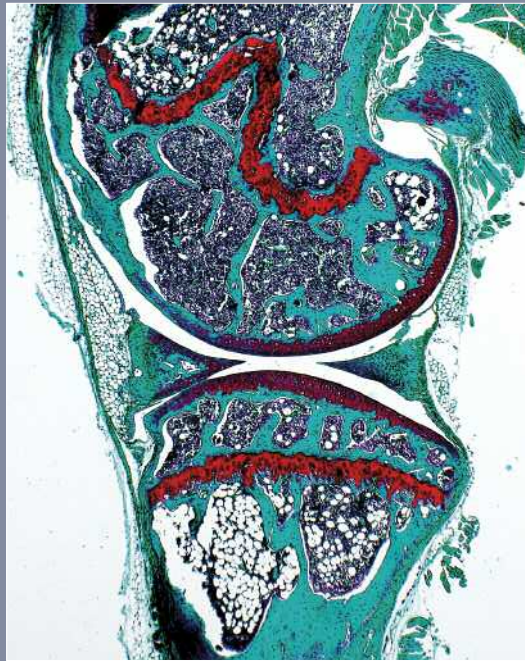


THE SCRIPPS RESEARCH INSTITUTE

Scientific Report 2007





On the cover: Section of a normal mouse knee joint. At the center is the joint space with the wedge-shaped menisci. The layers of deep-red tissue on either side of the joint space are the joint cartilage on the tibial plateau (left) and the femoral condyle (right). Cartilage is responsible for absorbing mechanical stress and for providing a surface for frictionless joint movement. Aging-associated changes and degradation of the articular cartilage lead to the development of osteoarthritis, the most common joint disease. Tissue sections prepared and provided by Lilo Creighton, research assistant, and Martin Lotz, Ph.D., professor, Division of Arthritis Research, Department of Molecular and Experimental Medicine. Digital photomicrograph created by Bob Turner, director, BioMedical Graphics, Scripps Research, using bright-field illumination and a didinium enhancement filter. The image was awarded a Citation of Merit, BioImages 2007, by the BioCommunications Association.

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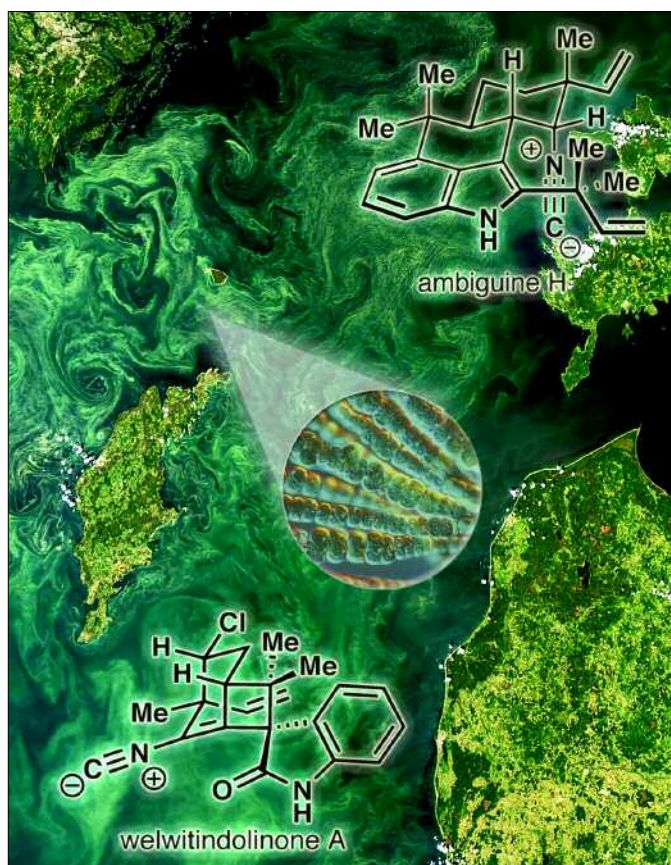
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Mass reproduction of cyanobacteria (blue-green algae) can sometimes result in large colorful algal blooms ("cyanoblooms"). Blue-green algae from the Stigonemataceae family also produce a large array of exotic indole alkaloid natural products that have inspired synthetic chemists for decades. Shown here are 2 representative members of the ambiguine (top) and welwitindolinone (bottom) families. Both compounds were prepared by unconventional total synthesis with no protecting groups and in gram quantities. Graphics by Paul Krawczuk, graduate student, in the laboratory of Phil S. Baran, Ph.D., associate professor, Department of Chemistry.

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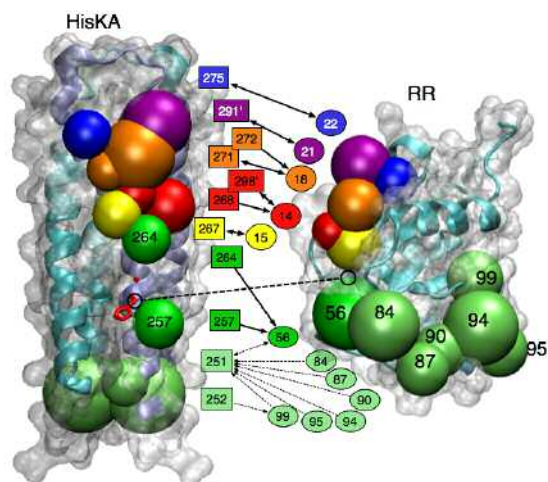
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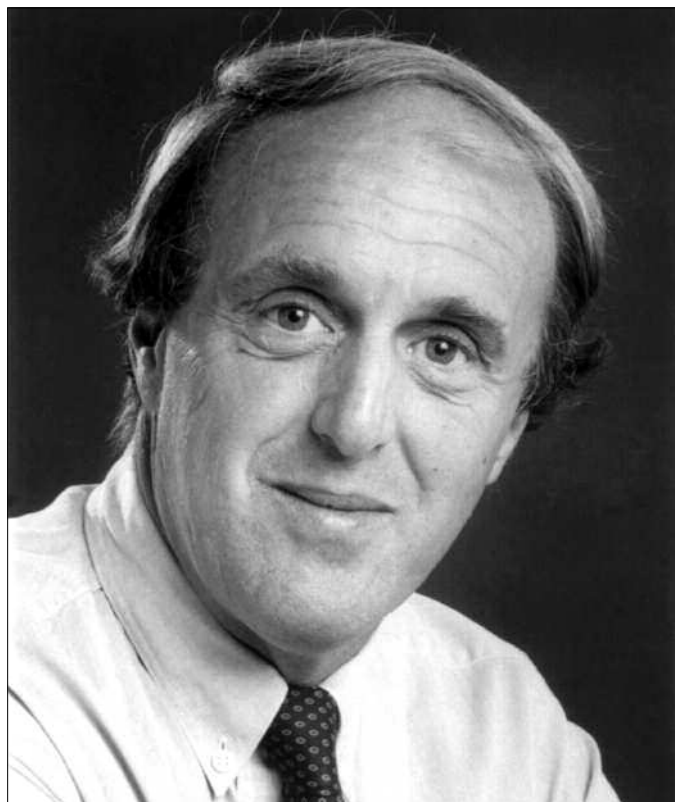
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Mapping of the couplet network obtained from mutual information-based covariance analysis of protein databases of sensor histidine kinases (HisKA) with their chromosomally adjacent response regulator (RR) mates. Covariance-coupled positions that are consistent with direct interactions between positions are shown in solid lines with arrows; potential long-range interactions are indicated by dotted lines with arrows. Work done in the laboratory of James A. Hoch, Ph.D., professor, Division of Cellular Biology, Department of Molecular and Experimental Medicine.



Richard A. Lerner, M.D.

President's Introduction

It is my pleasure to report on another extraordinary year at The Scripps Research Institute. In 2007, construction began on the permanent Scripps Florida campus in Jupiter, Palm Beach County; scientists at the institute continued to push the boundaries of discovery; and new collaborations positioned Scripps Research to thrive in the future.

SCRIPPS FLORIDA

In March, Scripps Research officially dedicated its Florida campus in Jupiter to "increasing human knowledge, advancing biomedical science, educating the researchers of the future, and improving the health of humanity." At the ceremony before some 400 Scripps Florida employees and guests at the construction site on the Jupiter campus of Florida Atlantic University, I had the opportunity to again thank the people and leaders of Palm Beach County and the State of Florida for their contributions to the establishment of Scripps Florida.

We were honored to have with us to share in this celebration Palm Beach County Commission Chair Addie Greene, former Governor Jeb Bush, and Governor Charlie Crist. Each has been instrumental in bringing Scripps Florida to where it is today and in establishing its

future positive impact on the community, science, and human health.

Construction on the first phase, 3 buildings totaling 350,000 square feet of laboratory and administrative space, is proceeding according to schedule. The buildings are expected to be ready for occupancy in early 2009. About 220 researchers, technicians, and administrative staff are already at work in 2 temporary buildings and several trailers adjacent to the construction site. The buildings will be turned over to Florida Atlantic University when the new permanent facilities open.

In 2007, we welcomed 2 new students to our graduate program in Florida. We were also proud to have chemistry student Porino Va become our first graduate from the Florida campus. Dr. Va marched down the aisle with 26 of his California colleagues to receive his doctorate of science as part of the Kellogg School of Science and Technology commencement celebration.

We have continued to expand our education outreach efforts in Florida. The summer internship at Scripps Florida, modeled on the California program and now in its third year, hosted 9 students and 3 high school teachers, thanks to support from the William R. Kenan, Jr., Charitable Trust. The Science Saturday program gave more than 300 Palm Beach County high school students an opportunity to use modern biotechnology tools. The hands-on Introduction to Science lesson has provided information to middle schools on what the world is made of and how it fits together. In addition, work has begun on a permanent exhibit at the South Florida Science Museum, illustrating how bioscience is shaping our lives and our future.

BREAKTHROUGHS OF 2007

Conducting innovative science is central to our mission as a leading biomedical research institution, so I am delighted to highlight a few of our researchers' many scientific accomplishments. In 2007, Scripps Research investigators did the following:

- Associate professors Anette Schneemann and Marianne Manchester and their colleagues developed a new and highly effective agent that provides protection against anthrax by combining a fast-acting inhibitor of anthrax toxin with a vaccine in a single compound. The immune response generated in rats protects against exposure to lethal toxin after only a single injection and is faster and stronger than any currently available vaccine.
- With Sydney Brenner, Tobin J. Dickerson, and other colleagues, I developed a breakthrough

method that can be used to rapidly predict how viruses such as avian influenza virus H5N1, a dangerous strain that causes “bird flu,” will mutate in response to attacks by the immune system. The new approach, dubbed “checkmate analysis,” may also be useful in predicting which antibodies or small-molecule therapeutic agents will best neutralize these viral mutations before the viruses can result in global epidemics. Because of its simplicity and low cost, this innovative approach will be accessible to scientists around the world.

- Professor Mark Yeager, research associate Barbie Ganser-Pornillos, and colleagues published a detailed molecular model of the full-length HIV capsid protein, a viral protein that forms a cone-shaped shell around the genome of HIV. This structure reveals a never-before-seen molecular interaction that may be a weakness at the core of the virus.
- Associate professor Phil Baran and colleagues developed new techniques that dramatically reduce the time, complexity, and cost of synthesizing natural products with pharmaceutical potential. The work dislodges previously entrenched beliefs in organic chemistry about how such products must be produced and could help advance and expand the use of natural products in drug discovery programs.
- Professor Corinne Lasmézas and colleagues showed for the first time that small clumps of abnormal prion proteins called oligomers cause the widespread death of neurons. In contrast, much larger prion aggregates known as fibrils are far less toxic. The findings suggest that small protein aggregates play a central role in prion diseases, such as bovine spongiform encephalitis (mad cow disease) and Creutzfeldt-Jakob disease; similar mechanisms have been proposed for the so-called amyloid neurodegenerative diseases, including Alzheimer’s disease.
- Professor Martin Friedlander and colleagues completely inhibited the growth of new blood vessels in animal models of a highly vascular brain tumor and of neovascular eye diseases with little or no effect on normal tissue vasculature. This combination therapy provides a new range of treatment options for patients with neovascular diseases.

- Professor Ulrich Müller and colleagues showed that 2 key proteins join at the precise location where energy of motion is turned into electrical impulses in the ear. These proteins, cadherin 23 and protocadherin 15, are part of a complex of proteins called “tip links” on hair cells in the inner ear.
- Professor Kim Janda and colleagues developed a new monoclonal antibody that destroys the highly addictive drug methamphetamine. The new antibody, called YX1-40H10, converts methamphetamine into a benign substance, pointing to an entirely new way to treat the global epidemic of substance abuse.
- George Koob, chair of the Committee on the Neurobiology of Addictive Disorders, research associate Olivier George, and colleagues identified a neurobiological mechanism that contributes to nicotine dependence, and to the anxiety and craving experienced upon withdrawal. The findings may lead to drugs that could help smokers quit.
- Julius Rebek, a professor at Scripps Research and the director of The Skaggs Institute for Chemical Biology, and colleagues described a new chemical tool that effectively pauses the formation of certain intermediate products never before seen, allowing them to be identified and studied. The technique will improve basic understanding of chemical processes and may aid in biosynthesis studies, drug development, and detection of pollutants.
- John L. Cleveland, professor and chair of the Department of Cancer Biology, and colleagues showed that targeting the autophagy pathway (an ancient cell survival pathway that cells use to survive conditions of metabolic stress) can prevent and cure cancer in mouse models of malignant lymphoma and leukemia.
- Associate professor Peiqing Sun, professor Jiahuai Han, and colleagues discovered a surprising new function of a well-known protein kinase signaling pathway. When activated, the pathway can inhibit tumor growth. This finding may lead to the development of drugs that can be used to effectively treat cancer by artificially activating this pathway in tumor cells.
- Professor Paul Wentworth, Jr., and colleagues furthered the ongoing search for better treat-

ments for devastating parasitic diseases such as Chagas' disease and African sleeping sickness. The group now understands better a critical DNA-protein binding event that if blocked can kill the parasites that cause the diseases. The researchers are already working to screen drugs that will block this mechanism.

- Associate professor Sheng Ding and colleagues generated a new type of embryonic stem cell and developed a chemical method to "reprogram" adult mouse somatic cells to become embryonic stem cells, thus opening up new research avenues. The results shed light on the detailed mechanisms that control how stem cells choose their specialized fate and how specialized cells can unwind that choice.
- Associate professor Mark Mayford and colleagues unlocked one of the secrets of how memory is formed. Working with a unique breed of transgenic mice, the researchers found that the same neurons activated during fear conditioning are reactivated during memory retrieval. The findings could help uncover precisely how drugs such as antidepressants work in the brain, allowing clinicians to better evaluate treatment options.
- Professor Tamas Bartfai, research associate Manuel Sánchez-Alavez, and colleagues discovered a pathway that appears to play a critical role in the onset of obesity. The team showed that mice genetically altered to lack a molecule known as the EP3 receptor tend to be more active during the animals' normal sleep cycle and to eat more. Further research could lead to better understanding of obesity and to new treatments.

NEW GRANTS FOR RESEARCH

In recognition of their potential for future breakthroughs, Scripps Research scientists received a number of new grants this year. In addition to support for individual research programs, the grants included funding for several consortiums and other notable projects.

A \$17 million, 5-year grant from the National Eye Institute will support the development of the use of adult stem cells as a therapy for treating the most common types of vision loss, including diabetic retinopathy, age-related macular degeneration, glaucoma, and retinitis pigmentosa. The team, led by Dr. Friedlander and scientists in the research groups of Laura Crisa, Glen Nemerow, Wolfram Ruf, Gary Siuzdak, Bruce

Torbett, and William Balch, will conduct the extensive and detailed preclinical work necessary for moving the potential therapy forward.

A \$51 million, 5-year contract from the National Institute of Allergy and Infectious Diseases will support the study of innate and adaptive immune responses to a number of dangerous pathogens, including those that cause influenza, smallpox, and anthrax. The project scientists, led by Richard Ulevitch, professor and chairman of the Department of Immunology at Scripps Research, and including researchers at the Institute for Systems Biology, Seattle, Washington; the Australian National University, Canberra, Australia; and Stanford University, Palo Alto, California, will develop innovative approaches to improving vaccines and immunotherapeutics.

A prestigious, 10-year MERIT grant to associate professor Cindy Ehlers from the National Institute on Alcohol Abuse and Alcoholism will support research on risk and protective factors for alcoholism in Southwest California Indians. Southwest California Indians have a 5-fold greater risk than the general population for alcohol dependency. In work funded by a separate 3-year, \$1.5 million grant from the National Institute on Alcohol Abuse and Alcoholism and the National Center on Minority Health and Health Disparities, Dr. Ehlers will help design, implement, and evaluate a program to build services and to prevent underage drinking in Native American young people.

PRIVATE GIFTS

In addition to government-sponsored grants and our corporate partners, we are grateful for the generosity of our many donors, whose gifts accelerate the progress of research on our campuses and leave a powerful legacy for future generations.

Always notable is the ongoing gift from Aline and Sam Skaggs through the Skaggs Institute for Research and their family foundation, the ALSAM Foundation. Their commitment of \$100 million created the The Skaggs Institute for Chemical Biology to improve human health by supporting research at the interface of chemistry and biology.

In 2007, philanthropist and entrepreneur Mark Pearson gave \$3 million to establish the Pearson Family Chair, an endowed position in alcohol and addiction research; the first recipient will be Professor Barbara Mason. The Pearson Family Chair builds on Pearson's previous gift of \$3 million in 2003, which created the Pearson Center for Alcoholism and Addiction Research. The center, codirected by Dr. Mason and Professor

George Koob, combines the latest biomedical research with new clinical treatments to fight the devastating, costly, and deadly diseases of alcohol and drug addiction.

Because of another far-reaching act of generosity, in 2007 we received the final payment from the estate of Norma and Frank Sugg, a California couple who included Scripps Research as a beneficiary of their will. The \$1.6 million gift from proceeds of the sale of the Suggs' home and other assets will support research on leukemia.

Long-time Scripps Research friend and supporter Daniel Koshland, Jr., gave \$100,000 to the Scripps Research Kellogg School of Science and Technology this year, forming the basis for a new student fellowship, the Koshland Graduate Fellowship in Enzyme Biochemistry. Sadly, Dr. Koshland passed away in July at the age of 87. An original thinker whose work changed the field of biochemistry, he will be remembered not only for his exemplary science but also for his deep commitment to the next generation.

NEW CORPORATE COLLABORATION

The year 2007 marked the first full year of our new research collaboration with Pfizer Global Research and Development. Under the terms of the agreement, Pfizer will pay Scripps Research \$100 million over a 5-year period. During that time, scientists from Pfizer and Scripps Research will work together to identify and perform specific projects of mutual interest. The goal of the agreement is to advance scientific knowledge of uncured diseases and novel ways to treat the diseases, making full use of emerging technologies and resident talent from both organizations. In a separate initiative, Pfizer is funding 8 postdoctoral fellowships in chemistry at Scripps Research.

AWARDS AND HONORS

In 2007, Scripps Research investigators, postdoctoral fellows, and graduate students were again lauded by numerous awards. To mention only a few, this year's honors include the following:

- Bruce Beutler, chair of the Department of Genetics, was awarded the prestigious Balzan Prize for his work with Jules Hoffmann of the Academie des Sciences in Paris. The International Balzan Prize Foundation of Italy and Switzerland cited the researchers for "their discovery of the genetic mechanisms responsible for innate immunity." Drs. Beutler and Hoffmann have collaborated to develop a new vision, across a wide evolutionary spectrum, of the molecular defense strategy deployed by animals against infectious agents.

The results of the research have led to promising medical applications.

- In June, I received an honorary doctor of science degree from the University of Oxford for my research on catalytic antibodies. The studies indicate that antibodies can be used as enzymes and are relevant for conditions such as atherosclerosis and Alzheimer's disease.
- Professor Benjamin Cravatt was elected a fellow of the American Association for the Advancement of Science "for the development of innovative chemical proteomic technologies to annotate enzymatic pathways in mammalian systems." Dr. Cravatt also won the 2007 Young Investigator Award from the Linda and Jack Gill Center at Indiana University in Bloomington.
- Professor Chi-Huey Wong was the recipient of a Humboldt Research Award from the Alexander von Humboldt Foundation in recognition of lifetime achievements in research. In addition, in 2007 Dr. Wong received the F.A. Cotton Medal from Texas A&M, an honorary degree from Technion-Israel Institute of Technology, and an honorary fellowship from the Chemical Research Society of India.
- Professor Francis Chisari won the Distinguished Scientist Award of the Hepatitis B Foundation for his "seminal work in the immunopathology of hepatitis B, which has contributed significantly to the current understanding of the disease and advanced medical research towards finding a cure."
- Professor William Roush, executive director of Medicinal Chemistry and associate dean of Scripps Florida graduate studies, was named Scientist of the Year by the South Florida Science Museum in the first of the museum's annual series of awards.
- Professor Linda Curtiss received the Distinguished Achievement Award from the American Heart Association Council on Arteriosclerosis, Thrombosis, and Vascular Biology for "immense contributions to the council for many years."
- Professor Dale Boger won the Ernest Guenther Award in the Chemistry of Natural Products from the American Chemical Society. The award was given "in recognition of contributions to the total synthesis of complex biologically active natural products and key analogs used to define their mode of action."
- Associate professor Dorian McGavern won a prestigious award from the Burroughs Wellcome Fund,

which named him 1 of 15 new Investigators in Pathogenesis of Infectious Disease. These highly competitive awards are given to scientists during the early years of the scientists' career.

- Assistant professor Kristin K. Baldwin was 1 of 20 exceptional researchers selected as 2007 Pew Scholars in the Biomedical Sciences by the Pew Charitable Trusts and the University of California, San Francisco.

I extend my sincerest thanks to trustees, donors, friends, faculty, staff, postdoctoral fellows, and students for their efforts in making 2007 another exemplary year at The Scripps Research Institute.