Immune MATTERS

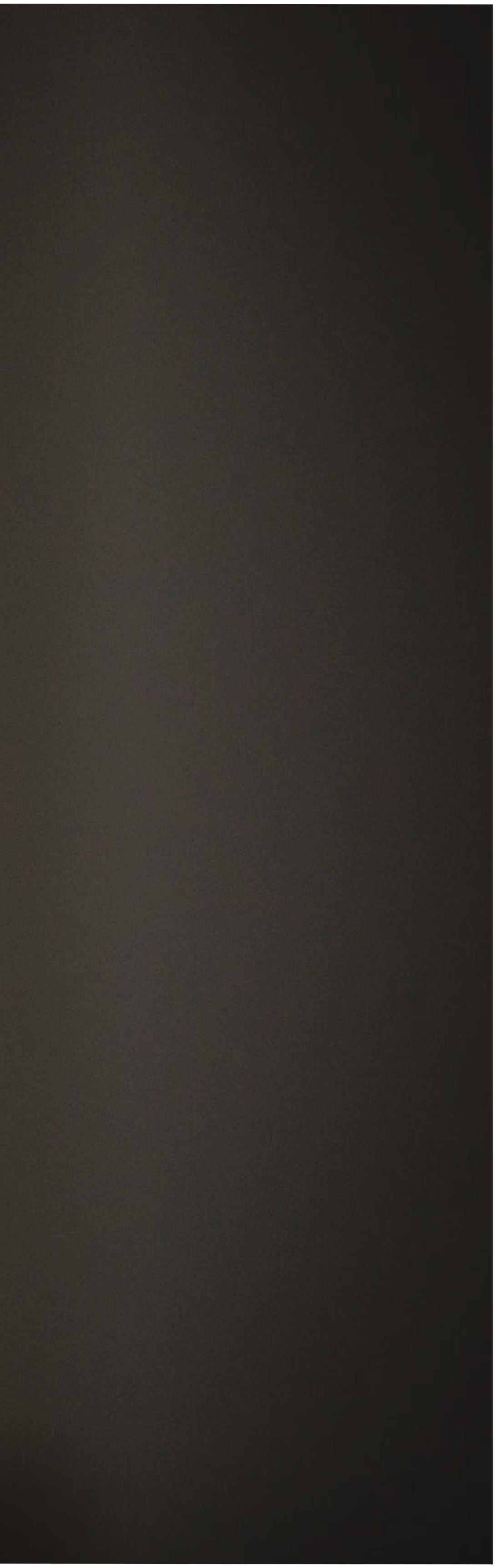
LA JOLLA INSTITUTE
FOR IMMUNOLOGY
FALL 2020

THE WORLD GOES CRAZY AROUND YOU

AN ORAL HISTORY OF HOW
LA JOLLA INSTITUTE SCIENTISTS
CAME TOGETHER AGAINST COVID-19

Above: As COVID-19 spread across the globe, LJI Instructor Kathryn Hastie, Ph.D., shifted her work from studying Lassa virus to studying antibodies against SARS-CoV-2.

Cover image: LJI Research Assistant Professor Daniela Weiskopf, Ph.D., works to uncover how T cells respond to SARS-CoV-2.



Immune MATTERS FALL 2020

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LID UNTIL ROTOR STOPS.

LETTER FROM THE PRESIDENT

When La Jolla Institute for Immunology (LJI) went into “maintenance mode” in mid-March, which meant limiting building access except for COVID-19 research, there had not been any fatal COVID-19 cases in San Diego County. Since then, there have been hundreds of COVID-19 deaths in the county and hundreds of thousands more nationwide. We are horrified by the loss of life and saddened by the pandemic-related social and economic disruptions that have occurred.

We have been horrified—but not helpless. As you’ll read in this issue’s cover story, LJI scientists and staff leapt into COVID-19 research. For example, their hard work showed how different types of immune cells work to fight the virus SARS-CoV-2, findings that will guide the development of vaccines and therapeutics. In this issue, you’ll also meet Haoyang Li, Ph.D., an LJI Postdoctoral Associate who had to quarantine during the SARS outbreak in China in 2003. He went on to investigate some of the world’s deadliest viruses and now is one of many LJI researchers who quickly shifted to studying COVID-19. The research has meant long hours and personal sacrifices for those working on COVID-19. I want to thank every member of the LJI research teams and staff for their efforts to adapt to social distancing in the labs and to work from home whenever possible. We are keeping the Institute safe as well as productive and have opened up to accommodate all types of research.

Of course, our mission is Life Without Disease®—not just life without COVID-19. All immunology research is related, and insights in one area can lead to advances in another. For example, treatments that failed to prevent bacterial infections in the blood (sepsis) led to the development of effective treatments for rheumatoid arthritis and other inflammatory diseases. LJI’s strengths in genetics and immune cell biology, which underpin our successes in cancer immunotherapy and autoimmune disease treatments, will also help us understand what constitutes a protective immune response to prevent COVID-19.

The pandemic has given the world a crash course in immunology. Scientific terms like herd immunity, and even T cells and B cells, are now commonplace. Will we see a new wave of scientists entering research in the coming years as students today grow up with immunology and virology in the news? The media

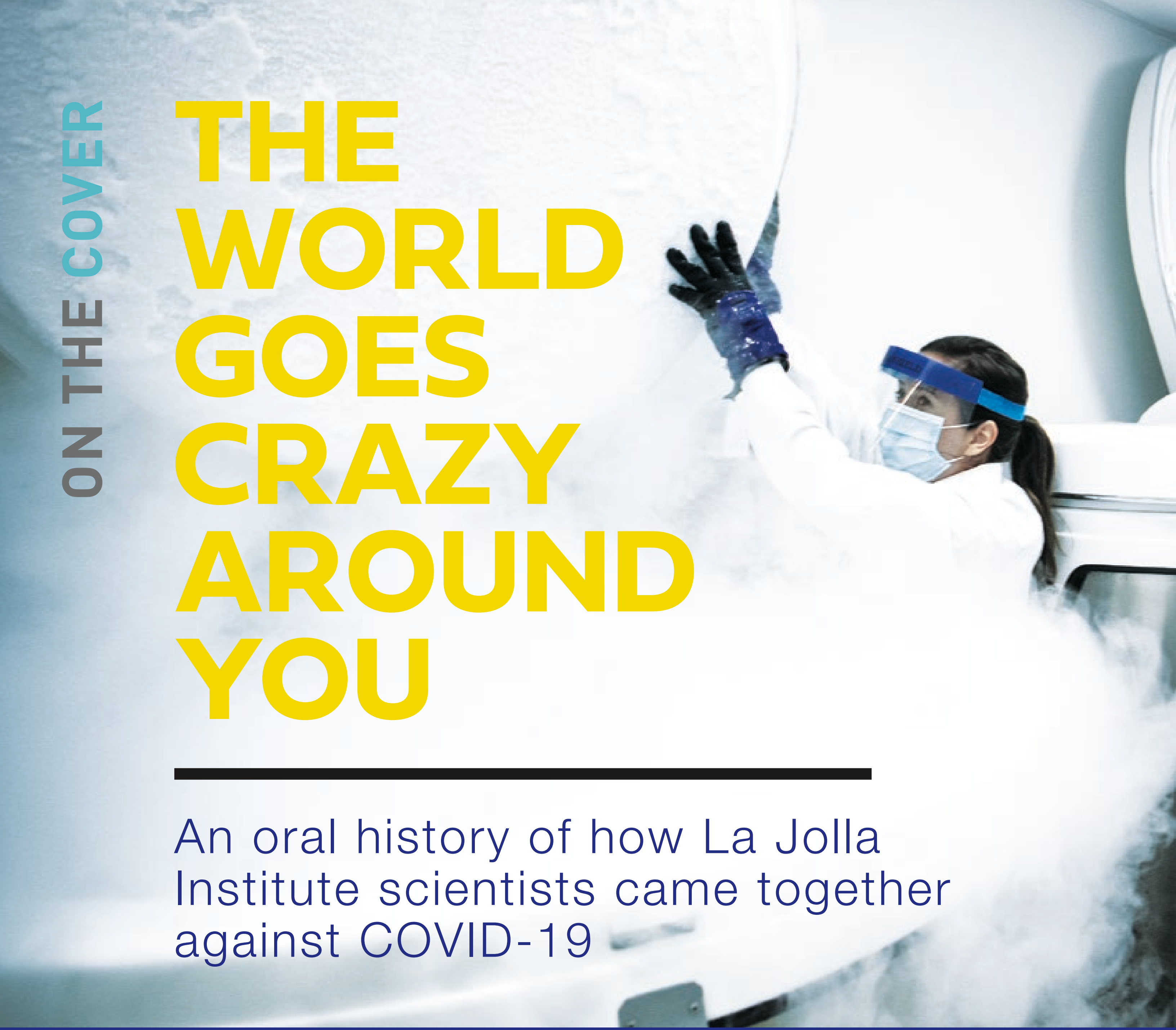
attention has certainly made communicating our mission much easier. The result has been philanthropic gifts that have fueled COVID-19 research before NIH grants could possibly start. Our Donor Honor Roll in this issue celebrates those who have given to life-saving research. I want to express my deepest gratitude to our community of supporters personally.

As I write this, several promising vaccine candidates are advancing through clinical trials. This pandemic will end through the development of vaccines, better treatments for people who are ill, and responsible social behavior. I hope that life will go back to normal as soon as possible, but I also hope that we can hold onto the knowledge that immunology is the key discipline for improving human health—and that scientific progress can lead to longer, happier lives for all.

Sincerely,

Mitchell Kronenberg

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



ON THE COVER

THE WORLD GOES CRAZY AROUND YOU

An oral history of how La Jolla Institute scientists came together against COVID-19

The pace of research for La Jolla Institute for Immunology's Coronavirus Task Force is intense. Samples come in, data come out. Some labs are running 24-7.

LJI scientists have brought us closer to ending the pandemic. They've also missed months of family dinners and bedtime stories. Missed sleep. Missed the *before* days.

This is the story—in the researchers' own words—of how LJI's dedicated scientists took on COVID-19.

Research Assistant Professor
Daniela Weiskopf, Ph.D.

Cover story images by Earnie Grafton

JANUARY AND FEBRUARY: A virus at the doorstep

Sydney Ramirez, M.D., Ph.D., Postdoctoral Researcher: My daughter, who is nine, was watching the evening news about the cases occurring in China. I think this was in December of 2019. She was scared.

Professor Lynn Hedrick, Ph.D.: When they shut down that area of China, we realized this was going to be a major issue if the virus escaped.

Professor Erica Ollmann Saphire, Ph.D.: We started thinking very seriously about the scientific questions that needed to be answered.

Instructor Alba Grifoni, Ph.D.: We started working on COVID-19 fairly early, around mid-January. I started doing bioinformatic analysis with Alessandro Sette and Bjoern Peters. I found that thrilling because the sequence of the virus had just come out. We were trying to predict which portions of the virus would be relevant for B cell and T cell responses.

Professor Bjoern Peters, Ph.D.: As part of the Immune Epitope Database (IEDB) mission, we routinely create meta analyses of new data for pathogens out there. We did this before for Zika. We did that for the novel coronavirus. That was our first scientific response.

Dr. Grifoni: We were doing analyses day and night. That's how we ended up publishing the *Cell Host & Microbe* paper in early March.

Professor Alessandro Sette, Dr. Biol. Sci.: The reason we got such a head start is because, based on completion of bioinformatic analysis, we were able to synthesize the peptides used to detect immune system responses to SARS-CoV-2.

Dr. Ramirez: Then there started to be reports of asymptomatic or mildly symptomatic individuals spreading the virus. The screening and containment strategies that were successful for SARS would not be successful with COVID-19.

Dr. Jose Angel Regla Nava, Ph.D., Postdoctoral Researcher: The difference for this virus, in my opinion, was the facility for transmission from person to person. That's how it got around the world so quickly. In only about five months, five million people in the world were positive.

By February, the Gates Foundation had approached Dr. Saphire to lead the Coronavirus Immunotherapy Consortium (CoVIC), a global effort to analyze virus-fighting antibodies. The National Institutes of Health required all companies wanting to participate in American clinical trials to first have their antibodies vetted by CoVIC at LJI.

MARCH: Full speed ahead

Jason Greenbaum, Ph.D., Director, Bioinformatics: Around the second week of March—the Wednesday night when the President got on TV to address the nation. That's when it started to get scary. The next day I asked all my staff to go home, because it seemed like it was getting worse.

Professor Shane Crotty, Ph.D.: This pandemic was not a surprise. I started my lab for this reason. It was apparent to virologists and plenty of vaccine researchers that emerging diseases are one of the few things that pose existential threats to the species.

Dr. Ramirez: I had been meeting with Shane regarding joining his lab in July. I met with him on a Wednesday in March just before the plans for the shutdown. He asked me if I was ready to commit to the lab, and I said that I was. Just two days later, I was rushing to get badge access to LJI before the planned shutdown that coming Monday.

The lab had only a skeleton crew due to the shutdown. Things picked up quickly, and other members of the lab were called in to help with the research. We started to collect more patient samples for analysis. Then it was full speed ahead.

Dr. Crotty: Everything we've been working on in the HIV vaccine community for the last 10 plus years, the tools and technologies to try to solve problems and move quickly, were immediately applicable to COVID-19—for studying the disease and for vaccine development.

Dr. Regla Nava: We used social distance. We stayed six feet from each other. In some labs, people worked in the morning or the afternoon and some at night.

Sharon Schendel, Ph.D., Program Manager, CoVIC: We had people who were even working from 11 p.m. to 7 a.m.

IN ONLY ABOUT FIVE MONTHS, 5 MILLION PEOPLE IN THE WORLD WERE POSITIVE.

Postdoctoral Associate Lindsey Padgett, Ph.D., and Professor Lynn Hedrick, Ph.D.

Dr. Greenbaum: The novel coronavirus didn't just change what I was working on—it was all that I was working on.

Professor Pandurangan Vijayanand, M.D. Ph.D.: We were already actively analyzing T cells reacting to different viruses using single-cell genomic approaches. In fact, we were examining T cells that react to a wide-range of respiratory viruses—so as COVID-19 spread, we were fully equipped to immediately understand the nature of SARS-CoV-2 reactive T cells.

Jennifer Dan, M.D., Ph.D., Clinical Associate: I was helping with the processing of blood specimens, but mainly I was running a lot of ELISAs [a blood testing technique] looking at anti-COVID responses.

Dr. Crotty: I was living in my office basically seven days a week. Analyzing COVID-19 patient data, figuring out experiment plans, and coordinating people. To figure out, as quickly as we could, what are the basic outlines of immune responses for COVID-19 patients.

Professor Sujan Shresta, Ph.D.: All of us were doing this research without dedicated funding, as it can take several months to get a new NIH grant. Time was of the essence and we just didn't have the luxury to wait for slower funding channels with this viral infection. As we creatively juggled resources to respond quickly to the pandemic, donors played—and still play—a tremendously important role, allowing us to quickly initiate and sustain COVID programs until labs can receive a new round of NIH grants.

Dr. Saphire: Our job is to do the science we need to do to get humanity out of this. You have to hold it together and focus on that while the world goes crazy around you.

Instructor Kathryn Hastie, Ph.D.: Antibody discovery is a new research avenue in our lab and we are pioneering new ways to get as much information from each cell as possible—and as quickly as possible. Just before the pandemic, we were starting to think of how to take the immune system's memory cells, which are of low abundance in blood samples, differentiate them into plasma cells that might secrete antibodies and then identify the individual cells and their targets in a day rather than weeks.

We wanted to do this with our African samples for Ebola antibody discovery and Lassa discovery. So I just sort of changed lanes again and started working with coronavirus samples.

Kristen Valentine, Ph.D., Postdoctoral Fellow: The scientific community really worked together. We started using several animal models—several mouse strains—to study T cell responses. We didn't know how long we would have immunity after infection. This disease had only been around for a few months. We needed time.

Daniela Weiskopf, Ph.D., Research Assistant Professor: You ran on adrenaline during those times, so you didn't even feel the long hours that much. Most of the time.

APRIL AND MAY: New discoveries and new hope

Dr. Weiskopf: By April, we had established a collaboration with UC San Diego, and they helped us collect samples from some of the people who had been exposed and recovered.

Dr. Grifoni: We needed to see if how we predicted the immune system would respond to the virus would actually work in samples.

Dr. Peters: We needed to know—if you have a certain immune response prior to exposure to the virus, does that make you less likely to develop symptoms? And then how does your immune response look after you are exposed?

Dr. Ramirez: Our *Cell* manuscript showed that the individuals who had recovered from mild COVID-19 formed antibodies and helper T cell responses to the SARS-CoV-2 spike protein and other portions of the virus, called antigens. It suggested that the majority of individuals who recover from COVID-19 will have formed an immune response specific to the virus.

All of these individuals responded to the viral spike protein. This is the protein being used in the majority of candidate vaccines, so it seems as though these vaccines may result in a similar response.

Professor Sujan Shresta, Ph.D.

Associate Professor Sonia Sharma, Ph.D.

By late March, LJI researchers had formed the LJI Coronavirus Task Force. The Institute had quickly become a hub for COVID-19 efforts.

INVESTIGATING SICK KIDS AND "STICKY" BLOOD

Dr. Sette: The *Cell* paper also clearly showed that, unexpectedly, people that had never seen the virus had preexisting immune reactivity to SARS-CoV-2.

Dr. Weiskopf: We realized that T cells recognize the entire virus and not just a certain protein. That was definitely important to know for therapeutics and vaccine development.

Dr. Shresta: We need to better understand how this one virus causes such a wide spectrum of symptoms. We also need to understand what makes it different from its closely related cousin, SARS, which causes severe symptoms in almost every patient. One ongoing approach is to conduct natural history studies in diverse populations, geographic locations, climatic zones—so that we understand the true epidemiology of this viral infection, including the impact of co-infections and diverse patient histories on the course of COVID-19.

My lab decided to study SARS-CoV-2 infection in Nepal. The major advantage is that I'm from there, so it's easy to navigate that world. The size of the country makes it easy to conduct our studies, and South Asia is really important to study because it houses a quarter of the world's population. The virus-host interaction may be different in clinical specimens in that part of the world.

Associate Professor Sonia Sharma, PhD.: When we started hearing about the first community spread in the States, that's when I thought, "This has pandemic potential."

Professor Lynn Hedrick, Ph.D.: There was this huge explosion of research, I think because the virus is so different and so serious. It was life-changing. It became the focus of our world.

Lindsey Padgett, M.D., Ph.D., Postdoctoral Associate: There was a lot we didn't know about the virus.

Dr. Sharma: People kept saying kids can't get COVID. And that never made sense to me. Then in May, cases of Pediatric Multisystem Inflammatory Syndrome came out of New York.

One of the cell types my lab has been particularly interested in is endothelial cells. When I started hearing that folks who were getting really sick with COVID-19 were having cardiovascular complications, pulmonary complications, kidney complications—it was very reminiscent of these multi-organ systemic inflammatory diseases that we study. We thought the virus might be infecting the endothelium in kids, as well as adults.

SUMMER: And the work went on

Members of the Coronavirus Task Force published paper after paper over the summer. Dr. Saphire's lab studied how mutations changed the virus and began a pilot study to test antibodies in precious human samples.

Dr. Hastie: We had to jump in with two feet. You can do all the studies you can with less valuable samples, but eventually you just have to take what you've learned and see what happens in a real environment.

Dr. Sette: Our *Science* paper that came out in July showed that the preexisting reactivity against SARS-CoV-2 that we and others had detected was directly related to immune memory cross-reactive with the common cold coronaviruses.

As the summer went on and cases began rising again, Anthony Fauci, M.D., Director of the National Institute for Allergy and Infectious Diseases, lauded the Sette and Crotty-led research in a Congressional hearing.

Dr. Grifoni: We have a fantastic coronavirus team. And we are so motivated. We want to find answers that are useful for the scientific community.

Dr. Weiskopf: It's been a really big team effort. Both the clinical core and flow cytometry core have been amazing.

Dr. Hedrick: Kudos to [LJI President and Chief Scientific Officer] Mitch Kronenberg and to [Vice President and Chief Operating Officer] Steve Wilson. We had very strict guidelines to follow, but we were allowed to come in and make progress and help. It took leadership to allow us to do that and help guide us so everyone was safe. And then there's been everyone behind the scenes in Operations making it work.

Dr. Saphire: I haven't had a work day less than 12 hours since February. Some of them are 18 hours. There are just hundreds of emails. We believe we're having a tremendous global impact.

Dr. Schendel: Members of my family say, "I so envy that you're able to actually do something."

IT TOOK LEADERSHIP TO ALLOW US TO DO THAT AND REALLY HELP GUIDE US SO EVERYONE WAS SAFE.

Continued from page 11...

So our lab started looking at the contribution of the endothelial immune response in COVID cases, and how this impacts vascular inflammation, particularly in children.

Dr. Hedrick: My lab focuses on cardiovascular research. We started working on COVID-19 when it got to the U.S. By that time, enough reports had come out in online journals that suggested that the virus was quite different from your normal virus or coronavirus, and that it caused a weird complication with blood clotting in many patients and serious thrombotic events in others, and that sparked our interest.

Only five to 10 percent of COVID patients have serious thrombotic events, like stroke or pulmonary thrombosis, but in almost everyone—even when they don't have to go into the hospital but they get their blood taken—in almost everyone, doctors have seen some kind of "sticky" blood or "clotted blood."

Dr. Padgett: We use a technology called CyTOF, which is kind of like flow cytometry on steroids. We use it to look at new immune cell populations, which could be very interesting in the context of COVID.

Dr. Hedrick: We hypothesized that COVID patients may have an increase in a type of immune cell called monocytes—and that these monocytes might be causing this unusual coagulation. I think we can help because we know very well how monocytes work.

Instructor Alba Grifoni, Ph.D.

FEATURE

Gearing up for the next pandemic

When COVID-19 hit, LJI's scientists and core staff were ready to fire up leading-edge technology in the search for treatments and vaccine candidates. With significant donor support, LJI even put together a new high containment (BSL-3) lab to expand its COVID-19 studies. These tools have made LJI a hub for infectious disease research, and they will prepare the Institute for the next emerging disease outbreak.

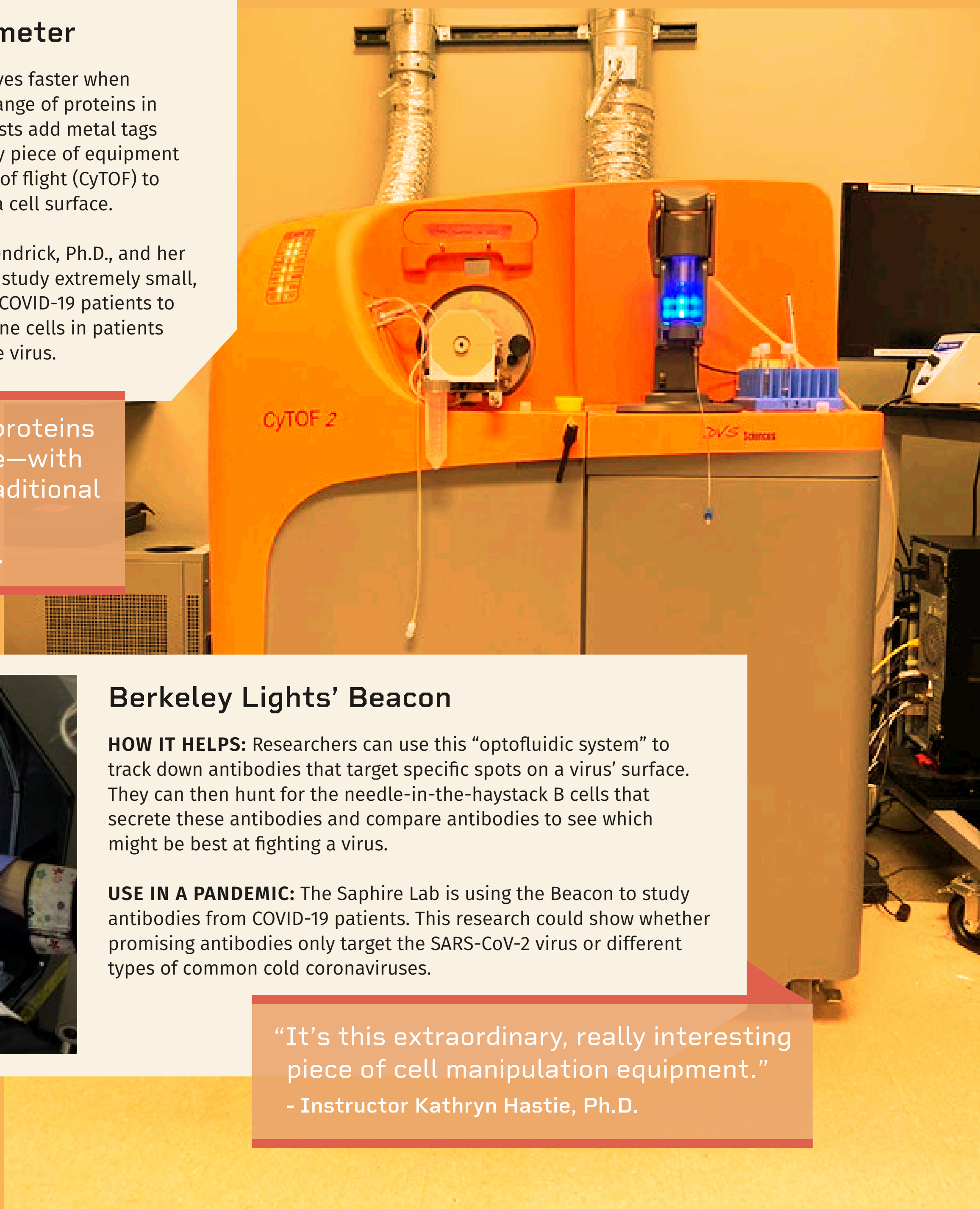
CyTOF Mass Cytometer

HOW IT HELPS: Research moves faster when scientists can detect a large range of proteins in very small samples. LJI scientists add metal tags to proteins and use this handy piece of equipment to perform cytometry by time of flight (CyTOF) to detect which proteins are on a cell surface.

USE IN A PANDEMIC: Lynn Hendrick, Ph.D., and her colleagues are using CyTOF to study extremely small, precious blood samples from COVID-19 patients to understand the roles of immune cells in patients with vascular symptoms of the virus.

"This lets us look at more proteins and get the bigger picture—with much more detail than traditional cytometry."

- Professor Lynn Hedrick, Ph.D.



Berkeley Lights' Beacon

HOW IT HELPS: Researchers can use this "optofluidic system" to track down antibodies that target specific spots on a virus' surface. They can then hunt for the needle-in-the-haystack B cells that secrete these antibodies and compare antibodies to see which might be best at fighting a virus.

USE IN A PANDEMIC: The Saphire Lab is using the Beacon to study antibodies from COVID-19 patients. This research could show whether promising antibodies only target the SARS-CoV-2 virus or different types of common cold coronaviruses.

"It's this extraordinary, really interesting piece of cell manipulation equipment."

- Instructor Kathryn Hastie, Ph.D.

"We really need to use the real virus to understand the basic science—so we need a BSL-3 facility."

- Postdoctoral Associate Haoyang Li, Ph.D.

Infectious Disease Exploration and Abatement (IDEA) Facility

HOW IT HELPS: The IDEA Facility is a Biosafety Level 3 (BSL-3) lab, meaning it meets the CDC's high containment requirements for pathogen control. Among the requirements: scientists must don personal protective equipment, experiments are performed in biosafety cabinets, and exhaust air cannot be recirculated.

USE IN A PANDEMIC: The IDEA facility is a key piece of infrastructure for studying potentially lethal infectious diseases. COVID-19 projects include the development of a more accurate clinical test. By building the IDEA Facility, the Institute will be able to take on many more studies of future emerging viruses.

Cytek Biosciences Aurora Flow Cytometer

HOW IT HELPS: This machine is a workhorse! The advanced flow cytometer gives scientists a highly sensitive way to analyze immune cell populations.

USE IN A PANDEMIC: The Sette and Crotty Labs at LJI use the Aurora Flow Cytometer to study which cells help COVID-19 patients fight off the virus. Their work has shown the key role of T cells in recovery and helped guide the development of vaccines.

The Titan Krios Transmission Electron Microscope (TEM)

HOW IT HELPS: Scientists freeze a sample in liquid nitrogen and shoot it with electron beams to capture images of how a virus changes its shape to infect cells, how antibodies target viral proteins, and much more.

USE IN A PANDEMIC: The Saphire Lab is using the Titan Krios TEM to quickly get high-resolution images that reveal how antibodies can neutralize SARS-CoV-2. By comparing antibodies sent in from labs around the world, they hope to find the antibodies (or combination of antibodies) that will work the best.

UP & COMING

Haoyang Li, Ph.D.

AN INSPIRED VACCINE

Postdoc's new vaccine project combines Ebola and coronavirus expertise

Haoyang Li, Ph.D., is no stranger to quarantine. He was in high school in China when SARS came knocking.

"My hometown was in one of the worst hit areas at that time. I know people who died," says Dr. Li. "We were quarantining at home for four months—from April to July."

During those days in quarantine in 2003, Dr. Li ended up picking up a book about viruses. And then another book. And another. He went on to pursue a Ph.D. in virology. The SARS outbreak had changed the course of his life.

Then, just as he started his graduate work, the biggest Ebola virus outbreak in history struck in West Africa. Dr. Li and his graduate advisor launched research into Ebola virus at a time when no other academic lab in China was focused on the virus. Dr. Li needed resources, and his search led him to studies from the lab of Erica Ollmann Saphire, Ph.D., who today serves as a professor at La Jolla Institute for Immunology (LJI).

"I read a lot of Dr. Saphire's papers and cited her work in my dissertation," says Dr. Li. Again, a virus had changed the course of his life. Once he earned his Ph.D., he moved to California to work in Dr. Saphire's lab as a postdoctoral researcher.

Dr. Saphire is an expert in structural virology. She and her lab members use high-resolution imaging tools to map viral structures in detail. These maps can reveal sites on a virus, called immunogens, that elicit human antibodies to stop an infection. Visualizing these viral targets is a crucial step in designing vaccines and therapies. "Nothing is better than seeing the details of the immunogen with your own eyes," says Dr. Li.

Dr. Li continued to study Ebola virus at LJI when another virus emerged: SARS-CoV-2. As the world began hearing more about lockdowns in China and infections on cruise ships, Dr. Li returned to an idea he had back in graduate school: a combined coronavirus/Ebola virus vaccine.


La Jolla Institute
CRAFT
TMC

"At that time, based on Dr. Saphire's structures, I found that we could design a novel vaccine against both Ebola virus and coronavirus," says Dr. Li.

"He came to me with this idea back in January, and I told him to go for it," says Dr. Saphire.

This kind of combined vaccine is called a multivalent vaccine. Some of the most widely used vaccines are multivalent vaccines which combine pathogens, such as MMR shots that combine measles, mumps, and rubella protection in one dose. The new generation multivalent vaccines not only combine pathogens in a single dose but in the same vaccine molecules—basically sticking immunogens from different viruses together.

Dr. Li hopes to take an existing Ebola virus vaccine, which has already been tested and approved for safety and efficacy, and add an important SARS-CoV-2 immunogen to the Ebola proteins used in the vaccine. "We hope to put them together to get a chimera immunogen," says Dr. Li.

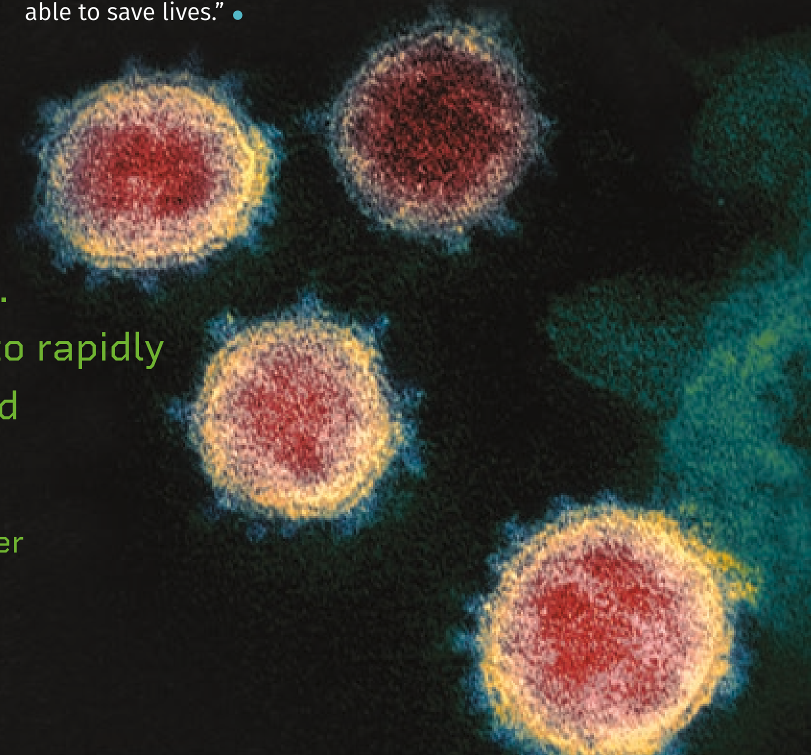
A multivalent Ebola/coronavirus vaccine might work well *because* the two viruses are so different. The viruses originated in different parts of the world, and most people have never been exposed to Ebola virus. This means their immune systems would go into high alert if they encountered unfamiliar Ebola virus immunogens delivered in a vaccine.

The idea is that as the body responds to the Ebola immunogens, it would also build a strong immune memory of SARS-CoV-2. Two birds, one very sophisticated stone.

"Multivalent vaccines are the future," says Dr. Li. "If this idea works, we would hope to rapidly design vaccines against unexpected pandemics in the future."

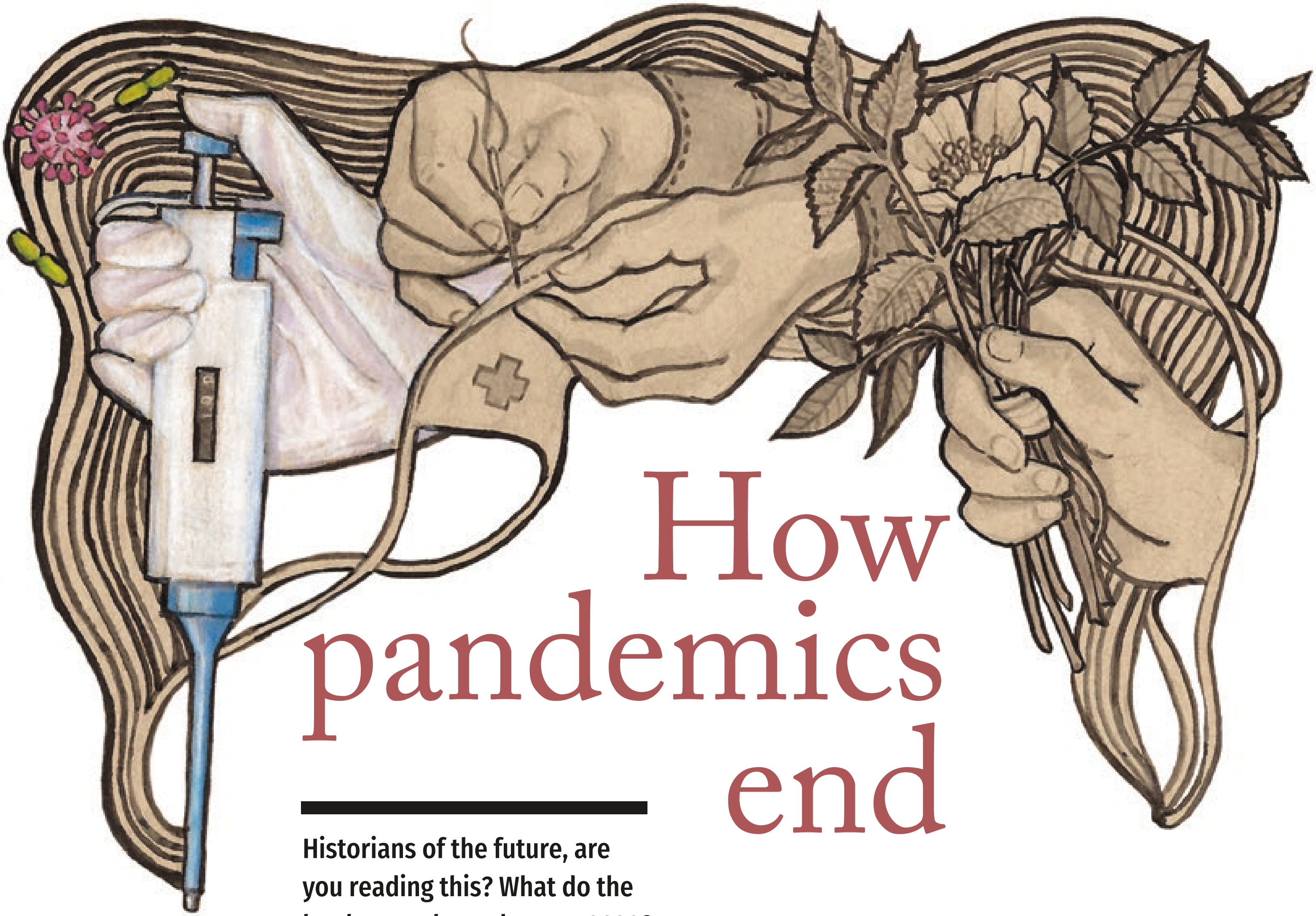
He's been spending long hours in the lab working on the new vaccine design and developing a test that might detect SARS-CoV-2 more reliably. Staying home was never an option.

"This time, I didn't quarantine even one day. We had to keep working," says Dr. Li. "We may be able to save lives." •



"Multivalent vaccines are the future. If this idea works, we would hope to rapidly design vaccines against unexpected pandemics in the future."

– Haoyang Li, Ph.D., Postdoctoral Researcher



How pandemics end

Historians of the future, are you reading this? What do the books say about the year 2020?

Nearly every pandemic has had an arc. A disease spreads, it kills, it stops. We don't yet know how the COVID-19 pandemic will end. But here are the lessons we've learned from past pandemics—and how infectious disease research has evolved.

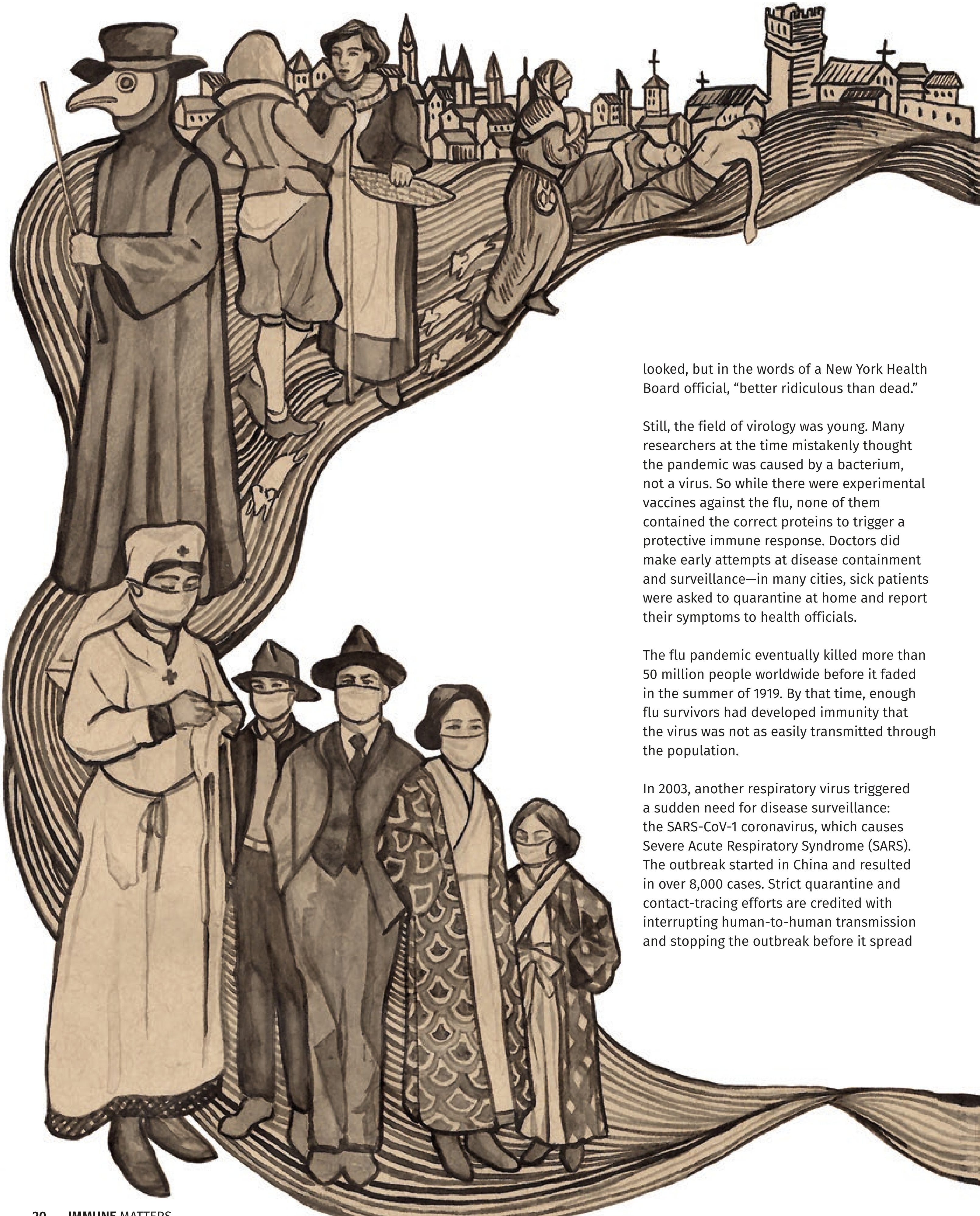
Let's start with the bubonic plague. The bacterial disease, also known as the Black Death, hurtled through Asia, Africa, the Middle East, and Europe during the Middle Ages. The pandemic peaked during the 14th century. Somewhere between 75 million and 200 million people died from the bubonic plague between 1347 and 1351. Some cities in Europe lost half of their population.

The great plague did end. While there are examples of towns spared because they maintained a strict quarantine, historians believe the disease eventually disappeared in many areas because everyone had either developed immunity or died.

Medicine was forever changed by that wave of death. Cities created the first-ever boards of health. Before the plague, many doctors relied on astrological projections to understand disease. Afterward, they turned to more testable theories. In the following centuries, the scientific method was born.

The bubonic plague continued to cause outbreaks through the 18th century, but never on the same scale. Along the way, some doctors designed early personal protective equipment (PPE) to avoid infection. The new head-to-toe coverings sometimes included beaked "plague doctor" masks.

Doctors understood a lot more about infectious diseases by the time the "Spanish flu" hit in 1918. The public was asked to avoid crowded places, stay home if they felt sick, and even wear a cloth face mask. And boy. Some hated how masks

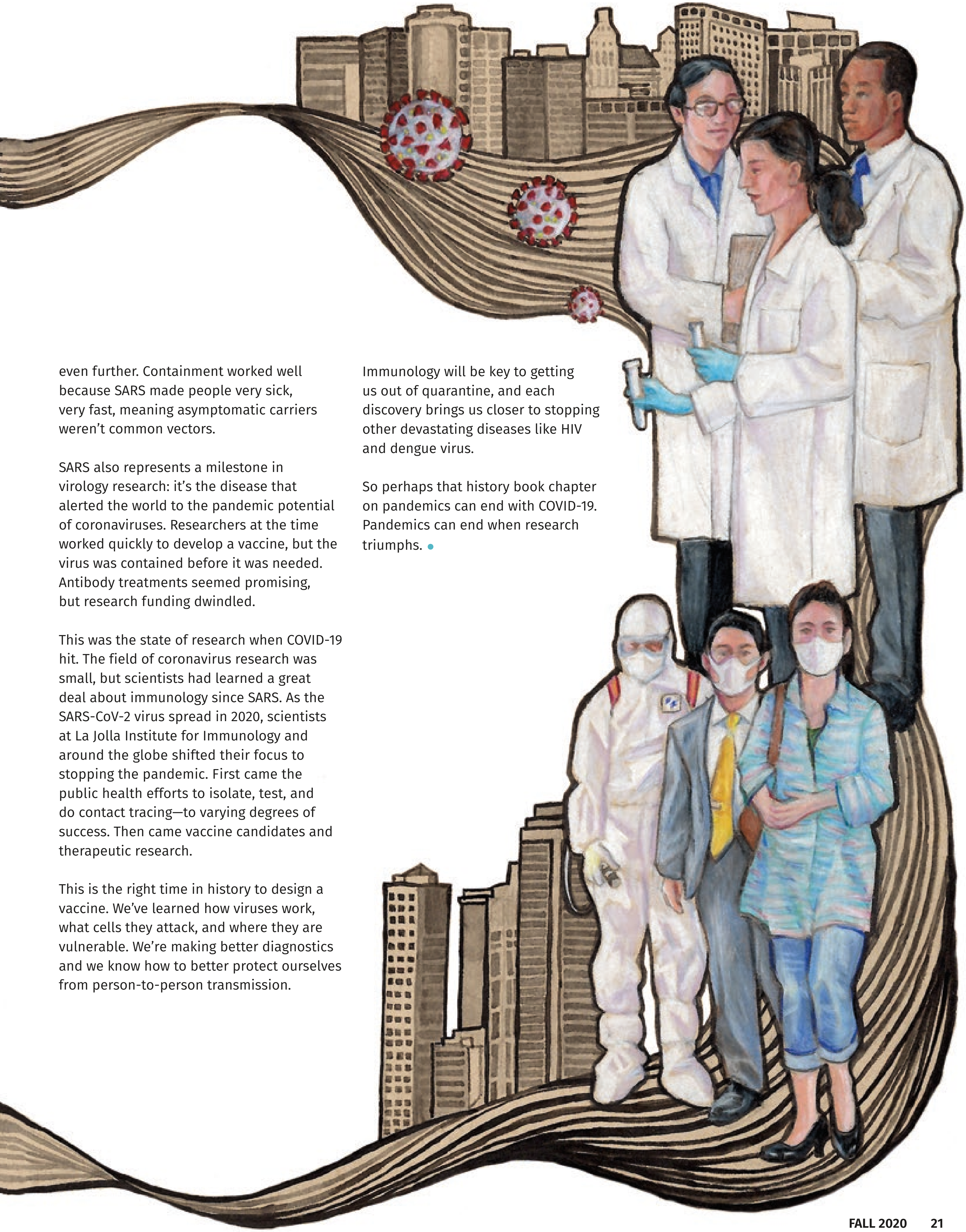


looked, but in the words of a New York Health Board official, “better ridiculous than dead.”

Still, the field of virology was young. Many researchers at the time mistakenly thought the pandemic was caused by a bacterium, not a virus. So while there were experimental vaccines against the flu, none of them contained the correct proteins to trigger a protective immune response. Doctors did make early attempts at disease containment and surveillance—in many cities, sick patients were asked to quarantine at home and report their symptoms to health officials.

The flu pandemic eventually killed more than 50 million people worldwide before it faded in the summer of 1919. By that time, enough flu survivors had developed immunity that the virus was not as easily transmitted through the population.

In 2003, another respiratory virus triggered a sudden need for disease surveillance: the SARS-CoV-1 coronavirus, which causes Severe Acute Respiratory Syndrome (SARS). The outbreak started in China and resulted in over 8,000 cases. Strict quarantine and contact-tracing efforts are credited with interrupting human-to-human transmission and stopping the outbreak before it spread



even further. Containment worked well because SARS made people very sick, very fast, meaning asymptomatic carriers weren't common vectors.

SARS also represents a milestone in virology research: it's the disease that alerted the world to the pandemic potential of coronaviruses. Researchers at the time worked quickly to develop a vaccine, but the virus was contained before it was needed. Antibody treatments seemed promising, but research funding dwindled.

This was the state of research when COVID-19 hit. The field of coronavirus research was small, but scientists had learned a great deal about immunology since SARS. As the SARS-CoV-2 virus spread in 2020, scientists at La Jolla Institute for Immunology and around the globe shifted their focus to stopping the pandemic. First came the public health efforts to isolate, test, and do contact tracing—to varying degrees of success. Then came vaccine candidates and therapeutic research.

This is the right time in history to design a vaccine. We've learned how viruses work, what cells they attack, and where they are vulnerable. We're making better diagnostics and we know how to better protect ourselves from person-to-person transmission.

Immunology will be key to getting us out of quarantine, and each discovery brings us closer to stopping other devastating diseases like HIV and dengue virus.

So perhaps that history book chapter on pandemics can end with COVID-19. Pandemics can end when research triumphs.

Fueling a cancer researcher's career

THE TULLIE AND RICKEY FAMILIES SPARK AWARDS FOR INNOVATIONS IN IMMUNOLOGY

In 2019, researcher Huy Dinh, Ph.D., was among five early career scientists at La Jolla Institute for Immunology to receive $25,000 in funding through the Tullie and Rickey Families SPARK Awards for Innovations in Immunology. Using data generated by his SPARK project, Dr. Dinh recently published groundbreaking research on a rare but vital stem cell connected to tumor growth. His findings are a step toward developing rapid, blood-based diagnostic tests for cancer, emphasizing the power of private philanthropy to advance bold ideas. Today, Dr. Dinh is building on this research as he starts his own lab at The University of Wisconsin–Madison.

"As I interviewed for faculty positions, I found that my SPARK project came up as a perfect example of how I could lead independent research."

Each year, the Tullie and Rickey Families SPARK Awards program supports the next generation of researchers as they pursue high-risk, high-reward projects. Dr. Dinh's project was funded by the generosity of LJI Board Director **Mark Bowles** and **Kathleen Bowles**, **Ira** and **Kathleen Robb** and other various donors to the program in 2018.

Learn more about Dr. Dinh's success and the results from his fellow awardees in the 2020 Annual Report on the Tullie and Rickey Families SPARK Awards for Innovations in Immunology coming out soon. For a preview of the digital report visit

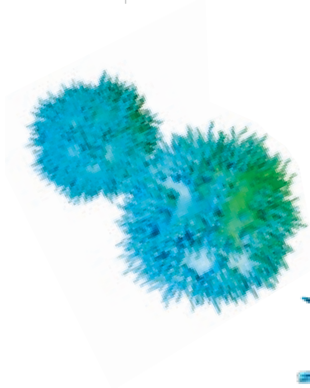
lji.org/SPARKAnnualReport

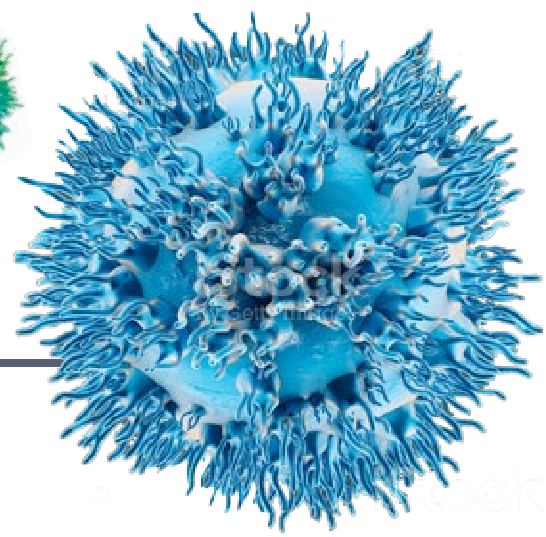
Tracking how SARS-CoV-2 mutates

In a recent *Cell* paper, LJI Professor Erica Ollmann Saphire, Ph.D., and researchers from Los Alamos National Laboratory and Duke University showed how a second strain of the SARS-CoV-2 virus quickly traveled around the globe in the early days of the pandemic.

This viral variant, called “G” virus, did not have a higher mortality rate than the original “D” virus. Further experiments showed that the G variant was linked to higher viral “titers,” meaning the virus grew more efficiently, even though it didn’t seem to cause worse symptoms.

Dr. Saphire and the study co-authors are continuing to monitor how SARS-CoV-2 may mutate. She explains that viruses regularly acquire mutations to help them “escape” antibodies made by the human immune system. “We’ll be keeping an eye on it,” says Dr. Saphire.





Shedding light on how T cells fight SARS-CoV-2

Scientists at LJI were the first to show the world how the immune system responds to SARS-CoV-2. Their detailed analysis, published in *Cell* in May, found that patients with COVID-19 could mount a robust T cell response against key vulnerable parts of the virus. This piece of good news helped guide vaccine efforts and dispelled fears that the virus may elude efforts to create an effective vaccine.

“All efforts to predict the best vaccine candidates and fine-tune pandemic control measures hinge on understanding the immune response to the virus,” says Professor Shane Crotty, Ph.D., who co-led the research with Professor Alessandro Sette, Dr. Biol. Sci.

“What we saw was a very robust T cell response against the spike protein, which is the target of most ongoing COVID-19 efforts, as well as other viral proteins,” added Dr. Sette.

In an August *Science* study, the team went on to show that exposure to common cold coronaviruses can teach the immune system to recognize SARS-CoV-2. The researchers could not say whether that reactivity equaled protection against the virus, but there is a chance it could explain why some people have milder symptoms of the disease.

“We have now proven that, in some people, pre-existing T cell memory against common cold coronaviruses can cross-recognize SARS-CoV-2, down to the exact molecular structures,” says LJI Research Assistant Professor Daniela Weiskopf, Ph.D., who co-led the new study with Dr. Sette.

“All efforts to predict the best vaccine candidates and fine-tune pandemic control measures hinge on understanding the immune response to the virus.”

– Shane Crotty, Ph.D.

When a common allergen turns deadly

Scientists at LJI are working to understand why some people develop allergies and asthma while others do not. This mission has led them to investigate house dust mites: an allergen that is everywhere and causes no symptoms in most people—but dangerous asthma attacks in others.

In a recent *Science Immunology* study, LJI researchers report that a previously unknown subset of T cells may keep allergic immune reactions and asthma from ever developing in response to house dust mites. People with this specific cell population, which is enriched for a gene that encodes a protein called TRAIL, could have less T cell-driven inflammation.

"We discovered new immune cell subsets and new therapeutic opportunities," says Grégory Seumois, Ph.D., Instructor and Director of LJI's Sequencing Core and co-leader of the new study.

"The study highlights the power of unbiased single-cell genomics approaches to uncover novel biology," adds Professor Pandurangan Vijayanand, M.D. Ph.D., senior author of the new study.

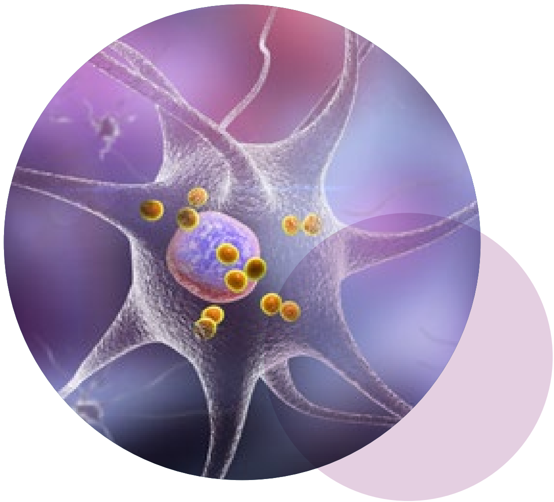
Detecting telltale T cells in Parkinson's patients

The brain cells that die in Parkinson's disease appeared to be marked for death by clumps of a damaged protein called alpha-synuclein. Now a new *Nature Communications* study shows that alpha-synuclein acts as a beacon for the T cells that contribute to cell death. The study, led by LJI Research Assistant Professor Cecilia Lindestam Arlehamn, Ph.D., and LJI Professor Alessandro Sette, Dr. Biol. Sci., gives further evidence that autoimmunity plays a role in Parkinson's disease.

The research could make it possible to someday detect Parkinson's disease before the onset of debilitating motor symptoms—and potentially intervene with therapies to protect neurons and slow disease progression.

"Once these cells are gone, they're gone. So if you are able to diagnose the disease as early as possible, it could make a huge difference," says Arlehamn.

Adds Sette, "This study tells us that detection of T cell responses could help in the diagnosis of people at risk or in early stages of disease development, when many of the symptoms have not been detected yet."



"Once these cells are gone, they're gone. If you are able to diagnose the disease as early as possible, it could make a huge difference."

– Cecilia Lindestam Arlehamn, Ph.D.

Stopping deadly inflammation

A recent LJI investigation offers a new strategy for treating DADA2, an inflammatory blood vessel disease in children. The *Science Advances* study, led by Associate Professor Sonia Sharma, Ph.D., showed that a previously poorly understood enzyme actually inhibits inflammation in blood vessels.

The newly explored enzyme, called ADA2, was not thought to have an important role in the body. Instead, Dr. Sharma's team showed that loss of the enzyme leads to too much of an immune molecule called signaling molecule called type 1 interferon beta, which causes harmful inflammation. "What we ended up identifying was a new immuno-metabolic axis," says Dr. Sharma. These findings suggest that doctors may one day treat DADA2 by reconstituting the enzyme in patients.

LJI gives back through

X-WOW initiative

Back in June, LJI Microscopy and Histology Core Director Zbigniew Mikulski, Ph.D., packed up a box, added a mailing label and sent it half-way around the world. The refurbished microscope inside landed in Ilorin, Nigeria, where a hematologist immediately put it to use at a local hospital.

Dr. Mikulski restored and donated the microscope as part of the X-WOW program. This global network, which mostly connects scientists through social media, brings crucial technology to scientists who couldn't normally access it. The ultimate goal is to improve cancer diagnosis around the world.

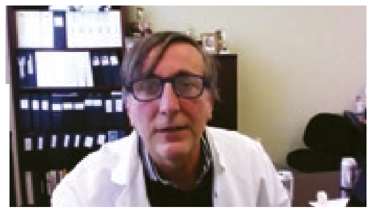
"The microscope was brought to me from a lab that was well-equipped and no longer needed it, so I was looking for a place to donate it," says Dr. Mikulski. "It gave me immense joy to work on this."

EVENTS

LJI scientists welcome virtual visitors

Staying safe during the pandemic meant canceling LJI's in-person events this year. Instead, our outreach shifted online, and we were proud to bring viewers into our labs virtually for COVID-19 research updates. The Institute's public "Live from the Laboratory" series alone has welcomed more than 2,000 live attendees since April. LJI plans to continue the online "Live from the Laboratory" series through the Fall and into 2021. We hope you will tune in. In case you missed a past event, recordings are posted online at lji.org/covid-19/videos.

Coronavirus Updates:
Live from the Laboratory with
Erica Ollmann Saphire, Ph.D.



Coronavirus Updates:
Live from the Laboratory with
Alessandro Sette, Dr. Biol. Sci.

Coronavirus Updates:
Live from the Laboratory with
Mitchell Kronenberg, Ph.D.

Coronavirus Updates:
Live from the Laboratory with
Shane Crotty, Ph.D.

» **lji.org/covid-19/videos**

Film premiere highlights LJI's COVID-19 research

The Visionaries, an award-winning public television series hosted by Sam Waterston, recently launched its twenty-fourth season, which included a half-hour documentary film featuring La Jolla Institute infectious disease researchers titled *Life Without Disease*. The film showcased the critical work of LJI scientists working on the frontlines of the COVID-19 pandemic. La Jolla Institute hosted a virtual premiere of the film on Aug. 25 that featured a Q&A with the scientists involved and filmmaker Jody Santos.

Images from: *The Visionaries*

Erica Ollmann Saphire leads Coronavirus Immunotherapy Consortium

CoVIC

In March, LJI announced the launch of the Coronavirus Immunotherapy Consortium (CoVIC), an international research effort established through funding from the COVID-19 Therapeutics Accelerator, a partnership between the Bill & Melinda Gates Foundation, Wellcome and the Mastercard Impact Fund.

Led by Professor Erica Ollmann Saphire, Ph.D., the CoVIC is fielding promising therapeutic antibody candidates against COVID-19—contributed by dozens of laboratories around the world—for side-by-side, apples-to-apples comparisons of antibody function. “The CoVIC provides an even platform for nonprofits, small biotechs and multinational corporations alike to accelerate their therapeutic candidates with complete and independent evaluation,” says Dr. Saphire. “CoVIC will also identify and mobilize antibody therapies to impoverished people around the world. The virus will return here again and again unless we can achieve global immune protection. No one is safe until everyone is safe.”

In August, the CoVIC received a significant $1 million gift from GHR Foundation, an independent philanthropic foundation based in Minneapolis, MN. This funding supports CoVIC partner lab studies into cell types and mechanisms involved in antibody neutralization of SARS-CoV-2.

The National Institute of Allergy and Infectious Diseases (NIAID) also granted $6.4 million to Dr. Saphire to support CoVIC efforts to analyze virus-fighting antibodies and track how SARS-CoV-2 may attempt to escape those antibodies.

> “No one is safe until everyone is safe.”
>
> – Erica Ollmann Saphire, Ph.D.

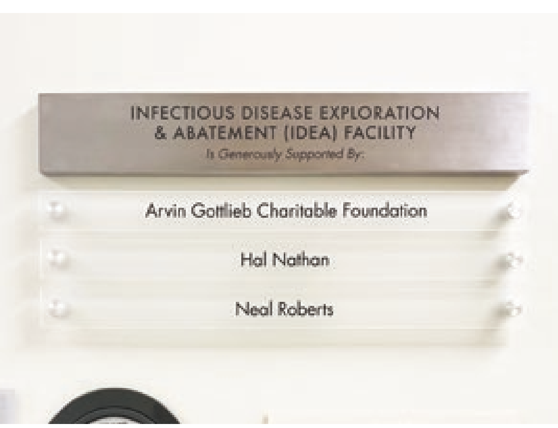
Klaus Ley joins Leducq Foundation Scientific Advisory Committee

Fondation Leducq

Professor Klaus Ley, M.D., has joined the Scientific Advisory Committee of the Leducq Foundation, an international charitable organization that aims to improve human health through international efforts to combat cardiovascular disease. Dr. Ley is a leading expert in how immune cells contribute to atherosclerosis, a disease of the arteries that causes heart attacks or stroke.

A new facility to fight COVID-19 and other infectious diseases

Infectious disease research at LJI took a huge leap forward this year with the construction of the Institute’s first-ever high containment facility. The new Infectious Disease Exploration and Abatement Facility (IDEA) was made possible thanks to the generous support of Hal Nathan, Ph.D., Neal Roberts, and the Arvin Gottlieb Charitable Foundation. For more information on the IDEA Facility, see our “Gearing Up for the Next Pandemic” feature on page 14.



La Jolla Institute

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

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

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

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WHY I GIVE

David Anderson on supporting accessible science

David Anderson was looking for ways to support research at La Jolla Institute for Immunology (LJI) long before the COVID-19 pandemic. He went from an Institute supporter to a leader when he took a position as Co-Chair of the LJI Planned Giving Advisory Council.

Why LJI? "The access LJI gives its supporters to the Institute's stunning science is unprecedented," he says. "Immunology is the key to controlling or curing many of our most dangerous diseases."

San Diego is Anderson's hometown. He grew up on Coronado before heading to college and law school on the East Coast. After college he became a Navy fighter pilot, and from 1965 to 67, flew the F-4 out of Miramar in San Diego and on the Kitty Hawk in Vietnam. In 1969, he left the Navy for law school at Harvard. He returned to San Diego in 1981 and began building his estate planning practice, which he continues today.

Anderson has watched the biomedical industry's growth here, starting with Hybritech, Inc. in the early 1980s. "I'm thrilled with what's been happening on the Torrey Pines Mesa for over 30 years. The collection of minds out there is stunning," says Anderson. "The spirit of collaboration is higher in San Diego than any place else I know. Scientists regularly pick up the phone and trade information with colleagues working at UC San Diego or other firms, just a few blocks or a continent away."

In Anderson's experience, LJI is an especially collaborative and accessible institute, and the COVID-19 pandemic brought it to the world's attention.

"LJI gives great seminars and webinars for the public—and they were doing so before the pandemic," says Anderson. As society went into lockdown, he was impressed by how LJI scientists took time from their work to explain the COVID-19 realities to the public. "There was a lot of misinformation out there, and good information was often hard to come by. LJI has provided useful and timely information to the public," he says.

Anderson's goal is to share LJI's progress with an even wider audience of supporters. In addition to giving to the Institute himself, he's worked closely with the LJI Advancement team to help labs get the financial boosts they need as they take on COVID-19 projects.

"At LJI, an individual's donation has an immediate and real impact on the scientists' work," says Anderson. "Giving to LJI enhances the quality, depth, and breadth of their work and significantly enhances their ability to do life-changing work."

> "LJI has provided useful and timely information to the public."

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WHY I GIVE

Barbara Donnell

on the importance of endurance—and hope

For Barbara Donnell, La Jolla Institute for Immunology (LJI) has always been a place for inspiration and collaboration. The San Diego philanthropist and fundraiser has enjoyed attending events, learning about research, and getting acquainted with staff and scientists over the years.

Together with the Juvenile Diabetes Research Institute (JDRF), Donnell has organized the annual "Meet the Scientists" event at LJI, at which kids diagnosed with diabetes and their families can meet diabetes researchers and learn about the latest science. "It's an all-day educational event," says Donnell. "It's very interactive and uplifting for the kids and families as well as the scientists."

The COVID-19 pandemic changed everything. "Meet the Scientists" was cancelled. The research funding world was reeling. With her experience in philanthropy, Donnell knew how hard it would be for researchers to get new projects off the ground.

Donnell has been a steady supporter of LJI labs, and she had given additional funding this year to LJI's SPARK Program for early career investigators. When she heard that LJI would be running the international Coronavirus Immunotherapy Consortium, she decided to make an additional gift to the institute.

"Every bit counts," says Donnell. "I just felt compelled to break my budget and give an additional gift of stock."

As the pandemic continues, Donnell is encouraged by LJI's "Live from the Laboratory" webinar series, which highlights LJI teams and their progress toward COVID-19 therapies and vaccines.

Donnell also understands the importance of every penny raised for scientific research. She began working with JDRF in 2001, when her daughter was diagnosed with type 1 diabetes. One of Donnell's roles was to act as a bridge between the foundation and San Diego's research institutes. That work brought her to LJI.

"I just fell in love with the place and the scientists," Donnell says. "La Jolla Institute shines for me."

Donnell is confident researchers will develop new therapies and vaccines for COVID-19. It will just take time. "I've been on a quest for a type 1 diabetes cure for years, so I understand that you have to have so much endurance and patience."

"I know how dedicated, how hardworking, how passionate these scientists are, and I know they are pushing the envelope. They are going way beyond," says Donnell. "La Jolla Institute researchers are in this, heart, and soul. And because I know that, I have hope." •

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WHY I GIVE

Neal Roberts and Hal Nathan on making a global impact

Neal Roberts and Hal Nathan, Ph.D., have been friends since 1964, when they first ran into each other in the dorms at the University of California, Santa Barbara. Since then, they've grown their businesses, traveled together, and joined forces to donate to important causes.

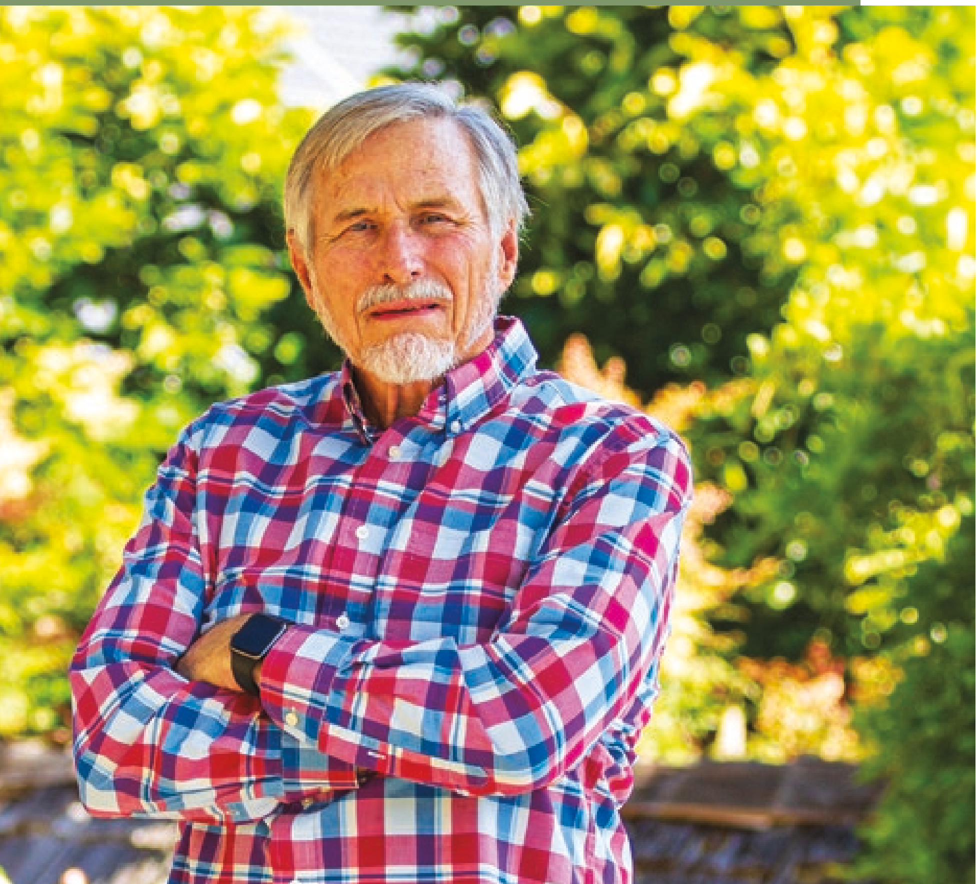
"Over the years, we've figured out various ways to do good in the world," says Roberts.

Their donation strategy always starts with research—they believe it's the best way to ensure their philanthropy can make the biggest difference. Both men have run small foundations. Roberts has established a scholarship program for high school students. Dr. Nathan chairs Partners Asia, a non-profit that supports the work of local organizations and schools in Myanmar and Thailand.

When the two saw the need for COVID-19 research funding, they investigated where their funds could do the most good. After speaking with a friend at the Bill & Melinda Gates Foundation and attending a La Jolla Institute for Immunology (LJI) webinar, presented by Professor Erica Ollmann Saphire, Ph.D., they settled on a plan: they would give to equipment purchases for a new high-containment facility at LJI.

"This was something we could do directly and immediately—something to help right away," says Dr. Nathan.

The new equipment is part of LJI's new Infectious Disease Exploration and Abatement (IDEA) Facility, a biosafety level 3 lab built to contain highly infectious agents. Scientists at LJI need this level of containment to study the virus that



causes COVID-19 and work toward better diagnostics and vaccine strategies. Roberts and Dr. Nathan are hopeful this work will also lead to antibody therapeutics for COVID-19, a major goal of the Saphire Lab.

"Neal and Hal had the vision to fund this important equipment at the Institute, which will help both Dr. Saphire and her work—and many infectious disease projects we're working on," says Christopher Lee, Chief Advancement Officer at LJI.

In so many ways, the two old friends have supported projects that will outlast them. Their gifts to LJI could save lives in the pandemic and for years to come.

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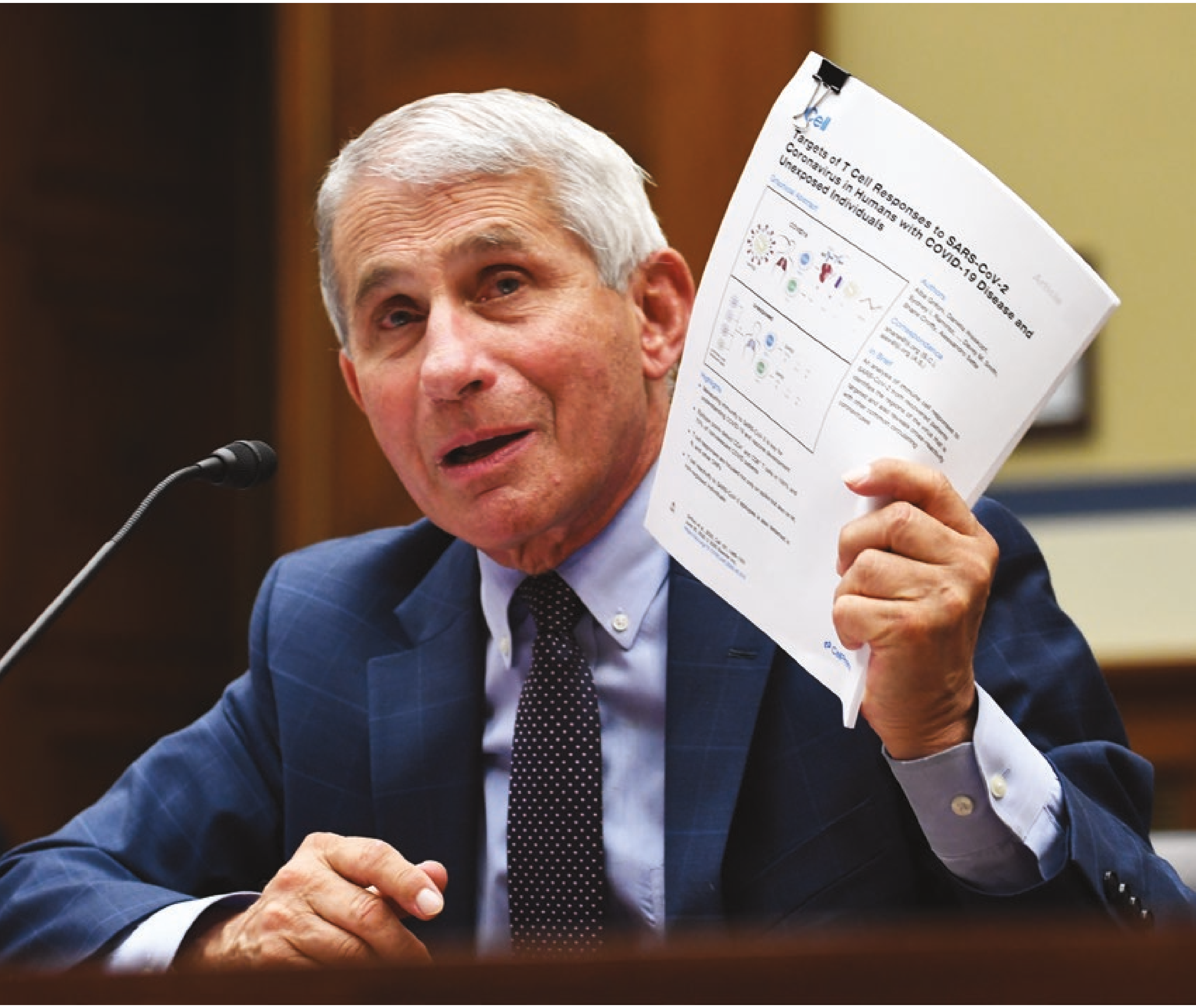

Dr. Fauci brings LJI research to Congress

Anthony Fauci, M.D., Director of the National Institute of Allergy and Infectious Diseases, came with an LJI study in hand when he testified before a House subcommittee on the nation's COVID-19 response on July 31. Holding up the *Cell* study, he called the T cell research from the labs of Alessandro Sette, Dr. Biol. Sci., and Shane Crotty, Ph.D., "work we really need to pursue. We're just at the cusp of really understanding the importance of this type of response in COVID."

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

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