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.

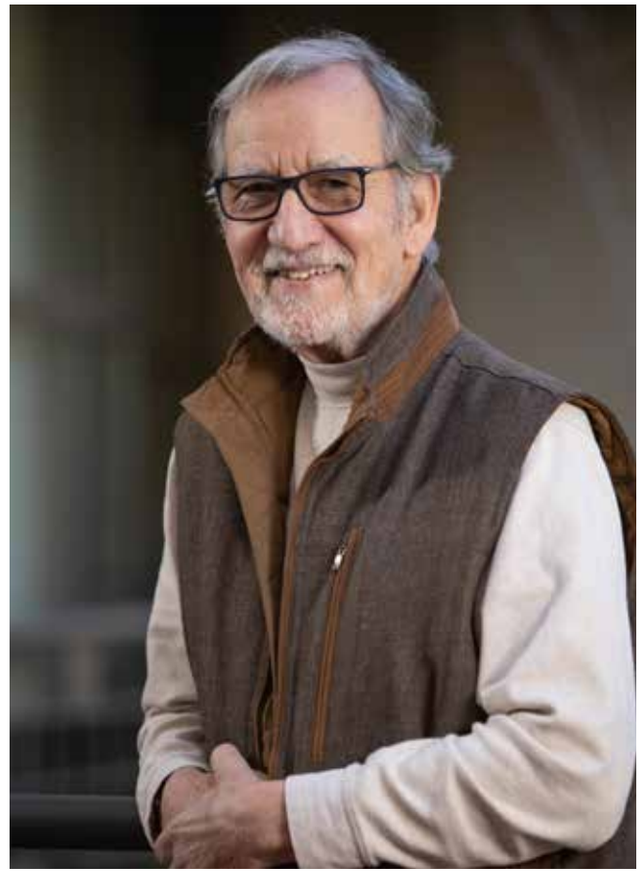
In addition to its heart failure drug, Cytokinetics has developed a molecule that activates skeletal muscle. This could benefit a variety of patients, including frail elderly and people with amyotrophic lateral sclerosis (ALS), which causes muscle atrophy. The agent is now in phase 2 clinical trials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

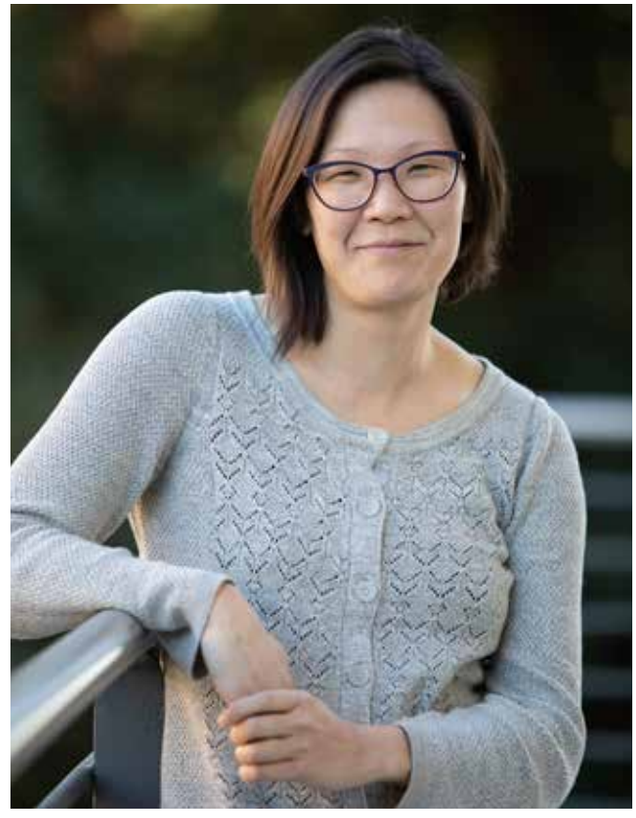
The apicoplast is an ancient plant-like plastid that is found in a number of different parasites, including the Plasmodium family of parasites that cause malaria. It's been found to be essential to the function of the parasite during human infection, particularly during the blood stage – the point when 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."

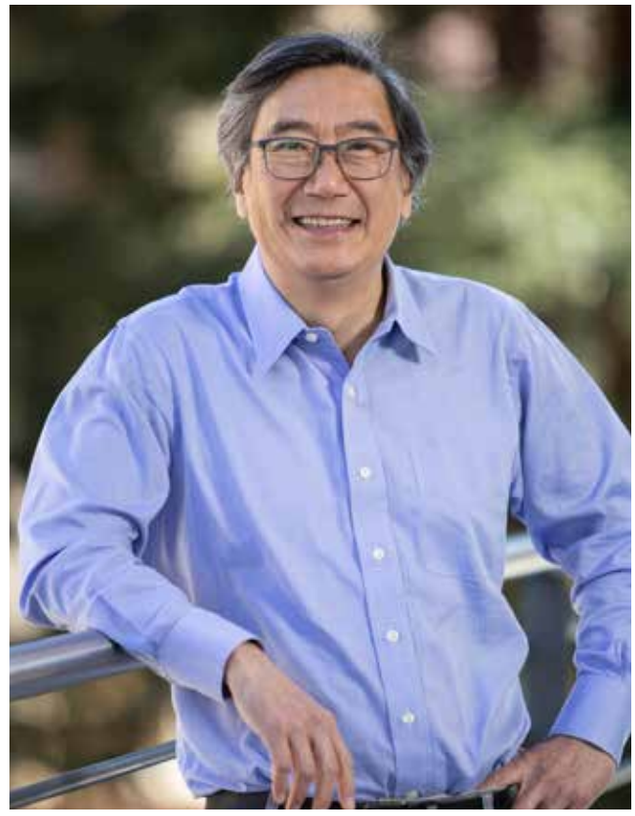
Peter S. Kim, PhD, has been focused on a global problem that has bedeviled the scientific community for three decades: the creation of an effective HIV vaccine.

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. ■