

The power of the
immune system.

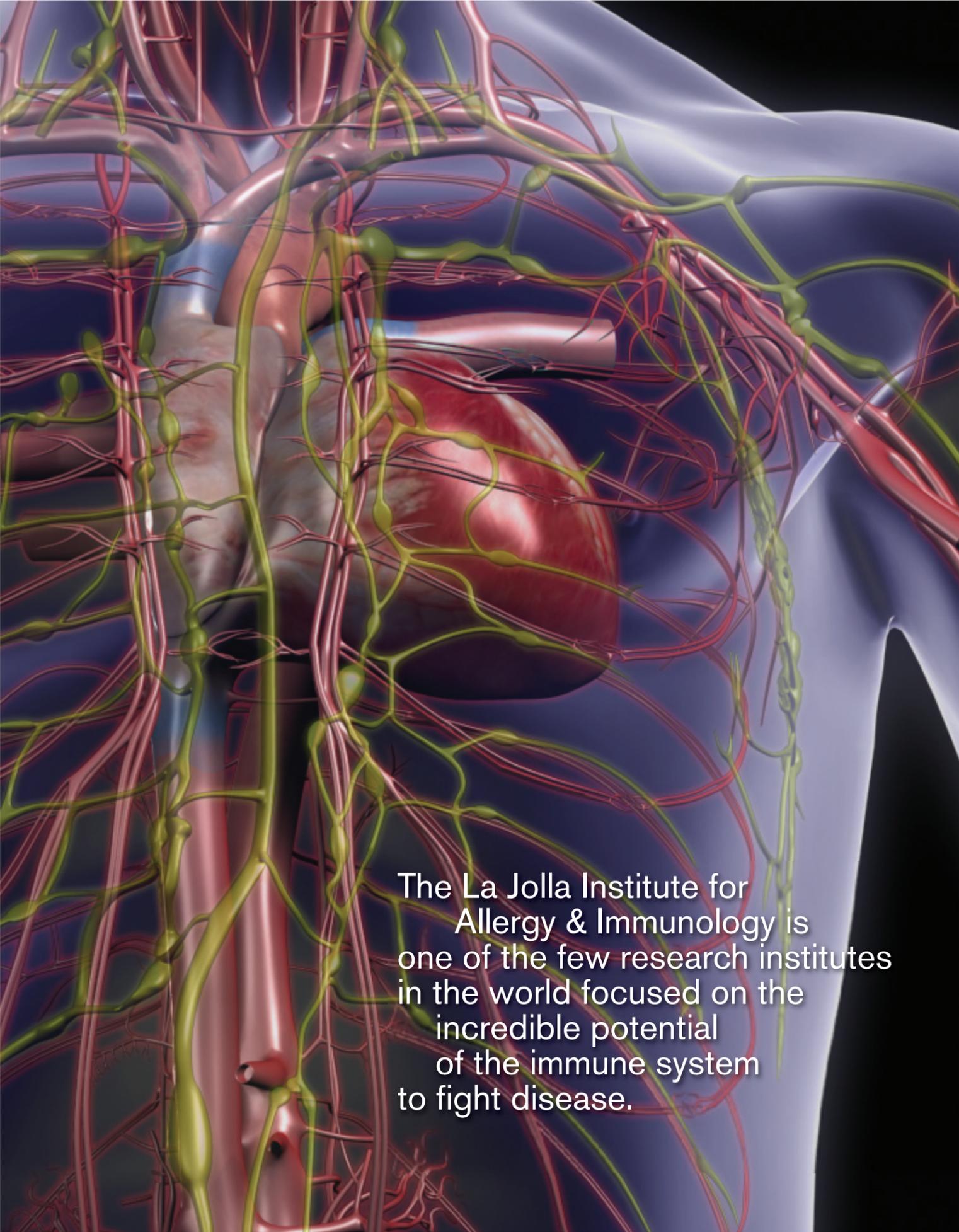


LA JOLLA INSTITUTE
for
ALLERGY & IMMUNOLOGY

The power of the
immune system
cannot be overstated.

Within its intricate
cellular pathways
lie amazing opportunities
for new treatments and cures
for a vast number of diseases.

No biomedical discipline
has greater implications
for improving human health.



The La Jolla Institute for
Allergy & Immunology is
one of the few research institutes
in the world focused on the
incredible potential
of the immune system
to fight disease.

The Immune System

What other single system offers the possibility of fighting infectious diseases, blocking diabetes and warding off cancer all at the same time?

The immune system is one of the most complex biological systems known to man. Yet within its extensive landscape is an extraordinary world of interconnected molecular mechanisms that simultaneously hold the key to a vast spectrum of diseases—more, in fact, than any other biomedical discipline. These range from infectious diseases like influenza to cancer to diabetes to heart disease. While on the surface these diseases may seem dissimilar, in reality each of them is heavily influenced

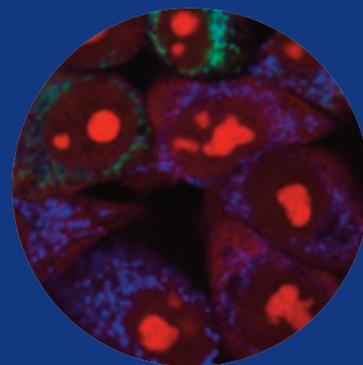
by the immune system and may one day be cured through targeting specific pathways in its seemingly infinite network. Its ability to impact such a broad array of diseases stems from the immune system's dual nature. On the one hand, it is your protector, defending you daily from a siege of viruses, bacteria and other infectious microorganisms. On the other hand, it can be your enemy, triggering a wide spectrum of autoimmune disorders ranging from multiple sclerosis to Crohn's disease to asthma. Even cancer

and heart disease have a strong immune system link. This intersection of the immune system's conflicting roles—in some cases protector, and in some cases assailant, gives it its incredible reach. It also gives the Institute's scientists an expansive opportunity to fight disease. It is a goal they pursue with passion and dedication as they seek new ways to boost the protective side of the immune system through vaccines and cancer therapies and to block its destructive side through new molecular therapies.

La Jolla Institute scientists, in focusing on the immune system, are zeroing in on one of the greatest single weapons that biomedical science has to offer.

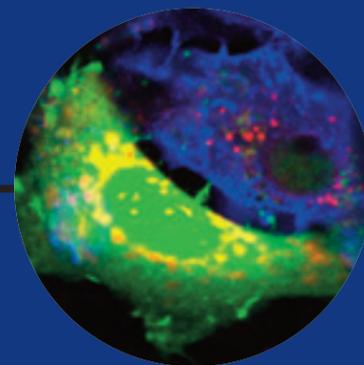
Immune system disorders affect millions and include many of society's most debilitating illnesses.

Our research focuses on five major disease areas:



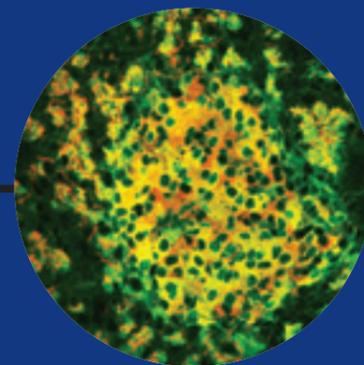
AUTOIMMUNE DISEASES

such as diabetes, multiple sclerosis, rheumatoid arthritis and Crohn's disease



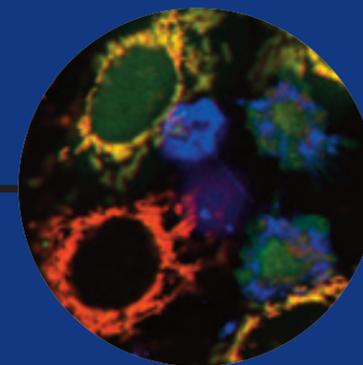
ALLERGY AND ASTHMA

and controlling harmful, hyperactive immune reactions



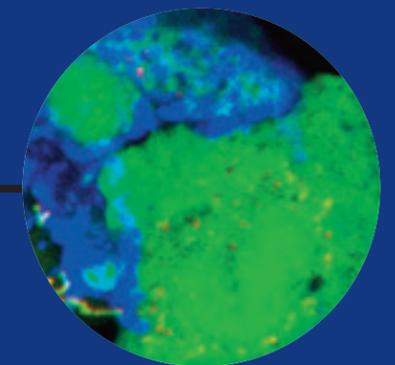
INFECTIOUS DISEASES

such as flu, dengue fever, tuberculosis and malaria



HEART DISEASE

and other cardiovascular disorders



CANCER

and stimulating immune response against tumors

We believe the true measure of success in research is how it will help people like you.

Interconnected. It is not only an accurate description of the body's complex immune system, but it is also an excellent way of describing how we continue to be successful as a biomedical research institute of the highest caliber.

Being interconnected starts with the faculty, our highly talented and productive scientific leaders and the culture of collaboration they have fostered. Furthermore, our focus on the immune system, which holds the key to understanding so many aspects of health and disease, ties us together. Our Board of Directors provides excellence in governance and leadership. Finally, our setting within UC San Diego's Science Research Park facilitates interactions with our neighbors. The result of being interconnected in these ways is a strong foundation for biomedical research critical to Finding Cures Faster.

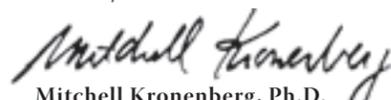
In 2010, we initiated the addition of powerful new technologies at the La Jolla Institute with the award of a substantial NIH grant, which is helping to establish an innovative RNAi Center (see story on page 7). This new facility utilizes modern genetics combined with high-throughput technology and, in effect, will become an engine for accelerating discovery. Importantly, it will also serve to connect scientists within the La Jolla Institute with those in the surrounding research organizations for collaborative new research.

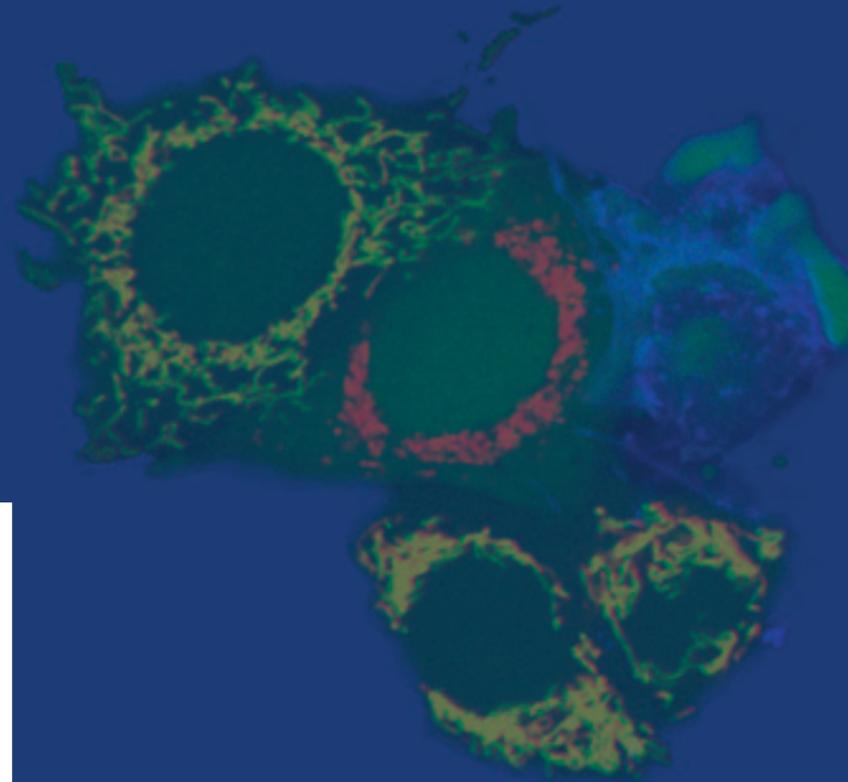
The year of 2010 also marked the end of a ten-year period in which the respected organization, Thomson-Reuters, measured the impact of the publications of organizations like ours: universities, hospitals and research institutes. Publications describing discoveries is the critical component for the advancement of scientific knowledge, and impact is a measure of how many times others have read the papers and acknowledged a direct influence on their research. I am quite pleased to share that the La Jolla Institute was determined to be in the top five in the world in Immunology by this measure.

Even with the excitement of new technologies and the recognized impact of our scientific discoveries, we understand that the true success of our work is how it will help people like you, your family, and your friends. More and better therapies for autoimmune diseases such as arthritis and avoiding disease, for example through new vaccines, are our true measures for success. I hope you will take time to review our Annual Report for 2010 to learn firsthand of our determination to Finding Cures Faster.

We thank you for your support.

Sincerely,

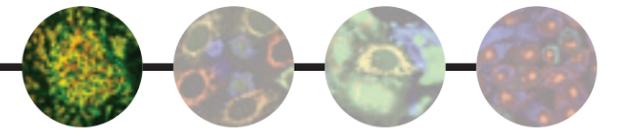

Mitchell Kronenberg, Ph.D.
President & Chief Scientific Officer



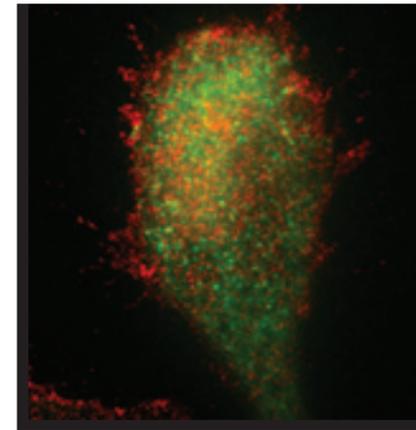
"Working on a broad spectrum of diseases, yet focused on the immune system, the La Jolla Institute is one of the world's finest research institutes."
—John E. Major
Chairman of the Board



La Jolla Institute for Allergy & Immunology Board of Directors (left to right): Samuel Strober, M.D., Toshifumi Mikayama, Ph.D., Michael J. Martin, Richard K. Kornfeld, Mark A. Fischer, Rhonda F. Rhyne, John E. Major, Mitchell Kronenberg, Ph.D., Robert C. Dynes, Ph.D., David Dominguez, William R. Rohn, Leroy Hood, M.D., Ph.D.



Genes are the blueprint of every individual. They determine the color of your eyes and other physical traits, and also have a strong influence on the diseases you may develop in your lifetime. Due to the Human Genome Project, we know more about our genetic makeup than ever before. And yet, we still know little about how genes work individually, and collectively, to affect disease processes. The La Jolla Institute, harnessing a revolutionary technology known as RNAi, is poised to change all that.



An RNAi whole genome screen, published in 2006 by Dr. Anjana Rao, co-lead investigator of the Institute's new RNAi Center, unlocked the puzzle of how calcium enters T cells, one of the most sought after mysteries in biomedical science. The cells pictured here illustrate this process. This photo shows a resting cell, in which the green and red dots mark two proteins (STIM and ORAI) involved in calcium entry.

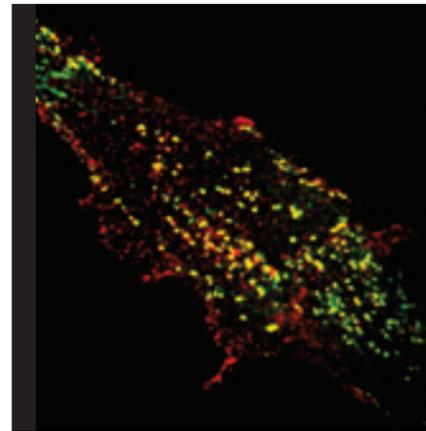
Institute to Develop Innovative Center for RNAi Genomics Research

Center will be One of the Few Dedicated RNAi Screening Facilities Nationwide

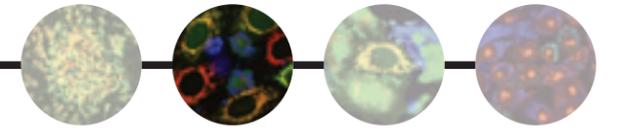
If you could participate in something with profound implications for benefitting mankind... If you could combat disease in ways never before possible... If you could use a breakthrough technology with implications for fighting nearly every imaginable disease... Would you do it?

At the La Jolla Institute, the answer is a resounding "yes." With backing from the National Institutes of Health (NIH), the La Jolla Institute has taken the lead in developing a dedicated RNA interference (RNAi) Screening Center, one of the few such centers in the United States. The NIH awarded the Institute \$12.6 million toward developing the Center, to be launched in 2011. "RNAi allows scientists to explore new ways of disrupting disease processes based on altering gene function," said Institute President & Chief Scientific Officer Mitchell Kronenberg, Ph.D., co-lead investigator of the Center along with Anjana Rao, Ph.D. "It is a powerful technology with the potential to transform human health and we are pleased that the NIH has entrusted us with bringing this publicly funded RNAi facility to San Diego and the nation."

The Institute will conduct its own cutting-edge immunology research at the Center, along with hosting projects from UCSD, The Scripps Research Institute and other San Diego research institutes. "We're going to use this great technology to make breakthroughs in biomedical research, along with making the Center available to the wonderful talent at our fellow San Diego research institutions," said Dr. Kronenberg. In receiving the NIH grant, the Institute succeeded against thousands of applicants in a highly competitive process. Dr. Kronenberg said he believes the Institute's proposal was accepted because of its research excellence and Dr. Rao's previous successes with RNAi while at Harvard Medical School, where she was recruited from last year. In addition, Dr. Kronenberg said the Institute has the drive and the specialized expertise in mouse models to take RNAi to the next level. "We intend to develop methods for RNAi screening in vivo that will allow us to analyze complex disease processes like Alzheimer's or cancer in ways never before possible. The in vivo screening will be truly revolutionary and will greatly expand the capabilities of RNAi worldwide."



In this photo, the cells have been stimulated: the yellow dots show the points at which the STIM and ORAI proteins come together. These are the places where calcium enters cells to trigger immune responses against disease.



Nowhere is the immune system's complicated molecular interplay more evident than in autoimmune diseases. Here, the same cellular soldiers that fight infection, instead begin inexplicably attacking normal cells. The result? Autoimmune diseases like type 1 diabetes, rheumatoid arthritis, multiple sclerosis and Crohn's disease. The La Jolla Institute is at the forefront of discovering ways to stop these misguided cellular sieges and relieve the suffering of millions.



Joel Linden, Ph.D., (top photo) is leading a human clinical trial on sickle cell disease, while a discovery by Michael Croft, Ph.D., (bottom) is the basis for a potential new asthma treatment in phase II clinical trials.

Five Institute Discoveries Advance in Pharmaceutical Translation

Asthma, Crohn's and Rheumatoid Arthritis are Among Targets of Potential Therapies

Five potential therapies that could improve the lives of millions of people around the world are now in the pharmaceutical pipeline due to novel discoveries by La Jolla Institute researchers. Three of the potential therapies have advanced to human clinical trials and two others are in pharmaceutical research. "We are proud to have five potential new treatments arising from our discoveries," said Mitchell Kronenberg, Ph.D., the Institute's president and chief scientific officer. "This is quite remarkable for an Institute of our size and years in existence and reflects the dedication and scientific excellence of our researchers."

While many hurdles still lie ahead on the road to approval, if successful, the therapies would provide new treatments for as many as eight immune-mediated diseases, among these Crohn's disease, asthma and rheumatoid arthritis. In addition, one of the therapies would target tissue rejection in organ transplants.

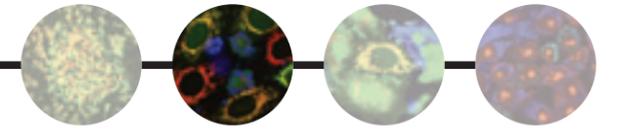
Joseph Panetta, president and CEO of BIOCOM, the regional trade group representing Southern California's life sciences industry, called the Institute's efforts noteworthy. "It takes years of work for a scientific discovery to get from the laboratory bench into the pharmaceutical pipeline," he said. "To have five discoveries, simultaneously in drug translation, shows that something very right is going on at the La Jolla Institute." The "something right" may have a lot to do with its area of focus and quality of researchers. "Our specialization on the immune system and our reputation for scientific excellence has allowed us to attract some of the brightest and most passionate immunology researchers in the world," said Dr. Kronenberg.

In addition, the immune system itself represents an amazing opportunity. "It affects all areas of the body and holds the key to treating a vast spectrum of disorders, ranging from infectious diseases to autoimmune diseases to cancer and heart disease," he said. "We're working in all these areas to develop new treatments. The five discoveries now in translation are only the beginning."

If ultimately approved for use, five potential therapies, arising from the Institute's discoveries, would collectively treat as many as eight diseases.

The eight diseases targeted are:

- >> Asthma
- >> Rheumatoid Arthritis
- >> Crohn's Disease & Ulcerative Colitis (collectively known as inflammatory bowel disease)
- >> Sickle Cell Disease
- >> Eczema
- >> Psoriasis
- >> Dermatitis
- >> Organ Transplant Rejection



A S T H M A

Institute Donor Recalls Ignorance Surrounding Asthma in the 1940s

Childhood Experiences Prompt Research Support



Institute donor Derry Eynon, who has suffered from asthma since childhood, enjoys a vacation spot with his wife of 50 years, Lois. Derry began giving charitable gifts to the Institute in 2008 after learning of its focus on immune system diseases, like asthma.

Seventy-seven-year-old Derry Eynon recalls wryly the day in 1944 when a doctor told him that his wheezing and other asthma symptoms were a consequence of a “well-known emotional instability in red-headed people.” Thankfully, many decades have passed since asthma was wrongfully regarded as a psychosomatic illness, and numerous advances have been made toward improving its treatment. Even so, Derry believes much work needs to be done to truly understand and better treat asthma, allergies and

many other immune-based disorders, a conviction that prompted his recent charitable gifts to the La Jolla Institute. “I chose the La Jolla Institute because it was one of only two Institutes I found nationwide that was really focused on the immune system, which is a foundation of body functions,” said Derry.

A retired journalism professor and Colorado resident, Derry’s once severe asthma and allergy symptoms are now under control. But the road to recovery was long and difficult. One of his earliest allergy memories is at age 10. “I was

out playing on a baseball field and broke out in hives. My mother had me get in the bathtub. She didn’t know what else to do.”

“That fall, I had my first asthma attack,” he continued. “I had no idea what it was and my parents didn’t either. In August, when the ragweed moved in, I was basically incapacitated for a month.”

By the late 1950s, asthma had been recognized as a physiological disorder and Derry, now entering adulthood, began seeing various specialists. However, it wasn’t until age 35 that Derry found a doctor who diagnosed his severe allergies to wheat and other foods, along with identifying various airborne asthma triggers. A special diet, along with regular allergy shots, has kept Derry in good stead over the years.

These days, Derry enjoys various hobbies, and stays abreast of the latest medical research. “My own experience with an illness that was once so misunderstood has taught me that we’re continually learning about disease.”

Researchers Continue Key Diabetes Findings

Brighter Outlook for Type 1 Sufferers; New Players in Type 2 Revealed

The deadly truth about diabetes is that it kills several million people worldwide each year and it’s the fastest growing disease in America today. It is also a major contributor to heart disease and stroke and is the leading cause of kidney failure, blindness and lower-limb amputations among U.S. adults. Such statistics paint a distressing picture, but one that the La Jolla Institute is working hard to counteract, with several major findings on type 1 (juvenile) and type 2 diabetes in 2010.

Ken Coppieters, Ph.D., and Matthias von Herrath, M.D., director of the Institute’s Diabetes Research Center, announced a surprising finding that trounced conventional wisdom on the absence of insulin-producing beta cells in longtime type 1 diabetes sufferers. Problems with insulin, which is needed to convert sugar from food into energy, underlie both type 1 and type 2 diabetes. Rather than no beta cells, the researchers found that more than 25 percent of type 1 sufferers still have some beta cells as long as 20 years after disease onset. “This is good news since several of the new treatments under investigation, including therapies aimed at beta cell regeneration, require some existing beta cells to work,” said Dr. Coppieters. In addition, Dr. von Herrath

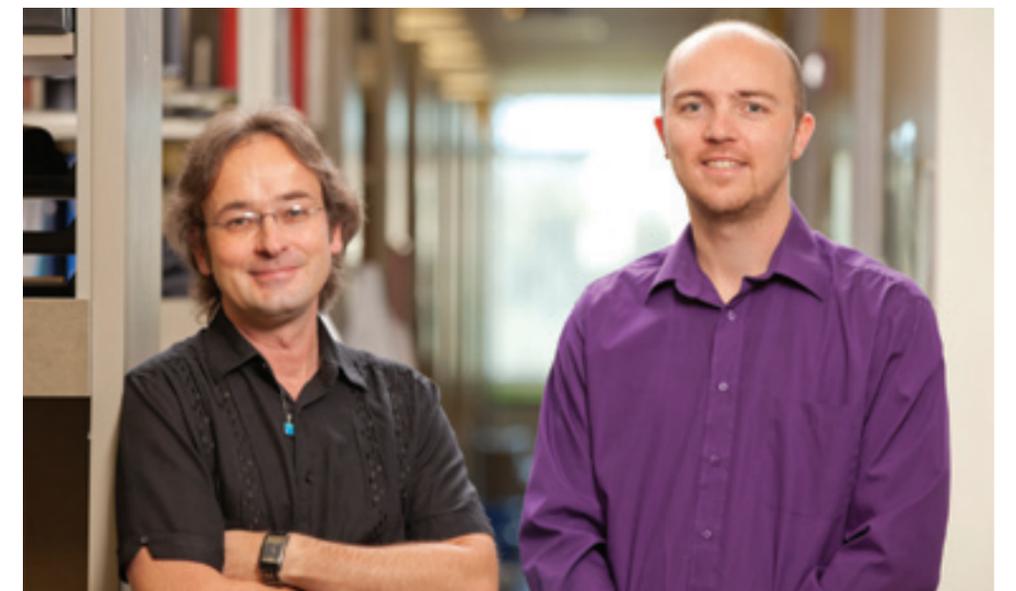
noted, the finding could open the door to previously inaccessible drug trials. “It used to be thought that long-term type 1 sufferers should not even be considered for trials involving stimulation of remaining beta cells,” he said. “Our finding suggests that 25 percent or more of them may be helped if these new therapies prove successful.”

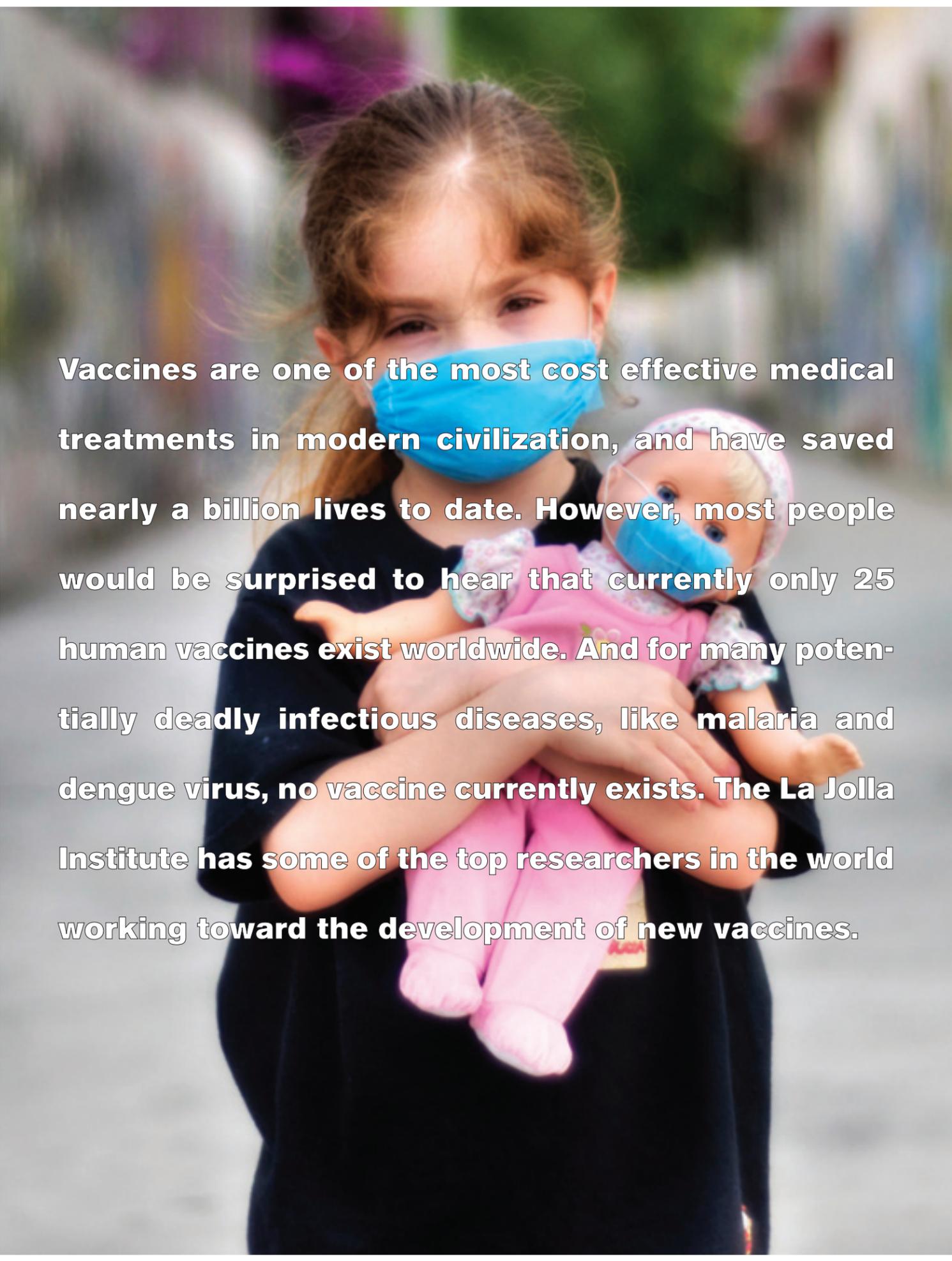
In the area of type 2 diabetes, Catherine Hedrick, Ph.D., unmasked a previously unknown cellular player, the ABCG1 protein, and showed that it is critical for proper insulin production. “Based on our studies, we think that many diabetes patients have reduced expression of ABCG1 in their beta cells which impairs insulin secretion,” she

said, adding that the finding also has application to type 1 diabetes. Dr. Hedrick’s discovery was called “very novel and extremely important” by a Columbia University expert on diabetes mechanisms, and could lead to new therapies that boost insulin secretion by artificially triggering more ABCG1 proteins.

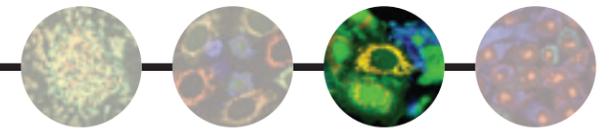
Joel Linden, Ph.D., meanwhile, proved the effectiveness of a molecular blocker to stop adenosine-fueled inflammation that impairs insulin action, and contributes to type 2 diabetes, the most common form of diabetes. “We found that if you use this molecule to block one of the adenosine receptors, insulin resistance is decreased and diabetes gets better,” said Dr. Linden.

A discovery by Matthias von Herrath, M.D., (left) director of the Diabetes Research Center, and Ken Coppieters, Ph.D., provided important new information for long-time type 1 sufferers.





Vaccines are one of the most cost effective medical treatments in modern civilization, and have saved nearly a billion lives to date. However, most people would be surprised to hear that currently only 25 human vaccines exist worldwide. And for many potentially deadly infectious diseases, like malaria and dengue virus, no vaccine currently exists. The La Jolla Institute has some of the top researchers in the world working toward the development of new vaccines.



Researchers Probe New Territory in Tuberculosis Battle

New Data to Close Giant Knowledge Gap; Could Lead to New and Better Vaccine

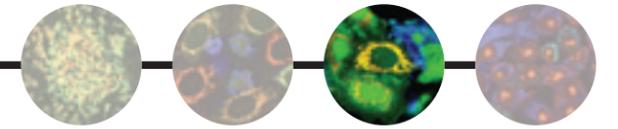
La Jolla Institute researchers are charting new territory in the worldwide scientific battle against tuberculosis, a dangerous infectious disease that kills about 1.7 million people worldwide each year. As part of a multi-million dollar project, funded by the National Institutes of Health, Institute researchers will map the body's immune response to the tuberculosis bacteria, marking the first time this massive effort has ever been undertaken. "By illuminating previously unknown cellular players in the body's tuberculosis defense, we hope to find important candidates for developing a new and better vaccine," said Alessandro Sette, Ph.D., principal investigator on the tuberculosis project and director of the Institute's Center for Infectious Disease.



Shane Crotty, Ph.D., (above) and Alessandro Sette, Ph.D., are co-investigators on a major study to advance progress toward a new tuberculosis vaccine.

According to the World Health Organization, there were 9.4 million new cases of tuberculosis worldwide in 2009, with the majority occurring in the developing world. Currently, only one tuberculosis vaccine is available, BCG, and is varied in its ability to protect. In addition, the emergence of multi-drug-resistant tuberculosis strains, which do not respond to standardized antibiotic treatments, has heightened worldwide concern. About 2,500 such cases have been reported in the U.S. within the last 15 years. In the Institute's study, researchers will identify thousands of epitopes targeted by the body's tuberculosis defenses. Shane Crotty, Ph.D., co-investigator on the tuberculosis contract, described epitopes as what the immune system "sees" on an infected cell and which causes it to attack and eliminate the cell. "By understanding which epitopes cause the immune system to attack a germ, scientists can focus on making sure those germ epitopes are in the vaccine to ward off illness—in this case tuberculosis," he said.

Along with identifying the epitopes, Dr. Sette said they will narrow down the group from thousands to the few which produce the strongest and most effective immune response. "This has always been a giant knowledge gap in the scientific community—which TB epitopes produce the strongest response." He added that significant advances in bioinformatics and genomic sequencing over the last 10 years are enabling the team to perform more comprehensive epitope identification than ever before.



D E N G U E F E V E R

Infectious Diseases Remain a Stealthy Foe for U.S. Military Abroad

La Jolla Institute Works on Dengue and Other Diseases of Concern

For U.S. armed forces, the threats faced on foreign soil don't always come from weapon-toting enemy soldiers. Sometimes, they are invisible foes that can weaken military operations through sickness and even death. Infectious diseases, acting as nature's own band of terrorists, are a significant concern for the U.S. military. "Throughout history, infectious diseases have threatened, and in some cases played a major role in military conflicts, due to their ability to cripple forces through rapidly spreading infection," said Alessandro Sette, Ph.D.,

director of the Institute's Center for Infectious Diseases (CID), which is focused on several diseases of major military importance, including dengue virus and malaria.

Dr. Sette said history shows many examples of wartime disease influence. "As far back as the 7th century, the devastating plague during the siege of Athens heavily influenced the war's outcome," he said. He also pointed to the 1918 Spanish flu pandemic, which was likely responsible for half the deaths of American military personnel stationed abroad during World

War I. Malaria has also played an undermining role in military operations. In fact, more person-days have been lost among U.S. military personnel due to malaria than to bullets during every military campaign fought in malaria-endemic regions during the 20th century. Dengue virus, meanwhile, has had a negative impact on military operations abroad dating back as far as World War II. (Dengue also recently reared its head in the U.S., with a small outbreak in Key West, Florida in 2010. While the outbreak produced only 27 cases and no deaths, dengue remains a U.S. concern, according to the Centers for Disease Control).

"Malaria and dengue virus are important diseases from many standpoints," said Dr. Sette. "They affect millions worldwide, threaten our military when deployed in subtropical areas of the world and weaken the economic and military stability of developing countries where they are endemic." CID researchers are working toward first-ever vaccines for malaria and dengue virus with NIH grant funding. The grant also funds CID work on tuberculosis, another military focus, and smallpox, which remains a U.S. bioterrorism concern.

Throughout history, infectious diseases have been a major concern for military leaders. U.S. soldiers on both military and humanitarian missions in foreign lands are at risk for contracting a number of serious diseases.



Institute Scientists Make Major Advances Toward First-Ever Dengue Virus Vaccine

Institute is Among World's Research Leaders Focused on this Dangerous Mosquito-Borne Disease

For those afflicted by the severest form of dengue infection—most often children in subtropical areas of the world—muscle and joint pain, rash, fever and nausea may seem minor compared to the fate that awaits those who don't recover—blood vessel leakage leading to shock, organ failure and death. It's a frightening scenario, but a real possibility for 500,000 people hospitalized each year with dengue hemorrhagic fever/dengue shock syndrome, the most acute form of the disease.

Recognizing its importance, La Jolla Institute scientists Sujan Shresta, Ph.D., an internationally recognized dengue expert, and Alessandro Sette, Ph.D., one of the world's top vaccine biologists, are working in concert toward the development of a first-ever dengue vaccine. The two scientists are co-investigators on a major NIH-funded project aimed at combating this dangerous mosquito-borne disease.

Dengue annually infects 50 to 100 million people worldwide, primarily in Southeast Asia and Latin America. While infection usually causes dengue fever, a flu-like illness, an estimated 500,000 people progress to the most dangerous



form, of which 26,000 die each year. "Dengue viral infection is a growing public health threat that leads to significant illness, death and economic cost in many parts of the world," said Dr. Shresta, who is credited with several major advances.

In 2008, her development of the first mouse model closely resembling human dengue virus infection was called a "breakthrough" in research tools. And in 2010, she proved that antibodies—usually the good guys in fighting infection—instead trigger dengue's severest form, a critical finding that is influencing dengue vaccine work worldwide.

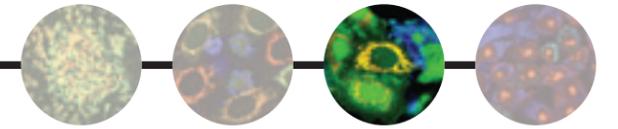
Meanwhile, Dr. Sette is using blood samples from people in Sri Lanka previously infected with dengue virus. He is focused on identifying small pieces of dengue virus, or epitopes, which are important



for the immune system's T cells to recognize, eradicate, and protect against future infection.

"The Sri Lankan samples are allowing us to take the situation from animal models to real cases," said Dr. Sette. "We are generating important data that suggests a T-cell based vaccine may provide protection from the prominent and severe complications of dengue infection."

Sujan Shresta, Ph.D., and Alessandro Sette, Ph.D., are leading research studies that are moving the world closer to a first-ever dengue virus vaccine.



Institute Researcher Fights Little Known—but Treacherous—Viral Foe

CMV is the Leading Infectious Cause of Congenital Birth Defects

Most people probably haven't ever heard of it. Yet, the vast majority of us walk around with the cytomegalovirus (CMV) tucked deep in our bodies. It doesn't produce problems in most of us, and yet it is the nation's No. 1 infectious cause of congenital birth defects. Because of CMV, 1 in 750 children are born with or develop permanent disabilities, such as hearing loss or brain damage. And, in fact, more children have disabilities from this disease than other well-known congenital problems, such as Down syndrome or fetal alcohol syndrome.

Chris Benedict, Ph.D., recognizes the havoc wrought by this seemingly mild virus, which also causes major problems for people with compromised immune systems, such as transplant recipients or AIDS patients. New information is also emerging that CMV may contribute to wearing down our immune system over time. "It used to be thought that CMV lay largely dormant in the body, but new research is showing that its presence may tire our immune system over time." Dr. Benedict said this erosion occurs over decades and can result in significant problems for people in their

60s, 70s and 80s, when trying to fight an infection. "It's estimated that as much as half of the immune system can be wasted fighting CMV," he said.

Dr. Benedict's research has provided major insights into CMV, including his discovery of components of the immune response that should aid in developing the first-ever CMV vaccine. In addition, in 2010 his lab was the first in the world to show that removing a specific CMV gene could significantly improve the ability to fight the infection by boosting T cells, a key component of immunity. "It's definitely a disease that warrants increased research," said Dr. Benedict. "If we can control or prevent CMV, the potential to prevent birth defects and aid the elderly in fighting infection is enormous."

Chris Benedict, Ph.D., focuses on cytomegalovirus, which causes more congenital birth defects in the U.S. than other, more well-known conditions, such as Down syndrome or fetal alcohol syndrome.



Scientist Explores Once Hidden Secrets of Disease Through 3-D Crystal Structures

Latest Study Reveals Molecular Structures Key in Lyme Disease

Dirk Zajonc, Ph.D., brings a penetrating vision to a realm too small to see with even the most powerful microscope. He uses X-ray crystallography, a state-of-the-art technology that captures three-dimensional molecular images at the atomic level—images that are revealing once hidden secrets of health and disease.

"Crystallography enables us to see a single atom in the highest resolution now in existence," said Dr. Zajonc, a protein crystallographer and structural biologist. "Having this detailed, structured image is a significant advantage in combating disease."

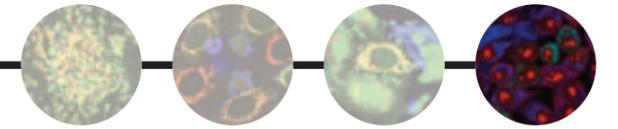
Dr. Zajonc focuses on a relatively new player recognized by the immune system to fight disease-causing bacteria—glycolipids—which are natural biochemicals made of fat and sugar. These molecules play the very important role of triggering the responses of natural killer T cells (NK) T cells, which destroy disease-causing microbes in the body. Over the years, Dr. Zajonc's studies also have provided important revelations on autoimmune diseases and cancer, and have led to his selection for a prestigious Cancer Research Institute Investigator Award in 2007.



In his latest study, Dr. Zajonc examined the structure and role of glycolipids in stimulating the immune response to *Borrelia burgdorferi*, the bacteria that cause Lyme disease. In Lyme disease, in the absence of prompt treatment, bacteria transmitted by tick bites cause a debilitating chronic disease that includes arthritis as well as neurologic and other symptoms. Dr. Zajonc's research stemmed from a 2008 discovery by fellow scientist and Institute President Mitchell Kronenberg, Ph.D., who showed that glycolipids contained in this bacterium trigger an attack by the (NK) T cells, which is key to destroying these disease-causing pathogens.

Dr. Zajonc tapped into his glycolipid expertise to make a breakthrough finding, revealing for the first time the exact steps by which the glycolipids bind to the (NK) T cells and incite them to attack the bacteria. "Dr. Kronenberg's finding demonstrated the importance of these glycolipids in triggering the immune system to fight Lyme disease," said Dr. Zajonc. "Our study illuminated the "how" of that process, and provided insights on cellular mechanisms that we hope will aid further efforts to find new vaccines and treatments for Lyme and other bacterial diseases."

Dirk Zajonc, Ph.D., a protein crystallographer, studies cells at the atomic level to uncover new information about disease processes.



On the surface, heart disease might seem to have little to do with the immune system. But, in fact, the body's disease-fighting immune cells play an important role in heart attacks and other cardiovascular problems. How? The same inflammation-causing immune cells that help heal a wound or kill off viruses can cause problems when they turn up in unwanted locations and stay for too long, as occurs in heart disease. The La Jolla Institute is pioneering immune-based approaches to fighting heart disease.

Institute Division Explores Novel Approaches to Fight Heart Disease

Researchers Look at Harnessing the Immune System to Reduce Cardiovascular Inflammation

A cell of the immune system with an odd-sounding name may hold the key to reducing the incidence of heart disease and other inflammation-provoked cardiovascular diseases. Such is the thinking of Klaus Ley, M.D., a pioneer in vascular immunology and director of the La Jolla Institute's Inflammation Biology Division.

The division explores new ways to fight heart disease—the nation's No. 1 killer—using the immense power of the immune system. It is one of the few such groups in the world. “It is now widely recognized that immune system-produced inflammation is a major contributor to arterial plaque buildup, also known as atherosclerosis, which is the underlying cause of most heart problems,” said Dr. Ley. He noted that research over the last 20 years has shown that one of the most important cell types controlling inflammation are macrophages, a role that has made these cells a major focus of his division. With a name partially derived from the Greek word “phagos,” meaning “one that eats,” these cells are aptly titled, serving as molecular scavenger hunters that eat up viruses and bacteria. In heart disease, however, their normally positive function turns destructive as the macrophages eat away at the artery wall, weakening it in some cases to the point of rupturing and producing a heart attack. “We believe if we can stop that process, we can stop the rupture,” said Dr. Ley, noting this would have major implications for combating heart disease.

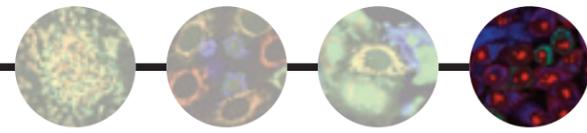
Dr. Ley has joined forces with Joel Linden, Ph.D., and Catherine Hedrick, Ph.D., two other Inflammation Biology Division faculty members, and UCSD researcher Chris Glass, Ph.D., to investigate the mysteries of macrophages. All four scientists are studying various aspects of how macrophages are formed and ultimately promote atherosclerosis. In addition, Drs. Linden and Hedrick are exploring connections between type 2 diabetes and heart disease, and how macrophages may contribute to both. “We think that what happens in type 2 diabetes and atherosclerosis is very similar,” said Dr. Linden, referring to the detrimental effects of inflammation on both diseases. “And we think the same cells—macrophages—may be causing the inflammation that leads to the worsening of both diseases.”



Klaus Ley, M.D., leads the Division of Inflammation Biology, which looks at harnessing immune mechanisms to battle heart disease and other cardiovascular disorders.



Catherine Hedrick, Ph.D., researches the correlation between type 2 diabetes and heart disease.



Scientist's New "Dynamic Footprinting" Method Provides Unprecedented Cellular View

Method Gives Researchers New Weapon Against Bacterial Infections, Heart Disease and Other Disorders

Dr. Ley used his "dynamic footprinting" technique to capture images of a neutrophil, pictured here, an inflammation-producing immune system cell, in the process of adhering to the blood vessel wall. This adherence is a key step in the neutrophil's ability to cause inflammation, which is helpful in fighting bacteria, but harmful in disorders like heart disease.

Like detectives seeking footprints and other clues on a television "whodunit," science can also benefit from analyzing the tracks of important players in the body's molecular landscape. Thanks to La Jolla Institute scientist Klaus Ley, M.D., and his breakthrough development of "dynamic footprinting," the scientific community now has a new weapon for examining key cellular soldiers—known as neutrophils—in greater detail than ever before possible.

"Neutrophils are the body's first line of defense and the main cell protecting us from bacterial infections," said Dr. Ley, head of the Institute's Division of Inflammation Biology. While neutrophils are the good guys in helping the body fight infection, their

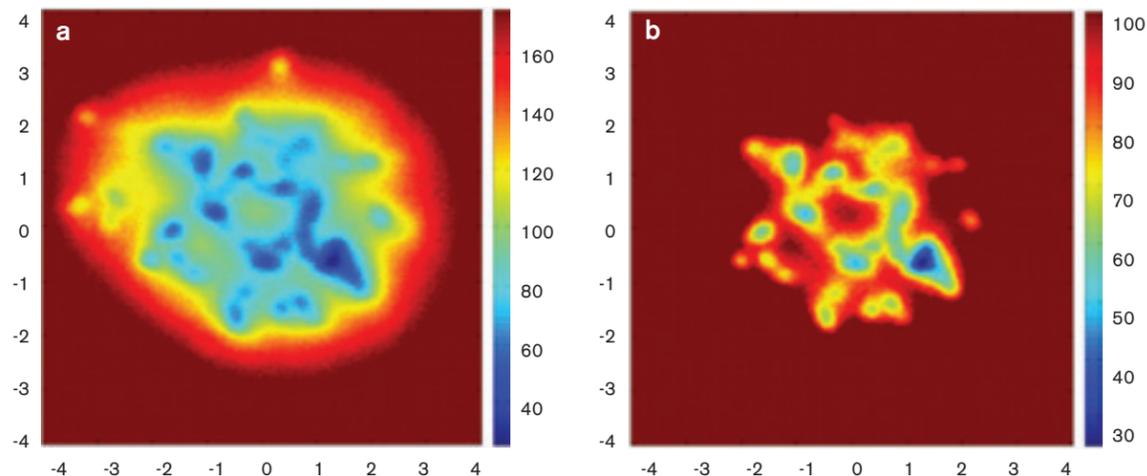
inflammation-producing properties cause problems in heart disease and a host of autoimmune diseases, such as lupus and multiple sclerosis.

"These cells play an important role in many diseases," said Dr. Ley. "Yet, it was not really known how neutrophils adhere to the blood vessel wall, which is a key step in causing inflammation."

To take a closer look, Dr. Ley collaborated with Dr. Alex Groisman at UCSD to develop a new micro fluidic flow chamber, a clear, glass holding unit 10,000 times smaller than the previous version. Along with the chamber, Dr. Ley developed the "dynamic footprinting" technique using special microscopes and light reflection technology to see and photo-

graph the neutrophil adhesion process with unprecedented clarity. "The ability to understand what is actually occurring is significantly enhanced," said Dr. Ley.

These studies have already revealed new insights about neutrophil adhesion, which could prove valuable in helping scientists understand how to reduce adhesion, where inflammation is unwanted, such as in heart disease and MS, or to enhance the process, where more neutrophils are desired, such as in bacterial infections like MRSA. "The body needs to get enough neutrophils into the blood vessels to fight off bacteria faster than they can grow," he said. "Better understanding of neutrophil adhesion could be very beneficial in that process."



HEART DISEASE

Board Chairman Cites Heart Disease as Another Important Area for Institute

John Major, Chairman of the La Jolla Institute Board of Directors, knows well the insidious nature of heart disease. He lost his mother, a type 2 diabetic, to a heart attack. "They call heart disease the 'silent killer' because it can build up quietly over time," said Major, a respected leader in San Diego's high-tech community. "In my mother's case, her type 2 diabetes created the conditions that led to her fatal heart attack."

For Major, the Institute's novel research on heart disease was another important reason he joined the Board in 2009. "When I was asked to sit on the Board, I took a close look at their research and was truly impressed by what I found," he said. "The Institute's work is among the finest in the world and covers an incredibly broad spectrum of diseases because of the immune system's role in so many disorders."

In 2010, Major was elected Board Chairman, and he's made raising community awareness one of his goals. "I want people to know that we are fortunate to have a world leader in immunology research as part of San Diego's life science community."



John Major's mother, Viola, suffered a fatal heart attack. She is pictured here with his father, John J. Major.

2010 Awards and Publications

For the La Jolla Institute, 2010 was a year of unparalleled discovery as evidenced by the 150 research papers published in various scientific journals—the highest annual total in the Institute's history. Scientific papers—in which researchers explain their latest findings—must go through a rigorous peer-review process prior to publication. Their publication validates that the scientist's work is of such importance that it should be shared with the international scientific community. Among the Institute's major published findings in 2010 were discoveries that may contribute to treatments for a range of diseases, including:

- 1) **White blood cell cancers, including myelomonocytic leukemia and acute myeloid leukemia:** Toshi Kawakami, M.D., Ph.D., discovered a previously unknown tumor suppressor mechanism that may be important in these cancers, while Anjana Rao, Ph.D., found that a mutation in the enzyme TET2 is a contributing factor to tumor formation in myeloid cancers.
- 2) **Sickle cell disease:** Joel Linden, Ph.D., showed, in animal models, that the signaling molecule adenosine inhibits inflammation that worsens the effects of sickle cell disease. He is currently leading human clinical trials on the disease.
- 3) **Type 2 diabetes:** Catherine Hedrick, Ph.D., discovered an important new cellular player in insulin secretion, which could lead to new therapies that reduce diabetes severity by boosting this molecule. Her finding may also ultimately help type 1 diabetes sufferers.
- 4) **Dengue hemorrhagic fever:** Sujan Shresta, Ph.D., proved a long-held and controversial hypothesis that some antibodies can be harmful in dengue infection. Her work is influencing dengue vaccine development worldwide.

Also in 2010, Institute scientist Klaus Ley, M.D., was awarded the prestigious Malpighi Medal at the World Congress for Microcirculation in Paris, France. A lifetime achievement award presented by the European Society for Microcirculation, Dr. Ley received the honor in recognition of his pioneering endeavors in vascular immunology, a scientific discipline that he helped to pioneer, which looks at novel immune-based approaches to combating heart disease. He is only the 17th recipient of the biennial award worldwide.

Mitchell Kronenberg, Ph.D., Institute president & chief scientific officer, said the award comes as no surprise. "Dr. Ley is undeniably one of the top researchers in the world in vascular immunology," he said. "His contributions to better understanding of inflammation's critical role in heart disease have led to new diagnostics and potential treatments for arterial diseases."

2010 Caps Five-Year Period of Sustained Growth



Over the past five years our nation has experienced the collapse of the housing bubble, followed by the Great Recession and a period of severe economic unrest. Through this period, La Jolla Institute not only weathered the storm, it grew and flourished.

During the five-year period ended December 31, 2010, the Institute's faculty expanded from 15 to 21 members, while our overall employee population grew from 200 to more than 300. At the same time, our total revenues and total assets increased by more than 50%, to all-time highs of \$43.38 million and \$30.92 million, respectively.

This period of sustained Institute growth was largely fueled by a five-year upward trend in grant revenue from the National Institutes of Health (NIH), as shown in the accompanying bar graph. Our growth in NIH funding is attributable not only to an increased number of faculty, but also our scientists' excellent track record in obtaining competitive, peer-reviewed research grants. Historically, La Jolla Institute's success rates in obtaining NIH grants have exceeded national averages.

Some highlights of our grant successes in 2010 include the Institute's receipt of its first stem cell research grants from the California Institute for Regenerative Medicine, and new grants awarded as part of the American Recovery and Reinvestment Act. These included a \$12.6 million award to help establish a new RNAi screening center that will lay the groundwork for the therapeutic use

of gene-regulating RNA interference. Developing and sustaining the center will depend on a variety of funding mechanisms, including philanthropy.

While the Institute has enjoyed growth and success, new challenges are on the horizon. An era of constrained federal budgets will make obtaining NIH grants an even more competitive endeavor in the years ahead. Just prior to this report's publication, Congress approved a 1 percent reduction in the NIH budget for 2011. More NIH cuts are being discussed for 2012. With nearly 80 percent of the Institute's budget funded through NIH grants, we remain cognizant of these economic pressures. As a result, we have initiated efforts to build the Institute's operating reserves, while maintaining our strategic goal to diversify and enhance revenues through technology licensing and philanthropy. In addition, we will make a concerted effort to husband our resources and reduce costs while keeping at full strength the superb faculty and staff that have put us at the leading edge of discovery.

In summary, La Jolla Institute's financial position and outlook remain positive. We would like to recognize and thank our long-time industry partner, Kyowa Hakko Kirin California, Inc., in providing a stable source of unrestricted research funding while facilitating the translation of our discoveries into potential treatments for human disease. We are also profoundly grateful to our expanding group of donors and loyal supporters, and to our talented and dedicated scientists and support staff.

Charles A. Carpowich, Jr.
Executive Vice President & COO/CFO

2010 Financial Data

STATEMENT OF FINANCIAL POSITION

Cash and investments	\$ 14,384,000
Grants receivable and other	8,776,000
Property, net	7,762,000
Total assets	\$ 30,922,000
Accounts payable and accrued expenses	\$ 8,299,000
Deferred revenue	6,547,000
Total liabilities	\$ 14,846,000
Total net assets	\$ 16,076,000
Total liabilities and net assets	\$ 30,922,000

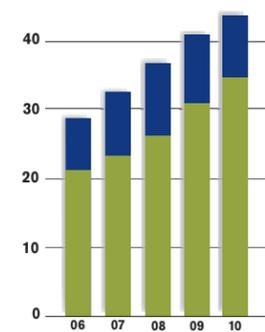
STATEMENT OF ACTIVITIES

Revenues:	
NIH grants and contracts	\$ 34,237,000
Private grants and contracts	8,257,000
Contributions	534,000
License revenue	137,000
Investment return and other	221,000
Total revenue	\$ 43,386,000

Expenses:	
Research	\$ 40,320,000
General and administrative	4,959,000
Fundraising	291,000
Total expenses	\$ 45,570,000
Change in net assets*	\$ (2,184,000)

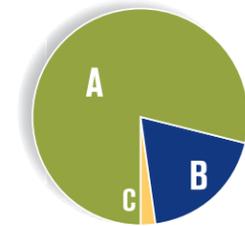
*In 2010 expenses exceeded revenues by \$2.184 million, primarily due to the expenditure of start-up funds for new faculty member labs. The expense was anticipated and financed with revenues earned and recorded in previous years.

2010 Financial Data summarized from LIAI's December 31, 2010 audited financial statements. To receive a copy of LIAI's audited financial statements, contact Charles Carpowich at 858-752-6510 or e-mail skip@liai.org.



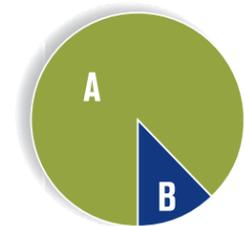
Revenue Growth
in millions of dollars

■ NIH GRANTS AND CONTRACTS
■ TOTAL REVENUES



Revenues

A) NIH and contracts 79%
B) Private grants and contracts 19%
C) Contributions and other revenue 2%



Expenses

A) Research 88%
B) G&A and Fundraising 12%

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DONOR PROFILE

Jerry Mohr Credits Medical Research With Adding Years to his Life

When asked about including the La Jolla Institute in his estate plans, Rancho Santa Fe resident Jerry Mohr said his own experiences, and those of his family, have made him a strong believer in medical research. “That’s where the cures are found. I wouldn’t even be here without medical research advances,” said Jerry, 70, who’s had several surgeries related to heart disease, one of the Institute’s disease focuses.

“Places like yours are near and dear to my heart,” said Jerry. “My 34-year-old niece was diagnosed with juvenile diabetes as a child, and has to take insulin four times a day.

I’m so glad that the Institute is working to eradicate this terrible disease.”

Upbeat and busy, Jerry runs a successful business and sees “giving back” through community organizations as a natural part of life. Over the years, he’s been very involved, serving as a Board member with Walden Family Services, Wounded Warriors, the Nice Guys and other charitable groups.

“Once I saw what the Institute was doing, I became very interested in their work,” he said. “I think those who want to make a difference should do what I did and put charitable gifts in their trusts.”



“My 34-year-old niece was diagnosed with juvenile diabetes as a child... I’m so glad that the Institute is working to eradicate this terrible disease.” —Jerry Mohr

New Friends

Autumn Sunset over Del Mar

On a picture perfect fall evening in October 2010, Board members of the La Jolla Institute hosted a friend-raising event at the Rancho Santa Fe home of Mark and Carol Fischer. The event was designed to help guests learn about the Institute's focused research and the extraordinary potential it holds for improving human health. Guests were treated to a spectacular view overlooking the Del Mar Country Club all the way to the Del Mar Fairgrounds as the sun set over the Pacific Ocean. In a brief program, Board Chairman John Major welcomed everyone, asking that they get to know the distinguished faculty who were present among the guests and their dedication to research on the immune system and Finding Cures Faster.



1.) Mark and Carol Fischer 2.) Mike Martin, Rhonda Rhyne with husband Peter Rosvall, David Dominguez and Rick Kornfeld 3.) John Major with Bill Rohn 4.) Duane and Renee Roth with Assemblyman Nathan Fletcher 5.) Joel Linden, Lynn Hedrick and Amnon Altman 6.) Mick Croft and Hilde Cheroutre with David Dominguez 7.) Jerry Mohr with MaryAnn Stewart 8.) Mitch Kronenberg with Mark Fischer 9.) Jim and Lisa Silverwood 10.) Jim and Diana Burdick 11.) Paula Martin with Randy Woods and Wendy Walker



Charitable Gifts— Funding that Can Have the Greatest Impact

This is our opportunity to say ‘thank you’ to our generous donors.

It gives all of us at the La Jolla Institute for Allergy & Immunology great pleasure to present the Donor Honor Roll listing those who have supported us in Finding Cures Faster. In fact, for the first time in our Annual Report, we’ve highlighted the stories of two of these charitable individuals and their very personal reasons for supporting the La Jolla Institute. I hope you’ve taken a few moments to get to know Derry Eynon (page 18) and Jerry Mohr (page 24). We have—and we think you will find them and their stories inspiring.

Charitable giving is not only important as a source of funding, but it is *the* funding that can have the greatest impact, and make the biggest difference in what a biomedical research non-profit can do. For example, the resources provided through gifts enable the La Jolla Institute to stay on the cutting edge of technology by leveraging the funding provided by the National Institutes of Health to purchase the

most advanced equipment and recruit the best people to operate the technology so that discovery can be accelerated. Or, when funds are given for research on certain diseases, it can provide valuable assistance to begin the data gathering process necessary to procure grant funding from the federal government. All of this is for the purpose of unraveling the complexities of one of the most interconnected systems known—the immune system—so that fewer people suffer, and more people are helped towards better human health.

It is our hope that you will join our donors, like Derry Eynon and Jerry Mohr in making an even greater impact in *Finding Cures Faster*. Again, thank you.

With kind regards,



MaryAnn F. Stewart
Vice President, External Relations
& Chief Development Officer



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2010 High School Summer Internship Program

(left to right) La Jolla Institute Board Member: Robert C. Dynes, Ph.D.;
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