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## **STATE GRANTS TOTALING \$49.2 MILLION AWARDED TO THREE UCLA STEM CELL SCIENTISTS TO FUND TRANSLATIONAL RESEARCH**

### **Grants will Fund Research to Develop New Therapies for Sickle Cell Disease, HIV/AIDS and Brain, Ovarian and Colorectal Cancers**

Three scientists with the Broad Stem Cell Research Center at UCLA were awarded grants today totaling \$49.2 million to take leading-edge stem cell science from the laboratory and translate it into new therapies for such devastating diseases as sickle cell, HIV/AIDS and brain, ovarian and colorectal cancers.

In all, 14 disease team grants totaling more than \$250 million were awarded today by the California Institute for Regenerative Medicine (CIRM), the state's stem cell agency. In all, scientists with the UCLA stem cell center have been awarded nearly \$122 million in state funding since 2005 for human pluripotent and adult stem cell research.

The four-year grants are part of CIRM's Disease Team Initiative, which seeks to explore new ways of integrating and organizing the highest quality basic, translational and clinical research with the aim of developing new therapies and diagnostic tools. As part of the approval process, disease teams must submit an investigational new drug application to the Food & Drug Administration within four years, fast-tracking stem cell-related drug development.

The UCLA disease teams include collaborations with other prominent stem cell institutions, industry and, in the case of the cancer disease team grant, a partnership with a Canadian research consortium. The Canadian government is matching the CIRM grant, bringing the total for the UCLA/Canada cancer disease team research project to nearly \$40 million.

"As one of the world's top research institutions, UCLA has long been a leader in translational research, taking the best laboratory science from the bench to the bedside to provide novel, more effective therapies that benefit the people of the world," said Chancellor Gene Block. "The fact that UCLA received three disease team grants today is a clear acknowledgement that UCLA is a leader in the field and will provide much needed new therapies for sickle cell disease, HIV/AIDS and brain, colorectal and ovarian cancers."

The UCLA disease team grants were awarded to:

- Irvin Chen, director of the UCLA AIDS Institute and a professor of microbiology, immunology and molecular genetics and medicine, who received \$19,999,580 to develop a method to block HIV infection and reproduction in the human body.
- Dr. Donald Kohn, a professor of microbiology, immunology and molecular genetics and pediatrics and director of the Human Gene Medicine Program at UCLA, who received \$9,212,365 to develop a blood stem cell transplant to cure sickle cell disease.

- Dr. Dennis Slamon, director of clinical/translational research at UCLA's Jonsson Comprehensive Cancer Center and chief of the division of hematology/oncology at UCLA, who received \$19,979,660 to develop drugs that target cancer stem cells, believed to be the cause of some cancers, including glioblastoma (brain), ovarian and colorectal cancers.

“We’re grateful to the California Institute of Regenerative Medicine and the people of California for these three grants, which will allow our scientists to translate their outstanding work in the basic sciences into revolutionary new therapies for people suffering from a variety of diseases,” said Dr. Owen Witte, director of the Broad Stem Cell Research Center. “These are pivotal grants that have the potential to change the way we practice medicine.”

UCLA has earned an international reputation for conducting translational research. The molecularly targeted therapies Herceptin for breast cancer and Gleevec and Sprycel for chronic myeloid leukemia, among others, were developed based on work done in UCLA laboratories. The three disease team projects funded by CIRM will now join many other innovative research projects being conducted here to try and bring new, more effective and less toxic therapies to patients with devastating diseases for which there currently are no successful treatments. Exploring stem cell therapies opens new avenues of medical possibility, as the biology of these cells is uncovered and understood.

“I applaud the UCLA stem cell center faculty for being chosen to conduct what will be groundbreaking translational research – with the potential to alleviate the suffering of millions affected by HIV/AIDS, cancer and sickle cell disease globally,” said philanthropist Eli Broad, whose foundation donated \$20 million to the UCLA stem cell center in 2007.

Other Broad Stem Cell Research Center scientists are collaborators in disease team projects based at other research institutions. Dr. Hanna Mikkola will work with a team seeking better treatments for leukemia, Dr. Tom Carmichael will work with a team developing a new treatment for stroke, while Drs. Paul Mischel, Tim Cloughesy and Linda Liau will collaborate with a team focusing on glioblastoma.

## **HIV/AIDS**

The need for novel approaches to the treatment of HIV infection has never been greater, Chen said. New infections continue to occur in California, nationally and worldwide despite decades of prevention efforts. Additionally, the number of people living with HIV is rising due to improved management of their infection. As a result, California, which ranks second in the nation behind only New York in diagnosed cases of HIV infection, has identified 102,800 men, women and children who carry the virus. Estimates of the number of state residents who are infected but have yet to be diagnosed are as high as 33,500. Worldwide, it’s estimated that 33 million people are living with HIV.

Chen’s disease team will focus on RNA interference, a means to block the function of genes in the human body. He proposes this RNA interference can be used to block HIV-1 infection, a sub-type of HIV, and its reproduction within the body. In this case, his team proposes blocking expression of CCR5, a key co-receptor used by HIV-1 to gain entry into host cells.

The approach is designed to mimic the effects of a naturally occurring mutation in humans that renders those individuals resistant to HIV-1 infection. When RNA interference is introduced into a stem cell, its blocking activity will be present throughout the lifetime of the stem cell, theoretically the lifespan of a human being, providing a lifelong therapy for HIV-1 infection.

“If you can artificially knock out CCR5, you can make the cells resistant to HIV,” Chen said. “We thought we could use RNA interference – and we proved in preclinical and animal models that it works. Now we are ready to test this theory in human clinical trials.”

In effect, researchers will be creating a new blood system that carries the RNA interference therapy in it. Chen said, in theory, an effective stem cell RNA interference therapy will require only a single treatment as opposed to the current lifetime administration of expensive anti-HIV-1 drugs, which often result in serious side effects.

“The goal of lifelong control or even, potentially, eradication of HIV via a stem cell therapy will not be straightforward,” Chen said. “We have assembled the combined AIDS and stem cell expertise of investigators from four California academic institutions as well as a corporate partner and a host of world renowned advisors. Each will contribute unique expertise towards the development of a safe and efficacious therapeutic path into patients.”

Independent reviewers of Chen’s grant said the proposal was very strong and “the resources and investigators are outstanding and the team is superb, both scientifically and in therapy development.”

### **Sickle Cell Disease**

Kohn, a renowned scientist who was recruited this year to UCLA, wants to alleviate the suffering of patients with sickle cell disease, which affects one in 500 African Americans and one in 1,000-1,400 Latinos. The disease results from an inherited mutation in the hemoglobin gene that causes red blood cells to "sickle" under conditions of low oxygen, meaning they become crescent shaped and have difficulty passing through small blood vessels. Median survival is 42 years for men, 48 years for women.

Kohn and his disease team seek to treat sickle cell patients by transplanting them with their own bone marrow, using adult blood stem cells that are genetically corrected by adding a hemoglobin gene that blocks the sickling of the red blood cells. This approach, Kohn said, has the potential to permanently cure sickle cell disease with significantly less toxicity than with a bone marrow transplant from a donor and would make treatment available to sickle patients who do not have a suitable matched bone marrow donor. A clinical trial using stem cell gene therapy for sickle cell patients will be developed through this award and be ready to be launched by its completion. Kohn’s multi-disciplinary disease team includes experts in stem cell gene therapy, clinical bone marrow transplantation and the care of patients with sickle cell disease.

“Successful use of stem cell gene therapy for sickle cell disease has the potential to provide a more effective and safe treatment for this disease to a larger proportion of affected patients,” Kohn said.

That would be wonderful news for Summer Harris, 24, of North Inglewood. Diagnosed with sickle cell disease at six months, Harris suffered her first major stroke at age 6 and a second, massive stroke at age 20. She lives daily with debilitating pain and has never led what most would consider a normal life. She could not attend school or play with her friends. She's been hospitalized more times than she can count.

"It would be fantastic if they could develop a new drug to cure sickle cell," Harris said. "It would be so great to have a normal life. It would make everything so much easier."

Mary Brown, president and chief executive officer of the Sickle Cell Disease Foundation of California, said it is "vitally important that researches continue to explore new avenues such as stem cell research."

"One of the hardest parts of my job is looking into the eyes of a young family with a newborn or an adult with sickle cell disease and being unable to tell them that a cure has been found," Brown said. "Sickle Cell Disease is mean and cruel and compromises the quality of life. Our clients and thousands of affected persons in the United States struggle to make sense out of lives riddled with pain. We remain hopeful that the efforts of Dr. Kohn and others will result in a positive outcome for persons living with sickle cell disease."

### **Glioblastoma, Ovarian and Colorectal Cancers**

Cancer is a major cause of human death worldwide. The majority of cancer patients suffer from solid tumors, whose growth destroys vital organs. Slamon's team proposes to develop novel drugs that target solid tumors affecting the brain, colon and ovaries, cancers that account for a significant proportion of the difficult-to-treat solid malignancies.

Scientists have made great strides in understanding the molecular and cellular changes that cause cancer, Slamon said, but the approval of new drugs that can kill cancer cells has lagged behind. This disparity suggests that there must be critical bottlenecks impeding the process of translating a basic research discovery into an effective anti-cancer drug. Over the last decade, research has given rise to the idea that one of these bottlenecks may be caused by the existence of cancer stem cells, which are not killed by conventional treatments.

Slamon said the cancer stem cell hypothesis proposes that there is a minor population of cancer stem cells that drive the growth of the tumor. These cells are very rare and difficult to identify. However, recent technical innovations have allowed for the identification, isolation and growth of these cancer stem cells in the laboratory. It is clear, Slamon said, that these cells have properties that are distinct from both the bulk of tumor cells and the cancer cell lines used to test anti-cancer drugs in the laboratory.

These cells, Slamon said, are most likely the reason that cancers come back after years of remission. They may also be behind the spread of cancer to other organs.

"A drug that specifically targets cancer stem cells could dramatically improve the chances of treatment success," said Slamon, whose research led to the development of Herceptin. "Our team is one of the few in the world that can identify cancer stem cells in brain, colon and ovarian tumors. Furthermore, we have developed assays that can accurately test the effectiveness of drug candidates in killing these cells."

Slamon's team seeks to develop a lead and backup compound for each of two kinase targets on cancer stem cells, and further, to develop a genetic analysis that would allow them to identify which patients with brain, ovarian and colorectal cancer are most likely to respond to treatment in clinical trials, thereby personalizing their therapy.

Preliminary data suggest that several known drug candidates can inhibit the growth of cancer stem cells in culture and block tumor initiation in animal models. Most importantly, Slamon said, these drug candidates appear to work through mechanisms that are different from those employed by current chemotherapeutics, meaning these drugs represent a fresh and potentially effective approach to cancer treatment.

Established in 1992, the UCLA AIDS Institute is a multidisciplinary think-tank drawing on the skills of top-flight researchers in the worldwide fight against HIV and AIDS, the first cases of which were reported in 1981 by UCLA physicians. Institute members include researchers in virology and immunology, genetics, cancer, neurology, ophthalmology, epidemiology, social science, public health, nursing and disease prevention. Their findings have led to advances in treating HIV as well as other diseases such as hepatitis B and C, influenza and cancer.

UCLA's Jonsson Comprehensive Cancer Center has more than 240 researchers and clinicians engaged in disease research, prevention, detection, control, treatment and education. One of the nation's largest comprehensive cancer centers, the Jonsson center is dedicated to promoting research and translating basic science into leading-edge clinical studies. In July 2009, the Jonsson Cancer Center was named among the top 12 cancer centers nationwide by U.S. News & World Report, a ranking it has held for 10 consecutive years.

The stem cell center was launched in 2005 with a UCLA commitment of \$20 million over five years. A \$20 million gift from the Eli and Edythe Broad Foundation in 2007 resulted in the renaming of the center. With more than 200 members, the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research is committed to a multi-disciplinary, integrated collaboration of scientific, academic and medical disciplines for the purpose of understanding adult and human embryonic stem cells. The center supports innovation, excellence and the highest ethical standards focused on stem cell research with the intent of facilitating basic scientific inquiry directed towards future clinical applications to treat disease. The center is a collaboration of the David Geffen School of Medicine, UCLA's Jonsson Cancer Center, the Henry Samueli School of Engineering and Applied Science and the UCLA College of Letters and Science. To learn more about the center, visit our web site at <http://www.stemcell.ucla.edu>.