PRESS RELEASE
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UCLA Scientists Taking Stem Cell Research to Patients

- Two prominent UCLA stem cell scientists receive CIRM Disease Team III awards for clinical trials scheduled to begin in 2014.
- Binational Phase I clinical trial to test a targeted anti-cancer drug approved to enroll patients in US and Canada.
- First-in-human testing of stem cell gene therapy for sickle cell disease that allows patients to be their own bone marrow donors.

Scientists from UCLA's Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research are bringing stem cell science funded by the California Institute of Regenerative Medicine (CIRM), the state stem cell agency, directly to patients in two exciting new clinical trials scheduled to begin in early 2014. The recipients of the Disease Team Therapy Development III awards were Dr. Dennis Slamon and Dr. Zev Wainberg, whose phase I clinical trial will test a new drug that targets cancer stem cells and has been approved to begin enrolling patients in the US and Canada, and Dr. Donald Kohn, whose first-in-human trial is on stem cell gene therapy for sickle cell disease (SCD).

The announcement of the new awards came on December 12, 2013 at the meeting of the CIRM Independent Citizen's Oversight Committee (ICOC) at the Luxe Hotel in Los Angeles. Dr. Owen Witte, Director of the UCLA Broad Stem Cell Research Center, highlighted that the "The CIRM support demonstrates that our multidisciplinary Center is at the forefront of translating basic scientific research to new drug and cellular therapies that will revolutionize medicine."

Targeting solid tumor stem cells

The Disease Team III grant to Dr. Dennis Slamon and Dr. Zev Wainberg and their US-Canadian collaborative team will support the first in human clinical trial scheduled to open in early 2014. The project builds on Dr. Slamon's previous work partially funded by CIRM to develop a drug that targets tumor initiating cells with UCLA's Dr. Zev Wainberg, assistant professor of hematology/oncology and Dr. Tak Mak, director, Campbell Family Institute of the University Health Network in Toronto, Canada. Dr. Slamon, renowned for his research that led to the development of Herceptin, the first FDA-approved targeted therapy for breast cancer, is the director of clinical and translational research at the UCLA Jonsson Comprehensive Cancer Center, and professor, chief and executive vice chair for research in the division of hematology/oncology.

With investigational new drug approval from the Food and Drug Administration (FDA) and Health Canada, the Canadian government's therapeutic regulatory agency, this trial is an international effort to bring leading-edge stem cell science to patients.

"We are delighted to receive this CIRM grant that will drive our translational research from the laboratory to the clinic," Slamon said, "and allow us to test our targeted drug in a phase I clinical trial."

The trial is based on the evidence built over the last decade for what has become known as the cancer stem cell hypothesis. According to this hypothesis, cancer stem cells are the main drivers of tumor growth and are also resistant

to standard cancer treatments. One view is that cancer stem cells inhabit a "niche" that prevents cancer drugs from reaching them. Another view is that tumors can become resistant to therapy by a process called cell fate decision, by which some tumor cells are killed by therapy and others become cancer stem cells. These cancer stem cells are believed to be capable of self-renewal and repopulation of tumor cells, resulting in the recurrence of cancer.

The target of the new drug is an enzyme in cancer stem cells and tumor cells called Polo-like kinase 4, which was selected because blocking it negatively affects cell fate decisions associated with cancer stem cell renewal and tumor cell growth, thus stopping tumor growth.

This potential anti-cancer drug is now ready to be tested in humans for the first time. "Our goal is to test this novel agent in patients in order to establish safety and then to proceed quickly to rapid clinical development. We are excited to continue this academic collaboration with our Canadian colleagues to test this drug in humans for the first time," said Wainberg. Drs. Slamon, Wainberg, Mak and colleagues will also look for biological indications, called biomarkers, that researchers can use to tell if and how the drug is working.

Stem cell gene therapy for sickle cell disease

Dr. Donald Kohn, professor of pediatrics and microbiology, immunology and molecular genetics in the life sciences and colleagues successfully established the foundation for using hematopoietic (blood-producing) stem cells (HSC) from the bone marrow of patients with SCD to treat the disease. Kohn's gene therapy approach using HSC from patient's own blood is a revolutionary alternative to current SCD treatments as it creates a self-renewing normal blood cell by inserting a gene that has anti-sickling properties into HSC. This approach also does not rely on the identification of a matched donor, thus avoiding the risk of rejection of donor cells. The anti-sickling HSC will be transplanted back into the patient's bone marrow and multiply the corrected cells that make red blood cells without sickling.

Dr. Kohn will begin enrolling patients in the clinical trial within the first three months after receiving the CIRM grant. The first subject will be enrolled and observed for safety for six months. The second subject will then be enrolled and observed for safety for three months. If evaluations show that no problems have arisen, the study will continue with two more subjects and another evaluation until six total subjects have been enrolled.

Affecting more than 90,000 patients in the US, SCD mostly affects people of Sub-Saharan African descent. It is caused by an inherited mutation in the beta-globin gene that makes red blood cells change from their normal shape, which is round and pliable (like a plastic bag filled with corn oil), into a rigid sickle-shaped cell (like a corn flake). Normal red blood cells are able to pass easily through the tiniest blood vessels, called capillaries, carrying oxygen to organs such as the lungs, liver and kidneys. But due to their rigid structure, sickled blood cells get stuck in the capillaries and deprive the organs of oxygen, which causes organ dysfunction and failure.

Current treatments include transplanting patients with donor HSC, which is a potential cure for SCD, but due to the serious risks of rejection, only a small number of patients have undergone this procedure and it is usually restricted to children with severe symptoms.

"Patients with sickle cell disease have had few therapeutic options. With this award, we will initiate a clinical trial that we hope will become a treatment for patients with this devastating disease," Kohn said.

CIRM Disease Team III Awards

The purpose of the CIRM Disease Team Therapy Development III Awards initiative is to advance early clinical development of novel therapies derived from or targeting stem cells. These novel therapies may offer unique

benefits with well-considered risk to those with disease or serious injury. The CIRM grants only support programs that include a clinical study that can be completed and analyzed within a four-year period.

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 Comprehensive 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.