THE IMPORTANCE OF FUNDAMENTAL IMMUNOLOGY

Researching fundamental immunology using sophisticated molecular and cellular technologies is the primary activity of scientists at LIAI, but at the same time most scientists at the institute have a passionate interest in a specific major human disease. Understanding the molecular mechanisms by which the immune system functions is a key to treating, curing, or preventing a wide range of illnesses. The list of human diseases with direct links to immune function continues to grow. For example, recent evidence indicates that immune system malfunction contributes to heart disease. Scientists understand that there are numerous layers of complexity to the immune system, and at LIAI we know that defeating difficult biological problems like sickness from infection or chronic diseases such as diabetes requires a great depth and breadth of knowledge. Moreover, some diseases that seem very different may actually have similar causes at their core. For example, an immune based treatment has recently been successful for both patients with arthritis and also those with inflammatory bowel disease.
Dr. Frank Dixon was a founding board member of LIAI and has served as Board Chairman for the last 14 years. A renowned leader in the scientific community, Dr. Dixon is a member of the prestigious National Academy of Sciences, and was a founder and long-time director of the Scripps Research Institute. “Dr. Dixon’s career has been one of pioneering endeavors and remarkable scientific achievement,” said Mitchell Kronenberg, Ph.D., LIAI President and Scientific Director. “The Institute has benefited greatly from his guiding hand, forthright style and keen insight. We owe much to his many years of service.”

Dr. Dixon became the first director of the Scripps Clinic (now TSRI) in 1961 and served as its director until 1987, guiding its growth into the largest private research institute in the United States. Dr. Dixon received the coveted Albert Lasker Medical Research Award in 1975 for his outstanding contributions to the creation of a new medical discipline — immunopathology — constituting a breakthrough in medicine that illuminated the underlying mechanisms of an entire class of human disease.

Dr. Dixon holds more than 20 major awards for his lifetime of scientific achievement, and continues to serve on numerous scientific advisory committees for major organizations, including the National Kidney Foundation, the World Health Organization, and the National Multiple Sclerosis Society.

Upon his retirement from the LIAI Board of Directors and from his position as Chairman of the Board, the Institute wishes to express its deep appreciation and gratitude for Dr. Dixon’s longstanding dedication and enduring contributions to the Institute. It is with great pride that we announce that Dr. Frank J. Dixon has been appointed as a Director Emeritus of the Institute for life.
THE LA JOLLA INSTITUTE FOR ALLERGY AND IMMUNOLOGY is a nonprofit, academic research institute dedicated to fighting disease through cutting-edge immunology research. Our internationally renowned team of scientists studies how the immune system normally defends us from infection, and how it may malfunction to cause an array of chronic diseases. In fact, the immune system affects all areas of the body, and with treatment or cures for infectious diseases, allergies, autoimmune diseases (such as diabetes), and even cancer dependent upon advances in immunology, there is probably no biomedical discipline that has greater implications for improving human health.

Founded in 1988, LIAI is a young and exceptionally dynamic institution that is at the forefront of innovation and discovery. We are passionate in our desire to address important problems of the immune system, and we were gratified that the Institute was recently ranked among the top five molecular biology and genetics research organizations in the world1. I am honored to serve as the third President and Scientific Director of this Institute, succeeding two giants in the field of immunology: Dr Kimishige Ishizaka and Dr. Howard Grey.

The past year has been marked by many accomplishments for the Institute. Highlights during 2004 include the successful recruitment of two new faculty members. Dr. David Lo is an expert on immune system development and mucosal vaccines, and Dr. Sujan Shresta studies Dengue virus, which causes the most prevalent mosquito-borne viral illness in humans. These two investigators add substantially to the Institute’s expertise in the area of infectious disease, which is enhanced by our new Emerging Infectious Disease and Biodefense Center. Also in 2004, we successfully completed negotiations to occupy a cornerstone property in the new Science Research Park of the University of California San Diego campus, where our new, much larger, research building is now under construction. Most importantly, during the past year our faculty continued to make important discoveries that could influence human health, and they published approximately 100 research studies, many of which were reported in the most prestigious scientific journals.

Because public support and understanding are important to us, we have begun to more actively publicize the goals, accomplishments, and activities of the Institute. Our scientists have been highly successful in obtaining competitive grants from both the U.S. National Institutes of Health (NIH) and private foundations. These sources of support are not sufficient to pay for all necessary scientific equipment and development of the new building, nor do they support highly innovative and risky projects. Therefore we are seeking private donations from interested individuals who wish to contribute to our intensive search for understanding, treatments, and cures of a broad range of human diseases.

The La Jolla Institute for Allergy and Immunology is a place with an especially pleasant and harmonious atmosphere, where a highly focused group of researchers function at the highest level, with a minimum of bureaucracy or distractions. I am obviously very proud of this unique Institute and grateful for your interest. As we make the transition to our new building in the next 12 months, we hope that you will help us to realize the potential for improving human health that will inevitably arise from research designed to achieve a better understanding of the immune system.

Mitchell Kronenberg, Ph.D.
President and Scientific Director

THE LA JOLLA INSTITUTE FOR ALLERGY AND IMMUNOLOGY (LIAI) is a nonprofit research center dedicated to increasing knowledge and improving human health through studies of the immune system. LIAI’s ongoing mission is to expand our understanding of how the immune system functions, with particular interest in four major areas of disease-related research:

- AUTOIMMUNE DISEASES such as diabetes, inflammatory bowel disease, and arthritis
- CANCER and stimulating immune responses against tumors
- INFECTIOUS DISEASES such as opportunistic infections, hepatitis C, and emerging biothreats like SARS
- ALLERGY AND ASTHMA and controlling life-altering or life-threatening reactions
Since its founding in 1988, LIAI has provided a unique intellectual environment with strong ties both to the University of California, San Diego and the biomedical industry. As such, it has grown to become one of the largest freestanding immunology research institutions in the world. LIAI has 15 independent laboratories with over 120 Ph.D.-level scientists.

The quality of science performed at LIAI is exceptional. A recent survey of productivity by research institutions and universities ranked LIAI 5th in the world for overall quality in molecular biology and genetics during the past decade. LIAI is now entering an era of expansion following major Institute discoveries in fundamental immunology, cancer, diabetes, and infectious diseases, with the confidence that these efforts will ultimately contribute to cures for human diseases.

**Kimishige Ishizaka, M.D., Ph.D.**

*Founding President and Scientific Director, 1989-1995*

Dr. Kimishige Ishizaka and his wife Dr. Teruko Ishizaka received worldwide recognition in 1966 when they discovered human immunoglobulin E (IgE), the form of antibody responsible for allergic reactions. Thereafter, Dr. Ishizaka devoted his efforts to determining the molecular character of IgE and why IgE is such a potent cause of allergic reactions. Dr. Ishizaka was a professor at Johns Hopkins University School of Medicine for two decades before joining the new La Jolla Institute for Allergy and Immunology in 1989 as its first Scientific Director. Dr. Ishizaka is the recipient of numerous prestigious scientific awards, including the Japan Prize (2000) and election to the U.S. National Academy of Sciences (1983). The Ishizakas now live in Japan, but Dr. Ishizaka still actively participates in the scientific affairs of the Institute and as a member of the Board of Directors.

**Howard Grey, M.D.**

*President and Scientific Director, 1995-2003*

Dr. Howard Grey was the second director of LIAI, and recently retired from that position in 2003 after eight very successful years. Dr. Grey is an exemplary laboratory scientist and is the author of more than 250 scientific papers. Early in his career, Dr. Grey made fundamental contributions to our understanding of how antibodies can react to such a wide range of foreign invaders. Later, his laboratory made seminal discoveries identifying the features of foreign molecules that T cells of the immune system “see” on a diseased cell. The nature of how a T cell “sees” foreign molecules is crucial for many aspects of immune reactions, including protection from infectious diseases, prevention of cancers, and autoimmunity. For these accomplishments, Dr. Grey was elected to the National Academy of Sciences, one of the highest honors in American science.
BANNER YEAR FOR LIAI RESEARCH

LIAI scientists continued to push the frontiers of knowledge in immunology in 2004, with an extremely productive research year. LIAI faculty published 96 research studies, many of which were reported in the most prestigious scientific journals in the world — Nature, Cell and Science. Faculty member Dr. Hilde Cheroutre made a major breakthrough on triggering long-term memory in immune cells, which was published in Science magazine and reported by media outlets throughout the world.

Two major findings by Dr. Doug Green (right), which further illuminated the molecular mechanisms of cell death, led to publications in Science and Cell magazines. Many other LIAI scientists had important findings published in the most prestigious scientific journals throughout the year. These ranged from Dr. Yun-Cai Liu’s research identifying a molecule that may prevent the development of arthritis, which was...
“The people who are going to make the breakthroughs, by analogy with history, are going to be...well-trained scientists working in unpredictable areas.” —David Baltimore, winner of the Nobel Prize in Medicine, President, California Institute of Technology

NEW FACULTY RECRUITMENT

Sujan Shresta, Ph.D. (top right), who specializes in Dengue virus, will join LIAI in 2005 after spending four years conducting research at the University of California, Berkeley. A potentially deadly disease, Dengue virus is part of the flavivirus family of diseases, which include yellow fever, Japanese encephalitis and the West Nile virus. Dengue virus kills thousands of people in Southeast Asia and Latin America each year, and also poses a potential threat to the United States. Along with the Dengue virus, Dr. Shresta will also work on the West Nile virus, another potentially deadly virus. As part of the Institute’s Vaccine Discovery division, Dr. Shresta will concentrate on better understanding the body’s immune response to these diseases, with the hope that her research may one day lead to the development of safe, effective vaccines and treatments for people in all countries.

The Institute also recently welcomed faculty member David Lo, M.D., Ph.D. (below left), who specializes in the study of how the body battles infections in the intestine and other mucosal sites. Dr. Lo spent 10 years at the Scripps Research Institute’s Department of Immunology and later served as vice president of integrative biology at San Diego biotech Digital Gene Technologies. Dr. Lo joined LIAI’s Developmental Immunology division in 2004, where his research has implications for flu, E. coli and HIV infections. He also has projects directed at autoimmune diabetes and chronic inflammatory bowel disease.

New faculty member Dr. Shane Crotty, who started at LIAI in 2003, was awarded a prestigious Cancer Research Institute Young Investigator Award in 2004. He was one of only six promising young scientists in the country to receive this award.
2004 HIGHLIGHTS

TOP 10 IN RESEARCH QUALITY

LIAI was recently recognized by The Scientist as one of the highest quality biology research organizations in the world. LIAI was ranked 5th in Molecular Biology and Genetics and 16th in Biology and Biochemistry during the past decade. This placed the Institute ahead of almost all university departments and other research institutes. This accomplishment is particularly impressive given the modest size of LIAI compared to many other research organizations.

NEW EMERGING INFECTIOUS DISEASE AND BIODEFENSE CENTER

The Institute launched a new research initiative in 2004, with the creation of its Emerging Infectious Disease and Biodefense Center. Researchers within the center will focus on the fight against new and re-emerging infectious diseases, such as West Nile virus, SARS and influenza, along with potential bioterrorist threats, such as smallpox. The center’s work has gained LIAI national prominence in the last year, and given the Institute a key role in the nation’s biodefense efforts due to its selection for several major research projects. The most prominent of these projects calls for the development of the world’s largest medical research database on immune responses to infectious agents, known as the Immune Epitope Database. The Institute was selected to lead this effort by the National Institute of Allergy & Infectious Diseases (NIAID) in 2003.
LIAI FACULTY: LEADERS IN THE SCIENTIFIC COMMUNITY

Several LIAI faculty members were involved in organizing major international conferences in 2004, bringing together researchers from around the world to focus on the latest scientific research in various areas. LIAI faculty members who organized these conferences were: Dr. Carl Ware, Dr. Mitchell Kronenberg, and Dr. Matthias von Herrath.

In addition, several faculty members have recently authored major scientific review articles. These articles are written by leaders in a scientific field and discuss the latest findings in a scientific research area. Frequently such articles point out new important areas of research and are often cited by other scientists. LIAI faculty authors and their places of publication were: Dr. Yun-Cai Liu, the Annual Review of Immunology; Dr. Doug Green, Science; Dr. Hilde Cheroutre, the Annual Review of Immunology; and Dr. Michael Croft (below), Nature Reviews Immunology.

LIAI INITIATES FUNDRAISING DRIVE

LIAI recently launched an initiative to raise funds for the Institute’s new research facility (see following pages), which began construction in early 2005. The new facility will provide increased space and cutting-edge equipment that will allow LIAI to significantly enhance and expand the scope of its research programs. In addition, the fundraising drive is also targeted at facilitating the establishment of LIAI’s new initiative in Emerging Infectious Diseases.
LIAI HAS ALREADY BEGUN construction of a new facility in La Jolla, California (shown above) to help solidify its place as one of the world’s leading freestanding immunology research centers. The building, which will be completed in May 2006, will allow the Institute to significantly enhance programs in its four strategic areas of scientific research: autoimmune diseases, cancer, infectious diseases, and allergy and asthma.

OPTIMAL RESEARCH ENVIRONMENT TO FUEL INNOVATION

By providing increased space and cutting-edge equipment for LIAI’s internationally renowned team of scientists, the new facility will increase the ability of Institute researchers to develop innovative solutions to some of the most pressing biomedical questions of our time — from diabetes to bioterrorism and from tumors to asthma.

Now enjoying a period of success-driven growth, the need for a new building has never been more evident for LIAI. As the scope of LIAI’s research has expanded through the years, the Institute has grown well beyond the research capacity of its current space of 45,000 square feet. The new facility will comprise 145,000 square feet, providing an optimal research environment for LIAI scientists. With new laboratory space housing cutting-edge equipment and supporting critical new technologies, LIAI researchers will have greatly expanded opportunities to pursue and solve complex problems of human health and disease.

UCSD LOCATION WILL ENHANCE COLLABORATION

LIAI’s new facility will be located in the University of California, San Diego’s (UCSD) Science Research Park. While LIAI will retain its independent identity, its
The new facility will comprise 145,000 square feet, providing an optimal research environment for LIAI scientists.

campus location will encourage a closer working relationship with UCSD scientists, thereby enhancing efforts to translate basic research findings into treatments and cures for human diseases.

“By locating in the UCSD Science Research Park, we will bring together the talents and knowledge of some of the world’s leaders in immunological research, clinical trials and patient care, concentrating immense biomedical expertise all in one location,” said Mitchell Kronenberg, Ph.D., LIAI President and Scientific Director. “This powerful combination will undoubtedly lead to research breakthroughs and, ultimately, new medical treatments.”

The connection with UCSD will also enhance LIAI’s access to world class instruments and facilities that can only be supported by a larger institution.

The La Jolla Institute for Allergy & Immunology relies on partners in government, industry and the private sector who support its important work. But as the Institute’s research has continued to expand, so too has its need for support. LIAI is asking those who believe in the Institute’s distinctive scientific mission to invest in its new research facility and our expansion, which will truly transform the way LIAI scientists address important problems in immunology that are deadly or debilitating problems for people throughout the world.
Most of the time, the immune system is the body’s protector, warding off invading viruses and tumors before they can lead to infection and disease. But in autoimmune disease, the immune system does an about face, turning on the body and attacking normal cells. Amnon Altman, Ph.D., and his lab are working to understand the biochemical mechanisms which cause this aberrant behavior. Ultimately, Dr. Altman hopes their discoveries may lead to the development of specific treatments for multiple sclerosis, arthritis, diabetes and other autoimmune disorders which attack, and potentially devastate, their victims.

Dr. Altman and his team focus their studies on T lymphocytes — white blood cells that are essential in the body’s fight against infection and disease. In particular, they are probing the process which occurs when a T lymphocyte encounters an antigen (any foreign substance, including disease causing agents).

“This triggers a cascade of complex biochemical changes, which activate the T lymphocyte and allow it to mount an effective immune response,” explained Dr. Altman. “If we understand this process, it will allow us to rationally design treatments aimed at either boosting an immune response, such as to fight cancer, or to suppress an unwanted immune attack on normal cells, which occurs in autoimmune disease.”

Dr. Altman’s studies have turned up several important findings, most notably the discovery of an enzyme — protein kinase C theta, which may hold the key to controlling immune response. “In more recent studies, we have found that this enzyme provides an important survival signal to T lymphocytes,” he said. “Conceivably, if we could find specific inhibitors of the enzyme, then we could prevent this survival signal, which may result in the death of potentially dangerous T lymphocytes capable of causing an autoimmune disease.” Dr. Altman and his lab

AUTOIMMUNE DISEASES

Amnon Altman, Ph.D. (left) and Yun-Cai Lui, Ph.D. (right) examine data involving signaling molecules relating to autoimmune disease.
“We concluded that the Cbl-b molecule critically blocks arthritis by giving the immune system of the normal mice the ability to ‘tolerate’ the arthritis antigens.”

Yun-Cai Liu, Ph.D.

continue to explore this, and other enzymes, hoping to unlock the mysteries of autoimmune disease.

Autoimmune arthritis is a debilitating disorder that can turn the everyday tasks of life — from tying one’s shoes to buttoning a shirt — into painful, difficult challenges. At its worst, arthritis can disable and cripple, leaving previously vibrant, independent people unable to fend for themselves. Yun-Cai Liu, Ph.D., has devoted much time and attention to understanding the biochemical basis of autoimmune arthritis, with the ultimate hope of finding better ways to treat this devastating illness. In 2004, Dr. Liu and his lab took a giant step in that direction. Working jointly with the Austrian Academy of Sciences, Dr. Liu made an important discovery — finding that the molecule Cbl-b plays a critical role in preventing the development of autoimmune arthritis. Cbl-b is a normal protein in the human body, produced and used in many organs.

In the study, researchers injected substances to induce arthritis in two groups of mice — one which had been genetically-targeted to remove the Cbl-b molecule; the other group consisted of normal mice with the Cbl-b molecule. Under these conditions, the normal group did not react, while the group without Cbl-b developed severe arthritis. "We concluded that the Cbl-b molecule critically blocks arthritis by giving the immune system of the normal mice the ability to ‘tolerate’ the arthritis antigens," he said. Dr. Liu’s lab continues to expand on the finding, which is viewed as an important advancement in scientific understanding of arthritis and also thought to have application for other autoimmune diseases, such as diabetes.
While the battle against cancer is being waged on many fronts, Stephen Schoenberger, Ph.D., believes significant promise for fighting this devastating disease lies in "educating" the immune system to attack cancerous cells — a concept known as immunotherapy. While more mainstream treatments such as chemotherapy, radiation and surgery remain important, Dr. Schoenberger says the body's natural defense system — the immune system — offers a powerful, and as yet still largely untapped, fourth modality of cancer treatment.

An American Cancer Society Research scholar, Dr. Schoenberger and his laboratory are focusing, in particular, on using immunotherapy to fight lymphoma and leukemia, which result from the unrestrained growth of B or T cells. Both are white blood cells that usually defend the body against disease, but which can also mutate into cancerous cells. He says, "Part of cancer is that the body begins to express a lot of mutated proteins, which the immune system should respond to and destroy, yet there's very little immune response to lymphoma or leukemia. Why?" Dr. Schoenberger's research seeks to find a way to teach the immune system to recognize the differences which distinguish cancerous cells from their normal counterparts, and then to eradicate those cancerous cells.

His studies are drawing significant interest in cancer research circles and recently led to his selection as a Leukemia and Lymphoma Society Scholar. "We have found that normal resting T and B cells of the body's immune system have the ability to induce tolerance — in other words, they stop or quiet down new immune responses in the body," he said, which is contrary to normal immune function. "We theorize that tumors derived from T and B cells (lymphomas and leukemias) use the same strategy to escape killer T cells, and killer T cells are powerful cells of the immune system that, if
functioning normally, would lead to the eradication of tumors. So, we believe the tumors work hard to stop or avoid killer T cell responses, and one devious way they do this is by inducing tolerance in the killer T cells.”

Dr. Schoenberger and his research team believe they have identified the molecular mechanism which allows the T and B cells to interfere with immune response. Currently, they are conducting experiments with a cancer prone transgenic mouse to see if the cancerous form of the cells use the same mechanism. “Once we figure that out, we can find a way to overcome it,” he said.

This could have major implications for fighting leukemia and lymphomas since it would enable the immune system to eradicate the cancerous cells.

Don Newmeyer, Ph.D., is studying one of the underlying mysteries of cancer — why some cells grow out of control and lose the capacity to die. The ability of cells to die on cue is very important and may hold the key to ultimately defeating cancer. Normally, unneeded or damaged cells in the body die off through a natural process of cell suicide, known as apoptosis or programmed cell death. But in cancer, the process is skewed and cells that should die off do not. Instead, these wayward cells multiply out of control, leading to tumors. Dr. Newmeyer and his laboratory are focusing on understanding the molecular mechanisms of cell death, principally the role of the mitochondria — the energy factory of the cell. In particular, his team is examining several proteins of the mitochondria — Bax, Bid, Bcl-2 and Bcl-XL — to see how they induce or, in some instances, block the death of a cell. “We study the fundamental mechanisms of cell death,” he said. “Understanding this would have major positive implications for cancer therapy.” By better understanding this process, Dr. Newmeyer believes it may be possible for scientists to learn how to artificially induce cell death in tumors, while leaving normal cells unharmed. “This is one of the problems of current cancer treatments — the inability to kill cancer cells without undesirable side effects.”
Carl Ware, Ph.D., is known the world over for his trailblazing work on tumor necrosis factor (TNF). TNF is one of a group of proteins found to play an important role in the immune system’s functions. Dr. Ware, in fact, was involved in the initial discovery of TNF in the 1980s, an extremely significant finding which eventually led to the development of new treatments for rheumatoid arthritis and Crohn’s disease, two autoimmune disorders. Dr. Ware’s research has also explored TNF’s role in infectious disease, particularly cytomegalovirus (CMV), one of the herpes family of viruses. “Over 90 percent of the population has CMV,” he said, explaining the virus is usually acquired as a childhood infection and produces mild or no symptoms — except in transplant patients who have heavily suppressed immune systems.

The virus can persist for the life of a normal person, quietly existing in the individual’s cells. It is this symbiotic relationship between virus and host that fascinates Dr. Ware and fuels his studies. “Normally, the immune system rejects a virus,” he said. “But it doesn’t reject this virus. Instead the virus and the immune system exist in a state of détente.”

Dr. Ware and his lab have found that TNF plays an important role in this co-existence. When CMV first enters a cell, “the body’s lymphotoxins (close relatives of TNF) induce another protective protein, an antiviral called interferon. But CMV inhibits the interferon response. The lymphotoxins and TNF then override that blockage.” The net result is that the cell survives, but the virus persists, although in a dormant state, he said. This battle of human and viral proteins results in the survival of the person and the “hibernation” of the virus.

By studying the molecular complexities of this process, Dr. Ware hopes that scientists can one day use this knowledge to intervene therapeutically in other diseases, which unlike CMV, are dangerous to their host. “We think that through the lymphotoxin system, we might...
LIAI is also the lead organization on developing the world’s largest Immune Epitope Database, which will explore how the immune system battles disease. Specifically, the database will categorize epitopes, which are the regions of infectious viruses and toxins that are the focus of an immune response.

LIAI and 12 other leading research institutions, which were selected for the discovery contracts, will provide much of the information to populate the database. “The NIH has shown great confidence in the Institute by entrusting us not only with creating and hosting this important database, but also with the work of gathering much of the data related to the smallpox and arena viruses,” Sette said. He added that no live smallpox or arena viruses will be used in the LIAI research. “Our work is based on computer modeling and algorithms and making small synthetic pieces for testing in the lab,” he said. “This allows us to work on very dangerous infectious agents without the risk of using the actual viruses.”
Following a research breakthrough last year that generated worldwide interest, Hilde Cheroutre, Ph.D., and her lab continue to probe the mysteries of immune memory. Immunological memory is the process by which the immune system remembers — and defends against — infectious agents it has encountered before. Dr. Cheroutre’s finding identified precursor cells, which are capable of becoming immune memory cells. The discovery has important implications for the future development of better vaccines and treatments for cancer, since it may one day enable scientists to trigger the development of more immune memory cells. With more of these memory cells, the body can better fight disease should it arise again.

Recently, Dr. Cheroutre’s immunological studies have further expanded, with an important new finding that could one day change the way vaccines are administered. “We’ve found that these memory cells (developed from the precursor cells) have the capacity to go and fight an invading pathogen where it enters the body, most often through the mucosal linings — mouth, nose, lungs, intestine,” she said. Their studies also revealed that specific dendritic cells, which instruct these memory cells, are located most abundantly in the mucosal linings and nearby draining lymph nodes full of immune system cells.

Doug Green, Ph.D., is one of the top scientists worldwide studying the process of how cells die. His findings have made him internationally renowned and earned him prominence as one of the most cited scientists in biomedical research. Dr. Green’s newest discovery is a identified a key protein (NDUSF1), which is an integral component of the pathway leading to programmed cell death. Dr. Green found that the protein’s destruction by the caspases, another cellular protein, accelerates the destruction of the entire cell. “This is one of the key steps for efficient dismantling of the cell,” Dr. Green said.

RESEARCH BREAKTHROUGHS

Combined, the research of Hilde Cheroutre, Ph.D. (left), Doug Green, Ph.D. (center) and Matthias von Herrath, M.D., Ph.D. (right) covers a broad range of human diseases. Their work has resulted in major discoveries for cancer, diabetes and immune memory.
“Since the complications from high blood sugar levels (diabetes) worsen with time, this therapy could reverse the disease in patients before they have too much multi-organ damage.”

Matthias von Herrath, M.D., Ph.D.

The finding offers another important piece in the complex molecular puzzle of cell death. Cell death plays a key role in a wide variety of debilitating illnesses — ranging from cancer to AIDS to Alzheimer’s. Most cells are meant to die off. They do this through apoptosis, a natural process of cell suicide which eliminates excess or damaged cells. But sometimes cells fail to die, such as occurs in cancer or too many die as happens with T cells in AIDS. Dr. Green’s research focuses on better understanding the molecular signals leading to cell death. Such knowledge could one day enable cell death to be controlled, which has major implications for many illnesses.

Matthias von Herrath, M.D., is a scientist whose “out-of-the-box” thinking could forever change the way type I (insulin-dependent) diabetes is treated. An internationally recognized expert on the molecular basis of type I diabetes, Dr. von Herrath has developed a combinatorial therapy that offers great promise as a new, safer approach to treating this dangerous autoimmune disorder. Currently in pre-clinical trials, the novel therapy already has been shown to reverse diabetes in lab animals and, within a year, will likely be ready for testing in humans. It also may have application for treating other autoimmune disorders, which occur when the body’s immune system mistakenly attacks normal body tissues.

Dr. von Herrath’s combinatorial approach focuses on teaching the immune system to tolerate, rather than attack, the insulin-producing cells of the pancreas. This is accomplished by injecting a combination of signaling molecules to calm the immune system and proteins from the pancreas. “This therapy is particularly attractive,” he said, since it could replace current insulin injection treatments altogether, which often cannot prevent the long-term detrimental effects of diabetes. “Since the complications from high blood sugar levels (diabetes) worsen with time, this therapy could reverse the disease in patients before they have too much multi-organ damage,” he said.
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Wenyi Piao, M.D., Ph.D.
Venuparasad K. Prasyp, Ph.D.
Diana Ratnabolsena, Ph.D.
Akihiro Sakai, Ph.D.
Masato Sakai, Ph.D.
Shahram Salek-Ardakani, Ph.D.
Elyes Salleh, Ph.D.
Yun Sun, Ph.D.
Hideaki Sato, Ph.D.

Research Technicians
Takaki Sa, Ph.D.
Ashu Sehgal, Ph.D.
Diana Spiery, Ph.D.
Marcus Sterenberg, Ph.D.
Barbara A. Sullivan, Ph.D.
Binggang Sun, Ph.D.
Misunakah Samudram, Ph.D.
Hironori Takeshita, Ph.D.
Shino S. To, Ph.D.
Kashibing Wang, Ph.D.
Wenbin Xiao, M.D.
Kyu Y. Yamasaki, Ph.D.
Chun Yang, Ph.D.
Kensuke Yamada, Ph.D.

Visiting Scientists
Michael Isaacson, Ph.D.
Sriram Sanda, M.D.

ADMINISTRATIVE STAFF
Mitchell Kronenberg, Ph.D.
President and Scientific Director
Charles Carperovich, Jr.
Vice President
Chief Operating Officer
Becky Reinhardt
Senior Director of Facilities and Operations
Matthew Davol
Director of Finance and Accounting
Melinda Diamond
Director of Human Resources
Stephen Wilson, Ph.D.
Director of Information and Research Technology
Samuel Connell
Manager, Imaging Facility and Technology
Jamel Fox
Environmental Health and Safety Manager
Denise O’Masters
Animal Facility Manager
Amy Peake
Manager of Sponsored Research and Intellectual Property
Eric Williams
Purchasing Manager

Johnny Andrade
Kathleen M. Burke
Mary G Caldeiron
Erica J. Chavin
Kassandrin Cooper
Jody Dang
Nicola M. Eaton
April Esquivel
Tanya R. Fantress
Patrick Fitzgerald
Edward C. Flori, Ph.D.
Michael Freeman
Diana L. Fray
Linda Gentry-Ro Dier Ahe
Richard Gibson
Tina Hereford
Tezal C. Hines
Jennifer A. Lagos
Victor J. Liao
Edward Lopez
Janelle R. Magana
Nancy L. Martorana
Rebecca M. Matheny
Malina N. Miller
Teresa E. Morgan
Thu Nguyen
Sarah R. Olopa
Vanessa Palma Gonzalez
Brusel L. Palmer
Jason Panning
Mary E. Park
Silvia A. Parage
Michael K. Peyer
Charles B. Prickett
Amanda J. Ramos
Kelly J. Riddle-Hilde
Bennett K. Roberts
Muthuraman Sathianathan
Michael T. Scarpelli
Vitorina Shagayyan
Sue J. Song
John Stillwagon
Alexandra U. Strong
Quyen T. Tran
Jean F. VanDenbroeck
Erik G. Winter
Ashley L. Winterton
Timothy Woodruff
Amaryon Zaki
Israel Zuniga
As a research institute, LIAI’s primary product is scientific publications. This is a complete list of the scientific publications achieved by the laboratories at LIAI in 2004.


Bansal-Pakala, P. Haihman, B., and M. Chong, M.H. and M. Krzysztof, M. 2004. Lck Depletion Induces T Cells To Enter An rP-10 gradient. 11:278-84.

Benedict, C.A., Angulo, A., Paterson, G., Ho, S., Huang, H., Messiaen, M., Ware, C.T., Ghazal, P. Neutrality Of The Canonical NF-kappaB-Dependent Pathway For Human And Murine Cryptomegalovirus Transcription And Replication In Vitro. 19:76274-50.


Baros, S., and M. von Harst, M. Prophylaxis Of Autoimmune Diabetes By Antigen-Based Immune Modulation: Are We There Yet? 95:105-16.


Barchet, H. Initiation Of Autoimmunity. 1:759-78.

Barchet, H. Initiation Of Autoimmunity. 1:759-78.

Barchet, H. Initiation Of Autoimmunity. 1:759-78.


LA JOLLA INSTITUTE FOR ALLERGY AND IMMUNOLOGY continues to operate in a strong financial position, with total revenues reaching a new high of over $25 million for fiscal year 2004. Our renowned scientists continue to be highly successful in obtaining competitive, peer-reviewed research funding from the National Institute’s of Health. As shown on the accompanying bar graph, federal funding and the Institute’s total revenues have increased steadily over the past five years, and we expect this trend to continue in 2005.

Since our inception in 1988, the Institute’s industry partner, Gemini Science, Inc., has provided a critical source of unrestricted research funding to our investigators. Sponsored research funding from Gemini Science continues to be our second largest source of revenue, and is committed through the year 2010.

In 2004, Gemini Science and its parent company, Kirin Brewery Company, Ltd., facilitated our planned relocation into a state-of-the-art research facility in the University of California, San Diego’s new Science Research Park. This facility, which is currently under construction, will provide a long-term home for the Institute and an optimal research environment for our scientists.

As we move forward on this exciting project, the Institute is working to meet the required costs for building and equipping its new space and for recruiting scientists. We have therefore embarked on a fundraising initiative to help secure our plans for relocation and expansion of the Institute. These efforts represent the first major fundraising initiative in the Institute’s 16-year history. At this critical time, we are extremely grateful for the generous support of donors who can help us fulfill our plans for relocation and expansion, and in doing so, advance our intensive search for understanding, treatments and cures of a broad range of human diseases.

Skip Carpowich, CPA
Vice President and Chief Operating Officer
FINANCIAL DATA
FISCAL YEAR ENDED DECEMBER 31, 2004

BALANCE SHEET

<table>
<thead>
<tr>
<th>Asset</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash and investments</td>
<td>$8,427,000</td>
</tr>
<tr>
<td>Grants receivable and other</td>
<td>$3,871,000</td>
</tr>
<tr>
<td>Property, net</td>
<td>$1,531,000</td>
</tr>
<tr>
<td><strong>Total assets</strong></td>
<td><strong>$13,829,000</strong></td>
</tr>
<tr>
<td>Accounts payable and accrued expenses</td>
<td>$3,298,000</td>
</tr>
<tr>
<td>Deferred revenue</td>
<td>$403,000</td>
</tr>
<tr>
<td><strong>Total liabilities</strong></td>
<td><strong>$3,701,000</strong></td>
</tr>
<tr>
<td><strong>Total net assets</strong></td>
<td><strong>$10,128,000</strong></td>
</tr>
<tr>
<td><strong>Total liabilities and net assets</strong></td>
<td><strong>$13,829,000</strong></td>
</tr>
</tbody>
</table>

STATEMENT OF ACTIVITIES

REVENUES:

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Federal grants and contracts</td>
<td>$19,253,000</td>
</tr>
<tr>
<td>Private grants and contracts</td>
<td>$5,879,000</td>
</tr>
<tr>
<td>License revenue</td>
<td>$13,000</td>
</tr>
<tr>
<td>Investment return and other</td>
<td>$189,000</td>
</tr>
<tr>
<td><strong>Total revenue</strong></td>
<td><strong>$25,334,000</strong></td>
</tr>
</tbody>
</table>

EXPENSES:

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>$23,321,000</td>
</tr>
<tr>
<td>General and administrative</td>
<td>$2,061,000</td>
</tr>
<tr>
<td><strong>Total expenses</strong></td>
<td><strong>$25,382,000</strong></td>
</tr>
<tr>
<td><strong>Change in net assets</strong></td>
<td><strong>($48,000)</strong></td>
</tr>
</tbody>
</table>

REVENUE GROWTH

<table>
<thead>
<tr>
<th>Year</th>
<th>Federal Grants</th>
<th>Total Revenues</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02</td>
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<tr>
<td>03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NET ASSET GROWTH

<table>
<thead>
<tr>
<th>Year</th>
<th>Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td></td>
</tr>
<tr>
<td>01</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td></td>
</tr>
<tr>
<td>03</td>
<td></td>
</tr>
<tr>
<td>04</td>
<td></td>
</tr>
</tbody>
</table>

REVENUES

Federal grants and contracts 76%
Private grants and contracts 23%
License revenue and investment return and other <1%

EXPENSES

Research 92%
General and administrative 8%
MAKING AN IMPACT

LIAI scientists are addressing some of the most important biological issues of our time, issues that will affect our lives in profound ways. The basic research at LIAI advances our understanding of an array of diseases, from cancer to diabetes, from infectious diseases to arthritis.

Gifts from those who believe in LIAI’s mission have a clear impact on our research efforts. Two-thirds of the Institute’s budget comes from federal funding sources, but philanthropy is an essential component of our budget, giving LIAI the flexibility to meet our most pressing needs.

Gifts to LIAI:
- Allow LIAI scientists to pursue promising, innovative research paths that are not covered by traditional funding
- Recruit world-renowned faculty and provide them with seed money to jump start their laboratories
- Acquire sophisticated new equipment, from DNA sequencers to robotics for lab automation, to give Institute researchers the tools they need for breakthroughs
- Educate future generations of leading scientists through the Institute’s superb graduate and postdoctoral training programs

BECOME PART OF OUR MISSION

We encourage those who believe in our mission — providing new insights on human disease and human health through a better understanding of the immune system — to invest in the Institute. Your gifts help to fuel our research programs, and philanthropy is vital to future successes and breakthroughs at LIAI.

To learn more about giving opportunities at the Institute, please contact:
Charles Carpowich, Vice President/COO, at 858-558-3510 or email skip@liai.org