

Proposition 71, The California Stem Cell Research and Cures Initiative: A Research Agenda

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Executive Summary

Since August 9, 2001, when President Bush decided to limit federal funds for human embryonic stem cell (HESC) research,¹ much debate has surfaced about the future of this type of research. In California, Proposition 71, The California Stem Cell Research and Cures Initiative, was passed in November 2005 in response to the federal funding limitations. This bond initiative (1) established the California Institute for Regenerative Medicine, a California surrogate for National Institute of Health, to regulate stem cell research and funding (2) appropriated \$3 billion from the General Fund to pay for bonds to finance this endeavor and (3) established a constitutional right to conduct stem cell research.

To date, lawsuits have stalled the funding of Proposition 71. Meanwhile, other states have initiated their own stem cell and HESC research projects and bipartisan Congressional support for HESC research has increased. These events may have substantially decreased California's "first-mover" advantage in HESC research and has called into question the economic returns of this bond measure. Many argue that this initiative will not pay for itself as its proponents claimed it would. Diverse groups who support HESC research have questioned the details of this policy experiment, focusing on ethical and oversight questions. Even when/if therapies are developed; the impact on California's healthcare system and consumers is uncertain and needs careful investigation.

Background on Embryonic Stem Cell Research

Since 1998, when James Thomson isolated the first embryonic stem cells in his lab, excitement has continued to build around this promising area of biology and medicine. All stem cells have three properties, which account for their biological and medical importance: (1) they are capable of dividing and renewing themselves for long periods; (2) they are unspecialized; and (3) they can give rise to specialized cell types.² Stem cells are classified by the developmental stage of the tissue (e.g. adult, fetal, embryonic) and/or the specific cell type from which they are derived (e.g. pancreatic, neural). HESCs differ from adult stem cells because they have the ability to develop into many different cell types of the body. In contrast, adult stem cells are generally limited to only differentiating into the cell type of their tissue of origin or cell types that are derived from their tissue of origin, i.e. progenitor stem cells.

Until recently, the most common type of stem cells came from adult blood and skin cells.³ HESCs are potentially more useful for medical and research purposes because they can produce cells for almost every type of tissue in the body and they are relatively easy to grow *in vitro*. Moreover, HESCs can also be customized for treatment of a specific patient through a procedure known as somatic cell nuclear transfer (SCNT).⁴ This property may be especially important for autoimmune diseases, such as type I diabetes or multiple sclerosis, for which patient-specific immunologic response is a barrier to treatment.

What Is Proposition 71?

In August of 2001, President Bush announced that he “would allow federal funding for research on the limited number of HESC lines that existed [at the time],”⁵ but not for the creation of more HESC lines. However, many people, including scientists, patients, and medical

practitioners, believed that HESC research could lead to new treatments of degenerative diseases in the future. The California Stem Cell Research and Cures Initiative, known as Proposition 71, was proposed as a response to the loss of federal funding. Proposition 71 consists of four key provisions:

- The California Institute for Regenerative Medicine (CIRM) was established to regulate stem cell research and funding, and the Independent Citizen’s Oversight Committee (ICOC) was established to govern CIRM.
- Loans up to \$3 million were provided for CIRM's initial administration and implementation costs and bonds to annually finance CIRM were authorized (an annual limit of \$350 million up to a total of \$3 billion).⁶
- A constitutional right to conduct stem cell research but one that prohibits funding of human reproductive cloning was established.
- No amendments are allowed to statutes for the first three years and any repeal or amendment thereafter requires a legislative supermajority (70%).

Emphasizing the public interest, advocates claimed that Proposition 71 was “an affordable solution that closes the research gap” left by the restrictions on federal funding so that “new treatments and cures can be found.”⁷ Because architects of the proposition expected to encounter strong opposition, even after the initiative passed, the constitutional amendment was included to separate science decisions from political intervention. In addition, the oversight committee for these new funds was comprised of 29 members appointed by elected officials and chancellors of the University of California system to ensure that allocation decisions would mainly be in the hands of scientists, technocrats, and experts.⁸

What Has Happened Since Proposition 71 Was Passed?

Even before the outcome of the California election, support for continued federal funding of HESC research was voiced in Congress.⁹ After Proposition 71 passed, several states initiated their own small-scale stem cell research projects, while conservative groups in California immediately filed a lawsuit to stop the disbursement of funds for Proposition 71. These groups challenged the initiative by claiming that CIRM, a private body potentially rife with conflicts of interest, could not effectively control taxpayer funds. Although some claimed that this lawsuit was just a tactic for opponents of HESC research, supporters of HESC research also acknowledged the lack of public oversight, limited transparency, and the potential for conflict of interest within ICOC and CIRM.¹⁰ A timeline documenting some major events in the stem cell debate, both nationally and in California, is outlined in Table 1.

Current Debate on Proposition 71

Economic Perspective

While Proposition 71 allocates State monies to fund scientific research, it is unclear whether this investment would pay for itself as advocates have argued. Even though California may benefit from direct and indirect revenues from intellectual property rights, the likelihood of realizing these financial gains has been questioned on several grounds. First, licensing income and royalties to academic institutes have historically been between 2.5% - 5.0% of research expenditure.¹¹ This calls into the question the large revenue stream necessary to pay for these bonds. Second, the Thompson Patents, which cover most commercial applications of HESC technology, may limit research incentives and profits for most cures/products because of licensing and royalty payments to the patent holders.¹² Third, cures/products from this research may take much longer to produce than initially expected, delaying prospective returns. Fourth, California may not be able to claim tax-exemption status for bonds issued as a result of

Proposition 71, as this conflicts with royalty payments to the State,¹³ channeling profits to researchers and businesses.

However, returns to the State's investment on stem cell research may be gained via other avenues. Some have claimed that the location of stem cell-based technology companies in California will give rise to an economic boom within the State, thereby increasing tax revenues and employment opportunities.¹⁴ Others point out that California's "head start" on this type of research will enable better access to future cures/products for Californians. However, advantages associated with this "head start" may be deteriorating as lawsuits stall the initiative's funding and other states develop their own research agendas.

Whether the initiative crowded out private capital investment or whether it was really necessary to get this technology started is still another debate altogether. Some argue that cures/products would have been developed without public investment, but others assert that there is a lack of venture capital even when research has produced promising results.

Many hope that at a minimum California will benefit from reductions in healthcare spending in the long run because of new medical treatments and cures derived from stem cell research. However, cell-based technologies, most likely in the form of more expensive biotherapeutics or cell-based therapeutics, will require more monitoring and specialized administration, contributing to rising healthcare spending. Although the health of patients in California may improve from these new technologies, it will likely come at a high price.

Ethics, Implementation, and Oversight

Proposition 71 also raises many ethical and organizational questions. Its passage intensified public debate on the definition of life, cloning, and the legal status of an embryo. Aside from these issues, additional ethical concerns are associated with the commoditization of eggs and the potential for unintended uses of the technology. Advocates for women's rights, in

particular, fear that women will be viewed as “egg producing machines,” as evidenced by what has already happened with the market for *in vitro fertilization* (IVF).¹⁵ The complexity of the IVF procedure and the requirement of several eggs per donation has created a market where young women aged 21-26 are compensated \$2,000-\$50,000 depending on their genetic desirability and endurance for intense hormone therapy. Egg donors for ES cell research may further exacerbate this trend toward commoditization because the genetic content of an egg for stem cell research has no value, whereas the genetic component has all the value in IVF egg donation. In particular, more economically disadvantaged women may disproportionately provide eggs while enduring the potential side effects of the egg donation process. Women’s rights advocates are calling for regulations to ensure all egg extraction is medically performed with follow-up and donated without compensation (to discourage the development of a market for eggs). Additionally, women’s rights advocates want more research on the side effects and long-term consequences of egg donation procedures. Still others fear that advancing HESC research will encourage more controversial research, such as reproductive cloning, creation of chimeric animals,¹⁶ or advancement of eugenics.¹⁷

Given these ethical concerns, the organizational structure and oversight of CIRM has also been contested. Many want CIRM’s guidelines modified to ensure that funds are used only for research that complies with ethical standards. Some have suggested that more decentralization, by having institutional or research funding contingent upon fulfillment of the National Academy of Science research standards,¹⁸ would require much less administration and would be self-enforcing. Yet, by sacrificing some flexibility, more centralization could help increase accountability, ensure uniformity of egg donation procedures and guidelines, and prioritize the allocation of funds.

Public involvement and administration of CIRM is also a concern. Some view the provisions of Proposition 71 as inherently resistant to legislative oversight and point to CIRM’s

initial violations of open meeting laws as questionable since public funds are used to finance CIRM's operations. CIRM has acknowledged these concerns and has been more responsive to the public's concerns.¹⁹ In the past year, CIRM had opened its meetings to more public involvement and will convene a conference to discuss the safety of egg donations procedures.²⁰ Nevertheless, questions over what kind of oversight best serves the public interest when decisions require extreme technical knowledge still remain.

Research Questions

The passage of Proposition 71 has already stimulated many debates without having even spent a single penny in research grants. Assuming the best-case scenario in which therapies are actually developed in the near future, a new set of questions will need to be investigated:

- What type of products will these new therapies be?
- What are the problems associated with these new products?
- Will these products demand an even more specialized medical workforce, such as MD/PhDs, to deliver them?
- What type of infrastructure will be needed to support these new therapies?

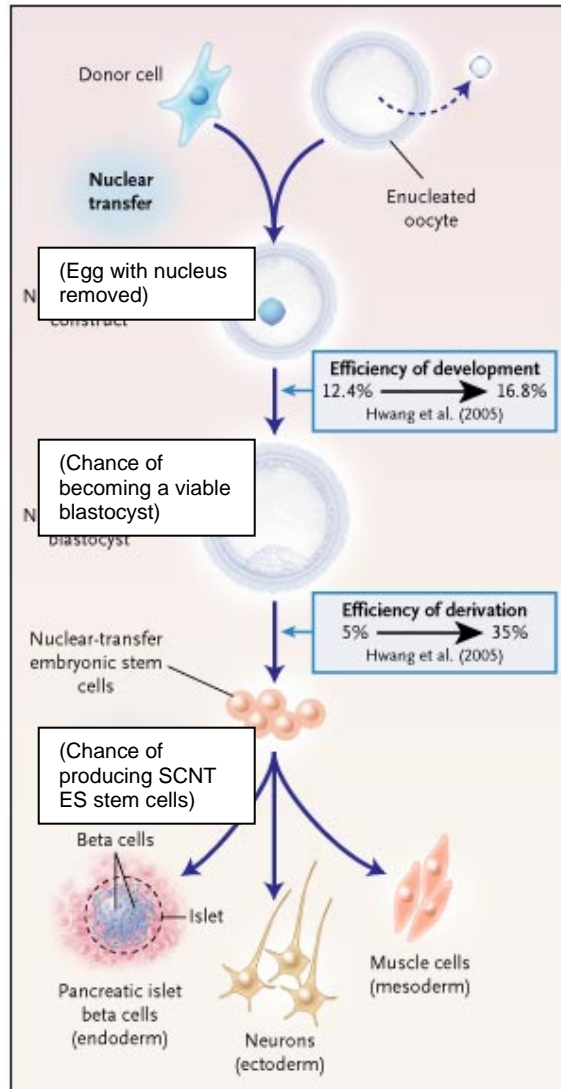
Looking ahead we also need to consider that these therapies might transform the healthcare sector:

- What will be the impact on the delivery system costs?
- How will insurance companies respond if therapies are more and more personalized (and therefore expensive)?
- If patients are expected to help finance these therapies what will be the demographic composition of these patients?
- How will we make these publicly financed products accessible?

Table 1: Timeline of Stem Cell Debate

National Timeline		California and CIRM Timeline
	2001	
President Bush declares federal funding will only go to research on currently available stem cell lines that were derived from destroyed embryos left over at fertility clinics. States retain the ability to appropriate money for research or to restrict it.	August 9, 2001	
Scientists in Massachusetts perform the first cloning of human embryos.	November 25, 2001	
	2004	
	November 2, 2004	California Proposition 71 passed with 59% of the vote.
	December 16, 2004	ICOC unanimously elected Proposition 71 campaign chairman Robert Klein II, stem cell initiative architect, as the ICOC chairman. The panel also voted Edward Penhoet, scientist and entrepreneur, committee's vice chairmanship.
	2005	
New Jersey's governor announces the state will fund a \$150 million stem cell research center and promises to champion a ballot initiative to allocate another \$230 million.	January 11, 2005	
	February 22, 2005	Taxpayer organizations and groups opposed to stem cell research filed two legal challenges with the Supreme Court to immediately stop CIRM from distributing funds. Supreme Court sent challenges to lower courts.
	May 6, 2005	CIRM chooses San Francisco as headquarters.
Connecticut lawmakers earmark \$100 million for stem cell research over 10 years in an effort to help its biotech industry compete with California and New Jersey.	May 31, 2005	
	June 6, 2005	CIRM accepts \$5 million in private donation from Ray Dolby, Dolby Laboratories' Chairman and founder.
Illinois Gov. Rod Blagojevich circumvents the legislature using an executive order to dedicate \$10 million for HESC studies after bills allocating funds for the research were voted down or shelved without a vote.	July 13, 2005	
Senate Majority Leader Bill Frist (R-Tenn.) announces his support of an effort to loosen Bush's restrictions on stem cell research, putting him at odds with the Bush administration.	July 29, 2005	
	September 9, 2005	CIRM grants training grants but can't finance them.
	September 29, 2005	Governor Schwarzenegger veto's SB18, a measure designed to protect the health of women donating their eggs for stem cell research and requiring performance audits of CIRM by the state auditor. In his veto message the Governor said he supported the main provisions of the bill but found it to be "in direct conflict" with a provision in Prop. 71 barring amendments until 2008.
	November 30, 2005	Alameda County Superior Court declined to dismiss two lawsuits that have blocked the state from issuing bonds to finance its \$3 billion stem cell research program.
	2006	
	February 28, 2006	Stem cell initiative trial opens. CIRM lawyers insist the program operates like many other state agencies and that voters knew exactly what they were getting when they created it.
	March 3, 2006	Stem cell initiative trial ends.

Figure 1: Schematic Depiction of Somatic Cell Nuclear Transfer



¹President Discusses Stem Cell Research. <http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html>. Accessed on April 7, 2006.

² NIH Report. *Stem Cells: Scientific Progress and Future Research Directions*. 2001. <http://stemcells.nih.gov/info/scireport/>.

³ In fact, hematopoietic stem cells (adult bone marrow stem cells) have been used for nearly 50 years in bone marrow transplants because of their regenerative properties, their ability to differentiate into multiple types of blood cells, and their numbers.

⁴ In the process of somatic cell nuclear transfer (SCNT), a nucleus from a patient's body cell (somatic cell) is transferred into an egg that has had its nucleus removed, producing a blastocyst that can generate ES cells that are immunologically compatible to a patient. See Figure 1.

⁵ Connolly, C. Calif. *Stem Cell Initiative Could Backfire Nationally*. *Washington Post*. November 14, 2004.

⁶ Appropriating monies from the General Fund to pay for bonds and imposing cost of about \$6 billion over 30 years to pay off both the principal (\$3 billion) and interest (\$3 billion) on the bonds. The attorney general's office estimated State payments to averaging about \$200 million per year.

⁷ Proposition 71 Stem Cell Research. Funding. Bonds. Initiative Constitutional Amendment and Statute. www.ss.ca.gov/elections/bp_nov04/prop_71_entire.pdf. Accessed on April 7, 2006.

⁸ Pollack, Andrew. "California's Stem Cell Program Is Hobbled but Staying the Course." *New York Times*. December 10, 2005.

⁹ On April 28, 2004, 206 members of the U.S. House Representatives sent a petition to President Bush requesting a removal or partial removal of restrictions on federal ES cell research. Fifty-eight Senators, including several key Republicans, sent a similar request in June 2004. On June 24, Representatives Castle (R-Delaware) and DeGette (D-Colorado) sponsored a bipartisan bill, H.R. 4682, the Stem Cell Research Enhancement Act of 2004, to increase federal support of embryonic stem cell research.

¹⁰ Korobkin, R. "The stem cell initiative, sabotaged." *Los Angeles Times*. March 3, 2006.

¹¹ AUTM U.S. Licensing Survey: FY2004. <http://www.autm.net/events/File/FY04%20Licensing%20Survey/04AUTM-USLicSrvy-public>. Accessed on April 7, 2006.

¹² Loring, J, and C. Campbell. "Science and law. Intellectual property and human embryonic stem cell research." *Science*. Mar 24, 2006; 311(5768):1716-7.

¹³ Tansey, B. "Tax law casts doubt on stem cell royalties; State may not reap billions promised to voters last fall." *The San Francisco Chronicle*. October 25, 2005.

¹⁴ Wade, N. "Stem Cell Researchers Feel The Pull of the Golden State." *The New York Times*. May 22, 2005.

¹⁵ Woodward, T. "Scrambled eggs - Could an international stem cell consortium make San Francisco the center of an emerging market in human ova?" *San Francisco Bay Guardian*. Vol.40, No.7. November 15-22, 2005.

¹⁶ Named for the mythical Greek monster with a lion's head, goat's body and serpent's tail, chimeric animals are generally defined as having cells from two or more different organisms. A typical chimera might be a mouse endowed with a few human brain cells to make it a better subject for experimentation on treatments for diseases like Parkinson's.

¹⁷ Eugenics is a social philosophy, which advocates the improvement of human genetic traits through social and scientific intervention.

¹⁸ National Academy of Science Report. "Guidelines For Human Embryonic Stem Cell Research: Committee on Guidelines for Human Embryonic Stem." <http://www.nap.edu/catalog/11278.html>. Accessed on April 7, 2006.

¹⁹ CIRM To Initiate Public Sessions On Guidelines For Stem Cell Research. <http://www.cirm.ca.gov/pressreleases/2005/08/08-26-05.asp>. Access on April 7, 2006.

²⁰ Somers, T. "Stem cell experts keep active while funds lag in limbo; Institute sidelined by court challenge." *The San Diego Union-Tribune*. January 13, 2006.