LA JOLLA INSTITUTE FOR ALLERGY & IMMUNOLOGY

Immune Matters

FALL 2012

Inflammation & Heart Disease

The internal fire that's fueling America's No. 1 killer

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A conversation with one of the world's top scientists

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A sister's untimely death spurs remarkable research progress

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LA JOLLA INSTITUTE
for
ALLERGY & IMMUNOLOGY
9420 Athena Circle • La Jolla, CA 92037

The La Jolla Institute for Allergy and Immunology (LIAI) 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, LIAI has made numerous major advances leading toward its goal: life without disease.

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Letter from the President

It's no secret that heart disease kills more Americans each year than any other medical disorder including cancer. But what is not well known is that inflammation—driven by the immune system—is a critical player in the process that leads to heart attack and stroke.

In this issue of our newly redesigned publication, we have invited some major cardiovascular experts from our Institute and other leading medical organizations to comment on inflammation's pivotal role in heart disease and on efforts researchers are making to control its deadly impact.

One of the most exciting initiatives currently under way involves our scientist Klaus Ley, M.D., who is pursuing a first-ever vaccine for heart disease—a long-held dream among cardiovascular researchers that is now moving closer to reality.

This issue also goes Up Close with faculty member Hilde Cheroutre, Ph.D., a world leader in research on the immune system's activity in the intestines. Hilde's passion is to prevent cancer and other diseases, fueled by her sister's early death from colon cancer.

You'll also have the opportunity to hear from one of the world's most renowned scientists—Leroy Hood, M.D., Ph.D., a board member—who discusses his involvement with the Human Genome Project, one of the most significant scientific undertakings of the past century. Dr. Hood also comments on the power and promise of the immune system in fighting disease—a key reason he joined our Institute's board.

Our Institute is universally recognized as a world leader in the study of the immune system. We focus our efforts on the immune system because we believe that harnessing its power to preserve health holds the key to conquering heart disease, diabetes, cancer, and many other disorders that have long plagued humankind. We are grateful for the generosity of individual donors, foundations, and federal funding sources that enable our critical work to proceed and invite all of our supporters to share our pride as we move closer toward life without disease.

Sincerely,

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

P.S. We'd love to hear your thoughts on our new magazine format… please email Institute_Relations@liai.org with your comments.

Highlights

Top Ten

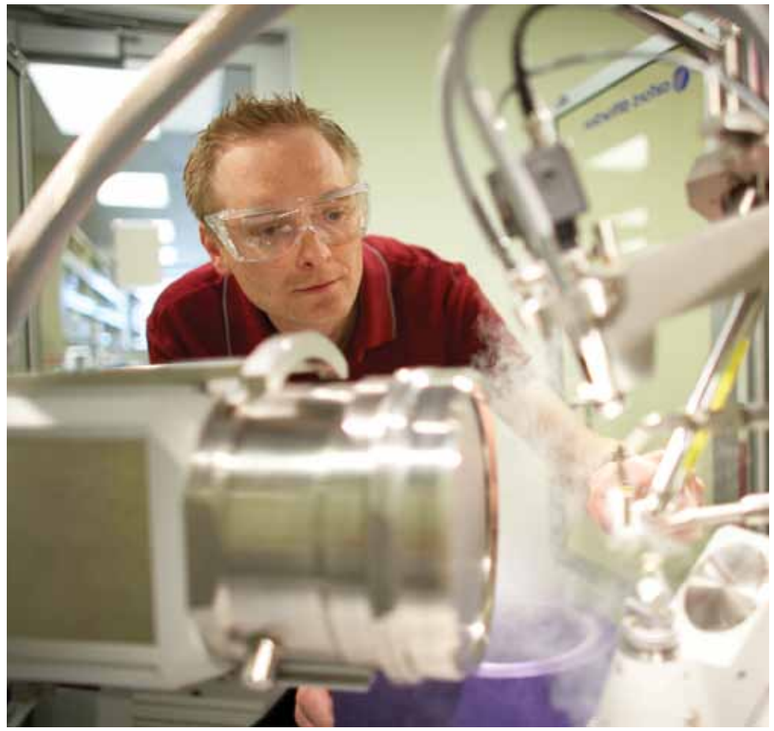
La Jolla Institute ranks among world's "Best Places to Work" in science.

For the second time this year, the La Jolla Institute has been ranked as one of the best places to work in the worldwide academic research community, according to surveys of research institutions conducted by *The Scientist* magazine.

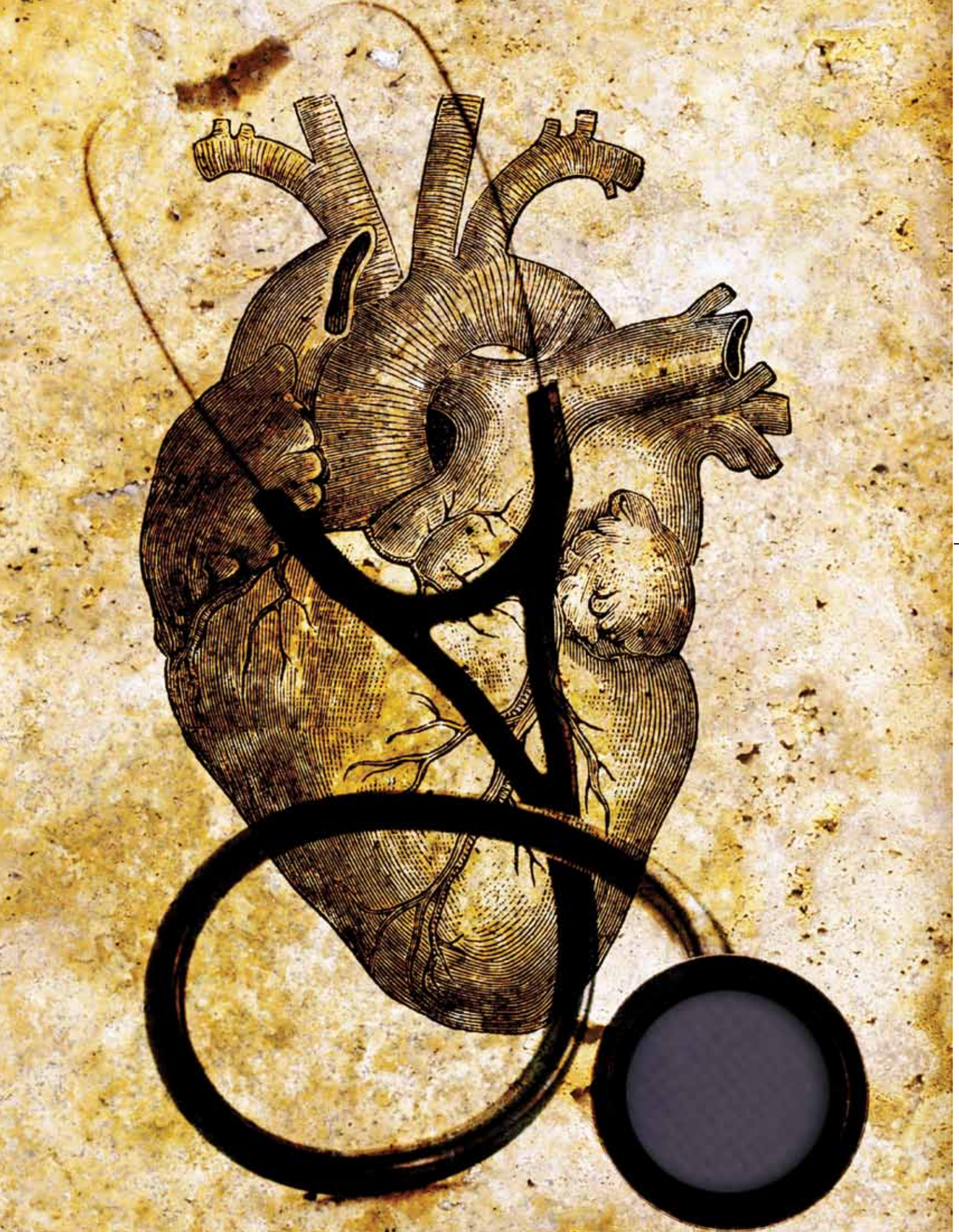
In the latest recognition, the La Jolla Institute ranked in the top 10 in *The Scientist's* annual "Best Places to Work in Academia" survey. The Institute came in at No. 6 on the list, which included such major institutions as Massachusetts General Hospital at No. 5 and St. Jude Children's Research Hospital in the No. 8 slot.

The "Best Places to Work in Academia" recognition comes on the heels of the La Jolla Institute's ranking as 7th in the nation for "Best Places to Work for Postdocs," announced by the *The Scientist* magazine in April. Postdoctoral fellows, called "postdocs," are researchers in training, who typically spend several years working under senior scientists.

"It's obvious that something very right is going on at the La Jolla Institute," said John Major, a prominent San Diego business executive who is Chairman of the Institute's Board of Directors. "These survey results are a reflection of the cutting-edge science and collegial environment that sets the Institute apart from many other research organizations."



Protein crystallographer Dirk Zajonc, Ph.D., operates the Institute's X-ray diffraction machine, a state-of-the art research tool that allows scientists to study molecular interactions at the atomic level.



Getting to the HEART *of the matter.*

Inflammation and Heart Disease. The fire within that's fanning the flames of our nation's top killer.

Your physician will probably tell you that high LDL cholesterol, high blood pressure, smoking, obesity, and a sedentary lifestyle are the major factors that increase the risk of a heart attack. But there's another serious threat often missing from this discussion—a force so powerful and insidious that many researchers now believe it may be one of the biggest cardiac dangers of all—inflammation. Yes, an internal fire—particularly the "smoldering" chronic variety—is fanning the flames of heart disease, a scourge that kills more Americans each year than any other disorder, including cancer.

"The scientific community used to think cholesterol alone led to plaque formation, but that is only part of the story," said Klaus Ley, M.D., a leading vascular immunologist and director of the La Jolla Institute's Inflammation Biology Division. "Research over the past 15 years has shown that inflammation is a major contributor to arterial plaque buildup, also known as atherosclerosis, which is the underlying cause of most heart problems."

Lynn Hedrick, Ph.D.

Thankfully, inflammation's key role in heart disease has become an important issue in the scientific community, and major strides are being made toward understanding and controlling its detrimental effects. In this article, cardiovascular leaders from the La Jolla Institute, Harvard Medical School, UC San Diego, and Scripps Health discuss some of the exciting approaches being explored.

How Inflammation Damages Our Arteries

Eric Topol, M.D., a renowned cardiologist and chief academic officer at Scripps Health, cites inflammation as "the major process by which arteries 'get sick,'" noting that inflammation greatly exacerbates the accumulation of cholesterol plaque. LDL, the so-called bad cholesterol, wreaks havoc

by leaving raw fatty deposits that slowly evolve into plaque on the inside of major coronary arteries. Then inflammation comes along and makes matters worse by fueling and destabilizing plaque buildup, says Dr. Topol.

Peter Libby, M.D., a Harvard professor and chief of Cardiology at Brigham and Women's Hospital in Boston, describes inflammation as a "transducer of risk factors," which doesn't replace traditional risk factors such as high blood pressure and cholesterol, but instead magnifies the initial problems they create. Notably, inflammation is believed to be the trigger that causes cholesterol-laden plaques to rupture, triggering formation of blood clots that impede blood flow, leading to a heart attack. "Inflammation is a central part of the process that leads to heart attack and stroke," says Dr. Libby.


Eric Topol, M.D.

Inflammation is so central to the process that its chronic presence can be used as an indicator of heart disease risk, adds Dr. Libby, whose colleague at Brigham and Women's Hospital Dr. Paul Ridker showed in 1997 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, in addition to total cholesterol and other factors.

Back to Basics—Inflammation's "Good Intentions"

The story of inflammation's role in heart disease might be more appropriately titled "Good Intentions Gone Bad." Inflammation is actually a good thing designed to promote healing, which one can witness as first hand 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." Trouble arises, however, when the inflammatory response is prolonged or shows up where it's not needed. In these instances, inflammation can harm body tissues.


Chris Glass, M.D., Ph.D.

Dr. Hedrick says that most researchers believe that much of the inflammation in heart disease is a response to cholesterol buildup in the arteries. "The endothelial cells lining the arteries perceive the LDL (bad) cholesterol as a problem or injury. So they send out chemical 'help" signals to recruit other cells to the site. It's the same process that occurs with a cut, where immune cells signal other cells to come and heal the wound."

However, the healing process can go awry. "It works for a while, but eventually the responding cells become overwhelmed and switch to become damaging cells that end up exacerbating heart disease. This is an area of major focus at the La Jolla Institute: what causes these otherwise helpful cells to become deleterious?"

Focusing on the Key Cellular Culprits

Most researchers agree that two immune cells produce most arterial inflammation—T cells, the body's cellular warriors, and macrophages, molecular scavenger hunters that survey the body, ridding it of viruses, bacteria, and other unwanted cells.

In a major recent finding, Dr. Ley identified the specific T cell type involved in the inflammatory attack. Presently, he is working on the possibility of a vaccine for heart disease that would stop the T cell onslaught by teaching the body to tolerate rather than destroy cells in the arterial wall. "That would fulfill a dream—an effective vaccine that prevents heart attacks," says Dr. Topol of the finding. (See related story, next page).


Peter Libby, M.D.

Other research efforts are aimed at taming the macrophages. "In the arterial wall, macrophages move in like a cleanup crew trying to eat up the fat (cholesterol)," said Dr. Hedrick. "Somewhere along the way, this normally positive function turns destructive. The macrophages start accumulating fat and get bogged down in the arteries where they fuel inflammation."

UC San Diego scientist Chris Glass, M.D., Ph.D., notes that macrophages are so important in heart disease that "studies in mice suggest that if you don't have macrophages you don't have atherosclerosis." Both Dr. Glass and Dr. Hedrick have recently made important findings on potential ways of controlling the macrophage's detrimental effects.

The Statin Drugs

In the 1990s, cholesterol-reducing statin drugs (e.g., Lipitor, Crestor, and many others) began to appear and now are among the most widely prescribed drugs in the world. Statins | *Continued on page 8* >>

A Vaccine for Heart Disease?

La Jolla Institute discovery advances long-held dream.

Creating a vaccine to prevent heart disease is a concept that has been kicked around the scientific community for years—more dream than possibility.

But a recent finding by La Jolla Institute scientist Klaus Ley, M.D., has taken a major step toward making that dream a reality.

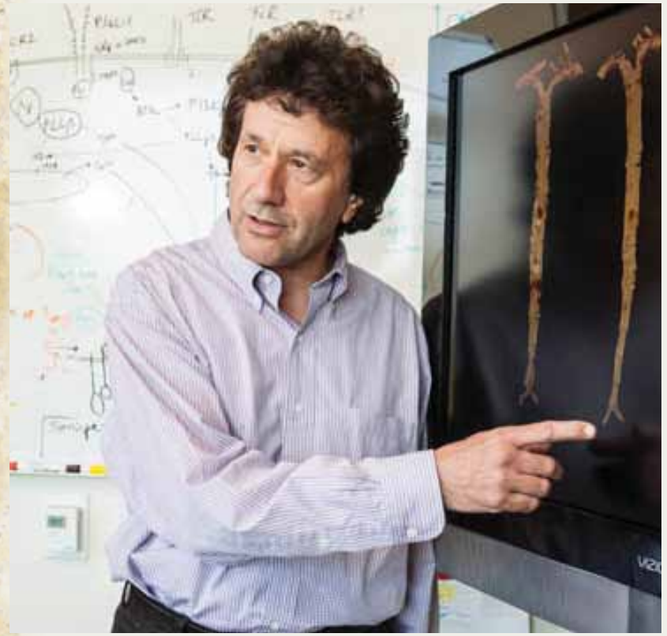
Dr. Ley identified the specific immune cells that orchestrate an attack on the artery wall, producing inflammation which is a major contributor to heart disease. Further, he found that the attack is launched against normal proteins that the body mistakenly perceives as foreign, essentially an autoimmune reaction like those that cause rheumatoid arthritis and other disorders.

"This strong autoimmune component means we can explore creating a "tolerogenic" vaccine, such as those now being looked at in diabetes, which could induce tolerance by the body of this self-protein to stop the inflammatory attack."

Eric Topol, M.D., a prominent cardiologist and chief academic officer of Scripps Health, praised Dr. Ley's finding, noting it advances the potential for a vaccine by pinpointing the most important cellular players. "This is quite an important discovery," he said. "There are so many biologic mediators of the inflammation process, and it is critical to understand which ones are especially dominant, driving factors."

Dr. Topol added that a vaccine would be "an ideal way to prevent atherosclerosis—the main culprit of heart disease."

These photos show early data from Dr. Ley's work toward a vaccine for heart disease. The images show two mouse arteries with plaque buildup (plaque lesions stained red). In the right image, the mouse has been inoculated with Dr. Ley's test vaccine, resulting in a significant reduction in plaque lesions. The other mouse received no vaccine. Arterial plaque buildup, caused by inflammation, cholesterol and other factors, is the underlying cause of most heart problems.


Klaus Ley, M.D.

Continued from page 6 | are credited with producing a striking reduction in heart disease deaths nationwide—nearly 30 percent.

Beginning in the 1990s, Dr. Libby and his research partner Dr. Paul M Ridker have conducted some major studies on statins, showing that statins not only reduce cholesterol but also reduce inflammation. Their continued efforts in the JUPITER clinical trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) have demonstrated that statins could decrease the rate of the first major cardiovascular events in people with chronic, elevated inflammation who otherwise have normal cholesterol levels. Indeed, half of all heart attacks occur in people with normal cholesterol levels.

"We found that, if you applied inflammation biology to people, you could save lives," said Dr. Libby. The trial's results, published in 2008, were met with both acclaim and controversy as they raised the question of whether statins should be broadly prescribed as a preventive measure against heart disease to people with chronic inflammation and normal cholesterol. The subject remains under debate and has been further complicated by recent reports that statins can increase the risk of diabetes. Dr. Libby maintains that the statins' potential life-saving benefits outweigh any diabetes risk.

Meanwhile, Dr. Ridker and Dr. Libby are exploring other inflammation-reducing drugs' potential in heart disease, having recently launched a trial of low-doses of methotrexate, which is widely prescribed for rheumatoid arthritis, and another trial that targets a pro-inflammatory messenger known as interleukin-1 beta. "We'll let you know what we find in four or five years," he said. ■

Dr. "Mimi" Guarneri at the Scripps Center for Integrative Medicine Offers Tips on Eating for Better Health

Chronic inflammation has now been linked to some of America's deadliest diseases, including heart disease, diabetes, stroke, some cancers, and even Alzheimer's. While many factors influence inflammation, lifestyle issues such as obesity, unhealthy diet, and stress also feed internal fires, says Erminia "Mimi" Guarneri, M.D., founder of the Scripps Center for Integrative Medicine, which combines conventional and complementary medicine. Dr. Guarneri said there is growing evidence about the anti-inflammatory properties of many foods. Based on this, she provides the following tips for healthy eating:

- **Eat plenty of fruits and vegetables. Green leafy vegetables—kale, broccoli, and brussel sprouts—are particularly good.**
- **Eliminate trans fats (found in vegetable shortenings, some margarines, crackers, cookies and other foods made with or fried in partially hydrogenated oils).**
- **Eat a good source of omega-3 fatty acids, such as fish or walnuts. Dr. Guarneri says remember "SMASH" (sardines, mackerel, anchovies, wild sockeye salmon, herring) are the fish highest in omega 3's.**
- **Eat foods low on the glycemic index. Avoid refined carbohydrates (pasta, white bread, etc.) and sugar. Switch brown rice for white rice and eliminate soda, fruit juice and alcohol.**
- **Eat plenty of whole grains such as brown rice, quinoa, and bulgur wheat.**
- **Eat lean protein sources such as chicken (use organic); cut back on red meat, full-fat dairy foods and other sources of saturated fats.**
- **Spice it up. Ginger, turmeric, rosemary, and basil can have an anti-inflammatory effect.**

Mimi Guarneri, M.D.

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News & Notes

Flu Hospitalizes 200,000 Americans Each Year

La Jolla Institute scientists urge flu vaccination—"It's the responsible thing to do."

It's that time of year again when that most unwelcome of visitors—the influenza virus—begins clobbering our friends, neighbors and loved ones, giving the non-vaccinated among us pause.

The good news is that it's not too late to get the vaccine, since flu season typically peaks in February and can last as late as May. What's another good reason to get vaccinated? "It's the responsible thing to do," said Alessandro Sette, Ph.D., director of the La Jolla Institute's Center for Infectious Disease and an internationally recognized leader in vaccine biology.

Alessandro Sette, Ph.D.

"We do not live on an island and the decisions we make can affect our loved ones and the people we interact with socially and at work," he said, noting that influenza poses a greater risk to certain groups, including the elderly, young children, and pregnant women. People with certain health conditions like asthma, heart disease and cancer are also more vulnerable. "Failing to vaccinate contributes to the spread of the germs, and it is the least responsible thing to do. Likewise, if one feels sick, they should stay home and not expose coworkers to infection."

La Jolla Institute scientist Bjoern Peters, Ph.D., a bioinformatics expert who studies viruses, said the problems caused by lack of vaccination not only relate to influenza, but to diseases like measles, which once was eliminated in the United States. "We've seen some measles flare-ups over the last few years, primarily due to unvaccinated people going to other countries and bringing the disease back to the U.S. and spreading it to others," he said.

Bjoern Peters, Ph.D.

According to the Centers for Disease Control, 222 measles cases and 17 measles outbreaks were reported in the U.S. in 2011. "This clearly illustrates the importance of vaccination," said Dr. Sette, noting that measles can lead to serious complications and death, an outcome that is also possible with influenza. Indeed, between 3,000 and 49,000 Americans die annually from the flu (depending on the severity and length of the season) and more than 200,000 are hospitalized.

Dr. Peters urged people to get vaccinated sooner rather than later, since it takes at least two weeks after flu vaccination for protective antibodies to develop.

Klaus Ley to Head North American Vascular Biology Association

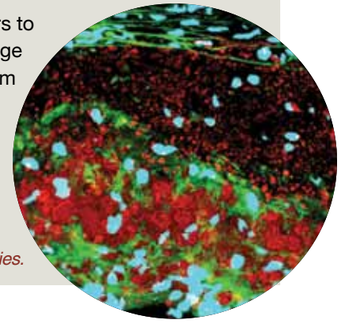
Klaus Ley, Ph.D., head of the La Jolla Institute's Division of Inflammation Biology, has been elected president of the North American Vascular Biology Organization (NAVBO), an association of more than 700 scientists worldwide working to promote research on the vascular system.

The vascular system, also called the circulatory system, delivers oxygen-carrying blood throughout the body. Heart attack, stroke and peripheral arterial disease are examples of vascular disorders.

"It's exciting to help shape vascular biology research at a national level," said Dr. Ley, a pioneering vascular immunologist, who assumes the President's position in 2013.

The organization provides a forum for members to share information and knowledge and to encourage the translation of vascular biology discoveries from basic science to clinical practice.

NAVBO supports and organizes meetings and workshops, including the national conference, a premier event in the field of vascular biology.



Fat (red areas) and inflammation-producing macrophages (green areas) shown in the arteries.

Shane Crotty to Play Key Role in Major AIDS Vaccine Initiative

Shane Crotty, Ph.D., a La Jolla Institute scientist recognized for his groundbreaking work in vaccine design, will participate as a key member in a major new center focused on using the immune system to fight HIV, the virus that causes AIDS.

The Center for HIV/AIDS Vaccine Immunology & Immunogen Discovery (CHAVI-ID), to be led by the Scripps Research Institute, will focus the collective talents of vaccine biology experts from several major U.S. research institutions. The multi-disciplinary team will work toward the development of an AIDS vaccine to prevent HIV infection, and also on ways to control the virus once an individual is already infected. The National Institutes of Health awarded Scripps a $77 million, seven-year grant to fund the Center's activities.

"For more than three decades, the scientific community has worked toward developing an AIDS vaccine," said Dr. Crotty. "This is a huge opportunity to fulfill that vision."

As a key team member, Dr. Crotty will contribute his significant knowledge on vaccine mechanisms, particularly his understanding of antibody production, which led to his landmark discovery in 2009 of the molecular trigger for generating potent antibodies. Antibodies are the body's disease-fighting warriors and the basis for most vaccines.

"Our earlier studies showed that follicular helper T (Tfh) cells are essential to the production of antibodies," said Dr. Crotty. "The next step is figuring out the best way to boost Tfh cell development to enable a good antibody response and a good vaccine, not only for HIV, but other dangerous pathogens for which we still have no vaccine."

Shane Crotty, Ph.D.

LA JOLLA INSTITUTE POSTDOC NEWS

Stephanie Stanford Receives Diabetes Research Fellowship

Stephanie Stanford, Ph.D, a postdoctoral researcher in the La Jolla Institute laboratory of Nunzio Bottini, M.D., Ph.D., has been awarded a three-year JDRF fellowship to fund her continued work toward a sophisticated new approach to target genes underlying the development of type 1 diabetes.

Type 1 diabetes is caused by an improper immune response, resulting in the elimination of beta cells in the pancreas by T cells. In recent years, a number of gene mutations have been identified that increase the risk of this occurring. These are Stephanie's targets.

Her approach will be utilizing antisense therapy, a method of introducing specialized strands of DNA, called oligonucleotides, into activated T cells. The strands bind to the targeted genes and effectively silence them without creating unwanted side effects.

The work Stephanie is undertaking takes advantage of newly developed technology, and is an exciting example of the momentum immune research is gathering. The potential benefits range from reversing the disease in recently diagnosed patients, to adding a new treatment option for combination therapies.

UP CLOSE Hilde Cheroutre, Ph.D.

A Sister's Tragic Death Fuels Quest to Prevent Cancer and Other Diseases

Every one of Hilde Cheroutre's scientific papers ends with thanks for "contributions" from M. Cheroutre—a name unknown to most readers. These contributions don't refer to technical assistance, a hard-to-find molecule, or special funding, but rather to an intangible gift that might best be called "inspiration," or perhaps even more accurately, "love."

"M. Cheroutre" is actually Marieke Cheroutre, Hilde's younger sister, who died in 1998 from colon cancer. Marieke's untimely death is the reason Hilde chose to study the immunology of the intestines, an area in which she is now regarded as one of the leading authorities in the world. Marieke is also the impetus behind Hilde's passion for finding ways to prevent cancer, inflammatory bowel disease, celiac disease, and other intestinal disorders.

Hilde Cheroutre, Ph.D.

"There isn't a day that goes by when I don't think of Marieke," Hilde said. "I thank her in every scientific paper because I feel that she's always helping me."

Cherished Memories

Growing up in Belgium, Hilde and Marieke were more like twins than regular sisters. Only a year apart, the two were nearly inseparable—biking to school together, studying together, laughing together, trading secrets as young girls do, and even sleeping in the same small bed.

"Marieke was much better in languages than me, but then I was good in math and physics so we'd do each other's homework," recalls Hilde with a laugh. "We had all these secrets and agreements…things we said to each other that no one else would understand."

Their special bond endured into adulthood. And when Marieke died in the prime of her life at age 40, she left behind a husband, two children, and a big loving family. "She wasn't gone from our hearts or forgotten," said Hilde. "I felt her closer than ever and from that day on I was determined to unravel the cellular mysteries that robbed Marieke, and millions like her, of many years of life."

The Road to Scientific Prominence

Hilde is one of eight children born to her "go-getter" engineer father and her elegant, serene mother. Her parents emphasized honesty and always "doing the right thing." The Cheroutre children also knew the value of hard work, spending summers working in the family's small yarn shops as a way to help make ends meet. Hilde and her sisters took in requests for garment making, continually knitting sweaters, skirts and so on.

Hilde excelled in school, particularly science and math, and attended the University of Ghent in Belgium to study botany and cellular biology, which led to her first encounter with genetics. "I loved it and was so happy when I got an opportunity to work in a lab," she said. She eventually earned her doctorate in Molecular Biology in 1984, graduating with highest honors, and moved to the U.S. later that year.

Hilde's early work in genetics laid the groundwork for her doctoral thesis, which she presented as a graduate student at a major scientific conference in the U.S. There Hilde wowed attendees with her identification of the gene encoding human interferon gamma, a major mediator of immune responses. "My presentation got a lot of attention at the conference. I met Lee Hood (current La Jolla Institute Board member) there and he invited me to work in his lab at Caltech."

Above: Hilde and Mitchell Kronenberg (center) and their sons (from left) Samy, Daniel, and Benjamin.

Family and Research Walking Hand in Hand

At Caltech, she met current La Jolla Institute President Mitchell Kronenberg, who was a post-doctoral Fellow in Lee Hood's lab at that time. Today, they have been married 26 years and have three wonderful sons, Daniel, 24, Samy, 22, and Benjamin, 19. Initially, Hilde worked with Mitch in his lab at UCLA, but when they moved to LIAI in 1998, then-Institute President Howard Grey, M.D. offered Hilde her own lab. She accepted and took on the challenge of combining the functions of a busy mom at home with those of building a strong research team at the Institute. She devoted her lab's study to intestinal problems, such as those that took the life of her 40-year-old sister that same year.

"It felt as if I had two families, one at home and one at the Institute," said Hilde. "It wasn't always a breeze and there were difficult moments and times when the next step was not certain. I could never have kept everything straight if it weren't for the unconditional love and support from Mitch and the great joy and happiness we receive from our children. I also had the good fortune of working with incredible researchers over the years that contributed and are still contributing to the continuous advances and successes of our research family at the Institute."

Marieke Cheroutre

"There isn't a day that goes by when I don't think of Marieke. I thank her in every scientific paper because I feel that she's always helping me."

Bucking Conventional Wisdom

It wasn't long before Hilde and her team were finding new insights that sometimes ran counter to conventional wisdom. Her first paper, as lab head, contradicted current thinking on T cell development in the gut, and it ruffled a lot of feathers among scientific leaders. Getting the paper published proved extremely difficult, but she endured. "I had to. I had proved my finding in many different ways. I knew it was true." Today, her discovery is recognized as a breakthrough in the understanding of disease processes in the intestines.

It was the first of many novel findings by Hilde, who is now a world-renowned thought leader in the field.

Architecture in her Spare Time

With two of her sons recently graduated from college and the youngest now attending the University of Colorado, Hilde now spends a little more of her free time on her other passions—architecture and fitness. For Hilde, maintaining a healthy body and mind involves regular 8-mile runs, biking and nightly Sudoku puzzles. Architecture, meanwhile, is a hands on endeavor. "I've designed a new addition to our house," said Hilde proudly.

As with everything in her life, Hilde approaches architecture with great enthusiasm. "Architecture is so important throughout history," she said. "Without the ability to create structures, we wouldn't have hospitals, train stations and schools, no meeting places for exchanging ideas."

"Everything happens in buildings," she added. "It's such an important, but taken for granted achievement of humanity."

Hilde thinks the same curiosity that hooked her on science—to try to understand how things fit together and create the whole picture—probably fuels her architecture interest. That interest hasn't dampened her passion for research, which recently received a prestigious national boost.

National Award for Visionary Approaches

In 2009, Hilde was one of a small, select group of scientists nationwide chosen for the Pioneer Award, presented by Francis S. Collins, director of the National Institutes of Health and the nation's top scientific leader. Hilde and 17 other highly creative scientists received major grants to fund their out-of-the-box ideas for solving major human health issues.

Hilde's idea of a mechanism to identify and treat autoimmune diseases at birth received an award of $5 million over five years.

Three years into her grant, Hilde says early data suggests that her theory—that certain cellular defects underlie autoimmunity—is correct. More work needs to be done, but Hilde remains optimistic and excited.

Her sister would undoubtedly be proud. ■

Q&A

A conversation with one of the world's top scientists

VISIONARY AND LA JOLLA INSTITUTE BOARD MEMBER: LEROY HOOD

In 2009, ***Rolling Stone*** magazine named Leroy Hood, M.D., Ph.D., "One of the 100 people who are changing America." This accolade comes with good reason. An inventor and visionary, Dr. Hood's key role in developing several pioneering technologies, most notably the automated DNA sequencer, has profoundly altered the face of human health and redefined "possible" in genomics research.

Dr. Hood's roster of accomplishments places him in an elite group of scientists. He is one of only seven scientists, out of more than 6000 nationwide, elected to all three branches of the National Academies of Sciences and Engineering. He is also the recipient of the renowned Lasker award, often called the "American Nobel Prize," and he received the prestigious Kyoto prize in 2002. His DNA sequencer is credited with enabling the Human Genome Project to proceed by radically transforming sequencing speed, making it possible to process in one day what once took one hundred scientists a year to complete. Dr. Hood has been featured in *Forbes*, *Newsweek*, and the *New York Times* and counts Microsoft co-founder Bill Gates among his friends.

A former professor at Caltech and the University of Washington, Dr. Hood is currently the Founder and President of the Institute for Systems Biology in Seattle, a first-of-its-kind endeavor he established in 2000 to tear down scientific silos and promote cross-disciplinary research for the betterment of human kind. He has served on the La Jolla Institute Board of Directors since 2009.

In this wide-ranging interview, Dr. Hood discusses the future of biomedicine, his current undertaking, and why the immune system is important in so many diseases.

Q: When were you first bitten by the "science bug"?

A: It was during the 1950s as a student at our small high school in Shelby, Montana. I had outstanding mathematics and chemistry teachers and their love of their subjects was infectious. As a senior, the chemistry teacher asked me to help him teach biology to sophomores, which I did using articles from *Scientific American*. One article was on the structure of DNA, discovered just three years earlier in 1953. Even at that young age, I was very taken by the elegance of the molecule, and I think that helped turn me toward a career in biology.

Q: That early fascination with DNA seems to have foreshadowed your later role in the Human Genome Project, a monumental scientific initiative that identified the 20,000 to 30,000 genes in human DNA. How would you describe the Human Genome Project in terms of its significance?

A: I would say it probably was one of the most transformational projects in biology the world has ever seen. In fact, I could go through and give you a list of 15 or 16 really significant things that it did. I think three of the most important are, number one, it democratized genes. That is, it made all genes available to all biologists. Two, it gave us a complete parts lists of genes and, therefore, we could carry out systems biology. And three, it drove the emergence of enormously important technologies.

Q: From your perspective, what were the greatest surprises to come from the Human Genome Project, and what were the major disappointments, if any?

A: I think the greatest surprise for me was the enormous animosity that 90% of the biologists that I spoke to initially felt toward this project when we started talking about it in the mid-1980's. What it said to me is how conservative most biologists are and, in fact, even the National Institutes of Health was initially opposed. The project was labeled as "big science" and, at the time, there was still a lot of opposition to that idea.

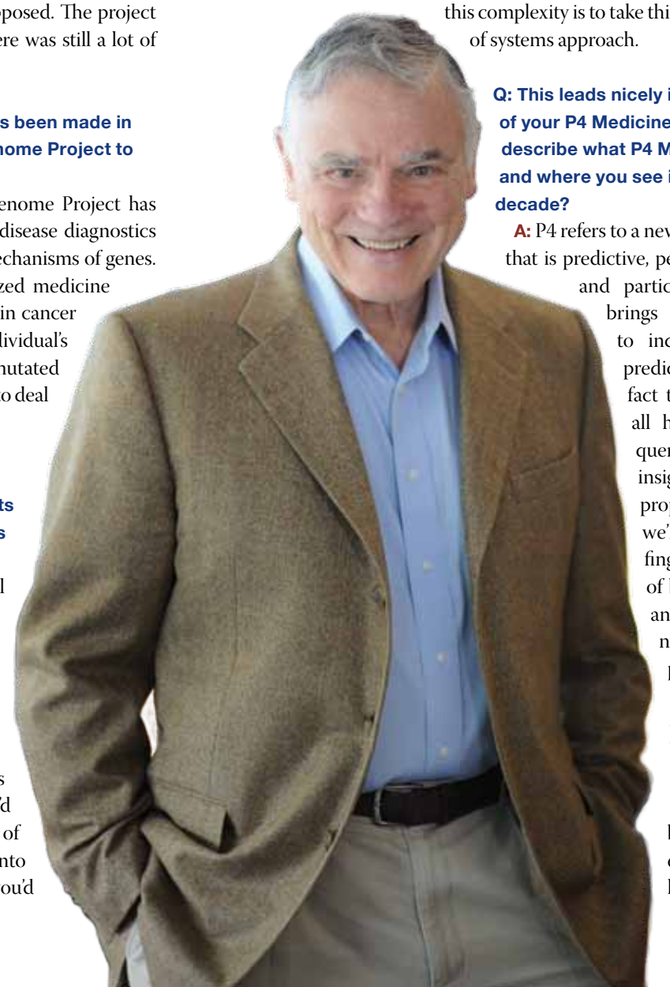
Q: How pleased are you with progress that has been made in applying new knowledge from the Human Genome Project to combat disease?

A: I'm really pleased. I think the Human Genome Project has given us the tools for transforming the field of disease diagnostics and for beginning to understand in detail the mechanisms of genes. In fact, the most recent advances in personalized medicine have come from gene sequencing. For example, in cancer biology, they've shown that by sequencing an individual's tumors, you can understand which genes have mutated and, in some cases, actually select effective drugs to deal with the genes.

Q: In 2000, you cofounded the Institute for Systems Biology in Seattle, the first center of its kind in the world. Can you explain the systems approach and why it is important?

A: Systems biology advocates studying all the elements in a system rather than studying one gene or one protein at a time, as biologists have done for the past 30 years. I'll give you an analogy. If you wanted to figure out how a radio converts radio waves into sound waves, you would take the radio apart and assess the individual parts and try and learn what they do. This approach is classic small science biology. But you'd realize from those studies that you haven't a wit of an idea of how that conversion of radio waves into sound waves actually occurs. So the next thing you'd have to do is assemble those parts into their circuits and to learn individually and collectively how the circuits carried out this conversion.

It works the same in living organisms. Living organisms have their biological circuits or networks that mediate information. The way to really understand how those systems work is to take them apart to learn the individual components and then put them back together, so you can understand how those networks transmit information to the molecular machines that actually execute the functions of life. Biology and disease are enormously complex, and the only powerful way to decipher this complexity is to take this kind of systems approach.



"...and hence the focus of medicine in the future has to be on the individual rather than on populations of individuals."

Q: This leads nicely into the discussion of your P4 Medicine concept. Could you describe what P4 Medicine is all about and where you see it going over the next decade?

A: P4 refers to a new approach to medicine that is predictive, personalized, preventive, and participatory. P4 Medicine brings the systems approach to individual patients. The predictive has to do with the fact that, in ten years, we'll all have our genomes sequenced and get enormous insights into our individual propensity for disease. Or we'll be able to prick our finger and from a droplet of blood be able to follow any transition from wellness into disease. The prevention part of P4 is new approaches to drug targets, which will be increasingly focused on wellness. The personalized side comes because, on average, we each differ by six million nucleotides from one another and hence the focus of medicine in the future has to be on the individual rather than on populations of individuals. And the fourth piece, the most difficult, the participatory, is creating the patient-activated social networks that I think will be the real drivers for acceptance of P4 Medicine.

Q: What do you view as the most important scientific advances in biology and medicine of the past half century?

A: I would say the sequencing of the whole human genome was a very, very important achievement. Also, the development of automated technologies that can capture many different types of information along with the development of analytic tools that allow us to mine, in a predictive sense, all this information. I also think the ability, and this is just emerging now, to analyze single cells is going to be absolutely revolutionary. The other technology that needs to be mentioned is the ability to do DNA sequencing in a cheap, rapid and very accurate manner that will eventually enable its widespread use in individualized health care. By applying this to a large number of people, I think this will be transformational and really impact our ability to decipher and address human disease.

Q: What led you to decide to serve on the La Jolla Institute's Board of Directors?

A: Frankly, the primary reason is my friendship with (La Jolla Institute President) Mitch Kronenberg and my deep affection for him. I'm enormously busy, but I've known Mitch for 30 years since he was a graduate student in my lab at Caltech. He was an exceptional graduate student and took on some really challenging problems and became a very central figure in my lab. I think it is both a respect for Mitch as a person and a respect for Mitch as a scientist that has created this enduring bond.

My second reason for joining is that I think the La Jolla Institute is a wonderful institute and that immunology is an extremely important discipline. Immunology, in fact, has been a central theme in my biological career and I think there's real value in having an institute focused exclusively on its study. The immune system is one of the deepest and most fundamental defense mechanisms that higher organisms have, and it interfaces directly or indirectly with virtually every type of disease. It's incredibly complex and enormously diverse in its operation, and has major implications for understanding health and improving medicine. ■

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Understanding the Immune System's Extraordinary Power in Health and Disease

The immune system is a vast network of cells that holds the amazing power to keep us well or make us sick. Composed of more than a trillion cells circulating throughout the body, the immune system offers one of the greatest scientific avenues for improving human health. In fact, the leading disease killers of Americans today (including heart disease, cancer, and chronic lower respiratory diseases) are caused largely or entirely by the immune system's failure to function properly.

And yet most of us only think of the immune system when catching a cold. But to researchers at the La Jolla Institute who are unmasking its mysteries to combat a multitude of diseases, its inner workings are a biomedical puzzle of vast importance. "Most people understand that our immune system protects us from colds, flu, and life threatening infections," said Mitchell Kronenberg, Ph.D., president & chief scientific officer. "But they may not realize the central role it plays in a vast array of other disorders—including heart disease, stroke, diabetes, and a large group of disorders known as autoimmune diseases. Dr. Kronenberg said autoimmune diseases result from the immune system's mistaken attack on healthy tissues, and affect up to 8 percent of the U. S. population. They include such disorders as type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease. Allergies and asthma also result from inappropriate immune responses. "This is the dark side of the immune system, which actually causes many terrible diseases," said Dr. Kronenberg. "On the other hand, the immune system is our defender against viruses and other foreign invaders. It's a yin and yang situation."

Dr. Kronenberg said Institute scientists are working to boost the helpful side of the immune system through the development of vaccines and cancer therapies, and also to correct its destructive aspects. Both pursuits are critically important. "That's why our founders formed this research institute 24 years ago," he said. "They saw the immune system's extraordinary potential for improving human health."