

# Immune Matters

SPRING 2015

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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



In La Jolla Institute's ambitious quest to progress towards a "*life without disease*," a key strategy is to prevent disease in the first place. That's why the study of vaccines—how they work, why they sometimes fail to protect, and how we can create new ones to protect against a host of challenging diseases—is a major focus of our research.

After control of water and sanitation, there is probably no more important public health advancement than the development of vaccines. Diseases like smallpox and polio that used to kill or cripple millions have been virtually eradicated. Unfortunately, there are also many infectious diseases—such as malaria, tuberculosis, HIV, and dengue fever—that have

proven resistant to vaccine development and continue to result in too many deaths and too much human suffering.

In this *Immune Matters*, we highlight how vaccine research at LJI is at the core of our mission as immunologists and why we are so optimistic that we're going to have a major impact on the field. You'll see how a dedicated group of scientists, all internationally recognized for their research skills, is leveraging their discoveries to create new ways of developing vaccines, including unique strategies that will harness the power of T cells to attack previously resistant diseases. You'll see how the innovative work of Sujana Shresta, Ph.D., has helped take a dengue fever vaccine into human clinical trials, and we'll show you how the deep scientific commitment of Alex Sette, Ph.D., led him to include himself and his family in a pertussis vaccine study.

We also look at the darker side of the vaccine story—the anti-vaccine movement and the alarming trend of parents not vaccinating their children and compromising immunity throughout society. As an immunologist with more than 30 years in this field, I find the trend disturbing and dangerous. Vaccines have been proven not only incredibly effective, but also remarkably safe. Every one of our LJI scientists shares my feelings and we raise awareness of this important issue with the public whenever possible.

I think you'll also enjoy our Q&A with Amnon Altman, Ph.D., one of our most distinguished and longest-serving faculty members whose expertise in T cells may hold the key to a vaccine against cancer. You'll also meet someone at the beginning of a promising career: Stephanie Stanford, Ph.D., who received a \$1.6 million *Initiator* grant, one of only two such awards given out by the American Diabetes Association each year.

Whenever I reflect on the extraordinary talent and commitment of our LJI scientists, I feel a tremendous sense of gratitude for their dedication, along with a genuine optimism about the positive impact their scientific efforts will have on the human condition. Working in collaboration with our many invaluable partners—the foundations, individual donors, and federal funding sources—I've never been more confident that La Jolla Institute is creating a true path to *life without disease*.

Sincerely,

A handwritten signature in blue ink that reads "Mitchell Kronenberg".

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

# In Pursuit of Next-Generation Vaccines



Across the span of human history, a handful of discoveries and inventions has transformed the lives of our species: fire, the wheel, the printing press, and electricity immediately come to mind. A more recent but no less potent discovery is often overlooked: vaccines. Immunizations have prevented mass suffering and the deaths of millions of people across the planet, while saving billions in medical costs and offering iron-clad health protection for generations to come.

Since Edward Jenner used cowpox to create immunity to smallpox in 1796 and Louis Pasteur developed a rabies vaccine in 1885, vaccines have become one of the most remarkable and powerful tools ever created. They successfully eradicated smallpox, one of the deadliest diseases known to humankind, and continue to save millions of lives each year.

Amazingly, thanks to groundbreaking research by scientists at La Jolla Institute, the field of immunology is on the threshold of an entirely new and exciting era of vaccine development that may lead to the treatment and prevention of some of the most serious infectious diseases afflicting the globe.

A small army of LJL researchers is engaged on multiple fronts: several are probing the basic mechanisms of how successful vaccines work so that the concepts can be applied to tackling new diseases; some are researching how T cell-based immunity may be the key to a vaccine against HIV and other pathogens that have eluded vaccine development efforts; other scientists are leveraging computational biology to track exactly how the immune system targets pathogens at the cellular and genetic level; still others have made key discoveries in animal models

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## History of Vaccines

<b>1000</b>	<b>1796</b>	<b>1885</b>	<b>1921</b>	<b>1922</b>	<b>1937</b>	<b>1938</b>	<b>1939</b>
The Chinese use smallpox inoculation or "variolation" to protect against smallpox	Edward Jenner uses cowpox material to protect against smallpox creating the first vaccine (after "vacca," Latin for "cow")	Louis Pasteur creates rabies vaccine	First test of tuberculosis vaccine	Schools in the U.S. start to require smallpox vaccination	Yellow fever vaccine developed	The <i>March of Dimes</i> , an enormous fundraising campaign to fight polio, is born	Whooping cough vaccine shown to be effective

that have shown such promise in preventing disease the research has advanced to clinical human trials.

This promising new wave comes at a time when vaccines, in the ultimate irony, are themselves under attack. With many life-threatening diseases only a distant memory, some parents have become wary of vaccines, worrying that they could harm their children. Some still believe that vaccines cause autism, despite multiple studies to the contrary. The resulting drop in vaccination rates has compromised “herd immunity” and allowed measles and whooping cough to gain a foothold in communities across the nation where they’d long been kept at bay.

Herd immunity, which offers protection to those who can’t get vaccinated—including newborns and people whose immune systems are compromised—only works if enough individuals in a community are vaccinated, resulting in too few individuals who are able to pass the infection along. This is important because vaccines are not 100 percent effective all the time in protecting those who receive them.

For the scientists at La Jolla Institute who have devoted their lives to studying immune response, the latest measles outbreak, which originated at Disneyland, just added fuel to their already passionate drive for discovering pathways to new vaccines.

“I focus on vaccines for a very simple reason: One out of every three deaths in the world today is the result of infectious disease,” says Shane Crotty, Ph.D., Professor in the Institute’s Division of Vaccine Discovery. “As a scientist working in this area, the potential for saving lives and reducing human misery is immense. But so is the challenge. Virtually no new vaccines have been developed in the past decade, mostly because the diseases we’re targeting are so challenging.”

Dr. Crotty just happens to be tackling one of the most difficult: HIV, which has proven to be particularly resistant to vaccine development.

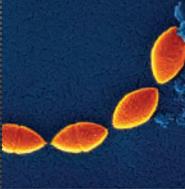
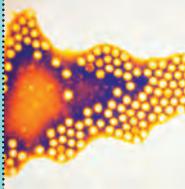
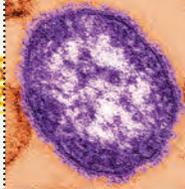
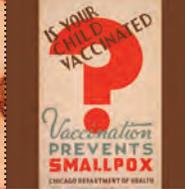
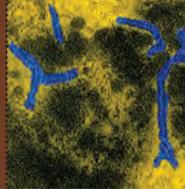
Yet in his quest to unravel the underlying immunology of vaccines, he has made a number of major discoveries that have placed him at the forefront of vaccine research internationally. The vaccine expert knew that attacking the problem traditionally through simply trial and error would not work against destructive microbes such as HIV. A much more promising approach, he believed, was to start with the fundamental immunology of T cells, the white blood cells that are crucial to the immune system at the cellular level. In recent years, that approach has paid major scientific dividends, most recently in late 2013, when Dr. Crotty announced a key discovery in the journal *Immunity*: certain helper T cells are critical for triggering a strong antibody response against HIV, the virus that causes AIDS. He showed that a specific type of these cells, known as follicular helper T (Tfh) cells, are not only necessary, but are a limiting factor that differentiates between an average and a potent antibody response to HIV.

Dr. Crotty’s research revealed that the frequency of the Tfh cells correlated with development of broadly neutralizing antibodies against HIV in a large group of HIV-infected individuals. His findings were hailed by experts in the field as “the kind of fundamental basic research that will eventually allow us to defeat HIV.”

Equally encouraging and exciting research, this time in the battle against tuberculosis, has come out of the lab of Alessandro Sette, Ph.D., Professor and Director of the Institute’s Division of Vaccine Discovery.

Dr. Sette’s research is helping unlock the mysteries of how the body fights infection by focusing on the identification of epitopes, small molecular features on the surface of pathogens that are recognized and targeted by antibodies and T cells. In addition to studying tuberculosis, Dr. Sette’s lab is heavily focused on threats posed by emerging diseases or bioterrorism, such as SARS, smallpox, influenza, and arena viruses, which cause

## History of

							
<b>1944</b> First Japanese Encephalitis vaccine becomes available	<b>1945</b> Influenza vaccine approved	<b>1945</b> Pneumococcal vaccine introduced but largely ignored because of the introduction of penicillin	<b>1948</b> First combination vaccine (diphtheria, tetanus and pertussis) introduced	<b>1955</b> Results of polio vaccine trial announced	<b>1963</b> Measles vaccine approved	<b>1966</b> WHO launches smallpox eradication program	<b>1967</b> Mumps vaccine approved

a range of hemorrhagic fevers.

Last year, Dr. Sette and his colleagues significantly expanded the understanding of the pathogenesis of TB when they announced in the journal *PLOS Pathogens* that they had identified a number of epitopes that are recognized by CD4 T cells, a subset of lymphocytes that is essential in defending against intracellular bacterial pathogens such as *mycobacterium tuberculosis* (Mtb).

Says Dr. Sette, “Very little had been known about the Mtb antigens that invade the body, but our findings provided a much greater understanding of how the immune system—through these CD4 T cells—recognizes and targets these intracellular pathogens. We’re optimistic that identifying and characterizing these epitopes will play a key role in developing an effective vaccine for TB, which remains one of the leading causes of infectious mortality around the world, and which is also the most frequent opportunistic infection in individuals with HIV/AIDS.”

Identifying epitopes—on a grand scale—is actually one of Dr. Sette’s primary areas of interest and expertise. Sette and his colleague, Bjoern Peters, Ph.D., Associate Professor in the Division of Vaccine Discovery, are the principal investigators who oversee the Institute-based Immune Epitope Database (IEDB), which provides an invaluable collaborative research tool by collecting and cataloging targets of immune responses identified by scientists around the world.

IEDB curators review thousands of scientific papers each year to determine what data can be pulled from



Bjoern Peters, Ph.D.

research papers, standardized through expert annotation, and placed into a searchable online information warehouse, resulting in a distilled and freely available resource to scientists worldwide.

For Dr. Peters, working with the IEDB the past decade has been one of the most rewarding phases of his career. “This database is one of the most remarkable tools ever created to assist the field of immunology,” he says. “With one mouse click, scientists can instantly access the results of hundreds of immune system studies revealing information that is saving them countless hours and dollars as they conduct their own research, much of it aimed at developing new vaccines.”

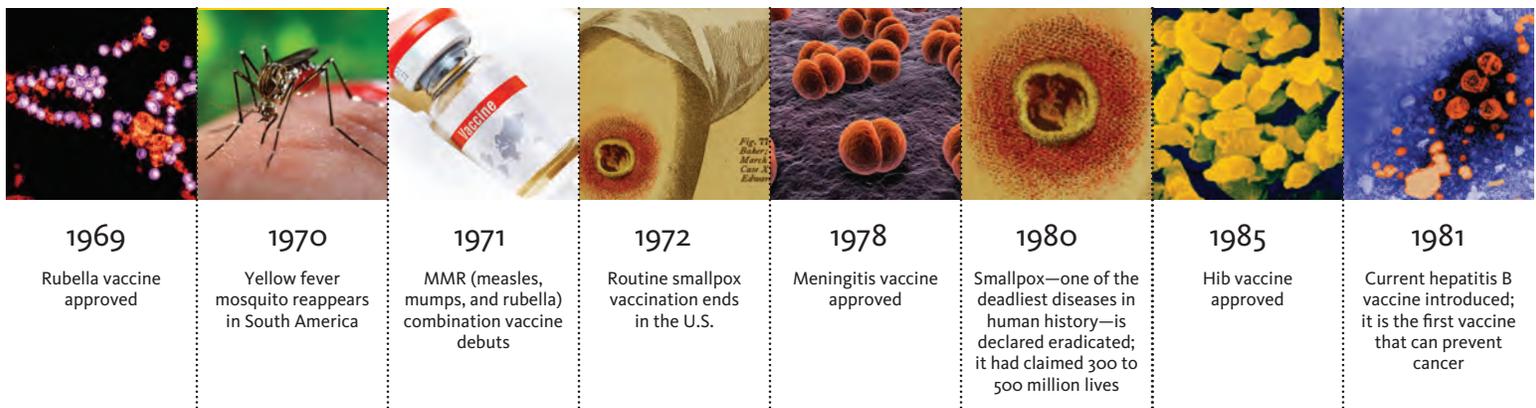
Funded by the National Institute of Allergy and Infectious Diseases (NIAID), the IEDB is accessed by thousands of scientists every month and cited as a crucial resource in more than 300 research papers every year. “There’s no question our database is vastly improving our chances to conquer infectious disease,” he says.

Dr. Peters’ particular expertise—bioinformatics—is perfect not only for overseeing the construction of the IEDB, but also for learning from the information being gathered. Bioinformatics research is an interdisciplinary field of science that develops methods and software tools to pull meaningful information from vast amounts of biological data.

Through the development of new tools to analyze what parts of a pathogen are targeted by immune responses, Dr. Peters’ research team has created predictive computational models that are providing vaccine developers with critical

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## Vaccines





# Whooping Cough Vaccine Study: All in the Family

*Alessandro Sette, Ph.D.*

There's a very interesting name on the list of blood donors participating in Dr. Alessandro Sette's whooping cough vaccine study at La Jolla Institute: Alessandro Sette. Look a little closer and you'll also see the names of Dr. Sette's son, his stepdaughter, his son's girlfriend, and her sister.

When Dr. Sette, Professor and Head of the Institute's Division of Vaccine Discovery, set out a few years ago to compare the old pertussis (whooping cough) vaccine versus the newer one, he knew he needed to look at individuals from both vaccinated groups.

"I realized that in my own family I had the perfect study group," Dr. Sette says. "I had received the old vaccine many years ago when I was a child, and my relatives and their friends are all teenagers who received the newer vaccine. It was helpful that the young people were excited and eager to participate in our study."

Dr. Sette launched the study in an effort to understand why the newer pertussis vaccine, introduced in the 1990s, is not as effective as the original one, which had been phased out because of infrequent side effects. Proof of waning immunity is that whooping cough, once considered a disease virtually eradicated, is once again on the rise. Just two years ago, the U.S. Centers for Disease Control and Prevention reported the U.S. had the highest number of whooping cough cases since 1959 with more than 41,000 infections and 18 deaths.

"When you add in the fact that growing numbers of parents are not vaccinating their children at all, we're now facing a potentially very dangerous public health situation in which we're certain to see even more new cases of whooping cough and more deaths," Dr. Sette says.

Hoping to play a role in countering that trend, Dr. Sette and his team are researching how the immune systems of those who received the old versus the newer vaccine react to booster shots.

"I believe we're going to see a significant difference in the way the T cells respond in each group's immune systems," he says. "By identifying and cataloging those differences we should gain a better understanding of the best way to attack pertussis. These findings could be valuable in improving the current vaccine so that we regain control of this very serious disease."

As for why he is participating in his own study, Dr. Sette says it's actually something he does frequently. "I've donated blood in our studies of the smallpox vaccine, our allergy research, and I'm about to do it again with the launch of our yellow fever protocol," he says. "I'm more than happy to be a guinea pig because I think that, if you believe strongly enough in the power of science, you have to be willing to actually be a part of the research process itself." ●

information that helps them target invading pathogens more effectively.

“Our work is increasingly important because it’s helping level the playing field in dealing with the more challenging infectious diseases out there today,” Dr. Peters says. “HIV, influenza, and other viruses are really tricky because of their ability to mutate in order to evade the immune response. Our ability to track and predict those shifts is a foundational tool in developing the kinds of sophisticated vaccines that will be required to prevent these diseases.”

Included on that list of challenging diseases is dengue fever, which is caused by four distinct, but closely related cousins. Borne by mosquitos, dengue virus infects 390 million people around the world each year. Most commonly, it causes a flu-like illness. However, subsequent infection with another serotype can cause potentially life-threatening dengue hemorrhagic fever.

One of those leading the Institute effort is Sujan Shresta, Ph.D., Associate Professor in the Division of Inflammation Biology. Dr. Shresta’s drive to fight infectious disease arises partly from her deep scientific curiosity, but also from a very personal and emotional source.

“Like so many people, my life has been affected by infectious disease,” she says. “My favorite aunt died of cholera when I was growing up and my dad has a limp because of polio. I also come from a third-world country, Nepal, where dengue has now spread. If I’m able to successfully fight dengue, it’s going to help my homeland



Sujan Shresta, Ph.D.

and the rest of the world at the same time.”

Dr. Shresta has already made impressive strides with her dengue research. In one major discovery, she validated a 50-year-old and controversial hypothesis that antibodies—usually the “good guys” in the body’s fight against pathogens—play a crucial role in the development of dengue hemorrhagic fever. She showed that through a phenomenon known as antibody-dependent enhancement, the first infection primes the immune system to trigger the severest form of the disease, dengue hemorrhagic fever, when it encounters the virus again.

But Dr. Shresta’s most important contribution is most likely the creation of unique mouse models for testing potential dengue vaccines. They allow her team to explore protective versus pathogenic aspects of the immune response to viral infection. Identifying the immune mediators that control primary and sequential dengue infections is a critical first step in developing vaccines and anti-viral therapies.

“Our mouse models are so effective we’ve been asked by a number of pharmaceutical companies to test compounds they believe may work as a dengue vaccine or anti-viral,” Dr. Shresta says. “What’s exciting is that we’ve already proven that one antiviral treatment completely wipes out the virus in mice and it has gone on to human trials. We’re currently also testing a number of compounds that show promise as live attenuated vaccines. This has made me extremely optimistic that we could see the first truly effective vaccine for dengue within five years.”

For “History of Vaccines” image credits please visit [LIAI.org/pages/credits](http://LIAI.org/pages/credits)

## History of Vaccines

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<b>1988</b>	<b>1994</b>	<b>1995</b>	<b>1995</b>	<b>2005</b>	<b>2006</b>	<b>2006</b>	<b>2006</b>
Global polio eradication campaign announced	Polio declared eradicated from U.S.	Chickenpox vaccine introduced	Hepatitis A vaccine approved	Pertussis booster for adults approved	HPV vaccine approved	Rotavirus vaccine approved	Shingles vaccine introduced

All of the Institute scientists working on the basic research that drives vaccine development share a similar optimism that more than 200 years after the first vaccine emerged the next era in preventing disease is upon us, due in part to their efforts in the scientific trenches.

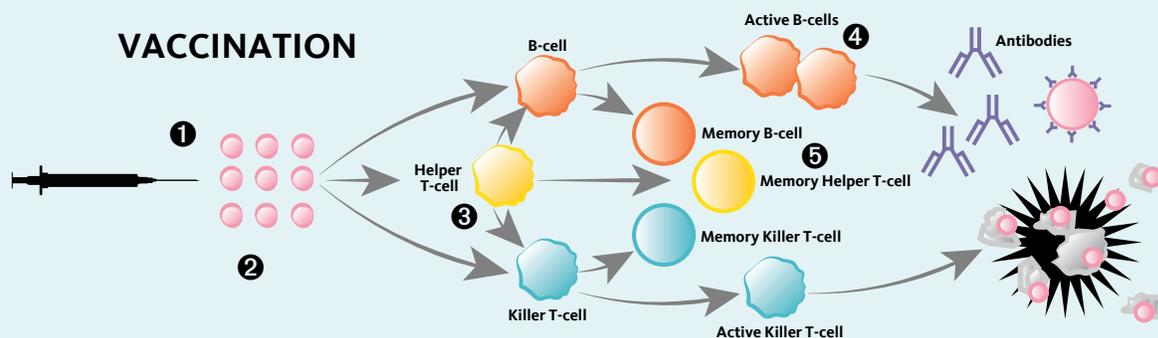
Dr. Peters reflects the feelings of all of his colleagues when he says, “To be involved in something that directly benefits human health gives us all a tremendous feeling of

accomplishment. It is not a fast process, and not everything will lead to an actual vaccine, but that’s also critical to know.

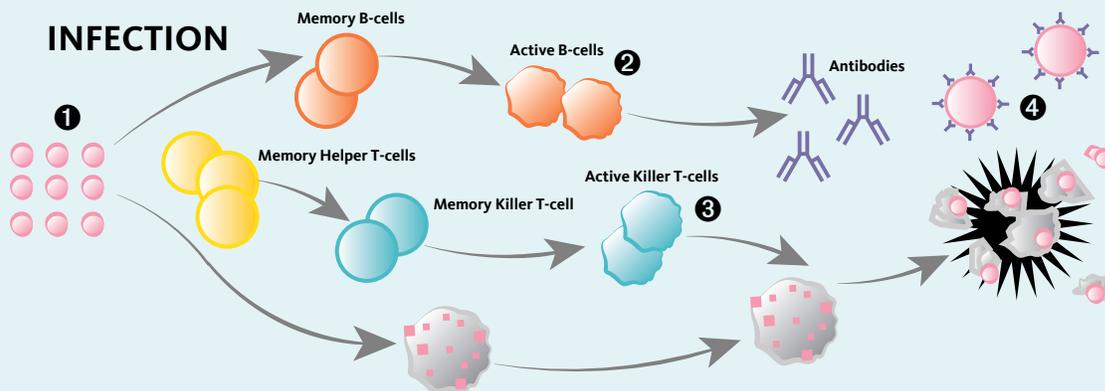
“Personally, I believe if we stay creative and keep working hard, our research will actually lead to vaccines to prevent a number of diseases and dramatically improve life on our planet. For me and every one of us working at this great Institute, that’s truly the holy grail.” ●

## How Vaccines Work

**Vaccines boost the body’s own defense system by inducing immunity that protects against infection. They are effective in preventing diseases that can cause severe illness, disability, or even death.**



❶ Vaccines contain weakened, inactivated, or partial forms of disease-causing germs. ❷ Vaccines activate various immune cells because they contain parts of bacteria or viruses, called antigens, that are recognized by the body’s immune system. ❸ Activated T helper cells send out chemical messengers that help activate other immune cells, such as antibody-producing B cell and T killer cells. ❹ Activated B cells multiply and start producing antibodies that recognize and trap antigens. ❺ Small but important subsets of B and T cells transform into memory cells that are able to react quickly when they encounter the same antigen again in the future.



❶ Exposure to a disease-causing microbe after vaccination activates memory B and T cells that remember the antigen from the vaccine. They respond quickly and efficiently to eliminate the pathogen before it can cause disease. ❷ Memory B cells start to proliferate and produce large amounts of antibodies. ❸ Memory T cells give rise to activated T killer cells that bind to and destroy any cells that contain the germ’s antigen. ❹ Antibodies bind and inactivate germs or mark infected cells for killing.

# Researchers Concerned Fear and Misinformation Over Vaccines are Jeopardizing Public Health

2000  
No Measles  
in the US

Most of the growing numbers of parents who choose not to have their children vaccinated have no idea their actions are seriously jeopardizing the health of people all around them.

That lack of awareness—along with the fear and misinformation about vaccines that led parents to that decision in the first place—must end, and soon, according to some very concerned scientists at La Jolla Institute who see the anti-vaccine movement as a ticking time bomb.

“Choosing not to vaccinate your children is not like deciding to go gluten-free, a decision that only affects yourself,” says Bjoern Peters, Ph.D., Associate Professor, Division of Vaccine Discovery. “These parents are actually damaging public health by reducing the herd immunity we’ve built up to diseases like measles and whooping cough, and giving these highly infectious diseases a chance to flourish again.”

A tiny fraction of people has always opposed vaccines on religious grounds, but over the past 15 years a sizable and vocal anti-vaccine movement has emerged. It was jumpstarted with the publication of a 1998 study in *The Lancet* by British physician Andrew Wakefield purportedly linking the measles, mumps, and rubella vaccine to autism. A media firestorm ensued,



Shane Crotty, Ph.D.

further inflamed when celebrity Jenny McCarthy claimed her son’s autism was caused by vaccines. Within five years, however, the research was proven to be a fraud, the journal retracted the study, and Wakefield was prosecuted and stripped of his medical license.

Far more serious has been the fallout from the recommendations of Robert Sears, M.D., a California pediatrician who in 2007 published *The Vaccine Book: Making the Right Decision For Your Child* recommending an alternative vaccination schedule that delayed shots to avoid “antigenic overload,” which he claimed could cause serious health consequences. The problem was that Sears was neither a

vaccine expert nor presented scientific evidence to back up his recommendations. That didn’t keep large numbers of parents from relying on Sears’ claims not only to delay vaccinations but eliminate them entirely.

Shane Crotty, Ph.D., Professor in the Institute’s Division of Vaccine Discovery, tracks vaccination rates across the U.S. and has been watching with growing alarm how the movement has taken on a life of its own. The rate of parents opting out of vaccination has doubled in California and is rising across the U.S. As a result, a disease like measles that was deemed eradicated in the

U.S. in 2000 had 644 cases in 27 states last year. And there are growing numbers of serious whooping cough outbreaks.

“Vaccines may be a victim of their own success because we seem to have forgotten just how devastating the diseases were before these incredible medicines were invented,” Dr. Crotty says. “But if we don’t want to see a surge in babies dying from whooping cough and youngsters going deaf from measles, we’re going to need to raise public awareness that there is no evidence that vaccines are harmful and that they offer the only real protection against a host of very dangerous infectious diseases.” ●

# Q&A

## Dr. Amnon Altman on Recent Milestones in Immunology and What to Expect in the Future

*For Professor Amnon Altman, Ph.D., who serves as Head of the Division of Cell Biology and Director, Scientific Affairs, immunology was love at second sight. As an undergraduate at Tel Aviv University in Israel, the biology major loved to go on field trips and envisioned himself as a biologist trekking through nature studying plants and animals. But a teaching assistant took a liking to the bright student and got him interested in immunology research at the Weizmann Institute, one of the premier research institutions in Israel.*

*Eventually, Dr. Altman did his masters and Ph.D. thesis in the Department of Cell Biology at the Weizmann Institute, where he helped develop a culture system for generating cytotoxic T cells, a major subset of T cells charged with killing virus-infected and otherwise compromised cells. "These were early days for modern immunology and at the time we knew almost nothing about cytotoxic T cells." During his Ph.D. thesis, Dr. Altman discovered that when you add fluid from a culture of activated T cells to naïve T cells it stimulated a much more effective cytotoxic T cell response. "Now of course we know that these supernatants contain a mixture of over 30 different cytokines, which act as chemical messengers that induce a broad range of biological activities and modulate the activity of many cells in the immune and other systems," Dr. Altman explains.*

*Since then, Dr. Altman has identified several proteins critical to the proper regulation of T cells. More recently, he shifted his attention to cancer immunology, a rapidly developing and promising area of cancer therapy.*

## Immunotherapies' Big Leap Forward

**Q:** Over the last few decades, we have made big strides in understanding how the immune system works. What were the biggest milestones?

**A:** Among the major advances in the last 20 to 25 years was certainly the discovery of the so-called innate immune system, which serves as the first line of defense against foreign invaders. Other important advances include the elucidation of the signaling pathways that T and B lymphocytes use in order to become functionally active cells that can expand and mount effective immune responses; appreciation of the important role of epigenetics in shaping immune responses; and, lastly, the realization that a number of diseases that we didn't think had anything to do with an aberrant immune system, for example coronary heart disease or type 2 diabetes, actually do have an immune or inflammatory basis.

**Q:** Regulatory T cells created a lot of excitement when they were discovered a few years ago. What is their role?

**A:** Regulatory T cells are one of the mechanisms that the immune system has developed over the course of evolution to terminate an immune response after its job is done or to put a damper on a hyperactive immune system, which can cause chronic inflammation. The other side of the coin is of course cancer. Regulatory T cells inhibit the

immune response against cancer, which in this case, is a disadvantage. This is a clear example of how developing an effective immune response comes at a certain cost to the individual.

**Q:** Why does cancer pose such a challenge for the immune system?

**A:** The first thing we have to remember is that cancer cells generally represent "self" and, therefore, their ability to stimulate an immune response is very limited. But the main reason is that over the course of evolution cancer cells have developed various mechanisms to escape an effective immune response.

**Q:** Lately, there has been a lot of talk about cancer immunotherapy. What is it?

**A:** Passive forms of cancer immunotherapy have been around for a while and they generally do not rely on stimulation of the patient's immune system. Some examples are monoclonal antibodies such as Herceptin® or the transfer of T lymphocytes after they have been genetically modified or their ability to kill cancer cells has been enhanced otherwise before they are returned into the patient's body. The other major category of cancer immunotherapy relies on waking up the cancer patient's immune system and making it more effective, as in the use of cancer vaccines.

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

**A:** Cancer vaccines aim at boosting the natural immune response, which is quite weak in most cases. Vaccines currently used in the clinic are mostly directed against molecules (proteins) that are highly expressed on the surface of cancer cells but at much lower levels on the surface of normal cells. There is currently an extensive effort to map the many genetic changes or mutations that occur in cancer cells, and use the resulting, highly tumor-specific proteins as vaccines.

**Q:** Vaccines have been incredibly successful against certain diseases but others have proven intractable. Why?

**A:** Historically, successful vaccines have worked well against those pathogens that are in themselves capable of inducing a naturally effective immune response. The reality is that in many cases the human immune system doesn't develop an effective immune response against certain pathogens for reasons that we still do not understand very well.

**Q:** Are we getting any closer to developing vaccines against these diseases?

**A:** Our understanding of the human immune system is still limited but there are major efforts underway to change that. For example, in 2010 the National Institute of Allergy and Infectious Disease launched the Human Immunology Project Consortium, which combines the efforts of many national and international academic institutes to answer questions such as: How can we induce an effective immune response in humans against a specific pathogen? Or what are the target antigens that would stimulate the most effective immune response?



*Amnon Altman, Ph.D.*

Later this year another initiative, the Human Vaccine Project, will likely be launched. It will focus on the improvement of existing vaccines and the development of vaccines against diseases that so far have eluded us, including malaria, dengue, and tuberculosis.

**Q:** In your opinion, what are currently the most exciting areas in immunology?

**A:** Cancer immunotherapy is at the top of my list. This is fueled by a better understanding of how the immune system deals with cancer. I am also very excited about novel technologies that were developed over the last 10 to 15 years. Mostly, these are technologies that allow us to look at different biological phenomena on a very large scale and provide unprecedented insights into the complexities of the immune system.

**Q:** Where is your own research headed?

**A:** For many years, and in fact until quite recently, our research asked very fundamental questions. We tried to understand the basic mechanisms of how cells in the immune system and specifically T lymphocytes are stimulated to become activated cells so that they can mount an effective immune response.

But based on some recent discoveries, we have become much more interested in cancer immunotherapy. We are trying to modulate the immune response by inhibiting the function of regulatory T cells in order to enhance the effectiveness of the immune system against cancer. At the moment, we are using a mouse model of cancer but we hope that in the not too distant future, we will be able to translate some of these studies to the human immune system. ●

# Type 1 Diabetes: When Genetics and Environment Collide



*Stephanie Stanford, Ph.D.*

Intrigued by how the human body works at the molecular level, immunologist Stephanie Stanford, Ph.D., zooms in on the interplay between our genetic makeup and the environment. Her vision and groundbreaking work caught the eye of the American Diabetes Association, which awarded her a \$1.6 million grant to investigate how genetic risk factors intertwine with environmental triggers to cause type 1 diabetes.

Human biology had always held great allure for Stephanie Stanford, but she found her true calling when she fell in love with molecular biology as an undergraduate at Azusa Pacific University in Azusa, California. “I loved studying things at the molecular level and solving problems,” she remembers. “I wanted to apply this passion to something I hoped would benefit people.”

After majoring in chemistry, Dr. Stanford applied to graduate programs with a strong focus on biomedical research. Impressed by the collegial environment, she enrolled in the University of Southern California in Los Angeles, and started looking for the right lab. “I knew for a fact that I wanted to work on signal transduction and I wanted it to be in immune cells,” she says.

Fellow students pointed her to the lab of Nunzio Bottini, M.D., Ph.D., a brand new assistant professor at USC whose research focused on just that. “The lab was a perfect match,” says Dr. Stanford. “Not only could I work on signaling in immune cells, but Nunzio is a wonderful mentor and his passion for science is infectious.”

In Dr. Bottini’s lab, Dr. Stanford was introduced to the cellular protein that would become a steady companion throughout her unfolding scientific career. Known as PTPN22, it plays a pivotal role in a range of autoimmune diseases in humans. “Mutations in PTPN22 are the third highest genetic risk factor for type 1 diabetes and the second highest for rheumatoid arthritis,” Dr. Stanford says.

Unlike type 2 diabetes, type 1 diabetes, also referred to as juvenile diabetes, is not triggered by diet or lifestyle. Instead, it is an autoimmune disease in which the body’s immune system attacks and destroys the insulin-producing cells in the pancreas, sometimes in the wake of a viral infection early in life. Each year, more than 15,000 children and 15,000 adults are diagnosed with type 1 diabetes in the U.S.

During her graduate work, Dr. Stanford studied how mutations in the PTPN22 gene ultimately influence the protein’s molecular structure and function. When she decided to follow Dr. Bottini to La Jolla Institute as a postdoctoral researcher, she began tracing the molecular thread that connects PTPN22 and type 1 diabetes.

She credits the unique environment found at the La Jolla Institute: “All of a sudden we were surrounded by the best immunologists in the world and an unbelievable wealth of

knowledge.” Dr. Stanford secured a postdoctoral fellowship from the Juvenile Diabetes Research Foundation and started tapping into her colleagues’ expertise.

In collaboration with several groups, she and Dr. Bottini discovered that PTPN22 promotes the production of type 1 interferon, which helps fight viral infections. It could explain why mutations in the PTPN22 gene—found in six to 10 percent of the U.S. population—significantly increase the risk of type 1 diabetes.

“When the PTPN22 gene is mutated, it impairs the body’s immune response to viral infections. We are especially concerned about a specific enterovirus that is known to trigger type 1 diabetes by leaving the body vulnerable to an attack on the pancreas,” says Dr. Stanford. She believes that certain environmental factors, including exposure to pathogens

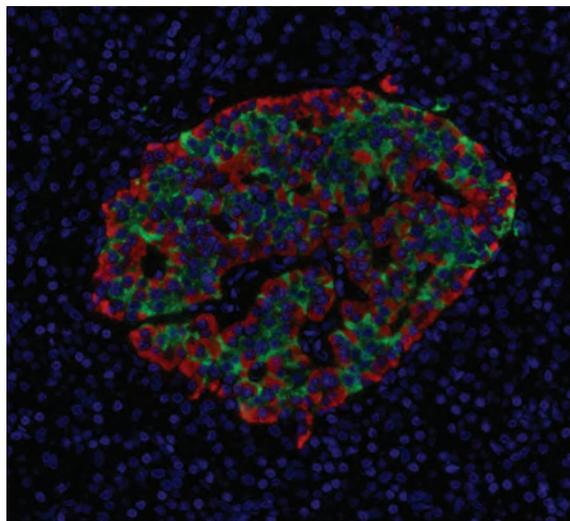
early in life, combine with genetic mutations to increase risk of type 1 diabetes.

“That’s what’s so intriguing about this finding. It sheds light on why some people with type 1 diabetes risk genes never develop diabetes, as they are not exposed to certain pathogens, while other people can develop the disease if they have genetic mutations that damage their response to infections.”

The American Diabetes Association (ADA) was intrigued as well and awarded Dr. Stanford an “*Initiator Award*”—one of only two such awards given nationally each year to support promising young scientists on the cusp of starting their independent research career. Funded through the ADA’s *Pathway to Stop Diabetes* initiative, the seven-year grant enables Stanford to expand her research program and establish her own lab.

Most importantly, it gives her the opportunity to connect the dots between genetic and environmental risk factors for type 1 diabetes and identify the molecular mechanism on which they converge.

“My long term goal is the prevention of type 1 diabetes,” she says. “Once we have a clearer picture of why the immune system is unable to successfully fight viral infections, we’ll be able to devise better strategies to prevent people who carry the mutated gene from developing type 1 diabetes. Such strategies could be prophylactic or aggressive treatment for enteroviral infections, or a vaccine against viruses associated with type 1 diabetes.” ●



*In most people with type 1 diabetes, the body’s own immune system mistakenly destroys the insulin-producing islet cells in the pancreas. (Image courtesy of Somayeh Sabouri and Florence Anquetil-Besnard, Matthias von Herrath Lab)*



# WELLNESS WRIT LARGE

LJI teams regularly participate in the annual JDRF Walk to Cure Diabetes. Back row: Annika Lindholm, Gustaf Christoffersson with Nils Lindholm, Florence Anquetil-Besnard with Arthur Besnard, Somayeh Sabouri, Kathrin Ehrhardt, Scott Westenberger, Daniel Moyer. Middle row: Sowie Sachithanantham, Diana Mason, Chris Romano, Anne Bresciani, Luise Sternberg, Jen Dan, John O'Sullivan. Front row: Pascal Bresnard, Takako Fujisaki, Michelle Fujisaki, Cristhiane Favero de Aguiar.

Reaching for fresh fruit instead of the candy bar when the afternoon slump hits; taking the bike instead of the car when running a quick errand; drinking water instead of sugar-laden soda—we all know the healthiest options, but old habits are hard to break. La Jolla Institute's wellness program is designed to make it easier for employees to overcome this hurdle and start making healthier choices.

Most people spend a majority of their waking hours at work and that's where they make a lot of their choices about nutrition and fitness," says Human Resources Manager Emily Gordon, who has run the healthy workplace program since it launched in 2012. "We wanted to create an environment where making the healthy choice is the easy choice."

Out went the traditional candy-laden vending machines and in came refrigerators stocked with "real food" such as carrots, yogurt, fruit, and salads. In addition, the Institute opened an in-house cafeteria where employees can choose between several healthy, freshly prepared meals four days a week. The cost is subsidized by the Institute to keep prices reasonably low. The wholesome offerings are complemented by healthy cooking classes, which were a huge success in the past.

A "bike share" program provides five Institute-owned bicycles, which employees can check out to get to meetings across campus, run errands, or just get some exercise. There are also free onsite fitness, yoga, martial arts, and stress reduction classes, a ping pong table, soccer, and a softball team, among various other

organized team outings that encourage LJI employees to get moving. "LJI teams regularly participate in fundraising walks that benefit charitable organizations, such as the Juvenile Diabetes Research Foundation," says Gordon.

Quarterly "team challenges" provide additional impetus to jump on the fitness bandwagon. Teams participate in a series of five to eight different weekly activities and can win prizes for the best team effort. "Sometimes people need a little extra incentive to participate," says Gordon, adding it can be as simple as water bottles with the Institute logo for members of the team that collected the most points. A committee composed of employees from every department plans the challenges and evaluates their success afterwards. In the past, these challenges have encouraged employees to walk more, replace sodas with water, go out into the community and volunteer for a good cause, give meditation a try, or be more diligent about applying sunscreen.

"We've made it priority to create a healthy work environment that mirrors our mission to improve human health and accelerate research toward life without disease," says Mitchell Kronenberg, Ph.D., the Institute's President and Chief Scientific Officer. "The benefits come in the form of healthier, happier, and more productive employees who are passionate about coming to work and making a difference. In a research environment focused on finding new breakthroughs to fight disease, that's an invaluable asset." ●

# Father's Illness, Lifelong Fascination with Medicine Motivates Newest Board Member

Watching her father battle multiple sclerosis was such a life-changing experience for Pamela Blakely, she has devoted much of her time in the decades since to supporting scientists who are trying to unravel the mysteries of autoimmune diseases.

It is a path that led the Rancho Santa Fe resident last November to eagerly accept an invitation to join the Board of Directors of the La Jolla Institute. In a few short months, Blakely has become one of the most engaged board members through her work on the board's Institute Relations committee.

For Blakely, her involvement with LJI feels like the culmination of a journey that began when she was growing up in the South, first in her native North Carolina where her father managed a textile plant, and then South Carolina where the family moved so her Dad, by then experiencing symptoms they later would learn were the first signs of MS, could have a less stressful job running his own office supply store. In MS, the body's own immune cells attack the myelin coating around the nerve fibers, which allows nerves to conduct signals between the brain, spinal cord, and the rest of the body.

While attending high school, Blakely took a job with a physician who had just opened a clinic to serve the underprivileged.

"That was truly eye-opening for me," Blakely recalls. "It gave me a keen interest in medicine, while instilling in me a deep respect and admiration for those in the medical profession who work so hard to help other people." Nothing, however, could prepare her for her father's illness.

"It started with fatigue and some balance issues we thought were work related," Blakely says. "Eventually, he had difficulty walking and after many tests he was diagnosed



*Pamela Blakely*

with MS. Because there was no real treatment for it back in the early 70s, we had to watch helplessly as Dad became more and more debilitated." Says Blakely, "Experiencing my father's decline provided me with a life purpose to learn everything I could about MS and other autoimmune disorders. I promised myself that whenever and wherever possible, I would help find treatments and cures for these devastating diseases."

As Blakely moved on to college and into a successful career as a licensed real estate broker in Florida, she kept her promise. She became a voracious reader of medical literature and began a long involvement with the National Multiple Sclerosis Society. In her local Naples community she

organized an MS event that raised \$130,000 and chaired a gala benefitting a hospital in Largo. In San Diego, she will chair Scripps Clinic's annual charity golf tournament this fall.

But it is at La Jolla Institute where Blakely feels she's found a true home for her philanthropic passion and skills. She's already immersed in ambitious plans to raise money and public awareness for the Institute's work. Both, she says, are vital if the Institute is going to be able to continue its groundbreaking scientific mission of understanding how the immune system works.

"I'm honored to advocate on behalf of the world-class scientists at La Jolla Institute because their research is transforming the field of immunology in ways not imaginable just a few years ago," Blakely says. "I've already had a chance to share with others all of the wonderful work of the Institute," she adds. "When others realize the Institute's incredible potential for treating and curing our most challenging diseases—and that it will help not only themselves and their families but the entire world—they've all become as excited and energized." ●

# La Jolla Institute

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## About La Jolla Institute for Allergy and Immunology

■ **MISSION:** La Jolla Institute for Allergy and Immunology is dedicated to understanding the intricacies and power of the immune system so that we may apply that knowledge to promote human health and prevent a wide range of diseases. Since its founding in 1988 as an independent, nonprofit research organization, the Institute has made numerous advances leading toward its goal: *life without disease*.

■ **SCIENTIFIC PRODUCTIVITY:** 23 faculty investigators and 145 postdoctoral fellows have 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.

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