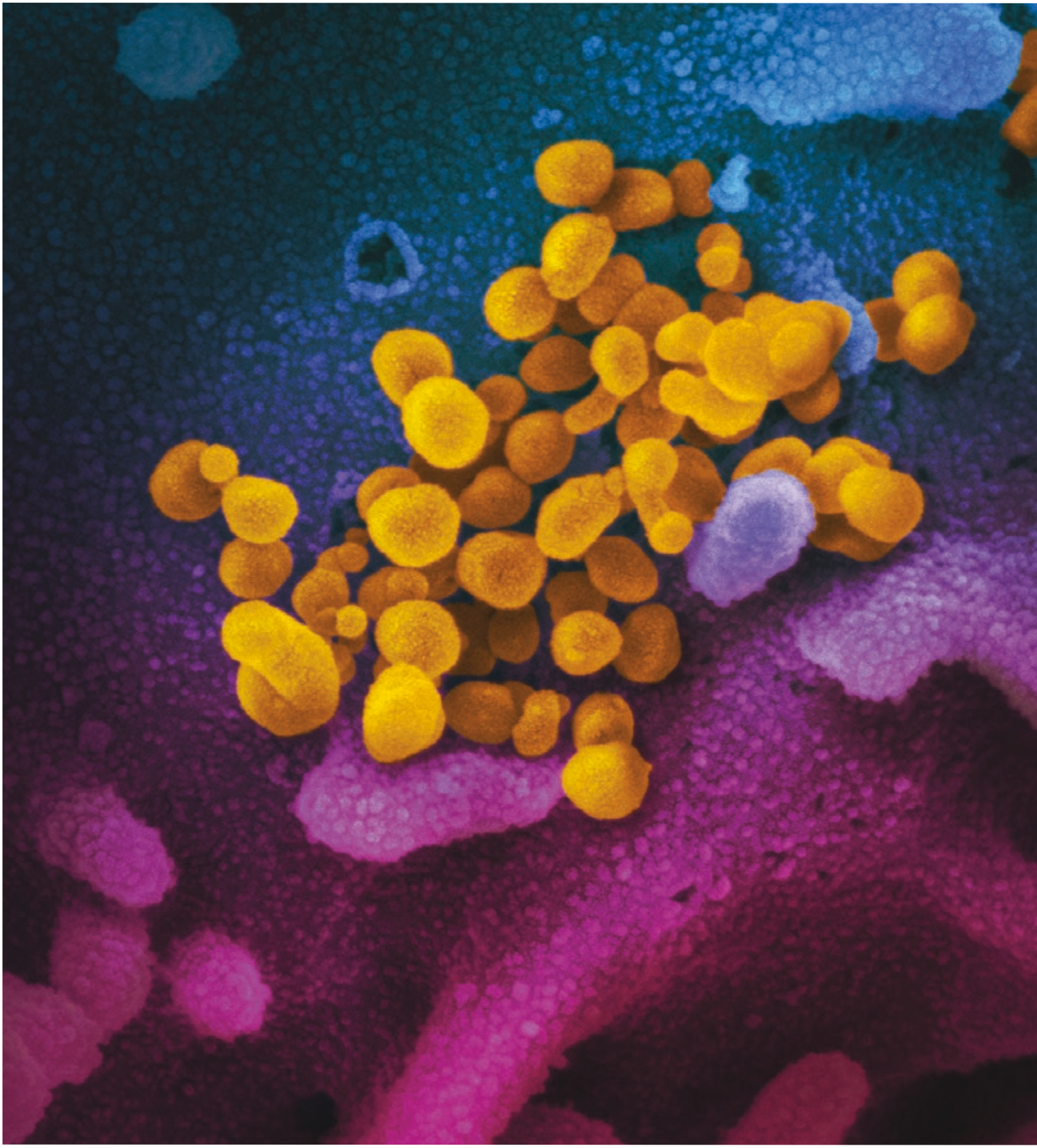
# Immune MATTERS

LA JOLLA INSTITUTE
FOR IMMUNOLOGY
SPRING 2020



## Novel Coronavirus SARS-CoV-2

COVID-19 is the official name for the disease that's paralyzing China and threatening the rest of the world. The first symptoms are similar to other respiratory illnesses—fever, a dry cough, and shortness of breath. But in a small percentage of infected people the disease can progress to life-threatening pneumonia. This scanning electron microscope image shows SARS-CoV-2 (yellow) emerging from the surface of cells cultured in the lab (see story on page 13).

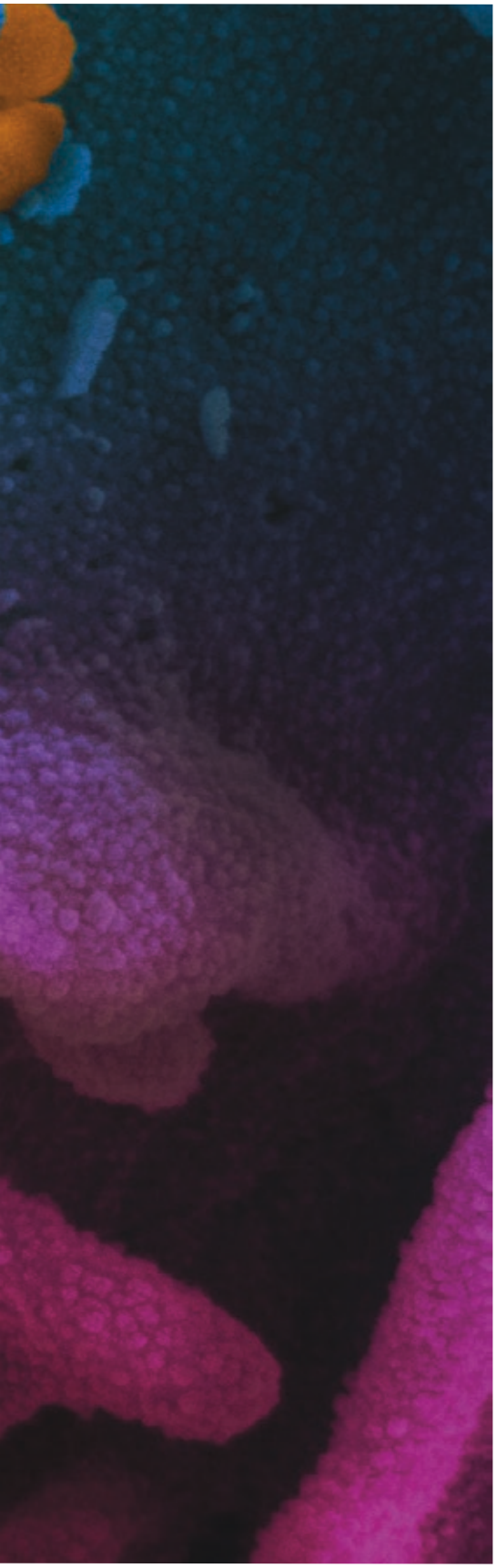


Image: Courtesy of NIAID-RML

# Immune MATTERS

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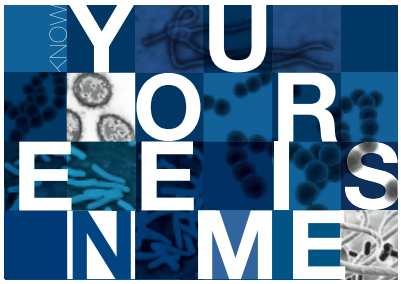








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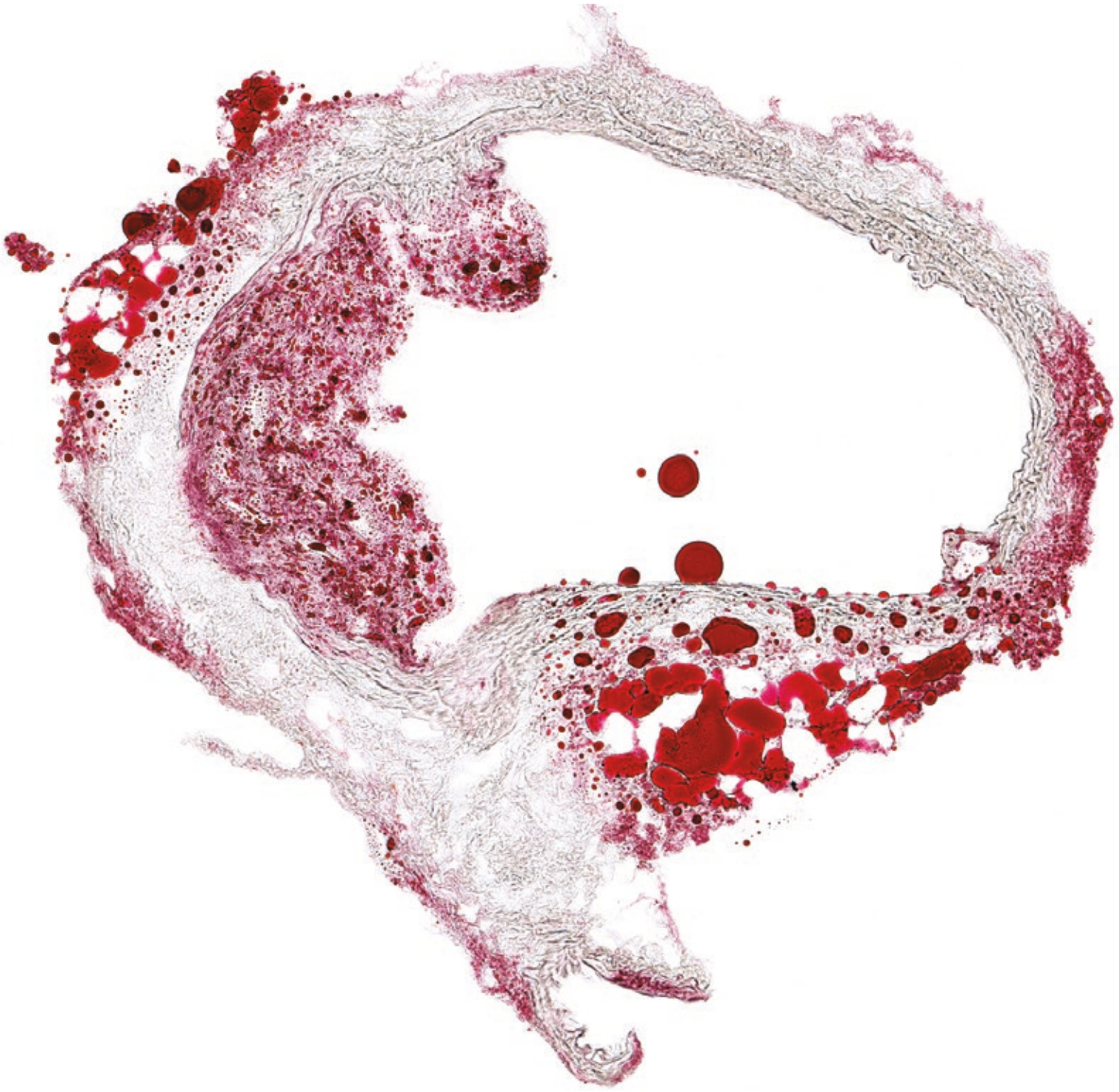


## Atherosclerosis

Atherosclerosis—the buildup of plaque inside arteries—is a chronic inflammatory disease and the immune system plays a critical role in the progression of the disease. Dr. Klaus Ley, one of the world's foremost experts on the immunobiology of vascular disease, is pioneering novel strategies to curb vascular inflammation (see page 18).

Image: Courtesy of Ley lab

# LETTER FROM THE PRESIDENT


In my many years of doing research in immunology, including 16 years as President and Chief Scientific Officer, there has never been a more thrilling time to study the immune system. Thanks to the groundbreaking research of our La Jolla Institute for Immunology scientists we are moving toward our vision of *Life Without Disease®*. Diseases we're attacking at the Institute include heart disease, cancer, autoimmune disorders like type 1 diabetes, multiple sclerosis, and inflammatory bowel disease, and infectious diseases such as HIV, Zika, and Ebola.

In our cover story on infectious diseases, you'll see how Institute researchers are developing vaccines and other treatments to address conditions that kill 17 million people annually. Our fundamental research that underlies the basis for protective immune responses is essential for creating vaccines against well-known infections, such as tuberculosis and AIDS, as well as newly emerging diseases such as COVID-19.

In our Q&A, you'll meet a world-class Institute scientist whose research may soon save millions of lives. Klaus Ley, M.D., is getting closer to perfecting an atherosclerosis prevention vaccine that has already proven to reduce inflammatory plaque, the cause of heart disease, in mice.

In this issue, we also mourn the passing of Howard Grey, M.D., who as President and Chief Scientific Officer from 1996 to 2003, was a signature figure in the history of the Institute. A renowned scientist, Howard recruited some of the world's leading immunologists, doubled the organization's size, and enhanced our reputation. La Jolla Institute has continued to grow in size and reputation, and today is among the top research organizations in the world.

To continue tackling diseases that afflict millions, we're looking for assistance from anyone who believes in the power of science—and specifically immunology research. While we're proud of the numerous federal National Institutes of Health grants we've been awarded, the truth is we need more support to have the kind of major impact on diseases that we envision.

We can make an extremely compelling case for support because there isn't a person who hasn't been touched by diseases related to immune system function, either themselves, their family members, friends, or colleagues. When you support the Institute, you partner with talented researchers who, among many efforts, are leveraging the power of the immune system to create a potential vaccine to halt atherosclerosis, cure cancers through immunotherapy, develop vaccines to protect against HIV and dengue, and more.

An infusion of support from the community will enable the Institute to recruit additional world-class investigators, purchase research equipment to open new insights, and expand our already leading-edge use of bioinformatics and creation of huge databases that are changing the face of immunology.

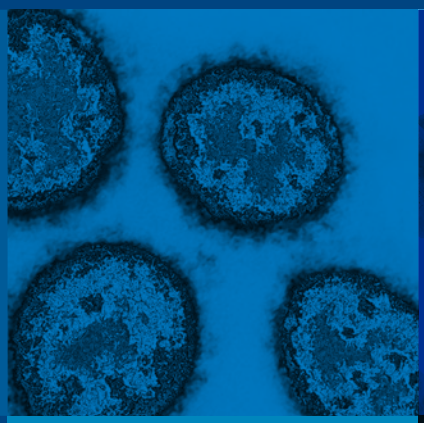
With your help we look forward to an even more exciting future with greater discoveries and impact on human health. As always, we appreciate our wonderful Institute partners—including individual donors, foundations, and federal funding sources—who play such a crucial role in supporting our research. We are indeed closing in on potentially lifesaving breakthroughs in treating many of the world's most devastating diseases and moving toward our vision of ***Life Without Disease®.***

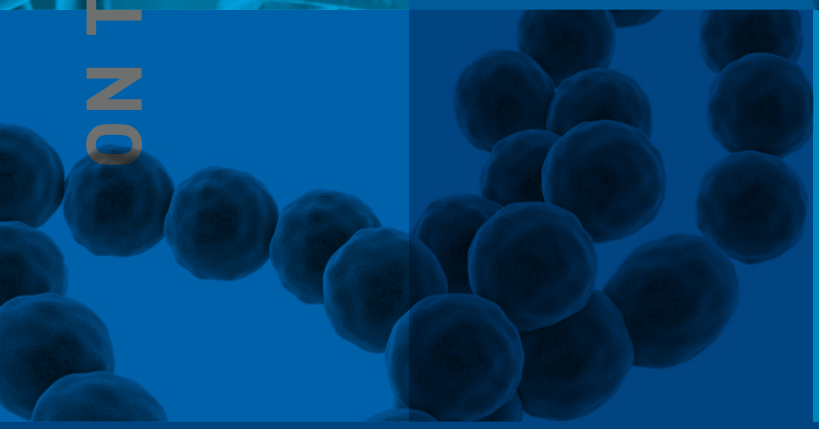
Sincerely,

Mitchell Kronenberg

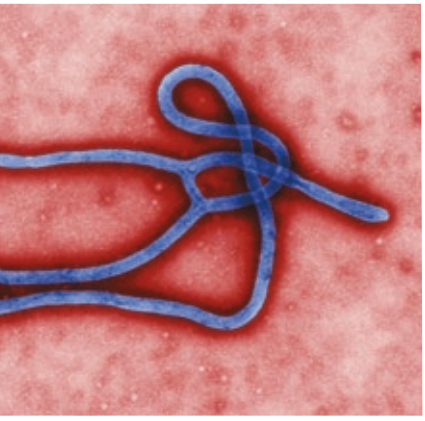
Mitchell Kronenberg, Ph.D.
President & Chief Scientific Officer
La Jolla Institute for Immunology

ON THE COVER





# KNOW YOUR ENEMIES



# Our bodies are home to trillions of microbes.

**They help us digest food, balance our immune system, and keep our hearts and brains healthy. But harmful viruses and bad bacteria can creep in at any time. Scientists at La Jolla Institute for Immunology are working to stop these infectious agents and learn more about the body's defense strategies.**

At first glance, dengue virus looks a bit like a kid's toy. The virus is shaped like a little ball, and the pieces of its outer shell fit together like puzzle pieces. But as soon as it invades, pieces of dengue's smooth shell pop open to release dengue's genetic material into our cells.

This sneak attack is extremely effective. According to the World Health Organization, there are an estimated 390 million dengue infections each year, and the disease is a leading cause of serious illness and death in some Asian and Latin American countries.

In fact, mosquito-borne diseases like dengue, malaria, and Zika are spreading around the globe as warmer temperatures allow mosquito species to migrate out of their usual habitats. Overall, many infectious diseases are reaching new territories. Scientists used to think Ebola virus was only a threat in Central Africa—until the virus crossed international borders and exploded into a 30,000-person epidemic.

Other microbes hide in plain sight. An estimated 50 percent of San Diegans harbor cytomegalovirus deep in their tissues. The virus will go unnoticed by most people, but when it infects pregnant women, it can cause serious birth defects. In fact, it is the most common infectious cause of birth defects in the United States.

We still need to know much more about infectious diseases and how to effectively treat, or better yet, prevent them. That's why several teams of LJI researchers have dedicated their careers to understanding and defeating dangerous microbes.

## THE RAPID KILLERS

Endemic in most of West Africa, Lassa fever tends to start out with a slight fever and general malaise like any old cold or flu. It doesn't seem like an emergency at first and for the majority of infected people it

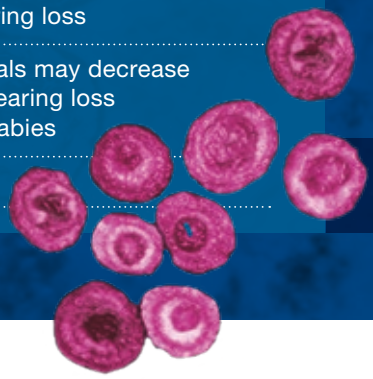
## ON THE COVER

### Bordetella Pertussis

| | |
|---|---|
| **Impact:** | 24 million cases/160,000 deaths |
| **Distribution:** | worldwide |
| **Transmission:** | respiratory droplets |
| **Symptoms:** | whooping cough |
| **Treatment:** | antibiotics |
| **Vaccine:** | yes |

### Cytomegalovirus (CMV)

| | |
|---|---|
| **Impact:** | >50% of the adult US population carry the virus, 1 out of every 200 babies is born with congenital CMV |
| **Distribution:** | worldwide |
| **Transmission:** | bodily fluids |
| **Symptoms:** | usually none; congenital CMV can lead to long-term health problems, such as hearing loss |
| **Treatment:** | none; antivirals may decrease severity of hearing loss in infected babies |
| **Vaccine:** | none |



is indeed nothing more than a blip of feeling unwell for a bit. But in 20 percent of patients, the disease progresses to full blown hemorrhagic fever, which can result in multi-organ failure and death. In West Africa, the virus causes 300,000 to 500,000 illnesses annually and kills thousands each year.

LJI Professor Erica Ollmann Saphire, Ph.D., is fascinated by the simplicity of Lassa virus and other hemorrhagic fever viruses, such as Ebola and Marburg. Lassa virus carries out a sophisticated attack using just four genes and four moving parts. Ebola virus has just seven genes and eight moving parts. “How can something so simple be so spectacularly pathogenic?” says Dr. Saphire. “On the other hand, with so few moving parts, we can find where it is vulnerable and launch a therapeutic.”

New cryo-electron microscopy imaging equipment at LJI makes it possible for Dr. Saphire and her colleagues to quickly see the smallest details of viral structures and where these pathogens are susceptible to human antibodies and drug therapies.

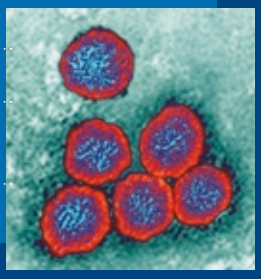
Another one of LJI’s strengths is its connections with experts in countries where many infectious diseases are endemic. Dr. Saphire is currently working alongside epidemiologists and medical professionals in Sierra Leone and the Democratic Republic of Congo. At the same time, LJI Associate Professor Sujan Shresta, Ph.D., is coordinating with experts in Nepal to study mosquito-borne diseases in that country. “We need their expertise and local knowledge,” says Dr. Shresta.

Dr. Shresta, who was born and raised in Nepal before she moved to the U.S. to continue her higher education, wants to help people in both regions. She’s seen how diseases such as dengue devastate communities in Nepal, and she says new mosquito-borne diseases could easily reach LJI’s home in Southern California. “The same mosquitoes that transmit dengue can be found right here in San Diego,” she says, “and to be prepared, we need to learn more about these diseases before they eventually reach the U.S.”

Dr. Shresta focuses on how viruses interact with the host immune system. She says the closely related dengue and Zika viruses show how complicated the host response can be. Studies suggest that when a person is infected with dengue, their response to a later Zika infection will be much worse and vice versa. This “cross-reactivity” poses a problem for

## Dengue Virus

| | |
|---|---|
| **Impact:** | 400 million infections/> 20,000 deaths per year |
| **Distribution:** | >100 countries |
| **Transmission:** | infected mosquitoes (*Aedes aegypti* or *A. albopictus*) |
| **Symptoms:** | nausea, vomiting, rash, pain, hemorrhage in severe forms |
| **Treatment:** | supportive care |
| **Vaccine:** | available with limitations |



## Ebola Virus

| | |
|---|---|
| **Impact:** | 3,351 cases/2,211 deaths in the current outbreak in the Democratic Republic of Congo (as of Dec. 18, 2019) |
| **Distribution:** | sub-Saharan Africa |
| **Transmission:** | direct contact with bodily fluids |
| **Symptoms:** | fever, body aches, diarrhea, hemorrhage |
| **Treatment:** | monoclonal antibodies |
| **Vaccine:** | first vaccine approved in Dec. 2019 but only effective against one type |

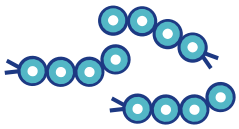
both dengue and Zika vaccine programs, where priming the body to fight one virus may leave it vulnerable to another closely related virus.

"This is really important to study because I believe the most effective way to solve the global dengue/Zika problem is going to be a vaccine, and we're showing that you can't approach vaccine development focusing on only one virus at a time." Dr. Shresta says.

## THE TURNCOATS

We're all home to viruses and bacteria. Some protect you or even help you digest food. And then there are the double agents, the microbes that are usually harmless, until the day they decide to attack. What makes these pathogens turn on us?

Take *group A Streptococcus*, a noodle-shaped bacterium that makes up a normal part of the body's microbiome—except when it turns on the body, triggering tonsillitis, which is commonly known as strep throat. Just about every kid gets strep throat at some point. But some kids get it over and over again, and it's more dangerous than you may think. Left untreated, strep throat can actually lead to rheumatic heart disease.



***Streptococcus pneumoniae***

**This bacterium can live harmlessly in the body but then turn around and cause disease in immuno-compromised individuals, such as babies and the elderly.**

LJI scientists are working to figure out why. "It's still unknown why children get recurrent group A strep," says Jennifer Dan, M.D., Ph.D.

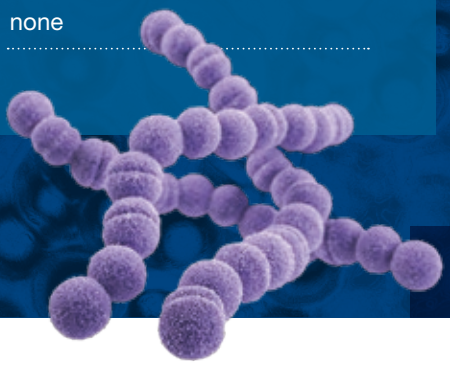
As a member of Professor Shane Crotty's lab at LJI (she also has an assistant professor appointment at the University of California, San Diego), Dr. Dan studies exactly how the body responds to group A strep. This project could provide insight into how we fight off many other infectious diseases.

Mitchell Kronenberg, Ph.D., LJI President and Chief Scientific Officer, says work on diseases like group A strep can help us understand how the body responds to a huge range of attacks. "The principles we learn can be applied across infections," he says.

ON THE COVER

## Group A Streptococcus

| | |
|---|---|
| **Impact:** | ~700 million infections/year |
| **Distribution:** | worldwide |
| **Transmission:** | airborne droplets, direct contact |
| **Symptoms:** | strep throat, scarlet fever, rheumatic fever |
| **Treatment:** | antibiotics |
| **Vaccine:** | none |



## HIV

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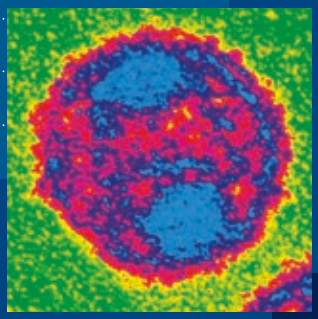
|---|---|
| **Impact:** | 37.9 million infected people worldwide/770,000 deaths in 2018 |
| **Distribution:** | worldwide |
| **Transmission:** | sexually, contaminated syringes |
| **Symptoms:** | acquired immunodeficiency syndrome (AIDS) |
| **Treatment:** | antiviral therapy |
| **Vaccine:** | none |



Dr. Kronenberg's own lab is very interested in another infectious turn-coat: *Streptococcus pneumoniae*. This bacterium can live harmlessly in the body but then turn around and cause disease in immunocompromised individuals, such as babies and the elderly. It is a leading cause of fatal pneumonia in older people.

"These bacteria live on the nutrients from mucus: sugar, fats, and proteins. They normally stay away from immune cells," says Dr. Kronenberg. "The real question is how does it decide to become invasive?"

Dr. Kronenberg says the Institute's expertise in the techniques of flow cytometry and genome sequencing is giving his team new insights into how better vaccines against *S. pneumoniae* might move forward.

## THE STANDING ARMIES

A tuberculosis infection can begin with a single sneeze from an infected person. With one sneeze, 40,000 droplets shoot into the air, and each droplet is loaded with *Mycobacterium tuberculosis*. You'd only need to inhale ten of these bacteria to contract the infection. And then the invaders lay low.

**"Tuberculosis is currently the number-one killer worldwide in terms of infectious diseases."**

Bjoern Peters, Ph.D.

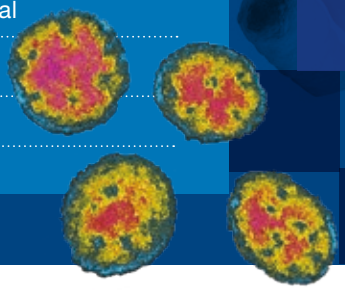
Tuberculosis is one of those diseases that mostly hangs out in a "latent" stage. The bacteria don't actually want to kill their host, and yet they can become deadly when the immune system stops working as it should. "Tuberculosis is currently the number-one killer worldwide in terms of infectious diseases," says LJI Professor Bjoern Peters, Ph.D.

Dr. Peters and his team are working closely with the lab of LJI Professor Alessandro Sette, Dr. Biol.Sci., to answer a big question in tuberculosis disease research: Why do some infected people get sick when so many don't show symptoms?

LJI researchers are searching for ways to catch tuberculosis cases before they turn deadly. Current therapies for tuberculosis tend to be harsh on the body, so they aren't given proactively in most countries. Dr. Peters wants to find a way to treat those most at risk—sooner.

## Lassa Virus

| | |
|---|---|
| **Impact:** | ~300,000 infections/thousands of deaths per year, long-lasting deafness and health complications; possible link to autoimmunity |
| **Distribution:** | endemic in West Africa |
| **Transmission:** | infected rodent (*Mastomys natalensis* or multimammate rat) |
| **Symptoms:** | usually mild; 20% of infected individuals develop hemorrhagic fever, which can be fatal |
| **Treatment:** | supportive care |
| **Vaccine:** | none |



## Mycobacterium Tuberculosis

| | |
|---|---|
| **Impact:** | 1.7 billion latent infections/ 1.2 million deaths per year ) |
| **Distribution:** | worldwide |
| **Transmission:** | respiratory droplets |
| **Symptoms:** | latent or active tuberculosis |
| **Treatment:** | antibiotics |
| **Vaccine:** | BCG (limited efficacy) |

"We want to identify the immune system signals of someone who is about to get sick," says Dr. Peters.

Drs. Peters and Sette have also established the Immune Epitope Database (IEDB), the largest existing collection of molecular targets or epitopes recognized by the immune system and an invaluable resource for infectious disease research around the world. The free database houses information on how immune cells such as T and B cells target pathogens.

"We can use these epitopes as bait to fish out the T cells that drive immune response and understand, for example, the type of immune response in people with good immune responses versus people whose immune response fails," says Dr. Sette.

Dr. Sette's work has also shed light on infectious diseases such as pertussis (whooping cough), Zika, dengue, malaria, chikungunya, cytomegalovirus (CMV), and shingles. The virus that causes shingles, called the varicella-zoster virus (VZV), is another one of those pathogens with a long latent period.

If you've had chicken pox, then you now have VZV hiding out in your nerve cells. "The virus is still in a bit of a battle with your immune system, but it's not really obvious that you're infected," says LJI Professor Chris Benedict, Ph.D. He says that shingles tends to be associated with elderly people because the virus becomes active again as the immune system weakens with age, but shingles also can occur in younger individuals, especially when they are stressed.

**1 in 5 deaths are caused by INFECTIOUS DISEASE**

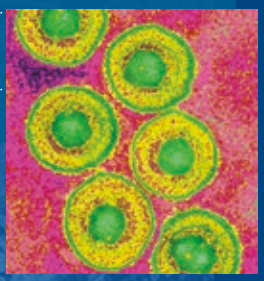
Dr. Benedict is also concerned with CMV, a common virus that can infect almost anyone.

The immune system of healthy people can keep the virus in check but can be very harmful to babies when their mother is infected during pregnancy. In adults with compromised immunity, especially due to organ transplantation, it can be fatal. A recent partnership with the Sette lab seeks to understand how immune "helper" cells called CD4 T cells respond specifically to CMV.

ON THE COVER

## Varicella Zoster Virus

| | |
|---|---|
| **Impact:** | normally mild disease |
| **Distribution:** | worldwide |
| **Transmission:** | air droplets, direct contact with rash |
| **Symptoms:** | chickenpox and shingles |
| **Treatment:** | typically not required; antivirals in high-risk population |
| **Vaccine:** | chickenpox and shingles |



## Zika

| | |
|---|---|
| **Impact:** | 2 out of 10 babies exposed to Zika before birth are born with Zika-associated birth defects |
| **Distribution:** | 87 tropical and subtropical countries with known previous or current transmission |
| **Transmission:** | infected mosquitoes (*Aedes aegypti* or *A. albopictus*), sex, to fetus during pregnancy |
| **Symptoms:** | none or mild such as fever, rash, joint and muscle pain, conjuctivitis |
| **Complications:** | Guillain-Barre syndrome, microcephaly, and other birth defects in babies infected *in utero* |
| **Treatment:** | none |
| **Vaccine:** | none |

Dr. Sette says LJI has the right team of scientists and bioinformatics experts in place to figure out how mysterious latent infections turn deadly. "We have fantastic faculty and scientists who collaborate in the studies and really help extract every piece of information possible from the data," he says.

## THE JACK-OF-ALL-TRADES

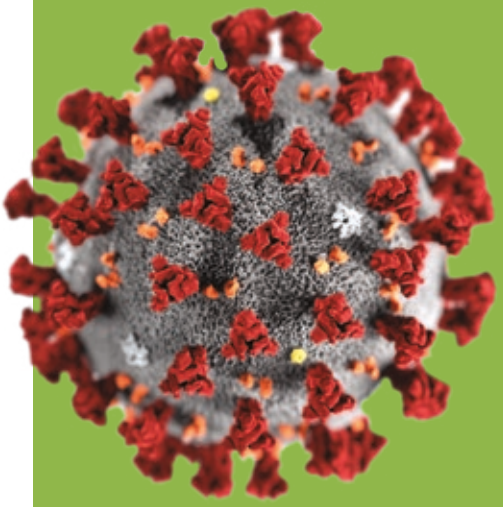
Some pathogens fit neatly into a category. And then there's HIV. It can kill a person within a few years, or it can hide out in the body for a decade or more. It adapts quickly and blocks the immune system from even keeping an eye on it.

"This virus is especially difficult to target," says J.H. Lee, Ph.D., a postdoctoral researcher in the Crotty lab. Dr. Lee says the immune system has trouble fighting off HIV because the virus is covered in a shield of sugar molecules called glycans. "It's like it's wearing an invisibility cloak," Dr. Lee says.

But there could be a way to outsmart HIV. The Crotty lab is part of an international consortium to develop an HIV vaccine. The group studies blood samples from some of the rare people who produce antibodies that are able to inactivate or neutralize the many strains of the virus. These unusual antibodies have given scientists a guide for what kinds of immune molecules an HIV vaccine would need to elicit in a person's body. The Crotty lab is now leading research in animal models to study how an effective vaccine could work. At the same time, they are also studying healthy people to determine whether the general population has the potential to make those rare antibody-producing cells in response to a vaccine.

LJI's state-of-the-art facilities and expertise make it the perfect place to spearhead this effort. "Because we have advanced molecular techniques here, we can do work on highly virulent pathogens like HIV or others, for example, using molecular pieces rather than the entire disease-causing organism. Therefore we can work safely without the need for super high levels of containment or fear that our scientists will be infected," says Dr. Kronenberg.

With the help of Institute supporters and international collaborators, LJI researchers are closing in on the best ways to defeat the world's worst pathogens. •



# Outbreak Alert: Coronavirus

Within weeks of its discovery, a novel **coronavirus (SARS-CoV-2)** has spread to six continents and infected over 80,000 people.

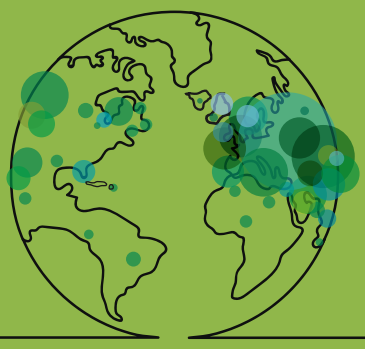
Most coronaviruses usually cause the common cold, but, as happened with the SARS virus in 2003 and the MERS virus in 2008, every few years a new coronavirus that can cause severe disease emerges. At the same time, we are still susceptible to older threats we have known for a long time. For example, last summer, the measles virus rapidly spread across several continents and the United States risked losing its measles-eradicated status.

Whether worldwide efforts to surround the outbreak of COVID-19, the disease caused by SARS-CoV-2, and develop a vaccine ultimately succeed or fail, one thing is certain: Infectious diseases caused by viruses will continue to emerge and pose a threat to human health. “What we need is permanent infrastructure that allows us to respond rapidly to these threats,” says LJI Professor Erica Ollmann Saphire, Ph.D. “Even if a future pandemic is caused by a different virus, the basics remain the same.”

Many of the necessary tools are already in place at the Institute. They include a broad effort to understand the fundamentals of how we can harness the immune system to protect against new infectious threats. The Immune Epitope Database (IEDB), which contains the world’s most comprehensive collection of immune targets, allows LJI Professor Alessandro Sette, Dr. Biol.Sci., to scour millions of entries for coronavirus-related information at a moment’s notice, and apply machine learning approaches to identify new potential targets. These data are made public to inform efforts to develop new diagnostics, therapeutics, and vaccines.

Dr. Saphire built a state-of-the-art cryo-electron microscopy and antibody discovery facility at LJI to reveal which parts of these emerging viruses, including SARS-CoV-2, can be targeted to inspire immune defense or new drugs. “With the right arsenal in place, we can accomplish what seemed inconceivable just a few years ago—create a treatment or vaccine fast enough to stop the next outbreak before it becomes a global threat to human health,” says Dr. Saphire.

Infectious diseases caused by viruses will continue to emerge and pose a threat to human health.



# WE ARE WHAT WE EAT

## Postdoc's exploration of olfactory receptor function could lead to therapies to prevent atherosclerosis.

When 16-year-old Marco Orecchioni, Ph.D., abandoned his dream of becoming a chef to pursue science, little did he know that years later food would play a major role is his quest to counter the pro-inflammatory effect poor diets have in triggering atherosclerosis.

Dr. Orecchioni, a postdoctoral fellow in the lab of professor Klaus Ley, M.D., at the La Jolla Institute for Immunology (LJI), is a rising star at the Institute, having already notched a number of key research successes in a little over two years since he arrived in La Jolla after receiving his Ph.D. in his native Sardinia, an Italian island in the Mediterranean.

One of the signs that Dr. Orecchioni is an outstanding young talent came last year when he was awarded one of the Institute's Tullie and Rickey Families SPARK Awards for Innovation in Immunology. SPARK awards provide $25,000 of 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.

Dr. Orecchioni's research expanded on the Institute's discovery that olfactory receptors are not restricted to our nose but can be found in other parts of the body in the form of macrophages, a type of white blood cell.

# MARCO ORECCHIONI, PH.D.

"At first, we couldn't understand what role these olfactory receptors could play outside the nose," Dr. Orecchioni says. "But then we discovered that mice fed cholesterol-rich diets expressed hundreds of these olfactory receptors on macrophages isolated from their atherosclerotic arteries.

"That's when I really began to get excited because I was able to demonstrate that vascular macrophages can sense certain odorants in response to which they induce a pro-inflammatory response. It still has to be proven in humans, but my theory is that these olfactory receptors expressed in macrophages just might be one of the missing links between high fat diets and the progression of atherosclerosis."

Another indication Dr. Orecchioni is on a fast track is that his SPARK project, which normally would remain a side effort to work on in his spare time, has now become part of the Ley lab's main research focus (see Q&A with Dr. Ley, page 18).

While Dr. Orecchioni is amazed at his success at LJI, he traces its origins to his decision in high school not to follow in the footsteps of his brother—who was a chef—after he took his first biology class.

"I remember studying a cell and realizing how complicated and fascinating it was and how I really wanted to understand everything I could about it," Dr. Orecchioni recalls. "And then when I began to study immunology that's when my real passion began. I was intrigued because the immune system is not only one of the most intricate and complex systems in the body, there's a delicate balance between its amazing power to protect us against disease and its destructive ability to turn on us and harm our bodies through autoimmune diseases."

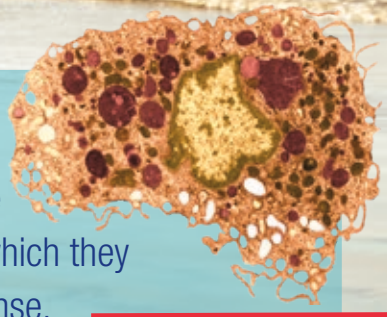
And Dr. Orecchioni is eager to tackle the autoimmunity issue head on. He knows his research on olfactory receptors is in the early stages, but he's optimistic enough to believe that within a few years it will lead to clinical trials with humans and ultimately development of a drug that would block the pro-inflammatory effect of the macrophages.

"One of the reasons I love being a scientist is that my research has the potential to help people," he says. "Nothing would be more exciting for me than to make a contribution to the health of millions around the world by coming up with a way to protect the human body against cardiovascular disease, which is still the leading killer around the world."

There is an even more personal reason Dr. Orecchioni wants his research to succeed.

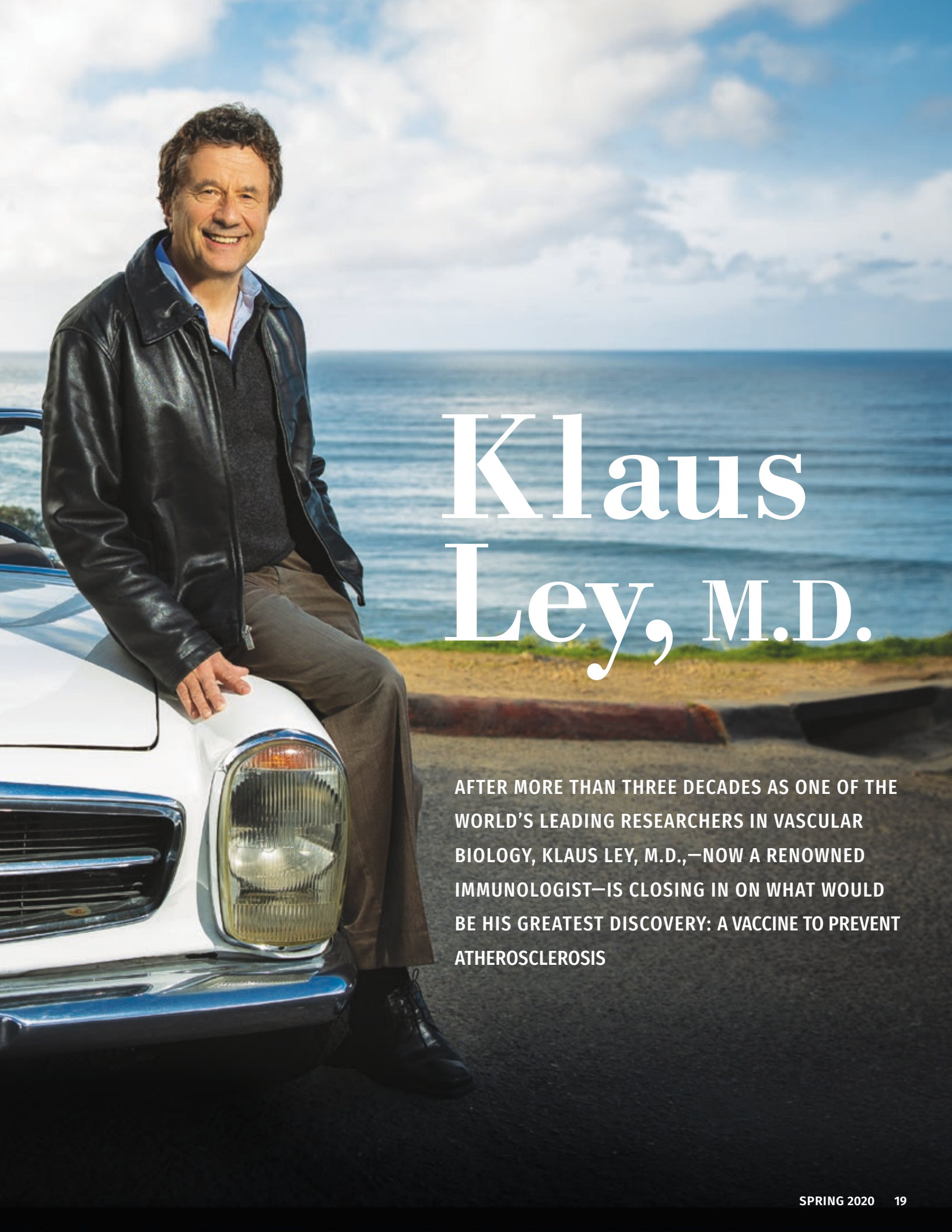
"I'd like to help my own family, which has a bad history of cardiovascular disease. My grandfather died of a heart attack at 54 and my uncle has heart disease. My mother has high blood pressure and high cholesterol and I'm always telling her to eat this and not that. Everyone in the family knows that I'm working on this and they're very happy for my success and very proud," Dr. Orecchioni adds, laughing, "but they want me to hurry up!" •

"One of the reasons I love being a scientist is that my research has the potential to help people."



I was able to demonstrate that vascular macrophages can sense certain odorants in response to which they induce a pro-inflammatory response.

# QUESTIONS & ANSWERS



# Klaus Ley, M.D.

AFTER MORE THAN THREE DECADES AS ONE OF THE WORLD'S LEADING RESEARCHERS IN VASCULAR BIOLOGY, KLAUS LEY, M.D.,—NOW A RENOWNED IMMUNOLOGIST—IS CLOSING IN ON WHAT WOULD BE HIS GREATEST DISCOVERY: A VACCINE TO PREVENT ATHEROSCLEROSIS

## IF FINDING A WAY TO PREVENT CARDIOVASCULAR DISEASE IS ONE OF THE HOLY GRAILS OF MEDICAL RESEARCH, PROFESSOR LEY MAY BE FURTHER ALONG THAN MOST IN THAT QUEST.

A vascular biologist-turned-immunologist, Dr. Ley has made huge strides by proving his vaccine successfully reduces atherosclerotic plaque in mice and he believes the same process will work in humans. The much-honored Dr. Ley was born and raised in Germany and received his medical degree from the Julius-Maximilians-Universität, Würzburg, Germany, in 1982. He trained as a postdoctoral researcher at the Freie Universität Berlin, to which he returned after a short stint as a visiting research scientist at the University of California, San Diego. In 1994, he joined the faculty of the University of Virginia where he served as Director of the Robert M. Berne Cardiovascular Research Center from 2001 until 2007 when he was recruited to LJI.

### How did you go from studying to be a physician to ending up as an internationally known biomedical researcher?

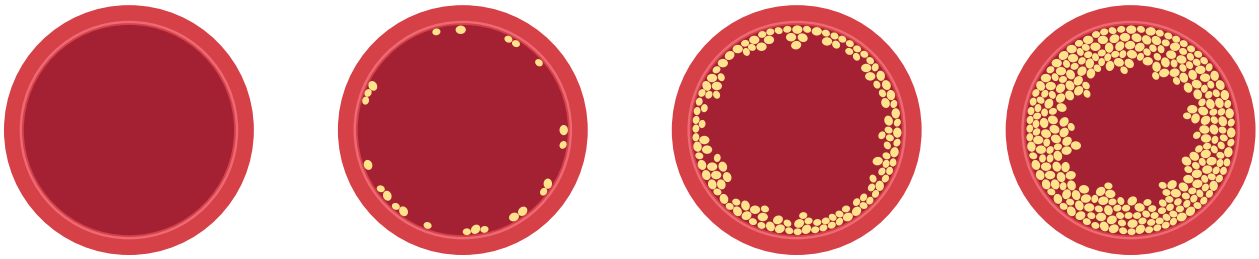
One day during a high school physics class my teacher said, "Klaus, you're going to be a scientist." Being a teenager and somewhat rebellious, I said, "No, I'm going to be a doctor" and I went to medical school. He was right, though. In my third year I started doing lab research and realized I'm very curious and love learning about all things in life, especially the scientific world. I knew then I didn't want to be a doctor and take care of patients but I still went ahead and completed my medical degree, knowing that every position I pursued after that would be pure research.

### How were you able to make that transition?

The challenge was that while medical school was an excellent education, and to this day continues to provide me with valuable insight into what the ultimate goal of my research is, the training is somewhat superficial in that you learn a little about everything but nothing in depth. It lacked the rigor I would have gained had I pursued a research Ph.D. I knew I had some catching up to do, so the solution I came up with was to do two postdocs: the first, in Berlin, helped me learn the basics, almost like a Ph.D., and the second at UC San Diego, prepared me to become a faculty member at a major research center.

# Immune attack

The immune system plays a critical role in the progression of atherosclerosis—the buildup of fatty deposits in arteries—but may also be the key to combat the disease.



**Your Berlin postdoc was before the Iron Curtain fell, wasn't it?**

Yes, and I almost didn't take it. You had to drive four hours through East Germany to get to West Berlin and they hold onto your passport until you return. It was November and in the northern latitudes the nights are long and wet. It was all very dreary and disconcerting and I didn't know if I could handle it. I decided to take the plunge and it turned out great. The research on microcirculation was narrow but deep and it gave me a real foundation for becoming a vascular biologist.

**You leveraged that foundation into a remarkable career that culminated with you heading up University of Virginia's Cardiovascular Research Center in the early 2000s. You were a pioneer in vascular biology, published countless papers, and won virtually every major award in your field. Why did you then take another right turn, this time into immunology?**

By that time our center was at the leading edge of discovering the inflammatory nature of atherosclerosis. But I also was beginning to believe there was an important connection between the immune system and its role in causing and controlling inflammation. I sensed we might be able to use the immune system to manipulate inflammation with the goal of possibly preventing or curing disease. The problem was that I was an expert in inflammation biology but I knew I needed more knowledge and experience on how the immune system works. I knew there was no better place to gain that knowledge than at one of the world's leading immunology institutes, so it was an easy decision to come to La Jolla Institute.

**In the 13 years since, you and your team have made a number of important discoveries—including your work on neutrophils and olfactory receptors (see Up and Coming article, page 14)—but the most important is probably your research on an atherosclerosis vaccine. How close is it to becoming a reality?**

The good news is we're making excellent progress, having already proven the vaccine works in mice. Even so, we're realistic enough to understand that we're still a number of years away from proving the vaccine works in humans, which is a far more complicated process. We are confident in our basic discovery that identified the type of immune cells (CD4 T cells) that orchestrate attacks on the artery walls, and that these immune cells act as if they have already seen the antigen that leads them to launch the attack. These immune cells seem to remember the molecule brought forth by the antigen-presenting cells, and this immune memory is what allowed us to create a vaccine prototype.

BASED ON HOW MUCH WE WERE ABLE TO REDUCE ATHEROSCLEROSIS IN MICE, WE BELIEVE WE MIGHT BE ABLE TO ACHIEVE A **50 PERCENT REDUCTION** IN ATHEROSCLEROSIS IN HUMANS.

### What is the biggest challenge in getting the vaccine to work in humans?

Let's start with the fact that mice and humans are completely different species and that the human body and its immune system is far more complicated. That makes mice limited in value as a disease model, but it's nevertheless a critically important starting point. Right now we're focusing a lot of our attention on a real challenge, something we call "the switch." That means that while the vaccine might be anti-inflammatory for most everyone we would give it to, there is a chance in some people the process could switch and actually turn pro-inflammatory and do real harm to the patient. Until we figure out why that switch occurs and how to prevent it, we've still got a ways to go before we can call the vaccine safe, effective, and durable.

### If you are able to perfect the vaccine, what is its potential value?

Based on how much we were able to reduce atherosclerosis in mice, we believe we might be able to achieve a 50 percent reduction in atherosclerosis in humans. That's why we're working so hard on it because we know it would have such a huge impact on human health. We believe it could literally save millions of lives around the world and it would definitely be the highlight of my career. Ironically, it would bring me full circle from my medical training in that I would actually be helping heal patients.

### Looking back on that career, do you think you made the right decision to become a researcher?

Absolutely. My life in scientific research has been everything I hoped it would be and much more. I love coming up with hypotheses and then designing experiments to kill those hypotheses as quickly as possible to get down to what is true and verifiable. That's the best and only way to conduct science. If you fall in love with your hypotheses and design irrelevant experiments that never challenge your theories, you'll never make any progress. I've been a scientist for nearly 40 years and I actually see that as a huge advantage in helping me create groundbreaking research. When you first start out you want to be very specific and focused in a small niche so you get your grants and get taken seriously by your fellow scientists. But now, after having gathered a huge amount of knowledge over the years, I have the wide experience that enables me to see science and research problems on a big picture level. That's really valuable because real-life diseases require broad approaches to attack, and I'm fully aware there is no single magic bullet that will suddenly solve a complex scientific problem.

### How do you relax when you're not in the lab?

I enjoy cooking and spending time working on my classic 1964 Mercedes 230SL convertible. I also like long distance running. I just finished a half marathon in December and will run another one in April. Going on long runs is a good time to think scientifically. I don't wear headphones or take my phone so I can concentrate. A lot of big ideas or breakthroughs to research problems have come when I'm out there on the road.

The power of mentoring

# When you give you get

If you want to know the power of mentoring to transform lives, look no further than a wonderful relationship that began in 2018 between a talented researcher at the La Jolla Institute for Immunology (LJI) and a bright young high school student.

Neither of them knew at the time how impactful the mentorship would be. Chan Wang "Jerry" Lio, Ph.D., at the time an instructor in the lab of Principal Investigator Anjana Rao, Ph.D., remembers volunteering to mentor summer intern Allison Bien, a 16-year-old from San Diego's Torrey Pines High School.

"I was impressed with her resume, but the challenge we faced was that this would be the first time I mentored a high school student, and Allison, while fascinated with science and having been honored for her high school experiments, understandably was a bit intimidated at the prospect of working at a major research institute."

"It was a little overwhelming at first," Allison admits. "I had recently discovered a love for biology, but this was the first time I actually held a pipette in my hands. It was also my first experience learning about immunology and epigenetics."

Fortunately, because both Dr. Lio and Allison are remarkable in their own ways, there were a lot of positives going in. Dr. Lio, who was born in Macau and educated in Taiwan and the U.S., was promoted as a Young Independent Investigator in 2018, and was awarded a $750,000 "Transition to Independence" grant from LJI partner Kyowa Kirin Pharmaceutical Research, Inc. And, significantly, he says, he has always had a passion for helping and teaching other people.

"I'm thrilled and honored to play a role in LJI's important mission of helping influence and prepare the next generation of scientists." — DR. LIO

Dr. Lio taught me patience, and persistence, and his encouragement has been critical to my success through all my mistakes and failed experiments." — ALLISON BIEN


## SILVER MEDAL BRONZE MEDAL

"We competed against 77 high schools around the world, and our Torrey Pines High School iGEM team won a bronze medal, a silver medal, and two nominations over the past two years. It's really exciting to be recognized on an international stage." —Allison Bien

**iGEM:** The International Genetically Engineered Machine (iGEM) competition is a worldwide contest that gives students the opportunity to push the boundaries of synthetic biology by tackling everyday issues facing the world.

Allison had always had a predisposition towards biology. In addition to her 4.0 grade average, she was a key team member on her school's iGEM project in 2018, and was captain of the iGEM team last year. iGEM—which stands for International Genetically Engineered Machine—is a synthetic biology research competition where high school, college, and graduate school students from around the world create sophisticated research projects and present their findings at an international conference.

With Dr. Lio's assistance, Allison was able to conduct research for her iGEM team at the Institute.

"The hundreds of hours spent in the lab, all the late nights, and the help that Dr. Lio provided really paid off," Allison says. "We competed against 77 high schools around the world, and our Torrey Pines High School iGEM team won a bronze medal, a silver medal, and two nominations over the past two years. It's really exciting to be recognized on an international stage."

Both Dr. Lio and Allison agree that from the very beginning the two had immediate chemistry.

"I think both Allison and I have a similar spark and passion for learning," Dr. Lio says. "From the beginning I could see how excited and motivated Allison was. She was an incredibly quick study. She also has a great mind for science with an outstanding ability to think logically while showing remarkable dedication and perseverance. I think Allison has what it takes to be a true superstar."

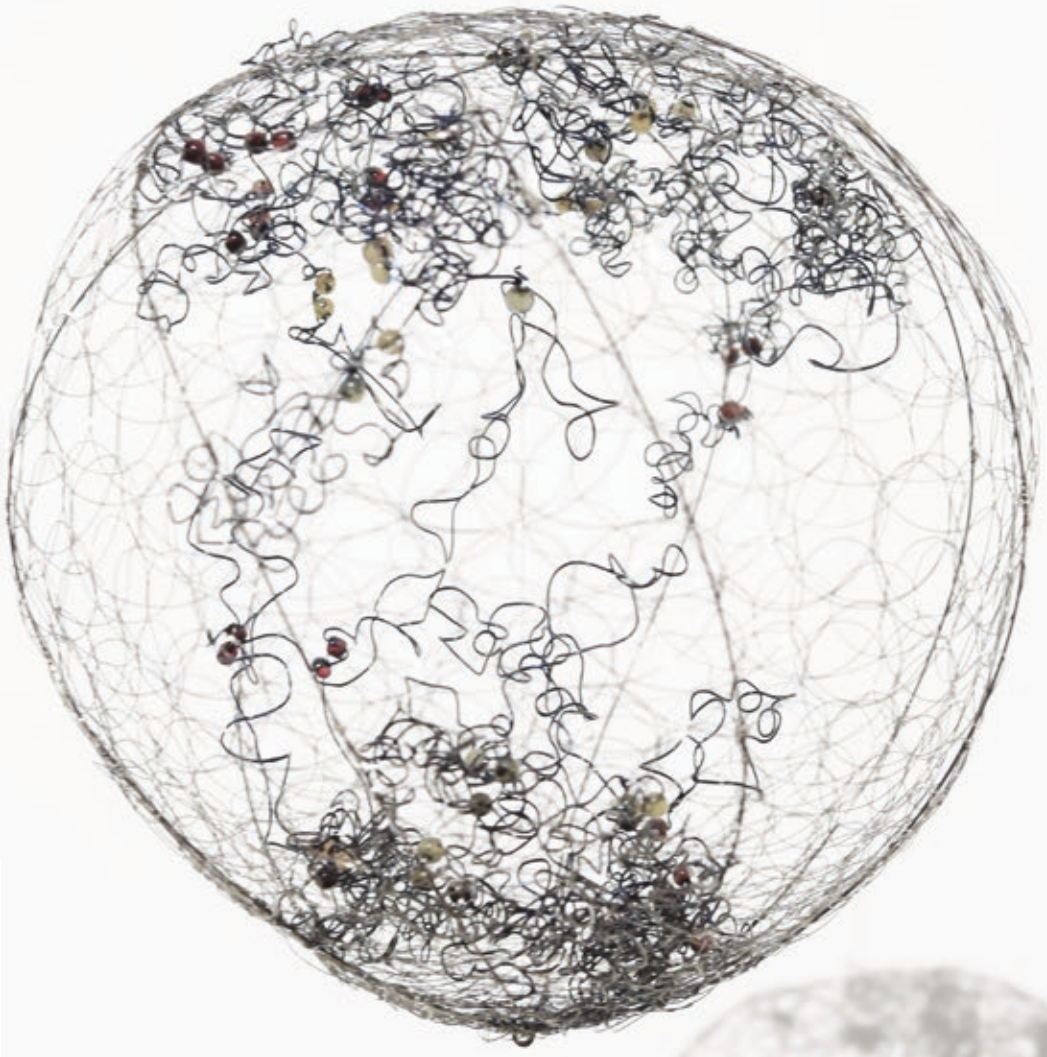
Allison recalls her first interaction with Dr. Lio. "When I first met Dr. Lio and he explained the research going on in the Rao lab, a new sense of urgency was ignited in me. I didn't understand what he was talking about, but the way he explained it made me believe to the core that it was important. Enough so that it made me go home and read every article on TET2/TET3 genes I could find."

From cracking jokes to discussing food to sharing serious moments of contemplation, a deeper relationship has developed between Allison and Dr. Lio. He now trusts her to assist him with his own research in a paid position in which she works 20 to 30 hours a week at the Institute during her senior year.

"Mentoring Allison has been a real highlight of my time here at LJI," Dr. Lio says. "I've learned so much about teaching and managing people that will help me for the rest of my career. I really have felt a lot of joy in sharing my knowledge with Allison and watching her develop. I'm also thrilled and honored to play a role in LJI's important mission of helping influence and prepare the next generation of scientists."

Allison is appreciative of the opportunity the Institute has provided her and she hopes it will help her achieve her goal of applying for a M.D.-Ph.D. program that will enable her to study cancer and hopefully benefit the lives of patients through her work. She says she could not have done it without the help of her mentor.

"Dr. Lio taught me patience and persistence, and his encouragement has been critical to my success through all my mistakes and failed experiments," Allison says. "I consider meeting Dr. Lio to be one of the most fortunate things that has happened to me because it has inspired me to pursue the dreams I have today. As a student and a friend, I am so grateful for Dr. Lio's teaching and support."



SAN DIEGO ART INSTITUTE

# ILLUMINATION

## 21st Century Interactions with **ART + SCIENCE + TECHNOLOGY**

**Anne Mudge | Dr. Ferhat Ay**

*Nucleus 1*

Anne Mudge explored the dynamics of DNA folding inside a cell's nucleus with spring wire, which measures two meters in length, precisely the length of an unfolded human genome.


**Margaret Noble | Dr. Matthias von Herrath**

*Dogma Roulette*

Margaret Noble created an interactive belief machine that makes players question their beliefs and world views through chance experiments with a roulette wheel.


**FOUR LJI RESEARCHERS PARTICIPATED IN THE PROJECT THAT PAIRED LOCAL ARTISTS WITH SCIENTISTS. THE RESULTING WORKS OF ART REFLECT ON THEIR INTERACTIONS IN SURPRISING WAYS.**

Just like art that forces us to see the world in new ways, science has changed our view of ourselves, our prejudices, and our culture. "It is my hope that by seeing science through the eyes of artists we are able to shift our focus outside of our worlds and consider novel ways we can impact each other and the planet," says Chi Essary, who curated the show.

For *Illumination: 21st Century Interactions with Art + Science + Technology* Essary played matchmaker for 16 artists with scientists from seven San Diego research organizations and invited 10 more artists working on their own interpretation of science, nature, and technology. The results are as varied and diverse as the collaborations that ensued.

When Margaret Noble met with LJI Professor Matthias von Herrath, M.D., who studies how the immune system destroys insulin-producing cells in type 1 diabetes, their conversation soon

**Cy Kuckenbaker | Dr. Zbigniew Mikulski and Dr. Sarah McArdle**

*Chromosome 22*

Seeing cell nuclei split under a high-tech microscope made Cy Kuckenbaker (right) wonder how much data is contained in the nucleus of a single cell. Using a familiar physical measurement, he printed the DNA sequence of chromosome 22, the smallest human chromosome, on 5,000 pages.

veered from immune cells to the power of dogmatic beliefs. “Science is considered to be based on facts, where hypotheses are either independently verified or refuted,” says Dr. von Herrath. “But some ideas can become so entrenched they effectively turn into articles of faith and prevent us from moving forward.”

Noble remembers thinking that the threat of dogma not only poses a challenge to biomedical research, but also plays an important role across the whole spectrum of human experience. “I wanted to explore all the areas where ingrained beliefs hold us back,” says Noble.

Cy Kuckenbaker concedes that he didn’t know much about biology when he visited the microscopy core facility at La Jolla Institute.

“My favorite science was astronomy—it was visual, philosophically challenging, and took place on a grand scale,” Kuckenbacker says. “During my encounters with Dr. Mikulski and Dr. McArdle, I experienced biology for the first time in a way that felt like astronomy. The world they are exploring is three-dimensional and inconceivably vast. It is breathtaking.” In his installation, he pays homage to his hosts for opening up a new world to him by featuring Drs. Mikulski and McArdle in the wallpaper’s repeating pattern.

The show will run until May 3 at the San Diego Art Institute in Balboa Park, 1439 El Prado, San Diego, CA 92101. **Admission is free.**

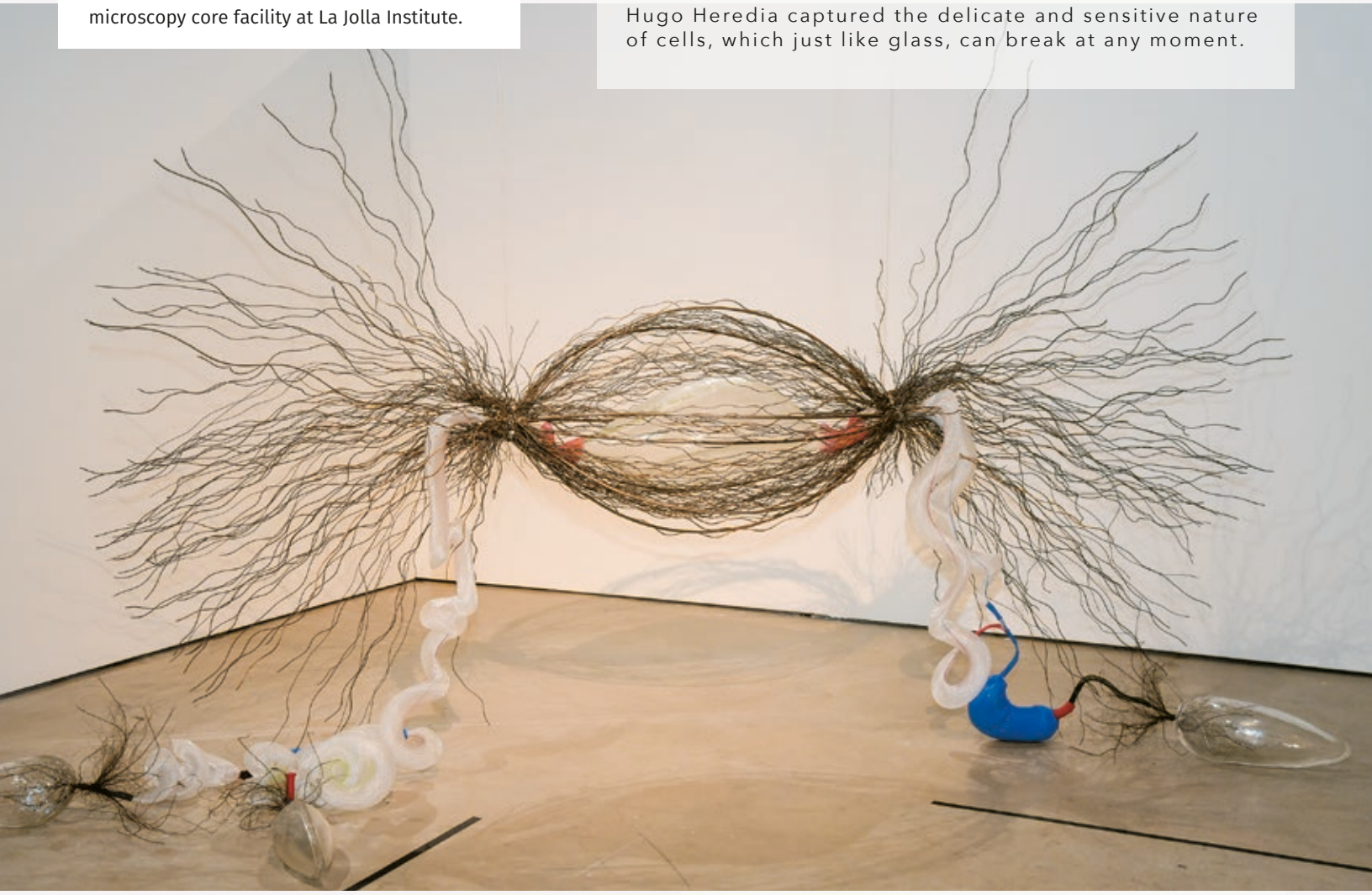
**“What inspired me the most was Dr. Shukla’s passion, his constant hard work in search for new information, and how critical and delicate his job is.”**

HUGO HEREDIA BARRERA

**Hugo Heredia Barrera | Dr. Vipul Shukla**

*Changes and Damage of DNA on a Cancer Cell*

Hugo Heredia captured the delicate and sensitive nature of cells, which just like glass, can break at any moment.



# Tremblay-Jacobs Symposium on Human Autoimmunity

La Jolla Institute for Immunology hosted the inaugural Tremblay-Jacobs Symposium on Human Autoimmunity on November 8, 2019, at the Institute. The event, spearheaded by LJI Board Director Geneviève Tremblay Jacobs, brought together global experts in the field of autoimmunity research with supporters and community leaders to share ideas to achieve the shared goal of creating a Life Without Autoimmune Disease.




**Top right:** LJI Board Director Geneviève Tremblay Jacobs shared her personal battle with a debilitating autoimmune condition and urged the research and medical community to put a bigger emphasis on human autoimmune research. **Top left** (from left): Pandurangan Vijayanand, M.D., Ph.D., (La Jolla Institute for Immunology), Stephen Targan, M.D., (Cedars Sinai), Martin Kriegel, M.D., Ph.D., (Yale University), Gary Firestein, M.D., (UC San Diego). **Bottom left** (from left): Paul and Geneviève Jacobs, LJI President Mitchell Kronenberg, Ph.D.

The next edition of the symposium will be held on **May 1, 2020**

**Register at lji.org/tremblay-jacobs**

## Women in STEM

On February 4, 2020, honors genetics students from the Academy of Our Lady of Peace visited La Jolla Institute to get a peek behind the scenes at a research organization. The group heard from female scientists and executives about their professional journeys that led them to careers in research or research-related fields, toured labs and core facilities, and got to ask a number of thoughtful questions.

## ACCESS CIRCLES

On February 7, 2020, Geneviève Tremblay Jacobs shared her personal story of fighting chronic illness and how it led her to push for novel approaches to study human autoimmunity with members of AccessCircles at their national symposium in Palm Beach. AccessCircles is a global network for women that aims to spur dialogue, action, and transformation through the sharing of collective knowledge and influence by tapping the wisdom of preeminent thinkers and industry pioneers.

From left to right: Dr. Anula Jayasuriya, Founder, EXXclaim Capital; Scientific Chair, WHAM!, Geneviève Tremblay Jacobs, Member, LJI Board of Directors, Dr. Alyson McGregor, Brown University.

## SWING FOR A CURE

The Bernardo Heights Country Club, under the auspices of their Women's Golf Association (WGA), raised over $26,000 in 2019 to support cancer research at La Jolla Institute for Immunology, more than doubling their fundraising efforts from the year prior. Each October, the WGA invites all club members to come together for a weeklong campaign to recognize cancer awareness month and raise funds to help support cancer research. It all culminates on Sunday with a Swing for a Cure Golf Tournament and Banquet. For the second year in a row, the participants chose to donate a major part of the proceeds to LJI. The Swing's other two beneficiaries, Salk Institute and American Cancer Society, shared the balance of $12,000.

"Bernardo Heights Country Club focuses on local organizations working on cancer research. LJI is a perfect fit for us. Our experience has served to educate our members to the wonders of immunotherapy. We even got to meet some of the scientists!"

**Julie Stone,** ***Chairperson for the Swing for a Cure***




## Fellows of the American Association for the Advancement of Science

Professors Shane Crotty, Ph.D., and Alessandro Sette, Dr. Biol.Sci., of La Jolla Institute for Immunology have been named as Fellows of the American Association for the Advancement of Science (AAAS). Election as an AAAS Fellow is an honor bestowed upon AAAS members by their peers for their scientifically or socially distinguished efforts to advance any field of science or its applications.

Dr. Crotty was elected an AAAS fellow in recognition of his distinguished contributions to the field of vaccine immunology, particularly defining and characterizing T follicular helper (Tfh) cells and their roles in humoral immunity.

Dr. Sette was recognized for his distinguished contributions to the field of immunology, particularly for providing insights into T-cell specificity and immune-profiling of T-cells in human disease, and for pioneering immuno-informatics.

New Fellows were announced during the 2020 AAAS Annual Meeting in Seattle, Washington, in February 2020. The election of Drs. Crotty and Sette brings the total number of AAAS fellows at LJI to four. The other two fellows are LJI President and Chief Scientific Officer Mitchell Kronenberg, Ph.D., and LJI Professor Erica Ollmann Saphire, Ph.D.

## Global Highly Cited Researchers 2019

Four researchers—or 19 percent of La Jolla Institute for Immunology's faculty—have been named in the Highly Cited Researchers 2019 list from the Web of Science Group. The 2019 Highly Cited Researchers list, released November 19 by the Web of Science Group, identifies scientists who produced multiple papers ranking in the top one percent by citations for their field and year of publication, demonstrating significant research influence among their peers.

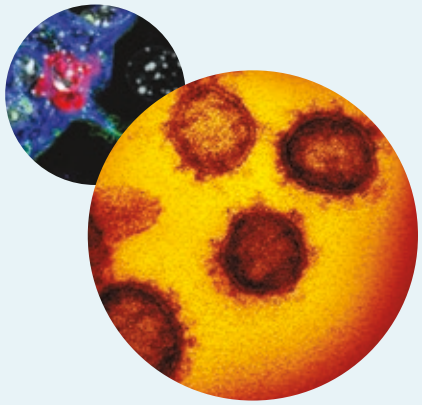
La Jolla Institute faculty on the list include Professor Shane Crotty, Ph.D., whose ground-breaking work on the immunology underlying vaccines earned him a spot on the list for the fourth year in a row; Professor Alessandro Sette, Dr. Biol.Sci., whose sustained efforts to systematically dissect the immune response to a wide range of microbes and allergens has a tremendous impact on the field of immunology, made the list for the second year.

This year, Drs. Crotty and Sette are joined by Professor Bjoern Peters, Ph.D., who helped establish the Immune Epitope Database, a free, searchable site that houses data from more than 1.6 million experiments, making it a one-stop shop for understanding and predicting the body's response to viruses, bacteria, cancer, allergens, and more, and Professor Anjana Rao, Ph.D., whose pioneering insights into the fundamentals of T cell biology have the potential to successfully address T cell exhaustion, which, in the past, has limited the success of cancer immunotherapies.

Drs. Peters, Rao, and Sette have been identified as researchers with cross-field impact, or exceptionally broad performance based on high impact papers across several fields, which is not only a testament to their research's prowess but also a strong signal of the increasing influence and importance of immunology on the broader scientific discourse.

**19 percent**

**of La Jolla Institute for Immunology's faculty have been named in the Highly Cited Researchers 2019 list from the Web of Science Group.**



# Semiconductor industry pioneer David M. Rickey joins Institute Board with commitment to help launch research careers of young scientists

Nothing excites David M. Rickey more about his involvement with the La Jolla Institute for Immunology than helping launch the research careers of young scientists and providing a path for their discoveries to one day lead to treatments and cures for diseases that afflict millions.

Rickey, who enjoyed a remarkable career in the semiconductor industry, including nearly a decade as chairman and CEO of Applied Micro Circuits Corporation (AMCC), was recently elected to the Institute Board of Directors.

Rickey already had established a philanthropic relationship with the Institute last year when he and his wife Brenda, along with Institute Board Member Tom Tullie and his wife, Judy, endowed the Institute's two-year-old program for developing the careers of young scientists.

Now named The Tullie and Rickey Families SPARK Awards for Innovation in Immunology, the program provides flexible start-up funding so that 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.

Each year the SPARK program receives dozens of proposals from Institute scientists. A panel that includes Institute scientists, the Rickeys and Tullies, board members, and top business leaders reviews the proposals, selects the finalists, and has each of them present their project in person. The winning proposals are each awarded $25,000 in start-up funding.

"Brenda and I have been inspired by the talent and drive of these young investigators and amazed at the sophistication and innovative excellence of their projects," Rickey says. "We're privileged to provide them with a stepping stone because we believe they're the future leaders of science."

Rickey, who lives in San Diego, was born in Geneva, a small town in western New York. He graduated with a BS in mathematics from Marietta College in Ohio, received a BS in metallurgy and materials science from Columbia University, and a masters in materials science from Stanford University.

After semiconductor engineering jobs with major companies like IBM and Northern Telecom, Rickey enjoyed his greatest success when he took the helm in 1996 of AMCC, a small and struggling company worth $30 million. Over the next decade, Rickey and his team turned AMCC around and grew the company into a high tech giant valued at more than $30 billion.

"I hope to leverage my experience to help the Institute achieve its ambitious but achievable mission of 'Life Without Disease,'" Rickey says. "Whether it's a young scientist with fresh ideas, or a seasoned principal investigator on the verge of a major discovery, I really believe the Institute's research is going to have a major impact on improving public health for millions around the world." •

# One of nation's top health care attorneys, J. Mark Waxman, is elected to La Jolla Institute Board of Directors

The process of biomedical science—from hypotheses that lead to research experiments that progress to clinical trials and ultimately result in successful treatments for disease—is extremely complicated. But surrounding that is a byzantine maze of regulations, safety and compliance requirements, intellectual property challenges, and a host of other issues that make it one of the most complex processes in the world.

The La Jolla Institute for Immunology recently elected to its Board of Directors a man with the expertise to help navigate that process. For the past four decades J. Mark Waxman has been one of the most respected and effective leaders in health care law at Foley & Lardner, where he is a partner in one of the nation's oldest and most prestigious firms.

"The depth of Mark's legal experience in both private health care settings as well as academic medicine will be invaluable to the Institute as our research discoveries increasingly emerge from the lab and enter the clinical realm and pharmaceutical marketplace," says Mitchell Kronenberg, Ph.D., Institute President and Chief Scientific Officer.

Waxman says he is looking forward using his four decades of experience to assist the Institute.

"These days you can't run any organization of any size without consideration of legal issues, and the biomedical and health care environments are particularly complex and unforgiving," Waxman says. "Everything the Institute is involved in, whether it's health and safety regulations, federal grants management, HIPA rules, IP opportunities and so much more, has myriad legal ramifications it has to stay on top of just to stay in business, let alone be successful in discovering treatments and cures for disease."

Waxman, who lives in San Diego, was born in Denver and raised in Los Angeles' San Fernando Valley. He majored in economics at UC San Diego and received his J.D. from the Boalt Hall School of Law at the University of California, Berkeley. After working as an Assistant U.S. Attorney in Los Angeles, Waxman joined the L.A.-based health care law firm Weissburg & Aronson, which merged with Foley & Lardner in 1996.

"One of the reasons I'm excited to become involved with the Institute is that I'm fascinated with the incredible progress their scientists are making in understanding and treating infectious disease," Waxman says. "Beyond the spike in headlines when something like the coronavirus arises, our planet has much larger and more serious problems with a host of infectious diseases that don't get as much publicity but that infect and kill millions every year. I really believe that the brilliance and commitment of the Institute's researchers will soon lead to a number of groundbreaking treatments and vaccines that will save many of those lives."

# Howard Grey, M.D.

**1932 - 2019**

## Dr. Howard Grey, former President and Scientific Director of La Jolla Institute for Immunology, died on December 23, 2019, in Denver, Colorado.

Dr. Grey, a highly respected biochemist who had helped lay the foundation for modern immunology, took over as Scientific Director and third President of LJI after the retirement of Dr. Kimishige Ishizaka in 1996. Over the next seven years, Dr. Grey strengthened LJI's ties with its business partners, expanded the faculty from six to 14 members, and initiated plans to move the Institute to LJI's current home in UC San Diego's Research Park. When he retired as CEO in 2003, he continued to be involved in immunological research at LJI until 2015.

"We deeply mourn the loss of Howard, who has left an indelible stamp on La Jolla Institute," said LJI President and Chief Scientific Officer Mitchell Kronenberg, whom Dr. Grey recruited as a faculty member to LJI in 1997. "For all of us who were fortunate enough to know and work with him, Howard was the embodiment of an incredibly sharp scientist and a wise leader, who guided a still young organization with a sure hand and ensured its place as one of the top immunology research institutes in the world."

Born in New York City, Dr. Grey earned a BA in Chemistry in 1953 from the University of Pennsylvania and then attended medical school, earning an M.D. from New York University and interning at Johns Hopkins. In 1958, however, he moved from the clinic to fundamental research and began a six-year research fellowship studying antigen-antibody interactions, first at University of Pittsburgh and then at the Scripps Clinic and Research Foundation in La Jolla. He was mentored in those early years by Dr. Frank Dixon, who later became well known for leading the Scripps Research Institute. After a short stint at Rockefeller University as an investigator and assistant professor in the mid-60s, he returned to Scripps in 1967.

In 1970, Dr. Grey joined the faculty of the University of Colorado Medical Center in Denver, where he embarked on two decades of high impact research and served as Head of the Basic Immunology Division from 1978 to 1988. In Denver, Dr. Grey was one of a group of trail-blazing immunologists who showed that MHC molecules—proteins that sit on the surface of cells and determine whether organ donors and recipients are a match—are crucial for activating T cells and initiating an efficient immune response. He then moved on to answer many biochemical questions that detailed the molecular mechanisms involved in the interaction between MHC molecules, bits of invading pathogens, and T cells.

Dr. Grey's contributions over this highly productive period of his career would earn him prestigious awards in the late 80s and 90s, including being named co-winner of the William B. Coley Award for distinguished research in basic and tumor immunology and culminating in membership in the National Academy of Sciences in 1999.

In 1988, Grey left Colorado to co-found the San Diego biotechnology company Cytel, in part to realize his work's clinical potential by creating and testing novel drugs that modulate the immune system, some to build better vaccines and others intended to dampen immune responses in autoimmune disease. Dr. Grey remained the company's Vice President for Research and Development until 1994, when he moved to LJI to become division head of Immunochemistry and, in 1996, LJI President.

Grey stepped down as LJI CEO in 2003 and at age 71 assumed a part-time position in LJI's Division of Vaccine Development working with Dr. Alessandro Sette, his former post-doc who had since joined the faculty. "Howard remained in my lab another 10 years as a partner and key contributor in driving grants and mentoring young students and postdocs," says Dr. Sette, who worked with Dr. Grey for almost 30 years. "He was my most influential mentor and one of the smartest people I ever met."

Dr. Grey served as LJI President Emeritus until his death.

Dr. Grey is survived by his wife Hilda, two of his three children, Allen and Stuart, and seven grandchildren. •

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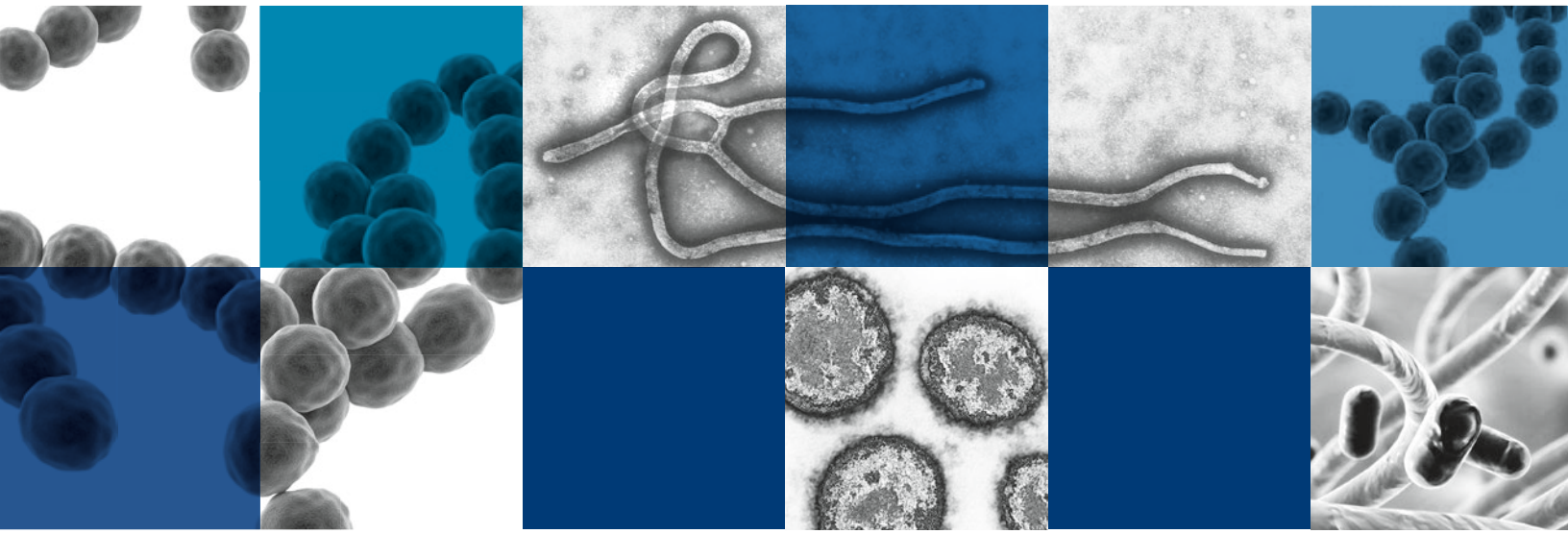

## OUR MISSION

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

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