USC Stem Cell NEWS

California's biggest stem cell experiment: Impact of the stem cell ballot proposition at USC

In 2008, USC broke ground on an $80 million building dedicated solely to stem cell research and regenerative medicine. The plans called for a monolithic structure clad in black marble and reflective glass, rising five stories and enclosing nearly 90,000 square feet. When it was completed, the university had a stunning new contemporary research space at the center of its Health Sciences Campus in Los Angeles—a place where scientists could edit genes, engineer tissues, and fulfill the promise of stem cells.

USC's stem cell research center (Photo by Ben Gibbs)

This building would never have existed without $27 million in funding from California taxpayers, who had voted in favor of the California Stem Cell Research and Cures Initiative, also known as Prop 71, in 2004. By approving this ballot proposition, voters created a state agency, the California Institute for Regenerative Medicine (CIRM), charged with distributing $3 billion of public money to accelerate stem cell treatments to patients with unmet medical needs.

The $27 million of CIRM funding attracted an additional $30 million gift from The Eli and Edythe Broad Foundation, dedicated to the construction of USC's stem cell research center. Eli and Edythe Broad also funded two other stem cell centers at the University of California, Los Angeles, and the University of California, San Francisco. At the USC stem cell research center's grand opening in 2010, the original author of Prop 71, Robert Klein, proudly announced: "The definition of 'possible' has changed. The stem cell revolution has begun."

CIRM has driven that revolution by granting $146.5 million of funding to USC—which transformed a university with a few scattered developmental biologists into one with a thriving stem cell research community.

USC's story is exemplary of CIRM's impact at major research universities across the state, with partnerships extending into the biotech and pharma industries and investment in at least 64 clinical trials.

"In California history, nothing like CIRM has ever happened before," said David Jensen, editor of the California Stem Cell Report. "And the scale is large, and its approach is large. It's created an agency that combines big business, big academia, big science, religion—all in one little agency."

About USC Stem Cell

USC Stem Cell is a collaborative and multidisciplinary effort working to translate the potential of stem cell research to the clinical imperative of regenerative medicine.

Centered at the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, the initiative brings together researchers and clinicians from USC and Children's Hospital Los Angeles.

Is this even legal?

In 1998, scientists succeeded in deriving and growing stem cells from human embryos. To achieve this, James Thomson and his colleagues at the University of Wisconsin used very early-stage embryos, where a fertilized egg had been developing for 5 days and had formed a ball of approximately 200 cells called a blastocyst. These blastocysts were generated from surplus embryos remaining after *in vitro* fertilization and donated by the patients.

Science magazine declared Thomson's discovery to be one of the major scientific breakthroughs of the year, and it was easy to understand why. Embryonic stem cells could provide an unlimited source for generating any type of cell in the human body. This could allow scientists to develop cell therapies, replace damaged tissues and organs, screen potential drugs or toxins, improve methods for genetic engineering, and solve the fundamental mysteries of human development. It didn't matter if you or your loved ones suffered from heart disease, cancer, diabetes, or arthritis. Regardless of the disease, stem cells could provide a solution.

Within a few years, stem cells derived from at least 60 embryos were growing in laboratories around the world. Scientists were just starting to explore their potential medical applications. Everyone was tuned into this new and exciting frontier of biomedical discoveries and bioethical quandaries, including the President of the United States.

In August 2001, George W. Bush addressed the American public from his family's ranch in Crawford, Texas.

"My administration must decide whether to allow federal funds, your tax dollars, to be used for scientific research on stem cells derived from human embryos," he said.

Citing his belief that "human life is a sacred gift from our Creator," President Bush decided to cut off federal funding for any research involving newly created embryonic stem cell lines. However, the federal

Stem cells have the ability to become any type of cell in the body. (Painting by Amanda Kwieraga)

government would continue to fund research involving the 60 existing stem cell lines, "where the life and death decision has already been made." He also dedicated $250 million to research involving stem cells derived from non-embryonic sources: the umbilical cord or placenta, adults, or animals.

"I have made this decision with great care, and I pray it is the right one," he said.

In response, Californians turned to the ballot initiative process to amend the state's Constitution and provide taxpayer support for all kinds of stem cell research—including projects involving embryonic stem cells.

The resulting coalition brought together powerful forces from Hollywood, Sacramento, and everywhere in between. There were Nobel laureates from academia, celebrity patient advocates including Michael J. Fox and Christopher Reeve, wealthy Silicon Valley moguls such as Microsoft co-founder Bill Gates and eBay founder Pierre Omidyar, and even Republican Governor Arnold Schwarzenegger. Bob Klein, a real estate developer from Palo Alto, led the charge, and donated $3 million of the

The California Institute for Regenerative Medicine in San Francisco (Photo courtesy of Creative Commons)

$25 million of support for the campaign.

Among the most important supporters of Prop 71 were more than 70 patient advocacy groups, ranging from the Juvenile Diabetes Research Foundation to the Alzheimer's Association.

In November 2004, 59 percent of Californians showed up at the polls in support of the initiative, and CIRM was created.

Just as CIRM had powerful supporters, it had equally powerful detractors, including a handful of groups involved in taxpayer advocacy and pro-life causes. These groups filed lawsuits arguing that CIRM violated the California Constitution by allowing a committee of unelected citizens to distribute tax money as research grants. The lawsuits further alleged that several committee members had conflicts of interest, because they were scientists from the same academic institutions eligible to receive CIRM grants.

Although the lawsuits were ultimately unsuccessful, they dragged on for years—temporarily blocking CIRM's access to the $3 billion in state bond funding provided by Prop 71.

To bridge the gap, then California Governor Arnold Schwarzenegger arranged a loan from the state's general fund, augmented by support from private individuals including billionaire Ray Dolby, who pioneered surround sound. CIRM relied on these loans to issue its first round of grants in April 2006. And after the lawsuits finally resolved in CIRM's favor, California issued its first bonds to fund stem cell research in October 2007—nearly three years after the voters had approved Prop 71.

CIRM 1.0: Laying foundations

CIRM was a new type of funding agency in a new scientific field. As CIRM began building its own enterprise by hiring staff, assembling an Independent Citizens Oversight Committee, and establishing its headquarters in San Francisco, it also began building the stem cell research enterprise throughout the state of California.

"What's often missed is the idea that science is a long road," said Gage Crump, a professor of stem cell biology and regenerative medicine at USC. "You have to develop the infrastructure for it to work and survive. And it's really developing that infrastructure, which is going to be the lasting effect of CIRM—not immediate cures."

CIRM had to start building this infrastructure from the ground up, training a workforce through a broad range of educational programs, building new research facilities and laboratories, and recruiting leading stem cell scientists to California universities.

Among CIRM's first investments were grants to fund programs to educate the next generation of stem cell scientists. USC and its affiliated pediatric hospital, Children's Hospital Los Angeles (CHLA), received a total of $13 million in CIRM funding to train PhD students, as well as postdoctoral and clinical fellows.

As a direct result of CIRM's training grants, USC launched key educational opportunities that are still offered to this day. These include courses in stem cell and

developmental biology, as well as an annual retreat and weekly seminars where PhD students and postdoctoral trainees share their research progress. These offerings created the educational framework for what eventually became USC's PhD Program in Development, Stem Cells and Regenerative Medicine.

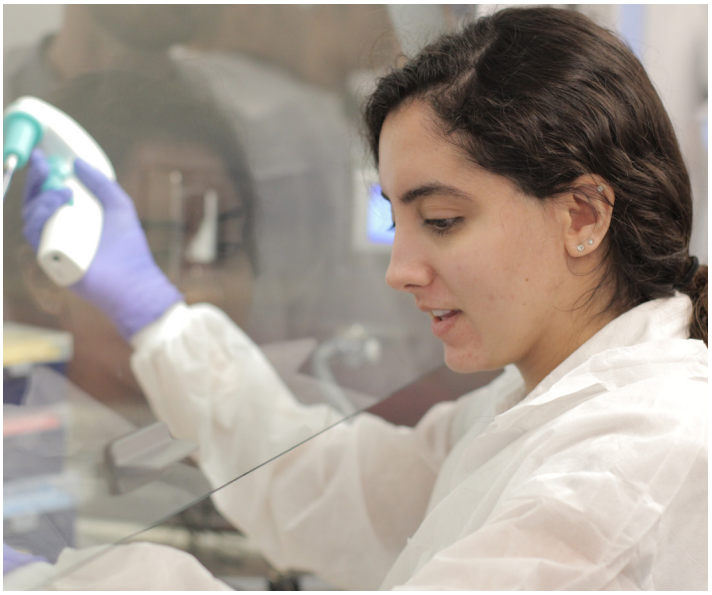
"What CIRM did was incredibly valuable," said Emeritus Professor Robert E. Maxson, who was in charge of USC's stem cell training grants. "And because the grants were big, and we were able to fund a lot of people, they really had a huge impact on helping us to jumpstart the program in stem cell biology."

Professor David Warburton, who directs the Developmental Biology and Regenerative Medicine Program at CHLA, added, "CIRM has had a huge impact on regenerative medicine for children at Children's Hospital Los Angeles and The Saban Research Institute here. We were able to award 20 or 30 training fellowships, mostly for physician-scientists, but some PhD scientists, working on different aspects of organ development, regeneration, tissue engineering, gene therapy, and cell-based therapy. And many of these people have gone on to successful careers, either at CHLA or at other places around the world."

The training grants also funded the CIRM Bridges to Stem Cell Research program, providing internships at USC's stem cell research center for students and recent graduates from Pasadena City College and other local institutions.

"It makes a huge difference for them, because they acquire training and exposure to new ideas that most people do not have access to," said Francesca Mariani, associate professor of stem cell biology and regenerative medicine, and integrative anatomical sciences at USC. "It's also terrific to have these trainees in our labs, because they can try experiments that are more adventurous and innovative. The outcomes of these experiments can be quite useful for charting new research directions."

In addition, CIRM invested in education on the high school level with the CIRM Science, Technology and Research (STAR) program, which provided local



CIRM's training grants supported efforts to educate the next generation of scientists (Photo by Cristy Lytal)

students with hands-on experience in stem cell research laboratories at USC.

In keeping with its long-term vision, CIRM invested not only in students and trainees, but also in faculty at the early stages of their careers. As these faculty established their new labs, CIRM funding provided a powerful incentive to focus their research energies on stem cell-related projects.

"We do a lot more work in adult regeneration of cartilage, bone and ligament, and really the main reason we got into that was because of our $2.2 million CIRM New Faculty Award to study these topics," said Crump. "It would've been very unlikely I would have gotten in that field, if it wasn't for that grant. And then once I got the award, we found some interesting results, and then it took off. And so the CIRM award fulfilled its purpose, because it shifted someone who was starting out, who had training in developmental biology, more towards regeneration and regenerative medicine."

To further encourage research involving human stem cells, CIRM created shared "core facilities" at USC and CHLA. These core facilities taught best practices for growing and maintaining human stem cells, and also directly provided these cells on a fee-for-service basis to

Andy McMahon, Director of USC's stem cell research center and Chair of the Department of Stem Cell Biology and Regenerative Medicine (Photo by Christina Gandolfo)

researchers across Southern California.

California's stem cell agency made even larger investments in brick-and-mortar infrastructure at universities across the state. In 2008, CIRM awarded $271 million to construct 12 major California facilities dedicated to stem cell research—including the Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research at USC.

"When I came to USC's medical school in 1983, I think I was the only developmental biologist," said Maxson. "And then Cheng-Ming Chuong was hired, and then Larry Kedes was recruited from Stanford to found the Institute for Genetic Medicine, and Hal Slavkin established the Center for Craniofacial Molecular Biology. The result of these recruitments was that by the late 90s, we had a small but active presence in developmental biology at USC's Health Sciences Campus, also including Henry Sucov, Yang Chai, and Malcolm Snead. But it was a quantum leap in growth when the Broad CIRM Center came about. That's had an enormous impact on developmental biology and stem cell biology."

USC's new stem cell building celebrated its grand opening in 2010, creating a center of gravity to draw scientists from around the world to its sunlight-filled laboratories.

CIRM exerted even more of a gravitational pull through its Research Leadership awards, designed to attract established stem cell investigators by providing the funding to expand into unexplored scientific territory.

The opportunity to try something new appealed to Andy McMahon, a well-known developmental biologist and founding faculty member of the Department of Stem Cells and Regenerative Biology at Harvard University. Despite his proven track record studying organ and kidney development in the embryo, the National Institutes of Health (NIH) considered it too risky to fund a foray into kidney repair and regeneration in the adult.

CIRM awarded McMahon a $5.7 million Research Leadership grant—enabling him to pursue new directions in his career. He left Harvard University to serve as the director of USC's stem cell research center, and shifted the focus of his lab to an area of great clinical need: exploring injury and repair in the adult kidney.

"There are a whole host of factors in a move," said McMahon. "And so one factor was to use the energy from a move to refocus and take the lab in a new direction. And another very big factor was not my lab, but to take on board a center with great potential in a fabulous city with collaborative opportunities amongst different institutes, and to build up this area of regenerative medicine. That was the big picture."

Upon arriving at USC, McMahon founded a new Department of Stem Cell Biology and Regenerative Medicine, and launched a university-wide USC Stem Cell initiative to encourage collaborations among scientists, engineers and clinicians from many disciplines across the university and CHLA. He recruited a strong cohort of early career faculty, and established a culture of intellectual exploration and collaboration to promote their success. He also established a first-of-its kind master's program, capitalizing on the excitement and promise of stem cell research.

"A key aspect of CIRM's mission was not just to see that the stem cell-based treatments that were ready for the clinic went into the clinic," said McMahon, "but to set in place a strong foundation for the future."

CIRM 2.0: Where are the cures?

In a 2004 television ad, actor Michael J. Fox entreated voters to support the effort to find cures by voting yes on Prop 71, the stem cell research initiative.

"71 will support research to find cures for diseases that affect millions of people, including cancer, diabetes, Alzheimer's and Parkinson's," said Fox, who was diagnosed with Parkinson's at the age of 29. "Please support the effort to find cures by voting yes on 71. It could save the life of someone you love."

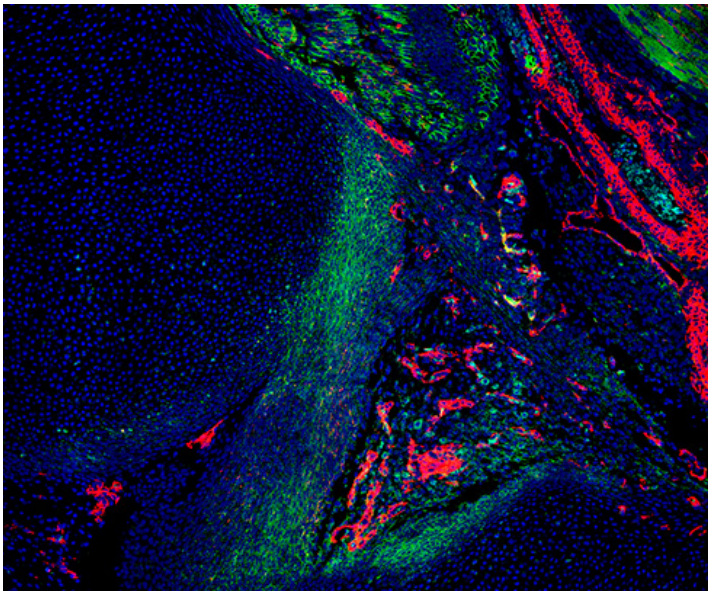
Ten years later, CIRM abruptly shifted its focus away from long-term strategic investments in education and basic scientific research. It would take years for the next generation of scientists to come of age, and decades for basic research discoveries to evolve into patient therapies. In the meantime, where were the cures?

In 2014, under the leadership of a new president and CEO, C. Randal Mills, California's state stem cell agency re-branded itself as CIRM 2.0. Mills outlined the principles of CIRM 2.0 at a series of public meetings, including one held at USC's stem cell research center.

At the meeting at USC, Mills explained that a project would have to pass four tests in order to receive funding from CIRM 2.0.

"The first test is that it has to accelerate the development of a stem cell therapy to a patient," he said. "Part two is that it has to increase the likelihood of success of a stem cell treatment. The third criteria is that there has to be an unmet medical need. And then fourth is [that it has to do so] efficiently."

He added, "I will be beating the better, faster drum as long as there are patients that need to be treated."



Knee joint (Image courtesy of the Evseenko Lab)

For USC Stem Cell scientists with a clinical focus, CIRM 2.0 was very good news.

USC researcher Denis Evseenko received a $2.5 million grant to use stem cells to develop cartilage implants to surgically repair sports-related knee injuries, which affect more than 10 percent of people under the age of 50. Thanks to CIRM's support, Evseenko has advanced the project to the stage of manufacturing the cartilage implants in preparation for human clinical trials, and has also founded a related company, PluroCart.

"I'm one of the examples of actually bringing things into the clinic," said Evseenko, an associate professor of orthopaedic surgery, and stem cell biology and regenerative medicine at USC. "It would probably not have been possible if CIRM considered me as too junior or too risky—if they took an NIH approach to it. CIRM took more of a venture capital type of approach: out of 10 funded projects, nine will fail. But the one that doesn't fail, will pay back. They're more outcome-oriented, and they want this research to develop something, to bring something, to convert into something financially."

This approach has led CIRM to put their money on at least 64 clinical trials treating conditions ranging from cancer to neurodegenerative disease to COVID-19. CIRM also funded discoveries that led to 30 additional

Anna Kuehl (Photo by Tracy + David Stills and Motion)

clinical trials, including an ongoing clinical trial for patients with HIV/AIDS based on discoveries made by USC researcher Paula Cannon.

"CIRM really provided me with both the opportunity and also the motivation to make quite a considerable shift in my research focus," said Cannon, a distinguished professor of molecular microbiology and immunology, and stem cell biology and regenerative medicine at USC. "I'd worked on the basic biology of HIV and hadn't really thought too much about whether anything I did could ever impact a treatment or could ever end up in a clinical trial. And so CIRM transformed my scientific life. It was like whiplash. I had this idea, I turned around, and in a very short period of time, they handed me a check to go do it."

To pursue this research, CIRM awarded $14.5 million to a team of scientists, led by John Zaia at City of Hope. As a key member of this team, Cannon pioneered a technique for genetically engineering a patient's own immune cells to resist HIV infection. This technique laid the groundwork for an ongoing clinical trial at the City of Hope, funded by an additional $5.6 million from CIRM and a matching amount from industry partner Sangamo Biosciences.

CIRM also invested heavily in stem cell research at CHLA. Researcher Tracy Grikscheit has received nearly $15 million to use stem cells to develop tissues for newborns with serious liver or intestinal problems.

"Without the support that CIRM gave to me and to my lab, I might not have ever gotten these projects off the ground, but now we are working to go to the FDA with a stem cell therapy for the children of California," said Grikscheit, who is chief of the Division of Pediatric Surgery at CHLA and a professor of surgery at USC. "It is truly remarkable to see what is possible when one state and all of her people decide that we should make progress together, and to support saving patients with stem cells."

At USC, one of CIRM's biggest investments has been over $40 million supporting in the development of a stem cell-based treatment for the leading cause of age-related blindness. Known as dry age-related macular degeneration or AMD, the debilitating condition causes the progressive loss of central vision—leaving people unable to read, drive or live independently.

To restore vision lost to AMD, USC Professor Mark Humayun is leading a team of scientists and partners from USC, the University of California, Santa Barbara (UCSB), the City of Hope, Caltech and Regenerative Patch Technologies. Together, they are using stem cells to generate more specialized cells that support the health of the retina. These retina-supporting cells grow on a membrane or "patch" that is surgically implanted into the eyes of subjects.

"Without CIRM's support, we could not have taken on this multidisciplinary effort to develop a novel stem cell-based treatment for AMD, which has led to FDA approval of an Investigational New Drug application and completion of a phase I/IIa clinical trial," said Humayun, director of the USC Ginsburg Institute for Biomedical Therapeutics and co-director of the USC Roski Eye Institute.

Some subjects have already recovered partial vision after receiving the implants during the clinical trials.

"After the procedure, my life changed in many ways," Anna Kuehl has said about her experience in the AMD

clinical trials at USC. "I could see whole faces on the TV and also the whole face of my husband and other people. My hope for the future is that these cells, these implanted cells, will stay alive and that many more people can experience the same as I have and can be helped."

An economic engine for California

With the worldwide economy in meltdown due to COVID-19, it seems counterintuitive to vote in favor of a ballot proposition allocating $5.5 billion to stem cell research and education. But to an economist, the 2020 stem cell ballot initiative, called Prop 14, is simply another stimulus package.

"Any injection of public or private funds for research helps provide a stimulus to the state economy, especially in a time of unemployment," said Adam Rose, research professor at the USC Price School of Public Policy.

Rose and Dan Wei, a research associate professor within the USC Price School, prepared an Economic Impact Report examining the effects of CIRM funding on the state and national economy between 2005 and the end of 2018. According to their analysis, in California alone, Prop 71 generated $10.7 billion in economic activity, and created an annual average of 2,974 jobs. Elsewhere in the U.S., Prop 71 generated $4.7 billion in economic activity, and created an annual average of 1,315 jobs. CIRM also led to significant state and federal tax revenues.

"In addition," said Wei, who is the lead author of the economic impact report, "the employment stimulated by CIRM funding created relatively higher paying jobs in the life sciences, health care and scientific research fields."

According to its supporters, Prop 14 could result in even greater payoffs for the state. And if CIRM pushes any of its clinical trials past the finish line, the resulting patient therapies have the potential to pay huge dividends by reducing the $3.5 trillion in U.S. health care expenditures, as well as by alleviating human suffering.

"It feels like a responsibility that California has, because we are the fifth largest economy in the world, and we have more world-class biomedical research institutions in this state than most countries," said Melissa King, executive director of Americans for Cures. "And so if we're not funding this at the state level, all kinds of opportunity for research will disappear."

Featured Image

University President Carol Folt visits the Eli and Edythe Broad CIRM Center for Regenerative Medicine and Stem Cell Research at USC. (Photo by Sergio Bianco)

Your Support

To learn how you can transform medicine by supporting USC Stem Cell, contact:

Keck School of Medicine of USC
stemcelldev@usc.edu
stemcell.keck.usc.edu/support

USC Stem Cell