Immune MATTERS

LA JOLLA INSTITUTE
FOR IMMUNOLOGY

FALL 2022

Academic Nomads

The international soul of science

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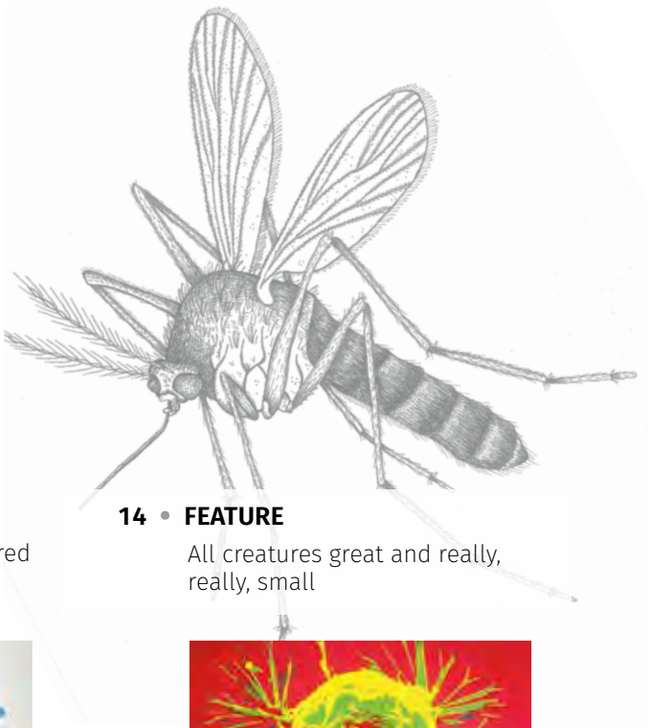
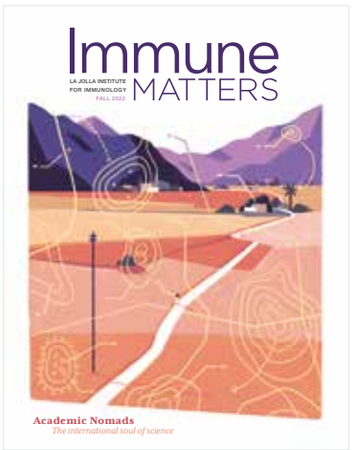
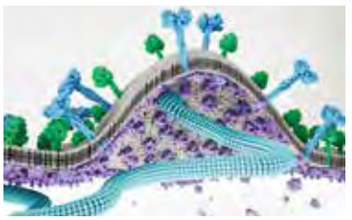
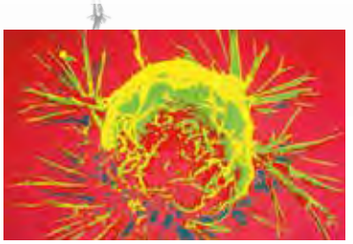
Fall 2022





What brings great minds in immunology to our Institute? International researchers share their stories.





OUR MISSION

The Institute will engage in a world-class biomedical research program with a focus on the immune system. It will conduct, share, and partner such that the results of its discovery program will make outsized contributions to the betterment of human health.

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The many roads to LJI

A while back, a member of my lab—a brilliant postdoc named Heather Callaway—described herself as an "academic nomad." This is a good way to describe a scientist's first decade or so in the field. Researchers often travel from institute to institute to earn their degrees and complete postdoctoral training, fellowships, internships, and a series of early career positions.

The nomadic life can be tough on families and leave scientists feeling like they are always just "settling in." Yet with each move comes a chance to work with new mentors, take on new projects, and learn new skills. I've enjoyed international research stays myself, and at home, have worked with many international colleagues who enriched both our research programs and our world view by sharing their cultures, their perspectives, and their scientific insights.

In this issue of *Immune Matters*, we focus on the new skills and ideas international scientists bring to La Jolla Institute for Immunology (LJI).

LJI is a global destination for scientists for many reasons. Read on to learn how LJI scientists are preparing for the next pandemic by investigating animal-borne diseases. Zoonotic diseases, which spread between humans and animals, are a particular interest of mine and the focus of my lab. We've all seen what happens when a pathogen "spills over" into humans.

We're also eager to share new insights into Alzheimer's disease—a neurodegenerative disorder not often thought of as immune-related. I also hope you'll enjoy a new profile of LJI Associate Professor Ferhat Ay, Ph.D. Ferhat's work to piece together the three-dimensional architecture of genomes is the kind of research that will rewrite textbooks.

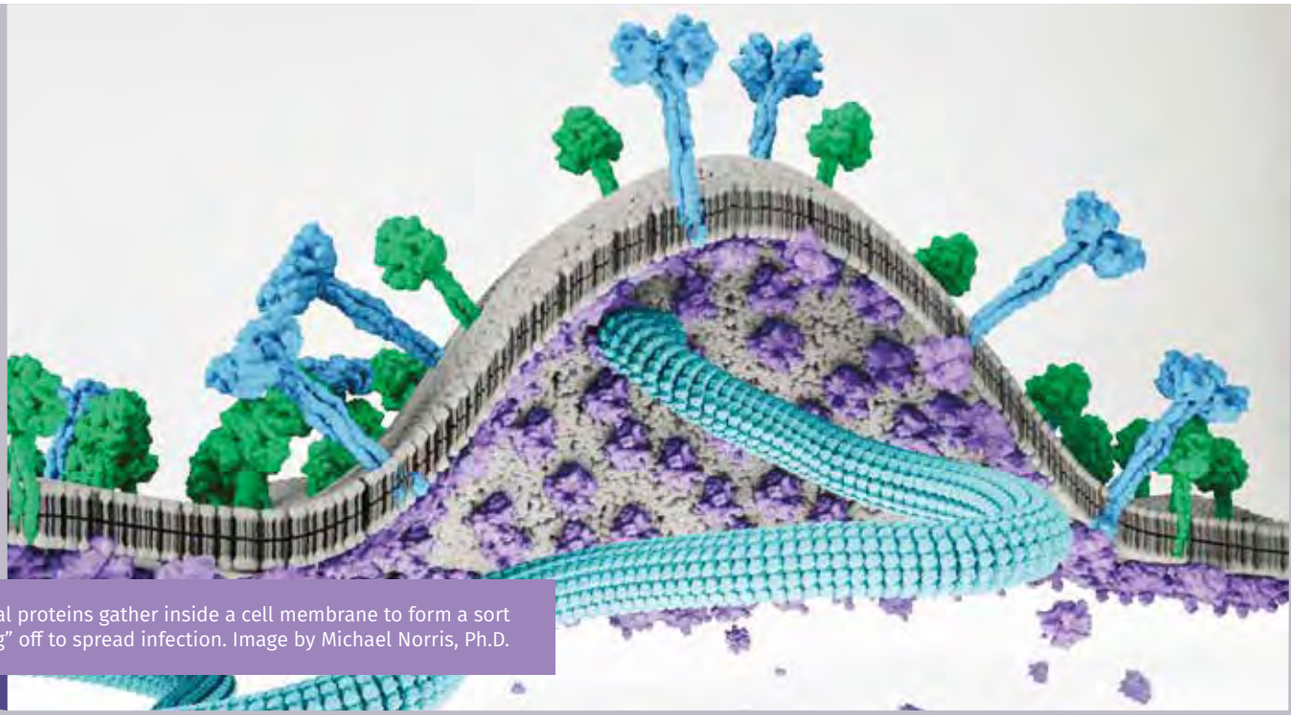
LJI's physical footprint may seem small. We're one building in the La Jolla biotech landscape. Still, LJI's intellectual mark is weighty in the world of biomedical research. Scientists here routinely publish in top scientific journals and lead global collaborations. We've become a gathering place for the academic nomads who want to share their expertise in a place that values diversity.

Today when I travel, I'm proud to say that LJI is my home. I hope LJI supporters like yourself can help us embrace the brilliant people who find their way here.

Sincerely,

Erica Ollmann Saphire, Ph.D.
President and CEO
La Jolla Institute for Immunology

RESEARCH BRIEFS



This image shows how viral proteins gather inside a cell membrane to form a sort of bubble before "budding" off to spread infection. Image by Michael Norris, Ph.D.

Measles, Nipah viruses captured in stunning detail

Some members of the *Paramyxovirus* viral family, such as measles, are incredibly contagious. Other members of the family, such as Nipah virus, have a shocking mortality rate of 40 to 90 percent. "Just imagine if a *Paramyxovirus* emerged that was as contagious as measles and as deadly as Nipah," says former La Jolla Institute for Immunology (LJI) postdoctoral researcher Michael Norris, Ph.D.

In a new study published in *Science Advances,* Dr. Norris worked with LJI Professor Erica Ollmann Saphire, Ph.D., and an international team of collaborators to study a key stage in the life cycles of measles and Nipah viruses. The scientists used high-resolution imaging techniques to catch these viruses in the process of viral assembly, when viral proteins form a "bud" so a new virus slips out of an infected cell

The research reveals how key pieces of these viruses, called matrix proteins, come together and bind with the host cell membrane while showing how future therapies might interrupt the viral assembly process to stop *Paramyxoviruses* in their tracks.

LJI scientists uncover dangerous "feedback loop" linked to inflammation in severe asthma

A lack of oxygen, called hypoxia, can be an "initial insult" that leads to future lung problems, including severe asthma, chronic obstructive pulmonary disease (COPD), and fibrosis.

Now, LJI Professor and Chief Scientific Officer Mitchell Kronenberg, Ph.D., has uncovered a clue to why hypoxia causes long-term health issues. Dr. Kronenberg and his colleagues used a mouse model to show how hypoxia activates the same immune cells that cause inflammation during asthma attacks. As a person gasps for breath, these cells flood the airways with molecules that damage the lungs. If a person can't breathe properly due to asthma, the resulting hypoxia appears to lead to a "feedback loop" that triggers even more inflammation.

Going forward, the researchers hope to study whether ADM, a molecule involved in hypoxia-driven inflammation, could be a target for treating inflammatory and allergic lung diseases.

COVID-19 vaccine comparison is first of its kind

Members of LJI's Coronavirus Taskforce have published a unique, in-depth study that compares the four COVID-19 vaccines: Pfizer-BioNTech, Moderna, Novavax, and Janssen/J&J.

The LJI team is the first to compare the strengths of T cell, B cell, and antibody responses over time to different vaccines against the same pathogen, targeting the same viral structure, using three different vaccine platforms. "This study is important because it lets us answer how different vaccine platforms perform in terms of inducing immune responses," says LJI Professor Alessandro Sette, Dr.Biol.Sci., who co-led the research with Research Assistant Professor Daniela Weiskopf, Ph.D., and Professor Shane Crotty, Ph.D.

The study, published in *Cell*, is not meant to provide a vaccine "scorecard." The researchers found that each vaccine provided valuable immune protection. "Just understanding the immune responses to these vaccines will help us integrate what is successful into vaccine designs going forward," says Dr. Weiskopf.

> "This study is important because it lets us answer how different vaccine platforms perform in terms of inducing immune responses."
>
> LJI PROFESSOR
> ALESSANDRO SETTE, DR.BIOL.SCI.

New drug shows promise for treating Ebola virus infections

In a new collaboration with Stanford University and Scripps Research scientists, Dr. Erica Ollmann Saphire's lab has shown the power of targeting an Ebola virus protein called polymerase. This research, led by Graduate Student Jingru Fang, suggests an experimental drug called CC-90009 can stop Ebola virus by targeting a human protein that partners with polymerase to help infections spread.

> "This study shows there are new targets we can go after to treat Ebola virus infection."
>
> LJI GRAD STUDENT
> JINGRU FANG

Zika virus all too ready to mutate

Scientists at LJI have shown the Zika virus can mutate to become more infectious—and potentially break through pre-existing immunity. "The world should monitor for the emergence of this Zika virus variant," says LJI Professor Sujan Shresta, Ph.D., who co-led the *Cell Reports* study with Professor Pei-Yong Shi, Ph.D., of the University of Texas Medical Branch (UTMB).

Dr. Shresta and her colleagues set out to understand how Zika evolves as it transmits back and forth between mosquito vectors and mammalian hosts. To study this, collaborators at UTMB transmitted Zika virus between mosquito cells and mice.

The researchers found it is relatively easy for Zika to acquire a single amino acid change that allows the virus to make more copies of itself and help infections take hold more easily. "A high replication rate in either a mosquito or human host could increase viral transmission or pathogenicity and cause a new outbreak," says Jose Angel Regla-Nava, Ph.D., former postdoctoral researcher at LJI and current Associate Professor at the University of Guadalajara, Mexico.

Academic Nomads

The international soul of science

Humans have been on the move since the dawn of time. Scientists are a peculiar migrant "species," as they move around the globe following their passion, looking for the best places to learn new skills, and carrying out their next projects. These migrations help push scientific progress forward.

La Jolla Institute for Immunology (LJI) could not flourish without its international researchers. In a recent survey conducted by LJI's diversity, equity, and inclusion committee, about 48 percent of the respondents reported they were born outside the United States. These respondents hailed from 32 different countries.

This is the story of four researchers from different parts of the world who followed different paths but all ended up at LJI.

Priyanka Saminathan, Ph.D.,

is an Indian postdoctoral fellow, originally from Kuwait, who leads research in the laboratory of Associate Professor Sonia Sharma, Ph.D.

Her interest in immunology was born during her undergraduate training in India when she attempted to set up a protocol to analyze her sister's mysterious allergic reaction to antibiotics that doctors were unable to characterize. The diagnostic device Dr. Saminathan thought up remains theoretical, but the project lit the spark for her future career.

Science drove her westward: Dr. Saminathan trained in India, Estonia, and Scotland before landing in the United States. She has been following LJI research since she moved to America to earn her Ph.D. at the University of Rochester Medical Center in New York. She finally had the opportunity to join Dr. Sharma's group in 2021. Here, she investigates sex-based differences in the immune response to SARS-CoV-2 and in Alzheimer's disease. To tackle those issues, Dr. Saminathan uses flow cytometry, a technique she describes as "the right hand of an immunologist."

"One of the reasons I moved to LJI and interviewed with both Dr. Lynn Hedrick and Dr. Sharma is because they are amazing female role models," she says. Dr. Saminathan knows from personal experience the importance of a good mentor, and she is trying to become one: At LJI she found a place where she can cultivate her passion for teaching, a fundamental skill to guide future scientists.

"One of the reasons I moved to LJI and interviewed with both Dr. Lynn Hedrick and Dr. Sharma is because they are amazing female role models."

Priyanka Saminathan, Ph.D.

Benjamin Schmiedel, Ph.D.,

is a German scientist who has been working at LJI for 10 years in the laboratory of Professor Pandurangan Vijayanand, M.D., Ph.D. He has worked his way up from postdoctoral fellow to instructor.

After completing his training in Germany, where he studied the functional role of immune cells in leukemia, Dr. Schmiedel looked for an opportunity to widen his horizons both personally and professionally.

An opening in the Vijayanand Laboratory to study the role of genetics in immune cells was the perfect opportunity for Dr. Schmiedel to explore a new aspect of immunology. When he joined LJI in 2012, Dr. Schmiedel was thrilled by the idea of being part of a community that studies so many different aspects of the immune system. He came from a lab where researchers followed a strict line of questioning, so he appreciated the more varied and creative approach to research at LJI. “Here things are freer. You get to explore more and ask questions in a more flexible way,” Dr. Schmiedel says.

Today, Dr. Schmiedel is researching how genetic differences affect a person’s susceptibility to autoimmune diseases, as well as the different clinical features of COVID-19 infections. To answer these questions, Dr. Schmiedel is using techniques such as cell culture, flow cytometry, and sequencing, “which are greatly supported by the LJI facilities,” he says.

Reika Watanabe, Ph.D.,

is a scientific associate from Japan who leads structural biology research in the laboratory of LJI President and CEO Erica Ollmann Saphire, Ph.D.

During her undergraduate studies she became fascinated by a rare autoimmune disease, called paroxysmal nocturnal hemoglobinuria, which she studied during her Ph.D. at Osaka University. “Science made me go to different places,” says Dr. Watanabe. After earning her Ph.D., she moved to Switzerland to continue studying a key protein involved in this rare disease.

During her first experience in the United States at the University of California, San Diego, she studied a protein structure in Parkinson’s disease, but after a few years she sought to return to immunology: “Joining the Saphire Lab in LJI in 2020 was like closing a circle,” Dr. Watanabe says. She was captivated by the way Dr. Saphire organizes her lab and by LJI’s wide range of cutting-edge research instruments, which open up many possibilities for new projects.

Dr. Watanabe wants to shed light on the various biological processes that regulate host-pathogen interaction. To do so she employs her extensive expertise in cryo-electron tomography (CET), a unique tool to visualize the structure of macromolecules in their natural environment. Solving the structures of both human proteins and pathogenic molecules is critical for future vaccine and drug development.

Fernanda Ana-Sosa-Batiz, Ph.D.,

is a Mexican postdoctoral fellow in the laboratory of Professor Sujan Shresta, Ph.D.

After completing her undergraduate studies in Mexico, Dr. Ana-Sosa-Batiz moved to Australia for her Ph.D., where she studied the antibody response to HIV and influenza virus infections. In 2017, she landed in the United States and spent the first three years focused on raising her daughter. The onset of the pandemic pushed her to return to science. "I wanted to contribute to our understanding of the immune response against this virus that caused so much damage," says Dr. Ana-Sosa-Batiz.

She joined Dr. Shresta's laboratory in 2021. "Since I was in grad school on the other side of the world I read and heard about the excellent research being done at LJI," says Dr. Ana-Sosa-Batiz. "I wanted to be in a place like this where there is no limitation to the scientific questions you can answer, and you have access to cutting-edge research."

> "I wanted to be in a place like this where there is no limitation to scientific questions you can answer…"
>
> **Fernanda Ana-Sosa-Batiz, Ph.D.**

Dr. Ana-Sosa-Batiz wants to have a full picture of antibody responses elicited by different COVID-19 vaccines and by viral infection. Her goal is to better understand which vaccines are the best tools against SARS-CoV-2. She is also hoping to learn how to design RNA vaccines.

LJI was born with an international perspective

In fact, Institute founding leaders Makoto Nonaka, Ph.D., and Kimishige Ishizaka, Ph.D., both trained in Japan before coming to California. Today, half of LJI laboratories are led by faculty members who grew up outside the United States.

Dr. Saminathan points out that international contributions are especially important in the field of immunology because scientists from different parts of the world bring first-hand experience of diseases not present in the United States. For example, Dr. Shresta's laboratory has hosted visiting scientists from Nepal who have shared their passion for confronting dengue virus, a pathogen that has infected millions of people around the world and could potentially emerge in the United States.

In return, the welcoming environment at LJI can change how scientists approach their work. Scientists here have the independence to pursue research directions that fascinate them—and they have access to the equipment, training, and experts to propel this research.

LJI administrative staff are there to help. The Institute works with an immigration attorney to set up the appropriate visas for international researchers and employee benefits include relocation services.

Working at LJI also leads to funding opportunities. Through LJI's Tullie and Rickey Families SPARK Awards for Innovations in Immunology, early career scientists can receive funding to launch new projects and gather data that can fuel their careers. Dr. Saminathan's ongoing COVID-19 research is supported by a SPARK Award.

By choosing to bring their expertise to LJI, a diverse and dedicated group of international researchers is changing how we combat disease around the world. •

All creatures great and really, really small

Mosquitoes hide. They bite. They kill. One million people die from mosquito-borne illnesses every year. The mosquito is the deadliest animal in the world.

So how does the human body react when it meets a mosquito-borne virus? That's a great question. "We know very little about the immunologic changes in the skin after a mosquito bites you," says Professor Sujan Shresta, Ph.D., an infectious disease researcher at La Jolla Institute for Immunology (LJI).

In fact, scientists face many big questions when it comes to the diseases spread by animals.

An estimated 80 percent of diseases are zoonotic, meaning they can be transmitted between humans and animals. Spillovers happen all the time. HIV came from other primates. MERS came from camels. "Zoonosis is everywhere. This is where pandemics come from," says LJI Professor Erica Ollmann Saphire, Ph.D. "We are constantly interacting with birds and mammals and insects. There are rats in the subways and birds that leave waste in our water sources."

The bubonic plague was a zoonotic disease. So was the 1918–1919 flu pandemic. And COVID-19. Monkeypox, potentially carried by rodents or other mammals, is the latest animal-borne threat.

Several LJI laboratories are dedicated to understanding how zoonotic diseases emerge—and how we can prevent them.

< > An estimated **80 percent** of diseases are zoonotic, meaning they can be transmitted between humans and animals.

Flaviviruses

As a kid growing up in Nepal, Dr. Shresta wasn't worried about dengue virus. The mountainous nation was too chilly for *Aedes* mosquitoes, which carry the virus. Then, as she trained as an immunologist, Dr. Shresta watched dengue march across Asia.

Today, dengue is endemic to Nepal, and Dr. Shresta is working closely with Nepalese research partners to understand the disease. She has devoted her career to studying how the immune system responds to dengue and other mosquito-borne flaviviruses, such as Zika and Japanese encephalitis virus.

"These diseases are major public health problems worldwide," says Dr. Shresta. "Dengue and Zika affect half the world's population. They are spreading in every tropical and subtropical country in the world."

Through pioneering work in mouse models, Dr. Shresta has shown how the immune system responds when it encounters flaviviruses and how exposure to these viruses can harm developing fetuses.

Dr. Shresta is also interested in a phenomenon called "antibody-dependent enhancement," or ADE. In ADE cases, subsequent infections by related viruses can accelerate, rather than blunt infection, leading to more severe disease. By studying ADE, Dr. Shresta is helping develop safe vaccines for people who live in areas where several flaviviruses overlap.

There's no time to waste as climate change and warmer temperatures drive a global mosquito migration. In recent years, three species of *Aedes* mosquitoes were spotted in San Diego County for the first time.

"Dengue and Zika **affect half the world's population**. They are spreading in every tropical and subtropical country in the world."

LJI Professor Sujan Shresta, Ph.D.

Rabies virus

Humans have always feared rabies. Think vampires, werewolves. “This is an ancient disease,” says Dr. Saphire.

Rabies spreads between mammals through their bodily fluids, like saliva and blood. The virus is especially common in bats, raccoons, skunks, and foxes.

“Regardless of where you live in the United States, somewhere in your state is a creature that has rabies,” says LJI Postdoctoral Fellow Heather Callaway, Ph.D. “If you are exposed, you must get treatment or you will die, because rabies is 100 percent lethal if not treated.”

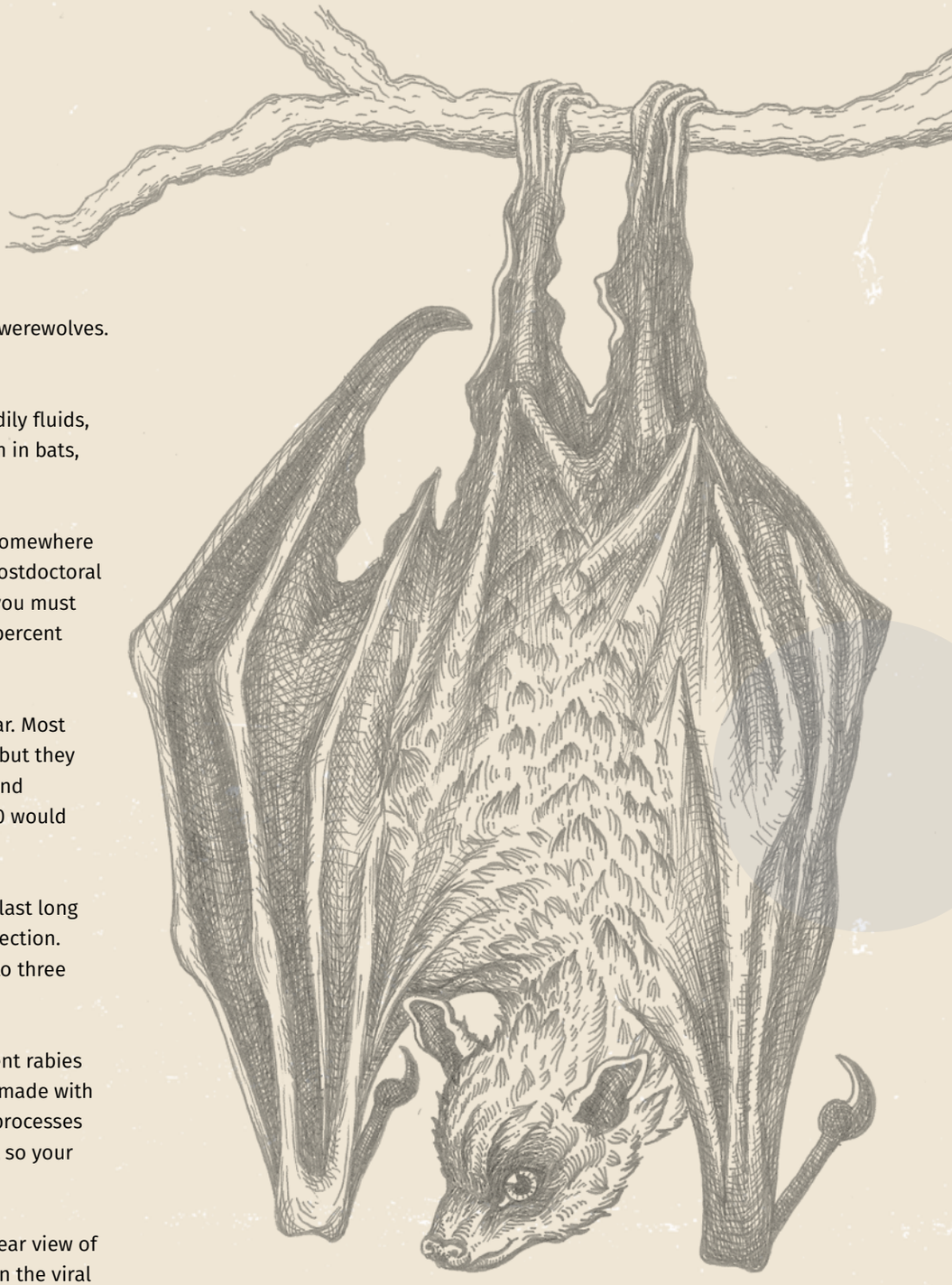
An estimated 59,000 people die from rabies each year. Most of the victims are children. Rabies treatments work, but they are inaccessible for most people around the world and unaffordable. (The treatment cost of $4,000 to $7,000 would devastate the average family).

Vaccines are a more realistic option—but they don’t last long enough. “Rabies vaccines don’t provide lifelong protection. You have to get your pets a booster shot every one to three years,” says Dr. Saphire.

To be frank: rabies vaccines are outdated. “The current rabies vaccines for humans and domesticated animals are made with killed or inactivated virus,” says Dr. Saphire. “These processes can spring the viral molecules into the wrong shape, so your immune system is distracted by the wrong thing.”

What rabies vaccine researchers have needed is a clear view of the rabies glycoprotein—a potential vaccine target on the viral surface. “It is important to understand that structure to make more effective vaccines and treatments—and to understand how rabies and other viruses like it enter cells,” says Dr. Saphire.

So Drs. Callaway and Saphire are using modern tools to solve an ancient problem. Thanks to advances in cryo-electron microscopy, they are capturing some of the first 3D images of the rabies glycoprotein, giving scientists the first glimpses of where the rabies virus might be vulnerable.



An estimated **59,000 people** die from rabies each year. Most of the victims are children.

COVID-19

A coronavirus was likely circulating in an animal population (perhaps civet cats) when it mutated to spread from animal to human—and then from human to human. Who knows how many coronavirus variants circulated in the wild before the wrong animal made it to Wuhan, China.

Scientists refer to a virus-carrying animal population as a reservoir. Reservoirs are a problem because a large group of infected animals makes a fertile proving ground for dangerous viral mutations.

We've already seen how mutations can change SARS-CoV-2: human immune cells have a harder time fighting some SARS-CoV-2 variants, even in people who have been vaccinated.

To make matters worse, humans are hopping on planes and going on with their daily lives, seeding SARS-CoV-2 back among animal populations. "We're the reservoir now," says Dr. Saphire.

Already, SARS-CoV-2 has sickened mink, hamsters, tigers, and gorillas, among others. SARS-CoV-2 is now common in white-tailed deer in the Eastern United States. We've created reservoirs for SARS-CoV-2 in animals that posed no danger before.

Ebola virus

Dr. Saphire has witnessed the threat of animal reservoirs in her Ebola virus research. Time and time again, Ebola virus will appear in a community, seemingly out of nowhere. Then the outbreak will end and the disease will appear eradicated—until the virus reappears years or decades later.

Ebola virus can disappear and reappear because it can survive in an animal reservoir. Many studies point to fruit bats as the probable source. By persisting in an animal reservoir, Ebola virus can travel to new areas undetected. So far, Ebola virus has five cousins (that we know of), and they all pose a threat.

Dr. Saphire and her colleagues are eager to help design vaccines or therapies that fight all five *ebolavirus* species. By comparing the molecular structures of these viruses, the researchers can spot antibody targets the viruses have in common.

Engineering immunity

We don't know which zoonotic disease will emerge next. No one expected monkeypox to spread so widely this year. LJI scientists want to be ready for anything. Their goal is to "engineer" immunity against specific viral targets—weak spots that a family of viruses may have in common.

"There are actually more than 70 known flaviviruses that could emerge and cause an explosive outbreak," says Dr. Shresta. Her research suggests a pan-flavivirus approach is the best option.

Dr. Saphire, who is LJI's President and Chief Executive Officer, leads the global Coronavirus Immunotherapy Consortium (CoVIC) and is working on a vaccine to tackle whichever coronavirus species emerges next. Dr. Shresta is a member of this consortium, and the two are collaborating to understand the best immunization strategies and key immune cells to activate with this kind of pan-coronavirus vaccine.

Meanwhile, Dr. Callaway has succeeded in capturing a clear 3D image of the rabies glycoprotein. Her recent work, published in *Science Advances*, may guide the development of better vaccines against rabies and the whole family of lyssaviruses.

These researchers are chipping away at the big questions—and they are making progress. Earlier this year, the Saphire Lab showed how a pair of antibodies can fight off Ebola virus and the closely related Sudan virus. This is a key step toward a pan-*ebolavirus* vaccine.

Doctors have a saying: "When you hear hoofbeats, think of horses, not zebras." It means doctors should consider the most likely diagnoses first.

But LJI immunologists have to prepare for the most far-fetched possibilities. "We can't play a game of whack-a-mole every time a virus emerges, where we shut down and try to make a vaccine against just that virus," says Dr. Saphire. •

Researchers set out to develop a dengue virus vaccine 80 years ago. We still don't have a good one. Read the online exclusive article "The dengue problem" to learn how Dr. Shresta has accelerated dengue research. >

About the artist: Liz Hui is a multimedia artist and gardener for the San Francisco Recreation and Parks Department. She finds a steady stream of inspiration in horticultural work, incorporating themes and imagery of nature into drawings, screen prints, murals, and sculptures.

DR. EMILY HOLMES JOINS LJI BOARD OF DIRECTORS

La Jolla Institute for Immunology (LJI) welcomes Emily Holmes, Ph.D., J.D., to the Institute's Board of Directors. Dr. Holmes has more than 30 years of experience in the areas of patent law, ethics, and research compliance. She brings with her in-depth knowledge of clinical trials and the challenges of taking research from bench to bedside.

"Serving as a LJI board member provides a unique opportunity for me to contribute in a governance leadership role to help guide LJI's vision, strategic planning, regulatory compliance, and sustainability in its global health initiatives," says Dr. Holmes.

Dr. Holmes currently serves as Senior Director of Research Compliance and Regulatory Affairs at Seattle Children's, where she and her team support the hospital's groundbreaking research by fostering a culture of research compliance, responsibility, and integrity,

Dr. Holmes previously led compliance efforts at Scripps Research in La Jolla, one of the largest biomedical research institutes in the world. For nearly two decades, Dr. Holmes served in various positions, including patent attorney and supervising the Scripps Research cores and research compliance. By the time she left Scripps Research, Dr. Holmes had risen to the position of Vice President of the institute's Office of Policy, Education, and Risk Administration.

Dr. Holmes also has extensive experience in drafting regulatory policy. She is registered with the U.S. Patent and Trademark Office and is a current member of the California Bar. She is certified in healthcare research compliance (CHRC).

SEQUENCING SPECIALIST HANNAH DOSE WINS XPRIZE-FUNDED FELLOWSHIP

Hannah Dose, Associate Manager for the LJI Next Generation Sequencing Core, was awarded an XPRIZE-funded fellowship to attend the OC program, a conference held in the Dominican Republic to bring together experts equipped to address global poverty and injustice. Dose is a sequencing specialist focused on looking for ways to share scientific tools with researchers around the world. "I feel honored to just be part of a collaborative movement like this," says Dose.

Dose's fellowship comes on the heels of a $500,000 XPRIZE win to the entire Next Generation Sequencing Core team for their development of a fast, inexpensive, highly accurate COVID-19 testing protocol.

CANCER RESEARCHER LEILA CHIHAB WINS PRESTIGIOUS NSF GRANT

Leila Chihab has received a National Science Foundation (NSF) Graduate Student Research Fellowship, one of the most competitive awards available to graduate students in the United States. The $138,000 award will fund three years of Chihab's tuition and stipend as a UC San Diego graduate student working in the laboratory of LJI Professor Bjoern Peters, Ph.D.

Chihab is working to improve cancer immunotherapies. She analyzes patient sequencing data—the genetic makeup of their individual tumors—to predict which neoantigens (new proteins on cells) can generate epitopes (vulnerable sites) that can be recognized by the immune system as cancerous. This research is critical for designing personalized cancer treatments.

She's also investigating what makes some T cells good at fighting cancer. A part of the secret potentially lies in a cell's TCR, the molecules on the outside of T cells that allow them to recognize antigens. While T cells are great at learning to target invading pathogens, they can struggle to recognize "neoantigens," the molecular markers that separate mutated cancer cells from normal cells nearby. Chihab is hunting for the most useful T cells by analyzing data from single-cell sequencing.

The NSF was interested in supporting Chihab's research because of her efforts to generate and harness massive datasets for bioinformatic research. In the end, Chihab hopes to help develop machine-learning algorithms that can detect TCR patterns in reams of single-cell data.

MARCO ORECCHIONI, PH.D., WINS PILOT GRANT FUNDING FOR OLFACTORY RECEPTOR RESEARCH

LJI Instructor Marco Orecchioni, Ph.D., has shown that olfactory receptors are important for much more than a person's sense of smell. His work in the Ley Lab at LJI has revealed that olfactory receptors in immune cells called macrophages actually "sniff" molecules in the arteries and drive the kind of inflammation seen in heart disease.

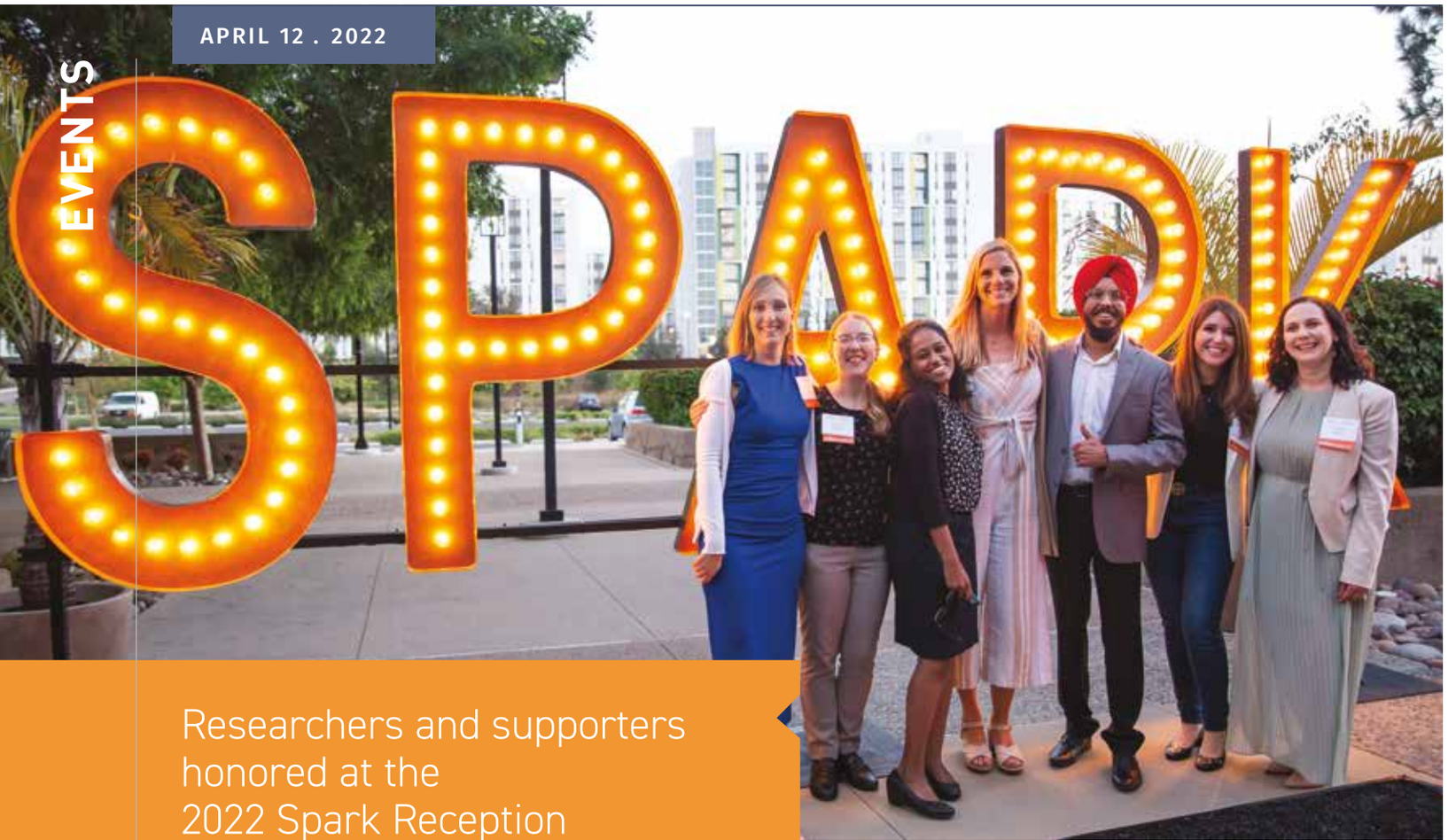
Now Dr. Orecchioni has received new funding to investigate the roles of olfactory receptors in the body's response to infectious disease. Dr. Orecchioni's new project is a collaboration with University of California, San Diego School of Medicine Professor Manuela Raffatellu, M.D. The two researchers will each receive $50,000 for this research, splitting a $100,000 Pilot Grant from the Program in Immunology, a partnership between LJI and UC San Diego.

The new funding will allow Dr. Orecchioni to build on his discovery that olfactory receptors in macrophages present in artery walls can respond to oxidative stress-derived molecules—and further trigger the inflammation that can lead to atherosclerosis. This surprising insight was made possible through the Tullie and Rickey Families SPARK Awards for Innovations in Immunology and funding from The Conrad Prebys Foundation.

APRIL 12 . 2022

Researchers and supporters honored at the 2022 Spark Reception

On April 12, 2022, LJI hosted guests to a dazzling reception celebrating five years of the Tullie and Rickey Families SPARK Awards for Innovations in Immunology. The event was held on LJI's back patio, in part to honor the brilliant winners of the 2022 Tullie and Rickey Families SPARK Awards, but also to recognize the donors and supporters of the Tullie and Rickey Families SPARK Awards program. Guests sipped on "spark"ling cocktails as LJI leadership shared highlights from current Institute endeavors and news from former SPARK winners about their ongoing research projects.



SPARK Program Manager Kelsey Dale with the '22 Tullie and Rickey Families SPARK Awards winners

'22 SPARK Awards winner Greet Verstichel, M.D., Ph.D., with SPARK donors Carol Streeter and Carolyn Nelson

Mitchell Kronenberg, Ph.D., LJI Chief Scientific Officer, with SPARK donors Tom and Judy Tullie, Sam Myers, Ph.D., and SPARK donor Vann Parker

'19 SPARK Awards winner Julie Burel, Ph.D., and SPARK donor Anne Hill

From left: LJI Professor and Chief Scientific Officer, Mitchell Kronenberg, Ph.D., Consul General of Mexico in San Diego Carlos González Gutiérrez, LJI Research Technician Cindy Manriquez-Rodriguez, M.Sc., LJI Managing Director and Chief Business Officer Joel Martin, Ph.D.

The group enjoyed a tour of the Institute, especially a stop by the Cryo-EM Facility where they learned about the Titan Krios microscope from Ruben Diaz Avalos, Ph.D., Senior Research Scientist at LJI.

Cindy Manriquez-Rodriguez, M.Sc., a research technician in the Myers Lab, shared her research and her educational pathway to LJI.

On June 16, 2022, the Mexican Consulate in San Diego brought a delegation of representatives of Mexico's biological sciences industry to LJI for a visit. The delegation was in San Diego representing Mexico for the first time at the BIO International Convention.

The visiting delegation included representatives of the Mexican Consulate in San Diego, the Border Philanthropy Partnership, biotech and pharmaceutical companies, and universities from across Mexico.

JUNE 1 . 2022

On June 1, 2022, LJI and partner Women's Health Access Matters (WHAM) welcomed supporters to a private inaugural event at the Rancho Valencia Resort & Spa celebrating a shared commitment to research focused on sex-based differences in the immune system. LJI President and CEO Erica Ollmann Saphire, Ph.D., and WHAM CEO and Founder Carolee Lee, an LJI Board Member, led a discussion and shared more about the two groups' recently launched partnership.

WHAM Founder and LJI Director Carolee Lee with Erica Ollmann Saphire, Ph.D., LJI President & Chief Executive Officer

Susan Davis and Elliot Feuerstein with Susan Ulevitch

Jacque Sokolov and Mitzi Krockover

AUGUST 5 . 2022

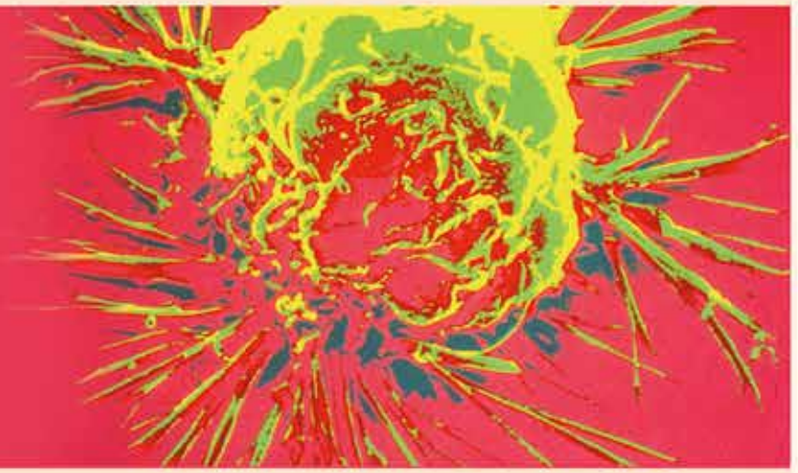
A DAY AT THE *Races*

August 5, 2022, marked the long-awaited 2nd annual "A Day at the Races" event at the renowned Del Mar Racetrack. Guests of LJI received exclusive access to the penthouse level of the Turf Club for a bird's-eye view of the horse races from il Palio Restaurant and Patio. Guests mingled with LJI scientists and leadership, experienced a virtual reality demo, and even had the opportunity to see a little magic.

LJI President and CEO Erica Ollmann Saphire, Ph.D., with UC San Diego Chancellor Pradeep Khosla, Ph.D.

Attorneys and guests from Rodriguez Horii Choi & Cafferata, LLP, showed their support at the event

Valuable lessons from a failed cancer drug trial



LJI and U.K. scientists investigate dangerous inflammation in clinical trial subjects and develop new strategy to avoid cancer immunotherapy side effects

Cancer immunotherapies can save lives, but they are also associated with harmful side effects and failed clinical trials. In fact, only 20 to 30 percent of solid cancer patients given immunotherapy end up in long-term remission.

New research shows how we can improve immunotherapies by examining exactly what is happening in the immune system when clinical trials go sideways.

When U.K. patients were struck with adverse effects during an immunotherapy trial testing for head and neck cancer, researchers at La Jolla Institute for Immunology (LJI) and the University of Liverpool went back to the bench to understand what went wrong.

Their findings may prove critical for improving immune treatments for patients with solid tumors. The research, published in *Nature*, was led by LJI Professor Pandurangan Vijayanand, M.D., Ph.D., and University of Liverpool Professor Christian H. Ottensmeier, M.D., Ph.D., FRCP, also adjunct professor at LJI.

The team investigated how immune cells respond to a cancer drug called a PI3Kδ inhibitor. This drug is meant to block "regulatory" T cells (Tregs), which would normally stop effector T cells from targeting the body's own tissues. By removing the brakes, the PI3Kδ inhibitor sets the immune system free to generate tumor-fighting T cells.

This drug has been approved for B cell lymphomas, and the recent clinical trial tested it in patients with solid tumors. Unfortunately, the trial came to a swift end when half of the study volunteers were hit with colon inflammation.

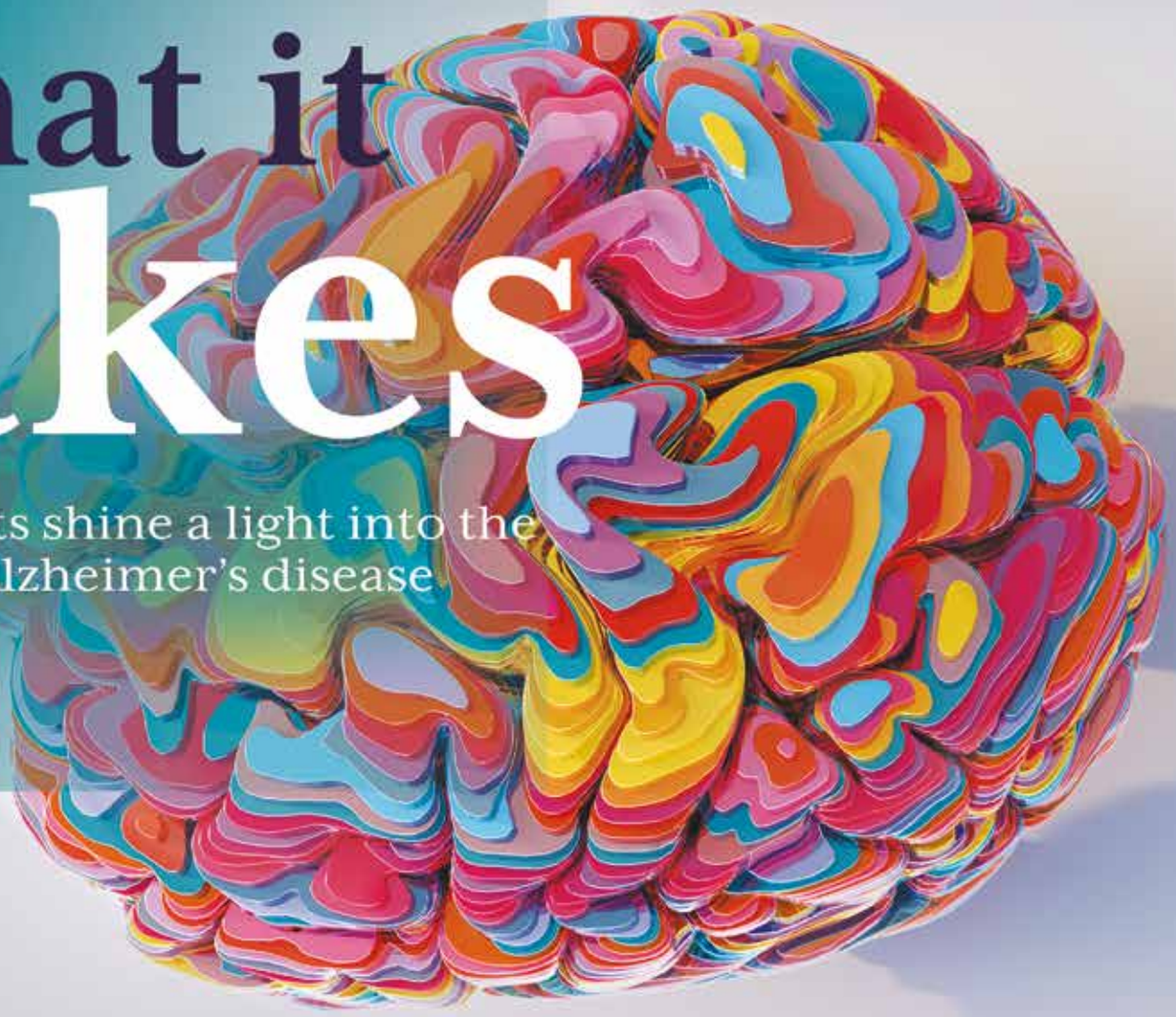
To understand why the treatment caused colon inflammation, LJI Instructor Simon Eschweiler, Ph.D., and colleagues took a closer look at how the PI3Kδ inhibitor affects immune cells. The scientists showed the drug also blocks a specific Treg cell subset from protecting the colon; without the right Tregs protecting the colon, pathogenic T cells caused gut inflammation and colitis.

Dr. Eschweiler explains that while B cell lymphoma patients receiving the drug were immunocompromised from previous treatments, the solid cancer patients still had functional immune cells. The harmful T cells in the gut were ready to swoop in and cause inflammation. This difference means the solid tumor patients showed unexpected immune-related side effects. The researchers think this discovery may help explain toxicity associated with cancer immunotherapies more broadly.

This study highlights the importance of designing personalized therapies based on ad hoc doses and schedules. Based on data from a mouse model experiment, the scientists came up with a new strategy to reduce drug toxicity in solid tumors: intermittent dosing, an approach that will soon be tested in the clinic. •

What it takes

LJI scientists shine a light into the depths of Alzheimer's disease



What a shock to be diagnosed with Alzheimer's disease. What a feeling to have one's memories stolen by a disease that seems to drift in from nowhere.

Still, every disease must come from somewhere. Associate Professor Sonia Sharma, Ph.D., is leading one of several promising efforts at La Jolla Institute for Immunology (LJI) to uncover the fundamental molecular drivers of Alzheimer's disease.

"In the last five years, it's become clear the immune system is a major factor in Alzheimer's disease," says Dr. Sharma.

Already, Dr. Sharma has found new clues to Alzheimer's by investigating an odd type of immune cell: the stromal cell. Stromal cells are interesting because they are barely immune cells at all.

They actually have a lot in common with the kind of stem cells that hang out in the bone marrow. But stromal cells are special because they help activate T cells and B cells. "In my lab, we consider stromal cells to be immune mediators," says Dr. Sharma.

Some stromal cells, called vascular endothelial cells, line the blood vessels in the brain. This puts them in contact with immune cells, signaling molecules, and pathogens. These stromal cells take their position seriously. They are ready to pump out signaling molecules to alert the immune system if they see anything suspicious.

Of these many signaling molecules, Dr. Sharma has chosen to focus on small molecule metabolites. Metabolites were once seen as minor players in immune activation, but Dr. Sharma's work highlights how metabolites can actually drive inflammation in the vascular system, leading to conditions like vasculitis and vascular dementia.

"In fact, both Alzheimer's and vascular dementia are characterized by vascular inflammation," says Dr. Sharma.

Dr. Sharma is following up on these findings by comparing metabolite levels in women who develop—or don't develop—Alzheimer's disease. According to the Alzheimer's Association, women account for two-thirds of Alzheimer's patients. Studying their blood may reveal clues to the disease.

By examining blood samples from a longitudinal study (where participants were followed for many years), Dr. Sharma and her collaborators at UC San Diego and Cedars-Sinai Medical Center in Los Angeles have uncovered a group of bioactive lipid metabolites that appears to protect some women from Alzheimer's disease. Other metabolites are pathogenic, and may predispose some women to the disease.

"There are some metabolites that are actually missing in males, and while they are present in females, they appear to be missing in females who develop Alzheimer's," says Dr. Sharma. "What's really interesting is that these are biologically active, dietary metabolites—which means we may be able to modulate the disease by giving these metabolites as supplements. That's a very intriguing possibility for treating the disease."

LJI Research Assistant Professor Cecilia Lindestam Arlehamn, Ph.D., is looking at an entirely different arm of the immune system: T cell responses.

Self-reactive T cells are the sort of T cells that mistakenly attack healthy tissues and cause autoimmune disease. As Dr. Lindestam Arlehamn has shown, in collaboration with LJI Professor Alessandro Sette, Dr.Biol.Sci., self-reactive

> **"In fact, both Alzheimer's and vascular dementia are characterized by vascular inflammation."**
>
> **LJI Associate Professor Sonia Sharma, Ph.D.**

T cells do appear to target key brain cells at the onset of Parkinson's disease, another age-related neurological condition. However, similar experiments did not show the same T cell activity in Alzheimer's disease.

"What we want to do now is to look at individuals at risk of developing Alzheimer's disease," says Dr. Lindestam Arlehamn. With this head start, she may be able to spot the fleeting moments when T cells do cause changes in the brain. "In Parkinson's, we see that T cell reactivity changes over time as the disease progresses," she says.

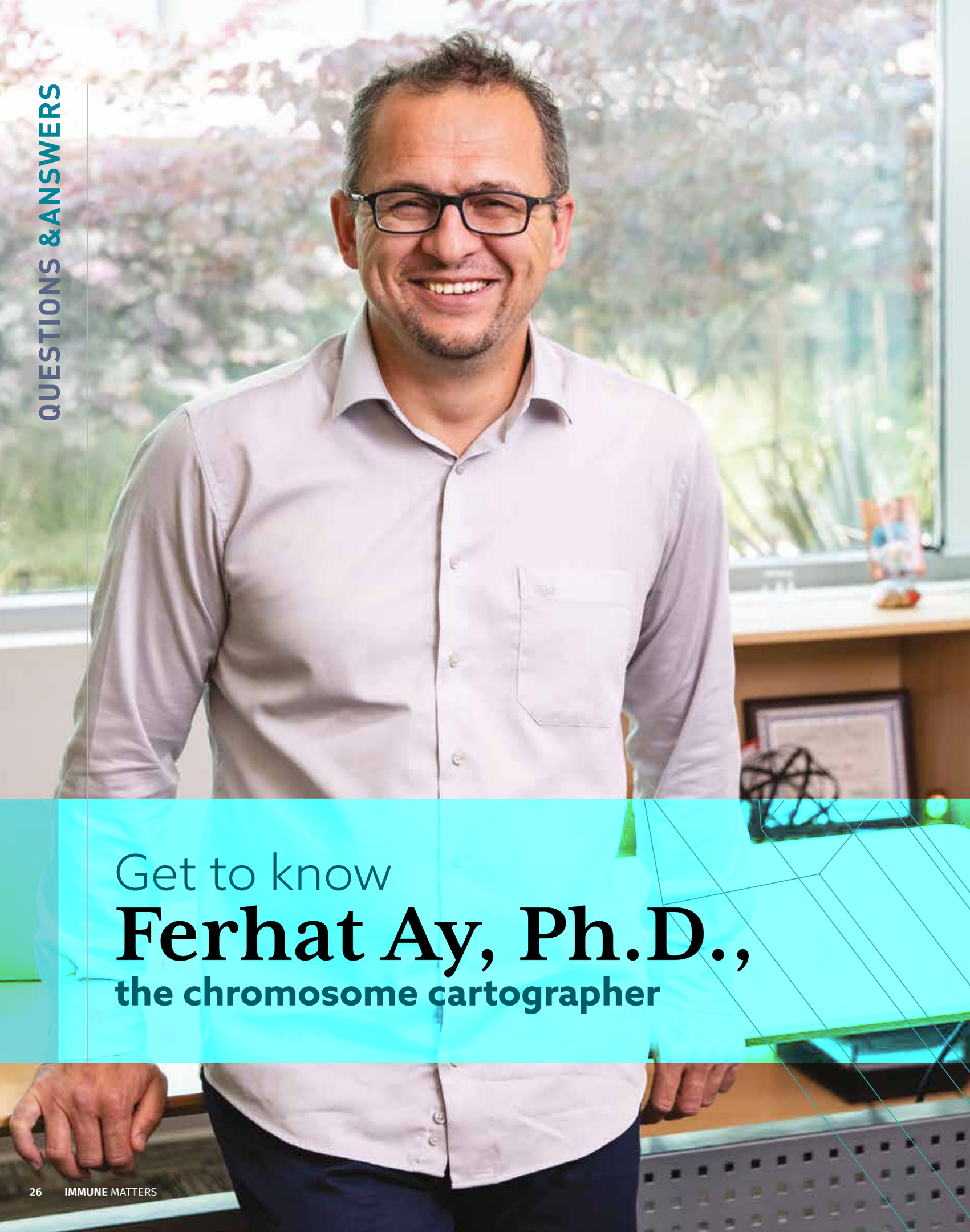
Dr. Lindestam Arlehamn is also interested in investigating whether Epstein Barr virus (EBV) could be involved in Alzheimer's disease. "Epstein Barr virus has been implicated by other groups and also in other similar diseases," she says. EBV, also known as human herpesvirus 4, is extremely common. Many people are infected in childhood and show only minor cold-like symptoms. But studies show the virus can linger in the body and reactivate years later. Like any virus, EBV has the power to activate the innate immune system, including stromal cells, and trigger a T cell response.

Could a virus drive a neurological disease? It wouldn't be the first time. Dengue virus and rabies virus attack the nervous system. CMV, the virus that causes chickenpox and shingles, can survive for years in the nervous system. Just last January, researchers at Harvard University published compelling evidence suggesting EBV may cause multiple sclerosis.

Alzheimer's disease research at LJI may also shed light on COVID-19 symptoms. Both Dr. Sharma and Dr. Lindestam Arlehamn see echoes of Alzheimer's symptoms in the growing number of Long COVID patients. Many Long COVID patients show cognitive changes and describe a "brain fog" that suggests SARS-CoV-2 (or the body's response to SARS-CoV-2) can lead to neurological issues.

"What does SARS-CoV-2 do to the brain? Could it have a role in the development of diseases like Alzheimer's?" asks Dr. Lindestam Arlehamn. Her research into T cell responses may lead to answers.

Meanwhile, Dr. Sharma has launched a new study into the power of bioactive lipid metabolites in a mouse model. "We're just at the early stages of this research, but we're working to ramp it up," she says.



Get to know

Ferhat Ay, Ph.D.,

the chromosome cartographer

La Jolla Institute for Immunology Associate Professor Ferhat Ay, Ph.D., is building some of the world's smallest maps. Dr. Ay harnesses computers to transform DNA genomic sequences into 3D maps. These maps can reveal how genes interact and how the body fights disease.

There is an urgent need for computational biologists like Dr. Ay. Thanks to new, more affordable sequencing tools, scientists today are generating bigger and bigger datasets. Dr. Ay has developed new methods to quickly sort through "big data" and uncover the patterns that matter.

Your lab looks a lot different from the usual immunology lab. What can you accomplish with computers?

We look at a number of different features of your DNA, including how it is folded and what parts of it carry marks of biochemical activity. All of these in concert determine the activity levels of your genes and how cells function. With recent methods, we can "see" how DNA, RNA, and proteins all come together to form chromatin.

It's important to understand how your chromatin is structured and folded inside a tiny cell nucleus and how that is different from one cell type to another. Changes in this intricate 3D organization may lead to disease.

What does it mean to build a genomic "map?"

We analyze data by placing each datapoint in a huge matrix. Sometimes a matrix can be a million by a million in size, over a trillion points. We've developed really efficient statistical models and image processing tools to scan the matrix—like it's a map—for specific patterns and then link these patterns to functions in different cells.

Once you sequence billions of reads to quantify proximities between different regions in the genome, you can start telling which genomic regions touch each other a lot. Using these points as anchors, we can turn that information into a three-dimensional map using computational modeling to show how genes interact.

By developing new computational algorithms and methods, we can analyze sequencing datasets to answer specific biological questions. For example, we can test hypotheses about a specific genomic region playing an important role in an autoimmune disease. Or we can test hypotheses about certain rearrangements in the chromosomes being important for cancer.

How would a chromosome get rearranged in cancer?

My lab is looking at an especially aggressive leukemia subset in pediatric patients. These patients have cells where a chromosome has actually shattered into pieces and those pieces came back together in a sort of random order.

We've developed a computational project to detect these rearrangements. Which genes are broken down, and which genes are fused to each other? We're focused on helping the pediatric patients who are most likely to not respond to treatment and most likely to relapse.

What can your research teach us about infectious disease?

In one collaboration, we were able to link genetic variants to COVID-19 case severity by first finding the genes that neighbor those genetic variants in specific immune cells. People had previously missed these associations because they were looking at the genome in one dimension. By adding these three-dimensional maps, we were able to identify genes that might be relevant to the body's response to certain diseases, such as COVID-19.

I imagine your field changes faster than most.

It's both exciting and scary that like every couple of years, we have new technologies that are emerging, essentially making some of the previous technologies obsolete. Each new technology produces data sets much larger and more complex than we have ever seen. As computational biologists, our task is to develop effective methods that best utilize these data and allow us to ask and answer questions that we could not have before. We really enjoy doing this!

Do you have any advice for students who may want to pursue a career in computational biology?

You should be able to work under the mentality that everything will change. The things that you're an expert in today—and tools you develop—will be useful for a while, but you should be able to accept they may become obsolete. You need to renew yourself. But it is important that you prepare yourself well by acquiring core computational skills and building a knowledge base that will stay with you wherever the research takes you.

LJI WORKS TO LEVEL THE **PLAYING FIELD**

New internship program is important step toward growing the careers of all scientists

Walter Green (upper right) with LJI scientists and interns

Stillman College student Ayana Green (left) in the Rao Laboratory.

As scientists and historians have documented, many Black students historically have been barred from leading scientific institutions, and Black scientists have been deprived of the facilities, funding, and platforms to support their careers and share their work.

La Jolla Institute for Immunology (LJI) is working to put new programs in place to address inequality in the sciences. "We have to do more," says LJI Chief Scientific Officer Mitchell Kronenberg, Ph.D.

With generous support from San Diego mentor, non-profit investor, and "gratitude messenger" Walter Green and philanthropic partner Lisa Ligouri, the Institute is making progress.

For the past two decades, Green and his wife, Lola, have funded scientific education in San Diego County for students ages eight through 18 years old. Over the last four years, Green and Liguori have joined forces to further these efforts on the behalf of their respective families.

Green and Liguori were first introduced to LJI when they gave support to a trainee in the lab of Erica Ollmann Saphire, Ph.D., Institute President and CEO. Shortly afterward, Dr. Kronenberg approached Green and Ligouri with the idea of funding a summer internship program for underserved students.

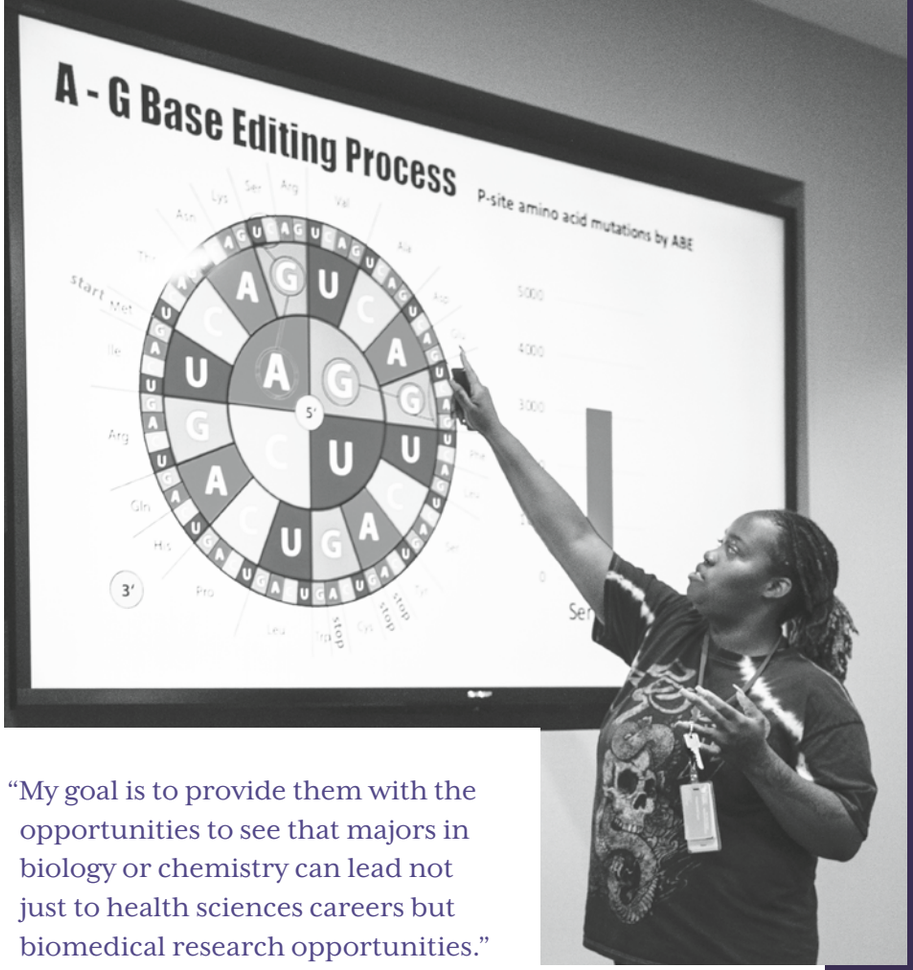
To bring students to La Jolla, Dr. Kronenberg coordinated with Cynthia Warrick, Ph.D., R.Ph., President of Stillman College, a prestigious liberal arts college in Tuscaloosa, Ala. Stillman College is one of America's leading Historically Black Colleges and Universities (HBCUs).

"There are so many health disparities for African Americans," Dr. Warrick says. Indeed, the community faces higher cancer mortality rates, higher diabetes and lupus rates, higher rates of maternal mortality, and more. "Through hands-on experiential learning at places like LJI, students can learn how to really make a difference in their communities through biomedical research."

Together, Dr. Warrick, LJI leadership, Green, and Ligouri launched an internship program where LJI scientists could welcome Stillman students into their labs. For the inaugural year, the Institute welcomed two interns from Stillman: Ayana Green and Tamia Little, who interned in the laboratories of Professor Anjana Rao, Ph.D., and Assistant Professor Sam Myers, Ph.D.

LJI also welcomed two students from the UC San Diego PATHways to STEM through Enhanced Access and Mentorship (PATHS) Program. These students were Arianna Girmai and Emi Sanchez, who interned in the laboratories of Dr. Rao and Professor Michael Croft, Ph.D. "By introducing the Stillman and UC San Diego students, we could combine the benefits of their respective programs. Two plus two is more than four in this case," Green says.

Green was keen to work with PATHS as an extension of his mission to work with local students from underserved communities. Green calls his approach "community-based investment." "I consider these investments, I don't consider them donations," says Green. "I'm attracted to really high-quality programs with great leadership."



Stillman College intern Tamia Little presents findings from the Myers Lab at LJI.

"My goal is to provide them with the opportunities to see that majors in biology or chemistry can lead not just to health sciences careers but biomedical research opportunities."

Dr. Cynthia Warrick

The four interns accomplished a lot in their time at LJI. Thanks to the simultaneous efforts of LJI's newly formed diversity, equity, and inclusion committee, LJIdea, the interns attended workshops in core facilities, including microscopy, sequencing, cryo-EM, and mass spectrometry. The interns were invited to lunches with faculty, post docs, and members of leadership and administrative staff. They even toured the IT Department at LJI and were treated to a private tour of San Diego-based biotech Illumina. They also attended a special talk on animal research.

After 10 weeks working in a laboratory setting at LJI, the interns presented what they learned. "These interns didn't just go through the motions," says Dr. Warrick. "They actually worked on real-world research projects." Dr. Warrick says it's been great to see the undergraduates connect their lab work with scientific concepts they've learned about in classrooms and textbooks.

Green appreciated the mentors who stepped up to share their work with the visiting interns. "You cannot overstate the talent and commitment that was brought to bear on this internship program," says Green.

The Stillman interns will use their research experiences in their senior thesis work at Stillman. Dr. Warrick hopes they will also consider applying for opportunities like graduate school going forward. •

A FOUNDATION OF GRATITUDE

Walter Green says supporting highly technical immunology research at LJI feels "a little bit like supporting the space program." Yet Green has given significant financial support to LJI's internship programs—and to STEM education throughout San Diego.

Alongside his wife, Lola, Green has given generously to the Elementary Institute of Science, an afterschool enrichment program that provides hands-on scientific activities for underserved students in southeast San Diego. His family's support also led to the expansion of a teen program to help students explore scientific careers as they head to college. "The irony of it is that I have no competency in the sciences myself," says Green.

Green has seen the life-saving power of biomedical research. He's also witnessed the life-changing power of something else: gratitude. For the last decade, Green has promoted the idea of sharing gratitude with loved ones while they are still alive. "We all too often wait until a person goes to honor them," says Green. "Knowing that they made a difference validates their lives."

In 2010, Green went on a year-long journey to visit with everyone who had a major impact in his life. His book, *This Is the Moment! How One Man's Yearlong Journey Captured the Power of Extraordinary Gratitude*, chronicled his journey around the globe to thank 44 people.

His latest gratitude initiative is "Say it Now," which inspires group events or Zoom-based "living tributes" where people can express gratitude before it's too late. The death toll of the COVID-19 pandemic has added a sense of urgency to Green's mission, and he hopes more and more young people will see the importance of "Say It Now."

La Jolla Institute | VANGUARD

GIVING SOCIETY

With your contribution of $1,000 or more to the La Jolla Institute for Immunology, you are joining our **Vanguard** and asserting your role at the forefront of the next breakthroughs in medical research. Our researchers are dedicated to assessing how the immune system can be harnessed to fight diseases ranging from asthma to Zika, so that one day we can all live free of the symptoms and frightening prognoses of many of the conditions we suffer from today. Your support ensures our scientists have the resources they need to accelerate the pace of their discoveries and turn "someday" into today.

As a member of LJI's Vanguard you are taking an active role in leading the way to **Life Without Disease®**.

van·guard | a group of people leading the way in new developments or ideas

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Why I give:
A tradition of American leadership

DICK AND KARNA BODMAN ESTABLISH A LEGACY AT LJI

Richard S. "Dick" Bodman and Karna Bodman know a lot about leadership. As a venture capitalist and engineering entrepreneur, Dick has served in positions including Assistant Secretary of the Interior under President Nixon, Chairman of TDF Ventures, and founder of AT&T Ventures.

Karna, currently a novelist, began her career as a TV news reporter and anchor. She then served six years in the Reagan White House, first as Deputy Press Secretary, later as Senior Director and Spokesman for the National Security Council.

The Rancho Santa Fe couple knows their resumes can be a mouthful.

"Dick has had several different careers," says Karna.

"All of which have been enjoyable!" adds Dick.

Always glad to give where they can, in recent years the Bodmans have focused much of their time and philanthropy on educational and scientific causes. Dick is a passionate supporter of biomedical research as a Trustee of the Buck Institute for Research on Aging. Karna is a member of the Board of Directors of the PBS stations in Washington, D.C., is the Founding Trustee of their church, and served as a member of the Board of Directors of Recording for the Blind & Dyslexic for over a decade.

The Bodmans have also given regular gifts to La Jolla Institute for Immunology (LJI), where their generosity fuels research into infectious diseases, autoimmune diseases, cancer immunotherapies, and much more. In 2016, Dick was elected to the LJI Board of Directors and helped guide the Institute as head of the finance committee.

"We want to support good causes through service," says Dick. "If one is really interested in getting rid of diseases, then LJI is one of the top places to look."

The Bodmans are also inspired by breakthroughs in biomedical technology. Dick is co-founder and Chairman of PurThread Technologies, Inc., a maker of antimicrobial textile fibers for healthcare and consumer use, and he has a keen understanding of the new technologies in use at LJI. Karna has even incorporated the gene-editing technique CRISPR into one of her award-winning political thrillers.

Advocacy for the sciences runs in the family. As Dick was growing up, his father served as Chairman of the Board at Henry Ford Hospital in Detroit. "Since then, I've always been interested in health and disease," says Dick. Philanthropy has also continued as a Bodman family tradition. The couple's sons serve on several non-profit boards.

Most recently, Dick and Karna established the endowed Richard S. and Karna S. Bodman Leadership Fund. This fund will be used at the discretion of the Institute's President and CEO to fund the most promising and often unanticipated scientific opportunities that arise. Their support gives LJI scientists a way to pursue new, often urgent research questions for which other, more rigid funding sources are not readily available.

"I always say, 'Put it where it's most useful'," says Dick. •

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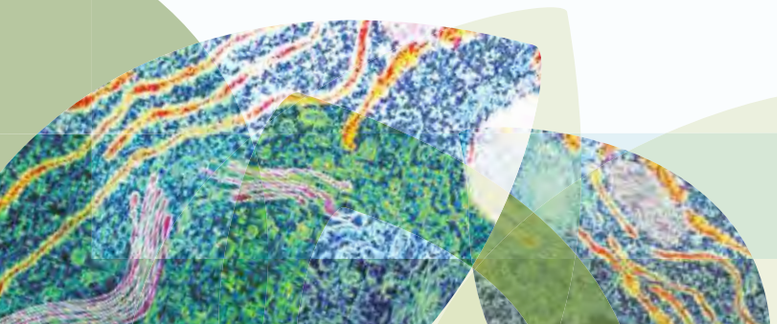

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