

# Stem Cell Research in California: The Game Is On

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**The California Initiative embodied in Proposition 71 was designed to boost embryonic stem cell research and its translation into cell therapies in the face of federal restrictions on such research. With funding starting to flow, the stem cell revolution is now underway.**

## A Bold Beginning

In 2004, California voters passed a ballot initiative providing \$3 billion in state monies over 10 years to support stem cell research carried out in California and to construct facilities to allow this research to take place unencumbered by federal restrictions. Born from the frustration of parents who recognized that the potential of stem cell therapy was being snuffed out by restrictive federal policies, Proposition 71 (The Stem Cell Research and Cures Initiative) was designed around the scientific needs of researchers, physicians, and academic administrators with the goal of using state bond financing to generate long-term, stable capital support for human embryonic stem cell research and its translation into cell therapies. Proposition 71 was a courageous initiative at a time of opposition by the Bush Administration to such research and was also a milestone demonstrating that ordinary citizens are willing to take bold steps when Washington fails to meet its obligations.

## Delays and Challenges

The California Institute for Regenerative Medicine (CIRM) was established by Proposition 71 to distribute the grant monies. However, grant distribution was held up for 16 months while opponents of human embryonic stem cell research hamstrung the Institute in the courts, claiming the ballot initiative was unconstitutional. During this time CIRM maintained momentum by donations from private philanthropists, followed by a life-giving loan of \$150 million from California Governor Arnold Schwarzenegger

2 days after President Bush vetoed the bill that would have loosened restrictions on federal funds for embryonic stem cell research in the United States. Now, a mere 3 years after Proposition 71's approval, the court challenges have been overcome, the funding is flowing, and Californians have begun to see their vision realized.

Throughout the legal delays, vital infrastructure was built up by CIRM's governing body, the 29-member Independent Citizens' Oversight Committee (ICOC), established by Proposition 71 to include patient advocates, research institutes, and the business and general community of California to act in public to govern and to award grants recommended by management. They established operating procedures and created committees to establish working groups to oversee grants, standards, facilities, medical ethics, conflicts of interest, governance, and intellectual property. CIRM's first President, Zach Hall, aided by Arlene Chiu, both veteran neuroscientists with NIH administrative experience, hired a talented and committed staff, spearheaded a visionary strategic plan, and established procedures for issuing research funding applications (RFAs) and processes for managing the grants. Concurrently, the ICOC selected a peer review group comprised of expert scientists from outside California, chaired by Harvard University's Stuart Orkin.

## Driving Research Forward

In 2006, CIRM's funding apparatus finally began turning its gears, issuing a call for RFAs from new and established researchers investigating fundamental

questions about embryonic stem cell biology. A total of \$45 million over 2 to 4 years has been awarded to 72 applicants. In addition, a stem cell training program was established in which \$40 million was awarded for 3 years to cover the salaries of 54 graduate students, 80 postdoctoral fellows, and 35 clinical fellows, all of whom, as part of their training, are required to be schooled in the ethics of working with human stem cells. An additional \$50 million was divided among 17 California institutions to construct shared research facilities where investigators can work together, and six institutions received funding to teach courses in stem cell techniques to scientists.

CIRM has recently announced additional programs to expand its research scope. For example, a competition has just been completed that provides generous 5-year young investigator grants for salary and operations to 22 assistant professors. For the six clinician-scientists successful in that competition, additional funds will be provided to repay their medical school tuition loans to encourage them to consider stem cell-related research as a viable career opportunity. A second round of new investigator grants targeting 14 or more investigators has been approved and will be evaluated in the coming months.

CIRM has also issued an RFA for establishing new pluripotent human stem cell lines and for new technologies to create them. We are interested in a multipronged approach that will include parallel lines of research not only on human embryonic stem cells but also on somatic cell reprogramming and induced

pluripotency (Lewitzky and Yamanaka, 2007). Human embryonic stem cells will remain the gold standard for characterizing innate pluripotency, despite claims to the contrary expressed by President Bush in his State of the Union address last month.

### Strengthening Research Facilities

CIRM panels are judging a \$262 million funding competition for the construction of major research facilities in California. Twelve academic institutions that successfully negotiated a scientific review are moving forward to qualify for designation as either CIRM "Institutes," which will carry out basic, preclinical, and clinical research; CIRM "Centres of Excellence," which will focus on two of those three areas; or CIRM "Special Programs," which will focus on one of the three programs. A requirement for matching funds from the candidate institutions will leverage CIRM's contribution considerably, with over \$700 million expected to flow into the program from all sources.

CIRM-funded "Institutes" will house, at one location, basic researchers, translational scientists, and clinicians who will also maintain links with colleagues within and between institutions in various regions of California. California institutions are already drawing key scientists from around the country as well as from overseas: among others, Martin Pera to the University of Southern California, Peter Donovan to UC Irvine, Stephan Heller to Stanford, and Nissan Benvenisty to Cedars-Sinai. In addition, James Thomson and Shinya Yamanaka have agreed to spend part of their time at UC Santa Barbara and the Gladstone Institute, respectively. The influx of such top researchers will hopefully induce a new generation of young scientists to seek training and faculty appointments in California.

Eight other states in the US have commitments in process that total just under \$2 billion for their own stem cell programs, in part to retain staff and to reduce emigration. We welcome their efforts, for increasing the number of stem cell researchers across the country stands to benefit all programs in the United States and to spur advances in stem cell research and cell therapy applications globally.

### Additional Funding Capacity

CIRM has also posted planning grants for Research Disease Teams to enable multidisciplinary teams of researchers in academia and business to write grants that integrate basic discoveries, translational research, and clinical trials for treating specific diseases or injuries with cell replacement therapy. Support for prospective planning grants is rarely provided by granting agencies, but this new program, by aligning basic and clinical research with the interests of for-profit companies, lies at the heart of CIRM's mission to translate basic research into improved clinical care. It is vital that we marshal all aspects of California's research capacity toward the development of stem cell therapeutics. The 2008 Disease Team Research Grants will require identification of an investigational new drug (IND) target that can reasonably be reached within 4–5 years, with funding potentially reaching \$20 million (subject to ICOC approval), if all milestones are achieved through to phase II clinical trials.

A key goal of CIRM is to integrate for-profit companies into its programs to lever and expand the capacity to generate cell therapeutics. For-profit companies are more experienced than nonprofits at seeing commercial opportunities, facilitating research by supplying laboratory reagents and materials, manufacturing cell products suitable for clinical use, understanding the regulatory processes involved in translational medicine, and opening the cell product pipeline to clinical application for patients. For this reason, the governing body of CIRM is investigating the possibility of allowing for-profit companies to compete for financial support from CIRM in an ambitious revolving loan program. In the proposed program, the grants to for-profit companies will be paid back to CIRM on a basis to be determined and will be reinvested for further grant or loan support to accelerate stem cell research applications. This support from CIRM may be expected to attract additional leverage funding for for-profit companies from venture capital or other financial institutions. The ICOC has now established a Loan Task Force to seek the advice of California's business, financing, and venture capital communities as to how such a program could work.

### National and International Collaborations

CIRM is eager to support collaborations among CIRM-sponsored investigators and institutions and other stem cell programs in the US and globally. We would like to create joint funding initiatives that will link international efforts with our own, for example, to standardize expansion, differentiation, and manufacturing methods and to assess the variant properties of different stem cell lines that may define their stability and clinical usefulness. Discussions with Canada on cancer stem cell research collaborations are already underway, and initiatives have been proposed with Australia, UK, France, and others. These early-stage negotiations seek working relationships that include joint programs funded by all partners and consistency with CIRM values in award and grant policy. Bioinformatics is another potential and valuable target for international collaborations and shared research findings.

CIRM plans to reach out to our national and international colleagues by hosting meetings and encouraging exchanges, visits, and sabbaticals to promote the sharing of information, to expand the network, and to reduce duplication of effort. We will seek to broaden the mandate to include all forms of science that will move the stem cell agenda forward, including, for example, an emphasis on immunology, which will be key for clinical applications. In sum, CIRM will work to dissolve any barriers that delay progress toward clinical applications. Mature programs of research, translation, and clinical trials under way in other locations can only enhance the ability of California researchers to develop and deliver therapeutics. CIRM is open to building bridges to other public and philanthropic organizations and to exploring joint efforts where they can assist us in delivering CIRM's mission for the Californian community.

### The Road Ahead

CIRM's future scientific programs will aim to maintain a wide range of interests, guided by the directions set by our grant applicants and by staff, who will be closely watching developments in all fields to identify needs and opportunities. For example, research propos-

als on deriving new pluripotent stem cell lines including disease-specific cell lines, induced pluripotent stem (iPS) cells, parthenogenetic and androgenetic stem cells, and placental stem cells have all been identified as potential areas to be funded. We will not be restricted by political conflicts that aim to separate research efforts on embryonic stem cells, fetal and placental stem cells, and adult tissue stem cells. We believe such distinctions are potential barriers to developing safe and effective therapies. In actuality, the fields overlap, as evidenced by the fact that derivation of iPS cells from adult somatic cells is based on information from expression profiling of embryonic stem cells. The identification of directed differentiation pathways and the growth factors, cytokines, and inducers necessary to yield specific cell types for therapy will also depend on data gathered from human embryonic stem cells. The clinical response of the body to cells introduced to repair damaged tissue will require the experience obtained from autologous and allogeneic transplantation. For these and other reasons, integrating the entire spectrum of stem cell experiences appears sensible and productive.

There will be particular emphasis on immunology as many diseases, such as multiple sclerosis and juvenile diabetes, include an autoimmune component that will require manipulation of the immune system before tissue repair with exogenous stem cell populations can be attempted. Strategies that involve reinstruction of tolerance and removal of activated immune cells may need to precede reintroduction of the target cells. This could involve chemotherapies, thymic stimulation, adult stem cell therapy (hematopoietic and/or mesenchymal stem cells), and eventually transplantation of progenitor cell types derived from pluripotent stem cells in culture. Autologous cell therapies are likely to be more effective than allogeneic therapies, unless immunological interventions can be developed to ensure tolerance to the transplanted cells (Seach et al., 2007).

The road ahead leading to stem cell therapies and possible cures may be long and arduous. But California has tremendous resources to apply to the problem, plus a populace that supports the effort. By April of this year, CIRM will have invested over \$500 million in California, making it the world's largest

funder of embryonic stem cell research. Matching donor and institutional funding in California is expected to bring in an additional \$550 million, bringing the total funding commitment to over \$1 billion. By creating a critical mass of stem cell researchers as well as synergy among the rich public and private sector intellectual assets, California will remain steadfast in its dedication to developing the stem cell therapies and cures that its citizens and patient families dreamed of when the community embraced Proposition 71. California's funding together with its scientific and clinical talent will ensure a major impact on medical research for treating chronic disease and injury.

#### ACKNOWLEDGMENTS

Alan Trounson is President of CIRM, Robert Klein is Chairman of the Independent Citizens' Oversight Committee (ICOC), and Richard Murphy was interim President of CIRM from September 2007 to February 2008.

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