

# Immune Matters

FALL 2013

La Jolla  
Institute  
FOR ALLERGY AND  
IMMUNOLOGY

Life  
Without  
Disease.



**The  
Microbiome  
Our New  
Understanding of  
Germs in Disease**

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**Revolutionary  
Advances Ahead!**

**A Look Into The Not-too-  
Distant Future of Immune  
System Research**

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La Jolla Institute for Allergy and Immunology is dedicated to understanding how the immune system works and to applying that knowledge to promote human health and prevent a wide range of serious diseases. Since its founding in 1988 as an independent, nonprofit research organization, La Jolla Institute has made numerous major advances leading toward its goal: life without disease.

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## Letter from the President

**M**ost people recognize that our environment is rife with bacteria and other microbes. However, they may not be aware that trillions of these microscopic organisms actually reside inside and outside of our bodies! Commonly referred to as the 'human microbiome,' our microbial co-inhabitants—which assist in digestion and many other crucial bodily functions—have lately become a hotbed of scientific interest. The reason? Emerging studies suggest that these resident microbes help to maintain our health, and when these microbial communities get out of balance, they may contribute to conditions ranging from obesity to autoimmune diseases. In this issue of *Immune Matters*, we talk with experts from La Jolla Institute and other leading research institutions about the microbiome's possible role in many diseases and how it might be manipulated to improve human health.



Also in this issue, we explore the past and future of immune system research. Many major medical advances, including widespread availability of antibiotics following World War II and the growing use of vaccines, are the result of major strides in immune system research over the last 50 years. Looking ahead to the not-too-distant future, we see the potential for enormous progress against many deadly diseases through a better understanding of the immune system.

We are also delighted to welcome and introduce one of our newest Board Members Herbert Wertheim, O.D., D.Sc., M.D. (hc), a noted inventor, philanthropist, and ophthalmic and visual science industry pioneer, who shares our passion for the immune system's unlimited potential for preventing disease. In addition, we are pleased to welcome our newest faculty member, Sonia Sharma, Ph.D., who is using RNA interference technology to explore anti-viral responses as well as other key disease-fighting processes.

And finally, we wish to share with you a recent honor of which we are very pleased: we have been recognized as the best place to work in the worldwide academic research community. We feel that the quality of our science, which is reflected by our universal recognition as a world leader in the study of the immune system, has a great deal to do with this top ranking.

We focus our efforts on the immune system because we believe that harnessing its power to preserve health holds the key to conquering heart disease, diabetes, cancer, and many other disorders that have long plagued humankind. We are grateful for the generosity of individual donors, foundations, and federal funding sources that enable our critical research to proceed, and we invite all of our supporters to share our pride as we work toward life without disease. I thank you for your support, and I hope you enjoy this issue of *Immune Matters*.

Sincerely,

A handwritten signature in black ink that reads "Mitchell Kronenberg". The signature is written in a cursive, flowing style.

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

## La Jolla Institute Ranks Number One in Worldwide “Best Places to Work” in Science Survey

Recognition Marks Second Top Ranking This Year for Best Research Workplace

La Jolla Institute for Allergy and Immunology has earned the Number 1 ranking in *The Scientist* magazine’s 2013 “Best Places to Work in Academia” survey of the worldwide academic research community.

La Jolla Institute is joined in the “Top Ten” by such major research institutions as the University of Pittsburgh at number 4, St. Jude Children’s Research Hospital at number 7, and Scripps Institution of Oceanography at number 8.

This first place finish comes on the heels of La Jolla Institute’s rank as number 2 in the “Best Places to Work for Postdocs,” *The Scientist’s* national survey of postdoctoral researchers who are junior-level scientists in training, which was announced in April.



The results of these surveys put La Jolla Institute in the unusual position of garnering two of the top research workplace rankings for 2013. President and Chief Scientific Officer Mitchell Kronenberg, Ph.D., was extremely pleased. “I think our collaborative atmosphere and the quality of our science are absolutely central to being regarded as a great place to work,” he says, noting that the Institute is now recognized as one of the top medical research organizations in the world, based on its highly cited immunology research.

More than 1,200 full-time life scientists working in academic or noncommercial research institutions worldwide participated in the “Best Places to Work in Academia” survey, covering topics such as scientific excellence, research resources, and job satisfaction. In the same survey in 2012, the Institute earned the number 6 ranking, while landing at number 7 in the 2012 postdoc survey.

“The two recent rankings combined really shout that La Jolla Institute is an exceptional place to conduct research,” says Stephen Wilson, Ph.D., an immunologist and Institute Executive Vice President. “After doing well in other years, it is also rewarding to know that we reached our highest rankings in this year’s competition, the final year that *The Scientist* is conducting the survey.”

John Major, a prominent San Diego business executive and Chairman of the Institute’s Board of Directors, says the recognitions speak volumes. “When you see this kind of positive feedback from employees, coupled with the Institute’s stellar scientific reputation, you realize that something special is going on at La Jolla Institute,” says Major. “We are fortunate to have an immunology leader of the Institute’s caliber as a member of San Diego’s world-renowned life science community.”



# THE Microbiome

New Research Links Our Microbial Co-Inhabitants to Everything from Obesity to Chronic Infections

**I**t may seem quite strange to learn that germs are actually critical to human survival. After all, this runs counter to childhood warnings that we should strive for constant cleanliness and do everything possible to avoid dirt, grime, and other sources of germs in order to remain healthy.

But a growing body of scientific evidence reveals that not all germs are bad for us and that many germs play a surprisingly important role in maintaining our health. As it turns out, germs—primarily bacteria—are our personal companions, with several thousand species of microbes, amounting to trillions of bacteria, living inside and outside of our bodies. This huge bacterial system and its genetic components, commonly referred to as the ‘human microbiome,’ is the focus of numerous studies that link our microbial co-inhabitants to everything from obesity to chronic infections. “It’s an extremely hot research area because it offers the potential to treat disease by manipulating the bacteria residing on our skin, in our mouths, in our

lungs, and in our intestines,” says La Jolla Institute President Mitchell Kronenberg, Ph.D., who studies how certain microbes in our gut may contribute to Crohn’s disease or leave us more vulnerable to *E. coli* and other infections.

## What on Earth are Bacteria Doing in Our Bodies?

“The bacterial cells that reside in our body vastly outnumber our human cells, and they influence our health status in extremely important ways,” says Kronenberg. Indeed, bacterial cells outnumber human cells 10 to 1! And in terms of sheer numbers of genes, the total number of genes in our microbial occupants is nearly 500 times larger than the approximately 22,000 genes in the human genome.

David Artis, Ph.D., a professor at the University of Pennsylvania and a prominent

microbiome researcher, describes these resident bacteria as “partners in our journey” which are essential to helping digest food and influencing other major functions such as our blood vessel development, metabolism and immune system operation. “We know, for example, that the healthy human intestine is colonized by trillions of beneficial bacteria,” says Artis.

La Jolla Institute scientist Hilde Cheroutre, Ph.D., notes that our bacterial occupants primarily live in the areas where our body is in contact with the outside world, such as the mouth, nose, skin, and most predominantly the intestine, and which are also the most common entry points for infectious agents. “These microbes are pivotal in building strong immunity at the body’s borders (called mucosal surfaces),” says Cheroutre, a



*Neisseria lactamicacac mitis*



*Escherichia coli*



*Staphylococcus epidermidis*



*Clostridium sordellii*

*Streptococcus anginosus*

**Common  
bacteria that  
are found  
hitchhiking  
in and on the  
human body.**

world renowned expert on mucosal immunity. She notes that numerous experiments have shown that germ-free mice have very few T cells—the body’s key disease-fighting cells—in the gut. “When we’re born, bacteria start to populate our gut. This serves as a ‘call to arms’ to our T cells to strengthen our intestinal borders against dangerous microbes that occasionally try to sneak past.”

The relationship between our immune system and the microbiome is very much a two-way street, she adds. “Just as microbes in our gut foster our immune system’s early development, our immune system affects the ongoing composition of our resident bacteria,” says Dr. Cheroutre, who notes that the immune system serves as the gatekeeper, not only preventing bacteria from crossing the gut barrier into the body, but influencing the

“You need the appropriate composition of species of bacteria to promote an immunologic balance.”

types of bacteria that can live inside the intestine or on other surfaces such as the skin.

**Microbial Imbalance Can Lead to Disease**

Serious health problems can arise, say researchers, when our microbial communities get out of balance from a lack of bacterial diversity or a proliferation of the ‘wrong’ kind of microbes.

One result appears to be chronic inflammation, explains Artis, who studies the ef-

fects of individual bacterial species on inflammation-fueled disorders such as asthma, allergies, and inflammatory bowel disease.

“Some bacterial species can be pro-inflammatory, while others dampen the body’s immune response. In a healthy human, you need the appropriate composition of species of bacteria to promote an immunologic balance.”

**Medication Effectiveness, Multiple Sclerosis, and More**

Recent advances in gene sequencing and computational technologies have revolutionized the study of the microbiome, with researchers now exploring its role in a vast number of areas including how we respond to medications.

Jeremy Nicholson, Ph.D., an internationally recognized scientist from Imperial College London, found that the production of a molecule called ‘4-cresol’ by gut-dwelling bacteria affects the absorption of acetaminophen (e.g., Tylenol) in humans. “It may also affect the sulfate chemistry of hundreds of other drugs as | *Continued on page 6* >>

## THE Microbiome

well,” says Nicholson.

He adds

that someday it may be possible to improve health outcomes by targeting bacteria whose byproducts influence the effectiveness of particular medications. “If we know which bugs go with which drugs,” says Nicholson, “we can think about ‘drugging the microbiome.’” He cites a 2010 study, published in *Science*, in which researchers showed that the toxic side-effects of a colon cancer drug called ‘CPT-11’ were lessened in mice by inhibiting the production of a specific bacterial enzyme.

Some other microbiome studies—though not necessarily appropriate subjects for dinner conversation—are also producing very interesting results:

- ◆ ‘Fecal transplants’ have been shown to effectively treat an antibiotic-resistant bacterium known as *C.difficile*, which kills 14,000 Americans each year. In this process, microbes harvested from a healthy person’s fecal matter are inserted into a sick person’s lower intestine to attack the deadly microbe.

- ◆ Worm therapy is now in clinical trials for the treatment of multiple sclerosis. Sci-

entists at the University of Nottingham in England are testing controlled exposure to the human intestinal parasite hook worm, known to stimulate beneficial immune responses which may be related to changes in gut microbes.

### The Microbiome-Obesity Link

One of the most talked-about areas in microbiome research is obesity—a subject intensified by a high-profile 2006 *Nature* paper from Jeffrey Gordon, Ph.D. and his colleagues at Washington University in St. Louis. In the study, the researchers looked at the mixture of bacteria in the guts of obese and thin Americans. Obese people, they discovered, had more of a gut bacterial type known as ‘Firmicutes’ and fewer ‘Bacteroidetes’ than did thin test subjects. And if dieting made an obese person thin, the individual’s proportion of Bacteroidetes increased to resemble that of a thin test subject.

Harvard University researcher Peter Turnbaugh, Ph.D., who authored this study as a graduate student in Gordon’s lab, today continues to explore the obesity-microbe connection. In another surprising finding,

he showed that lean mice transplanted with the intestinal microbes of obese mice gain weight.

While these are intriguing results, Turnbaugh readily admits that there’s “still a lot we don’t know” about how, why, and to what extent microbial communities influence obesity. “We think that microbes may play a significant role in how food is metabolized, processed, and stored,” he says. For instance, “some bacteria may hasten weight gain by helping people extract extra calories from their food.”

If this proves true, then another, even larger issue remains: why do some people harbor ‘bad’ fat-leaning bacteria and others ‘good’ beneficial bacteria?

“That’s really the million dollar question,” says Turnbaugh, who is particularly interested in the role of one’s diet in shaping microbial communities. “If you take mice from a standard low-fat diet and transfer them to a typical Western diet (high fat and high sugar), the structure of the microbial community changes radically in a single day,” he says. Results in humans are more complicated, but “there is definitely evidence that diet,

## Too Clean for Our Own Good? *The Hygiene Hypothesis*

Television commercials featuring talking mops, animated bacteria, and gleaming kitchen counters are constant reminders of the importance of maintaining a clean and pristine environment.

But is society’s heavy emphasis on cleanliness producing some unintended, negative consequences in the U.S. and other developed countries? Some scientists think so, while others say more study is needed.

Originating in the late 1980s, the ‘hygiene hypothesis’ suggests that excessive cleanliness may be causing a rise in allergies, asthma, and various autoimmune diseases in the developed world. They point to rising U.S. allergy statistics as reflecting this trend. According to the National Institutes of Health, more than 50 percent of Americans aged 6 to 59 are sensitive to at least one allergen. That’s two to five times higher than rates found in a survey from 1976 to 1980!

While researchers can’t definitively link this trend to our fastidious habits, they note a shift towards more sterile home environments since the early 19th century, a steady population movement from

rural to urban areas, and couples having fewer children—all of which have contributed to children being exposed to fewer ‘germs.’ This lack of exposure interferes with the natural development of our immune system, according to the hypothesis.

“Viral infections, when you undergo them, ‘tune’ the immune system, and this tuning is lost when you avoid the infection,” explains Matthias von Herrath, M.D., director of La Jolla Institute’s Diabetes Research Center. “You’re better off, because you don’t



to some degree, can shape the composition of microbes in the human gut.”

Another prominent finding from Belgian researcher Patrice D. Cani, Ph.D. points to a

**Adding prebiotic plant (dietary) fibers found in foods such as bananas, garlic, and asparagus into the mouse diet tames the junk food-fueled rise of endotoxins and resulting inflammation and weight gain.**



particular culprit in the diet-microbe-obesity cascade. His study in mice found that a molecule known as ‘endotoxin,’ located in the cellular membrane of certain gut bacteria, could leak into the blood stream, triggering inflammation that leads to metabolic syndrome and ultimately weight gain. Junk food fuels this cascade, according to Cani’s study.

Along with diet, Turnbaugh says that one’s genetics and physical environment, an excessive use of antibiotics, and the societal emphasis on cleanliness are also believed to affect microbial balance (see sidebar on hygiene hypothesis).

### **Keeping our Gut Bacteria Happy— Is Improving our Diet the Answer?**

A number of research studies are exploring whether microbial gut balance, and in turn our health, can be improved through healthier food choices.

Primary among the research is probiotics, certain bacteria that have long been thought to have healthful properties.

“Probiotics such as ‘Lactobacilli’ in yogurt and other food stuffs are an attempt to deliver more of the beneficial bacteria

that promote balanced immune responses,” says Artis. Prebiotics—food that is likely to increase the growth of good bacteria—are also gaining interest. This work is in its early stages, but there are initial reports of some beneficial effects.

Cani, for instance, has showed that adding prebiotic plant (dietary) fibers found in foods such as bananas, garlic, and asparagus into the mouse diet tames the junk food-fueled rise of endotoxins and resulting inflammation and weight gain.

Some scientists caution against overblown expectations from probiotics, while others say that more testing is needed to determine proper dosage and develop more targeted approaches. Still others, particularly in the integrative medicine community, advocate an ‘anti-inflammatory’ diet which avoids processed foods and sugars that are shown to increase inflammation.

Kronenberg says the jury is still out on this and other approaches. But the possibilities are exciting. “It may one day be possible, with rather simple biologic remedies or even food additives, to alter our immunological status in order to treat disease.” ■

have the risk of dying from the virus infection. But the immune system evolved to defend us from these things, and thus it loses its practice, or its tuning aspect.”

The hygiene hypothesis says this lack of tuning early in life skews immune system balance, causing it to overreact to environmental agents, such as dust, pollen, and mites, leading to allergies. The reduced immune prepping can also cause unwarranted immune attacks against our own cells, contributing to Crohn’s disease, other autoimmune diseases, and asthma, according to the hypothesis.

La Jolla Institute President and Chief Scientific Officer Mitchell Kronenberg, Ph.D., says the link between immune problems and excessive cleanliness is under intense investigation, but remains unproven. He notes that more study is needed. “Even in modern ultra-clean environments, humans carry literally trillions of microbes on and in their bodies, but only some may prevent excessive immune reactions,” says Kronenberg. “Therefore a critical issue is which types of microbes are responsible for tuning or educating

the immune system to achieve the proper balance early in life.”

While many questions remain, numerous research studies are turning up interesting findings. A study by German researchers found that children exposed to farm animals are about half as likely as other children to develop the immune-mediated illness Crohn’s disease. Even children who are raised with domestic animals see health benefits. For example, children who live in a home with two or more dogs or cats during their first year of life are much less likely to develop allergic diseases compared with children raised without pets, according a 2002 study published in the *Journal of the American Medical Association*.

Supporters of the hypothesis also point to a markedly lower incidence of allergies, asthma, and autoimmune diseases in undeveloped countries. On the other hand, they say that higher rates of infectious diseases in these countries point up the need for a balance between maintaining proper sanitation and allowing exposure to relatively harmless pathogens.

## Only 26 Vaccines in the Entire World? Award-winning Scientist Discusses Challenges in Vaccine Design



*La Jolla Institute faculty member Shane Crotty, Ph.D., focuses on infectious diseases, which kill more people worldwide than any other single cause. Throughout his career, Crotty has earned a number of accolades for his breakthrough discoveries that have advanced worldwide efforts to create new and more effective vaccines. In 2005, Crotty was chosen as one of America's "Most Promising Biomedical Researchers" by the Pew Charitable Trusts for his early work on immune mechanisms. And in 2009, his seminal discovery of the molecular trigger for antibodies landed him on National Public Radio and the San Diego Union Tribune's front page. In 2012, he received the Biosciences Investigator Award from the American Association of Immunologists, a prestigious honor recognizing early-career scientists for outstanding research contributions. In the following article, Crotty discusses current challenges in developing vaccines, which remain one of the greatest health interventions ever invented.*

**Q:** Only 26 vaccines currently exist worldwide. Why don't we have more vaccines, especially considering that many dangerous diseases such as malaria, AIDS, and tuberculosis still have no effective vaccines?

**A:** The simple answer is that all the easy ones already exist. By that I mean the scientific community has developed vaccines for the diseases that we knew how to address. So what's left are the 'hard ones,' in other words extremely complex diseases that present special challenges for vaccine researchers.

This brings me to the subject of vaccine design and its lack of a structured process, which I see as the biggest obstacle to new vaccine development today. Almost all of our current vaccines work on the basis of antibody responses. However, most of these have been made in a hit or miss, trial and error process, instead of using a scientific approach based on in-depth knowledge of cellular mechanisms, or what I refer to as 'rational vaccine design.' So despite their critical importance, vaccine development still involves a lot of guesswork. The papillomavirus vaccine, for example, involved people trying a variety of different ways to make a vaccine. Basically all of them failed except one. It's wonderful that this vaccine works, but I think we could be much faster and more effective if we had a step-by-step engineering-based approach for vaccine design.

That's one of the reasons my lab focuses on identifying the key cellular mechanisms involved. We're trying to understand enough about the process to develop straightforward principles for creating great antibody-based vaccines.

**Q:** How do most vaccines work?

**A:** All vaccines are based on immune memory, which refers to our immune system's ability to remember and protect us against viruses, bacteria, or other invading pathogens.

Here's how it works: A previous encounter with a virus 'teaches' the immune system to recognize and remember that exact pathogen should it ever show up again. A vaccine's purpose is to do the same thing without the person being infected. To accomplish this, vaccines contain pieces of the pathogen or a similar virus which cement themselves in the immune system's memory without making the receiver sick. As part of that process, the immune system builds up antibodies, which seek out and destroy the virus if it reappears.

**Q: Which diseases currently receive the greatest emphasis for vaccine development?**

**A:** HIV, malaria, and tuberculosis are the big three killers among infectious diseases, so they are the major areas of focus right now.

**Q: What has made these diseases particularly challenging for vaccine developers?**

**A:** **HIV – the virus that causes AIDS.** For the first time in 30 years, there is a lot of excitement about creating an antibody-based vaccine for HIV-infected people. For a long time, it wasn't thought possible. This was due to a belief that humans just don't make good antibodies against HIV and also because the virus is extremely changeable. But over the years people began to turn up who could make antibodies capable of neutralizing nearly all of the HIV varieties. Researchers began testing their antibodies in animals and found them protective against HIV-like disease. These studies renewed hope about developing a potent antibody vaccine. In 2012, the NIH funded two major HIV/AIDS vaccine research consortiums, including one at The Scripps Research Institute. I'm one of Scripps' collaborators, and my lab focuses on cells needed to generate a strong antibody-based AIDS vaccine (T follicular helper (TFH)).

**Malaria.** There are a number of problems with malaria. Malaria has several different stages of its life cycle, and each stage is really hard to vaccinate against. Another problem is that people don't

develop strong immune memory to malaria infection, and can get infected multiple times. Most kids in malaria-endemic countries catch malaria many times before they enter high school. Another thing is that antibodies may not be very good at protecting against malaria. Animal experiments indicate that a certain type of T cell (CD8 T cells, which are disease-fighting immune cells) are important in controlling malaria infections, but the scientific community is not skilled at developing T cell-based vaccines. In fact, there is no licensed vaccine that works on the basis of CD8 T cells, although there have been several attempts. The results of a major malaria vaccine trial in Africa were recently announced, and it failed. Many people believe this occurred because the vaccine focused on generating antibodies, not CD8 T cells. A number of our Institute's researchers study how to generate these cells, so we are among those trying to find answers.

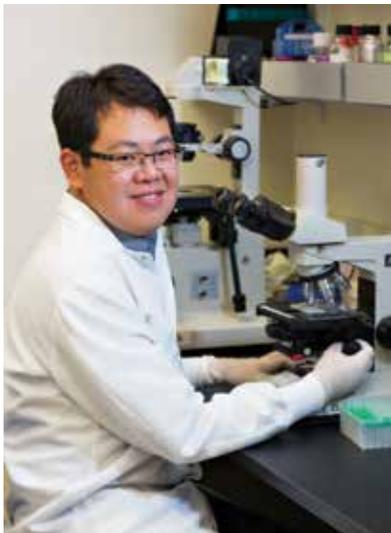
**Tuberculosis (TB).** TB is interesting because there is a vaccine against TB called the 'BCG vaccine.' It's not used in the U.S. because basically it doesn't work in adults and provides only a little protection in very young kids. There are several theories about why it's been so difficult to create a strong TB vaccine. One theory is that, like malaria, antibodies may not work in stopping a TB infection, and that a T cell vaccine may be needed. This gets back to my earlier comment about the need for more work on T cell-based vaccines for certain infections. I think we're going to see more emphasis on that in the future. ■

**FACTS ABOUT INFECTIOUS DISEASE**

## Did You Know?

- >> **More than 200,000 Americans are hospitalized with the flu each year, and approximately 36,000 people die from it annually.**
- >> **Tuberculosis kills about 1.7 million people worldwide annually.**
- >> **There are 250 million malaria cases every year and it results in nearly 1 million deaths. In Africa, one of the hardest hit areas, every 30 seconds a child dies from this dreaded disease.**
- >> **About 2,500 cases of multidrug-resistant tuberculosis have been reported in the U.S. within the last 15 years.**
- >> **Infectious diseases kill more people worldwide than any other single cause.**





Kok-Fai Kong, Ph.D.

## Scientist Receives Research Grant from Major Melanoma Alliance

**T**he Melanoma Research Alliance (MRA), the largest private funder of melanoma research, has selected La Jolla Institute scientist Kok-Fai Kong, Ph.D. for a grant award designed to support promising research efforts against melanoma, one of the fastest growing cancers in the U.S. today.

Kong is one of 49 scientists at leading academic institutions throughout the world to receive the MRA's 2013 awards, which the organization hopes will accelerate the creation of new therapies for preventing, detecting, and treating melanoma.

"This year's grants are at the cutting edge of the most promising areas of inquiry in the field of melanoma research," says Wendy K.D. Selig, president and CEO of MRA, who notes that 80,000 new cases of melanoma are diagnosed annually, with the numbers rising—particularly among young people.

"I am very honored to receive this award," says Kong, a researcher in the lab of senior faculty member Amnon Altman, Ph.D., who is also the Institute's director of scientific affairs. Kong's melanoma project builds on Altman's groundbreaking discoveries on novel mechanisms involved in triggering T cells to destroy diseased cells. T cells are the body's key 'soldiers' in combating disease. "This grant will propel my research in tumor immunology, with a focus in melanoma, and may also have implications for other cancers," adds Kong.

Altman calls Kong "a well-deserving candidate" for this award. He notes that "since joining my laboratory, Kok-Fai has made major contributions to our research projects. He is an independent thinker and his original ideas often represent a starting point for promising new projects in the lab."

## Patrick Hogan Discovers Molecular Feat Essential to Disease-Fighting T Cells

**W**hile hard to imagine, our body's cells must sometimes engage in near herculean efforts to make the connections needed for our survival. Such is the case with certain molecular proteins necessary for activating T cells, the body's most important disease-fighting cells.

La Jolla Institute scientist Patrick Hogan, Ph.D. has discovered how a protein called 'STIM' reaches across to the T cell's plasma membrane, from its position inside the cell, to open a calcium channel on the surface of the T cell. This vitally important channel allows calcium to enter T cells from the blood stream, a process that is essential for triggering T cells to fight disease.

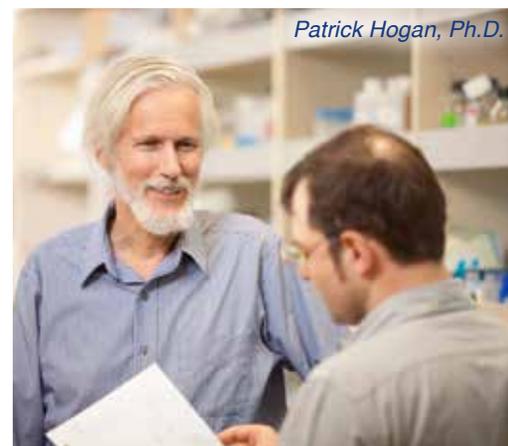
"The distance is extremely small, only 15 or 20 nanometers, but that's a big gap for a protein," says Hogan. "If you compare it to

humans, it would be like asking us to reach up three stories."

In his study, published July 14th in the prestigious journal *Nature Structural & Molecular Biology*, Hogan illuminates this process, likening it to a spring-loaded mechanism, in which STIM reaches across, opens the channel, and then later snaps back into place. Yubin Zhou, Ph.D., formerly of La Jolla Institute and now an independent faculty member at Texas A&M Health Science Center, was the study's first author. Hogan was senior author.

While opening the channel may seem like a tiny step in a T cell's life, it actually represents a biological process of immense importance, considered key in human health and disease. Hogan and fellow scientist Anjana Rao, Ph.D. are world leaders in the study of the calcium channel. Their

groundbreaking discovery in 2006 of the protein that forms the calcium channel solved one of the biggest mysteries in biomedical science because it is the gateway to T cell functioning. Hogan's latest study is a continuation of these research efforts.



Patrick Hogan, Ph.D.



*Sonia Sharma, Ph.D.*

## Sonia Sharma Appointed to Faculty

**S**onia Sharma, Ph.D., an expert in high throughput genomic screening using RNA interference (RNAi), has been promoted to assistant professor in the Division of Cell Biology. Sharma has published groundbreaking work on the biology of gene functions in the immune

system and came to La Jolla Institute in 2011 to serve as scientific director of its new RNAi Center. Prior to joining the Institute, she was a scientist and instructor at Harvard Medical School.

The Institute's RNAi Center is a centralized, state-of-the-art platform for carrying out cutting-edge genomic research. It is one of the few facilities of its kind in the world, and represents an important local resource for La Jolla Institute and the San Diego academic research community. Using the Center's innovative technologies, scientists can 'turn off' individual genes one at a time to evaluate how they contribute to cancer and other diseases with underlying genetic origins. Sharma will continue as the Center's scientific director, while also establishing her own laboratory.

"Dr. Sharma is an exceptionally talented and creative young scientist whose innovative studies using RNAi screens have made her a recognized leader in understanding how white blood cells are activated to carry out immune responses that protect us from disease," says Institute President & Chief Scientific Officer Mitchell Kronenberg, Ph.D. "As a member of our faculty, I think she will continue to tackle problems of great biomedical importance as she expands her research to systematically dissect the mechanisms by which our body rapidly mobilizes its innate immune defenses against infections such as influenza and hepatitis C."

Sharma's work also has implications for understanding the immune system's role in complex inflammatory diseases such as lupus, rheumatoid arthritis, and asthma, notes Kronenberg.

Sharma began her career in basic science doing undergraduate honors work at McGill University in Montreal, Canada, where she investigated the genetic basis of a rare form of adult T-cell leukemia (ATL). She received a B.Sc. degree from McGill, followed by a Ph.D. in 2004, for which she received the Wilfred Yaphe Award for outstanding academic achievement in a graduate program for work that identified an elusive cellular 'on-switch' for triggering immune response to viral infections. She was also the recipient of several postdoctoral fellowship awards from the Canadian Institutes of Health Research and received a special fellow award from the Leukemia and Lymphoma Society to continue her work investigating gene functions in the immune system and the genetic causes of disease.

## Michael Croft Speaks on Breakthrough TNF Research at Major Symposium

**M**ichael Croft, Ph.D., an internationally recognized scientist in the field of immune cell stimulation, was a featured speaker at the annual meeting of the American Association of Immunologists (AAI) in May. Croft was one of four scientists invited to speak during the event's President's Symposium, an honor bestowed by the AAI President. AAI is a highly respected worldwide scientific association whose members focus on advancing immune research to combat disease.

The four President's Symposium speakers were experts on the tumor necrosis factor (TNF) family of molecules, a hot area of scientific study due to their potential importance in diseases ranging from cancer to asthma. Croft spoke about TNF molecules, which have been prominent in his lab studies. One of his discoveries is the basis for a new asthma drug now in pharmaceutical development. His finding was considered a breakthrough because it has the potential to control asthma longer and more effectively than existing therapies.



*Michael Croft, Ph.D.*

# What Lies Ahead?

## Immune System Discoveries Will Completely Redefine

In the early 1900s, many children didn't live to see their first birthday. Life expectancy was nearly half of what it is today. And diseases such as diphtheria killed more people in the United States than did cancer. "Before we understood how to avoid or treat infection, two out of 10 children died in the first few years of life," says Stephen Wilson, Ph.D., an immunologist and La Jolla Institute Executive Vice President.

But public health measures, the widespread availability of antibiotics after World War II, and growth in the types and use of vaccines have led to improvements in health and life expectancy which our great-grandparents could only dream about. "When you consider that polio contagion was still a very real fear in the U.S. in the 1950s, or that the measles vaccine wasn't licensed until 1963, you realize that immunology research has made enormous strides

in the last 50 years," says Wilson. "It's exciting to consider what may lie ahead in the next 30, 40, or even 50 years."

### THE NOT-TOO-DISTANT FUTURE OF IMMUNE SYSTEM RESEARCH

Just as our ancestors couldn't imagine life without diphtheria, smallpox, and many other deadly diseases, the next 30 to 50 years hold the potential for major advances or even the elimination of many devastating illnesses currently regarded as an inevitable reality in our world. "Our ability to control microbes through the advent of antibiotics changed the world," says Mitchell Kronenberg, Ph.D., La Jolla Institute President & Chief Scientific Officer. "One day we may be able to say the same thing about chronic inflammation, which is an immune system function at the heart of many of today's deadliest disorders."



### DEVELOPING A FIRST-EVER VACCINE FOR HEART DISEASE

Though it may not be obvious, inflammation plays a pivotal role in heart disease. Research over the past 15 years has shown that inflammation is a major contributor to arterial plaque buildup, also known as atherosclerosis, which is the underlying cause of most heart problems. Inflammation not only worsens plaque buildup, it weakens and destabilizes plaque formations. This in turn causes cholesterol-laden plaques to rupture, triggering formation of blood clots that impede blood flow, ultimately leading to a heart attack. Institute scientist Klaus Ley, Ph.D., a pioneer in vascular immunology, is currently testing the world's first heart disease vaccine, which aims to dampen inflammation by halting the body's mistaken attack on certain arterial proteins, a battle whose byproduct is inflammation. Noted Scripps cardiologist Eric Topol, M.D., has praise for Ley's efforts, calling a vaccine "an ideal way to prevent atherosclerosis—the main culprit of heart disease." Ley's early work shows great promise, with plaque lesions significantly reduced in mouse studies.

### PREVENTING THE IMMUNE SYSTEM FROM ATTACKING HEALTHY CELLS

In an apparent case of mistaken identity, our immune system sometimes attacks and destroys healthy cells, leading to a variety of autoimmune diseases. The specific type of autoimmune disease depends on the part of the body attacked—for instance, type 1 diabetes results from an attack on the insulin-producing beta cells in the pancreas, whereas multiple sclerosis is caused by attacks on the insulation surrounding nerve cells. A number of La Jolla Institute researchers are probing new ways to stop these unwarranted attacks. A particularly intriguing breakthrough involves the work of Amnon Altman, Ph.D., who discovered an enzyme that is essential for instigating T cell attacks involved in autoimmune and many other diseases. Altman has shown that blocking the enzyme's activity in T cells could stop the immune onslaught. He is now working on therapeutic targets for blocking this interaction, which could lead to a new treatment for autoimmune disease.



# Health Care in the Next 30 Years

Indeed, heart disease, stroke, diabetes, and autoimmune diseases such as multiple sclerosis and rheumatoid arthritis are all inflammation-fueled disorders. Meanwhile, cancer and infectious diseases could also become a thing of the past if the immune system's immense powers can be harnessed. "If we can control the immune system, we'll be able to create vaccines against any new or existing pathogens, cure autoimmunity, limit inflammation's effects on heart disease, stroke, and other vascular disorders, and provide a major weapon in the war on cancer," says Kronenberg.

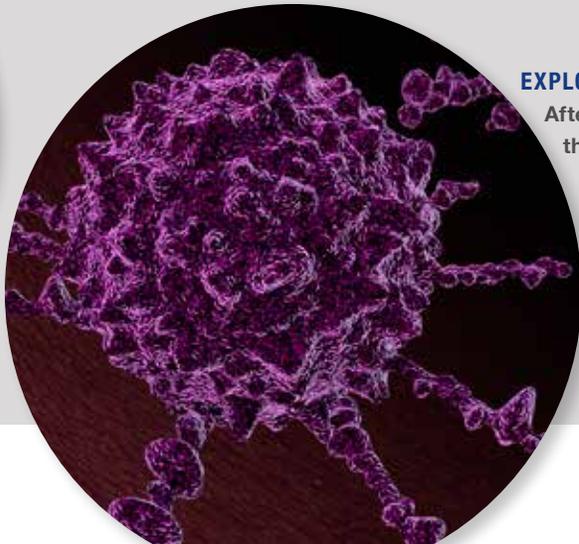
At La Jolla Institute, which recently adopted the motto "Life Without Disease," exciting research is underway to bring the world closer to that goal. "Life Without Disease' is our vision, a destination we work toward and which we believe is the true mission of biomedical

research," says Wilson. "As one of the world's leaders in immune system research, we believe we are focused on the one system that could most quickly lead to that goal."

Below are just a few examples of how La Jolla Institute researchers are helping tackle the major health problems of today through focused research on the immune system. In the same way that many of the health threats of the past were conquered by discoveries that led to treatments like antibiotics, improved sanitation, and an understanding of infectious disease transmission, La Jolla Institute scientists are working on the front lines of our current-era health scourges. With continued funding support and a stimulating and encouraging research environment, great progress is expected toward the goal of Life Without Disease. ■

## LEADING INNOVATIONS IN VACCINE DESIGN

La Jolla Institute researchers include some of the top vaccine specialists in the world. Their breakthroughs are advancing worldwide efforts to create vaccines for tuberculosis, AIDS, dengue virus, and other deadly pathogens. For instance, a landmark discovery by Shane Crotty, Ph.D. in 2009 identifying the molecular switch required for generating protective antibodies—essential for a successful vaccine—marked an enormous advance in understanding effective vaccine design. In addition, a study by Alessandro Sette, Ph.D., and Institute faculty colleagues Howard Grey, Bjoern Peters, and Sujana Shresta, Ph.D.s, published in April, demonstrated the need for a new approach to dengue vaccine development, challenging current scientific theory. Along with these groundbreaking studies, the Institute hosts the world's largest database on how the body responds to infectious and autoimmune diseases. Selected by the National Institutes of Health (NIH) to design and host this amazing data treasure trove, the Institute has gained a prominent voice in international vaccine efforts through the development of this critical resource. Funded by the NIH, the database is freely available to researchers around the globe.



## EXPLORING IMMUNE-BASED APPROACHES TO BATTLING CANCER

After years of debate, cancer immunotherapies have finally come of age, and new therapies that enable immune cells to recognize and destroy cancer cells are rapidly emerging. Immune therapies for prostate cancer and melanoma were introduced over the last two years, and in 2012, an experimental immune therapy saved a six-year-old girl who was near death from leukemia. Other cancer immunotherapies are in clinical trials and show impressive results in skin, lung, and kidney cancers. La Jolla Institute researchers have helped to reveal some of the key immune mechanisms underlying the new therapies, and Institute scientists have more novel studies underway, several of them focused on unleashing T cells against tumors.

# La Jolla Institute Board Welcomes Herbert Wertheim

Inventor, Philanthropist, Clinician, and Visual Science Pioneer Shares Institute's Passion for Disease Prevention

**N**oted scientist and ophthalmic industry leader Herbert Wertheim, O.D., D.Sc., M.D. (hc), whose inventions have saved millions from blindness and other debilitating eye conditions, harbors a deep respect for the value of time. His philosophy of life is to make every minute count.

"The only common denominators for all of us are time and our humanity," says Dr. Wertheim, who recently joined La Jolla Institute's Board of Directors. "It's what we do with these precious resources that define who we are."

What Dr. Wertheim has chosen to do—and continues to do—with his "precious resources" makes for a remarkable story of outstanding personal and professional accomplishment despite a life of early adversity.

Today, approaching his 75th year, Dr. Wertheim is founder and president of Brain Power Inc., the world's largest manufacturer of ophthalmic instruments and chemicals, has a medical college and a 1000-seat concert hall and performing arts theater bearing his name, holds more than 100 patents and trademarks, and has invented some of the most important ultraviolet and therapeutic lens technologies of our time. Dr. Wertheim was recently inducted into the Horatio Alger Association of Distinguished Americans, joining the ranks of Oprah Winfrey, Senator Bob Dole, Carol Burnett, and his good friend astronaut Buzz Aldrin as Americans who have made extraordinary achievements despite humble beginnings.

In talking with Dr. Wertheim, you'll find a man brimming with a thousand ideas and extreme positivity. "I don't believe in sustained negative thoughts," says Dr. Wertheim, who continues to research longevity and new vision technologies, particularly those focused on diminishing age-related damage and extending the usefulness of body and mind well beyond 100 years. This goal is also reflected in his strong belief in educating young doctors-to-be and the medical profession about the benefits of wellness and preventive medicine—a primary reason he joined La Jolla Institute's Board of Directors.

"La Jolla Institute is the world leader in immunology research, which offers amazing potential for preventing disease," says Dr. Wertheim, noting the Institute's motto of Life Without Disease. "The potential to avert disease, rather than treating it after significant damage has already occurred, is exciting and something I have pursued in my own research. I feel a real kinship with its mission."

Dr. Wertheim's emphasis on prevention started early in his op-



**"I don't believe in sustaining negative thoughts."**

**—Herbie Wertheim**

tometric career as he witnessed the tragedy of blindness in the elderly caused by macular degeneration. "The most important thing I could see in my practice was the need to prevent eye damage, so people wouldn't go blind in their later years."

He made a major discovery toward that goal in the 1970s, when he was the first to reveal the dangers of ultraviolet (UV) light. "Before I started publicizing it, the medical profession and population weren't aware that absorption of UV light contributed to eye problems and possible blindness," says Dr. Wertheim, who was the first to develop UV-absorbing lens tinting technology, which has helped prevent cataracts and other eye diseases in millions of people.

Dr. Wertheim's focus on preventive medicine is also evidenced in several of his philanthropic endeavors. In 1985, he joined the board

of Florida International University (FIU), a major public university in Miami, and later championed the University's creation of a medical college. Dr. Wertheim also led FIU's Medical College Initiative, which he and his wife Nicole personally supported with a \$40 million gift in 2009 including a state match of \$20 million.

FIU's Board of Trustees named the new college "Herbert Wertheim College of Medicine" in his honor, and also adopted an innovative curriculum reflecting his focus on wellness and longevity. At the Medical College's first graduation in June, Dr. Wertheim presented their MD diplomas along with the University President and deans, calling it "very heart-warming and the beginning of a new era in medicine."

Being the impetus behind a new medical school would be an incredible accomplishment for anyone, but is even more impressive considering Dr. Wertheim's challenging early years. Born to German immigrants in 1939, Dr. Wertheim describes a wonderful mother and an abusive father whose violence led to his parent's divorce. Ordered by the court to remain with his father to help run the family bakery, Dr. Wertheim often ran away from home at a very young age to avoid his father's wrath. This tumultuous upbringing eventually led to his enlistment in the Navy at age 17, which proved to be a pivotal decision. "To this day, it was one of the most important, life-changing experiences of my life," says Dr. Wertheim.

He thrived under the Navy's guidance and encouragement, excelling in avionics engineering and eventually becoming a naval aviator and later a NASA engineer. After his discharge from the Navy, he graduated from Brevard Community College and the University of

# Institute Community

Florida, earning a bachelor's degree in optical engineering, followed by a Doctor of Optometry from the Southern College of Optometry. In recent years, he has been awarded an M.D. degree, Honoris Causa (hc), from FIU in recognition of his 45 years of clinical eye research and inventions, as well as the University's Doctor of Science (hc) degree for his distinguished scientific career.

Over the years, Dr. and Mrs. Wertheim have contributed to hundreds of charities and Dr. Wertheim also is or has been a majority shareholder, chairman, or board member of 18 private, NYSE or NASDAQ companies in banking, health care, aerospace, and other industries.

In addition to staying busy with his business, research, and philanthropic interests, Dr. Wertheim focuses on family, and notes that he is blessed with a loving wife, two wonderful daughters and four grandchildren. He also maintains a strong belief in the importance of giving back to family and society.

"I want to do as much as I can to make a difference in this world," he says, always mindful of the precious nature of time. "I am 74 now and I figure if I live 20 more years, then I have 7,000 days ahead of me. I still have a lot I want to accomplish in those 7,000 days. None of us knows how many ticks remain on our clocks." ■

# 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:

For more information contact Rachel Jonte at [rjonte@lji.org](mailto:rjonte@lji.org) or 858-752-6542.

### 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



# La Jolla Institute

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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:** 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.

