

Immune Matters

SPRING 2014

**A Line You'll Want
to Stand In:
A Vaccine for
Heart Disease**

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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

Heat disease takes an enormous toll in human life and suffering in this country and throughout the world. In the U.S., where heart disease still outpaces cancer as the number one cause of death, more than 600,000 Americans die each year. It is also the leading cause of death worldwide, killing 7 million people annually. Medical science has made many significant strides against this terrible illness over the last 20 years, yet it still claims the lives of our friends and loved ones in alarming numbers.

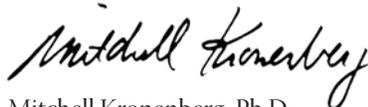
Given this rather grim backdrop, I am extremely pleased to share with you the story of some pioneering cardiovascular research in this issue of *Immune Matters*. Klaus Ley, M.D., head of our Division of Inflammation Biology, together with Dr. Alessandro Sette, head of our Vaccine Discovery Division, are making extraordinary progress toward developing the world's first successful vaccine for heart disease. Now in early concept testing in mice, this groundbreaking work is already producing remarkably encouraging results, with vaccinated mice showing 50 percent less arterial plaque than their non-vaccinated counterparts. Since plaque buildup, also known as 'atherosclerosis,' is the underlying cause of most heart problems, this vaccine holds the potential to one day reduce or even prevent this devastating disease. Our cover story describes this work in more detail and we will keep our supporters informed as this project advances.

Also in this issue, you will learn about the efforts of Stephen Schoenberger, Ph.D. to harness the immune system's amazing potential to fight cancer. Known as 'immunotherapy,' this approach is gaining major momentum as a powerful new weapon in the war on cancer. Schoenberger focuses on CD8 cells and how they can be activated to kill targets, including cancer cells. Along with this research, you will receive an update on the work of scientist Joel Linden, Ph.D., who has joined forces with Rady Children's Hospital in a joint study aimed at reducing excruciatingly painful episodes suffered by children with sickle cell anemia. Sickle cell anemia is a life-threatening blood disorder that affects 100,000 Americans and several million people worldwide.

This issue also provides an opportunity to meet our three new Board members—Sergio Jinich, Timothy Wollaeger and Tina Nova, Ph.D. All are prominent San Diego business executives who bring their insight, experience, and leadership skills to our Board of Directors. In doing so, they and the other outstanding members of our Board of Directors generously give of their time and talent to advance our mission to promote health and prevent disease.

La Jolla Institute is a world leader in the study of the immune system, which we believe holds unmatched potential for preserving health and ultimately conquering heart disease, cancer, diabetes, and myriad other devastating disorders. We are grateful for the generosity of individual donors, foundations, and federal funding sources that enable our critical research to proceed, and we invite all of our supporters to share our excitement as we work toward life without disease.

Sincerely,



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



LJI Researcher Alex Sette Recognized as One of World's Most Influential Researchers



In a new study, that analyzed the work of millions of researchers over a 15-year period, La Jolla Institute scientist Alessandro "Alex" Sette, Ph.D., has been identified as one of the world's 400 most influential researchers, including those performing research in any biomedical discipline.

The ranking is based on a study conducted by scientists from Stanford and Temple universities, which measured research impact, and was published in a recent issue of the *European Journal of Clinical Investigation*. Sette is a renowned specialist in vaccine development whose work has advanced efforts against a vast array of life-threatening illnesses.

"The ranking is not a great surprise given the breadth and prominence of Sette's work," says Mitchell Kronenberg, Ph.D., La Jolla Institute President & Chief Scientific Officer. "I can say without hesitation that he is the world's most prominent researcher in the area of epitope identification, which is critical for understanding how the immune system's T cells—which are the body's most important disease fighting cells—respond to viruses, bacteria, and substances that trigger dangerous allergic reactions. A deep understanding of T cell responses and their ability

to recognize infectious agents is central to curing the most devastating diseases of our time."

The study looked at the research publications of biomedical researchers worldwide, published from 1996 through 2011, to assess their level of impact on the work of the greater scientific community. The survey included a staggering total of more than 15 million names, out of which the top 400 were recognized.

Level of impact in the scientific community is measured by the number of times the findings of each scientist are cited in journal articles written by other scientists. "The citation appears as a detailed footnote and is an acknowledgement of the previous work on which a scientist is building his study," explains Kronenberg. "It is used as a measure of impact because it shows that the cited research was of such magnitude that it influenced the work of other scientists."

The study also measured the relative prestige of the scientific publications in which the researcher's original articles were published. In Sette's case, his outstanding rating was based on 18,219 times that other scientists cited findings from his 365 scientific papers during the 15-year period.

Sette was in impressive company in the top 400 list, which included La Jolla Institute Board member Leroy Hood, M.D., Ph.D., regarded as one of our nation's most prominent scientists, and 17 other distinguished scientists from the Institute's neighboring research institutions—UCSD, Salk Institute, The Scripps Research Institute, and Sanford-Burnham Medical Research Institute.

"Together, these 18 scientists constitute nearly 5% of the entire list of 400 top scientists world wide—a remarkable and commendable achievement for any one community," Kronenberg notes. ■

A POTENTIALLY TRANSFORMATIVE INITIATIVE: LA JOLLA INSTITUTE RESEARCHING WORLD'S FIRST VACCINE FOR **HEART DISEASE**

In the not-too-distant future, people lining up for their annual flu vaccine may see a startling new offering—a vaccine for heart disease.

Yes, emerging research shows that a vaccine—that routine instrument of American health—may be the tool that finally tames the most deadly disease of our time.

La Jolla Institute scientist Klaus Ley, M.D., a pioneer in vascular immunology, is researching the development of a vaccine that could prevent or stop the progression of heart disease, a widespread malady that kills more Americans each year than any other medical disorder including cancer.

Ley's vaccine would focus on reducing inflammation in the arteries and, in turn, plaque buildup. "The scientific community used to think cholesterol alone led to plaque formation, but that is only part of the story," says Ley. "Research over the last 15 years has shown that inflammation is a major contributor to arterial plaque buildup, also known as atherosclerosis, the underlying cause of most heart problems." In addition to heart disease, the vaccine could target the type of stroke which results from plaque buildup in the arteries.

Slashing Plaque Buildup by Fifty Percent

In early testing of the concept in mice, vaccinated mice experienced about 50 percent less arterial plaque than mice that did not receive the vaccine. "We found that we could prevent the development of atherosclerosis by giving mice the vaccine," says Ley, whose findings were recently published in the journal *Frontiers in Immunology*.

Prominent cardiologist Eric Topol, M.D., chief academic officer of Scripps Health, stressed the importance of Ley's work. "If successful, the potential development of a vaccine to prevent atherosclerosis

would be a monumental advance in medicine," says Topol, also a professor of genomics at The Scripps Research Institute.

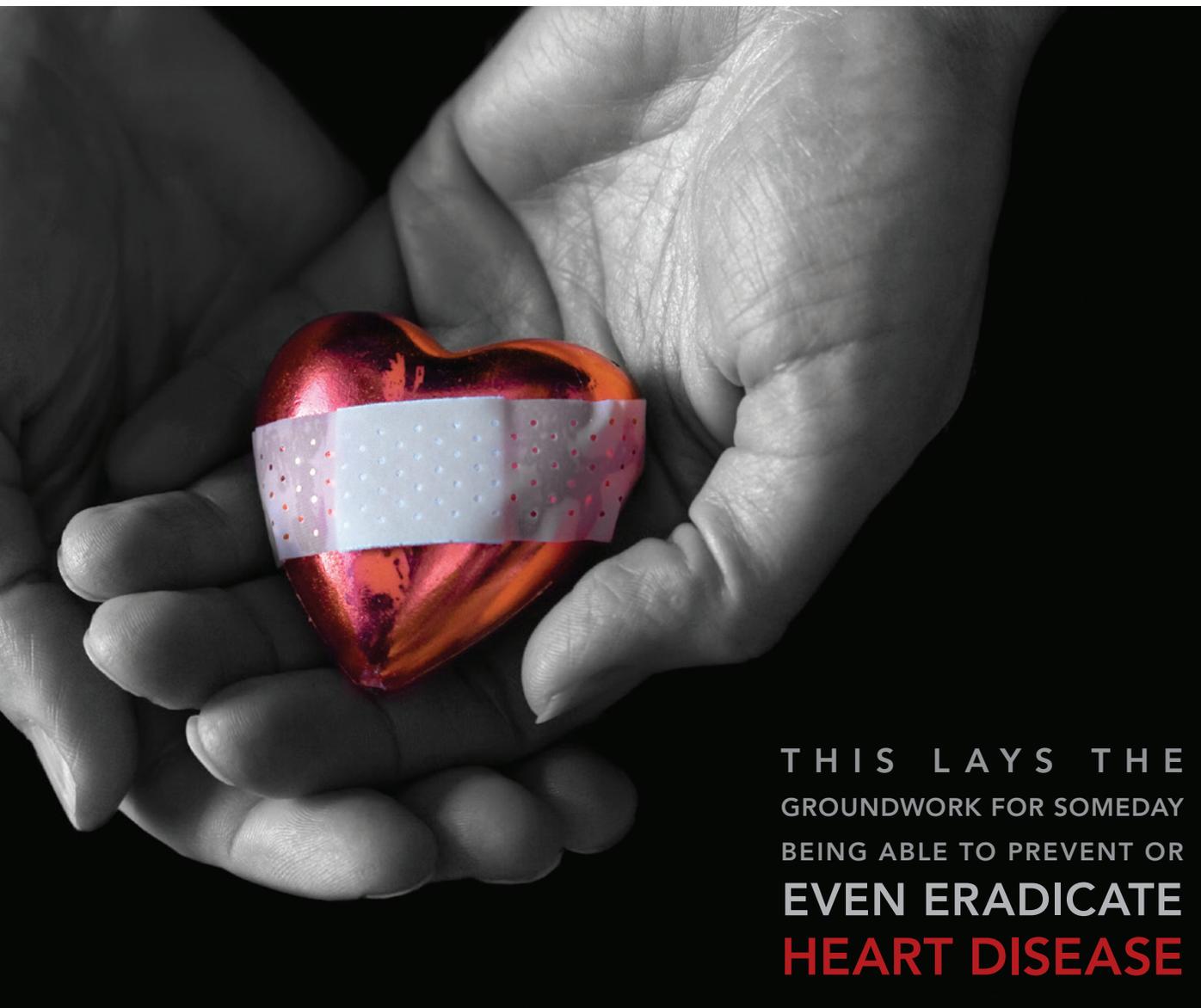
Stanley Hazen, M.D., Ph.D., section head of Preventive Cardiology at the Cleveland Clinic, one of the nation's top cardiology hospitals, also had praise for Ley's research, calling the study "elegant and tremendously exciting."

"This lays the groundwork for someday being able to prevent or even eradicate heart disease by giving a vaccine," says Hazen, also chairman of the Department of Cellular & Molecular Medicine. "This is truly a remarkably important advance."

Not Your Typical Vaccine

The vaccine type Ley is exploring is different than those people receive for the flu and other infections. "A flu vaccine's purpose is to teach your immune system to launch an attack if it encounters the





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virus,” he says. “Our vaccine would work more like the desensitization process used in allergy shots. Allergy shots are designed to teach the individual’s immune system to tolerate the allergen. Our vaccine would use the same principle—only in this case we’d be teaching the immune system to tolerate certain molecules of our own bodies that it mistakenly attacks, which causes inflammation.”

The molecule to be targeted is a protein that wraps itself around “bad” cholesterol in the bloodstream. “Immune molecules, in particular T cells, perceive this cholesterol-laden protein in the artery wall as a problem and attack,” says Ley. “Our vaccine would teach the immune cells to ignore this protein, thereby stopping the attack and the resulting inflammation that worsens plaque formation.”

La Jolla Institute President & Chief Scientific Officer Mitchell Kronenberg, Ph.D., says the vaccine research is the result of Ley’s ability to see things a little differently. “Dr. Ley has combined the

knowledge that T cells are important in atherosclerosis, something that was known partly because of his earlier work, with the idea that we can induce tolerance or prevent a response by the immune system by certain types of vaccination,” says Kronenberg. “Both of these concepts were already recognized, but he put them together. It’s a simple, yet really clever approach that has game-changing potential for treating heart disease.”

If successful, Ley says, the vaccine could significantly reduce the inflammation component of heart disease. He envisions that it could be used in conjunction with statins, cholesterol-lowering drugs that have already significantly reduced the number of people with heart disease. “If the vaccine were combined with statin drugs, I think medical science could deliver a nice one-two punch that would knock out the leading culprits in heart disease—cholesterol and inflammation,” says Ley. | *Continued on page 6* >>

How Inflammation Joined the Heart Disease Discussion

Inflammation's role in heart disease—a once little known topic on the cardiology landscape and still a relatively new awareness in the medical community—is increasingly sharing center stage with cholesterol as a key factor in causing heart disease.

Cardiologist Paul Ridker, M.D., a Harvard professor whose research is widely credited with bringing the link between heart disease and inflammation to the forefront, began looking at the issue in the 1990s. “Since half of all heart attacks were occurring in those with normal cholesterol levels, we thought some other process must be involved,” says Ridker, also director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston. He and his team began pouring over stored blood samples from previous heart studies and, in a landmark 1997 paper, showed that C-reactive protein (CRP), a biomarker of inflammation found in the blood, can be used to predict future risk of heart attack and stroke, along with total cholesterol and other factors. “Our studies showed that elevated levels of either cholesterol or CRP indicated an increased risk for a major cardiovascular event and elevation of both put people at very high risk,” says Ridker.

In effect, Ridker's study had demonstrated that heart disease, in addition to being a disease of cholesterol accumulation, also represents a chronic inflammatory process. “High cholesterol levels and a proinflammatory immune system conspire together to aggressively promote this disease,” says Ridker.

Inflammation's Role—How it Wreaks Havoc in our Arteries

Inflammation is a double-edged sword, whose benefit vs. harm ‘quotient’ is often-times directly related to its duration. For

example, inflammation is the hallmark of an alerted immune system, as witnessed firsthand when you cut your finger. “The initial swelling and redness (inflammation) are basically immune cells swarming to the injured site, working to heal the damage,” explains Catherine “Lynn” Hedrick, Ph.D., a scientist in the La Jolla Institute's Inflammation Biology Division, which explores new ways to fight heart disease using the power of

the immune system. “Inflammation is actually a wound repair response.”

However, when your finger is healed, the inflammation subsides. Trouble arises when the inflammatory response is prolonged or shows up where it's not needed. In these

instances, inflammation can harm body tissues, says Hedrick.

Such is the case in heart disease. “Cholesterol-laden plaques attract an inflammatory response,” says Hazen of the Cleveland Clinic, explaining that the immune system perceives the plaque as an injury and sends in cells to heal the wound. Unfortunately, the healing process goes awry. The immune cells get bogged down and end up worsening and destabilizing the plaque buildup, adds Hazen.

Even worse, says Topol, eventually this sustained inflammation can weaken the plaque to the point of rupturing. “Inflammation is really the critical piece that leads to heart attack and strokes,” explains Topol. “When inflammation is really acute, it can crack the plaque and then you get a clot that impedes blood flow to the heart. It's the clot that's the killer.”

Ridker is so convinced of inflammation's importance that he is currently running two major clinical trials to test the effects of targeted anti-inflammatory therapies in heart disease. The trials follow other high-profile research by Ridker and his Brigham and Women's colleague, Peter Libby, M.D., showing that statins can reduce inflammation in addition to cholesterol, and can lower the incidence of a first heart attack in people with chronic elevated inflammation, but normal cholesterol.

In the latest trials, Ridker is focusing on two drugs that specifically target inflammation. Trial participants have already had a heart attack and are currently being treated with all the “gold standard” medications, such as statins, beta blockers and aspirin. “We look at these (two trials) as two swings of the bat,” says Ridker. “They ask the fundamental question, ‘can lowering inflammation per se actually lower major cardiac risk events?’”

Such is the question that Ley is also asking with his vaccine research.

The Road Ahead

Ley is currently working with fellow La Jolla Institute scientist Alessandro Sette, Ph.D., an internationally recognized vaccine biologist, to identify more candidate proteins for

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Left: Mouse artery, no vaccine.
Right: Vaccinated mouse has greatly reduced arterial plaque (stained red).

CHOLESTEROL-LADEN PLAQUES ATTRACT AN INFLAMMATORY RESPONSE

creating a vaccine for people. “The next step is to do testing in specially engineered mice with an immune system more similar to humans,” he says. With continued refinement and adequate funding, the vaccine could begin human clinical trials in as little as three years, Ley adds.

Ley says the heart disease vaccine initiative has been primarily funded thus far by competitively awarded grants from the National Institutes of Health. However, the

cost of pursuing the vaccine’s development on schedule will require several million dollars in funding from private sources. As a result, the Institute is now seeking sources who might be interested in funding a portion or all of the initiative.

Kronenberg says he is excited by Ley’s efforts and also credits the Institute’s immunology leadership and collaborative environment for fueling this innovation (see related story below). “Heart disease remains

our nation’s number one killer,” says Kronenberg. “Dr. Ley’s studies show promise for creating a vaccine that may one day reduce or even prevent this terrible illness. That’s the kind of breakthrough that would transform human health.” ■

An Unexpected Alliance Advances Groundbreaking Vaccine for Heart Disease

Two Experts in Seemingly Unrelated Areas Unite Toward Novel Goal

Pioneering scientist Klaus Ley, M.D., who specializes in the immune system’s role in heart disease, readily admits that he didn’t used to focus much on the work of fellow scientist Alessandro Sette, Ph.D., an expert in infectious diseases.

After all, given the expansiveness of the immune system, many of his La Jolla Institute colleagues work in areas that seem far removed from his study of cardiovascular diseases.

“I used to think, ‘Alex does infectious disease research. It’s interesting, but not really related to what I do.’”

That was until he attended a talk by Sette on identifying molecular targets for developing a tuberculosis (TB) vaccine. Sette, a world leader in vaccine development, who specializes in emerging infectious threats, was discussing how he used high-powered computer modeling to pinpoint the best peptides for building a TB vaccine. Peptides are tiny fragments of viruses, bacteria and other antigens that prompt the immune system to launch an attack.

Coincidentally, Ley was also working to identify peptides, only in his case the peptides didn’t involve tuberculosis or other infections, but rather non-infectious cells underlying heart disease.

“We were trying to screen 600 peptides, but we didn’t have the tools to do it quickly,” says Ley. A light bulb went off in Ley’s head and he was soon in Sette’s office, one of the benefits of being in a research institute with a singular mission uniting immunology experts under one roof.

Before long, Sette and his team had used sophisticated predictive technology, known as bioinformatics, to narrow Ley’s 600 candidate epitopes down to 30—a critical step toward developing the heart vaccine. “Without these tools, this process would be incredibly slow if not impossible,” says Sette.



Alessandro Sette, Ph.D., left, and Klaus Ley, M.D.

So began a collaboration between two prominent scientists, both leaders in their respective areas, that has significantly accelerated progress toward the world’s first vaccine for heart disease.

“I don’t think this could have happened anywhere else,” says Ley. He credits the Institute’s dedicated immunology focus for bringing together the “perfect storm” of researchers that enable such breakthroughs to happen.

“This is a great example of why I moved here from the University of Virginia,” adds Ley. “There is so much immunology expertise in one location. It’s really amazing.”

As a world leader in the study of the immune system, the Institute attracts top immunologists from around the globe. The immunologists bring a spectrum of expertise—ranging from infectious diseases to cancer to autoimmune diseases to inflammatory disorders like heart disease. In other words, their scientific specialties reflect the broad disease spectrum of the immune system.

“This collaboration allowed the expertise that my lab has developed in the context of infectious diseases to be used in heart disease,” says Sette. “It’s another illustration of how understanding the immune system’s molecular underpinnings can bring new insights in a wide array of diseases.” ■

Heart Disease Survivor Shares Her Story to Help Others

Just before drifting off under anesthesia for triple bypass surgery, Rae Arnold recalls the last words uttered by her husband of 42 years—“Don’t let go.”

It was a solemn and serious admonition because Rae knew that her major coronary artery was 95 percent blocked and two other key arteries were nearly closed off.

Thus began Rae’s tenuous medical odyssey that would entail two triple bypass surgeries, aspirin desensitization therapy, and nine arterial stents before returning to a healthy state. Today, the 65-year-old Rae looks calm and radiant, but she keeps her experience and those who helped her through it close at hand. A dainty bracelet with a single heart charm dangles from her wrist, inscribed with her husband’s loving plea, “Don’t let go.”

“I never take it off,” says Rae with a smile.

For the retired pastoral assistant and grandmother of eight, her ordeal has led to new experiences and a new passion—educating the community, particularly women, about heart disease as a volunteer speaker for the American Heart Association. “A lot of women don’t realize that heart disease is the number one killer of women,” says Rae, a longtime Vista resident and church volunteer. “Most of us assume its breast cancer.”

Women may also be unaware of the warning signs of a heart attack, continues Rae, noting that these signs differ from those

for men. Her experience, which began on a typical day in February 2011, illustrates the issue.

Rae was out on a training walk in preparation for the Susan G. Komen three-day fundraising event, which she’d participated in for seven years in a row. “I walked up a small incline and noticed that I had a slight shortness of breath, which wasn’t typical for me,” recalls Rae. A short time later, she felt a little pain in her jaw and down her neck and a slight burning in her throat. Rae didn’t think too much about it, but decided to visit her primary care doctor a few days later, just in case.

While she didn’t know it or even consider it at the time, Rae had experienced some of the classic warning signs for heart disease in women. “I didn’t have high cholesterol or blood pressure. I ate right and exercised. My only known risk factor was a family history of heart disease.”

Suspecting exercise-induced asthma, Rae’s doctor sent her to a pulmonologist who discovered Rae’s vascular blockages during a routine cardiac stress test. A stunned Rae was told she had angina, a problem resulting from restricted blood flow to the heart, and that she needed triple bypass surgery, which she soon underwent.

Following surgery, everything went great for 12 weeks, says Rae, until symptoms returned and doctors discovered that two of her three bypass grafts had failed. A second bypass surgery ensued but had to be stopped mid-way when a hole was torn in her right ventricle, caused by scar tissue from the previous bypass.

Rae’s situation looked grim, but hope was on the horizon. She was transferred to the newly opened UC San Diego Sulpizio Cardiovascular Center, where doctors administered intensive IV therapy to help Rae overcome a severe hypersensitivity to aspirin. “You have to be able to tolerate aspirin in order to be a candidate for a stent,” explains Rae. The procedure was a success, and the next day Dr. Ehtisham Mahmud “literally saved my life,” says Rae, when he implanted the first two of nine stents to open up her clogged arteries.

Today, nearly three years later, Rae has shared her story with hundreds of San Diegans at AHA-sponsored talks at club gatherings, churches, and businesses. “I try to educate people about disease prevention and also about the warning signs, particularly women, who tend to just ‘push through’ and ignore symptoms.”

Rae says she also looks forward to sharing news of La Jolla Institute’s work toward a vaccine for heart disease, which she describes as “amazing.”

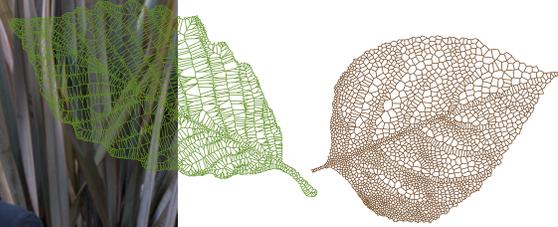
“To think that we could one day live in a world where there is no heart disease,” says Rae. “I can’t even fathom it. It would be so miraculous.” ■

DON'T
LET
GO



Institute's "Go Green" INITIATIVE

Preserves Resources, Cuts Costs



(L to R) Joel Seliger and John Keegan

A "green" initiative to ramp up eco-friendly practices at La Jolla Institute has led to creative ways to preserve water, electricity and other resources, along with saving \$150,000 since launching in August, 2012. "I'd say the most amazing part of going through this process has been the surprises—the various ways to preserve resources that you'd never realize until you delve deeper," says John Keegan, senior director of Facilities & Operations, who led the effort.

Key in the process has been strong support from Institute President Mitchell Kronenberg, who championed the initiative, adds Keegan.

The Institute is part of a growing U.S. trend, with a recent survey showing that 69 percent of American businesses have instituted energy-saving and waste- and carbon-reducing programs.

While long practicing recycling and other environmentally friendly measures, Keegan

says the Institute decided to launch an expanded effort in 2012, starting with small efforts and strong employee communication to encourage participation.

First up was removing most paper and plastic products from the employee lunch room, which vastly reduced the mounds of disposable plates, glasses, and utensils (about 392,000 items in a typical year) headed for the landfill, while also saving \$13,000 in product cost. Since the launch, Keegan says use has dropped by about 2/3, with most employees easily adapting to bringing reusable utensils from home.

The lunch room program also had unexpected benefits. "The bigger impact was that our waste stream dropped by 10 to 15 percent," he adds.

The Initiative also led the Institute to target water waste by installing portable water meters to pinpoint areas of heaviest use. Joel Seliger, assistant chief engineer, handled data monitoring, which provided key insights. "We found that much of the

waste related to inefficiencies in how washers and other cleaning equipment were operated, not in the equipment itself," says Keegan. Enhanced operator education solved the problem and resulted in a huge drop in water use followed shortly by natural gas. "Because we use a lot of extremely hot water for sterilization purposes, reductions in water use translated into a major drop in our natural gas heating costs," he explains.

Other measures included: a new vendor recycling program which handles a broader array of plastics; a new focus on better temperature control in little used areas and after hours to reduce energy consumption, switching out employee drinking water to a lower-waste system, and making loaner bicycles available to employees who need to run local errands on the UCSD campus or elsewhere during the work day. Overall, about 50 measures, large and small, have been adopted and more are planned in 2014. "We had a great team and wonderful employee support," says Keegan. "It just speaks to the conscientious kind of people who work at the La Jolla Institute."

All of these measures combine to do more than make a positive environmental impact; the resulting savings are one more way that LJI is putting our donor's dollars to work in the most efficient way possible, allowing us to focus funding where it is needed—scientific research. ■

Immunotherapy: Rediscovery of our Natural Weapon Against Cancer



La Jolla Institute faculty member Stephen Schoenberger, Ph.D., is one of the nation's leading researchers in how organisms regulate immune responses at the cellular and molecular level. Among his achievements, Schoenberger's early work led to the development of a transplantation drug, now in clinical trials, designed to prevent organ graft rejection. Schoenberger earned both a B.S. and Ph.D. from UCLA and joined the Institute in 1998 as an Assistant Professor in the Division of Immune Regulation. He became an Associate Professor in the Division of Cellular Immunology in 2002 and was promoted to Professor in 2007. One of Schoenberger's goals is to expand public awareness of the burgeoning potential of cancer immunotherapy.

Q: Surgery, radiation and chemotherapy have been the traditional tools to fight cancer, but recent news suggests that a new therapy called “immunotherapy” has the potential to revolutionize the treatment of this deadly disease, leading to outright cures in some cases. What does your research suggest is the future of this treatment?

A: Our research is flying a little under the radar right now, but that's going to change. That's because we're on the threshold of an incredibly important and exciting period in which the research we're doing here at the Institute—along with work being conducted by scientists all over the world—will harness the power of the immune system to transform how we treat cancer. The many years of basic scientific investigation we've invested in unraveling the mechanisms of how immune systems work at the cellular level—combined with the discoveries showing the genetic basis of cancer—are finally paying off with breakthroughs that will allow us to attack cancer on multiple new fronts and in ways we could barely imagine 10 years ago.

Q: How will your research contribute to that effort?

A: Working now in mouse models, we're studying the process by which an organism's immune system, through “killer” cells—(cytotoxic) T lymphocytes—attack and destroy target cells, including cancer cells. We're beginning to understand the rules by which these killer T cells are activated and regulated, and most importantly, how they can be manipulated for therapeutic goals. Now that we fully understand the signals that guide T cell activation, development, and long term protective memory, we are starting to deploy them to attack a variety of cancers. The idea is to educate the immune system—either through the use of targeted vaccines or the use of T cells that are trained to distinguish a malignant cell from a normal cell—to eradicate only the cancer cells while sparing the surrounding healthy cell tissue. This would represent a huge advancement over the debilitating side effects currently caused by chemotherapy and radiation.

Q: How do you see this playing out with cancer patients?

A: We envision that in the not-too-distant future, an oncologist will be able to take a sample of the patient's cancer and very quickly and inexpensively have it analyzed to determine its specific mutations and how the patient's immune system reacts to the tumor at the molecular level. An immuno-

therapy will be designed in the space of a few weeks that will be customized specifically to the patient's unique immune system and cancer. This will be delivered to the patient and, if everything is done correctly, the cancer should be eradicated or at least neutralized with minimal side effects. Our research currently is focusing on a model for ovarian cancer, which is the fifth-most prevalent among women right now, but causes the most mortality. If our approach works, we plan to expand to models for melanoma, prostate and breast cancer.

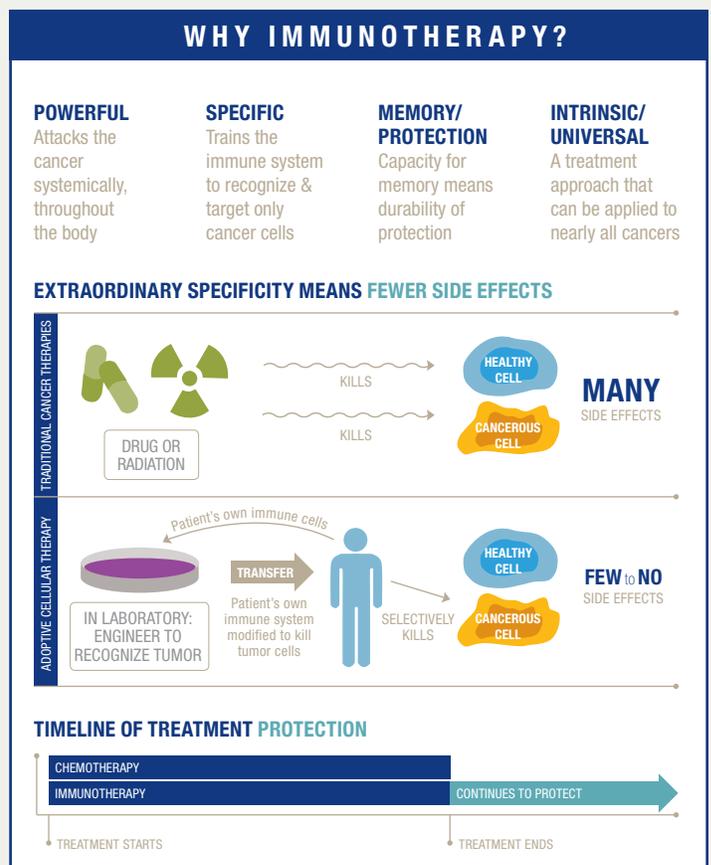
Q: La Jolla Institute isn't focused solely on cancer. Is that an advantage or disadvantage?

A: It's been a tremendous advantage. I can say without hesitation that the remarkable environment here at the Institute has been critically important to my success and that of our research objectives. If I had been at a smaller institution with fewer resources, or at an organization with bureaucratic red tape, my research might never have advanced as far and as quickly as it has here. This is the most collegial, interactive and helpful group of scientists I've ever worked with. The world-class facilities, infrastructure, and support from our administration free us to focus on an amazing breadth of immunological research. It's why the Institute remains on the cutting edge nationally and why our reputation in the scientific community is absolutely first rate.

The one dark cloud that really concerns me, and which I believe threatens future discoveries, is that funding for research is becoming much more difficult to obtain. We're dependent on NIH funding from the Federal government, and in years past we've had tremendous success attracting grants. We could submit five grant applications and be pretty sure we would secure funding for at least one; this led us to propose "risky" or cutting-edge ideas. Today, we have to write 15 grants to get just one funded even when we stay "safe", not to mention the vast amount of time this process takes away from our research. I bring up the funding issue because I think we need to develop a new model for supporting our research: we need to add back what we're losing in terms of time and progress for those people who suffer now—and in the future—until we can finally live without the constant threat of a devastating or incurable disease. One of the reasons I like to share my research with the public is that I believe we need to capture the imagination of philanthropists, foundations, and those in the private sector who might be interested in providing financial support to something that will absolutely improve their community.

Q: Even with the funding challenge, are you optimistic about the future impact of your research?

A: So much so that we're already planning ahead. We've entered into a partnership with the Moores Cancer Center at UC San Diego that has brought Dr. Aaron Miller, an M.D./Ph.D., to work side-by-side with us to ensure our discoveries will be translated properly to the clinical setting with real patients. From a personal standpoint, I'm so confident about our work that I've actually shifted gears myself, moving from basic research that illuminated the principles of immunity, which I did for 25 years, to now conducting translational research that can be adapted to the treatment of patients. Much of that has to do with the magnitude of the disease we're battling. Cancer ends productive lives far too often and far too soon and I'd like to play a role in stopping it. I have no doubt that when we're finally able to take our knowledge and therapies into the clinic it will be the most rewarding phase of my career, as I'll actually be able to witness the results of our research and how it enhances and saves lives. ■

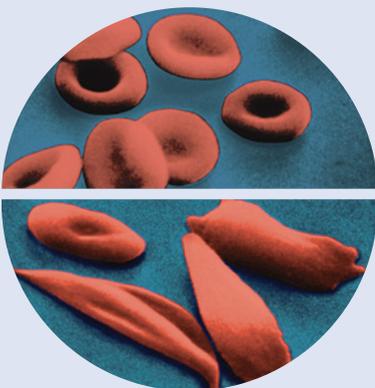


LA JOLLA INSTITUTE AND RADY CHILDREN'S COLLABORATE TO FIGHT SICKLE CELL ANEMIA

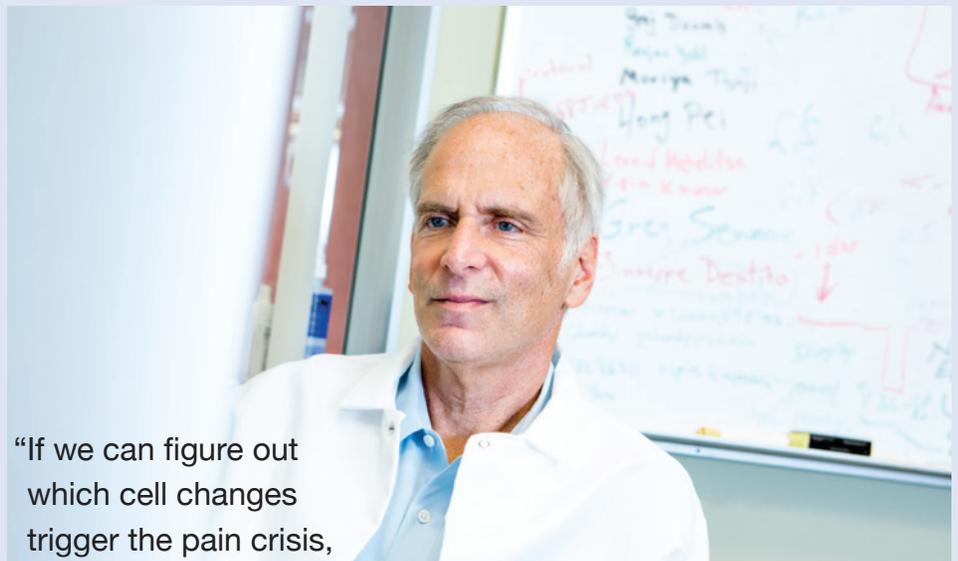
Joint Research Project Hopes to Reduce Severe Pain Episodes in Children

La Jolla Institute for Allergy and Immunology researchers have joined forces with Rady Children's Hospital-San Diego doctors to study ways to improve the lives of children with sickle cell anemia, in particular reducing the extreme pain episodes that ravage many sufferers.

More than 100,000 Americans and several million people worldwide suffer from sickle cell anemia, an inherited disorder that causes the oxygen-carrying red blood cells to become stiff, sticky and misshapen or "sickled" in appearance. This leads to poor blood flow that deprives tissues of oxygen, which can cause severe pain, difficulty breathing and organ damage that leads to a shortened lifespan. Sickle cell is most common in people of African descent, but is also found in Hispanics of Caribbean ancestry and people of Middle Eastern, Asian, Indian, Latin American, Native American, and Mediterranean heritage.



Healthy red blood cells (above) and elongated, or "sickled" cells (below) after they have become stiffy, sticky and misshapen.



"If we can figure out which cell changes trigger the pain crisis, then we can potentially develop ways to block these changes and significantly lessen the severity and frequency of pain."

—Joel Linden, Ph.D.

The two organizations are conducting a joint research project to study ways to reduce the incidence of "pain crisis," a periodic worsening of the disease that causes severe pain and often leads to hospitalization. The study is analyzing the blood cell changes that occur in children with sickle cell anemia during the painful periods. "We're hoping this research may enable us to find ways to shorten or eliminate these episodes that can produce acute suffering for patients," says Jenny Kim, M.D., medical director of Rady Children's Hospital Comprehensive Sickle Cell Center and associate clinical professor of pediatrics, UC San Diego.

A number of patients from the Rady center are providing blood samples for the study, which are then sent to the laboratory of Joel Linden, Ph.D., and his team at the La Jolla Institute for analysis. "If we can figure out which cell changes trigger the pain crisis, then we can potentially develop ways to block these changes and significantly lessen the severity and frequency of pain," says Linden, a prominent inflammation biology researcher.

The collaboration is particularly effective, adds Linden, due to the proximity of the two organizations, which enables samples to be obtained and analyzed quickly. "This minimizes cellular changes that begin after blood is collected and provides my lab with more accurate information for understanding this disease," says Linden.

Linden says the joint study focuses on pain because it is one of the most difficult and common symptoms faced by sufferers. While the study will use blood samples from children, he believes the knowledge gained will help adult sufferers as well. "Sickle cell

anemia is a devastating disease and current therapies to improve the lives of these patients are very limited," says Linden, adding that the pain experienced by sufferers is a reflection of tissue injury.

The study is one of two projects being championed by Linden to combat sickle cell anemia. He is also co-leading a nationwide clinical trial—involving trial sites in 10 eastern U.S. cities—to test a potential therapy for reducing the disorder's severest symptoms, including pain and difficulty breathing. "I hope that this study with Rady Children's, as well as the ongoing clinical trial, will help us to identify new ways to relieve the pain and other complications faced by sickle cell patients." The trial began in 2010 and is now in Phase II.

Kim says pain crises can occur every month or two for many sickle cell patients. The episodes, which are treated with intravenous pain medication or blood transfusions, can last from several hours to several days. Factors such as heavy physical activity, stress, infection, dehydration, and altitude changes can trigger the painful episodes, so patients must be cognizant of their illness. "It's something these kids have to deal with all their lives," says Kim. "Sickle cell is not silent."

Rady Children's sickle cell center uses a multi-disciplinary approach involving neurologists, pulmonologists, hematologists, and a pain clinic to address the many aspects of the disease. Most patients are treated on an outpatient basis, and many undergo monthly blood transfusions to reduce sickled cells. Others take a host of medications to help control the various disease complications. Only one drug is currently licensed to treat sickle cell disease, and it has limited success. ■

Meet the Scientists

JDRF and LJI Collaborate on Type 1 Diabetes Event

More than 300 type 1 diabetes sufferers and their families got an opportunity to meet and learn from scientists working to fight their disease at the "Meet the Scientists" event on February 9th.

Attendees enjoyed laboratory tours, an educational panel, research update, vendor show and games for the kids.

Parker Poston, 7, conducts a laboratory "volcano" experiment, while kid sister Madison, 4, and friend Aiden Birney, 6, look on. The three youngsters, all of whom have type 1 diabetes, and their families were among more than 300 people who attended the "Meet the Scientists" event on Feb. 9th.



(L to R) Sean McParland, executive director of JDRF San Diego; Mitchell Kronenberg, Ph.D., La Jolla Institute president & chief scientific officer, and Matthias von Herrath, director of the La Jolla Institute's Diabetes Research Center. The "Meet the Scientists" event is a collaboration between JDRF San Diego and the La Jolla Institute for Allergy and Immunology.

La Jolla Institute scientist Grzegorz Chodaczek shows a young visitor a laboratory microscope.



Three Prominent San Diego Executives Elected to La Jolla Institute Board of Directors

The new members are: Sergio Jinich, a distinguished real estate and construction executive in the U.S. and Mexico; Tina Nova, Ph.D., a scientist and successful co-founder of three San Diego biotechnology companies; and Timothy Wollaeger, a biotechnology industry veteran with extensive experience in corporate finance, management and venture capital, who has co-founded numerous San Diego biotech. “We are honored to attract these high-caliber individuals to our Board of Directors,” says Mitchell Kronenberg, Ph.D., La Jolla Institute President & Chief Scientific Officer. “Each brings a track record of extraordinary success, experience, and leadership that is a perfect complement to our existing Board of respected business and scientific leaders.”



Sergio Jinich

CURRENT POSITION

Chairman of Paragon Management Company, a real estate investment firm established in 1998 after he and his family moved from Mexico to San Diego.

PAST PROFESSIONAL EXPERIENCE

» 24 years as chairman of Grupo COIN in Mexico, a major construction

and real estate firm that developed bridges, highways, and numerous other public infrastructure projects over 24 years

- » President of the Mexican Chamber of the Construction Industry
- » Vice president for Concamin, the Confederation of Industrial Chambers of Commerce in Mexico

EDUCATION

- » B.S. degree in civil engineering from the National University of Mexico
- » Completed graduate studies at the National College of Hydraulic Agriculture in Paris
- » Executive MBA from the the Instituto Panamericano de Alta Dirección de Empresa (IPADE) in Mexico City, one of the world's top-ranked business schools

COMMUNITY INVOLVEMENT

- » Executive Committee Policy Board for USD's Burnham-Moores Center for Real Estate
- » Chairman of the American Israel Public Affairs Committee in San Diego

REASON FOR JOINING LJI BOARD OF DIRECTORS

“The purpose of the Institute is fascinating, in particular their goal for everyone to live life healthy and I think they do excellent work for very good reasons. I've learned that the immune system either protects you or attacks you. They're researching how to get the best of it.”



Tina Nova

CURRENT POSITION

Co-founder, president and CEO of Genoptix, Inc., a laboratory diagnostics company specializing in blood cancers, and acquired by Novartis Pharmaceuticals in March 2011. Nova continues to serve as Genoptix president and CEO.

PAST PROFESSIONAL EXPERIENCE

- » Co-founded Nanogen, Inc., a provider of molecular diagnostic tests
- » Co-founded Selective Genetics in 1992, a biotech focused on eye diseases

EDUCATION

- » B.S. degree in Biological Sciences from UC Irvine
- » Ph.D. in Biochemistry from UC Riverside

COMMUNITY INVOLVEMENT & RECOGNITION

- » Board member of Rady Children's Hospital
- » Board member of Arena Pharmaceuticals and Adamis Pharmaceuticals
- » Former Board Member of the University of San Diego (USD)
- » Chair of BIOCOM, a major life science industry association, from 2001 to 2002
- » Business Leader of the Year Award from Cal State San Marcos
- » Ernst & Young Entrepreneur of the Year Award in life sciences
- » “One of the Top 10 Women in Biotechnology” by FierceBiotech news

REASON FOR JOINING LJI BOARD OF DIRECTORS

“As a scientist, I have long admired the La Jolla Institute and the incredible work that they accomplish. I also feel a kinship with their area of research. I've spent the majority of my career in oncology research. You can't think about cancer without thinking of the immune system.”

Join Us



Timothy Wollaeger

CURRENT POSITION

Managing Director of Sanderling Ventures, one of the oldest investment firms dedicated to building new bio-medical companies.

PAST PROFESSIONAL EXPERIENCE

» Vice President & CFO of Hybritech, Inc., San Diego's first biotechnology

company, which was acquired by Eli Lilly

- » Founded and served as general partner of venture capital firm, Kingsbury Capital
- » Helped found Columbia/HCA Healthcare Corporation
- » Founding general partner of Biovest, a venture capital firm
- » One of the founders of San Diego biotechnology companies: Pyxis, Biosite, Vical, Amylin Pharmaceuticals, Aurora Biosciences, Digirad, Senomyx, Althea Technologies, Sotera Wireless, and Chimerix (now headquartered in North Carolina).

EDUCATION

- » B.A. Degree in Economics from Yale University
- » M.B.A. from Stanford
- » Officer in the U.S. Navy for three years

COMMUNITY INVOLVEMENT & RECOGNITION

- » Board member for several Sanderling portfolio companies including, CalciMedica, and Chimerix
- » Chairman of the board of Sotera Wireless and Asteres
- » Ernst & Young Entrepreneur of the Year and Corporate Director of the Year
- » Lifetime Achievement Award from the San Diego Corporate Directors Forum

REASON FOR JOINING LJI BOARD OF DIRECTORS

"Why not do something that's interesting and positive? The Institute is an excellent group and I hope that my background in drug development can serve as a resource as they continue to develop and license their discoveries."

La Jolla Institute Membership

La Jolla Institute for Allergy and Immunology conducts groundbreaking and innovative research focused on understanding and optimizing the immune system—the essential component for maintaining human health and preventing a wide variety of diseases.

We are especially grateful for our annual donors and Members who share our commitment to focused research on the immune system and support our efforts to strive toward Life Without Disease.

Join the Search—Become a Member!

The Institute offers special benefits and opportunities for involvement to those who donate \$250 or more annually. These Membership levels and benefits are listed here:

Friends: \$250 - \$999

- Invitations to a stimulating series of community lectures describing the latest scientific discoveries at the Institute and their potential impact on human health
- Advance invitations to the Life Without Disease Lecture Series and reception events
- Subscription to the Institute's magazine *Immune Matters*
- Listing on the annual donor roster in the *Immune Matters* magazine

President's Council: \$1,000 - \$9,999

- All "Friends"-level benefits, plus:
- Listing on the Institute's permanent Donor Wall
- Private tour of the Institute
- Annual President's Council luncheon with Institute President Dr. Mitchell Kronenberg
- President's Council lapel pin
- Invitations to special presentations in private homes
- Advance notice of important Institute scientific discoveries and other news

Chairman's Circle: \$10,000 and up

- All "President's Council"-level benefits, plus:
- Private roundtable lunch with a scientist for up to four of your friends and family members, to ask all of your immune health-related questions

For more information contact Rachel Jonte at rjonte@lji.org or 858-752-6542.

La Jolla Institute

FOR ALLERGY AND IMMUNOLOGY

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for the latest news
and updates.

About La Jolla Institute for Allergy and Immunology

MOTTO: Life Without Disease.

MISSION: To understand how the immune system works, and to apply that knowledge to promote human health and prevent disease.

VISION: To become the world's preeminent scientific organization engaged in research on the immune system.

FOUNDED: November 14, 1988 in San Diego as a nonprofit 501(c)(3) public benefit corporation.

RESEARCH STAFF: 23 faculty investigators, 145 postdoctoral fellows and other trainees, and 180 technicians and support staff.

SCIENTIFIC PRODUCTIVITY: 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.

