

LA JOLLA INSTITUTE FOR ALLERGY AND IMMUNOLOGY

Immune

SPRING 2018

MATTERS

VACCINES

Dawn of a New Era
in Vaccines

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Immune MATTERS

SPRING 2018



VACCINES

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LETTER FROM THE PRESIDENT

As proud as we are of the remarkable discoveries you'll read about in this issue of *Immune Matters*, we're equally proud that La Jolla Institute for Allergy and Immunology has earned a reputation as one of the best-run scientific organizations of its kind in the country. The two go hand in hand.

As other organizations struggle with funding challenges, debt, frequent turnover of leadership, overexpansion, and even litigation from faculty and staff, La Jolla Institute has worked hard to provide a stable, creative environment that encourages groundbreaking research from our principal investigators.

It starts at the top with one of the strongest and most engaged Boards of Directors anywhere, along with solid executive leadership that has been in place for 15 years. Financially, we're in outstanding shape with no debt and a unique ability to secure government funding that puts us at the top per capita among local institutions in acquiring grants from the National Institutes of Health.

We've also chosen steady growth instead of overextending and expanding into scientific and commercial areas where we're not experts. We've strengthened the Institute by establishing an academic partnership with UC San Diego and commercial partnerships, especially with Kyowa Hakko Kirin, and we've steadily built up our philanthropic efforts to the point where contributions big and small play a critical role in our ability to sponsor novel science and acquire equipment not funded by NIH.

All of this effort has enabled La Jolla Institute scientists the freedom to focus on what they do best: study the immune system to understand the cause of a wide range of diseases and leverage that research into immunological therapies that will prevent or eradicate illness.

Our cover story on vaccines is a great example of that process at work. The knowledge we've gained in two decades of unraveling the immune system is about to pay off in a handful of new vaccines that could, if confirmed in human clinical studies over the next few years, change the face of medicine. You'll read about the amazing work of four of our PIs who are closing in on vaccines for heart disease, cancer, HIV, and the dengue and Zika viruses.



In this issue you'll also read about another one of our outstanding researchers, Catherine "Lynn" Hedrick, Ph.D., whose remarkable work in studying a type of immune cells called monocytes is breaking new ground in understanding cardiovascular disease and cancer metastasis.

You'll also learn first hand why our board is so effective through profiles of our newest members, Pam Wasserman, MPH, and Geneviève Tremblay Jacobs. Pam is a highly successful business leader and pioneer in creating HMOs, while Montreal-born Geneviève brings international and cultural diversity to our board through a wonderfully varied career that includes a stint as a Canadian army medic.

As strong as we believe La Jolla Institute is today, we will always strive to be more effective as a scientific organization. And we will always need help. That's why we continue to be so appreciative of the foundations, individual donors, federal funding sources, and other partners who have been vital to fulfilling our mission of *Life Without Disease*®.

Sincerely,

Mitchell Kronenberg, Ph.D.
President & Chief Scientific Officer
La Jolla Institute for Allergy and Immunology

DAWN OF A NEW ERA — IN — VACCINES

La Jolla Institute scientists are
leveraging their advances in immunotherapy
to create the next generation of vaccines

As they peel away the complex layers that form the human immune system, scientists at La Jolla Institute for Allergy and Immunology are revealing a fascinating path to a new generation of powerful vaccines they believe will soon turn the tide against some of the world's deadliest diseases, including cancer and heart disease.

The potential for these vaccines is vast because they are far more advanced and in some cases function differently than traditional vaccines—the type that for many decades has relied on producing antibodies to prevent people from contracting polio, smallpox, and other infectious diseases. The new vaccines are much more therapeutic than preventive, and rely on advances in immunotherapy at the Institute to ramp up the human immune system and its T cells to actually attack tumors, viruses, and other diseases already afflicting the body.

“Thanks to the progress we’ve made in understanding the immune system, La Jolla Institute is on the cusp of one of the most important periods not just in our 30-year history, but potentially in the history of medical science,” says Mitchell Kronenberg, Ph.D., Institute President and Chief Scientific Officer. “The idea that Institute scientists are on the verge of developing vaccines for heart disease, cancer, Zika, and even HIV would have been unimaginable just a few years ago. We’re excited that in the near future these vaccines will emerge from the lab and enter the clinic where they will be used to save lives around the world.”

There is no Institute scientist more eager to see his vaccine help patients than Klaus Ley, M.D., founding head of the Division Inflammation Biology and a much-honored researcher who has been awarded “Distinguished Scientist” status by the American Heart Association. After decades of trying to understand the causes of atherosclerosis, Dr. Ley believes he and his team are close to developing a vaccine that will reduce



Klaus Ley, M.D.

or prevent inflammation in the arteries and, in turn, the buildup of plaque that causes deadly heart attacks and strokes.

One of the keys to Dr. Ley’s progress was a groundbreaking discovery several years ago in which he found that a specific type of immune cells known as CD4 T cells orchestrates inflammatory attacks on artery walls by receiving antigen-specific signals from other inflammatory cells in the vessel wall. He also showed that these immune cells behave as if they had previously seen the antigen that causes them to launch the attack.

an·ti·gen | any substance capable of inducing an immune response

“This was critical because it meant that the immune cells had memory of the molecule brought forth by the antigen-presenting cells,” Dr. Ley says. “That kind of immune memory is the underlying basis of successful vaccines and it was extremely promising because it demonstrated conceptually that it might be possible to develop a vaccine that could significantly dampen that inflammatory process.”

» [READ MORE ON IMMUNOTHERAPY REGIMES | PAGES 7 & 10](#)

While vaccines traditionally have been thought of in terms of boosting the strength of the immune response, the concept here is entirely different, in that the vaccine is designed to enhance immune regulation to reduce the harmful immune response leading to inflammation.

A couple of years later, in 2014, Dr. Ley used those findings to conduct one of the most exciting experiments in his career. He demonstrated that a sample vaccine his lab tested in mice resulted in a remarkable 40 percent reduction in arterial plaque. Today, Dr. Ley is gearing up to try his atherosclerosis vaccine in humans, possibly as soon as the end of 2018.

“Mice are not people and I assure you there will be setbacks and failures as we try to see what kind of results we can achieve in real patients with serious heart disease,” Dr. Ley says. “I want to stress this can’t succeed unless you have a large team of dedicated researchers all working together and with the assistance of expert collaborators like Alessandro Sette, Ph.D., a pioneer in vaccine development here at the Institute.”

Saving millions

With that proviso, Dr. Ley allows himself a few moments to imagine the impact of his vaccine if it does work in humans.

“If we achieve just a 30 percent reduction in plaque with this vaccine, we could potentially prevent 20 million heart attacks and strokes each year around the world if we gave it to all those at risk,” Dr. Ley says. “That would save millions of lives, which would fulfill the reason I went into immunology research in the first place. As optimistic as I am, I can’t predict what will happen, but I can tell you making this vaccine work has become the singular focus of my career. And, if it’s successful, it will be the most important thing I ever do in my life.”

That same kind of passion infuses the research of Sujan Shresta, Ph.D., Associate Professor in the Institute’s Center for Infectious Disease. Dr. Shresta’s quest is an area that doesn’t get as much attention as heart disease and cancer, but the reality is that one in three deaths worldwide is caused by infectious disease.



Sujan Shresta, Ph.D.

Dr. Shresta is a pioneering researcher in dengue virus infection, a mosquito-borne disease that afflicts nearly 400 million people around the globe annually. More recently, she has used her vast experience and applied it to researching dengue’s close cousin, the Zika virus, another mosquito-borne global threat that two years ago caused widespread panic.

Based on her outstanding scientific track record, and the fact that she always seems to be one step ahead in her research, it is a safe bet Dr. Shresta and her team will be among the first to develop a vaccine that works against both diseases. An example of one of her key discoveries was that antibodies, normally the immune system’s warriors in fighting pathogens, can actually cause harm. She proved the existence of a phenomenon known as antibody-dependent enhancement in which antibodies created in a mild form of dengue can prime the immune system to trigger the severest form of the disease, dengue hemorrhagic fever, when it encounters the virus again.

This research has made Dr. Shresta extremely cautious about basing potential dengue and Zika vaccines solely on an antibody response produced by the immune system's B cells.

"I wasn't at all surprised when it was revealed recently that a major dengue vaccine that took 20 years and \$2 billion to develop can actually cause people to come down with a severe form of the disease," Dr. Shresta says. "And I was disappointed that following the panic caused by the Zika outbreak two years ago that almost all companies rushing to launch vaccine projects based their research only on antibodies."

Calling in T cells

It has motivated Dr. Shresta to pursue a different path to a vaccine, one she believes offers a much better chance of success. While retaining some of the best features of the traditional B cell antibody approach, she is investing much of her effort in developing a vaccine that relies on the response of T cells, the other major player in the body's immune system. In a paper published last fall in *Nature Communications*, Dr. Shresta showed that mice rendered immune to dengue show "cross-protection" from subsequent Zika infection.

"We're excited because we identified specific types of T cells capable of defending against both dengue and Zika without the danger of releasing the harmful cytokines T cells sometimes produce," Dr. Shresta says. "Since we see these two as almost sister diseases, we now believe it's possible to create one vaccine that would protect people against both dengue and Zika."

WE'RE EXCITED BECAUSE WE IDENTIFIED SPECIFIC TYPES OF T CELLS CAPABLE OF DEFENDING AGAINST BOTH DENGUE AND ZIKA WITHOUT THE DANGER OF RELEASING THE HARMFUL CYTOKINES T CELLS SOMETIMES PRODUCE.



Cancer

IMAGINE A PERSONALIZED CANCER VACCINE SO POWERFUL THAT IT TARGETS AND DESTROYS THE SPECIFIC TUMOR ATTACKING YOUR BODY—AND THEN PROTECTS YOU FROM THE MALIGNANCY RECURRING FOR THE REST OF YOUR LIFE.

Until recently, such a scientific concept would have been unthinkable. Yet sometime this fall, a vaccine just like it will be tested in 20 patients with advanced cancer.

If this vaccine—which stimulates the body's own T cells to specifically zoom in on a tumor's mutations—works as planned, there will be an amazing bonus feature that would launch the vaccine into the realm of one of the greatest discoveries in modern medical science.

"What makes this kind of cancer vaccine potentially game-changing is that it can be deployed not just against one type of cancer but almost every type of solid-tumor cancer that afflicts humans," says La Jolla Institute Professor Stephen Schoenberger, Ph.D., the scientist whose pioneering T cell research paved the way for the development of the vaccine.

The reason the vaccine offers so much hope, and why it would work against many types of cancer, is the ability of T cells to recognize signature features that set tumors apart from normal tissues. Called neoantigens, these "molecular red flags" result from the highly variable mix of mutations harbored by each tumor. One of Dr. Schoenberger's breakthroughs was learning through genomic sequencing and bioinformatic analysis that these neoantigens are detectable much more frequently than previously thought.





“What is exciting and makes this vaccine potentially game-changing is that it would be effective not just against one type of cancer but almost every type of solid-tumor cancer that afflicts humans.”

– STEPHEN SCHOENBERGER, PH.D.

The key discovery came when Dr. Schoenberger and his team learned they could take a small sample of a patient’s tumor, sequence its DNA and RNA to determine which neoantigens were the most recognizable, and then design a personalized vaccine for each patient that would help guide T cells toward their target. The T cells would then not only shrink and eliminate the tumor, they would also be on guard to offer future immunity if any cancer cells ever recurred.

Ezra Cohen, M.D., who co-directs the San Diego Center for Precision Immunotherapy together with Dr. Schoenberger, will oversee the clinical trial. As a Professor of Medicine at the Moores Cancer Center and translational specialist, Dr. Cohen is hoping the results will confirm the team’s research so he can offer real hope to the type of patients whose lives he’s seen devastated by cancer.

“This is a potentially world-changing vaccine because it would enable us to remove the death sentences patients have been given and actually give them a future where they can resume normal productive lives with their loved ones and not have to worry about their cancer coming back,” Dr. Cohen says. “It’s exciting personally because helping bring this type of incredible research into the clinic is why I went into translational medicine in the first place.”

Dr. Schoenberger says if the vaccine is successful, it would be “a 12 on a scale of 10” personally, and likely the major achievement of his long career.

“We’re particularly proud of this work because it’s not the result of government funding,” Dr. Schoenberger says. “It came about through the amazing generosity of non-profit organizations and individual donors who have believed in and supported our research over the years. We could not be more appreciative, and it demonstrates the remarkable power of philanthropy to advance science.”

Although she acknowledges proving her theories will require a number of years of intensive research, Dr. Shresta is thrilled for the opportunity to fulfill her dream of using her scientific skills to help people most in need around the world.

“Dengue is now in 128 countries, afflicting half the world’s population, and is spreading from tropical regions to more temperate countries, including my homeland Nepal,” she says. “It’s only a matter of time before Zika reaches all these countries as well. The toll on human health and resources has already been devastating. I can’t tell you how rewarding it would be for me to play a role in stopping these two diseases in their tracks and relieving some of this tremendous burden.”

As difficult as it has been to develop a vaccine for dengue and Zika, the quest for an HIV vaccine has been several orders of magnitude more complicated and challenging. In fact, after decades of trying, a number of researchers around the world have abandoned the effort, deeming it impossible.

Rising to the challenge

Fortunately, for the field of medical research, Shane Crotty, Ph.D., Professor in the Institute’s Division of Vaccine Discovery, is a most resilient and tenacious investigator. As a leading expert on how vaccines work, Dr. Crotty in recent years has invested significant time and energy on HIV, and says he’s committed to finding a vaccine no matter how long it takes.

“This is one of the most challenging scientific problems we as immunologists will likely ever face,” Dr. Crotty says. “We’re taking on a chameleon-like virus that for several reasons is very hard to see for the human immune system, unlike almost all other pathogens that invade the body. Even as an optimist I acknowledge the strong possibility of failure. At the same time, the hard work we’ve been putting in is beginning to pay off, and I think we have a real moral imperative to keep trying, whatever the odds.”

Dr. Crotty, whose reputation as a leading expert in T cell function and vaccine development led Thomson Reuters to include him in its annual list of the world’s most influential scientific minds, says the key to the progress so far has been breaking down the effort into smaller pieces that can be attacked and solved individually before moving on. That, and working with equally talented researchers like



Shane Crotty, Ph.D.

William Schief, Ph.D., at The Scripps Research Institute, along with Dr. Crotty's other colleagues in the International AIDS Vaccine Initiative.

One of Dr. Crotty's own discoveries was foundational in launching the effort. His discovery of a pivotal piece of the body's mechanism for switching on the production of antibodies—published in *Science* in 2009—showed the BCL6 gene was like an on and off switch, or master regulator, that triggers the production of a certain group of helper T helper cells known as follicular helper T (Tfh) cells, which in turn tell B cells to make more protective antibodies.

More key discoveries followed: Dr. Crotty demonstrated that Tfh cells are critical for triggering broadly neutralizing antibodies that might combat HIV. The team also discovered that the type of B cell that produces the antibodies is rare in humans but that a vaccine could stimulate them to produce more and stronger antibodies. A major advance came when these antibodies were injected into healthy monkeys and prevented the animals from contracting an HIV-like virus. This string of successes has Dr. Crotty envisioning human clinical trials in the not-too-distant future.

“We’re realistic enough to know we’ve got years of work ahead but it was really exciting to show that an HIV vaccine is possible in concept,” Dr. Crotty says. “With all of the steps we’re taking, including the setbacks, we learn more about the intricate processes at work in the immune system and that’s critical to informing our future research.

“I’m often asked why I’m pursuing something so difficult, especially when anti-retroviral drugs have turned AIDS into more of a chronic, manageable disease. The truth is that HIV is still a tremendous global burden. Only half of the 36 million people infected with HIV are able to get the medications needed to control the virus. One million people still get infected with HIV every year, and a million still die annually from AIDS-related illnesses.

“This is why finding an HIV vaccine is such a priority for La Jolla Institute and our partners,” Dr. Crotty adds. “Participating in this huge, complex collaborative effort has been incredibly rewarding and the thought that I’m contributing to an effort that might positively impact the lives of millions around the world is extremely gratifying.” ●

HIV IS STILL A TREMENDOUS GLOBAL BURDEN...ONLY HALF OF THE 36 MILLION PEOPLE INFECTED WITH HIV ARE ABLE TO GET THE MEDICATIONS NEEDED TO CONTROL THE VIRUS.

Clinical Associates Program connects bench scientists with clinicians

RESEARCHERS DEFINE TRANSLATIONAL MEDICINE AS THE TRANSFER OF KNOWLEDGE FROM “BENCH-TO-BEDSIDE.”

In this scenario, scientists working in biology labs make discoveries that suggest a novel therapy, which then undergoes development and makes a one-way trip to the clinic, where it is tested in patients by white-coated physicians. The metaphor is apt because, like quarterbacks and receivers, people who conduct experiments at lab benches generally do differ markedly in training and temperament from those who carry them across the clinical goal line.

Yet, as translational medicine successes increase, players on both ends of this continuum are realizing that a unidirectional flow of information is too simple a model for modern biomedicine. Notably, in an age that promises patient-specific therapies, devising effective cures will require that transfer of knowledge and the unique perspectives gained at the bedside transit continuously back to the lab for investigation and improvement.

The La Jolla Institute for Allergy and Immunology (LJI) Clinical Associates Program emerged from the recognition that the clinic is an extension of the lab. Created two years ago, its goal is to bridge bench and bedside cultures by embedding physicians in LJI labs to conduct immunology-related research alongside mechanistic scientists. If successful, these programs will facilitate collaborations between physicians and LJI scientists that produce innovations with a greater likelihood of reaching the clinic.

Practically, the program provides Clinical Associates, as these scholars are called, with LJI lab space, greater opportunities to apply for grants, and daily conversations with the kinds of scientists they might not normally associate with. The hope is that when they return to the clinic, Associates will remain permanently affiliated with LJI, and they and their former basic science mentors will see themselves as players on the same team.

Stephen Wilson, Ph.D., Executive Vice President and Chief Operating Officer at LJI, recalls the founding of the program. “A few years ago it became obvious that our program would benefit from having physician-scientists conduct research here, a deep-dive that would support a lasting connection. Before that, we had relationships with clinicians who themselves had no intention of running a lab full-time to the exclusion of seeing patients, but they were less immersive, and often based around the sharing of clinical samples,” Wilson says. “We decided to create something resembling a postdoc program but one that would foster enduring personal and professional relationships with physicians who return to the clinic with a full clinical workload.”

Creating a cohesive force

The first recruit was Aaron Miller. After earning both an M.D. and Ph.D. at Northwestern University, Dr. Miller completed a hematology-oncology fellowship and residency through the Physician Scientist Training Program at the UC San Diego School of Medicine. He now holds an academic appointment as an Assistant Clinical Professor of Medicine at UC San Diego and is a board-certified medical oncologist who specializes in diagnosing and treating patients with gastrointestinal cancers. Dr. Miller had a career epiphany five years ago, when reports of immunotherapy success against intractable cancers like melanoma became front-page news.

“I knew I needed to learn more about immunology, so I sought a world-class T cell biologist who could help me do that and contribute to these efforts. That’s how I found Steve,” he says, referring to Stephen Schoenberger, Ph.D., an LJI immunologist who focuses on T cell responses in the context of tumor development.

In 2015, Dr. Miller joined Dr. Schoenberger’s lab. He spends one day a week in clinic seeing patients at UC San Diego, but the rest of his time is devoted to conducting research in Dr. Schoenberger’s lab.

There, Dr. Miller searches for novel “neoantigens”, or proteins aberrantly expressed on patients’ tumor cells that could be recognized by T cells as part of immunotherapy regimes.

These therapies are highly personalized: one patient’s tumor neoantigen may differ from that displayed by another. For example, Dr. Miller says we can now take tumors from patients (at the bedside), expand populations of T cells that target tumor-specific neoantigens (at the bench), and then infuse those cells back into patients (at the bedside) as anti-cancer cellular therapy.

For the benefit of patients

In fact, working with colleagues in the Schoenberger lab and nearby UC San Diego Moore’s Cancer Center, Dr. Miller has already conducted preclinical studies required for an Investigational New Drug application to the Food and Drug Administration for a phase I trial of adoptive cell transfer of neoantigen-specific tumor infiltrating lymphocytes into patients with advanced melanoma and head and neck cancer. This investigator-initiated trial will be conducted by a multidisciplinary team of physicians and scientists, typifying the intent of the program, and a testament to the cohesive force generated by Dr. Miller’s physician-scientist role. Going forward, Dr. Miller will possess extensive experience and insight needed to lead a mechanistic lab, and LJI will count him as a valued member of its extended research program. And as such, the team has extended its playbook.

LJI’s Dr. Wilson says the program has an eye toward treatment needs that non-scientists may not realize exist. “People have a notion that life in a hospital halts while physicians rush to their lab when they need to develop a better way to treat each patient,” he says. “But hospitals don’t necessarily work that way: they apply current standards of care, and run clinical trials. Our Clinical Associates will have a direct connection to LJI, and together we will push back on the status quo by bringing the capabilities of a mechanistic research lab to bear on limitations that remain in the clinic with existing treatments. Physicians bring ‘front line’ access to our research, and in return, we bring the state of the art in experimental research to the problem.”

Recently, the program enrolled its newest Clinical Associate, Dr. Ryan Nelson, who now works in the lab of LJI’s Pandurangan Vijayanand, M.D., Ph.D. Having earned his M.D. at the University of Chicago, Nelson did his residency at Northwestern and is now a fellow



Aaron Miller, M.D. Ph.D.

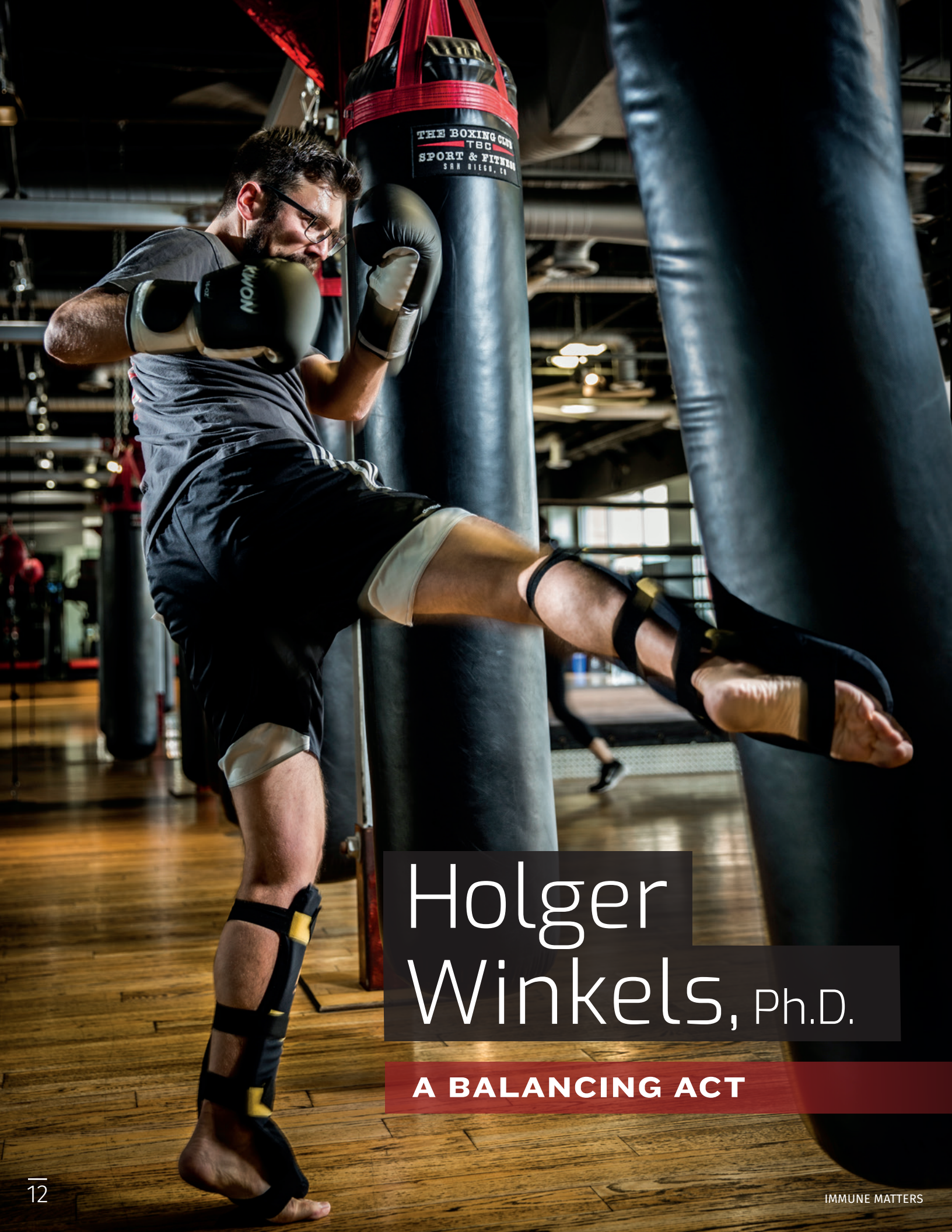
at UC San Diego’s Division of Pulmonary, Critical Care & Sleep Medicine. At LJI, Nelson will conduct genomic studies as part of LJI’s asthma center “smart trials.”

Now about halfway through his five-year Clinical Associate stint, Dr. Miller attests to the program’s success. “Over the last two years I’ve learned a lot of immunology,” he says. “But the lab has also learned a lot about cancer! The Clinical Associate Program formalizes these kinds of synergies that can lead to treatment success. Without it, they might emerge only from informal collaborations.” ●

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“PHYSICIANS BRING ‘FRONT LINE’ ACCESS TO OUR RESEARCH, AND IN RETURN, WE BRING THE STATE OF THE ART IN EXPERIMENTAL RESEARCH TO THE PROBLEM.”

– STEPHEN WILSON, PH.D.



Holger Winkels, Ph.D.

A BALANCING ACT

Whether in the lab or the dojo, Holger Winkels, Ph.D., spends a lot of time thinking about balance. As a devoted martial arts practitioner with many years of jiu jitsu, krav maga, and muay thai under his belt, Dr. Winkels reads his opponents, finding an opening to push them off balance. As a postdoctoral researcher in the lab of Professor Klaus Ley, M.D., he studies the immune system to figure out how to achieve the perfect balance between pro-inflammatory and anti-inflammatory T cells to prevent atherosclerosis.

Born and raised in Germany, Dr. Winkels had always been interested in science. As a high school student he hesitated between chemistry and biology when an internship at Bayer propelled him toward biology. “I actually got to synthesize aspirin and it was fascinating,” remembers Dr. Winkels. But it left him uninspired—unlike his first immunology lecture, “I immediately knew immunology was it!” Dr. Winkels’ course was set and he never wavered.

During his diploma (undergraduate) thesis, Dr. Winkels studied T cell homeostasis in atherosclerosis before he dug deeper into T cell activation during his graduate studies in the lab of Professor Esther Lutgens, M.D., Ph.D., and Professor Norbert Gerdes, Ph.D., at the Institute for Cardiovascular Prevention in Munich. “I got into my current field very early on,” he says. The added advantage of being able to split his time between Munich, Amsterdam, and Boston, Mass., “was fantastic,” he says and adds with a laugh, “when I first arrived in Boston, I wasn’t even sure I had landed in the U.S. since a lot of the announcements were in Spanish.” He quickly fell in love with the city and Americans’ cheerful and positive attitude. “It was the first thing I noticed and it was very refreshing,” he says.

After finishing his graduate studies in 2016, the newly minted Ph.D. joined the lab of Dr. Ley. “If you are in immunology, you can’t do much better than La Jolla Institute,” he states as one of the reasons. The other one was Dr. Ley.

“Klaus has an outstanding reputation and is very well known in Germany,” he says. Dr. Winkels’ extensive expertise in T cell biology in the context of atherosclerosis was the perfect match for Dr. Ley’s heart vaccine project. “We are looking at the question why a certain subset of T cells, so called regulatory T cells, is unstable in cardiovascular disease,” he says. “The balance is skewed and our goal is to almost surgically dissect the immune system and find the dials that we can turn to stabilize regulatory T cells.”

In an unexpected twist, Dr. Winkels’ experiments turned up hitherto unknown immune cells that seem to play a role in atherosclerosis. Dr. Winkels successfully competed for a SPARK grant to follow up on his finding.

When he is not in the lab, Dr. Winkels is trying to find his own balance out in nature, at a music festival, a local bar, or in the muay thai boxing gym. Probably even more than the physical aspects, he values the mental workout martial arts provide him. “It forces me to focus and really be in the moment,” he says. “It quiets my mind and gives me a feeling of peace.” ●



Lori and Paul Thiel present Dr. Holger Winkels with a check on behalf of the Advisor of the Year Awards Program, which will fund his successful SPARK proposal. From left to right: Dr. Mitchell Kronenberg, Dr. Winkels, Lori and Paul Thiel.

» READ MORE ON DR. LEY'S HEART VACCINE | PAGE 5

WE ARE LOOKING AT THE QUESTION WHY A CERTAIN SUBSET OF T CELLS, SO CALLED REGULATORY T CELLS, IS UNSTABLE IN CARDIOVASCULAR DISEASE.

Catherine “Lynn” Hedrick

As a trailblazing scientist, Catherine “Lynn” Hedrick, Ph.D., radically changed the way we think about cardiovascular disease and cancer metastasis. As a devoted mentor, Dr. Hedrick gently transforms the way young scientists think about research experiments and their results.

Among the many responsibilities of a research scientist, mentoring the next generation of young researchers is probably the least recognized. But even the most naturally gifted and independent-minded young researchers benefit from some guidance to channel their often boundless energy toward reaching critical milestones. “I take it very seriously because they are putting their future in my hands,” says Dr. Hedrick, Professor in the Division of Inflammation Biology. “I really care about how well they do, how fast they progress. So, I try to help them keep their research projects focused and moving forward.”

Just as her protégés transform under Dr. Hedrick’s guiding hand, her own research keeps evolving. Dr. Hedrick started her research career studying cardiovascular disease, which is one of the complications of diabetes. Slowly, her work pivoted toward understanding the role of immune cells, such as monocytes and T lymphocytes, in cardiovascular disease and cancer. A recognized leader in her field, Dr. Hedrick was recently awarded a five-year, \$13 million grant by the National Institutes of Health to lead a collaborative research program to study how the metabolism and function of these immune cells change during cardiovascular disease progression in humans. And she just added another large collaborative research grant from the National Cancer Institute to understand how immune cells transform in cancer.

How did you become interested in science?

My mother had type 1 diabetes, and when I was about 7 years old I decided that I would either become a doctor or a scientist, cure diabetes, and help my mom.

That’s a long way from what you are studying now?

It set the stage and I just kept going down that path. As a graduate student I worked in a lab that studied heart disease, which is a complication of diabetes, but it wasn’t really diabetes research per se. When I started my own lab, I initially focused on type 1 diabetes, which was what my mother had. Ultimately, I started working on type 2 diabetes, but I was always more interested in studying the complications of the disease.

What are the main research findings from that period?

We discovered that even in type 1 diabetics there is an accelerated incidence of cardiovascular disease, which hadn’t been known at the time. It had been well known for type 2 diabetes but not type 1. We looked at the

consequences of elevated glucose levels on blood vessels and vascular wall function and how this contributed to heart disease. Over time, immunology started to play a bigger role in my research. It was still cardiovascular-based but my research became more and more immune cell-based.

When did the critical role of the immune system become apparent?

For me, it changed about 15 years ago. I remember going to research conferences on cardiovascular disease in the early ’90s. Back then, there was only one immunologist in our field and he was very famous. He said, “Look, there are T cells involved in cardiovascular disease and we should really treat it as an immunological disease.” People stood up telling him that he was absolutely wrong and that his work was an artifact. Now we know that he was right all along. That was one of the reasons I moved to La Jolla Institute, to study the immunology of cardiovascular disease in a world-class research environment.



Q&A



Left to right: Dalia Gaddis, Ph.D., Graham Thomas, Ph.D., Catherine “Lynn” Hedrick, Ph.D.

Has moving to an immunology-focused institute changed how you approach certain questions?

This move was the best thing I ever did, both personally and professionally. Professionally, it is a world-class immunology institute, so I knew that I would have the tools to explore the disease from a new perspective. Although we knew that the immune system played an important role, we had barely scratched the surface. At LJI, I could immerse myself in immunology and it really helped.

Are there any advantages to LJI's small size?

When I came here, I had more freedom and more time to think, which made me more creative. But the most important difference is that people here have a different attitude: anything's possible. You may fail but you go for it. That is a completely different attitude than I know many of my colleagues across the country have, and it has changed the way I run my lab. It propelled my lab to make larger, more important discoveries and allowed us to publish in higher-quality journals. We could never have made our discovery about patrolling monocytes and cancer anywhere else.

Why is mentoring young scientists so important to you?

Trainees come to my lab because they like my science and they trust me to help propel them toward an independent research career. I tend to hire postdocs who are just starting their training. Their research abilities are still not very polished but I can see the potential in them. Everybody has a different personality and a different approach to their experiments and it is very satisfying to watch these trainees grow and develop.

What do you look for before you invite a postdoc to join your lab?

I first look at what they've done so far in terms of science and what they are interested in studying. But then I try to have people interview in person because then you see their personality and personality is actually very important. I get a feel for whether I can mentor that person effectively because if I can't then he or she will not do very well in the lab.

What does it take for a young scientist to be successful?

They are all really smart, so that's not what distinguishes them. When I was a postdoc at UCLA, I was taught by my mentor that if you took scientific risks and did challenging experiments that many times you would fail, but in the long run it could pay off and lead to a major discovery, and that's what I've seen in my lab. The postdocs who are really successful are creative, determined, and not afraid to tackle that challenging experiment that's going to take them six months to figure out how to do. Those are the trainees that will make it. And those qualities are what I look for.

What is the most fulfilling aspect of being a scientist for you?

For me, it's twofold. We study cancer and cardiovascular disease and any discovery we make that could lead to a new treatment, a new biomarker, or help patients in some other form is a huge thing for me. The other is watching these “kids” of mine, these postdocs, develop into amazing young scientists under my watch and then step out on their own and become really successful.

How do you balance your busy life as a scientist?

I don't read science textbooks [laughs]. I work out a lot. I especially like running on the beach. It is great for my health and it is good for my brain. I have written many a grant in my head while running on the beach. It really helps me clear my mind. Another important part is spending time with my family. I have a 14-year-old son who is a wonderful kid. He can talk about “monocytes and immune cells” with his friends, and he is very proud of what I do but he is not scientifically inclined himself. He says I work too hard! ●



Dr. Shane Crotty

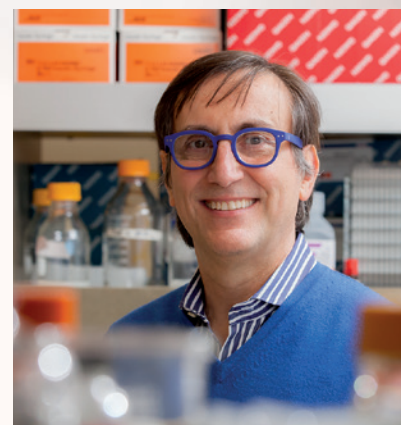
DR. SHANE CROTTY AGAIN MAKES THE LIST OF "HIGHLY CITED RESEARCHERS"

For the second year in a row, Dr. Shane Crotty's pioneering studies on vaccine-related immunology have earned him a spot among "The World's Most Influential Minds." The list of highly cited researchers is compiled annually and singles out scientists whose work has inspired their peers and shaped a whole field of inquiry. Researchers given this honor have been in the top one percent of citations for their field of study spanning the last decade. Dr. Crotty, a professor in the Division of Vaccine Discovery at La Jolla Institute for Allergy and Immunology, is driven by his desire to fundamentally change how vaccines are designed. With that goal in mind, Dr. Crotty has dedicated himself to understanding the fundamentals of what makes a good immune response to help tailor vaccine candidates so they elicit a protective immune response.

» READ MORE ABOUT DR. CROTTY'S HIV RESEARCH | PAGE 8

MICHAEL J. FOX FOUNDATION FUNDS GROUNDBREAKING PARKINSON'S RESEARCH AT LJI

Professor Alessandro Sette, Dr. Biol. Sci., has been awarded a two-year, \$340,000 grant by The Michael J. Fox Foundation for Parkinson's Research (MJFF) to expand an earlier MJFF-supported study, which provided the strongest evidence to date that autoimmunity plays a role in Parkinson's disease. Part of the new study, a collaborative effort that brings together immunologists, Parkinson's clinicians, and neuroscientists at the La Jolla Institute, UC San Diego, Rush University Medical Center, and Columbia University Medical School, will focus on the in-depth characterization of T cells that recognize fragments of alpha-synuclein, a protein that accumulates in the brain cells of people with Parkinson's disease. Defining the T cell-based autoimmune features of Parkinson's could provide new directions in therapy, including their use as biomarkers to identify individuals who are at risk or in the early stages of the disease.



Dr. Alessandro Sette



Dr. Sonia Sharma

DR. SONIA SHARMA RECEIVES GRANT FROM VASCULITIS FOUNDATION

The Vasculitis Foundation has awarded Assistant Professor Sonia Sharma, Ph.D., a \$50,000 grant to study the connection between vasculitis and pro-inflammatory immune responses. Vasculitis is an autoimmune condition characterized by inflammation and damage to the blood vessels, which precipitates multi-organ damage due to restricted blood flow to affected tissues. Dr. Sharma's lab has recently shown that the metabolic enzyme adenosine deaminase 2 (ADA2), which is mutated in certain patients with vasculitis, directly controls inflammatory immune responses. Dr. Sharma's lab is now exploring new treatments for vascular inflammation aimed at dampening pro-inflammatory immune responses by correcting the metabolic defect caused by low ADA2 activity.

SUSAN WEBBER

1952 – 2017



La Jolla Institute for Allergy and Immunology mourns the passing of Susan Webber, 65, who along with husband Scott had recently become a significant supporter of the Institute's groundbreaking research into understanding and treating cancer.

Even as Webber waged a brave battle with stage 4 colorectal cancer, her concern for the needs of others overrode her own, according to Aaron Miller, M.D., Ph.D., Clinical Associate at La Jolla Institute and Webber's oncologist at UC San Diego's Moores Cancer Center.

"Sue not only kept her condition from even her closest friends to shield them from her painful reality, she was also determined to find a way to help protect others in the future from colorectal and other types of cancer," Dr. Miller says. "When she learned about the advances we're making at the Institute using immunotherapy to create a potential cancer vaccine, she and Scott became excited and asked how they could support the research."

Dr. Miller explained that the more leading-edge immunological-based cancer research conducted at the Institute rarely qualifies for government funding and relies instead on philanthropic support. After hearing this, the Webbers decided to support this effort with a significant gift. Their donation will specifically fund Dr. Miller's research in the lab of Stephen Schoenberger, Ph.D., the Institute principal investigator whose discoveries form the basis of the vaccine.

"I think Sue would be very happy to know that her contribution will be extremely valuable in furthering this important research," Dr. Miller says. "I only wish she could have lived to see what we believe will be transformative advances in our ability to fight and eradicate some of the most difficult-to-treat cancers."

Webber, a native of Chicago, had a successful career with a number of companies, including IGA, Keebler,

"I only wish she could have lived to see what we believe will be transformative advances in our ability to fight and eradicate some of the most difficult-to-treat cancers."

– AARON MILLER, M.D., PH.D.

and a start-up software company, Applied Decision Systems. She met her husband in Illinois where he also was in the software industry. Upon the birth of their first child, Webber switched her career to that of mother and homemaker and participated in numerous school and charitable activities after the family moved to Carmel, Ind.

The Webbers' generosity actually went beyond their initial gift, according to Chris Lee, Institute Chief Advancement Officer.

"When Sue passed we were honored and appreciative to learn her family had asked that memorial gifts be made to La Jolla Institute in lieu of flowers," Lee says. "We received more than forty donations and nearly \$10,000. It's a tribute to what a beloved and inspiring person Sue was."

No one knows better than her husband what a special person Webber was.

"Sue was one of the strongest and most considerate people the majority of us will ever have the pleasure of meeting," Scott Webber says. "She was truly excited by the concept that our family could play a role in supporting innovative cancer research that may someday save millions of lives. It was typical of Sue that she could turn something so sad and tragic as her illness into something so positive and potentially world-changing." ●

» [READ MORE ON CANCER VACCINE | PAGES 7 AND 10](#)

CHARLES D. SURH

1961 - 2017

With great sadness, La Jolla Institute for Allergy and Immunology (LJI) marks the untimely passing of noted immunologist Charles "Charlie" Surh, Ph.D., who died of colon cancer at his San Diego home in October of 2017. He was 56.

Dr. Surh, a researcher at LJI, was best known for revealing how interactions with their environment determine whether T cells will grow or undergo elimination, a field now referred to as T cell homeostasis.

"Charlie was a great colleague, a pillar of San Diego's immunology community," said LJI President and Chief Scientific Officer Mitchell Kronenberg, Ph.D., who invited Dr. Surh to join the LJI faculty in 2012. "When he came to LJI he brought not just a grant and grad students but his excellent reputation and solid record of accomplishment."

Born in Seoul, South Korea, Dr. Surh came to California with his parents at age 11 and ultimately earned a B.S. in chemistry from the University of California, San Diego, and a Ph.D. in immunology from the University of California, Davis. He then completed postdoctoral training with Jonathan Sprent, then at The Scripps Research Institute (TSRI), where in 1994 he published a classic study applying then-novel TUNEL staining to prove that autoreactive T cells bound for elimination in the thymus underwent programmed cell death.

Dr. Surh ultimately became a TSRI faculty member, serving as full professor in the Department of Immunology from 2008 to 2012. In his years there, Dr. Surh's work focused primarily on how various cytokines controlled T cell survival.

In 2012, Dr. Surh became adjunct professor in LJI's Division of Developmental Immunology, and until the end of his career divided work

time between LJI and Pohang University of Science and Technology (POSTECH) in South Korea, where he simultaneously served as director of the Academy of Immunology and Microbiology. In Korea, Dr. Surh developed a unique facility in which germ-free mice were provided a limited diet in order to explore the role of the microbiome and the diet on the immune system. He spent the last five years of his career exploring the molecular basis of food allergy, publishing a 2016 groundbreaking *Science* paper reporting a molecular basis for food tolerance. That work provided insight into why children may become susceptible to food allergy.

Dr. Surh was greatly honored in South Korea, where in 2007 he received the Samsung-sponsored Ho-Am Prize in Medicine to honor Korean scientists making significant contributions to combat disease. And in 2017, he posthumously received the Scientist of the Year award from Korean science journalists.

Dr. Surh's family organized a celebration of his life at LJI last November attended by over 200 friends from LJI, TSRI, and all over North America and Australia, including Dr. Surh's parents, who survive him. Dr. Kronenberg, who had shared lab office space and day-to-day conversations with Dr. Surh, was among colleagues and family members who eulogized Dr. Surh, most praising his ethos as highly as his science.

"There was no pretense about Charlie," says Dr. Kronenberg. "He wasn't about showmanship or prestige or reputation. For him, the human world was flat: he spoke to the most honored professor or neophyte graduate student in the same way, without arrogance or condescension."

Dr. Surh's conviviality in no way hampered his productivity. He published 145 papers over

his life, including an astonishing 12 as a graduate student and 19 as a postdoctoral fellow. He continued work on the intestinal microbiome despite a cancer diagnosis, publishing his last paper in *Immunity* three months before his death.

In addition to his parents, Dr. Surh is survived by his wife, Helen Oh-Surh, and their three children. •



"Charlie was a great colleague, a pillar of San Diego's immunology community." – MITCHELL KRONENBERG, PH.D.

Pam Wasserman

When Pam Wasserman, MPH, was invited to join the Board of Directors of the La Jolla Institute for Allergy and Immunology, she didn't have just one reason to become involved with the scientific organization, she had many.

First and foremost, Wasserman is so passionate about the Institute's mission, she wanted to ensure her family's deep involvement with the Institute continued after her husband, Fred, recently resigned from the board to devote more time to his service to the Rancho Santa Fe Association. Wasserman herself had already become involved with the Institute through volunteering and hosting events, but now she can devote more of her considerable talents to directly assisting the Institute.

"In his many years of serving the Institute, Fred had become one of the most engaged and valuable members on the board, and I have every intention of continuing his legacy," says Wasserman, a Rancho Santa Fe resident who is Co-General Partner of Wasserman Companies. "My goal is to be every bit as committed to helping this organization realize its very ambitious but achievable goal of 'Life Without Disease.'"

One way Wasserman will accomplish that is by continuing her family's extremely valuable tradition of making the board stronger by recruiting outstanding new members from their circle of acquaintances. In recent years, Fred, with Pam's assistance, helped recruit high-profile leaders whose wide-ranging talents and philanthropic interests have been important assets on the board.

Another reason Wasserman wanted to join the board was so she could advance the Institute by leveraging her own extensive set of skills as a public health expert, health care pioneer, and talented business leader. Wasserman understands the world of health through her academic training and co-founding of one of the earliest HMOs; she has deep experience in starting and operating businesses; and she has an excellent track record of raising money for non-profit organizations. Born in Los Angeles, where her father worked in the exhibitor department of the movie studio RKO Pictures, Wasserman attended UCLA, receiving a BA (cum laude) in psychology and an MPH in Health Services Management.

In 1973, the Wassermans founded Maxicare Health Plans, Inc., one of the nation's early HMOs. She served as president and director of the HMO, which grew to operate in 26 states with 7,000 employees. After retiring from the HMO in 1988,



the couple would subsequently purchase Christopher Creek Winery, an award-winning Sonoma County-based winery, which they operated for 16 years. Wasserman is still actively involved in business today, owning and managing commercial and residential real estate and growing oranges in the Central Valley.

Wasserman has also been involved with a number of non-profit organizations. She was a director of the Robert Kennedy Community Hospital, the Healdsburg Community Hospital, and a member of the Dean's Council at the UCLA School of Public Health.

If Wasserman didn't already have enough reasons for her involvement with the Institute, there's yet another and this one is extremely practical.

"Fred and I both suffer from allergies, so we're thrilled the Institute's leading-edge research in this area will one day soon provide us and millions of others with relief," she says with a laugh.

"I firmly believe La Jolla Institute is one of the most important scientific organizations in the world," Wasserman adds. "From the moment Fred and I became involved with the Institute we've been intrigued and excited about the groundbreaking research being conducted on the complexities of the immune system." •

“The Institute’s scientists are some of the most talented and committed researchers in the world and we really do believe they’re on the verge of coming up with actual cures for some of the most challenging diseases humans face.”

Geneviève Tremblay Jacobs

There are few things in life more important to Geneviève Tremblay Jacobs than the health of her family and helping others who face steep medical challenges. That is why she recently—and eagerly—accepted an invitation to become the newest board member of the La Jolla Institute for Allergy and Immunology, whose goal as a scientific organization is “Life Without Disease.”

Tremblay Jacobs is particularly thrilled about the opportunity to contribute to the Institute’s work because she personally has seen the devastating impact some of the diseases the Institute studies can have on a family. Her mother is waging a brave battle with uterine cancer, her father suffers from the autoimmune disease vasculitis, a serious inflammation of the blood vessels, and she has only recently begun to regain her own health after a long struggle with autoimmune disorders.

“We’re no different than the countless other families who are facing similar health issues,” Tremblay Jacobs says. “It’s just that my involvement with La Jolla Institute has suddenly given me an entirely new perspective and hope for the future. I’ve been fascinated by science my whole life, so meeting the Institute’s brilliant and dedicated scientists and hearing about the incredible scope of their research has been really exciting. I learned that the Institute is truly on a unique path that is transforming the way we diagnose and treat disease.”

Interestingly, in Tremblay Jacobs’ wide-ranging education and career, science and health—along with a talent for business—have been constants. Born and raised in Montreal, she served as a medic in the Canadian army for three years before entering Concordia University in Montreal

where she studied physical geography. She then became fascinated with the ocean and majored in marine science at the Université du Québec à Rimouski. While there she worked as an oceanographer in Italy on the Corilla Project in the Venice lagoon.

In hopes of becoming a teacher, she pursued a degree in education from the University of Ottawa, then taught elementary and high school in Ontario. Eventually, Tremblay Jacobs found her way into pharmaceutical sales where she discovered she could combine her love of business with her interest in science by helping provide Canadian doctors with drugs that would help their patients. In just three years as a representative for Warner Chilcott, she became one of the company’s highest-performing employees.

Tremblay Jacobs would likely still be there had it not been for a fateful day at the Grand Prix Montreal when she met an American businessman. She had no idea the man was Paul Jacobs, a top executive at Qualcomm, one of the world’s biggest and most important telecommunications companies. The two would ultimately marry, and today are the proud parents of a two-year-old daughter.

Although her life has changed significantly, Tremblay Jacobs, who divides her time between La Jolla and Montreal, remains the same energetic and down-to-earth person she has always been. If anything her passions for the environment, human rights, children, and education are stronger than ever, and her new life has given her a more global perspective on the importance of those causes. And as always, science and health will continue as priorities in her life.



“I’m honored to serve on the La Jolla Institute board and my primary goal will be to help spread awareness so that as many people as possible understand—and support, if possible—the phenomenal science these wonderful investigators are conducting,” Tremblay Jacobs says. “I’m hopeful that one day soon, research will demystify the immune system and that millions of people will finally stop suffering from autoimmune disease and cancer.” •

“My involvement with La Jolla Institute has suddenly given me an entirely new perspective and hope for the future.”

State of the Institute address launches new giving society

van•guard | n. a group of people leading the way in new developments or ideas

La Jolla Institute launched the Vanguard Giving Society with a “State of the Institute” address by Dr. Mitchell Kronenberg, President and Chief Scientific Officer, and a luncheon for the top long-term supporters of the Institute in February of this year.

During his presentation, Dr. Kronenberg reported on the Institute’s solid financial health, highlighted some of the Institute’s recent successes, and outlined the Institute’s bold mission: *Life Without Disease*®. “Life without disease sounds illogical but in fact it is a direction,” Dr. Kronenberg said. “We don’t know when and if the destination will be reached but we can eliminate diseases through biomedical research. Right now, there are real breakthroughs occurring in immunology research that are going to have a major impact on human health. We can already see it in cancer immunotherapy and it’s going to happen for other diseases as well.”

Dr. Kronenberg also emphasized the critical role of philanthropic support to help ensure LJI researchers’ role at the forefront of the next breakthroughs in medical research. “Our supporters take an active role in leading the way to life without disease by ensuring our scientists have the resources they need to take risks and accelerate the pace of discovery.”

Donors whose lifetime contributions reach \$1,000 automatically become members of the La Jolla Institute Vanguard Giving Society and enjoy a number of exclusive benefits:

\$100,000+

- Private dinner with the LJI President/Chief Scientific Officer for you and up to six of your friends and family members to ask all of your immune health-related questions
- Personal disease-area research landscape review and analysis

\$25,000-99,999

- Private roundtable lunch with a scientist for up to four of your friends and family members to ask about their specific research focus
- Individual report on the impact of your annual gift or pledge

\$10,000-24,999

- Reserved parking when visiting the Institute
- Invitations to special events with LJI faculty, LJI Board Members and LJI senior leadership at private residences and off-site venues

\$5,000-9,999

- Private lab tour of your choice
- Invitations to VIP receptions with Life Without Disease Seminar Series speakers

\$1,000-4,999

- Invitation to annual LJI State of the Institute event
- Special communications for LJI Vanguard members
- Recognition of LJI Vanguard membership at LJI events
- Listing in LJI Donor Honor Roll



Cedar pollen

After World War II, an ambitious project by the Japanese government called for the replacement of large swaths of natural forests with Japanese cedar, which was considered economically superior. As the trees matured, clouds of pollen started to waft across the country each spring, triggering widespread cedar pollen allergies.

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Our Mission

La Jolla Institute for Allergy and Immunology is dedicated to understanding the intricacies and power of the immune system so that we may apply that knowledge to promote human health and prevent a wide range of diseases. Since its founding in 1988 as an independent, nonprofit research organization, the Institute has made numerous advances leading toward its goal: *Life Without Disease*[®].



www.lji.org