La Jolla Institute FOR ALLERGY AND IMMUNOLOGY | Life Without Disease.

Immune Matters

WINTER 2013-14

Too Much of a Good Thing

Misdirected Immune Activity Tips the Scales Towards Disease

HEART DISEASE
MULTIPLE SCLEROSIS
RHEUMATOID ARTHRITIS
TYPE 1 DIABETES
ASTHMA
AND
MUCH MORE

See page 4

La Jolla Institute FOR ALLERGY AND IMMUNOLOGY | Life Without Disease.

9420 Athena Circle • La Jolla, CA 92037

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.

***Immune Matters* Contributors**

Bonnie Ward, Editor
Chris Benedict, Ph.D.
Jessica Colby
Rachel Jonte
David L. Mitchell
Annie Morley, Design
Bob Ross
Stephen Wilson, Ph.D.

STAY UPDATED! If you would like to receive email updates from the La Jolla Institute, please email us at:

institute_relations@lji.org

858.752.6542

Letter from the President

The immune system is one of the human body's most complex and important biological systems. It is absolutely central to our survival and protects us daily from billions of bacteria, viruses, and other microorganisms that circulate around us. While this is the immune system's crucial protective role, its well-intended efforts can sometimes go awry when our healthy cells are mistaken as foreign. This leads to the immune system's inadvertent destruction of normal cells, resulting in autoimmune and inflammatory diseases. These disorders can affect any organ and they run the gamut from rheumatoid arthritis (an attack on the joints) to type 1 diabetes (an attack on the pancreas). Even heart disease has been found to be largely an inflammatory disease. In this issue, we discuss these disorders and efforts at La Jolla Institute and other research centers to bring these diseases under control. As one of the world's most highly ranked immunology research institutes, we are uniquely positioned to address these disorders and we are proud to be at the forefront.

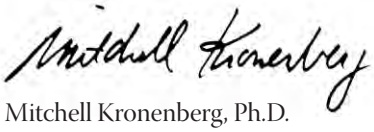
Also in this issue, you'll find an update on infectious diseases, another pivotal area of our institute's research. Internationally recognized vaccine biologist Alessandro Sette, Ph.D. discusses infectious diseases most relevant to the U.S. He also discusses international concerns, such as tuberculosis, which remain a threat to Americans due to the globalization of health issues.

This issue of *Immune Matters* provides an opportunity to meet three of our new Board members—all prominent San Diego executives. Gene Ray, Ph.D., Anthony Carr, and Fred Wasserman, DrPH, have generously brought their insight and leadership skills to our Board of Directors, which plays a key role in our mission to promote health and prevent disease.

We are also delighted to share with you the personal story of a type 1 diabetes sufferer, whom you may recognize from both the professional sports and political arenas. Former NBA basketball star and Oregon gubernatorial candidate Chris Dudley graciously shares his experience with type 1 diabetes, an insidious disorder that affects millions worldwide and is one of La Jolla Institute's areas of focus. A strong diabetes advocate and recent San Diego transplant, Dudley talks about his efforts to raise awareness of type 1 diabetes as part of his continuing community efforts in Oregon and now San Diego.

In closing, we would like to express our gratitude for the continued support of our individual donors, foundations, and federal sources. Without this funding, our research would simply not be possible. We are proud to be a world leader in the study of the immune system, which holds amazing potential for preserving health and ultimately conquering heart disease, cancer, diabetes, and myriad other devastating disorders. We hope you find this issue of *Immune Matters* informative and stimulating, as we value the opportunity to share with you our ongoing efforts to achieve 'life without disease.'

Sincerely,



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

Three Scientists Receive Fellowships to Explore Cancer Immunotherapies

Harnessing the Immune System to Fight Cancer Offers Promising New Approach

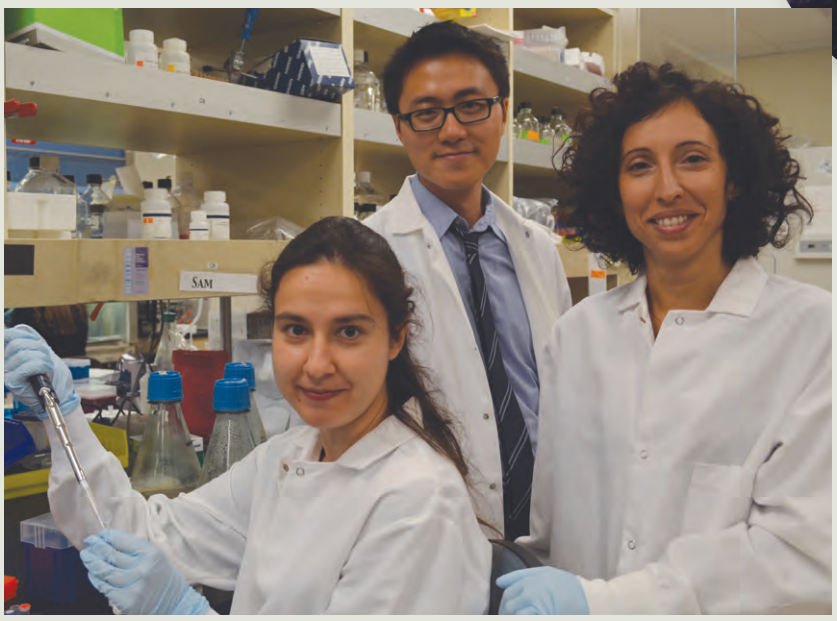
The Cancer Research Institute, a New York-based nonprofit organization committed to developing immune system-based cancer treatments, has awarded major fellowships to three La Jolla Institute researchers. The funding supports pioneering clinical and laboratory research to harness the immune system to fight cancer.

All three recipients are postdoctoral fellows in the lab of Anjana Rao, Ph.D., a prominent genetics and cell biology researcher and member of the National Academy of Sciences. Collectively, the fellowships total $450,000 over three years.

"The field of cancer immunotherapy is exciting because it's growing so quickly and turning up so many promising results," says Jill O'Donnell-Tormey, CEO and director of scientific affairs at the Cancer Research Institute. "We're eager to see the new breakthroughs coming from these grants and fellowships."

The awardees are: Ageliki Tsangaratou, Ph.D., who is working to define the role of DNA modifications produced by certain enzymes involved in T-cell leukemias; Sara Trifari, Ph.D., who explores genetic changes in killer T cells, the body's primary disease-fighting cells, which are crucial for anti-viral and anti-tumor responses; and Chan-Wang "Jerry" Lio, who is studying novel molecules believed to influence leukemia development.

"We are very grateful for this funding from the Cancer Research Institute," says Dr. Rao. "It will help us explore genetic aspects of cancer as well as immunotherapies that could enable new treatments to stop cancer in its earliest stages."



(ABOVE) Computer illustration of cancer cells splitting. (LEFT) Three La Jolla Institute researchers received fellowships to study immune-based approaches to fighting cancer. The recipients are: Ageliki Tsangaratou, Ph.D., (seated), Chan-Wang "Jerry" Lio, Ph.D., and Sara Trifari, Ph.D.

TOO MUCH OF A *Good Thing*

Millions Suffer the Consequences

A top immunologist talks about how inflammatory and autoimmune diseases result from the immune system's good intentions gone bad

The old adage "too much of a good thing" is something every person has experienced from time to time. Sunlight provides healthy doses of Vitamin D, which is necessary for sustaining life, but too much sunlight can cause sunburn—or with enough exposure, cancer. Similarly, exercise is important for health but over-exercising can lead to muscle tears and joint replacements. And who doesn't consider the occasional enjoyment of chocolate a good thing? But too much can cause weight gain. This concept can also be aptly applied to autoimmune and inflammatory diseases—serious disorders that result from the immune system's well-intended destruction of "bad cells" being mistakenly directed at our own healthy cells or being overzealous and causing harm. The fallout from these unwarranted onslaughts produces over 80 chronic diseases that affect the health and well-being of countless millions of people. In the following article, La Jolla Institute President & Chief Scientific Officer Mitchell Kronenberg, Ph.D., discusses the challenges of autoimmune and inflammatory diseases and the Institute's pioneering research to stop them.

A Massive Problem

"Autoimmune and inflammatory diseases are very diverse, and they can affect almost any organ in the body," says Kronenberg, one of the world's most highly cited immunologists. "These include diseases such as rheumatoid arthritis, multiple sclerosis, and Crohn's disease, but they also involve disorders typically not thought to have an inflammatory component, such as heart disease and Alzheimer's."

Kronenberg says that inflammation-fueled diseases are on the rise in the United States and other developed countries, and that no one knows exactly why. "Eight percent of the U.S. population is estimated to have an autoimmune disease," says Kronenberg, noting that the percentage would climb even higher if disorders not widely recognized to have an immune-mediated cause, such as heart disease, were included.

Various theories seek to explain this rise.

Examining Possible Causes

"There's a longstanding theory that certain infections, particularly viral infections, may trigger autoimmunity," explains Kronenberg.

Autoimmune and Inflammatory Diseases:

Autoimmune and inflammatory diseases produce debilitating symptoms for millions and also can be life-threatening. Listed here are some of the more common inflammation-fueled disorders. La Jolla Institute's research on the immune system touches all of these diseases—and many more:

Heart Disease
Rheumatoid Arthritis
Multiple Sclerosis
Diabetes
Crohn's Disease and Colitis (Inflammatory Bowel Disease)
Alzheimer's
Lupus
Asthma
Allergies
COPD
Psoriasis
Eczema

"One hypothesis, called mimicry, holds that some viruses may resemble our own cells and that our immune system destroys them by mistake." While this theory remains unproven, Kronenberg indicates that studies in the lab of Institute scientist Matthias von Herrath, M.D., support this hypothesis. (see sidebar on type 1 diabetes, pg. 7).

Kronenberg says that emerging evidence about environmental factors is also noteworthy. "Many studies show a higher prevalence of asthma in poor urban neighborhoods, while other research reveals that if you grow up on a farm, you may be protected. Both of these results suggest that changes in the environment play an important role in autoimmunity."

Other possible factors include the rising rate of obesity, as excess weight has been shown to worsen inflammation in some diseases, although not others.

The bottom line, states Kronenberg, is that inflammatory diseases likely result from a combination of factors. "Even though a malfunction of the immune system is the underlying cause in every case, the way the malfunction occurs is not the same," he says, noting that autoimmunity arises in widely varied areas of the body, such as in the joints in rheumatoid arthritis or in the pancreas in type 1 diabetes.

Zeroing In On the Prime Inflammation Controllers

Kronenberg explains that autoimmune and inflammatory diseases are both disorders fueled by inflammation. Inflammation is a normal part of the healing process to tissue damage, but it can cause chronic disease and activate the T cells of the immune system when there is too much inflammation or it is misdirected. Immune system T cells are among the most important disease-fighting cells, but are also the chief architects of an autoimmune attack on the body's own cells. "The same cells that help you fight infections can hurt you in autoimmune diseases," says Kronenberg. Consequently, the Institute devotes significant attention | *Continued on page 6* >>

Inflammation

to T cells as "the primary controllers of the immune response."

Breaking a Link in the Inflammation Chain

The process for inciting a T cell attack involves a massive web of intricate molecular interactions between many different cell types. In much the same way that a chain reaction would be stopped if a link in the chain were broken, researchers can block or lessen a T cell's action by interrupting a critical step in its activation or sustained action. "Our T cell studies look at key molecules that regulate key interactions," says Kronenberg.

In this vein, several La Jolla Institute labs explore the tumor necrosis factor (TNF) family of molecules, which carry messages that are important for T cell survival and expansion. The TNF family is widely considered to be one of the most exciting areas in autoimmune research today—a field in which the Institute is at the forefront. "The TNF family has become a virtual hotbed of research activity because it has been shown to have profound effects on inflammation," says Kronenberg. Several blockbuster TNF-inhibitors are in use to treat rheumatoid arthritis and other autoimmune disorders, although they do not help all sufferers. Institute discoveries underlie several new TNF therapies to help that group. "Because of our focus in this area, we now have four TNF-related discoveries in pharmaceutical development to treat various autoimmune diseases. This is quite a remarkable achievement for an Institute of our size." The potential therapies include a treatment for Crohn's disease and colitis, the skin disease psoriasis,

The Institute's Novel Research on Inflammation-Fueled Diseases

La Jolla Institute for Allergy and Immunology is a world leader in understanding and solving complex problems of immune function underlying autoimmune and inflammatory diseases. The following are a few examples of some of our work in these areas:

HEART DISEASE :: IMMUNIZING AGAINST AMERICA'S #1 KILLER

It might come as a surprise, but according to La Jolla Institute researcher Klaus Ley, M.D., there is a strong autoimmune component to heart disease. Autoimmune diseases result from the immune system's attack on normal cells and, in the case of heart disease, this destruction involves proteins in the artery wall which the immune system mistakenly identifies as foreign. The byproduct of this attack is chronic inflammation that worsens and destabilizes artery-clogging plaque that can trigger a heart attack.

Ley, a pioneer in vascular immunology, has seized upon this emerging knowledge with a first-of-its-kind solution—a vaccine for heart disease. Now in early testing, Ley's vaccine is designed to induce immune tolerance of the arterial proteins, similar in concept to the tolerance induced by allergy shots. Early results are promising. It has significantly reduced plaque buildup in mice and has drawn praise from top cardiologists.

RHEUMATOID ARTHRITIS :: TACKLING THE DISEASE WHERE IT LIVES

Nunzio Bottini, M.D., Ph.D., is a La Jolla Institute researcher and part-time physician at UCSD Medical Center, whose rheumatoid arthritis (RA) patients serve as a constant reminder of the critical need for a cure. About 2 million Americans suffer from RA, a chronic autoimmune disease that gradually destroys joint function.

Bottini is aggressively pursuing two lines of research: one that aims to block a gene known to quadruple the odds of developing RA; the other effort seeks to attack RA in the joints rather than by globally suppressing the immune system. The levels of immune suppression currently used to treat RA are considered safe, but they are not effective in a large fraction of patients, says Bottini. "I would like to add the option to treat the disease at the site of the joint damage, without further increasing systemic immune suppression that might lead to problems fighting infections and tumors," he adds. To accomplish this, Bottini explores blocking disease-causing cells directly in the synovial membrane, the soft tissue between joints, in hopes of halting joint destruction.

and an organ transplant anti-rejection drug, all in clinical trials.

Institute labs also explore many other groundbreaking approaches for shutting down the T cell's unwanted attack. These include work by Anjana Rao, Ph.D., and Patrick Hogan, Ph.D., to control the T cell by regulating its internal machinery; Amnon Altman, Ph.D.'s research to block a critical enzyme essential for unleashing T cells; and work by Hilde Cheroutre, Ph.D., who received the prestigious Pioneer award from the National Institutes of Health to fund her studies on controlling T cell behavior by intervening during the formation of these cells.

A Look into Future Areas of Focus

Kronenberg says several new factors have come into play in recent years which will greatly affect autoimmune research in the future. These include emerging studies on the microbiome—the huge bacterial contingent residing in and on the human body. Research suggests that the microbiome may influence various health conditions ranging from autoimmunity to obesity. Researchers are exploring possible ways to treat diseases by manipulating the makeup of the microbiome.

Another area of growing importance is genetics, which the La Jolla Institute is actively pursuing in its RNA interference (RNAi) center, one of the few such centers of its kind in the world. "The sheer genetic diversity involved in particular diseases is surprising," says Kronenberg. For instance, more than 160 genes have been associated with Inflammatory Bowel Disease. In any one person, 10 to 20 of these genes may be at play. | *Continued on page 8* >>

TYPE 1 DIABETES :: COULD A VIRUS BE THE CULPRIT?

What if a particular virus could trigger the onset of type 1 diabetes in those who are genetically pre-disposed to the disease? Matthias von Herrath, M.D., director of La Jolla Institute's Diabetes Research Center and a world leader in type 1 diabetes research, has made several major discoveries that point to just such a possibility. The viral connection is based on the 'molecular mimicry' hypothesis that the immune system may confuse normal cells with certain virally infected cells, leading to the unintended destruction of healthy cells. While the unwarranted destruction of healthy cells is the hallmark of type 1 diabetes and other autoimmune diseases, von Herrath's research would, for the first time, establish a specific cause and a possible means of prevention, if the viral culprits in type 1 diabetes can be identified. "By building on this research, one day we may be able to advise people who are genetically predisposed to type 1 diabetes to be vaccinated against certain viruses to prevent the development of the disease," says von Herrath. The research is the latest in a series of groundbreaking discoveries by von Herrath, whose work on a combination therapy to prevent type 1 diabetes has also drawn worldwide interest.

ASTHMA :: DISRUPTING IMMUNE "CONVERSATIONS"

Asthma is a serious chronic disease that currently affects 25 million Americans, including 5 million children. Existing therapies primarily provide short-term relief, but La Jolla Institute researcher Michael Croft, Ph.D. has a much more ambitious goal—to reeducate the immune system to stop the reoccurring assault on the airways which causes asthma. Put simply, he wants a permanent end, not a band-aid, to asthma's vicious cycle. Croft is an internationally recognized scientist specializing in immune cell co-stimulation, or understanding how cells communicate with each other. Understanding these 'conversations' has proven critical in multiple diseases, and has led to a potential new drug, now in pharmaceutical development, to treat asthma based on Croft's discovery. Croft's finding showed that blocking the chatter between two key immune proteins (both members of the tumor necrosis factor (TNF) family of molecules) substantially suppressed the lung inflammation and accompanying symptoms of an asthma attack. Croft's work doesn't stop with asthma. He has also shown that disrupting other TNF family molecular conversations may aid in controlling several autoimmune diseases and chronic obstructive pulmonary disease. Conversely, he has also demonstrated that promoting these conversations can be used in cancer therapy.

This brings up the promise and potential of personalized medicine, states Kronenberg. "The medical community has a fundamental problem of specifically targeting affected areas in autoimmune treatment," he says. "We already have drugs (steroids, etc.) that will dampen inflammation. Unfortunately they do this on a systemic basis, which can cause increased susceptibility to infection or cancer."

Kronenberg says a personalized medical approach could involve treating the specific defects in the immune system of the patient leading to autoimmunity, rather than doing system-wide immune suppression. Such treatments may also act locally, meaning only at the site of disease. Institute scientist Nunzio Bottini, M.D., Ph.D., is exploring this localized treatment approach in rheumatoid arthritis, Kronenberg notes. (see sidebar, pg. 6)

Gene-based treatments, inspired by the rapidly increasing number of people having their genomes sequenced, will also play a prominent role in future autoimmune treatment efforts, says Kronenberg. As researchers gain insights into controlling genes in disease, it will be possible to provide different drugs based on an individual's specific genes. "Because of the genetic diversity in chronic autoimmune and inflammatory diseases, you can't really have a one-size-fits-all approach to medical treatment," adds Kronenberg. "I think the ultimate answer for mastering these diseases may lie in personalized medicine."

Optimal health is achieved when the immune system is doing its job—not too much, but not too little. The goal, therefore, is to understand how these immune processes work so that we might be able to manipulate the system to keep the proper balance. One thing that will never be "too much of a good thing" is research in this area. ■

What is Inflammation? And Why Are People Talking About It?

You can't pick up a newspaper or watch TV without hearing something about the perils of inflammation. What exactly is this extraordinary force that is being implicated in an ever-increasing number of diseases?

Stephen Wilson, Ph.D., an immunologist and La Jolla Institute Executive Vice President, says inflammation is not a troublesome invader, but rather the hallmark of an alerted immune system. "Inflammation is your immune system picking a place and doing something," Wilson says. Whether that 'something' is good or bad depends on the context, explains Wilson.

For instance, when you cut your finger, cells from the immune system rush in to heal the wound. The initial swelling and redness (inflammation) is a byproduct of the swarming cells. The same is true in fighting infections. Immune cells attack the virus or bacteria, causing temporary inflammation, says Wilson, noting this is a positive inflammatory action.

The bad effects occur when immune cells show up where they are not needed or when they stay too long. "Chronic inflammation is the party that doesn't end," quips Wilson.

This results in autoimmune and inflammatory diseases such as multiple sclerosis, type 1 diabetes, and asthma. Even heart disease and Alzheimer's have been found to be chronic inflammatory diseases, adds Wilson. The list continues to grow as inflammation's role in disease is better understood through research at La Jolla Institute and other major institutions.

Three Prominent San Diego Executives Elected to La Jolla Institute Board

La Jolla Institute has elected three distinguished San Diego business executives as new members of its Board of Directors. The new members—Tony Carr, a real estate executive, Gene Ray, Ph.D., a founder of the Titan Corporation, and Fred Wasserman, DrPH, a founder of Maxicare Health Plans—bring a wealth of knowledge, insight and leadership skills to their role as board members. "The Institute is honored to attract this exceptional group of new board members," says Mitchell Kronenberg, Ph.D., president and chief scientific officer. "Our Board plays a key role in advancing the Institute's mission to promote health and prevent disease through groundbreaking immune system research. We look forward to working with these new members and appreciate their willingness to serve." The new trustees are:

Anthony "Tony" Carr is the managing partner of Carlo Development, a southern California based real estate development company. Carlo Development owns and operates multi-family and self storage/industrial properties throughout California. Carr is also a managing member and co-owner of San Diego Self Storage (SDSS), the largest self storage company in San Diego County with 18 locations. Prior to this, Carr was a registered principal for C & L Securities Corp., a wealth management firm, and an investment advisor licensed with the Securities and Exchange Commission. He received his B.A. degree from UCLA and attended the UCLA Anderson School of Management before beginning his career in finance and real estate.

Carr has been active in several community organizations including service with the following groups: the advisory board for the University of San Diego (USD) Burnham-Moores Center for Real Estate, the UCSD Athletic Advisory Board, the Board of Trustees for The Grauer School, the Board of Directors for Big Brothers of Greater Los Angeles, the Board of Directors of International Relief Teams, UCLA Chancellor's Associates, and The Los Angeles BIA Multi-Family Housing Council.

Gene Ray is the owner and CEO of GMT Ventures, an investment firm in San Diego. In the 1980s, he was one of the founders of The Titan Corporation, a leading national security solutions provider, and served as its CEO and on its Board of Directors from the company's inception in 1981 until its merger with L-3 Communications in 2005. He was elected chairman of the board in 1999 and also served in that capacity until 2005.

Prior to launching Titan, Ray was executive vice president, general manager and board member of Science Applications International Corporation, Inc. (SAIC) for 11 years. SAIC, a multi-billion dollar science and engineering company serving the defense and other industries, was founded in San Diego, and moved its headquarters to McLean, Va. in 2009. The company still maintains a large presence here.

Ray received his Ph.D. in theoretical physics at the University of Tennessee in 1965; an M.S. in physics at the University of Tennessee in 1962; and a B.S. in mathematics, physics and chemistry at Murray State University in 1960. He is or has been involved on a number of community boards, including: chairman of the board, Decision Sciences Corporation; chairman, Heart, Lung & Vascular Advisory Board, Scripps Clinic; advisory board member, Scripps Clinic/Green Hospital; foundation board member, Murray State University, and as an advisory board member at various early-stage technology companies.

Fred Wasserman has a broad business background with leadership experience in health care, real estate, agriculture, and as a faculty member at several major universities. Wasserman and his wife, Pamela, are co-general partners in the Wasserman Companies, which own and operate commercial and residential real estate and agricultural properties in California. Wasserman is a founder of Maxicare Health Plans, Inc., the first federally qualified health maintenance organization in California and served as CEO from 1973 to 1988. In the decade following 1988, he was a consultant to senior management at several major health care companies and startups advising on strategic positioning, health service systems, and product innovations and introductions. Wasserman has also served on the faculties of USC's School of Public Administration, UCLA's School of Public Health, and Cal State University Northridge.

Wasserman has been active in a number of professional and community organizations. He is a current member of the World Presidents Organization and previously served on the Dean's Council at UCLA's School of Public Health, where he and his wife Pamela funded an endowed chair in Health Services. He has also served on the boards of the UCLA Foundation and the Jewish Home for the Aging. Wasserman holds a B.S. degree in business administration from UCLA; an MBA in general management from USC; and a DrPH in Health Services from UCLA.

Q+A

Infectious Disease Expert Discusses Challenges in the U.S. and Around the World

Renowned vaccine scientist Alessandro Sette, Ph.D., heads La Jolla Institute's Division of Vaccine Discovery and also serves as director of the Institute's Center for Infectious Disease. Sette's expertise has catapulted him into the international forefront of infectious disease research as co-lead scientist on the National Institutes of Health's Immune Epitope Database. Sette led the La Jolla Institute team that designed, developed and now hosts this global research resource—the world's largest collection of data on how the body responds to infectious and autoimmune diseases. In the following article, Sette discusses infectious disease challenges in the U.S. and other parts of the world, as well as ongoing research efforts to prevent or better treat these diseases.

Q: Which infectious diseases are currently of particular concern in the U.S.?

A: There are ongoing concerns about influenza and other respiratory viruses, sexually transmitted diseases, like HIV and Chlamydia, which is on the rise. There is also major concern about many preventable diseases, particularly pertussis (whooping cough) and measles, which are increasing because of a lower degree of compliance with vaccination. Measles was once eliminated in the United States, but we've seen flare-ups over the last few years. This is a real problem since measles can lead to serious complications and death. The same is true for pertussis, which can be deadly, particularly in infants.

Q: The H1NI (swine) flu outbreak in 2009 thankfully turned out to be milder than originally feared, but served as a wakeup call to the potential threat of novel influenza strains. Are there currently emerging flu strains of which we should be aware?

A: The H7N9 avian influenza strain is raising some concern. However, the research community is paying close attention and the epidemiological and public health surveillance scientists are very much involved in following this virus worldwide. Luckily, it's not a major threat right now in terms of having jumped from birds to humans and causing widespread infection. Of course, we know that viruses can mutate and become more easily transmissible. So in addition to ongoing surveillance, the key issue is to develop technologies to rapidly progress vaccine candidates through the pipeline.

Q: We know that in the event of a dangerous flu outbreak, time is of the essence. What types of technologies would enable more rapid vaccine development?

A: The process by which the flu vaccine is made is based on identifying the particular influenza subtypes in circulation and then manufacturing vaccines containing non-infectious viral pieces that will stimulate a protective response. The manufacturing, testing and so forth takes time.

Several technologies are under development to speed this process. One would enable influenza to be grown in cell culture systems instead of in chicken eggs, which is the current practice because birds are natural hosts for influenza. If feasible, cell cultures would be much faster. Another key technology under development would enable genetic manipulation of flu strains to develop vaccines more rapidly.

Q: What about infectious diseases occurring in other parts of the world? Are there any to which the U.S. is especially vulnerable?

A: Since the U.S. is not on a separate planet, our health, just like our economy, is interconnected with the rest of the world. So diseases like tuberculosis that are of major concern in Africa, India, Russia and many other parts of the world also remain a concern here.

Also changes in climate may bring diseases of a more tropical nature to the U.S. Dengue virus, for instance, is already seen in Hawaii and Puerto Rico and in 2010 there was a small outbreak in Florida. Malaria is not a concern in the U.S., although this was not always the case. People might be surprised to learn that the CDC originated from the Malaria Control in War Areas agency that existed from 1942-1945. Atlanta was chosen as the agency's headquarters because of its central location and proximity to the more humid southern areas, where malaria was problematic. A concentrated mosquito eradication campaign was undertaken in 1947 and by 1951, malaria was declared eliminated in the U.S. So while the type of mosquito that spreads malaria is gone from the United States, the variety that causes dengue virus is here. Consequently, this disease is closely monitored in the U.S. and its territories. There are also very aggressive efforts to develop the first dengue virus vaccine, in which the La Jolla Institute is a major participant.

Q: Can you talk more about tuberculosis (TB) and what kind of incidence we see here?

A: The first thing to understand about TB is that there are two forms—the active TB where people are infectious and severely affected and might eventually die, and latent TB. One third of the world's population is infected with latent TB. Of those, it is estimated that about 1 percent will go on to develop active TB. If you are latently infected, you are healthy, not infectious, have no bacteria in your blood, and are pretty much impossible to tell from the next person. That is because your immune system keeps the TB in check. However, in cases where people have a weakened immune system, then TB can progress from the latent to the active form. The number of active cases in the U.S. is low compared to the rest of the world. For instance, 9,945 active TB cases were reported in the U.S. in 2012. This compares to 9 million cases elsewhere in the world in 2011 and 1.4 million deaths worldwide.

Q: How have we been able to keep it in check here? And are we at risk for increasing TB incidence?

A: TB can be successfully treated. There are standard antibiotic regimens that work very well. And even in the case of multi-drug resistant TB, the vast majority of cases are effectively treated with more advanced and sophisticated mixtures of antibiotics.

But the concern worldwide is that we could run out of antibiotics that work. Then it could be something that is very much drug resistant. This is another example of the interconnection between the U.S., where TB is not a major problem, and the 2.3 billion people worldwide estimated to have latent TB infection. How do drug resistant strains originate? They evolve or mutate. The chance that a mutant will evolve is greatly enhanced if there are large reservoirs of people with latent TB infection.

Q: This of course makes the search for an effective TB vaccine even more important. Can you discuss your current research in this area?

A: A vaccine exists for TB called the 'BCG vaccine.' It's not used in the U.S. because it provides only limited protection in very young kids and no protection in adults. So there is a significant push worldwide to create an effective TB vaccine. In my lab, we are very interested in trying to understand if there are early signs of someone who is going to evolve from latent disease to active TB disease. This would allow targeted treatment for the most at-risk group (the estimated 1 percent of the latently infected) and also reduce the cost of vaccine trials through smaller trials focused on this at-risk subset. We are working with scientific collaborators throughout the world to study this issue.

Q: So in closing, what do you think is the most important thing for people to remember about infectious diseases?

A: That we must remain continually vigilant. There are always going to be new pathogens such as the H7N9 avian flu or old pathogens that mutate and produce new drug resistant strains. We must continually work to stay one step ahead of these dangerous agents. ■

a distinguished scientist's *persistence* rewarded with major advancement in *asthma research*

For several millennia, dating at least back to the ancient Egyptians, the human race has been plagued by asthma. Seen by many as primarily a childhood disease affecting a relative few number of people—and overshadowed by cancer, heart disease and diabetes in today's biomedical research arena—asthma receives a fraction of the attention it deserves.

In reality, the chronic inflammatory lung disease afflicts more than 300 million people worldwide, causing 250,000 deaths annually. In the U.S., 25 million people—one in 12 Americans—suffer from asthma at a cost of $50 billion a year. Worse, the prevalence of asthma has been increasing the past few decades, reaching epidemic proportions in the U.S. and other industrialized nations.

And while the prevalence in children is relatively high, asthma affects all age groups, from young adults to seniors. To varying degrees, all suffer the often debilitating symptoms of narrowed, inflamed and mucus-filled airways that result in wheezing, coughing, and shortness of breath.

Unfortunately, not only is asthma incurable, it has proven exceedingly resistant to scientific attempts to determine its cause, let alone develop therapeutic remedies. That is changing thanks to La Jolla Institute researchers. Distinguished molecular biologist, **Toshiaki Kawakami, M.D., Ph.D.**, and his team of talented researchers, have made several pioneering discoveries that are unraveling the underlying mechanisms that cause the symptoms of asthma and many allergies.

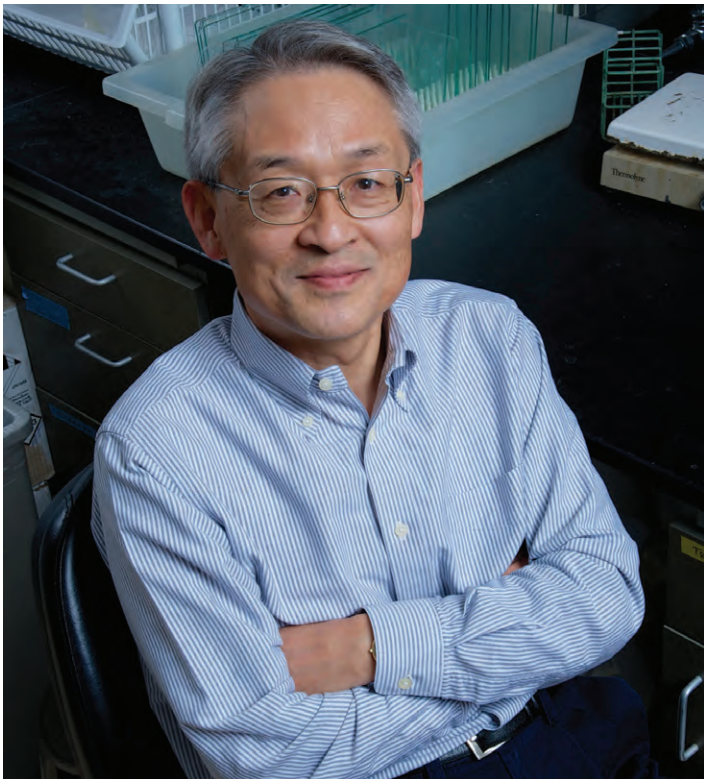


PHOTO: BOB ROSS

"In simplest terms, we have identified some of the molecular factors that trigger certain cells within an organism to become activated and cause allergic reactions, like those many asthma patients suffer," says Dr. Kawakami. "We've also identified a number of ways in which these reactions might be blocked, which is even more exciting because it should allow us to eventually develop therapeutic strategies to stop those reactions in their tracks before they ever reach the symptomatic stage."

A PASSION FOR DISCOVERY

To appreciate the evolution of these discoveries, and the groundbreaking work behind them, it is essential to understand how Dr. Kawakami himself evolved as a researcher, and how he developed the scientific creativity and equally important persistence, if not doggedness, that has marked his career. Born in northern Japan to a government worker and homemaker, Dr. Kawakami decided he wanted to be a doctor. But as he pursued his medical degree at the University of Tokyo, he assisted a friend with a neuroscience research project and became hooked on the process of scientific inquiry.

"I found pure research to be far more intellectually stimulating than medicine," Dr. Kawakami recalls. "I loved the idea that I could discover things that were completely new, and that some of them hopefully might be important enough to help people."

Dr. Kawakami still got his medical degree but then shifted careers entirely to put himself on a molecular biology track, pursuing a Ph.D. It wasn't long before he had an emotional confirmation that he had not only made the right decision, he had a real passion for the work.

"I was an assistant professor in the lab of the well-known Japanese molecular biologist Tasuku Honjo where I was working on an immunoglobulin chain cloning project searching for a particular sequence," Dr. Kawakami recalls. "One day, when I developed the film and saw I had found a previously undiscovered sequence, I physically shook with excitement. It was a minor discovery, but no one had done it before. It's those kinds of moments that keep you going through the long and often many years of really challenging research that's required to develop true scientific breakthroughs."

PUSHING THE BOUNDARIES OF RESEARCH

Dr. Kawakami brought that ambition and talent for discovery with him when he came to the U.S in 1984 to work as a cancer researcher at

the National Institutes of Health. He joined La Jolla Institute in 1990 in the early days of the organization when there were just 30 employees. In the 23 years since, Kawakami and his team have pushed the boundaries of molecular research, especially in the area of signal transduction in the immune and hematopoietic (blood-producing) systems.

The team has also made significant progress in understanding the function of mast cells, a key immune cell that is found in mucosal as well as connective tissues, and which is responsible for some allergic reactions that trigger itching, wheezing, and sneezing. The team's most recent groundbreaking discovery came when it identified the histamine releasing factor (HRF) molecule—including its receptor—as a promising target for developing new treatments for asthma and allergic reactions.

Dr. Kawakami says the research is extremely promising because it could lead to the development of new therapies based on blocking HRF interactions with certain antibody (IgE) molecules, long known to be central causes of allergies. The study also found two novel peptides (N19 and H3) as strong therapeutic candidates for blocking the HRF and IgE interactions.

The findings earned praise from the research community around the world. Hannah Gould, Ph.D., a professor and prominent allergy researcher at King's College in London, said, "the identity of the primary binding partner, the HRF receptor, the unique characteristics of the IgE in these individuals, and the mechanisms involved in HRF activity have remained elusive until the present study by Dr. Kawakami and his team."

Gould added, "These findings suggest a potential treatment for allergy and asthma patients who have HRF reactive IgE. We can look forward to the future results of pre-clinical and clinical studies in the human system."

While pleased with the response, Dr. Kawakami characteristically gives much of the credit for his success to his team and a warmly collegial environment at the Institute he believes encourages scientists to inspire and collaborate with each other, even across disciplines. "Most important," Dr. Kawakami says, "is the Institute's singular focus on immunology. Every day we're finding more about how the immune system is involved not just in asthma and allergies, but heart disease, diabetes, cancer, and many other diseases. The potential for our work to make a difference is vast."

"The potential for our work to make a difference is vast."

Dr. Kawakami is optimistic that within five to 10 years we could see the first therapeutic dividends of his scientific investment. He is confident that eventually his work will help neutralize a devastating disease that has been such a challenge for scientists to understand.

"I look forward to the day when our findings will help relieve the terrible symptoms and suffering of asthmatic patients. For scientists like us who have spent such a long time in the trenches searching for answers, that will be a truly happy moment for all of us." ■

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 here:

Friends: $250 - $999

- Invitations to a stimulating series of community lectures describing the latest scientific discoveries at the Institute and their potential impact on human health
- Advance invitations to the Life Without Disease Lecture Series and reception events
- Subscription to the Institute's magazine Immune Matters
- 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@lji.org or 858-752-6542.

Former NBA Basketball Star Chris Dudley Channels His Competitive Spirit into the Battle Against Diabetes

Once you get to know Chris Dudley, a couple of things quickly become apparent: first, you should never challenge him to a game of 'one-on-one,' as you wouldn't stand a chance against the 6-foot-11 former NBA center; second, you'll probably never meet anyone more dedicated to fighting diabetes, whether it's increasing awareness of the disease, showing young people how to cope with their own diabetes, or supporting those searching for a cure for what he calls a 'modern epidemic.'

Dudley has some very personal and emotional reasons for devoting much of his post-basketball life to his own one-on-one battle with the disease. Diagnosed with type 1 diabetes at age 16 when he was a sophomore at Torrey Pines High School in Del Mar, Dudley recalls being shell-shocked and worried that his life might be over. Far from it. He not only learned how to deal with his disease, he went on to star at Yale and play 16 seasons as a center for the Portland Trailblazers and several other NBA teams.

"I get really choked up when they tell me the only time they feel normal is when they're at the camp with kids like themselves."

—Chris Dudley

That was the personal side. The emotional side comes every year when he holds his Chris Dudley Basketball Camp in Oregon for 80 kids with type 1 diabetes. Over the 18 years that he's staged the camp, Dudley has helped more than 1,500 young athletes improve their basketball skills and learn how to better handle the medical and practical logistics of their disease, all the while becoming part of a unique community.

"It's heartbreaking when I hear the stories of how these kids feel so isolated and ostracized in their schools and community because they're the only ones with diabetes," Dudley. "I really get choked up when they tell me the only time they feel normal is when they're at the camp with kids like themselves. So when I talk about a cure for diabetes, it's not because I want it for me, I want it for all the young people who are just starting out in life with this horrible disease."

In Chris Dudley, camp participants could not have a better role model. More valuable than the basketball wisdom he imparts is the 30 years of hard-won experience he can share with them on how he "never let diabetes get the best of him." Almost from the time Dudley was diagnosed, he took the disease seriously, learning how to monitor his blood sugar, improve his diet, and stick religiously to his insulin injection regimen.

"I learned how my body worked. On game days, I would take my blood sugar at least 15 times to make sure I was dialed in, but I also kept juice or a power bar handy if my levels dropped too low," Dudley says. "I'm proud to say I never once missed a practice or a game at any level of basketball because of my diabetes."

That success is why Dudley is always eager to share his most important message for anyone—youth or adult—who has type 1 diabetes: "I want them to know they absolutely don't have to give up their dreams if they have the disease. But they need to know that they can't let diabetes take control of their lives. They have to take control of it. If they do, there's no goal in life they can't achieve."

One of Dudley's own goals is to raise as much awareness as possible about diabetes treatment and prevention, not just type 1, but also type 2, which he says has the potential to become the nation's number one health—and fiscal—nightmare. Dudley participates in events such as the recent Pacific Northwest Diabetes Heath and Wellness Week in addition to speaking to civic groups, distributing podcasts, and testifying before Congress.

"I told the senators we have to get ahead of this disease, which has become a true modern epidemic. I shared the scary numbers: one out of three people born today are expected to have diabetes in their lifetime. A third of all Medicare costs are related to diabetes.

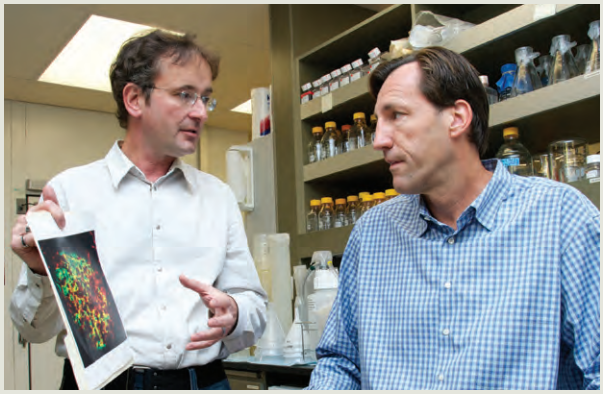
If we fail to deal with this now, we run the risk of bankrupting the system and that will mean millions could go untreated."

Research offers the best and only real hope of winning the war against diabetes, Dudley says, which is why he was eager to accept an invitation earlier this year to tour La Jolla Institute and meet with Matthias von Herrath, M.D., one of the foremost diabetes researchers in the world.

"I was impressed to see the huge scope of work the Institute is engaged in, and how it's helping understand how a lot of different diseases work. But I was totally thrilled about the potential of Matthias' research because it appears he is getting close to understanding what causes diabetes in the first place. What was so exciting about Matthias was that beyond his scientific skills and obvious brainpower, here's a man who is really passionate about his research. He's obsessed with finding a cure for diabetes."

Dudley will be able keep a closer eye on Dr. von Herrath's research now that he and wife Chris and their three children have moved back to San Diego from Oregon, where he ran for governor in 2010, losing by only one percentage point. He doesn't rule out another run at politics, but it won't be until after his kids—ages 11, 13, and 14—are grown. Until then, he will continue in his day job as a certified financial planner and overseeing his foundation, balancing that with what he sees as his real mission in life.

"I've told my family and camp kids that I'm going to stay in the fight against diabetes as long as the disease exists," Dudley says, adding with a smile. "But I've told them as soon as there's a cure, we're going to have a heck of a party!" ■



Immunologist's Research Success Inspires Hope for Treatments, Possible Cure for Type 1 Diabetes

The energy, excitement, and optimism emanating from Matthias von Herrath, M.D., are palpable when you visit the renowned diabetes researcher at his La Jolla Institute lab. They are certainly what NBA player Chris Dudley (see main story) noticed—and was inspired by—during the Institute tour von Herrath gave him earlier this year.

While Dr. von Herrath's personality is naturally confident and positive, it is the groundbreaking success he's achieved in understanding type 1 diabetes that is the real source of his passion—and why he has received so many honors, including the 2008 American Diabetes Association's Outstanding Scientific Achievement Award.

Dr. von Herrath and his team have made significant strides in understanding why the body's own immune system attacks insulin-producing beta cells, which is one of the causes of type 1 diabetes, as well as other diseases caused by viral infections. Dr. von Herrath discovered that stimulating the immune system with beta cell proteins in animals via DNA vaccines resulted in a beneficial immune response that he believes may eventually prevent type 1 diabetes in humans.

In related research, Dr. von Herrath has shown that introducing immune response modifiers, such as small molecules named "cytokines," or certain antibodies, can put the immune system back on track and prevent it from attacking the body's own cells.

"This is a disease that has been virtually impenetrable scientifically for most of the past 100 years," Dr. von Herrath says. "But now we're really on an exciting path that I believe will soon lead us to some effective therapeutic interventions for type 1 diabetics. I'm even more hopeful that we'll be able to go even further and come up with a cure for the disease through a reliable vaccine. Thinking of how many patients now and in the future who would benefit these from types of breakthroughs is really why I love this work and won't stop until we've achieved our goals."

La Jolla Institute
FOR ALLERGY AND IMMUNOLOGY

9420 Athena Circle
La Jolla, CA 92037

Non-Profit Org.
U.S. Postage
PAID
Permit No. 2325
San Diego, CA

Visit our web site at www.lji.org for the latest news and updates.

About La Jolla Institute for Allergy and Immunology

MOTTO: Life Without Disease.

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

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

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

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

SCIENTIFIC PRODUCTIVITY: Published nearly 2,000 scholarly papers in prestigious scientific journals since 1988. Numerous patents (and patents pending) for discoveries designed to yield revolutionary clinical applications.

ACCOLADES: Ranked #5 in the world in scientific impact in immunology. In 2013, ranked #1 in the "Best Places to Work in Academia" and #2 in the "Best Places to Work for Postdoctoral Researchers" in the annual survey of research institutions throughout the world, conducted by *The Scientist* magazine.