Impact Report

THE ELI AND EDYTHE BROAD CENTER FOR REGENERATIVE MEDICINE AND STEM CELL RESEARCH AT USC

Keck School of Medicine of USC

OCTOBER 2013

LETTER FROM THE DIRECTOR

On my desk, I have small model of a human kidney, made of plain gray plastic. What's interesting about this particular kidney is how it was made: it was fashioned by a 3D printer.

Not so long ago, it would not have been possible to build a plastic kidney this way. For me, this curious trinket serves as a reminder that so many things that were once thought impossible have already been realized.

At the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, we're constantly redefining what's possible.

To achieve this, our center brings together thinkers and doers from across this great university to translate discoveries into therapies for the patients who need them most. Our investigators are exploring kidney, digestive and metabolic, respiratory and circulatory, craniofacial and musculoskeletal, and neural and sensory diseases — harnessing the power of stem cell biology to develop new treatments. As with normal tissues, cancers are fueled by stem cells. Researchers are targeting cancer stem cells to cure cancer.

In partnership with the Eli and Edythe Broad Foundation and our supporters, USC has made a demonstrated commitment to developing tomorrow's stem cell therapies — working to attract world-class scientists, build state-of-the-art research facilities, form scientific collaborations, communicate our mission and, most of all, prove that anything is possible.

Restoring and repairing injured, diseased and worn out body systems is the medicine of the future. We are creating the knowledge base and developing the translational approaches that will make this medicine a reality. I look forward to the time when we build kidneys that aren't made of plastic.

Sincerely,

Andrew P. McMahon, PhD
Director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC

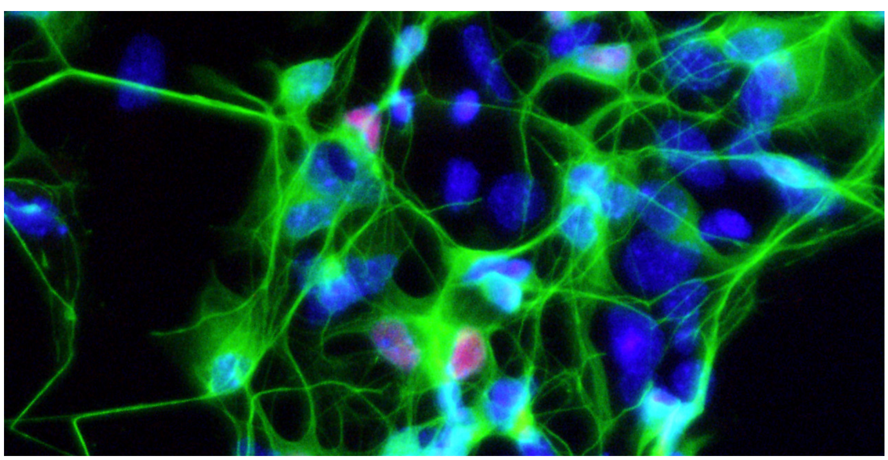
OVERVIEW

Under the visionary new leadership of Dr. Andrew P. McMahon, the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC has entered a phase of dynamic growth and change.

Recent research highlights from center scientists include:

- the discovery of new ways to program stem cells and model diseases;
- the identification of delicate controls that balance the maintenance and commitment of stem cells to control the ordered assembly of functioning organ systems; and
- the uncovering of the secrets of non-mammalian systems in which the ability to repair and regenerate body systems greatly exceeds our own.

The discovery process is complemented by translational approaches to pioneer stem cell-aided treatments when the time is right. Curing blindness resulting from macular degeneration and stopping the spread of the HIV/AIDS virus are in the sight-lines of translational teams.



With the center as its hub, the USC Stem Cell initiative (stemcell.usc.edu) has brought together researchers across the university's many schools and disciplines as well as at the House Research Institute and at Children's Hospital Los Angeles.

In August 2013, USC Stem Cell hosted the first Regenerative Medicine Initiative Awards, which provides $1.2 million in seed funding to collaborative, multidisciplinary research projects focused on early-stage translational approaches.

This interdisciplinary effort extends far beyond medical research. Center scientists will partner with the USC Roski School of Fine Arts, for example, to bring art students into its laboratories. While scientists improve their ability to communicate with non-scientists, art students will learn the beauty of science through hands-on research, creating stem cell-inspired works of art to cap their experience. Collaborations with the world-renowned USC School of Cinematic Arts are under development — to use their special talents to develop animations that demystify regenerative medicine for the general public, enhance understanding for our students, and attract non-scientists to the center.

USC students aren't the only ones to benefit. Last summer, 20 local high school students, including several scholarship winners from disadvantaged areas, had the opportunity to engage in hands-on stem cell research and host a CIRM-sponsored forum featuring retired State Senator Art Torres and CIRM Chair Jon Thomas.

Under Dr. McMahon's watch, the center has also enhanced its core services, which now include world-class capabilities in imaging as well as stem cell sorting, culture and programming. In addition, the center has established a therapeutic screening facility, where researchers test potential drugs on reprogrammed stem cells from actual patients.

Recruiting new research teams strengthens existing programs and broadens the centers research programs. Dr. Justin Ichida, a talented young researcher recruited from Harvard University in January 2013, is spearheading the therapeutic screening facility. An expert in neurodegenerative conditions, he is conducting some of the first screenings on Lou Gehrig's disease — testing potential drugs on motor neurons formed by directly reprogramming patients' skin cells.

Two other stellar young faculty recruits will arrive at USC in January 2014. Dr. Rong Lu from Stanford University studies what makes one blood stem cell outcompete another, which has significant ramifications for improving transplants and preventing blood cancers. Dr. Min Yu from Harvard University, recruited in conjunction with the USC Norris Comprehensive Cancer Center, focuses on filtering out circulating cancer stem cells from billions of other blood cells in breast cancer patients to understand how cancer spreads and stop it in its tracks.

In the months and years ahead, the center will continue to grow, change and differentiate — solidifying USC's place as a leader in regenerative medicine and developing approaches that will improve the lives of patients around the world.

DISCOVERY

TITLE	PRINCIPAL INVESTIGATOR(S)	DISEASE PROGRAM	IMPACT
Discovering how blood-forming stem cells give rise to lymphoma	Michael R. Lieber, M.D., Ph.D.	Cancer	This study explains how hematopoietic, or blood-forming stem cells, and lymphoid precursors give rise to most human B-cell lymphomas.
Exploring the relationship between colon stem cells, aging and disease	Michael R. Lieber, M.D., Ph.D.	Cancer	This study investigates how human colonic stem cells give rise to potential tumorous progeny with genetic changes that increase with human age.
Understanding the role of cancer stem cell marker TLR4-NANOG in liver cancer	Keigo Machida, Ph.D.	Cancer	This research identifies the role of the TLR4-NANOG signaling pathway, a group of molecules that work together to control the renewal and proliferation of liver cancer stem cells in alcohol-associated cancers.
Developing zebrafish jaw repair model	Gage J. Crump, Ph.D.	Craniofacial and Musculoskeletal	This study aims at developing a zebrafish jaw bone repair model, which provides new insight into how bone is repaired at the genetic level. The group identified a new cell population that is specific for bone repair and is planning to identify small molecules that would increase this cell population and could potentially be used to promote mammalian bone repair.
Developing a new mouse model to study mammalian cartilage and bone repair	Francesca Mariani, Ph.D.	Craniofacial and Musculoskeletal	This research identifies the key role of a stem/progenitor cell population surrounding the mouse ribs that is important for rib bone repair.

DISCOVERY

TITLE	PRINCIPAL INVESTIGATOR(S)	DISEASE PROGRAM	IMPACT
Isolating a stable neural crest cell line from mouse	Robert E. Maxson, Ph.D.	Craniofacial and Musculoskeletal	This research isolates cranial neural crests cells before they have differentiated, enabling the team to potentially cure defects in structures that are derived from these stem-like cells, such as the skull. This provides an important tool for research and potentially future therapy for facial reconstruction. EMD Millipore has agreed to license this technology for commercial distribution.
Enhancing bone regeneration with drugs targeting the host immune system	Songtao Shi, Ph.D., D.D.S.	Craniofacial and Musculoskeletal	This study uncovers a previously unrecognized role of recipient T-cells, or immune cells, in stem cell-based bone repair, and suggests a pharmacological approach for enhancing bone regeneration.
Generating induced pluripotent stem (iPS) cells from patients suffering peroxisome biogenesis disorders for drug screen	Joseph Hacia, Ph.D.	Digestive and Metabolic	This collaborative study generates iPS cells from patients suffering from peroxisome biogenesis disorders and uses these cells to screen for small molecule compounds that will improve the disease.
Generating hepatocytes (liver cells) from human pluriopotent stem cells and placental stem cells	Toshio Miki, Ph.D.	Digestive and Metabolic	This study generates liver cells, called hepatocytes, from human pluripotent stem cells and placental stem cells with the goal of curing congenital metabolic disorders.
Identifying the origin of liver fibrosis	Kinji Asahina, Ph.D.	Digestive and Metabolic	This research identifies that the thin layer of cells on the surface of the liver, mesothelial cells, are the origin of liver fibrosis. They provide the therapeutic target for the supression of liver fibrosis and cirrhosis.
Discovering key factors involved in generating insulin-producing pancreatic beta cells	Senta Georgia, Ph.D.	Digestive and Metabolic	This study identifies that a key enzyme, DNMT1, regulating cellular memory is important for the generation of insulin-producing pancreatic beta cells during the development of the pancreas. This discovery could be important in regenerating beta cells damaged in patients with diabetes.

DISCOVERY

TITLE	PRINCIPAL INVESTIGATOR(S)	DISEASE PROGRAM	IMPACT
Deriving embryonic stem cells from rat blastocysts	Qi-Long Ying, Ph.D.	Stem Cell Research	For the first time, this research establishes authentic embryonic stem cells from the rat, the most widely used species in biomedical research. Published in Cell in December 2008 this major breakthrough received widespread acclaim from the scientific community as well as mainstream media.
Developing the first "knockout" rats	Qi-Long Ying, Ph.D.	Stem Cell Research	This study uses embryonic stem cell-based technology to produce the world's first "knockout" rats, laboratory animals modified to lack the tumor related gene P53. Selected by Science magazine as one of the top 10 breakthroughs of 2010, this technology will accelerate discovery and applied research across a range of biomedical disciplines.
Using direct reprogramming to study amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases	Justin Ichida, Ph.D.	Neural and Sensory	This study uses motor neurons generated from ALS patient skin cells by direct reprogramming to understand the disease. The group is also doing small molecule screens to identify compounds that can slow or stop the death of patients' motor neurons.
Identifying novel mechanisms of hair follicle stem cell regulation	Kris Kobielak, M.D., Ph.D.	Neural and Sensory	This study reveals that the competitive balance of two important signaling pathways - BMP and Wnt - important to regulate hair stem cell proliferation and differentiation. This work may lead to future therapies for alopecia, wound regeneration and skin cancer.

DISCOVERY

TITLE	PRINCIPAL INVESTIGATOR(S)	DISEASE PROGRAM	IMPACT
Characterizing sweat gland stem cells	Kris Kobielak, M.D., Ph.D.	Neural and Sensory	This research focuses on sweat gland stem cells. By isolating these cells for the first time, the lab identified molecular markers for these cells and showed that under the right condition, these cells can differentiate into sweat gland cells, skin cells and hair follicle cells. This has important implications for wound healing and treating burn patients.
Discovering the mechanisms of neural stem cell differentiation and self-renewal	Wange Lu, Ph.D.	Neural and Sensory	This study reveals the role of a gene called RYK in regulating the differentiation of neurons during brain development.
Understanding how reprogramming works	Wange Lu, Ph.D.	Neural and Sensory	The study investigates how a skin cell is reprogrammed to become an induced pluripotent cell. The result shows that one of the four factors, KLF4, organizes long-range chromosomal interactions in cell reprogramming and pluripotency
Identifying a novel approach for embryonic stem cell self-renewal	Qi-Long Ying, Ph.D.	Neural and Sensory	This research identifies a novel mechanism by which the protein B-catenin regulates human embryonic stem (ES) cell self-renewal. This allows for the efficient propagation of human ES cells, and derivation of pluripotent stem cells from different species.
Regenerating neural stem cells in patients with Alzheimer's	Roberta H. Brinton, Ph.D.	Neural and Sensory	This study shows that the neurosteroid Allopregnanolone (Allo) activates neural stem cells in the brain to generate new nerve cells and to restore cognitive function while also reducing the pathology of Alzheimer's disease. Allo is the first regenerative therapeutic for Alzheimer's with the potential to regenerate nerve cells and the pathways necessary for memory. The team has obtained FDA approval and NIH funding for a phase I clinical trial.

DISCOVERY

TITLE	PRINCIPAL INVESTIGATOR(S)	DISEASE PROGRAM	IMPACT
Using human embryonic stem cell-derived retinal pigment epithelial cells to treat age-related macular degeneration	Mark Humayan, M.D., Ph.D.	Neural and Sensory	The study performs all necessary pre-clinical research that will lead to a successful Investigational New Drug (IND) filing. This includes deriving retinal pigment epithelial cells from human embryonic stem cells, developing bio-memberanes to seed these cells for transplantation and testing these cells in animal models of age-related macular degeneration.
Improving bone marrow therapies by modulating calcium-sensing receptors	Gregor Adams, Ph.D.	Respiratory and Circulatory	A major problem in bone marrow transplant is the poor engraftment/homing of the donor bone marrow into patients. The study examines the role of calcium sensing receptors (CaR) in blood-forming stem cells. Stimulating CaR receptors increases the ability of these cells to lodge into the recipient bone marrow niche.
Understanding the molecular mechanisms of mouse heart development	Mohammad Pashmforoush, M.D., Ph.D.	Respiratory and Circulatory	The group studies the role of a molecular modulator R-spondin3 in regulating the Wnt pathway, and heart progenitor cell proliferation and differentiation. The study may potentially lead to better treatment for heart attacks.
Mammalian heart development and disease	Henry Sucov, Ph.D.	Respiratory and Circulatory	This research defines the major signal that induces heart muscle cells to divide during fetal heart development. The same pathway may be harnessed to induce heart regeneration in adult patients with heart failure.
Treating HIV/AIDS with stem cell therapy	Paula Cannon, Ph.D.	Respiratory and Circulatory	As part of a multi-group CIRM disease team, the group is performing pre-clinical research for an Investigational New Drug (IND) filing. Specifically, the group is testing whether transplanting human bone marrow stem cells with the HIV receptor CCR5 detected can cure HIV/AIDS in mice.

DISCOVERY

TITLE	PRINCIPAL INVESTIGATOR(S)	DISEASE PROGRAM	IMPACT
Repairing the heart after an attack	Robert A. Kloner, M.D., Ph.D., Michael Kahn, Ph.D .	Respiratory and Circulatory	This study examines the effect of a small molecule signaling modulator that may be important in enhancing heart function after a heart attack. It also shows the regenerative capability of the epicardium, or outer layer of tissue, after a heart attack.
Improving heart function after an attack through an injection of heart tissue-derived extracellular matrices	Robert A. Kloner, M.D., Ph.D.	Respiratory and Circulatory	This study shows that the strengthening of a myocardial infarct (heart attack) scar with extra cellular matrix results in some of the same benefits as observed with cell therapy. Thickening the scar improves overall left ventricular function.
Regenerating zebrafish hearts using PDGF signaling	Ching-Ling Lien, Ph.D.	Respiratory and Circulatory	This study examines the role of an important signaling pathway in regenerating a zebrafish heart. The study shows that this pathway is important for the proliferation of epicardial cells, or cells from the outer layer of heart tissue, as well as new heart blood vessel formation. These cells are important for the regrowth of the heart.
Demonstrating the role of amniotic fluid stem cells in tissue repair	Laura Perin, Ph.D.	Respiratory and Circulatory, Kidney	Using a mouse model of Alport Syndrome (chronic kidney failure), this study showed that injecting amniotic fluid stem cells could modify the course of progressive renal fibrosis, prolong animal survival, and ameliorate the decline in kidney function.
Understanding kidney stem cells and nephrogenesis	Andrew McMahon, Ph.D.	Kidney	The functional unit of the kidney is a long filtering tube, the nephron. A million nephrons form in fetal life. We have identified the nephron forming stem cells and the regulatory processes controlling expansion and nephron commitment of these cells, enabling steps towards the long-term goal of kidney biogenesis.

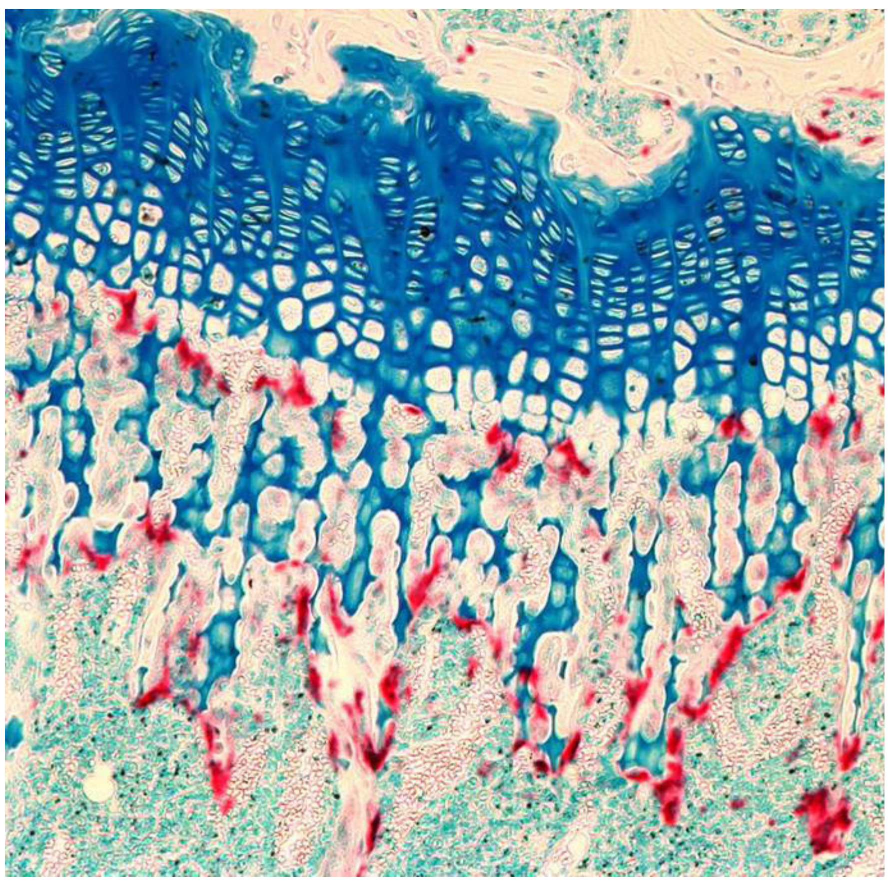
DISCOVERY

TITLE	PRINCIPAL INVESTIGATOR(S)	DISEASE PROGRAM	IMPACT
Identifying mechanisms of adult kidney repair	Andrew P. McMahon, Ph.D.	Kidney	This study establishes an acute kidney injury mouse model. By using genetic techniques, the study provides a deep, cell-based view of early injury-associated molecular events in acute kidney injury. This is important for identifying the cellular processes of kidney repair, early injury biomarkers to help identify patients at risk and novel targets for therapeutic intervention.
Understanding kidney function in health and disease	Janos Peti-Peterdi, M.D., Ph.D.	Kidney	Using complex imaging technique (multiphoton microscopy), the study focus on how kidneys regulate blood pressure and body fluid balance under normal and disease conditions (hypertension and diabetes). By studying the response of various cell types and molecular pathways within the kidney under various physiological conditions, the study has the potential to identify therapeutic targets for diseases such as hypertension and diabetes.
Understanding the role of Wnt signaling pathway in stem cell maintenance and cancer	Michael Kahn, Ph.D.	Cancer	The study identifies small molecular modulators of the Wnt signaling pathway to see how they influence stem cell differentiation and self-renewal — to examine how they affect cancer growth in animal models and to observe how they influence tissue repair in animal disease models such as heart attack.

TRANSLATION

Regenerative Medicine Initiative Awards

Last year, Carmen A. Puliafito, M.D., M.B.A., dean of the Keck School of Medicine of USC, committed $1.2 million for three Regenerative Medicine Initiative Awards for interdisciplinary, translational stem cell research projects in the areas of hearing loss, cancer and bone repair. These awards are part of USC Stem Cell, the university-wide initiative in regenerative medicine led by the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC. The center is committed to supporting these and other multidisciplinary research ventures that show promise for improving the lives of patients.



TRANSLATION

TITLE	PRINCIPAL INVESTIGATORS	SUMMARY
"Differentiation of Inner Ear Sensory Neurons and Hair Cells through Direct Reprogramming"	Neil Segil, Ph.D. Professor, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC Takahiro Ohyama, Ph.D. Assistant Professor of Research, Department of Otolaryngology, Keck School of Medicine of USC Justin Ichida, Ph.D. Assistant Professor, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC	This research aims at curing deafness by using cellular reprogramming to create inner ear cells, including sensory hair cells. The death of these delicate structures, which humans and other mammals cannot regenerate, is the most common cause of deafness.
"Healing of Critical Sized Bone Defects with Periosteal Dual Fate Skeletal Progenitors"	Gage Crump, Ph.D. Associate Professor, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC Jay R. Lieberman, M.D. Professor and Chair, Department of Orthopaedic Surgery, Keck School of Medicine of USC Francesca Mariani, PhD Assistant Professor, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC	This study focuses on potential ways to repair human bones through discoveries made from in vivo studies in mice and zebrafish. When mouse ribs or zebrafish jaws are damaged, special cartilage cells transform themselves into bone-producing cells called osteoblasts. The research team hopes to show that these cells can more effectively heal severe bone damage that is a challenge to current therapeutic approaches.
"The Impact of CD22E12 Genetic Defect on Fate of Lymphoid-biased Stem Cells in the Hematopoietic Stem Cell Niche"	Gregor Adams, Ph.D. Assistant Professor, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC Fatih Uckun, M.D. Professor, Pediatrics, Keck School of Medicine of USC Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles	This research aims to develop a targeted therapy for the most common form of cancer in children and adolescents, which is called B-precursor acute lymphoblastic leukemia. Some children with the disease have a genetic defect that results in the production of an abnormal form of the protein CD22E12, which causes their cancer stem cells to proliferate and resist chemotherapy. The team will leverage the insights gained from their studies of this abnormal protein to design new and more effective treatment strategies.

THE CHOI FAMILY THERAPEUTIC SCREENING FACILITY

With generous philanthropic support from the Choi Family, the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC will for the first time be able to screen a large collection of small chemical libraries. This ability will result in discoveries that will transform patient care in our lifetime.

Researchers will discover how stem cells differentiate themselves into other cell types, how various compounds and therapies have an impact on patient cells, and which compounds and therapies are safe and effective.

Integrated with the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC core laboratories, the therapeutic screening facility is comprised of chemical libraries, specialized equipment for screening a menu of chemical compounds and imaging their reactions to cells, and highly trained technicians to run the facility and support investigators.

EDUCATION

Department of Stem Cell Biology and Regenerative Medicine

With the transformative recruitment of Dr. Andrew P. McMahon, USC established a new department in stem cell biology and regenerative medicine that will play an important role in spearheading new educational initiatives across the university.

Development, Stem Cells and Regenerative Medicine Doctoral Program

Building upon the strengths, momentum and investment in regenerative medicine and stem cell research from the Keck School of Medicine of USC, the stem cell research center is the home of a new doctoral degree in development, stem cells and regenerative medicine. This unique program incorporates a re-vamped curriculum that emphasizes hands-on training, critical thinking about the literature and extensive laboratory experience working with embryos and stem cells.

More than 40 Ph.D. students from the Keck School of Medicine of USC participate in this program, with support and partnership from affiliated faculty at Children's Hospital Los Angeles, the Ostrow School of Dentistry of USC, and USC's Biochemistry Department.

Microanatomy Course in Medical Education

As part of a mandatory course for incoming first-year medical students, faculty from the stem cell research center lead a semester-long course in microanatomy to empower students with knowledge in cellular biology. In addition, several laboratories at the center host medical students and fellows for hands-on stem cell and regenerative medicine research.

Stem Cell Core Training Facility

Training and education are pivotal to the advancement of stem cell research. Sponsored by a CIRM Core Facility grant, the Stem Cell Core offers a broad range of educational services including technical protocols, one-on-one customized training and a week-long course covering human pluripotent stem cell culture techniques.

OUTREACH

USC's Early Investigator High School Program in Stem Cell Research

The USC Early Investigator High School Program in Stem Cell Research is a science education and outreach program run in partnership with high schools in Los Angeles. More than 20 students receive hands-on training and mentorship at the USC Stem Cell Core Facility and research laboratories. Students also attend weekly forums, which provide a foundation in the ethical and political issues relating to stem cell science and regenerative medicine.

Participating Schools

Bravo Medical Magnet High School
Harvard-Westlake School
Lifeline Education Charter School
Milken Community High School
Mira Costa High School

Supporters

USC CIRM Science, Technology and Research (STAR) Program
USC School of Pharmacy
Ambassadors for Stem Cell Research at USC
California Institute for Regenerative Medicine (CIRM)
USC Neighborhood Outreach

CORE FACILITIES

The Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research at USC received high honors from R&D magazine as a 2011 Laboratory of the Year. Featuring architecture and interior design by ZGF Architects LLP of Los Angeles, the center is the first building on the USC Health Sciences Campus to receive a silver Leadership in Energy and Environmental Design (LEED) designation based on its eco-friendly features.

The Eli and Edythe Broad CIRM Center for Stem Cell and Regenerative Medicine at USC has four core laboratories that provide access to specialized equipment as well as technical experts who maintain the equipment and train and assist scientists in its use. The core facilities support not only the center's scientists, but also investigators from the larger Regenerative Medicine Initiative at USC to translate discoveries from laboratory benches to patient bedsides.

Imaging Core

The Imaging Facility is equipped with a wide range of cutting-edge microscopes, which allow researchers to study high-resolution cellular dynamics in diverse systems such as mouse embryos, living zebrafish and human stem cell cultures.

The Choi Family Therapeutic Screening Facility

At the therapeutic screening facility, researchers can screen a large collection of chemicals or biological entities to see how they affect different cell types generated from patients with a particular disease patient. They can then determine whether these compounds or agents "cure" the disease in a petri dish and identify safe and effective dosages.

Flow Cytometry Core

With the recent acquisition of the BioRad S3 cell sorter, the FACS Core Facility has become one of the best cell sorting facilities at USC. The Flow Cytometry Core currently serves more than 150 laboratories across the USC campus.

Stem Cell Core

The Stem Cell Core Facility serves as the center of excellence at USC for all uses of human embryo stem cells. The Stem Cell Core provides researchers with the ability to generate patient-specific induced pluripotent stem cells and to genetically engineer these and other stem cell types. This facility offers comprehensive support and is a central hub for technical expertise, resources and state-of-the-art technology for researchers working with stem cells.

Genome Modification Core

Plans are underway, and support is being sought, for a state-of-the art core to generate animal models to aid and promote translational research.

USC University of Southern California