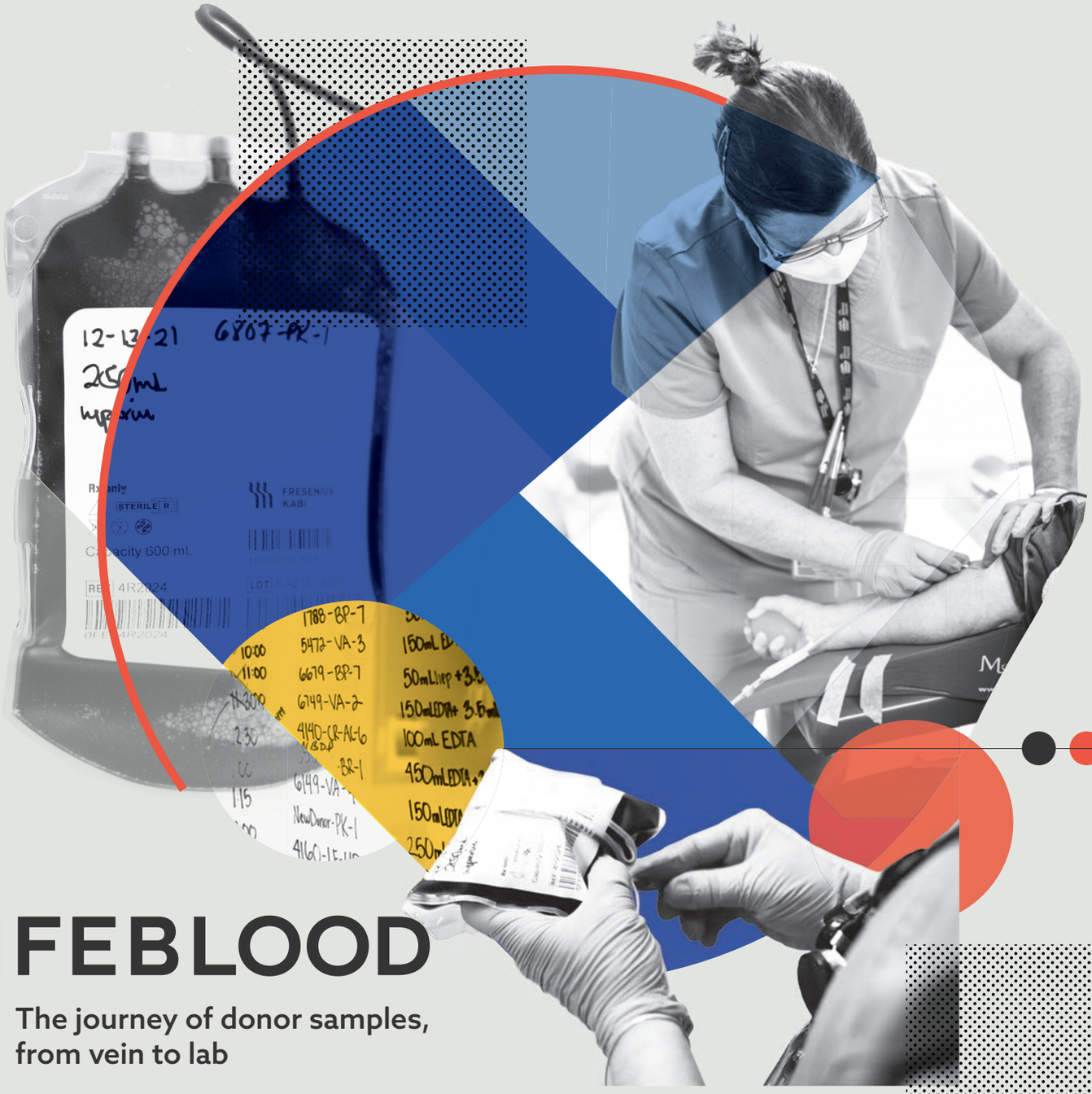
Immune MATTERS

LA JOLLA INSTITUTE
FOR IMMUNOLOGY
SPRING 2022



LIFEBLOOD

The journey of donor samples, from vein to lab

+ more stories from the unseen side of immunology

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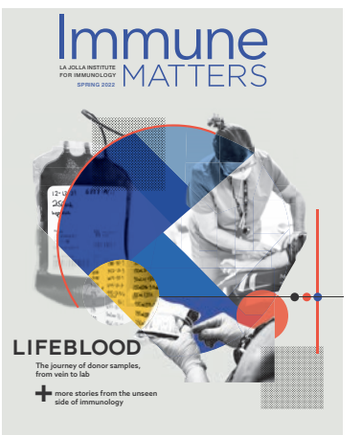
LIFEBLOOD



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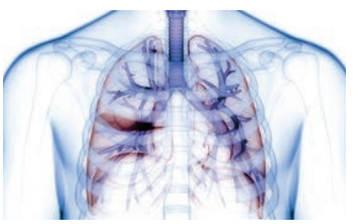

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OUR MISSION

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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La Jolla
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FOR IMMUNOLOGY

Fresh perspectives come from LJI scientists

Back in 2019, my lab members were the new folks at La Jolla Institute for Immunology. We were coming from a larger institute with a longer history, but we knew LJI was an exciting place where immunologists could thrive.

As newcomers, we saw LJI with fresh eyes—and we saw something very special. LJI is a place where community is key. At LJI, supporters can share their own life experiences with the very researchers focused on a specific disease or a promising new therapy.

With this issue of *Immune Matters,* I want to invite you to come through the front door of LJI. Look through the hallways and through the microscopes. Be on the front lines with us.

You'll meet the team behind The John and Susan Major Center for Clinical Investigation. These scientists and medical professionals draw blood from local volunteers who qualify for clinical research studies. Their priceless blood samples have given LJI scientists a window into the roots of Parkinson's disease and the life-saving power of COVID-19 vaccines.

You'll see Dawid Zyla's, Ph.D., striking photographs from inside the Institute. These photos show the cutting-edge equipment that make discoveries possible. You'll also get a fascinating glimpse into the world of histopathology and Kenneth Kim's, Dipl. ACVP vivid images of disease processes inside tissues.

This issue's "Up & Coming" piece highlights the work of Jermaine Khumalo Ph.D., a researcher who came to LJI last year after many years studying immunology in South Africa. Dr. Khumalo is bridging the fields of immunology and bioinformatics to make new asthma therapies a reality. As he explains, asthma kills half a million people a year. This isn't a small problem, and science needs Dr. Khumalo's fresh perspective.

Breakthroughs happen inside LJI laboratories every day. I hope you enjoy this new look at what we've discovered—and how your support fuels research.

Sincerely,

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

Genes hold secrets to COVID-19 case severity

A recent *Nature Communications* study by researchers at La Jolla Institute for Immunolgy (LJI) is one of the first in-depth looks at the connection between COVID-19 severity and gene expression in many types of immune cells. This work could guide the development of new COVID-19 therapies to boost immune cell function.

Among the findings, the LJI team reports that a gene in a type of cells called non-classical monocytes, which are part of the body's "first responder" team of innate immune cells, could be a potential target for COVID-19 therapies.

> **"This study highlights the power of human genetics to uncover novel pathways linked to disease."**
>
> LJI PROFESSOR
> PANDURANGAN VIJAYANAND, M.D., PH.D.,
> SENIOR AUTHOR OF THE STUDY

T cells can fight SARS-CoV-2 variants

As we see SARS-CoV-2 variants rise and fall, the good news is that four COVID-19 vaccines (Pfizer-BioNTech, Moderna, J&J/Janssen, and Novavax) can prompt the body to produce long-lasting T cells that are effective against many SARS-CoV-2 Variants of Concern, including Delta and Omicron.

"The vast majority of T cell responses are still effective against Omicron," says LJI Professor and study co-leader Alessandro Sette, Dr.Biol.Sci.

"These cells won't stop you from getting infected, but in many cases they are likely to keep you from getting very ill," adds LJI Professor Shane Crotty, Ph.D.

"And this is true in all the types of COVID-19 vaccines we studied—and up to six months after vaccination," says LJI Instructor Alba Grifoni, Ph.D., who co-led the work with Drs. Sette and Crotty.

These data come from adults who were fully vaccinated, but not yet boosted. The researchers are now investigating T cell responses in boosted individuals and people who have experienced "breakthrough" COVID-19 cases.

The study in *Cell* also shows that fully vaccinated people still show a drop over time in memory B cells and neutralizing antibodies against the Omicron variant. The main take-away for the public: Get your booster, says Dr. Sette.

Better treatments for psoriasis

Psoriasis can be painful and persistent. LJI Professor Michael Croft, Ph.D., is working to change that. “Current therapies don’t reduce disease by 100 percent, and they don’t cure the disease,” says Dr. Croft.

Dr. Croft and his team in the LJI Center for Autoimmunity and Inflammation have discovered how a key protein called TWEAK damages skin cells in psoriasis patients. Their findings, in mice and with human skin cells, suggest targeting TWEAK may help control the disease.

As the researchers report in *Science Immunology*, TWEAK teams up with two other proteins, called tumor necrosis factor (TNF) and interleukin-17 (IL-17), to trigger inflammation. This trio of proteins appears to control the production of inflammatory molecules and the expression of additional inflammation-associated proteins in patients with psoriasis.

“The primary implication is that TWEAK will also be a good drug target, as has already been proven for TNF and IL-17,” says Dr. Croft.

A new look at targeting malignant cells in many cancers

An LJI study, published in *Nature Immunology,* could potentially open opportunities for designing drug treatment strategies to target malignant cells in many cancers.

The researchers show how loss of TET enzymes can lead to B cell lymphoma. Without TET enzymes regulating normal gene expression, cells can end up with genomic fragility and their DNA can get stuck in strange loops and knot-like structures, called R-loops and G-quadruplexes. The researchers are now studying ways to stop these harmful structures from forming.

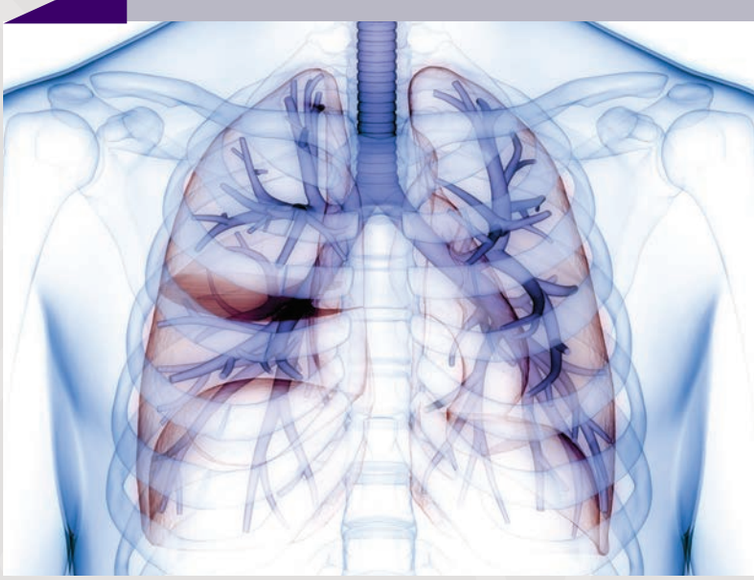
The work was led by LJI Professor Anjana Rao, Ph.D., in the LJI Center for Cancer Immunotherapy, and experiments were spearheaded by LJI Instructor Vipul Shukla, Ph.D. (now an Assistant Professor at Northwestern University), and UC San Diego Graduate Student Daniela Samaniego-Castruita.

Taking on cystic fibrosis

Scientists at LJI have found they can dramatically improve survival of mice with cystic fibrosis through a partial bone marrow transplant. Their new study in the *Journal of Immunology* shows that a partial bone marrow transplant helps these mice by introducing a population of healthy immune cells called monocytes.

Although this therapy is still in preclinical stages, the technique could be ideal for treating patients when cystic fibrosis symptoms first appear.

> **“The transplant is enough for a better life—at least in mice.”**
>
> LJI PROFESSOR KLAUS LEY, M.D., MEMBER OF THE LJI CENTER FOR AUTOIMMUNITY AND INFLAMMATION

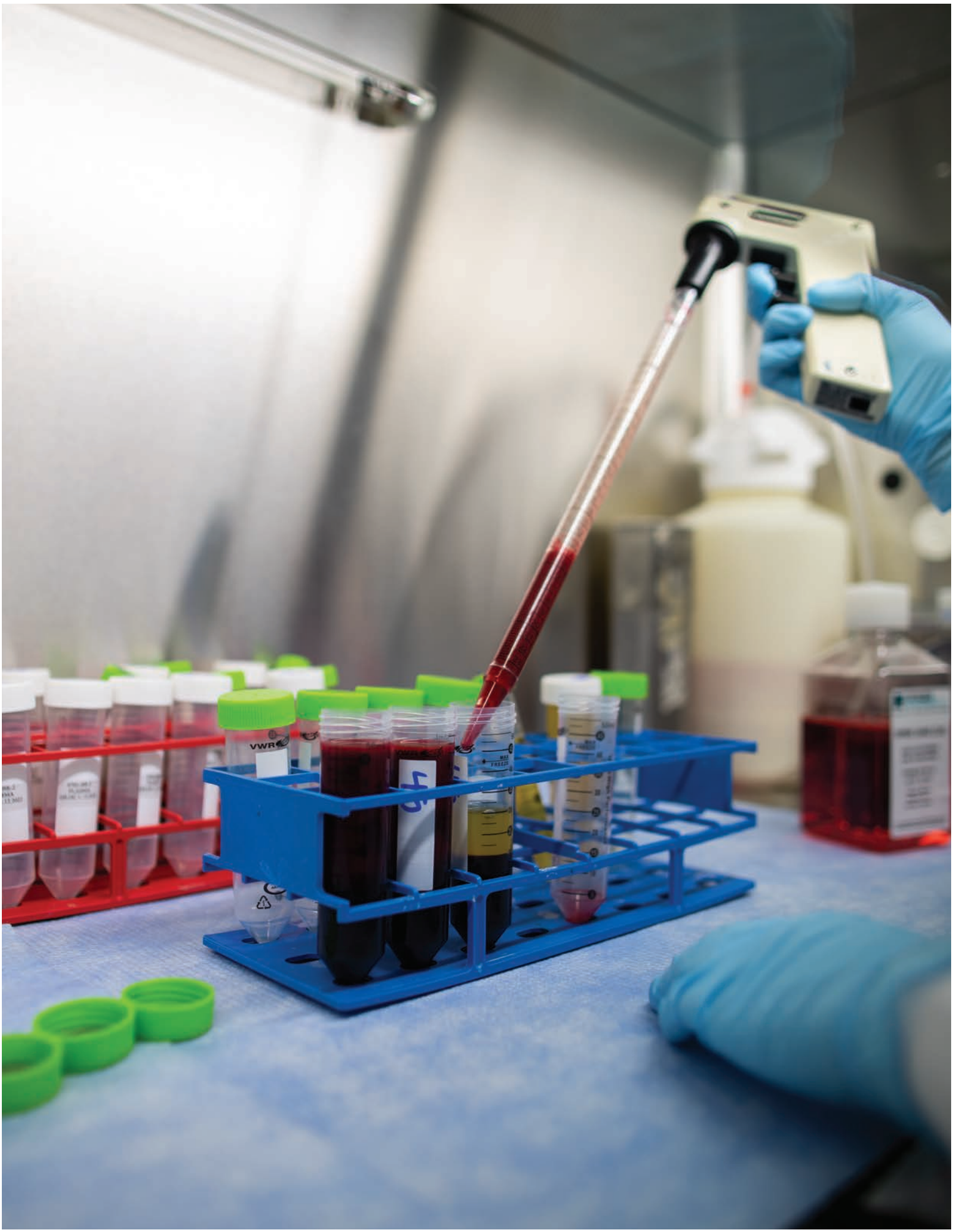


LIFE BLOOD

IT ALL STARTS WITH BLOOD. In 2020 alone, nearly half of the studies published by La Jolla Institute for Immunology (LJI) researchers relied on human blood samples. Through blood, they witnessed the immune system's battle against SARS-CoV-2 and the power of COVID-19 vaccines. Through blood, they tracked responses to yellow fever and dengue virus. They even uncovered potential drivers of heart disease.

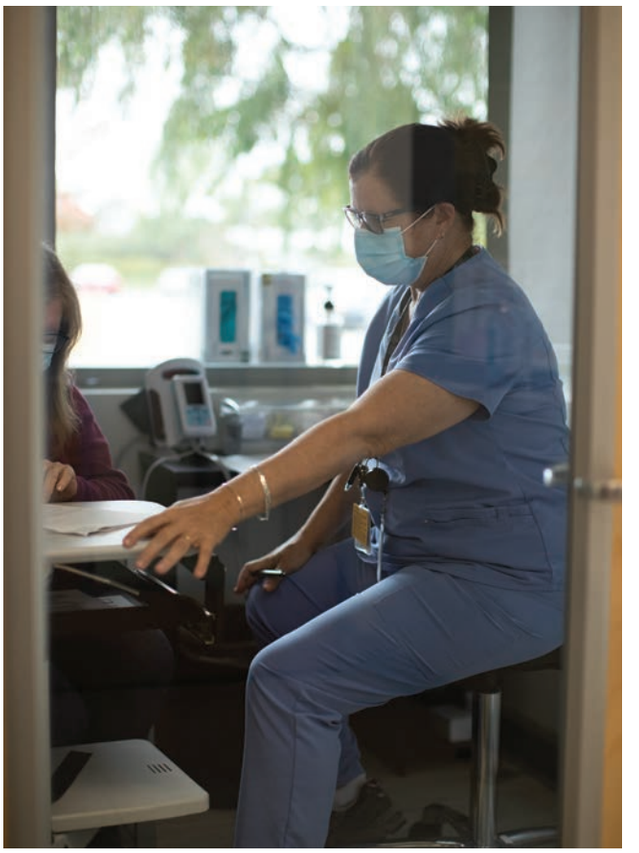
In 2021, the Institute opened the John and Susan Major Center for Clinical Investigation. In this new, highly efficient space LJI staff can see up to 35 donors a day.

This is where generous blood donors meet the hardworking Clinical Core staff.

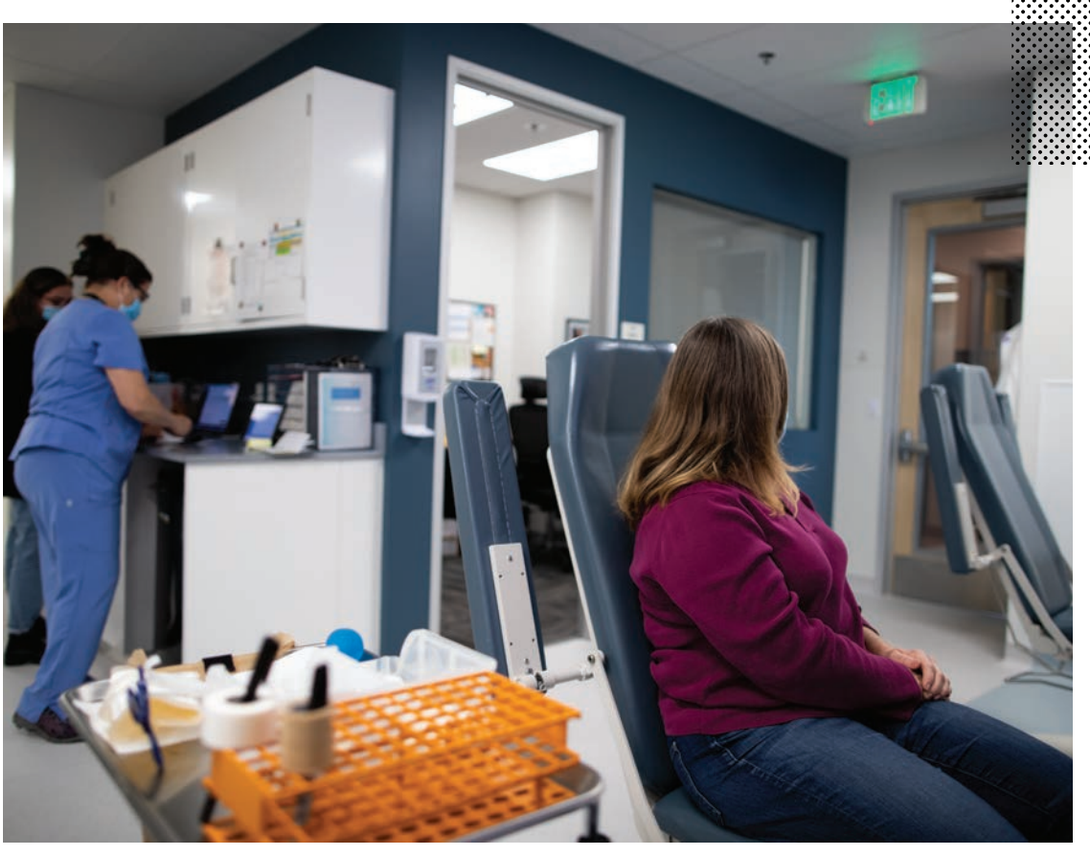

VWR

Core Director Gina Levi, R.N., welcomes blood donor Rachel M. to the clinic on a crisp winter day. They sit down in a screening room to go over the clinical research requirements and Rachel's health history. Rachel is healthy, but her family history of Parkinson's disease means her blood may hold clues to the origins of the disease—and possible treatments.

Levi understands Rachel's urge to help. "Advances in Parkinson's research, specifically, have been very meaningful to me as my father had Parkinson's disease," Levi says. "I watched as it slowly robbed a once vital and strong man of his ability to move and think."



Levi prescreens Rachel M. for the study.



Levi prepares Rachel M. for her blood donation.

INSIDE THE CLINICAL CORE:

13 LABS
served in 2021

282,853 ML
of blood processed in 2021

1,699
COVID-19 patient samples collected

25 PROJECTS
currently enrolling donors

Blood has many ingredients, and most LJI scientists aren't interested in the red stuff. Immunologists here focus on white blood cells, also called leukocytes, which include T cells, B cells, macrophages, and other key immune cells. Find these leukocytes, and you'll uncover clues to how immune cells do their jobs.

With Rachel's blood donation complete, it's time to process the blood before it heads to an LJI laboratory.

THE CLINICAL CORE LAB STAFF ARE IN CHARGE NOW

Isabella Simmons, Lab Processing Technician

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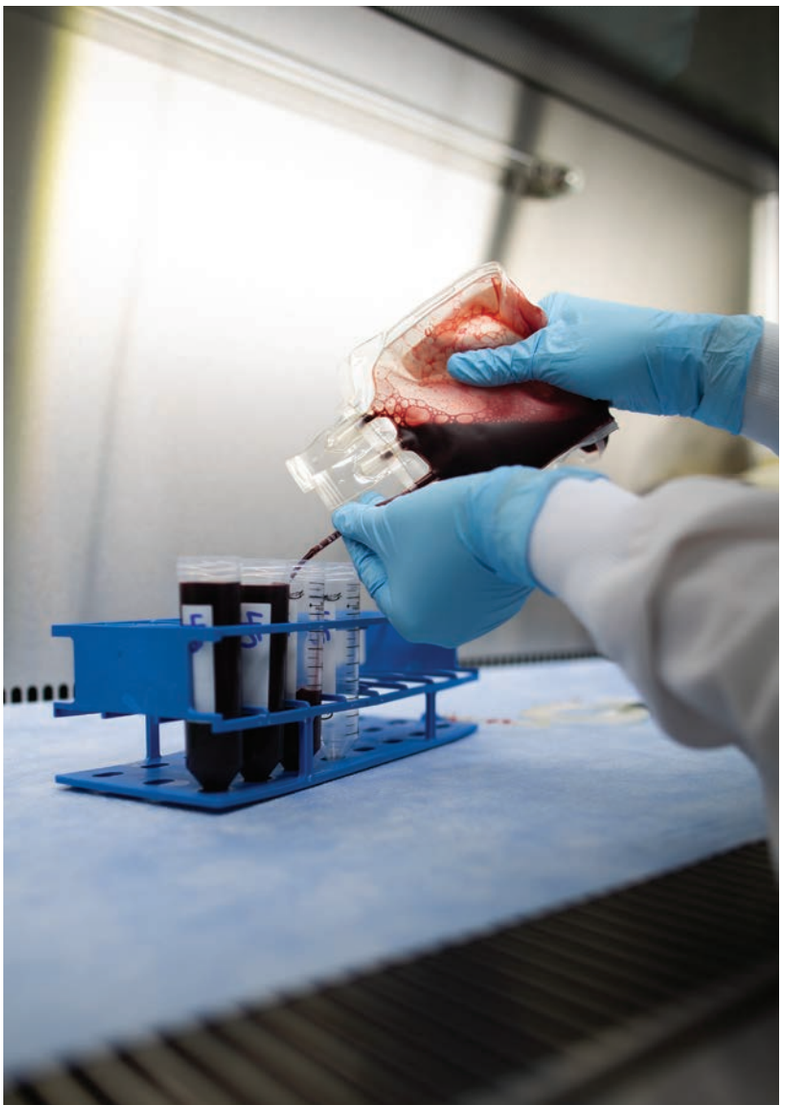
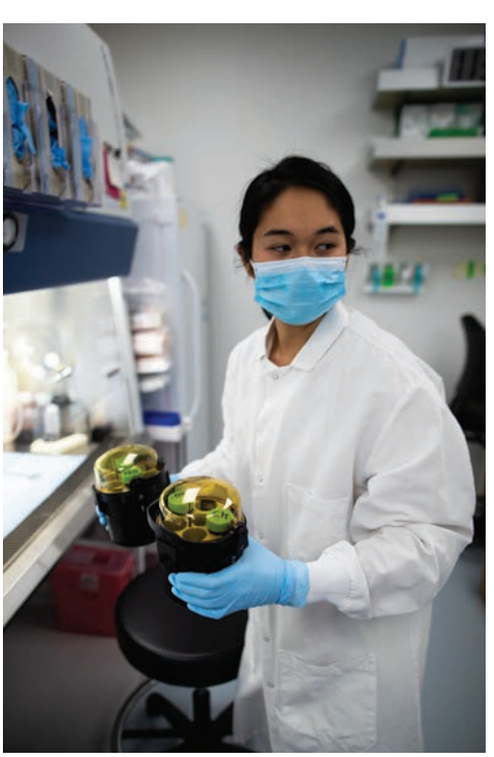
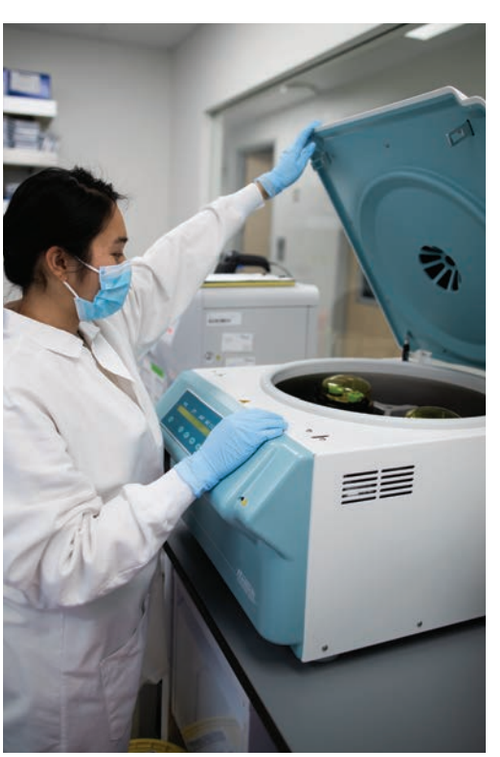




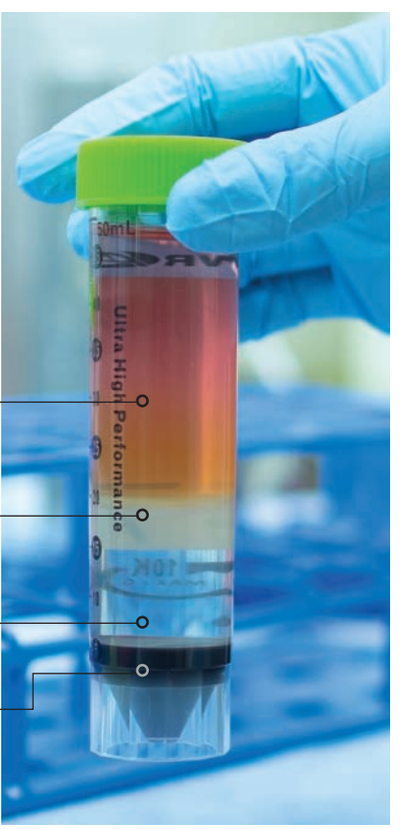


To isolate Rachel's immune cells, the highly skilled Clinical Core staff start by spinning the blood sample in a centrifuge. Heavier red and white blood cells will settle at the bottom of the tube, while a layer of blood plasma stays at the top. The blood cells are then separated by density (red blood cells are heavier than white blood cells).

The layer of precious white blood cells is washed with a special mix of chemicals used to keep cells healthy and then the cells are frozen.

"It is amazing to watch how the Clinical Core directly connects the public to the research happening at LJI. The work we do here goes on to answer vital questions about allergies, infectious diseases, and neurodegenerative diseases. It is an honor to work alongside the many brilliant people of LJI."

Quinn Bui, Clinical Laboratory Technician



PINK LAYER
Blood serum, which contains proteins such as coagulation factors and antibodies

WHITE LAYER
White blood cells, also called leukocytes or immune cells

CLEAR LAYER
Media added by Clinical Core staff

REDDISH-BLACK LAYER
Red blood cells

LJI Postdoctoral Fellow Gregory Williams, Ph.D., picks up Rachel's cells from the Clinical Core freezer.

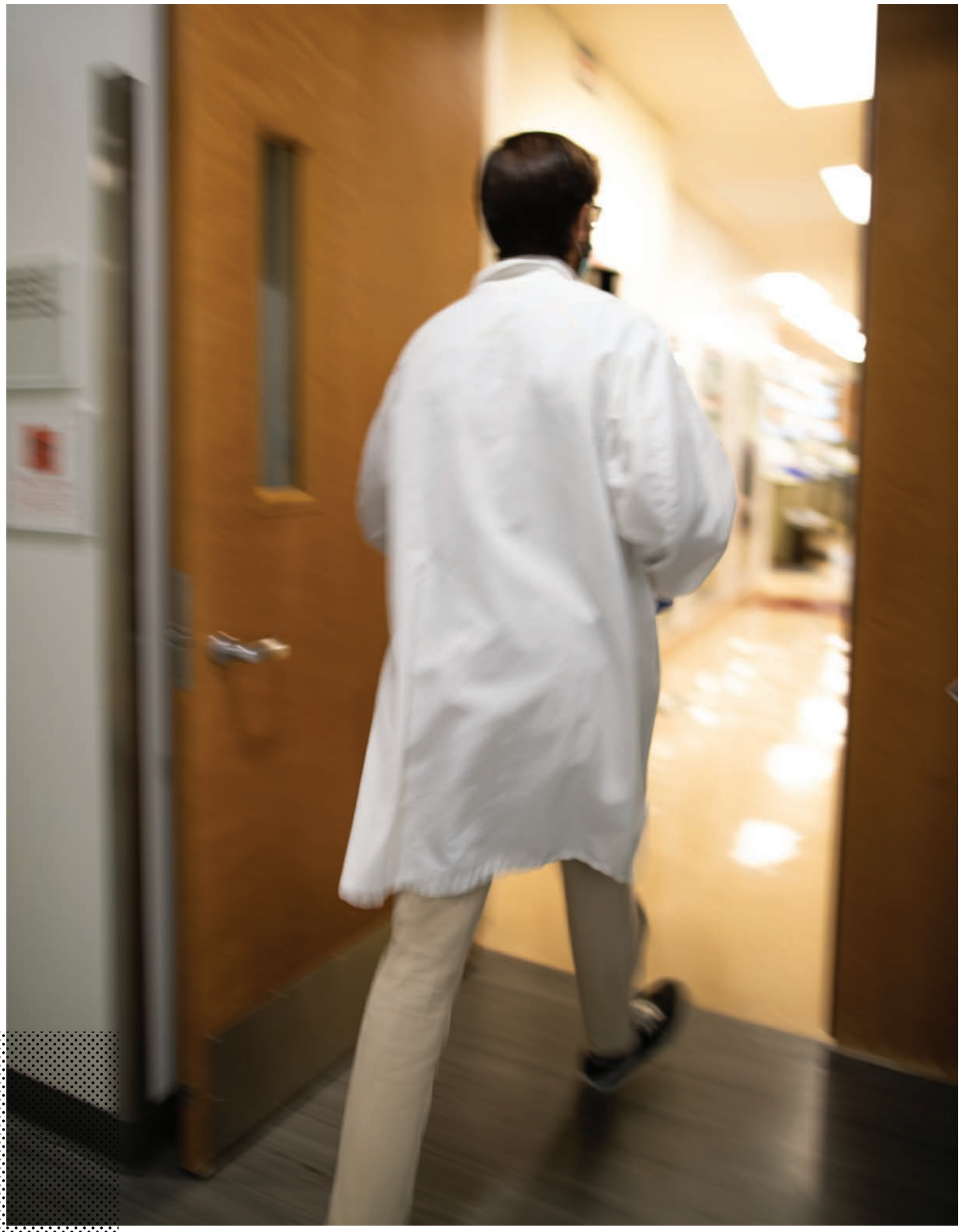
Dr. Williams is spearheading a Parkinson's study in the lab of LJI Research Assistant Professor Cecilia Lindestam Arlehamn, Ph.D.

Already, LJI researchers working with human blood samples have uncovered something surprising: Parkinson's disease looks a lot like an autoimmune disease, at least at the disease onset. That finding has sparked many, many more questions—and paths to potential Parkinson's diagnostics and therapies.

In the end, what Dr. Lindestam Arlehamn's team finds in Rachel's blood may appear as a single data point in a scientific paper. What the world doesn't get to see are the many personal stories that propel citizens and scientists to contribute to research.

Every breakthrough begins with a quest to solve a mystery in human health—and a personal mission to help people. Blood holds the clues. •

Scan for behind-the-scenes videos and a closer look at Rachel M.'s blood journey. Plus, get a view through the microscope with Quinn Bui.



NO PATIENT OVERLOOKED

An LJI scientist crosses the globe to help stop asthma deaths

The community had a meningitis problem. When kids were brought into a referral hospital in Cape Town, South Africa, with a suspected clinical case of meningitis, the only way to diagnose them was to do a lumbar puncture and test their spinal fluid. The puncture was excruciating for kids—but it could save their lives. Meningitis can be fatal if left improperly diagnosed.

The problem was that too many laboratory tests came back inconclusive. The doctors couldn't tell whether cases were bacterial or viral, which delayed proper treatment. In fact, out of more than 3,000 lumbar punctures performed at that hospital annually, only one percent of samples came back positive for bacterial meningitis. Kids weren't getting the antibiotics they needed in time.

Jermaine Khumalo, Ph.D., was a masters student at the University of Cape Town when he saw these puzzling results from the nearby hospital. Dr. Khumalo's job was to re-run these samples and help devise a faster and more accurate way to test spinal fluid.

"My job was to come up with a real-time diagnostic tool that could distinguish between the major common causes of meningitis in children," says Dr. Khumalo.

His PCR test (which detected genetic material from six possible pathogens) proved accurate and practical for use in a hospital setting. His analysis also showed doctors had missed another 30 percent of viral meningitis cases and five percent of bacterial meningitis cases in that initial group of patients. Tragically, some of those overlooked children had died.

"They died because they couldn't get conclusive results," says Dr. Khumalo. "That spurred on my work. I saw that if one improves diagnosis, one can improve therapy and save lives."

Dr. Khumalo hadn't set out to become an immunologist. As a kid in the newly independent country of Zimbabwe, he hadn't known being a scientist was even a career option. The adults he knew were becoming lawyers, accountants, or medical doctors, so he thought he'd train as a physician as well.

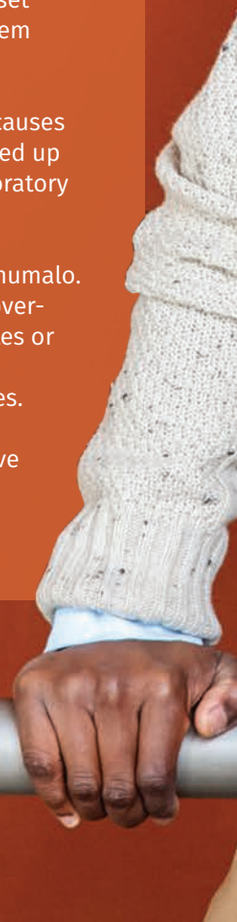
"I was always fascinated with the human body and biology as a whole," he says. As an undergraduate at Zimbabwe's National University of Science and Technology, he realized life as a doctor wasn't for him after a professor warned him of the grisly scenes he would encounter in a hospital. "That kind of trauma wasn't for me," says Dr. Khumalo.

Instead, Dr. Khumalo focused on saving lives through clinical research. "As an undergraduate, one of my favorite lecturers always talked about 'demystifying' immunology," he says. "That was contagious, and I fell in love with the aspect of solving problems and finding things out."

Working through the meningitis problem showed Dr. Khumalo the impact his work could have, so he set out to learn a lot more about how the immune system responds to disease.

"I looked for a lab that was attempting to uncover causes of disease pathogenesis," says Dr. Khumalo. He ended up pursuing his Ph.D. in a University of Cape Town laboratory focused on tuberculosis and allergy research.

Allergy research presented another puzzle for Dr. Khumalo. In an allergic reaction, the body's immune system over-reacts to the molecules in an allergen, like dust mites or pollen. Immune cells go on the warpath, activating inflammatory molecules and wrecking healthy issues. "That fascinated me," he says. "How could the body mount this highly pathogenic immune and disruptive immune response against something harmless?"



"I SAW THAT IF ONE IMPROVES DIAGNOSIS, ONE CAN IMPROVE THERAPY AND SAVE LIVES."

This work led to a passion for studying asthma. Asthma is a tough nut to crack because it looks different in almost every patient. The disease is driven by different allergens and can cause wheezing—or even death.

Dr. Khumalo's graduate research revealed specific cell types important in asthma and clues to which treatments might work best in different patients. Still, Dr. Khumalo saw a problem. His work in mouse models showed a segment of mice resistant to treatment, just like many humans with severe asthma.

"Fifty percent of people with asthma respond perfectly to corticosteroid treatment, but there is a significant portion who don't respond," says Dr. Khumalo. Similar to meningitis, patients with asthma can die without good medications. "There are 300 million people affected by asthma in the world, and about half a million die every year from severe forms of the disease."

Dr. Khumalo's interest in these individual differences in asthma patients led him to apply for a postdoctoral position in the Vijayanand Lab at La Jolla Institute for Immunology (LJI).

Led by LJI Professor Pandurangan Vijayanand, M.D., Ph.D., the lab has pioneered the use of a technique called single-cell gene expression profiling. By looking at genetic expression in immune cells, the researchers can investigate how different human immune cells operate in diseases such as asthma.

Dr. Khumalo is studying samples from patients with and without severe asthma. This broad patient group is key, since Dr. Khumalo knows that any immune cell could hold important clues. No patient, no immune signature, is overlooked. "With high-throughput, single-cell sequencing, we are then able to isolate the responsible cells," says Dr. Khumalo. This research has led him to focus on T cells, which can drive inflammation.

Dr. Khumalo's work doesn't stop there. In 2020, Khumalo was named an Intersect Fellow by the American Association of Immunologists and won support to pursue interdisciplinary research in a second LJI lab. In collaboration with the laboratory of LJI Associate Professor Ferhat Ay, Ph.D., Dr. Khumalo uses his skills in bioinformatics to analyze his immune cell data to find any disease-specific biomarkers.

By looking at asthma from every angle—through new patient groups, animal models, genetic factors, immune cell interactions, and environmental triggers—Dr. Khumalo hopes to spot what other researchers have missed. His end goal is to track down new drug targets for treating the disease.

"Once you solve a problem, you need to move on to the next one," says Dr. Khumalo. "And it's always exciting, even if an experiment fails. You fail and get back up, fail and get back up. But then an experiment finally works and you buy a bottle of wine." •

WHAT IS SINGLE-CELL GENE EXPRESSION PROFILING?

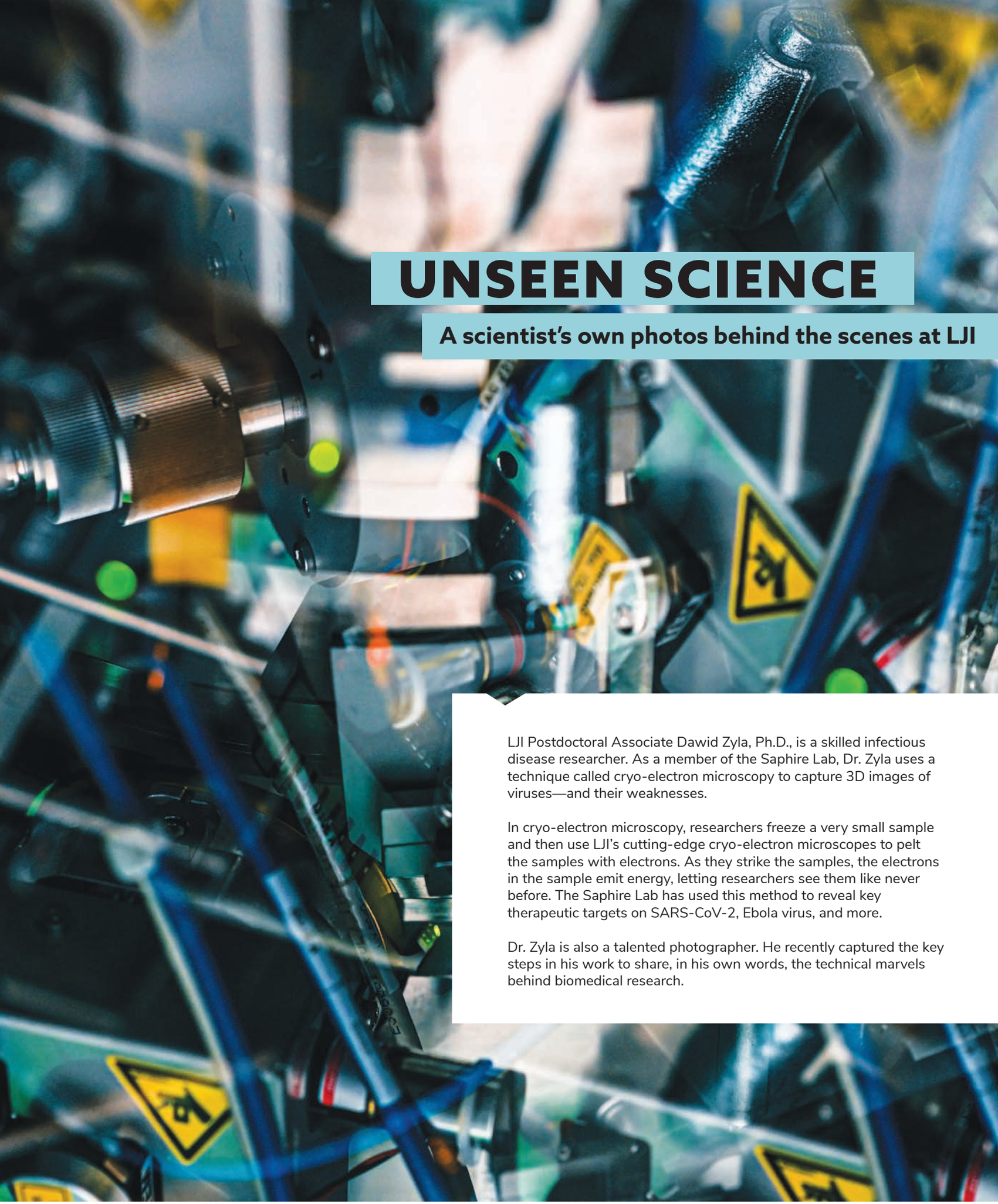
Your cells all have nearly the same DNA code, but they don't do the same jobs. For example, cells called nociceptors help sense pain, while beta cells in your pancreas make insulin.

Your cells play their different roles thanks to changes in gene expression. This means a cell only "reads" a subset of genes to make certain proteins.

Immune cells do the same thing—that's why there are so many different flavors of immune cells. For example, macrophages and T cells both fight pathogens, but they use different strategies, thanks to differences in their gene expression.

With single-cell gene expression profiling, scientists can discover exactly which genes are being expressed by individual immune cells in a sample. They can also figure out how gene expression changes, on a cell-by-cell basis, as they fight disease. This cutting-edge method is changing the field of immunology.

Using single-cell gene expression profiling, scientists in LJI's Vijayanand Lab have uncovered new subsets of immune cells with jobs no one had ever witnessed before. In Dr. Khumalo's research, single-cell gene expression profiling can reveal which immune cells overreact in cases of asthma—and how these haywire immune cells communicate with each other.



UNSEEN SCIENCE

A scientist's own photos behind the scenes at LJI

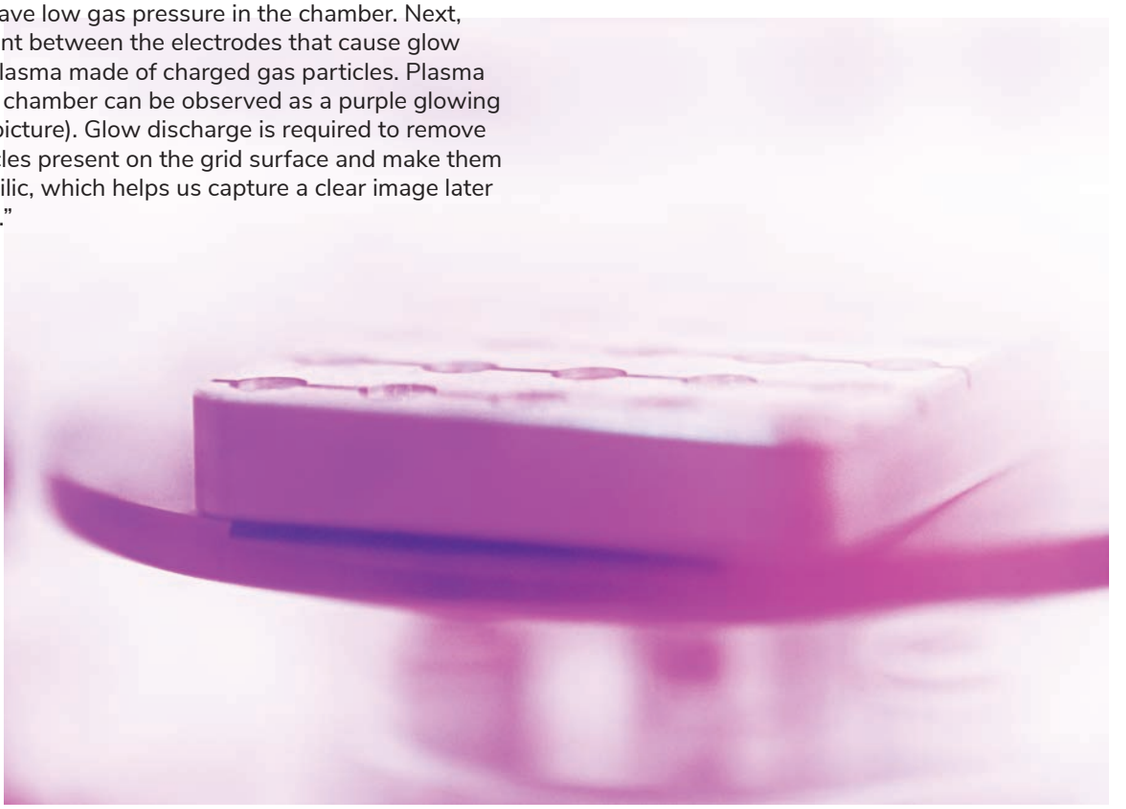
LJI Postdoctoral Associate Dawid Zyla, Ph.D., is a skilled infectious disease researcher. As a member of the Saphire Lab, Dr. Zyla uses a technique called cryo-electron microscopy to capture 3D images of viruses—and their weaknesses.

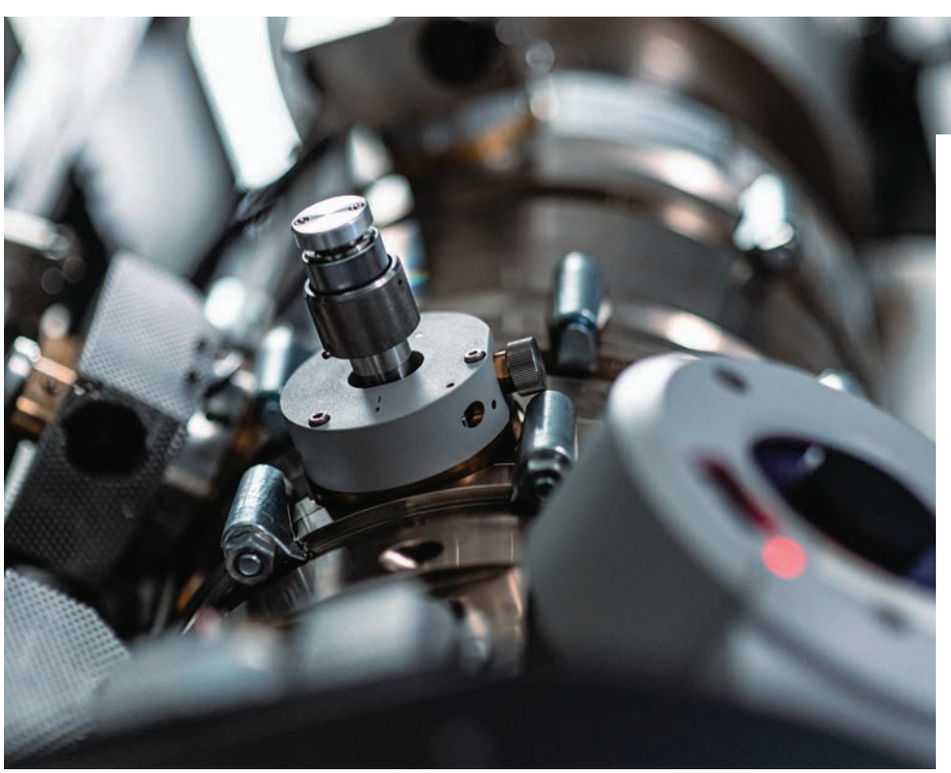
In cryo-electron microscopy, researchers freeze a very small sample and then use LJI's cutting-edge cryo-electron microscopes to pelt the samples with electrons. As they strike the samples, the electrons in the sample emit energy, letting researchers see them like never before. The Saphire Lab has used this method to reveal key therapeutic targets on SARS-CoV-2, Ebola virus, and more.

Dr. Zyla is also a talented photographer. He recently captured the key steps in his work to share, in his own words, the technical marvels behind biomedical research.

"BEGINNING IN PLASMA"

Dr. Zyla: "In cryogenic electron microscopy, everything starts in plasma. To prepare a sample, grids with small pieces of copper covered with a thin amorphous carbon film are cleaned and coated with charged particles. This is called the 'glow discharge' step. We do this work in a device called a plasma cleaner, which is connected to a vacuum pump that allows us to have low gas pressure in the chamber. Next, I apply a current between the electrodes that cause glow discharge: a plasma made of charged gas particles. Plasma present in the chamber can be observed as a purple glowing effect (in the picture). Glow discharge is required to remove residual particles present on the grid surface and make them more hydrophilic, which helps us capture a clear image later in the process."



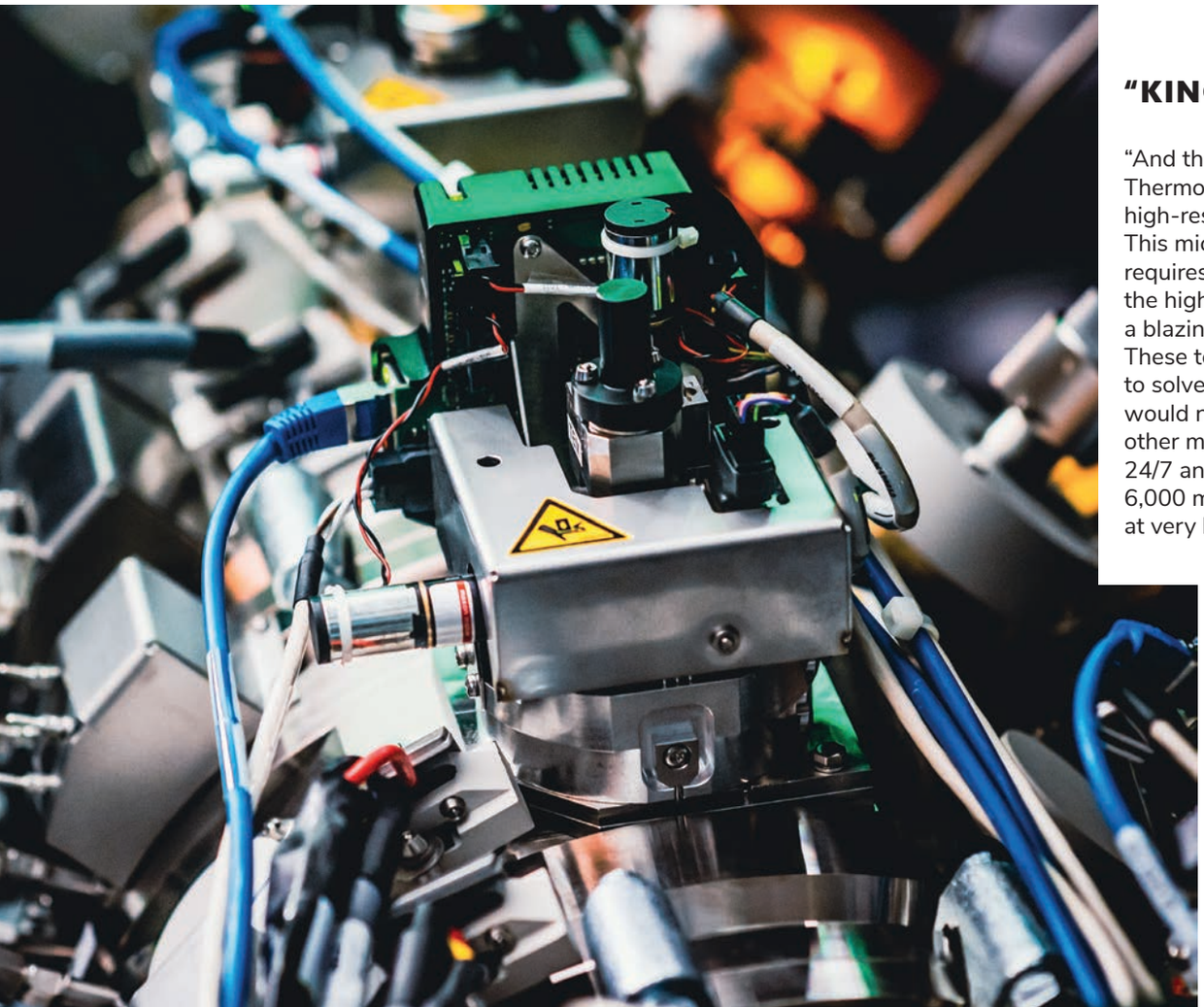


"SCREENING FIRST"

"Preparing cryo-electron microscopy grids is knotty and it is relatively easy to make poor quality grids. It gets even harder when we factor in protein samples and their quality. Before we can solve any protein structure, we have to check grid quality using a cryogenic transmission electron microscope. This is the Titan Halo. The data we get from this microscope help us optimize samples and solve low-resolution reconstructions—which guides us toward other protein structures to pursue."

"ART OF BLOTTING"

"Most of the cryo-EM samples are proteins in an aqueous solution, so we need to blot them to remove excess fluid. Manual blotting is a highly imprecise method. Thus various automated devices have been developed to standardize the task. Here is a close-up picture of one of them: a Thermo Vitrobot Mark IV. Vitrobot has a humidity-controlled chamber with two blotting pads and tweezers to hold the grid for the sample application (in the picture). Good blotting conditions are tricky to get, and we usually have to try several times before we get it right. The blotted grid is quickly transferred to a container filled with liquid ethane placed below the humidity chamber and flash frozen. Fast freezing is a crucial step in cryo-electron microscopy."



"KING OF THEM ALL"

"And there it is, the mightiest of them all. Thermo Titan Krios. The workhorse of high-resolution cryo-electron microscopy. This microscope is fully automated yet requires highly trained staff. It provides the highest quality of data possible with a blazingly fast direct electron detector. These technologies allow LJI scientists to solve macromolecule structures that would never be possible to tackle with other methods. The Krios works almost 24/7 and enables us to collect over 6,000 micrographs, images of the sample at very high magnification, per day."

Amazing mucosa

Let's visit the guts and the lungs

Mucosal surfaces get their name from their flagship product: **mucus.**

These membranes line the airways, lungs, reproductive, and gastrointestinal tracts—the parts of the body that come into direct contact with the outside world.

"Along with the skin, a non-mucosal surface, these barriers are a critical deterrent to infection and inflammation," says La Jolla Institute of Immunology (LJI) Professor and Chief Scientific Officer Mitchell Kronenberg, Ph.D.

Other organs just don't have as much contact with visitors. Yet mucosal surfaces come in contact with dirt, smoke, microflora, spaghetti, cheesecake, and broccoli. With these visitors come countless potential pathogens.

So a team of cells, called the mucosal immune system, has to be on standby on these surfaces where your innards meet the world. Mucus helps flush away some invaders, but it's just one part of the elaborate defenses of the mucosa.

"The whole mucosal immune system is so fascinating," says LJI Professor Hilde Cheroutre, Ph.D. "It has to operate in an environment of extremes."

Guts and glory

For each of these organs, a very thin layer of special epithelial cells separates your insides from outside threats (on the skin, cells called keratinocytes play the role of epithelial cells. Instead of mucus, an oil called sebum adds to the skin's protective power).

"In the intestines, this wall is just one cell thick," says Dr. Cheroutre. "Can you imagine?"

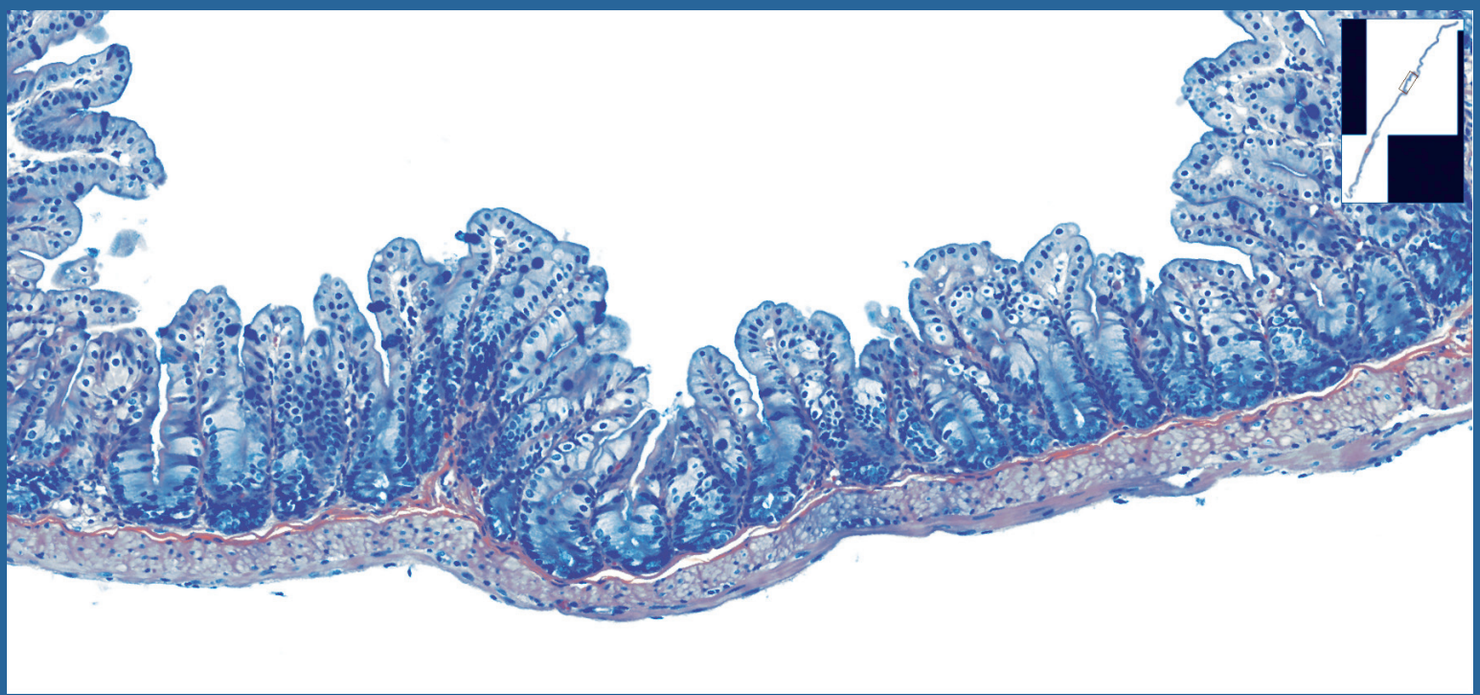
Dr. Cheroutre's lab has shed light on how the epithelial layer in the small intestine "talks" to nearby T cells. These are resident, rather than circulating, T cells trained to know, very generally, that something is wrong with a cell.

For example, an epithelial cell can't tell the difference between a blueberry and *Salmonella*. Both contain "foreign" proteins and other molecules, so epithelial cells rely on these resident T cells to tell the difference. Epithelial cells do this by analyzing the invader and then "presenting" a peptide that resembles the invader—somewhat like a mugshot.

The T cells see these peptides and determine either that an unfamiliar molecule is safe or RED ALERT. After all, *Salmonella* bacteria trigger certain molecules associated with cellular invasion. A blueberry does not. An effector T cell then swoops in to immediately kill an infected epithelial cell.

This kind of speed is unheard of in organs like the heart or liver. With an infection in these organs, the adaptive immune system will detect a pathogen only when an alert reaches the lymph nodes. The

« In this illustration, artist Brad Krajina Ph.D., imagines epithelial cells as fortresses protecting the body from missile-like pathogens. Spiky blue T cells are poised—ready to stop any infection from spreading.



In this image, we can see how the thin epithelial layer weaves up and down to maximize the surface area in the bowel.

immune system will then spend several days perfecting an immune response, where T cells and B cells learn to attack that specific pathogen, and only that pathogen.

The gut doesn't have time to wait for more specialized immune cells to travel down from the lymph nodes whenever it senses something weird. It needs to act immediately to tell blueberry from *Salmonella*. This speed saves lives.

Mucosal surfaces also get help from special antibodies and innate lymphoid cells. These fighters are not specialized either. Instead, like a Chihuahua hearing a doorbell, these cells get jumpy around anything unfamiliar and can quickly respond to a pathogen.

Yet the mucosal immune system must also tread lightly. While an inflammatory response in another organ, like the spleen, might result in a lot of dead tissue cells (what Dr. Cheroutre calls "collateral damage"), the body usually recovers.

The body can't mount a massive inflammatory response in the fragile epithelium of the gut and risk friendly fire. Too many dead epithelial cells leads to a break in the barrier, leaky gut, nutrient deficiencies, inflammation, and severe infections.

When things go wrong

Diseases such as ulcerative colitis and inflammatory bowel disease strike when immune cells mistakenly see the intestine cells as a threat—or when these intestinal cells respond inappropriately to a harmless molecule.

"Immune cells might also respond to the contents of the intestines, for example the microbiota," says Dr. Kronenberg.

Dr. Kronenberg wants to help the gut get better. He says it's likely immune cells begin attacking the gut when they mix up the signals between pathogens, food peptides, and beneficial microbes (the gut bacteria that keep us healthy).

"The relationship between the body and the microbiome is mediated in part by

> "These barriers are a critical deterrent to infection and inflammation."
>
> **Mitchell Kronenberg, Ph.D., LJI Professor**

epithelial cells," says Dr. Kronenberg. "But sometimes epithelial cells signal the immune system to over respond, which contributes to the problem."

In Dr. Kronenberg's lab, researchers have found that an anti-inflammatory molecule called IL-10 is extremely important for keeping the peace between epithelial cells and the gut's beneficial microbes.

Today, Dr. Kronenberg is working closely with LJI Professor Pandurangan Vijayanand, M.D., Ph.D., to study the roles of T cells in human mucosal surfaces. Dr. Kronenberg and his LJI colleagues also work hand-in-hand with the Institute's core facilities, and they often collaborate with nearby researchers at UC San Diego and the San Diego Digestive Diseases Research Center, as well as researchers and clinicians in the United Kingdom.

Battling for breath

Mucosal immunity in the airways is pretty gnarly, too. LJI Professor Michael Croft, Ph.D., studies airway inflammation seen in asthma and diseases such as idiopathic pulmonary fibrosis (IPF), an autoimmune disease that leaves thick scar tissue in the lungs.

During an asthma attack, for example, immune cells mistake a harmless trigger, such as pollen, for an invader. As immune cells flood the lungs, muscles in the bronchial tubes start to thicken. Epithelial cells add excess mucus to the mix, and cells called fibroblasts churn out sticky collagen that stops the lungs from expanding. "That gums things up further," says Dr. Croft.

In asthma attacks, the famed speed and sensitivity of the mucosal immune system is a huge problem. Rescue inhalers help, but 10 Americans still die every day from asthma. Patients with IPF and similar diseases have even fewer options.

Dr. Croft's lab is working on ways to return mucosal membranes to a healthy state.

The Croft Lab has found that a protein called LIGHT can trigger inflammation and scarring of the lungs. His lab has also discovered that a different protein, called TL1A, can cause the kind of fibrosis seen in IPF. By manipulating molecules like LIGHT and TL1A in combination, scientists could potentially shut down detrimental immune responses.

"We need to really dampen the immune system to stop these diseases from coming back—and that applies to essentially all mucosalimmunity, including the inflammatory diseases of the gut," says Dr. Croft.

Team Mucus

Fun fact: "Snot" only refers to mucus made in the nasal passage.

Clearly, there's a lot we need to understand about mucosal membranes. Studying mucosal immunity has become especially important during the pandemic. Today, scientists are testing how to deliver COVID-19 vaccines directly to mucosal surfaces in the airways and recruit virus-fighting immune cells to the lungs.

Because the cells of the mucosal immune system sometimes live by different rules than circulating white blood cells in the blood and lymph, a better understanding of interactions in the mucosal immune system may lead to many new therapeutic avenues. After all, many pathogens specialize in attacking mucosal membranes. Bacterial pneumonias and tuberculosis are deadly mucosal bacterial infections of the lungs. HIV usually begins as a mucosal infection of the rectum or reproductive tract.

"I think we're just beginning to understand how the immune cells, the barrier cells in the epithelium, and the microbiome talk to each other," says Dr. Kronenberg. •

» T cells must defend the small intestine without overreacting to beneficial microbes.

The Conrad Prebys Foundation grants more than $1.5 million to support critical LJI infrastructure and research

The Conrad Prebys Foundation has given more than $1.17 million to support La Jolla Institute for Immunology's (LJI) Flow Cytometry Core and more than $415,000 to fuel infectious disease research led by LJI Instructor Julie Burel, Ph.D.

"This support allows LJI scientists to buy essential equipment and pursue fascinating early career research," says LJI President and CEO Erica Ollmann Saphire, Ph.D. "We are proud to strengthen our relationship with The Conrad Prebys Foundation as we lead immunology research here in San Diego."

The Conrad Prebys Foundation works to improve quality of life—primarily in San Diego County—through the distribution of grants to support medical research, healthcare, visual and performing arts, and other charitable causes. These new grants carry on founder Conrad Prebys' legacy of supporting truly innovative research in the health sciences.

The new funding to LJI's Flow Cytometry Core will allow the Institute to purchase new cutting-edge equipment for research into diseases such as cancers, COVID-19, and heart disease.

"The Foundation is pleased to support this world-renowned institute," says Erin Decker, Director of Grantmaking at The Conrad Prebys Foundation. "LJI is driving understanding and progress across a wide range of diseases. The Institute's vanguard flow cytometry core and its top team of technicians are poised for future breakthroughs, and this funding means LJI scientists, and the entire San Diego research community, will have access to enhanced equipment."

Flow cytometry is a method for sorting individual immune cells and analyzing their roles in fighting disease or contributing to autoimmunity. Skilled technicians in the Flow Cytometry Core carry out experiments for LJI scientists and offer services to nearby research collaborators at UC San Diego, Moores Cancer Center, the Sanford Burnham Prebys Medical Discovery Institute, Scripps Research, and more.

The Conrad Prebys Foundation's support will also allow Dr. Burel to build on the surprising findings of her 2019 Tullie and Rickey Families SPARK Award for Innovations in Immunology. Dr. Burel, a member of the Peters Lab, has pioneered the study of doublets. Doublets occur when two immune cells are stuck together. For decades, researchers thought doublets were an accidental artifact of certain laboratory procedures commonly used for analyzing clinical samples. Dr. Burel's work, in collaboration with the LJI Flow Cytometry Core, has shown that some doublets do have a role in the body—and may even be a sign that the immune system is fighting an infection.

Dr. Burel's research so far suggests doublets do not form randomly, but instead are enriched for certain immune cell subsets with unique gene expression patterns, suggesting a previously uncharacterized form of communication between immune cells. "Doublets are found at increased frequency in the blood of individuals with diseases such as tuberculosis or dengue fever," says Dr. Burel.

Detecting doublets and analyzing their content could show researchers how well an individual is fighting an infection or responding to a vaccine.

"Dr. Burel and her exciting early stage research is a wonderful illustration of the type of groundbreaking work that Conrad Prebys would have been fascinated with and eager to help move forward," says Decker. •

LJI's Flow Cytometry Core is a resource for scientists across San Diego.

ARCS San Diego recognizes promising graduate students

La Jolla Institute for Immunology (LJI) and ARCS San Diego are strengthening ties in an effort to advance graduate training in immunology. In 2021, Gabriel Antonio Ascui Gac and Sonya Haupt—who are both UC San Diego graduate students training in LJI labs—became the first students at the Institute to be named ARCS Scholars.

Gac is a mucosal immunity researcher in the Kronenberg Lab, and Haupt is an HIV vaccine researcher in the Crotty Lab. The award recognizes their research achievements and comes with $10,000 in funding to support their careers.

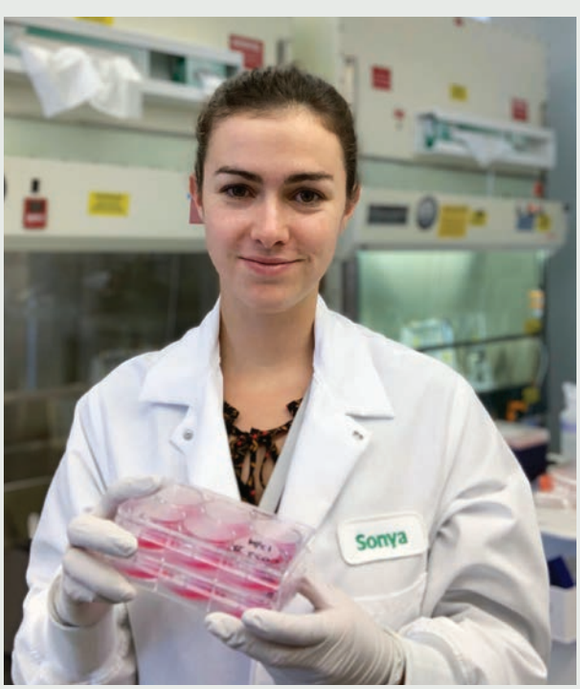
"Training the next generation of scientists to study immunology and human health is a core part of the La Jolla Institute mission," says LJI President and CEO Erica Ollmann Saphire, Ph.D. "We are delighted to partner with ARCS and UC San Diego to advance discovery and opportunity."

ARCS (Achievement Rewards for College Scientists) is a nationally recognized nonprofit organization founded and administered by women who volunteer their time and talent to advance science and technology in the United States by providing financial awards to academically outstanding students completing degrees in STEM (science, technology, engineering, and math) and in medical research. The organization is comprised of 15 chapters across the nation.

"Investing in the next generation of scientists, engineers, and medical researchers is crucial and will provide ongoing benefits to society as these young scientists become tomorrow's leaders," says Holly Heaton, President of ARCS San Diego.

The ARCS San Diego chapter was founded in 1985 and has granted more than 1,400 awards totaling over $11 million. In 2021, Dr. Saphire was named the 2021 ARCS San Diego Scientist of the Year honoree for her infectious disease research and leadership. •

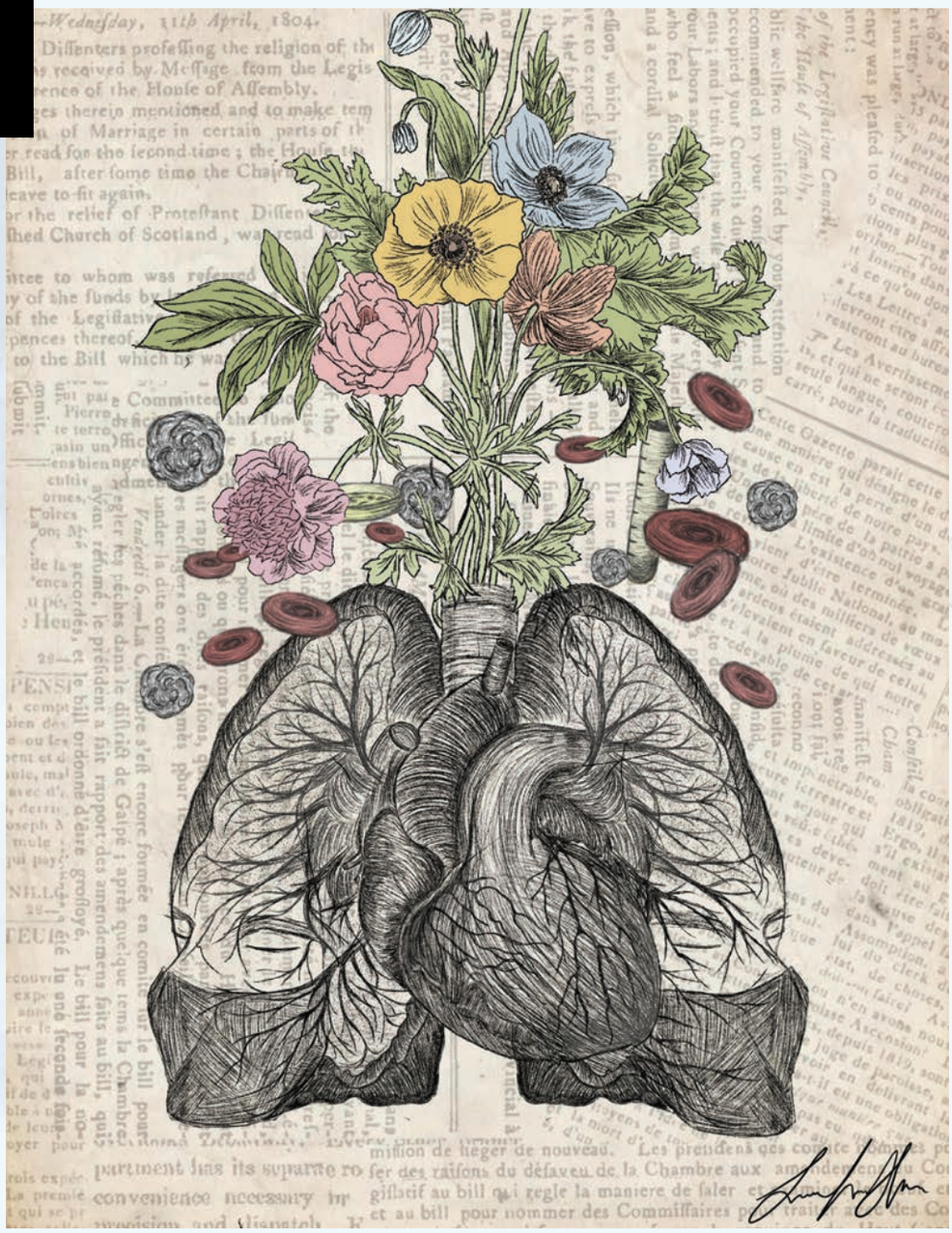
> "Investing in the next generation of scientists, engineers and medical researchers is crucial and will provide ongoing benefits to society as these young scientists become tomorrow's leaders."
>
> **Holly Heaton, President, ARCS San Diego**



Left is Gabriel Antonio-Ascui Gac and right is Sonya Haupt

San Diego students capture the pandemic era through art

The LJI Art of the Immune System Student Competition gives students a chance to learn about medical research while creating something stunning. The 2021-2022 competition was open to high school students across San Diego County. For inspiration, the student artists were invited to attend a series of live Q&A sessions with LJI researchers.



FIRST PLACE

JENNIFER HU

CANYON CREST ACADEMY

Hu's winning piece is a digital painting showing the lungs and heart blooming with flowers, test tubes, and red and white blood cells.

"Flowers are displayed to highlight the importance of the immune system in maintaining our health, especially when facing viruses," explains Hu. "The lungs contain faces with masks to recognize the vital researchers and healthcare workers and their significant contributions in maintaining health and safety during the pandemic."

Second-place winner Neshama Reed chose to use colored pencils to illustrate the evolution of vaccines throughout history. From left to right, she depicted smallpox and the 1796 cowpox inoculation, rabies and the 1885 rabies vaccine, polio and the Salk vaccine, HPV and the 2008 HPV vaccine, and COVID-19 and the current vaccines.

SECOND PLACE

NESHAMA REED

IDEA CENTER HIGH SCHOOL

THIRD PLACE

KELLY DAI

CANYON CREST ACADEMY

Third-place winner Kelly Dai focused on the importance of collective responsibility in stopping COVID-19. Her piece shows how a masked man is reducing the spread of SARS-CoV-2 to people around him, while an unmasked woman is putting her community at risk.

As she assembled her piece, Dai looked into the research behind mask wearing and how SARS-CoV-2 spreads. “I concluded that it is extremely important that everybody contributes and wears a mask, regardless of whether they believe they have COVID-19 or not,” says Dai.

DR. FERNANDA ANA-SOSA-BATIZ WINS AAI FELLOWSHIP

The American Association of Immunologists (AAI) has awarded a Career Reentry Fellowship to Fernanda Ana-Sosa-Batiz, Ph.D., a Postdoctoral Fellow at La Jolla Institute for Immunology (LJI). The fellowship will fund Dr. Ana-Sosa-Batiz's salary for a year and support her COVID-19 vaccine research in the lab of LJI Professor Sujan Shresta, Ph.D.

The AAI Career Reentry Fellowship goes to postdoctoral researchers who have taken a leave of absence from their positions for more than one year. Awardees may have taken time off for military obligations, medical, or family leave. "This fellowship means a lot to me," says Dr. Ana-Sosa-Batiz. "Coming back to work after three years of taking care of my family was really rewarding, and this fellowship opens up a lot of future opportunities."

Fernanda Ana-Sosa-Batiz, Ph.D.

LJI CELEBRATES RENEWED COLLABORATION WITH KYOWA KIRIN, INC.

In January, LJI and Kyowa Kirin, Inc., announced the signing of a new collaboration agreement, strengthening their alliance forged over 30 years ago.

Kyowa Kirin, Inc. is a global specialty pharmaceutical company with labs based in La Jolla. The renewed agreement increases annual funding and provides for more engagement of LJI faculty and Kyowa Kirin scientists as they work to translate basic immunology research into clinical applications.

"Faculty at LJI stand out as thought leaders in immunological research, driving a better understanding of how immune responses are coordinated to fight disease and also the adverse effects of unchecked immune activation," says Andrew McKnight, Ph.D., Chief Research Officer and Head of Open Innovation, Kyowa Kirin North America. "Our research team has worked to apply these novel ideas to develop new treatments for diseases, including acute respiratory distress and atopic dermatitis. We see great potential for further collaboration as we continue to grow our respective organizations."

LJI PARTNERS WITH WHAM TO ADVANCE WOMEN'S HEALTH RESEARCH

Scientists at LJI are partnering with Women's Health Access Matters (WHAM) to fuel research into sex-based differences in the immune system. The new collaboration brings LJI scientists together with experts focused on differences in women's health and related impacts on the U.S. economy. Already, WHAM has sponsored research showing diseases that predominantly affect women, such as rheumatoid arthritis and Alzheimer's disease, are understudied despite their profound effects on women in the workplace and women's healthcare costs.

At LJI, researchers are taking a close look at how diseases such as COVID-19, Parkinson's, and autoimmune diseases lead to different symptoms—and may require different diagnostic tools or therapies—in women and men. By working with WHAM, LJI can accelerate this research and help improve quality of life for all.

"Studying sex-based differences in a systematic manner will help uncover the causes and allow for treatments that are in tune with biology," says LJI President and CEO Erica Ollmann Saphire, Ph.D. "This is an exciting and growing area of research."

DR. ALBA GRIFONI AND DR. ALESSANDRO SETTE EARN TOP HONORS FROM THE SPANISH SOCIETY OF IMMUNOLOGY

LJI Instructor Alba Grifoni, Ph.D., and Professor Alessandro Sette, Dr.Biol.Sci., have received the Boulle-SEI International Award. This award, presented by La Sociedad Española de Inmunología (Spanish Society of Immunology) and the Jean Boulle Group, recognizes the global impact of the pair's studies into how T cells respond to SARS-CoV-2.

Alba Grifoni, Ph.D.

Alessandro Sette, Dr.Biol.Sci.

"I am very honored and humbled to receive this award, which also recognizes the importance of T cells in SARS-CoV-2," says Dr. Grifoni. "Like us scientists, the immune system works as a team, and we need all the possible components to properly fight this virus."

"I am very proud of the award that recognized a strong team effort at LJI, and several other groups in the United States, Europe, and Asia, with whom we regularly exchange information and collaborate," adds Dr. Sette. "The response to COVID has been truly a global undertaking."

"Like us scientists, the immune system works as a team, and we need all the possible components to properly fight this virus." LJI Instructor Alba Grifoni, Ph.D.

SIX LJI SCIENTISTS NAMED "HIGHLY CITED RESEARCHERS"

One of the best ways to measure the impact of research at LJI is through the recognition of scientific peers.

Last year, a record number of scientists at LJI were named "Highly Cited Researchers" by Clarivate. This recognition goes to researchers whose peer-reviewed papers have been cited most often by their scientific colleagues.

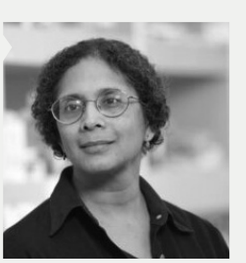
Clarivate named LJI Professors Shane Crotty, Ph.D., Klaus Ley, M.D., Bjoern Peters, Ph.D., Anjana Rao, Ph.D., and Alessandro Sette, Dr.Biol.Sci., and LJI Associate Scientist John Sidney, as scientists whose papers have ranked in the top 1% of citations for their field of study between 2010 and 2020.

"Citations are the best compliment you can get from your scientific peers," says Dr. Peters. "We cite each other's work to give credit and build on it."

Shane Crotty, Ph.D.

Klaus Ley, M.D.

Bjoern Peters, Ph.D.


Anjana Rao, Ph.D.

Alessandro Sette, Dr.Biol.Sci.

John Sidney, Associate Scientist

WHY I GIVE

Love & Science

Jaime and Sylvia Liwerant had a rare kind of love. “We always said magic was there,” says Sylvia. “Even after 63 years, we would watch TV holding hands. He gave me a wonderful life.”

“I wanted to create a memorial to a man who was so kind, so loving, so generous.”

Sylvia Liwerant

When Jaime Liwerant passed away in 2019, Sylvia wanted his community to remember who he was and what he stood for. Jamie was born in Mexico in 1931. He trained as a civil engineer at the Universidad Nacional Autónoma de México and moved to San Diego in 1974 with Sylvia and their sons, Maury and Gery. He was known for co-founding the Sylmar Development Company—and for his humor and warmth.

"I wanted to create a memorial to a man who was so kind, so loving, so generous," says Sylvia.

Through the Jewish Community Foundation, Sylvia was introduced to the mission of the La Jolla Institute for Immunology (LJI). "I was looking for a place where I could honor my husband's memory," she says. "LJI has a purpose that is hard to beat."

In September 2021, Sylvia and her friends and family gathered at LJI for a heartfelt memorial service and presentation in honor of Jaime. Sylvia also shared with LJI a generous donation, of an undisclosed amount, to support biomedical science for decades to come.

The new Liwerant Family Endowed Research Technology Fund at LJI will provide critical support for the technology and tools used in all 21 labs and four research cores at the Institute. These tools include high-resolution imaging equipment, sequencing platforms, and much more.

"This gift supports the technology that makes discoveries possible," says LJI President and CEO Erica Ollmann Saphire, Ph.D. "When we can see further, when we can see at higher resolution and see cells we've never seen before, it's because of these instruments."

Jaime and Sylvia Liwerant's love and legacy will be woven into countless studies, advancing research into cancer, autoimmune diseases, allergy, and some of the world's most devastating pathogens.

"What better way to help others," says Sylvia. •

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November 17 . 2021

A toast to Mitch

On Nov. 17, friends, supporters, and colleagues gathered at the Alila Marea Beach Resort for a special happy hour in honor of former LJI President Mitchell Kronenberg, Ph.D. Dr. Kronenberg strengthened LJI's impact and expanded the Institute during his 18-year tenure as LJI President, and he will continue to advance immunology in his new role as LJI's Chief Scientific Officer.

Mitchell Kronenberg, Ph.D., (right) and son Daniel Kronenberg, M.D.

JANUARY 25 . 2022

Women's Health Research Day

On Jan. 25, LJI and Women's Health Access Matters (WHAM) celebrated Women's Health Research Day by sharing the facts on the importance of women's health research for improving quality of life—and the American economy. The groups hosted a free, live webinar featuring experts on sex-based differences in diseases such as rheumatoid arthritis. The joint event also kicked off LJI's new partnership with WHAM to advance critical research into sex-based differences in the immune system.

The Jan. 25 expert panel included (clockwise from top right) LJI President and CEO Erica Ollmann Saphire, Ph.D., WHAM Founder and LJI Board Director Carolee Lee, LJI Board Chair Gail K. Naughton, Ph.D., and Lori Frank, Ph.D., of the RAND Corporation.

Women's Health Access Matters®

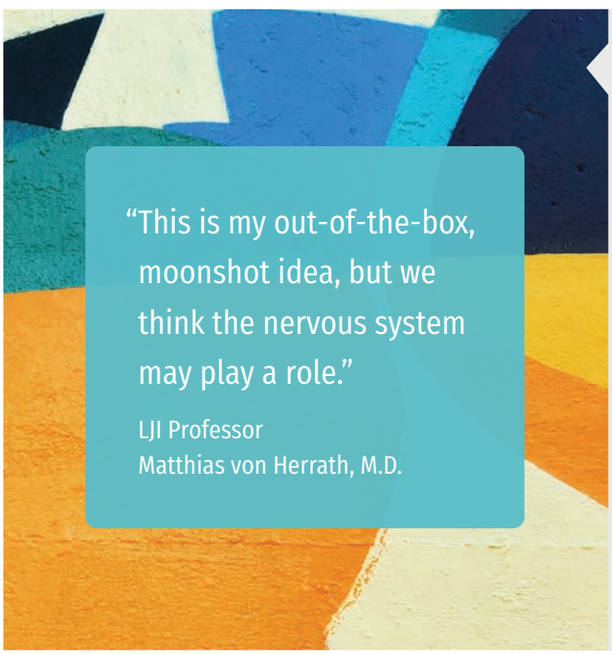
La Jolla Institute FOR IMMUNOLOGY | Life Without Disease.®

Scan QR code to watch webinar

MARCH 31 . 2022

LIVE FROM THE LAB

Exploring a fresh perspective on the causes of type 1 diabetes



On March 3, LJI Professor Matthias von Herrath, M.D., shared his latest type 1 diabetes research in the LJI *Live from the Lab* series. Type 1 diabetes affects an estimated 1.6 million Americans and there is no cure. The von Herrath Lab is working to understand what causes immune cells to attack the body's own cells in type 1 diabetes—and in similar autoimmune diseases. Their goal is to shed light on the basic mechanisms of autoimmunity.

Dr. von Herrath's research suggests the nervous system may play a role in triggering T cells to attack beta cells in the pancreas. He is leading work with industry partners to translate these findings to new therapies.

Scan QR code to watch webinar

AUGUST 5 . 2022

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A DAY AT THE Races

HOSTED BY
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5 | FRIDAY | AUGUST 5, 2022

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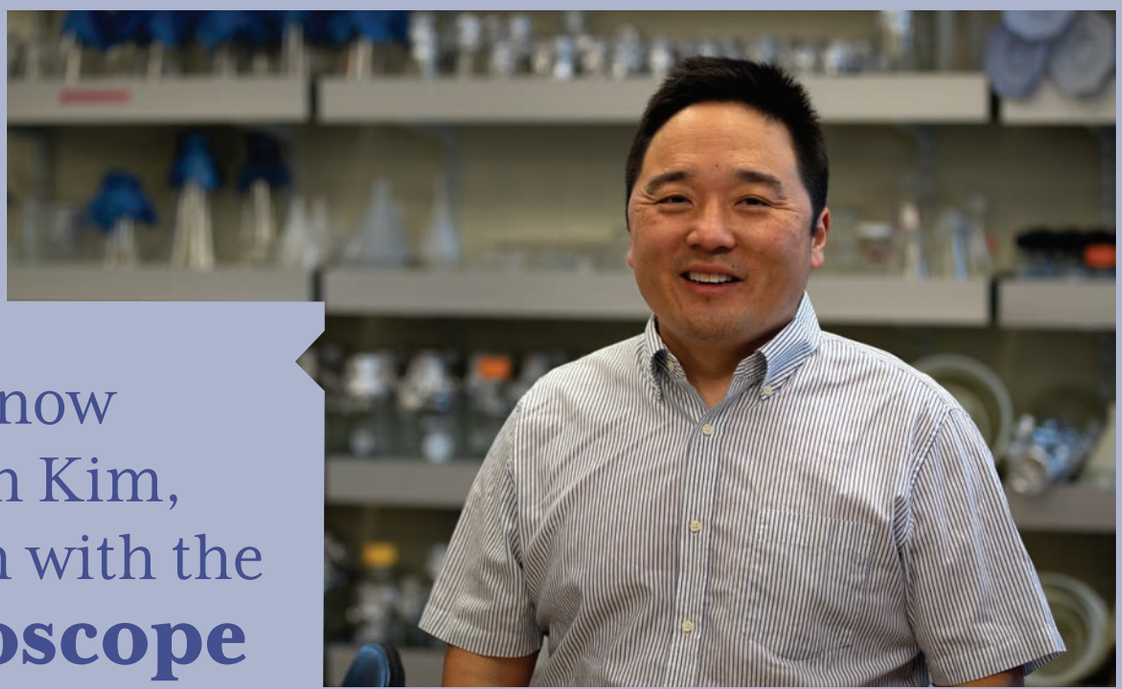


Get to know Kenneth Kim, the man with the **microscope**

Histopathologists are detectives on the lookout for microscopic signs of disease in the body's tissues. Histopathology comes from the Greek *histos*, for tissue, and *pathos*, for disease or suffering.

At La Jolla Institute for Immunology (LJI), histopathologic investigations are led by Kenneth Kim, Dipl. ACVP, Histopathology Core Director. Dr. Kim has collaborated with LJI scientists for many years, shedding light on diseases from dengue to ulcerative colitis. He has an eagle eye for spotting the important players in diseased tissues.

Why did you become a histopathologist?

I practiced veterinary medicine for about 10 years, but surprisingly clinical medicine became routine, and I missed the discovery side of science. I had always enjoyed pathology and remembered that one of my professors at UC Davis had mentioned the coming revolution in medicine, which would be driven by the genetically engineered mouse. He was right, and before I knew it a mouse pathology course at UC San Diego School of Medicine had me on the road to a pathology residency.

What can scientists learn from these mouse tissues?

I am trained to pick out the interesting or alarming parts of diseased tissues. One thing I can do is help investigators pick which regions of a tissue show the most injury. This lets them focus on the right sites for their follow-up analyses.

Other times, I'll look at a tissue and say, "Where is the normal stomach lining?" Those are the tricky ones, where something that should be there is missing.

What I'm trying to do is give researchers the big picture. The researchers are then going to open the doors and figure out how the immune system is reacting in these areas.

What do you like about being a histopathologist?

It's fascinating. If investigators decide to have me look at their tissues, it's almost like pure discovery. The investigators know something is different about their mice, but I'm the one who gets to put it together for them.

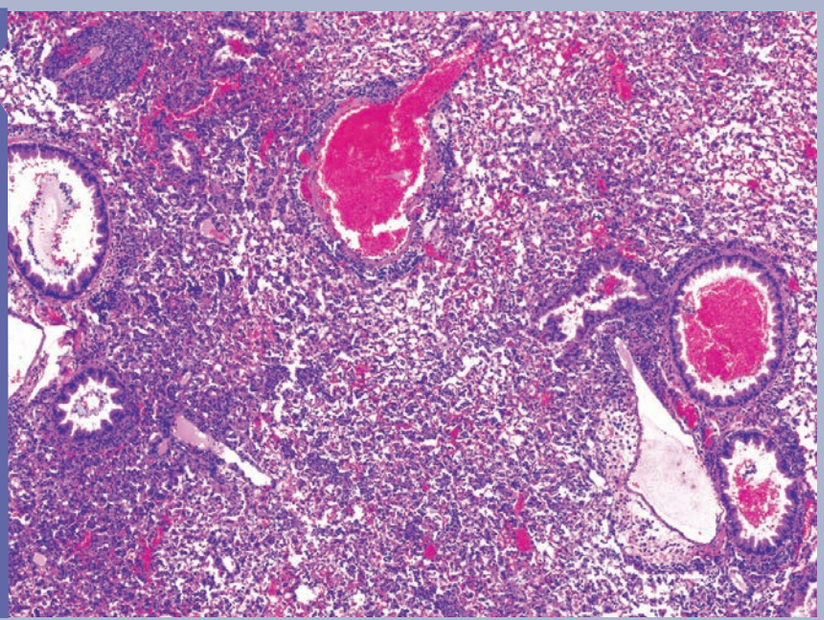
What's the coolest thing you've seen under your microscope?

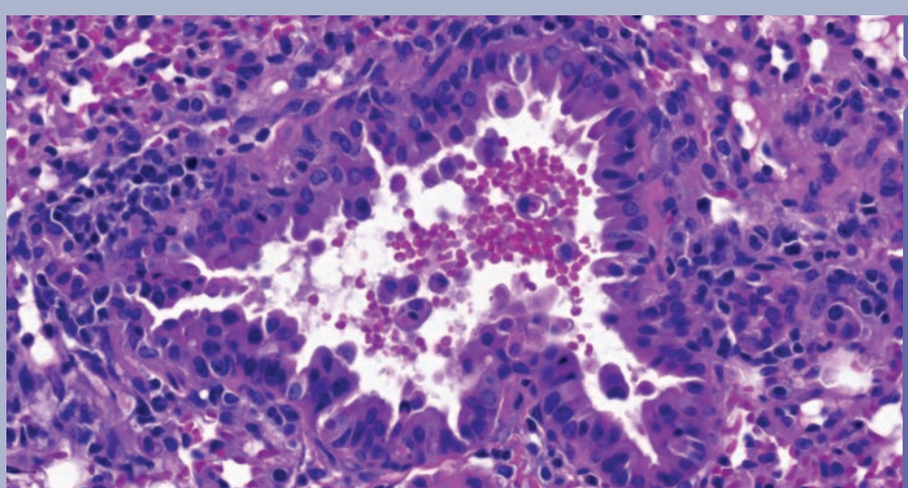
Microanatomy is in itself beautiful. Immune cells are always interesting because whenever there's an injury, immune cells or inflammatory cells are at the scene.

You never know what moment in time—or what moment in life—you're going to capture. I got this image once of a blood vessel. The red cells were at the bottom, white cells on top of them, with the serum above that. It was all in perfect order—like I captured a tube of settled blood. •

The purple and pink hues in this image are the signature colors of histopathology. Scientists like Dr. Kim use a special technique called an H&E stain to get these colors, which help them distinguish between different cell types.

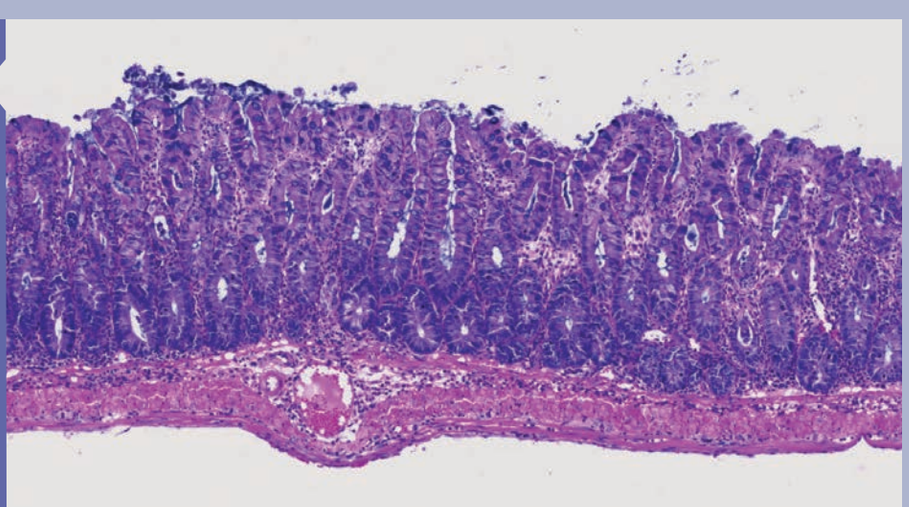
The dark purple dots in this image are individual bacteria colonizing lung tissue in a case of severe pneumonia. The dark clumps are florid bacterial colonies.





In this image of lung bronchiole, cells called phagoctyes (large pink and purple circles in the center) consume invading bacteria (small pink circles).

This diseased colon has been infiltrated with immune cells that drive inflammation. The dark structures are “goblet” cells, which produce mucus so waste can pass through the intestines.



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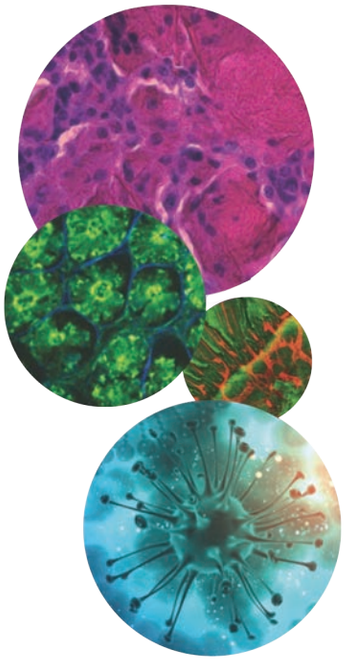

With your contribution to the La Jolla Institute for Immunology, you are joining our Vanguard and asserting your role at the forefront of the next breakthroughs in medical research. Our researchers are dedicated to assessing how the immune system can be harnessed to fight diseases ranging from asthma to Zika, so that one day we can all live free of the symptoms and frightening prognoses of many of the conditions we suffer from today. Your support ensures our scientists have the resources they need to accelerate the pace of their discoveries and turn "someday" into today. As a member of LJI's Vanguard you are taking an active role in leading the way to *Life Without Disease*®.

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Treating inflammation in the arteries

Atherosclerosis can start with minor inflammation. The disease leads to chronic inflammation of the arteries, dangerous lesions, and plaque deposits that clog the cardiovascular system and trigger heart attacks, strokes, and more.

New research in a mouse model suggests "smell" receptors in immune cells may trigger the initial inflammation that leads to atherosclerosis. This research, published in the journal *Science*, was led by La Jolla Institute for Immunology (LJI) Professor Klaus Ley, M.D., and LJI Instructor Marco Orecchioni, Ph.D., whose work was supported through the Rickey and Tullie Families SPARK Awards for Innovations in Immunology program and The Conrad Prebys Foundation.

No one expected to find smelling immune cells—until their existence was proven by LJI Scientific Associate Sara McArdle, Ph.D., also a previous SPARK Award winner. The fact that macrophages in the artery walls have olfactory receptors was reported by LJI scientists in 2019.

Thanks to an olfactory receptor called OR6A2, these macrophages sense octanal, a colorless, organic compound (which Dr. Ley describes as smelling like warmed-up chicken).

"Macrophages are some of the most important cells in our immune system," says Dr. Orecchioni. "They are constantly checking for signals. We could say they 'sniff' their environment and respond."

Everyone has a small amount of octanal in their blood, but LJI scientists have shown that people with markers of cardiovascular disease, such as high LDL cholesterol, also have higher levels of octanal. This extra octanal can end up in blood due to diet or a phenomenon in cells called oxidative stress.

The new research reveals that when macrophages in the arteries sense octanal, they cause inflammation, which can lead to cardiovascular disease and atherosclerosis in mice. "Smelly molecules can be pro-inflammatory," says Dr. Ley.

Drs. Ley and Orecchioni found they could reverse this inflammation by stopping the macrophages from sensing octanal. The team thinks it may be possible to block OR6A2 in humans, too. "These receptors are very well known as drug targets," says Ley. "In fact, most drugs on the market today act on this type of receptor, called a GPCR."

Dr. Orecchioni is also curious whether olfactory receptors may play a role in metabolic diseases, such as type 2 diabetes. "This study is just the first hint of something new," he says. "It's opened up years of research ahead of us."

"Macrophages are some of the most important cells in our immune system. They are constantly checking for signals. We could say they 'sniff' their environment and respond."

Marco Orecchioni, Ph.D., LJI Instructor

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