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# The California Stem Cell Initiative: Persuasion, Politics, and Public Science

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The California Institute for Regenerative Medicine (CIRM) was created by a California ballot initiative to make stem cell research a constitutional right, in response to Bush administration restrictions on stem cell research. The initiative created a taxpayer-funded, multibillion-dollar institution, intended to advance public health by developing cures and treatments for diabetes, cancer, paralysis, and other conditions. The initiative has been highly controversial among stakeholders and watchdog groups concerned with organizational transparency, accountability, and the ethics of stem cell research. We interviewed major stakeholders—both supporters and opponents—and analyzed documents and meeting notes. We found that the CIRM has overcome start-up challenges, been selectively influenced by criticism, and adhered to its core mission. (*Am J Public Health*. Published online ahead of print January 14, 2010: e1–e6. doi:10.2105/AJPH.2009.168120)

In 2001, President George W. Bush issued a rule limiting federal funding for research involving human embryonic stem cells (hereafter, "stem cells"), including funds from the National Institutes of Health (NIH), the world's largest single source of funds for stem cell research.[1] For institutions that used nonfederal funding sources to continue stem cell research, the rule required the use of alternative laboratory space and equipment that had not been purchased or built with federal funds.[2] In reaction to the federal policy, the citizens of California took stem cell research into their own hands: in 2004 voters passed the California Research and Cures Initiative, which amended the state constitution to make stem cell research a constitutional right and created an institution—the California Institute for Regenerative Medicine (CIRM)—to fund, facilitate, and provide oversight for stem cell research in the state.[3] The initiative provided a mechanism to fund stem cell research with $3 billion over a decade through the sale of public bonds, with interest payable from the state's general fund, amounting to an additional $3 billion.

The initiative was specifically designed to protect stem cell research in California from many typical impediments, including unpredictability of funding, legislative interference, and regulatory restrictions. The CIRM is a semiautonomous institution; although it operates as an agency of the state executive branch, its governing board, the Independent Citizens Oversight Committee (ICOC), is responsible for the CIRM's governance and administration. The ICOC also administers the CIRM's financing, together with the California Stem Cell Research and Cures Finance Committee, a state agency created by the initiative to handle the bond issues. The ICOC also coordinates the 3 policy-setting working groups mandated by the initiative: Scientific and Medical Research Funding, Scientific and Medical Research Facilities, and Scientific and Medical Accountability Standards.

We undertook a subjective review of the CIRM's history, including its political and legal aspects and present status. We conducted semistructured interviews and discussions with 17 key stakeholders: principal supporters and opponents of the initiative campaign; past and present CIRM officers and staff; ICOC members; state legislators; critics of the CIRM; and representatives of watchdog organizations. The interviews were tailored to elicit information or opinions on aspects of the subject most germane to each interviewee's knowledge of and role in CIRM activities. We followed the initial stages of the interviews with discussion and further questions to pursue in greater depth significant themes that arose during the interviews. Four respondents interviewed early in the project were subsequently reinterviewed. All respondents gave informed consent and were guaranteed confidentiality. No requested interviews were refused.

We also analyzed government documents, litigation briefs and opinions, transcripts of CIRM meetings and other materials from the CIRM Web site, media accounts, and policy papers and materials from other sources, including advocacy organizations and watchdog groups. We did not attempt formal tabulation of the interview responses beyond listing several relevant themes, to ensure that they were covered in future interviews or reinterviews. Here we review the general outlines of stem cell research, describe selected aspects of the initiative from political and legal perspectives, describe the actions and roles of key stakeholders in support or opposition before and after passage of the initiative, and look at the progress made to date.

It is difficult to find anything quite like the California stem cell endeavor—the rationale for its origin, its enabling ballot initiative, the extent of state funding for research, and the public's vigorous engagement with the process are all unprecedented. We found that the CIRM, after a difficult beginning, and despite institutional turbulence, economic uncertainty, and constant public scrutiny, has become well-established and has both maintained and strengthened its core mission, partially aided by the pressures and criticism.

## HUMAN EMBRYONIC STEM CELLS

In the early stages of embryonic development, all cells are pluripotent. As development proceeds, cells differentiate to serve specific functions: they become neurons in the brain and spinal cord, for example, or glomerular

cells in the kidney. Researchers use stem cells obtained from previously frozen human embryos very early in development at the blastocyst stage; the embryos are produced by in vitro fertilization of donor eggs.[4,5] The process of obtaining the stem cells destroys the possibility of further development of the embryo.

The number of currently frozen embryos in the United States has been conservatively estimated at approximately 400 000, and more continue to accumulate.. Many are awaiting possible implantation or are considered excess embryos.[6] Embryos may be kept frozen for years, and donation of embryos to research is an issue of heated ethical debate. An alternative method of producing embryonic stem cells is somatic cell nuclear transfer, in which a somatic donor cell nucleus is transferred into an enucleated egg and allowed to develop into a blastocyst. This process requires hyperstimulation of egg production in the donor and surgical removal of her eggs, both of which carry certain health risks to the donor.[7]

Research on stem cells began well before the presidential order limiting federal funding. This field was and is highly attractive to biological and medical researchers and to the public, for obvious reasons: (1) stem cell research promises to shed light on basic foundations of human biology, and (2) if stem cells were implanted or injected under as-yet-to-be-developed ideal conditions, they might cure or greatly ameliorate diseases and conditions that are unresponsive to standard treatments.

## THE CALIFORNIA RESEARCH AND CURES INITIATIVE

Researchers have long sought funding for all types of stem cell research (e.g., with nonhuman cells, human adult stem cells, cells derived from umbilical cord blood, and stem cell-like cells developed from adult cells); this research has been included in the broad objectives of contributing to public health in the United States and globally. As it became evident that a restriction on federal funding of stem cell research was likely to occur, leaders at universities and research institutes and in the biotechnology and pharmacological industries began to consider alternative funding sources. At the national level, leading scientists met to discuss possibilities for continuation of the work. Prominent biomedical scientists, including professors Irving Weisman of Stanford University and Lawrence Goldstein of the University of California, San Diego, continued discussions in California. Potential wealthy donors, with a broad range of influential connections—from the entertainment industry, the financial sector, and politics—met with advocates for disease-specific research to formulate a state-based strategy.

Robert N. Klein Jr, a prominent real estate developer, networked vigorously among these stakeholders.[8] No single name is as closely associated with the initiative or the CIRM as Klein's. His supporters and admirers and even his critics credit him for the success of the initiative, from his original concept of the project, through the development and funding of the ballot measure, to his present leadership as chairperson of the ICOC. Klein is noted for facilitating the carefully focused use of the California ballot initiative process to create a stable, funded structure to promote and conduct stem cell research on a highly predictable, steady basis and for recruiting the intense participation and influence of disease- or injury-specific research advocates along with leading scientists. His associates and detractors alike have acknowledged his single-minded and at times autocratic leadership style as well as the accomplishments that have resulted. After training as an attorney, Klein earned his wealth as a real estate developer and used his experience to steer legislation and joint initiatives to encourage and support combined government and private financing of low-income housing. He has strategically allied his own wealth and influence with those of others to sponsor support for medical research. Prior to his involvement in the creation and support of the initiative and the CIRM, and after his son was diagnosed with juvenile-onset diabetes, he worked with the Juvenile Diabetes Research Foundation to lobby for congressional approval of a supplementary NIH appropriation for diabetes research.

The ballot initiative enterprise was notable for its California style. The most populous state, California is located far from Washington, DC, and Bethesda, Maryland (the seats of research funding legislation and the NIH), and has a history of breaking new ground in the social, political, and commercial sectors. The state has some of the nation's most highly regarded academic medical and scientific institutions and is home to a very large biotechnology industry. More than in any other state, voters in California have turned to ballot initiatives to overcome legislative deadlock and lack of confidence in the state legislature and its processes. Initiatives requiring statewide approval may reflect a more equitable cross-section of voters than do legislators, who are elected by local geographic districts. Initiatives can institute new legislation, amend existing statutes, or amend the state constitution,[9] as was the case with Proposition 71, the stem cell initiative.

Republican governor Arnold Schwarzenegger enthusiastically endorsed the initiative, as did more than 20 Nobel laureates, and some $30 million was raised in support of the campaign. The proponents of the initiative were careful to cast the issue as nonpartisan and to emphasize that it would engender highly desirable medical progress and possibly cures, often casting it in a general, public health–related context. Panels of respected medical and biological scientists also supported the initiative and participated in public discussion forums, with all points of view represented. In October 2004, for example, *Scientific American* sponsored a discussion about the initiative in Washington, DC, with a panel of prominent scientists, ethicists, and politicians, among them Elias Zerhouni, then director of the NIH, and California state senator Deborah Ortiz (D, 6).[10]

The campaign encountered difficulties, however, in the California State Legislature. Although stem cell research was already legal in California, funding of the research was elusive. In 2002, prior to the initiative, Senator Ortiz sponsored a bill that became law declaring that it was "state policy that stem cell research in all forms shall be permitted in California."[11] No funding was attached to the legislation, however, and it was clear that no funding would be forthcoming, because California law requires that state tax increases must be passed by a supermajority (more than 70%) of the legislature.

It was readily apparent to many stakeholders in the legislature and members of the public that a ballot initiative would be the most effective way to bring the issue of funding stem cell research directly to the voters (a ballot initiative that originates from the general public, once written and qualified for the ballot, is

not subject to further modification by the legislature prior to the vote). For several months, as the movement toward an initiative coalesced, Senator Ortiz and her legislative staff worked with groups that had become advocates of the initiative through Robert Klein. Over time, however, philosophical and political differences led to a struggle for control of the initiative campaign and ultimately for control of the initiative itself. This caused a deep rift between Senator Ortiz and others associated with the legislature and the supporters of what eventually became the CIRM.

Over the past decade, ballot measures tended to fail if they proposed expanding government-related bureaucracies or adding new financial obligations to the burdens of the state's taxpayers. The initiative incited heated debate, with opposition from the California Republican Party on the grounds that it would increase costs to taxpayers and from the Catholic Church and other antiabortion groups on religious and ethical grounds. The measure ultimately passed by a margin of approximately 3 to 2.[12] This was undoubtedly attributable to a confluence of factors, among them hope for success against otherwise untreatable diseases, opposition to the president's injection of personal religious values and conservative ideology into stem cell research, and the opportunity to fund stem cell research specifically, independent of funding targeted at single diseases.

The initiative affected the state government in complex ways, modifying both the state constitution and the California Government Code. In addition to creating the CIRM and the ICOC, the initiative specified a detailed organizational model requiring that the ICOC comprise 27 members, chosen by specific elected officials according to a detailed formula, with California's medical schools, research institutes, biotechnology and pharmaceutical industries, and advocacy groups for research on specific diseases and conditions all represented. The state legislature was prohibited from amending the initiative until 2008, after which the initiative could be changed only by a supermajority vote of the legislature, along with the signature of the governor. The CIRM's governance structure was created by the ICOC, through regulations developed by its working groups.

Despite these manifestations of autonomy, the CIRM is required to comply with certain features of state law, such as the Bagley-Keene Open Meeting Act, and with additional state requirements, such as independent financial audits by the state controller.[13,14] Thus, the CIRM is both part of the state government and independent from it, further complicating the relationship.

## POLITICAL AND ETHICAL LIGHTNING RODS

Research on stem cells continues to be highly controversial. Numerous ethical and religious concerns have not been resolved, and conflation and confusion with other biopolitical issues have been inevitable; these arguments have concerned human cloning, therapeutic abortion, and reproductive rights in general. Stem cell research has fallen squarely into the arena where science, politics, and public policy intersect. The initiative before its passage and the CIRM after its establishment have been public lightening rods for a panoply of opinions and actions from technically sophisticated and informed scientists, socially and emotionally motivated advocates for disease research, and politicians and policymakers acting as proponents, defenders, or antagonists of the effort.[15] The issues raised by the initiative have engaged the public in a multilevel discourse about embryos, medicine, ethics, and public policy. This discourse was conducted in the political arena, in highly visible opposition to the policies and practices of the Bush administration. Through its prominent place in the public consciousness, stem cell research has provided grounds upon which the stakeholders—both supporters and opponents—could bring their various viewpoints to bear, and they have done so vigorously.

Following passage of the initiative, opponents and taxpayer advocates sued in state court to block its implementation. Initially 2 lawsuits were filed, both challenging the initiative on state constitutional grounds; these were ultimately combined. The plaintiffs argued that (1) the initiative created a taxpayer-funded entity that was not under the direct control or management of the state, (2) the ICOC had an inherent conflict of interest because it would both award grants and include representatives of institutions that might receive grants, and (3) the initiative violated California's single-subject requirement for initiatives, because some of the provisions were broader than funding for stem cell research only.[16] Although the plaintiffs did not elect to directly challenge the morality or legality of stem cell research, several antiabortion organizations, led by the Life Legal Defense Foundation, were involved in initiating and supporting the litigation. Ultimately, the California Supreme Court, denying review of the California Court of Appeals decision holding the initiative constitutional, established what appears to be a secure legal foundation for the CIRM and stem cell research in the state.

The litigation delayed the sale of bonds for funding for 3 years, and no large-scale mechanism for CIRM operations existed during this period, although private loans and donations and loans from the state helped keep the core administration afloat. Although the delay was dispiriting to those who had hoped for rapid funding of stem cell research, it is generally agreed that the delay allowed the concerns of the critical stakeholders to be heard and the CIRM to focus on the rational development of ethical standards and administrative procedures. During the California budget crisis in the summer of 2009, bond sales were briefly interrupted, and some grantee institutions were reported to be having difficulty securing funding from outside sources to build facilities to house CIRM-funded research, resulting in some delays. As of this writing, bonds are again selling.[17]

## CRITICS, WATCHDOGS, AND BLOGGERS

Since the initiative passed, continuous criticism and scrutiny has come from sources opposed not to stem cell research itself but rather to other aspects of the endeavor. Some critics raised concerns about the protection of egg donors (for somatic cell nuclear transfer), others about limited attention to donors' physical health and potential exploitation because of their economic status.[18] Strong objections have been raised to the manipulation and commercialization of human genes. The Center for Genetics and Society has been a frequent critic, questioning possible conflicts of interest of ICOC members and grant recipients, the risks of

egg retrieval and gene transfer, and numerous related issues.[19] Many of these objections relate to biopolitics, a debate about manipulation of the natural state of humanity to gain commercial profit or power.[20]

Although many critics readily concede the value of medical research, they are concerned about how often the results of publicly funded research have been exploited by the corporate sector and the degree to which commercial interests engage in questionable or illegal practices to maximize profits. They have also raised the specter of unintended hazards arising from the research and of extreme and frightening future research, such as cloning humans or creating animal–human chimeras. Although many physicians and scientists find these views to be discomforting or irrational and tend to summarily dismiss them as highly improbable or extreme, they are broadly worthy of consideration, especially in a world in which both the wonders and the horrors of science frequently arise side by side.[21] The CIRM, because of its visibility and public exposure to comment and criticism, has provided an ideal opportunity for the airing of these views.

The CIRM expects to engage in partnerships and joint investments with biotechnology and pharmaceutical firms and has incorporated a specific mechanism for this in its draft Revised Strategic Plan.[22] Although much can be gained from collaboration between academic research and industry, it also has potential for conflicts of interest if publicly funded research is used to increase corporate investors' wealth. Critics have worried that corporate interests in protecting intellectual property may conflict with the initiative's mandate that California citizens cannot be excluded from access to treatments and cures developed at taxpayers' expense. Some are concerned that the costs of the taxpayer-financed investment will not be repaid because the profits from the sale of bonds may not be realized or that future licensing, patenting, and other agreements will not benefit the public. Both the CIRM and its critics are apprehensive about the possible overselling or exaggeration of potential gains or cures that may prove to be difficult, slow, or impossible to achieve.

Perhaps the closest attention to the conduct of the CIRM's affairs has been paid by individuals and groups concerned about the CIRM's potential conflicts of interest and lack of transparency. Watchdogs and consumer advocates have kept steady pressure on the CIRM to maintain transparency in spending taxpayers' funds, including awarding of research grants, and to be publicly accountable for adherence to ethical and other standards. The CIRM, which may only fund research to be conducted in California, also had to address several potential conflicts of interest in funding decisions. The relatively narrow composition and size of the ICOC, and the limited number of institutions qualified to conduct CIRM-funded research, guarantee a large overlap among those seeking and those awarding funds. Many potential grantee institutions have representatives on the ICOC, because the initiative requires the appointment of representatives from 5 University of California campuses and from other California research institutions. Although peer review of research applications takes place outside California, the CIRM Grants Working Group reviews the recommendations of the external peer reviewers, and the ICOC makes the final decision on funding.[23] ICOC members are required to reveal potential conflicts of interest and to recuse themselves from certain votes; on a few occasions, this has left a relatively small pool of board members to decide on highly charged matters. The initiative mandated little legislative or official regulatory oversight of the CIRM's internal affairs. Thus, to a large degree, external watchdogs, advocacy organizations, and the media have taken on critical oversight functions that might otherwise be considered a role for government.

We encountered little agreement among internal CIRM and ICOC interviewees about the influence of the critics on the content and adoption of ethical standards of research by the CIRM or on the ICOC's conduct of its activities and operations. ICOC members have publicly differed about whether critics' influence has been largely constructive. Some members have lauded watchdogs' positive influence on the development of research standards and credited critics with helping to ensure that the organization remained alert to the concerns of racial and ethnic minorities, to matters of social class and women's concerns, and to overall accountability and transparency. But other ICOC members have disagreed and have derided the influence of the critics, using such terms as "Luddite" and challenging their objectivity on the grounds that the watchdogs were funded by sources politically or ethically opposed to the CIRM's basic mission.

Strong arguments can be made for and against aspects of institutional transparency. The public is paying for the research and thus has a legitimate interest in the fairness, efficiency, and effectiveness of the granting process in bringing about the goals of the initiative. However, transparency in peer review is antithetical to broadly recognized and accepted procedures and therefore is generally not acceptable to reviewers because it undermines their privacy and anonymity. Absolute transparency might also discourage the biotechnology and pharmaceutical sectors from making the capital investments needed to bring therapeutic products to market. The CIRM has been highly protective of its flexibility in creating collaborations with these profit-generating sectors. Long-standing and generally accepted conventions govern the academic, research, and technology sectors regarding peer review, intellectual property, proprietary information, and other customary practices. It is unlikely that the CIRM could institute or accept fundamental changes in these conventions, even if it were permitted to do so under the structure and language of the initiative.

## FURTHER LEGISLATIVE INVOLVEMENT

In the fall of 2008, after the 3-year ban on amendments to the initiative expired, state senators Sheila Kuehl (D, 23) and George Runner (R, 17) introduced a bill to ensure access for low-income Californians to drugs whose development stemmed entirely or partly from CIRM-supported research. The bill passed both houses of the legislature with the requisite supermajority but was vetoed by the governor; under the terms of the initiative, the amendment therefore could not become law.[24] The CIRM opposed the bill on the grounds that it would discourage biotech firms from developing therapies and would therefore limit the agency's flexibility in negotiating affordability issues, among other things. During the debate on the bill, the CIRM leadership attacked Senator Kuehl, alleging that she interfered with the CIRM's core mission.[25] Tensions like these continue between those who, for numerous and

at times highly practical or pragmatic reasons, believe that any attempt to exert legislative control over the CIRM would impede its core mission and those who would place it under the regulation of the legislature as an agency of state government.

ICOC members have differing and at times conflicting motivations for particular policy decisions; at times, some of these views have also conflicted with those of the CIRM's administrative leadership. These conflicts, however, provide further evidence of the productive intellectual and political ferment at the CIRM. Among the basic perspectives represented are those of the advocates for research on specific diseases, who want and even demand rapid progress on the diseases of greatest interest to themselves or their loved ones and who believe that any dedication of research funds to building, for example, multimillion-dollar stem cell research facilities is a diversion of research funds away from rapid cures. Others, primarily scientists, university administrators, and biotechnology experts, advocate building a broad, rational knowledge and technical base, along with a bricks-and-mortar laboratory infrastructure with which to attract scientists to conduct research that produces incremental advances leading to long-term goals. These goals—acquisition of a broadly relevant scientific knowledge base, construction of large-scale laboratory facilities in which to house the research, and the immediate conduct of research and testing activities to bring about cures—are perpetually in a degree of competition with each other. However, the initiative has resulted in a sufficiency of funds and donations to pursue all these ambitions. The CIRM has awarded several hundred million dollars, extended by matching funds from outside sources, and tensions between advocates of short-term and long-term research objectives have eased as time has passed.

## VISIONS AND POSSIBILITIES

Because the CIRM was created to fund research that the NIH and other federal sources were proscribed from supporting, many of its advocates have seen the CIRM as a surrogate for, and potential improvement upon, the NIH. Not only has the CIRM been an alternative funding source for stem cell research, but it has also formulated research priorities and established ethical standards, intellectual property regulations, and other functions that would otherwise have been the responsibility of the NIH and other federal government agencies. Some stakeholders hoped that the CIRM might make funding decisions more quickly and flexibly than traditional agencies such as the NIH, that its peer reviewers might be more creative and open to new ideas than the scientific review panels at the NIH, and that the overall enterprise might be more creative. Finally, the organizational structure of the CIRM was designed to facilitate interinstitutional collaboration, creating a research and development framework from basic bench research to final development, testing, and licensing of therapeutic agents.

California has established itself as a major center for stem cell research. Recruitment of world-class stem cell scientists from across the globe has been a direct result of CIRM funding. Through 2008, according to its annual report, the CIRM had awarded more than $500 million in scientific grants, with another $300 million to come.[26] Another $1.15 billion has been approved for the construction of new stem cell research facilities. Global collaborations are in place with research institutions in Australia, the United Kingdom, Canada, and Spain.

Measuring the CIRM's success by its highly ambitious goals for research and cures is a challenge for the future. The federal administration under President Barack Obama has begun to lift the Bush-era restrictions on stem cell research, although some legislative barriers remain at the federal level.[27] Once federal funding of stem cell research resumes, California stem cell researchers can apply for both federal and state funding. Duplicate facilities to separate human embryonic stem cell research from other stem cell or cell biological work will no longer be required, allowing funds for facilities to be invested more flexibly in California and elsewhere to expand research facilities at universities and research institutes. As of this writing, the NIH has increased the number of stem cell lines eligible for research, opening up new possibilities for CIRM researchers.[28] The CIRM anticipates that access to federal funding and a cooperative relationship with federal funding sources will be of mutual advantage. At its March 2009 meeting, the ICOC voted to prioritize funding for translational grants, which focus on quickly moving results of basic science investigations from the laboratory to the clinic, a program "designed to be a jewel in CIRM's crown, demonstrating the agency's special role in translating stem cell science into treatments."[29]

Scientific success and development of therapies are usually the result of a branching pathway of investigations, which lead through numerous geographic locations. Recently, considerable progress has been made in the use of adult cells to generate embryonic stem cell–like pluripotential cells in mice and humans.[30] Whether these cells, apparently acceptable to the Catholic Church and others, may eventually be used to largely or entirely substitute for stem cells generated from frozen embryos remains to be seen, but their use will benefit the field of stem cell research.

In its short history, the CIRM has taken on a vigorous life of its own. It is apparent that the shift of a major focus for stem cell research to California will have a significant effect into the future on the geographic distribution of biological science and biotechnology infrastructure in the United States; on the location of university, biotechnology, and pharmaceutical research and start-up firms; and on the investment of venture capital. Evidence for this is the $300 million the CIRM has invested in stem cell facilities, already leveraged to more than $1 billion in linked donations. The CIRM has also directly stimulated the formation of a consortium of otherwise separate institutions to meld resources and facilities in San Diego, and has begun to develop international collaborative partners. California is host to a steadily growing cadre of world-class scientists, dedicated state-of-the-art facilities, training programs, and support programs, such as a large-animal facility for the testing and development of drugs to facilitate the translational pathway leading from basic stem cell research findings in the laboratory to treatments and cures. ■


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## Contributors

Both authors contributed to all aspects of this work.

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