

Immune

SPRING 2017

MATTERS



It takes a village

A community of non-scientists provides a network of scientific support functions that allows research to flourish unimpeded

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Letter from the President

As successful as La Jolla Institute has been in conducting research on the immune system for almost 30 years, we are excited to report the best is yet to come.

The Institute is right in the middle of a recent scientific eruption that has seen the field of immunology rise into a leadership role in the quest to understand and treat disease. The effect of immunotherapy on cancer treatment alone, for example, has been nothing less than thunderous, and we are proud many of our principal investigators are contributing to that revolution.

That is just the tip of the iceberg. In the next few years, the kind of research that has earned us an international reputation for great science is going to pay huge dividends in transforming the way many diseases are treated, especially the chronic, inflammation-based ailments we specialize in studying here at the Institute.

As always, the talent and commitment of our 23 Principal Investigators and their outstanding research teams are the driving force in generating groundbreaking science. In this issue of *Immune Matters*, however, we want to highlight a group of Institute staff, virtually unknown to the public, whose support for science plays a critical role in our achievements. In acknowledging their vital contributions in our cover story, we show how we intentionally built an effective support infrastructure designed to foster discovery.

In our Q&A, you will learn about Ferhat Ay, Ph.D., one of an increasingly important type of scientist specializing not in lab experiments, but in analyzing the vast amounts of data that are being generated using statistical and mathematical methods. As a computational biologist, Dr. Ay is a pioneer in understanding the genetic basis of malaria and other diseases.

You will also read about Colin Havenar-Daughton, Ph.D., in our “Up-and-Coming” feature. As a research associate in the lab of Shane Crotty, Ph.D., Dr. Havenar-Daughton is investigating immunization strategies that could lead to a preventative HIV vaccine. Speaking of Dr. Crotty, you will see an article identifying him as one of the world’s most



influential scientific minds thanks to his place on the annual “Highly Cited Researchers” list compiled by Thompson Reuters.

In this issue, we also take a moment to mark the passing of two generous Institute supporters. William K. Bowes Jr., a Bay Area venture capitalist and biotech pioneer, provided the largest individual philanthropic gift in our organization’s history, one that allowed us to greatly expand our research on human immune responses through the recruitment of faculty member Dr. Pandurangan Vijayanand. Ralph Whitworth, an activist investor, founded the Immunotherapy Foundation, which supported cancer research at the Institute, especially the work of Professor Stephen Schoenberger, Ph.D.

In our optimism about the future, we know our success will continue to rely on the contributions of our many dedicated partners. We are privileged to have one of the most prestigious and engaged boards anywhere, and I hope you will read about our three outstanding new members inside. We are also deeply appreciative of the foundations, individual donors, and federal funding sources that will continue to assist La Jolla Institute as we draw ever closer to achieving our mission of *Life Without Disease*®.

Sincerely,

A handwritten signature in dark ink that reads "Mitchell Kronenberg". The signature is written in a cursive, flowing style.

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



It takes a village

A small but passionate group of support staff use their remarkable professional skills to free up Institute scientists to focus solely on groundbreaking discovery.

Rarely in view of the general public, a small but unique group of La Jolla Institute employees works passionately to help advance some of the most groundbreaking immunology research in the world. Most are not classically trained scientists but it is their joint effort that creates the robust support infrastructure that is so critical to the Institute's scientific success.

DR. STEPHEN WILSON, COO AND EVP, AND ALBIN SOARES, DIRECTOR OF RESEARCH ADMINISTRATION

“The principal investigators and their research teams are just the leading edge of a massive effort that includes large numbers of non-scientific personnel whose support is fundamental to the scientists’ ability to achieve true discovery.”

— Mitchell Kronenberg, Ph.D.

Though “outside the lab,” the scientific support staff’s deep pride and commitment to helping unravel the mysteries of the immune system parallels that of their scientific colleagues. Their contributions range far and wide: from helping attract millions in government grants, securing the most sophisticated scientific equipment, safeguarding vast amounts of data, protecting the health and safety of both staff and animals, stewarding intellectual property, fundraising, and communicating the Institute’s discoveries to the world, to mention just a fraction of the important functions that propel La Jolla Institute’s mission (see stories on pages 6 to 12).

“To some, biomedical research may seem as simple as a brilliant mind going into a lab with a hypothesis and in a solo effort attempting experiments that will hopefully uncover the secrets of nature,” says Mitchell Kronenberg, Ph.D., Institute President and Chief Scientific Officer. “That will always be the foundation, but in today’s modern world, most people are unaware that science has become an incredibly complex social enterprise. The principal investigators and their research teams are just the leading edge of a massive effort that includes large numbers of non-scientific personnel whose support is fundamental to the scientists’ ability to achieve true discovery.”

The person who oversees this effort is immunologist Stephen Wilson, Ph.D., and as Executive Vice President and Chief Operating Officer, he and his team approach scientific support as an opportunity to partner with labs, not just administer from afar.

“We’re fortunate to have such a clear and admirable mandate: empower scientific staff with cutting-edge technology and expertise so that their research environment has the fewest possible barriers to discovery,” says Dr. Wilson. “While we

constantly search for ways to improve, it’s our belief that from a scientist’s perspective, LJI is among the most streamlined and effective institutes in the world.”

Facilities and financial support aside, the biggest factor helping the Institute stand apart: the individuals providing scientific support. Highly trained professionals with a passionate interest in science and discovery, they are dedicated to facilitating research and smoothing the road to discovery. Although not scientists themselves, they carry out critical jobs within a heavily regulated business environment and are held to the highest standards.

“We take our mission very seriously, and every day, together, we’re fighting the clock,” says Dr. Wilson. “So, when we boil it down, everything our support staff does has to be with the intent of making life easier for our scientists to remain focused and effective, saving them that most precious of commodities, time.”

“Can a researcher conduct science with just a lab, some lab technicians and some tissue and no other support?” asks Principal Investigator Sonia Sharma, Ph.D., Assistant Professor and Director of the Functional Genomics Center. “I will always say ‘yes’, but if the question is whether that same researcher can produce great science, and in high quantities without support, the answer is ‘absolutely not.’”

Dr. Sharma says that in today’s environment, the pursuit of science is so complex, competitive, and technological, researchers would simply be overwhelmed and their research productivity and quality would suffer tremendously without support. Having worked at several other scientific organizations, she says the Institute is far and away the best at providing that support.

“La Jolla Institute is truly unique,” Dr. Sharma said. “I think I speak for just about all of the research staff here at the Institute when I say that top to bottom our support staff are stellar. I don’t think there’s any question they’ve played a crucial role in both the volume and quality of the research my lab has been able to conduct. They really do help us become better scientists.”

MEET SOME OF LJI’S SUPPORTERS OF SCIENCE ON THE FOLLOWING PAGES.

Administration Mission Statement

The administrative departments at La Jolla Institute are dedicated to creating the foundation on which our investigations of immune system function can thrive, ensuring best-in-class laboratories and facilities, providing access to advanced technology and equipment, recruiting talented professionals who deliver lab-centric service, and fostering a culture of innovation, collaboration, and mutual respect. This is all in keeping with our greater commitment to *Life Without Disease*®.

Albin Soares, MBA

DIRECTOR OF RESEARCH ADMINISTRATION

In every successful organization you'll find "go-to" people—those to whom others turn to help get things sorted out. As the Institute's Director of Research Administration, Albin Soares is the epitome of that person: smart, highly motivated, and amazingly resourceful.

When Soares recently listened to Principal Investigator Sujana Shrestha, Ph.D., ask whether her lab had the finances to add both a postdoc and some new equipment, he knew it would overburden her lab in the short-term.

"Dr. Shrestha wanted to hire a postdoc from Nepal to help expand her human study efforts, but she also needed to replace a failing -80 degree freezer and a six-foot lab hood. I recommended that she use available funds to hire the postdoc, and that we would beg, borrow, and steal for the equipment. In the end, Dr. Shrestha was able to accomplish all three."

Soares engages in that kind of problem solving virtually every day as he serves as the Institute's key administrative liaison with the scientists. Just to name a few of his duties: He is responsible for the financial success of scientists' portfolio of grants and contracts; advises the PIs on the impact of personnel decisions and equipment acquisition; helps them create financial plans for operating their labs and drafts strategic plans for future expansion; supervises all the labs' administrative assistants; informally serves as administrative support for the joint LJI-UC San Diego immunology program, and as the Institute's government relations specialist, conducts Institute tours for members of Congress and other state and local elected leaders.

Soares' education and professional experience, along with his passion for the Institute's scientific mission, made him well suited for the dynamic job when he was hired three years ago. He has a B.A. from George Washington University, an MBA from Tulane University, has worked for a U.S. congressman on Capitol Hill, served as a consultant to the Office of Management and Budget, and has worked in private businesses ranging from startups to Fortune 500 companies.

"Our scientists are brilliant when it comes to their research. But they are not formally trained in business, and that can put them at a disadvantage in running their labs, which are essentially enterprise operations experiencing many of the same issues facing small businesses," Soares says. "I do wear a lot of hats in this job, but I really like what I do because I enjoy seeing just how much of a positive impact I can have in helping the labs. If I can free up even 10 percent of the principal investigators' bandwidth, that translates into 10 percent more of their time that can be focused on science."

Margaret Ng Thow Hing, J.D.

SENIOR DIRECTOR, TECHNOLOGY DEVELOPMENT

There's nothing more thrilling at La Jolla Institute than those moments when research leads to a groundbreaking scientific discovery that may help to understand the cause or to treat a disease. Once the excitement and celebration have subsided, however, two questions emerge: First, is there an application in industry for this technology and, second, is there any novel intellectual property that should be protected?

Intellectual property protection is a critical step in translating discoveries into actual drugs and therapies and, in the process, generating commercial research funding, licensing fees, and royalties for the Institute.

The many complexities and details of the discovery protection process at the Institute are handled by the highly skilled team in the Technology Development department, led by Patrick Ho, J.D., Vice President and Chief Business Officer. The department members, each of whom is a legal specialist, a trained scientist, or both, all share a love of science and truly enjoy the process of helping protect the Institute's key discoveries.

Senior Director Margaret Ng Thow Hing is a perfect example. She has both a J.D. and a master's degree in molecular genetics from the University of Toronto, and calls on both disciplines daily in working with scientists.

"One of our key responsibilities is to make sure the Institute's discoveries are protected with patents and other legal safeguards, and that's a process we work on with the scientists, often at a very early stage in the research," Hing says. "As a scientist, I love the opportunity to observe all kinds of outstanding research evolve and come to fruition, and as a lawyer, I enjoy employing my legal skills to make sure those discoveries are properly protected." In addition to putting the proper intellectual property protections in place, Hing works closely with members of the department responsible for business development functions to identify commercial applications for the technology and develop strategies to move the discovery out of the research lab and into industry.

As complicated and time consuming as the above process is, however, it represents only a fraction of the services Hing and her colleagues provide. They draft the contracts necessary to acquire compounds and technical tools the scientists use in their labs. They manage the necessary legal framework for the Institute's many relationships with corporate partners and other scientific institutions. They write the agreements that allow the Institute to license research discoveries to pharmaceutical companies for drug development or contract with companies to conduct research on compounds they provide.

"One reason our department is so committed to doing the best job we can is because these corporate partnerships and contracted research agreements are not only important for advancing science, they're also critical to the Institute financially," Hing says.

As busy as she is, Hing says she will never regret her decision to leave private intellectual property law in 2011 and join the Institute. "I feel particularly lucky to be working here," she says. "It may sound hokey, but I really believe this is a very special place with amazingly talented scientists and staff. I realize I'm not the person generating the science, but I'm completely invested in the success of our researchers and the Institute. I get excited when there is a new discovery and I have the opportunity to contribute to a process that enables great science to emerge from the lab and be delivered out into the world to benefit public health."





Lisa Young, CIP

SENIOR COMPLIANCE ADMINISTRATOR

When asked about the intellectual thrill of being a scientist, one topic never comes up: navigating a maze of research regulations designed to safeguard research integrity and protect the physical wellbeing of scientists and research subjects alike.

That's where Lisa Young, a 14-year veteran of the Institute, comes into play. A senior compliance administrator with a bachelor's in science from National University of Ireland, Young administers three separate internal committees that oversee biosafety, lab animal welfare, and human subjects research. She sees herself as a guide and facilitator, who educates researchers and helps scientists comply with the regulatory requirements surrounding their research. "The work our faculty does carries with it a great deal of responsibility and, as a result, a great deal of paperwork," she explains. "We strive to make the oversight process as efficient as possible, so that our researchers can return their focus to what's most important to them and that's investigating the immune system."

In many cases, before any actual research takes place at the bench, the proposed project has to be reviewed by the appropriate committee to ensure it meets all internal safety standards, complies with federal, state, and local regulations, and is designed in accordance with the highest ethical principles. The committees include LJI scientists, independent outside scientists, subject matter experts as well as members of the general public. Young works with these diverse groups of members to help the committees operate smoothly and with researchers to facilitate submission of research proposals. She confirms the correct forms are filled out, coordinates the submission and review process, and generally lends a helping and reassuring hand.

As part of their research, scientists routinely handle laboratory mice, pathogens, potentially hazardous chemicals, and human blood samples from clinical research volunteers. Add in that all of this is subject to massive amounts of government regulation and oversight and it is easy to understand why some researchers may feel burdened by all the rules and regulations governing their work.

"It can be logistically challenging to ensure that all of our research complies with all applicable regulations given the wide scope and nature of immunology research conducted here," says Young, who started her career at LJI at a laboratory bench and thus is intimately familiar with the day-to-day operation of an active research lab. "But the Institute has an elaborate infrastructure in place to address all of the logistics and we strive to make the process as efficient as possible. For me, it is very rewarding to be part of the team supporting our researchers in the great work they do."

John Stillwagen, MBA

DIRECTOR OF MANAGEMENT SYSTEMS

La Jolla Institute has continued to expand and improve the quality of its research into the immune system because it is made up of people like John Stillwagen, who are driven to continue to grow and get better professionally.

If you could flash back 16 years, you would see Stillwagen arrive at the Institute as an eager but largely inexperienced young tech department employee. Today, you will find Stillwagen has risen all the way to the top, serving as Director of Management Systems, an IT position critical to the Institute's ability to organize its business systems and manage burgeoning scientific data.

What happened in between is a tribute both to the Institute's willingness to support staff professional development and Stillwagen's motivation to succeed.

"I started out in tech support, but when they were looking for a web developer I taught myself how to build web pages and got the job," Stillwagen recalls. "Then I moved up to be our primary Windows system administrator, learned enough to become database manager, and then expanded my skill set so I could take on the job of designing and overseeing our primary data storage systems."

Stillwagen's outstanding performance in carrying out the latter job is especially appreciated by the scientific staff and Institute administration because managing the Institute's rapidly growing scientific data is vital to the organization.

"This one was a real challenge because the Institute's data doubles every year and was threatening to overwhelm us if we didn't stay on top of it," Stillwagen says. "By constantly investigating new technologies we've been able to come up with what we think is the most secure and lowest cost data system among all of the scientific institutions in the area."

As director, Stillwagen's duties continue to expand. He is responsible for crafting the Institute's overall technology strategy, developing new technologies, and rolling them out to the workplace. Typical of people like Stillwagen, however,

he isn't satisfied and believes he can do more to help the Institute. To improve his business planning skills, he has just finished up his MBA in an online program from the Kelly School of Business at Indiana University. He also launched a trial project with Principal Investigator Lynn Hedrick, Ph.D., in which he serves as a business consultant to help create the most streamlined technology-based processes for her lab, including inventory, purchasing, and personnel.

"My measure of success is whether I can improve the quality of the work life at the Institute, especially for our scientists," Stillwagen says. "If I can equip them with a technology-based solution to help them become more efficient and enjoy their job more, they're going to be happier and more productive. That's the best way I can help them have more impact in their research."



Gina Kirchweger, Ph.D.

CHIEF COMMUNICATIONS OFFICER

It wasn't until after Gina Kirchweger earned a Ph.D. in biochemistry at the University of Vienna and worked as a scientist for a number of years that she realized she had missed her calling. Fortunately for her and La Jolla Institute, she didn't miss it by much.

"I'm lucky because I discovered my true passion was actually writing about science and sharing with the world the discoveries that come out of the amazing work of talented researchers like we have here at the Institute," says Dr. Kirchweger, who joined the organization as Chief Communications Officer in 2015.

Once Dr. Kirchweger made the decision to take a different path in the late 1990s, she enrolled in the Science Communication program at the University of California, Santa Cruz, and then launched her second career by working as a foreign science correspondent for European newspapers and magazines for a number of years. She then shifted to working in-house, leading the science communications teams at prestigious scientific organizations such as the Salk Institute for Biological Studies in La Jolla and the Stowers Institute for Medical Research in Kansas City, Mo.

Over the last two years, Dr. Kirchweger has had a significant impact on the substance and quantity of the communications coming out of the Institute. Her credibility as a trained scientist and talent as a communicator have helped her gain the confidence of scientists throughout the Institute. They're impressed with her ability to translate the most technical and difficult-to-comprehend research into plain, understandable English accessible to all audiences, but especially those in the general public who have little or no science background.

What makes Dr. Kirchweger so valuable to the Institute is that she isn't just a science writer, she is a communications force. She and her colleagues have built the equivalent of an entire communications agency that utilizes a wide variety of tactics to share the Institute's work and achievements. Among her many duties, Kirchweger writes and distributes press releases; handles media relations and works with reporters covering the Institute; serves as editor and writer for *Immune Matters* magazine; manages LJI's website, including overseeing its re-design last year; writes fundraising brochures; develops communications strategic plans; polishes the visuals on

presentations given to lay audiences and just recently helped develop the Institute's first mobile app.

"I love that I still have a foot in science but get to use all of my creativity," she says. "To me it's all about communicating the excitement and critical nature of immune system research. I'm thrilled we have such a fantastic story to tell about the groundbreaking science here and how it affects every aspect of human health. Our scientists' research here has always been recognized and admired within the scientific community, but awareness of their work is reaching a wider audience regionally and nationally. My ultimate goal is that someday anyone who thinks of immune system research thinks first of La Jolla Institute."



Chris Lee, MBA

CHIEF ADVANCEMENT OFFICER

In a recent meeting, a potential donor suddenly looked Chris Lee in the eye and asked, “If La Jolla Institute is so successful in attracting highly competitive federal government research funding, why do you need a contribution from me?”

It is a question Chris Lee hears often in his job as Chief Advancement Officer, and it’s one he’s always eager to answer as the person primarily responsible for raising philanthropic support for the Institute from private sources. “I really enjoy letting people know that while the Institute thankfully has stable core funding based on the strength

of our work, as a donor they have a tremendous opportunity to significantly grow the Institute’s research on the immune system,” says Lee. “I love seeing them get excited about the idea of their philanthropy helping our scientists make those pivotal discoveries that change people’s lives.”

Lee, who graduated with a bachelor’s degree in political science from West Virginia University and an MBA in marketing from Villanova University, started his career as a staffer on Capitol Hill. Today, he is a 20-year development veteran with experience at top-level scientific organizations. Although he has only been on board at the Institute since last fall, he has already gained the confidence of many organizational stakeholders through a genial style and almost charismatic ability to capture the imagination of donors and encourage them to manifest their deep commitment to helping others by supporting the Institute financially.

“Philanthropic dollars are like an injection of accelerant because they often allow our researchers to dramatically expand their scientific vision and capabilities to complement the research they can achieve with competitive grants,” Lee says. “That outside money can be used to spark unusual and innovative research that can’t yet be funded with a grant, it can pay for recruiting the brightest and best postdocs and technicians, and it can fund the purchase of the most technologically advanced equipment and facilities.”

Lee and his team are succeeding in attracting more donors because they have a true passion for the Institute and its mission and a laser-sharp focus on the message they want to impart to donors.

“In raising awareness of La Jolla Institute and bringing in as many private philanthropic dollars as we can for our scientists, we want people to know three things: who we are, what we do, and why it matters,” Lee says. “It’s crucial they know we are proudly and singularly focused on studying the immune system and the role it plays in virtually all disease. And that contributing to our work is one of the best scientific investments they will ever make, and finally, that the payoff, especially if they’ve had family or friends suffer from disease, is the chance to contribute to a process that has the very real potential to transform human health.”





Brandon Fabritzky, CRA

SENIOR MANAGER, OFFICE OF SPONSORED RESEARCH

Late last year, Sara McArdle, Ph.D., was getting excited about applying for a grant she hoped would enable La Jolla Institute to purchase a sophisticated laser scanning research microscope. That was until she opened the necessary forms to complete the grant application.

“It was more than 150 pages long, had five pages alone of confusing rules, and required accompanying letters from 20 scientists around the building,” says Dr. McArdle, a microscopy specialist in the Institute’s Microscopy Core. “If I had been working anywhere else but the Institute, I wouldn’t have even tried to complete the application.”

Yet Dr. McArdle wasn’t at all concerned because she knew she had a huge advantage: the Institute’s Office of Sponsored Research. She contacted and received immediate assistance from one of the members of Senior Manager Brandon Fabritzky’s veteran staff, among the most talented and dedicated grant assistance teams on the Torrey Pines Mesa.

“I remember showing the application to Maya Sarinana in the department and she wasn’t intimidated at all,” Dr. McArdle recalls. “She went right to work, and over a period of a few weeks made sure everything was collected and put in its proper place with the right format. We even had a glitch on deadline day, but she came up with a solution and we submitted the application with only five minutes to spare.

By contrast, most places I’ve worked in the past offered me almost no assistance at all.”

Dr. McArdle’s praise is echoed by virtually all of the scientists at the Institute who receive similar assistance from Fabritzky’s team in submitting upwards of 130 grant applications a year, mostly to the National Institutes of Health, from which the Institute receives about 70 percent of its annual funding. LJI has one of the higher success rates in attracting NIH funding, which is why Fabritzky can’t understand why other institutions don’t invest the same kind of resources and effort that the Institute does.

“With grant funding being one of the vital lifelines of our Institute, we know just how important every one of them is to the health of our organization,” Fabritzky says. “That’s why my team and I always go the extra mile, handling every application with the utmost care—down to the smallest detail—while making every effort right to the very last minute before a deadline to support our scientists to make sure their entire application is the best it can possibly be.”

Fabritzky and his team are always excited when news of a grant award is received. “We feel very much like LJI’s maternity ward,” Fabritzky says with a smile. “We’re thrilled to play a role in helping deliver a service that is so critical to our researchers’ ability to fund great science.”

Colin Havenar-Daughton

IN SEARCH OF A VACCINE TO PROTECT AGAINST HIV/AIDS

Colin Havenar-Daughton, Ph.D., defied the odds. He grew up in Oakland long before hipsters flocked across the Bay Bridge into the “Brooklyn of the West Coast”. “It was rough,” recalls Dr. Havenar-Daughton, but an intense and inspiring high school program focused on the humanities kept him on the straight and narrow. “It was set up by a couple of teachers and shielded about 50 kids each year from what was going on all around us—truancy, drugs, violence.” It also nurtured his interest in politics and government affairs.

When Dr. Havenar-Daughton enrolled at Pomona College, a small liberal arts college in Claremont, Calif., he initially chose the Public Policy Analysis program before his interest in biology won over. After graduation, Dr. Havenar-Daughton took a job with the HIV Vaccine Trials Network (HVTN), the world’s largest publicly funded collaboration dedicated to developing a vaccine for HIV. “It fit right in with my goal of pursuing a career with a purpose,” he says.

After analyzing HIV clinical trials data for HVTN for four years, Dr. Havenar-Daughton went back to school to get his Ph.D. in immunology from the University of Washington in Seattle. “When I graduated, I was ready for a bit of adventure and went to France for my postdoc,” he says. Three years later he returned to the U.S. and his scientific roots—the quest for an HIV vaccine.

As a research associate in the lab of Shane Crotty, Ph.D., Dr. Havenar-Daughton has a front seat at the Scripps Center for HIV/AIDS Vaccine Immunology & Immunogen Discovery (CHAVI-ID), which develops immunization strategies for a preventative HIV vaccine. His most recent paper revealed important immunological features and bottlenecks that determine whether immunization is successful. Most importantly, it provides a valuable tool to track the potential of novel HIV vaccine candidates in upcoming human phase I clinical trials. “The work we are doing on the HIV vaccine in collaboration with the consortium is everything I want to do in science,” he says.

Dr. Havenar-Daughton may have found his scientific happy place, but his adventurous streak is as strong as ever. He recently started rock climbing and travels the world with his wife Laure, whom he met in France. “I adopted the French attitude: During your work hours you focus on your work and don’t mess around but when you take vacation—and you do take vacation—then you are on vacation.”

Microscopy Core

Science is propelled by curiosity and technology and nothing illustrates this better than microscopy

Despite microscopy's long history—the first microscopes date back more than 400 years—new innovations push the limits of what we can see. Yet, increased magnification by itself doesn't mean much. "Blowing up a tiny picture doesn't reveal more details, there is a physical limit of how much we can see," says Zbigniew Mikulski, Ph.D., who directs LJI's Microscopy and Histology Core. "However, there are some smart ways in which we can break through that barrier. The goal of all technical advances is to improve resolution, be gentler with our samples, penetrate tissues deeper, and in some cases to do so in living animals."

Today's microscopes are marvels of engineering—and mind bogglingly expensive—but it still takes human ingenuity to bring never before seen details into view. Dr. Mikulski and his team of microscopy experts stay up-to-date on the latest technology, advise, write software, and even experiment with 3D-printers to help LJI researchers expand their gaze into uncharted depths of living tissues to better understand how the immune system works. The following are some examples of pioneering images that had a powerful impact on LJI scientists' work.



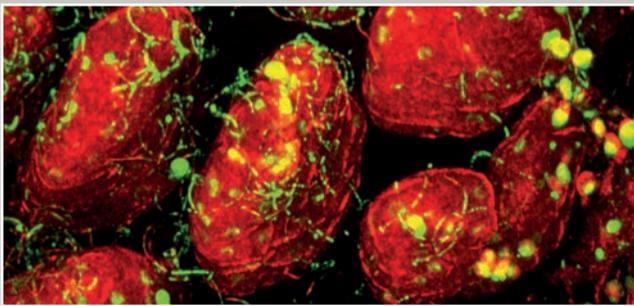
ATHEROSCLEROTIC MOUSE CAROTID ARTERY.
IMMUNE CELLS (YELLOW), COLLAGEN (BLUE).

Skipping the beat

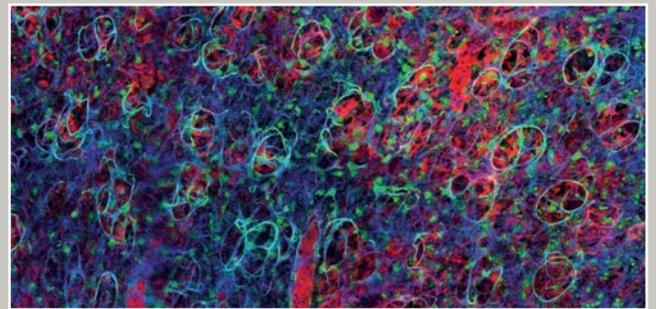
As part of her graduate studies, Sara McArdle, Ph.D., explored the role of immune cells in atherosclerosis, the buildup of fatty substances and cholesterol deposits on the inside of arteries. Specifically, she wanted to use intravital microscopy to track immune cells inside the carotid artery in living mice, but the ebb and flow of blood pulsing through the vessel would inevitably thwart any efforts to record clear videos.

To compensate for the heartbeat, Dr. McArdle designed and custom-built a clever system that links the frequency of the animal's pulse with the acquisition speed of a 2-photon microscope. This allows the microscope to skip the heart's beat and acquire a series of stable images. "Right now, nobody in the world does this better than the LJI imaging core," says Dr. Mikulski. After some computational fine-tuning of the collected data, Dr. McArdle was able to watch as a specific type of immune cell orchestrates the inflammatory assault on the artery wall.

“The goal of all technical advances is to improve resolution, be gentler with our samples, penetrate tissues deeper.”



INTESTINAL VILLI (RED) AND SEGMENTED FILAMENTOUS BACTERIA (GREEN).



LUNG ARCHITECTURE; ACTIN (GREEN), VASCULATURE (RED), CONFOCAL REFLECTION (DARK BLUE).

Reflecting the invisible

When Gooyoung Seo, Ph.D., wanted to study T cells within intestinal villi, the finger-like projections extending into the interior of the small intestine, she used confocal reflection microscopy (CRM) to trace the villis' surface relative to the T cells. While most modern microscopes rely on fluorescent tags to identify and visualize molecules, CRM—a technique often used in material sciences—uses polarized light to form images of unlabeled objects placed close to a glass surface.

Much to Dr. Seo's surprise, CRM revealed that in the ileum, the section of the small intestine next to the appendix, the villi were covered with tiny fibers. Further experiments confirmed that these fibers were segmented filamentous bacteria (SFB), elusive members of the gut microbiome. Dr. Seo is now following up on her unexpected discovery, hoping to learn whether there is a connection between intestinal T cells, the presence or absence of SFBs, and inflammatory bowel disease.

A picture worth more than a thousand words

Catie Crosby, Ph.D., is interested in how a special class of immune cells known as invariant natural killer T cells (iNKT) function in the lung during infection with *Streptococcus pneumoniae*. The bacterium is part of our body's natural ecosystem but when the immune system is weakened it can turn into a formidable foe. Not only is it the most common cause of community-acquired pneumonia and meningitis in the elderly, it can also manifest itself in myriad different ways.

When Dr. Crosby submitted a grant application to the American Lung Association, she proposed an ambitious project: a combination of intravital microscopy and flow cytometry to study why iNKT cells are so critical for protection against *S. pneumoniae* with the ultimate goal of harnessing the potential of these cells for human therapeutics. Submitting visual proof that LJI's imaging core was more than up to the task of probing lung tissue of living, breathing mice convinced the selection committee to award her the grant. ●



Ferhat Ay

Computational Biologist

Before Ferhat Ay, Ph.D., entered first grade, he had already announced to the world that he wanted to become a computer engineer. By the time he enrolled at the Middle East Technical University in Ankara, Turkey, the avid gamer had narrowed his career path to video game developer and soon was busy taking math and computer graphics classes. In the midst of his undergraduate studies, an inspiring bioinformatics class captured his imagination and Dr. Ay found himself veering off into a new direction. Instead of dreaming up fantasy worlds, he redirected his focus to the string of four letters that make up our DNA.

“You are playing with A, T, G, and Cs and they all have meaning. You can look at them in very creative ways,” says Dr. Ay, who joined La Jolla Institute as Institute Leadership Assistant Professor of Computational Biology a little more than a year ago. “When I applied to Ph.D. programs, I specifically sought out bioinformatics programs and then it picked up from there.”

When fully extended, the DNA encoding our genes measures about two yards, yet it is tucked into a cell nucleus with a diameter more than a 100,000 times smaller. To fit it all in, the DNA is coiled up and carefully folded. Dr. Ay’s trailblazing work in the parasite *Plasmodium falciparum*, which causes the most lethal form of malaria, provided the first evidence that the three-dimensional shape of the resulting DNA folds can coordinately repress or activate genes. “It was great to be in the right lab at the right time and be part of it when it all started,” he says. Since then the field of genome architecture has taken off and the genome’s three-dimensional structure has emerged as a universal tool to understand the regulation of gene function. At La Jolla Institute, Dr. Ay has expanded his research to uncover new links between disrupted genome folding patterns and disease.

HOW WOULD YOU DESCRIBE THE FOCUS OF YOUR RESEARCH?

I am interested in epigenetics. By definition, epigenetics is anything beyond the sequence of the four letters in DNA that controls the activity of genes. That would be chemical modifications of DNA and proteins intimately associated with DNA, and in my case specifically, how the DNA is folded in the nucleus.

WHY IS THE FOLDING IMPORTANT?

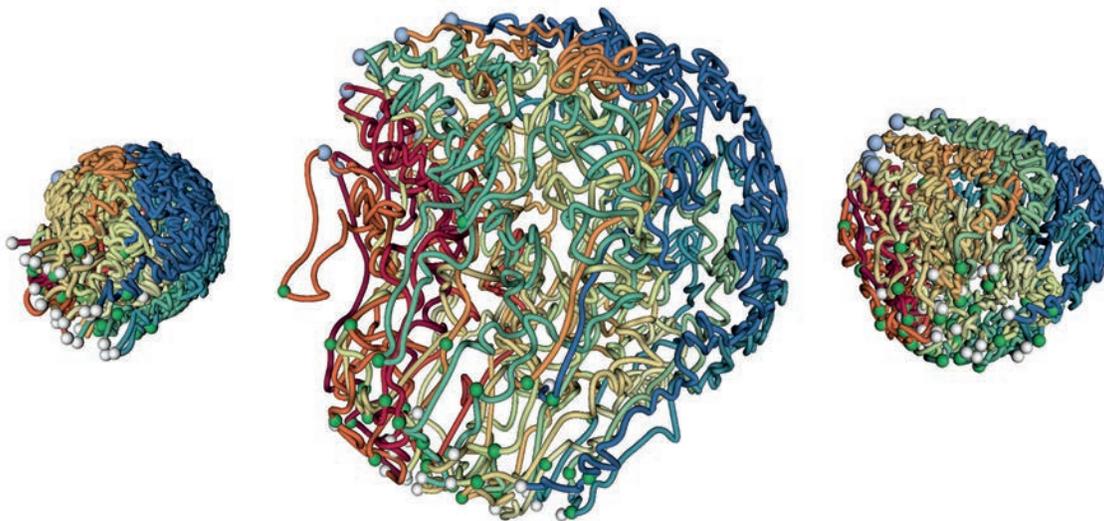
If you stretched out the DNA from all of your body’s cells and lined it up end-to-end, it would cover the distance between earth and sun a hundred times. While this is certainly an intriguing tidbit of information, most importantly it goes to show how much information needs to be compacted into a tiny nucleus.

HOW DOES IT ALL FIT?

The DNA is not randomly jammed into the nucleus. Instead, the packing follows a strict hierarchy, which is controlled by regulatory elements all over the genome. We want to understand how these regions control the packing of the genome and ultimately gene activity.

WHY WOULD THE PACKING INFLUENCE GENE EXPRESSION?

Control switches that regulate gene activity are found all over the genome, but they are not necessarily lined up next to the gene they control. By merely looking at the one-dimensional organization of the genome, we are unable to tell which gene a specific control switch is actually controlling. When a chromosome dynamically folds it brings distant control switches close to their targets, which are ready to respond to signals from control regions.



IS THE THREE-DIMENSIONAL ARCHITECTURE OF THE GENOME RELEVANT BEYOND ENSURING THAT IT ALL FITS?

It sounds like a very abstract concept when we talk about looking at the 3D structure of the genome, but that is not the case. We were able to show that activities of multiple genes that are implicated in disease are actually controlled by the three-dimensional folding. In our latest collaboration with Vijay (*Associate Professor Pandurangan Vijayanand, M.D., Ph.D.*) we found that the three-dimensional folding of a stretch of DNA is different in certain individuals who show increased susceptibility to asthma. Just five years ago, we wouldn't have been able to measure such differences and we wouldn't have considered such events to be relevant to gene regulation and disease.

HOW DO YOU ACTUALLY DETERMINE THE THREE-DIMENSIONAL STRUCTURE?

Traditionally, this was done through imaging, but imaging only gives you a limited number of reference points that tell you about the overall structure of a chromosome or the whole genome. Nowadays, you can take a snapshot of the nucleus by cross-linking cells, which chemically holds together the regions that are in close proximity. We then sequence the DNA to find out what the involved DNA regions are. We can now do this genome-wide by using many cells at once in order to look at all of the regions and how many times they get in touch with each other. However, these measurements don't tell you the 3D structure or connections between genes and regulatory switches right away. That's where the computational part comes into play and where I am having all the fun.

WHAT SET YOU ON YOUR PATH TO BIOINFORMATICS?

Biology was never a strong suit of mine. I was more interested in mathematics and abstract concepts such as computational complexity. Then I took a bioinformatics class from an inspiring young professor, and I had this 'Aha!' moment when I realized that many biological concepts

could be modeled as computational problems—problems with a huge impact.

WHERE DID YOUR INTEREST IN THE ARCHITECTURE OF THE GENOME ORIGINATE?

Originally, I came from a computer science background, which by its very nature dealt with more abstract problems. When I started my postdoctoral training I wanted to be closer to data that had a direct relevance for understanding disease. I had several options, but the one project I was most interested in was the three-dimensional structure of the malaria parasite's genome, which was then uncharacterized. That's when I realized this is a lot of fun as well as an up-and-coming area of science and that there would be a lot of opportunities to develop new methods that will be widely used.

WHAT INSPIRES YOU AS A SCIENTIST?

As a computational scientist, I am wearing many different hats and I love them all: One day I might be working on malaria, the next day I might be working on cancer or asthma. Trying to catch up on the latest on all these different topics by immersing myself keeps things fresh and exciting. Plus, being able to come up with computational methods, which lots of people use in their day-to-day research, is very rewarding.

SCIENCE CAN BE ALL CONSUMING. HOW DO YOU KEEP A HEALTHY BALANCE?

[Laughs] I don't know that I do. I love playing soccer and hiking and those really clear my mind. But with the new baby in the family it just doesn't happen as much. Family is very important for me and I make every effort to spend more time with them. Having a family has made me very flexible in terms of the places, positions, or ways that I can work in and be creative. I try to multifunction often and push the lines of what you can do with one hand when the other hand is holding a five-month-old.●



VACCINE EXPERT SHANE CROTTY JOINS RANKS OF “THE WORLD’S MOST INFLUENTIAL MINDS”

Shane Crotty, Ph.D., Professor in the Division of Vaccine Discovery, has been named a Highly Cited Researcher, a select group of scientists whose research papers wield outsize influence in their respective fields of study. The list of highly cited researchers is compiled annually by Thomson Reuters and tracks how often others reference a specific paper in their subsequent work to reflect the extent to which a scientist’s research has assisted, inspired, or challenged other investigators.

Dr. Crotty drew national attention when he discovered a pivotal piece of the body’s mechanism for switching on the production of antibodies, which underlies almost all successful vaccines available today. This seminal finding led to Dr. Crotty’s recognition as an expert in vaccine design, and to his inclusion as a T cell expert in one of the nation’s top AIDS vaccine consortiums.



AMERICAN HEART ASSOCIATION HONORS PROFESSOR KLAUS LEY

Klaus Ley, M.D., Professor and Head of the Division of Inflammation Biology, was awarded the Distinguished Scientist designation by the American Heart Association and American Stroke Association. Dr. Ley was recognized for his efforts to develop a vaccine that reduces or prevents inflammation in arteries and, in turn, plaque buildup. If successful, his work will result in the first vaccine to protect against heart disease, which is recognized as the deadliest disease of our time.

“Dr. Ley’s vaccine research is the result of his ability to see things differently,” says Mitchell Kronenberg, Ph.D., President and Chief Scientific Officer. “His vision and pioneering spirit allowed him to combine seemingly unrelated concepts and come up with a clever and potentially game-changing approach to treating heart disease. Klaus embodies the best qualities of a creative scientist and is richly deserving of this honor.”



ASSISTANT PROFESSOR SONIA SHARMA RECEIVES JEFFREY MODELL GRANT

Sonia Sharma, Ph.D., Assistant Professor in the Division of Cellular Biology and Director of the Functional Genomics Center, has been awarded a two-year research grant by the Jeffrey Modell Foundation to identify specific immune defects in primary immunodeficiency disease. “Unraveling the molecular basis of primary immunodeficiency disorders has provided valuable insight into the function of the immune system, which is crucial for developing effective therapies to treat these debilitating diseases,” says Dr. Sharma.

XMEN immunodeficiency patients experience persistent infections with a broad spectrum of viruses and bacteria, and are highly susceptible to developing Epstein Barr Virus-induced lymphoma. The recently discovered disease is a rare genetic disorder, which is caused by a faulty magnesium transporter. How the resulting magnesium deficiency affects the immune system is not yet fully understood and will be the subject of Dr. Sharma’s research.



La Jolla Institute elects new members to Board of Directors



Michael D. Coit

A native of Norwich, Conn., Michael D. Coit has been a highly successful executive in a number of different areas of business over his 50-year career. Out of college, Coit opened a small advertising firm in Connecticut and then moved to Texas, becoming involved in the textile and real estate business. One of the highlights of that period was founding Decorp, Inc., a manufacturer of women's apparel, which he eventually sold to a Fortune 500 company.

Coit then moved into real estate development specializing in multi-family, affordable housing development projects, much of it funded through the U.S. Department of Housing and Urban Development. Coit is involved in numerous companies, and currently serves as President of MDC Investments Inc., which provides multi-family housing in Texas and surrounding states; managing member of Coit Acquisition Group, LLC; President of Finco Development; and sole manager of Coit Energy LLC.

Throughout his career, Coit has combined business with giving back to his community. As a continuing board member of the Pacific Ridge School in Carlsbad, Calif., he served as chairman of the Campus Committee, helping to plan and oversee construction of the non-profit high school and its athletic center. Additionally, he was a trustee of the Rancho Santa Fe, Calif., Education Foundation and a board member of the Vogel Alcove for Homeless Children in Dallas.

The La Jolla Institute recently elected three outstanding leaders with diverse backgrounds and talents, including biomedical research and its commercial application, as well as real estate development, to its Board of Directors. This reflects LJI's continuing effort to expand the breadth and depth of the expertise guiding the Institute's scientific vision and business strategy.

Elected to the board for three-year terms were Robert W. Mahley, M.D., Ph.D., Founder and President Emeritus of the Gladstone Institutes, François Ferré, Ph.D., one of San Diego's leading biotech entrepreneurs and angel investors, and Michael D. Coit, real estate developer, bringing the total number of directors to 25.

"I am delighted that individuals of our new directors' caliber decided to join our board," says Mitchell Kronenberg, Ph.D., Institute President and Chief Scientific Officer. "Their global experience and expertise in strategic business management, research funding, academic research, and biotech will strengthen LJI's ability to take innovation to the next level and increase our impact around the world."



François Ferré, Ph.D.

François Ferré, Ph.D., is one of San Diego's leading biotech entrepreneurs and angel investors. Born in France, Dr. Ferré received his Ph.D. in molecular oncology from the Pasteur Institute before coming to the U.S., where he did his postdoctoral work at UC San Diego. During his first decade in San Diego, Dr. Ferré worked as a scientist in the biotech industry specializing in gene quantification and biomarker development. Among the highlights of that period were Dr. Ferré's co-editing a book on polymerase chain reaction with Nobel Prize winner Dr. Kary Mullis, and working with Dr. Jonas Salk on the development of a therapeutic HIV vaccine.

In 1998, Dr. Ferré and his wife, Magda Marquet, Ph.D., started their first company, Althea Technologies, which became a leading provider of contract services to the biotechnology field in the U.S. and Europe. That company was acquired in 2013 by the Japanese group Ajinomoto. Dr. Ferré also co-founded a spinoff company, AltheaDX, which specializes in personalized medicine and pharmacogenomics. Four years ago, Dr. Ferré and Dr. Marquet co-founded ALMA Life Sciences, LLC., an early-stage investment firm focusing on the creation and growth of health care companies in San Diego.

Dr. Ferré has also been active in the non-profit arena, serving on the boards of the Keck Graduate Institute of Applied Life Sciences, the Chopra Foundation, and the San Diego Museum of Art. He received the 2005 Ernst & Young Entrepreneur of the Year award in life sciences, and in 2016, he and Dr. Marquet were inducted into San Diego's CONNECT Entrepreneur Hall of Fame.



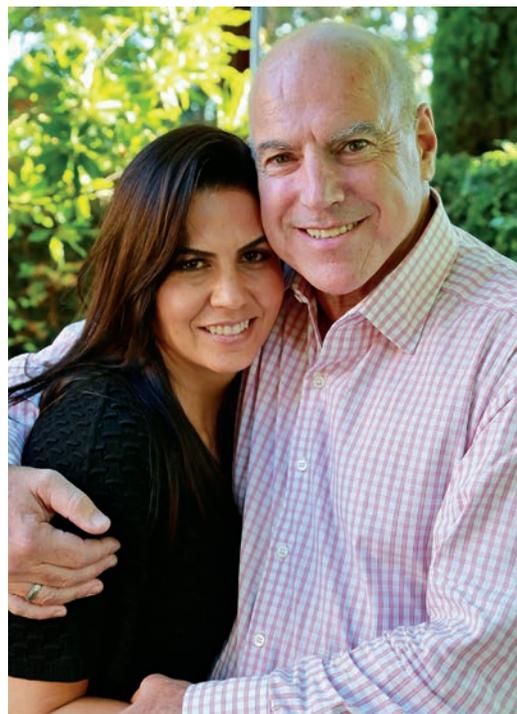
Robert W. Mahley, M.D., Ph.D.

Robert W. Mahley, M.D., Ph.D. has had a long and distinguished career in biomedical research. In addition to his nearly four decades of developing the San Francisco-based Gladstone Institutes into one of the nation's top independent research institutes, Dr. Mahley is a professor of pathology and medicine at the University of California, San Francisco (UCSF), and a member of the National Academy of Sciences.

In the late 1970s, Dr. Mahley was a cardiovascular researcher at the National Institutes of Health when he was approached by UCSF to start a scientific research institute affiliated with the university with funding from the estate of J. David Gladstone, a Southern California developer of shopping malls.

Over the years, Dr. Mahley, with his vision of "basic science with a purpose," built Gladstone into a major research institution that today has 30 principal investigators, a staff of 470, and an annual budget of nearly \$90 million. Gladstone began as a single institute studying cardiovascular disease, but significantly expanded its research focus by adding virology, immunology, and neurology institutes.

Dr. Mahley, who stepped down as Gladstone's president in 2010 to pursue research full time, is an internationally known expert on heart disease, cholesterol metabolism, and, more recently, Alzheimer's disease. He studies plasmalipoproteins and particularly apolipoprotein E (apoE), the major genetic risk factor for Alzheimer's disease. His seminal research has defined apoE's critical role in cholesterol homeostasis and atherosclerosis.●



Ralph Whitworth (1955 – 2016)



“Ralph keenly understood both the promise and the urgency of precision immunotherapy, and the need to make meaningful advances that could help patients now rather than later.”

– STEPHEN SCHOENBERGER, PH.D.

Ralph Whitworth, an activist investor who sparked change at companies ranging from Home Depot to Hewlett Packard by championing the rights of shareholders, died from the complications of cancer at the age of 60 on September 29, 2016.

Widely admired for his focus, enthusiasm, compassion, and love of life, Whitworth was the co-founder of Relational Investors, which led the way for shareholder activism. After being diagnosed with head and neck cancer, Whitworth turned from activist investor into activist patient and channeled the same tenacious persistence he had brought to the boardrooms of struggling companies to investing in immunotherapy research for cancer treatment.

“Ralph was like a force of nature. He precipitated change by relentlessly asking the right questions and bringing people together at the same table in the boardroom as well as the lab,” says Mitchell Kronenberg, Ph.D., Institute President and Chief Scientific Officer. “He was a strong public advocate for the research at LJI and attended and spoke at several of our events.”

In 2015, he and his wife Fernanda created the nonprofit Immunotherapy Foundation to fund

cancer research at UC San Diego and the La Jolla Institute.

“Ralph keenly understood both the promise and the urgency of precision immunotherapy, and the need to make meaningful advances that could help patients now rather than later,” says LJI Professor Stephen Schoenberger, Ph.D., whose research is actively supported through the Immunotherapy Foundation. “As a member of our team, he provided the bold vision, focus, and leadership needed to achieve that.”

Whitworth graduated from the University of Nevada, Reno, in 1982. He worked as a legislative aide for Senator Paul Laxalt from Nevada, while earning his law degree from Georgetown University. Shortly after graduating, he joined investor and financier T. Boone Pickens at Mesa Petroleum, where he ran a group that promoted shareholder rights. He became an expert, petitioning the U.S. Securities and Exchange Commission in 1992 to overhaul executive compensation disclosure rules. In 2013, he received the Lifetime Achievement Award from the International Corporate Governance Network. ●

William K. Bowes, Jr.

(1926 – 2016)

The La Jolla Institute mourns the loss of William K. Bowes, Jr., a Bay Area venture capitalist and biotech trailblazer whose leadership and quiet philanthropy supported medical research, access to college and higher education, the environment, and the arts. He passed away December 28, 2016, at the age of 90.

Bowes' gift to La Jolla Institute, the largest individual philanthropic gift in Institute history, established the William K. Bowes, Jr. Foundation Distinguished Professorship, currently held by Associate Professor Dr. Pandurangan Vijayanand. "Bill's passion for basic biomedical research was matched by his passion for philanthropy," says Mitchell Kronenberg, Ph.D. President and Chief Scientific Officer. "As the most important philanthropist on the West Coast, he quietly invested in improving health by advancing science. We will deeply miss him."

Born in San Francisco in 1926, Bowes graduated from Lowell High School in 1942, a magnet school for that city's brightest students. He earned a B.A. in economics from Stanford University and an MBA from Harvard University, and served in the U.S. Army infantry in the South Pacific and Japan during and after World War II.

Bowes predicted early on that biotechnology had the potential to make a difference in the world and in 1980 became the founding shareholder of Amgen, which would grow into one of the world's largest independent biotechnology firms. Later he founded U.S. Venture Partners, building it into one of the most important venture capital firms in the world, ensuring his legacy as one of the pioneers of Silicon Valley venture capital. In 1991, he created the William K. Bowes, Jr. Foundation, which has discreetly donated hundreds of millions of dollars to various causes. Among the science and educational organizations receiving grants, in addition to LJI, were Stanford University, the California Institute of Technology, Harvard University, UCSF, UC Santa Barbara, and the American Asthma Foundation. ●



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Our Mission

La Jolla Institute for Allergy and Immunology is dedicated to understanding the intricacies and power of the immune system so that we may apply that knowledge to promote human health and prevent a wide range of diseases. Since its founding in 1988 as an independent, nonprofit research organization, the Institute has made numerous advances leading toward its goal:

Life Without Disease®.

