facility User*
Bottom: *Alan Hebert, Facility User*

Academic Departments



Overview of Academic Departments

Department of Biochemistry

Under the leadership of department chair Suzanne Pfeffer, research in the Department of Biochemistry encompasses very diverse questions and uses a wide variety of approaches, experimental systems, and techniques. Nevertheless, what bonds members of the department is an interest in understanding fundamental biological questions at the level of how molecules act and interact to accomplish highly complex, intra- and intercellular processes. The diversity of the department enriches the intellectual environment and provides an incredibly broad spectrum of expertise that benefits everyone, as members of the department tackle a wide variety of important questions. All researchers in the department study molecules: proteins, RNA, DNA, and polyphosphate; and analyze their synthesis, structure, actions and interactions. They use physical techniques such as spectroscopy, laser light traps and crystallography, cell biological techniques such as light microscopy and cell fractionation, biochemical techniques such as enzyme purification and characterization, along with molecular biological techniques and genetics. By attacking problems using these complementary approaches, departmental researchers are best suited to pave the way towards solving the questions at hand.

Suzanne Pfeffer, PhD
Professor and Chair of Biochemistry

Two features about the department are especially noteworthy. First, members of the department share all of the space and major equipment. Thus, students and postdocs from different groups are intermixed. This enhances interactions at all levels and guarantees equality in terms of access to all resources and equipment. Second, everyone works hard to maintain a collegial, cooperative and supportive environment. All faculty are engaged in the

operation and mission of the department, and share and uphold philosophies of operation and community spirit that all members hold dear.

FACULTY RESEARCH

Steve Artandi's lab is interested in unraveling the molecular and cellular mechanisms which telomeres and telomerase modulate stem cell function and carcinogenesis. **Onn Brandman**'s lab studies how cells ensure protein quality and how they signal stress. The lab uses an integrated set of techniques including single cell analysis of proteotoxic stress pathways, structural studies, in vitro translation, and full genome screens. **Gil Chu**'s laboratory studies cellular responses to damaged DNA. The group focuses on pathways for the repair of UV-damaged DNA and the repair of DNA double-strand breaks induced by ionizing radiation and V(D)J recombination in order to understand the mechanisms that generates immunological diversity. **Rhiju Das**'s research group strives to predict how RNA sequence determines the folding properties of proteins, nucleic acids and heteropolymers, and establishes their ultimate structure. **Ron Davis** is using Saccharomyces cerevisiae and Human DNA to conduct whole genome analysis projects. The **James Ferrell** lab has been studying the system of regulatory proteins that drives the cell cycle, through a combination of quantitative experimental approaches, computational modeling, and the theory of nonlinear dynamics. **Pehr Harbury** aims to measure and understand dynamic structural changes in proteins, and their role in the functional biology of macromolecular machines. **Dan Herschlag**'s laboratory is aimed at understanding the chemical and physical behavior underlying biological macromolecules and systems, behaviors that define the capabilities and limitations of biology. **Peter Kim** studies the process by which proteins cause viral membranes to fuse with cells, designs molecules that stop membrane fusion by HIV, and pioneers efforts to develop vaccines based on similar principles. The research in **Mark Krasnow**'s laboratory is focused on understanding lung development, stem cells and disease, including cancer, and the neural circuits that control lung function, including breathing and speaking. **Ling Yin Li** uses chemical biology to uncover biochemical mechanisms in innate immunity and, in parallel, develop therapeutic hypotheses and lead compounds. **Suzanne Pfeffer**'s group is investigating the molecular mechanisms by which proteins are targeted to specific membrane compartments. They seek to understand how transport vesicles select their contents, bud, translocate through cytoplasm, and then fuse with their targets, as well as other similar processes. **Rajat Rohatgi**'s lab is working to elucidate the biochemical and cell biological principles that govern signaling pathways that sit at the intersection between developmental biology and cancer. **Julia Salzman**'s research group develops statistical and experimental tools to construct a high dimensional picture of gene regulation, including cis and trans control of the full repertoire of RNAs expressed by cells. The general research interest of the **James Spudich** lab is the molecular basis of cell motility. Research interests include the molecular basis of energy transduction that leads to ATP-driven myosin movement on actin, the biochemical basis of regulation of actin and myosin interaction and their assembly states, and the roles these proteins play *in vivo*, in cell movement and changes in cell shape. The **Aaron Straight** group studies the process of cell division in eukaryotes focusing on the mechanisms of chromosome segregation. **Ellen Yeh**'s research goal is the elucidation of apicoplast biology, function, and role in pathogenesis with the ultimate goal of realizing the potential of the apicoplast as a therapeutic target.

2018-2019 FACULTY HONORS, AWARDS AND APPOINTMENTS

Steven Artandi—professor of biochemistry and of medicine, was named the new Laurie Kraus Lacob Director of the Stanford Cancer Institute, effective October 1, 2018. A medical oncologist and cancer biologist, Artandi studies the role of telomerase in stem cells and cancer.

Gil Chu—professor of biochemistry and of medicine (oncology) was named a member of the American Physical Society in 2018.

Dr. Chu also received the 2018 Asian American Community Faculty Award. The award recognizes the contributions of an outstanding professor who has represented the Asian American community at Stanford by enhancing undergraduate and/or graduate education or community.

Daniel Herschlag—professor of biochemistry, was among the 84 members elected in 2018 to the National Academy of Sciences at the 155th annual meeting in 2018.

Peter Kim—the Virginia and D.K. Ludwig Professor of Biochemistry, received an Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences from the Stanford Medicine Alumni Association. Established in 2010, the award recognizes the lifetime achievements of School of Medicine alumni in the biomedical sciences.

Mark Krasnow—professor of biochemistry, was appointed the Paul and Mildred Berg Professor, effective April 10, 2018. He is the executive director of the Wall Center for Pulmonary Vascular Disease and a Howard Hughes Medical Institute investigator.

Dr. Krasnow was also elected a member of the National Academy of Sciences at the academy's 156th annual meeting in 2019.

Ling Yin Li—assistant professor of biochemistry, received a 2018 DOD Breast Cancer Breakthrough Award, Level 2. The awards are made to support promising research that has the potential to lead to or make breakthroughs in breast cancer.

Suzanne Pfeffer—the Emma Pfeiffer Merner Professor in the Medical Sciences, and professor and chair of biochemistry, was awarded the Martin and Winifred Ehlers Named Professorship at the Mayo Clinic.

Rojat Rohatgi—associate professor of biochemistry and of medicine (oncology), was elected to membership in the American Society for Clinical Investigation in 2018.

James Spudich—the Douglass M. and Nola Leishman Professor of Cardiovascular Disease, and professor of biochemistry, was awarded the 2018 Founders Award by the Biophysical Society. The Founders Award is given to scientists for outstanding achievement in any area of biophysics.

Dr. Spudich also received a 2018 Alumni Achievement Award from the University of Illinois.

Ellen Yeh—assistant professor of biochemistry, of pathology and of microbiology and immunology, was the recipient of a Scholar-Innovator Award from the Harrington Discovery Institute. The awards recognize physician-scientist innovators throughout the U.S. and Canada, whose research has the potential to change standard of care.

HISTORICAL FACULTY HONORS AND AWARDS

Steven Artandi

Association of American Physicians	2015
American Association for the Advancement of Science	2008
American Society for Clinical Investigation	2008

Robert L. Baldwin, Emeritus

Founders Award, Biophysical Society	1999
Merck Award, American Society for Biochemistry and Molecular Biology	1999
Wheland Award in Chemistry, University of Chicago	1995
Stein & Moore Award, Protein Society	1992
American Academy of Arts and Sciences	1981
National Academy of Sciences	1980

Paul Berg, Emeritus

American Institute of Chemistry Gold Medal	2008
Lifetime Achievement Award, Association for Molecular Pathology Award	2008
Pontifical Academy of Sciences	1996
Honorary Doctor of Sciences, Pennsylvania State University	1995
Foreign Member, Royal Society, UK	1992
Honorary Member, Academy of National Sciences of the Russian Federal Republic	1991
Honorary Doctor of Sciences, Oregon State University	1989
National Library of Medicine Medal	1986
Honorary Doctor of Sciences, Washington University, St. Louis	1986
National Medal of Science	1983
American Philosophical Society	1983
American Association for the Advancement of Science Award for Scientific Freedom and Responsibility	1982
Foreign Member, French Academy of Sciences	1981
Canada Gairdner International Award	1980
Albert Lasker Basic Medical Research Award	1980
Nobel Prize in Chemistry (shared with Drs. Walter Gilbert and Frederick Sanger)	1980
Honorary Doctor of Sciences, University of Rochester and Yale University	1978
V.D. Mattia Prize of the Roche Institute for Molecular Biology, National Academy of Medicine	1974
National Academy of Sciences	1966
American Academy of Arts and Sciences	1966
California Scientist of the Year	1963
Eli Lilly Award in Biochemistry	1959

Onn Brandman

Helen Hay Whitney Postdoctoral Fellowship	2009

Patrick Brown, Emeritus

CEO and Founder, Impossible Burger	2011
National Academy of Medicine	2009
Medal of Honor, American Cancer Society	2006
Curt Stern Award, American Society for Human Genetics	2005
Rave Award, WIRED Magazine	2004
ASM-Promega Biotechnology Award, American Society for Microbiology	2003

Biotech Helsinki Prize, Finnish National Fund for R & D	2003
Innovation Award, Discover Magazine	2002
National Academy of Sciences	2002
Takeda Award, Takeda Foundation	2002
America's Best - Genomics, TIME Magazine	2001
NAS Award in Molecular Biology, National Academy of Sciences	2000
Jacob Heskel Gabbay Award, Brandeis University	1998

Douglas L. Brutlag, Emeritus

Fellow, American College of Medical Informatics	2001
Honorary Professor of Bioinformatics, Keio University	2000
ComputerWorld-Smithsonian Award in Science	1992
Henry and Camille Dreyfus Teacher-Scholar	1979

Gil Chu

American Physical Society	2018
Asian American Community Faculty Award	2018
Kaiser Award for Excellence in Preclinical Teaching	2015
Lawrence H. Mathers Award for Exceptional Commitment to Teaching	2014
Burroughs Wellcome Clinical Scientist Award for Translational Research	1997
Leutje-Stubbs Faculty Scholar	1990
Robert W. Cahill Faculty Prize in Cancer Research, Stanford University	1989

Rhiju Das

American Chemical Society OpenEye Outstanding Junior Faculty Award, Stanford University	2015
W.M. Keck Foundation Medical Research Grant Award, Stanford University	2012
Burroughs Wellcome Career Award at the Scientific Interface	2008
British Marshall Scholar, Harvard University	1998

Ron Davis

Named among the top 7 of "Today's Greatest Inventors", Atlantic Magazine	2013
Warren Alpert Foundation Prize	2013
Gruber Genetics Prize	2011
Inventor of the Year, Silicon Valley Intellectual Property Law Association (SVIPLA)	2011
Distinguished Alumni Award, California Institute of Technology	2007
Recipient of Dickson Prize in Medicine, University of Pittsburgh	2005
Herbert A. Sober Award, ASBMB/IUBMB	2004
Lifetime Achievement Award, Genetics Society of America	2004
Senior Scholar Award in Global Infectious Disease, Ellison Medical Foundation	2002
Biotechnology Research Award, Chiron Corporation	1998
Genetics Society of America Medal	1998
Louis S. Rosentiel Award	1992
National Academy of Sciences	1983
United States Steel Award	1981
Award in Microbiology and Immunology, Eli Lilly and Co.	1976

James Ferrel

Moosa Award, Korean Society for Molecular Biology	2009
Leutje-Stubbs Faculty Scholar	1994
Searle Scholars Award	1991

Pehr Harbury

MacArthur Fellow	2005
NIH Director's Pioneer Award	2005
Schering-Plough Awardee, American Society for Biochemistry and Molecular Biology	2004
Burroughs Wellcome Young Investigator in the Pharmacological Sciences	2003
Searle Scholars Award	2002
MIT Technology Review Magazine's 100 Young Innovators	1999

Dan Herschlag

National Academy of Sciences	2018
ASBMB William Rose Award	2010
Cope Scholar Award, American Chemical Society	2000
Pfizer Award in Enzyme Chemistry	1997
David and Lucile Packard Fellowship in Science and Engineering	1995
Searle Scholars Award	1993
Lucille P. Markey Scholar Award	1990
Helen Hay Whitney Postdoctoral Fellowship	1989
American Institute of Chemists Award in Biochemistry, SUNY-Binghamton	1982
Award for Excellence in Biochemistry, SUNY-Binghamton	1982

David S. Hogness, Emeritus

International Prize for Biology	2007
Thomas Hunt Morgan Medal	2003
March of Dimes Prize in Developmental Biology	1997
Humboldt Research Award	1995
European Molecular Biology Organization	1992
Genetics Society of America Medal	1984
Howard Taylor Ricketts Award	1977
American Academy of Arts and Sciences	1976
National Academy of Sciences	1976
Newcomb Cleveland Prize	1965

A. Dale Kaiser, Emeritus

Abbott Lifetime Achievement Award	1997
Thomas Hunt Morgan Award, Genetics Society of America	1992
Prize for Basic Medical Research, Waterford	1981
Lasker Award, Basic Medical Research	1980
American Academy of Arts and Sciences	1970
National Academy of Sciences	1970
US Steel Award in Molecular Biology	1970

Peter S. Kim

Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences	2018
National Academy of Engineering	2016
Doctor of Science, Honoris Causa, Pohang University of Science and Technology	2011
Korean Academy of Sciences and Technology	2011
American Academy of Arts and Sciences	2008
National Academy of Medicine	2000
Hans Neurath Award, The Protein Society	1999
American Academy of Microbiology	1997

National Academy of Sciences	1997
Mack Award, Ohio State University	1995
DuPont Merck Young Investigator Award, The Protein Society	1994
Eli Lilly Award in Biological Chemistry	1994
Ilchun Award, Korean Society of Molecular Biology	1994
NAS Award in Molecular Biology, National Academy of Sciences	1993
Excellence in Chemistry Award, ICI Pharmaceuticals	1989

Arthur Kornberg, Emeritus (1918-2007)

Honorary Member, Japan Society	2004
Arthur Kornberg Medical Research Building, University of Rochester, NY	1999
Canada Gairdner International Award	1995
Cosmos Club Award	1995
National Medal of Science	1979
American Philosophical Society	1970
Foreign Member, Royal Society, UK	1970
Nobel Prize in Medicine (shared with Dr. Severo Ochoa)	1959
National Academy of Sciences	1957
Paul-Lewis Award in Enzyme Chemistry	1951

Mark Krasnow

National Academy of Sciences	2019
National Academy of Medicine	2016
Kaiser Family Foundation Award for Preclinical Teaching	2012
American Academy of Arts and Sciences	2009
NSF Presidential Young Investigator Award	1991
Lucille P. Markey Scholar Award	1987
Helen Hay Whitney Postdoctoral Fellowship	1985
Medical Alumni Prize, University of Chicago	1985

I. Robert Lehman, Emeritus

Herbert Tabor Research Award of the American Society for Biochemistry and Molecular Biology	2008
Merck Award, American Society for Biochemistry and Molecular Biology	1995
National Academy of Sciences	1977
American Academy of Arts and Sciences	1973
Honorary Doctor of Medicine, University of Gothenburg	
Honorary Doctor of Sciences, University of Paris	

Lingyin Li

DOD Breakthrough Award Level 2	2018
Baxter Faculty Scholar, Donald E. and Delia B. Baxter Foundation	2017
NIH Director's New Innovator Award	2017
Ono Pharma Foundation Breakthrough Science Initiative Award	2017
NIH Pathway to Independence Award (K99/R00)	2015
The Jane Coffin Childs Memorial Fund for Medical Research Fellowship	2012

Suzanne Pfeffer

Martin and Winifred Ehlers Named Professorship, Mayo Clinic	2019
American Academy of Arts and Sciences	2013

President, American Society for Biochemistry and Molecular Biology	2010
President, American Society for Cell Biology	2003
NSF Presidential Young Investigator Award	1988
Basil O'Connor Scholar Award	1987
William M. Hume Faculty Scholar	1986
Helen Hay Whitney Postdoctoral Fellowship	1984

Rojat Rohatgi

American Society for Clinical Investigation	2018
NIH Director's New Innovator Award	2012
Pew Scholar Fellow	2010
Basil O'Connor Scholar Award	2010
Distinguished Scientist Award, Sontag Foundation	2010
Martin D. Abeloff Scholar, V Foundation for Cancer Research	2009

Julia Salzman

NSF CAREER Award	2016
McCormick-Gabilan Fellowship	2015
Alfred P. Sloan Fellow	2014
Baxter Faculty Scholar Grantee, Donald E. and Delia B. Baxter Foundation	2014
NCI K99/R00 Pathway to Independence Award	2012

James Spudich

Alumni Achievement Award, University of Illinois	2018
Founders Award, Biophysical Society	2018
Liberal Arts and Sciences Alumni Achievement Award, University of Illinois	2015
Honorary Doctor of Sciences, Guelph University	2014
Ahmed H. Zewail Award Gold Medal, Wayne State University	2013
Massry Prize, Massry Foundation	2013
Albert Lasker Basic Medical Research Award	2012
Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences	2012
Wiley Prize in Biomedical Sciences, Rockefeller University	2012
E.B. Wilson Medal, The American Society for Cell Biology	2011
US Genomics Award for Outstanding Investigator, Single Molecule Biology, Biophysical Society	2006
American Academy of Arts and Sciences	1997
Repligen Award in Chemistry of Biological Processes, American Chemical Society	1996
Lewis S. Rosenstiel Award, Brandeis University	1996
Biophysical Society Lifetime Research Career Award, Biophysical Society	1995
Alexander von Humboldt Research Award	1991
American Heart Association Research Prize	1991
National Academy of Sciences	1991

Aaron Straight

Stanford Faculty Excellence in Teaching Award	2014
American Cancer Society Research Scholar Award	2011
Gordon Family Scholar of the Damon Runyon Foundation	2005
Frederick E. Terman Fellowship, Stanford University	2005

Julie Theriot, Emeritus

Professor of Biology, University of Washington	2018
Kaiser Foundation Award for Excellence in Preclinical Teaching	2010
John D. and Catherine T. MacArthur Foundation Fellow	2004
David and Lucile Packard Foundation Fellowship for Science and Engineering	1998
Junior Award, Women In Cell Biology Committee of the ASCB	1994
Whitehead Fellow, Whitehead Institute for Biomedical Research	1993
Fellow, Howard Hughes Medical Institute Predoctoral	1988

Ellen Yeh

Harrington Scholar-Innovator Award	2019
Burroughs Wellcome Career Award for Medical Scientists	2012

Department of Developmental Biology

Developmental Biology are working at the forefront of basic science research to understand the molecular mechanisms that generate and maintain diverse cell types during development. Research groups use a variety of innovative approaches including genomics, computation, biochemistry, and advanced imaging, and study organisms ranging from microbes to humans, with a primary interest in the evolution of these organisms. This work has connections to many areas of human health and disease, including stem cell biology, aging, cancer, diabetes, and novel strategies for stimulating repair or regeneration of body tissues. The department is a dynamic, interactive research community situated in one of the world's best environments for biomedical research.

Roel Nusse, PhD
Professor and Chair of Developmental Biology and Howard Hughes Medical Institute Investigator

FACULTY RESEARCH

Maria Barna is investigating ribosome-mediated control of gene expression in space and time during cellular differentiation and organismal development. Her research group is also employing state-of-the-art live cell imaging to visualize call signaling and cellular control of organogenesis. **Philip Beachy**'s group studies the function of Hedgehog proteins and other extracellular signals in injury repair and regeneration, primarily through effects on stem cell physiology. They also study abnormal signaling and perturbed stem cell physiology as it occurs in tissue disorder and in the formation and expansion of cancer stem cells. The members of **Gill Bejerano**'s lab focus on a fundamental question in human genomics: the relationship between geno(me) type and phenotype. The group studies genome function in human and related species by mapping genome sequence (variation) to phenotype (differences) and extracting specific genetic insights from deep sequencing measurements. **Alistair Boettiger**'s lab aims to understand how long-range interactions between non-consecutive parts of the genome are regulated to control gene expression. **James Chen**'s group integrates synthetic chemistry and developmental biology to interrogate the molecular mechanisms that control embryonic patterning, tissue regeneration, and oncogenesis. The focus of research in the **Gerald Crabtree** laboratory is the role of chromatin regulation in development and human cancer. **Margaret Fuller**'s research group seeks to understand the mechanisms that regulate stem cell behavior and in particular the mechanisms that regulate and mediate cellular differentiation during

male gametogenesis, using spermatogenesis in Drosophila as a powerful genetic model system. **Daniel Jarosz**'s lab aims to gain insight into the interplay among genetic variation, phenotypic diversity, and environmental fluctuations in complex cellular systems. **Seung K. Kim** lab has created unprecedented opportunities for harnessing knowledge about the molecular and cellular basis of pancreatic development and growth to restore pancreas islet function and to diagnose pancreas cancers. They trust their discoveries will provide the tools and expertise needed to produce islet regeneration therapies for type 1 diabetes, improve treatments and tests to mitigate or prevent type 2 diabetes, and generate new therapeutic strategies for endocrine or exocrine pancreas cancers. **David Kingsley** is using a combination of genetic and genomic approaches to identify the detailed molecular mechanisms that control evolutionary change in vertebrates. **Kyle M. Loh**'s lab aspires to understand how different human cell-types form from stem cells, and how developing tissues incipiently take shape and form. **Roeland Nusse**'s laboratory is interested in the growth, development and integrity of animal tissues. The group studies multiple different organs, trying to identify common principles, and extend these investigations to cancer and injury repair. The laboratory has a long-standing interest in the activity of Wnt proteins during embryogenesis and other processes. **Lucy Shapiro**'s laboratory studies the mechanisms used to generate the three-dimensional organization of a cell from a one-dimensional genetic code. Their goal is to define the complete genetic circuitry that regulates cell cycle progression in time and space. **Will Talbot**'s lab focuses on the development and function of glial cells in the vertebrate nervous system. **Anne Villeneuve**'s lab group is interested in elucidating the events required for the orderly segregation of homologous chromosomes during meiosis, the crucial process by which diploid germ cells generate haploid gametes. **Bo Wang**'s research group is working at the interface between statistical physics, developmental biology, and bioengineering. They seek to understand, quantitatively, the fundamental rules that control stem cell collective behavior to optimize tissue regeneration, remolding, and adaptation. **Irving Weissman's**'s lab studies the phylogeny and developmental biology of the cells that make up the blood-forming and immune systems. The focus of the research in **Joanna Wysocka**'s lab is to understand how regulatory information encoded by the genome is integrated with the transcriptional machinery and chromatin context to allow for emergence of form and function during human embryogenesis and evolution, and how perturbations in this process lead to disease.

2018-2019 FACULTY HONORS, AWARDS AND APPOINTMENTS

Maria Barna—assistant professor of developmental biology and genetics, was awarded a 2019 Early Career Award by the RNA Society.

Alistair Boettiger—assistant professor of developmental biology, was awarded a New Innovator Award by the National Institutes of Health.

Dr. Boettiger was also awarded a 2018 Packard Fellowship in Science and Engineering from the David and Lucile Packard Foundation. Boettiger will investigate how the three-dimensional structure and organization of the genome regulates gene expression and cell fate in embryonic development.

Dr. Boettiger was also named a Fellow of the Kavli Frontiers of Science Program of the National Academy of Sciences, which brings together outstanding young scientists to discuss exciting advances and opportunities in a broad range of disciplines.

Dr. Boettiger also received a 2018 Beckman Young Investigator Award from the Arnold and Mabel Beckman Foundation.

David Kingsley—professor of developmental biology, was appointed the Rudy J. and Daphne Donohue Munzer Professor in the School of Medicine, effective October 16, 2018. His research examines the molecular mechanisms that underlie evolutionary traits and common diseases in vertebrates.

Kyle Loh— assistant professor of developmental biology, has received the Fannie and John Hertz Foundation's 2018 Thesis Prize for his work, "A developmental roadmap for the diversification of human tissue fates from pluripotent cells."

Roeland Nusse—professor of developmental biology, was appointed the Reed-Hodgson Professor of Human Biology, effective September 1, 2018.

Anne Villeneuve—professor of developmental biology and of genetics, was awarded the 2019 Genetics Society of America Medal. The Medal is awarded to an individual member of the Society for outstanding contributions to the field of genetics in the last 15 years.

Irving Weissman—the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research and professor of developmental biology, was the recipient of the 2019 Arthur Kornberg and Paul Berg Lifetime Achievement Award in the Biomedical Sciences. Established in 2010, the award recognizes lifetime achievements of Stanford University School of Medicine alumni in the biomedical sciences.

Joanna K. Wysocka —professor of developmental biology and chemical and systems biology, and Howard Hughes Medical Institute investigator, was elected to membership in the American Academy of Arts and Sciences.

Dr. Wysocka was also appointed the Lorry Lokey Professor in the School of Medicine, effective December 4, 2018.

HISTORICAL FACULTY HONORS AND AWARDS

Maria Barna

RNA Society Early Career Award, RNA Society	2019
H.W. Mossman Award in Developmental Biology, American Association of Anatomists	2017
Inaugural Elizabeth Hay Award, Society of Developmental Biology	2017
Tsuneko and Reiji Okazaki Award, Japan	2017
Emerging Leader Prize, American Society for Cell Biology	2016
Rosalind Franklin Young Investigator Award, Gruber Foundation and Genetics Society of America	2016
Alfred P. Sloan Fellow	2014
Mallinckrodt Foundation Award, Edward Mallinckrodt Jr. Foundation	2014
Pew Scholar Fellow	2014
Top '40 under 40', Cell Press	2014

Philip A. Beachy

Katharine Berkan Judd Award for Cancer Research, Sloan Kettering Institute	2016
Keio Medical Science Prize	2011
March of Dimes Prize in Developmental Biology (shared with Cliff Tabin)	2008
American Academy of Arts and Sciences	2003
National Academy of Sciences	2002
NAS Award in Molecular Biology, National Academy of Sciences	1998

Gill Bejerano

Sony Faculty Scholar Award	2014
Microsoft New Faculty Fellowship	2009
Alfred P. Sloan Fellow	2008
Packard Fellowship for Science and Engineering	2008
Searle Scholars Award	2008
Young Investigator Award, Human Frontier Science Program	2008

Alistair Boettiger

Beckman Young Investigator Award, Arnold and Mabel Beckman Foundation	2018
Kavli Fellow	2018
NIH Director's New Innovator Award	2018
Packard Fellow	2018
Searle Scholars Award	2017
Dale F. Frey Award for Breakthrough Scientists	2016
Burroughs Wellcome Fund CASI Fellow	2015

James K. Chen

NSF INSPIRE Award	2013
Nature SciCafe Award for Outstanding Research Achievement	2009
NIH Director's Pioneer Award	2008
American Cancer Society Research Scholar Award	2008
Brain Tumor Society/Rachel Molly Markoff Research Chair	2006
Astellas USA Foundation Award	2005
Kimmel Scholar, Sidney Kimmel Foundation for Cancer Research	2004

Gerald R. Crabtree

Javits Neuroscience Investigator Award	2013
Thomas Scientific Laureate in Chemistry with Stuart Schreiber	2006
Outstanding Inventor, Stanford University	2004
National Academy of Sciences	1997
Warner Lambert Parke Davis Award	1986

Margaret T. Fuller

Invited Graduation Ceremony Speaker for Human Biology, Stanford University	2015
Excellence in Teaching Award, Stanford Biosciences	2014
National Academy of Medicine	2011
American Academy of Arts and Sciences	2008
National Academy of Sciences	2008
Mary Ingraham Bunting Fellowship, Radcliffe College	1994
Scholar in Cancer Research Award, American Cancer Society	1994
Searle Scholars Award	1985

Daniel Jarosz

Faculty Scholar, Bert and Kuggie Vallee Foundation	2017
Glenn Award for Research in Biological Mechanisms of Aging	2016
CAREER Award, National Science Foundation	2015
David and Lucile Packard Fellowship in Science and Engineering	2015
Director's New Innovator Award, National Institutes of Health	2015
Kimmel Scholar, Sidney Kimmel Foundation for Cancer Research	2015
Louis Pasteur Award, Belgian Brewing Society	2015
Searle Scholars Award	2014
Pathway to Independence (K99/R00) Award, National Institutes of Health	2011
MIT Center for Environmental Health Sciences Research Award	2006

Seung K. Kim

Ho-Am Award in Medicine	2014
Gerald and Kayla Grodsky Basic Science Research Award, JDRF	2013
Pew Scholar Fellow	1999
Baxter Junior Faculty Career Development Award, Donald E. and Delia B. Baxter Foundation	1999
Howard Hughes Medical Institute Junior Faculty Scholar Award	1999
SmithKline Beecham Junior Faculty Scholar Award, Stanford University	1998

Stuart Kim, Emeritus

Glenn Award for Research in Biological Mechanisms of Aging	2008
Ho-Am Award in Medicine	2004
Ellison Scholar	2002
Searle Scholars Award	1990
Lucille P. Markey Scholar Award	1988
Helen Hay Whitney Postdoctoral Fellowship	1985

David Kingsley

GSA Medal, Genetics Society of America	2017
National Academy of Sciences	2011
Conklin Medal for Outstanding Research in Developmental Biology, Society for Developmental Biology	2009

American Academy of Arts and Sciences	2005
Investigator, Howard Hughes Medical Institute	1997
Scholar in Biomedical Research, Lucille P. Markey Foundation	1989

Kyle M. Loh

Human Frontier Science Program Young Investigator	2019
Pew Biomedical Scholar	2019
The Anthony DiGenova Endowed Faculty Scholar, Stanford University	2018

Harley McAdams

John Scott Award, Philadelphia City Trust (shared with Lucy Shapiro)	2009
American Academy of Microbiology	2006

Roeland Nusse

Breakthrough Prize in Life Sciences	2017
Feodor Lynen Medal, Miami Winter Symposium	2015
Flexner Discovery Lecturer Vanderbilt University	2015
National Academy of Sciences	2010
Named "Research Leader in Medical Physiology" in Annual Scientific American 50	2003
American Academy of Arts and Sciences	2001
Peter Debeye Prize, University of Maastricht, The Netherlands	2000
Honorary Member, Japanese Historical Society	1998
Royal Danish Academy of Sciences and Letters	1997
European Molecular Biology Organization	

Matthew P. Scott, Emeritus

President, Carnegie Institution for Science (2014-2017)	2014
Pasarow Award in Cancer Research	2013
National Academy of Medicine	2007
The Conklin Medal, Society for Developmental Biology	2004
National Academy of Sciences	1999
American Academy of Arts & Sciences	1996
Passano Award	1990

Lucy Shapiro

Pearl Meister Greengaard Prize	2013
National Medal of Science	2013
Louisa Gross Horwitz Prize	2012
Abbott Lifetime Achievement Award	2010
Canada Gairdner International Award	2009
John Scott Award, Philadelphia City Trust (shared with Harley McAdams)	2009
Selman Waksman Award, National Academy of Sciences	2005
American Philosophical Society	2003
FASEB Excellence in Science Award	1994
National Academy of Sciences	1994
American Academy of Microbiology	1993
American Academy of Arts and Sciences	1992
National Academy of Medicine	1991

Will Talbot

Award for Excellence in Faculty Advising in Human Biology	2017
Catherine R. Kennedy & Daniel L. Grossman Fellow in Human Biology	2014
Rita Allen Foundation Scholar	2002
NYU Whitehead Fellowship for Junior Faculty	1997

Anne Villeneuve

GSA Medal, Genetics Society of America	2019
National Academy of Sciences	2017
American Cancer Society Research Professor Award	2016
American Academy of Arts and Sciences	2016
Kirsch Investigator Award	2003
HHMI Junior Faculty Scholar Award	1999
Searle Scholars Award	1996

Bo Wang

Beckman Young Investigator Award, Arnold and Mabel Beckman Foundation	2017
Hellman Faculty Scholar Award, Hellman Fellows Fund	2017
Baxter Faculty Scholar Award, Donald E. and Delia B. Baxter Foundation	2016

Irving Weissman

Arthur Kornberg and Paul Berg Lifetime Achievement Award in Biomedical Sciences	2019
Donald Metcalf Award, International Society of Experimental Hematology (ISEH)	2017
Helmholtz International Fellow Award, Helmholtz Zentrum Munchen	2017
Honorary Doctorate, University of Turku	2017
Charles Rodolphe Brupbacher Prize for Cancer Research	2015
Chinese-American BioPharmaceutical Society (CABS) K. Phong Award in Life Sciences	2015
McEwen Innovation Award, International Society for Stem Cell Research	2015
Agency for Science, Technology and Research (A*Star) National Day Award, The Public Service Medal (Friends of Singapore), A*Star	2013
Alumni Achievement Award, Montana State University	2013
Award of Honor, Radiological Society of North America	2013
Max Delbruck Medal of the Max Delbruck Center, Berlin	2013
Bennett J. Cohen Award, University of Michigan	2012
Hall of Fame, Montana BioScience Alliance	2012
Honorary Professor, Peking Union Medical College	2010
Simon M. Shubitz Award for Excellence in the Field of Cancer Research, University of Chicago	2010
Physician Scientists Award, The Passano Foundation	2009
Rosenstiel Award, Brandies University (shared with Shinya Yamanaka and John Gurdon)	2009
The Cockrell Foundation Award in Clinical or Translational Research	2009
American Philosophical Society	2008
Robert Koch Award (shared with Shinya Yamanaka and Hans Scholer)	2008
Doctor of Science, Honoris Causa, Mount Sinai School of Medicine	2007
American-Italian Cancer Foundation Prize for Scientific Excellence in Medicine	2006
Honorary Doctorate, Columbia University	2006
John Scott Award, Philadelphia City Trust	2006
The Linus Pauling Medal for Outstanding Contributions to Science	2005
Alan Cranston Awardee, Alliance for Aging Research	2004
Jessie Stevenson Kovalenko Medal, National Academy of Sciences Council	2004
American Diabetes Association Elliott Proctor Joslin Medal	2003

J. Allyn Taylor International Prize in Medicine	2003
Society of Neurological Surgeons Bass Award	2003
California Scientist of the Year	2002
Distinguished Scientist Award, Association of American Cancer Institute	2002
National Academy of Medicine	2002
Van Bekkum Stem Cell Award	2002
Ellen Browning Scripps Society Medal	2001
Irvington Institute Immunologist of the Year	2001
E. Donnall Thomas Prize	1999
Leukemia Society of America de Villier's International Achievement Award	1999
American Academy of Microbiology	1997
American Academy of Arts and Sciences	1990
National Academy of Sciences	1989
Pasarow Award for Outstanding Contribution to Cancer Biology	1989
Kaiser Award for Excellence in Preclinical Teaching	1987

Joanna Wysocka

American Academy of Arts and Sciences	2018
Valkhof Chair Award, Radboud University Nijmegen, the Netherlands	2017
AAA's Harland Winfield Mossman Award in Developmental Biology	2013
Vilcek Prize for Creative Promise	2013
International Society for Stem Cell Research Outstanding Young Investigator Award	2010
W.M. Keck Distinguished Young Scholar in Biomedical Research Award	2008
Searle Scholars Award	2007
Baxter Faculty Scholar Award, Donald E. and Delia B. Baxter Foundation	2007
Frederick E. Terman Fellowship, Stanford University	2006

Department of Molecular and Cellular Physiology

The Department of Molecular and Cellular Physiology (MCP), under department chair Miriam Goodman seeks to understand how cells communicate, interact and enable complex physiological function. MCP labs take an interdisciplinary approach, with an emphasis on quantitative and structural approaches drawn from multiple scientific disciplines, including structural biology, biophysics, cell biology, immunology and neuroscience. By uncovering molecular and cellular processes, MCP scientists have established new paradigms in the biology of signaling and communication, such as the relationship between the structure and function of G-protein-coupled receptors (GPCRs), and the presynaptic molecular mechanisms underlying neuronal communication. Key research areas include understanding how cell signaling occurs and enables complex physiological function and response to the environment. The department conducts studies at every level of life, ranging from atoms and molecules, to macromolecular assemblies, to cells and cellular networks, to organ systems and entire organisms. They have established new paradigms in the biology of signaling and communication by practicing across multiple scientific disciplines including: structural biology, biophysics, cell biology and neuroscience.

Miriam Goodman, PhD
Professor and Chair of Molecular and Cellular Physiology

By uncovering molecular and cellular processes, MCP scientists have established new paradigms in the biology of signaling and communication, such as the relationship between the structure and function of GPCRs and the presynaptic molecular mechanisms underlying neuronal communication.

FACULTY RESEARCH

The goal of research in **Axel Brunger**'s lab is to understand the molecular mechanism of synaptic neurotransmission by conducting single-molecule/particle reconstitution and imaging experiments, combined with high-resolution structural studies (by X-ray crystallography and electron cryo-microscopy) of the synaptic vesicle fusion machinery. Other interests include the development of advanced methods for biomolecular structure determination. **Steven Chu**'s areas of research include tests of fundamental theories in physics, atom interferometry, the study of polymers and biological systems at the single molecule level, and biomedical research.

Liang Feng is interested in the structure, dynamics and function of eukaryotic transport proteins that mediate ions and major nutrients across the membrane, the kinetics and regulation of transport processes, the catalytic mechanism of membrane embedded enzymes and the development of small molecule modulations based on the structure and function of membrane proteins. **Christopher Garcia**'s group studies the structural and functional studies of transmembrane receptor interactions with their ligands in systems relevant to human health and disease -primarily in immunity, infection, and neurobiology. **Miriam Goodman**'s research investigates the biophysics and mechanics of touch sensation by combining *in vivo* electrophysiology with genetics and novel tools for mechanical stimulation, through quantitative behavioral studies, light and electron microscopy. **Brian Kobilka**'s laboratory investigates the molecular mechanisms of G-protein-coupled receptor signaling. G-protein-coupled receptors are responsible for the majority of cellular responses to hormones and neurotransmitters, as well as the senses of sight, olfaction and taste. The laboratory of **Richard Lewis** investigates calcium signaling mechanisms and their consequences for cell behavior, with a focus on store-operated calcium channels. **Daniel Madison**'s laboratory uses electrophysiological techniques to study the mechanisms of synaptic transmission and plasticity in the mammalian hippocampus. A major focus in the lab is in the study of long-term potentiation and mechanisms underlying memory formation in the central nervous system. The goal of research in **Merritt Maduke**'s lab is to determine the molecular mechanisms of chloride-selective ion channels and transporters. These membrane proteins are ubiquitously expressed in humans and are necessary for proper cardiovascular, muscular, neuronal, and epithelial function. **Lucy O'Brien**'s lab uses a stem cell-based Drosophila epithelium, the intestinal lining of the adult midgut, as a system to explore the regulatory interface of stem cell and epithelial tissue biology. **Georgios Skiniotis** and his research group are using electron cryo-microscopy (cryoEM) to study the mechanisms of transmembrane signal instigation with a particular focus on G-protein-coupled receptors and cytokine receptors. **Thomas Südhof**'s laboratory studies how synapses form in the brain, how synapses work at a molecular level and change during synaptic plasticity, and how synapses become dysfunctional in diseases such as autism and other neuropsychiatric disorders. **William Weis**'s research group studies molecular interactions that underlie the establishment and maintenance of cell and tissue structure including cadherin-based adhesion and its interaction with the cytoskeleton, the relationship between cell-cell junction formation and generation of cell polarity, and the Wnt signaling pathway.

2018-2019 FACULTY HONORS, AWARDS AND APPOINTMENTS

Steven Chu—the William R. Kenan, Jr. Professor and professor of molecular and cellular physiology, and of physics, was awarded the 2018 Pioneer Award by the Fitzpatrick Institute for Photonics. The award recognizes the dedicated contributions that researchers have made in the photonics community.

Dr. Chu was also named a member of the Pontifical Academy of Sciences in 2018.

Merritt Maduke—associate professor of molecular and cellular physiology, was named president of the Society of General Physiologists in 2018.

Thomas Südof—the Avram Goldstein Professor in the School of Medicine, and professor of molecular and cellular physiology, was awarded the 2018 Pericles Prize by the Pericles International Academy, Rome, Italy.

William Weis—the William M. Hume Professor in the School of Medicine, and professor of structural biology and of molecular and cellular physiology and of Photon Science, was elected a member of the National Academy of Sciences at the academy's 156th annual meeting in 2019.

HISTORICAL FACULTY HONORS AND AWARDS

Axel Brunger

Trueblood Award, American Crystallographic Association	2016
Bernard Katz Award, Exocytosis & Endocytosis Group, Biophysical Society	2014
Carl Hermann Medal of the German Crystallographic Society (DGK)	2014
DeLano Award, American Society for Chemistry and Molecular Biology	2011
National Academy of Sciences	2005
Gregori Aminoff Prize, The Royal Swedish Academy of Sciences	2003
Röntgen Prize in Biosciences, University of Würzburg, Germany	1995

Steven Chu

Pioneer Award, Fitzpatrick Institute for Photonics	2018
Pontifical Academy of Sciences	2018
Foreign Member, National Academy of Sciences of Belarus	2017
Richard Ernst Medal	2015
Robert Fletcher Award	2015
Silk Road Award	2015
Foreign Member, Royal Society, UK	2014
George Eastman Medal, University of Rochester	2013
Foreign Member, Royal Academy of Engineering	2011
Arthur L. Schawlow Award, The Laser Institute of America	2010
Honorary Fellow, Institute of Physics	2009
Honorary Lifetime Member, Optical Society of America	2004
American Philosophical Society	1998
Foreign Member, Chinese Academy of Sciences	1998
Korean Academy of Sciences and Technology	1998
Nobel Prize in Physics (shared with Drs. Claude Cohen-Tannoudji and William D. Phillips)	1997
Academia Sinica	1994

Arthur Schawlow Prize for Laser Science, American Physical Society	1994
King Faisal International Prize for Science, Co-winner, King Faisal Foundation	1993
National Academy of Sciences	1993
American Academy of Arts and Sciences	1992
Optical Society of America	1990
Richtmyer Memorial Prize Lecturer, American Physical Society/American Association of Physics Teachers	1990
American Physical Society	1987
Broida Prize for Laser Spectroscopy, American Physical Society	1987

Liang Feng

Klingenstein-Simons Fellow, The Klingenstein Fund and the Simons Foundation	2015
NIH Director's New Innovator Award	2015
Sloan Research Fellow	2014

K. Christopher Garcia

National Academy of Medicine	2016
National Academy of Sciences	2012
Keck Distinguished Medical Scholar	2002
Pew Scholar Fellow	2001
Frederick J. Terman Junior Faculty Award, Stanford University	1999
Rita Allen Foundation Scholar	1999
Basil O'Connor Scholar Award	1999

Miriam Goodman

Excellence in Diversity and Inclusion Award, Stanford Medicine	2015
Excellence in Teaching, Faculty Teaching Award, Stanford Medicine	2014
Kate and Michael Bárány Young Investigator Award, Biophysical Society	2014
McKnight Foundation Scholar	2005
Eppendorf & Science Prize in Neurobiology	2004
Alfred P. Sloan Fellow	2002
Baxter Faculty Scholar, Donald E. and Delia B. Baxter Foundation	2002

Brian Kobilka

Fellow of the Biophysical Society	2017
Louis and Artur Lucian Award, McGill University	2016
Royal Danish Academy of Sciences and Letters	2016
American Academy of Arts and Sciences	2015
Mendel Medal, Villanova University	2015
Docteur Honoris Causa, Monash University, Melbourne, Australia	2014
National Academy of Medicine	2014
Earl and Thressa Stadtman Distinguished Scientist Award, American Society for Biochemistry Molecular Biology	2013
Honorary Member, Royal Irish Academy	2013
Raymond and Beverly Sackler Distinguished Visiting Neuroscientist, University of Toronto	2013
Docteur Honoris Causa, Free University, Brussels, Belgium	2012
Lecturer of the Year, Oxford University Biochemical Society, Oxford, UK	2012
Nobel Prize in Chemistry (shared with Dr. Robert J. Lefkowitz)	2012
National Academy of Sciences	2011
Ariëns Award, Dutch Pharmacological Society	2010

Julius Axelrod Award, American Society for Pharmacology and Experimental Therapeutics	2010
Javits Investigator Award, National Institute of Neurological Disorders and Stroke	2004
Young Investigator Award, Western Society for Clinical Investigation	1995
John Jacob Abel Award, American Society for Pharmacology and Experimental Therapeutics	1994

Richard Lewis

Howard Hughes Medical Institute Junior Faculty Scholar Award	1996-1998

Daniel Madison

Young Investigator Award, Society for Neuroscience	1994
Lucille P. Markey Scholar Award	1987

Merritt Maduke

President, Society of General Physiologists	2018
Cranefield Award, Society of General Physiologists	2008
Scientist Development Award, American Heart Association	2004
Esther Ehrman Lazard Faculty Scholar	2003

William James Nelson

American Academy of Arts and Sciences	2009
Burroughs Wellcome Visiting Professorship in the Basic Medical Sciences	1999
Max-Planck Research Prize (with Rolf Kemler), Max-Planck Gessellschaft, Germany; Alexander von Humboldt Professorship	1992
Established Investigator Award, American Heart Association	1988

Lucy O'Brien

Life Sciences Research Foundation, Genentech Foundation Fellow	2007
Harvard College Detur Prize	1989
Westinghouse (now Intel) Science Talent Search, National Scholarship Winner	1988

Georgios Skiniotis

SBMB Earl and Thressa Stadtman Scholar Award	2016
Presidential Early Career Award for Scientists and Engineers, White House/National Institutes of Health	2012
Pew Scholar Fellow	2011
K. R. Porter Award of the Society of General Physiologists on Molecular Motors	2001

Stephen J. Smith, Emeritus

Senior Investigator, Allen Institute for Brain Science	2014
Board of Directors, Aratome, LLC	2011
Board of Directors, Nanometrics, Inc. (Nano)	2004
Scientific Advisory Board, Max Planck Institute	2000
Board of Scientific Counselors, NICHD, NIH	1999

Thomas Südof

Pericles Prize, Pericles International Academy, Rome Italy	2018
Foreign Member, Royal Society, UK	2017
La Grande Médaille de la Ville de Paris	2014
Lasker Award, Basic Medical Research	2013
Nobel Prize in Physiology or Medicine (shared with James E. Rothman and Randy W. Schekman)	2013

American Academy of Arts & Sciences	2010
Albert Einstein Honorary Professorship, Chinese Academy of Sciences, Beijing	2010
Kavli Prize in Neuroscience	2010
Bernard Katz Award, Biophysical Society	2008
Physician Scientists Award, The Passano Foundation	2008
National Academy of Medicine	2007
Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research	2004
MetLife Award in Alzheimer's Disease Research	2004
National Academy of Sciences	2002
US National Academy Award in Molecular Biology	1997
Wilhelm Feldberg Award	1994
W. Alden Spencer Award, Columbia University	1993

Richard W. Tsien, Emeritus

Chair, Department of Neuroscience and Physiology, NYU Medical School	2012
Alan C. Beering Award, University of Indiana	2000
Charter Member, Biophysical Society	1999
American Academy of Arts and Sciences	1998
National Academy of Sciences	1997
Academia Sinica	1996
National Academy of Medicine	1994
Kaiser Award for Outstanding and Innovative Teaching	1991, 1995, 1999
Kenneth S. Cole Award	1985

OTHER BECKMAN FACULTY HISTORICAL HONORS AND AWARDS

DEPARTMENT OF GENETICS

Aaron Gitler

American Academy of Neurology Sheila Essey Award	2019
Friedrich Merz Guest Professorship Award	2017
Glenn Award for Research in Biological Mechanisms of Aging	2015
Addgene Innovation Award Winner	2011
Instituto Paulo Gontijo International Medicine PG Award	2011
"Scientist to Watch," Aug. 2010, The Scientist	2010
Rita Allen Foundation Scholar	2009
NIH Director's New Innovator Award	2008

William James Greenleaf

Wilson Prize, Harvard University	2016
Baxter Faculty Scholar Award, Donald E. and Delia B. Baxter Foundation	2014
Rita Allen Foundation Scholar	2011
Gates Cambridge Trust Scholar, Gates Foundation	2002

Leonard Herzenberg (1931-2013)

Fellow, American Institute for Medical and Biological Engineering	2008
"Ruggero Ceppellini" – Torino Medical Award	2007
Kyoto Prize in Biotechnology and Medical Technology, The Inamori Foundation	2006

Abbott Laboratories Award in Clinical and Diagnostic Immunology, American Society for Microbiology	2005
Novartis Special Prize in Immunology	2004
American Association of Clinical Chemistry	2002
Lifetime Achievement Award, American Association of Immunologists	1998
ComputerWorld Smithsonian Award	1996
International Cytometry Symposium Award	1994
Honored Guest, New York Academy of Sciences Conference	1993
National Cancer Institute Outstanding Investigator Award	1993
Honorary Life Fellow, American Society for Microbiology	1992
Smithsonian Institution, acquisition of the Herzenberg Laboratory Fluorescence Activated Cell Sorter (FACS)	1989
Honorary Life Fellow, American Association for the Advancement of Science	1987
Guggenheim Fellow	1986
Awarded for FACS and Immunology Studies, Pasteur Institute, France	1986
National Cancer Institute Outstanding Investigator Award	1985
National Academy of Sciences (US), elected for life	1982
Distinguished Alumnus, New York City University, Brooklyn College	1980
Awarded for studies with Dr. Cesar Milstein coupling hybridoma and FACS technology and applications, Cambridge University	1978
Guggenheim Fellow	1976
Life Fellow, Clare Hall, Cambridge University	1976

Leonore Herzenberg

Honorary Fellow, Royal Microscopical Society	2015
Visionary Use of Information Technology, Medicine, Torino Medical Sciences Award	2007
Heroic Achievement in Information Technology, The ComputerWorld Smithsonian Award	1996

Lars Steinmetz

Ira Herskowitz Award, Genetics Society of America	2016
Dr. V. Ramalingaswami Chair, Indian National Science Academy	2014
European Molecular Biology Organization (EMBO) Member	2013
Enhanced Recovery Company (ERC) Advanced Investigator	2012
Emmy Noether-Program Young Investigator, Deutsche Forschungsgemeinschaft	2004

Monte Meier Winslow

Pancreas Cancer Action Network Career Development Award	2013
Donald E. and Delia B. Baxter Foundation Faculty Fellow Award	2012
V Scholar Award, V Foundation for Cancer Research Martin D. Abeloff, M.D.	2012

DEPARTMENT OF MEDICINE (INFECTIOUS DISEASES) AND MICROBIOLOGY AND IMMUNOLOGY

Paul L. Bollyky

Transformative Research Award, Dr. Ralph and Marian Falk Medical Research Trust	2017
Grand Challenges Award, Bill and Melinda Gates Foundation	2016
Catalyst Research Award, Dr. Ralph and Marian Falk Medical Research Trust	2015

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Mark Davis

Henry Kunkel Society	2018
Foreign Member of the Royal Society, London	2017
Distinguished Alumni Award, California Institute of Technology	2005
National Institute of Medicine	2004
Paul Ehrlich Prize	2004
Ernst W. Bertner Award, M.D.Anderson Cancer Center/Univ. Texas	2003
The Rose Payne Award, American Society for Histocompatibility and Immunogenetics	2002
William B. Coley Award, Cancer Research Institute	2000
Novartis Prize for Basic Immunology, International Union of Immunology Societies	1998
Alfred P. Sloan Jr. Prize, General Motors Cancer Research Foundation	1996
Pius XI Medal, Pontifical Academy of Sciences	1996
King Faisal International Prize for Science	1995
National Academy of Sciences	1993
Canada Gairdner International Award	1989
Howard Taylor Ricketts Award	1988
Eli Lilly Award in Microbiology and Immunology	1986
Young Scientist Award, The Passano Foundation	1985

Bali Pulendran

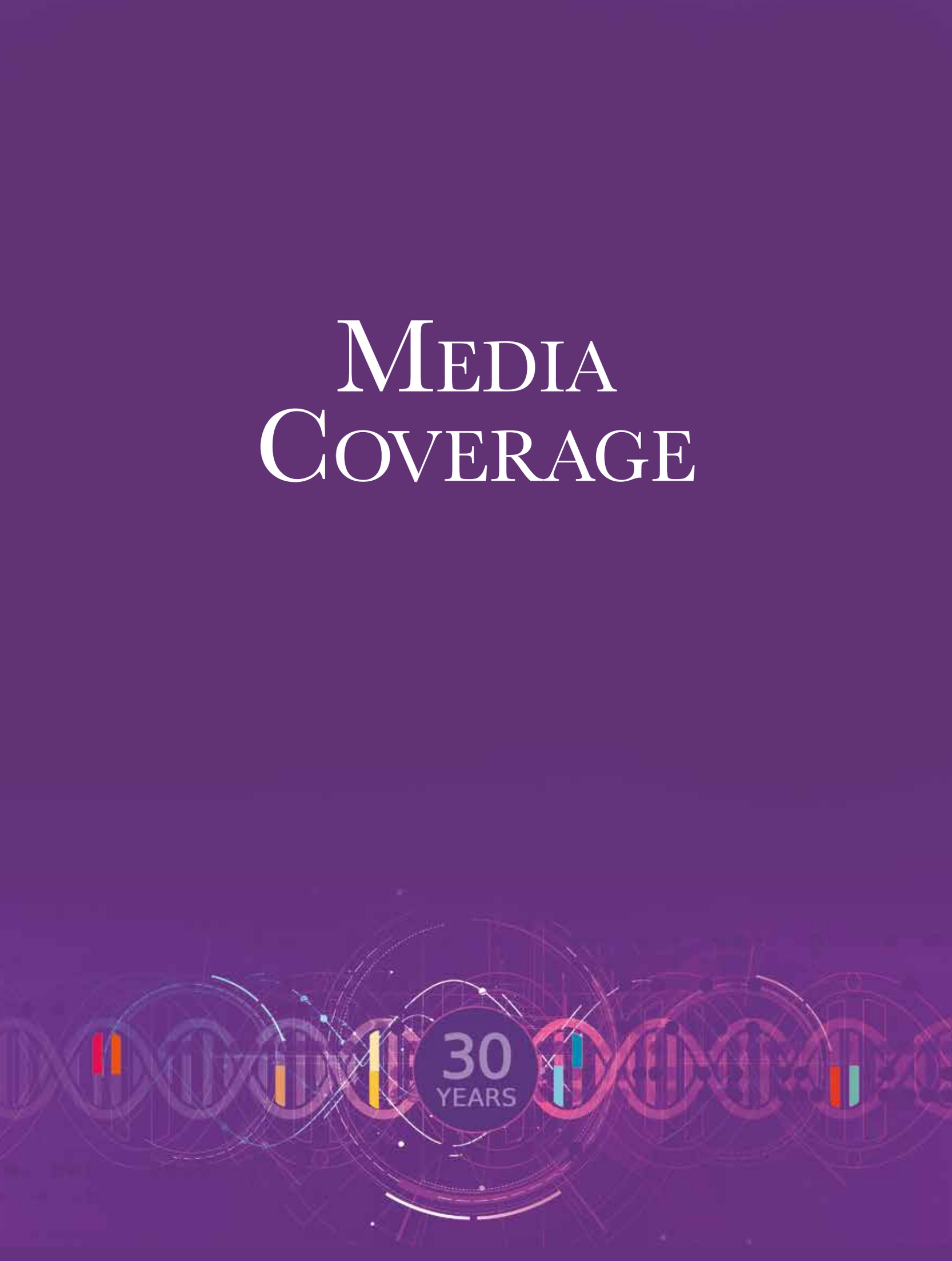
Albert E. Levy Scientific Research Award, Emory University	2011
Paper of the Year Award, International Society for Vaccines	2011
Millipub Club Award, Emory University	2010
Collegium Internationale Alloergologicum	2008

DEPARTMENT OF NEUROLOGY

Lawrence Steinman

Cerami Prize in Translational Medicine	2016
Charcot Prize for Lifetime Achievement in MS	2015
National Academy of Sciences	2015
National Academy of Medicine	2009
Dystel Prize	2004

Media Coverage



Media Coverage

THE FOLLOWING ARTICLES ARE REFERENCED IN THE HIGHLIGHTS SECTION

"The Cell's Integrated Circuit: A Profile of Lucy Shapiro"

THE SCIENTIST, AUGUST 1, 2018.

"Beckman Center for Molecular and Genetic Medicine Awards Seed Funding to Five Projects"

NEWS, HTTP://MED.STANFORD.EDU/BECKMAN.HTML, NOVEMBER 6, 2018.

"Hidden DNA Sequences Tied to Schizophrenia, Bipolar Risk"

INSIDE STANFORD MEDICINE, AUGUST 20, 2018, VOL. 10, NO. 15.

"In Apoptosis, Cell Death Spreads Through Perpetuating Waves"

INSIDE STANFORD MEDICINE, AUGUST 20, 2018, VOL. 10, NO. 15.

"New Algorithm Could Improve Diagnosis of Rare Diseases"

INSIDE STANFORD MEDICINE, AUGUST 20, 2018, VOL. 10, NO. 15.

"Osteoporosis, Fracture Risk Predicted with Genetic Screen"

INSIDE STANFORD MEDICINE, AUGUST 6, 2018, VOL. 10, NO. 14.

"Scientists Deploy Worms to Investigate Neurological Drugs"

INSIDE STANFORD MEDICINE, JANUARY 28, 2019, VOL. 11, NO. 2.

"Team Seeks to Decipher Vulnerability to Virus"

INSIDE STANFORD MEDICINE, AUGUST 6, 2018, VOL. 10, NO. 14.

"Revealed: The Molecular Mechanism Underlying Hypertrophic Cardiomyopathy"

INSIDE STANFORD MEDICINE, AUGUST 20, 2018, VOL. 10, NO. 15.

"The Puzzle of a Mutated Gene Lurking Behind Many Parkinson's Cases"

INSIDE STANFORD MEDICINE, NOVEMBER 19, 2018, VOL. 10, NO. 21.

"Beckman Center Secures $1-Million Grant for Cutting-Edge Lattice Light Sheet Microscope"

NEWS, HTTP://MED.STANFORD.EDU/BECKMAN.HTML, APRIL 5, 2019.

"How Do You See the Inner Working of a Cancer Cell: Stanford's Cell Sciences Imaging Facility"

STANFORD CANCER INSTITUTE NEWS, FALL 2018.

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