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RESEARCH UPDATE

Scripps Research Scientists Find New Way to Attack Cancerous Cells

> Findings Open the Door to the Development of More Effective Therapies for Lymphomas and Leukemias



Professor James Paulson

Scripps Research Institute scientists have discovered a new way to target and destroy a type of cancerous cell. The findings may lead to the development of new therapies to treat lymphomas, leukemias, and related cancers.

The study showed that in animal models the new technique was successful in drastically reducing B cell lymphoma, a cancer of immune molecules called B cells.

“[The method] worked immediately,” said Scripps Research Professor James Paulson, who led the research. “We are very interested in moving this technology forward to see if it would be applicable to treatment of humans and to investigate other applications for this kind of targeting.”

In his research program at Scripps Research, Paulson has studied glycoproteins, which are proteins decorated with sugars, for many years.

While these molecules have traditionally proven challenging to understand, limiting their pharmaceutical applications, Paulson has pioneered new techniques to study and manipulate these enigmatic molecules.

In the new research, Paulson and his colleagues applied some of the lab’s insights to a problem with great medical relevance—finding a new way to target and destroy cancer cells.

Specifically, in the new study the team set out to attack B cell lymphoma (which includes Hodgkin lymphoma and non-Hodgkin lymphoma), a type of cancer diagnosed most frequently in older individuals and those with compromised immune systems. Each year approximately 70,000 people are diagnosed with B cell lymphomas in the United States alone, according to the American

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Scripps Research Institute and Dana-Farber Scientists Uncover Novel Anti-Diabetes Mechanism

> Findings Could Lead to Next Generation of Improved Therapies

In a joint study, scientists from The Scripps Research Institute and the Dana-Farber Cancer Institute at Harvard University have uncovered a novel mechanism that dramatically increases insulin sensitivity and reduces the risk of developing type 2 diabetes and cardiovascular disease.

These findings offer a potent new target in the continuing search for new and improved anti-diabetic treatments. Currently, nearly 24 million children and adults in the United States have some form of the disease, according to the American Diabetes Association.

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Cancer Society. While the drug rituximab is often effective at treating the disease, each year 22,000 patients still die from B cell malignancies.

Normally, B cells provide an important immune function circulating throughout the bloodstream to help in the attack of infectious agents. But when B cells become cancerous, the question becomes how to pick them out of the crowd of other molecules in the body to target them for destruction, ideally without affecting surrounding tissues.

Because of his previous research, Paulson knew that B cells had a unique receptor protein on their surfaces that recognized certain sugars found on glycoproteins. Could the team create a viable potential therapeutic that carried these same sugars to identify and target these cells?

Paulson and colleagues decided to try a unique approach to this problem.

The scientists combined two different types of molecules into one, using both new and tried-and-true technology. One part of the potential therapeutic was composed of a specialized sugar (ligand) recognized by the B cell receptor, called CD22,

expressed on the surface of B cells. This was attached to the surface of the other portion of the potential therapeutic, a nanoparticle called a "liposome," loaded with a potent dose of a proven chemotherapy drug.

"The advantage is that we already know a lot about how liposomes act in the body because they are approved drugs," said Paulson. "They have a long circulatory half-life. They are formulated so they are not taken up by the macrophages in the liver. So we just used the same formulation, attached these ligands, and went right into *in vivo* studies."

The chemotherapy drug chosen was doxorubicin, which is used in the treatment of a wide range of cancers. First identified in the 1950s, doxorubicin was originally isolated from bacteria found in soil samples taken from a 13th-century Italian castle. The team used a nanoparticle formulation of doxorubicin called Doxil, in which the drug is encapsulated inside the liposomal nanoparticle, which Paulson explains protects normal cells from the drug until it reaches the cancer.

Normally Doxil is passively delivered to tumors by exiting

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Diabetes, CONTINUED

"The field has become interested in finding drugs that can promote increased insulin sensitization but not activate the classical fat cell generating pathway of the protein, PPAR γ ," said Patrick R. Griffin, chairman of the Department of Molecular Therapeutics at Scripps Florida who headed up the Scripps Research part of the study. "We examined the mechanism of action of compounds that bind to PPAR γ that improve insulin sensitivity but have minimal induction of fat. It was clear from the studies that these compounds have a unique but overlapping mechanism with the class of drugs used clinically that target PPAR γ ."



Professor Patrick Griffin

Adipose or fat tissue lies at the center of the metabolic syndrome, a cluster of risk factors that increases the possibility of type 2 diabetes, as well as stroke, coronary artery disease, and even certain cancers. Of those risk factors, excessive body fat is considered the most problematic. PPAR γ can be considered the master gene of fat cell biology because it drives the conversion of cellular precursors into fat cells.

The collaborative studies showed obesity causes a modification on PPAR γ that leads to alterations in the expression of a number of genes, including a reduction in the production of an insulin-sensitizing protein (adiponectin). This leads to an increase in insulin resistance. The reprogramming of genes controlled by PPAR γ occurs when it undergoes phosphorylation (a phosphate group is added to a protein) by the cdk5 kinase, an enzyme that is involved

in a number of important sensory pathways and that can be activated by pro-inflammatory proteins.

The scientists were able to use both full and partial agonists (compounds that activate a cellular response) to reverse these phosphorylation effects and improve the production of adiponectin. These results strongly suggest that cdk5-mediated phosphorylation is involved in the development of insulin-resistance and open the door to a novel opportunity for creating an improved generation of anti-diabetic drugs.

In 2007, Griffin and his colleagues published a study that explained the difference between how full and partial agonists interacted with PPAR γ . Full agonists interacted strongly with a region of the receptor known to be important for the classical fat generation program. On the other hand, partial agonists, which are poor agonists of the receptor, did not interact with this region at all but interacted more strongly with a potentially critical region of the receptor. From a drug development point of view, these results offered a new area of the protein to focus on to optimize therapeutic molecules that would be potent insulin sensitizers without driving fat generation.

"Bruce Spiegelman at Dana-Farber was starting to uncover the fact that the phosphorylation of PPAR γ takes place in the very region where MRL-24, one of the partial agonists interacted," Griffin said. "I suggested that compounds like MRL-24 might be better at antagonizing the cdk5 site given their strong interaction in this region of the receptor. For the new study, we provided significant amounts of compound to support the animal studies and provided a plausible mechanism for how partial agonists might recruit co-activator proteins to the cdk5 surface of PPAR γ ."

While the team found that PPAR γ phosphorylation effects were reversed by both full and partial agonists, partial agonists

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Richard and Helen DeVos: Philanthropists and Champions of Free Enterprise

In 1959, Rich DeVos and his high school friend and fellow World War II veteran Jay Van Andel formed Amway, which today is one of the largest privately held companies in America. Known for being champions of free enterprise, Rich and his wife, Helen, are also among the foremost philanthropists in the United States. Numerous organizations have been touched by their generosity, including Scripps Research.

Rich and Helen, through their foundation, recently donated \$100,000 to Scripps Research to jump start a philanthropic drive to expand the graduate school program at Scripps Florida. The program, part of Scripps Research's Kellogg School of Science and Technology, offers a doctoral program with an emphasis on chemistry, chemical biology, biophysics, or the biological sciences.

"We have watched Scripps Florida grow from a single idea to a high-tech center for world-class biomedical research, right here in Jupiter," said Rich. "We hope our gift will help Scripps Florida keep attracting the best young scholars to its graduate program."

As the owner of the Orlando Magic NBA basketball team, Rich has a special interest in the state of Florida. The DeVoses were early supporters of the vision of then-governor Jeb Bush to develop a thriving biotechnology industry in the state.

Scripps Research's commitment to improving human health through advanced biomedical research, its entrepreneurial approach to research, and its culture of innovation made it a natural partner for the DeVoses charitable giving and their philosophy of helping individuals fulfill their potential so they can contribute to society.

Out of a total of 30 students currently enrolled in the Scripps Florida graduate program, half a dozen have a connection to Florida. So far, five students have completed their Ph.D. degrees on the Florida campus. The entire institute's graduate program encompasses approximately 200 Ph.D. candidates on both the California and Florida campuses.

"The level of excellence and accomplishment of our Scripps Florida graduate students is exceptional," said William R. Roush,

associate dean for the Scripps Florida graduate program, as well as professor of chemistry and executive director of Medicinal Chemistry at Scripps Florida. "The DeVos contribution will help us continue to identify and recruit top notch candidates, especially those who come from Florida."

The quality of the Scripps Research graduate program has been widely recognized by independent sources. For one, U.S. News & World Report, which periodically reviews the nation's colleges, has ranked The Scripps Research Institute among the best graduate schools in the country. The graduate program is provided at no cost to the students, who are given a stipend to cover living and other expenses.

Rich, who serves on the Scripps Florida Council, is also especially fascinated with the work of Ron Davis, chair of the Scripps Florida Neuroscience Department, who uses fruit flies to study neurological diseases.

"We cannot begin to thank Rich and Helen enough for their gift and Rich's service on the Scripps Florida Council," said Alex Dreyfoos, Scripps Research trustee. "The investment will serve to further life changing research, and inspire students in their scientific studies."

Natives of the Grand Rapids area, Rich and Helen have transformed the quality of life in that region, in Florida, and beyond through their time, philanthropy, and the impact of fifty years of economic development driven by Amway's remarkable success.



Richard and Helen DeVos

Diabetes, CONTINUED

indeed accomplished this as well or better than the full agonists. Mimicking the effects of just blocking the phosphorylation event by mutation of the site on the receptor showed improvements in the production of adiponectin.

The new study also suggests a unified framework for understanding the relationship between fat cell dysfunction in obesity and anti-diabetic therapies based on PPAR γ . In animal studies, high fat diets activate the cdk5 kinase, initiating phosphorylation, disrupting a number of key metabolic regulators including *adiponectin* and *adipsin*, a fat cell-selective gene whose expression is altered in obesity.

"The great paradox of this whole effort is we're targeting a receptor critical for fat production to offset the *problem* of fat overproduction," Griffin said. "Unfortunately, current drugs that target PPAR γ increase fat as one of their unwanted long-term side effects."

While the study is a big step forward, important questions still remain such as does a high fat diet and obesity lead to activation of cdk5 in non-fat tissues, Griffin said, since the negative effects of obesity extend far beyond metabolic syndrome to diseases like cancer and neurodegeneration.

Peter K. Vogt: A Groundbreaking Pioneer in Cancer Research

> As a teenager, Peter K. Vogt wanted to study philosophy and become a monk. After his undergraduate studies, he thought of becoming a high school teacher. And his love for painting also once made him consider a career as an artist. But instead he went into science – and became an internationally renowned cancer researcher whose work has profoundly changed biology and medicine.

But how did this pioneering scientist get his start? The first decision to pave the way was made in 1950, when Dr. Vogt as a teenager escaped from his East German home to the West. It was a dangerous step, something he and a friend had been preparing to do for some time. “We knew how to get across the border,” Dr. Vogt said of that first dramatic journey. “We’d gone across the border in previous summers – to taste freedom. By the time I finished high school, even before that, I knew that I had to leave.”

He went to Würzburg, a city which had been almost completely destroyed during World War II, but was about to be rebuilt. “I liked the spirit of this city and knew that this was the place to be.” He studied biology at the University of Würzburg and also took classes with the painter Josef Versl. After receiving his degree, he did not know what to do next and took a friend’s advice to do a summer internship at a research institute. “The institute was in a very small town. It was so boring, there was nothing you could do on a weekend, other than working and reading.” In the institute’s library he came across a book that changed his life – “*General Virology*” by S. E. Luria. It was the first book on virology he read and it hooked him. He decided to stay in science and joined the Max Planck Institute for Virus Research in Tübingen – the only institute in Germany working in the field of virology at that time – for his graduate studies.



Professor Peter Vogt

The ultimate goal of his work has long been to apply the genetic knowledge of cancer to the development of novel therapies that will be effective in the treatment of the disease.

In 1959 he moved to America, where he had been accepted for postdoctoral training at the University of California in Berkeley. During his postdoctoral studies in the laboratory of Dr. Harry Rubin he started to work on a virus that induces cancer. Dr. Rubin had just developed a method to study cancer in cell culture. This method became the starting point for much of the scientific developments that have shaped cancer research today.

In the late 60s, Dr. Vogt discovered mutants in cancer viruses that proved they carry a single cancer causing gene. Drs. Michael Bishop and Harold Varmus at UCSF used these mutants to show that humans carry these cancer genes in an inactive form. We now know that human cancer essentially involves the activation of these oncogenes in the body. Our current understanding of cancer as a disease of genes is based on these seminal discoveries. Humans and animals carry many different cancer genes, and several that play critical roles in cancer were discovered by Dr. Vogt in the course of his studies with cancer viruses. His most recent discovery is a protein called PI 3-kinase which regulates numerous body functions. This protein is often mutated in common cancers; it increases its activity and then drives the development of the tumor. PI 3-kinase is now considered one of the most promising cancer targets.

In 1993 he joined The Scripps Research Institute as a Professor in the Department of Molecular and Experimental Medicine. He was attracted by the interaction of world class chemistry with the traditionally outstanding biomedical sciences at Scripps. “It was a genius decision to integrate these two branches of science in the fabric of the Institute. Here, I can hope to translate genetic knowledge and insights into new therapies. At Scripps, I can concentrate on my work with a minimum of distraction, collaborate with top scientists, and receive amazing institutional support. It’s the ideal environment for my work, and I think it points the way to the future of cancer research.”

The scientific community has honored Dr. Vogt with several distinguished awards including the Ernst Jung Prize for Medicine (1985), the Robert J. and Claire Pasarow Award (1987), the ICN International Prize in Virology (1989), the Bristol Myers Award (1989), the Paul-Ehrlich and Ludwig-Darmstaedter Prize (1988), the Charles S. Mott Prize (1991) and most recently the Albert Szent-Györgyi Prize for Progress in Cancer Research.

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Scripps Research Scientist Wins 2010 NIH Director's Pioneer Award

Carlos F. Barbas III, Ph.D., professor at The Scripps Research Institute, has been named one of the winners of the National Institutes of Health's 2010 National Institutes of Health (NIH) Director's Pioneer Awards, which includes a research budget of up to \$500,000 in direct costs per year for five years.

A key component of the NIH Roadmap for Medical Research, the Pioneer Award supports exceptionally creative scientists who take innovative approaches to major challenges in biomedical research.



Professor Carlos Barbas

Barbas is one of 17 scientists named by NIH Director Francis S. Collins, M.D., Ph.D., as new recipients of the prize, designed to give awardees the intellectual freedom to pursue groundbreaking new research directions.

"NIH is pleased to be supporting scientists from across the country who are taking considered risks in a wide range of areas in order to accelerate research," said Collins. "We look forward to the results of their work."

Barbas, who holds the Janet and Keith Kellogg II Chair in Molecular Biology and Chemistry and joint appointments in the Departments of Molecular Biology and Chemistry and the Skaggs Institute for Chemical Biology at Scripps Research,

was selected for the award on the basis of his proposal for future bold and high-impact work. Specifically, his proposal concerns chemically programming immunity, research that could lead to "instant immunity" vaccines for the flu, HIV-1, and cancer. The new approach would overcome a major drawback of current vaccinations—the lag time of days, or even weeks, that it normally takes for immunity to build against pathogens such as bacteria and viruses.

The NIH selects recipients through special application and evaluation processes. Distinguished outside experts identify the most competitive applicants.

"This is a tremendous recognition that Carlos is doing outstanding work," said Peter Wright, chair of the Scripps Research Department of Molecular Biology. "His laboratory continues to tackle some extremely important scientific questions that lay the foundations for future therapeutics and vaccines."

Barbas's research program and wide-ranging scientific inventions span a number of topics. His team invented human and synthetic phage antibody technology, the first artificial transcription factors capable of regulating endogenous genes for gene discovery and gene therapy. The group also pioneered a new approach to catalytic asymmetric synthesis called organocatalysis; developed directed evolution approaches for antibodies and zinc finger recombinases and nucleases to create novel therapeutics and gene therapy strategies; and invented chemically programmed antibodies and vaccines. Barbas's scientific inventions are behind numerous drugs in clinical testing for diseases such as cancer, diabetes, and AIDS.

The NIH Roadmap for Medical Research is a series of far-reaching initiatives designed to transform the nation's medical research capabilities and speed the movement of research discoveries from the bench to the bedside.

For more information about Barbas's work, see the Barbas lab website (<http://www.scripps.edu/mb/barbas/>).

Vogt, CONTINUED

Dr. Vogt's 50 years in science were marked with exciting and groundbreaking discoveries. Looking back, he feels he made the right decision when he fell in love with virology – but this does not mean he neglected his passion for art. Painting still remains a significant part of his life. "Speed and spontaneity are of essence in my art, and I favor watercolor as a medium. Watercolor tools are also readily portable, facilitating work en plein air – my strongest source of inspiration..."

Driven by a curiosity to discover, Dr. Vogt continues to be a leader in multiple aspects of cancer research, including initiatives that use some of the most important oncogenes as therapeutic targets – initiatives that are bringing renewed hope to cancer patients.

Please see Dr. Vogt's website at <http://www.scripps.edu/mem/vogt/> for more information on his research and a link to his gallery website.

Scripps Research Scientists Share \$2 Million in Florida State Research Grants

> The Florida Biomedical Research Program has awarded \$2 million in biomedical research grants to three scientists from the Florida campus of The Scripps Research Institute.

This year's awards went to Glenn Micalizio, an associate professor in the Scripps Research Department of Chemistry, who will receive \$1,199,600 over five years; Thomas Bannister, assistant professor of medicinal chemistry and associate scientific director of Scripps Florida's Translational Research Institute, who won a grant of \$400,000 over three years; and Douglas Kojetin, an assistant professor in the Molecular Therapeutics Department, who also won \$400,000 over three years.

The highly competitive grants from the Florida Biomedical Research Programs support innovative research into the prevention, diagnosis, treatment, and/or cure of cancer and tobacco-related diseases. Funding comes primarily from taxes collected from the sale of tobacco products.

Micalizio's five-year grant will make it possible for him to study naturally occurring anticancer agents that could become potential chemotherapeutic agents.

"We're looking at a protein called Hsp90, which is of considerable interest in cancer," Micalizio said, "because it plays a central role in controlling the function of a host of other proteins that are known to be oncogenic or cancer causing. Inhibiting Hsp90 results in the selective destruction of cancer cells. Unfortunately, the chemical structures of various natural products have proven difficult to optimize as therapeutic agents. Our aim is to develop ways to overcome those barriers. It's an exciting opportunity for chemists to help drive the search for the next generation of anticancer chemotherapeutic agents."

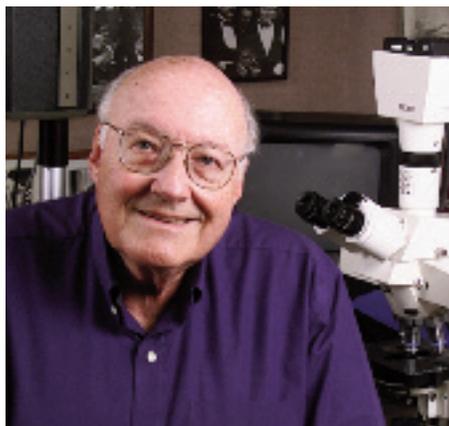
For Bannister, the grant is an opportunity to pursue an equally novel form of potential cancer treatment as part of

a collaborative research program in cancer therapy with William Roush, who is a professor in the Department of Chemistry, executive director of the Translational Research Institute Medical Chemistry Division, and associate dean of the Kellogg School of Science and Technology, and John Cleveland, chair of the Department of Cancer Biology.

"Cancer cells differ from most healthy cells in using one pathway, called glycolysis, to acquire nearly all of their energy from glucose," Bannister said. "The pathway makes lactic acid, a byproduct they must pump out in order to survive. Our research is aimed at improving molecules we have discovered that block lactic acid export and acidify the tumor cells. Cancer cells also recognize our compounds as an amino acid that they need in abundance. This tricks tumor cells into taking in something that will kill them."

The major focus of Kojetin's work is to understand how the structural dynamics of proteins contribute to their biological function. Modulation of a protein's dynamic shape or conformation represents an avenue for drug discovery.

"For this grant, we're looking at nuclear receptor transcription factor proteins, which are receptors for small molecules and important drug discovery targets for a variety of human diseases, including cancer and type II diabetes," he said. "When compounds bind to these receptors, other proteins called transcriptional co-regulator proteins also bind, all of which helps regulate expression of target genes. Hopefully, our work will help in the development of drugs targeting a specific receptor we've identified as promising."



Professor Michael Oldstone

Michael Oldstone's *Viruses, Plagues, and History* Named San Diego Book Awards Finalist

The revised and updated edition of Scripps Research Professor Michael Oldstone's book *Viruses, Plagues, and History: Past, Present, and Future* (Oxford University Press) has been named a finalist in the General Nonfiction category of the San Diego Book and Writing Awards. The book, published by Oxford University Press, paints a portrait of humanity's long-standing conflict with our unseen viral enemies. First released in 1998 to positive reviews in the *New York Times*, *Nature*, and *Science*, as well as other publications, the book has been translated into five languages (Japanese, Chinese, Hungarian, Polish, and Spanish).

Scripps Research SMART Teams Present Work at High Tech Fair

Students participating in the high school SMART team program at The Scripps Research Institute showcased their work at the San Diego High Tech Fair recently, presenting posters and molecular models at the Del Mar Fairgrounds to thousands of parents and students from around the region.

“They were a big hit,” said Marisela Chevez, the Scripps Research science outreach coordinator who spearheaded the SMART team program in San Diego with Ange Mason of the University of California, San Diego (UCSD) Super Computer Center. “All the hard work the students did throughout the year showed.”

The program—called “Students Modeling a Research Topic or “SMART” for short—was originally developed at the Milwaukee School of Engineering to provide students with the opportunity to learn more about science on their own time, after school and on weekends.

Now in its second year in San Diego thanks to efforts at Scripps Research and the UCSD Super Computer Center and a grant from the Howard Hughes Medical Institute, the number of schools participating has increased to six. New to the SMART team program are Lutheran High School of San Diego and Francis Parker School. Returning are teams from El Capitan High School, Lincoln High School, Arroyo Paseo Academy, and Audeo Charter, now called North San Diego Girls Cooperative. Some students from these schools opted to participate for their second year.

In the SMART team program, students delve in depth into a research topic over the course of an academic year, with the support and input of a teacher from the team’s school, SMART team program directors, and laboratory scientists. The students’ activities center around a specific molecule that is important to the scientists’ research.

Participants started the year by learning the basics of protein structure and folding, crystallography, and molecular modeling. In November, each team was paired with a volunteer lab from Scripps Research. “Thanks so much to the mentors in the Wilson, Kuhn, Wright/Dyson, Stout, and Stevens groups for volunteering to work with the students,” said Chevez.

Over the winter months, the teams met with the scientists from “their” lab, learned about the lab’s work, and created posters explaining their molecule. The teams also worked on creating physical models of their molecule using cutting-edge molecular

modeling technology, available from the Scripps Research Olson lab, to give to their SMART team teachers and scientific mentors. The students used software called RasMol to design their models, which were later “printed” out in eight to 12 inch structures that can be examined up close and passed from person to person.

“Marisela has brought together a great team of people to guide the teams through various parts of the project,” said David Goodsell of the Olson lab, who is scientific advisor for the San Diego initiative. “I have been helping with the design of models. As in the past years, the students have done a great job with their designs. I’m always amazed at the creativity they put into their designs—each team comes up with something unique.”

In the final phase of the program, students shared their work with each other and with the community. In addition to showing their work at the High Tech Fair—which was also attended by representatives of the Olson lab—the SMART teams participated in presentations on the Scripps California campus and at the San Diego Science Festival.

Susan Moerder, a teacher and SMART team leader at the Francis Parker School, said, “I have students on my SMART Team who range in all academic levels. The program has been beneficial for all of them. My top student has had the opportunity to work closely in the lab with our mentor, Dr. Gira Bhabha, while my students who typically struggle academically have found an area where they can shine. Whether it was designing the model, the poster, or the power point for their presentation, every student on the team had a job to do and had the chance to show their talent. This has been a great experience for all of us and I look forward to continuing our participation in future years.”

For more information on the SMART team program, contact Chevez, at mchevez@scripps.edu or (858) 784-2171.



Models created by SMART team participants help explain how specific molecules work.

Christine Crumbley Wins American Heart Association Fellowship

Christine Crumbley, a graduate student in the Kellogg School of Science and Technology and a member of the Scripps Florida Burris laboratory, has been awarded a two-year American Heart Association predoctoral fellowship. The title of her project is “Retinoic Acid Receptor-Related Orphan Receptor Alpha Regulation of the Hypoxia Response.”

Partners



1 Since the Scripps Florida Education Outreach Program began in 2006, over 76 teachers and students from over 15 Palm Beach County public high schools have taken part in the summer intern program. Pictured here representing the 2010 Class of Kenan Fellow Summer Interns, are 26 students, teachers, undergraduates, and returning alumni. (top photo)

2 To honor the Scripps Florida talent and scientific minds who now call Palm Beach their home, Elizabeth Fago, William Meyer, Steven Tendrich, and Paul Walczak II of Palm Health Partners hosted an evening of expression at Arcature Fine Arts, Palm Beach. The theme for the reception and dinner was one of talent – “The Art of Science” – in the form of inspiring painting, sculpture, music and science. After introductions by the hosts, eighty-five guests learned of the latest advancements and research initiatives underway at the nonprofit institute from three of its leading chairmen: Professor Charles Weissmann, Chairman, Department of Infectology; Professor Roy Smith, Chairman, Department of Metabolism and Aging; and Professor Ronald Davis, Chairman, Department of Neuroscience. Pictured here is Elizabeth Fago, a Scripps Florida Founder, with her children (l to r) Paul, Stephanie, and Joey. (bottom photo)

Cancer, CONTINUED

leaky tumor vasculature, and the drug slowly leaks out to kill the tumor. But by decorating the nanoparticles with the CD22 ligand, the team made the nanoparticles into a type of Trojan horse that is actively targeted to and taken up by human lymphoma B cells, carrying the drug inside the cell.

In the current research, the team administered their new compound to immune-compromised mice that had been infected with B cell lymphoma cells (Daudi Burkitt type). The team used two different formulations of the molecule, one decorated with two percent ligands, the other with five percent. The mice received only one dose.

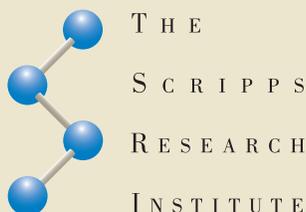
The results were remarkable. No mouse in the control group lived to the end of the 100-day trial, but five of the eight mice receiving the higher ligand dose of the compound survived.

The scientists then looked to see if they could detect any residual tumor cells in the survivors, knowing that in a mouse that is paralyzed by the disease 95 percent of the cells in the bone marrow are tumor cells.

“When we looked at the bone marrow of those that had survived to 100 days, we couldn’t detect any [tumor cells],” said Paulson. “Our detection limit was down to 0.3 percent. It was pretty impressive.”

To extend the results, the scientists examined their compound’s activity in blood samples from human patients with three types of B cell lymphomas—hairy cell leukemia, marginal zone lymphoma, and chronic lymphocytic leukemia. The scientists found that the compound also effectively bound to and destroyed these diseased B cells.

Encouraged by the results, the team is now working to further improve the drug platform, looking for ways to increase the specificity of B cell targeting as well as exploring the technology’s use with other chemotherapy agents.



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