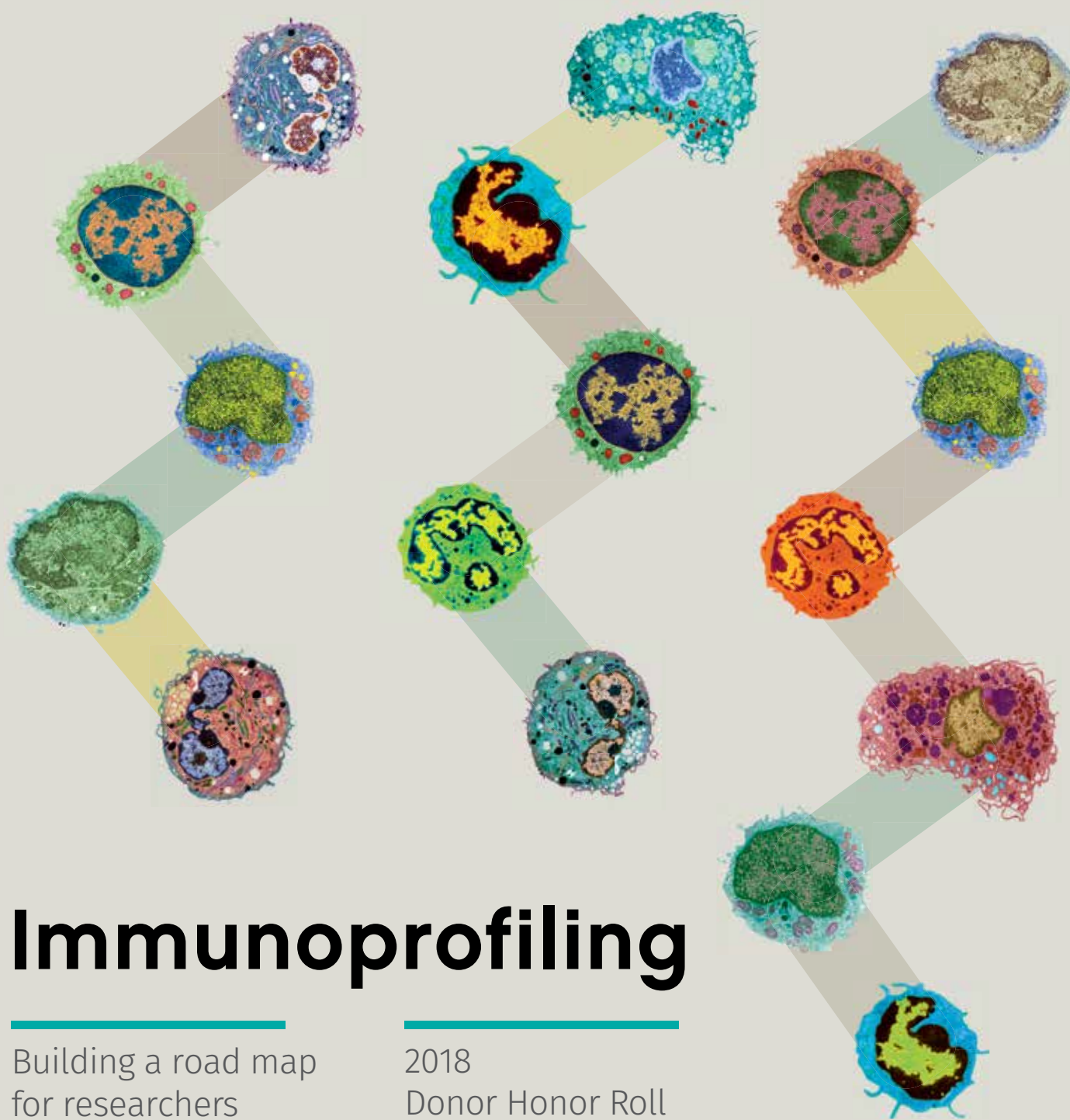


# Immune

FALL 2018

# MATTERS



## Immunoprofiling

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Building a road map  
for researchers

PAGE 4

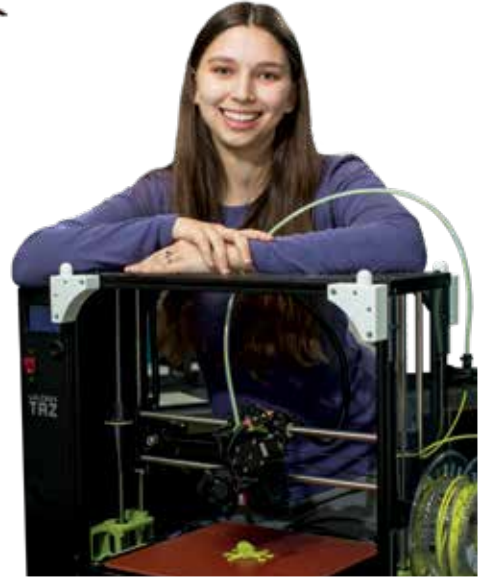
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2018  
Donor Honor Roll

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# Immune MATTERS

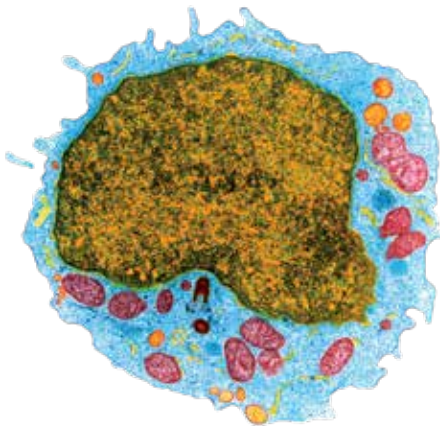
FALL 2018



 SPARK

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GIVING SOCIETY



## 4 ON THE COVER IMMUNOPROFILING

LJI scientists are building a road map for researchers worldwide probing the immune system's role in health and disease.

### IMMUNE MATTERS CONTRIBUTORS

Nick Abadilla  
Chris Benedict, Ph.D.  
Jenna Hambrick  
Lisa Huppert  
Gina Kirchweger, Ph.D.

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Bob Ross  
Stephen Wilson, Ph.D.

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## LETTER FROM THE PRESIDENT

In just the past few years, immunology and its importance to bioscience has broken into the public consciousness, thanks in part to remarkable advances in immunotherapy that have led to dramatically improved treatment—and in some cases cures—for cancer and other diseases.

At La Jolla Institute, we're excited immunology is making headlines and capturing the public's imagination. What we want people to know, however, is the recent successes are just the leading edge of a far bigger and even more thrilling story that promises to fundamentally transform human health in the coming years.

We've learned the power of the immune system extends far beyond its traditionally understood role of fighting infection. Through analysis at the atomic, protein, cellular, and most recently, genetic levels, we've discovered the immune system and inflammation play crucial roles in virtually all diseases, including triggering a number of serious autoimmune ailments.

That knowledge has put LJI's principal investigators on the precipice of a number of major breakthroughs, including novel immunotherapy treatments that train immune cells to attack multiple types of cancers; new types of vaccines to prevent heart disease, HIV, and the Zika virus; inflammation-inhibiting factors that improve asthma treatments; and understanding how T cells, rather than boosting immunity, actually mobilize inappropriately to exacerbate multiple sclerosis and other autoimmune diseases.

These breakthroughs would not have been possible without the highly sophisticated instrumentation LJI has invested in to provide our scientists with the latest technology to reveal the intricacies of the immune system. As you will read in our *Immune Matters* cover story, one of the most powerful is a suite of methods we are calling immunoprofiling. Institute researchers are creating detailed molecular profiles of the immune system in individuals that will provide a detailed and customized roadmap for diagnosis and treatment of diseases.

Our own innovative staff has created some of LJI's most effective scientific tools. Sara McArdle, Ph.D., who you'll read about in our "Up and Coming" feature, found a solution to the problem of keeping pulsating mouse coronary arteries in focus by creating a unique software program that keeps the images sharp by synchronizing the frequency of image captures through the microscope with the mouse's heartbeat.



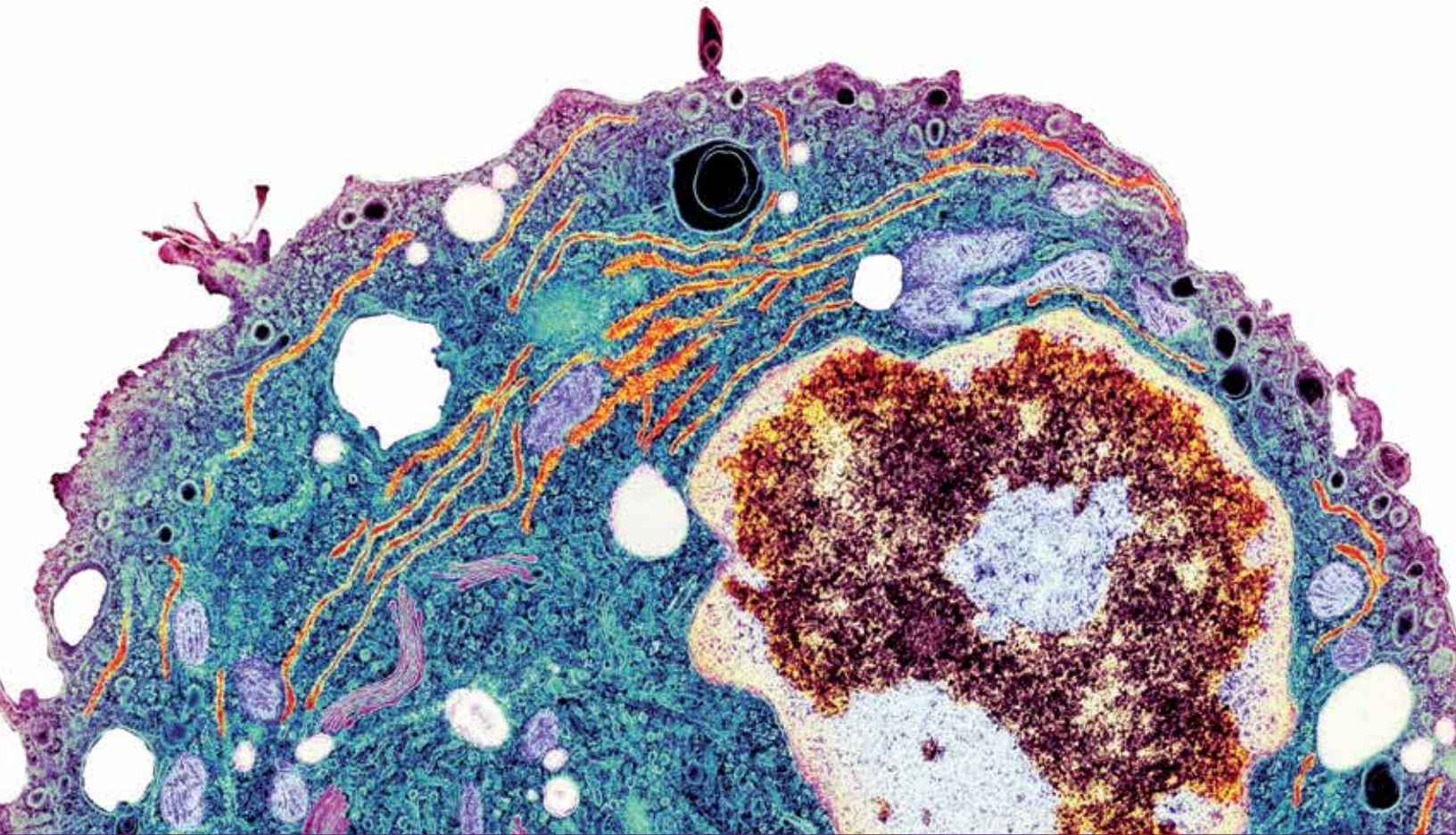
In this issue you'll learn about three outstanding new members of LJI's Board of Directors: Lynda Stuart, M.D., Ph.D., is a Deputy Director at the Bill & Melinda Gates Foundation and an internationally recognized immunology researcher; Mitsuo Satoh, Ph.D., is Executive Officer, Vice President Head of Research and Development for the global specialty pharmaceutical company Kyowa Hakko Kirin Co., Ltd.; and Sandor W. Shapery, J.D., is one of San Diego's most respected real estate developers and business leaders.

One of the benefits of increased awareness of LJI and the rapidly expanding role of immunology is that our work inspires donors to contribute to our work. As you'll read in our donor profile, LJI contributor Bridget Cresto was motivated by the death of her husband from cancer to find an organization she believes can help save others.

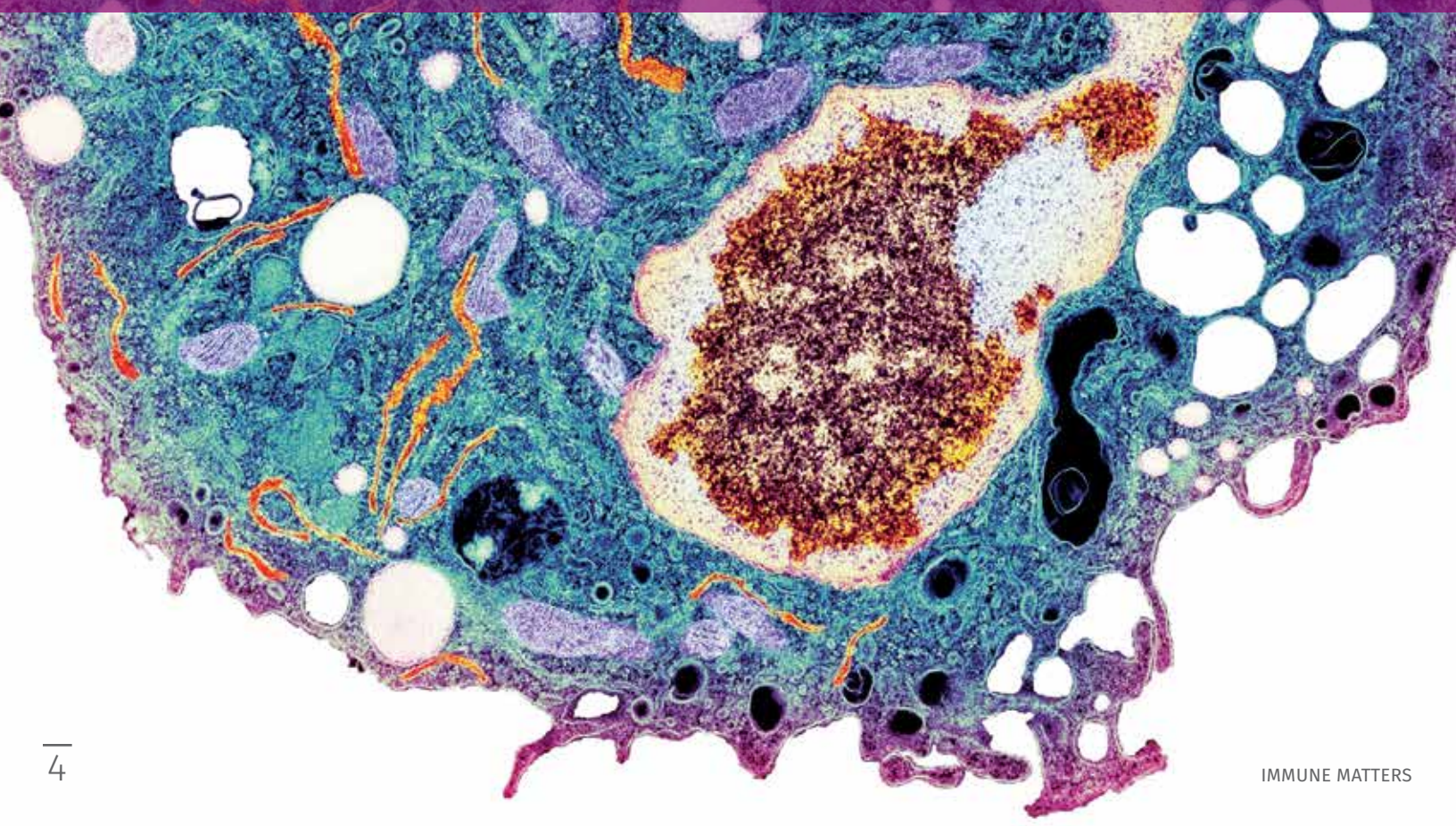
As always, La Jolla Institute appreciates all of our wonderful partners—including individual donors, foundations, and federal funding sources—who play such a crucial role in supporting research we believe is leading us closer to achieving our mission of *Life Without Disease*®.

Sincerely,

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



# Immunoprofiling



Billions of highly diverse and specialized immune cells work together to keep us healthy. LJI scientists are deciphering the molecular code that defines who these cells are and how they interact with each other, ushering in a new era of high-resolution immunoprofiling.

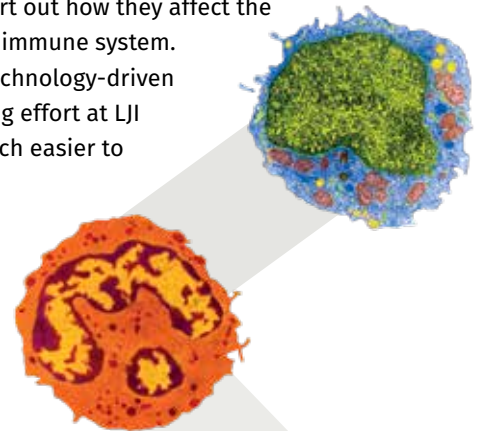
The composition of the immune system varies not just from person to person, but over time—shifting as our health changes, as we encounter different viruses and bacteria, and as we age. Within that variability lie important clues to improving human health: The presence or absence of certain cells may hint at whether a person is at risk for heart disease, tell us how someone is likely to respond to an influenza vaccine, or suggest whether a new immunotherapy is the best way to treat their cancer.

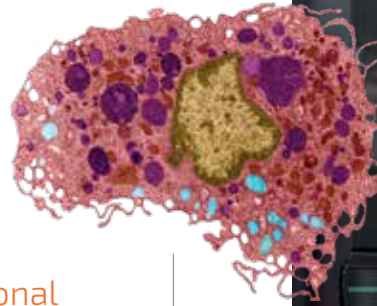
For now, many of those clues remain concealed within the immune system's staggering complexity, but LJI researchers are accelerating the search. They are creating detailed profiles of the immune system, breaking it down into its constituent parts and examining its cells' molecular makeup in health and disease. They are mapping out the genetic factors that drive the immune system's variability and finding out which kinds of cells control infections and which ones fail. The knowledge they are uncovering is forming a roadmap for researchers worldwide probing the immune system's role in disease.

These immunoprofiling efforts are already generating vast amounts of data that will elucidate how the immune system impacts our health. "This isn't just an interesting discovery tool, this is something that can educate people who are treating disease," says LJI Executive Vice President and Chief Operating Officer Stephen Wilson, Ph.D. "It both powers your diagnostic capabilities and functions as a compass that points to places where you can intervene therapeutically."

One of LJI's major immunoprofiling projects is a deep analysis of 15 different types of immune cells led by Pandurangan Vijayanand, M.D., Ph.D., an Associate Professor in the Division of Vaccine Discovery. Dr. Vijayanand and his team are creating detailed molecular profiles of these cell types as they are found in each of 100 healthy volunteers. The resource will be so vital to the research community that the National Institutes of Health is supporting its development with a \$4 million grant.

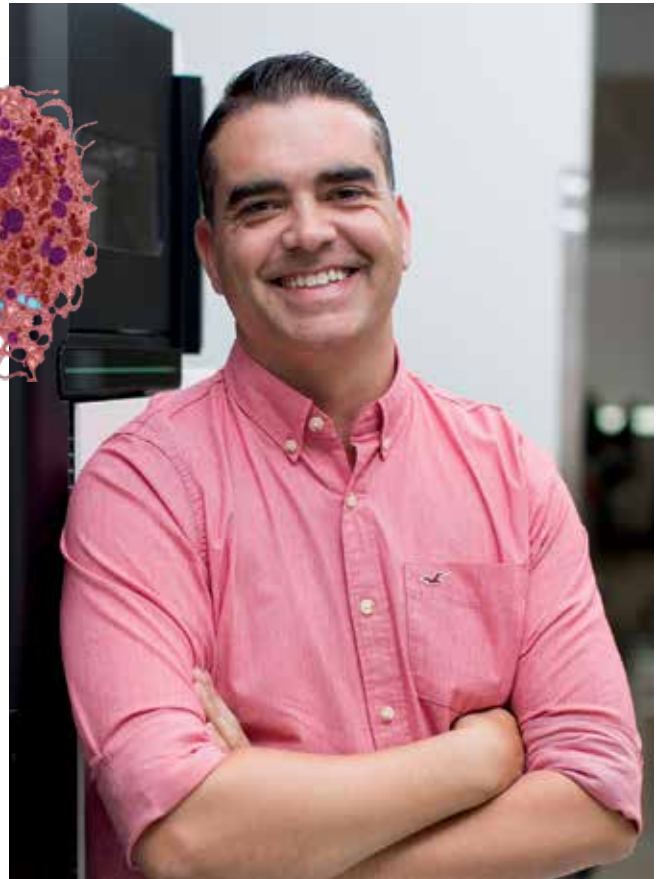
The team's goal is to examine the consequences of genetic differences on the immune system and learn how that variability impacts our susceptibility to a range of diseases, from asthma and cancer to autoimmune disorders and infectious diseases. Genetic studies have tied specific variations in the genome to all of these conditions. Most occur in the largely uncharted DNA between genes, where subtle sequence variations can have profound effects on when, where, and how strongly genes are switched on. Without the kind of high-resolution immunoprofiling taking place at LJI, most of these disease-associated genetic factors would remain mysterious: Scientists wouldn't know which genes they affect or in which cell types they matter, making it difficult to sort out how they affect the function of the immune system. The massive, technology-driven immunoprofiling effort at LJI will make it much easier to





“Every immune cell is classified as a functional subtype and at the same time can display a unique set of super-specialized features.”

– Greg Seumoio, Ph.D.



Dr. Greg Seumoio

interpret these genetic clues and bridge the gap to clinical advances.

Dr. Vijayanand and his team are essentially creating an atlas that will lay out, for every cell type, which genes are affected by specific genetic variants. To do that, they have worked with LJI’s core facilities to measure the activity of every gene in each of the 15 cell types, for each of the 100 donated samples. Now, adding an additional layer of information, the team is mapping exactly where activity-modulating marks called histone modifications dot the genome in each cell type. That will help them to determine which genes are under the influence of each histone marker, and might hint at ways to modify gene activity to treat disease.

Sorting 15 different types of cells out of each donor’s blood sample and analyzing them individually is an ambitious undertaking, but an essential one. For many years, researchers studied the immune system as if all of its parts behaved the same—but we know now that it is characterized by layer upon layer of complexity. “Every immune cell is classified as a functional subtype and at the same time can display a unique set of super-specialized features,” says Greg Seumoio, Ph.D., who

directs LJI’s sequencing core facility and has overseen all the sequencing for the project. Consequently, a lot of information is lost when mixed populations of cells are analyzed together.

This multilayered profiling is generating a staggering amount of data, and making sense of it all requires both computational expertise and deep knowledge of the immune system. That analysis, led by computational biologist Bjoern Peters, Ph.D., also a Professor in the Vaccine Discovery Division, is already paying off, revealing key distinctions between cell types and pointing the team to genes worthy of deeper investigation. Genetic variation impacts the activity of about 10,000 of the 22,000 genes that are switched on in immune cells, the team has found—but about half of these are affected in just one of the 15 cell types.

It’s been gratifying to find so many variations between cell types, says postdoctoral researcher Benjamin Schmiedel, Ph.D., who is managing the project. “It kind of makes me wonder how little details here and there can cause so much trouble, ending up in autoimmune disease or allergies or cancer. It’s exciting to have a look at these data now and dig through it.”



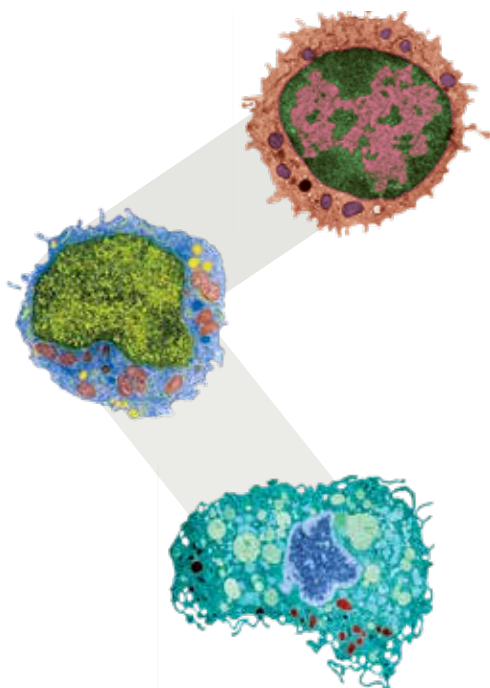
## Immunoprofiling in cancer

Cancer immunotherapies empower patients' own immune systems to fight tumors, but so far, these treatments don't work for everybody. Immune profiling could be an effective way to identify the best candidates for the treatment. Researchers in Dr. Catherine Hedrick's lab in the Laboratory of Inflammation Biology examined a group of immune cells known as myeloid cells in patients with non-small cell lung cancer, characterizing the cells according to the presence of 40 different surface markers. After donating blood for the analysis, all patients received immunotherapy designed to release the brakes on their immune systems by targeting a protein called PD-1. The team's analysis found one cell type whose presence was a reliable indicator of patients' response to the treatment. "It seems that this monocyte subset is associated with a healthy immune system and predicts whether a patient can mount a robust antitumor immune response," says Claire Olingy, Ph.D., a postdoctoral researcher in Dr. Hedrick's lab who led the study. "We may be able to predict this response before the patient ever starts immunotherapy and save valuable time for patients who wouldn't see a benefit." •

With gene activity profiles complete for the first 15 cell types, the team is already expanding the scope of their project—returning to the frozen stocks prepared from the blood samples to analyze additional cell types and test how cells' gene activity changes under different conditions. They're also starting to follow up on leads that have emerged from their data—testing the function of genes whose activity patterns sparked their curiosity or suggested a role in disease.

But they have uncovered such a wealth of information, it's going to require a lot of people with a wide range of expertise to take advantage of it all. "We are generating a huge resource that the entire world will have access to. The challenge is to try to make sense of all this information. Understanding the basic biological processes will ultimately help us to find a cure for disease," says Dr. Seumois.

All of the cell profiles are freely available to the research community, and word of the resource is beginning to spread. Dr. Schmiedel says when he first tells people about the project they are impressed by the sheer volume of data LJI has produced—and then they quickly begin seeking specific information about the genes or



diseases they study in their own labs. That's exactly what the team had hoped. Ultimately, the data will be accessible through an interactive database that Dr. Peters is developing so users can easily search by gene or cell type. "We'll give people this information and they can take it from there," Schmiedel says.

While Dr. Vijayanand's team profiles the cells of healthy individuals, LJI researchers are also taking a similarly comprehensive approach to figuring out which features of the immune system are critical for protecting the body against specific pathogens. Since 2014, teams led by Dr. Peters and Alessandro Sette, Dr. Biol. Sci., head of the Division of Vaccine Discovery, have been focusing on two pathogens that have major impacts on global health: the mosquito-borne dengue virus and *Mycobacterium tuberculosis*.

Hundreds of millions of people are infected by dengue and tuberculosis every year. Drs. Sette and Peters want to know what's different about the immune systems of people who control these infections compared to those for whom the same microbes cause life-threatening illness. As one of eight centers collaborating to characterize the immune system through the nationwide Human Immunology Project Consortium (HIPC), LJI has received \$18 million of support from the National Institute of Allergy and Infectious Disease to find out.

The strategy for these teams is to first isolate the subsets of T cells that recognize dengue and tuberculosis from the blood of people who have been exposed, either through vaccination or natural infection. Then they create detailed



Dr. Benjamin Schmiedel (front) and Dr. Pandurangan Vijayanand

profiles of those cells, comprehensively surveying their gene activity and determining whether key protein markers are present on their surfaces.

"From all the T cells in the body, we are pulling out those that have actually been in contact with the bacterium or virus," Dr. Peters says. "That allows us to detect signals and differences that you often lose if you look at whole T cell populations or whole blood, because the important cells are very few."

Then they sift through the data, comparing the immune responses of various groups. What's different about dengue-detecting T cells in people who develop natural immunity to the virus after a few infections, as compared to people whose infection leads to hemorrhagic fever, the



severe form of the disease, for example? As these analyses begin to reveal the hallmarks of effective immune responses, that information will guide the development and testing of new vaccines.

Defining the features of a healthy immune response might also allow clinicians to predict the outcome of an individual patient's infection—and manage their condition accordingly. One quarter of the people in the world are infected with tuberculosis, and 5 to 10 percent will become sick if they are left untreated. In others, the infection will remain latent. "If you could pick up the people who are at risk of getting really sick and spreading the disease, you could treat those before they develop active disease, then you could really get rid of it at the population level," Dr. Peters says. "That would be a massive public health breakthrough."

Blood samples for the dengue and tuberculosis projects come to LJI from around the world, and since 2014, LJI's sequencing core facility has analyzed more than 4,000 of them. It's important that diverse groups of people are represented in the analysis because so many factors influence the makeup and effectiveness of the immune system. Some subsets of T cells may be well equipped to fight strains of tuberculosis that are prevalent in Nicaragua, for example, but do little to protect someone who becomes infected in Sweden. "We want to make sure what we see is reproducible in different geographical locations, because we don't want to make a vaccine that works only in South America but not in Africa or vice versa," Dr. Sette says.

As with the profiles of healthy immune systems, the biggest challenge these teams face may be taking advantage of all the data they are producing. "It's really a flood," Dr. Peters says. "Right now, we have too many interesting things to follow up on." But here too, data sharing is a priority, and the knowledge coming out of LJI will spur progress in labs around the world.

LJI researchers hope their pioneering efforts will spur more immunoprofiling, too. With the immune system's almost infinite complexity, there will always be another cell type or infection or condition to explore. But as these efforts continue, we're gaining a clearer picture of this vast network, and giving researchers who haven't thought deeply about the immune system's intricacies new tools to unravel how it protects our health. •

"We want to make sure what we see is reproducible in different geographical locations, because we don't want to make a vaccine that works only in South America but not in Africa or vice versa."

– Alessandro Sette, Dr. Biol. Sci.

Dr. Alessandro Sette (left) and Dr. Bjoern Peters





Matthias von Herrath,  
M.D.

QRA

## Considered the top type 1 diabetes expert in the world, Matthias von Herrath, M.D., feels equally at home in academia and big pharma.

When Novo Nordisk, a global pharmaceutical company headquartered in Denmark and best known for its diabetes products, wanted to reinvigorate its type 1 diabetes (T1D) research program, it looked no further than La Jolla Institute (LJI). It was the work of LJI Professor Dr. Matthias von Herrath that had caught their attention. A latecomer to biomedical research, the trained virologist was running an innovative and world-renowned research program on the pathology of type 1 and type 2 diabetes as part of the national Pancreatic Organ Donor network (nPOD). Dr. von Herrath accepted Novo Nordisk's offer to head up the company's new T1D research center in Seattle on one condition: He would keep his lab at LJI. Realizing the potential benefits of having closer interactions with a big pharma company, LJI agreed to the joint appointment, which is atypical in academic organizations.

Born and raised in Germany, Dr. von Herrath received his M.D. from the University of Freiburg and spent several years working in infectious diseases, internal medicine, and intensive care before his passion for bench research brought him to San Diego. Inspired by his patients, many of whom struggled with type 1 diabetes, Dr. von Herrath founded the Center for Type 1 Diabetes at La Jolla Institute and began studying the causes of the disease. "I got into type 1 diabetes research because I really thought it might be a problem that we can tackle in our lifetime," he says.

### **What made the job offer from Novo Nordisk so appealing?**

I always wanted to have an effective arm to get new treatments into the clinic. Clinical trials for type 1 diabetes are very expensive because of patient heterogeneity.

### **Can you explain?**

The disease progresses at different speeds in different people and because of that the trials have to be bigger, which makes them very expensive. Going into big pharma was very purpose-driven with the main goal of catalyzing large clinical investigations and helping to develop new treatments.

### **Why did you decide to keep your lab at LJI?**

You just cannot make drugs without a solid mechanistic and pathological understanding of the disease at hand. The fundamental research we do at LJI—trying to understand the pathology of type 1 and to a certain extent type 2 diabetes—lays the foundation for better therapeutics, which is super important. Without this basic, mechanistic research we would choose poor drug targets.

### **What's the current thinking on the cause or causes of T1D?**

We know that many different genes contribute to the disease but, in addition to the genetic predisposition, there's a very strong environmental component.



### **What is known about the environmental factors that contribute to T1D?**

This is a very complex area and we don't know enough to even begin to pinpoint what the cause may be. The environment probably works via the immune system and it is something we are working on quite extensively here at LJI. Ultimately, the immune system attacks and destroys beta cells and that's why we ask what influences the visibility of the beta cell to the immune system. But we still don't know why the immune system starts seeing beta cells.

### **Are there any clues as to what might be going on?**

For one, there's evidence that the response to viral infections may be altered in the islets of Langerhans, which are tiny clusters of cells scattered throughout the pancreas that contain the insulin-producing beta cells. It seems islet cells are hyper responsive. Understanding why would help us a great deal. It would also mean that it is not one particular virus but that it is a more general way of how beta cells as an organ respond to viruses in type 1 diabetes.

### **Are there any other factors?**

There is also heterogeneity across the pancreas, which means that not all islets are affected the same way. That may have to do with the innervation of single islets, which signals the immune system some form of stress and that's why certain areas of the pancreas become a target of the immune system.

### **How did becoming a member of the nPOD consortium impact your research?**

Without the pancreatic organ donor consortium we wouldn't be doing what we are doing. We were one of the first labs to use this incredible resource and it allowed me to switch the whole lab around to studying clinical pathology in humans, which is fundamental to understanding what's actually happening in patients. Novo Nordisk acknowledged that this is really important work and agreed to let me continue basic research at LJI.

### **Between two jobs and a family, how do you find time to unwind?**

I play violin. It puts good colors into my head and makes me feel relaxed.

### **Wait, what?**

I see colors when I play music and every key has a different color. It's called synesthesia. Playing music completely changes my mindset, it balances me, and keeps me sane. Riding my bike does the same thing. Usually, when I am done with my Novo Nordisk responsibilities in the morning—the headquarters are in Copenhagen and there is a nine-hour time difference—I take a bike ride or play some violin and then come to La Jolla Institute. That way I have a clear break in between and can refocus my mind on something else.

### **Many scientists are also accomplished musicians. Is there a connection?**

That's an interesting question but I don't have a good answer. Both are creative endeavors but certain forms of music like playing in a band are more fun because you can write your own music and then see the sound coming together. When I play the violin I also like to put my own interpretation on pieces and that's why I never enjoyed playing in an orchestra. I couldn't express myself.

### **Have you ever considered becoming a professional musician?**

As a teenager I thought about playing the violin professionally but quickly realized I wasn't going to hack it. Mostly because Anne-Sophie Mutter was born the day before I was born. We are from the same area, Germany's Black Forest, and at the time she was very visible in Southern Germany. When she started recording with Herbert von Karajan and the Berlin Philharmonic I knew it wouldn't work. I also played guitar for a very long time because I thought there was more creative freedom. I came to the U.S. after working in intensive care oncology for several years for two reasons: To do research and to see what I could do with music. After one year we had a record offer from Arista Records and that's as far as we pushed it. ●

# Lighting Sparks

When the inaugural SPARK campaign launched late last year two calls went out: one to young La Jolla Institute (LJI) researchers asking for their boldest ideas and the other to the community to help get the most innovative research projects off the ground. Scientists and supporters alike responded with great enthusiasm and proposals and funds poured in. After several Shark Tank-like pitching sessions, the list of projects had been whittled down and enough funds had accumulated to provide each of the eight top finalists—twice as many as originally hoped—with \$25,000 in flexible start-up funding. ✨

Below is a roundup of the winning research projects from the 2017 SPARK campaign:



Dr. Nadine Hartmann

## Can the environment give you cancer?

**Nadine Hartmann, Ph.D. & Angeliki Tsangaratou, Ph.D.**

Humans with a defect in a gene known as TET2 have an increased risk of developing acute myeloid leukemia. Interestingly, mice with the same defect can be either healthy or develop myeloid tumors depending on the environment they are kept in. As part of their SPARK project, Drs. Hartmann and Tsangaratou sequenced the microbiome of normal mice and mice lacking TET2 (tet2KO). Compared to normal mice, mutated mice seem to have reduced microbiome diversity. In a next step, the researchers will compare the microbiomes of healthy and sick tet2KO mice to determine the influence of the environment on their susceptibility to disease.

## Nanoparticles to deliver cancer immunotherapy

**Yuan Lin, Ph.D.**

Tumors use molecular signals to hide from the immune system and recent cancer immunotherapies yank away the tumor cells' "invisibility cloak." However, one of the protective molecules deployed by tumors accumulates in such high concentrations that it renders traditional immunotherapy ineffective. To overcome that hurdle, Dr. Lin is using specially designed nanoparticles to deliver specific inhibitors directly into tumors. The data collected so far show that the nanoparticles reach cancer cells, deliver their payload, and effectively shrink the targeted tumors.





## New immune cells in atherosclerosis

**Holger Winkels, Ph.D.**

The main driver of heart disease—the leading cause of death worldwide—is atherosclerosis, the build-up of plaques in arteries. Since arterial plaque build-up is initiated and perpetuated by immune cells accumulating at sites of vessel tissue damage, Dr. Winkels studies the role of immune cells in atherosclerotic plaques. Unexpectedly, his experiments turned up hitherto unknown immune cells that seem to be involved in the development of atherosclerosis. He is now defining their role further, hoping to open up new therapeutic avenues.

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## Pro/antibiotics to cure allergy

**Rana Herro, Ph.D.**

The human microbiome is closely tied to our overall health. Not surprisingly, an altered microbiome has been linked to chronic inflammatory diseases including allergies. Dr. Herro has sampled the microbiomes of allergic patients as well as mice prone to house dust allergies. Once she receives the microbiome sequences from both the human and mouse studies, she hopes to be able to define an “allergic microbial signature.” She believes that depending on the signature, antibiotics or probiotics could be used to restore a healthy microbiome and thus hopefully cure allergies.

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## The battle against Strep pneumonia

**Catherine Crosby, Ph.D.**

Despite available vaccines, *Streptococcus pneumoniae*, the most common cause of community-acquired pneumonia and meningitis in the elderly, remains a serious threat. Dr. Crosby is observing immune cells in real time as they fight off *S. pneumoniae* infection in the lung. So far, she has found that several different cell types take up the bacteria and that one of them—a special kind of dendritic cell—clusters together with bacteria around the major airways in the lungs. This suggests that this particular cell type plays an important role in the protection against *S. pneumoniae*. Dr. Crosby is now exploring her observation further.

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## Predicting dengue disease severity

**Daniela Weiskopf, Ph.D.**

A small percentage of the roughly 390 million people infected each year with dengue virus develops life-threatening dengue hemorrhagic fever. Dr. Weiskopf has identified a handful of genes, whose activity correlates with disease severity. She is now working on a simple diagnostic test that can quickly identify patients who are most likely to come down with severe disease to ensure they receive adequate care early on.



## Flaviviral infections in Nepal

**Melanie McCauley, M.D.**

*Aedes aegypti* and *Aedes albopictus*, the main mosquito species that transmit dengue and the closely related Zika virus, are quickly spreading from tropical to temperate zones and with them the viruses they carry. Tropical disease specialist Dr. McCauley is exploring how climatic shift impacts mosquito-virus interactions and how pre-existing immunity to other viruses of the same virus family effects dengue severity. During the height of mosquito season, Dr. McCauley will collect blood samples in Nepal, which provides an ideal natural laboratory to study the implications of the rapid spread of dengue virus and its kin because of the geographical proximity of the country's tropical plains region with the temperate foothills of the Himalayas.

## Predicting patient responses to cancer immunotherapy

**Ian T. Mathews, Ph.D.**

Despite astounding successes, cancer immunotherapy currently only works in some patients. Also, once unleashed, the immune system can cause severe immune-related side effects. Dr. Mathews is developing a simple blood test based on small molecules that can predict who will respond favorably and who is at risk of potentially life-threatening adverse effects. His early results are already pointing to promising new biomarkers of severe immune-related side effects, as well as molecules that could protect against these dangerous forms of autoimmunity.



To find out more about the SPARK program and how you can help 2018 SPARK Program finalists put bold ideas into action visit [lji.org/SPARK](http://lji.org/SPARK). ✨



Sara  
McArdle, Ph.D.



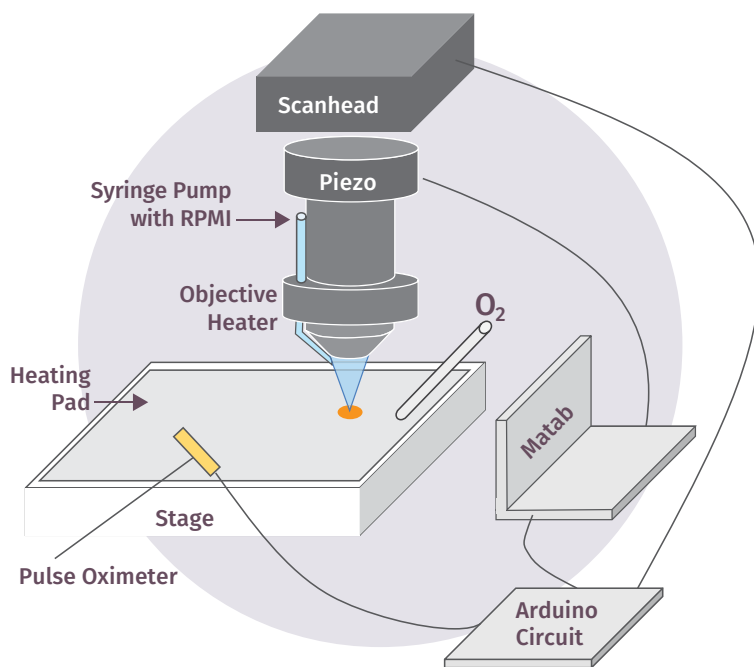
# The Art of Tinkering

When the first prototype designed to follow immune cells in the arteries of living mice failed, Sara McArdle, Ph.D., nabbed a handful of coffee stirrers at a nearby coffee shop and started tinkering. “Constructing with the little wooden sticks helped me think through the problem and figure out the solution,” says Dr. McArdle, a microscopy specialist in La Jolla Institute’s (LJI) imaging core.

Trained as a medical bioengineer, Dr. McArdle feels most at home at the intersection of biomedical research and technology. It satisfies her desire to make an impact on people’s lives while taking comfort in the predictability of engineering. “There aren’t biological laws in the way that there are mathematical laws or physical laws,” she says. “A computer does exactly what you tell it to and if something doesn’t work you told it the wrong thing. But it also means you can fix it.”

Cue the coffee stirrers. After rethinking her first attempt, Dr. McArdle, then a graduate student in the lab of LJI Professor Klaus Ley, M.D., ended up building a device that combined circuits and programming software to synchronize the image frequency of a high-tech microscope with a mouse’s heart beat.

“A big part of atherosclerosis research looks at blood flow and how it influences what’s going on in the blood vessel,” says Dr. McArdle. “The big complication is that some of the large arteries, the kind that are affected by atherosclerosis, move with every pulse, which makes it really hard to keep things in focus.” All of a sudden, Dr. McArdle’s cleverly designed contraption allowed scientists for the first time to catch a glimpse of immune



cells weaving in and out of arterial plaques. “It was a really cool project that changed how we look at the role of the immune system in cardiovascular disease,” she says.

It also changed Dr. McArdle’s career trajectory. “I realized that I didn’t want to follow the standard academic track,” she says. “I love being in the lab and developing new tools.” Since Dr. McArdle already spent most of her time in the imaging core, it was only natural that she would move there permanently.

Today, she works as a microscopy specialist in the imaging core and regularly does deep dives into the newest imaging technologies to push the limits of what scientists can see. “Once you realize how major things can change, it changes the way you think,” Dr. McArdle says. “Suddenly, you don’t just think about how to adjust the project to fit the resources. Instead you think about the resources we need to fit the project.”

In her spare time, Dr. McArdle likes to bake and is widely known for her deliciously chewy chocolate chip cookies. Whether she likes to tinker with cookie recipes as well, she wouldn’t say. •

## La Jolla Institute Board of Directors elects three new members

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A global health leader, the head of research and development for an international specialty pharmaceutical company, and a leading real estate developer have been elected to the La Jolla Institute for Allergy and Immunology Board of Directors.

Joining the Institute board are Lynda Stuart, M.D., Ph.D., Deputy Director at the Bill & Melinda Gates Foundation and an internationally recognized immunology researcher; Mitsuo Satoh, Ph.D., Executive Officer, Vice President Head of Research and Development for the global specialty pharmaceutical company Kyowa Hakko Kirin Co., Ltd.; and Sandor W. Shapery, J.D., one of San Diego's most respected real estate developers and business leaders.

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**“We are pleased to welcome Dr. Stuart, Dr. Satoh and Sandy Shapery to the Institute Board. They are all recognized as outstanding leaders in their respective fields and their vast experience and interest and commitment to advancing immunology research will make them extremely valuable members of our board.”**

**– Mitchell Kronenberg, Ph.D.**  
La Jolla Institute President and Chief Scientific Officer



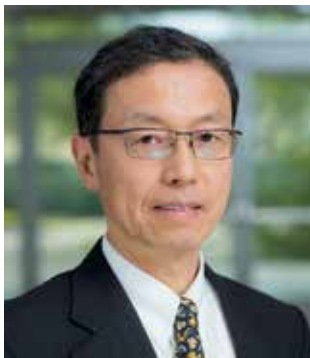
### **Sandor Shapery, J.D.**

Shapery is the founder of San Diego-based Shapery Enterprises, a real estate holding company involved in the ownership, design, and development of high-rise office buildings, high-rise hotels, commercial centers, and raw land. Emerald Plaza, which he developed on West Broadway in the early 1990s, was architecturally innovative with its futuristic, multi-tower hexagonal design.

Born in Chicago, Shapery moved in 1947 with his family to San Diego where his father took over a wholesale food distributorship. He graduated from San Diego State University with a degree in political science and earned his J.D. cum laude from the University of San Diego School of Law. Shapery worked as a law clerk with famed attorney Melvin Belli and later argued a case before the U.S. Supreme Court.

On the technology side, Shapery designed a vertical takeoff aircraft engine system that he developed with the help of a NASA grant. More recently, through his Transportation Systems Corporation, Shapery is developing advanced transportation infrastructure technology, including zero emissions induction-powered rail and magnetic levitation trains capable of traveling 300 miles an hour on existing railroad platforms. One of his patents has been licensed to the Elon Musk-designed Hyperloop transportation project.

“I’m thrilled to become involved with the Institute because I believe immunology is now at the absolute forefront of humankind’s ability to treat and prevent disease,” said Shapery.



### Mitsuo Satoh, Ph.D.

Dr. Satoh is a much-honored scientist and one of the leading pharmaceutical research scientists in the world. His company's American subsidiary, Kyowa Hakko Kirin California, Inc., and La Jolla Institute have been longtime industry and research partners whose collaboration has led to pharmaceutical translation of many of the Institute's promising discoveries into new treatments for disease.

"I am very proud of the successful partnership between Kyowa Hakko Kirin and La Jolla Institute and look forward to working with the tremendously gifted and pioneering scientists at the Institute," said Dr. Satoh. "The engrained culture of innovation creates important opportunities to improve people's health around the globe."

Dr. Satoh, who assumed his current position at Kyowa Hakko Kirin in March of 2017, began his scientific career with the Japanese company in 1987. In 1996, he became a visiting scientist at the Texas Medical Center where he studied chromosome engineering and subsequently contributed to the development of Potelligent® Technology after returning to Japan. Dr. Satoh was involved in glyco-engineered biological pipeline developments, including Mogamulizumab, Benralizumab, and Acoalan.

Dr. Satoh holds a Master of Pharmacy and Ph.D. from Hokkaido University. Dr. Satoh received the Kei Arima Memorial Award from the Japan Bioindustry Association in 2005 and the 62nd Okochi Memorial Technology Prize from The Okochi Memorial Foundation in 2016.



### Lynda Stuart, M.D., Ph.D.

Dr. Stuart, who was born in Jamaica and raised in the United Kingdom, received a BA in Medicine and her M.D. from the University of Cambridge and the University of London. She subsequently received training as a nephrologist and practiced for 10 years. She acquired a Ph.D. in Microbiological Sciences and Immunology from the University of Edinburgh. In 2003, Dr. Stuart moved to the United States to join the faculty of Harvard Medical School and Massachusetts General Hospital.

In 2016, Dr. Stuart joined the foundation, where she leads the Vaccine and Host Pathogen Biology domain of Discovery and Translational Sciences. The group works across all infectious diseases of interest to the foundation and sponsors novel approaches that accelerate the discovery, development, and translation of new passive and active immunization for targeted diseases. Dr. Stuart is also an affiliate professor with the Benaroya Research Institute at Virginia Mason.

"My love of science and commitment to discovery is identical to the passion and dedication the remarkable scientists at La Jolla Institute have for advancing immunology to a point where it very soon will have a profound impact on health around the world," Dr. Stuart said. "Immunology-based organizations like La Jolla Institute are on the threshold of developing some of the most effective treatments, if not actual cures, in medical history."



### HUGO SEPÚLVEDA NAMED PEW LATIN AMERICAN FELLOW

In recognition of his innovative research, postdoctoral researcher Hugo Sepúlveda, Ph.D., has been named a 2018 Pew Latin American Fellow. Only one of 10 awardees, Sepúlveda will receive two years of funding to probe how regulatory proteins called TETs that modify DNA influence the formation of specialized cell types and how dysregulation of their activity is involved in cancer. A better understanding of how TET proteins control cell proliferation and cell fate could provide new targets for the treatment of cancer and help advance stem cell therapies.

After the fellowship ends, Pew provides additional funding to awardees who return to Latin America to launch their own labs. “We’re delighted to help these outstanding researchers secure training and mentorship in some of the world’s leading laboratories,” said Rebecca W. Rimel, Pew’s President and CEO. “They make up an exemplary group committed to building biomedical expertise in Latin America and advancing human health around the globe.”

### MALLORY PAYNICH NAMED TO AAI PUBLIC POLICY FELLOWS PROGRAM

Postdoctoral fellow Mallory Paynich, Ph.D., was named a Public Policy Fellow by the American Association of Immunologists (AAI). The goal of the program is to engage postdoctoral fellows and junior scientists in public policy activities that have an impact on biomedical research. During her one-year term as a fellow, Dr. Paynich will have the opportunity to visit Capitol Hill and to delve more deeply into key issues related to biomedical research through the AAI public affairs program.

“As young scientists we must learn how to advocate for science education and continued investment in biomedical research, and it is our responsibility to inform the public of the crucial benefits of this research,” Dr. Paynich said. “I look forward to this experience with AAI to gain insight on issues pertaining to biomedical research and communication among scientists, politicians, and the public.”



### LA JOLLA INSTITUTE HONORED BY JUVENILE DIABETES RESEARCH FOUNDATION

La Jolla Institute for Allergy and Immunology (LJI) was honored for its outstanding diabetes research at this year’s JDRF Promise Ball. The annual event raises awareness and funds for type 1 diabetes (T1D) research and celebrates the progress JDRF is making toward finding a cure for T1D. LJI and JDRF share a long and successful history. JDRF has been a loyal supporter of T1D research in the lab of LJI professor Matthias von Herrath, M.D., who directs LJI’s Type 1 Diabetes Center (see Q&A, page 10). For many years, LJI has hosted the local JDRF chapter’s annual “Meet the Scientists” Day, where several hundred guests, including children with T1D and their parents, get to meet scientists in their natural laboratory habitat and learn more about the latest T1D research at LJI and elsewhere.



## Kimishige Ishizaka, Ph.D. (1925 - 2018)

**La Jolla Institute (LJI) mourns the loss of Dr. Kimishige Ishizaka, who led the nascent Institute through its formative years and left an indelible stamp on its culture. He died on July 6 in Yamagata City, Japan.**

"Dr. Ishizaka was a true founding father of our Institute," said LJI President and Chief Scientific Officer Mitchell Kronenberg, Ph.D. "As our first scientific director and later as president, he instituted a culture of collaboration and caring, while promoting innovative, high quality research."

Known as "Kimi" to colleagues, Dr. Ishizaka was already famous for his discovery of a novel class of antibodies when he moved to La Jolla in 1989 to accept the position of scientific director at the newly founded Institute. Courted by the Kirin Brewing Company and Dr. Makoto Nonaka to guide the immunology research center it was building on Torrey Pines Mesa, Dr. Ishizaka arrived from Johns Hopkins University School of Medicine with his wife Teruko, an accomplished scientist in her own right.

In 1962, Dr. Ishizaka and Teruko, already partners in marriage and science, came to the U.S. from Japan to do immunology research at the Children's Asthma Research Institute and Hospital. There, in 1966 they co-authored a paper in the *Journal of Immunology* that unveiled a brand new class of antibodies, one associated with allergy (now called immunoglobulin E or IgE and distinct from the previously characterized IgA or IgG immunoglobulins that drive immune responses to pathogens). That groundbreaking finding would establish Dr. Ishizaka as a pioneer in his field and win him prestigious scientific prizes over the next 40 years.

At LJI, Dr. Ishizaka continued laboratory work but also assumed an administrative role as scientific director and led the Institute through its formative years, taking on the additional role of president in 1991. He was particularly renowned for his generosity in guiding the careers of young scientists he recruited there, among them Toshiaki Kawakami, M.D., Ph.D., now a full professor at the Institute. Another early recruit was Amnon Altman, Ph.D., who Dr. Ishizaka lured from a faculty position "across the street" at what was then called the Scripps Clinic and Research Foundation (now Scripps Research).

"The positive thing about Kimi from the beginning was his scientific stature, which automatically accorded the Institute

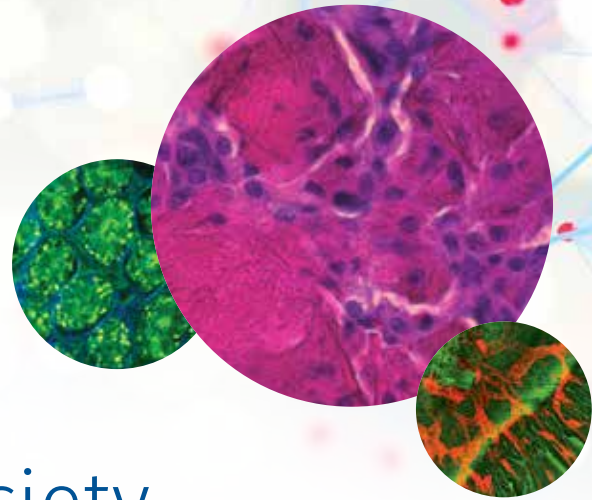


very high esteem," said Dr. Altman, Professor and Director of Scientific Affairs. "Later, we realized Kimi and his wife were unique not only in doing excellent science but in inspiring people to work collaboratively. That emphasis on harmony seemed to be part of coming from a Japanese culture. It still is in place here today—it's why the Institute has done so well."

Dr. Kawakami, who co-authored papers with the Ishizakas in the early 1990s and still focuses on mast cell signaling, concurs. "Kimi and Terry succeeded in making this initially small group of scientists and administrative folks extremely interactive, almost like an extended family," he says. "This warm and collegial environment has been sustained though the entire history of the Institute."

Science, like any profession crowded with overachievers, is ferociously competitive: other institutes may attain the level of scientific prestige that now defines LJI, but achieving that and collegiality is extraordinary. Thus, Dr. Ishizaka's legacy as a leader is as enduring as his work at the lab bench.

Dr. Ishizaka won numerous scientific prizes for discovering IgE. Among them were the 1972 Passano Award and the 1973 Gairdner Foundation International Award, both shared with Teruko; election in 1983 to the National Academy of Sciences; the 1974 Order of Culture, which is the most prestigious scientific award in Japan; and the 1985 American College of Physicians Award for Achievement in Medical Science. After he retired, he won the 2000 Japan Prize for achievements in science and enhancing worldwide prosperity from the Science and Technology Foundation of Japan. ●



# La Jolla Institute Vanguard Giving Society

## \$5,000,000+

Pfizer, Inc.

## \$3,000,000 - \$4,999,999

The William K. Bowes, Jr. Foundation

## \$1,000,000 - \$2,999,999

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Arvin Gottlieb Charitable Foundation

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Praespero - An Autoimmune  
Research Fund

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Immunotherapy Foundation

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Hilde Cheroutre

Legler Benbough Foundation

Gail K. Naughton

Hunt and Laura Pettit

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Takeda Pharmaceuticals

Nancy L. Vaughan

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Family Foundation

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Timothy and Cindy Wollaeger



## Laurie Venning

### From oil field to research field

Laurie Venning, a Canadian entrepreneur and business man, was running a successful business—Regent Energy Group Ltd., an oil field downhole tool and sand control equipment manufacturer—and playing up to 140 hockey games a year, when he was diagnosed with rheumatoid arthritis at the age of 45.

“When you have an autoimmune disease, your whole life changes overnight,” says Venning. “One day you still think you are in the NHL and the next day, your arms don’t work, your legs don’t work, your ankles swell up, and you are in incredible pain. And you wonder, what’s wrong with me?” It would take two years before his doctors arrived at the correct diagnosis and even longer before they found the right treatment that would keep Venning’s symptoms under control.

After he sold his company, Venning decided to redirect some of his seemingly boundless energy to funding and supporting medical and scientific research into the causes, treatments, and cure of autoimmune diseases. He dedicates the rest to running the VennWest group of companies, which encompasses widespread interests in the entertainment, fashion, and energy industries.

Venning started the Praespero Foundation, which is dedicated to funding autoimmune research, assembled a Scientific Advisory Council, and brought accomplished engineer Whitney A. Dueck on board to run the foundation. “We want to raise money and awareness. We are also looking into autoimmune research at different institutions

in the hopes of forming partnerships that can help us to formulate a better understanding of what happens when the immune system turns against your own body,” says Venning.

“We did our research and the work of Dr. Hilde Cheroutre at La Jolla Institute really stood out,” says Dueck. “Hilde and all the others at LJI really want to discover the truth and make humanity better. They are fully on board with the mission of Life without Disease.”

The group’s enthusiasm for the research conducted at La Jolla Institute only grew when they visited the Institute earlier this year. “We brought a member of our scientific advisory board and he was so impressed with the way the Institute is structured and equipped to successfully execute research, and that really convinced us to keep supporting La Jolla Institute,” says Dueck. “If a fellow immunologist is so excited about you, you are obviously doing something right.”

For Venning the most important aspect is that the research is discovery-driven and not directed by the pharma industry. ●

“It is a very special place and it is a real honor to be associated with a group of people whose whole life is based on improving others’ health and wellness.”

– Laurie Venning

# Bridget Cresto

Transforming loss into hope



After years of watching cancer claim the lives of a dozen friends and family members—including her husband—Bridget Cresto decided she would only invest her philanthropic dollars in research that seeks cures for the devastating disease.

“I appreciate that treatments are improving and they helped my husband John live for almost three years after he was diagnosed with lung cancer, but now I believe the only way to battle this modern scourge is to develop actual cures that eradicate the disease once and for all,” says Cresto, a retired schoolteacher from Austin, Texas. “What’s thrilling is that I believe we’re very close to seeing it happen.”

That is why Cresto has become a donor to the La Jolla Institute for Allergy and Immunology (LJI), specifically earmarking her gifts for the lab of Principal Investigator Stephen Schoenberger, Ph.D., who actually is on a path to a potential cure for certain kinds of cancer through the use of personalized immunotherapeutic vaccines.

“I really became excited when I met Dr. Schoenberger and he told me about his research and how he’s on the verge of being able to save the lives of terminal cancer patients through vaccines customized to attack their tumors based on their individual genetic profiles,” Cresto says. “I was also fascinated to learn that Stephen’s work is just one of the many research projects underway at LJI that are close to finding solutions for other types of cancer and even heart disease and HIV.”

Cresto’s commitment to LJI is interesting, given the fact that she had never heard of the organization before her husband, a 3M executive, was diagnosed in 2012 with stage 4 lung cancer at age 56. A friend referred Cresto to Tom Marsilje, Ph.D., a cancer researcher whose own

colorectal cancer diagnosis spurred him to become one of the nation’s leading advocates for patients through his website “Colontown.”

Dr. Marsilje became a mentor and friend of the Crestos and referred them to La Jolla Institute, where Dr. Marsilje had developed a professional relationship with Dr. Schoenberger and hoped to be included in one of the researcher’s clinical trials.

“Unfortunately, time ran out for Tom, who tragically passed away at age 45 before he could take advantage of Dr. Schoenberger’s discoveries,” Cresto says. “It was heartbreaking, but Tom helped countless numbers of cancer patients and I’ll always be thankful to him for bringing us to La Jolla Institute.”

Cresto says she has been so inspired by the research at LJI she will continue to give to the organization every year. And while she acknowledges she’s not a major donor, she plans to leverage her contribution by recruiting as many others to give to LJI as possible.

“I know that what I’ve given so far isn’t much, but when you combine a lot of these donations, they can become very powerful,” Cresto says. “These private, unencumbered gifts are particularly critical for the Institute and Dr. Schoenberger because they make possible the kind of highly creative, novel research that doesn’t qualify for government science grants.”

Cresto adds, “For me, if there is one consolation to losing loved ones to cancer, it’s the satisfaction of knowing I will have played a small but important role in helping find a cure for one of the most devastating diseases human beings have ever faced.” •





### \$5,000 - \$9,999

Steven and Lisa Altman  
David and Dode Anderson  
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The Thomas C. Ackerman Foundation  
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### \$1,000 - \$4,999

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Patrick Hogan  
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“For me, if there is one consolation to losing loved ones to cancer, it's the satisfaction of knowing I will have played a small but important role in helping find a cure for one of the most devastating diseases human beings have ever faced.”

– Bridget Cresto

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Paul and Laureen Mirabella  
Joseph and Barbara Mize



## Gail Naughton

### Nurturing the next generation

There are few things in life Gail K. Naughton, Ph.D., is more passionate about than advancing bioscience research and helping develop the next generation of groundbreaking scientists.

That's why the noted San Diego scientist-entrepreneur—and longtime member of the La Jolla Institute of Allergy and Immunology (LJI) Board of Directors—jumped at the opportunity to help launch LJI's new SPARK campaign. The program provides young scientists with financial assistance to develop their best scientific ideas (see story page 13).

"SPARK is one of the most exciting and inspiring programs I've ever been involved with," Dr. Naughton says. "I remember how challenging it was for me as a young scientist to have my ideas heard. SPARK not only listens to the scientists, it provides the critical monetary and scientific support to help their brilliant ideas potentially develop into important scientific discoveries. It's a tremendous boost to the careers and confidence of these talented researchers while making the Institute even stronger scientifically."

Supporting SPARK with a donation and helping judge the proposals is just the latest example of Dr. Naughton's unwavering support of LJI. In addition to being a major donor, she's been deeply involved with board activities, including serving as chair of the nominating committee. The Institute president's office is named in her honor.

Dr. Naughton's multifaceted professional expertise has been invaluable to LJI. A legend in San Diego's scientific, business, and academic communities, Dr. Naughton is a pioneer in tissue engineering research for wound care and reconstructive purposes. A holder of more than 100 patents, Dr. Naughton co-founded Advanced Tissue Sciences in the 1980s and currently serves as Founder, CSO and CBDO of Histogen, Inc., which creates regenerative medical products based on a process she developed. For nearly a decade, Dr. Naughton served as Dean of the College of Business Administration at San Diego State University.

In addition to all of the professional reasons Dr. Naughton decided to become involved with LJI, there was one that was extremely personal: One of her daughters suffers from scleroderma, a debilitating autoimmune connective tissue disease.

"I believe even more strongly today that La Jolla Institute is at the absolute forefront of immunological research and that their amazing scientists are leading the way in finding incredible new treatments and even cures to a host of autoimmune diseases that plague our world.

"What's thrilling for me is that I have a chance to play a role in supporting that kind of science as well as nurturing the development of the brilliant young scientists who will be coming up with the wonderful discoveries that will help my daughter and millions more around the world." •

## \$1,000 - \$4,999 continued...

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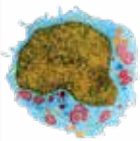
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*The donor list above represents lifetime contributions to LJI as of August 2018*

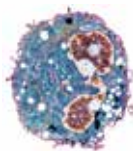
\*Deceased

## Meet the cover models:



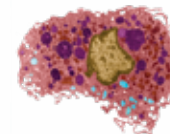
### B cell

B cells produce antibodies, which recognize and trap invading bacteria and viruses in large clumps.



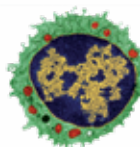
### Eosinophil

Eosinophils help fight off multicellular pathogens and play an important role in asthma and allergies.



### Macrophage

Macrophages engulf cellular debris, foreign substances, microbes, cancer cells and anything else that doesn't belong.



### T cell

T cells help coordinate the body's immune response and kill compromised cells such as malignant or virus-infected cells.



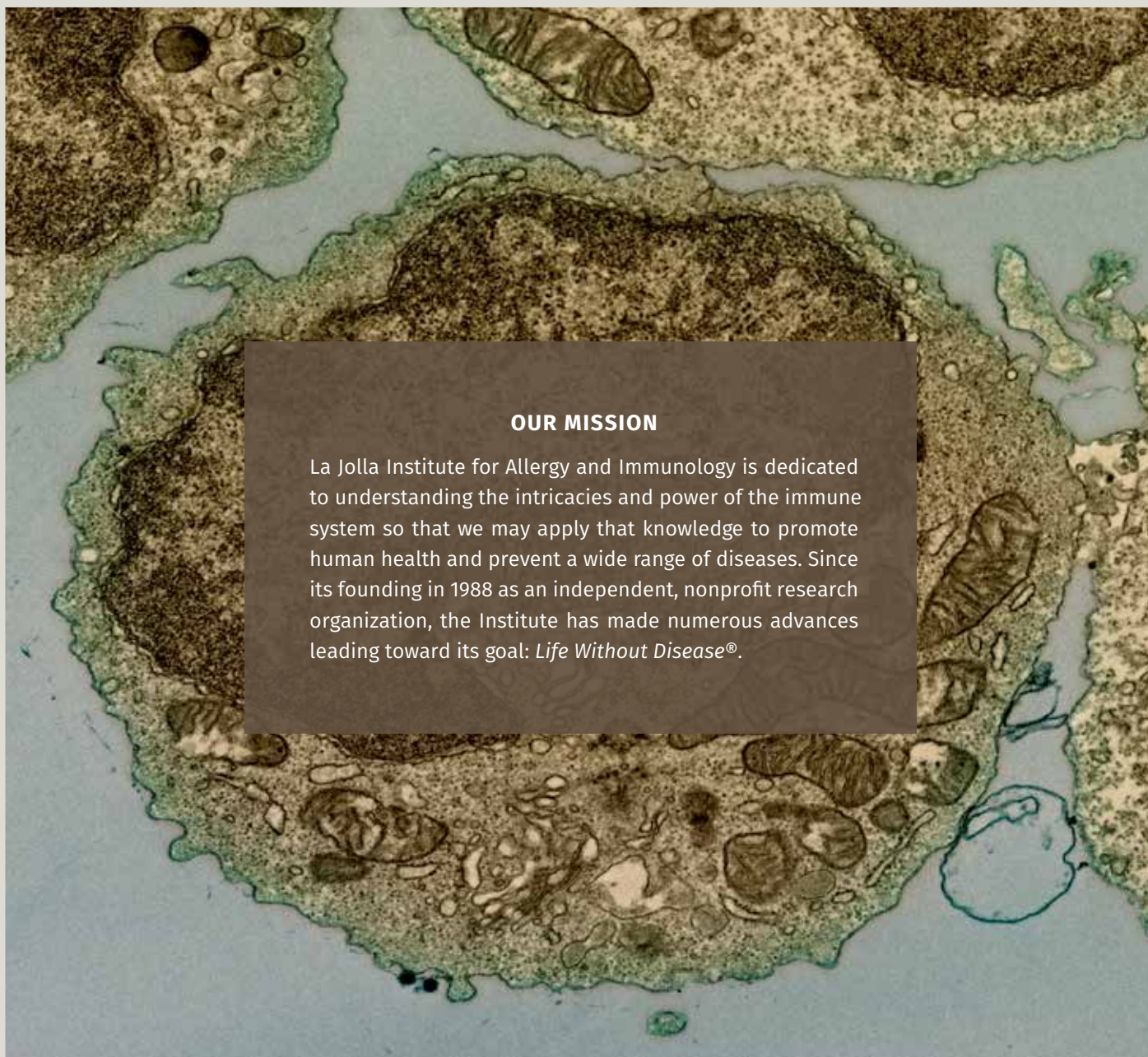
### Neutrophil

Neutrophils, the most abundant type of white blood cell, are among the first immune cells to arrive at the scene of a foreign invasion.

### ON THE BACK COVER:

Transmission electron micrograph of a B cell from a human donor.

Credit: NIAID



#### OUR MISSION

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