



SCRIPPS DISCOVERS

Improving Lives Through Research

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INSTITUTE UPDATE

Scripps Research Team Dramatically Simplifies Synthetic Production of Potential Pharmaceuticals

> A team of researchers at The Scripps Research Institute, led by Associate Professor **Phil Baran, Ph.D.**, has developed new techniques that dramatically reduce the time, complexity, and cost of synthesizing natural products with pharmaceutical potential.

The work dislodges previously entrenched beliefs in the organic chemistry field about how such products must be produced, and could help to advance and expand the use of natural products in drug discovery programs.

Chemists are currently able to synthetically produce almost any compound, but they must typically resort to expensive, complex processes that can require dozens of steps.

To synthesize their products, the Scripps Research team designed a variety of chemical reactions that maximize the bonding of carbon atoms

between different molecules. In many cases, the products were synthesized in gram quantities in less than 10 steps, as compared to traditional syntheses using protecting groups that have taken as many as 30 steps to produce milligrams of product.

Use of the techniques the Scripps Research group has developed could lead to substantially reduced production costs for natural products. This is a critical concern, as identification of a reasonably economic means of production for marine and

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BACK COVER:

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Scripps Florida Forms Molecular Therapeutics Department

In anticipation of Scripps Florida's continued expansion, The Scripps Research Institute has created a new academic department, the Department of Molecular Therapeutics.

"We will recruit faculty to the Department of Molecular Therapeutics capable of utilizing the advanced

drug discovery technology at Scripps Florida," says **Patrick Griffin, Ph.D.**, the new department's chair. "Our goal is to discover new chemical probes that have immediate therapeutic implications."

In addition to Molecular Therapeutics, Scripps Research

departments based primarily on the Jupiter, Florida site are Infectology, chaired by **Charles Weissmann, Ph.D.**, and Cancer Biology, chaired by **John Cleveland, Ph.D.**



Dr. Patrick Griffin

Additional departments are anticipated as the permanent Scripps Florida campus, scheduled to open in 2009, nears completion.

other natural products is typically one of the most challenging hurdles in a potential drug's commercial development. An overly complex and expensive synthesis can even slow or halt the development of an otherwise promising drug candidate.

Beyond economic ramifications, Baran hopes the research will offer additional benefits to the drug discovery field. Many pharmaceutical companies' potential drug pipelines are

drying up, leading some to suggest that interest in natural products should be renewed. A range of drugs from aspirin to the widely used cancer treatment Taxol has been discovered in nature, but the complexity of producing natural products has made some companies reluctant to focus on them.

"There is this far-ranging and damaging perception that natural products are too complex to be used in a drug discovery setting, despite their

overwhelming track record in medicine," says Baran. "I think if our work has helped in even a small way to revive the use of natural products, then we've served our purpose."

The Baran team has focused its work to date on marine natural products, because these chemical compounds from sponges, algae, and other organisms have proven a rich source of bioactivity with pharmaceutical potential, but have also been challenging to work with. Marine natural products are ideal targets for simplified synthesis techniques because they tend to be exceptionally complex, and because they are typically difficult to collect. Researchers often struggle to amass marine organism samples in quantities great enough to yield the volume of a given compound needed for research and clinical trials, much less commercial production, making better and cheaper production means all the more critical.



"... if our work has helped in even a small way to revive the use of natural products, then we've served our purpose."

— Dr. Phil Baran

RESEARCH UPDATE

Cancer-Specific Mutations May Offer Path to Treatments

> Three years ago, Scripps Research Professor Peter Vogt, Ph.D., was astonished to read a paper that identified three cancer-specific mutations in the gene known as PIK3CA.

He was surprised, because his laboratory had been studying the role played by the same gene, along with the enzyme whose production it codes, in causing cancer in chickens. Until the paper was published, though, the team had no idea of the gene's significance in humans.

"We immediately took up the challenge of these cancer-specific mutations," says Vogt, head of the Division of Oncovirology in the Department of Molecular and

Experimental Medicine. In short order he and his team were able to show that each of the three mutations identified was in fact capable of inducing the onset of cancer. Later research by the group, published recently, has led to some remarkable discoveries about related mutations in the same gene, broadening understanding of how the mutations cause cancerous cell proliferation. Collectively, the work has revealed a tantalizing potential pathway for cancer-specific drug treatments.

PIK3CA codes for the production of an enzyme called PI3 kinase, which, in its normal state, plays a variety of critical roles



Dr. Peter Vogt

in cell signaling, regulating such aspects of cell growth as glucose metabolism and cell survival. PIK3CA mutations are found in about 30 percent of cancer cases, and are especially common in colon, breast, and endometrial cancers.

The three mutations first identified in PIK3CA are by far the most common, making up some 80 percent of the gene's mutations, but more than 80 additional mutations have also been discovered, and the Vogt team's recent work focused on 15 of these.

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At the outset, the researchers fully expected that the rare mutations would not be oncogenic (causing the creation of tumors). Instead, they found that 14 of these 15 mutations examined could in fact induce cancer, though not quite as strongly as the three more common mutations. “That was a complete surprise,” says Vogt, “and it gave us a

This new understanding of the common and rare mutations and their effects opens a promising new path for the discovery of potential new cancer treatments.

terrific tool for looking at all these mutations and their relation to the functioning of the protein.”

A possible conclusion based on the pervasive oncogenicity discovered was that the gene simply has a propensity to turn oncogenic in response to almost any mutation. To test this idea, the group made random mutations to the gene, none of which proved capable of causing cancer.

In hopes of discovering why the rare mutations cause cancer, the Vogt lab worked with Marc Elsiger, from Scripps Research Professor Ian Wilson’s lab, to develop a 3-D map of the PI3 kinase and its mutations. This effort revealed that the rare oncogenic mutations produce changes clustered at various positions, but always on the surface of the protein. The three common mutations also induce surface changes on the protein.

Marco Gymnopoulos from the Vogt lab, says that, based on this discovery, there exist several molecular mechanisms that can lead to a gain of function in PI3K. These include enhanced affinity for the plasma membrane of the cell where PI3K is active, altered interaction with regulatory proteins, and structural changes that enhance the function of the catalytic domain of the protein.

This new understanding of the common and rare mutations and their effects opens a promising new

path for the discovery of potential new cancer treatments. One possibility would be to identify small molecules that specifically target the mutations to prevent increased cell division. The most obvious initial focus would be drugs that target the three most common mutations to block their impacts.

Treatments aimed at the rare mutations might also be possible, but this would be a more daunting prospect because there would be so many potential targets, and because far fewer cancer cases involve these mutations. Gymnopoulos says the main benefit of

the discoveries regarding the rare mutations may instead take another form.

“The rare mutations are very important, because they tell us how this whole signaling cascade functions,” says Gymnopoulos. Understanding the various mechanisms involved may well lead to broader understanding of interactions between the protein and cells, he says, and, hence, broader treatments. For instance, the work could illuminate a method for blocking the interaction between the enzyme in a variety of mutated forms and other cells, preventing the cancerous increase in cell division.

The Vogt team is awaiting word on a proposal for funding from the National Cancer Institute to begin screening for drugs that target the mutations, and is also in discussions with pharmaceutical companies interested in pursuing potential treatments based on the team’s research.

DONOR PROFILE

Norma and Frank Sugg: Making a Difference in the Fight against Leukemia

Norma and Frank Sugg led wonderful lives. Their lives revolved around each other, and both were generous philanthropists.

Unfortunately, they each passed away from leukemia, but they have left a powerful legacy for leukemia research — after Frank’s death, Norma decided to name The Scripps Research Institute as the beneficiary of their home in Nipomo, near Santa Barbara. The \$600,000 in proceeds from the home’s sale, as well as an additional \$1,000,000 in cash, after Norma’s death in 2005 is making an impact by accelerating the progress of acute leukemia research here — with the goal of an eventual cure. During her life, Norma was a regular donor to Scripps Research, providing approximately \$10,000 cumulatively over the years.

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Norma and Frank Sugg

Norma and Frank Sugg met at a U.S.O. function while Frank was in the Air Force. Frank, who enlisted early at age 16, had an illustrious Air Force career of over 20 years. He was in charge of ground maintenance crews all over the world, keeping Air Force jets flying. Although he had never finished high school, Frank went on to earn an engineering degree while in the Air Force.

After leaving the Air Force, Frank was hired by Rockwell in Southern California to work in their Space Program. In 1977, while at Rockwell, Frank developed an improved

radiographic inspection capability for detecting flaws in materials — using sound waves to examine their structural integrity without destroying the material. Plus, he was one of the developers of the tiles used in the Space Shuttle that stop burning upon reentry to the earth's atmosphere. He also developed several other patent applications and presented numerous seminars at other Rockwell facilities.

Norma was a devoted philanthropist. Aside from Scripps Research, she donated to many other organizations involved with leukemia and lymphoma, as well as St. Joseph's

Catholic Church in Nipomo, and a variety of other charities.

"Frank was a brilliant man, but he never gave you the impression that he was smarter than you," said Tom Etzel, Norma and Frank's nephew and the trustee for Norma's estate. "And Norma was a wonderful woman who had the vision and foresight to support charitable causes and community needs into the future."

If you would like information about including The Scripps Research Institute in your estate plans, please contact Cheryl H. Dean at (858) 784-2380 or cdean@scripps.edu.

SCIENTIST PROFILE

Dennis Burton: *A Pioneer in HIV Vaccine Research*

> Dennis Burton is widely considered a leader in the HIV vaccine field and one of the world's primary masters in antibodies.

Burton is the director of the International AIDS Vaccine Initiative Neutralizing Antibody Consortium to speed the discovery of a vaccine to prevent AIDS worldwide, an effort which includes a number of research dignitaries.

His most recent finding, which appeared in the February 15 issue of *Nature*, could have profound implications for AIDS vaccine design. It delineates a component of an HIV surface protein, that unlike much of the constantly mutating virus, is stable and appears vulnerable to attack from a specific antibody, known as b12, that can broadly neutralize HIV.

"I really think he's doing great work and people should stand up and pay attention," says Ronald Desrosiers, an HIV vaccine researcher at Harvard Medical School. "I don't give

compliments easily, but I've been saying a lot of good things about Dennis lately."

Burton says he hopes to contribute in some significant way to finding an effective AIDS vaccine. He and others have characterized a few antibodies that can broadly neutralize HIV.

Yet, two days every week, you'll find Burton adorned in soccer apparel in his lab. The immunologist has played soccer most of his life. Off the field, Burton is very easy to get along with and has a laid back attitude. Burton has fostered a spirit of teamwork and because of his bright, acceptable attitude, many of his current lab members have either always worked with him, or have left and returned after postdoctoral appointments elsewhere. Since he established his own lab at Scripps Research in 1991,



Dr. Dennis Burton

"A strong, analytical scientist like Burton is particularly valuable in the HIV field."

—Richard Lerner,
president of Scripps Research

his research team has skyrocketed from two people to eighteen.

A strong, analytical scientist like Burton is particularly valuable in the HIV field, says Richard Lerner, president of Scripps Research. "Burton takes a very calm scientific approach to the problem."

Burton received his Ph.D. from the University of Lund in Sweden. He began his career at the University of Sheffield in the UK. In 1989, he arrived at Scripps Research to work in

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Dr. Lerner's lab. At the time, Burton and several others in the Lerner lab were trying to make recombinant antibodies using a new technology.

During this time, Burton made his largest breakthrough and a much-praised paper in *Science*. Even today, Burton still describes the finding with excitement and feeling. One morning that October, he says, he came in and saw a series of spots on radioactive plates. "What that meant is we'd made recombinant antibodies outside of animals and here they were for the first time," Burton says. That afternoon, the lab rejoiced with champagne and Burton wrote the date on the bottle. He still keeps the bottle in his kitchen cupboard.

Burton values collaboration above all else. "In the [HIV] vaccine field, there is a duty of researchers to help one another get to [a common] goal—I think most people feel that. You can do more working together than in isolation."

In fact, the biggest attraction of Scripps Research to Burton is that he can work with multiple individuals who are world leaders in virology, immunology, chemistry and structural biology. "It's possible to get advice and collaborate with people who are amazingly gifted and dedicated."

When asked what drives him day to day, Burton said, "Like most scientists, I'm driven by the curiosity and satisfaction of being able to explain how nature works and by the excitement of seeing data that helps to put the puzzle together. Plus, I find myself increasingly driven by the goal of developing an AIDS vaccine."

Burton and his colleague at Scripps, Ian Wilson, led the research that solved 4E10, which was named Molecule of the Year 2005 by the International Society of Molecular and Cell Biology Protocols and Researches "for being the broadest acting neutralizing antibody against HIV."

In addition to his work on HIV, Burton has worked on respiratory syncytial virus, Ebola virus, and prion infections, such as mad cow disease.

William Roush Wins Award from South Florida Science Museum

> The Scripps Research Institute's William Roush, Ph.D., has been named Scientist of the Year by the South Florida Science Museum in the first of the museum's annual series of awards.



Dr. William Roush

Roush and other award winners were honored at an event sponsored by Friends of The South Florida Science Museum and the future Dekelbourn Science Center on March 28.

"Dr. Roush is a leading light in the research and development of biochemistry solutions to address critical health care challenges," said James Rosebush, Dekelbourn Science Center CEO.

Roush, who is professor of chemistry and biochemistry, executive director of Medicinal Chemistry and associate dean of Scripps Florida graduate studies, focuses his research on the total synthesis of structurally complex and biologically interesting natural products, development of new synthetic methods and strategies, and on problems in medicinal and bioorganic chemistry. His research might prove useful in developing drugs for tropical diseases such as malaria.

Francis V. Chisari Presented with Hepatitis B Award



Dr. Frank Chisari

The Hepatitis B Foundation (HBF) presented its prestigious "Distinguished Scientist Award 2007" to Francis V. Chisari, M.D., at its annual Crystal Ball Gala held on April 28 in Bucks County, Pennsylvania. Dr. Chisari is Professor and Head of the Division of Experimental Pathology in the Department of Molecular and Experimental Medicine at The Scripps Research Institute. He was honored with the foundation's highest scientific award in recognition of his extraordinary contributions to the science and medicine of hepatitis B.

Give Online You can make your gift to Scripps Research online at www.scripps.edu/philanthropy. All information sent online is encrypted to protect your information and privacy. Your gift is tax deductible in the manner and to the extent allowed by law and a receipt will be mailed to you following our processing of your gift. Thank you for your generosity!

Science on Display

> This spring, more than 2,500 San Diego County middle and high school students flocked to the Del Mar Fairgrounds for the annual Educational Technology Fair, sponsored by the San Diego Science Alliance.



Among the displays, whose topics included semi-conductors, aerospace, environmental sciences, and robotics, was a booth staffed by a group from The Scripps Research Institute.

The Scripps Research booth offered students the opportunity to view several 3-D models of proteins, DNA, and other tiny biological molecules. The display was set up and staffed by volunteers from the lab of Professor **Art Olson, Ph.D.**, to show students a new side of the world of science and to share their knowledge about careers in the biosciences.

The Olson lab's molecular models often capture people's attention because of their versatility—not only can they be viewed from more than one angle, they can be touched, twisted, and passed from person to

person. The models are created with cutting-edge fabricators that “print” solid objects out of thousands of layers of plaster or plastic.

Another popular visualization that Olson uses to explain the molecular world is a system, called “augmented reality,” that uses a simple digital video camera to capture the image of an object, which is then tracked in an artificial computer environment.

The Scripps Research Educational Outreach Program also recently participated in the San Diego Reuben H. Fleet Science Museum's Biosciences day. There, volunteers from different labs provided hands-on demonstrations and public talks on topics including the importance of protein folding, what's in a genome, and why viruses are like tiny bottles of champagne.

Students examine molecular models from the lab of Scripps Research's Dr. Art Olson at the annual Educational Technology Fair.

Partners

1 The Frontiers in Science series continued this spring at the Estancia La Jolla Hotel & Spa with a presentation by Doctors John Griffin, Jeffery Kelly, and Martin Lotz on *Current Research and Developing New Treatments for Cardiovascular Disease, Stroke, Alzheimer's, and Arthritis—On the Front Lines of Hope*. The series features lectures from Scripps Research scientists followed by a reception, where participants can mingle and ask further questions of the researchers. Pictured in the top photo are **Douglas A. Bingham**, Executive

Vice President & Chief Operating Officer of The Scripps Research Institute, with **Helen Dorris**, whose gifts to Scripps Research created both the Helen L. Dorris Child and Adolescent Neuro-Psychiatric Disorder Institute and the Harold L. Dorris Neurological Research Institute.

Pictured in the bottom photo is donor **Marilyn Howe** and **Patricia Hawkins**.



Partners

2 **Barbara J. Mason, Ph.D.**, Professor and Director of the Division of Clinical Psychopharmacology in the Department of Neuropharmacology at The Scripps Research Institute and Co-Director of The Pearson Center for Alcoholism and Addiction Research, addressed *An Evidence-Based Evaluation of the New Pharmacotherapies for Alcoholism* at the Scripps Florida Corporate Club luncheon in March. While visiting the Scripps Florida campus, Dr. Mason also shared her neuroscience research knowledge, presenting a special session to professional practitioners working in Florida's alcoholism and addiction clinical care community. Pictured at the event are **Barbara S. Noble**, director of external affairs, Scripps Florida, with attendees **Kenneth Kirby**, president,

TransDermal Technologies Inc.; **Mark Fleisher**, Broad and Cassel Attorneys at Law, and **Michael Mitrione**, shareholder at Gunster, Yoakley & Stewart, P.A.

3 Following the dedication of its new campus, Scripps Florida continued to celebrate with an *Evening of New Friendships*, at the Admirals Cove home of **Dr. William and Lori Schacter**, with a reception to welcome the Scripps Florida family to its permanent campus in Jupiter, Florida. The Schacters, **Dr. Laszlo and Rubye Mate, Max and Cookie Cohen, Andrew and Irene Russo, James and Deborah Lysaght, and Jacob and Mary Uittenbogaard** hosted the reception. Approximately 125 guests were entertained in the Schacters' new home with cocktails, hors d'oeuvres and music. **Dr. Harry Orf**, vice president of

scientific operations, spoke of Scripps's endeavors. Guests of Scripps Florida included many faculty scientists such as **Dr. Charles Weissmann**, chair of infectology, **Dr. John Cleveland**, professor of cancer biology, and a special guest visiting from the La Jolla campus of The Scripps Research Institute, **Dr. Barbara Mason**, co-director of the Pearson Center for Alcoholism and Addiction Research.

Pictured in the top photo are **Christopher Rosen**, chairman & CEO, EffRx Inc.; Scripps Research's **Dr. Barbara Mason**, and Scripps Florida's **Dr. Claes Wahlestedt**, professor of biochemistry and director, CNS Discovery.

Pictured in the bottom photo are **Mrs. Cookie Cohen, Mrs. Dorothy Sullivan, Dr. Harry Orf, Mrs. Lori Schacter, and Mrs. Rubye Mate.**



The Scripps Council of 100

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