

# Immune Matters

SPRING 2013



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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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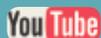
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## Letter from the President

Americans are living longer today than ever before in our history. The U.S. Census Bureau predicts that, by 2050, those 60 years and older will constitute 25% of our nation's population. While living longer is certainly good news, elderly Americans are more susceptible to infection and chronic diseases that can severely diminish their quality of life. Why? Because our immune system is less equipped to fight disease as we grow older. I'm happy to report, however, that there is plenty of room for optimism on the research front. In this issue of *Immune Matters*, you'll read the comments of experts from La Jolla Institute, National Institute on Aging, and other leading medical organizations regarding their promising research efforts to rejuvenate our aging immune systems.

Also in this issue, we discuss the emerging therapeutic potential of the immune system in fighting cancer. After years of debate, this approach has finally come of age and immune therapies are blazing a new trail in the ongoing battle to combat one of the world's most challenging diseases.

This issue of *Immune Matters* also describes two members of our Board of Directors who generously support our institute's efforts to understand and prevent disease: Leroy Hood, M.D., Ph.D., who recently received the National Medal of Science from President Obama; and Rick Kornfeld, an inventor and successful entrepreneur, who has played a pivotal role in the formation of San Diego's wireless industry.

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. But our research would not be possible without funding support from our individual donors, foundations, and federal sources. We wish to express our gratitude for this support which plays a critical role in our continuing efforts to achieve life without disease.

Sincerely,

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



## La Jolla Institute Board Member Leroy Hood Awarded National Medal of Science

### White House Recognizes Visionary Researcher With Nation's Highest Honor for Scientists

Renowned scientist Leroy Hood, M.D., Ph.D., a member of the Board of Directors of the La Jolla Institute, has been awarded the National Medal of Science, the nation's highest honor bestowed upon scientists.

President Obama presented the award to Dr. Hood and 11 other eminent U.S. scientists in a White House ceremony on February 1. "I am proud to honor these inspiring American innovators," said President Obama. "They represent the ingenuity and imagination that has long made this nation great."

An inventor and visionary, Dr. Hood is president and co-founder of the Institute for Systems Biology in Seattle, and has served on La Jolla

Institute's Board since 2009. His key role in developing several pioneering technologies, most notably the automated DNA sequencer, redefined "possible" in genomics research and made him a revered scientific figure worldwide. High speed DNA sequencers were central to the Human Genome Project, one of the most important scientific achievements of the past half century, which identified the 25,000 genes in human DNA.

Mitchell Kronenberg, Ph.D., La Jolla Institute president and chief scientific officer, said Dr. Hood's receipt of the national award is extremely well-deserved, noting his extraordinary record of scientific achievement. "Lee is a scientist whose work has truly changed the world," said Dr. Kronenberg. "Not only did his DNA sequencer enable the Human Genome Project to proceed, but he is also credited with launching the field of proteomics, the large-scale study of proteins—the body's amazing cellular workhorses—and with creating several technologies that form the core of modern molecular biology. Lee's expansive ideas have and continue to revolutionize the future of medicine, and we are honored that he is a member of our Board of Directors."

In a recent interview, Dr. Hood said his longtime friendship and respect for Dr. Kronenberg as well as his belief in the La Jolla Institute and its focus on immune system research, led him to join the Institute's Board of Directors.



**La Jolla  
Institute**  
FOR ALLERGY AND  
IMMUNOLOGY

**Life  
Without  
Disease.**

The Institute has recently adopted a new look and tagline. 'Life Without Disease' points to the Institute's goal that will be achieved through intensive and highly focused research on the body's natural power source for maintaining health and protection against disease: the immune system. The Institute is one of the world's top centers for immune system research, and boldly declares a vision of what harnessing the power of the immune system can mean: Life Without Disease.





## Can Scientists Turn Back the Clock?

From Infancy to Old Age—Our Immune System Never Stops Changing

The immune system—when it's working optimally—protects us from an onslaught of bacteria, viruses, and other pathogens. When it's not working properly, it contributes to allergies, chronic inflammation, and a laundry list of diseases. But we aren't just born with a full set of blueprints for fighting disease. The development of this incredibly complex system starts when an embryo is about five weeks old. Once it starts, the immune system never stops changing.

A baby is born with temporary immunity, borrowed from its mother *in utero* and through breast milk. This “passive immunity” slowly fades over the first six to eight months, but by this time the immune system has already been stimulated by germs in the environment and has begun producing its own protective antibodies. In fact, by the age of one, a child will already have adult-level immunity to some diseases. But this is just the beginning of the story.

### What causes immune aging?

Two major branches of our immune system collaborate to protect us from the billions of viruses, bacteria, and other pathogens we encounter during our lifetimes. Our first line of defense—known as our innate immune system—is made up of natural barriers (skin, mucous

membranes, etc.) and specific cells that keep harmful invaders from entering the body. For any pathogens that make it past this first barrier, a second line of defense—our adaptive immune system—takes over the fight.

Throughout life, our bodies are exposed to a variety of antigens (the cellular triggers that cause our immune system to react) causing us to adapt to the diseases we encounter and leading to a healthy buildup of antibodies.

Some of this exposure is the result of vaccinations—such as measles, hepatitis B, and tetanus—and some is a byproduct of illnesses, such as common colds and chicken pox.

In addition to antibodies, the ability of the immune system to function properly relies on a multitude of elaborately orchestrated

The ability of the immune system to function properly relies on a multitude of elaborately orchestrated cellular functions.

cellular functions involving organs and cells in the entire body, most notably T cells which develop in the thymus. T cells travel throughout the body, seeking out and destroying foreign, abnormal, and infected cells. Because of their key role in combating diseases ranging from flu to cancer, “the major focus in aging research has been on T cells,” says Mitchell Kronenberg, Ph.D., president and chief scientific officer, who leads La Jolla Institute’s renowned immunology research program, which focuses significantly on T cells. | *Continued on page 6* >>



Elderly individuals are at greater risk of dying of a new strain of influenza or an emerging disease.

tact with a strain of virus or another pathogen they haven't encountered before, they aren't able to launch a robust immune response. This is why elderly individuals are at greater risk of dying of a new strain of influenza or an emerging disease such as West Nile virus."

Indeed, about 90% percent of the approximately 36,000 Americans who die from influenza each year fall into the 65+ age group.

Also, the incidence of cancer, heart disease, diabetes, and chronic inflammation/autoimmunity also increases with age—all of which have strong links to our immune system.

Several clinical trials are showing promise for jump-starting T cell production in the thymus, while other research delves into the mechanistic problems that erode T cell function. More on that in a moment, but first, any discussion of immune aging is incomplete without mention of an insidious virus, well known to experts in the field.

### **Crafty Virus That Steals Years from Our Lives**

A virus you've probably never heard of—but that the majority of us carry—may be one of the single greatest purveyors of immune system decline. Once contracted, cytomegalovirus (CMV) never goes away, silently occupying the time and energy of our immune systems. This is because CMV is part of the herpes family of viruses that cause cold

The problem with T cells, say researchers, is that their numbers decline over time, gradually losing their gusto. "In your teens, your body decides you've made most of the T cells you'll ever need, and production begins tapering off. By the time you reach your 40s or 50s, the thymus stops producing T cells altogether," says Dr. Kronenberg.

Unfortunately, this leaves the body with an insufficient supply of "naïve" T cells, which are those geared to fight new, previously unseen infections. In addition, the T cells that do remain are weaker and slower to respond. "This presents a significant problem for the elderly," says Rebecca Fuldner, Ph.D., director of the National Institute of Aging's Immunology Program. "When elderly people come into con-

## Immune System Milestones

### IN UTERO

Immune system development begins in the womb. When an embryo is about five weeks old, this complex system begins to grow.



### BIRTH

A baby is born with temporary immunity borrowed from its mother and partially developed in utero. Very quickly the immune system begins to "learn" through exposure about the environment.



### INFANCY



Childhood vaccines begin at birth and continue over the next few years. In addition, germs in the environment start helping to stimulate protective antibodies and T cells.

sores, chicken pox, and other maladies. As we all learned in health class, ‘herpes is forever.’ Transmission is believed to occur through saliva, feces, and other body fluids and about 50 percent of Americans are infected by age 20, increasing to more than 80 percent by age 80. There is no cure and most people won’t exhibit symptoms, although research shows that the immune system stays busy keeping CMV at bay. Along with using immune resources, CMV also has the unfortunate distinction of being the nation’s number one infectious cause of congenital birth defects. Because of CMV, 1 in 750 children are born with or develop permanent disabilities such as hearing loss or brain damage.

How does a single virus wreak so much havoc? “It used to be thought that CMV lay largely dormant in the body, but new research is showing that its presence may tire our immune system over time,” says La Jolla Institute scientist Chris Benedict, Ph.D., an expert in CMV. Dr. Benedict says this erosion occurs over decades and can result in significant problems for people in their 60s, 70s, and 80s when trying to fight an infection.

Allison E. Aiello, Ph.D., associate professor of Epidemiology at University of Michigan School of Public Health, notes that some scientists believe that the immune system only has a certain amount of immunological memory available for the many pathogens we face. “A lot of those (memory) T cells become specific to CMV in order to keep it at bay,” she says. “Therefore we may not have as many T cell defenses available for other infections.”

Dr. Benedict said it’s estimated that approximately 10 to 20 percent of our T cell immunity may be used up fighting CMV.

As further evidence of its problematic nature, people infected with CMV have a 1.2 times greater rate of earlier death than those not infected, according to a major population study published in 2011 by Dr. Aiello. With this growing detrimental evidence, the search for a CMV vaccine is gaining traction, says Dr. Benedict, whose research has produced novel insights boosting vaccine development. “If we can control or prevent CMV, the potential to prevent birth defects and aid the elderly in fighting infection is enormous,” he adds.

### More Innovative Work to Rejuvenate the Immune System

Researchers are focused on a number of ways to boost immunity, in particular improving vaccine effectiveness in the elderly. “As people age their ability to respond to vaccines for new strains of flu, or new pathogens that begin to circulate, becomes compromised,” says Susan Swain, Ph.D., a professor at the University of Massachusetts School of Medicine and a leader in aging research. Statistics tell the story. “While 90 percent of young adults respond to vaccines, that response rate declines to around 40 to 45 percent after age 60,” says Jorg Goronzy, M.D., Ph.D., a prominent aging researcher from Stanford University School of Medicine.

Various approaches are being explored, including increasing vaccine dosage to bolster potency. Using | *Continued on page 8* >>

## TEENS

By puberty, the thymus starts slowing down production of T cells, the immune system’s most important disease-fighting cells. In your teens, your body decides you’ve made most of the T cells you’ll ever need, and production begins to slowly decline.



## 20s



In our 20s, 30s and 40s, T cells numbers are still plentiful and immunity remains strong.

## 50s

By our 50s, the thymus stops producing T cells altogether...this can lead to a shortage of “naïve” T cells, which are geared to fight new, previously unseen infections. With fewer available, combating the flu and other new infections gets harder by the time we enter our 60s.



## 70s



By our 70s and 80s, our immune system’s effectiveness has noticeably declined. We now have fewer T cells and those that do remain are weaker and slower to respond, making it tougher to launch a robust immune attack against infections. This makes leading a healthy lifestyle all the more important in our older years.



*Chris Benedict, Ph.D.*

If we can control or prevent CMV, the potential to prevent birth defects and aid the elderly in fighting infection is enormous.

this method, the CDC is offering a special flu vaccine for seniors for the first time this year. A second popular approach is using new adjuvants, special chemicals designed to boost vaccine protection.

A big part of this equation is B cell production of antibodies, a critical component for vaccine effectiveness. “We’ve found that the numbers and quality of B cells decrease with age along with their ability to be stimulated,” says Bonnie Blomberg, Ph.D., a professor at the University of Miami, who has identified the enzyme (AID) as a possible therapeutic target for improving B cell function. In addition, Dr. Blomberg has pinpointed autonomous B cell biomarkers in the blood that can predict a good vaccine response. “Using this information, it would be possible before a vaccine is given to test whether the individual should get a second dose or adjuvant,” she states, noting that this could improve protection.

Dr. Goronzy, meanwhile, discovered that an age-related increase in a specific protein inhibits the production of protective antibodies following vaccination. In a recently published study, he showed that blocking this protein could improve vaccine effectiveness in the elderly, but added that more testing is needed. “We need to keep tweaking the compound and testing it in mice to make absolutely sure it’s safe enough to try in humans.” Nonetheless, he acknowledges that these and other studies indicate that “it may someday be possible to pharmacologically counter aging’s effects on our immune systems.”

Other major efforts to boost vaccine protection are also under way. La Jolla Institute scientist Shane Crotty, Ph.D., nationally known for his research on vaccine mechanisms, notes that not all vaccines or other forms of immune memory decline with age. “We found that the smallpox vaccine may protect people 60 years after inoculation,” says Dr. Crotty, who has studied the smallpox vaccine extensively as many consider it to be the “gold standard” of vaccines. His research led to the discovery of a molecular trigger

for antibodies in 2009, considered a seminal advance in the field. He continues to study immune memory to determine how to build vaccines that provide better protection against infection, regardless of the recipient’s age.

Several other exciting research efforts focus on firing up dendritic cells, known as the sentinels of the immune system that alert T cells to the presence of viruses and other invaders.

Dr. Swain, a former La Jolla Institute board member who served on the National Advisory Council on Aging, showed in mouse models that aged T cell responses could be increased, and a good immune response restored, by inducing the body’s dendritic cells to make more interleukin 6 (IL-6), a molecule important for stimulating T cell immune responses.

Meanwhile Laura Santambrogio, M.D., Ph.D., a professor at Albert Einstein College of Medicine in New York, put antioxidants to the test to see their effect on the aging immune system. By injecting old mice with a potent antioxidant for two weeks, Dr. Santambrogio was able to reverse some of the effects of oxidative stress and improve immune response. While more study is needed, she says her results point to the possibility of one day using antioxidant therapy before vaccination to increase vaccine effectiveness in the elderly.

With childhood vaccines and ongoing studies such as these, there is hope for better health at both ends of the age spectrum. As a group, Americans are not only living longer but are healthier than generations past. And many are taking active steps to stay that way. Today, people of all ages recognize that exercise, eating well, and timely vaccinations can do much to stave off disease. ■

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# Latest Breakthroughs

at La Jolla Institute  
for Allergy and Immunology

## Discovery Continues La Jolla Institute's Rich History of Allergy Innovation

### Finding Could Lead to New, Safer Allergy Desensitization Therapies

Allergies are miserable, costly, and increasing in number while treatment options are limited. Fortunately, a path to a new allergy treatment has been discovered by La Jolla Institute researchers, who continue to make important allergy advances.

A team led by Bjoern Peters, Ph.D. has discovered a novel cellular approach that could translate into new, safer allergy desensitization immunotherapies. La Jolla Institute's cutting-edge expertise in bioinformatics and gene sequencing enabled this important finding. "We have discovered that allergens are much more complex than previously thought," says Dr. Peters, who looked at allergy reactions to timothy grass, a common cause of hay fever. "We've found different parts of the allergen that won't trigger a severe allergic reaction. By targeting these areas, we believe we can avoid the danger of potentially deadly reactions to immunotherapies."

The finding was published February 11 in the *Proceedings of the National Academy of Sciences*. La Jolla Institute scientist Alessandro Sette, Ph.D., was a major contributor. An estimated 50 million Americans suffer from hay fever, and treatment for allergies in the U.S. cost \$21 billion annually. Over the counter and prescription treatments abound, providing temporary relief, but only immunotherapy offers the possibility of permanently ending allergy symptoms.

Dr. Peters says that current immunotherapies work by exposing the body to increasing doses of the allergen. This gradually overcomes the allergic immune reaction, which at the molecular level is triggered by IgE, a type of antibody that recognizes parts of the allergen. This immune response is the same as normally used by the body to identify and neutralize unwanted invaders such as bacteria or viruses. People who are severely allergic can't use immunotherapy due to the risk of triggering potentially deadly antibody reactions such as anaphylactic shock, even with a very small exposure.

"People have previously studied those parts of timothy grass that cause the antibody reaction," says Peters. "Instead, we looked at the molecular pieces that cause T cell reactions." T cells are important disease-fighting cells, but they also help to establish and maintain antibody activity.

To their surprise, the researchers found pieces of timothy grass molecules that only trigger T cells and not IgE antibodies. "This opens the door to using these pieces to develop safer

T cell based immunotherapies that won't run the risk of triggering a potentially fatal antibody reaction," says Dr. Peters.

Dr. Sette says the research team's use of gene sequencing and bioinformatics enabled a more comprehensive look at the timothy grass allergen than ever previously undertaken. "Before it was a painstaking process—people looked at one protein (in the allergen) at a time," he says. "Now we can go in and sequence the entire set of proteins in grass pollens. This is enabling novel insights about new ways to treat allergies."

Mitchell Kronenberg, Ph.D., president and chief scientific officer, praised the finding as yet another important step in the Institute's rich history of allergy innovation. "A seminal discovery by two of our founding scientists changed the face of allergy research more than 40 years ago," he says, referring to the discovery of the immunoglobulin E (IgE) antibody in 1966 by Kimishige and Teruko Ishizaka, both M.D.s and Ph.D.s., who later helped launch the Institute.

"Dr. Peters' finding is a continuation of our tradition of exploring new approaches to improving the lives of allergy sufferers." ■

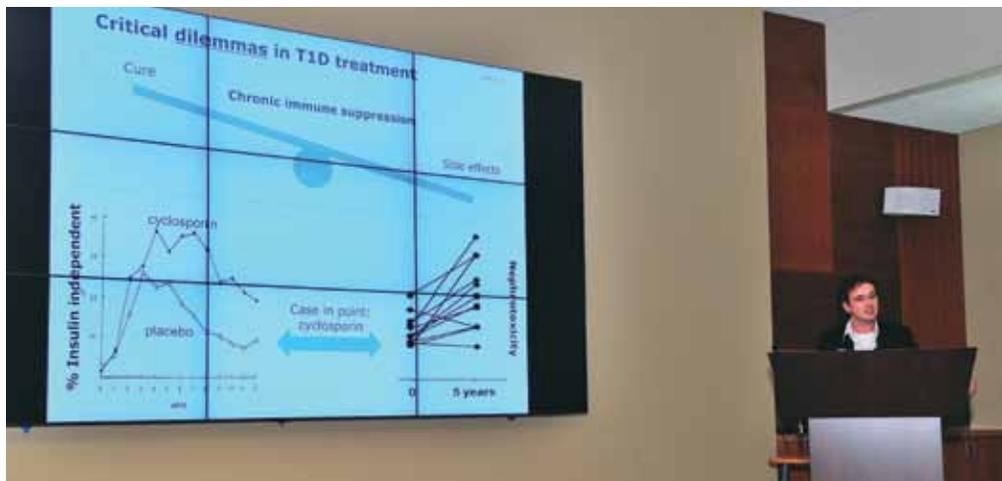


## JDRF “Meet the Scientists” Day at La Jolla Institute Draws Nearly 300

Saturday, March 2nd was a day of hope, learning, and fun at La Jolla Institute. The annual “Meet the Scientists” day, co-sponsored by La Jolla Institute and the Juvenile Diabetes Research Foundation’s San Diego chapter, brought together researchers and type 1 diabetes sufferers for a lively and educational event.

Nearly 300 children and adults with type 1 diabetes and their families got to meet scientists and learn more about their disease throughout the day, which was highlighted by laboratory tours, speakers, games, and other educational and fun activities. More than 3 million Americans suffer from type 1 diabetes, a life-threatening and chronic disease affecting children and adults. JDRF is the world’s leading funder of type 1 diabetes research and works with top research organizations like La Jolla Institute in hopes of one day finding a cure.

The San Diego Chapter of JDRF recently honored La Jolla Institute with a community partner award for their terrific collaborative efforts. Working together, both organizations are hopeful that through research, a cure may be found for this devastating disease.



**Clockwise from left: Dr. Matthias von Herrath presents the latest on the research front; lab tour participant has fun with science; an up close look at cells in the pancreas; participants have fun in the La Jolla Institute atrium.**



## Klaus Ley Receives American Heart Association Vascular

**L**a Jolla Institute scientist Klaus Ley, Ph.D. has been honored with a Special Recognition Award in Vascular Biology from the American Heart Association (AHA). The award was presented by the AHA’s Council on Atherosclerosis, Thrombosis and Vascular Biology at the AHA’s annual meeting in Los Angeles.

“This is a career award which recognizes Dr. Ley’s important contributions to the field of vascular biology,” said Council Chairman Nigel Mackman, Ph.D., director of the

McAllister Heart Institute at the University of North Carolina at Chapel Hill. Heart attack, stroke, and peripheral arterial disease are examples of vascular disorders.

A pioneering vascular immunologist, Dr. Ley is head of La Jolla Institute’s Inflammation Biology Division, which explores new ways to fight heart disease using the immense power of the immune system. His discoveries have shed new light on how inflammation worsens heart disease and stroke and revealed possible therapeutic mechanisms for reducing its detrimental effects in these disorders.



Photos by Rick Keller

## NEWS POSTDOCTORAL FELLOWS INSTITUTE LA JOLLA

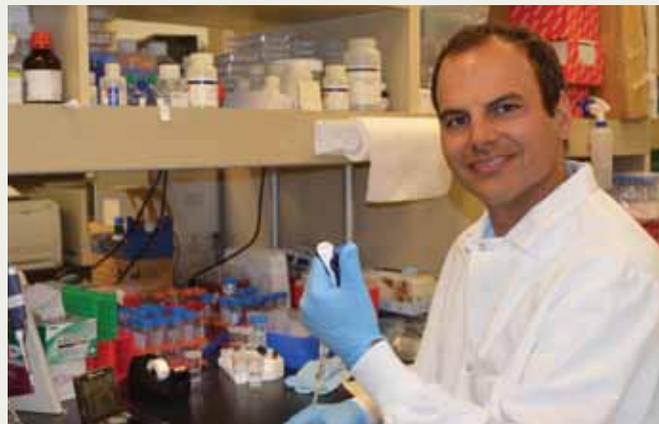
### Richard Hanna's Heart Disease Work Fueled by Board of Directors Award

Postdoctoral Fellow Richard Hanna, Ph.D. is focused on a single protein that may have a huge impact on combating heart disease. His work received a major boost through funding from a "Director's Choice" award, supported by donations from La Jolla Institute's Board of Directors.

"We showed that mice that didn't have the NUR77 protein developed more plaque in their arteries, while the mice with this protein had significantly less plaque," he said, noting that the Board's award funded this study. Based on these promising results, Dr. Hanna recently received a four-year, \$300,000 grant from the American Heart Association to continue this research.

"We were so pleased to provide funding to advance Dr. Hanna's promising studies on heart disease, which remains our nation's number one killer," said John Major, chairman of La Jolla Institute's Board of Directors. "Postdoctoral fellows are the next generation of researchers, and it is essential to provide funding and encouragement so their critical work may proceed." Board members selected Dr. Hanna for the one-year award from applications submitted by postdoctoral fellows describing their work.

Dr. Hanna works under the supervision of faculty member Catherine Hedrick, Ph.D. in the Institute's Division of Inflammation Biology, which explores how immune-fueled inflammation is a major contributor to arterial plaque buildup underlying heart disease. Postdoctoral fellows are researchers in training who have received their doctorate degrees. "I am very grateful for the Director's Choice award," said Dr. Hanna, who recently presented his study results to the Board. "It was a great opportunity to extend our earlier findings, which then resulted in our selection for a major American Heart Association grant."



LA JOLLA INSTITUTE POSTDOCTORAL FELLOWS NEWS

## Biology Award

Dr. Mackman says the AHA award also recognizes Dr. Ley's groundbreaking work in imaging. "Vascular biologists like to talk about atherosclerosis, but it's happening in a mouse where we can't see," says Dr. Mackman. "Thanks to Dr. Ley, we now have imaging techniques that enable scientists to view the cellular interactions of atherosclerotic plaque in mice in real time. This is very exciting and allows us to learn a great deal about the disease process."

## The Immune System Opens a Promising New Front in the

# WAR ON CANCER

Cancer Immunotherapies  
“Arrive” in 2012

The December 10, 2012 edition of *The New York Times* seemingly shouted the joyous news: “*In Girl’s Last Hope, Altered Immune Cells Beat Leukemia.*”

The story reported on a new type of cancer treatment that had pulled a 6-year-old girl back from the brink of death. Instead of lying limply in bed, barely clinging to life, the spunky, straight ‘A’ student was bounding through her home just months after an experimental treatment at Children’s Hospital of Philadelphia that turned a monumental corner in the world fight against cancer.

Known as immunotherapy, this new form of cancer treatment is coming of age after years of debate and painstaking research, says Mitchell Kronenberg, Ph.D., president and chief scientific officer of La Jolla Institute, a world leader in the study of the immune system. “For me, 2012 was the breakthrough year that proved that the immune system can be harnessed to create powerful new treatments to fight cancer,” he says.

The Children’s Hospital of Philadelphia treatment, pioneered by Carl June, Ph.D., the keynote speaker at a major immunology conference co-organized by La Jolla Institute last October, represents the first time this type of immunotherapy has ever been tried in a child. Its success, and promising results from several other immune-based therapeutic approaches, is creating new hope for stamping out cancer.

“The era of immune therapy is here and now,” says Thomas Kipps, M.D., Ph.D., deputy director for research at UC San Diego Moores Cancer Center. “We’re very excited about the immune system’s potential in cancer and are already using some of these emerging approaches to enhance our patient treatment,” he says.

The new drugs enable the immune system to recognize cancer cells as an enemy and then attack them, countering decades of controversy about the immune system’s viability in cancer treatment. La Jolla Institute researchers have helped to reveal some of the key immune mechanisms underlying the new therapies. “Many of us in the field have long believed that the immune system could be taught to recognize and kill cancer cells, while others thought it was impossible because cancer cells look too much like our own cells,” says Dr. Kronenberg.

Recent clinical trials as well as two approved therapies demonstrate that researchers are successfully addressing these challenges—with exciting results. While side effects remain a concern, a significant

number of patients are showing marked improvement. For example, in June 2012, two experimental immunotherapy drugs by Bristol-Myers Squibb significantly shrunk tumors in some patients with advanced skin, lung, and kidney cancers, and are now headed for Phase III trials. In addition, approaches designed to amplify

the ability of T cells to attack tumors, like those at Children’s Hospital of Philadelphia, are being explored at several major medical institutions and are showing impressive results. Additionally, two cancer immunotherapies have arrived on the market—Provenge launched in 2010 for advanced prostate cancer and Yervoy in 2011, which has extended survival in more than 20 percent of patients with advanced melanoma. Several cancer vaccines are also in the works.

La Jolla Institute scientist Stephen Schoenberger, Ph.D., who has a longstanding interest in cancer immunology, isn’t surprised by the results, noting that the scientific knowledge of immune system mechanisms has reached a tipping point. “We’ve attained a level of knowledge that allows us to manipulate the immune system in ways never before thought possible,” says Dr. Schoenberger, who received a five-year Leukemia and Lymphoma Society Scholar award. He sees more discoveries on the horizon and is representing the Institute in talks with the Moores Cancer Center regarding establishing some joint immunotherapy research projects.

La Jolla Institute scientist Michael Croft, Ph.D., explains that immunotherapies take a different tack than most cancer treatments. “Unlike chemotherapy, which directly attacks cancer cells, the primary target in immunotherapies is the immune system,” says Dr. Croft, an internationally recognized expert on co-stimulatory molecules that promote the activities of immune cells and are the focus of some of the current tumor immunotherapies.

“The goal of these therapies is to stimulate T cells (immune system warrior cells), either directly or indirectly, to kill the tumor cells,” he says. One particularly exciting approach targets molecules, known as check-point modulators, which conspire with tumor cells to shut down the T cell attack. “Blocking this inhibitory mechanism frees the T cells to eradicate the tumor,” says Dr. Croft, adding that this technique is the basis for the melanoma drug Yervoy.

Dr. Croft says another major method for goading T cells into action is to stimulate molecules that boost immune activity. Several of these molecules are now being studied in Dr. Croft’s lab (see related story next page for more info). ■



The new drugs enable the immune system to recognize cancer cells as an enemy and then attack them.

## La Jolla Institute Scientists Explore New Cancer Therapy Approaches

Leveraging the immune system to battle cancer represents a very exciting and hopeful new approach to one of the greatest scourges of our time. As a world leader in immunology research, La Jolla Institute is uniquely equipped to explore ways to manipulate the immune system to battle cancer and other diseases. Some of its cancer efforts include:

- **Shutting down the tumor escape mechanism.** A Leukemia and Lymphoma Society Scholar, Stephen Schoenberger, Ph.D. has shown how blood cancers evade T cell destruction and has pinpointed mechanisms that could shut down their escape from the T cell onslaught. His work has also revealed new roles for certain molecules (TRAIL, CD27, and CD40) that are key to unleashing a T cell attack. This research has led to current clinical trials on a drug that blocks CD40 to ease immune rejection problems in patients following organ transplantation. CD40 continues to be studied as a potential drug target in cancer. In another major effort, Dr. Schoenberger is working to engineer T cells that zero in on tumors, without damaging normal cells to minimize possible side effects.
- **Strengthening T cell soldiers for cancer battle.** Michael Croft, Ph.D., who describes cancer as “a battle between different cell populations,” focuses on ways to help the primary soldiers in that battle—the T cells—to function more effectively. Dr. Croft has explored certain molecules (OX40, 4-1BB, and GITR) which can be stimulated to boost T cell activity. His research has made him a world-renowned expert on immune cell co-stimulation and has greatly enhanced the scientific understanding of how these molecules can be manipulated in tackling diseases ranging from cancer to asthma. One of his discoveries concerning OX40 is now in pharmaceutical development as a new asthma treatment, and his work on 4-1BB
- and OX40 has significantly advanced knowledge required for developing some of the new cancer immunotherapies.
- **Taking the brakes off the immune system.** Joel Linden, Ph.D. is exploring ways to block the immune suppressive effects of adenosine, a signaling molecule that hampers efforts by T cells, macrophages, and other key immune cells to wipe out tumors. Dr. Linden explains that tumors have increased adenosine levels; this suppresses the immune system’s attack. He is investigating the effects of deleting or blocking certain adenosine receptors to restore the tumor attack. Using this approach, Dr. Linden has slowed tumor growth in mice. His research continues in hopes of translating these exciting results into human therapies.
- **Bringing out Hercules in helper T cells.** Hilde Cheroutre, Ph.D. recently identified the molecular switch that enables helper T cells—which normally only assist other cells of the immune system—to transform into killer T cells, the true warriors that directly attack tumors. Understanding this mechanism could eventually enable the creation of drugs to build larger and more powerful T cell armies to fight cancer and other diseases.
- **Other cancer research efforts designed to understand what makes these cells grow uncontrollably include:** Don Newmeyer, Ph.D., seeks to understand the fundamental mechanisms of the ways cells die, in the hope of developing new drugs that specifically kill tumor cells, while leaving normal cells unharmed; Toshiaki Kawakami, M.D., Ph.D., explores an enzyme that appears to be important in lymphoma and leukemia. He discovered the enzyme’s previously unknown tumor suppressor function in 2009; and Anjana Rao, Ph.D., studies the TET proteins and has found that a genetic mutation in TET2 is a major contributing factor to tumor formation in certain blood cancers.

# Join Us

## 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 below:



### 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*
- Quarterly "Members Only" email newsletter with LIAI announcements and updates on the latest immune health and research news
- Listing on the annual donor roster in the *Immune Matters* magazine

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

- All "Friends"-level benefits, plus:
- 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:
- Listing on the Institute's permanent Donor Wall
- 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@liai.org](mailto:rjonte@liai.org) or 858-752-6542.



## San Diego Wireless Executive Rick Kornfeld Serves on La Jolla Institute Board of Directors

**A**s a youngster growing up in San Diego, Rick Kornfeld loved to ride his bike down to the Industrial Liquidation yard at 40th and University, where he would acquire parts and other “treasures” for his innumerable building projects. By age 10, Rick’s insatiable curiosity had filled his home with self-built gadgets—a radio, a blinking light, and a carbon arc welder for melting glass, bricks, and other items of great fascination to 10-year-old boys. Even the family dryer did not escape his inquisitive mind. “I took it apart because I wanted to see how it worked,” Rick recalls with a smile. “My parents took it really well. They didn’t come unglued or anything.”

This early appetite for figuring out how machines work undoubtedly foreshadowed Rick’s extraordinary success as an inventor and a leader in San Diego’s wireless industry. It may also say something about his role as a member of the Board of Directors of La Jolla Institute for Allergy and Immunology (the Institute), a world leader in the study of the immune system. Rick acknowledges a certain like-mindedness among people in the sciences. “When you have a background in one of the sciences—in my case electrical engineering—I think you have an innate curiosity about how things work,” he says. “You want to look underneath the hood.”

Looking underneath the hood is exactly what the Institute’s scientists do daily as they explore ways to harness the immune system to prevent and treat diseases ranging from cancer to heart disease. “Everyone knows we have an immune system,” says Rick. “But when you really start thinking about it, how does it really work? How does it have memory that protects us from disease? Why does it sometimes cause disease? The Institute’s scientists really get to the core of how the immune system functions, and that’s extremely important in health and disease.”

Rick, who has worked for some of San Diego’s most notable technology companies, says learning about the Institute’s science has turned out to be the most enjoyable aspect of his board service. Of particular interest, he says, are the Institute’s plans to converge bioinformatics and gene sequencing technologies to make major medical advances. Bioinformatics uses computer modeling and analysis to significantly accelerate disease research, while gene sequencing



“The Institute is beautifully positioned to take advantage of these technologies in a way that really can disrupt this field and all of medicine.”

—Rick Kornfeld

allows scientists to unravel the secrets of disease buried deep in our genes. Such research is considered the foundation of medicine. “The Institute is beautifully positioned to take advantage of these technologies in a way that really can disrupt this field and all of medicine,” he says.

Rick’s admiration for disruptive technologies isn’t surprising considering his major role in the formation of San Diego’s wireless industry. Rick’s career began in the early 1980s when he was an undergraduate electrical engineering student at UCSD. He started with a summer internship at Linkabit, one of San Diego’s founding wireless companies, and before long he was talking to a small group of technology savvy entrepreneurs, many from Linkabit, who had formed Qualcomm. “When I interviewed at Qualcomm, they were located over a dry cleaner in La Jolla,” he recalls.

A small start-up with only 20 people, Qualcomm’s desire to launch a new wireless technology appealed to Rick’s brilliant and inventive mind. “We were developing the first CDMA cellular phones,” says Rick. “A lot of people said we couldn’t do it. CDMA was considered a disruptive technology and some friends told me I should get out because it might fail.”

But Rick didn’t flinch and went on to become Qualcomm’s Vice President of Engineering, serving as a key member of the core group that launched CDMA phones. “I still have the first CDMA portable phone ever built,” says Rick. Qualcomm’s CDMA technology became the industry standard and launched the company’s stratospheric rise to its current status as a leading worldwide force in wireless technology.

After 10 years with Qualcomm, Rick served as an executive at NextWave Wireless before co-founding Dot Wireless in 1997. Dot Wireless was an extremely successful company which developed chipsets (the core components) for CDMA phones. Dot Wireless was bought by Texas Instruments in 2000 after which Rick founded his latest venture, Grid2Home, a leading provider of new smart grid technology for the home.

Rick holds 17 patents and still enjoys building things, but he also makes time for bicycle racing and various community activities. These include serving on the UCSD Jacobs School Council of Advisors and the National Council of the American Israel Public Affairs Committee. He and his wife Carol have three children. ■

# La Jolla Institute

FOR ALLERGY AND IMMUNOLOGY

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## 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:** 22 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 2012, ranked #6 in the "Best Places to Work in Academia" and #7 in the "Best Places to Work for Postdoctoral Fellows" in the annual survey of research institutions throughout the world, conducted by *The Scientist* magazine.

