SCRIPPS DISCOVERS

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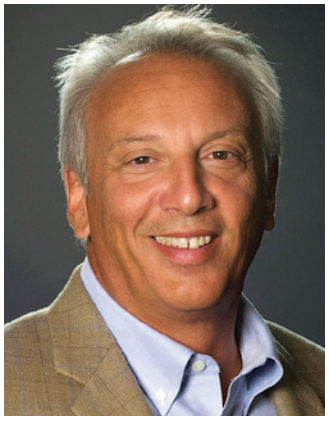
RESEARCH UPDATE

Scripps Florida Scientists Identify a Critical Tumor Suppressor for Cancer

Scientists from the Florida campus of The Scripps Research Institute have identified a protein that impairs the development and maintenance of lymphoma (cancer of the lymph nodes), but is repressed during the initial stages of the disease, allowing for rapid tumor growth.

While the study, published in the August 3, 2012 edition of the journal *Cell*, largely focuses on the role of this new tumor suppressor in lymphoma induced by Myc oncoproteins (the cancer-promoting products of Myc oncogenes), the authors show this circuit is apparently operational in all human tumors with *MYC* involvement, which is more than half of all human tumor types.

"This opens a new therapeutic avenue to exploit for cancers with Myc involvement— including relapsed metastatic tumors and refractory tumors, those that have not responded to treatment," said



"This opens a new therapeutic avenue to exploit for cancers with Myc involvement—including relapsed metastatic tumors and refractory tumors, those that have not responded to treatment."

Professor John Cleveland

John Cleveland, a Scripps Research professor and chair of the Department of Cancer Biology, who led the study.

The Myc family of oncoproteins (c-Myc, N-Myc, and L-Myc) regulate critical pathways that contribute to tumors; c-Myc expression, which is activated in human Burkitt lymphoma, is sufficient to induce the growth of several tumor types in animal models.

In the new study, the scientists focused on precancerous and malignant Myc-expressing B cells, part of the

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New Technique Reveals Cross-Talk between Two Essential Cellular Processes

> The Research Provides Insights into Programmed Cell Death and Opens Door to New Approaches to Cancer Treatment

Scientists at The Scripps Research Institute have simultaneously mapped two of the most important types of protein-modification in cells, revealing their extensive cooperation during an essential cellular process.

Phosphorylation, the attachment of a phosphate group to a protein, and proteolysis, the cleavage of a protein, had almost always been studied independently. The new research combines techniques for mapping these events across all proteins in a cell population to show how they work together to execute the cellular "auto-destruct program" known as apoptosis.

The specific findings on apoptosis may lead to the development of new cancer

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Inside:

Professor Benjamin Cravatt

diagnostics and drugs, since cancer treatments often aim to induce apoptosis in malignant cells. The study also marks the development of a basic new tool of "proteomics"—the large-scale study of proteins—that should provide useful insights into many cellular processes.

"Detecting the cross-talk between protein regulation pathways has long been a challenge, and so with this new technique we can start to do analyses that were difficult or impossible before," said Benjamin F. Cravatt, professor and chair of the Department of Chemical Physiology at Scripps Research, member of Scripps Research's Skaggs Institute for Chemical Biology, and professor in Scripps Research's Dorris Neuroscience Center. Cravatt was the senior investigator for the study, published in the July 20, 2012 edition of the journal *Cell.*

Phosphorylation and proteolysis are among the most important mechanisms of protein modification in cells. They are mediated by enzymes, and occur after a protein has been translated from genetic material and folded. Some proteolysis and phosphorylation events serve to activate a protein so that it can take part in a purposeful cellular process; others have the effect of deactivating a protein.

Previous studies of phosphorylation and proteolysis had suggested that the two mechanisms sometimes work in tandem, especially during apoptosis. But those studies had been focused on individual apoptosis-driving enzymes and their biochemical partners, rather than on the "global" apoptosis process within cells.

"In this study, we wanted to develop a global method to let us see all the signs of cross-talk between proteolysis and phosphorylation during apoptosis," said Melissa M. Dix, a research associate in the Cravatt laboratory. Dix was a lead author of the paper, along with then-graduate student Gabriel M. Simon, who is now a postdoctoral researcher at Washington University, St. Louis.

Dix and Simon built on an earlier proteolysis-mapping method that they had described in *Cell* in 2008. Known as PROTOMAP, it can be used to generate a detailed picture of the protein cleavage events in cells during a process of interest. For the new study, the researchers added a technique for detecting phosphorylation events, plus another recently-developed proteomics technology, SILAC, which enables researchers to distinguish, within a given sample, copies of proteins that have come from different cell populations. The researchers then applied the combined techniques to populations of control cells and apoptotic cells, in order to find the proteolysis and phosphorylation events that happened only during apoptosis.

They detected more than 700 apoptosis-specific proteolysis events—mostly mediated by apoptosis-driving enzymes known as caspases—including many that had not been reported before. The new mapping also revealed for the first time an extensive, apoptosis-specific network of phosphorylation events, many of which were clearly connected to proteolysis events. "Just looking at the map of phosphorylation events, we could see that they were unusually common around sites of known caspase cleavage," said Dix.

Previous studies had hinted that the phosphorylation of a protein near one of its caspase cleavage sites would always tend to block that cleavage. The new evidence suggested otherwise. "We could see that these apoptosis-specific phosphorylations sometimes persisted on caspase-cleaved fragments," said Dix.

Dix and Simon showed that these phosphorylations in some cases had enabled the caspase cleavage events; in others, cleavage events had enabled the phosphorylations. Similarly, they confirmed that some of the kinase enzymes that phosphorylate proteins during apoptosis can't do their jobs until they are cleavage-activated by caspases. "We've tended to study proteolysis and phosphorylation separately, but it's clear that they're intimately associated and need to be looked at as such," Dix said.

The Cravatt laboratory is now applying the techniques developed in this study to other analyses, starting with studies of apoptosis in a variety of cell types. The cells they used in the just-published study, Jurkat T-cells, are often used to investigate apoptosis because they can be easily induced to undergo the process. "But each cell type has its own set of working proteins, which will give it a distinct signature when it undergoes apoptosis," Cravatt said.

Techniques to detect apoptosis in specific cell types would be useful in cancer diagnostics and therapy. Tumor cells typically have evolved resistance to apoptosis, whereas chemotherapies often kill tumor cells by overcoming that resistance.

Dix, Cravatt, and their colleagues are now trying to determine whether certain phosphorylated protein fragments can be used as highly specific "biomarkers" of apoptosis in cancer cells, detectable in a simple blood test. "Such a test would tell you whether or not your cancer drug is working," Cravatt said.

The wealth of data from these apoptosis studies may also help researchers devise new apoptosis-inducing cancer drugs, he notes—and apoptosis is merely one cellular process that the new mapping technique can be used to illuminate.

The research was funded by the National Institutes of Health, the California Breast Cancer Foundation, ActivX Biosciences, the ARCS Foundation and the Skaggs Institute for Chemical Biology at Scripps Research.

Scripps Research Scientists Show Potent New Compound Virtually Eliminates HIV in Cell Culture

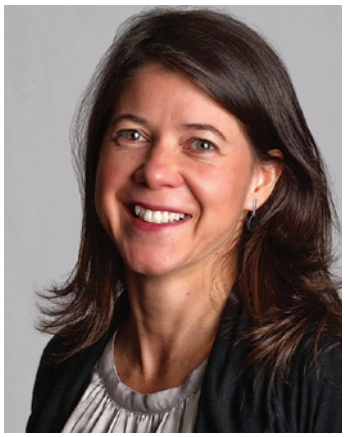
> A new study by scientists on the Florida campus of The Scripps Research Institute shows, in cell culture, a natural compound can virtually eliminate human immunodeficiency virus (HIV) in infected cells.

The compound defines a novel class of HIV anti-viral drugs endowed with the capacity to repress viral replication in acutely and chronically infected cells.

The HIV/AIDS pandemic continues to affect 34 million individuals worldwide, including more than 3 million children, according to the World Health Organization. Current treatment involves the use of several antiretroviral drugs, termed Highly Active Antiretroviral Therapy (HAART), which can extend the life expectancy of HIV-positive individuals and decrease viral load without, however, eradicating the virus.

"We know that there are reservoirs of HIV that aren't being eliminated by current treatment and that keep replenishing the infection," said Susana Valente, a Scripps Research biologist who led the study.

"Viral production from these cellular reservoirs that harbor an integrated viral genome is not affected by current antiretroviral drugs, which only stop novel rounds of infection. The compound in the current study virtually eliminates all viral replication from already-infected cells where HIV hides."



Assistant Professor Susana Valente

The new study, published in the July 20, 2012 issue of the journal *Cell Host and Microbe,* focused on a medically promising compound known as Cortistatin A. This natural product was isolated in 2006 from a marine sponge, *Corticium simplex,* discovered more than 100 years ago. In 2008, Scripps Research chemist Phil Baran and his team won the global race to synthesize the compound, presenting an efficient and economical method.

In the new study, Valente and her colleagues collaborated with the Baran lab, using a synthetic version of the compound, didehydro-Cortistatin A, to study the compound's effect on two strains of HIV. The strains were HIV-1, the most common form of the virus, and HIV-2, which is concentrated in West Africa and some parts of Europe.

The results showed that the compound reduced viral production by 99.7 percent from primary CD4+T cells (a type of immune cell) isolated from patients without levels of the virus in their bloodstream and who had been under HAART treatment for a long period of time. When the compound was added to other antiviral treatments, it further reduced by 20 percent viral replication from CD4+T cells isolated from patients with detectable amounts of virus in their bloodstreams.

The inhibitor works by binding tightly to the viral protein known as Tat, a potent activator of HIV gene expression, effectively preventing the virus from replicating even at miniscule concentrations—making it the most potent anti-Tat inhibitor described to date, Valente said.

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Tumor Suppressor, CONTINUED

immune system affected in human lymphoma. Using transgenic animal models, Cleveland and his team, led by the efforts of senior postdoctoral fellow Robert Rounbehler, showed that Myc-directed repression of a protein called tristetraprolin (TTP/ZFP36) was important for both the development and maintenance of cancer. The suppression of TTP is a hallmark of human cancers with MYC involvement, Cleveland noted.

The scientists' results showed that overriding this pathway by forced expression of TTP more than doubled the lifespan of Myc transgenic mice. Strikingly, Rounbehler discovered that re-introduction of TTP into Myc-driven lymphoma totally disabled these tumors, indicating an important therapeutic target.

The authors showed that Myc regulates hundreds of genes that contain adenylate-uridylate-rich elements (AU-rich elements), which play an important role in RNA stability and are found in many messenger RNAs (mRNAs) that code for oncogenes, nuclear transcription factors, and cytokines. AU-rich elements direct the mRNA for degradation; they are thought to be vital for controlling expression during cell growth.

"Myc regulates the expression of select AU-binding proteins to control the destruction of certain mRNAs," Cleveland said. "Also, our study strongly suggests that other AU-binding proteins may also, in fact, function as tumor suppressors in other cancers."

The study was supported by the National Institutes of Health, ThinkPink Kids Foundation, the State of Florida, the National City Charitable Contributions Committee, the Glenn W. Bailey Graduate Fellowship, and the PGA National Women's Cancer Foundation.

DONOR PROFILE

Joyce McLendon: A Stalwart Supporter of the Quest to Eliminate Disease

Joyce McLendon

Palm Beach resident Joyce McLendon knows how to keep busy—to put it mildly. A well-known and humble philanthropist for many years, Joyce, now 86 years old, is extremely involved with Scripps Florida. Her many volunteer commitments include serving as Board Chair for the Lord's Place (which fights homelessness), the Mideast Arthritis Foundation, and the Palm Beach Chamber Music Festival; being the incoming Chair for the Florida Arthritis Foundation Chapter; serving as First Vice President for the Arthur R. Marshall Foundation, which champions the restoration and preservation of the greater Everglades ecosystem; and sitting on the boards of the Palm Beach United Way, Alzheimer's Association, and the Fellowship of Christians and Jews.

She has been named "Executive Woman Volunteer of the Year" by the Palm Beach Chamber of Commerce and "2006 Outstanding Volunteer Fundraiser" by the Palm Beach County Chapter of the Association of Fundraising Professionals.

Asked why she gets so involved in the community and nonprofit causes, Joyce said, "I don't need anything…but lots of people do."

Joyce is a firm believer in supporting health causes. "I'm convinced that good health and eliminating diseases are our greatest needs," she said.

Joyce, who is a breast cancer survivor, is extremely interested in finding treatments and cures for Alzheimer's disease, arthritis, and cancer.

Her late husband Sam, who passed away from Alzheimer's, was a former Palm Beach Town Council member who was known for his warm demeanor and sense of humor, always putting others first. He was a partner in the consulting engineering firm Holzmacher, McLendon and Murrell, which became H2M Group. He helped design and create the operational systems for a number of water plants on Long Island, as well as a few in New Jersey.

Joyce moved to Palm Beach in 1991 from the town of Auburn, Indiana, where she grew up as Joyce Wiley and later became Joyce McIntyre. She met Sam on a tennis court in 1993, after he had retired and moved to Palm Beach. They were married in 1994. Sam later developed Alzheimer's disease. With his memory slipping badly, Joyce comforted him for five years during a very difficult time, until he passed away.

"There's nothing else you could do," said Joyce. "You couldn't take him to the ends of the earth and get a cure. I tried to make him as happy as I could for as long as possible. The experience really brought home the devastation of the disease and the need for a cure."

Joyce is a strong supporter of Scripps Florida. She has contributed a major gift and is a member of the Scripps Florida Council which has been instrumental in introducing the leaders of the Palm Beach business and philanthropic communities to the work of Scripps.

"I contributed to Scripps Florida in order to eliminate diseases," said Joyce. "It's a very impressive and inspiring place, and its young graduate students are launching science into the future."

Joyce initiated the idea for the Scripps Florida Science of Health lecture series, and serves as its Chairwoman. The series, which plays to packed houses, is held at the Royal Ponciana Chapel in Palm Beach.

"So many families are impacted by health issues," said Joyce. "I hope the series introduces Scripps to Palm Beach, so they know we're up in Jupiter, and what we are working on," said Joyce.

Outside of her philanthropic and volunteer efforts, Joyce can lay claim to a couple of very interesting distinctions. She is one of the founders of the largest automobile museums in the world, the Auburn Cord Dusenberg Automobile Museum, in her hometown of Auburn, Indiana. And she holds the world record as the oldest woman ever to fly a combat jet, which she did in her 70's. She was the one brave person to sign up for the flight in a Historical Society of Palm Beach County auction, and flew the jet in Orlando through an association of retired air force and airline pilots.

Joyce McLendon is a truly inspirational community leader, whose impact is being felt in so many vital areas.

HIV, CONTINUED

Another interesting feature of this compound is that withdrawal of the drug from cell culture does not result in virus rebound, which is normally observed with other antiretrovirals.

While most antiretroviral compounds block only new infections, didehydro-Cortistatin A reduces viral replication from already-infected cells, potentially limiting cell-to-cell transmission.

The new inhibitor already has a drug-like structure, is effective at very low concentrations, and has no toxicity associated with it, at least at the cellular level, the study noted.

The study was supported by the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) and the Landenberger Foundation.

Jeanne Loring: Creating New Opportunities to Treat Diseases through Stem Cell Research

> There are certain scientific advances that have had the power to change the human experience: the development of penicillin, the polio vaccine, the Human Genome project … many scientists expect that stem cell advances will soon be added to this list.

Leading the way in this burgeoning area of research is Professor Jeanne Loring, an internationally recognized authority in stem cell research, at Scripps Research's Center for Regenerative Medicine.

Stem cell research explores the potential of these cells to differentiate into various cell types that may be used to treat diseases and conditions such as Parkinson's disease and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis. It holds remarkable potential.

"Stem cells have such great ability to help science in so many ways," said Jeanne. "We're able to test drugs for certain diseases using stem cells from people who have the diseases. We've never had this opportunity before."

Normally, cells develop from stem cells into a myriad of increasingly more specialized cell types during early development and throughout a lifetime. In humans and other mammals, these developmental events are usually irreversible. This means that when tissues are damaged or cells are lost, the body has limited means by which to replenish them.

Having a source of stem cells would be useful in many medical situations because these cells are "pluripotent," having the ability to become any of the body's cell types. Pluripotent stem cells would potentially provide physicians with the ability to replace or repair damaged tissues throughout the body. In some cases, pluripotent stem cells may be differentiated into the damaged cell type and transplanted to the patient.

Much research on pluripotent stem cells to date has been conducted on human embryonic stem cells, which are harvested from discarded embryos (those created but not used for the purposes of *in vitro* fertilization, a technique to help couples conceive). However, recently another source of pluripotent stem cells has come onto the scene. These cells—called induced pluripotent stem cells—are created by taking a sample of skin cells or another type of differentiated cell and using molecular biology techniques to coax them back into a pluripotent state.

"We've never been able to do this before," said Jeanne. "If people have diseases such as heart disease, liver disease, or diseases of the brain, we can study the disease in a culture dish using their cells, and then screen for drugs that can correct the problem and feed into the pharmaceutical pipeline—it's the highest impact, short-term use for cells." One such project of Jeanne's, funded by the National Institutes of Health, is an effort to understand autism by studying development of nerve cells in culture dishes.

Professor Jeanne Loring

Jeanne is very involved in community efforts. "Stem cell research allows you to have a broad social impact," she said. "I don't work behind closed doors. I like to meet patients and understand the problems they face."

She is the recipient of funding from the Parkinson's Association of San Diego. A team of 16 people, including three people with Parkinson's disease, recently climbed to the top of Mount Kilimanjaro to raise the necessary funds for a pilot project using stem cells. Working with Melissa Houser at Scripps Clinic, Jeanne is taking skin cells from six Parkinson's patients, "reprogramming" them into stem cells, and making the stem cells into dopamine neurons that may eventually be used to repair their brains. Many of the patients and members of their families have visited Jeanne's lab to meet the scientists and better understand the research. "The involvement of the patients has really inspired and motivated our lab members," said Jeanne.

Jeanne is currently involved in two cell transplantation projects with the aim of producing investigational new drugs within a few years. The two projects are partnerships with University of California, Irvine scientists, Thomas Lane on a study of multiple sclerosis and Frank LaFerla on Alzheimer's disease.

Both projects have been successful in experiments with mice, and both involve the use of neural precursor cells produced in Jeanne's lab from human pluripotent stem cells. In the Alzheimer's disease project, the idea is to use the cells to deliver growth-enhancing molecules to the brains of Alzheimer's patients. Mice with Alzheimer's-like disease have regained their ability to form short-term memories. For the multiple sclerosis project, transplanted human neural precursor cells have allowed mice with multiple sclerosis-like disease to regain use of their limbs.

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In both cases, the launching of the project was based on the surprising results of early experiments. "It's important to try experiments in which we don't know what results to expect," said Jeanne. "Risk taking often leads to new directions in research."

Jeanne's drive to make a difference has taken her from academic research to the biotech industry and back to academia. As director of Scripps Research's Center for Regenerative Medicine, she is producing groundbreaking research like her Parkinson's disease, Alzheimer's disease, and multiple sclerosis projects, and focusing her expertise on work that may have extraordinary implications.

"A single idea has the capacity to make a significant impact in the world," said Jeanne. "Our team attempts to transform ideas into reality. Ever since I was a grad student, I believed that scientists should be responsible to the public—and I wanted my research to have an impact on human disease."

In another major breakthrough with Oliver Ryder of the San Diego Zoo Institute for Conservation Research, Jeanne's lab produced the first stem cells from two highly endangered animals—a rare African monkey called the drill and the nearly extinct northern white rhinoceros—transforming the animals' skin cells into pluripotent stem cells. There are only seven northern white rhinos still in existence, two of which reside at the San Diego Zoo Safari Park.

Viewed as a first step toward greater advancements, the stem cells could eventually make it possible to improve reproduction and genetic diversity for some species, possibly saving them from extinction, or to bolster the health on endangered animals in captivity. The best way to manage extinctions is to preserve species and their habitats, but that's not working all the time, with the rhinos being a perfect example. Stem cell technology provides some level of hope that these animals won't have to become extinct even though they've been completely eliminated from their habitats. The research, which received substantial funding from the Esther B. O'Keeffe Charitable Foundation, was named by Discover magazine as one of the top 100 stories of 2011.

"Because Scripps Research has a tradition of being on the cutting edge of research, the institute's scientists are always ready to take on the next big challenge," said Jeanne. Designed to foster scientific partnership, train the next generation of stem cell scientists, and inform the public about stem cell research, the Center for Regenerative Medicine is a key player in this important field.

"I appreciate the independence we're given here at Scripps Research as well as my incredible colleagues," said Jeanne. "They're the best and most diverse in the world—we have experts here in so many different areas. If I need to learn something, I don't have to go far."

Jeanne and her colleagues have gained a reputation in the stem cell community for their experimental rigor. They are continuously examining and inventing new methodologies and novel approaches to study some of life's most debilitating diseases. "We specialize in big projects that produce a huge amount of high quality data," said Jeanne. "As a result of our focus on quality control, our work answers scientific questions conclusively."

In addition to the Parkinson's Association of San Diego and the Esther B. O'Keeffe Charitable Foundation, Jeanne has received philanthropic support from Marie and Jimmy Mayer, the Millipore Foundation, and Autism Speaks. She believes that because of the potential for breakthrough discoveries, stem cell research is a great place for philanthropists to place their support. "Government grants tend to be restrictive. With private support, we've been able to take risks and make progress in technologies that could result in life-saving discoveries. It has allowed us to accomplish things that would not have been possible with classic research grants."

Jeanne has a B.S. in Molecular Biology from the University of Washington and a Ph.D. in Developmental Neurobiology from the University of Oregon. She served on the faculty of the University of California, Davis and has held research and management positions at biotechnology companies including Hana Biologics, GenPharm International, Molecular Dynamics, and Incyte Genomics, and was founder and chief scientific officer of Arcos BioScience (now part of ViaCyte). She joined the faculty of the Burnham Institute for Medical Research as a principal investigator in January 2004. She joined Scripps Research in October 2007.

Jeanne's lab has 35 scientists, and like a biotech firm, emphasizes team science. "My goal is to help my researchers launch their own labs one day," said Jeanne. "The people who have trained in my lab have all gone on to other jobs, many in biotech, or to graduate school."

Jeanne has always had an interest in science. "My dad was an exploration geologist and he sometimes took me on his prospecting trips," she said. "I have fond memories of going out in his pick-up truck with a Geiger counter. I started college with a major in comparative literature, but found that my science classes were so much easier. I've never looked back—science is exciting!"

Jeanne's interest in the social impact of science has led to her being asked to serve on ethics committees, often as the only scientist among professional ethicists, politicians, and community leaders. She currently serves on one such committee for Merck Serono and recently completed a term on the Ethics and Regulatory Board for the Bill and Melinda Gates Foundation. The goal of the Gates Foundation board was to oversee a stem cell project in Beijing, helping the researchers there conform to worldwide ethical standards.

Ever the scientist, Jeanne's chief hobby focuses on a different field of science. I've seen ten total solar eclipses in Bolivia, Aruba, Libya, Zambia, and other locales," she said "Over the years, I've spent more than 30 minutes in the shadow of the moon completely covering the sun. This November, I'll be viewing the solar eclipse in Papua, New Guinea. Why solar eclipses? It's hard to take vacations away from the lab; I don't want to miss an exciting discovery. The good thing about eclipses is that they take place at times and places that you can't change! They are an amazing experience, and there's always something new. In Bolivia, there are people who believe that the sun is being eaten by a jaguar during an eclipse, and they bang pots and pans to frighten the jaguar and make the sun come back! In Libya, our college-educated guide laid face down in prayer during the darkness of the eclipse."

When asked about her goals, Jeanne said, "I want to leave behind a legacy of doing great science and taking chances, but with a solid infrastructure. I feel strongly about being ethical in science, and I train my lab members to carry on that tradition."

Team Describes Antibodies that Protect Against Large Variety of Flu Viruses

> The work is a key step toward 'universal' vaccine and therapies against flu

A team led by scientists at The Scripps Research Institute and Crucell Vaccine Institute in the Netherlands has described three human antibodies that provide broad protection against Influenza B virus strains. The same team had previously reported finding broadly neutralizing antibodies against Influenza A strains.

The isolation of the new broadly neutralizing antibodies, which was reported in the journal *Science's* advance online edition, *Science Express,* on August 9, paves the way for researchers to develop a universal antibody-based flu therapy for use in severe infections or to protect hospital staff during an outbreak.

Importantly, these antibodies may provide key clues to the design of an active universal flu vaccine—designed to protect long-term against flu viruses, not just against the current season's strains.

"To develop a truly universal flu vaccine or therapy, one needs to be able to provide protection against influenza A and influenza B viruses, and with this report we now have broadly neutralizing antibodies against both," said Ian A. Wilson, the Hansen Professor of Structural Biology at Scripps Research, who was senior investigator for the new study with Crucell's Jaap Goudsmit and Robert Friesen.

One of the newly discovered antibodies will be of special interest to flu researchers, because it appears to protect against essentially all influenza B and influenza A strains. "It's the only one in the world that we know of that has been found to do this," said Wilson.

Influenza B viruses are considered less dangerous than Influenza A viruses, and have been less intensively studied because they have less capacity to mutate into deadly pandemic strains. However, influenza B viruses account for a significant part of the annual flu illness burden in humans.

To find broadly protective antibodies against Influenza B, the team at Crucell generated a large collection of flu antibodies from the immune cells of volunteers who had been given a seasonal flu vaccine. The researchers then screened this collection for antibodies that could bind to a wide variety of influenza B strains.

Three of the antibodies they found in this manner—CR8033, CR8071, and CR9114—protected mice against normally lethal doses of the two major influenza B strains. CR9114 also protected mice against influenza A viruses, including the H1N1 subtype that killed about 17,000 people in a 2009 pandemic. The fact that these antibodies protected against a variety of flu strains suggested they mark functionally important sites, or "epitopes," on the virus that are relatively unchanging (conserved) from one flu strain to the next.

Wilson's team at Scripps Research characterized the newly discovered antibodies' binding sites on influenza viruses using electron microscopy and X-ray crystallography techniques. They found that CR8033 binds to a highly conserved epitope—a functionally important site—on the "head" of the hemagglutinin protein, a structure that studs the outer coat of flu viruses and allows the viruses to stick to vulnerable cells. CR8071 binds to the base of the hemagglutinin head. Most antibodies that bind to the hemagglutinin head and neutralize influenza do so by blocking the virus's attachment to host cells.

"The unique thing about these two antibodies is that they neutralize flu viruses chiefly by preventing virus particles from exiting infected cells," said Nick Laursen, a research associate in Wilson's laboratory who was a lead author of the study.

Professor Ian Wilson

Antibody CR9114 turned out to bind to a site on the hemagglutinin stem. "It prevents the hemagglutinin protein from undergoing the shape-change needed for the virus to fuse to the outer membrane of a host cell," said Cyrille Dreyfus, a Wilson lab research associate who also was a lead author of the study. "This appears to be a real weak point of the virus, because this epitope is highly conserved among influenza A subtypes as well as influenza B."

Wilson notes that in a study published in 2009 his laboratory determined the structure of another Crucell antibody that broadly neutralizes influenza A viruses by binding to essentially the same site on the hemagglutinin stem— but in a subtly different way, so that it fails to get a grip on influenza B viruses, too. "With some tweaking of that antibody's binding domains, we might have been able to get a broader effect like CR9114's," Wilson said.

The viral epitope to which CR9114 binds will now be studied extensively by researchers as a target for vaccines and therapies, because it is the only one found so far that is broadly vulnerable to neutralization on both influenza A and B viruses.

Remarkably, CR9114 performed poorly against influenza B viruses in initial lab-dish tests known as microneutralization assays, which test the ability of an antibody to protect cells from viral infection. Yet CR9114 was clearly effective under more realistic conditions in mice, even at low doses. Because it attacks the stem rather than the head of flu virus hemagglutinins, CR9114 also failed to show effects in a widely used test known as the hemagglutinin-inhibition assay.

"As we move towards design of a universal flu vaccine, we need to find more inclusive assays to screen for antibodies such as CR9114, which may be highly effective but have novel mechanisms for neutralization that cannot be detected by the current methods used in influenza vaccine development," Goudsmit said.

An Income That Can't Shrink

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- The same plan freed you from worries about outliving your resources, fluctuating interest rates and the performance of your investments?
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Answer: Charitable Gift Annuity

GIFT ANNUITY PAYMENT RATES *For illustrative purposes only.*

Selected Rates for One Person		Selected Rates for Two People of the Same Age	
AGE	RATE	AGES	RATE
70	5.1	70/70	4.6
75	5.8	75/75	5.0
80	6.8	80/80	5.7
85	7.8	85/85	6.7
90+	9.0	90/90	8.2

How does it work?

A charitable gift annuity is a contract between you and Scripps Research. You make a gift of cash or appreciated securities and in return Scripps Research provides to you an annuity for the rest of your life. These payments never decrease in size or frequency, regardless of the changes in the economy. *See table for rates that you may currently receive.*

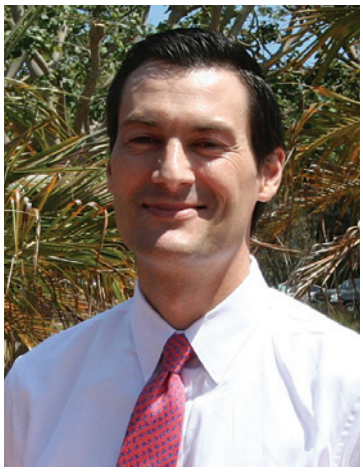
Other benefits of a Charitable Gift Annuity

- An income tax deduction is available for a portion of your charitable gift.
- Part of each payment is tax free from federal income tax for a period of time.
- You may enjoy capital gains tax savings.
- Estate taxes generally will not be due on amounts used to fund your annuity.
- Payments could also benefit loved ones and friends.

Also, another option might be a deferred gift annuity which pays out at a later date and provides for slightly higher annuity rates. For confidential consultation, and to find out more about our Scripps Research charitable gift annuity program and how an annuity might work for you, please contact Geoff Graham at (858) 784-9365 or gcgraham@scripps.edu.

When considering charitable gifts, you are urged to seek the advice of your own financial and legal advisor(s) about your specific situation.

Nick Burchfield Named Director of Corporate and Foundation Relations



Nick Burchfield

Scripps Research is pleased to welcome Nick Burchfield as its new Director of Corporate and Foundation Relations. Nick comes to Scripps Research after serving as Foundation Development Officer at Sanford-Burnham Medical Research Institute for six years. Nick is responsible for securing foundation and corporate funding to support Scripps Research's medical research, graduate school, and other programs that help the Institute fulfill its mission.

Nick has a successful history working with local and national foundations, and brings a wealth of experience in grant writing and proposal development.

As Nick explains, "With National Institutes of Health grant funding becoming more competitive and increasingly difficult to secure, private foundations and corporations play a critically important role in providing Scripps Research the funds we need to make important scientific discoveries and support the next generation of world-class scientists. I am thrilled to be a part of the incredible things happening here at Scripps Research, and I look forward to helping the Institute in its quest to improve human health."

Nick earned a bachelor's degree in sociology from Trinity College in Hartford, Connecticut. For further information about the Corporate and Foundation Relations program at Scripps Research, please contact Nick at (858) 784-2874 or nburch@scripps.edu.

The Scripps Research Institute

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