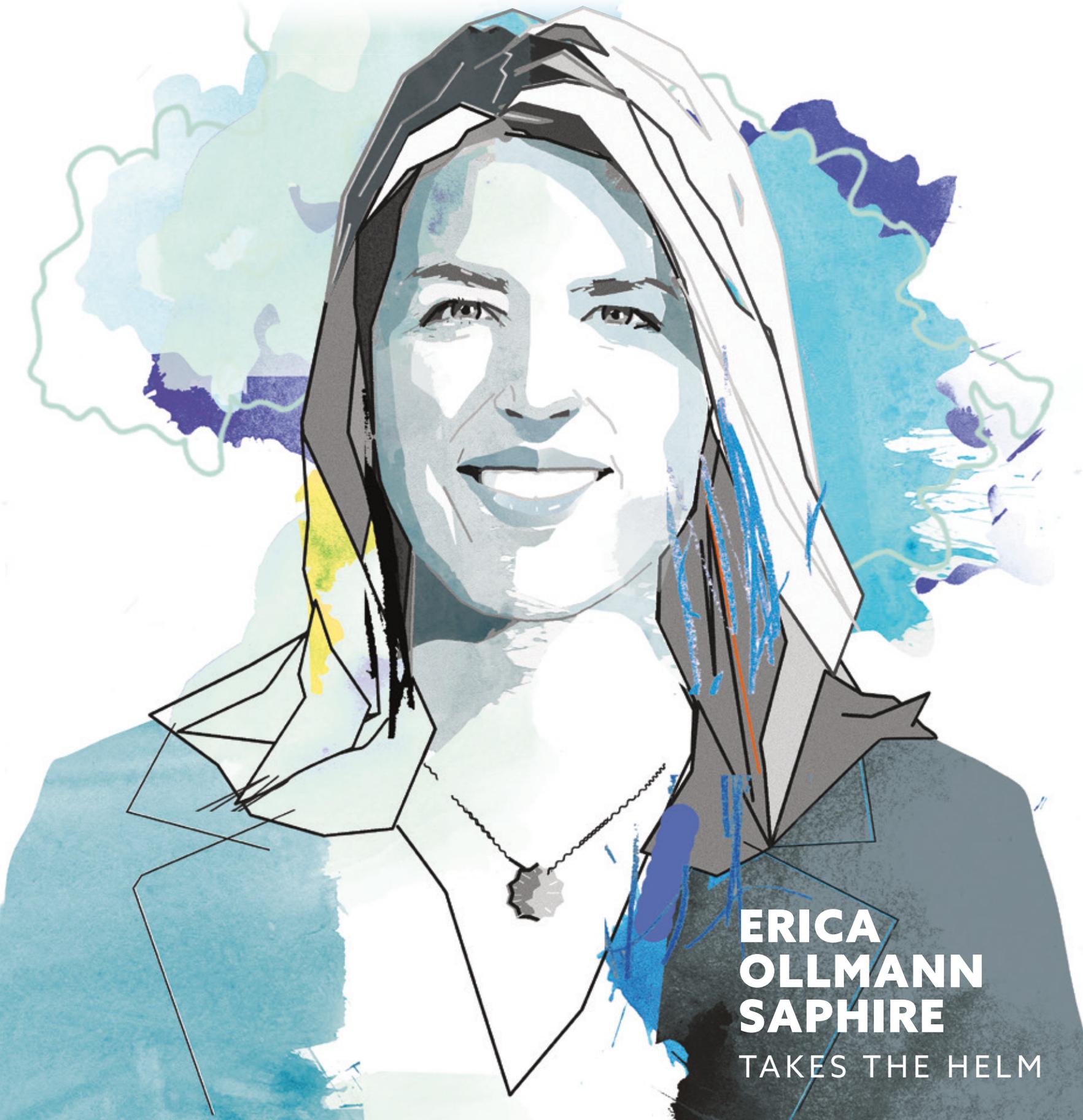


Immune

LA JOLLA INSTITUTE
FOR IMMUNOLOGY

FALL 2021

MATTERS



**ERICA
OLLMANN
SAPHIRE**

TAKES THE HELM



IMMUNE MATTERS CONTRIBUTORS

Gina Kirchweger, Ph.D.

Madeline McCurry-Schmidt

Jenna Hambrick

Chris Romano

Matt Ellenbogen

Lisa Huppert

Chris Lee

Kelsey Dale

Eileen Timken

Clare Grotting

Bob Ross

Jenny Siegart

Stacy Nixon

Cover art by Paddy Mills

How I see LJI

As a beacon. A leading light. I see discoveries and opportunities at LJI for the betterment of human health that don't exist anywhere else. Our faculty and core directors are internationally recognized. Our state-of-the-art facilities allow us to see with greater depth and complexity into individuals' immune functions. Woven in between, a golden core of collaboration and shared vision allows us to pivot those tools where needed, to address the pandemic and find new mechanisms of immune protection and immune control in cancer, heart disease, and autoimmunity.

What sets LJI apart is its focus. We are the best in the world at understanding the individuality and opportunity of the human immune response. As just one example, drugs that interact with the immune system, such as immunotherapies that fight cancer, are not one-size-fits-all.

LJI scientists can learn from our individual immune system differences to find new ways to treat and prevent disease.

I came to the Institute for Mitch Kronenberg, our outgoing President, and I would like to use my first letter as President to thank him. Mitch, you set a high bar for what it means to lead this Institute, and I'm honored to continue working side-by-side with you as LJI's Chief Scientific Officer.

In this issue of *Immune Matters*, you'll learn more about our vision for LJI.

You'll also read about the latest in cancer research at LJI, and how physician-scientist Estefania Quesada Masachs has launched paradigm-shifting research into type 1 diabetes. As you read, I hope you'll



take a moment to get to know our newest Board member, Carolee Lee. Carolee is dedicated to advancing women's health research across the country, and I am thrilled she's sharing her time and expertise with LJI.

Science can't get far without community support. In the last year, LJI has become more visible around the world, and we're in a position to reach more people.

Community and outreach are essential parts of LJI. As I've come into my role and spoken with each lab about their needs, I've heard how much donor support means to our staff and scientists. It's transformative and it's heartwarming.

As an Institute supporter, you have a voice here, too.

Sincerely,

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

Immune

FALL 2021 MATTERS

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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.

STAY UPDATED! If you would like to receive email updates from La Jolla Institute, please contact us at: communications@lji.org or 858.752.6645.



www.lji.org



A letter from Eric Zwisler, Chair, La Jolla Institute for Immunology Board of Directors

On behalf of the La Jolla Institute Board of Directors, I want to extend my sincerest gratitude to LJI's outgoing president, Dr. Mitch Kronenberg. Under Mitch's inspiring leadership and steady hand, LJI blossomed into a globally renowned scientific powerhouse and took its rightful place among the world leaders in immunology.

As LJI President from 2003–2021, Mitch led the Institute through a period of rapid growth, including the transition to the current, beautiful building in the UC San Diego Science Research Park. During his tenure, LJI's faculty doubled and the Institute's operating budget tripled. By 2019, the Institute was not only ranked #5 in the world in the field of immunology based on its scientific impact, but was also widely regarded as one of the best places to work in academia.

But Mitch's most enduring legacy is the culture of camaraderie and collegiality he established at the Institute. Leading by example, he got to know people and made sure they were well taken care of—scientifically and personally. It was no surprise when he was named “most admired” CEO by the *San Diego Business Journal*. When the Institute went into maintenance mode in the early days of COVID-19, Mitch made sure LJI scientists had what they needed to work safely and sent out weekly video updates to share, in his own heartfelt words, how the Institute was moving forward.

We are fortunate to have Mitch's continued leadership as he transitions from President to Chief Scientific Officer. And all of us will unquestionably benefit from his ability to spend more time in his lab and scientific pursuits.

We have all been lucky to work with Mitch, and I know President Erica Ollmann Saphire is the right person to carry his legacy forward.

On behalf of the Board of Directors and personally, a heartfelt thank you for making LJI a great place to advance science, and for shepherding all our important scientific discoveries as we pursue a *Life Without Disease*.

Sincerely,

A handwritten signature in black ink, appearing to read 'Eric Zwisler', written in a cursive style.

Eric Zwisler
Chair, La Jolla Institute for Immunology Board of Directors

ON THE COVER

ERICA OLLMANN SAPHIRE

*Takes
the helm*



When Erica Ollmann Saphire, Ph.D., was a kid, her house caught fire.

It was the middle of the night in the tiny town of Lago Vista, Texas. There was no professional fire department, so the call was answered by volunteers: friends and neighbors.

“They got themselves out of bed at 3 a.m. and, at risk to themselves, fought that fire,” says Dr. Saphire.

Dr. Saphire’s family never forgot. “That volunteer fire department had no budget, so whenever they needed a new truck or a new hose, we had to raise the money ourselves,” Dr. Saphire recalls. “And every year at the annual barbecue, in recognition for what they did for us, my family was on that line serving the brisket, the cole slaw, the potatoes.”

See a problem, take action. That’s how she was raised.

“You build a community together. You do for others what needs to be done,” she says.

As the new President and CEO of La Jolla Institute for Immunology (LJI), Dr. Saphire aims to bring together the best researchers to address the biggest question out there: Why does a person get sick?

A person’s immune system may be as unique as their fingerprint. The COVID-19 pandemic taught all of us that lesson. For Dr. Saphire, the next decade of immunology is about figuring out the power of these individual differences.

“La Jolla Institute has the best minds in the world for untangling that complexity, and there are now better tools than we ever had before,” says Dr. Saphire.

Dr. Saphire’s own work has revealed the inner workings of devastating viruses such as Ebola, Lassa, measles, and SARS-CoV-2. She’s also well known for turning rival laboratories into close collaborators.

In 2014, as the Ebola virus took lives across West Africa, Dr. Saphire rallied 43 previously competing laboratories from five continents to come together, rethink a fragmentary research pipeline, and accelerate promising human antibodies against the disease. Instead of accepting the delays and gaps, Dr. Saphire united researchers into the Viral Hemorrhagic Fever Immunotherapeutic Consortium, and found ways to protect individual interests while developing the data and understanding they all needed to move forward.

“There are lots of problems that are too big for one lab and one tool to solve alone,” says Dr. Saphire. “The only way forward is to build structures and systems that allow us to pool resources.”

So it made sense that when the COVID-19 pandemic struck, the Bill & Melinda Gates Foundation sought Dr. Saphire’s expertise in building a virus-fighting team. Dr. Saphire now helms The Coronavirus Immunotherapy Consortium, called CoVIC, a global collaboration that brings academic, non-profit, and commercial laboratories together to develop the best antibody therapeutics against COVID-19.

“A pandemic brings out the best in some and the worst in others,” says Dr. Saphire. “You find where you have clear thinkers. You put your resources behind them and empower them to make the right decisions.”

Dr. Saphire earned her Ph.D. from Scripps Research in 2000. She stayed at Scripps Research to open her own lab and swiftly advanced to the position of full professor. In 2019, the lab moved to LJI and established the Institute as a leader in cryo-electron microscopy, an imaging technique that can reveal how human cells and pathogens interact.

Many of her lab members have worked with her for years. They’ve raised their children together and published in top journals together. The lab is built

on trust, not competition. “I give them the resources they need, and I get out of their way,” says Dr. Sapphire. “I understand that if they have boots on the ground and hands in the research, they see things that I don’t.”

Dr. Sapphire’s field requires persistence and patience. She is an expert in stabilizing viral proteins and capturing their structures through high-resolution imaging. These images work like blueprints of a virus and can reveal where the virus is vulnerable to human antibodies.

Until recently, the best way to get a clear image of a viral protein was to use a technique called x-ray crystallography. Although the images from x-ray crystallography are incredibly useful, the process of getting the images is grueling. It might take thousands of attempts before a scientist can prompt viral proteins to align and form a crystal.

In 2017, Sapphire Lab member and LJI Instructor Kathryn Hastie, Ph.D., achieved the feat of determining the structure of Lassa’s outer shell protein, called the glycoprotein, together with a human antibody. The study, published as the cover story in *Science*, took 10 years.

“You just need the right kind of person with the right kind of tools to stick with it,” says Dr. Sapphire. “It takes a person with tenacity.”

Dr. Sapphire has a few scars—mostly from playing rugby. She helped start a women’s rugby team at her Texas university. They had seen the men playing and thought it looked like fun.

A rugby team wins possession of the ball as a unit called a “scrum.” Dr. Sapphire is tall, so she played in the second row of the scrum, using leverage to hold ground or propel the group forward.

“I liked that there was a position for every skill and every body. Me, I was just muscle,” says Dr. Sapphire.

Her job was to push the offensive players forward while using her entire body to keep the other team from getting too close. “We would use electrical tape to pin our ears down so they wouldn’t tear in the scrum,” says Dr. Sapphire. “I’m very pleased I have all my teeth and both ears.”

Dr. Sapphire stuck with rugby, and then played for the Bay Area Shehawks, the national champions at the time. She went on to play for two leading West Coast teams and also managed the United States Eagles.

“You can’t get rugby players down,” says Dr. Sapphire. “If it’s 40 degrees and raining, and the field is full of mud, they start singing a song.”

Dr. Sapphire had two herniated disks from playing rugby. But it was worth it, she says.

Dr. Sapphire’s drive is also born of loss. As she was earning her Ph.D., her grandfather lay dying of colon and lung cancer. “I felt powerless,” she says. “At the time, the doctors had nothing else to offer him and no explanation why a nonsmoker would develop tumors in his lungs. That inspired a career in research. I wanted to put something in the hands of those doctors so that someone else wouldn’t lose family member like that.”

Since then, Dr. Sapphire has taken on every project she can to strengthen her work and research around the globe. She gets up early to take conference calls with the World Health Organization. She entered an MBA program while running her lab. She recently launched a new project to understand retroviral causes of cancers and autoimmunity.

Her work has saved lives—and yet the human body still betrays.



“La Jolla Institute has the brainpower, the tools, and the technology to address that question: Why do we get sick?” says Dr. Saphire.

A few years ago, Dr. Saphire met a San Diego couple who helped Dr. Saphire purchase a piece of equipment that her lab desperately needed to develop a rapid Ebola test. “Ebola at the start can look like food poisoning or malaria,” says Dr. Saphire. “The test, with rapid lines like a pregnancy test, gave doctors a way to know who has Ebola and who doesn’t have Ebola, so you don’t put the wrong patient in the Ebola ward or inadvertently release an Ebola patient to infect others.”

That gift saved thousands of lives in West Africa, according to a report from Doctors Without Borders. A friendship grew between Dr. Saphire and the family. One of them in particular became Dr. Saphire’s mentor and sounding board.

“He totally got it,” says Dr. Saphire. “He was a good man. He used his good fortune to propel other people and their lives and discoveries.”

In April 2021, he died of bile duct cancer. “There was a revolving door of good friends coming to say goodbye at the end,” Dr. Saphire says. “It’s not right that we don’t know why he got it, and it’s not right that we couldn’t do anything about it. We just had to say goodbye to a great human.

“There is a reason why that cell turned into cancer. It’s not an unexplainable event,” says Saphire. “There is a scientifically explainable reason, and we can study those reasons in a way that we couldn’t just ten years ago.”

“Why do some people get sick while others don’t?” asks Dr. Saphire. “Why does a person’s immune system turn against them and cause autoimmunity? Why does one person get diabetes when their twin doesn’t? The genes are the same, the environment is the same.”

At LJI, scientists are working to demystify the immune system. Flow cytometry specialists analyze cell populations. The imaging core is down the hall from the bioinformatics team. The Institute excels in microscopy, disease model development, antibody discovery, and database design. Sequencing experts shed light on immune cells and viral threats—they can even track gene expression at different points in an infection.

“La Jolla Institute has the brainpower, the tools, and the technology to address that question: Why do we get sick?” says Dr. Saphire. “If we understand the why, then we can find the markers to arrest it, the drugs to stop it, and the vaccine to prevent it.”

Dr. Saphire knows how to unite people, and she knows how to get people what they need. Through pandemics. Through the decades. Through the rain and mud. ●

Dr. Saphire’s honors include the Presidential Early Career Award in Science and Engineering, an Investigator in the Pathogenesis for Infectious Disease Award from the Burroughs Wellcome Fund, a Mercator Award from Deutsche Forschungsgemeinschaft, a Fulbright Global Scholar fellowship from the U.S. Department of State, a scientific leadership award from the Global Virus Network, and the 2021 Scientist of the Year Award from ARCS Foundation - San Diego.



IMMUNE CELLS CAN DETECT CANCER

Now we can see what they see—and help

Living with an immune system is like carrying a tool belt. Your body can whip out specialized immune cells if you encounter a virus, eat rotten food, or get a paper cut.

The immune system is equipped for just about everything, except maybe cancer. Although immune cells regularly snuff out small cancerous growths, tumors can overwhelm the body.

And yet immune cells can detect cancer, even if they sometimes fail to defeat it. To devise better defenses against cancer, researchers at La Jolla Institute for Immunology (LJI) are shifting their approach and treating immune cells less like tools and more like partners.

We need to be able to check in and ask immune cells, “What do you see? And how can we help?”

What *can* immune cells see?

The immune system constantly scans the body for threats. With a new grant of \$4.2 million from the National Cancer Institute, LJI researchers are now able to catalogue the telltale markers immune cells rely on to tell whether a cell has turned cancerous.

In June 2021, LJI Professors Alessandro Sette, Dr.Biol.Sci., and Bjoern Peters, Ph.D., got the green light to launch the Cancer Epitope Database and Analysis Resource (CEDAR). CEDAR gives scientists a centralized database showing which sites on a cancer cell, called epitopes, the immune system responds to.

With CEDAR up and running, researchers from anywhere in the world can compare how immune cells respond to different cancer targets—across any cancer type—for the first time in history.

“This will make everything easier for cancer researchers,” says LJI Instructor Zeynep Koşaloğlu-Yalçın, Ph.D., a bioinformatics expert working in the Peters Lab.

CEDAR is a new approach to a lingering problem, Dr. Koşaloğlu-Yalçın says. For years, scientists have gathered cancer epitope data,

Local artist spotlight:

This illustration is by Stacy Nixon. Creating from her ranch in Northern New Mexico and the San Diego backcountry, Nixon explores the magical realities of life and the subconscious through her painting and sculptural practices.

but these databases and analysis resources are scattered across the internet. Labs around the world have put their tools online, but it's hard to know which actually work—or which one is right for a project.

“You can't find your way through this jungle of tools,” says Dr. Koşaloğlu-Yalçın. “We want to change that.” “There is a real need for a centralized resource that integrates all these new data and experiments,” adds Dr. Sette. The free, online resource will streamline investigations into cancer immunotherapies, personalized cancer vaccines, and more.

The initial CEDAR website should come online in the next year. So far, the process is running smoothly in the hands of LJI's bioinformatics team. To build CEDAR, LJI is relying on the years of experience the Sette and Peters labs have gained as they built a similar database for infectious disease research, called the Immune Epitope Database (IEDB).

“To launch the same effort for cancer that we've done for immune system findings in the IEDB is really a breakthrough,” says Dr. Peters. “It will be great to have these resources under the same roof.”

Helping cells do more

Professors Patrick Hogan, Ph.D., and Anjana Rao, Ph.D., are closing in on a problem called T cell exhaustion. T cell exhaustion is a remarkably simple concept: The body's T cells fight a tumor. The tumor is hard to kill. The T cells lose power and stop working.

“What if we can think of a way to protect these cells from ever becoming exhausted in the first place?” asks Dr. Hogan.

In a study out earlier this year, Drs. Hogan and Rao reported that T cells can be taken out of the body and engineered to overexpress a key protein that shields them from exhaustion. This approach, a form of CAR T therapy, worked in a mouse model and there is evidence these engineered T cells can also respond to fight recurring cancers.

“We didn't just increase the ability of T cells to fight exhaustion—we increased the ability of cells to fight tumors,” says LJI graduate student Edahí González-Avalos, who co-led the study.

Down the hall, LJI researchers are devising a one-two punch strategy to help immune cells fight cancer.

It's common for cancer patients to receive two kinds of immunotherapy at once: anti-PD-1 therapies and CTLA4 therapies. A recent study led by LJI Professor Pandurangan Vijayanand, M.D., Ph.D., shows how this double whammy can actually backfire.

His lab has shown that anti-PD-1 therapies lead to more T follicular regulatory (Tfr) cells in tumors. In a healthy person, Tfr cells do the important job of stopping haywire T cells and autoantibodies from attacking the body's own tissues. But in a cancer patient, Tfr cells suppress the body's ability to kill cancer cells.

This means anti-PD-1 therapies may cancel out the benefits of CTLA4 therapies. Dr. Vijayanand compares the combination treatment to hitting the gas pedal and the brakes at the same time. “You aren't going to go anywhere,” he says.

The conclusion: It may be more effective to first use CTLA4 therapy to deplete the Tfr population and then give patients anti-PD-1 therapy to further boost the immune system's cancer-fighting power.

Preliminary data suggest this sequential therapy approach can improve survival outcomes in melanoma patients. Dr. Vijayanand and study co-leader Christian H. Ottensmeier, M.D., Ph.D., FRCP, a professor at the University of Liverpool and adjunct professor at LJI, are now working to set up new clinical trials to test this sequential approach, and they are collaborating with Cancer Research UK to develop therapeutics that target Tfr cells.

Making cancer immunotherapy work for everyone

New discoveries at LJI will directly improve patient responses to cancer immunotherapy. Currently, only a minority of cancer patients actually benefit from transformative immunotherapy due to two main problems: poor response and immune-related inflammatory side effects. A recent \$3.6 million grant from the National Cancer Institute will allow LJI scientists to study cancer patient responses to immunotherapy in order to drive better clinical outcomes.

LJI Associate Professor Sonia Sharma, Ph.D., is taking a new approach to uncover hidden players in cancer immunology: metabolites. Her laboratory applied state-of-the-art mass spectrometry metabolomics technology to profile thousands of small molecule metabolites in the blood of cancer patients receiving immunotherapy for melanoma, lung cancer, and other solid tumors. They discovered certain metabolite molecules are enriched in patients with good responses to cancer immunotherapy and found molecules are missing in patients with poor outcomes.

For example, Dr. Sharma's group has found cancer patients who experienced severe immune-related side effects after receiving immune checkpoint blockers have unusually low levels of a metabolite called LPC. Without LPC, these patients developed life-threatening, autoimmune-like conditions which required them to stop receiving these life-saving treatments. Interestingly, this observation is mirrored in patients with natural autoimmune diseases, who also have low levels of LPC in their blood.

Dr. Sharma's lab is already looking at turning this exciting observation into an actual therapy. Experiments in a humanized mouse model of cancer treated with the immune checkpoint blocker Yervoy indicate that supplementing LPC restores normal blood levels and reduces immune-related side effects—without affecting the anti-tumor activity.

"Is it as simple as providing LPC supplements to patients receiving immune checkpoint blockers?" she asks. "We think it might be, so stay tuned."

Back in the Rao Lab, postdoctoral researchers Timothy Baffi, Ph.D., and Isaac F. López-Moyado, Ph.D., are closing in on TET2, a gene often found mutated in patients with acute myeloid leukemia (AML).

"Cancer genomes display aberrant DNA methylation, an epigenetic mark which can be imagined as an 'off' switch," says Dr. López-Moyado. "Patients with AML, as well as those with other myeloid malignancies, often display mutations in the TET2 gene."

Dr. López-Moyado has shown that patients with TET2 mutations exhibit DNA methylation in places of the genome that should be in an "on" state, but they can also have regions where these methylation marks are abnormally missing. This "hypomethylation" tends to pop up in areas of the genome where sequences are repeated. Scientists used to call these repeats "junk" DNA, but Dr. López-Moyado's work suggests changes in these overlooked regions may seed the beginnings of cancer.

"Currently, my research aims to understand the role of these repeat elements in AML initiation, since it has been previously shown these elements can 'jump' and insert themselves in new places in the genome, causing mutations," says Dr. López-Moyado.

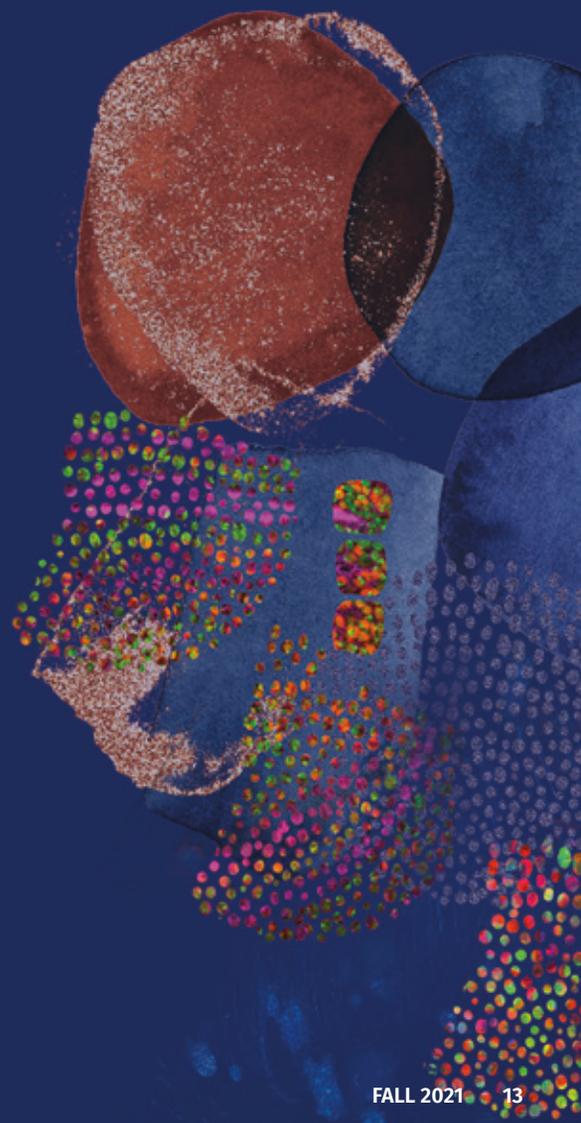
Meanwhile, Dr. Baffi is looking at the roles of different kinds of TET2 mutations in AML. Patients with AML can have TET2 mutations and secondary mutations that make their blood cells develop too quickly. This accumulation of mutations is one reason the rate of cancer recurrence is so high for patients with AML.

While therapeutics kill the cells with the secondary, "fast growing" mutations, therapeutics don't target the primary TET2 mutations in the hematopoietic stem cells living deep within the bone marrow. "That's like trimming a tree but leaving the branches to regrow," Dr. Baffi says. "We want to target the primary source of the cancer and stop that relapse."

By investigating an important genetic driver of AML, Dr. Baffi may shed light on the hidden roles of many genes. "Studying acute myeloid leukemia presents an opportunity to better understand many types of cancer," he says.

Across the Institute, LJI scientists are making important connections between what immune cells can do and how we can help them do their jobs better.

Dr. Hogan sums it up in the context of his T cell exhaustion research, "We're making cells a little bit different from anything nature made, but not so different they are non-functional or do bad things. They are just different enough to deal with chronic tumors." •



A cold case no longer.

What happened when an LJI scientist revisited a diabetes mystery.

Estefania Quesada Masachs, M.D., Ph.D., wanted to take on a scientific controversy. She'd read studies from the 1970s and 1980s showing that blood serum of patients with type 1 diabetes could damage healthy cells and cause the signs of the disease in samples from healthy people. This effect was initially attributed to self-targeting "autoantibodies," but Dr. Quesada Masachs always thought this research was suspect. "The results weren't really conclusive," she says. "They were quite controversial."

The major issue was that past studies were mostly done with fast-growing animal cell lines. These cell lines didn't necessarily mimic what actually happens in the human body. "It was probably their only option at the time, but nowadays we are able to study the effects directly on isolated human islets, which is a big advance," says Dr. Quesada Masachs, a postdoctoral fellow at La Jolla Institute for Immunology (LJI).

She decided to revisit these old studies using new technology to uncover the truth.

"We need to find the culprit that triggers type 1 diabetes," says Dr. Quesada Masachs.

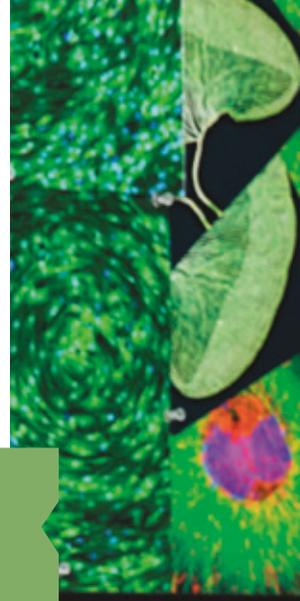
Are autoantibodies the culprits?

In type 1 diabetes, harmful immune cells move into structures in the pancreas, called the islets, and kill insulin-producing beta cells.

"Healthy people also have these immune cells, but they do not attack their pancreas, and we actually still do not know why this happens," says Dr. Quesada Masachs.

For years, researchers have known that autoantibodies are a red flag. These antibodies are made by B cells and can mistakenly target a person's own tissues. For some people, autoantibodies in the bloodstream are an early warning sign that they are "pre-diabetic," or at high risk of type 1 diabetes. Diabetes researchers need to know whether autoantibodies contribute to the disease or if they are merely a sign that something is wrong.

To see if something in blood serum was causing this attack, Dr. Quesada Masachs wanted to study whether the response of the healthy islets to the serum of patients with type 1 diabetes was





by the numbers

In the U.S., an estimated **64,000** people are diagnosed with type 1 diabetes each year.

200,000 people under the age of 20 years old have type 1 diabetes.

Source: Beyond Type 1



“Autoimmune diseases are very connected. Some of them share genetic similarities and errors in the immune system.”

different from the serum of healthy people. She won funding to pursue this pilot study through LJI’s Tullie and Rickey Families Awards for Innovations in Immunology program, which funds high-risk, high-reward projects led by early-career researchers at the Institute.

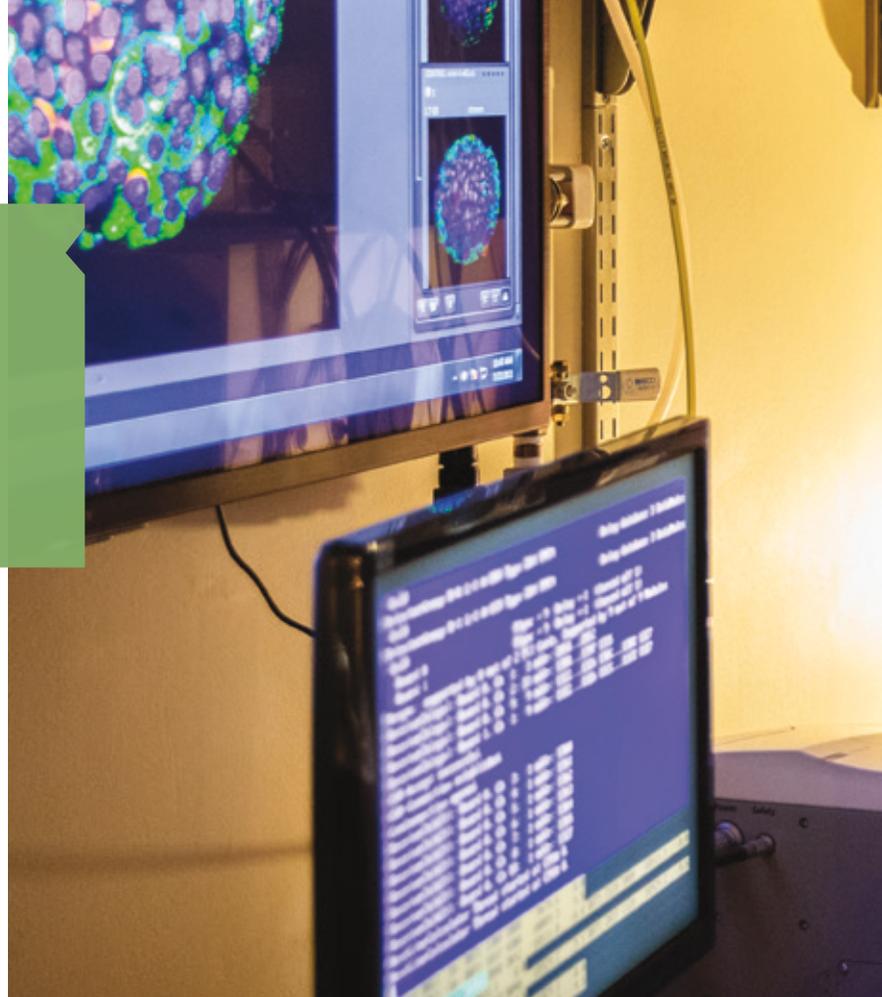
Ultimately, Dr. Quesada Masachs wants to develop treatments for type 1 diabetes. She’s an experienced physician and brilliant immunologist armed with cutting-edge research tools. For Dr. Quesada Masachs, launching this project was the next step in an impressive career in medicine.

Dr. Quesada Masachs grew up in Barcelona, the large, coastal capital city of the autonomous community of Catalonia, in the northeastern corner of Spain. Dr. Quesada Masachs remembers having a deep personal curiosity about medicine from an early age. “I wanted to know how scientists answer questions, and how they find drugs to treat diseases,” she says.

Once she got to college, at the University of Barcelona (UB) campus clinic, she interned in the pharmacology department and in the Apoptosis and Cancer Unit, a lab focused on studying leukemia. As she completed her undergraduate classes, she found herself leafing through books on rheumatology and immunology in her free time. Diving into these subjects became a hobby for her, a break from her usual course load. “To me, it was fun to study,” she says.

Dr. Quesada Masachs went on to medical school and ended up choosing rheumatology as her specialty. She completed her four-year residency at the Vall d’Hebron University Hospital and practiced medicine for five years as a pediatric rheumatologist at the Vall d’Hebron University Hospital and at the University Hospital Quiron-Dexeus. She focused on helping patients with juvenile idiopathic arthritis, an autoimmune condition that leaves children with joint pain, swelling, stiffness, and even blindness.

There are seven subtypes of juvenile idiopathic arthritis that affect specific joints while leaving others untouched.



Dr. Quesada Masachs saw similarities between these cases and other autoimmune diseases. She was especially fascinated by the diseases where tissue damage tends to be organ-specific.

“Autoimmune diseases are very connected. Some of them share genetic similarities and errors in the immune system,” she says. “But why would the immune system decide to attack a joint or to attack the pancreas?”

Dr. Quesada Masachs wasn’t done learning about the body. As she treated patients, she also took classes and conducted research to earn a Ph.D. in medicine. As a doctor she could help one patient at a time, she figured. But as a scientist she could potentially help millions.

Today, Dr. Quesada Masachs works in the lab of LJI Professor Matthias von Herrath, M.D. Her current research is a project with that kind of life-saving potential.

As part of her research, Dr. Quesada Masachs compared four groups of healthy islets. One group was kept in conditions that made them healthy and happy. A second group was flooded with blood serum from patients with type 1 diabetes—complete with potentially damaging elements, including autoantibodies. A third group received blood serum from healthy volunteers (matching the same age and sex as the patients). Dr. Quesada Masachs then exposed a fourth



group of islets to inflammatory proteins—a sure-fire way to study what islets look like when stressed.

Dr. Quesada Masachs found that islets exposed to blood serum from patients with type 1 diabetes behaved similarly to the islets that were purposefully stressed. On the other hand, the serum from healthy patients did not change how islets functioned.

“There is something there, in the serum of patients with type 1 diabetes, that may be making the beta cells unhappy. Something may be inducing the dysfunction of these beta cells,” says Dr. Quesada Masachs.

More research needs to be done before Dr. Quesada Masachs can confirm whether the serum of patients with type 1 diabetes consistently impairs the function of healthy islets and before she can identify the culprits.

Already, Dr. Quesada Masachs has shown how to run experiments using innovative 3D platforms with human islets and human organoids, using state-of-the-art technology to push past the confusion and controversy caused by the older studies.

Now that she’s broken through that wall, Dr. Quesada Masachs has a list of follow-up studies that need to be done to finally understand what damages islets.

“The last step will be to modify the culprits in this disease, to intervene on the elements that caused this dysfunction in the first place,” she says. “And this is the importance of the study, because if I can modify them, I can modify the disease, which means this study may open the door for future therapies or therapeutic strategies.” ●

BEAUTY IN SCIENCE

COVID-19, 2020

On display at La Jolla Institute for Immunology

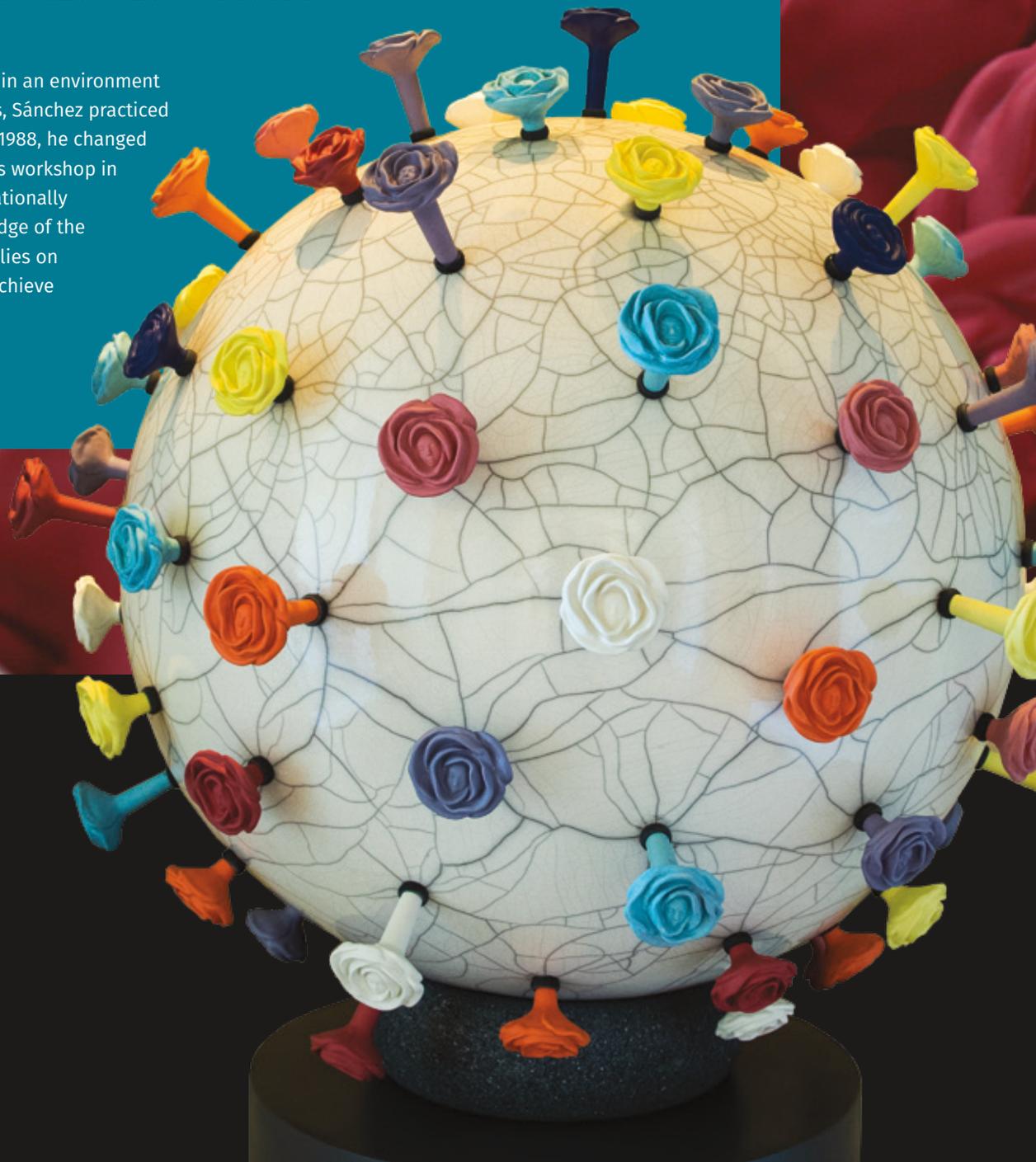
After reading about La Jolla Institute for Immunology's efforts to fight COVID-19, sculptor Juan de Dios Sánchez Arce (pictured right), generously gifted to the Institute a large-scale ceramic interpretation of the SARS-CoV-2 structure, adorned with multicolored roses, in appreciation of the researchers' dedication.

"Let us never forget the faces of COVID-19," says Sánchez. "In honor of the loved ones we've lost, the heroes on the frontlines, and those bound and determined to find the answers."

Born in Mexico City, Sánchez grew up in an environment of both art and medicine. For 17 years, Sánchez practiced as a doctor of anesthesiology, but in 1988, he changed professions to become a ceramist. His workshop in Cuernavaca, Mexico, has been internationally recognized for its quality and knowledge of the Raku fire technique, a process that relies on manipulating chemical reactions to achieve a colorful, smooth glaze.

Sánchez sees many parallels between science and art. Both endeavors are a team effort studded with the heartbreak of seeing experiments fail—and the thrill of finally putting months or years of work out into the world.

"The failures that you had and the problems and discussions and arguments and fights—when you get to the point where you can see the piece, you say, well, it was worth making that effort because the piece is beautiful." •





Scan to watch an original LJI video about this sculpture.





TET enzymes keep immune cells healthy

La Jolla Institute of Immunology (LJI) Professor Anjana Rao, Ph.D., published new research into a process in immune cells that may explain why some people develop cardiovascular diseases. Earlier studies had shown that people bearing TET2 mutations in immune cells called macrophages have a 40 percent increase in their risk of developing cardiovascular disease but the reason why had remained unexplained.

Research from Dr. Rao's lab, published in *Genome Biology*, showed that TET enzymes carry the main burden of keeping immune cells on a healthy track as they mature and preventing dangerous inflammation. The Rao Lab's deeper understanding of how TET enzymes work could help researchers determine where to intervene and help patients with this kind of mutation.

Ebola virus: A clever shape-shifter

In a *Cell Reports* study, a team led by LJI Professor and President Erica Ollmann Saphire, Ph.D., demonstrated how the proteins that form Ebola virus change their structure to complete the viral life cycle. The new study shows how one of Ebola virus's key proteins, VP40, uses molecular triggers in the human cell to transform itself.

The researchers found that VP40 senses and relies on particular human mRNA to make the transformation from a two-molecule "dimer" structure to an eight-molecule "octamer" structure. "We were very excited and surprised to see that the RNA that triggers this change comes from the host cell and not the virus," says study co-first author Sara Landeras Bueno, Ph.D. "The virus is hijacking the host cell—this is another example of a virus acting like a parasite."

The new study also offers further evidence that VP40 is a promising target for effective therapies. Because Ebola virus cannot spread without VP40, the virus is unlikely to acquire VP40 mutations that let it "escape" antibody therapies. This vulnerability has led the LJI team to think of VP40 as Ebola's Achilles' heel.



Shedding light on lupus

New LJI findings in *Genome Research* show how many types of immune cells coordinate to drive the development of systemic lupus erythematosus (SLE), an autoimmune disease that primarily affects women. The team, led by LJI Associate Professors Ferhat Ay, Ph.D., and Pandurangan Vijayanand M.D., Ph.D., developed a new computational method, which allowed them to show that for some patients, all six of the studied immune cell types were enriched for a common molecular program. This program is a known driver of SLE, called the interferon (IFN) pathway. Their analyses confirmed findings from previous studies showing that one SLE subtype had a high IFN signature and the other had virtually none.

These findings highlight the possibility that disease-driven changes in one cell type can cascade into others through intercellular messages. The team's new computational approach to studying genes expressed in multiple immune cells in individual patients could shed light on why many autoimmune diseases lead to such widely varying symptoms in patients—and why these diseases are so hard to treat.



Alessandro Sette, Dr. Biol. Sci.



Shane Crotty, Ph.D.

COVID-19 vaccines prep body to fight viral variants

LJI Professors Alessandro Sette, Dr. Biol. Sci., and Shane Crotty, Ph.D., have found that T cells from people who have recovered from COVID-19 or received the Moderna or Pfizer-BioNTech vaccines are able to mobilize against several concerning SARS-CoV-2 variants. Their study, published in *Cell Reports Medicine*, shows that both CD4+ “helper” T cells and CD8+ “killer” T cells can still recognize mutated forms of the virus. This reactivity is key to the body's complex immune response to the virus, which allows the body to kill infected cells and stop severe infections.

The labs are now analyzing a larger panel of variants, including the Delta (B.1.617.2) variant, which became prevalent after this study was initiated. The team has also established relationships with more than 20 different laboratories around the world to help monitor T cell reactivity to viral variants of concern.



LA JOLLA INSTITUTE FOR IMMUNOLOGY OPENS CENTER FOR CLINICAL INVESTIGATION

On May 18, La Jolla Institute for Immunology (LJI) celebrated the opening of the John and Susan Major Center for Clinical Investigation. The new space, built with support from local philanthropists John and Susan Major, greatly expands the Institute's capacity to collect human blood samples and launch new research into allergies, infectious diseases, cancer, autoimmune diseases, and more.

SYDNEY RAMIREZ RECEIVES FELLOWSHIP TO STUDY SARS-COV-2

Scientists suspect that COVID-19 case severity has a lot to do with how quickly the body's T and B cells spring into action to fight the virus. Sydney Ramirez, M.D., Ph.D., a postdoctoral associate at LJI, is taking a closer look at this theory, thanks to a new three-year fellowship from the A.P. Giannini Foundation.

Dr. Ramirez will study adaptive immunity to SARS-CoV-2, the activity of T cells, B cells, and the antibodies made by B cells. She wants to know how the development of SARS-CoV-2 specific B cell and T cell immunity in acute cases of COVID-19 correlates with viral loads, symptoms, and disease severity.



ADRIAN ENRIQUEZ WINS FUNDING TO INVESTIGATE LASSA VIRUS

Adrian Enriquez, Ph.D., a postdoctoral fellow at LJI, recently received a Postdoctoral Enrichment Program Award from the Burroughs Wellcome Fund to study how the immune system responds to Lassa virus.

“I’m very honored,” says Dr. Enriquez. “The Burroughs Wellcome Fund is really committed to their recipients’ careers, so this is an amazing opportunity.”

Researchers have noticed that even though Lassa virus infects rodents, the animals don’t seem to get sick. Dr. Enriquez is setting out to understand the differences between the human and rodent immune responses to the virus. Solving this mystery could guide the development of immunotherapies or even a vaccine that elicits an effective immune response.



LJI AND SYNBAL, INC. PARTNER TO DEVELOP MOUSE MODELS FOR BETTER COVID-19 RESEARCH

LJI is partnering with Synbal, Inc., a preclinical biotechnology company based in San Diego, to develop multi-gene, humanized mouse models for COVID-19 research. The research at LJI will be led by Professor Sujan Shresta, Ph.D., a member of the Institute’s Center for Infectious Disease and Vaccine Research.

“With this partnership, we are helping tackle the COVID-19 pandemic and establishing a strong collaboration

between academia and industry,” says Dr. Shresta. “The mouse models we develop will be important tools for all scientists as we develop next generation COVID-19 vaccines and therapies.”

The partnership is made possible through a competitive award to Synbal, Inc. via the National Institutes of Health Small Business Innovation Research (NIH SBIR) program. The multi-gene, humanized mouse models generated

through this partnership will be made available to the wider research community.

“With this partnership, we are helping tackle the COVID-19 pandemic and establishing a strong collaboration between academia and industry.”

Sujan Shresta, Ph.D.

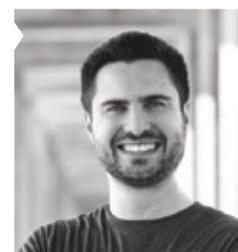
THE CONRAD PREBYS FOUNDATION GRANTS MORE THAN \$450,000 FOR STUDIES INTO CHILDHOOD CANCER AND CARDIOVASCULAR DISEASE

The Conrad Prebys Foundation has awarded more than \$450,000 in funding to support two early-career researchers at the Institute. LJI Instructor Abhijit Chakraborty, Ph.D., is using the funding to investigate how genomic instability can lead to childhood cancer. LJI Postdoctoral Fellow Marco Orecchioni, Ph.D., is leading a project to uncover how human immune cells may trigger atherosclerosis, the cause of heart attacks and strokes.

These grants support the expansion of research based on data that Drs. Chakraborty and Orecchioni were able to collect thanks to seed-investment grants they won from LJI’s Tullie and Rickey Families SPARK Awards for Innovations in Immunology in 2020 and 2019 respectively.



Abhijit Chakraborty, Ph.D.



Marco Orecchioni, Ph.D.

LJI welcomes Carolee Lee to the Board of Directors

Women’s health research has a new supporter at La Jolla Institute for Immunology (LJI). In July, LJI welcomed business leader Carolee Lee to the Institute’s Board of Directors. Lee is an innovator, entrepreneur, and thought leader dedicated to improving women’s opportunities to succeed by advancing their health and well-being.

“Carolee’s support for women’s health research is strongly in line with the LJI mission,” says LJI President and CEO Erica Ollmann Saphire, Ph.D. “LJI scientists are focused on women’s health in the areas of infectious disease, heart disease, and autoimmune disease. We look forward to launching more research that can end diseases that disproportionately affect women—and lead to better health for all.”

Lee was founder and CEO of Carolee Designs, one of the world’s leading accessories brands. After selling the company, Lee focused her energies on women’s health and life planning. In 2008, she founded AccessCircles, a global, by-invitation network committed to facilitating women’s access, to leaders, resources, and experiences that can help transform their lives.

Lee brings to the Board a deep understanding of how scientific advances fuel economic growth. In 2018, Lee launched Women’s Health Access Matters (WHAM), a non-profit organization on a mission to invest in

“LJI’s leadership in women’s health research is a differentiator from many other institutions in the field. The commitment to this issue means that stakeholders, from researchers to doctors to funders, are taking notice—and it’s driving real action and change.”

Carolee Lee



women’s health research. WHAM’s goal is to transform women’s lives and to show that fixing disparities in health research by increasing investment is in our best interest—not only for our health but for our economy.

Through WHAM, Lee has emphasized the urgent need for more medical research focused on health conditions that occur exclusively or predominantly in women. The knowledge gap is vast, and the medical community has a lot of catching up to do. As Lee points out, the National Institutes of Health didn’t mandate that women and minorities be included in any government-funded health research until 1993.

“When I learned about the glaring gap in medical research focused on women, my mind went to the economic impacts. I wanted to know how much this impacted our workforce and our economy. As a business leader, I know change starts with data and we lacked evidence; we lacked data about the economic costs, benefits, and social impacts of attention to sex and gender in health research,” Lee says.

Lee commissioned the RAND Corporation to analyze the impact of women’s health research on the economy and society. Earlier this year, the group published the WHAM Report, a set of studies that evaluated, for the first time, the massive economic benefits of accelerating research and investment in women’s health in the areas of Alzheimer’s disease, rheumatoid arthritis, and cardiovascular disease.

LJI was a lead partner on the WHAM report, which showed that, in every area, women’s health research produces higher economic returns than general research.

“LJI’s leadership in women’s health research is a differentiator from many other institutions in the field,” says Lee. “The commitment to this issue means that stakeholders, from researchers to doctors to funders, are taking notice—and it’s driving real action and change.”

As a member of the LJI Board of Directors, Lee is dedicated to supporting women’s health research across the Institute, especially in the area of autoimmune disease.

“Over 50 million people in the United States have an autoimmune disease, and 78 percent of those patients are women,” says Lee. “Yet, women are still underrepresented in research for these diseases which so clearly disproportionately affect them. LJI is on the forefront of understanding and researching sex and gender differences for autoimmune and so many other disease areas.”

Lee is also a mentor and leader in business, philanthropic, and educational organizations.

She is a past Chair of the Committee of 200, a community of the most successful women in business as well as Chair of its Foundation, and has served as a Director on the Board of DSW, Inc., a leading shoe retailer. Lee is a founding board member of The Breast Cancer Research Foundation, where she has served since 1986. She currently sits on the Women’s Leadership Board at The John F. Kennedy School of Government at Harvard University.



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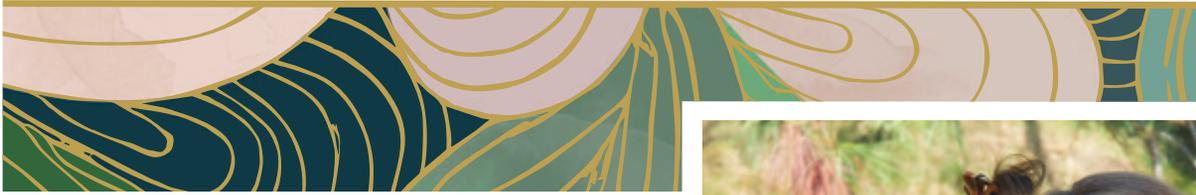
Left to right: Michael Norris, Ph.D., Simon Brunel, Ph.D., Annie Elong Ngonu, Ph.D., Jacqueline Tullie, Tom Tullie, Judy Tullie, Mehdi Benkahla, Ph.D., Payel Roy, Ph.D., Artem Romanov, Ph.D., Nicolas Thiault, Ph.D.

The Tullie and Rickey Families SPARK Awards for Innovations in Immunology 2021 Awardee Celebration

La Jolla Institute for Immunology welcomed guests to an outdoor reception on June 29 in celebration of the brilliant winners of the 2021 Tullie and Rickey Families SPARK Awards who were announced earlier this winter. The reception was a chance for LJLI to recognize supporters of the Tullie and Rickey Families SPARK Awards program and honor the newest class of SPARK Award winners. Attendees had the opportunity to hear from former SPARK winners about their research, recent achievements, and the program's impact.



Left to right: Abhijit Chakraborty, Ph.D., Marco Orecchioni, Ph.D., Nicolas Thiault, Ph.D., Joani Nelson



LJI President and CEO Erica Ollmann Saphire, Ph.D.



Tanya Shaffer and Erica Ollmann Saphire, Ph.D.

President's Reception

On Sept. 9, leading local scientists and supporters gathered at The Lodge at Torrey Pines for a celebration honoring the appointment of Erica Ollmann Saphire, Ph.D., as La Jolla Institute for Immunology President and CEO.



Left to right: LJI Board Member Anthony Carr, Erica Ollmann Saphire, Ph.D., and Sandra Jones



Left to right: David Webb Ph.D., LJI Chief Scientific Officer Mitchell Kronenberg, Ph.D., Lila Webb, Ellen Moxham Ph.D.



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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®**.

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Why we give Raydene and Peter St. Clair

Behind every “eureka!” science headline is a story of perseverance. At La Jolla Institute for Immunology (LJI), donor support sustains many long-term studies and funds “high risk, high reward” projects from many of immunology’s brightest minds.

LJI is where supporters Raydene and Peter St. Clair really get to see the nuts and bolts behind scientific breakthroughs. The San Diego philanthropists started attending the LJI “Life Without Disease” lecture series a few years ago and were immediately enthralled.

“I could feel the excitement,” says Raydene. “What the scientists were doing had ‘tomorrow’ applications. I could see immediately how these studies could lead to new drugs or treatments for diseases like cancer.”

Peter was struck by how the culture at LJI fueled research breakthroughs. “What really makes LJI stand out is the focus on collaboration,” says Peter. “LJI is both an example and a beacon to the other professional groups around the world, demonstrating on a daily basis what scientists are able to accomplish by working together.”

Peter is a retired leader in banking and real estate finance. Raydene is a trained nurse and teacher who worked as a special education

administrator. This duo knows about long work hours—and still, the work ethic at LJI has impressed them.

At one evening lecture, Peter noted how the scientists spoke passionately about their science and then headed right back up to their laboratories to keep working. The St. Clairs also appreciate how experts at LJI have dedicated time to speaking publicly during the COVID-19 pandemic.

The St. Clairs support LJI researchers through regular donations, including funding for early career researchers via The Tullie and Rickey Families SPARK Awards for Innovations in Immunology.

“It may sound trite to say this, but giving to LJI gets you a big bang for your buck,” says Raydene. “People sharing ideas at LJI results in exponential growth once these projects launch.”

The St. Clairs are eager for more people to see the excellent effort of scientists of LJI as they research cancer immunotherapies, diabetes, viral infections, and more.

“That is an important part of the process,” says Peter. “New support comes through friends talking to friends and letting them come and listen—and see for themselves the value of the incredible science underway at LJI.”

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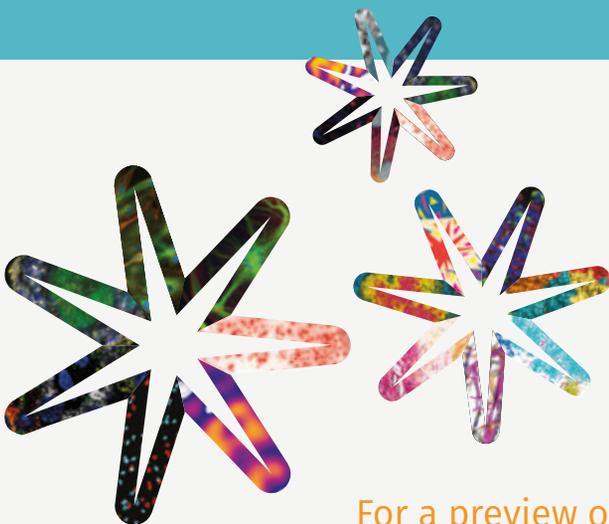
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SPARK AWARDS FOR
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Abhijit Chakraborty, Ph.D., peers into cancer

In 2020, researcher Abhijit Chakraborty, Ph.D., was among nine early career scientists at La Jolla Institute for Immunology to receive \$25,000 in funding through the Tullie and Rickey Families SPARK Awards for Innovations in Immunology. Using SPARK funding, Dr. Chakraborty has devised new methods to understand 3D maps of the human genome. This research is critical for understanding chromothripsis, a devastating phenomenon in cells where shattered chromosomes can lead to especially aggressive cancer tumors. Dr. Chakraborty leveraged the data he generated from his SPARK project to secure a \$245,000 research grant from **The Conrad Prebys Foundation** to continue his investigations. ✨

“I would consider receiving a SPARK Award as a pivotal moment in my career. The Tullie and Rickey Families SPARK Awards program has given me the confidence as a scientist to independently carry out my experiments.”



Each year, the Tullie and Rickey Families SPARK Awards program supports the next generation of researchers as they pursue high-risk, high-reward projects. Dr. Chakraborty's project was funded by the generosity of LJI Board member **François Ferré, Ph.D.**, and his wife **Magda Marquet, Ph.D.**, as well as various other donors to the program in 2019-2020.

Learn more about Dr. Chakraborty's success and the results from his fellow awardees in the 2021 Annual Report on the Tullie and Rickey Families SPARK Awards for Innovations in Immunology coming out soon.

For a preview of the digital report visit lji.org/SPARKAnnualReport

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"I was first introduced to La Jolla Institute more than 15 years ago by a friend. I was immediately hooked by all of the interesting scientific research on autoimmune disorders and with their goal of *Life Without Disease*®!"

"I personally believe in having a plan for my estate, since I feel it is important not only to remember those close to me when I am gone, but to make certain that the nonprofits that are most important to me are included as well (my interests vary from animal welfare to science to civil rights, education, and beyond). I created my living trust so that I would not worry about my family or my wishes, and I am happy to say that La Jolla Institute remains as a beneficiary after all of these years!"

- Nancy Vaughan

Have you named LJI as a beneficiary in your will, trust or retirement plan?

If so, contact Kelsey Dale, Deputy Director of Advancement, at kdale@lji.org or 858.752.6542 so that we can honor your gift and officially welcome you to...

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LJI Legacy Society members receive a number of benefits, including breaking research updates from LJI, exclusive invitations to private events, and special recognition.

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