

Immune Matters

WINTER 2014-15

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Putting Your Health
in the Spotlight

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La Jolla Institute for Allergy and Immunology is dedicated to understanding how the immune system works and to applying that knowledge to promote human health and prevent a wide range of serious diseases. Since its founding in 1988 as an independent, nonprofit research organization, La Jolla Institute has made numerous major advances leading toward its goal: life without disease.

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Letter From the President



Personalized medicine—the use of an individual’s genetic makeup to customize disease treatment and prevention—was heralded as one of the great benefits of the Human Genome Project. It’s been more than a decade now since that remarkable project was completed, and technologic advances have made genomic sequencing thousands-fold cheaper and more efficient, providing a torrent of data. Except for a handful of successes, the dream of truly effective personalized medicine has remained elusive.

The good news is that immunology research at La Jolla Institute is just a few years from reviving that dream in a way that will dramatically change the way the medical community diagnoses and treats disease. Even more exciting is that further down the road, we believe our research will contribute to the development of individualized vaccines and other preventive strategies that will keep people from contracting many diseases in the first place.

Personalized medicine has not progressed faster because having a person’s complete genetic picture isn’t nearly enough. It’s a crucial first step, but the next step for our research is even more challenging: understanding how the immune system contributes to the underlying cause of diseases at the cellular level, and then discovering how differences in each person’s genetic makeup contributes or prevents disease.

As a world leader in the study of the immune system, La Jolla Institute has a significant advantage in this area. For the past quarter century—recognizing that so many diseases have an immunological or inflammatory basis—we’ve begun to unravel some of the mechanisms through which diabetes, heart disease, cancer, asthma and a host of other diseases attack the body, and how the immune system reacts.

In this issue of *Immune Matters*, we’ll give you a closer look at the major strides La Jolla Institute is making in personalized medicine. Stephen Wilson, Ph.D., our Executive Vice President and Chief Administrative officer—and an outstanding scientist himself—will provide an overview of our efforts, as well as a glimpse of just how dramatic the changes in medicine will be at the patient level when our research is fully realized.

We are also pleased to share the groundbreaking research that Sujana Shrestha, Ph.D., is conducting at the Institute on dengue fever. Like other hemorrhagic diseases such as Ebola and Lassa, dengue fever is a serious infectious disease. Though many people have not heard of it, it afflicts 100 million people a year, largely because it’s so easily spread by mosquitos in tropical and subtropical regions.

We are continually sustained and energized by the knowledge that our work at La Jolla Institute has the potential to transform lives. As always, we share that path—and our successes—with many partners. We are proud of the scientific and corporate partnerships we’ve established, and we appreciate the generosity of individual donors, foundations, and federal funding sources that support the critical research that one day will lead to *life without disease*.

Sincerely,

A handwritten signature in blue ink that reads "Mitchell Kronenberg".

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

NEW LAB

This year La Jolla Institute finished construction of a new lab space that will be available for new faculty recruits. The first occupant is Sonia Sharma, Ph.D., the most recent appointment to the faculty. This 6,500 sq. ft. lab space was completed on time and under budget and is the first lab in the building to utilize LED lighting technology, which cuts down on utility consumption and maintenance. The layout of the lab space was arranged to take advantage of natural light, which is also abundant in the office spaces due to their sound-dampening glass doors. ●



At the Bench: Postdocs of La Jolla Institute

Postdoctoral fellows are the heart of La Jolla Institute. Guided by a faculty mentor, postdocs have achieved a Ph.D. and are conducting research under the supervision of a senior scientist. They make up over a third of the Institute's staff and perform crucial day-to-day research in our laboratories. Here, we spotlight the life of postdoc Shilpi Verma.

By day, Shilpi Verma is elbow deep in mouse cages and studying immune cells. By night, she gardens and organizes her household (after washing her hands, of course). She's a postdoctoral fellow in the lab of Dr. Chris Benedict, is married to a fellow scientist, and is a mother of two children.

Shilpi grew up traveling around India yet hadn't left her native country until she moved to the United States for graduate school. Nancy Drew, and other protagonists from her cherished childhood novels, first introduced her to life in the United States. Once Shilpi and her future husband, Shyam Sarikonda, graduated from college in India, they



Shilpi with her husband Shyam, their son Aadi and daughter Ria

decided on graduate school in the U.S. They each applied to different schools so they wouldn't be competing for the same limited spots for foreign students. After receiving Masters degrees, and then Ph.D.s, they joined different laboratories at La Jolla Institute for their postdoctoral work. Shilpi began studying the body's innate defense to cytomegalovirus, a member of the herpesvirus family that infects nearly 60 percent of the U.S. population, though most have never heard of it.

Recently her research on the disease was published in the high profile publication, *PLoS Pathogens*. She also received the American Association of Immunologists Young Investigator Award in October 2014.

It's a busy life, but Shilpi and her husband make science happen. In the past, they even brought their children to sleep in the postdoc office while they both completed experiments. "We balance each other," Shilpi describes how she and Shyam manage their busy scientific and home schedules. ●

La Jolla Institute's Personalized Medicine-Based Research Focus Offers Real Hope of Lifelong Health

Personalized MEDICINE

In all of human history, a perceptible decline in health—the feeling of disease—has been an ever-present concern. Even those who generally feel healthy are sure to know a friend, loved one, acquaintance, or family member who suffers from a significant disease—from infectious to chronic illnesses, from mild to seriously debilitating or even fatal sicknesses. So it stands to reason that the following statement might seem audacious or even unfathomable, but it is nonetheless true: in the not too distant future, many diseases we are familiar with will be stopped in their tracks by treatments that have been custom designed to eradicate the ailment based on each individual's specific biologic profile.

As impressive and exciting as that sounds, just a little further down the road looms the prospect of something even more remarkable, something that is no less than the Holy Grail of medical care: people early in their lives may one day be able to receive a series of preventative treatments, much the same as vaccinations—again, based on their genetic makeup—that will prevent them from ever developing many of these diseases in the first place. They likely will die from old age or accident, not from the chronic inflammatory and infectious diseases that claim so many lives today.

Immune cells are found everywhere in the body: blood, organs, brain, muscle, fat, every part is touched. This is why immune-based therapies will be at the root of personalized medicine, and why the claim above is not unrealistic. The key to triggering such a healthful outcome is an immune system that is perfectly tuned to protect us from the ravages of disease; an immune system that can respond

quickly and effectively to outside threats, and simultaneously sort out healthy and diseased cells in our bodies without causing unwanted damage. We would not feel threats to our health, our immune system would fight silently on our behalf and we would live a life without feeling symptoms of disease.

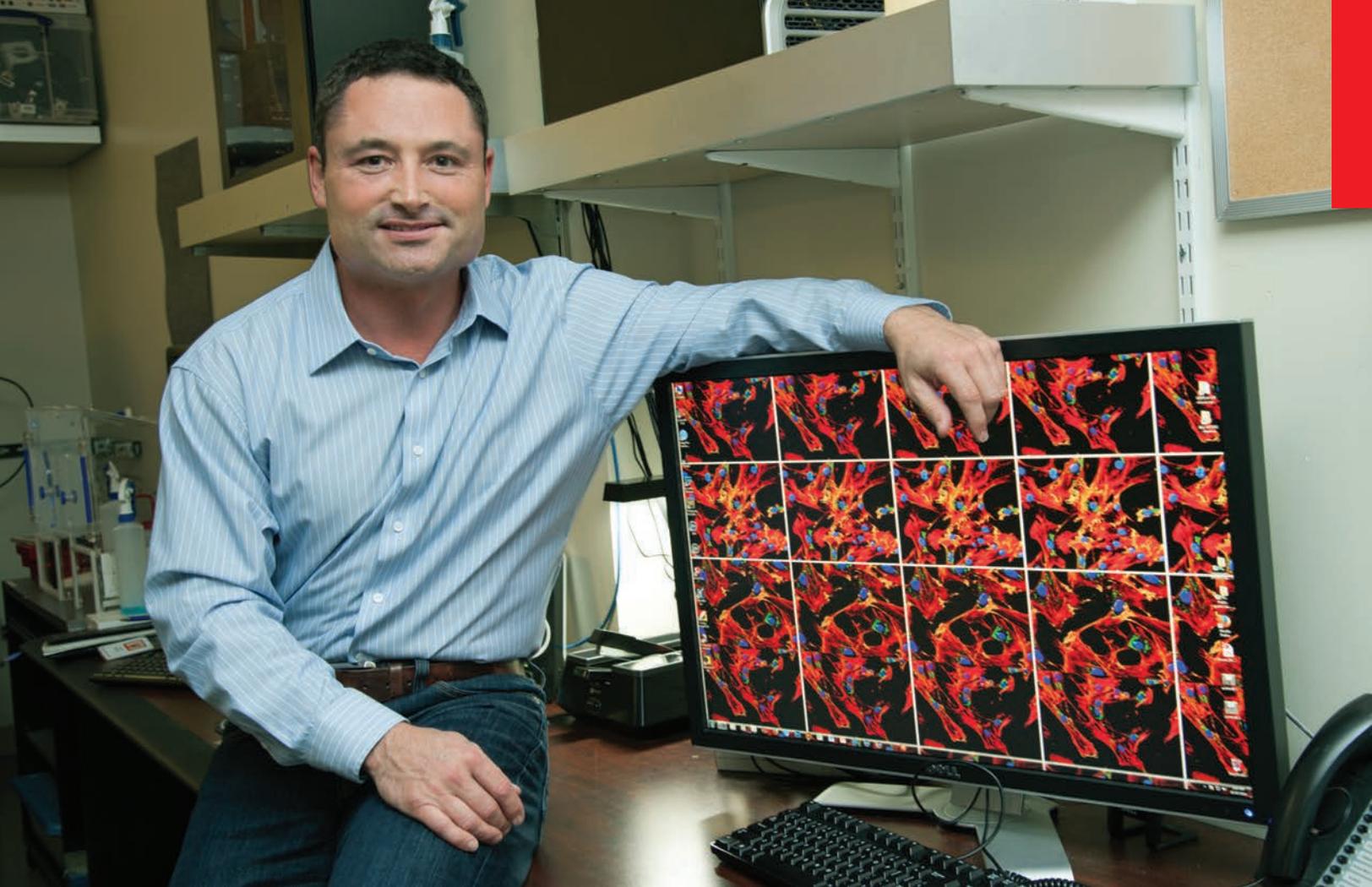
World-class scientists at La Jolla Institute are conducting research that is laying the foundation for this

THE GENOME PROJECT WAS AN IMPORTANT AND EXCITING FIRST STEP, BUT IT HAS ONLY ADVANCED THE FIELD SO FAR

simple scenario. Whether it's solving the mysteries of how our immune system works right down to the molecular level, or using computational biology (see story page 8) to sort through vast amounts of genomic and proteomic data from huge population groups to help scientists target the cause of disease, the Institute is among the leaders nationally in building a framework for personalized medicine centered on the body's system most responsible for health.

The challenge up until now has been that the term “personalized medicine” has largely remained a catch phrase to describe the potential of using genetic data and profiling to improve human health. The reality has been something quite different, according to Stephen Wilson, Ph.D., the Institute's Executive Vice President and Chief Administrative Officer.

“The successful sequencing of the human genome was supposed to be the launching point for a personalized medicine approach that would lead to treatments and cures for disease, but that has yet to happen,” Dr. Wilson says. “And it's fairly easy to describe why. It's true that the genome project was an important and exciting first step, but it has gotten us more information, not answers.



Stephen Wilson, Ph.D.

“I liken it to taking a huge box of Lego pieces and dumping them on the table. The genome project was the equivalent of telling us what pieces of Lego we had. Yes, it could identify some pieces—or genes—that are missing or malformed, which would explain a few problems caused by mutation in a single gene, such as the one causing cystic fibrosis. But sequencing alone did little to explain how virtually all of the other genes and other regions in our genomes work together to preserve our health or fail as we succumb to disease.”

The reason progress has not been rapid enough since the genome project is that answering those types of questions requires some of the most complicated and multidimensional research capabilities in scientific research, and the technology is only now coming up to speed. Also missing was a sufficient understanding of the immune system—the body’s sentinel in guarding us against disease—and its interplay with the body’s genes. Fortunately, La Jolla Institute has spent the past 25 years dedicated to understanding the immune system’s intricate workings. And because it has the necessary resources in its outstanding scientists and state-of-the-art

facilities, the Institute finds itself among the leaders in bringing personalized medicine to the clinical stage.

“We’re well on the way because we know the road to personalized medicine goes through an understanding of the intricate mechanisms of the immune system,” Dr. Wilson says. “The progress we’ve made in learning why the immune system turns on and off, why it protects the body in some cases and attacks it in other cases, and how so many diseases have an immunological or inflammatory underpinning, has already enabled us to take research concepts to the level of clinical testing across a range of diseases.”

Dr. Wilson believes the Institute’s research will result in two waves of progress in achieving real personalized medicine. The first will be the development of therapies that modulate the immune system to deal with illnesses after the patient has become afflicted; the second wave will actually prevent the disease from occurring in the first place by tuning the immune system ahead of time. As an example, Wilson highlighted Crohn’s Disease, an inflammatory bowel disease in which the body’s immune system attacks the gastrointestinal tract.

YOUR NAME



When Personalized Medicine is a Reality – A Glimpse Into the Future

A number of years in the future . . . a young family walks into what appears to have been a hospital. Actually, it had been hospital but it had to change business years before because there were more hospitals than patients to fill them. The facility had long since been converted into a “preventive medicine sanctuary.”

Inside, a genetic immunology conducts a series of tests on the two children that analyze their genetic and immunological makeup, a process that the parents had also gone through when they were kids.

Within minutes, the results are back. On a wall-sized screen, the specialist outlines precisely what each child’s future looks like in terms of encountering and susceptibility to every known disease (many infectious diseases have been eradicated). While he is talking, technicians in the lab are preparing a multi-target vaccine for each child, engineered snippets of pathogens, “practice” for the immune system. Before

the family leaves, the children receive the vaccine painlessly without needles. Along with their parents, the children go on to enjoy disease-free lives and all live well past 100.

This scenario may sound unrealistically futuristic, but conversations with some of the world’s leading immunology researchers at La Jolla Institute would lead you to believe otherwise. They are passionate in their belief that if given enough time and resources, they will not only discover how the immune system works down to the most minute molecular detail, they will use that knowledge to develop preventative treatments that can be custom designed for each individual so that they will never become victim to the diseases that impact our health today.

“Based on the remarkable progress in science and that which we’ve made at the Institute in understanding the mechanisms underlying human immunity, we don’t think a scenario like that is far-fetched at all. I

believe we’ll begin to see it happen in my lifetime,” says Stephen Wilson, Ph.D., the Institute’s Executive Vice President and Chief Administrative Officer, who is 44.

Dr. Wilson cites a number of human clinical trials already being conducted on potential vaccines, including several for infectious diseases he believes doctors may be able to check off in a few years as having been neutralized as well as an experimental effort to develop a vaccine to prevent heart disease.

“When this incredible transformation finally takes place, there will be countless advantages for humankind,” Dr. Wilson adds. “Not the least will be the savings of trillions of dollars in health care costs, an expense that could be plowed back into the prevention of suffering and disease rather than its treatment. But the biggest benefit is one you can’t put a price tag on: a full and long life without the prospect of disease. It will fundamentally change what it is to be human.” ●

Personalized MEDICINE

“For those patients already suffering from the disease, we’re looking at how their specific immune cells activate and cause disease. We will then be able to create an immunotherapy custom-designed for each individual that is able to target molecules on the immune cells to dampen those cells central to the patient’s symptoms and ease the attack without dampening the entire immune system and making the patient overly susceptible to viral infections,” Dr. Wilson says.

That type of therapy could be available in the next few years. And just beyond that is the even more exciting wave of the Institute’s research that has the potential to prevent Crohn’s from occurring in the first place.

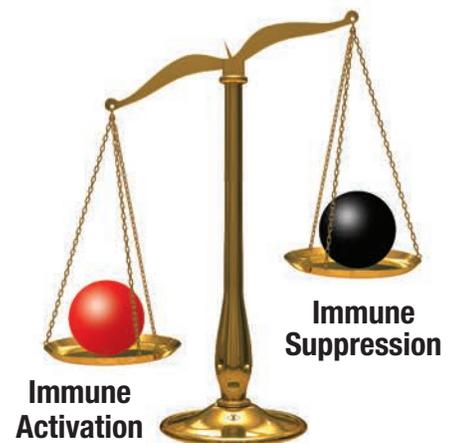
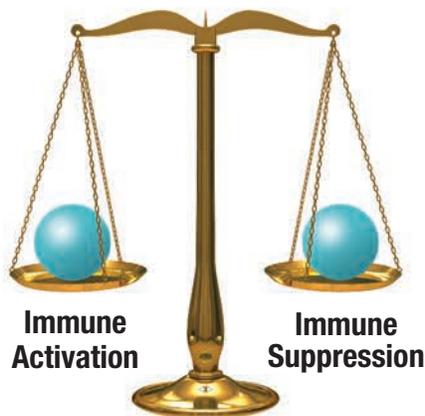
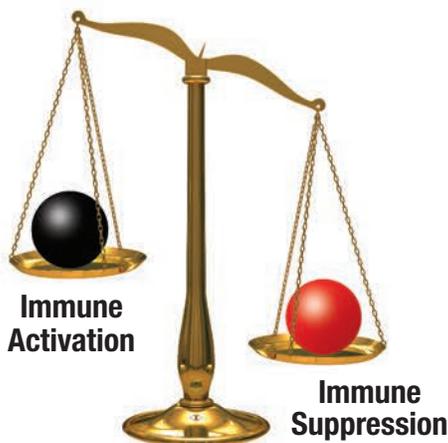
“What we’ve already learned about Crohn’s immunologically, and how and why it occurs in individuals, will provide scientists with an incredible foundation for ultimately developing a preventative approach to the disease,” Dr. Wilson adds. “Imagine that there will be a test you’ll be able to give a person that will reveal if they have genetic and immunologic biomarkers predisposing them to the disease years before they would ever fall victim to it.

“If they have those biomarkers, we’ll be able to give them what amounts to a vaccine that is custom designed

to blunt the over-reactive part of the immune system that normally would attack and cause Crohn’s. Essentially, what will happen is that when it comes time for the body to develop the disease by ramping up, the person’s immune system has already been programmed to specifically go the other way.”

Because the immune system is central to health, Wilson says the Institute’s research potentially will lead to treatments and preventative vaccines for diabetes, asthma, heart disease and even some forms of cancer. He said the success of the polio vaccine and more recently, the Human Papillomavirus vaccine that prevents virally induced cervical cancer, should persuade people to recognize the potential of an immunological approach to early treatment for life-long prevention.

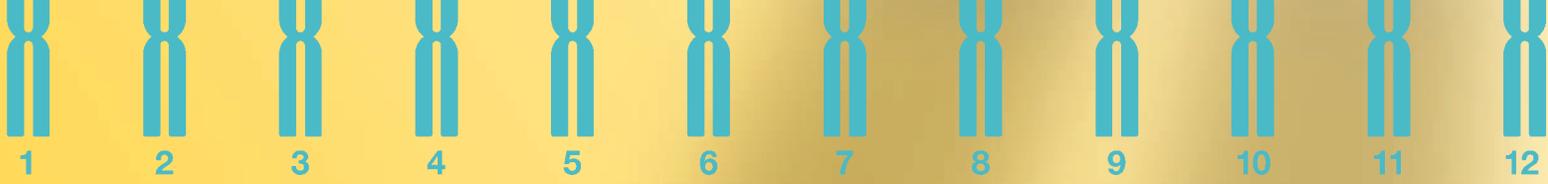
Says Dr. Wilson, “What motivates us every day is that we know that there’s something so basic and vital about us as living beings: We like to be alive, we want to thrive, and the feeling of health should be our normal state. I truly believe that by staying on this path of discovery and continuing to roll up our sleeves to carry out this really challenging work, La Jolla Institute has an incredible opportunity to help medical science reach a point where we really can enjoy life without disease.” ●



- Cancer
- Chronic Infection
- Influenza
- Pneumonia
- Meningitis
- AIDS

Life TM
Without
Disease.

- Allergy
- Heart Disease
- Diabetes
- Asthma
- Rheumatoid Arthritis
- Irritable Bowel Syndrome



New Genomic Database Will Provide Scientists Worldwide With Unprecedented Insight Into How Genes Fight Disease

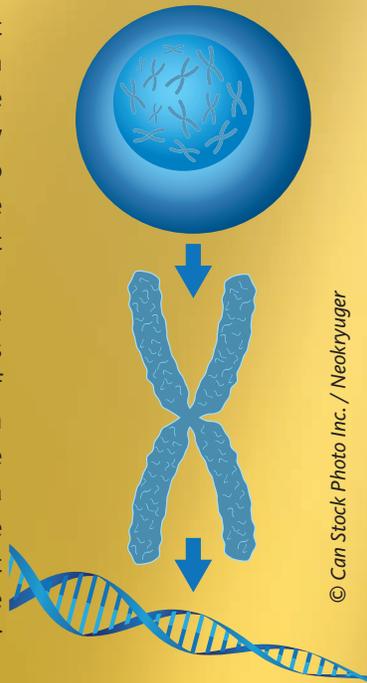
La Jolla Institute is creating a most remarkable scientific treasure map. Much like a guide to where precious metals are buried, the Institute's map will soon show scientists around the world where to "dig" to find the secrets of how genes act in the immune system to protect the body against a variety of diseases.

This tool could not have come at more opportune time. In recent years, scientists around the world who once dreamed of leveraging the sequencing of the human genome to help them investigate the pathology of disease have encountered a frustrating stumbling block: the massive amounts of genetic data collected don't actually reveal what is occurring at the cellular level of the immune system or elsewhere to cause or prevent disease.

The good news for those same researchers is that they will soon have access to a remarkable new tool created by LJI that will re-energize their research by equipping them with precisely the critical information they were unable to glean from the genetic data. Not only will the project save them months if not years of intensive research, it could well provide the tipping point for helping them develop innovative new treatments, vaccines and possibly cures, for a number of diseases.

The National Institutes of Health this past summer approved a \$4 million grant that will fund the Institute's construction of a genomic database of human immune cells. As an open resource project, all results will be available online to scientists anywhere in the world immediately after they become available.

"We're extremely proud of this grant because it's a recognition by the federal government of the Institute's deep expertise in understanding how the immune system works, and in particular how immune cells carry out their job—or sometimes fail to—at the molecular level," says Mitchell Kronenberg, Ph.D., Institute President and Chief Scientific Officer. "What's so exciting about this immune



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genomic database is its vast potential. The scientific data that it will generate on immune cell activity will be so exhaustive and useful, we believe it could well transform immunological research and lead scientists around the world to some amazing breakthroughs."

So exactly what is the immune genomic database, how does it work, and how will it achieve those kind of impressive results?

The Institute's Pandurangan Vijayanand, M.D., Ph.D., Adjunct Assistant Professor and one of four principal investigators (PIs) heading up the immune genomic database, said much of the genesis for the program resides in those massive and expensive genome-wide association studies (GWAS) that many scientists believed would help them identify the genes involved in human disease.

"It turned out those studies could reliably identify only a handful of genes whose function was affected by genetic variants associated with immune disease such as asthma and diabetes," Dr. Vijayanand says. "The problem was that only one percent of our genome contains the instructions for making proteins. We had little idea what the other 99 percent was doing. Researchers could see that the majority of the disease-associated genetic variants identified were far away from the genes they suspected were connected to the diseases, but they had no way of actually understanding the connection."

Fortunately, based on pioneering work identifying genes that contribute to asthma, Dr. Vijayanand, working with another PI on the grant, Anjana Rao, Ph.D., Professor and Head of the Division of Signaling and Gene Expression, had the ability to extend their experimental system to look at genes involving multiple diseases. The first step was to create a database in 13 different key immune (white) blood cells from a sample population of 85 healthy individuals as a baseline.



“We already had all disease-related genetic variances supplied by GWAS, now we needed the disease-free genomic data to compare it with,” Dr. Vijayanand says. “The challenge was human immune cells contain hundreds of thousands of enhancers or epigenetic switches. They act almost like amplifiers in an electrical circuit in their ability to turn genes on and off, which determines how the immune system will respond—or fail to respond—to viruses and other biological challenges.”

Because variations in more than one gene contribute to complex diseases like asthma or diabetes, normal individuals can carry some of these variants without manifesting disease. The project will determine where the epigenetic switches are located, which of the key cell types they act in, and if variants associated with a higher risk of disease contribute to the effectiveness of the switch in regulating the gene. Therefore, the approach taken, which uses sequencing technology and high-speed computers, is extremely efficient in not only cataloging all of the switches controlling the genes, but going a critical step further and identifying specific functions they carry out within the immune system—and on a disease-specific basis.

Bjoern Peters, Ph.D., Associate Professor at LJI and another PI on the grant, will lead the computational analysis of the generated data. “We’ve been able to narrow things down to such a fine point that we’re able to see what’s transpiring in the immune system right down to the molecular

“The database takes the hope of genomics and actualizes it into a real understanding of the immune system in action”

level,” Dr. Peters says. “We can look into specific immune cells and observe that when they’re activated and fighting a virus, they’re using these types of genes. We can look at it from the standpoint of a particular disease and see which genes are expressed in the face of that specific threat.

Conversely, we can also see when immune cells fail to respond and allow pathogens to invade the body.

“This will be a very powerful discovery tool,” Dr. Peters says. “Scientists who previously didn’t know where to search for the cause of disease will soon be able to go to their computers, click on a particular disease on the website, and it will

open up a richly detailed atlas of the key immune cell types and which genes are affected by specific disease-related genetic variants.”

To a scientist, this information will be “pure gold,” Dr. Kronenberg says.

“The database takes the hope of genomics and actualizes it into a real understanding of the immune system in action,” he says. “Instead of investing time searching for pathways, scientists will already have an invaluable genetic map in hand and can focus instead on applying this new knowledge to develop treatments and vaccines that attack or prevent disease and promote human health.” ●

Immune Epitope Database has Helped Scientists Easily Access Leading-Edge Research From Around the World

The National Human Immune Genomic Database project is not the first program at La Jolla Institute to collect and catalog massive amounts of data in order to enhance scientific understanding of how the immune system works. For more than a decade, the Institute’s Immune Epitope Database (IEDB) has served as an invaluable collaborative research tool by collecting and cataloguing the immune-based findings of scientists around the world.

Sponsored by National Institute for Allergy and Infectious Diseases, IEDB curators review thousands of scientific papers and journals each year to determine what data can be pulled from these research papers, standardized through expert annotation, and placed into a searchable online information warehouse which is freely available to scientific researchers worldwide.

“In a time of rapidly emerging diseases and potential bio-terrorism concerns, IEDB has served as a critical repository for the most important research being conducted in labs around the world,” says Alessandro Sette, Ph.D., who along with Bjoern Peters, Ph.D., is a principal investigator on this project. “It’s really a tool to foster global scientific collaboration. The technical efficiency of IEDB’s collection system, combined with the curators’ analytical abilities to discern which research is most important, has enabled scientists everywhere to access the findings of their peers and put them to use to make their own research more effective.”



Sujan Shresta, Ph.D.

The fact that La Jolla Institute faculty member Sujan Shresta, Ph.D., left her native Nepal for a better education abroad is a tribute to her mother, who encouraged her to break tradition and seek her own destiny. That she would become a world-class immunologist and pioneer in the search for a vaccine for dengue fever defies all odds and is a tribute to Dr. Shresta's sheer desire to achieve breakthroughs in science that will benefit the health of millions around the globe. Dr. Shresta obtained her B.A. in Biological Sciences from Smith College and Ph.D. in Immunology from Washington University in St. Louis. She completed her post-doctoral training in Virology at the University of California, Berkeley. She received a Research Scholar Development award from the NIAID in 2005. Dr. Shresta joined LJI in 2005 as an Assistant Professor in the Vaccine Discovery Division and was promoted to Associate Professor in 2011. Her research focuses on the interface between immunology and virology, with particular interest in viral immunopathogenesis.

Q&A

Researcher's Passion for Battling Dengue Fever Could Lead to Vaccine for Disease Infecting 100 Million World Wide Each Year

Q: Your main area of research is the dengue virus, but the headlines are dominated by another infectious disease, Ebola.

What are your thoughts about this potential global health crisis?

A: There are actually a lot of explosive viruses that are wreaking havoc across the planet, but this most recent Ebola outbreak is getting most of the attention because it's a particularly lethal disease. As with dengue and many other viruses, there's no effective anti-viral treatment or vaccine, so it highlights the critical need for the kind of research we're doing here at the Institute into the underlying mechanisms of how these diseases attack the human body and circumvent the immune system. It also shows how infectious diseases often thrive in areas where there's a perfect storm of poverty, war, substandard health infrastructure, economic stress and even climate change. That said, developed nations should not feel comfortable that these are only third-world health problems. Infectious diseases have no geographic boundaries as we've seen with Ebola spreading to the U.S and dengue fever arriving in Florida.

Q: Can you give us a snapshot of the dengue virus and its impact?

A: There are actually four separate dengue viruses causing different levels of severity of disease. They're all mosquito-borne and all are found in

tropical and subtropical areas of the world. The mild form, dengue fever, causes high fever, severe headaches, muscle and joint pain and rashes. The most severe form, dengue hemorrhagic fever, can cause severe bleeding, a sudden drop in blood pressure, and sometimes death. Half the world's population, or about 3.6 billion people, is exposed to the dengue virus and it's spreading rapidly. While the fatality rate is small—less than one percent—it's a devastating disease because each year it infects 100 million people, most of whom are bedridden in a hospital for up to a month, which causes massive economic loss for families and workforces.

Q: What have you learned about the virus from your research?

A: Our biggest breakthrough came when we validated a 50-year-old and controversial hypothesis that antibodies—usually the “good guys” in the body's fight against pathogens—can actually contribute to people contracting a severe form of the disease.

Scientifically, it's fascinating: a person can be infected with the mild form of the disease, and then nine months later, not only have they not built any immunity from having had the infection, they can come down with the much more severe dengue hemorrhagic fever. We've made significant progress in understanding how this phenomenon—called antibody dependent enhancement—occurs.

We're studying the mechanism of how the virus seems to be able to manipulate the host immune system and actually turn off the antibody response to allow more of the virus to flood the body than if it had never had antibodies to begin with.

Q: What is the potential for your research to lead to antiviral treatments and vaccines?

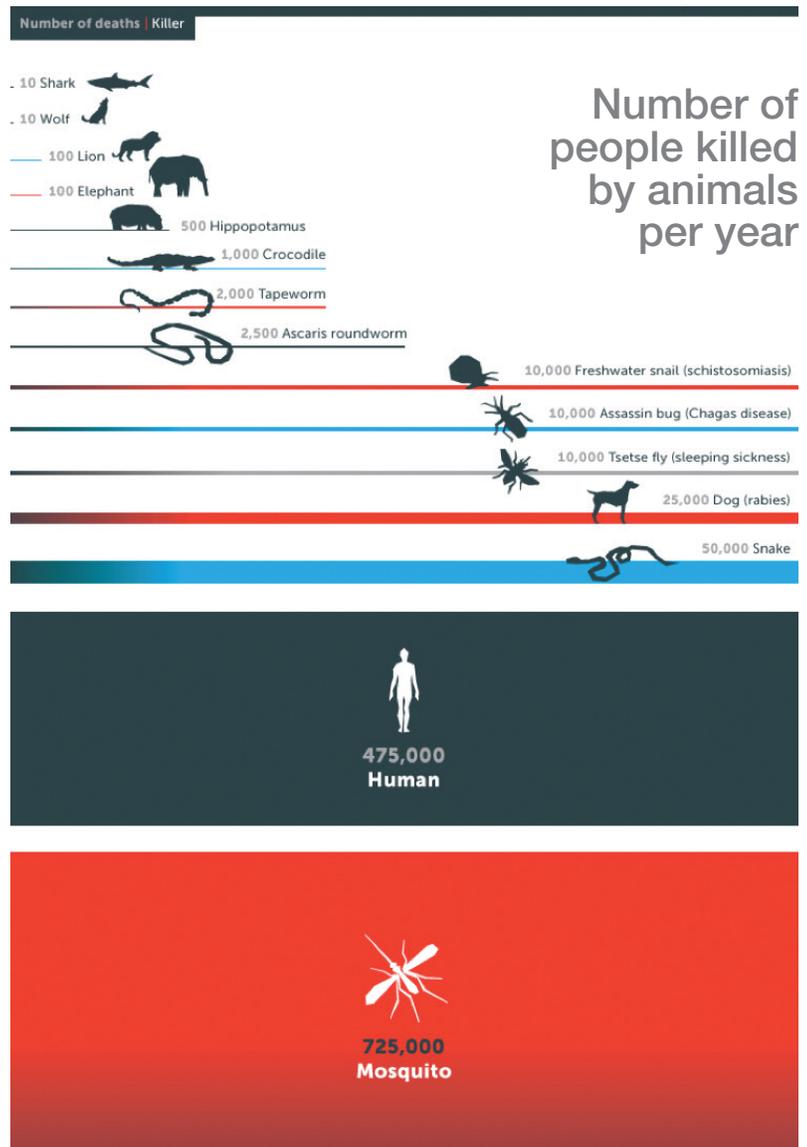
A: I'm optimistic we'll see some excellent therapies for dengue virus in a few years and some effective vaccines five to 10 years the road. My lab is actually making some important contributions in this area because we're partnering with several pharmaceutical companies that are relying on our unique mouse models to test a number of compounds they've developed. We're able to help fine tune whether antibodies or the body's own t cells, or white blood cells, offer the best way to attack or prevent the disease. We've already proven that one antiviral treatment completely wipes out the virus in mice and it's gone on to human trials. We're also testing a number of compounds that show promise as live attenuated vaccines, which are, vaccines in which the disease-producing ability of a virus has been weakened.

Q: Is there any benefit to conducting your research at LJI?

A: For me, the La Jolla Institute is a fantastic place for research. With many of the world's leading immunologists on the faculty, you would think there might be divas and turf protection. It's actually the opposite. Everyone is incredibly collaborative and eager to help each other succeed in producing the best possible science. The Institute has enabled me to pursue my dream of conducting research to help improve the health not only of the people of my homeland in Nepal, but dengue fever sufferers everywhere. I'm sometimes asked why it's important to support organizations like the Institute and I have a very simple answer: supporting this institution offers people the opportunity to assist an effort that is having a global impact by improving the ability of millions to battle and survive disease. There's almost nothing more important than that. ●



World's Deadliest Animals



Dear Friends,

La Jolla Institute is extremely grateful to those individuals and organizations that choose to support our research on the immune system with monetary donations. While the majority of the Institute's annual budget (\$52 million in 2013) is funded by U.S. government agencies, funding from individual donors represents some of the most powerful support, leveraging researchers' most exciting and innovative ideas.

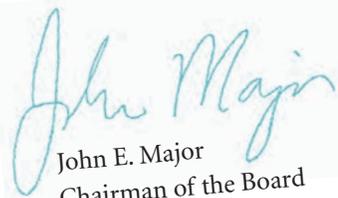
In the past year, with the help of contributions from our generous donors, La Jolla Institute scientists embarked on exciting new projects in areas relating to asthma, allergies, cancer, Crohn's disease, diabetes, heart disease, infectious diseases, including tuberculosis and dengue and chronic virus infections, irritable bowel syndrome, psoriasis, rheumatoid arthritis, scleroderma, and many other major health concerns.

Our researcher's groundbreaking work resulted in over 150 publications in important scientific journals. LJI Faculty members were invited to present their research to their colleagues at more than 100 scientific conferences around the world—a vital part of the scientific process. La Jolla Institute is also one of the most widely cited organizations in the world for immune system research, meaning that our work makes a great impact on scientists around the world and contributes to the direction of their own research pursuits.

La Jolla Institute not only has a significant impact on the worldwide body of scientific knowledge, our research has a direct impact on our modern lives and truly represents the frontier of medicine and health. Individual funding is crucial to ensure that our innovative research is able to continue, allowing flexibility, collaboration between researchers, and freedom to pursue projects that are free from the restraints present with government funding. Unrestricted funding supports science in its truest, most organic form.

We gratefully acknowledge the following donors with sincere appreciation for their visionary support, which helps us to strive toward our dream: life without disease.

Warm wishes,



John E. Major
Chairman of the Board
La Jolla Institute for Allergy and Immunology

With Thanks to Our Donors



Robert and Rachel Perlmutter,
Matthias von Herrath, M.D.



Linda Fox, Mary Harker



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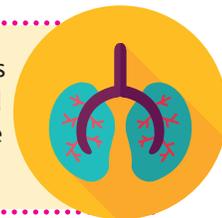
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Institute's Personalized Medicine-Focused Research Will Translate Into Effective Treatment, Prevention of Disease

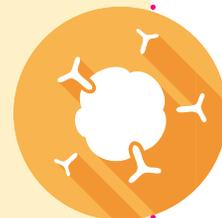
La Jolla Institute's immunological approach to personalized medicine is paying off in research breakthroughs that will someday transform the way physicians diagnose and treat a variety of serious diseases.

Here's a snapshot of just a few key discoveries by Institute researchers and their potential impact:

Asthma By studying the genetic makeup of the immune cells from the blood of healthy individuals as well as asthmatic patients, **Pandurangan Vijayanand, M.D., Ph.D.**, Adjunct Assistant Professor, and his team were able to search through 1,500 target regions associated with asthmatic disease and reduce the number to a handful that may respond to novel therapeutic interventions (see related story page 8).



Autoimmune Disease **Amnon Altman, Ph.D.**, has demonstrated how T lymphocyte cells, a type of white blood cell, spring into action when they encounter an infected cell. This has turned up several important findings, most notably the discovery of an enzyme-protein kinase C theta—which may hold the key to controlling immune response. It could lead to the design of treatments aimed at either suppressing an individual's immune response to fight off unwanted attack on normal cells, which happens in autoimmune disease, or boost the response to attack cancer cells.



Cancer **Stephen Schoenberger, Ph.D.**, and his team have discovered the way the immune system organizes an effective attack in the body. Two types of killer T cells that the immune system employs must both be engaged for the body to properly attack a pathogen invasion and to ensure a proper immune memory response. Immune memory is the way in which the body "remembers" previous infections so that on future occurrences of an illness it can mount a fast, efficient response. This discovery could be key to understanding why the body sometimes fails to destroy a tumor with an immune attack.



Diabetes **Matthias von Herrath, M.D.**, named the world's number one expert in type 1 diabetes by the healthcare information website Expertscape, discovered that introducing immune response modifiers, such as small molecules named "cytokines," or certain antibodies, can put the immune system back on track and prevent it from attacking the body's own insulin-producing cells.



Heart Disease **Klaus Ley, M.D.**, a pioneer in vascular immunology, is leading an effort to find a vaccine by reducing plaque buildup in the arteries by targeting inflammation. In his latest finding, published recently in the journal *Frontiers in Immunology*, Ley showed vaccinated mice had about 40 percent less arterial plaque than mice that didn't receive the vaccine.



La Jolla Institute

FOR ALLERGY AND IMMUNOLOGY

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■ **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*.

■ **SCIENTIFIC PRODUCTIVITY:** 23 faculty investigators and 145 postdoctoral fellows have published nearly 2,000 scholarly papers in prestigious scientific journals since 1988. Numerous patents (and patents pending) for discoveries designed to yield revolutionary clinical applications.

■ **ACCOLADES:** Ranked #5 in the world in scientific impact in immunology. In 2013, ranked #1 in the “Best Places to Work in Academia” and #2 in the “Best Places to Work for Postdoctoral Researchers” in the annual survey of research institutions throughout the world, conducted by *The Scientist* magazine.

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