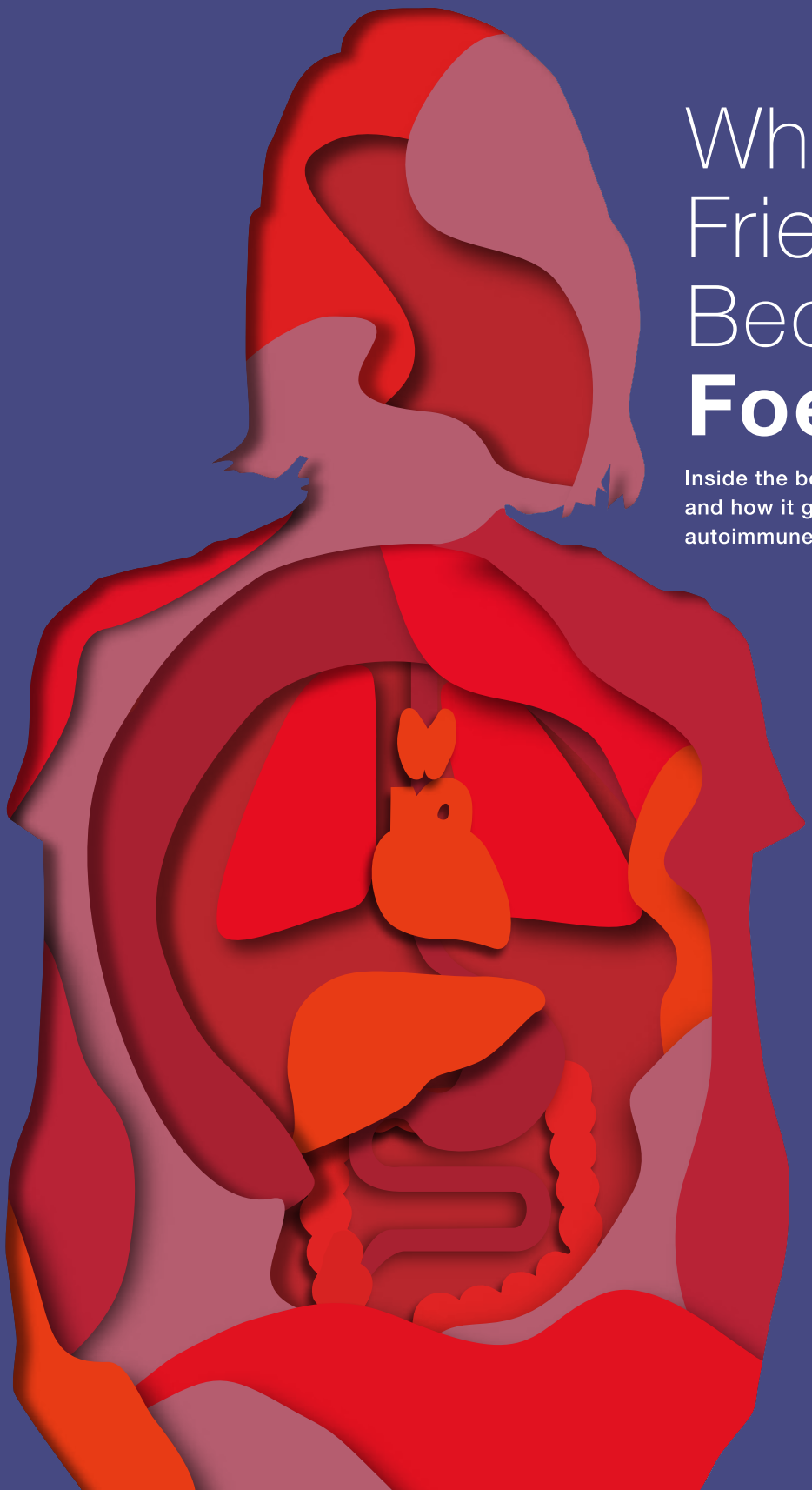
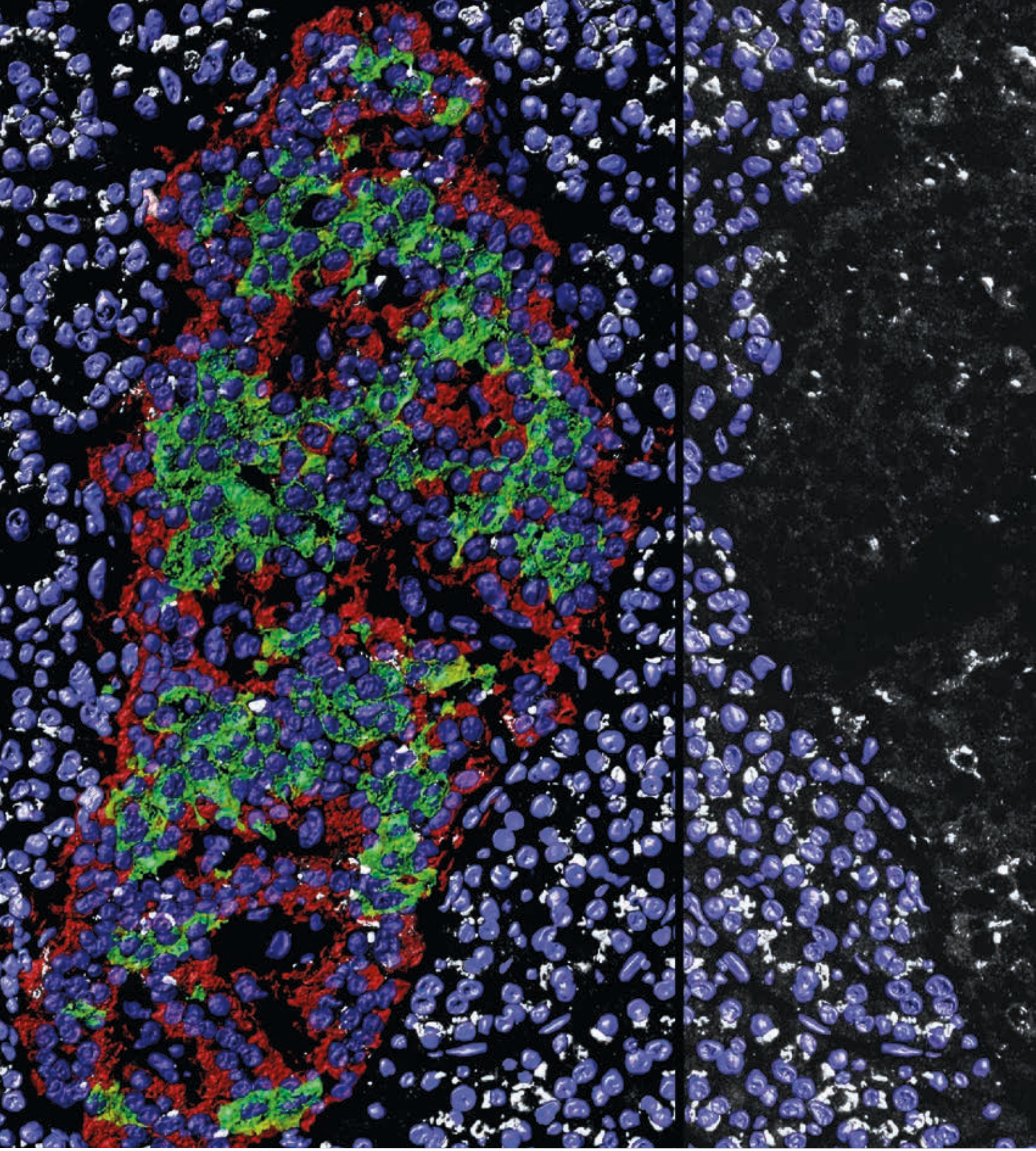
Immune MATTERS

LA JOLLA INSTITUTE
FOR IMMUNOLOGY
FALL 2019



When Friend Becomes **Foe**

Inside the body's defense system—and how it goes haywire in autoimmune diseases



Ink Blot Butterfly

On the “left wing” of the mirror image of a pancreatic islet from a donor with type 1 diabetes (T1D) cell nuclei are labeled blue, insulin-containing beta cells green, glucagon-containing alpha cells red, and human herpesvirus 6 (HHV-6) glycoproteins in white. On the right “wing” only cell nuclei and HHV-6 glycoproteins are visible demonstrating that human herpesvirus-6 is present at higher levels in the pancreatic tissues of donors with T1D.

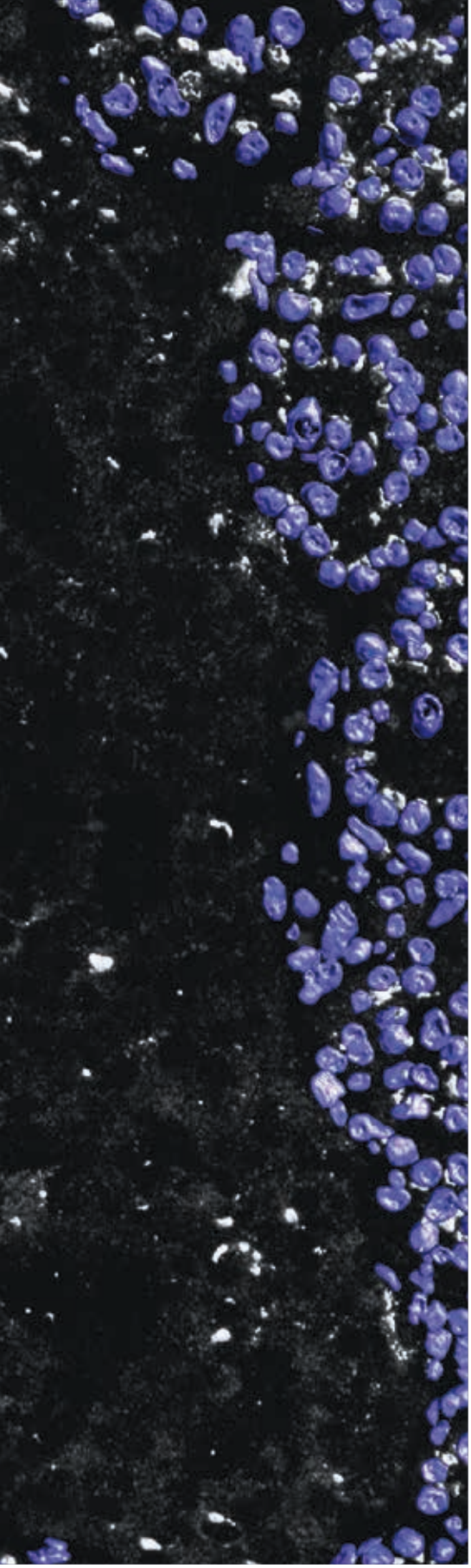


Image: Courtesy of Dr. William B. Kiosses

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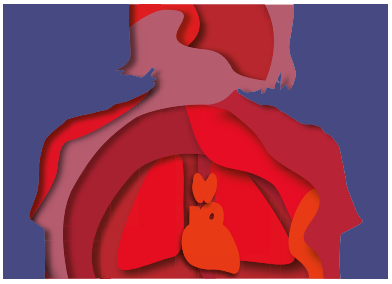

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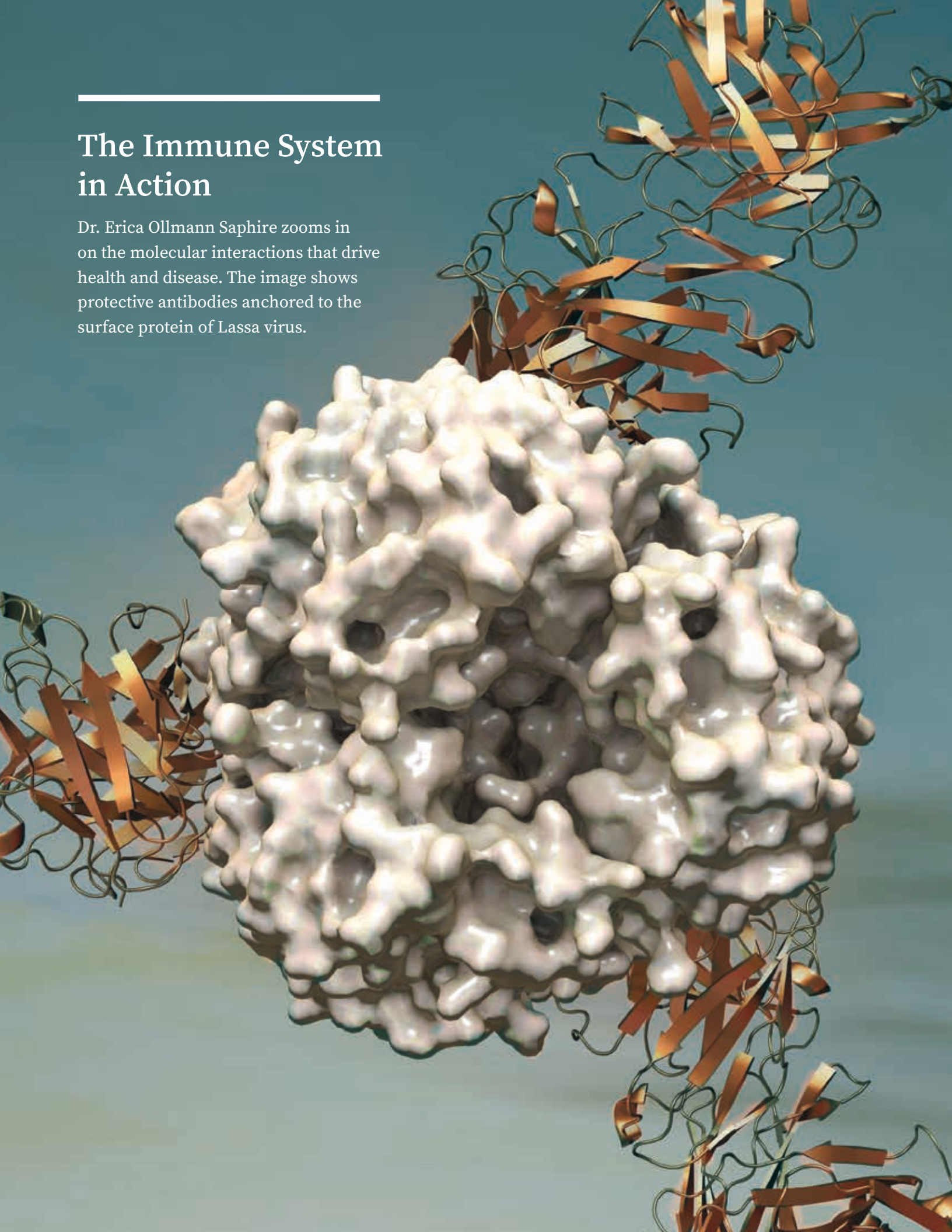
The Immune System in Action

Dr. Erica Ollmann Saphire zooms in on the molecular interactions that drive health and disease. The image shows protective antibodies anchored to the surface protein of Lassa virus.



LETTER FROM THE PRESIDENT

Of the three major research areas La Jolla Institute for Immunology focuses on—infectious disease, cancer, and autoimmune disease—the latter is least understood by the general public, but also the one whose incidence is increasing most evidently. With 23 million Americans suffering from 80-plus different disorders, autoimmunity affects more lives than any disease category.

Our cover story in this issue of *Immune Matters* reveals how the Institute is unraveling the mystery of how an immune system that normally protects us from harmful viruses, bacteria, and cancer cells can mistakenly turn on our bodies and attack healthy cells. The resulting inflammation and tissue damage wreaks havoc in the form of diseases ranging from type 1 diabetes, rheumatoid arthritis, and psoriasis, to multiple sclerosis, lupus, and inflammatory bowel disease.

You'll learn how Institute scientists are conducting groundbreaking research on these debilitating diseases by expanding our knowledge of one piece of good news. The mechanisms causing immune system T cells to attack healthy cells seem to work similarly in many of these diseases, despite the diverse target organs.

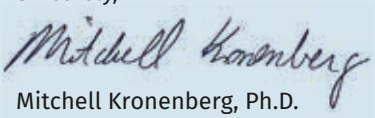
In this issue, we also profile three of our scientists who embody the Institute's world-leading reputation in immunology. In our Q&A with Principal Investigator Alessandro Sette, Dr. Biol. Sci., you'll read about an internationally renowned scientist who has devoted 30 years to understanding the immune response and using that research to develop interventional strategies against a variety of diseases. Dr. Sette is also the force behind the Immune Epitope Database (IEDB), an invaluable searchable site that gives scientists around the world free access to data from more than 1.6 million immunology experiments.

We also welcome the newest member of our faculty, Professor Erica Ollmann Saphire, Ph.D., whose innovative research explains, at the molecular level, how and why viruses like Ebola and Lassa are pathogenic and provides a roadmap for vaccines and cures. In our "Up and Coming" section we profile postdoctoral researcher Julie Burel, Ph.D., a native of France whose research on how the body responds to infections is gaining wide attention. Dr. Burel's imaginative scientific mind led her to winning one of the Institute's Tullie and Rickey Families SPARK Awards for Innovation in Immunology in 2019.

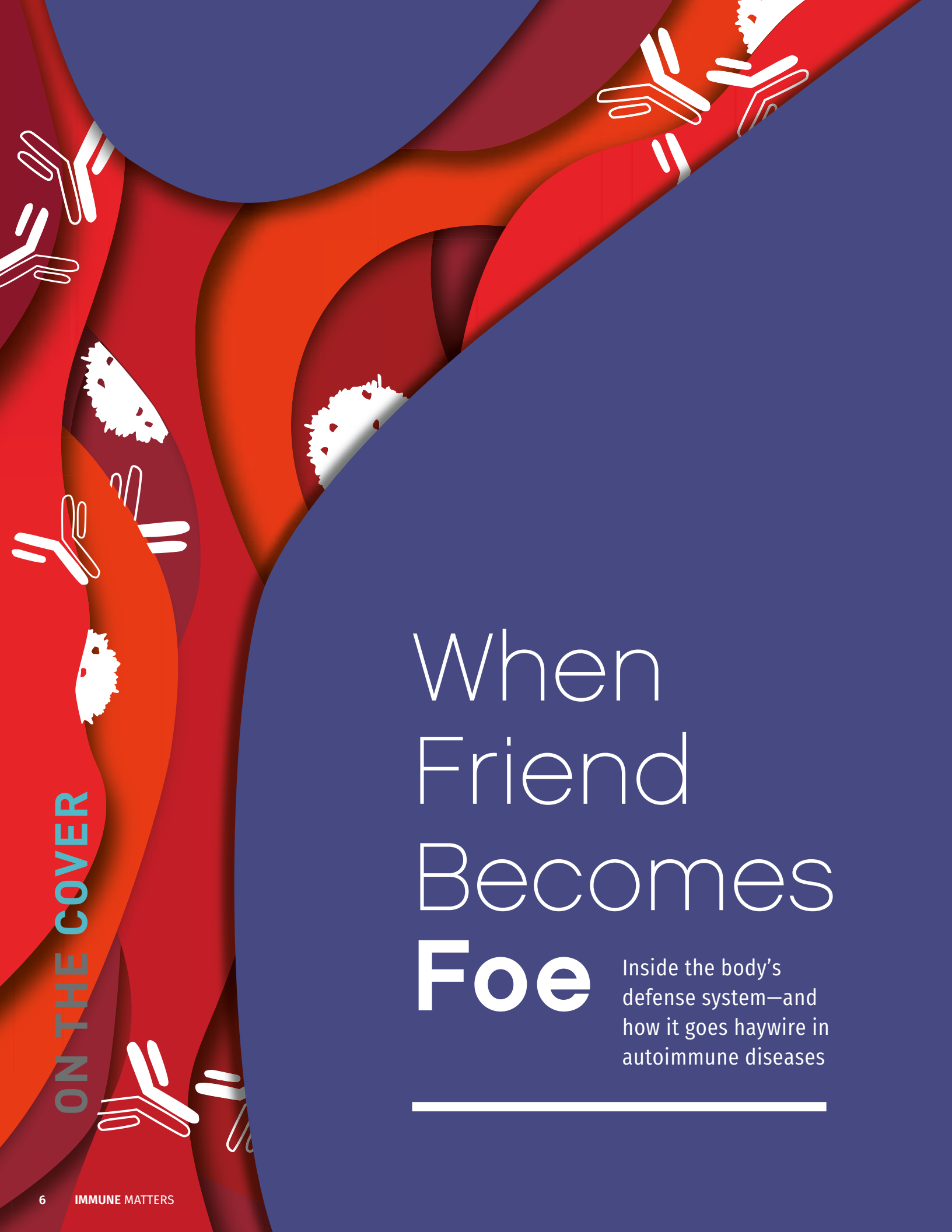
Finally, we profile Eric Zwisler, new chair of our Board of Directors, as we express appreciation to his predecessor, John Major. The Institute would not be where it is today without John's visionary leadership and guidance in his nine outstanding years as chair. With his deep international experience in business and leading organizations, Eric is the perfect choice to help the Institute reach its greatest potential.

Whether it's our dedicated researchers or our committed board members, the Institute is fortunate to have a remarkable team of collaborators working toward the same important scientific goals. As always, joining us in that effort are all of our wonderful Institute partners—including individual donors, foundations, and federal funding sources—who play such a crucial role in supporting research we believe will one day soon help us achieve our mission of ***Life Without Disease®***.

Sincerely,



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



ON THE COVER

When Friend Becomes **Foe**

Inside the body's defense system—and how it goes haywire in autoimmune diseases

Your immune system is **you.**

You were born with the inklings of immune protection, and this protection grew and grew as your body learned to fight off bacteria and viruses.

Your T cells are key to immune protection. T cells race through your bloodstream, and some nestle into your organs. These T cells are supposed to follow a basic rule: Don't attack this body. This body is you. It is self.

And yet millions of people suffer from autoimmune diseases, where T cells start attacking the body's own tissue. There are around 80 autoimmune diseases. Each has different targets—the skin, the lungs, the bowel—but they have much in common.

"In all autoimmune diseases, you have a revved-up immune system that is responding too well, or it is responding to something it shouldn't respond to," says Professor Michael Croft, Ph.D., Director of Scientific Affairs and Head of the Division of Immune Regulation at La Jolla Institute for Immunology (LJI).

To cure these diseases, LJI scientists need to know exactly what triggers T cells to turn on the body. This mission has led them to explore the power of genetics, cell development, and signaling molecules in one of the most complex systems in the galaxy: the human body.

What is **your** genetic risk?

Immunologist Pandurangan Vijayanand, M.D., Ph.D., the William K. Bowes Distinguished Professor at LJI, is putting together the genetic puzzle behind autoimmune diseases.

"We know that genes play a role in autoimmune diseases," Dr. Vijayanand says. "If you have a twin with type 1 diabetes, for example, your risk of also having type 1 diabetes is about 50 percent—much higher than the typical risk. Scientists have also found that risk of autoimmune disease can be linked to certain populations. For example, people of African or Chinese origin have a higher risk of developing lupus.

"The challenge is to track down these risk factors in the DNA code," he adds. "There are diseases where a single genetic mutation—one little DNA "letter" out of place—triggers disease. But few autoimmune diseases have such a simple clear genetic culprit. Instead, researchers believe subtle variations in groups of genes usually work together to increase risk."

Many studies have compared the full genomes of people with and without autoimmune diseases. Each person will naturally have numerous genetic variations, so Dr. Vijayanand and many others are sorting through thousands of people to see which commonly found genetic variants are more prevalent in people with different diseases.

From there, Dr. Vijayanand's team is going further to connect genetic variations to their effects in specific immune cells. Maybe a variation linked to lupus will have no effect in T cells but will be important in another immune cell type, B cells. "Once we know there's a gene effect in a particular cell type, then people can investigate further in humans or in model organisms," says Dr. Vijayanand.

There are

80+

autoimmune diseases

with very different targets:

joints

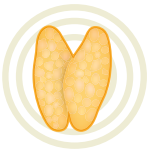
lungs

skin

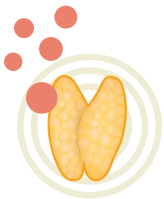
DICE

Database of Immune Cell Expression,
Expression of quantitative trait loci, and Epigenomics

T cells actually mature in an organ called the thymus.



thymus



The immune system takes a risk when it releases naïve cells from the thymus, since they have the potential to turn into extremely destructive cells when they respond in the wrong way or to the wrong antigen.

Already, Dr. Vijayanand and his LJI colleagues have built a database called DICE (Database of Immune Cell Expression, Expression of quantitative trait loci, and Epigenomics), which scientists can use to share pieces of the genetic puzzle. In 2018, the team published data from 91 healthy donors showing profiles of genetic activity for the 15 most abundant types of immune cells found in human blood. This database gives scientists a guide for comparing healthy variations to disease-associated mutations.

"To understand autoimmunity, you need to take a fresh look at it," says Dr. Vijayanand. "Then you are likely to find new players, new pathways."

Why do good **T cells** go bad?

So your genes control how your immune system is built, but then there's the matter of how T cells actually mature in an organ called the thymus. In adults, the thymus weighs about three grams. That's because its glory days are over. The thymus' real time to shine is in infancy and toddlerhood, when it weighs about 70 grams and lays like a blanket over the heart. Every pathogen is new to a baby, so the thymus works non-stop to prepare T cells for the challenges ahead.

T cells that leave the thymus have shown potential, but they are untested. These cells are called naïve cells. "T cells go to school in the thymus, if you will," says LJI President and Chief Scientific Officer Mitchell Kronenberg, Ph.D. While most come out ready to function, others "might become the T cell equivalent of juvenile delinquents."

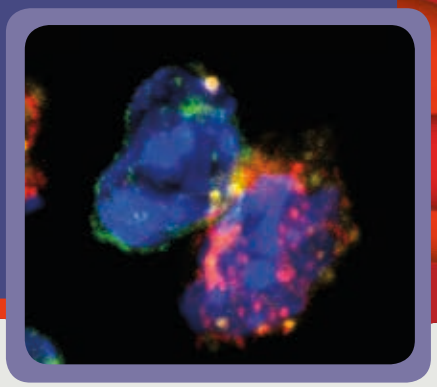
Dr. Kronenberg and LJI Professor Hilde Cheroutre, Ph.D., Head of the Division of Developmental Immunology, have dedicated their careers to better understanding T cells.

Dr. Cheroutre explains there is a big difference between autoimmunity and autoimmune diseases. "Autoimmunity in itself is not necessarily bad and autoreactive T cells are normally present in healthy people." T cells in the body are looking for cellular markers called antigens. All cells have self-antigens that signal 'hi, it's me and I'm a healthy cell.' An infected cell or a cancer cell will also have antigens derived from the pathogen (non-self) or tumor-specific antigens (abnormal self-antigens) that distinguish these cells from healthy cells. The presence of those foreign or abnormal antigens alerts the T cells and they fight the infection or remove the cancer cells. T cells first learn to distinguish self from non-self in the thymus, where they are tested against self-antigens. Those that do not react to those self-antigens leave the thymus as

Hello, Antigen!

When a T cell meets another cell, it scans that cell to detect molecular flags called antigens. Your cells should all have similar antigens that signal that the cell is "self." If a T cell encounters a "foreign" antigen it doesn't recognize, such as from a virus or bacteria, it may sound the alarm—the body is under attack! However, signals from other cells, such as macrophages, the white blood cells that "eat" foreign substances or cells lining the mucosal tissues, are usually required with antigens to activate T cells.

Cancer researchers would actually like to take advantage of antigen recognition. If they can prompt T cells to see antigens on cancer cells as foreign, they may be able to get the immune system to better fight tumors.



so-called naïve T cells. When these naïve T cells detect an antigen that alerts them to a threat like an infected cell, they mature and turn into protective cells that fight the infection.

"The immune system however takes a risk when it releases these naïve cells from the thymus, since they do have the potential to turn into extremely destructive cells when they respond in the wrong way or to the wrong antigen in the periphery, causing tissue destruction and autoimmune diseases," says Dr. Cheroutre.

But everyone also has autoreactive T cells that are specifically trained in the thymus to recognize "self." These "educated" autoreactive T cells are important players in beneficial autoimmunity by regulating immune responses and they often also emerge as critical protective cells to eliminate cancer cells or infected cells when mechanisms to alert conventional T cells fail. Still, a naïve T cell may encounter a self-antigen that it thinks is an invader. "If that happens under the wrong circumstances, that T cell can become a very dangerous autoreactive cell," Dr. Cheroutre explains.

To better understand what goes wrong in autoimmune diseases, Dr. Cheroutre and her team are working with doctors at Rady Children's Hospital-San Diego. When surgeons at the hospital have to perform heart surgery on young children, they must cut out a piece of the thymus to reach the heart. The surgeons leave a good part of the thymus in the patient, and Dr. Cheroutre can study those discarded pieces of thymus to learn more about the early days of T cell development.

"We hope to be able to identify autoimmune disease susceptibility in infants and even prevent autoimmune disease from ever happening," Dr. Cheroutre says.

"We hope to be able to identify autoimmune disease susceptibility in infants and even prevent autoimmune disease from ever happening."

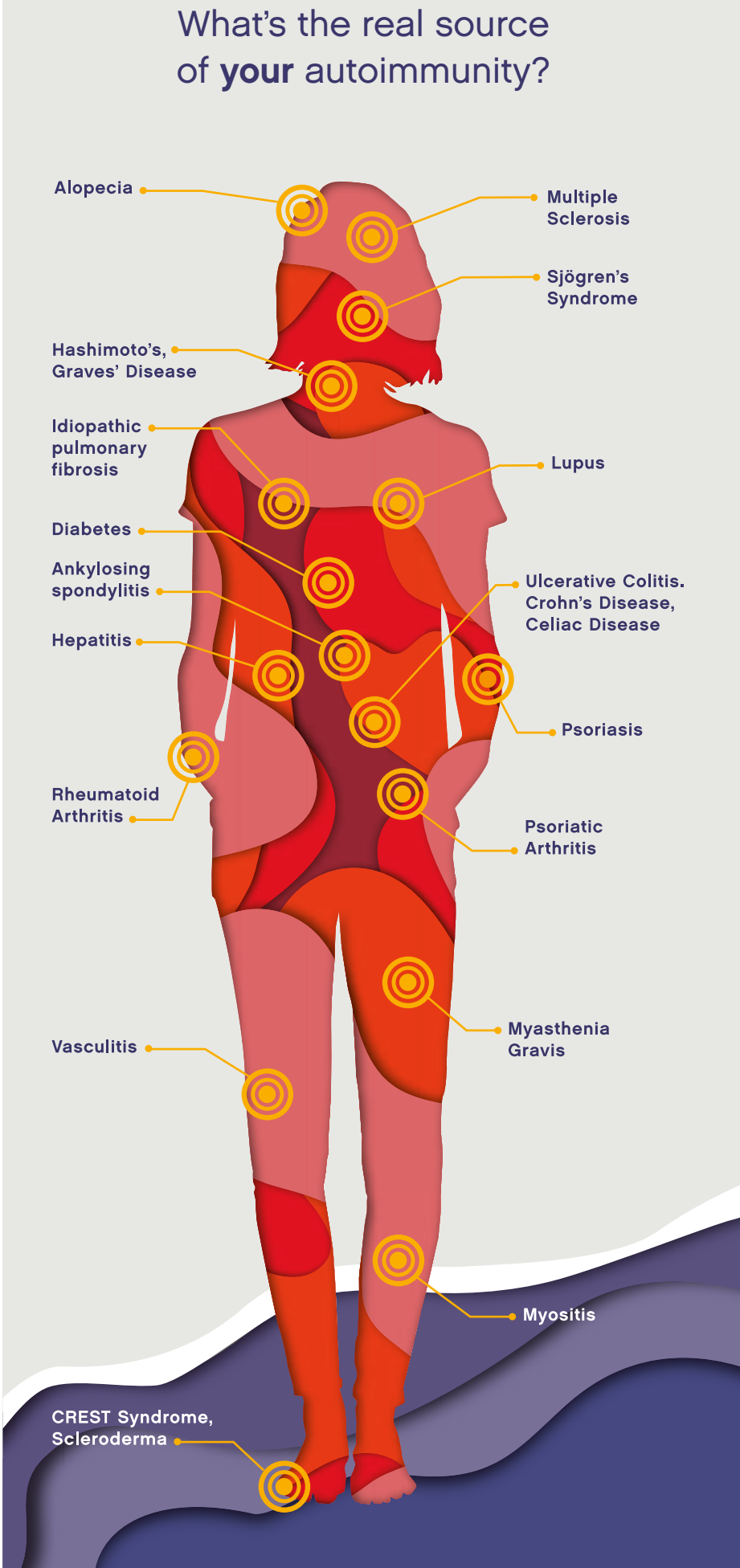
Hilde Cheroutre, Ph.D.

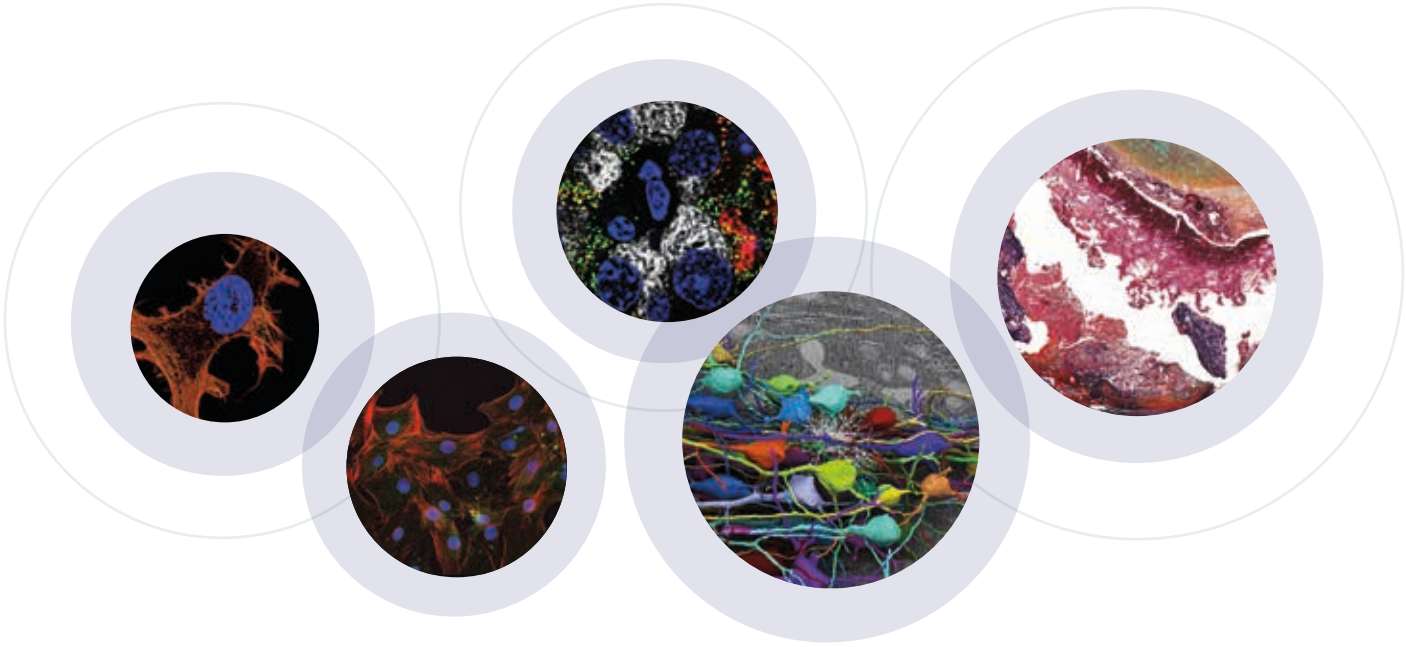
Why are only some tissues in the line of fire?

Autoimmune diseases have a lot in common. If something is altered in T cells and genes, it really ought to affect the whole body. This is the case for systemic autoimmune diseases, such as lupus. Yet many autoimmune diseases are known for primarily affecting just one type of tissue: the skin (psoriasis), nerve fibers (multiple sclerosis), spinal joints (ankylosing spondylitis), the tissue that lines joints (rheumatoid arthritis), and salivary and tear glands (Sjögren's Syndrome).

"By and large, these diseases occur somewhat in isolation," says Matthias von Herrath, M.D., Director of the Center for Type 1 Diabetes Research and Professor in the Division of Developmental Immunology at LJI.

To understand why so many diseases affect just one tissue, Dr. von Herrath is taking a closer look at type 1 diabetes. In this disease, self-reactive T cells kill beta cells in the pancreas, destroying the body's ability to produce insulin. Dr. von Herrath is exploring the hypothesis that there's something in the pancreas driving its own destruction. He's testing the theory that there's something wrong with the beta cells themselves. Prior to the onset of clinical signs of diabetes, the beta cells are drawing T cells to the area. These beta cells may have genetic mutations—or perhaps the cells are fighting off some type of virus.





Either way, the cells seem to want to die. Dr. von Herrath thinks understanding why could be key to unlocking the root of many autoimmune diseases.

But T cells certainly encounter other signals from inside the body. Dr. Croft is investigating how proteins called costimulatory molecules affect T cell function. Costimulatory molecules act on individual T cells, and research is indicating they play a role in causing T cells to attack tissues in autoimmune disease.

"We need to understand how these proteins cooperate together," says Dr. Croft. "Are there proteins that we don't know about that can be relevant for interventions?"

Hormones also seem to play a role. Women are more susceptible to most autoimmune diseases than men. Researchers believe this is tied to the female body's ability to sustain a pregnancy, since pregnancy requires that the body tone down immune responses in order to not reject foreign tissue (the developing fetus). This adds a layer of complexity to the female immune system and may lead to more opportunities for T cells to attack the wrong tissues.

Researchers at LJI are working to understand the flow of signals around the body and how this affects where destructive T cells are headed.

Many autoimmune diseases primarily affect just one type of tissue.

Above from left to right: lining of joints, skin, pancreas, nerve cells, blood vessels.

Hormones:
Women are more susceptible to most autoimmune diseases than men.

Researchers believe this is tied to the female body's ability to sustain a pregnancy.

A shared **hope**

Every day, LJI scientists make progress in answering the big questions about autoimmune diseases, and they find hope in recent breakthroughs.

Dr. Kronenberg thinks it's interesting that a biologic drug shown to treat inflammatory bowel disease has also proven effective against arthritis. Bowels and joints don't tend to have a lot in common, but in this case, the effective treatment for an autoimmune disease in one tissue also works in other tissues.

In the end, it's more about studying what makes autoimmune diseases the same than what makes them different. "The end organ is important, but the underlying cause is immune system dysfunction, and attacking that can be most effective," says Dr. Kronenberg.

Basic research is unlocking the secrets of autoimmune diseases, and LJI researchers have brought their expertise together to answer the biggest questions in the field. "We don't come at the problem from one angle, and we don't know where the next insight is going to come from," says Dr. Croft.

"I think the future is bright," adds Dr. Kronenberg. •

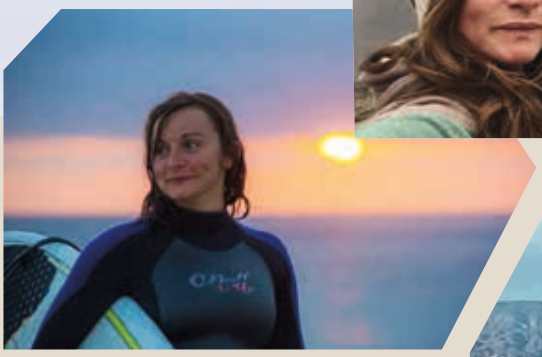
A SCIENTIST ABROAD

LJI postdoctoral researcher

Julie Burel

is changing the way we think about

INFECTIOUS DISEASE



When La Jolla Institute (LJI) postdoctoral researcher Julie Burel, Ph.D., isn't in the lab, she's adventuring. She's gone diving in Australia and hiked all over the world. A recent trip to Colombia included a four-day high-altitude trek in the Paramo, a unique alpine tundra ecosystem in the Northern Andes.

But it was a vacation to the South Pacific nation of Vanuatu that really stuck with Dr. Burel. "It's a fantastic place," she says. Her backpacking group stopped in a village, and Dr. Burel—who is originally from France—found the people there spoke a little French. Dr. Burel quickly made friends with a local teacher, and her group was welcomed by the chief.

Walking through the village, Dr. Burel saw what looked like a grave. A child had recently died of malaria, she was told.

Dr. Burel's research focuses on better understanding immune responses to infectious diseases to improve diagnosis, treatment, and vaccine efficiency. She stared at the grave. *This is why I'm doing what I'm doing*, she thought.

Although she is still early in her career, Dr. Burel's work has already forced immunologists to look more closely at how the body responds to infections. Earlier this year, Dr. Burel and her mentor, Bjoern Peters, Ph.D., Professor in the Vaccine Discovery Division, published a study in the journal *eLife* showing that monocytes and T cells, two key cell players in the immune system, appear more likely to stick together as "doublets" when the body is facing a threat, such as tuberculosis or dengue fever.

Dr. Burel thinks that looking for this signature in the blood could help doctors more quickly diagnose deadly diseases, and highlight which patients are more likely to face severe disease progression or treatment failure. She says LJI is uniquely set up to encourage her to pursue these kinds of unexpected discoveries. It's a place where collaboration makes every project stronger. For example, Dr. Burel's research often takes her down to LJI's Flow Cytometry Core, where the team seems just as excited as her to see new data.

"You have a sense of community because of the Institute's small size," says Dr. Burel. "Everything you need is on site. There are strong core facilities, and you have a lot of communication between the administration teams and the research teams. That's really important."

LJI's generous donor community has fueled this work. In 2019, Dr. Burel received $25,000 in unrestricted research funding through the Tullie and Rickey

"LJI lets you really focus 100 percent on doing research. I think that's what makes this place really successful."

Why are some people able to fight off infections while others are not?

Samples collected from geographically diverse populations provide insight into human immune diversity.

GOAL

To isolate white blood cells from samples and analyze which specific genes are turned off and on.

These gene patterns can reveal exactly how the immune system has reacted to the disease.

Families SPARK Awards for Innovation in Immunology. The SPARK Program allows researchers to pursue bold ideas that traditional funding agencies often see as too risky.

LJI has found that this research often leads to unexpected breakthroughs, such as Dr. Burel's "doublet" cell findings, so donors have stepped in to make SPARK funding available to early career scientists.

The SPARK Program was Dr. Burel's first experience in earning grant money. She said she learned a lot from presenting her work to non-scientists during the award selection process. "I think communicating with the public is really important, and scientists don't do it enough," Dr. Burel says.

Dr. Burel's next goal is to dive into one of the biggest questions in immunology: Why are some people able to fight off infections while others are not? To answer this question, researchers need to know more about the mechanisms driving immune system variability. Dr. Burel wants to know exactly what goes wrong in some patients. Which immune cells aren't working?

"That's very important for us to know to do more personalized medicine," Dr. Burel says.

Malaria is a good example of this variability. Most people can control the disease and may just experience a bad fever. But the disease can prove deadly for pregnant women and children, who may not have as strong an immune system.

Tuberculosis is another example. Most people can control the disease in an asymptomatic stage, called latent tuberculosis. But in a small fraction of individuals, mostly those with a weakened immune system, such as children and HIV-seropositive people, the tuberculosis bacteria can develop into a deadly lung disease. Dr. Burel wants to know what to test for in the blood to predict how the body will react to the disease.

"We still don't know how it works in most cases," she says. "That is why we can't have one therapeutic approach that works for everyone."

Studying individual variability comes with the challenge of processing many, many human samples. These days, Dr. Burel spends hours hunkered down in a tissue culture room, working with samples from patients with tuberculosis. Her goal is to isolate white blood cells from the samples and analyze which specific genes are turned off and on. These gene patterns can reveal exactly how the immune system has reacted to the disease. She's handling samples right now from patients in Peru, Sri Lanka, and South Africa. "It's quite geographically diverse, which is important if we want to understand human variability at a global level," Dr. Burel says. She's also working hard to strengthen her skills in bioinformatics, a field that will help her better analyze the large datasets that come from her research.

"LJI lets you really focus 100 percent on doing research," says Dr. Burel. "I think that's what makes this place really successful."

As she forges ahead, Dr. Burel knows there are lives on the line. As she meets people during her travels, they often ask what she does back home.

"Whenever I tell them, they say, 'this is good, this is helping.'" •

ALESSANDRO SETTE, DR. BIOL. SCI.

Throughout his career, Alessandro Sette, Dr. Biol. Sci., has been on a quest to define and understand what the immune system really sees and how it helps shape the resulting immune response.

QUESTIONS & ANSWERS

Raised in Rome, Italy, in a family of lawyers, Dr. Sette started his science career as a young boy in a spare room at his father's law firm, where he kept a "chemistry cabinet" and smelled up the firm from time to time with failed experiments. He soon left his trial-and-error days behind and quickly became known for his pioneering efforts to systematically dissect how the immune system responds to some of the most prevalent and dangerous infectious agents, such as those that cause malaria, tuberculosis, and dengue fever.

Dr. Sette spent 14 years in biotechnology, first at Cytel Corporation and later at Epimmune, as founder, Vice President for Research, and Chief Scientific Officer. The goal of these two companies was to develop highly specific immunotherapies for autoimmune diseases and better vaccines for hepatitis B infection. In 2002, Dr. Sette joined La Jolla Institute for Immunology to head the new Center for Emerging Diseases. There, Dr. Sette oversaw the design, development, and implementation of the national Immune Epitope Database (IEDB), a freely available database that catalogues all the specific structures that the immune system recognizes—which are known as epitopes—for humans, non-human primates, rodents, and other vertebrates, from allergens, infectious diseases, autoantigens, and transplants.

Q. *You came from a family of lawyers. How did you become interested in science?*

After finishing high school, I wanted to make an impact and change the world. In a philosophical sense, you can bring about change by changing people's minds. It doesn't change anything material but it changes the way we think. Or you change the world through tangible things, which is what science does. It invents new things, different medicines, or develops new ways to manufacture things. My desire was more to make an impact through changing the real world, the world of artifacts rather than being a lawyer or politician.

Q. *You were immediately captivated by immunology. Why?*

I was originally drawn more to chemistry because I liked the exact nature of chemistry. Back in the 80s, biology was more of a black box, but I was very impressed by immunology. People were trying to understand all the different genes that code for immunoglobulins and went into great molecular detail. At the same time, immunology's connection to human health made it a discipline with a high potential of practical applicability and having impact.

Q. *Did you ever consider medical school?*

That was one of the options but my perception back then was that medicine tackled problems one infection at a time, while science can give you a vaccine and solve the problem once and for all.

Q. *You were using bioinformatics before the term had even been coined. What sparked your interest in programming?*

I had always been attracted to statistics and mathematics. We already had Fortran machines and I started a little bit of computer programming. It's not that I foresaw bioinformatics, it was more of a nerd thing for me. I liked immunology, so it was only natural to see if I could combine them.

Q. *How did you pick your postdoc lab?*

At the time, the National Jewish Hospital was really one of the best places in the world for what I was interested in. My mentor knew John Kappler and Philippa Marrack, and he arranged for an interview. I flew out there, but they did not end up offering me a job. But Howard Grey, who was the head of the Department of Medicine there, came to the seminar. After the seminar, I spoke with him and told him that I wrote computer programs to look for patterns in peptides, and he thought maybe I was the right guy and he offered me a job on the spot.

Q. *Had you considered his lab before?*

It was a risky move. Howard was starting to get real biochemical evidence that epitopes bind to MHC, which are molecules on the cell surface. The idea had been out there for quite some time but it was still very controversial. What if he was wrong? I would have been wrong together with him. But Howard had such a sterling reputation and anybody I talked with said that his word

was rock solid. If he said something you could hang your hat on it and so I said, okay, sure. In the end, he was right. (Howard Grey later became president of La Jolla Institute.)

Q. *Why did you switch to industry after your postdoc?*

From there it became apparent that maybe you could use the fact that peptides bind MHC to inhibit autoimmune disease, and that's how Cytel was started. For technical reasons, it was too difficult to inhibit the autoimmune response and the company pivoted to trying to stimulate an immune response with peptides. The idea of epitope-based vaccines and a new company—Epimmune—was born.

"You change the world through tangible things, which is what science does. It invents new things, different medicines, or develops new ways to manufacture things. My desire was more to make an impact through changing the real world."

Alessandro Sette, Dr. Biol. Sci.

www.IEDB.org

The free, searchable database is home to data from more than

1.6 million

immunology experiments, making it a one-stop shop for understanding and predicting the body's response to viruses, bacteria, cancer, allergens, and more.

***Q.** You ultimately left Epimmune to join LJI. What propelled you?*

Epimmune had evolved—just like Cytel before—and the focus was increasingly on clinical trials and the manufacture of vaccines, which wasn't what I was interested in. I really enjoy being involved in the earliest stages of translational science—the transition between pure basic research and more fully applied research. And that's what I've been doing at La Jolla Institute ever since.

***Q.** You switched from academia to industry and back. Is there an overarching question guiding your research?*

The basic question is always the same: What does the immune system do? What kind of immune response is associated with good outcomes versus bad outcomes? It means understanding why some people infected with dengue get hemorrhagic fever while others only get a mild fever. Why some people breathe pollen and they are totally fine while somebody else gets asthma. What determines that? Once we understand that we can design treatments and vaccines that reproduce a good outcome or nudge the outcome in the right direction.

***Q.** Where did the idea for an immune database originate?*

The concept of a database to keep epitope data organized was born during our Epimmune years. Back then, we and others filed patents with thousands of different epitope sequences, and after a while it became very difficult to keep everything organized because of the sheer volume. What data were available for a certain epitope? Was it a prediction? Was it tested? Was it shown to bind? Antigenic in humans? So, we started to develop early concepts to corral the flood of data. When I left Epimmune, the NIH coincidentally advertised for a contract to develop an Immune Epitope Database and I thought we had a good shot at it because of my previous experience.

***Q.** You are an avid fencer. That's somewhat unusual, isn't it?*

Italy has a long tradition of world class fencing athletes and coaches, so it wasn't that uncommon in Italy when I was a young boy. I fenced for a few years but as I grew up other interests took over and I forgot about it until much later here in the U.S.

***Q.** What makes fencing so enjoyable for you?*

It is a good aerobic exercise, but your physical condition only matters up to a point. In a sense, it is like a chess game. Just like a good chess player who can visualize what is going to happen three moves down the line, a good fencer has to think ahead and to force his or her opponent to do something that creates an opening down the line. What's particularly interesting for me is that as scientists we tend to analyze or over analyze everything, but during a fencing bout you only have a split second to make a decision and then you hope for the best.

***Q.** How do you spend your time when you are not in the lab or the fencing gym?*

I love to cook for friends and family, the more the merrier. Back in the early 2000s, I also cooked for a local restaurant a few nights a week before it became impossible to spend two to three nights a week cooking and have a day job. I also like to travel and often go to Italy, where I still have a farm. The farm is in Pulia and has been in the family forever. It is run by Antonio, and Antonio's grandfather ran the farm for my grandfather. We keep it because we have a deep emotional connection. •

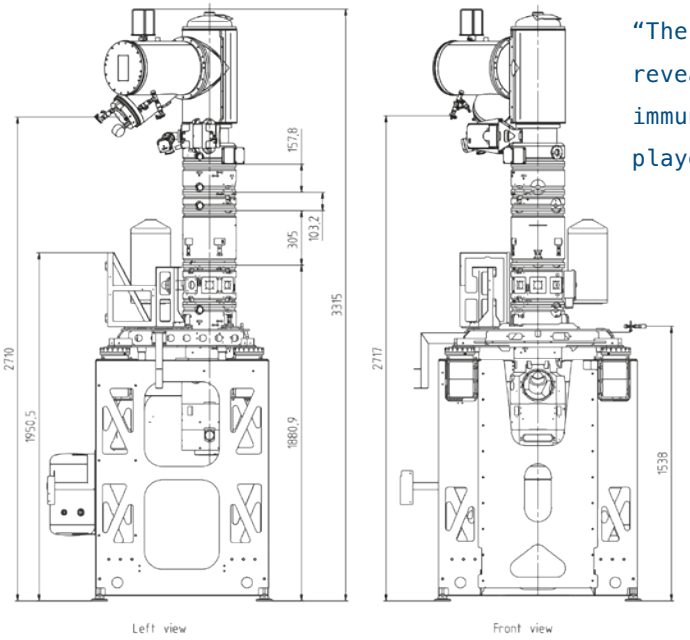
BUILDING A WORLD-CLASS imaging facility

When renowned structural immunologist Erica Ollmann Saphire, Ph.D., joined La Jolla Institute, she had a singular vision: to bring the most important new approach in molecular imaging to La Jolla Institute.

During the last week of August, the trucks finally started to arrive. Carefully nestled inside 22 huge wooden crates was what's casually referred to as the Krios—shorthand for the world's most advanced cryo-electron microscope. The Krios is the cornerstone of what soon will become a state-of-the-art molecular imaging facility at La Jolla Institute.

"What's most remarkable is that it has been barely a year since LJI and I started talking about the idea of building a cryo-EM facility," said Professor Erica Ollmann Saphire, Ph.D., a widely recognized structural biologists and one of the world's leading experts in pandemic and emerging viruses, who joined LJI faculty this spring. "What was a mere concept back then has progressed to assembly of the microscope in a newly constructed facility, and electrifying opportunities."

"We are thrilled to welcome Erica to the Institute. She is a truly exceptional scientist who uses molecular insights to bring together scientists and policymakers for scientific advancement and social change," says Mitchell Kronenberg, Ph.D., LJI President and Chief Scientific Officer. "Having her here will accelerate the Institute's efforts to solve humanity's most pressing health challenges, and continue to elevate the remarkable science on the Torrey Pines Mesa."



"The extremely detailed images produced by cryo-EM reveal precisely how essential mechanisms of the immune system operate and what goes wrong when one player is out of tune." **DR. ERICA OLLMANN SAPHIRE**

Standing over 10 feet tall, the Krios is a giant tool to help scientists visualize biological molecules at an atomic scale.

Dr. Ollmann Saphire's decision to move her lab to La Jolla Institute was, in part, driven by the opportunity to build a world-class molecular imaging facility. For decades, biologists have relied on x-ray crystallography—blasting x-rays at crystallized proteins—to determine the structure of biomolecules. But over the last couple of years, cryo-EM has taken the world by storm.

Cryo-EM had long been derided as "blobology" for the indistinct images it delivered, but a perfect storm of improvements in camera technology, image processing, reduced cost, and increased computing power has transformed cryo-EM from low-resolution technique to the most important new way to gain high-resolution insights. Crucially, cryo-EM can also visualize moving parts.

Cryo-EM uses electron beams to image flash-frozen biological molecules and lay bare their three-dimensional shapes. Not surprisingly, labs around the world are racing to adopt cryo-EM, because it can provide scientists with a blue print of large, complex proteins' structures that can't easily be formed into large crystals.

"At the heart of all advances in immunology is the fundamental understanding of the molecular interactions that drive health and disease," says Dr. Ollmann Saphire. "The extremely detailed images produced by cryo-EM reveal precisely how essential mechanisms of the immune system operate and what goes wrong when one player is out of tune."

As part of her own work, Dr. Ollmann Saphire studies the three-dimensional structures of viral proteins to understand, at the molecular level, how viruses like Ebola, Marburg, and Lassa are so deadly. In a series of groundbreaking discoveries, her team has identified the molecular structures of the Ebola, Sudan, Bundibugyo, Marburg, LCMV, and Lassa virus surface glycoproteins; how these viruses suppress immune function; and where human antibodies dock to defeat these viruses. This was the roadmap science needed to develop potent therapeutics and vaccines.

She showed that certain viral proteins are surprisingly dynamic and can twist themselves into new shapes at critical stages during a virus' life cycle to perform different functions. The discovery of what she calls "transformer" proteins expanded the central dogma of molecular biology, which states that a protein's sequence determines its one-and-only shape and thus its function.

Dr. Ollmann Saphire is also the galvanizing force behind the Viral Hemorrhagic Fever Immunotherapeutic Consortium (VIC). Under her leadership, the global consortium—now headquartered at La Jolla Institute—brings together the expertise of leading structural biologists, virologists, immunologists, clinicians, and public health practitioners to effectively combat disease in humans infected with Ebola and other related filoviruses; arenaviruses such as Lassa virus; as well as a third major global threat, alphaviruses, which infect millions of people across the world.


MADE IN THE
NETHERLANDS

"The recent resurgence of Lassa, the difficulties in containing Ebola outbreaks, and the re-emergence of alphaviruses in multiple locations, including the United States, makes the development of therapies against these threats an urgent local and global concern," says Dr. Ollmann Saphire.

Earlier this year, the VIC was awarded up to $35 million by the Centers of Excellence for Translational Research (CETR) program at the National Institute of Allergy and Infectious Disease to continue the tremendously successful international program for another five years.

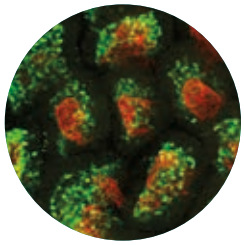
Dr. Ollmann Saphire's work has been recognized at the White House with the Presidential Early Career Award in Science and Engineering, with young investigator awards from the International Congress of Antiviral Research, the American Society for Microbiology, and the MRC Centre for Virus Research in the United Kingdom. She has also been recognized with an Investigators in the Pathogenesis of Infectious Disease Award from the Burroughs Welcome Fund, and by the Surhain Sidhu award for the most outstanding contribution to the field of diffraction by a person within five years of their Ph.D.

She has been awarded a Fulbright Global Scholar fellowship from the U.S. Department of State and a Mercator Fellowship from the German Research foundation, Deutsche Forschungsgemeinschaft, to develop international collaborations around human health and molecular imaging through cryo-EM.

Dr. Mitchell Kronenberg elected Distinguished Fellow by the American Association of Immunologist

The American Association of Immunologists (AAI) has named La Jolla Institute for Immunology (LJI) President and Chief Scientific Officer Mitchell Kronenberg, Ph.D., a world expert in T cell biology, as an AAI 2019 Distinguished Fellow. He is among 52 immunologists, including five Nobel Laureates, selected for the inaugural class of fellows.

Election as a Distinguished Fellow is among the highest honors bestowed by AAI and recognizes members for distinguished careers and outstanding scientific contributions as well as their service to AAI and the immunology community.



Dr. Kronenberg is best known for his extensive studies of a subset of specialized T cells known as invariant natural killer T (iNKT) cells and their brethren, mucosal-associated invariant T (MAIT) cells. Both cell types are an integral part of the innate immune response, which reacts almost immediately to foreign invaders.

In a different area, Dr. Kronenberg's pioneering studies focus on understanding the immune defense mechanisms at the body's largest "interface" with the outside world, the intestines.

In addition to forming a physical barrier separating us from many billions of resident microbes, known as the microbiome, the mucosal epithelium lining the intestine also carries out vital digestive functions. Therefore, any tissue damage induced by invading pathogens or excessive inflammation can jeopardize the integrity of this critical border, spread devastating infection, and cause inflammatory bowel disease.

Dr. Shane Crotty honored with 2019 Frederick W. Alt Award

Professor Shane Crotty, Ph.D., has been selected to receive the 2019 Frederick W. Alt Award for New Discoveries in Immunology for his pioneering insights in the fundamentals of what makes a good immune response to help custom-engineer vaccine candidates so they elicit a protective immune response.

The award is given annually to a former Cancer Research Institute postdoctoral fellow in recognition of outstanding success in academia or industry for research that has had a major impact in the field of immunology.

"It is a real honor, personally, to win this award," says Dr. Crotty. "Fred Alt is a doyen of modern molecular immunology and I have great respect for the Cancer Research Institute and previous winners of this award." Dr. Crotty is driven by his desire to fundamentally change how vaccines are designed. His work has been instrumental in spurring a shift from the trial-and-error approach that has dominated the field of vaccine development in the past and paved the way for the rational design of immune-based treatments.

In 2009, Dr. Crotty discovered a pivotal master switch that ignites the production of a certain group of helper T cells known as follicular helper T (Tfh) cells, which in turn help B cells make more antibodies. Subsequently, Dr. Crotty's team systematically unraveled the molecular mechanisms that drive

the differentiation and maturation of Tfh and antibody-producing B cells.

Most importantly, he demonstrated that Tfh cells are crucially important for triggering broadly neutralizing antibodies against HIV, the virus that causes AIDS.

Business leader Paul Thiel appointed to Board of Directors, expanding his involvement with La Jolla Institute

Paul Thiel is so passionate about the mission of La Jolla Institute for Immunology he is expanding his already deep involvement with the organization by accepting appointment as the newest member of the Institute Board of Directors.

"When you see as many family members and friends suffer from serious autoimmune diseases as I have, you jump at any opportunity to support a world-class immunology research institute like LJI," Thiel says. "I really want to leverage my business and finance expertise to help attract new resources and philanthropy to fund even more groundbreaking science and help LJI achieve its ambitious mission of 'Life Without Disease.'"

Thiel, who is President of Northern Trust Wealth Management's San Diego Region, first became involved with LJI six years ago as a donor after he and his wife, Lori, were captivated by the talented scientists and pioneering research they observed at LJI.

That was just the beginning of the La Jolla couple's involvement with LJI. Lori became an Institute Ambassador and Paul agreed to co-chair LJI's Planned Giving Advisory Council, a highly respected group of 29 professional advisors who volunteer their combined expertise in financial, estate, and charitable gift planning to generate philanthropic support for La Jolla Institute.

"We're introducing La Jolla Institute to the broader community and increasing awareness of the Institute's impressive scientific accomplishments, including several of which are saving and improving the lives of those battling immune system-related diseases," Thiel says.

The Thiels also organized the San Diego Advisor of the Year, a not-for-profit educational organization that hosted an awards event that raised funds for the Institute. Last year, Lori and Paul presented a $25,000 check to LJI's SPARK program, which provides funding to help young Institute researchers get their most promising scientific ideas off the ground.

"We're introducing La Jolla Institute to the broader community and increasing awareness of the Institute's impressive scientific accomplishments."

Eric Zwisler named Chair of La Jolla Institute's Board of Directors; John Major steps down after nine years of outstanding service

Eric Zwisler, former President and Chairman of Cardinal Health China, has been elected Chairman of the Board of Directors of La Jolla Institute for Immunology. He succeeds John Major, whose nine years of outstanding service help advance the Institute in a number of key areas.

"I am deeply moved by the confidence put in me by Institute colleagues on the Board to be named the fifth chair of LJI's Board of Directors," says Zwisler. "La Jolla Institute is one of the elite immunology-focused research organizations in the world, and I am honored to serve in this role at this important time in the Institute's history."

After joining the Institute's board in 2014, Zwisler quickly became deeply involved with the Institute and led the Institute's strategic planning initiative. "We are thrilled and extremely fortunate to have Eric agree to serve as Chair of the Board," says Mitchell Kronenberg, Ph.D., President and Chief Scientific Officer. "Eric has been a determined and a widely respected leader within the health care industry, who broke new ground in Asia. He brings that same passion and determination to La Jolla Institute and we are looking forward to breaking new ground together as we move more of our discoveries into clinical development and ultimately to patients."

Zwisler was involved in healthcare businesses in Asia and particularly China for over 30 years. In 1994, he established the China business for Zuellig Pharma Asia Pacific, a groundbreaking healthcare distribution company, and rose to CEO of Zuellig Pharma Asia Pacific, leading a multibillion-dollar company with 8,000 employees in 15 Asian countries. Most recently, Zwisler was Chairman of Cardinal Health China, a subsidiary of Cardinal Health (CAH), a US Fortune 15 healthcare distribution company.

In 2017, Zwisler participated in the sale of Cardinal Health China, and retired from Cardinal Health a year later. He now spends his time serving on various corporate and non-profit boards, including the advisory board of UC San Diego's School of International Relations and Pacific Studies.

Zwisler, who speaks fluent Mandarin, has been recognized for his contributions to business and society in China, including the Friendship Medal, the highest national level award bestowed on foreigners in China. He is also an Honorary Citizen of Shanghai, a silver and gold Magnolia Medal honoree, and one of the first foreigners given permanent residence in China.

When Major joined the board in 2009 and became chair a year later, he brought with him a distinguished background as a business leader and one of the most influential forces in wireless communications history. Trained as an engineer who also holds MBA and JD degrees, Major held top executive positions at Motorola, QUALCOMM, and Novatel Wireless, and was board chair at Broadcom, Inc. He and his wife Susan are active philanthropists who have supported a number of causes, including STEM education. This past May, he was awarded an honorary doctorate of engineering from the University of Illinois at Chicago.

Eric Zwisler

"John transformed the board at a critical time in our history and he has been invaluable to the Institute on many fronts during his years of visionary leadership, including as a major donor," Dr. Kronenberg says. "John expanded the board from a small group interested in science to a larger diversified group of members with major business and financial experience.

"Another of John's key contributions was his push to expand the Institute's philanthropic efforts," Dr. Kronenberg adds. "He knew that in order to produce the best immunology research in the world we would need significant resources beyond our government grants. John also encouraged us to share the Institute's science and discoveries with the larger pubic in a way that they could understand and support. Thanks to John's many contributions we can look forward to an even stronger future for the Institute."•

"John transformed the board at a critical time in our history and he has been invaluable to the Institute on many fronts during his years of visionary leadership."

– DR. MITCHELL KRONENBERG

Mitchell Kronenberg, Michael Crawford, LJI Board member Anthony Carr

Jason Mitchell, Alexis Lewis, Pat Walsh

A DAY AT THE *Races*

La Jolla Institute for Immunology hosted their inaugural Day at the Races event at the Del Mar Turf Club's il Palio Restaurant on August 2, 2019. This unique event treated more than 350 guests—including members of the LJI Board of Directors, leadership and faculty, and other prominent business leaders and community influencers—to panoramic views of the world-famous Del Mar Racetrack while simultaneously supporting a great cause. Proceeds from event sponsorships and table sales supported the La Jolla Institute's groundbreaking research, contributing to help millions of people live *Life Without Disease®*.

For more information or to learn about upcoming events contact Chelsea Luedeke at cluedeke@lji.org or 858-752-6896.

LJI Board member Kristine Charton, Joan Scott

Mark Mays, Alessandro Sette, Karna Bodman, LJI Board member Richard Bodman, Suzanne Sette, Gale Krauss

Kathleen Bowles, Jeffrey Miller, Hilde Cheroutre, Mitchell Kronenberg, Denny Sanford, Ingrid Velasquez, LJI Board member Mark Bowles

Samantha Durfee, Ian Mathews

Andy Head, Laura Kreiss, Fernanda Whitworth

LJI Supporters Hugh Mclean and Mary Harker

LJI Supporters Lee and Juniper Stein

LJI Board Chairman Eric Zwisler with Paul and Jane Krikorian

Salon Event Showcases

Cutting-Edge Science and Chocolates

Jim and Tanya Shaffer hosted an intimate garden party for friends and supporters of La Jolla Institute for Immunology at their home on Sunday, September 15, 2019.

LJI Professor Erica Ollmann Saphire, Ph.D., shared the results of her pioneering studies of Ebola and Lassa virus with a rapt audience. She explained how her research into the 3D structure of viral proteins provides the blueprint for the design of novel treatments and vaccines for emerging viral diseases that pose global health problems.

The informal research update was followed by a reception, where attendees had the opportunity to meet Dr. Ollmann Saphire in person and sweeten their day with Tanya's exquisite handmade chocolates.

LJI Board Member Geneviève Tremblay Jacobs with her husband, Paul Jacobs

LJI Board Member Michael Coit with his wife Ellise Coit

Erica Ollmann Saphire, between Jim and Tanya Shaffer

LJI Board Member Francois Ferré and his wife Magda Marquet

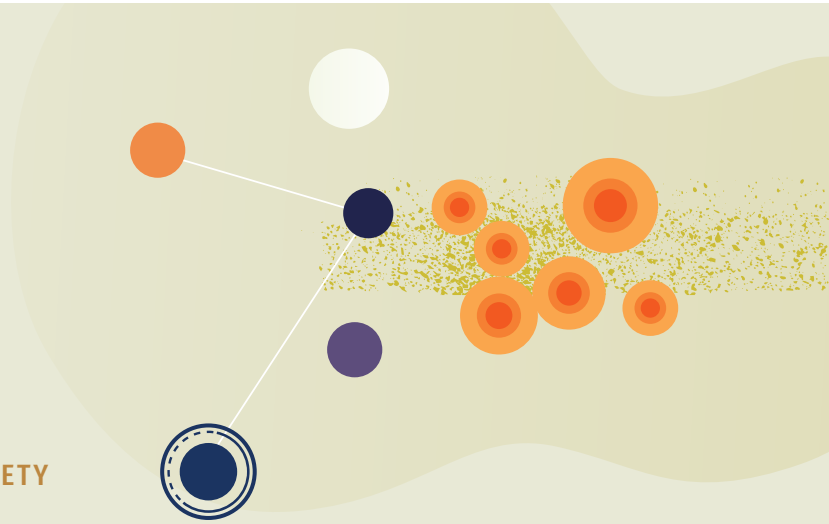
La Jolla Institute

VANGUARD

GIVING SOCIETY

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

With your contribution 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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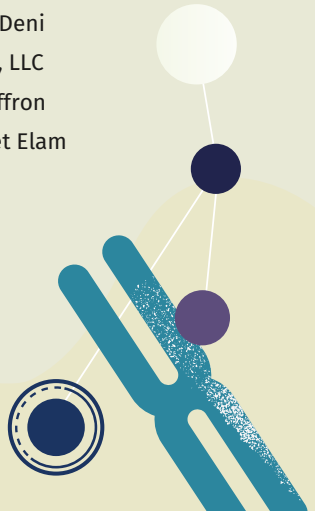

Patient takes charge of his treatment path and partners with LJI researchers to create a fully personalized cancer vaccine

Considering that Stephen Aldrich was diagnosed with a swift-moving terminal cancer in early 2017, the 63-year-old Vermont resident should not be alive today.

But Aldrich was not a normal patient. After the retired entrepreneur learned he had metastatic adenocarcinoma of the esophagus—and learned that 90 percent of patients die within two years—he rejected the palliative standard of care treatment recommendation he received.

"The only reason I'm still here today is that I decided I would look at highly experimental options I knew were exploding in the field of cancer immunotherapy, including some remarkable discoveries at the La Jolla Institute for Immunology (LJI)," says the former founder and CEO of Bio Economic Research Associates (bio-era).

The fascinating medical journey on which Aldrich embarked was not without at least one major obstacle. Hoping to use the genetic research conducted on his malignancy in his quest, Aldrich learned to his dismay that the Dana-Faber Cancer Institute legally owned his data and had no plans to release it to him. Out of his own pocket, he paid Human Longevity Inc., to sequence both his healthy and cancer genomes.

Armed with full genetic data, Aldrich first identified a Phase II clinical trial in Connecticut that was testing a combination of two promising immunotherapies—Pembrolizumab and Epacadastat—that were well matched genetically to his cancer and actually held his disease at bay for 14 months.

Ultimately, Aldrich was looking for a treatment path that would put him into radical remission, and he has achieved that after enrolling in a clinical study conducted by LJI Principal Investigator Stephen P. Schoenberger, Ph.D., and UC San Diego's Moore's Cancer Center. A personalized neoantigen cancer vaccine was custom-designed for Aldrich's cancer to train T cells in his body to specifically target tumor cells.

While not completely cancer free yet, Aldrich says he has achieved a radical remission in which his disease has not progressed for over two years, he feels great, and he's looking forward to the future. He's also so appreciative of LJI he has used his story and new website to raise tens of thousands of dollars to support Dr. Schoenberger's research.

"Stephen Schoenberger and the La Jolla Institute team are true heroes of mine, and I don't think I would be alive today without their pioneering research," Aldrich says. "The work they're doing is some of the most important in the world of immunotherapy and has the potential to completely revolutionize how we treat certain kinds of cancer."

Aldrich is also taking steps to transform every patient's ability to take control of their own data and easily make it used and useful on their own behalfs—just as he did. He has formed a company, myCancerDB (www.mycancerdb.com), owned and operated by late-stage cancer patients, that enables patients to store and access all of their fundamental health data in one secure online site, to query the data with useful tools, and allows researchers and the patient's care team to collaborate around the data.

"Ownership and control over your fundamental health data, especially genetic sequencing data, should be a universal human right," Aldrich says. "As I just showed, the ability to provide research institutes like LJI with that information can mean the difference between life and death."

www.mycancerdb.com

Owned and operated by late-stage cancer patients Stephen Aldrich, Brad Power, Joerg Matthiessen, and Lorraine McClellan.

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From left to right: Judy and Tom Tullie, Dave and Brenda Rickey

Donors endow SPARK Program to fund innovative research by Institute's young scientists

Some of the most exciting and potentially life-saving immunology research never sees the light of day because it lies only in the imaginations of young scientists who have no path to develop their innovative ideas.

Two San Diego high tech executives with deep entrepreneurial experience are determined to provide that path. Tom Tullie and Dave Rickey, who worked together as chief operating officer and chairman/CEO, respectively, of Applied Micro Circuits Corporation, have made substantial donations to endow La Jolla Institute for Immunology's two-year old SPARK program over the next decade.

The Tullie and Rickey Families SPARK Awards for Innovation in Immunology provides flexible start-up funding so that young scientists just beginning their careers can launch their ideas and generate enough data to attract scientific grants, enabling them to take their projects to the next level.

Tullie says he and his wife, Judy, are thrilled to support a program they believe will lead to groundbreaking science.

"I've been an entrepreneur and involved in innovation my entire career, but this is the most exciting program I've seen because the ideas these young scientists have are not only fascinating, they have the potential to generate breakthrough discoveries that will someday save lives," says Tullie, who also serves on the Institute's board.

Each year, the SPARK program receives dozens of proposals from Institute scientists. A panel that includes Institute scientists, board members, and top business leaders reviews the proposals, selects the finalists, and has each of them present their projects in person. Four award winners are selected and each are provided $25,000 in start-up funding.

The projects now under way range from using nanoparticles to deliver cancer immunotherapy and developing a universal molecular diagnostic test for infectious diseases, to using pro/antibiotics to treat and cure allergies and targeting the microbiome to prevent the infection and chronic inflammation that cause cancer.

For the Rickeys, involvement in the SPARK program was spurred by the couple's belief in the Institute's mission itself.

"Brenda and I love the idea of 'life without disease' because so many of our friends and family have suffered or died from cancer, heart problems, dementia, and other ailments," Rickey says. "A lot of non-profits don't have clear goals, but the Institute's mission is concise while being extremely bold and ambitious. It may not be fully realized in our lifetime, but we believe with the amazing talent of their scientists, the Institute's mission is achievable."

Both Tullie and Rickey have helped attract other donors to join forces with them on SPARK, bringing the total amount of the fund to approximately $1 million.

"A lot of other young scientists have proposed really worthy projects that are potential home runs, but we just couldn't fund them all," Tullie says. "We are hoping others will join us and provide additional seed funding to advance some more of these promising ideas."

IN MEMORIAM

Teruko Ishizaka, M.D., Ph.D.

(1926 – 2019)

La Jolla Institute mourns the loss of Dr. Teruko Ishizaka, trailblazing female scientist and co-discoverer of a novel class of antibodies known as IgE. She died on June 4, 2019.

Born in Yamagata, Japan, in 1926, Teruko stayed deeply connected to her birth country throughout her life. Yet, she defied the cultural expectations of her era early on when she earned an M.D. at Tokyo Women's Medical University in 1949, the same year she married Kimishige Ishizaka and set her eyes on a career in research. She went on to earn a Ph.D. in medical science from University of Tokyo in 1957 and undertook postdoctoral training at the California Institute of Technology from 1957-1959.

Teruko Ishizaka arrived in La Jolla in 1989 to become a member and head of the Division of Allergy at the then brand-new Institute. She came here from the Johns Hopkins University School of Medicine with her husband Kimishige, who had just been named the Institute's first Scientific Director. Prior to joining LJI, both conducted immunology research as faculty members at Johns Hopkins University.

But the scientific discovery that defined their careers occurred well before that when Teruko, working with Kimishige as a research immunologist at Children's Asthma Research Institute and Hospital in Denver, co-discovered allergen-specific antibody proteins called immunoglobulin E (or IgE). The finding defined a new class of antibodies that trigger allergic reactions.

Later, the Ishizakas reported that IgE proteins provoke allergic responses by binding to mast cells, a type of white blood cell, prompting them to release histamine to cause the physiological symptoms associated with allergy. Now, routine blood tests used to validate an allergic response actually detect levels of IgE antibodies in response to a test stimulus.

After the discovery of IgE, Teruko conducted allergy-related research for the next 25 years, first in Denver and then at Hopkins, where she moved in 1970 and where she eventually became a full professor of Medicine and Microbiology in the medical school. Between 1953 and 1992—the period encompassing her career as a bench scientist—Teruko published over 100 papers and reviews on allergy-related topics, most co-authored with Kimishige. Even in retirement, the couple occasionally co-authored reviews of the history of IgE research and mast cell biology.

Teruko Ishizaka earned several prestigious scientific prizes for discovering IgE. Among them were the 1972 Passano Award and the 1973 Gairdner Foundation International Award; the 1985 American College of Physicians Award for Achievement in Medical Science; the Pioneer of Modern Allergy Award from the American College of Allergists in 1982; and a Scientific Achievement Award from the International Association of Allergy and Clinical Immunology in 1994. In 1990, she won the Behring Kitasato Prize for "The study of mast cells and elucidating the mechanism of allergy." She was the first woman scientist in Japan to be so honored.

When she retired from LJI in 1993 she continued to live in La Jolla until she and her husband returned home to Japan in 1996. There, they resided in Yamagata City, in northern Japan. At the time of her death she served as Member Emeritus in the LJI Division of Allergy.

"After retirement, Terry had two dreams," recalls Yuko Kawakami, a colleague and close friend of Teruko. "One was to return to Japan and live a happy life in her hometown of Yamagata, and the other was to go on a gourmet tour around the world with their first postdoc, Tomio Tada." Tada, who after training with the Ishizakas in Denver and becoming a prominent immunologist himself, was a colorful personality who later switched careers to become a playwright of traditional Japanese Noh dramas. Teruko evidently harbored a few out-of-the-box notions herself, having entered tango competitions in Argentina in her youth.

Half of her dreams came true. Sadly, the worldwide gourmet tour never came to pass. But Teruko and her husband did build a house with a gorgeous mountain view in the countryside outside Yamagata and were officially fêted by their community as "honorable residents of Yamagata prefecture."•

The image shows a partial, artistic interpretation of the IgE (immunoglobulin) antibody molecule, which was discovered by Dr. Teruko Ishizaka and her husband Kimishige in 1966.

IMMUNE MATTERS CONTRIBUTORS

Nick Abadilla
Amelia Aldrich
Ruben Diaz Avalos
Chris Benedict, Ph.D.
Matt Ellenbogen
Jenna Hambrick
Lisa Huppert
Gina Kirchweger, Ph.D.
Elise Lamar, Ph.D.
Melissa Jacobs
Madeline McCurry-Schmidt
Jenny Siegwart
Bob Ross

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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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