Building a path to discovery
The journey. The road to discovery is not for the faint of heart. It is fraught with obstacles and gnarled with complexity—it winds through a land of peaks and valleys and seemingly insurmountable challenges. It frustrates and beguiles the greatest of intellects and truly tests the determination of its travelers.
The scientists of the La Jolla Institute for Allergy & Immunology (LIAI) know well the trials and tribulations of the road to discovery. But for our investigators, who daily fight disease through cutting-edge immunology research, the demanding journey is well worth the effort.

LIAI is a not-for-profit medical research institution, and San Diego’s only institute solely dedicated to unraveling the complexities of the immune system. Each day, our researchers analyze how immune system functioning influences a broad array of disorders – from rheumatoid arthritis to infectious diseases to cancer.

In 2005, that quest for knowledge resulted in important findings on type 1 diabetes, avian flu, smallpox, cancer and more – findings that we believe will one day help to improve—or even save – the lives of millions.

The Institute’s journey continues in 2006 with a new building, expanded university collaboration, and an infectious disease center of national import. Underlying it all is a young and exceptionally dynamic institution that was recently ranked among the top five molecular biology and genetics research organizations in the world. Please read on to learn more about our journey.

Mitchell Kronenberg, Ph.D.,
President and Scientific Director

* Read on to learn more about our journey.
The role of the immune system in determining your health cannot be overestimated. The many cells in the immune system work together to combat infection. At times, paradoxically, they can attack our own tissues causing so-called autoimmune diseases such as rheumatoid arthritis. Immunology is the study of the immune system and how our body fights infection, cancer or causes autoimmune disease.
LIAI’s internationally renowned team of scientists know that the key to many of society’s most debilitating illnesses lies in understanding the immune system. In fact, 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.

Despite its importance to our health, most of us know relatively little about how our immune system works. The immune system can be described as the body’s guardian or protecting army. In constant circulation, white blood cells of the immune system patrol like soldiers – programmed to attack viruses, bacteria or any “foreign” substance that enters the body.

Because the immune system touches so many organs and tissues, the pain and suffering caused by its malfunction can arrive in many forms—the once vibrant neighbor crippled by rheumatoid arthritis, an elderly relative struck down by influenza or the epidemic of asthma that affects young and old. These illnesses—and others—are tied to the failure of the immune system to function properly.

So important, in fact, is the role of the immune system in combating disease that the National Institute of Allergy and Infectious Diseases selected LIAI, in 2003, as the lead organization to develop the world’s largest research database on the immune response to infectious microbes. The database, to be launched in 2006, focuses particular attention on infectious diseases that pose grave threats to the U.S. and will be an important asset in vaccine development.

*1.5 trillion cells: Unlike an organ system, such as your digestive tract, the immune system is composed of individual cells and tissues throughout your body. This system – with over a trillion moving parts – is what immunologists study.
A journey filled with innovation. Each day our researchers analyze how immune system functioning influences a broad array of disorders – from rheumatoid arthritis to infectious diseases to cancer. As judged by the scientific community, the discoveries made at LIAI are among the most innovative and recognized in the world.
LIAI is pioneering and passionate—modest in size, but an international standout in terms of its impact. Despite a relatively short history, this Institute has emerged as a national leader in immunology research. Prestigious scientific awards and frequent citation by researchers worldwide prove that LIAI is a scientific powerhouse. It has also carved new territory in San Diego’s bioscience community as the only research organization focused solely on the study of the immune system.

The reason? Its founders saw immunology’s unique promise as a biomedical discipline that could contribute to reducing disease. Current research priorities that span studies of diabetes to avian flu to cancer bear out the immune system’s incredible affect on health.

The Institute owes much of its success to its founders, who laid the groundwork for its collegial and innovative environment. Key among those were Drs. Kimishige and Tenko Ishizaka, two world-renowned immunologists recruited from Johns Hopkins Medical School, who launched the Institute’s operations in 1989. The Ishizaka’s helped to create a standard of excellence and a collaborative environment that continues at LIAI to this day.

* LIAI was recently ranked 5th in the world among all research institutions in Molecular Biology and Genetics and 16th in the world in Biology and Biochemistry by The Scientist.
Soaring to new heights. A measure of LIAI's achievement is the application of its research to new ways of improving human health. To get there, LIAI scientists share their findings with great minds here and abroad by publishing in the world's greatest scientific journals.
For LIAI researchers, 2005 was a year of major discoveries ranging from a definition of the antibodies that fight smallpox to insights into the formation of immune memory, the basis of all successful vaccinations.

LIAI faculty produced an impressive 114 research papers in 2005. Several of these studies received significant media coverage and over the past two years, LIAI researchers have had an exceptional five papers published in *Nature* or *Science*, the leading scientific journals.

Reports in 2005 ranged from an investigation by Mitchell Kronenberg’s group on how NKT cells, a unique white blood cell population, fight disease-causing bacteria, to studies of the molecular mechanisms that limit the function of so-called immune memory cells from the groups of Stephen Schoenberger, Ph.D., and Doug Green, Ph.D. The laboratories of Chris Benedict, Ph.D., and Carl Ware, Ph.D., uncovered a new pathway by which herpes viruses evade the immune response, and the groups of Don Newmeyer, Ph.D., and Doug Green, showed a novel means by which the protein p53, implicated in so many cancers, causes uncontrolled cell growth.

* 16 labs are each led by one of our distinguished faculty members, and each pursues topics of its choosing. Labs typically include students, and post-doctoral fellows with M.D. or Ph.D. degrees, and technical staff.
Autoimmune disease. Type 1 diabetes is an autoimmune disease that often starts in early childhood, causing lifelong challenges. While daily insulin injections keep those with diabetes alive, dreadful complications are inevitable. Immunology research provides the hope that injections and special diets can be replaced by a carefree childhood and a long and healthy life.
Matthias von Herrath, M.D., and his research team’s recent finding of a potential cure for early stage type 1 diabetes generated headlines across the world. The excitement was no wonder, as the search for a true diabetes cure has challenged researchers since the first insulin injection in 1922.

Type 1 diabetes, also known as juvenile onset diabetes, accounts for up to 2 million U.S. cases and occurs when the immune system mistakenly destroys insulin-producing cells in the pancreas. Diabetes is immediately life-threating and is estimated to shorten the life span of sufferers by 15 years. Dr. von Herrath’s study in mice used a combination of a vaccine to stimulate beneficial immune cells that can prevent pancreatic cell destruction and an immunosuppressant that prevents this destruction. The combination reversed recent onset type 1 diabetes in the majority of animals tested.

The finding, which applies to type 1 diabetes caught in the early stages, was particularly significant because both treatments have previously been tested separately in humans. In those earlier studies, however, pancreas destruction was stopped for more than a year, but then resumed, and significant side effects occurred. Dr. von Herrath’s insight was to combine the two therapies, producing a strong synergy with better effectiveness and fewer side effects. Particularly exciting – the diabetes never reoccurred in the lifespan of the mice. Human clinical trials are planned for late 2006.

* According to the National Institute of Diabetes and Digestive and Kidney Disorders, 200,000 of the 2 million type 1 diabetes sufferers are children under the age of 20.
Infectious diseases. The specter of infectious disease is ever present. Older diseases such as tuberculosis stubbornly persist due to the development of drug resistant strains, while new agents, such as West Nile virus and the influenza strain that causes avian flu, emerge. The need to fight dangerous infectious agents remains constant.
Worldwide outbreaks are not a modern phenomena, but frequent travel and the emergence of previously unseen infectious organisms are reasons to prepare now, when prevention is still an option. Immunologists at LIAI address infectious disease from many angles, looking closely at how to engineer vaccines to protect people when they are exposed. In our Emerging Infectious Disease and Biodefense Center, we have placed special emphasis on combating bacteria and viruses, including avian flu and other forms of influenza, that cause major health concerns.

Consider the efforts of David Lo, M.D., Ph.D., who is working to produce an oral flu vaccine that could be used effectively around the world. The research is funded by a $3.9 million grant from the Bill & Melinda Gates Foundation, a prestigious program awarded to select researchers worldwide.

Meanwhile, Alessandro Sette, Ph.D., is investigating the development of a “universal” flu vaccine that would protect against numerous flu strains. Dr. Sette is using powerful biomedical research tools to measure the immune response of former flu sufferers in hopes of finding immune targets common to many flu viruses.

Another important effort involves a potential avian flu cure conceived by Hilde Cherourte, Ph.D. and with research carried forward by Gemini Science, a biopharmaceutical company and LIAI corporate partner.

Newly hired faculty have boosted LIAI’s expertise in the study of viral infections. Sujan Shresta, Ph.D., is researching ways to generate effective vaccines against Dengue fever, while Chris Benedict, Ph.D., is studying the myriad strategies that herpes viruses use to evade the immune response.

★ 18 pathogens were newly recognized in the last two decades as reported by the National Institute of Allergy and Infectious Diseases.
Yin and yang. Good health requires a balance between those signals that stimulate and those that suppress immunity. The thousands of proteins in every immune cell act in networks to govern the function of these cells, and ultimately, the immune system itself. An inappropriate or over-exuberant immune response can lead to allergy, asthma or autoimmunity. On the other hand, beneficial immune responses, such as those to infectious agents or to cancers, may require enhancement.
LIAI scientists are among the world experts in unraveling the connections between the thousands of proteins located in all parts of white blood cells in order to understand how they regulate the behavior of the immune system. The lab of Amnon Altman, Ph.D., has pioneered work at the white blood cell membrane, the outer boundary of the cell, to discover the role of a molecule called PKC0 that is required for immune activation. By contrast, the laboratory of Yun-Cai Liu, Ph.D., is a leading innovator in understanding how the “off switch” for immune activation works, through studies of molecules called ubiquitin ligases.

The laboratory of Donald Newmeyer, Ph.D., studies proteins in another, deeper part of the cell, the mitochondria, which is the powerhouse that provides cells with energy. Dr. Newmeyer has shown that this energy powerhouse also has molecules that actually tell a cell when to die, and they are part of a very important “off” switch to prevent the uncontrolled cell growth which is cancer.

The laboratory of Toshiaki Kawakami, M.D., Ph.D., carries on the LIAI tradition of studying allergy, and they have identified novel ways in which a protein called the Fc receptor can transmit signals that lead to allergic disease. In each case, these basic science studies have led to the identification of potential new targets for enhancing or inhibiting the immune response, which in some cases are being pursued by pharmaceutical companies.

* It is estimated that humans have 30,000 or more genes, each encoding a single protein. Specialized cells such as white blood cells do not need all of these proteins, however, it is estimated they may contain 10,000 or more.
Friend or foe... problem or salvation. The same chemical signals and cellular pathways can elicit different outcomes depending on how they act in the body. The potential for therapeutics is great, as is the need for complete understanding.
While the name tumor necrosis factor (TNF) is not a household phrase, scientists consider the TNF family of proteins to be one of the most important elements of immune function. Blocking TNF itself, which is the earliest known family member, is an effective treatment for rheumatoid arthritis and Crohn’s disease. It is estimated that more than one million people have used anti-TNF therapies for help with a variety of medical conditions.

Carl Ware, Ph.D., knows well the power of TNF molecules. A recognized expert in the field, Dr. Ware was involved in the discovery and modes of action of several TNF family members and the receptors to which they bind.

Five LIAI labs have an interdisciplinary and highly collaborative approach to studying the TNF family. In addition to Dr. Ware, the laboratories of Mitchell Kronenberg, Ph.D., Mick Croft, Ph.D. Stephen Schoenberger, Ph.D., and Chris Benedict, Ph.D., are conducting research on the TNF family as it relates to Crohn’s disease, allergic reactions, asthma, viral infections and cancer.

In particular, Mick Croft’s work on OX-40, one of the TNF family members, suggests that OX-40 is particularly critical for sustaining beneficial immune responses, such as those against cancers, while blocking OX-40 proved to be remarkably helpful in reducing inflammation in an animal model of asthma.

* Scientists use chemical techniques and computers to classify genes and the proteins they encode into families, based on resemblance or similarity. The estimated 30 genes of the TNF family are among the most important for controlling the immune response.
A new destination, building for the future. Immunologists equipped with the latest research technology, in facilities that invite some of the brightest minds in science to work together, can push forward medical research at an unprecedented rate. LIAI's new building will be an important address in cutting-edge science.
In 2006, LIAI’s path to discovery will lead to a new destination – a state-of-the-art facility in the University of California, San Diego (UCSD) Science Research Park, within walking distance to clinics and lecture halls. Retaining its financial independence and identity, LIAI is the first to locate in the Science Research Park, which is designed to encourage collaboration between the private sector, including nonprofit and profit-making organizations and UCSD, a great public university. The new 145,000-square-foot building will replace the Institute’s current cramped quarters. Using an “open laboratory” floor plan and larger group meeting areas, it is designed to nurture LIAI’s highly collaborative research environment.

It will offer specialized rooms for all aspects of molecular and cellular biology, including a Biosafety Level 3 Lab that will enable researchers to work at the highest level of safety with infectious organisms. LIAI is one of the very few not-for-profit research institutions in San Diego to have such a facility. The building will also house the Emerging Infectious Disease and Biodefense Center and will be home to the world’s largest database on the immune response to infections.

The four floors will also feature an array of instrumentation for genetic analysis, microscopy, and instruments for determining molecular structures at the atomic level. Informatics scientists will work alongside researchers to analyze and even predict immune responses using advanced computational systems.

Built for immunologists, the building is a new catalyst, enabling LIAI researchers with modern laboratories and the latest technology to examine the intricate workings of the immune system.

* 145,000 square feet of space is divided among the labs, administration, a corporate research partner and additional “shell” space for expansion.
percent of expenses used for research

2005 Financial Highlights. Our renowned scientists continue to be highly successful in obtaining competitive, peer-reviewed research funding from the National Institutes of Health. Unrestricted biomedical research funding from Gemini Science continues to be our second largest source of revenue, and is committed through the year 2010.
La Jolla Institute for Allergy & Immunology continues to operate in a strong financial position, with total revenues reaching a new high of over $30 million for fiscal year 2005. Our renowned scientists continue to be highly successful in obtaining competitive, peer-reviewed research funding from the National Institutes of Health (NIH). As shown on the accompanying bar graphs (see page 20), LIAI’s federal funding, total revenues and net assets have increased steadily over the past five years.

Since our inception in 1988, the Institute’s industry partner, Gemini Science, has provided us with a critical source of unrestricted research funding while facilitating the translation of our discoveries into potential treatments for human disease. Unrestricted biomedical research funding from Gemini Science continues to be our second largest source of revenue, and is committed through the year 2010.

LIAI’s new research facility, located in the University of California, San Diego’s Science Research Park, will provide us with a long-term home and an optimal environment for

(continued on page 21)

* This percentage reflects LIAI’s intense concentration on research activities, while administrative costs are kept to a minimum. (Refer to 2005 expense data on page 20)
### 2005 Financial Data

#### BALANCE SHEET

<table>
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<th>Description</th>
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<tr>
<td>Cash and investments</td>
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<tr>
<td><strong>Total net assets</strong></td>
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<tr>
<td><strong>Total liabilities and net assets</strong></td>
<td><strong>$16,184,000</strong></td>
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#### STATEMENT OF ACTIVITIES

**REVENUES:**

- Federal grants and contracts: $22,203,000
- Private grants and contracts: 6,474,000
- License revenue: 607,000
- Contributions: 508,000
- Investment return and other: 360,000
- **Total revenue**: $30,152,000

**EXPENSES:**

- Research: $25,454,000
- General and administrative: 2,423,000
- Fundraising: 28,000
- **Total expenses**: $27,905,000
- **Change in net assets**: $2,247,000

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#### Revenue Growth

- Federal Grants: [Graph]

#### Net Asset Growth

- [Graph]
our scientists to pursue medical research breakthroughs. As we move forward on the path of discovery, we also enter a period of expected decline in the NIH budget due to competing federal priorities. Further, we are working to meet cost requirements associated with our relocation and expansion. These include costs for building space improvements, recruiting prominent scientists, acquiring new technologies and instrumentation, and providing start-up funds for new research programs.

To help meet these immediate funding requirements and diversify our future sources of revenue, the Institute recently established a philanthropic giving program (see page 22). We are encouraging new donors to help support our intensive search for understanding, treatments and cures of a broad range of human diseases. We look to the future with optimism, and invite you to join us in realizing a new era in human health.

Charles A. Carpowich, Jr., CPA
Vice President and Chief Operating Officer

* 2005 Financial Data summarized from LIAI’s December 31, 2005 audited financial statements. To receive a copy of LIAI’s audited financial statements, contact Charles Carpowich at 866-752-6510 or e-mail skip@liai.org.
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. Gifts from those who believe in LIAI’s mission have a clear impact on our research efforts, giving LIAI the flexibility to meet our most pressing needs.
LIAI scientists are addressing some of the most important biological issues of our time, issues that will affect our lives in profound ways.

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 pursue some of our most exciting projects.

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
- Expand laboratory areas and finance building improvements needed to pursue important new avenues of research
- Educate future generations of leading scientists through the Institute’s superb graduate and postdoctoral training programs

Become a part of our mission
We encourage those who believe in our mission – fighting human disease 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 Cargowich, VP/COO, at 858.752.6510 or email skip@liai.org.
Total number of employees as of December 31, 2005. The names listed here include all those who were employed by LIAI from January 1, 2005 through June 1, 2006.