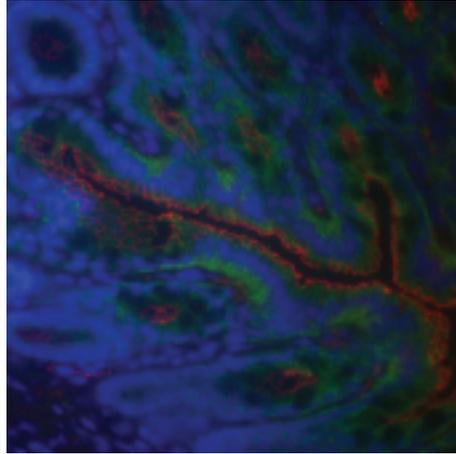
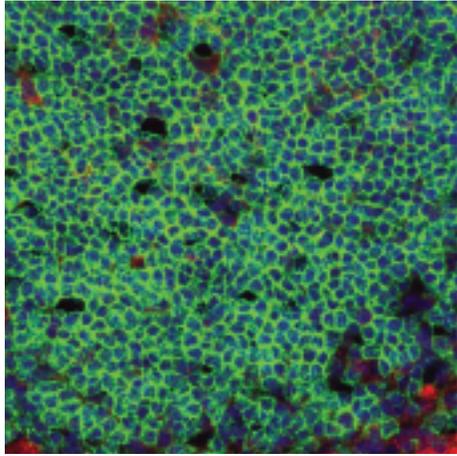
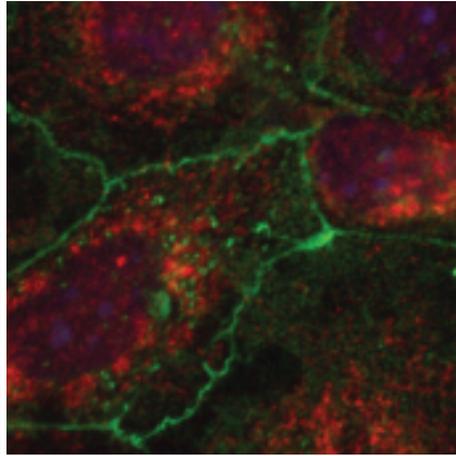
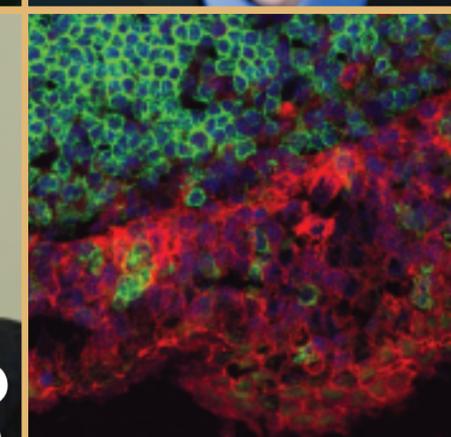
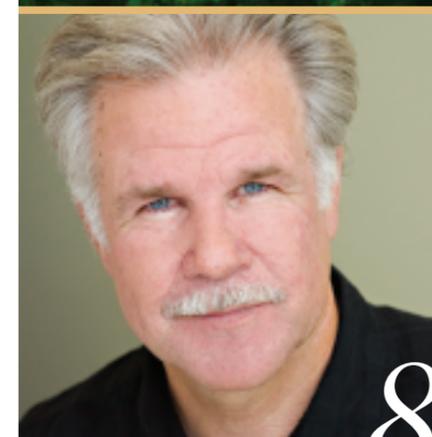
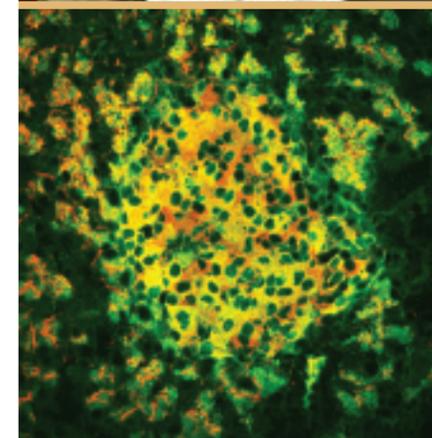
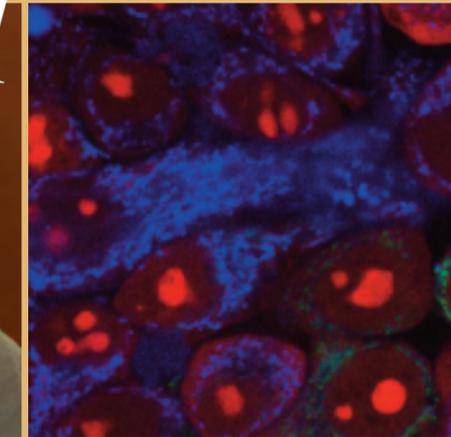


FINDING
CURES
FASTER



LA JOLLA INSTITUTE
for
ALLERGY & IMMUNOLOGY

Finding Cures Faster. Scientists at the La Jolla Institute for Allergy & Immunology (LIAI) work on the front lines of medical research—at the cellular level—where cures and new treatments first come to light. Their vista is the body's immune system, which time has shown plays a role in a host of human diseases. From infectious diseases to cancer, type 1 juvenile diabetes, heart disease and more—the immune system holds the key to end the suffering brought by these and many other disorders. Recognizing its incredible power, LIAI, a nonprofit biomedical research center, has devoted itself to the study of the immune system, emerging as a world leader and as San Diego's only institute focused solely on this remarkable biological vantage point. While the immune system's role in vaccines has long been known, tremendous medical advances over the last 10 years have shown that the body's defense system offers great promise for new medical interventions against disease. New immune-based therapies are emerging for rheumatoid arthritis, cancer, type 1 diabetes and more that weren't thought possible a decade ago. Immunology's application in medicine is still unfolding, with many exciting new therapies just over the horizon. Please read on to learn more about how LIAI is finding cures faster by harnessing the power of the immune system.



THE IMMUNE SYSTEM IS KEY

The people of the **La Jolla Institute for Allergy & Immunology (LIAI)** are passionate about finding cures faster through scientific discovery. Our researchers, many of whom you will meet on the following pages, believe deeply that their work to uncover new knowledge and a better understanding of the body's immune system is key to decrease human suffering and improve human health.

I am pleased to present our 2007 Annual Report in which we share with you the progress we've made in this pursuit. For example, Hilde Cheroutre, Ph.D., and her research team found that a derivative of vitamin A could play a significant role in controlling inflammation found in diseases such as rheumatoid arthritis and inflammatory bowel disease. This discovery was named one of the top

ten research advances in *all* of biomedical research in 2007 by *Nature Medicine*. Another example of research excellence can be found in the work of Don Newmeyer, Ph.D., on how cells survive and how cells die. Knowing more about cell death is extremely important in learning how to stop cancer before it spreads.

While remaining true to our focus on immunology, we have also broadened our scope with the arrival of an outstanding senior scientist, Klaus Ley, M.D., to head a new Division of Inflammation Biology. Dr. Ley comes from the University of Virginia where he served as Director of the Berne Cardiovascular Research Center. He and his team bring immense experience in imaging in living tissues, a critical technology in the study of inflammation, but also



with application to many of the diseases of the immune system being researched at LIAI.

Lastly, 2007 also saw the expansion of our efforts to encourage and develop philanthropy as a critical means of financial support at the La Jolla Institute for Allergy & Immunology. As a nonprofit organization, our primary source of funding (nearly 75%) is in the form of grants from the National Institutes of Health (NIH).

However, the NIH does not support the start-up funding for creative young scientists nor most of the funding for the high technology instruments needed for cutting-edge research. Therefore, philanthropic support makes a substantial difference to fulfill these needs and propel scientific discoveries forward. I invite you to get to know the people of the La Jolla Institute for Allergy & Immunology. Please join us and be part of Finding Cures Faster.

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 & Scientific Director

An anatomical illustration of the human immune system. It shows a blue-tinted human torso with a complex network of red and green lines representing the circulatory and lymphatic systems. The heart is visible in the center, and the network of vessels extends throughout the body.

What is Immunology?

The immune system's incredible power to affect our health cannot be overstated. Whether it be infectious diseases, cancer, type 1 diabetes or heart disease—all of these disorders and many more are heavily influenced by the immune system. Medical advancements over the last 20 years have shown that the immune system plays

a role in many diseases. And, in fact, there is no biomedical discipline that has greater implications for improving human health. But what is this system that plays such a major role in our health? The immune system is a vast network of cells—estimated to number more than a trillion—that circulate throughout the body

attacking and destroying viruses, bacteria and other foreign invaders. This is the helpful side of the immune system, which protects us from diseases and which scientists seek to boost through vaccines and cancer therapies. But the immune system also has a dark side. In a case of apparent mistaken identity, it occasionally launches

attacks against normal cells, unleashing a torrent of disorders, including type 1 diabetes, rheumatoid arthritis and other autoimmune diseases. LIAI is among the world's research leaders seeking to understand and correct the destructive aspects of the immune system as well as to boost its protective side.

FACULTY

Left to right, top to bottom:

Amnon Altman, Ph.D.

Christopher A. Benedict, Ph.D.

Hilde Cheroutre, Ph.D.

Michael Croft, Ph.D.

Shane Crotty, Ph.D.

Howard M. Grey, M.D.

Toshiaki Kawakami, M.D., Ph.D.

Mitchell Kronenberg, Ph.D.

Klaus F. Ley, M.D.

Yun-Cai Liu, Ph.D.

Donald D. Newmeyer, Ph.D.

Bjoern M. Peters, Ph.D.

Alessandro Sette, Ph.D.

Stephen P. Schoenberger, Ph.D.

Sujan Shresta, Ph.D.

Matthias von Herrath, M.D.

Carl F. Ware, Ph.D.

Dirk M. Zajonc, Ph.D.



2007 AWARDS

The Juvenile Diabetes Research Foundation, the world's largest charitable funder of type 1 diabetes research, selected **Matthias von Herrath, M.D.**, as a recipient of its 2007 Scholar Award. The award provides support for individual scientists of "extraordinary talent and creativity who pursue pioneering research toward finding a cure for type 1 diabetes and its complications." Dr. von Herrath was selected as one of six recipients worldwide for this prestigious award because of his "groundbreaking ideas, unique research direction, willingness to take risks, and commitment to accelerating type 1 diabetes research." Each of the recipients will receive \$250,000 annually for up to five years for their research efforts. "The Scholar Award is designed to encourage and support innovative, high-risk and high-reward, paradigm-shifting, challenging research," said Richard Insel, JDRF's executive vice president of research. "To fulfill its mission and find a cure fast, JDRF depends on the creativity and excellence of individual scientists like Dr. von Herrath."

Dirk Zajonc, Ph.D., received a 2007 Investigator Award from the Cancer Research Institute in recognition of his novel work exploring a possible connection between cancer and glycolipids, naturally occurring biochemicals made of linked fat and sugar. Only seven investigators worldwide received the award designed to encourage innovative cancer research by newly independent scientists. Recipients are selected based on their entire past body of work as well as their potential for making exceptional contributions to the field of cancer immunology.

Chris Benedict, Ph.D., was honored in 2007 with the Eng Tan Scholar award by the Arthritis National Research Foundation. Dr. Benedict was selected for the prestigious award for his "innovative approach" to research on rheumatoid arthritis. The award is given to only one researcher nationwide each year and is named for Eng Tan, a professor emeritus at the Scripps Research Institute, who did seminal work on various autoimmune disorders. Dr. Benedict was honored for his work on a newly discovered cytokine which is similar, but possibly more effective, than the most popular current rheumatoid arthritis therapy.

WHY AWARDS AND PUBLICATIONS MATTER

For LIAI, 2007 was a year of impressive research advancements and major discovery as evidenced by the receipt of several prestigious awards and the publication of more than 75 research papers in various scientific journals. Scientific papers—in which researchers explain their latest findings—must go through a rigorous peer-review process prior to publication. "The publication of a scientific paper is a milestone for researchers and validates that their work is of such importance that it should be shared with the international scientific community," said Mitchell Kronenberg, Ph.D., president & scientific director. LIAI's major published findings in 2007 ranged from Hilde Cheroutre, Ph.D.'s discovery of a connection between retinoic acid and inflammation published in *Science*, one of the most renowned scientific journals, to a comprehensive analysis of influenza virus data worldwide published by Huynh-Hoa Bui, and Alessandro Sette, Ph.D.'s, in the *Proceedings of the National Academy of Sciences USA*.

For the full 2007 publications listing, please visit www.liai.org.

LIAI Finding Named One of Year's Key Research Advances

COULD LEAD TO NEW TREATMENTS FOR INFLAMMATORY BOWEL DISEASE, RHEUMATOID ARTHRITIS

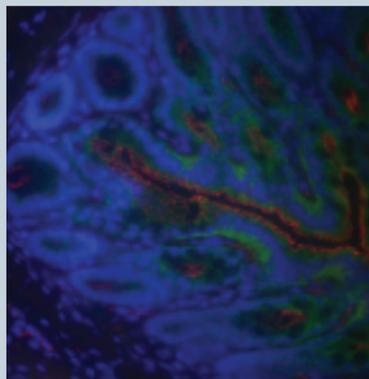
When **Hilde Cheroutre, Ph.D.**, realized that her research team had found something quite extraordinary that could lead to new ways to treat devastating inflammatory diseases, she swallowed hard and double checked the results. It was confirmed. She and her research team had made the startling discovery that retinoic acid, a vitamin A derivative, can play a critical role in controlling inflam-

mation in the body, which is the chief cause of inflammatory bowel disease, rheumatoid arthritis and other autoimmune diseases. The finding, initially published in the prestigious journal *Science*, was later named as one of the key biomedical research advances of 2007 by *Nature Medicine*, a highly respected and internationally renowned journal for biomedical research. It also served to

open a new frontier in inflammatory disease research. Already used to treat some leukemias, which are blood cancers, Dr. Cheroutre's discovery demonstrated—for the first time—that retinoic acid may also have the potential for treating a host of autoimmune diseases. "I realized that it was a very profound finding and that it had a lot of potential," said Dr. Cheroutre who led the research team, entirely from LIAI. **Yunji Park, Ph.D.**, and **Daniel Mucida, Ph.D.**, were key contributors. In the study, the researchers showed that by manipulating the amount of retinoic acid in mice, they could reduce the cellular inflammation characteristic of autoimmune diseases. The mice in the study were successfully treated for inflammatory bowel disease, but Dr. Cheroutre believes the retinoic acid manipulation also may have the potential to affect rheumatoid arthritis and other autoimmune diseases. As her lab continues their studies, Dr. Cheroutre notes the finding was an important first step, but further

testing is needed to determine retinoic acid's safety and applicability for treating autoimmune diseases in humans. Smiling, Dr. Cheroutre recalls that she is still amazed by the discovery because she and her team were studying other types of cellular activity when they noticed anomalies that eventually led to the retinoic acid finding. "We were not really looking for that," she said. "To stumble on to something like this is stunning...I'd have to say it was really quite beautiful."

Rheumatoid Arthritis Primer



For 1.3 million Americans, rheumatoid arthritis is an unwelcome constant companion that slowly tears down joint function. The inflammation of arthritis limits people in various ways, with damage sometimes leading to range of motion problems, making activities like turning a water faucet, grasping a fork or buttoning a shirt painful. At its worst, it can disable and cripple, leaving previously vibrant, independent people unable to fend for

themselves. Thankfully, research advancements over the past 10 years are improving the lives of rheumatoid arthritis sufferers. LIAI scientists are among those currently leading the way, with more advances on the horizon.



HILDE CHEROUTRE, PH.D., AND HER LAB HAVE OPENED A NEW FRONTIER IN AUTOIMMUNE DISEASE RESEARCH

Clinical Trials Under Way

RESEARCHER'S DISCOVERY OFFERS HOPE FOR MANY RHEUMATOID ARTHRITIS SUFFERERS

Rheumatoid arthritis can cripple not only the body, but the spirit as well. Marked by swelling, stiffness, weakness and joint pain—oftentimes in the hands—rheumatoid arthritis can debilitate its sufferers, turning the everyday tasks of life into painful, difficult challenges. LIAI researcher **Carl Ware, Ph.D.**, is well aware of the challenges faced by rheumatoid arthritis sufferers and has devoted much of his scientific career to finding new ways to help them. Known internationally for his trailblazing research on inflammation—the underlying cause of rheumatoid arthritis and many other autoimmune diseases—Dr. Ware has two important discoveries entering the drug development process. One of those discoveries is the lymphotoxin- β receptor, a protein that controls inflammation, which is the basis for a new drug currently in Phase II clinical trials for people with severe rheumatoid arthritis and Crohn's disease. The other discovery, an inflammatory protein known as LIGHT, is being pursued by a pharmaceutical company for possible use in various inflammatory diseases. Both are

members of the tumor necrosis factor (TNF) family of proteins, which are lines of communication used by inflammation-causing white blood cells that are linked to a variety of autoimmune diseases. Although TNF inhibitors like Enbrel™ and Remicade™ are now being prescribed to help alleviate inflammation, there is a signifi-



CARL WARE, PH.D., IS TRAILBLAZING NEW THERAPIES FOR SEVERAL INFLAMMATORY DISEASES

cant portion of rheumatoid arthritis and Crohn's disease patients whose disease does not respond to these TNF blockers. Dr. Ware, who serves as chairman of the Scientific Advisory Board for the Arthritis National Research Foundation, hopes that his lymphotoxin- β receptor discovery will help these patients. "There's an unmet need," he said. "I hope my work can help those rheumatoid arthritis and Crohn's disease sufferers who don't respond to the current therapies."



Ground-breaking LIAI Study to Shed New Light on Type 1 Diabetes

NEW TECHNOLOGY ENABLES AS-IT-HAPPENS CELLULAR VIEW

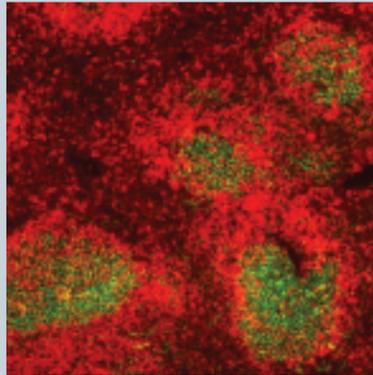
If a picture is worth a thousand words, what about a movie? If you ask LIAI researcher **Matthias von Herrath, M.D.**, he'll tell you it's priceless—especially when the movie is giving the world its first-ever look at type 1 diabetes cellular activity occurring live in the pancreas.

Thanks to the Institute's new two-photon microscope—and a new procedure developed by Dr. von Herrath—Institute researchers are now seeing an as-it-happens view of the cellular interactions that destroy insulin-producing beta cells in the

(continued on page 10)

MATTHIAS VON HERRATH, M.D.'S, TWO-PHOTON MICROSCOPE "MOVIES" ARE GIVING THE WORLD NEW INSIGHTS INTO TYPE 1 DIABETES

Type 1 Diabetes Primer



Type 1 diabetes, also known as juvenile diabetes, usually strikes in childhood, turning the world of previously healthy children upside down. Suddenly, the baseball gloves, Barbies and other childhood joys are joined by the harsh reality of daily insulin injections and rigorous dietary requirements. While daily insulin injections keep those with type 1 diabetes alive, dreadful complications can result and the disease often shortens

the lifespan of its sufferers. An estimated 2 million Americans suffer from this disease. LIAI researchers are among the world's leaders in type 1 diabetes research and are working diligently in hopes that its suffering can become a thing of the past.

pancreas, the cause of type 1 diabetes. The studies, being conducted in mice, are illuminating cell processes that previously had to be extrapolated from photos, computer modeling or lab experiments. The results may profoundly affect future directions in type 1 diabetes research.

“Being able to view these insulin-producing cells while they interact in the pancreas, rather than in a static state under the microscope, will greatly enhance our ability to find interventions for type 1 diabetes,” said Dr. von Herrath, who created a method allowing the microscope’s use in the pancreas. Up to this point,

the scientific community has used the two-photon to study lymph nodes, the liver and other organs in vivo, but never the pancreas.

Ken Coppieters, Ph.D., who is assisting Dr. von Herrath with the pancreas study, said the two-photon microscope enables researchers to “see” into living tissues at a much greater depth than conventional imaging methods. “It uses intense pulses of light that enable us to monitor interactions of cells without destroying them,” he said.

The state-of-the-art microscope is also expected to shed new light on cancerous tumors, infectious diseases

and other disorders being studied by Institute researchers by revealing new information on how immune cells coordinate attacks or defenses to protect the body.

Mitchell Kronenberg, Ph.D., president & scientific director, said the microscope is an important tool that will greatly enhance the Institute’s research activities. “The ability to make movies in living organs such as the pancreas allows us to track events in real time as inflammation develops, as opposed to the classic still photographs that medical investigators have been making for more than 100 years,” Dr. Kronenberg said. “The ability to visualize and analyze events as they happen inevitably will lead to great insights into the pathogenesis of diabetes and other immune-mediated diseases.”

KLAUS LEY, M.D., IS INTERNATIONALLY RECOGNIZED FOR HIS NOVEL RESEARCH ON HEART DISEASE

Institute Launches New Inflammation Biology Division

RESEARCHES PIONEERING IMMUNE-BASED APPROACHES TO HEART DISEASE

When **Klaus Ley, M.D.**, entered the biomedical research field some 25 years ago, the bioscience community had not yet conceived of the discipline that he would help pioneer—vascular immunology. Today, Dr. Ley is an internationally recognized scientist and among the world’s leaders in vascular immunology, which offers novel approaches for fighting heart disease—the nation’s No. 1 killer—via the immune system. Dr. Ley joined the Institute in late 2007 to lead the newly created Division of Inflammation

Biology, which taps into his vast knowledge of the vascular system along with his expansive experience in inflammation research. “We are excited to have a scientist of Dr. Ley’s stature lead this new research division,” said Mitchell Kronenberg, Ph.D., president & scientific director. “It puts us in a very select group of immunology institutions worldwide that are exploring new ways of fighting heart disease using the immense power of the immune system.” Prior to joining LIAI, Dr. Ley worked for eight years as

director of the Berne Cardiovascular Research Center at the University of Virginia, where he oversaw the efforts of 100 faculty members while continuing his work on atherosclerosis, Crohn’s disease and acute lung inflammation. “Atherosclerosis (hardening of the arteries) is the underlying disease for most heart problems,” he said, noting that inflammation of the artery wall is a key component of that process. While inflammation is usually an immune system defensive action designed to heal, it becomes chronic in atherosclerosis. “You can think of it as a lesion that doesn’t heal,” Dr. Ley explained. This eventually leads to weakening of the artery wall, which is further exacerbated by macrophages, white blood cells that are molecular scavenger hunters that rid the body of worn-out cells. “The macrophages switch on a very specific program that we are trying to understand and to decipher why it weakens, rather than heals, the artery wall,” said Dr. Ley, adding that the macrophages weaken the artery wall to the point of rupturing, which produces a heart attack. “We believe if we can stop that process, we can stop the rupture,” said Dr. Ley, noting this would have major implications for combating heart disease.



LIAI Research Takes Aim at ‘Viral Time Bomb’

POINTS TO POTENTIAL NEW THERAPIES FOR HEPATITIS C, AIDS AND OTHER CHRONIC VIRUS INFECTIONS

Hepatitis C is often compared to a “viral time bomb” ticking away on the world’s horizon. The World Health Organization estimates that about 180 million people, some 3% of the world’s population, are infected with hepatitis C virus, 130 million of whom are chronic carriers at risk of developing liver cirrhosis and/or liver cancer. In fact, 50-76% of all liver cancer cases can be attributed to this virus, and two thirds of all liver transplants in the developed world.

A recent discovery by LIAI researcher **Matthias von Herrath, M.D.**, has made major inroads toward finding new treatments for this disease, which chronically infects an estimated 3.9 million Americans. His findings, based on a chronic virus infection model similar to hepatitis C, also may have implications for HIV, the virus that causes AIDS, and other chronic virus infections. Dr. von Herrath and his research team used the approach of “killing the messenger” so to speak, by blocking in mice the activity of the interleukin-10 (IL-10)

messenger molecule. Normally, this molecule stops the immune system’s T cells—the body’s warriors against disease—from attacking chronic virus infections. Blocking its action caused the T cells to launch an assault against the disease.

Mitchell Kronenberg, Ph.D., president & scientific director, called the finding a “significant advance,” noting the scientific team was able to completely eradicate the chronic infection in the mice, not just tone it down, like many of the current treatment methods for such infections. The finding is under consideration for further testing by a major pharmaceutical company.

LIAI RESEARCHERS ARE MAKING STRIDES AGAINST VARIOUS CHRONIC VIRUS INFECTIONS. (L TO R) CARL WARE AND MICHAEL CROFT, PH.D.’S, STUDY CMV, WHILE MATTHIAS VON HERRATH, M.D., FOCUSES ON HEPATITIS C



Advancing on Cytomegalovirus

SCIENTISTS TREAT INFECTION BY BLOCKING MESSENGER MOLECULE

LIAI researchers took a major step towards unraveling the mystery of cytomegalovirus (CMV) in 2007, by reducing—and in some cases eliminating—CMV in the salivary glands by blocking the IL-10 messenger molecule.

CMV is a virus that affects the majority of the world’s population, but produces little or no symptoms in healthy individuals. However, it can cause multi-organ disease in newborns or persons who have weakened immune systems such as organ transplant recipients or AIDS patients.

Researchers **Ian Humphreys, Carl Ware** and **Michael Croft, Ph.D.’s**, used an antibody to block the action of IL-10 in infected mice, which enabled disease-fighting T cells to attack the

cytomegalovirus-infected cells and resolve the infection.

The findings of the team parallel those of LIAI’s **Matthias von Herrath, M.D.**, who successfully eliminated a chronic virus infection similar to hepatitis C in mice by blocking the IL-10 receptor. “Dr. von Herrath’s findings suggested that the IL-10 molecule plays a pretty important role in small RNA viruses, while our study looked at its impact in large DNA viruses,” Dr. Ware said. “I think both of these studies lend credibility to the idea that the medical community should be looking at IL-10 as a molecular candidate that might be targeted to control persistent viral infections.”

Infectious Disease Primer

Infectious diseases kill more people worldwide than any other single cause. And in our increasingly interconnected world, new infectious diseases are emerging at an unprecedented rate, often with the ability to cross borders rapidly and spread. Since 1967, at least 39 new pathogens have been identified, including HIV, Ebola hemorrhagic fever and SARS. Other centuries-old threats, such as pandemic influenza, malaria and tuberculosis, continue to pose a threat to health through a combination of mutation, rising resistance to antibiotics and weak health systems in many parts of the world. The worldwide research community is acutely aware of the need for new treatments and vaccines to battle these diseases and LIAI is a key player in the ongoing siege.

LIAI Center for Infectious Disease Remains Vigilant

RESEARCHERS CAN REACT QUICKLY TO DANGEROUS NEW STRAINS

Tuberculosis strains that defy existing drugs, San Diego's recent measles outbreak and the emergence of the staph infection superbug (methicillin-resistant *Staphylococcus aureus* or MRSA) remind us daily that infectious diseases remain a significant threat. "It's a perennial race between the research community and infectious microbes," said **Alessandro Sette, Ph.D.**, a world renowned vaccine expert and director of the Institute's Center for Infectious Disease (CID). "There's always going to be new pathogens such as avian flu or old pathogens that mutate and produce new drug resistant strains," said Dr. Sette, noting that drug resistant TB cases are being recorded globally at the highest rates ever seen. "You can never let your guard down. We must continually work to stay one step ahead of these dangerous agents."

Each day, the Center's researchers move closer to unlocking the mysteries of many potentially devastating infectious diseases, including West



RENOWNED VACCINE EXPERT ALESSANDRO SETTE, PH.D., HEADS LIAI'S CENTER FOR INFECTIOUS DISEASE

Nile virus, avian flu and SARS, along with potential bioterrorist agents such as smallpox and the arena viruses.

Dr. Sette said the need to react quickly to new disease strains is paramount and that the CID, one of the few such dedicated research centers in California, is uniquely positioned to do so. "There is a problem in infec-

tious disease research of lag time between the disease being recognized and people writing proposals, hopefully being funded and taking action," he said. "By having a Center to continually monitor new diseases, it allows specialists in the field to quickly rally and start to react to potential threats in real time."

Infectious Disease Research Highlights

The Institute's Center for Infectious Disease (CID) is a world-wide leader in battling infectious diseases through cutting-edge research. The following are a few examples of recent activity:

- **Development of World's Largest Infectious Disease Database.**

The Center has the distinction of hosting the National Institutes of Health's Immune Epitope Database (IEDB), the world's largest database on infectious disease research, created to accelerate vaccine-development on a global scale. The Institute's selection in 2004 by the National Institutes of Health (NIH) to develop the novel research tool, now available freely to scientists worldwide, catapulted the CID into the national forefront of infectious disease research.

- **TB, Influenza and Malaria Data Analyses.**

The Institute continues in the spotlight due to its creation of NIH-requested disease analyses based on IEDB data. The analyses include recommendations for future research targets for the worldwide scientific community. "In the last year, we've issued reports on influenza and tuberculosis and are currently working on malaria," said CID Director **Alessandro Sette, Ph.D.** "Our knowledge base has exploded because of the IEDB activities, and our research reflects this up-to-the-minute information."

- **Smallpox Treatment/Potential Vaccine.**

CID investigator **Shane Crotty, Ph.D.**, has made a major breakthrough in smallpox treatment. Dr. Crotty identified an antibody that could become the nation's first line of defense in protecting against a terrorist-induced smallpox outbreak. This is vital since the younger portion of the U.S. population is not vaccinated. The NIH is considering stockpiling the antibody treatment nationwide alongside the smallpox vaccine. Meanwhile, Dr. Sette is conducting research toward a new and better smallpox vaccine. His research is particularly important since up to 10 percent of the U.S. population should not receive the current vaccine.

- **Dengue/West Nile Virus Advances.** **Sujan Shresta, Ph.D.**, is making significant strides toward first-ever vaccines for the dreaded dengue and West Nile viruses. Dengue virus causes the most significant mosquito-borne viral diseases in the world today in terms of illness, death and economic cost. With 250,000 cases of the severest form reported annually in Southeast Asia and Latin America, dengue virus also poses a potential threat to the United States, since mosquitoes capable of transmitting the virus have been found here.

- **Universal Flu Vaccine.** Dr. Sette is conducting studies that could lead to the development of a "universal" flu vaccine, meaning one that would protect against a broad cross section of flu viruses. Dr. Sette is using powerful biomedical research tools to determine if there are certain molecular "pieces" that are common to all flu viruses and which don't change over time. If so, it may be possible to develop a vaccine that focuses on those pieces, versus the whole virus, part of which changes every year, requiring the development of a new flu vaccine annually.

- **Major Lyme Disease Discovery.** The work of **Mitchell Kronenberg, Ph.D.**, LIAI president & scientific director, is drawing international interest due to his novel finding of an apparent connection between NKT cells and Lyme disease. Lyme disease is transmitted to humans by the bite of infected ticks and can lead to serious health problems. Dr. Kronenberg's finding that a glycolipid in the bacteria that causes Lyme disease triggers an immune attack by the NKT cells has led to hope for a new vaccine.

- **Arena Viruses.** Dr. Sette and his lab were selected by the NIH to conduct research into a first-ever vaccine for the arena viruses, which cause hemorrhagic fevers and meningitis in Africa, South America and, more recently, Europe. Under the multi-million dollar NIH grant, Dr. Sette will map the immune system's response to the arena viruses, which could lead to the development of a vaccine and treatments.

Institute Once Again Advances New and Innovative Allergy Approaches

NIH SELECTS LIAI TO CONDUCT PIONEERING ALLERGY STUDY

Allergies have long been a cornerstone of LIAI's research activities, so it seems fitting that the Institute should lead the way toward a novel treatment approach that could improve the lives of allergy sufferers everywhere. "The pioneering research of our two founding scientists altered the direction of allergy research 42 years ago," said Mitchell Kronenberg, Ph.D., president & scientific director. "Our latest allergy study, which looks at revolutionary new approaches for treating allergies, is a continuation of that spirit of innovation."

In late 2007, the National Institute of Allergy & Infectious Diseases (NIAID) selected the Institute to conduct a five-year study that looks at new methods for treating allergies based on targeting T cells, white blood cells that regulate the immune response and which are some of the principal soldiers in the body's defense.

Alessandro Sette, Ph.D., principal investigator on the allergy contract, said the project will identify the specific allergy epitopes that cause T cells to launch an attack against the allergens. Epitopes are tiny sites on a protein or other molecule that instigate a T cell response. "This opens the possibility of developing therapies around those epitopes," Sette said, noting that several clinical trials have already shown promise to the approach of treating patients with allergy-related epitopes.

According to the NIAID, allergic diseases affect as many as 40 to 50 million Americans, and they are among the major causes of illness and disability in the United States.

Howard Grey, M.D., project co-investigator and president emeritus, said the study will push knowledge of allergies to a deeper level. "The whole field has been dominated by the analysis of the antibody response,

because that's what causes many of the symptoms of the disease—the sneezing, sniffing, coughing and so forth," he said, noting that the discovery of the immunoglobulin E (IgE) antibody in 1966 by **Kimishige Ishizaka, M.D., Ph.D.**, and his wife, **Teruko Ishizaka, M.D., Ph.D.**, who later helped launch LIAI, revolutionized allergy research.

"Now the scientific community has the tools to take our knowledge even further by analyzing T cell responses," he said. "It seems in keeping with our history that LIAI will now lead the next step—breaking down the allergy response to its most basic molecular level."

Results from the project will be available to scientists worldwide.



Researcher's Discovery Pursued for New Asthma Drug

FINDING MARKED AN ASTHMA RESEARCH MILESTONE

For the millions of Americans who suffer from the wheezing, coughing and difficulty breathing that is characteristic of asthma, the pioneering research of scientist **Michael Croft, Ph.D.**, may offer some good news. Dr. Croft's discovery of a cellular mechanism to suppress asthma is now in the development pipeline at a major pharmaceutical company.

"Dr. Croft's finding marked a major milestone in asthma research,"

MICHAEL CROFT, PH.D., HAS DISCOVERED A CELLULAR MECHANISM TO SUPPRESS ASTHMA

said Mitchell Kronenberg, Ph.D., president & scientific director. "He demonstrated in mouse models that the lung inflammation and accompanying symptoms of an asthma attack could be dramatically suppressed by blocking the interaction of the OX40 ligand with its receptor.

"We were not surprised to see that Dr. Croft's discovery generated major interest and are hopeful that it will lead to new therapies that improve the lives of asthma sufferers."

Dr. Croft's finding was particularly exciting because it offers the potential to control asthma for longer periods of time than current therapies.

Asthma is a chronic inflammatory lung disease that results, in many cases, from the overzealous response of the immune system's T cells, due to contact with an external allergen such as those from pollen. The T cells are usu-

ally the body's defenders against disease, but with asthma they mistakenly mount an attack where none is needed.

Dr. Croft began studying OX40, a protein essential to communication between immune cells, in the 1990s because of its strong effect on T cells. "The fact that asthma is a T cell controlled disease made me look at whether OX40 and its ligand were key participants in asthma onset."

Dr. Croft's insight proved true. In his groundbreaking study, he found that using an antibody to block the action of OX40 and its ligand in mice halted the T cell response to the asthma allergen and dramatically suppressed inflammation in the lungs.

Dr. Croft said those findings dealt with asthma onset, and he continues to examine OX40 for its potential in combating chronic asthma and other inflammatory diseases.

Asthma Primer

Asthma is a respiratory disease of the lungs that affects more than 20 million Americans, including nine million children. It is, in fact, the most common serious chronic disease of childhood and is the third-ranking cause of hospitalization among U.S. children under age 15. LIAI's research history is rich in important findings that have advanced the fight against asthma and allergies, which are related disorders marked by overactive immune responses. Both are extremely troublesome maladies that disrupt work and school and continue to grow in numbers. It is estimated that 10 to 20 percent of the population of industrialized countries suffers from some form of allergies.

Immune System Offers Powerful Ally Against Cancer

LIAI RESEARCHERS TARGETING CANCERS WITH IMMUNOTHERAPIES

Lymphoma and leukemia are two aggressive blood cancers that often show no mercy to their victims. While survival rates are improving, leukemia still causes more deaths than any other cancer among children under age 20. In addition, the incidence of lymphoma has increased significantly over the past 20 years—

taking it from a relatively uncommon disease to the fifth most common cancer in the United States.

Such statistics don't deter **Stephen Schoenberger, Ph.D.**, a Leukemia and Lymphoma Society Scholar. They only enhance his resolve that these two blood cancers can be defeated using the enormous disease-fighting

potential of the immune system. "The immune system has emerged as a key player in the ongoing war on cancer," said Dr. Schoenberger, noting that cancer vaccines, lymphocyte transfers, antibody therapy and other immune-based modalities are now being used successfully against a variety of cancers. "The introduction of



STEPHEN SCHOENBERGER, PH.D., FOCUSES ON USING THE IMMUNE SYSTEM TO COMBAT **BLOOD CANCERS**

cancer immunotherapy over the last 10 years has shown that the body's defense system can offer one of the most powerful avenues for fighting this disease. The time is now for aggressive translation of promising immunological findings into clinical use against cancer."

Dr. Schoenberger has spent several years focusing on the immunological puzzle of lymphoma and leukemia, which result from the unrestrained growth of B or T cells. Dr. Schoenberger has been unraveling the process through which normal B and T cells induce a state of tolerance to avoid recognition by killer T cells. His laboratory has found that lymphomas and leukemias can deviously appropriate this mechanism to shut down the killer T cells that would otherwise eradicate them. "We've made some critical insights into this process and have devised methods to interfere with the ability of cancer B and T cells to circumvent their own destruction. We believe this will lead to more effective clinical therapies against these types of cancers in the near future."

LIAI researcher **Don Newmeyer, Ph.D.**, is also engaged in the fight against cancer. However, his research comes from a different angle—understanding the process of cell death.

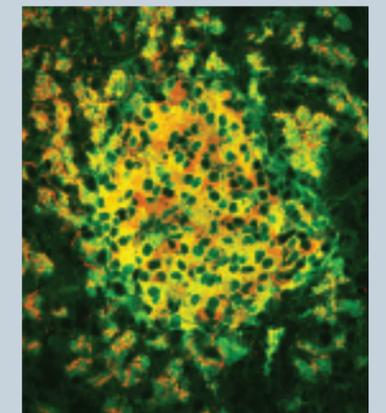
Cell death is important in battling cancer because cancer results from the multiplication of genetically altered cells that under normal conditions would die.

Dr. Newmeyer analyzes the functions of mitochondria—the energy factories of the cell—to determine how they help cells die. Cell death is a natural process in the body to remove excess or defective cells and to allow for the proper development of tissues. His studies have shed light on extremely important steps in the process of cell death that could ultimately be used to create new cancer treatments. In the late 1990s, Dr. Newmeyer's research showed that mitochondria initiate cell death by releasing key proteins, and that certain cancer genes can prevent this protein release, thus permitting the cancer cells to escape death. More recently, his laboratory has found another way in which mitochondria cause cell death—by shutting off energy production that would normally be necessary to the cell's survival.

In 2007, Dr. Newmeyer co-authored a major study demonstrating that some cancer cells can survive this energy loss by expressing the GAPDH protein. "GAPDH somehow keeps these cells alive long enough to generate new mitochondria, which are

Cancer Primer

In the 1980s, the American government declared war on cancer, a devastating disorder that encompasses about 200 different strains. While significant scientific progress has been made, cancer still remains the second leading cause of death in the U.S. In this year alone, more than half a million Americans will die at the hands of this terrible disease. But hope for a cure remains strong, especially considering major treatment advances over the last 10 years. Figuring prominently in that progress are new immunotherapies, which marshal the immune system's colossal forces against this disease. LIAI researchers are working diligently to advance this promising modality of cancer treatment.



necessary to sustain the growth of cancer cells," he explained. "If we could block or subvert the GAPDH protein's action, then we may be able to stop the survival of these cancerous cells."

Lipids Showing Promise as Potent Cancer Fighter

MOLECULES TRIGGER IMMUNE ATTACKS AGAINST INVADING ANTIGENS

Cancer remains a mystery that is still unfolding. Researchers attack it from a myriad of angles, with one of the more recent focuses being immunotherapies that utilize the power of the immune system to fight this often-deadly disease.

LIAI researcher **Dirk Zajonc, Ph.D.**, is studying a relatively new player in the immune system army—glycolipids—which are natural biochemicals made of linked fat and sugar. Some of these molecules play the very important role of triggering natural killer T cells (NK T cells) to attack viruses, bacteria and other foreign antigens invading the body. “If natural killer T cells are like soldiers in the body’s defending army, then glycolipids are like messengers telling the soldiers it’s time to attack,” Dr. Zajonc explained.

The fact that glycolipids can activate immune cells was only discovered about 15 years ago and has become the subject of intense research interest because of its potential use in fighting cancer and other diseases.



“These fats play a much bigger role in disease than previously realized,” said Dr. Zajonc. “They have implications for all kinds of things—autoimmune diseases, infectious diseases, cancer and tuberculosis.”

Prior to the discovery of glycolipids as NK T cell stimulators, scientists believed that peptides, which are protein pieces recognized by the immune system, were the only triggers of immune system attacks by T cells. In fact, two distinct disease-fighting pathways exist like parallel universes within the immune system. One path uses the killer T cells,

DIRK ZAJONC, PH.D., IS EXPLORING HOW GLYCOLIPIDS PLAY AN IMPORTANT ROLE IN CANCER AND OTHER DISEASES

which are activated by peptides, to attack and destroy antigens. The other path uses the NK T cells, which are activated by glycolipids.

Dr. Zajonc is studying how the glycolipid activates the NK T cells. “By better understanding this process, we may be able to design drugs that would stimulate more NK T cells to destroy cancerous cells.”

GIVING

Just as we believe that greater knowledge of the immune system is key to better human health, so we also believe in the power of philanthropy to make a difference.

The people we meet encourage us constantly—people like you who are willing to get to know us at the La Jolla Institute for Allergy & Immunology, learn about what we do—and subsequently support our important research.

We are most appreciative of our donors who share our passion for the significant contributions of our Institute to basic biomedical research. Every gift we receive does make a difference in our ability to conduct world-class science on a daily basis. Our greatest needs are to secure funding for new and innovative ideas, cutting-edge technology, and recruitment of the very best scientists—all so that we can fight the devastating effects of disease and suffering.

We thank you for taking the time to learn about us in this Annual Report and by viewing our newly revised web site. Please click on the “How to Help—Donate Now” button at www.liai.org for an easy, safe, and efficient way of supporting the La Jolla Institute for Allergy & Immunology. We welcome you to join our very special donors and make a gift in support of *Finding Cures Faster*.

Kind regards,



MaryAnn F. Stewart
Vice President, External Relations & Chief Development Officer

WHY GIFTS ARE SO CRITICAL

The rigorous and technological demands of academic biomedical research can no longer rely on the federal grants process to fund all of the needs of cutting edge science in the U.S.

Charitable gifts, especially from individuals and foundations, play an increasingly critical role in the development of new discoveries with the potential to benefit human health.



“You can lose a generation of researchers pretty fast—in five or ten years. You create such a discouraging atmosphere they just go somewhere else instead of academic research. We don’t have to lose 50,000 researchers, just 50 really good ones. Once it happens, we won’t get those people back.”

Joshua Boger, Ph.D.
Founder, Vertex Pharmaceuticals, and Chair, Biotechnology Industry Organization (BIO)

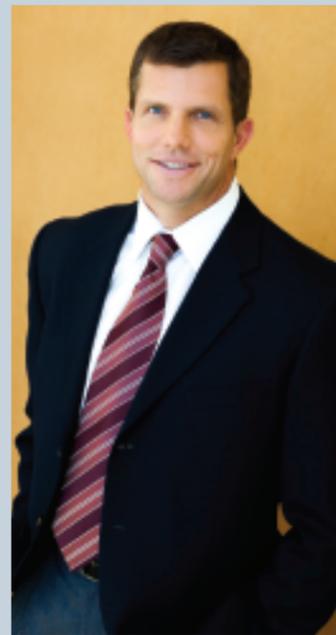
(from www.BrokenPipeline.org)

2007 FINANCIAL HIGHLIGHTS

FISCAL YEAR ENDED DECEMBER 31, 2007

2007 FINANCIAL PICTURE REMAINS STRONG

La Jolla Institute for Allergy & Immunology continues to operate in a strong financial position, with total revenues reaching a new high of \$32.1 million for fiscal year 2007. As shown on the accompanying bar graphs, LIAI's federal funding, total revenues and net assets have increased steadily during the past five years. This is largely due to the success of our renowned scientists in obtaining competitive peer-reviewed research funding from the National Institutes of



Health (NIH). However, we remain cognizant of a decline in NIH funding levels that has and will continue to affect biomedical research nationwide.

Since our inception in 1988, the Institute's industry partner, Kirin Pharma USA, Inc., has provided us with a critical source of unrestricted research funding while facilitating the translation of our discoveries into potential treatments for human disease. Sponsored research funding from Kirin Pharma remains an important source of revenue, and provides our scientists with the freedom to pursue the most promising research.

During 2007, the Institute made strides toward diversifying and enhancing

revenues from philanthropy and technology transfer. The addition of new departments for external relations and intellectual property has provided focus and experienced leadership in these areas.

While efforts to enhance revenue sources are under way, the Institute continues its intense concentration on research while operating with a lean and effective administration.

As shown on the accompanying pie chart, 88 percent of total expenses were used for research in 2007.

The Institute's financial position and outlook remain strong. This, coupled with our extraordinary scientists, dedicated staff, and world-class research facility provide a foundation that will enable us to continue our accelerated pace of discovery toward new treatments and cures for many debilitating diseases.

Charles A. Carpowich, Jr., CPA
Executive Vice President & COO/CFO

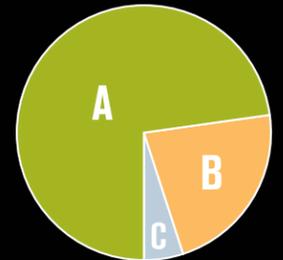
STATEMENT OF FINANCIAL POSITION

Cash and investments	\$ 9,003,000
Grants receivable and other	6,673,000
Property, net	5,414,000
Total assets	\$ 21,090,000
Accounts payable and accrued expenses	\$ 4,611,000
Deferred revenue	252,000
Total liabilities	4,863,000
Total net assets	\$ 16,227,000
Total liabilities and net assets	\$ 21,090,000

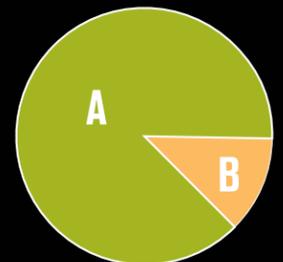
STATEMENT OF ACTIVITIES

Revenues:	
Federal grants and contracts	\$ 23,476,000
Private grants and contracts	7,047,000
License revenue	484,000
Contributions	340,000
Investment return and other	748,000
Total revenue	\$ 32,095,000

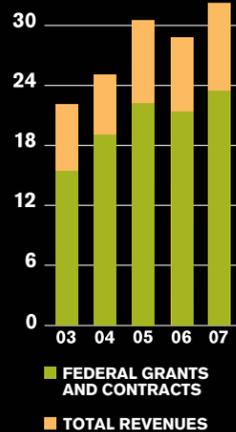
Expenses:	
Research	\$ 26,606,000
General and administrative	3,521,000
Fundraising	86,000
Total expenses	\$ 30,213,000
Change in net assets	\$ 1,882,000



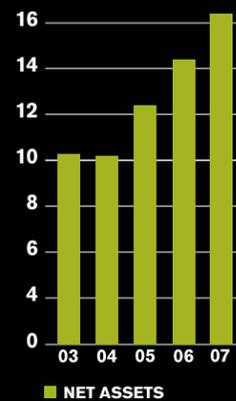
Revenues
A) Federal grants and contracts 73%
B) Private grants and contracts 22%
C) Other 5%



Expenses
A) Research 88%
B) G&A and Fundraising 12%



Revenue Growth
in millions of dollars



Net Asset Growth
in millions of dollars

* 2007 Financial Data summarized from LIAI's December 31, 2007 audited financial statements. To receive a copy of LIAI's audited financial statements, contact Charles Carpowich at 858-752-6510 or e-mail skip@liai.org.

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Kristi M. Vonderloh
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† Deceased

www.liai.org

In November 2007, the seminar room at the La Jolla Institute for Allergy & Immunology was formally named the “Kimishige and Teruko Ishizaka Seminar Room” in honor of the La Jolla Institute’s founding Scientific Director and second President, Kimishige Ishizaka, M.D., Ph.D. and his wife, Teruko Ishizaka, M.D., Ph.D., two extraordinary scientists in the field of immunology. The Ishizakas have also been very generous to the La Jolla Institute with gifts to support a lecture series for outstanding visiting scientists and to help in the construction of the new building in 2006.



LA JOLLA INSTITUTE
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ALLERGY & IMMUNOLOGY

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