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INSTITUTE UPDATE

Scripps Research Holds 15th Commencement

> In a joyful ceremony, The Scripps Research Institute celebrated its 15th commencement in May, graduating 27 Ph.D. students—among them the first from Scripps Florida.

Speaking at the event was University of California, San Diego (UCSD) Chancellor Marye Anne Fox, who also received an honorary degree.

After a colorful procession of students and faculty across the ocean-side La Jolla, California campus, Scripps Research President Richard Lerner offered welcoming remarks and Professor Jeffery Kelly, dean of graduate studies, spoke about the Scripps Research Kellogg School of Science and Technology, emphasizing its reputation for excellence.

Kelly noted that, from its inception, the Scripps Research program was able to attract the very best students because of the power of its mission—to train the next generation of scientists as individuals capable of bringing together the principles of various scientific disciplines, in Kelly's words, "the skill set required to solve the complex problems of today and especially tomorrow."

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Inside:

RESEARCH UPDATE

New "Checkmate" Method Provides Powerful New Tool for Preventing Spread of Future Epidemics

Novel Scripps Research Approach Could Help Efforts of Scientists Worldwide

Dr. Richard Lerner

> Scientists from The Scripps Research Institute have developed a breakthrough methodology that can be used to rapidly predict how viruses such as avian influenza H5N1, a dangerous strain of "bird flu," will mutate in response to attacks by the immune system.

The new approach, dubbed "checkmate analysis," may also predict which antibodies or small molecule therapeutics will best neutralize these viral mutations before they can develop into global epidemics.

In a high-powered collaboration, **Richard A. Lerner, M.D.,** president of The Scripps Research Institute, **Sydney Brenner, M.B.B.C.H., D.Phil.,** recipient of the 2002 Nobel Prize in Medicine and a faculty

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The continuing quality of the program is confirmed by stellar rankings from various organizations, including *U.S. News & World Report,* which has released its latest report on the nation's graduate schools. The publication again ranked the Kellogg School among the top ten programs in both biology and chemistry. (The Scripps Research program was ranked sixth overall in the country for chemistry, with the specialties of biochemistry and organic chemistry also each ranking sixth; the program was ranked seventh in the nation for biological sciences, with specialties of cell biology ranked 15th, and molecular biology, 12th, respectively.)

Compared to other prestigious graduate programs, the Kellogg School is a young upstart, having opened its doors in 1989. Since then, the Kellogg School program has expanded greatly in both size and reputation. The Kellogg School currently trains more than 225 doctoral students, who attend classes, complete lab rotations, and write a dissertation that offers an original contribution to their field. The school can now boast of 279 accomplished alumni, including the 2007 graduates.

"It is important to note that many of the major scientific discoveries that come out of this institute are work of graduate students—something that makes us feel enormously proud," said Kelly. "Extraordinary quality… is the standard and hallmark of this program."

Now, those affiliated with the Kellogg School can also be proud of the accomplishments of students from the program's Palm Beach County, Florida branch. Porino Va—the first graduate from Scripps Florida—was among those taking part in the 2007 commencement ceremony.

"The first student to complete the requirements for the Ph. D. degree at Scripps Florida… is a milestone event for Scripps Florida and the Kellogg School of Science and Technology," noted William Roush, professor, executive director of Medicinal Chemistry, and associate dean for Florida graduate studies.

The establishment of graduate education at Scripps Florida has been a key goal for the graduate program and for Scripps Flordia. In 2005, several students (including Va) transferred to Scripps Florida from the University of Michigan with Roush's lab. In 2006, the Kellogg School accepted its first new student to the Florida campus. And, in the fall of 2007, two new students are scheduled to begin graduate studies in Florida.

Va, who completed his dissertation on the stereocontrolled total synthesis of amphidinolide E and three additional amphidinolide stereoisomers, is delighted with his decision to complete doctoral work at Scripps Florida.

"I feel very fortunate to have the honor of being Professor Roush's first Scripps Florida Ph.D. graduate," he said in the days leading up to graduation. "The facilities and the science being conducted at Scripps Florida are truly world-class. It is really exciting to be a part of the genesis of a new research institution and I am certain that a few years from now, Scripps Florida will be even more recognizable for its novel discoveries in science."

As the ceremony continued, Fox—a physical organic chemist who is UCSD's seventh chancellor and the first woman to be permanent chancellor of that institution—stepped up to the podium to congratulate the graduates and address the audience.

"You are a very diverse graduating class," she said to the graduates. "You are from all over the United States and abroad, including Germany, China, Canada, Korea, Taiwan, and Switzerland. Before arriving at [Scripps Research], you studied at MIT, Peking University, and Penn State, among other elite institutions. But something brought all of you together here—your love of science."

Kellogg School graduates go on to work in both academia and industry. Members of this year's class will hold positions at institutions including: McKinsey & Co., Merck & Co., Memorial Sloan-Kettering Cancer Center, Columbia University, Washington University, Korea Institute of Science and Technology, Dynavax Technologies, Achaogen, and Harvard University.

A joyful ceremony

member of The Salk Institute for Biological Studies, **Tobin J. Dickerson, Ph.D.,** assistant professor of chemistry at Scripps Research, and several Scripps Research colleagues developed the methodology. Because of its simplicity and low cost, this innovative approach will be accessible to scientists around the world.

To date, new vaccines and other treatments have been designed against what the virus has done rather than what it might do —but the new methodology devised by Lerner, Brenner, Dickerson, and colleagues could change that.

"Our new 'checkmate analysis' allows scientists to explore all the possible routes that a virus might take to escape an immune response or a small molecule therapeutic," Lerner said. "The result is a detailed chemical map of the trajectories of viral escape and antibody response."

During the course of an infection, new viruses and new neutralizing antibodies are selected and discarded, as the microbe and the host struggle for dominance. During this process, the immune system operates largely in a reactive mode instead of anticipating the next viral mutation. To date, new vaccines and other treatments have also been designed against what the virus has done rather than what it might do —but the new methodology devised by Lerner, Brenner, Dickerson, and colleagues could change that.

The new method starts with large libraries of mutant viral proteins and antibodies that are expressed on a phage surface. (Phages, also called "bacteriophages," are single-stranded DNA viruses, which infect only bacteria.) These two factions are then used to challenge each other.

Because this approach is both simple and inexpensive, the new methodology is within reach of almost any biomedical laboratory on the planet.

"Currently, high-throughput screening is limited to those who have access to expensive equipment," Lerner said. "This work will put high-throughput screening into the hands of the worldwide scientific community."

That was the idea from the start, according to Dickerson. "We envisioned that this could be utilized in almost any environment—in a field laboratory in the Arctic or a research hospital in Africa," he said. "That's the real power of these findings, that we've reduced everything to a simple bacteriophage assay."

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Scripps is already noted for its pioneering work in combinatorial antibody libraries. But, before this study, no one had succeeded in expressing functional viral proteins on phages. While methods for generating combinatorial small molecules and antibody libraries were well established, the expression of functional viral proteins on phages posed additional challenges. These proteins are frequently assembled in cell membranes and often composed of various subunits, as is the case with hemagglutinin (HA), a glycoprotein on the influenza virus surface that binds the virus to infected cells.

Lerner, Brenner, Dickerson, and colleagues bridged this technological gap using some elegant chemistry to design a new system, which they then successfully applied to expressing hemagglutinin on the phage surface.

A sample protocol, the study suggested, might involve starting with a population of hemagglutinin-containing phages plus a similar population of antibodies or small molecules that prevent binding. The hemagglutinin would be mutated and the viral escape variants (which preserve binding capacity), selected. These new viral mutations could then be used to screen for new antibodies or small molecules that can bind and hold the escaped mutants.

As a result, the threat to the virus escalates as the population of new antibodies and small molecule antagonists grows and are added to each new analytical cycle. In the case of an immunological checkmate analysis, the sequence analysis of successful viral mutants provides a map of escape routes the virus can use, while the antibody sequences provide information about the chemical basis of a successful immune response.

"This really is a new way to think about the study of viral evolution," Dickerson said. "The ultimate scenario is that, in a single series of experiments, you can look forward and backward in evolutionary time to see where the avian flu virus has been and where it's going."

The new methodology, the study emphasizes, isn't limited to viruses but could be applied to any protein-ligand interaction that was open to disruption. For instance, the checkmate analysis of escape mutants could be useful in profiling trajectories of enzymes important to shifting cancer phenotypes or changes leading to antibiotic resistance in bacteria. The methodology also has potential for evaluating organic compounds or small peptides rather than antibodies that disrupt the interaction between protein and ligand. In that case, the new methodology would allow analysis of direct binding at the level of single molecules without special reagents or complicated equipment.

The study was supported by the Skaggs Institute for Chemical Biology and the National Institutes of Health.

Proteomics to Transform the Diagnosis and Treatment of Disease

Functional Proteomics Center a Goal of Scripps Research to Assist in this Quest

> There's little doubt that proteomics—the study of an organism's complete complement of proteins—will have great impact in all areas of the life sciences in the years to come.

And the reason is clear. "To really understand biological processes, we need to understand how proteins function in and around cells since they are the functioning units," said Scripps Research Professor **John Yates, Ph.D.,** who is pushing new frontiers in the proteomics field.

Proteomics is often considered the next step in the study of biological systems, after genomics. The task of studying the proteome has its share of challenges. One involves the sheer number of proteins that need to be identified. The approximate 25,000 genes in the human genome can code for at least ten times as many proteins; in extreme cases a single gene alone can code for over 1,000. Another challenge is that amino acids—the base units of proteins—are so small. Each amino acid is made from anywhere between 7 and 24 atoms. This is far beyond the reach of even the most powerful microscopes.

While an organism's genome is rather constant, a proteome differs from cell to cell and constantly changes through its biochemical interactions with the genome and the environment. One organism has radically different protein interactions in different parts of the body, different stages of its life cycle and different environmental conditions. Another major difficulty is the complexity of proteins relative to nucleic acids.

Most diseases result from malfunctions of proteins leading to dysregulated metabolic and signaling pathways in cells and tissues. Proteomics has become a paramount tool in biology in the last decade because it offers the possibility of identifying proteins associated with specific diseases. These proteins can then potentially be used as markers for detection or prevention or as targets for the design of new drugs to treat the disease. Proteomics promises to provide the new technologies that will transform the process of diagnosing and treating human diseases.

"Understanding the proteome, the structure and function of each protein and the complexities of protein-protein interactions will be critical for developing the most effective diagnostic techniques at early stages to stop disease in its tracks, and treat disease in the future, said Scripps Research Professor **Ben Cravatt, Ph.D.** Proteomics is fundamental to translating genomic information into knowledge that will allow us to predict and manage diseases such as cancer, diabetes, and neurodegenerative disorders."

Yates and Cravatt are two of the world's foremost leaders in the burgeoning field of functional proteomics. They have, for example, looked at dozens of samples of human tumors from breast cancer patients, and analyzed them with proteomics. The scientists were able to detect human proteins that may be associated with breast cancer—including some that have never before been associated with the disease.

"We have found some known and novel markers of breast cancer pathogenesis," said Cravatt.

Left: Dr. John Yates
Right: Dr. Ben Cravatt

"This method could potentially be applied to other human diseases to discover new markers currently evading detection by other methods."

Yates was also the lead scientist in a collaborative project involving 18 researchers at half a dozen laboratories in the United States and Great Britain to determine the proteome of the most deadly form of the malaria pathogen—*Plasmodium falciparum.*

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DONOR PROFILE

Alafi Foundation Funds Infectology Research at Scripps Florida

Dr. Charles Weissmann was beaming. Surrounded by the staff of his Scripps Florida Department of Infectology laboratory, he waited for quiet before announcing the award of his first-ever grant from the National Institutes of Health (NIH). This is always exciting news in any Scripps Research laboratory, for it marks a rite of passage for a rising young scientist, the time when one's scientific peers have recognized talent and the promise of a productive career.

In this case, it marks a different milestone, for Dr. Weissmann holds six honorary degrees and a cabinet full of medals and numerous honors including election to medical and scientific academies across Europe and the United States. His first of more than 300 scientific papers was published in 1953; he was one of the founders of Biogen, the first major European biotechnology firm; and has served as a scientific advisor to a number of pharmaceutical firms.

Dr. Margaret Alafi and her son, Chris Alafi, Ph.D., two of the founders of the Alafi Family Foundation.

Crucial to the support of Dr. Weissmann's work during his time

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Proteomics, CONTINUED

"This was the first instance that I know of where these proteomics studies have gone along side-by-side with the genome sequencing project," said Yates.

Proteomics promises to provide the new technologies that will transform the process of diagnosing and treating human diseases.

The effort identified the proteins in the single-celled *Plasmodium* that cause malaria. These efforts will pay huge dividends in global healthcare if even a few of the newly identified proteins lead to the development of new malaria vaccines—and Yates and his colleagues found an unprecedented total of more than 2,400 proteins. Knowing which proteins are expressed by *Plasmodium falciparum* should help scientists understand how the pathogen causes malaria and, with luck, how to thwart it.

Yates has also applied proteomics in working with Scripps Research Professor **William Balch, Ph.D.,** in understanding and treating the many protein-folding diseases that affect human health, notably cystic fibrosis—providing targets for therapeutic intervention.

In a direct effort to capitalize on the unique proteomics expertise that Yates and Cravatt bring to Scripps Research, the Institute is currently seeking private philanthropists who will contribute to a new Functional Proteomics Center that would employ state of the art mass spectrometry techniques, the collaborative nature of Scripps scientists, additional personnel, and powerful bioinformatic capabilities to address complex problems in biology and medicine. This dedicated center of excellence would enable the Institute to pursue numerous more research opportunities currently limited by capacity.

Through private philanthropy, Yates and Cravatt could acquire the necessary state of the art proteomic technology and further scientific staff support that will be required to receive larger-scale National Institutes of Health (NIH) funding for proteomics research projects in such areas as diabetes, cancer, drug abuse, and aging research, as well as other medical areas. The NIH is strongly pushing proteomics, but to receive federal funding, a solid proteomics infrastructure must be in place first. A private contribution to the Center is thus a "seed" investment in a proven, world-class research program whose work will continue to push the frontiers of biomedical research.

For further information on funding the Functional Proteomics Center, please contact Wendy Scott Keeney, Vice President of Philanthropy, (858) 784-7083, wkeeney@scripps.edu.

at Scripps Florida is a major grant from the Alafi Family Foundation of Berkeley, California. The Foundation was established in 1999 by Margaret and Moshe Alafi, and their two children Chris and Shireen, all great friends of science, education, and the arts. In her letter to Dr. Weissmann announcing the Foundation's grant, Mrs. Alafi wrote, "You have no idea how delighted we are to be able to make this gift . . . we have followed your achievements for over a quarter of a century with great interest and admiration."

The Alafi's achievements are remarkable in their own right. In the 1950's, Dr. Margaret Alafi founded a progressive grade school and directed it for over 25 years. She later established and served as president of The Center for Psychological Studies, a graduate program for clinical psychologists. Both schools introduced substantial innovative concepts in the fields of education. She met her husband Moshe at University of California, Berkeley where they both studied.

Mr. Alafi, who grew up in Baghdad, is considered one of the founders of biotechnology. He has founded over 60 companies through his firm Alafi Capital Company, LLC. The Alafis have been seed investors, both in start-up for-profit ventures and in charitable organizations that serve the public and advance knowledge such as Scripps Research. One of their early investments was to help in the founding of Biogen which led to their introduction to Dr. Weissmann in 1978.

Chris Alafi, a managing partner of Alafi Capital Company, LLC, has been participating in the foundation's decisions before he finished his Ph.D., in Biochemistry at Oxford University in Great Britain. Perhaps his most remarkable contributions were in identifying the potentials of new instruments in the medical field.

As for Charles Weissmann, his big day as an NIH grantee came after many years of research because the bulk of his career was centered in Europe, at the University of Zurich and in England at St. Mary's Hospital and University College, London. In the 1980's, Weissmann synthesized interferon in E.coli using a new cloning approach that led the way to large-scale production of human alpha interferon (IFN), today an important therapeutic agent for hepatitis C.

His path-breaking work on prions, infectious protein particles, has been fundamental to research that made it possible to breed cattle to be resistant to mad cow disease. In 2004, he was the first scientist appointed to Scripps Florida's faculty and now chairs the Department of Infectology on the Jupiter campus. Among Professor Weissmann's research interests at Scripps Florida are his continuing work on prion disease and hepatitis C.

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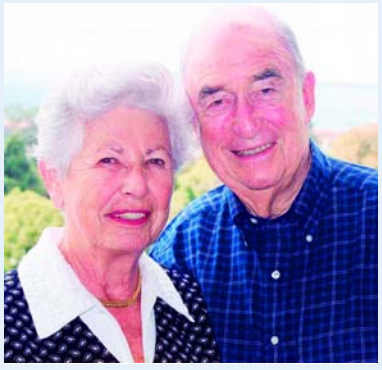
Two life rates are slightly less. Deferred gift annuities are available for younger individuals.

For example, if you are 80 years old and establish a $50,000 gift annuity with Scripps Research, you will receive $4,000 per year for the rest of your life, some of it tax-free, while also receiving an immediate tax deduction of $25,618.

Hans and Dagny Wiener have taken advantage of this option and established a charitable gift annuity with The Scripps Research Institute. "I've always been aware of the importance of medical research," said Dagny. "We had many doctors in the family, including my father, one of my sons, and my uncle — in fact, I worked for my uncle performing research on the effects of radium at the Karolinska Institute in Sweden."

"My husband, Hans, and I, wanted to create a lasting legacy for the future of medical research at Scripps Research by creating this charitable gift annuity, while also enjoying increased income in our retirement years," said Dagny. Hans, who has since passed away, had an illustrious career in international relations and received the Commander of the Swedish Royal Order of the North Star from the King of Sweden.



Dagny and Hans Wiener

Please call (858) 784-2380 or email cdean@scripps.edu for more information on setting up your own charitable gift annuity.

Partners

1 In celebration of the third annual gathering of The Scripps Legacy Society this spring, Scripps Research planned giving donors and Kellogg School of Science and Technology students enjoyed a luncheon and laboratory tours at the Beckman Center for Chemical Sciences atrium. The Scripps Legacy Society is composed of individuals who have included Scripps Research as a beneficiary in their estate plans. **Dr. Ray Stevens** (pictured) spoke about Scripps Research success stories, most notably his research on phenylketonuria (PKU), an inherited metabolic disorder that affects almost 30,000 children and adults in the United States. His research has led to one compound in Phase III trials for mild PKU and the development of another therapeutic in pre-clinical studies to treat severe or classical PKU.

AWARDS AND HONORS

Dorian McGavern Wins Burroughs Wellcome Fund Prize

Dorian McGavern, Ph.D., an associate professor in the Scripps Research Molecular and Integrative Neurosciences Department, has won a prestigious award from Burroughs Wellcome Fund, which has named him one of 15 new Investigators in Pathogenesis of Infectious Disease. These highly competitive awards are given to early career U.S. and Canadian scientists.

McGavern's research addresses questions at the intersection of immunology and neurobiology. He is currently focusing on how the central nervous system can rid itself of a persistent viral infection—which, in humans, can be caused by pathogens such as HIV, herpesvirus, measles virus, and human T-lymphotrophic virus type I.

2 Scripps Research benefited from an event called Hot Topz, a dance party, fashion show, and "Taste of San Diego" held this summer in downtown San Diego. Hot Topz, which was put together by musician and performing artist **Kathy Yuhl,** under the auspices of Desert Rock Productions, was held at the Manchester Grand Hyatt and raised money from a younger generation of donors for research on AIDS and cancer being done at the institute. Yuhl first became interested in Scripps Research after learning of its four-star rating by Charity Navigator, an internet rating service that evaluates the efficiency and and financial accountability of nonprofit groups. As part of the fundraising effort, photos of the evening's guests arriving on a Pink Carpet were developed onsite and made available for donations to the institute. The event honored three Scripps Research investigators: **Dr. Dennis Burton, Dr. Ben Cravatt,** and **Dr. Peter Kuhn.** Pictured at the event are Dr. Cravatt, Dr. Burton, Kathy Yuhl, and Dr. Kuhn.

The Scripps Council of 100

> The Scripps Council of 100 consists of individuals, couples, and representatives of corporations or foundations that contribute $100,000 annually or make a single contribution of $1 million or more to The Scripps Research Institute.

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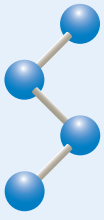

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