Inflammation & Heart Disease
The internal fire that’s fueling America’s No. 1 killer
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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 underway 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 systems 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—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.

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.
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.”

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...
Immune matters

Immune matters (inflammation) are basically immune cells swarming to the injured first hand when you cut your finger. "The initial swelling and redness are a good thing designed to promote healing, which one can witness 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 problem 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.

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.

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 overwhelming, so that they 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).

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

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.
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8 tips for healthy eating:

Koyna Haako Kim
Counsyl, Inc.
Koyna Haako Kim, M.D.
Susan and John Major Donor
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Dr. “Mimi” Guarneri offers tips on eating for better health.

Dr. “Mimi” Guarneri at the Scripps Center for Integrative Medicine.

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.** Fish or walnuts. Dr. Guarneri also suggests adding rosemary, thyme, sage, and basil can have an anti-inflammatory effect.
- **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.

In 2008, we 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 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. Libby and Dr. Guarneri 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 five or four years,” he said. ■
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 cloaking 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.

“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. ”

“Flu causes serious complications and death, and an outbreak is possible with influenza. Indeed, between 3,000 and 19,000 Americans die annually from the flu (depending on the severity and length of the season) and more than 200,000 are hospitalized.”

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

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 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.”

The Center for HIV/AIDS Vaccine Immunology & Immuno- gen 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.

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.

Stephanie Stanford Receives Diabetes Research Fellowship

Stephanie Stanford, Ph.D, a postdoctoral researcher in the La Jolla Institute laboratory of Nunzio Iozzoti, 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.
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,” 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 advancement and successes of our research family at the Institute.”

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.

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.
I'm molecule, and I think that helped turn me toward a career in biology. In 1953. Even at that young age, I was very taken by the elegance of the was on the structure of DNA, discovered just three years earlier in . One article in terms of its significance? 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: 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 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: If you could 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 well- ness into disease. The prevention part of P4 is new approaches to drug targets, which will be increasingly focused on wellness. The per- sonalized side comes because, on average, we each differ by six mil- lion 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 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.

Q&A

A conversation with one of the world’s top scientists

VISIONARY AND LA JOLLA INSTITUTE
BOARD MEMBER: LEROY HOOD

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 important achievement. Also, the development of automated tech- nologies 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 oth- er 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 trans- formational and really impact our ability to decipher and address human disease.

Q: What is your 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 have to do is assemble those parts into their cir- cuits and to learn individually and collectively how the circuits carried out this conversion. It works the same in living organisms. Living or- ganisms have their biological circuits or networks that mediate information. The way to really un- derstand 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 func- tions 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.

Q: How do you project the immediate impact of P4 Medicine? A: It works the same in living organisms. Living or- ganisms have their biological circuits or networks that mediate information. The way to really un- derstand 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 func- tions 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.

Q: What was the most influential scientific idea you ever learned? A: My second reason for joining is that I think the La Jolla Insti- tute 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 understand- ing health and improving medicine.
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.”