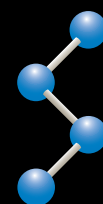


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Scientific Report 2006

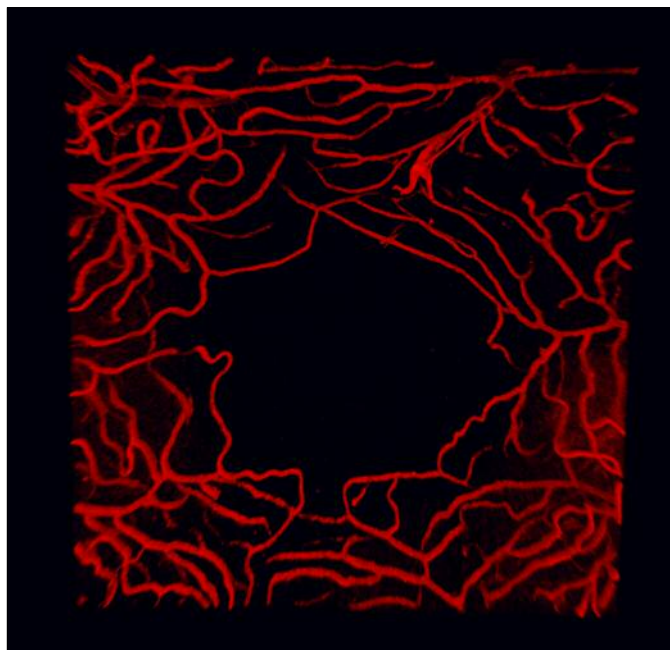


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ON THE COVER: "Click" chemistry refers to the development and use of highly reliable chemical reactions to make molecules that perform a desired function. The most successful click reaction is the copper-catalyzed azide-alkyne cycloaddition (CuAAC) process, an abstract representation of which is shown here. Blue (azide) and red (alkyne) components are efficiently joined by spherical copper ions to give pentagonal 1,4-triazoles. Surrounding the large triazole motif in the foreground are energy diagrams highlighting favorable aspects of the reaction, and its biological applications are represented by icosahedral virus particles. The brick-like mosaic tying the entire image together suggests both the highly modular nature of the CuAAC reaction and its usefulness in the creation of functional small molecules, polymers, and materials. The overall theme celebrates the importance of connections: in chemistry, as in life, while individuals may be unique and pleasing, it is when they "click" together that true art is created. Painting by Yeon-Hee Lim, Ph.D., research associate in the laboratory of M.G. Finn, Ph.D., Department of Chemistry.

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Vessels of a human retina (macula). The image shows the avascular zone of the fovea. Image provided by Edith Aguilar de Diaz, M.D., Scientific Associate, Matthew Ritter, Ph.D., Research Associate, and Martin Friedlander, M.D., Ph.D., Professor. Work done in the Friedlander laboratory in the Department of Cell Biology.

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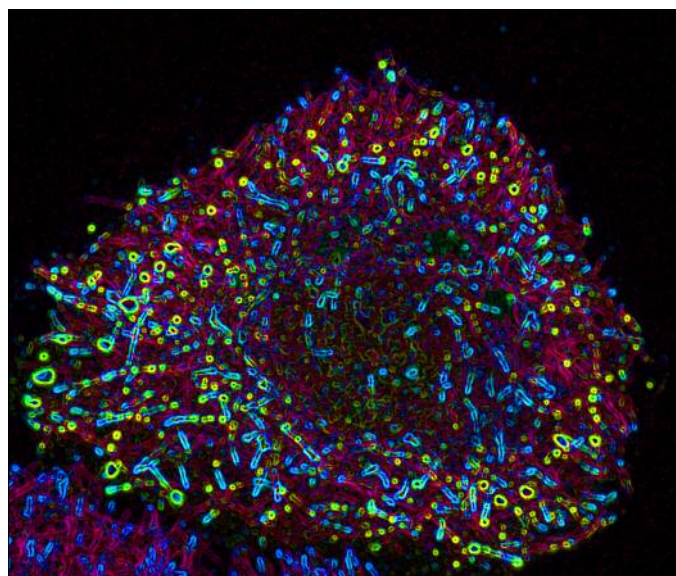
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Human keratinocyte polarising in response to EGF-1. Microtubules are shown in red, Clip170 a microtubule +end binding protein in yellow, and EB1 different microtubule +end binding protein in blue. Work done by Ann Wheeler, Ph.D., Research Associate, in the laboratory of Clare Waterman-Storer, Ph.D., Department of Cell Biology.

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The synapse revealed. The artist created a pencil sketch based on micrograph data, but opted to cut the number of neuronal interactions to ~30% in order to clarify the physiology. He constructed 3-dimensional models of two cells to render on top of the approved sketch. He designed a texture map to skin the two primary neurons that would insinuate a proteinated bilayer and simultaneously simulate organelles deep to the surface. Lighting sweeps attention over the entire image before settling it on the synapse by reflecting hints of color from the focus into peripheral regions of the drawing. Cool desaturated colors in the background allow the warm synapse region to command attention as it glows with a hint of anticipatory presynaptic transmission. This image received a Certificate of Merit award from the Association of Medical Illustrators and won first place in the National Science Foundation's Scientific Visualization Challenge of 2005 competition. Illustration by Graham Johnson, courtesy of the Howard Hughes Medical Institute ©2004.

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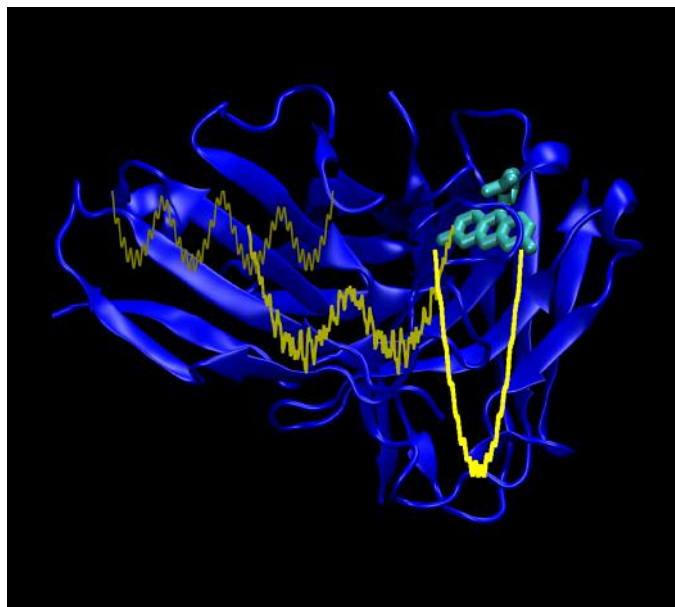
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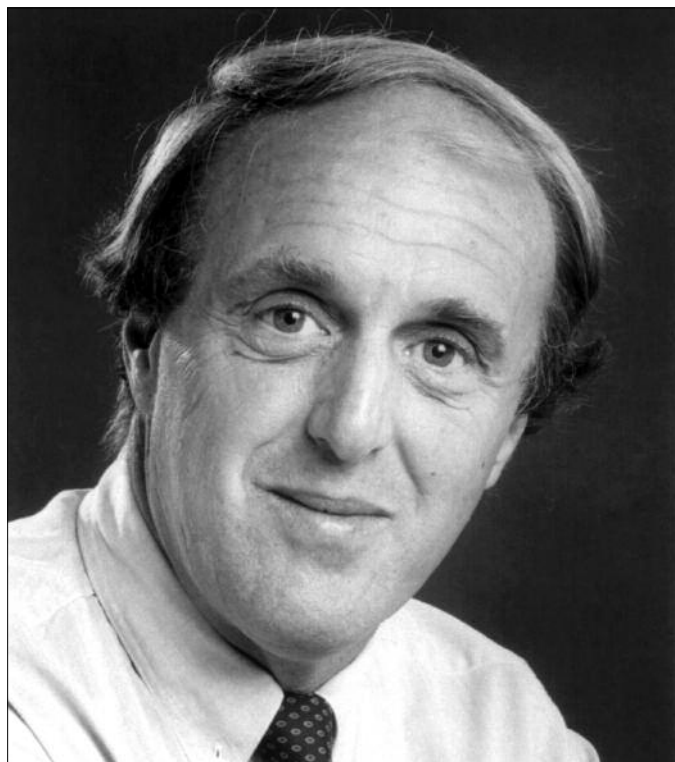
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The figure shows the variable domain of antibody 4-4-20, which binds the antigen fluorescein, and its free-energy surfaces at various stages of evolution. Work carried out in the laboratory of Floyd Romesberg showed that 4-4-20's binding site has evolved from a flexible progenitor that populates many conformations into a rigid binding site with only one conformation, thus confirming a longstanding hypothesis in immunology. The image depicts collaborative research between Floyd Romesberg, Ph.D., Charles Brooks, Ph.D., and their colleagues. Graphics by Joerg Zimmermann, Ph.D., and Floyd E. Romesberg, Ph.D., Department of Chemistry.



Richard A. Lerner, M.D.

President's Introduction

One of the pleasures of being associated with Scripps Research is that we so often have good news to report. So it is this year, when we can share progress on the Florida campus; new contributions of our faculty, staff, and trustees in both Florida and California; and groundbreaking research in our understanding of health and disease.

FLORIDA ADVANCES

With the Palm Beach County commissioners' selection in February of a new site for Scripps Florida—on the north campus of Florida Atlantic University in Jupiter—we have moved forward with plans for a permanent facility. Scheduled to open in 2009, the facility will be a world-class, 350,000-square-foot biomedical research operation focusing on basic biomedical science, drug discovery, and technology development.

In the meantime, Scripps Florida opened a second temporary building this fall on the Florida Atlantic University site. The structure will provide 33,000 square feet of space to house our growing faculty and staff while the permanent campus is under construction.

The state-of-the-art screening technologies at Scripps Florida have begun to make contributions to science as evidenced by published papers this year. The system,

which relies on automated robots to analyze a large number of compounds at once, is available to Scripps Research faculty on both coasts. In January, the Access to Technologies Program also opened the system to scientists from universities and research institutions throughout Florida, enhancing our other collaborations in the state.

The State of Florida awarded its first research grant to 1 of our faculty members this year. Awarded on the basis of scientific merit, the Florida Department of Health's James & Esther King Biomedical Research grant will provide support for Layton Smith, associate director of Pharmacology at Scripps Florida, who is conducting research in the field of metabolism.

In another Florida development this year, we welcomed the first entering classman to our graduate program in Jupiter, where he joins several students who transferred from other institutions. A new 2-way, web-based conferencing technology is enabling Florida students to participate in California lectures in real time, as well as open future Florida classes to interested California students.

NEW RESEARCH ALLIANCES

In 2006, we forged a number of new alliances that will advance science at the institute in the years ahead.

In February, we announced a collaborative initiative with IBM, called "Project Check-mate," that will conduct research on pandemic viruses to develop ways to anticipate, manage, and contain infectious diseases. Check-mate capitalizes on Scripps Research's world-class research in biochemical modeling and drug discovery and on IBM's expertise in computational biology biopatterning and supercomputing. The joint research team will harness both IBM's Blue Gene supercomputer and Scripps Florida's screening technology.

In March, we joined forces with 3 preeminent San Diego research institutions—the Burnham Institute for Medical Research, the Salk Institute for Biological Studies, and the University of California, San Diego—to establish an independent, nonprofit consortium dedicated to stem cell research. The alliance, called the San Diego Consortium for Regenerative Medicine, will explore the tremendous therapeutic potential of stem cells to repair and replace damaged tissue.

In April, we became part of Microsoft's new BioIT Alliance, a cross-industry group working to integrate science and technology to speed the pace of drug discovery and development. The alliance's first project, Collaborative Molecular Environment, strives to make

research more efficient through a data management solution targeting common technology problems faced in the life sciences.

In May, a new robotic crystallization facility opened on the California campus, thanks to support from the Joint Center for Structural Genomics (funded through the National Institutes of Health's Protein Structure Initiative) and global nonprofit group International AIDS Vaccine Initiative. One of the largest machines of its kind, the integrated robotics system will enhance scientists' ability to solve molecular structures, increasing our understanding of basic biology and strategies for combating a variety of diseases.

GROUNDBREAKING RESEARCH

The institute's science stands at the forefront of basic biomedical research, a vital endeavor that seeks to comprehend the most fundamental processes of life.

In addition to well-publicized research on an anti-obesity vaccine, reactivation of the gene responsible for Friedreich's ataxia, heart damage from prion disease, and the threat of the avian flu virus, Scripps Research scientists made many significant contributions in 2006. A few key studies are highlighted below.

- Scientists demonstrated an innovative combination of immunotherapy and small-molecule drug design for producing anticancer targeting antibodies. One study, led by Professor Carlos Barbas III, highlighted the potential of such an approach against melanoma. In another study, Associate Professor Subhash Sinha and I developed a compound against metastatic breast cancer.
- Professor Chi-Huey Wong and colleagues discovered a class of compounds that block the SARS virus from replicating, a finding that may open the door to new drug targets against the deadly disease.
- Professor Dale Boger and Kellogg School Ph.D. candidate Brendan Crowley re-engineered a well-known antibiotic to ensure its effectiveness against both sensitive and resistant enterococci, a common strain of bacteria responsible for widespread hospital infections.
- Professor John Tainer and colleagues determined the crystal structure and molecular mechanisms of a key part of WRN, a protein that protects humans from premature aging and cancer. They also uncovered the structural chemistry behind the bacterial GC Type IV pilus filament, which plays an essential role in allowing antibiotic-resistant strains of *N. gonorrhoeae* to escape the

immune system and cause persistent and recurrent gonorrhea infections.

- Professor Hugh Rosen and colleagues developed a chemical tool that allows manipulation of the passage of substances through the barriers between blood and organ tissues, findings that have therapeutic implications for organ transplants, autoimmune disease, multiple sclerosis, and adult respiratory distress syndrome.
- Immunology Department Chair Richard Ulevitch and colleagues uncovered a new and potentially important function for the protein Nod1, inhibiting the growth of estrogen-sensitive human breast cancer cells.
- Associate Professor Elizabeth Winzeler and colleagues discovered hundreds of novel genes that may help the malaria parasite evade destruction by the human immune system and antimalarial drugs. The findings could lead to the development of new therapies or vaccines for the deadly disease.

OTHER NOTEWORTHY DEVELOPMENTS

New agreements with Novartis and the Genomics Institute of the Novartis Research Foundation (GNF) will provide approximately \$50 million over the next 5 years to fund the Scripps Research laboratories of 20 investigators, including Professor Peter Schultz, 5 scientists moving to Scripps Research from GNF, and 14 assistant professors. Terms also facilitate the future funding of Scripps Research faculty by Novartis.

The Consortium for Functional Glycomics, led by Scripps Research Professor James Paulson, received a \$40.7 million "glue" grant for the international group of some 300 participating scientists to continue collaborative study of the complex dynamics of protein-carbohydrate interactions. The 5-year grant from the National Institute of General Medical Science of the National Institutes of Health follows a grant of \$34 million awarded in 2001.

The Integrative Neuroscience Initiative on Alcoholism, led by Scripps Research Professor George Koob, won renewal of support from the National Institutes of Health's National Institute on Alcohol Abuse and Alcoholism. The grant, which is expected to total \$38 million over 5 years, supports the efforts of a multi-institutional consortium of investigators to identify the molecular basis of alcoholism.

Scripps Research launched a research and educational initiative with McDonald's to drive progress toward a solution to childhood obesity and type 2 dia-

betes. McDonald's will contribute \$2 million to the institute to address these critical health issues.

PEOPLE NEWS

In 2006, Scripps Research continued to be served by an outstanding group of trustees and administrators.

At our commencement ceremony in May that graduated 31 students from the Kellogg School of Science and Technology, we conferred 2 honorary degrees in recognition of Hon. Alice Sullivan (Ret.), retiring chair of the Scripps Research Board of Trustees who will continue as a trustee, and Alexander Dreyfoos, also a member of the Board of Trustees.

The business leader and philanthropist John Moores was unanimously elected new chair of the board—he will bring enormous skill and energy to the position. We also have the pleasure of welcoming back Ralph J. Shapiro of Beverly Hills, California, chair of Avondale Investment Company, and of welcoming new member Marjorie Fink of Palm Beach County, Florida.

With the appointment of Professor Gerald Joyce as dean of the faculty and Professor Jeffery W. Kelly as dean of graduate and postgraduate studies, in July we formalized a new distribution of administrative responsibilities. This change will enhance efficiency and communication in our academic programs.

Barbara Suflas Noble, who has been part of our administrative team in Florida, will assume the position of director of external affairs for Scripps Florida, reaching out to our generous and enthusiastic base of donors in the state. Peter Policastro joins our team as senior director of business development for Scripps Florida.

We also welcome investigator John Cleveland, who will head the new Cancer Biology department on the Scripps Florida campus.

AWARDS AND HONORS

Many awards and honors lauded our faculty, postdoctoral fellows, and graduate students in 2006.

Among the faculty recognitions:

- Professor Dale Boger was elected to the American Academy of Arts and Sciences. Fellows are selected through a highly competitive process that recognizes individuals who have made pre-eminent contributions to their disciplines and to society at large.
- Chair of the Scripps Florida Department of Infectology, Charles Weissmann, received the prestigious DART/NYU Biotechnology Achievement Award from the Biotechnology Study Center of the New York University School of Medicine for

his elucidation of multiple interferon genes and the pharmaceutical development of Intron A (interferon alpha2b).

- Chair of the Department of Chemistry, K.C. Nicolaou, won both the 2006 American Chemical Society Auburn G.M. Kosolapoff Award and Germany's Burkhardt-Helferich Prize. He is also an author of 1 of Chemical Abstracts Service's 10 most requested papers (second quarter), "Palladium-catalyzed cross-coupling reactions in total synthesis," in *Angewandte Chemie*.
- Two patents on "click chemistry" by Professor K. Barry Sharpless, Associate Professor Valery Fokin, and Associate Professor M.G. Finn were among the Chemical Abstracts Service's 10 most requested patent families (second quarter).
- Associate Professor Clare Waterman-Storer won the 2006 R.R. Bensley Award in Cell Biology from the American Association of Anatomists, which recognized her for innovation in molecular microscopy and contributions to the understanding of cytoskeletal dynamics in cell motility.
- Professor Argyrios Theofilopoulos was honored several times this year for lifetime contributions to medicine and autoimmune research; he received honorary doctoral degrees from the Aristotle University of Thessaloniki Medical School and the Democritos Medical School of Alexandroupolis and was elected a corresponding member of the Academy of Athens.
- Professor Bruce Beutler won the Cancer Research Institute's 2006 William B. Coley Award for Distinguished Research in Basic Immunology for his contribution to our understanding of the events leading to the initiation of innate immunity.
- Associate Professor Phil Baran received the Sloan Research Fellowship for "outstanding researchers early in their academic careers." He also received the Bristol-Myers Squibb Unrestricted Freedom to Discover Grant (2006–2010) and a National Science Foundation CAREER award (2006–2010).
- Norman Klinman, who became professor emeritus this year, received the 2006 Excellence in Mentoring Award from the American Association of Immunologists for exemplary career contributions to a future generation of scientists.

Our hardworking postdoctoral fellows were also recognized by numerous grants and awards. As a few examples, Ian Schneider of the Waterman-Storer lab

won a Damon Runyon Fellowship Award; Adam Mullick of the Curtiss-Tobias lab, a fellowship from the American Heart Association; Terry Meehan of the Havran lab, a Crohn's & Colitis Foundation of America Research Fellowship Award; Jeff Lee of the Ollmann Sapphire lab, the Canadian Governor General's Gold Medal; and David Edmonds of the Nicolaou lab, a European Merck Postdoctoral Fellowship.

As for our Ph.D. candidates in the Kellogg School of Science and Technology, an unprecedented 5 students—Dan Bachovchin, Christine Fang, Graham Johnson, Costas Lyssiotis, and Adrian Ortiz—were awarded National Science Foundation Fellowships this year. In addition, students garnered prestigious awards from private donors, the National Institutes of Health, Novartis, and many other organizations including the Hertz Foundation, the American Heart Association, the California Breast Cancer Research Program, and the American Chemical Society.

This year's achievements make me proud to be part of The Scripps Research Institute. My congratulations go out to faculty, staff, postdoctoral fellows, students, trustees, and loyal supporters for another year well done.