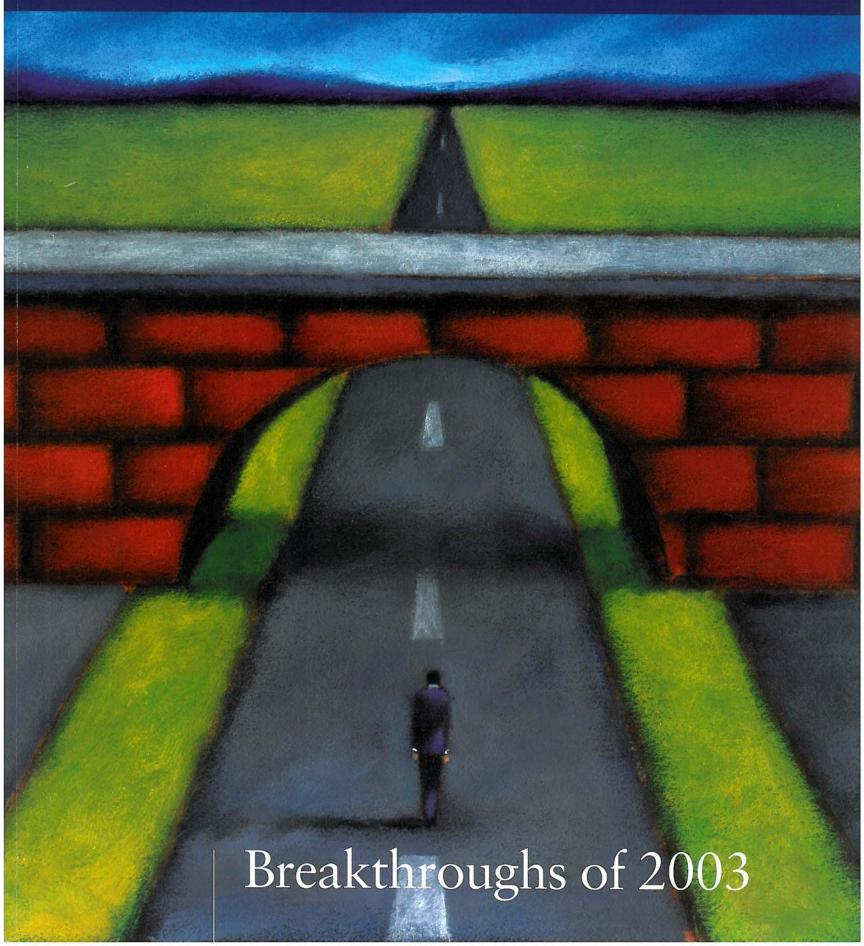


# THE SCRIPPS RESEARCH INSTITUTE Winter 2003/04 Cavolity Winter 2003/04



# Endeavor

VOLUME SIX NUMBER THREE

Winter 2003/04

This issue of Endeavor magazine features breakthroughs of 2003 at The Scripps Research Institute. Among many significant scientific milestones were the discovery of ozone in human biology, the solution of an unusual antibody to the virus that causes AIDS, and the first-ever creation of a 21-amino-acid organism. In addition, 2003 was marked by several historic turning points for the institute, including the establishment of a new campus in Florida and the launch of a joint doctoral program with Oxford University.



# featured Ozone at the Heart of Human Health Basic Research Leads to a Surprising Discovery



# Pushing the Limits of the Genetic Code Biology Isn't What it Used to Be



# It Had to Work Determination Fuels Scripps Research Scientists' Quest for AIDS Vaccine

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# Year in Review 2003

# President's Introduction

Like many things in life, science is a serendipitous enterprise. Although we conduct experiments according to well-prescribed methods, the surprises that come to the diligent and the prepared are often those moments that yield the most unexpected and exceptional insights. And so it is this year in the life of The Scripps Research Institute that we find ourselves, somewhat serendipitously, in collaborations with two unique partners in what will be truly exciting and profoundly meaningful experiments.

After months of discussions with Florida Governor Jeb Bush, Scripps Research recently began negotiations that will lead to the establishment of a new research

science center in Palm Beach County, with an emphasis on biomedical research, advanced technology, and drug discovery. I fully expect that the extension of Scripps Research's activities in this new scientific arena will increase the scope and depth of

scientific inquiry in the biomedical sciences; the synergy between the two research centers most likely will lead to major new developments to improve human health.



Scripps Research will establish a center in Palm Beach County, Florida, with an emphasis on biomedical research, technology development, and drug design.

This enterprise is expected to serve as a stimulus to Florida's economic development in biotechnology, because Scripps Research and other academic institutions have been the engine driving the burgeoning biosciences industry in San Diego County. Further,

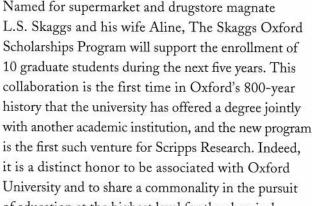
Scripps Research will be involved with the business community, the university system, and school districts in the Palm Beach area.

We are particularly grateful to Governor Bush for his foresight, his confidence in Scripps Research, and this unprecedented opportunity to play an important part in creating and transforming the scientific landscape in South Florida. I have every hope that this initiative will contribute not only to economic development, job creation, and educational enrichment but also to the overall growth of biomedical knowledge.

In another development that simultaneously acknowledges the reputation of Scripps Research in

> the international scientific community and elevates it to the next level, Scripps Research and the University of Oxford Department of Biochemistry have announced the establishment of a joint graduate program to train young

doctoral candidates at both acclaimed institutions. Named for supermarket and drugstore magnate Scholarships Program will support the enrollment of 10 graduate students during the next five years. This collaboration is the first time in Oxford's 800-year University and to share a commonality in the pursuit of education at the highest level for the chemical biologists of the future.



## **CHANGES IN BOARD OF TRUSTEES**

A change in board leadership in any organization is a double-edged sword. Although the change brings with it the opportunity for new ideas, a new perspective, and innovative thinking, it also acknowledges the closing of >



Richard A. Lerner, M.D., president of The Scripps Research Institute

"I have every hope that this initiative [to establish

a Scripps Research center in Palm Beach County,

Florida] will contribute not only to economic

development, job creation, and educational

enrichment but also to the overall growth of

biomedical knowledge." — Richard A. Lerner



The Hon. Alice D.
Sullivan is now
chair of The Scripps
Research Institute
Board of Trustees.

a chapter in the history of an institution. And so it is that we welcome the Honorable Alice D. Sullivan, a former Alameda County superior court judge, as chair of the Scripps Research Board of Trustees and thank John Diekman, former chairman of the board of Affymetrix and Bay City Capital, for his many years of extraordinary leadership. Judge Sullivan has served with distinction as a member of our board for the past several years and for the past decade has worked in private practice in the resolution of business disputes, particularly in the life sciences and technology fields.

In addition, this year we welcomed the following new members to the Board of Trustees: Rod Dammeyer, president of CAC, L.L.C., a private company offering capital investment and management advisory services; Thomas Insley, former managing partner of the San Diego office of PricewaterhouseCoopers L.L.P., and current vice president and chief financial officer of SkinMedica, Inc., a specialty pharmaceutical company; Richard J. Elkus, Jr., an executive and entrepreneur whose career has been closely connected with the

development and evolution of Silicon Valley; Warren Beatty, Academy Award-winning film actor, director, screenwriter, and producer; and Mervin Morris, founder of Mervyn's chain of retail stores. in New York City. The group's charge is to create an "encyclopedia" of innate immunity, a comprehensive picture of this ancient, essential first line of defense against bacterial and fungal diseases that is mustered by all living creatures. The knowledge generated could help scientists develop treatments for septic shock, certain auto-immune disorders, and diseases caused by potential agents of bioterrorism.



Two new multi-million-dollar grants will fund studies at Scripps Research on anthrax toxins. (File photo courtesy of Centers for Disease Control and Prevention.)

Later in 2003, the National Institute of Allergy and Infectious Diseases awarded a \$9.2 million, multicenter program project grant to a team of scientists at Scripps Research, Harvard Medical School, and the

Salk Institute for Biological
Studies to discover and develop
novel anthrax antitoxins and
ways of delivering them. The
overall goal of the program
is to design antianthrax nanosponges, antitoxin particles
that could be administered
to someone who has been

exposed to anthrax. In addition, another government agency, the U.S. Centers for Disease Control and Prevention, awarded a group of Scripps Research investigators a multiyear, \$11.4 million grant to study the interaction of the human immune system with toxins of the microorganism that causes anthrax. The goal is to understand how these toxins suppress immune responses in humans, circumventing the usual mechanisms by which the body would destroy the bacterium.

## MAJOR RESEARCH GRANTS

Scripps Research continues to attract large-scale consortia grants from the National Institutes of Health, an accomplishment that reflects its leadership position in numerous fields of study in the biomedical sciences and its collaborative relationships with centers of scientific excellence throughout the United States. Early in 2003, the National Institute of Allergy and Infectious Diseases awarded a multiyear, \$24 million grant to a group of researchers at Scripps Research, the Institute for Systems Biology in Seattle, and Rockefeller University

"Scripps Research continues to attract large-scale

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throughout the United States."

#### SIGNIFICANT SCIENTIFIC DISCOVERIES

As is the norm, the institute's researchers this year contributed a prodigious volume of work to the body of scientific knowledge in a broad range of disciplines, work that changes the way we think about biological mechanisms and the course of human disease. The following merely skims the surface of knowledge they created and the importance of their discoveries.

Work in the laboratory of Peter Schultz, professor of chemistry and Scripps Family Chair of The Skaggs

Institute for Chemical Biology, effectively removed a billion-year constraint on the ability to manipulate the structure and function of proteins. Dr. Schultz and his research group completed the synthesis of a form of the

manipulate the function of
Schultz and group completed of a form of the scherichia coli with a genetic code that to the body of scientific knowledge in a broad range of disciplines, work that changes the way we think about biological mechanisms and the course of human disease."

"As is the norm, the institute's researchers this

year contributed a prodigious volume of work

bacterium *Escherichia coli* with a genetic code that uses 21 basic amino acid building blocks to synthesize proteins, instead of the 20 found in nature. This creation was the first one of an autonomous organism that uses 21 amino acids and has the metabolic machinery to build those amino acids. Further, the group introduced revolutionary changes into the genetic code of organisms such as yeast that allow the mass production of proteins with unnatural amino acids. By so doing, Dr. Schultz and his team set the stage for an entirely new approach to applying the same technology to other eukaryotic cells, and even to multicellular organisms. Simply stated, these scientists have opened up the whole pathway to higher organisms.

Researchers in the laboratory of Stephen Mayfield and in my laboratory used algae to express an antibody that targets herpesvirus. The usefulness of the antibody lies not only in the potential production of an antiherpes topical cream or treatment but also in the development of technology that could facilitate the production of multiple human antibodies and other proteins on a massive scale. This technology enables the generation

of antibodies, soluble receptors, and other proteins so much more cheaply than previous technology that an entire new class of therapeutic agents may become available.

Jeffery Kelly and his colleagues in the Department of Chemistry and The Skaggs Institute for Chemical Biology discovered a new approach for treating amyloid diseases, particularly transthyretin amyloid diseases, which are similar to Parkinson's and Alzheimer's diseases. Amyloid diseases are caused by misfolding

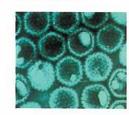
> of proteins into a structure that leads the proteins to cluster, forming microscopic fibril plaques that are deposited in internal organs and interfere with normal function. Dr. Kelly and his team showed the efficacy of using small

molecules to stabilize the normal fold of transthyretin, preventing this protein from misfolding. By so doing, they were able to inhibit the formation of fibrils by a mechanism that can ameliorate disease.

In what was a first for biology, researchers in my laboratory, including Paul Wentworth in collaboration with Bernard Babior, reported that the human body makes ozone. Ozone appears to be produced in a process involving human immune cells known as neutrophils and human antibodies. The presence of ozone in the body may be linked to inflammation, and the research may have important ramifications for treating inflammatory diseases. In addition to killing bacteria, the neutrophils feed singlet oxygen to the antibodies, which convert it into ozone.

Carlos Barbas, Janet and W. Keith Kellogg II Chair in Molecular Biology, designed a hybrid anticancer compound that combines the efficacy of a cancer cell-targeting agent with the long-lasting dose of an antibody. This potent combination has a profound effect on the size of tumors in animal models, shrinking both Kaposi sarcomas and colon cancers in preclinical studies. The

Using a promising new method to produce antibodies on a massive scale, Scripps Research scientists used algae to express an antibody that targets herpesvirus, pictured in an electron micrograph, below.



approach is general enough to be used to design hybrids against numerous different cancers; a single antibody can be mixed with multiple small molecules, resulting in a multiplicity of therapeutic agents.

A group of researchers led by Immunology Professor Bruce Beutler discovered rare genetic mutations in a subset of patients who have a severe form of sepsis, an acute and often deadly disease. These mutations, in a gene called Tlr4, predispose persons to susceptibility to meningococcal sepsis, which strikes more than 2,500 persons each year in the United States and has an overall fatality rate of 12 percent. Besides indicating the increased risk of severe sepsis in patients with these mutations, the results suggest that protection of patients at risk may be possible. Eventually, persons with these mutations might be given prophylactic treatment, for example, before undergoing surgery or traveling to a location where exposure to meningococcal bacteria is likely.

Scientists led by Kim D. Janda, Ely Callaway, Jr., Chair in Chemistry and an investigator in The Skaggs Institute, designed a new way to make a vaccine against nicotine that could become a valuable tool for treating addiction by helping the body clear the drug from the bloodstream. The vaccine, which eventually would be given to persons in smoking cessation programs, greatly suppresses the reinforcing aspect of nicotine. The researchers used an "immunopharmacotherapy" approach, by designing a drug that stimulates the immune system to clear the nicotine from the body.

In a related research study, Dr. Janda and his group discovered that a chemical called nornicotine, a major metabolite of nicotine, modifies proteins that misfold and form the fibril plaques found in abundance in the brains of patients who have Alzheimer's disease. Simply stated, this process physically inhibits the formation of the fibrils. The research is promising—not because nornicotine likely would be an effective therapeutic agent, but because it shows how a single molecule can cause a chemical interaction that may alter a mechanism

important in Alzheimer's disease. This research could lead to the development of small molecules similar to nornicotine that are not toxic but could interact in a similar fashion, preventing the aggregation of amyloid-b protein and perhaps Alzheimer's disease.

A group of scientists including John Tainer, Lisa Craig, Mark Yeager, and Mike Pique solved two key structures of a bacterial protein called pilin, which is required for infection by pathogens that cause diseases such as meningitis, gonorrhea, pneumonia, and cholera. The members of the group think that the research provides essential knowledge to help scientists develop novel antibiotics and vaccines against these deadly and emerging bacterial diseases. Because the structures are too large and flexible to be solved by using the traditional techniques of structural biology, the team used both x-ray crystallography and electron microscopy to build a model of the pili that would have otherwise been impossible at that level of molecular detail.

In another structural achievement, a multi-institutional group of researchers led by Ian Wilson and Dennis Burton solved the structure of an antibody that effectively neutralizes HIV, an important step toward the goal of designing an effective vaccine against HIV and a new means by which scientists may design antibodies in general. The structure of the antibody has never been seen before, prompting the scientists to speculate on whether they can use this knowledge to engineer antibodies with higher affinity against other antigens.

In a development that could improve the prospects for designing new ways to fight malaria, a group of researchers led by Elizabeth Winzeler described a comprehensive global profile of genes in the parasite that causes malaria, associating the function of a few such known genes with the thousands that have no known function. The researchers think that these data will accelerate our understanding of the malaria parasite and its interaction with humans and should provide new avenues for more effective drugs and



Research on a chemica called nornicotine may have implications for the treatment of Alzheimer's disease.

vaccines. In collaboration with researchers at the Genomics Institute of the Novartis Research Foundation, Dr. Winzeler created a malaria-specific gene chip with probes specific for the entire genome of the malaria parasite, enabling her to examine the expression of genes at each stage of the parasite's life cycle. This accomplishment should accelerate the pace of research on the parasite by categorizing uncharacterized genes in functional ways.

Using a new technique known as subtractive proteomics, Larry Gerace and John Yates recently identified more than 50 previously unknown proteins, several of which are associated with rare human muscle and nerve degenerative diseases. Recognizing the proteins that may cause or contribute to diseases such as congenital muscular dystrophy and spinal muscular

dystrophy is a first step in the long process of looking for ways to detect, prevent, or treat diseases. The study may clarify a significant number of

the more than 300 human dystrophies for which a causative gene has not been identified. The researchers think understanding how these diseases occur requires understanding more about the network of interlinked proteins.

## **FACULTY HONORS AND AWARDS**

Many Scripps Research scientists, at various stages of their careers, were honored by their peers this year with awards for achievement in numerous areas of scientific endeavor. Dale L. Boger and Bernard Babior were elected to membership in the American Association for the Advancement of Science, Francis Chisari and Peter Vogt were elected to the Institute of Medicine of the National Academies, and Michael B.A. Oldstone won the Pioneer in NeuroVirology Award of the International Society for NeuroVirology. Ernest Beutler was awarded the E. Donnall Thomas Lecture and Prize of the American Society of Hematology,

Tamas Bartfai received a Distinguished Investigator Award from the National Alliance for Research on Schizophrenia and Depression, Eng Tan was selected for the Japan Rheumatism Foundation/Wyeth Lederle Japan International RA Award, and Ben Cravatt won the Eli Lilly Award in Biological Chemistry from the American Chemical Society. Clare Waterman-Storer was awarded a Keith Porter Fellowship of the Porter Endowment for Cell Biology and Erica Ollman Saphire won the Burroughs Wellcome Fund Career Award in the Biomedical Sciences.

The events of this year have been nothing short of extraordinary, with profound and far-reaching implications for the future of Scripps Research. In an organization that often exceeds expectations on multiple levels and whose faculty and staff remain at

> the leading edge of science in an era in which the pace of discovery accelerates on a continual basis, these new developments will provide

greater impetus for Scripps Research to play an even larger role on the international stage of scientific discovery. I could not be more proud of our faculty, employees, trustees, donors, and friends, all of whom make me grateful to have the opportunity to work with them every day.

R.A. Jenny

Richard A. Lerner, M.D.



A group of researchers described a comprehensive global profile of genes in the malaria parasite, which is transmitted through mosquitoes. (Photo courtesy of Centers for Disease Control and Prevention.)

"The events of this year have been nothing short

of extraordinary, with profound and far-reaching

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# Ozone at the Heart of Human Health

# Basic Research Leads to a Surprising Discovery

Basic science is like the Tour de France. It takes place in many different stages with teams of scientists enduring long uphill climbs, weathering lengthy plateaus, and sprinting to the finish line amid cheering crowds. Not surprisingly, a story about a basic science discovery often ignores the climbs and focuses on the finish line—the publication in *Science* or one of the other top research journals.

This is a story about a basic science discovery in chemical biology that is still an event in progress. The team players include Scripps Research President Richard A. Lerner, M.D., Associate Professor Paul Wentworth, Ph.D., and several other members of The Skaggs Institute for Chemical Biology. Their discoveries in basic chemical biology may eventually lead to important changes in the way we diagnose and treat heart disease.

In the laboratory, Lerner and Wentworth were working with a protein known as a catalytic antibody, a special version of the antibodies the immune system generates to fight infections. What makes catalytic antibodies special is that they have the ability to chemically react with other molecules in the body and in the test tube in ways that might one day make them useful for everything from synthesizing cancer drugs to delivering them to a tumor.

Lerner, who is Lita Annenberg Hazen Professor of Immunochemistry and holds the Cecil H. and Ida M.

Green Chair in Chemistry at Scripps Research, discovered catalytic antibodies several years ago with Peter Schultz, who was then an investigator

at the University of California, Berkeley and is now the Scripps Family Chair and member of Scripps Research's Skaggs Institute.

Wentworth was working with an antibody that was designed to bind to a chemical called stilbene. These antibodies had the unusual property of displaying blue fluorescence when irradiated with ultraviolet light. It was a neat trick, but Lerner, Wentworth, and their colleagues wanted to find applications. "We were

simply asking," says Wentworth, "what chemistry can we do with this system?"

That's when they made their discovery.

They found that this antibody had the unusual ability to generate hydrogen peroxide—the familiar antiseptic and bleaching agent—under UV light. Moreover, they were surprised to discover that all antibodies have this ability.

This led them to ask if antibodies produce hydrogen peroxide under normal conditions in the body. In fact, Lerner, Wentworth, and their colleagues found that antibodies did indeed generate hydrogen peroxide when fed another form of oxygen, called singlet oxygen, which is available in the body because it is produced by cells of the immune system as part of our mechanism for defense.

Singlet oxygen is an electronically excited and highly reactive form of oxygen that can potentially destroy any cell, making it dangerous to an organism. Throughout evolution, animals have developed various mechanisms for removing singlet oxygen in order to survive.

In their 2001 Science paper, Wentworth, Lerner, and their colleagues suggested that ancient antibodies may have once played a role in biology by controlling the release of this potentially dangerous singlet oxygen. Moreover, the scientists postulated that this process may be part of a previously unrecognized mechanism

that enhances the defensive role of antibodies by subjecting pathogens to hydrogen peroxide and killing them.

For the last hundred years, immunologists have firmly believed that the sole purpose of antibodies was to recognize pathogens and trigger cells in the immune system to kill the pathogen. This previously unrecognized ability of antibodies to kill pathogens directly offered exciting possibilities for new antibody-mediated therapies for conditions ranging from bacterial and viral infection to cancer. Furthermore, this process could be linked to a number of other diseases.

|These| discoveries in basic chemical biology may eventually lead to important changes in the way we diagnose and treat heart disease. The researchers decided to investigate further.

## ANTIBODIES MAKE OZONE AND KILL BACTERIA

To further explore the mechanism of how antibodies produce hydrogen peroxide, Lerner and Wentworth collaborated with Skaggs Institute investigator Albert Eschenmoser, Ph.D., and the group of William A. Goddard III, Ph.D., at the California Institute of Technology.

A completely unexpected discovery from the quantum mechanics calculations by the Goddard group was that the antibodies reacting with singlet oxygen could generate a product with the chemical signature of ozone.

Ozone is a particularly reactive form of oxygen that exists naturally as a trace gas in the atmosphere, constituting on average fewer than one part per million air molecules. The gas plays a crucial role in protecting life on earth from damaging solar radiation by concentrating in the upper reaches of Earth's stratosphere—about 25 kilometers above the surface—and absorbing ultraviolet radiation. Ozone is also a familiar component of air in industrial and urban settings where the highly reactive gas is a hazardous component of smog in the summer months.

"Could we have found ozone in the human body?" Lerner asked himself at the time. Ozone had never been considered a part of biology before.

By the summer of 2002, the work of the Scripps Research scientists really began to heat up. Not only had they started to refine the approaches and the experiments to demonstrate how and where the ozone is produced in the human body, but they had begun to get a sense for what it was doing there—that it was involved in the immune response.

This conviction grew with the discovery they published late last year in *Science* that antibodies specific to *E. coli* bacteria could kill those bacteria when fed singlet oxygen, which the antibodies would catalyze into hydrogen peroxide. Because the amount of hydrogen peroxide the antibodies generated was not enough to kill the bacteria alone, ozone became implicated as a mediator in killing the bacteria. Ozone together with hydrogen peroxide destroys bacteria by poking holes in their cell walls.

The Scripps Research team also established a new and fruitful collaboration with Scripps Research Professor Bernard M. Babior, M.D., Ph.D., to explore a potential source of the singlet oxygen—a type of white blood cell

called a neutrophil, a key cellular component in the inflammatory response. In a study published in early 2003, the team suggested that during the inflammatory process, neutrophils and antibodies work together to produce human ozone. The neutrophils feed singlet oxygen to the antibodies, which convert it into ozone, enhancing the antibacterial effect of the neutrophils.

But the team wanted to know more.

For instance, if ozone is generated in the body's inflammatory response, could it also be involved in any of the human diseases in which inflammation plays a role—such as lupus, multiple sclerosis, rheumatoid arthritis, and atherosclerosis?

If so, this discovery would open up exciting possibilities for new therapies. Lerner, Wentworth, and their colleagues immediately began thinking of ways to look for ozone in inflammation—perhaps even in a clinical setting.

#### WHAT'S IN AN ARTERY?

Says Wentworth, "Given that atherosclerosis is an inflammatory disease, we asked the question, 'Is ozone generated in atherosclerosis?"

Atherosclerosis is a common vascular disease that increases the risk of heart attacks and strokes. In fact, heart disease is the most common cause of death in the United States. The Centers for Disease Control and Prevention statistics for 2000 list 878,471 deaths from heart disease and stroke, followed by 553,091 for cancer. Over the last few years, evidence has been accumulating that the process of atherosclerosis has a significant inflammatory component. Given this evidence, Lerner, Wentworth, and their colleagues thought they might look at tissue involved in the disease for evidence of ozone.

The name of the disease comes from the Greek athero (which means gruel or paste) and sclerosis (which means hardness). And, as the name implies, it is a disease that is characterized by a hardening of the arteries over time due to the buildup of hard plaques—fibrous tissue, calcium, fat, cholesterol, proteins, cells, and other materials—on the inner "endothelial" walls of an artery. These plaques feel something like cartilage to the touch, which explains why atherosclerosis is commonly called hardening of the arteries.

The open cross-section of the artery shrinks as this buildup occurs, and the reduction in blood flow can



Atherosclerosis is a common vascular disease that increases the risk of heart attacks and strokes.

become so significant that a thrombus or blood clot can form at the site. When this process occurs within the coronary arteries that provide the blood supply to the heart, the result is a myocardial infarction, a socalled heart attack. Heart attacks can also result from rupture of the plaque and obstruction of blood flow.

When the carotid arteries are involved, patients may often be asymptomatic, in which case the atherosclerotic plaques are discovered during a physical examination and confirmed by ultrasound. Symptomatic patients may experience lightheadedness and fainting, transient loss of vision in one eye or the other, weakness of the hands, transient loss of the ability to speak, or even stroke. In either case, patients who have their blood flow reduced by 60 to 70 percent or more are good candidates for an operation to remove the plaques from the inner walls of arteries. Known as an endarterectomy, this is a time-tested procedure performed by vascular surgeons that has been around since the 1950s, and it is a common procedure for patients in their 60s and beyond.

Atherosclerotic plaques have all the ingredients needed to make ozone. They contain white blood cells, which have the ability to generate the singlet oxygen that the antibodies need to produce ozone—and plenty of antibodies passing by in the blood stream.

Mix antibodies with singlet oxygen in the test tube and you get ozone. But does it really happen in vivo?

## THE DISCOVERY OF HUMAN OZONE

Lerner and Wentworth approached Giacomo DeLaria, M.D., who is a vascular surgeon at nearby Scripps Clinic, and asked if they could obtain samples of carotid atherosclerotic plaques. DeLaria provided a sample of plaque material from a patient who recently underwent an endarterectomy, generously enabling Wentworth, Lerner, and their colleagues to perform their studies.

"These are specimens we normally just inspect and throw away," says DeLaria. "Within themselves, they have no diagnostic value, and they don't change what we do after the procedure."

Wentworth and Lerner tested this sample, and the results proved promising. They did find some abnormalities that could be associated with the presence of ozone in these plaques. But they wanted to be sure. So DeLaria and his fellow vascular surgeon Ralph Dilley, M.D., provided several more samples.

When Lerner, Wentworth, and their colleagues studied the atherosclerotic plaque samples, they found evidence that ozone had been generated. Chemicals that would be produced when the highly reactive ozone mixed with the other components of the plaque were evident.

The researchers also found in the atherosclerotic plaques a completely new class of dangerous steroids never before found in human tissue. These are believed to be generated only when cholesterol is exposed to ozone. They may be a good specific marker for late-stage arterial inflammation, enabling doctors to determine how life-threatening a patient's plaques are.

Moreover, these findings are highly suggestive of a role for ozone in the pathology of atherosclerosis. These newly identified compounds are toxic to white blood cells, smooth muscle cells, and cells from the arterial walls—all the major types of cells in and around the plaques.

"The fact that [these toxins] are generated in proximity to cells that are destroyed I think is going to prove critical to part of the pathogenesis of atherosclerosis," says Wentworth. "We're going to pursue a hunt, now, for all these [toxins] and what they do."

Currently, physicians rely on easily measurable risk factors to identify patients who are more likely to suffer from vascular disease: elevated cholesterol, hypertension, diabetes, smoking, obesity, and a family history of vascular disease at an age less than 55. Nevertheless, there is a substantial fraction of patients who do not have these risk factors and yet who develop atherosclerosis. There is considerable interest in developing other sensitive markers that would allow early identification of patients at risk.

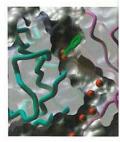
Could ozone or one of its side products be such a marker?

Lerner, Wentworth, and their colleagues found that one of the toxic steroids is present in the blood of patients who have late-stage atherosclerosis, but not in healthy individuals.

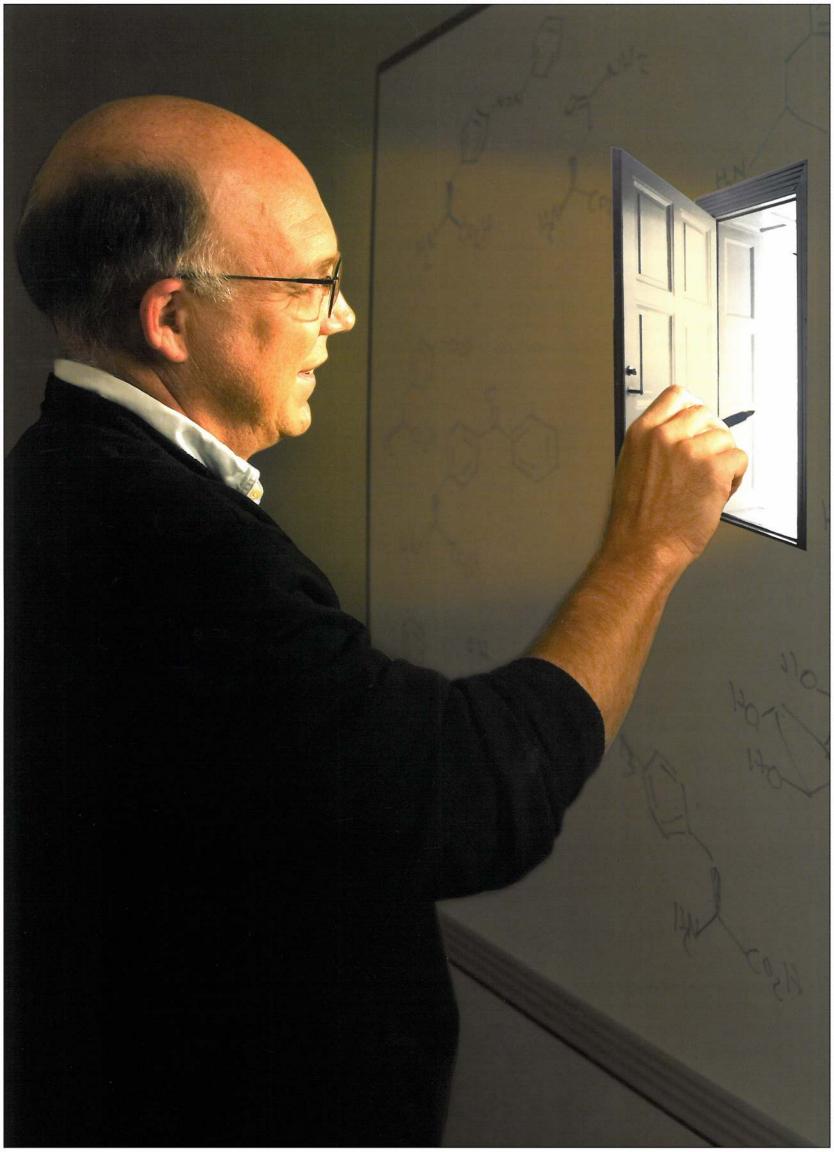
Are the toxins just bystanders or are they linked to the progression of the disease? If ozone and its byproducts are linked to the disease, then how can they be reduced or eliminated? Could the research come full circle by pointing to a therapeutic role for catalytic antibodies?

As in the Tour de France, each stage of this story has its own finish line. And with each exciting finish grows the anticipation of what's to come.

Jason Socrates Bardi



An illustration of the channel through which ozone travels from one side of an antibody, where it is made, to the other side, where it is released.



# Pushing the Limits of the Genetic Code

Biology Isn't What it Used to Be

The King of Sardis, who lived roughly 2,500 years ago, was once visited by a wise man named Solon, and he treated Solon to a tour of his immense palaces and fabulous treasures that lasted several days. At the end of this opulent display, he asked Solon one question: who is the happiest man alive? To the chagrin of the King of Sardis, Solon named an obscure character, Tellos of Athens.

Why? demanded the King of Sardis, Why is Tellos so happy?

According to Herodotus, who tells this story in his famous *Histories*, Tellos was the happiest man alive because he lived in Athens, had a long life, did well in business, had healthy children, achieved glory in battle, and won the honor of his peers. Tellos had lived his life to its fullest potential.

Herodotus's story is rich with ancient Greek moral subtext about accepting limitations, but does this mean that all limitations are good and all attempts to surpass them are bad?

Much in the modern world depends on using science to improve our lives, and change is at the heart of science. The basis for experimentation, after all, is to

change one variable while keeping the others constant and observing the effect. There are whole scientific disciplines, like physical

organic chemistry, devoted to making changes to molecules and observing what effects these changes have on molecular structure and function. For chemists, these are powerful tools. Chemists routinely change the structure of small organic molecules to enhance the activity of that chemical—to turn something found in a mold or tree bark, for example, into a powerful drug.

But physical organic chemistry has its limitations.

It is not easy to do physical organic chemistry on certain large biological molecules, such as proteins. While chemists have a huge diversity of building blocks to work with, biologists—like nature—have made proteins with 20—and only 20—amino acids. Almost without exception, life as we know it is composed, at the molecular level, of the same basic building blocks.

"Limiting [chemists] to only 20 synthetic building blocks would bring most labs to a grinding halt," says Peter G. Schultz, who holds the Scripps Family Chair and is a member of The Skaggs Institute for Chemical Biology at The Scripps Research Institute.

Schultz was not one to be satisfied with such limitations. To him, the answer was clear.

"One has to figure out how to add amino acids to the genetic code," says Schultz. In the late 1990s, while still a professor at the University of California at Berkeley, Schultz began working out how to do this.

## TWENTY-ONE UP

Schultz was not the first scientist to think of adding unnatural amino acids to proteins. Through the years, scientists have looked for chemical methods to incor-

> porate them into proteins, and they have been successful in the synthesis of peptides and small proteins that contain novel amino acids. Proteins

have been chemically synthesized step by step in the test tube, for instance, with unnatural amino acids inserted where desired—like a chain of silver paper clips with an occasional green one.

Incorporating unusual amino acids into polypeptides has turned out to be a powerful research tool and has allowed chemists to synthesize important therapeutic peptides. The technique provides a way of studying and controlling the biological processes that form the

"Limiting [chemists] to only 20 synthetic building blocks would bring most labs to a grinding balt."

- Peter Schultz

basis of some of the most intriguing problems in modern biophysics and cell biology, like signal transduction, protein trafficking in the cell, protein folding, and protein—protein interactions. The more scientists can control proteins in the cell, the more information they can get about what proteins are doing in their natural environment, and the more they can use proteins to affect biological processes in both natural and unnatural ways.

However, Schultz was not aiming to make unnatural amino acid proteins in the test tube. His goal was to be able to incorporate unnatural amino acids in vivo— which in Latin literally means "in the living." Instead of simply making proteins with unnatural amino acids by chemical synthesis in the laboratory, Schultz and his colleagues desired to generate organisms with expanded genetic codes so that living cells would themselves make proteins with unnatural amino acids.

That, Schultz knew, would open up whole new avenues of research. He began working on this project in 1996 and continued this effort when he

came to Scripps Research in 1999. It was not the easiest exercise in the world.

"The strategy was rather pie in the sky and involved the evolution of new components of the cellular biosynthetic machinery," says Schultz. He admits that he had his share of critics who doubted whether it could be done. But he proved them wrong.

Schultz's team had its first real breakthrough in 2001, when lab members managed to get a strain of the bacterium *Escherichia coli* to incorporate the unnatural amino acid O-methyl-L-tyrosine into its proteins when fed a supply of it. This was more than a proof-of-principle, as derivatives of O-methyl-L-tyrosine can be used to study protein folding in nuclear magnetic resonance studies—a method for imaging proteins based on the same technology as the familiar hospital MRI.

In 2003, the work to expand the genetic code *in vivo* really took off.

### FROM BACTERIA TO YEAST

In January, Schultz and his colleagues published a paper describing their synthesis of a form of the bacterium *E. coli* with a genetic code that uses 21 amino acids. It had

the metabolic machinery to build all 21 amino acids, and did not need to be fed any. This was the first time that anyone had created a completely autonomous 21-amino-acid organism.

"We have effectively removed a billion-year constraint on the structure and function of proteins and perhaps even whole organisms," Schultz said at the time.

Then, in August, Schultz and his laboratory published a paper describing a general method for adding unnatural amino acids to the genetic code of a type of yeast called *Saccharomyces cerevisiae*. They incorporated five different unnatural amino acids into the yeast, a "eukaryotic" organism that has cells with membrane-bound nuclei, rather than the "prokaryotic" bacterial cells, which lack membrane-bound nuclei. This was an important step because it set the stage for a applying the same technology to other eukaryotic cells.

"Yeast is the gateway to mammalian cells. We've opened up the whole pathway to higher multicellular organisms," says Schultz.

In another line of research, Schultz has developed a system that uses four-base codons. A codon is a combination of RNA bases (in nature, three bases) that are used by all biological systems to translate genes into proteins. Since there are four types of RNA bases, there are 64 three-base codons (4 x 4 x 4).

The way that Schultz inserts unnatural amino acids into proteins is by subverting one of these 64 codons to encode for his unnatural amino acid. But the three-base system only lets him use one or potentially two different amino acids per protein.

The advantage of using the longer codon is diversity. The four-base system would read out four bases at a time, and this would mean that there would be 256 four-base codons possible  $(4 \times 4 \times 4 \times 4)$ . Many of these additional codons could be re-assigned to a new unnatural amino acid, potentially creating a technology where one organism could make proteins with several unnatural amino acids.

In fact, as 2003 came to a close, Schultz was in the process of writing a manuscript that details the successful use of four-base codons to expand the genetic code of *E. coli*.





Almost without exception, life as we know it is composed of 20 amino acids, among them valine (top), and arginine, shown above through microscopic images of crystals.

"There are a number of things we can do that go

far beyond what anybody thought we could do

five years ago." - Peter Schultz

#### THE UNNATURALS

In 2003, Schultz and his laboratory found a number of unnatural amino acids that can be inserted into proteins *in vivo*, with a wide variety of uses in chemistry and biology. These amino acids include:

- A dihydroxy-phenylalanine amino acid. This provides an effective way to perform powerful redox reactions in proteins. Redox reactions, in which electrons are transferred from one atom to another, form the basis of everything from the combustion of gasoline to the action of household bleach. Natural amino acid side chains generally lack the ability to perform redox reactions.
- An "iodo" amino acid. This unnatural amino acid contains a heavy atom, which is useful for x-ray crystallography—a standard technique used to probe the structure of proteins.
- "Benzophenone" and "azide" containing amino acids that can be used as photo crosslinkers. These could be used for studying protein—protein interactions inside cells. Purifying these linked proteins would enable scientists to see what proteins interact with in living cells—even those with weak interactions that are difficult to detect by current methods.
- \* A "ketone" amino acid and an "acetylene" amino acid, both of which provide a molecular hook to which other molecules, like sugars or dyes, can be attached. This will provide tools for basic technologies and enteresearch and may allow the "This [work] will have a huge impact on the use

production of therapeutic proteins with improved pharmacological properties,

selectivities, and potencies. For example, these amino acids can be used to cross-link a protein with a toxin to target cancer cells.

### **MAKING THERAPEUTIC PROTEINS**

Also important for therapeutics is the work that Schultz and his laboratory have been doing with unnatural amino acids with "glycosylated" side chains. In nature, proteins are often glycosylated—a string of sugar molecules is attached to them—and chemists would like to be able to reproduce these sorts of sugary proteins in the laboratory. Therapeutic proteins often need to be glycosylated.



Incorporating unusual amino acids into polypeptides enables chemists to synthesize important therapeutic peptides.

It's not easy, however, to make glycosylated proteins in the test tube, and Schultz's technology may give scientists the tools they need to be able to do this more readily. Earlier this year, Schultz and his Scripps Research colleagues showed that glycosylated amino acids could be incorporated site-specifically to make glycosylated proteins—an important step in the preparation of some medicines.

"This will have a huge impact on the use of proteins as therapeutics," says Schultz.

Recently, Schultz co-founded a company called Ambrx, Inc. in La Jolla that seeks to apply his technologies and engineer proteins with new

> biological, physical, and chemical properties. Schultz is hoping that the technology will open up

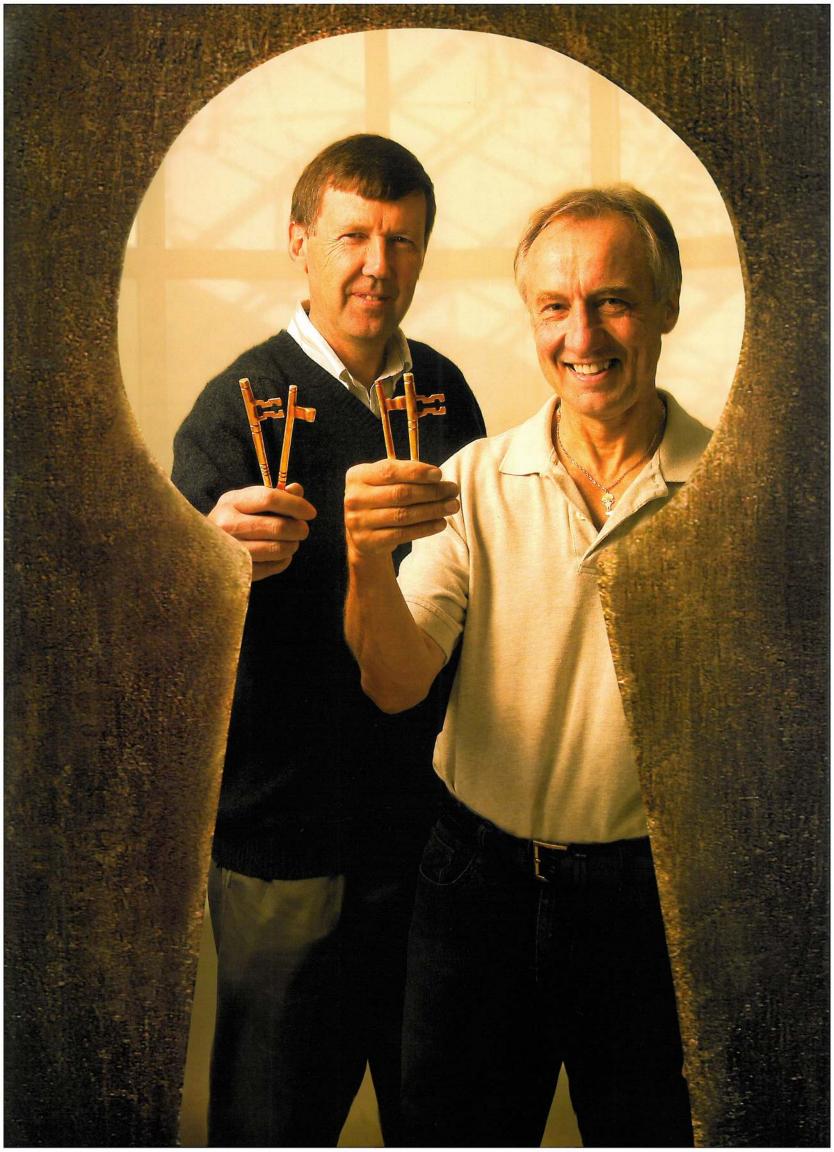
new opportunities for making human therapeutics—longer-lasting medicines as well as entirely new ones with activities that cannot be had by other means.

"There are a number of things we can do that go far beyond what anybody thought we could do five years ago," says Schultz. All told, they have added some 15 different amino acids to the genetic code of *E. coli* and yeast, and are beginning to tackle multi-cellular organisms such as *C. elegans*.

"Five years from now," he adds. "We'd basically like to be able to say, "The genetic code is obsolete."

Jason Socrates Bardi

of proteins as therapeutics." - Peter Schultz



# It Had to Work

# Determination Fuels Scripps Research Scientists' Quest for AIDS Vaccine

The Dennis Burton-Ian Wilson research collaboration that solved the structure of a unique antibody that effectively neutralizes HIV, the virus that causes AIDS, and made headlines around the globe began long before the groundbreaking announcement last June. Burton and Wilson, both veteran members of The Scripps Research Institute faculty—Burton is a professor of immunology,

Wilson a professor of molecular biology—have worked together since the early 1990s.

In an age when everyone wants everything to work on

media time—that is, instantaneously—the Burton-Wilson discovery began to bear fruit after what one researcher described as yet another last resort, which opened the door to a clearer understanding of the structure of the neutralizing HIV antibody 2G12. Given the goal of their work, the length of time it took to unravel the structural mystery of 2G12 doesn't seem all that surprising.

Of all the known antibodies, this was the first seen with such a structure.

"Nobody has come up with a vaccine candidate that will trigger neutralizing antibodies in animals or people," Burton says, describing what is perhaps the world's most elusive scientific goal. "But there is a small group of monoclonal antibodies that are neutralizing. It shows that such antibodies do exist and gives some hope for a future HIV vaccine. Our approach was to say, 'Well,

we don't have a good candidate for a vaccine, but we have these antibodies that do what we want. Can we work backwards from that?"

For Burton and Wilson, the path to the 2G12 antibody led directly through the human monoclonal antibody b12, one capable of broad and potent neutralization of different HIV-1 strains. To crystallize the

antibody, Wilson turned to one of his graduate students, Erica Ollmann Saphire, who now heads her own lab at Scripps Research.

but you just have to keep beating on it."

— Erica Ollmann Saphire

"Crystallography is tough. It can look hopeless,

#### **LAST RESORT NUMBER 128**

She began work in December 1994—with the sobering knowledge that several people had tried to crystallize b12 before, but had given up. It wasn't until nearly four years later, in August 1998, that she actually succeeded, but only after trying "last resort number 128" out of what she described as "sheer desperation."

Up until that moment, Saphire had been using the classic antibody approach—breaking the antibody into fragments and trying to crystallize the fragments. But that approach had proved frustratingly futile.

"That's when we suggested trying to crystallize the whole antibody," Burton says, "which was kind of a crazy idea because no one had ever crystallized a whole human antibody before. We all thought she would have had more problems with the bigger molecule, but it worked. And that just cracked open the whole problem. It was an amazing feat of perseverance that she stuck with it."

As Saphire explains it, there was no other alternative: "Crystallography is tough. It can look hopeless, but you just have to keep beating on it. It had to work. We had to have the b12 structure to see how it interacted with HIV."

With the initial crystallization complete, it took another year and a half to complete the work on b12. Shortly thereafter, Burton and Wilson moved on to

Main photo: Scripps Research Professors Dennis Burton (left) and Ian Wilson have collaborated on research projects for a decade. 2G12, a unique antibody taken from an HIV-positive individual a decade earlier by Hermann Katinger, a doctor at the Institute for Applied Microbiology of the University of Agriculture in Vienna, Austria.

Unlike b12, it took only a few months to crystallize

2G12, Saphire says. But then the real mystery began. Dan Calarese, another of Wilson's graduate students, noticed something odd about the molecule itself. What they

"Our approach was to say, 'Well, we don't have a good candidate for a vaccine, but we have these antibodies that do what we want. Can we work backwards from that?" — Dennis Burton

eventually discovered was a structural anomaly. The Fab, or antigen recognition arms, of the 2G12 antibody were interlocked to form multiple binding sites capable of recognizing the sugars that cover the surface of HIV, something it should not have been capable of doing because the sugars were human. However, their arrangement was foreign, and it was this arrangement that the antibody recognized as part of an alien pathogen.



A molecular detail of the novel antibody.

Of all the known antibodies in the world, this was the first the researchers had seen with such a structure.

For his part, Wilson wondered if they weren't looking at some anomaly associated with the crystallization process. He and his colleagues spent the next year making sure they weren't.

"After we took a good look at its structure," Wilson says, "we spent a year making certain it wasn't a crystallization artifact. That was the painful part, verifying what we believed to be true—that the antibody had multiple binding sites that allowed it to bind to HIV with such high avidity."

During that year, Burton and his colleagues collected biochemical and biophysical data to support their belief in its unusual structure. Burton was largely convinced from the start: "What Ian was doing was good science. While I was somewhat surprised by the structure, I did think it was probably right. So many things fell into

place with that explanation—that it could recognize these sugars so effectively. Also, the mapping that we'd done suggested that the footprint of the antibody was bigger than a normal antibody and that made sense given this extended array of binding sites."

The announcement of their discovery, and the surrounding media coverage, brought comments from friends, colleagues, and even rivals.

All praised Burton and

Wilson's work as a milestone in HIV research. The scientists, especially Wilson, worried that even the most legitimate publicity would get blown out of proportion and ultimately hurt the entire HIV research effort by raising false hopes.

Because the truly difficult work lies ahead.

#### THE ROAD AHEAD

The trouble lies with the nature of HIV itself.

"The real problem with HIV is that it has taken the evolutionary process and speeded it up," Burton says. "Evolution generally occurs over thousands of years, but HIV evolves in days and that is hard to deal with. It's a dead piece of genetic material that can't survive outside of living cells, but it incorporates all kinds of evolutionary tricks to survive in the human body."

What usually happens over the course of evolution, Burton explains, is that a virus will adapt to its host. That seems to be what happened with monkey viruses similar to HIV, but when HIV jumped species it turned deadly and it will remain so for quite awhile. "Perhaps HIV will reach an evolutionary compromise with its human host," Burton says, "but we're not at that stage yet."

So, the search for a vaccine against the virus goes on. The public seems to understand the strengths and weaknesses of anti-viral drugs against HIV but perhaps not the magnitude of the vaccine challenge. "In HIV research, there's enormous pressure to come up with a vaccine," Wilson says, "because of the widespread belief that vaccines are not that difficult to make. But the classic approaches that work so well in polio and influenza don't work with HIV."

An HIV vaccine, by definition, will have to be completely different. The influenza virus mutates

almost as quickly as HIV but doesn't integrate with human DNA. HIV does, so what may be needed is sterilizing immunity—the absence of any infection of a human host cell by the virus. In other words, HIV is best combated outside the cell. Once it invades, HIV goes about eliminating T helper cells, immune cells that are needed to fight infections. As these helper cells die, even common pathogens can turn lethal.

Now with a neutralizing antibody like 2G12 as a template, vaccine development may be accelerated. But this is by no means the whole answer. The 2G12 antibody, while remarkable, appears to neutralize only 25 to 50 percent of the known strains of HIV, so it could contribute only part of any viable vaccine solution.

"With 2G12, we have a new paradigm for recognizing molecular clusters, a new prototype," Wilson says. "Now that we know the arrangement of sugars that the antibody recognizes, perhaps we can find the clues we need to decide how to proceed with a vaccine."

Both Burton and Wilson underscore the desperate need to solve the mystery of how this particular neutralizing antibody developed and the incredible difficulty of this task.

## MOVING AS QUICKLY AS POSSIBLE

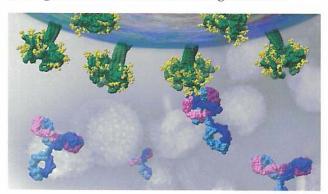
Perhaps the mystery could be solved more quickly if more people were working on these antibodies, Burton

argues thoughtfully. Despite the fact that interest in HIV antibodies has risen over the past few years, antibody research is still a slow process, as the crystallization of b12

shows. Burton says, "You can't always go as fast as you'd like because there are certain things that have to be done before you can move to the next step. You can't solve the structure until you crystallize the protein. Our first antibody took five years."

The task may be helped by a new group, the International AIDS Vaccine Initiative (IAVI), a consortium that combines the world's leading antibody experts with the financial resources and project management skills to get the job done. One of the primary goals of the consortium's five-year, multi-million dollar undertaking is to make sure that research moves as quickly as possible through cooperation and collaborative action.

As director of IAVI's Neutralizing Antibody Consortium, Burton sees his position as a catalytic one, helping to accelerate the whole field by encouraging the sharing of data and information on a global scale.



A model of how HIV-I neutralizing antibody 2GI2 is capable of recognizing a cluster of carbohydrate on envelope glycoproten gpI2O. (Image courtesy of Dan Calarese.)

"A lot of individual researchers are trying to make things go more quickly," Burton says of his consortium colleagues. "What you're seeing now is a sense that the problem is bigger than any of us. We need to share and get things to move more quickly."

The Scripps Research collaborative model may be a prototype for antibody research, the kind that both men want to see expanded.

"There are a lot of good ideas out there," Wilson says. "Dennis and I have a lot of ideas; our colleagues in the consortium have got good ideas as well. If you're

collaborating with experts in all areas, you can move the research along. For example, there were direct benefits of Dennis and I seeing the problem of 2G12 from different

angles. Working together, we can start to tackle the really difficult problems that lie ahead."

For Burton, the urgency of what he's doing is something palatable, a presence that he seems to carry around with him.

"We always have to remember that there is a major health issue here," he says, "a vaccine for AIDS. For me, that's the acid test. We can do a lot of nice science but we don't have time to sit around admiring our antibodies. We have to turn these antibodies into a vaccine. That's what I think about all the time so we keep pressing on."

You just have to keep beating on it because in the end, it *has* to work. 

Eric Sauter

"In HIV research, there's enormous pressure to

that work so well in polio and influenza don't

work with HIV." - Ian Wilson

come up with a vaccine... But the classic approaches

# Scripps Research Plans to Open Major Science Center in Palm Beach County, Florida

The Scripps Research Institute has announced plans to establish a major science center in Palm Beach County, Florida, focusing on biomedical research, technology development, and drug design.

The announcement comes after months of discussions with Florida Governor Jeb Bush and state and local leaders. The facilities and initial staffing for the new center will be supported by Florida state and local government.

Scripps Research will continue to operate and expand its activities and programs at its campus in La Jolla, California.

"Based on our history and experience in La Jolla, the extension of Scripps activities will increase the scope and depth of significant research in biomedical science," says Scripps Research President Richard A. Lerner, M.D. "The synergy between Scripps biomedical research in California and Florida is expected to lead to major new developments to improve human health."

The expansion is expected to boost Florida's economic development in biotechnology, just as the Scripps campus in La Jolla has served as the seeding ground and economic stimulus for the burgeoning bioscience industries in Southern California.

Approximately 40 companies have grown out of the institute's research and technology developments.

Governor Bush says, "Scripps is the brand name in biomedical research and we are honored they have chosen Florida to expand their current research facilities. Already known for breakthroughs for cancer and Alzheimer's disease, this new bi-coastal presence will bring even greater opportunities for life-saving and life-enhancing research."

Scripps Research will also collaborate with and support local industry and businesses, the university system, and school districts in the region, as it has done in San Diego.

Beginning in 2004, Scripps Research expects to occupy temporary laboratory space while it constructs a state-of-the-art, 364,000-square-foot facility to be occupied in 2006.

# Scripps Research and Oxford University Establish Joint Doctoral Program

Scripps Research and the University of Oxford have announced a joint graduate program in biology, chemistry, and biochemistry, named the Skaggs Oxford Scholarships Program.

This is the first time in its 800-year history that Britain's Oxford University has offered a degree jointly with another institution of higher learning. It is also the first such degree offered by Scripps Research.

The Skaggs Oxford Scholarships Program, named for supermarket and drugstore leader L.S. Skaggs and his wife, Aline, will support 10 students during a five-year program of study. Upon completion of the program, Skaggs Oxford Scholars will receive a doctoral degree from Scripps Research and Oxford University.

"It is an honor to be associated with Oxford University and its Department of Biochemistry," says Lerner. "Despite having quite different histories, our two institutions will now share a common path in this one regard—the education of the chemical biologists of the future."

"The Skaggs Oxford Scholarships create unique opportunities for multidisciplinary research and learning at the highest level," says Oxford University Professor Raymond A. Dwek, D.Phil., "The Department of Biochemistry at Oxford is one of the largest in the world with outstanding scientists in structural biology, cell biology, and molecular genetics, who welcome



On November 3, Florida Governor Jeb Bush signed a bill into law appropriating \$310 million to fund the opening of a Florida branch of The Scripps Research Institute. The Palm Beach County government will provide an additional \$200 million for the project.

The Scripps
Research
Institute's
2003 Highlights

# Campus News

these ties with Scripps Research and believe that many important research collaborations will result from these scholars having access to faculty on both campuses."

Chemical biology is an emerging interdisciplinary field that combines specialties including organic chemistry, biology, and biophysics. It seeks to find answers to some of the most pressing scientific questions of our day—such as discovering the identities, structures, and mechanisms of proteins and genes implicated in human health and finding ways to exploit this knowledge to develop drugs and treatments to alleviate human suffering.

Doctoral candidates selected as Skaggs Oxford Scholars will be enrolled at both institutions and spend two to three years studying biochemistry at Oxford University in the United Kingdom and two to three years exploring chemistry or biology at Scripps Research in La Jolla, California.



Oxford University and Scripps Research will offer a joint doctoral degree—a first in Oxford's 800-year history.

# Kellogg School Launches Restructured Graduate Program

The Kellogg School of Science and Technology at Scripps Research launched a restructured graduate program—the Scripps Research Doctoral Programs

in Chemical and Biological Sciences. The new program will offer Ph.D. candidates a wide range of courses and increased flexibility in course selection.

"[This program] will take advantage of Scripps Research's scientific strengths and will position our students to be leaders in science now and a decade from now," says Jeffery Kelly, dean of the program and vice president for academic affairs. "The new curriculum prepares students for a scientific environment that is ever-changing, fast-paced, and integrated across disciplines."

Previously, Scripps Research offered two largely independent graduate programs: Chemistry, and Macromolecular and Cellular Structure in Chemistry, which were ranked sixth and ninth in the nation, respectively, by U.S. News & World Report. In addition, Scripps Research's graduate programs were ranked second in the specialty of organic chemistry. Students who came to Scripps Research prior to 2003 will continue to fulfill these programs' requirements.

Beginning with the entering class, however, students will participate in the new Scripps Research Doctoral Programs in Chemical and Biological Sciences. In the new program, students will select from among four curricular tracks: Chemistry, Chemical Biology, Biology, and Biophysics. In addition, the students will meet new requirements designed to raise academic standards and further promote a well-rounded scientific education.

The review of the graduate program began about a year ago and involved input from more than 20 Scripps Research faculty and 170 graduate students. Student input was also sought and received in a town meeting format. Three meetings of the faculty group and four subcommittee meetings resulted in a proposal that was presented to the entire student body and faculty.

The proposal for curriculum changes was endorsed by a vote of the Scripps Research faculty and students and approved by the Western Association of Schools and Colleges.





Jeffery Kelly, dean of the Kellogg School of Science and Technology.

# "Riding the Tiger"

Excerpts from the 2003 Commencement Address





Distinguished scientist Daniel E. Koshland, Jr., Ph.D., gave the 2003 commencement address.

Twenty-nine young men and women of The Scripps Research Institute Kellogg School of Science and Technology were awarded Ph.D.s on May 16 in the institute's 11th commencement ceremony. Also receiving honorary degrees were businessman, philanthropist, and trustee John Moores and distinguished scientist Daniel E. Koshland, Jr., of the University of California at Berkeley, who gave the keynote address.

Following are excerpts from Koshland's remarks:

"It was the best of times; it was the worst of times." Those sentences in a Charles Dickens novel might well be applied to science today. Never have the frontiers of science been more extensive and more exciting, and never more relevant to our daily lives. Yet to read some headlines, all is gloomy.

Scientists are, from one point of view, the heroes who have brought us television, automobiles, modern medicine, and modern agriculture. From another point of view, scientists are the villains who have brought us television, automobiles, modern medicine, and modern agriculture. So today, at this memorable graduation, I'd like to discuss the fears, the fantasies, and the future of science.

There are stories on the oversupply of scientists and fraud in high places, and the accusations that scientists are cruel to animals and that they are responsible for pollution, cloning, and oat bran. That accumulation of horrors reminds me of a similar construction by a neighbor of Charles Darwin. A little boy who lived down the block decided he would fool the great naturalist. So he constructed with paste and scissors a bug with the body of a beetle, the legs of a spider, and the wings of a butterfly, and brought it to Darwin for identification. Darwin looked at it for quite a while, and then said to the boy, "I'm puzzled—does this bug hum?" The little boy was taken aback at the question, but said, "Oh, yes, it hums. I heard it myself." "Then," said Mr. Darwin, "I know what it is. It's a humbug."

And I believe the gloomy construction of the future

of science is also humbug. The funding of chemical sciences has never been higher; the number of problems that need solutions has never been greater; the amount of technological unemployment among chemists is less than one percent. It is true that society has funding problems, environmental problems, ethical problems, and medical problems. But the really terrible state, from the point of view of this class, would be if there were no problems. Then we wouldn't need you at all. So my generation has been kind enough, not only to give you an education, but also to produce problems for you to solve, and we expect you to be more productive and more effective than your parents or your faculty in solving them. Why do I say that? Because you are smarter or more diligent or wiser than we are? Certainly not. But you are certainly just as good, and you will have more powerful tools to work withbetter computers, better combinatorial chemistry, better molecular biology, and better nanotechnology....

But some of you will ask if we scientists are causing pollution and pesticides and increasing percentages of cancer are we really making progress or just replacing old problems with new ones? The answer is that we

are replacing old problems, but in solving old problems we are producing solutions that are so popular that we create new ones. There is an old Indian proverb: "He who

rides the tiger can never get off." Society has been riding the tiger of science and it can never get off.

The automobile is such a good replacement of the horse and buggy, there are now too many of them and we have traffic congestion and air pollution. The miracles of modern medicine are saving so many lives and the miracles of modern agriculture are feeding so many people that we have an overpopulation problem. Those are big problems and more science is going to be needed to solve them....

Similarly, improved agriculture by genetic engineer-

ing, which was called "crop selection" in previous eras, has many more people living healthier and longer. Today, we are providing food on an acreage one sixth of that we would have required with the old fashioned crops before genetic selection—extra land that can be used for habitats and parks or houses and high rises,



Koshland called on members of the Class of '03 to do their part in making the world better than it is today.

but nevertheless extra land provided by science which society must decide how to use....

That brings us to the future, and that future belongs to you, the Class of '03. You won't solve all the problems, but we expect you to do your bit at making the

world better than it is today. There is a little matter, like getting a job. But what you will accomplish will largely depend on your own motivation. The optimist says, "This

is the best of all possible worlds," and the pessimist says, "I'm afraid you're right." What we need is neither an extreme optimist who thinks all is well, nor an extreme pessimist who despairs, but a scientific activist who says, "Let's get going!"

There are massive problems that need solutions—waste disposal, diseases of old age like arthritis and Alzheimer's, plagues like the Ebola virus, SARS, and AIDS—and more science is clearly needed for each of these. Society is not yet ready to get off the tiger of science and we will need the Scripps Class of '03 to help.

"What we need is neither an extreme optimist

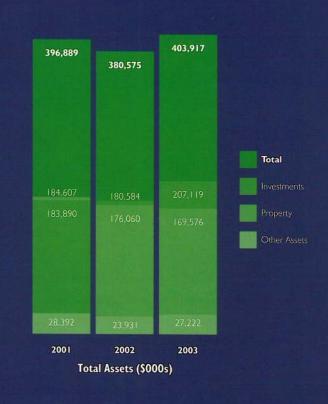
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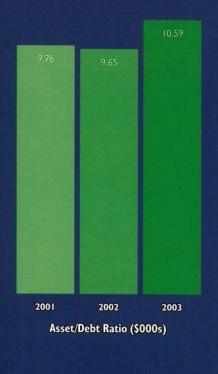
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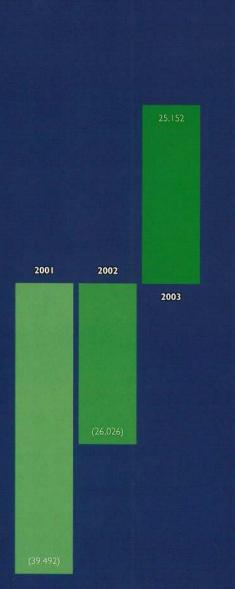
'Let's get going!" - Daniel E. Koshland, Jr.

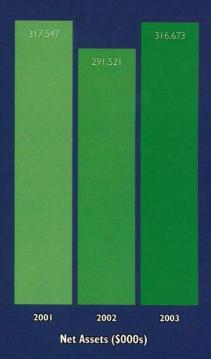
# Financial Highlights Years ended September 30











Net Income (\$000s)

# Development Report

Dear Friends

The year 2003 marked a noteworthy collaboration that clearly demonstrates the importance of private philanthropy to The Scripps Research Institute. Scripps Research established a joint graduate program in biology, chemistry, and biochemistry with Oxford University. This Skaggs Oxford Scholarships Program marks the first time in its 800-year history that Britain's Oxford University has offered a joint degree with another institution of higher learning. It is also the first such degree offered by Scripps Research. This new initiative was made possible by the generosity of L.S. and Aline W. Skaggs.

The Skaggs Institute for Research, a charitable foundation created by the Skaggs in 1996, is Scripps Research's largest benefactor and to date has provided grants of more than \$75 million to fund the Skaggs Institute for Chemical Biology, as well as graduate, postdoctoral, and clinical research programs.

Creating new opportunities for collaboration and forging new areas of research require the spirit of innovation and funding. Private philanthropy provides a critical source of funding that fuels the entrepreneurial drive of scientists to constantly seek new directions in research.

The following pages reflect those who have contributed gifts supporting biomedical research or educational and community programs at Scripps Research in 2003, as well as individuals who have informed us they have included the institute in their estate plans.

We are indeed fortunate to have such committed partners who understand the value of basic scientific research and its application towards diagnosis, prevention, and treatment of disease. It is your support that makes breakthroughs in basic research and our innovative educational and community programs possible.

The support of our philanthropic community has always been a key element in our ability to rapidly respond to emerging priorities in science and medicine. You have our deepest gratitude for being a part of that philanthropic community.

Sincerely

Charles C. Edwards, M.D.

Chair of the Development Committee

The Scripps Research Institute Board of Trustees

Mark C Mund

Friends of The Scripps Research Institute have demonstrated time and time again how their kind actions of generosity impact the institute's ability to remain at the forefront of cutting-edge basic biomedical research. On the following pages, we recognize those who have contributed to our success this year. We give special recognition on the sidebars to some of the people and organizations who have shown how private philanthropy carries forward the work of Scripps Research scientists and educational and community programs.

# Major Donors to The **Scripps Research Institute**

#### SPECIAL ACKNOWLEDGMENT

The following are those individuals and organizations who, over the years, have given \$1 million or more in support of investigations at the research institute. We specially honor them and recognize their dedication to the advancement of medical science.

Aline W. and L. S. Skaggs/ The ALSAM Foundation -The Skaggs Institute for Research American Cancer Society, Inc. American Heart Association Anonymous (17) Gordon M. Anderson Charitable Lead Trust Arthritis Foundation Donald E. and Delia B. Baxter Foundation Dr. and Mrs. Arnold O. Beckman Arnold and Mabel Beckman Foundation Becton Dickinson and Company Cancer Research Institute, Inc. The Council for Tobacco Research Mr. and Mrs. Richard A. Cramer Cytel Corporation Damon Runyon Walter Winchell Cancer Research Foundation

Harold L. Dorris Neuroscience

Helen L. Dorris Foundation

Ellison Medical Foundation

Mr. Walter Fitch III

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rosity of the many friends of The Scripps Research Institute who contributed during Graduate Education | The Fletcher Jones Foundation has continued its tradition of philanthropy at Scripps Research by permanently endowing a second fellowship for a first-year graduate student enrolled in the Kellogg School of Science and Technology. The foundation was established in 1969 by Computer Associates founder Fletcher Jones just two years before his untimely death. Endowments for the graduate program are an important means of supporting future scientists during their first year of graduate studies.

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Tradition | Claudia Skaggs Luttrell continues the tradition her family established at Scripps Research by serving as a member of the Board of Trustees. Her belief in the efficacy of the Skaggs Oxford Scholarships Program is demonstrated by her willingness to serve as the board's chair for this newly established and historic program supporting the education of the chemical biologists of the future.

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Legacy | Donors Jack and Deanna Hanes and the late Robert Kahse and Virginia Kahse made noteworthy decisions long ago to designate proceeds from their estates to fund basic scientific research at the institute in perpetuity, making a difference for the betterment of health and the human condition for generations to come. The Hanes and the Kahses are recognized as members in the Scripps Heritage Circle who have arranged for the future philanthropic support of the institute as part of their estate plans.

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Vision | Mark Pearson set out to find an institute partner to provide opportunities to conduct research across scientific domains in the pursuit of treatments for alcoholism. After visiting several other renowned facilities, he made the decision that Dr. George Koob and Dr. Barbara Mason of the Scripps Research alcohol center were at the forefront of innovative, multidisciplinary approaches to medication development for the treatment of alcoholism with a focus on the prevention of relapse. The Pearson Center for **Alcoholism and Addiction Research** at Scripps Research will work to fulfill his vision of a day when an alcoholic can move forward to a life that is free of alcohol consumption.

Mr. and Mrs. Philip J. Bergmann

In Memoriam | Helen Sachs was a strong believer in the importance of basic and clinical research and she appreciated the idea of "bench to bedside" research. She is supporting vital medical research beyond her own lifetime by the gift of half of her home to Scripps Research. Her generous contribution will help further medical progress that will benefit many future generations. She will be missed.

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Foresight | In 1987, the late Lita Annenberg Hazen funded an endowed professorship in immunochemistry at Scripps Research. With remarkable foresight, she made another significant gift a couple of years later to establish the Lita Annenberg Hazen Science Center at the institute. Her gift helped provide for the expansion of the Scripps Research campus to the east side of Torrey Pines Road, a critical move for the future of the institute's basic research efforts especially given the growth of the biotechnology industry on the Torrey Pines mesa. Today, the Lita Annenberg Hazen Foundation under the leadership of Mrs. Hazen's daughter, Cynthia Polsky, continues to be a strong institutional ally through its support of the Lita Annenberg Hazen Professorship in Chemistry held by Vice President of Academic Affairs and Dean of the Kellogg School of Science and Technology Jeffery Kelly, Ph.D.

Ms. Beverly P. Cohan

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Trustee Ralph Shapiro and his wife, Shirley,
have endowed a position in the Scripps

Research Summer Research Internship

Program—once again enriching the

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that at least one undergraduate student
participate in an Education Outreach

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will enable young people, especially
women and minority students, to come
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# **Opportunities for Giving**

### UNRESTRICTED FUNDS

The success of any research institution rests in its ability to identify promising new research programs in their infancy. Unfortunately, new programs generally do not qualify for federal grant support until they are fully developed. Similarly, young scientists who have not yet achieved prominence are also at a disadvantage in competing for grants. Their search for funds can delay their work and inhibit them from striking out in new directions. Consequently, unrestricted gifts constitute one of the most valuable resources for the institute as they allow the underwriting of important new projects that might not otherwise receive funding.

Giving Opportunities Gifts of all sizes are welcome. Contributions of \$1,000 or more entitle a donor to annual membership in The Presidents' Council.

## IMMUNOLOGY DEPARTMENT BUILDING

In 1961, the Department of Experimental Pathology was the cornerstone of the newly established Scripps Clinic and Research Foundation. With the arrival of Dr. Frank Dixon Jr., this department began investigations in the fledgling field of immunology that would be the genesis of The Scripps Research Institute.

In just a few decades, Scripps Research has become one of the preeminent leaders in the field of immunology. The scope of study has grown dramatically—from basic research in the 1960s to groundbreaking investigations into diseases affecting millions of people worldwide. Diseases such as diabetes, cancer, septic shock, Ebola, arthritis, lupus, multiple sclerosis, tuberculosis, hepatitis C, prion disease, and blood disorders such as HIV are but a few that come under the scientific investigation of the one of the largest immunology research departments in the world. At the same time, the department has expanded its work into early clinical development, giving Scripps Research scientists an even greater opportunity to aid patients directly.

Scripps Research has a one-time opportunity to purchase the building that houses the Department of Immunology at a price below current market value. The building, which has been leased by Scripps Research since 1980, is the southern anchor to the main campus and houses the institute's oldest and largest department, the Department of Immunology, comprising some 60 faculty, 100 postdocs, and 340 staff members. Since 1980, the Immunology Building has been home to world leaders in unlocking the secrets of the complex human immune system and in developing potential treatments for various global killers.

A naming gift will assure a donor a high level of recognition in the world of biomedical science.

**Giving Opportunities** Gifts of all sizes are welcome. Naming opportunities are available as follows:

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## INSTITUTE FOR CHILDHOOD AND NEGLECTED DISEASES

The Institute for Childhood and Neglected Diseases at The Scripps Research Institute applies the new molecular understanding of biology to address, reduce, and successfully treat illnesses in two major categories—childhood diseases, including childhood cancers, and neglected diseases that affect populations primarily in developing countries.

The time has come to apply the burgeoning knowledge of genes to specific childhood and early-onset diseases. For a number of years, researchers have attempted to use new therapies like gene therapy against many of these diseases—cystic fibrosis and muscular dystrophy, for example, and certain forms of cancer. Unfortunately, none of these efforts has led to consistent success. But in each case, there is reason to believe that the work done thus far has laid the groundwork for approaches that will succeed. And in other cases, such as autism, scientists are only now uncovering genetic clues that might lead to better treatments.

The majority of the world's population lives in developing countries, and has yet to reap the benefits of the genetic revolution. As biologists have begun to learn how human genes function, they also have begun to investigate the genes of parasites and other disease-causing organisms. The Institute for Childhood and Neglected Disease will build on Scripps Research's previous successes, and will use the latest advances in biology to help vanquish parasitic diseases.

Giving Opportunities Gifts of all sizes are welcome. Some naming opportunities are still available. A commitment of \$150,000 will establish a senior research fellowship that supports the work of a senior scientist for two years at the institute. A commitment of \$75,000 will support a laboratory that will bear the name of the donor or loved one.

# THE HELEN L. DORRIS INSTITUTE FOR THE STUDY OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS OF CHILDREN AND ADOLESCENTS

The Helen L. Dorris Institute for the Study of Neurological and Psychiatric Disorders of Children and Adolescents was recently established with another generous gift from mental health advocate and San Diego State University professor emeritus Helen L. Dorris. This new initiative was launched to uncover the pathological basis of neurological and psychiatric disorders and to enable therapeutic approaches to be developed. Benjamin Cravatt, Ph.D., director of the new institute, will be leading the effort to recruit an interdisciplinary team of scientists to focus on understanding neuropathology in children and adolescents.

Giving Opportunities Gifts of all sizes are welcome. A commitment of \$150,000 will establish a senior research fellowship that supports the work of a senior scientist for two years at the institute. A commitment of \$75,000 will support a laboratory that will bear the name of the donor or loved one.

## **FACULTY CHAIRS**

An endowment gift to establish a named faculty chair at Scripps Research is one of the most meaningful, and lasting, gifts available to the private donor. Such a gift perpetuates the donor's philanthropy by creating a permanently funded position, named by or for the donor, which may be occupied in succession by major figures in the world of biomedical science. The benefits far outlast the life of the donor, and will be enjoyed by successive generations of family members.

**Giving Opportunities** Gifts of all sizes are welcome. A commitment of \$1,500,000 will establish a senior faculty chair bearing the name of the donor or loved one. A

commitment of \$2,000,000 will establish a named faculty chair to be occupied by a dean, director, or department chair.

### SENIOR RESEARCH FELLOWSHIPS

Sometimes the implications for discoveries in basic research are unknown. Often, though, discoveries by geneticists, neuroscientists, immunologists, and other basic scientists become the foundation for the most important breakthroughs in medical treatments and diagnostic technologies.

A gift to fund a senior research fellowship provides a scientist with the opportunity to pursue new directions that would have been otherwise left uncharted and could possibly lead to better therapeutics and medical advances. Funding a senior research fellowship would also be a great way of participating in one of the great scientific adventures of our time.

Giving Opportunities Gifts of all sizes are welcome. A commitment of \$75,000 or more will establish a senior research fellowship that supports the work of a faculty member or a senior scientist for one year. A gift in the amount of \$1,250,000 or more will endow a senior research fellowship ensuring the ongoing funding of a scientist's research work or initiative.

# HAROLD L. DORRIS NEUROLOGICAL RESEARCH CENTER

The Harold L. Dorris Neurological Research Center was founded in 1999 as the result of a major naming gift and long-term commitment by the Harold L. Dorris Foundation under the direction of Helen L. Dorris.

The center is dedicated to conducting research and education into neurological disorders, including schizophrenia and Alzheimer's disease, as well as advancing knowledge of the process of aging of the brain. The center has attracted an international cadre of brain scientists, led by Tamas Bartfai, Ph.D. Dr. Bartfai is former head of central nervous system research at Hoffman-LaRoche in Basel, Switzerland, and former chairman of the Department of Neurochemistry and Neurotoxicity at Stockholm University.

The center seeks contributions to supplement the original gift of \$10,000,000 to recruit additional senior faculty, establish named fellowships, and create visiting professorship appointments.

Giving Opportunities Gifts of all sizes are welcome. A gift of \$1,500,000 will permanently name and support faculty chairs while a gift of \$1,250,000 will endow and name a senior research fellowship and a gift of \$50,0000 will establish a visiting professorship. Specific program funding in the range of \$50,000 to \$300,000 for new scholars is also a priority.

## THE KELLOGG SCHOOL OF SCIENCE AND TECHNOLOGY

The Scripps Research Institute, with its emphasis on individualized instruction, adherence to the highest scientific standards, and reputation for research excellence, provides an unparalleled environment for advanced study and outstanding preparation for successful careers in science.

In 1989, Scripps Research established a Ph.D. program in Macromolecular and Cellular Structure and Chemistry. A second Ph.D. program in Chemistry was established three years later to focus on synthetic and bio-organic chemistry. In 2003, the institute restructured the program to provide its students with a wide range of courses and increased flexibility in course selection. The new program is referred to as the institute's Doctoral Programs in Chemical and Biological Sciences. The program provides an exceptional training opportunity in a unique learning environment for a select group of outstanding and intellectually diverse students.

In honor of their extraordinary contributions to science and education, Scripps Research named its graduate college "The Kellogg School of Science and Technology" for philanthropists Janet R. ("Jean") Kellogg and W. Keith Kellogg II.

Giving Opportunities Gifts of all sizes are welcome. A gift of \$24,500 will name and support a graduate stipend for one year. A commitment of \$425,000 will endow a graduate student stipend in perpetuity. A commitment of \$10,000,000 will endow the graduate program.

# **EDUCATIONAL OUTREACH PROGRAMS**

As one of the country's leading basic biomedical research institutions, The Scripps Research Institute has made a commitment to the local science education community. The institute is using its intellectual and material resources to expose high school and undergraduate students and middle and high school science teachers to contemporary issues in biomedical research and intensive, hands-on

laboratory experiences, as well as to encourage students to pursue careers in the biological and chemical sciences. These multifaceted Educational Outreach Programs represent a cornerstone of the institute's commitment to training the next generation of scientists and perpetuating scientific knowledge.

At this time, the capacity of the Scripps Research summer internship program has grown to as many as 40 slots. With the demand and popularity of this program in local high schools, one of the limiting factors for filling these slots is availability of funding.

Giving Opportunities Gifts of all sizes are welcome. A contribution of \$2,500 supports the participation of one high school or undergraduate student in the summer internship program. A contribution of \$5,000 supports the participation of one middle or high school teacher in the summer internship program. A contribution of \$1,000,000 can name and endow the entire program.

#### **ENDOWMENTS**

The Scripps Research Institute seeks to enhance its endowment base from private contributions to provide ongoing income each year that can complement federal support. An endowment gift is one of the most meaningful, and lasting, gifts available to the private donor. The benefits far outlast the life of the donor, and will be enjoyed by successive generations of family members.

Giving Opportunities Gifts of all sizes are welcome. A gift of \$1,500,000 or more will permanently name and support a senior-level faculty position while a gift of \$2,000,000 will establish a named faculty chair to be occupied by a dean, director, or department chair.

Other endowment opportunities exist throughout the institute's departments and centers. Specific programs and needs within our Educational Outreach Programs can be endowed with gifts of \$100,000 and up.

# **EQUIPMENT ACQUISITION**

Scripps Research enjoys one of the world's leading private computational capabilities with an array of computers, including a Cray supercomputer. Research is further supported by x-ray crystallography laboratories, high performance NMR spectrometry including state-of-the-art 900 and 750 MHz instruments, electron microscopy, optical spectroscopy, a centralized DNA

sequencing laboratory, and a fluorescence activated cell-sorting facility. Scientists are able to make new discoveries and advances in research with the help of modern technology.

Scripps Research scientists require state-of-the-art facilities and equipment to remain on the cutting edge of research and rapidly changing technology. New laboratory equipment and tools are constantly being developed to improve the efficiency and effectiveness of the scientists. Gifts of discretionary funding are needed to support the continuous modernization of laboratories and equipment at the institute.

Giving Opportunities Gifts of all sizes are welcome.

# THE KRESGE LIBRARY

Gifts of discretionary funding are needed to fund the revamping of the Kresge Library. The library's furnishings, specifically its study carrels and chairs, have served students and faculty since the 1970s and are in need of replacement.

Giving Opportunities Gifts of all sizes are welcome.

# Gifts to The Scripps Research Institute

Gifts to The Scripps Research Institute provide the assurance that the institution will continue its mission of striving for excellence in biomedical research. Unrestricted gifts are particularly useful as they can be applied to programs and areas of urgent need. Gifts may also be designated for specific purposes, such as research, educational programs, or equipment. They may also be made in tribute to or in memory of a relative or friend.

# GIFTS OF CASH

An outright gift of cash is usually the simplest method of giving. It is not subject to gift or estate taxes, and you can deduct the gift amount from your federal income tax return up to 50 percent of your adjusted gross income. Should the gift total exceed your gift ceiling for that year, you can carry over the remaining deduction to succeeding tax years. This means that with careful planning, nearly every outright gift to Scripps Research can be fully deducted.

### **GIFTS OF SECURITIES**

Giving appreciated stocks or bonds is a superb way to show support for the institution. You can deduct the full fair market value of long-term appreciated securities, and avoid any tax on the capital gain. A gift of securities is deductible up to 30 percent of your adjusted gross income, with the five-year carry-over option. Under certain circumstances, however, you can choose to qualify for a 50 percent annual deduction by reducing the value of your gift by 100 percent of the appreciation in the contributed property—that is, to the cost basis.

## GIFT OF REAL ESTATE

Almost any type of real property—a personal residence, a farm, a vacation home, a commercial building, or an undeveloped parcel of land—can constitute a gift. A gift of real estate can be made either outright or through other methods.

If the property has appreciated in value and is given outright, you will avoid any tax on the capital gain, reduce your taxable estate by the value of the gift, and receive a charitable contribution deduction for 100 percent of the fair market value of the property. Your actual income tax savings will depend on your tax bracket. You may deduct the value of the gift up to 30 percent of your adjusted gross income. Under certain circumstances, however, you can choose to qualify for a 50 percent annual deduction by reducing the value of your gift by 100 percent of the appreciation—that is, to the cost basis.

# GIFTS OF RESIDENCE

The tax laws enable you to donate your personal residence or ranch and still live there for the remainder of your life. Furthermore, you can stipulate that your spouse may live there for his/her lifetime, or you may continue to live on the property for a set number of years. Either way, you will receive an immediate income tax deduction for the contribution.

The property does not have to be your primary residence—it can be a vacation or second home. Further, you do not have to reside on the property. You can also give stock in a cooperative apartment if the apartment is used as a primary residence.

The charitable deduction is less than the full value of the property and equals the value of the remainder interest given to Scripps Research. There are also charitable deductions available for estate or gift tax purposes if the life interest is given to one or two individuals and the remainder interest given to charity.

# GIFTS OF UNDIVIDED INTEREST IN PROPERTY

You are allowed a charitable deduction for the value of an undivided portion of your entire interest in a property. This consists of a fraction or a percentage of each substantial right or interest in the property. The fraction must extend over the entire term of your interest.

#### GIFT BY BARGAIN SALE

This entails transferring ownership of an appreciated asset (real estate, securities and the like) to Scripps Research. In return, the institute would pay an agreed-upon amount that is less than the full fair market value—usually your original cost. Essentially, you are selling your asset to Scripps Research for less than its fair market value, so the transaction is part gift and part sale.

You might want to consider this method if the current value of the property exceeds the amount you wish to give or if it is not practical or economical to divide the property. You are entitled to a charitable deduction based on the difference between the sale price and the full fair market value. You incur tax only on the part of the appreciation attributable to the sale.

## GIFT OF LIFE INSURANCE

You may reach a point where life insurance no longer has the financial significance for your family that it once did. In that case, you may wish to make a gift of the policy to Scripps Research. There are two ways to do this.

First, you may make Scripps Research the owner of the policy. This allows you an immediate income tax deduction. If the policy is fully paid, your deduction is equal to the replacement value of the policy unless that value exceeds the tax or cost basis. If premiums remain to be paid, the deduction is approximately equal to the cash surrender value. If you continue to pay the premiums on such policies, you will be entitled to a charitable contribution deduction. Or you may wish to contribute the amount of the premiums to Scripps Research; Scripps Research, in turn, could pay the premiums. As long as

the institute is not under any obligation to pay the premiums, your contribution would be fully deductible.

Secondly, you also may name Scripps Research as the beneficiary of your policy. Since the designation is revocable, it cannot be counted for any immediate tax savings. At your death, however, your executor may take federal estate tax charitable deduction for the entire amount.

Life insurance interacts well with other gift mechanisms. For instance, you can use all or part of your trust or annuity income to establish an irrevocable life insurance trust. The trust could purchase insurance on your life—perhaps an amount equal to the charitable gift—and you could name a spouse or child as the beneficiary. This way you can make a charitable gift and replace the assets with life insurance for the benefit of a loved one.

Alternatively, you could take all or a portion of the income for a set term of years and purchase a universal life insurance policy naming a family member the beneficiary. This is another excellent way to replace the wealth transferred to charity.

## LIFE INCOME GIFT

Another way to make a gift to Scripps Research is to transfer property (e.g., cash, securities, real estate) to the management of a trustee (for example, Scripps Research as an independent agent), and establish a life income arrangement. After the lifetimes of the beneficiaries, Scripps Research receives the assets in the trust. Life income trusts provide many benefits to you as a donor: an income tax charitable deduction, a reduction in estate taxed, avoidance of capital gains taxes, freedom from investment worries, and, of course, income for life.

There are several types of life income arrangements for different circumstances: unitrust, annuity trust, pooled income fund, gift annuity. Information about each gift arrangement is readily obtained from the Development Office at Scripps Research.

# **GIFT IN TRUST-WEALTH TRANSFER**

A trust may be funded with property (e.g., cash, securities, real estate). The terms of the trust will provide for specific payments to Scripps Research for a number of years, after which time the property is passed to a relative or friend of the donor. The donor receives sizeable estate

and gift tax advantages, and Scripps Research immediately receives funds for its programs. This arrangement is called a lead trust.

#### CORPORATE MATCHING GIFT

Many companies encourage philanthropic giving among their employees by offering to match an employee's gift with a corporate contribution. Donors interested in this opportunity should obtain the necessary matching gift form from their employer (usually the personnel office).

# GIFT BY BEQUEST

One of the easiest and most common ways to make a gift to Scripps Research is through a bequest in your will. The tax laws encourage bequests; consequently, a bequest is an excellent way to support the institute's programs. Bequests work particularly well for those who are unable to make an immediate outright gift, but would like to aid Scripps Research in the future. There are several types of bequests:

- Specific bequests take the form of an outright gift of money, securities or other property.
- With a residuary bequest, Scripps Research can receive the residue of your estate after all other bequests have been made.
- A contingent bequest takes effect only in the event that all other bequests, for whatever reason, fail.
- A bequest may also take the form of a testamentary trust; to receive the tax benefits, however, the trust must either be solely for charity or be a qualified charitable remainder or lead trust.
- When you make a bequest to Scripps Research, your taxable estate is reduced by a 100 percent deduction for the amount of a cash bequest, or the fair market value of appreciated assets.

This deduction results in tax savings whenever the taxable estate—after other deductions—exceeds the amount offset by individual estate tax credits. Because the estate tax rate schedule is progressive, the larger the taxable estate, the greater the potential tax savings per dollar given.

For more information regarding any of these ways of giving, please contact:

The Scripps Research Institute Development Office 10550 N. Torrey Pines Road Mail Drop TPC-2 La Jolla, CA 92037 (858) 784-9367 (800) 788-4931 (858) 784-2608 FAX

# **Benefits of Giving**

## SCRIPPS PRESIDENTS' COUNCIL

Founded in 1984, the Scripps Presidents' Council was created to serve two basic objectives: first, to provide a perpetual source of private resources for new and ongoing medical and research programs; and second, to provide a medium for sharing the excitement of our programs with those who invest in these undertakings.

Annual membership in the Scripps Presidents' Council is extended to individuals who contribute \$1,000 or more in a given year. Gifts may be earmarked for either specific research purposes, or left undesignated for use where the need is greatest.

Special privileges unique to the Scripps Presidents' Council are extended to all members:

- On request, personal assistance from a member of the Scripps Research Development Office in obtaining information or medical services at a Scripps Health hospital
- · A yearly report outlining the impact of donors' gifts
- An invitation to The Scripps Presidents' Council Special Event, an exclusive annual gathering
- Special invitations to scientific briefings, receptions, and lectures, where fellow members meet to learn more about the vital work their contributions support
- The Scripps Foundation Annual Report, which includes a listing of all Scripps Presidents' Council members
- Selected press releases on topics of general interest to help keep members informed about news-worthy activities at Scripps Research
- The Scripps Foundation quarterly newsletter update, which discusses developments at Scripps Research, the latest clinical procedures available to Scripps Hospital patients, and overall advances made at Scripps Research and Scripps Health
- The Scripps Research publication *Endeavor*, which covers scientific progress, awards, and publications, as well as *Endeavor Year In Review*, which recognizes supporters of Scripps Research.

#### SCRIPPS LEGACY

The Scripps Research Development Office also recognizes lifetime cumulative giving at the following levels:

Associate

\$25,000 - \$99,999

Advocate

\$100,000 - \$249,999

Ambassador

\$250,000 - \$499,999

Sponsor

\$500,000 - \$999,999

Guarantor

\$1,000,000 - \$2,499,999

Patron

\$2,500,000 - \$4,999,999

Benefactor

\$5,000,000 - \$9,999,999

Founder

\$10,000,000 - \$49,999,999

Laureate

\$50,000,000 or more

Additional benefits include:

 Name listed on the Scripps Foundation's Annual Report on Philanthropic Support.

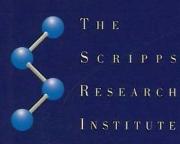
Those giving at the Advocate level or above also receive:

 Name recognition on the Honor Roll Boards in the lobbies of all Scripps Health Hospitals.

And, of course, the satisfaction members receive from knowing they have personally contributed to the advancement of medical knowledge through their gifts.

If you are interested in joining the Scripps Presidents' Council or the Legacy Program, please contact:

The Scripps Research Institute Development Office 10550 N. Torrey Pines Road Mail Drop TPC-2 La Jolla, CA 92037 (858) 784-9367 (800) 788-4931 (858) 784-2608 (FAX)



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