**On the Cover:**

The human immune system at work. T cells, B cells, macrophages, neutrophils, basophils, and dendritic cells are battling invading bacteria (orange circles and dark blue rods). Upper right, Antigens of extracellular origin are presented on MHC class II molecules to CD4⁺ T cells. Lower right, cells display antigen of intracellular origin on MHC I molecules to CD8⁺ T cells. These antigens are cleaved by proteasomes and are transported across the membrane of the endoplasmic reticulum by the protein TAP (transporter associated with antigen processing). Antibody neutralization, opsonization, and apoptosis are additionally visible.

Artwork by Katie Bauer, research technician in the laboratory of Michael Zwick, Ph.D., assistant professor, Department of Immunology and Microbial Science.
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Crystal structure of the trimeric, prefusion form of the Ebola virus glycoprotein (blue and white) bound by a human antibody (yellow) derived from the serum of a survivor of an Ebola virus outbreak. View is inside the virus, looking out, so that the trimer interface is visible at the center. Image created by Christina Corbaci, administrative assistant, in the laboratory of Erica Ollmann Saphire, assistant professor, Department of Immunology and Microbial Science.
Treatment of NIH3T3 cells with chloroquine for 4 hours induces the accumulation and enlargement of lysosomes (blue) within the cell and induces the fusion of autophagosomes (green) with lysosomes. Work done by Frank C. Dorsey, Ph.D., research associate, in the laboratory of John L. Cleveland, Ph.D., professor and chairman, Department of Cancer Biology.

† Deceased
President’s Introduction

I am proud to report on some of the many accomplishments at The Scripps Research Institute during the past year. Our investigators on both coasts made extraordinary advances in their fields, our education and community outreach programs continued to thrive, and Scripps Research teams won major grants to fund innovative projects.

NEW GRANTS

Despite the difficult funding environment for science in general, scientists at Scripps Research won several large federal grants in 2008, building on our cornerstone strengths of scientific excellence and interdisciplinary collaboration. These grants are a validation of the quality of the research on the California and Florida campuses.

The largest federal grant in 2008—and in the history of the institute—was an $80 million award to expand efforts to screen molecules for possible drug development at the Scripps Research Molecular Screening Center. The 6-year grant from the National Institutes of Health (NIH) provides funds to uncover “proof-of-concept molecules” that could bring new treatments for many human diseases closer to reality. Led by Professor Hugh Rosen, the recipients of the grant will use high-throughput robotics at the Florida campus to test discoveries made in laboratories in California and Florida and in other research institutions against various biological targets.

The NIH also awarded $20 million to the Scripps Translational Science Institute, a collaborative program between Scripps Research and Scripps Health and researchers at other institutions in San Diego. The purpose of the grant, a Clinical and Translational Science Award, is to accelerate the translation of scientific discoveries to improvements in medicine. In addition to funding studies relevant to developing individualized treatment and prevention strategies, the grant will support advanced research training. Led by Eric Topol, the Scripps Translational Science Institute is 1 of only 4 California programs to receive this type of funding and the first in Southern California.

The National Institute of Neurological Disorders and Stroke awarded $7.6 million to investigators at the Florida campus to develop the next generation of medications to treat Parkinson’s disease. Research funded by this 5-year grant will be led by Philip LoGrasso, associate professor and senior director for drug discovery. He and his colleagues hope to advance the potential treatment so that an application can be filed for an investigational new drug, the first step in the lengthy clinical trials required by the Food and Drug Administration.

The National Institute on Drug Abuse awarded $4 million to a group of investigators on the California campus for research on the effects of chronic marijuana use, including influence on brain function and the consequences of withdrawal. Scientists at the new Translational Center on the Clinical Neurobiology of Cannabis Addiction, led by Barbara Mason, professor and codirector of the Pearson Institute for Alcoholism and Addiction Research, will help develop novel approaches for the prevention, diagnosis, and treatment of marijuana addiction.

PRIVATE FUNDING

Thanks to the generosity of individuals and foundations, Scripps Research also received noteworthy support from the private and nonprofit sectors in 2008, accelerating the progress of our research.

The International AIDS Vaccine Initiative, a global nonprofit organization, awarded $30 million to Scripps Research to create a new research center at the California campus that will be linked to a network of research institutions in Africa, Asia, Europe, and the United States. The focus of the center, led by Dennis Burton, a professor at Scripps Research and the scientific director of the Neutralizing Antibody Consortium of the initiative, will be on expanding efforts to find the crucial antibody-inducing components necessary to make an effective vaccine against HIV and AIDS.

In another act of generosity and foresight, San Diego philanthropist, businessman, and community leader John J. Moores contributed the first donation, a gift of $2.1 million, to the Scripps Research $50 million initiative to recruit new world-class researchers and to sustain and expand the work of our current scientists. Moores, chairman and owner of the San Diego Padres baseball team, has served as a member of the Scripps Research Board of Trustees since 1997 and as chair of the board since 2006.

Miami physician, businessman, and philanthropist Phillip Frost and his wife, Patricia Frost, an ardent supporter of education and the arts, donated $1 million
to the Florida campus. In recognition of their donation, the foyer of the building that will house laboratories for a key component of research in Florida, making strategic scientific discoveries and then expediting their development into new drugs and treatments to improve human health, will be named the Frost Lobby.

We are deeply grateful for all the support we receive. We recognize that gifts and grants make possible our scientists’ extraordinary efforts to expand knowledge and improve human health.

**Scientific Breakthroughs**

Once again, scientists in our laboratories have made extraordinary findings. Recent breakthroughs in 2008 are described in the following list:

- Assistant Professor Erica Ollmann Saphire and colleagues revealed the shape of the Ebola virus spike protein, which is necessary for entry of the virus into human cells, bound to an antibody acting to neutralize the virus. The structure provides a major step forward in understanding how the virus works and may be useful in the development of Ebola virus vaccines or treatments for patients infected with the virus.

- Huntington’s disease has no cure, or even treatments that can reverse or slow progression of the movement deficits and cognitive dysfunction that occur with the condition. So, it was particularly good news when Assistant Professor Elizabeth Thomas and colleagues showed that an agent they developed has dramatic therapeutic efficacy and minimal toxicity in a mouse model of Huntington’s disease. The compound has been licensed for further testing and development.

- Bruce Beutler, chairman of the Department of Genetics; Ulrich Müller, a professor in the Department of Cell Biology; and colleagues found that a mutation in a new gene, which they named COMT2, causes a form of deafness that has nothing to do with structural proteins in the inner ear, which are commonly altered in hereditary deafness. The finding that the mutation affects an enzyme with a known catalytic function suggests how the deafness caused by COMT2 might be preventable with novel drug therapy.

- Professor Wolfram Ruf and colleagues uncovered a connection between blood coagulation and the immune system that may have important implications for patients with sepsis, a severe and difficult-to-treat disease that kills tens of thousands of in the United States each year. The scientists identified a new cross talk involving the vascular coagulation system and certain cells in the immune system. By disrupting this cross talk, they were able to rescue mice from death due to sepsis.

- Professor Chi-Huey Wong and colleagues developed a new 2-punch strategy against HIV infection and successfully tested aspects of the strategy in the laboratory. The investigators created devices they call glycodendrons that are designed to do 2 things at once: (1) inhibit the transport of HIV from its traditional sites of entry into the body, preventing it from moving deeper inside where it can infect immune cells, and (2) set up an immune antibody response to a unique carbohydrate structure on the surface of the virus.

- Professor James Quigley’s group identified a potential new target for treating metastatic cancer in humans. By blocking the action of the protein CD151, the team stopped cancer cells from spreading from one site to establish new tumors elsewhere.

- Professor Claes Wahlestedt and colleagues discovered a new gene involved in fragile X syndrome, a condition with many signs and symptoms similar to those of autism. The discovery of the new gene, FMR4, may lead to new tests or treatments for several neurologic disorders.

- Assistant Professor Timothy Tellinghuisen and his colleagues discovered a method to disrupt the production of infectious virus particles that cause hepatitis C, a blood-borne liver disease. This discovery might be a first step in developing new and more effective therapies against hepatitis C virus. Current antiviral agents are ineffective for many patients infected with the hepatitis C viral strains most prevalent in the United States.

- Professor Raymond Stevens and his group determined the structure of the human A2A adenosine receptor, sometimes referred to as the “caffeine receptor,” which is a member of the large, medically important family of G protein–coupled receptors. The findings could lead to the development of a new class of therapeutics for treating numerous neurologic disorders, including Parkinson’s and Huntington diseases.

- Professor Phil Baran and investigators in his laboratory developed an inexpensive new method for
economically producing a promising pharmaceutical steroid. The molecule, cortistatin A, which was isolated in 2006 from a marine sponge, has great promise for treating conditions ranging from macular degeneration to cancer.

- Associate Professor Mark Mayford and colleagues showed that in a situation that required learning, neurons in the brain's memory hub, the hippocampus, had an increased ability to retain newly synthesized proteins called AMPA receptors.

- Using samples from survivors of the 2005–2006 "bird flu" outbreak in Turkey, an international team, including researchers at Sea Lane Biotechnologies and me, created the first comprehensive monoclonal antibody libraries against avian influenza virus (type H5N1) These antibody libraries may be useful in developing a therapy that could stop an influenza pandemic and provide treatment to those infected and in pointing the way to the development of a universal flu vaccine.

- Kim Janda, Scripps Research professor and member of the Skaggs Institute for Chemical Biology; Eric Zorrilla, Scripps Research associate professor; and colleagues discovered a catalytic antibody that degrades a known appetite stimulant. The antibody works against the gastric hormone ghrelin, which has been linked to weight gain and fat storage. These findings may lead to a novel treatment for obesity.

**COMMITMENT TO EDUCATION**

In addition to our dedication to research, we are committed to educating the next generation of scientists. At our commencement ceremony in May, 28 doctoral candidates graduated from the Kellogg School of Science and Technology, and Scripps Research trustee Claudia S. Luttrell was awarded an honorary degree. The school can now boast of more than 300 accomplished alumni. Among these, 3 alumni—2 from this year’s graduating class—conducted their studies on the Florida campus.

The fall brought a record number of entering graduate students to both the Florida and the California campuses. In Florida, an unprecedented 75% of offers extended to students were accepted; 9 of 12 offers made. Of these 9 students, 4 are from Florida universities.

In addition, we continue to build programs to support our valued postdoctoral fellows, and to make strides in reaching out to high school students and teachers to share our excitement about the scientific endeavor.

**PEOPLE NEWS**

The year brought a variety of transitions for people at Scripps Research. We welcomed international business leader and entrepreneur Amin J. Khoury to the board of trustees. Khoury, who is chair of the board and chief executive officer of B/E Aerospace, Inc., of Wellington, Florida, brings his talents as a business executive and his experience as a founder of companies in aerospace, scientific instruments, medical services, and medical devices.

Roy Smith from Baylor College of Medicine joined Scripps Research at the Florida campus to head our new Department of Metabolism and Aging. I look forward to his contributions to this exciting field, which is advancing our knowledge of aging and age-related diseases.

Hollis Cline joined the California campus as part of the Departments of Cell Biology and Chemical Physiology. Dr. Cline’s expertise in the neuroscience of vision will be a significant contribution to our world-class neuroscience research.

Professor Jeanne F. Loring, renowned in the field of stem cell research, joined the faculty at the California campus. Dr. Loring will apply her extensive knowledge and experience to lead a team to new discoveries that will benefit human health.

Richard Ulevitch, an internationally renowned researcher in the field of innate immunity, stepped down as chair of the Department of Immunology this year. He is continuing to maintain a laboratory at Scripps Research as professor and chair emeritus while joining 5AM Ventures of Menlo Park, California. Professor Argyrios Theofilopoulos is acting chair as we conduct an international search to fill this position.

Ernest Beutler, chair of the Department of Molecular and Experimental Medicine since 1978, stepped down from this role in 2008. Filling the position is Jeffery Kelly, Lita Annenberg Hazen Professor of Chemistry and a member of the Skaggs Institute for Chemical Biology, who also recently became chair of the board of trustees of the Skaggs Institute for Research (one of the Skaggs family’s major mechanisms for its philanthropy). It is with great sadness I report that Ernie Beutler, who was planning to continue to run his research program, passed away in October. His passing is a great loss to science, to Scripps Research, and to all who knew and worked with him during his long, brilliant career.

Assuming the deanship of the Kellogg School from Jeff Kelly is Professor Jamie Williamson, also a member of the Skaggs Institute, who will build on his 7 years as associate dean and 10 years as a Scripps Research
faculty member to lead this top-ranked graduate program into the future.

FACULTY HONORS

In 2008, our esteemed faculty again received many honors and awards.

• Three of our faculty members, Bruce Beutler, Mike Oldstone, and Peter Wright, were acknowledged for their outstanding research achievements by election to the National Academy of Sciences. Their election brings to 19 the number of National Academy members among our faculty. To have had 3 such deserving researchers elected in a single year is truly remarkable for an organization of our size.

• Professor Albert Eschenmoser won the Benjamin Franklin Medal in Chemistry. Franklin Institute Awards are given for outstanding achievements that have enhanced the quality of human life and deepened our understanding of the universe; Dr. Eschenmoser was recognized for his research on nucleic acid structure, leading to the understanding of why RNA and DNA have the structures they do.

• Professor Ian Wilson was showered with honors, including an honorary degree from the University of St. Andrews in recognition of achievements “at the forefront of research to understand the immune system and influenza”; election as a corresponding fellow of the Royal Society of Edinburgh, Scotland’s National Academy of Science and Letters; and election to the board of directors of the Keystone Symposia.

• Professor Carlos Barbas received the 2009 Tetrahedron Young Investigator Award, Bioorganic and Medicinal Chemistry, an award for individuals less than 45 years old who have exhibited “exceptional creativity and dedication” in their fields. In addition, Dr. Barbas was chosen for the American Chemical Society Arthur C. Cope Scholar Award, which recognizes excellence in organic chemistry.

• Jeffery Kelly received the American Peptide Society Vincent du Vigneaud Award, sponsored by Bachem, Inc., for “fundamental, visionary research on folding and aggregation processes in peptides and proteins, and for courageous, insightful exploration of the biological and medical implications of his discoveries.”

• Sandra Schmid, chair of the Department of Cell Biology, was chosen by the American Society for Biochemistry and Molecular Biology to receive the William C. Rose Award, which recognizes outstanding contributions to biochemical and molecular biological research and a demonstrated commitment to the training of younger scientists.

• Associate Professor Gaudenz Danuser won the Michael and Kate Bárány Award for Young Investigators from the Biophysical Society for his “outstanding seminal contributions in diverse areas of cell biology, particularly . . . our understanding of cell cytoskeleton dynamics and function using speckle microscopy.”

• Assistant Professor Ian MacRae was selected as a 2008 Pew Scholar in the Biomedical Sciences by the Pew Charitable Trusts and the University of California at San Francisco. Dr. MacRae will receive 4 years of support for his research, which combines structural biology, biochemistry, and cell biology to understand mechanisms of gene regulation by RNA interference.

As we look forward to celebrating the opening of the permanent Florida campus in February 2009, I am delighted to take this moment to appreciate the many, significant accomplishments that have brought us this far. Thank you to trustees, donors, friends, faculty, staff, postdoctoral fellows, and students of Scripps Research for your dedication, hard work, and vision.