

Case Study Fall 2005

*Proposition 71:
A Model for
State Involvement
in Biomedical
Research?*

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I. Introduction

Proposition 71: A Model for State Involvement in Biomedical Research?

Since 1998, when James Thomson and his colleagues at the University of Wisconsin first successfully isolated human embryonic stem cells, the volume of research being conducted with these cells has expanded. This has occurred primarily through the use of private funds, because presidential and congressional restrictions have been placed on the use of federal funds for such research. California voters saw a void in support for this promising area of research and in 2004 passed a \$3 billion stem cell bond measure:

- establishing the California Institute for Regenerative Medicine (CIRM) to regulate stem cell research and provide funding, through grants and loans, for such research and for research facilities;
- establishing a constitutional right to conduct stem cell research, while prohibiting the institute's funding of human reproductive cloning research;
- establishing an oversight committee to govern the institute;
- providing a General Fund loan up to \$3 million for the institute's initial administration and implementation costs; and
- appropriating monies from the General Fund to pay for bonds.

Proposition 71, the California Stem Cell Research and Cures Act, explicitly places priority for research grant funding on stem cell research that meets CIRM's criteria and that is unlikely to receive federal funding. In some cases, funding also could be provided for other types of research that were determined to be for the purpose of curing or providing new types of treatment for diseases and injuries.

This high-stakes gamble on a promising and controversial area of biomedical research provides a new model for public investment in research. **Although states have a long history of investing in research and development (R&D) as part of their economic development programs, few have focused on basic**

research, and none has done so to compensate for a lack of federal funds. In addition, most states have had to dramatically cut budgets for R&D in recent years as fiscal constraints have increased.

Thus, California's stem cell initiative stands out for its courage—not only because of the size of the investment, but also because it is in an area of research that has been fraught with political controversy and legislative wrangling at the federal level for several years. The California stem cell initiative is unique because it is the first time state taxpayers have directly funded specific scientific research to compensate for federal restrictions.

The language of the act made it clear that one of its goals was to “benefit the California economy by creating projects, jobs, and therapies that will generate millions of dollars in new tax revenues in our state.” It was also intended to “[a]dvance the biotech industry in California to world leadership, as an economic engine for California's future.”

One of the premises of Proposition 71 was that the time had come to support research in a different way and discard old, crippling constructs that stymied controversial but clinically significant areas of research. Furthermore, it made the clear statement that government can and should fund controversial research through the formation of partnerships with scientists and business in innovative ways that benefit all.

Nobelist Paul Berg, Emeritus Professor in Biochemistry at Stanford University School of Medicine and former director of its Beckman Center, asserts that in this critical area of research, you “cannot count on the vagaries of the federal government.” Citing AIDS research as an example of a field that suffered first from poor funding, then from an over-infusion of funds, then from a lower and more restrictive drop in funding levels, Berg emphasizes the importance of continuity. “Stability is what is needed when an exciting new field or pressing public health need emerges,” says Berg. “Three hundred million dollars a year for 10 years is pretty stable.”

CIRM, created through Proposition 71, is currently the single most important source of stem cell research funding in the world. As such, what can we learn from this activist approach to advancing the search for new therapies? Several other states are moving toward establishing similar, if smaller, stem cell initiatives. Each will have to grapple with many of the issues facing the institute, including the following:

- developing a new model of civic leadership and oversight for science;
- devising strategies for priority setting and research funding in a political climate;
- building an infrastructure, including the need to isolate activities from federal funding pools (i.e., “National Institutes of Health (NIH)-free” space);
- locating headquarters and research sites;
- managing ethical and legal issues, including conflicts of interest; and
- meeting public expectations.

FasterCures believes that a better understanding of the California stem cell initiative will serve to educate other states as they consider similar or related investments in embryonic stem cell research or other areas of research not supported by the federal government for ideological or political reasons. This paper explores the development of state activities in this promising and controversial research on at least three levels:

First, how did the end of the covenant between the federal government and the public with regard to funding important public health research create this new landscape for biomedical research? How are the states, with California leading the way, assuming the mantle of first-to-fund, which used to be the foundational role of the federal government?

Second, has this new configuration for advancing science opened up new opportunities and strategies for pursuing cutting-edge research? Absent the federal infrastructure and oversight system, how is California re-creating or innovating in the area of research policymaking? Will this result in a better way to accelerate promising new research?

Third, does this new model of public financing of research create an opportunity to move quickly in critical areas of research considered too controversial for risk-averse politicians and federal bureaucrats?

This report is based on interviews conducted with individuals affiliated with CIRM, either as staff or as working group members, discussions with journalists who have been following the progress of CIRM since the passage of Proposition 71, and an extensive review of media reports, both print and online, between November 2004 and September 2005.¹

The California stem cell initiative is unique because it is the first time state taxpayers have directly funded specific scientific research to compensate for federal restrictions.

¹ See acknowledgments on the final page.

II. Failure to Fund: Or How We Got from Washington, D.C. to Sacramento

Public debates about embryo research, of which stem cell research is a subset, and the use of federal funds to support it have been ongoing for the past 30 years (see timeline). To understand the unique role that Californians have accepted in promoting stem cell research, it is helpful to understand how the federal government abandoned its traditional role of funding long-term, high-risk research. What follows is a brief summary of the position that has evolved in federal public policy debates since 1975, bringing us to where we are today.

The Emergence of Embryo and Infertility Research

In 1975, Caspar Weinberger, Secretary of the Department of Health, Education, and Welfare (HEW), announced that HEW would fund no proposal for research on human embryos or on in vitro fertilization (IVF) unless it was reviewed and approved by a federal ethics advisory board (EAB), to be appointed by the

HEW Secretary. In 1977, NIH received an application from an academic researcher for support of a study involving IVF. After the application had undergone scientific review, it was forwarded to the EAB, which had been appointed by the new Secretary of HEW, Joseph Califano, where the proposal was approved for initiation.

With the increased public interest that followed the birth of “test-tube baby” Louise Brown that summer, Califano asked the EAB to study the broader social, legal, and ethical issues raised by IVF research, including research involving embryos. In its 1979 report to the Secretary, the EAB concluded that federal support for IVF research was “acceptable from an ethical standpoint,” provided that certain conditions were met, including employing informed consent for the use of gametes; ensuring that the purpose of the research would be to attain an important scientific goal “not reasonably attainable by other means”; and ensuring that no embryo would be maintained “*in vitro* beyond the stage normally associated

Timeline: Evolving Human Embryo Research Policies: 1974-2005

Congress establishes the National Commission, which examines research using the human fetus.

HEW issues regulations regarding research with fetuses, pregnant women, and IVF, requiring review by an Ethics Advisory Board.

HEW Ethics Advisory Board concludes it is ethical for the federal government to support IVF research.

Ethics Advisory Board disbanded.

1974 1975 1976 1977 1978 1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989

with the completion of implantation (14 days after fertilization).” No action was ever taken by the Secretary with respect to the board’s report, and following the election of Ronald Reagan in 1980, the department dissolved the EAB. Because it failed to appoint another EAB to consider additional research proposals, HEW effectively forestalled any attempts to support IVF research using federal funds, and no experimentation involving human embryos was ever funded pursuant to the conditions set forth by the EAB or through any further EAB review.

The Beginning of the Endless Divide

Congressional interest during the late 1980s in the causes of infertility and the lack of reproductive research, including embryo research, led to a promise from HEW to re-establish an EAB. However, although a new charter was published, it was never signed following the election of President George H.W. Bush, thus extending a 12-year lapse in the availability of a federal mechanism for the review of these controversial research protocols.

This *de facto* moratorium would continue until 1993, when the NIH Revitalization Act effectively permitted the use of federal funds for IVF and other types of research involving human embryos by nullifying the regulatory provision that mandated EAB review. In response, NIH Director Harold Varmus convened an external panel to develop standards for determining which projects could be funded ethically and which should be considered unacceptable for federal funding. In addition to describing areas of research that were acceptable and unacceptable for federal funding, the panel made the recommendation that under certain conditions, federal funding should be made available to create embryos specifically for research purposes.

However, in December 1994, President William J. Clinton intervened to clarify an earlier endorsement of embryo research, stating that, “I do not believe that Federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such requests.”

NIH Director Varmus proceeded immediately to implement the panel’s recommendations that were not proscribed by the President’s clarification, concluding that NIH could begin to fund research activities involving “surplus” embryos—that is, embryos remaining after the conclusion of infertility treatments. Before any NIH funding decisions could be made, however, Congress used the Department of Health and Human Services (HHS) appropriations process to specify that “any activity involving the creation, destruction, or exposure to risk of injury or death to human embryos for research purposes may not be supported with federal funds under any circumstances.” Additional legislative riders have been inserted into subsequent annual HHS appropriating statutes, enacting identically worded provisions into law. Thus, **to date, no federal funds have been used for research that directly involves the destruction of a human embryo, whether created originally for reproductive or for research purposes.**

Current Federal Policy

So how did this legislative order come to restrict research involving embryonic stem cells, which are not embryos but rather cell lines derived from them? This restriction occurred because the act of deriving the stem cells effectively destroys the embryo, and federal funds cannot be used for such destruction.

Revitalization Act nullifies need for Ethics Advisory Board review, ending the de facto moratorium on embryo research.

Congress attaches rider to HHS appropriations bill prohibiting use of federal funds for embryo research.

President Bush limits federal funding of embryonic stem cell research to approved lines created before August 9, 2001.

California voters pass Proposition 71, providing \$3 billion over 10 years to support embryonic stem cell research.

1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005

When reports of the successful isolation of human embryonic stem cell lines were published in 1998, the scientific community asked if it could receive federal funding for human embryonic stem cell research using cell lines that had been obtained from surplus IVF embryos using private funding. Varmus sought the opinion of the HHS General Counsel on this issue, who responded that the legislation did not prevent NIH from supporting research that uses cells derived using private funds because the cells themselves do not meet the statutory, medical, or biological definition of a human embryo.

Varmus delayed the funding of any research until he convened a working group to develop guidelines for the conduct of ethical research in this area, a move that some scientists would later come to regret, given that some guidelines already in existence in other countries could have provided a useful point of departure while the research got under way.

Before any NIH grants could be funded, however, the 2000 election produced a new Administration. Varmus had already stepped down as NIH Director, and **on August 9, 2001 President George W. Bush announced that NIH could fund research using human embryonic stem cells, but only if the cell lines had been derived prior to that date and were registered with NIH.** This policy was intended to distance the Administration from complicity in any further destruction of embryos for stem cell research. Although NIH first announced that 60 such cell lines were available, it now appears that fewer than 22 cell lines are actually viable and available, at a cost of at least \$5,000 per line.

In 2003 (the most recent year for which complete data are available) NIH provided \$24.8 million for human embryonic stem cell research using the approved lines. It also provided \$190.7 million for human nonembryonic stem cell research (i.e., research involving adult stem cells, including those from umbilical cord blood, placenta, and bone marrow). The agency has also issued detailed guidance to research institutions regarding the need to “wall off” privately funded embryonic stem cell research programs. In laboratories with both federal and nonfederal funding, investigators and their staffs must separate allowable and unallowable activities in such a way that the costs incurred in the research can be charged consistently to the appropriate funding source. For example, the time and effort of laboratory personnel working on a stem cell line created after August 9, 2001 may not be charged to any federal grant.

Acquisition of equipment, use of cell and tissue culture supplies in the project, and travel to a conference to discuss or present this work likewise may not be federally supported. This policy creates a large administrative burden for research institutions that would like to continue to receive NIH funds for some of their work.

Cloning Debates

Debates about cloning are intricately related to those about embryonic stem cell research. Somatic cell nuclear transfer (a type of cloning) provides another approach to deriving stem cells. This method, perfected by Ian Wilmut in the cloning of Dolly the sheep, involves the insertion of a somatic cell (e.g., skin, bone, muscle) into an ovum (egg) that has had its nucleus removed. The fused egg and cell are then stimulated to divide, creating a blastocyst and then a late-stage embryo that is genetically identical to the individual from whom the somatic cell was obtained.

This technique could be used to create a blastocyst from which a scientist could derive stem cells that could be used to study a particular disease, test new drugs, or be manipulated and reinserted into an individual to repair or regenerate damaged cells or tissues. If allowed to continue to grow beyond the blastocyst stage to full term—so-called reproductive cloning—the resulting child would be genetically identical to the individual from whom the somatic cell was obtained. There is widespread support among scientists to forbid the use of somatic cell nuclear transfer for reproductive purposes.

Congress has been pursuing legislative measures to regulate cloning research for more than eight years. Since 1997, more than 44 bills have been introduced in Congress seeking to ban or regulate cloning research. Despite such seemingly zealous legislative actions, congressional efforts have failed because of differences over whether or not to allow cloning for creating embryonic stem cells. **Although there is an overwhelming consensus among members of Congress to prohibit reproductive cloning, lawmakers are almost evenly split on whether to allow the less controversial therapeutic cloning research.** This has led to a legislative stalemate.

In the meantime, several states have passed laws banning cloning for reproductive purposes, while allowing the use of the technique for stem cell research. These states include California, Connecticut, Massachusetts, Missouri, New Jersey, and Rhode Island.

III. California's Response to the Federal Void

In the wake of the President's August 2001 announcement, scientists and health advocacy groups started discussing the implications of the policy for stem cell research. The view was that this area of research was so promising that it required an accelerated effort to explore its potential, not what amounted to a federal ban.

Much of the pressure to move forward came from patient groups, although scientists also were involved. Researchers pursuing this line of work were not only anxious about the level of uncertainty at the federal level (some bills introduced in Congress would send scientists to jail for conducting the research), but they were also concerned that the political uncertainty and lack of federal funds would scare young scientists away from the field. Biomedical scientists rely heavily on NIH funds for training programs, and science survives only through the regular and consistent infusion of young minds and new ideas. ***The absence of federal support would essentially dry up the personnel pipeline.***

Several individuals would emerge as leaders in an effort to put California out in front in stem cell research. Filmmaker Jerry Zucker and his wife Janet have two daughters with juvenile diabetes. They understood that the lack of federal support in a new scientific field that also lacks the promise of immediate profit (thereby not attracting industry dollars) would cripple the field. Subsequently, they teamed up with film producer Douglas Wick and his wife Lucy Fisher and real estate developer Robert Klein, who also has a son with juvenile diabetes, to determine what could be done to ensure that the research could be pursued in California legally and aggressively.

Meanwhile, California State Senator Deborah Ortiz—who had successfully marshaled the passage of legislation making somatic cell nuclear transfer (“therapeutic cloning”) explicitly legal in California—introduced a bill to provide \$1 billion in stem cell research funding through the sale of revenue bonds approved by the state legislature. The measure's failure to pass further sowed the seeds for Proposition 71.

Klein, the Zuckers, and the Wicks mobilized a coalition to draft and pass Proposition 71, spending almost \$30 million in the process. In interviews, Zucker has said that the drafting of Proposition 71 was a long and difficult process, because its supporters wanted to make it an initiative that could not be blocked on legal grounds. It involved extensive consultation with patient advocates, attorneys, and scientists, who were particularly watchful that the language of the measure would not limit the field. The drafters also wanted to impose mandatory deadlines in implementing the proposition, which resulted in the state having only approximately six months to solve some of the thorniest issues raised by the measure, such as those involving the processes used for receiving advice and developing intellectual property policies that would be satisfactory to all. Speed was always an issue.

Proposition 71 appeared on the November 2004 ballot and was endorsed by Governor Arnold Schwarzenegger, former First Lady Nancy Reagan, and many other celebrities. It was also supported by all state constitutional officers, most Chambers of Commerce, and several newspapers. But California has one thing no one else has—Hollywood. The measure won by a healthy margin.

IV. Stem Cells and Economic Development

California is by no means the first state to actively support biomedical research. State funding for biomedical research has been on the rise since the late 1970s, although most states have had to dramatically cut budgets in recent years in response to increasing fiscal constraints. Typically, states support R&D through various mechanisms, including direct appropriations to universities, R&D tax credits, the establishment of endowment funds, and the formation of nonprofit corporations.

States, like industry, are generally more interested in research with immediate commercial applications, because this helps to build a state's biotechnology industry and thus increase the number of jobs. States also are investing in the biomedical R&D capacity of their universities and other research institutions to help them compete more effectively for support from federal agencies—especially NIH—and from industry and foundations. Most state economic development funds aim to leverage multiple federal dollars for each state dollar, not the other way around. Thus, for any state to intentionally set out to invest in basic research is highly unusual.

Nonetheless, states with major research centers are not going to sit idly by and watch their programs in embryonic stem cell research, no matter how fundamental, move to or become overshadowed by California. For example, following the California vote, Governor Jim Doyle of Wisconsin (academic home of James Thomson, a pioneer in embryonic stem cell research) proposed spending \$750 million through a public-private partnership in stem cell research and biotechnology to keep Wisconsin competitive.

Although a small investment in comparison to California's, New Jersey's initial investment of \$6.5 million in a stem cell research institute actually beat out California in 2004 in terms of actually providing funds for stem cell work. New Jersey, which plans to spend \$50 million on human embryonic stem cell research

over the next five years, is home to some of the largest pharmaceutical and biotechnology companies in the world, including Merck & Co., whose subsidiaries conduct stem cell research, and Johnson & Johnson, which is also involved in the research. New Jersey also has some state-of-the-art hospitals, universities, and institutions that conduct stem cell research, such as the University of Medicine and Dentistry of New Jersey, Saint Barnabas Medical Center, and Coriell Institute for Medical Research, a nonprofit biomedical research institution.

Like Proposition 71, the New Jersey initiative is explicit about its intent to boost the state's biotechnology industry, stating, "The biomedical industry is a critical and growing component of New Jersey's economy, and would be significantly diminished by limitations imposed on stem cell research." New Jersey legislators were no doubt watching California, where since the passage of Proposition 71 California researchers have already benefited as millions of private dollars were pumped into the research. Stanford University received a \$12 million grant from one anonymous Bay Area donor. University of California-San Francisco has created a \$30 million target for private money. And Hong Kong philanthropist Li Ka Shing donated \$40 million to the University of California-Berkeley for a new research center focused on emerging scientific fields, including stem cell biology.

Some states are betting on the fact that by putting a legal stamp on the research they will become a favored place for all biomedical research. Thus, states with a large biotechnology industry are under pressure to enact laws legalizing stem cell research and therapeutic cloning, lest they risk losing research—and jobs—to the two pioneer states, California and New Jersey. Moreover, the biotechnology industry has tried to play states against each other to win concessions on stem cell research.

Over the past two years, state legislatures have considered nearly 100 bills related to cloning and/or embryo research. Eight states have enacted laws addressing issues related to human cloning, and many more have embryonic and fetal research regulations, according to the National Conference of State Legislatures (NCSL). NCSL also reports that approaches to state policy range from the laws in California, Connecticut, Massachusetts, and New Jersey encouraging embryonic stem cell research, including research on cloned embryos, to South Dakota's law, which strictly forbids research on embryos regardless of the source. States that specifically permit embryonic stem cell research have established guidelines for scientists, including consent requirements and approval and review processes for projects.

Legislators in Massachusetts and four other states have introduced bills with language nearly identical to that of the California law, although none has yet been signed. With a few variations, Illinois, Maryland, New York, and Washington legislators have all authored bills with the same preamble. A new grassroots effort in Florida, Floridians for Stem Cell Research and Cures, Inc., has launched a statewide initiative similar to Proposition 71. Several states have committed to funding the research through executive orders and earmarking:

- In Connecticut, Governor Jodi Rell signed legislation earmarking \$100 million in funding over 10 years for embryonic stem cell research. The money will be funneled through Yale University and the University of Connecticut.
- On July 12, 2005, Illinois Governor Rod Blagojevich issued an executive order directing \$10 million in state money to be used for stem cell research, including research using embryonic stem cells. The money is to be given in grants to medical research facilities and would be part of a program the governor has called the Illinois Regenerative Medicine Institute. The Illinois Department of Public Health is to oversee the program, which is expected to be up and running by the end of 2005. The cash was included in the state budget as money for medical research. Thus, Illinois

became the fourth state—behind New Jersey, California, and Connecticut—to provide state funding for stem cell research. It is also notable that the money is to be directed to an existing agency and is earmarked for medical research.

- In July 2005, Ohio Governor Bob Taft signed the state's \$51.25 billion, two-year state budget bill. He exercised his line-item veto authority on 27 provisions, including striking a provision from the bill that would have restricted state funding of embryonic stem cell research. The provision in the bill would have prohibited the use of "Third Frontier"² initiative funds on any type of embryonic stem cell research, including those lines approved by the federal government.
- In June 2005, the Massachusetts legislature overwhelmingly and successfully voted to override Governor Mitt Romney's veto of the state's stem cell research bill.

Luring scientists into a state or preventing them from fleeing to California or New Jersey is another focus of state efforts to promote stem cell research. Because of the novelty of the field and the lack of sufficient federal funds for research in this area, there are few scientists with human embryonic stem cell experience. In addition, the President's policy has further discouraged students and young scientists from pursuing the research. Thus, ***the existing pool of qualified researchers is still relatively small, and competition for the top researchers has been keen.***

For example, Harvard University, home to a skilled stem cell laboratory directed by Douglas Melton and Kevin Eggan, announced that it was forming an ambitious new stem cell research institute using millions in private money, with Melton as co-director. Last year Melton announced that he had used private money to create 17 new human embryonic stem cell lines and would offer them free to researchers around the world. That number has since grown to 28 lines, more than the entire list of cells available to researchers under the current Bush Administration policy. The Harvard Stem Cell Institute has now raised \$26 million, according to a Harvard official.

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2 This project is Ohio's largest-ever commitment (10 years, \$1.1 billion) to expanding the state's high-technology research capabilities.

In Illinois, State Senator Sara Feigenholtz sponsored a stem cell bill, arguing that the state should increase its support for stem cell research because Illinois was already attracting researchers from neighboring Iowa, where therapeutic cloning is illegal. Iowa is one of at least four states—Arkansas, Michigan, and North Dakota are the others—that have banned both reproductive and therapeutic cloning through the enactment of laws that the biotechnology industry and others have lobbied against.

Despite the many state-level efforts, however, most scientists would prefer that NIH lead the way in this area, because it has the needed infrastructure and expertise, as well as the respect and the attention of the entire scientific community, not just that of California. Former NIH Director Harold Varmus, now President of Memorial-Sloan Kettering Cancer Center in New York, has said, “There really is no substitute for the NIH....It’s a bad precedent...to say we’ll solve the problems of the NIH by doing this state-by-state.”³

The real question is whether voters and policymakers will have the patience to wait for the breakthrough applications that will bring business and money to their state. There is likely to be intense political pressure on research institutions in California, New Jersey, and Connecticut to favor research projects that are commercially interesting over those that are more basic and long term. ***Those who have elected to be the first to provide such funding will face high expectations from state legislators, governors, and the public.***

“There really is no substitute for the NIH....It’s a bad precedent...to say we’ll solve the problems of the NIH by doing this state-by-state.” **Former NIH Director Harold Varmus**

³ See C. Bruck, “On the Ballot: Hollywood Science,” *The New Yorker*, October 18, 2004, 62-84.

V. Post-Election Challenges to CIRM

Passing Proposition 71 was just the first step Californians took to forge a leadership position in stem cell research. Several obstacles have cropped up since the election.

On December 6, 2004, a little more than a month after Proposition 71 was passed, State Senator Deborah Ortiz introduced a bill, SB 18, intended to address some of the criticisms that had been leveled against the proposition during the campaign.

SB 18 addressed four major areas of Ortiz's concern and, if enacted, would have supplemented Proposition 71. Supplemental legislation was needed because Proposition 71 was written in such a way that modifications could occur only through a constitutional amendment. Some believe this is an essential strength of the referendum. Ortiz's bill addressed:

- 1 the entitlement of the people of the state of California** to a certain proportion of the royalties that may accrue as a consequence of biomedical discoveries made with Proposition 71 funds and/or to forms of assured access at reduced or no cost to the treatments derived from these discoveries;
- 2 a further clarification of the obligations** of members of the CIRM working groups in terms of their need to file financial disclosure documents, observe various anti-conflict of interest rules, and/or recuse themselves from certain deliberations from which they stand to benefit personally, directly or indirectly;
- 3 the number of public meetings required** of the Independent Citizens' Oversight Committee (ICOC) responsible for overseeing the dispersal of the \$3 billion, and the method and amount of notice that needs to be given to the public of these meetings; and
- 4 the need to assure the safety of the "patients"** (i.e., women donating eggs) in the experiments financed by Proposition 71 money.

On this last point, Senator Ortiz said that the drafters of Proposition 71 had inadvertently left open the questions of informed consent from donors and rules regarding payment to women for undergoing hyper-ovulation treatments and egg extractions, including the issue of whether they would be required to waive their right to compensation for damages they might suffer as a result of these procedures. In fact, this was not the case. The Proposition 71 language made quite clear that review of consent procedures by an Institutional Review Board (IRB) was required and that there was to be no compensation beyond expenses for egg donation. Originally, Ortiz wanted to seek a three-year moratorium on multiple egg extractions for embryonic stem cell studies and other research, but she later abandoned this in favor of requiring a more extensive consent process.

Ortiz's intentions eventually morphed into two bills. SCA 13, a proposal to amend the state constitution, would have required that the ICOC be subject to open meeting and record laws; that appointees, employees, and working group members would have to follow the conflict of interest rules adopted by NIH; and that research grants would have to include provisions for possible state royalties. SB 18 in its final form would have required a state audit of CIRM and that egg donors sign a summary of health and consumer issues before donating. SB 18 required only a majority vote and the governor's signature to become law. SCA 13 was a constitutional amendment that required a two-thirds vote from each legislative house in order to be placed on the next statewide ballot. It did not need approval from the governor.

CIRM leadership believes that most of these issues could be addressed easily given the existing structure of CIRM. One editorial stated that, "The proposed amendment...would hold the California Institute of Regenerative Medicine to ethical standards and governance guidelines that the institute has already

adopted or exceeded independently. So at best it's redundant. At worst it holds the institute to a standard no pioneering medical research efforts could possibly meet.”⁴

For example, the ICOC could draw up acceptable rules governing conflicts of interest and public meetings without legislative intervention. And because Proposition 71 explicitly requires IRB approval of studies requiring egg donation, IRBs already would be addressing the issues of informed consent, risks, and compensation as required by existing federal regulations (45 CFR 46).

The issues of royalties and access to healthcare, however, were more troubling, as discussed further below. Critics of these requirements said that the stem cell initiative was not the place to secure a revenue stream through royalties and licenses or to propose a comprehensive healthcare plan for California.

In June 2005, Ortiz agreed not to push for a vote on SCA 13 at this time. And in September, Governor Schwarzenegger vetoed SB 18. But these bills are not the only impediment to CIRM. The courts also have to rule on several lawsuits before the state can begin selling the bonds that will finance the initiative. One suit claims that Proposition 71 is an unconstitutional delegation of spending authority to a body (CIRM) that is not adequately controlled by elected officials. Another suit argues that fertilized eggs should be treated as “persons.” Although the odds of either suit meeting success are slim, they will cause substantial delays.⁵

The suit challenging the constitutionality of Proposition 71 will test the model of states taking on a role and policies normally assumed by a federal basic science agency, such as NIH or the National Science Foundation. The question being raised involves whether a basic science funding agency can operate independently and effectively if forced to comply with overly restrictive oversight and requirements for conflict of interest policies and open meetings that exceed those of the federal government.

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⁴ See www.presstelegram.com/Stories/0,1413,204%257E21479%257E2920464,00.html.

⁵ Pending Litigation: *People's Advocate v. Independent Citizens' Oversight Committee*, Alameda County Superior Court, Case No. HG05206766, and *Mary Scott Doe v. Robert Klein, et al.*, U.S. District Court, Central District, Case No. ED CV 05-00438 (Government Code section 11126, subdivision (e)).

VI. Growing Pains: The Devil Is in the Details

At the center of Proposition 71 is the establishment of CIRM to award grants and loans for stem cell research and research facilities. CIRM does not conduct research in-house (while the New Jersey initiative establishes a new state research institution jointly operated by two universities).

The institute is also responsible for establishing regulatory standards for stem cell research funded by the grants and loans and managing the research and the development of related facilities. The institute could have a staff of up to 50 employees who would be exempt from state civil service requirements under the measure. It is important to underscore the intention to remove CIRM and its operations from the reach of political interference. By incorporating the initiative's core clauses as amendments to the California constitution, the initiative was removed from legislative oversight and the reach of the governor's office. In an October 18, 2004 interview with *The New Yorker* magazine, **Klein said the ballot measure aimed to "take politics out of medicine."**

Exemptions were also made from existing law concerning state agencies for a variety of reasons, but primarily to move the ICOC away from political intrusions and to allow it freedom to operate. In addition, severe and unprecedented restrictions were made on the ability of the legislature to make changes in the agency. However, apparently this independence was not to be easily granted, as evidenced by Ortiz's efforts to enforce some level of oversight. Independence is something CIRM has been fighting to maintain, and this has consumed much of its time and energy during the first six months of its existence.

Location

A first order of business was finding a site for CIRM, certainly a plum for any city in the state. As part of a bidding process to determine the location of its permanent headquarters, CIRM asked local governments, working in partnership with building owners, to provide approximately 17,000 square feet of office space at little or no cost. San Francisco was selected as the permanent headquarters by the ICOC at the May 6 meeting in Fresno.

Zach Hall, President of CIRM, said during an interview that despite the importance of finding a permanent home for the institute, he considered the headquarters search a distraction from the more pressing business of getting employees and advisors in place. Nonetheless, Hall recognizes the symbolic importance of a city becoming home to CIRM and was grateful for the amount of civic pride each community exhibited in submitting its proposal.

Oversight

The language of Proposition 71 stipulates that CIRM is to be governed by the 29-member ICOC, comprised of representatives of specified University of California campuses, another public or private California university, nonprofit academic and medical research institutions, companies with expertise in developing medical therapies, and disease research advocacy groups. The Governor, Lieutenant Governor, Treasurer, Controller, Speaker of the Assembly, President pro Tempore of the Senate, and certain University of California campus chancellors make appointments to the ICOC. According to Gerald Levey, Provost and

Dean of the University of California-Los Angeles School of Medicine and an ICOC working group member, the appointment process is so diffuse that it is difficult for any one member or constituent to have too much influence (which was the intent).

Nonetheless, the first round of appointments received the criticism that it was too insular and too political, that the universities had too much control, or that industry was over-represented. But it is difficult to imagine how such criticism could be avoided, given the nature of the mandate. The intent of Proposition 71 was to bring academic, industrial, and patient groups to the table, and all of these groups represented some California interest group with a stake in the success of the initiative and the advancement of the science.

Conflicts of Interest

California is a big state but not so big that the likely candidates for ICOC membership (university scientists, industrialists) would not know each other. Paul Berg finds it incredible that some opponents of the initiative would rather the ICOC be constituted of members who have no expertise or interest in the success of this large state investment. “This was a huge investment by the citizens of California,” said Berg. “Putting ‘second stringers’ or people with no interest in the research or relative expertise on the ICOC would guarantee we’ll lose the game.” Berg emphasized that CIRM is an unusual agency in that conflicts of interest were built into it. Scientists, business executives, and patient advocates are all directly involved. Some even have personal health issues at stake.

However, whenever there is a “land grab”—whether it’s gold, tobacco settlement money, or research dollars—some will argue that decisionmaking should be based on distributive politics—that is, everyone gets to play and no one gets to win.

Thus, it is no surprise that conflict of interest policies were among the first issues that CIRM had to address. Not only was the Ortiz legislation calling for a highly restrictive policy, but NIH also was mired in an

ongoing controversy about its own policies in this area, including a congressional investigation of whether NIH scientists were violating the government’s ethics rules.

The ICOC, however, recognized that it had to have clear policies in place to disclose and manage conflicts of interest because the ultimate decisions about both grants and standards for CIRM rest with that body. And decisions had to be able to withstand scrutiny. In June 2005, the ICOC approved a policy that:

- requires divestment by ICOC members of financial investments in any business entity with more than five percent of its annual budget in stem cell therapies and in any business organization receiving a grant involving stem cell research;
- broadens conflict of interest provisions for working group members; and
- provides earlier public availability of full disclosure of working group funding recommendations.

At its August 2005 meeting, the ICOC agreed to refinements of these policies, including:

- making the conflict of interest policies for the working groups consistent with respect to financial threshold (\$5,000) and family members;
- including a threshold of financial interest held in private companies.

The policies are in line with those of other research institutions, and CIRM is hopeful that these changes will assuage political opponents who believe that these restrictions must be legislated rather than merely adopted by the ICOC. Levey and Hall both believe that the ICOC’s response has been responsible and sufficient, given the intended independent stature granted the CIRM by Proposition 71. Hall notes that CIRM policies already go beyond NIH requirements by asking research grant reviewers to list any companies in which they have more than a \$5,000 investment. That information would not be made public, consistent with federal ethics rules.

“Putting ‘second stringers’ or people with no interest in the research or relative expertise on the ICOC would guarantee we’ll lose the game.”

Nobelist Paul Berg

Peer Review, Openness, and Transparency

One of the tenets of research grantsmanship is the use of peer review to decide which proposals merit funding. Peer review is employed by virtually every federal science agency. It subjects an investigator's proposal and prior work to the scrutiny of one or more experts in the field. These referees each return an evaluation of the work, including suggestions for improvement, to an intermediary (typically, most of the referees' comments, stripped of identifiers, are eventually seen by the investigator as well). The anonymity and independence of reviewers are intended to foster unvarnished criticism and discourage cronyism in funding and publication decisions. It is not a perfect system, but no one has yet developed a better one.

Hall says the concept of peer review has been a tough sell for CIRM. State politicians have expressed suspicion about the process, charging that it leads to "scientists making deals in the back room." SCA 13 would require open public records and open meetings when funding decisions are being made. This would essentially prevent blind peer review and cripple the process.

CIRM leadership has spent a good part of the last four months explaining that science is both collegial and competitive and that one can get frank evaluation of proposals only if the process protects confidentiality. In response, the language of SCA 13 was watered down, and the ICOC adopted some compromise policies that would:

- provide earlier public availability of working group funding recommendations;
- require comprehensive reports to the state legislature summarizing grant awards and recipients;
- ensure increased public access to meetings of the Standards Working Group and the Facilities Working Group; and
- provide public access to the Grants Working Group, except for discussions related to scientific and medical evaluations of grant applications and other mission-critical exceptions.

It is not clear whether this strategy will appease those who rigidly adhere to the principle that the process by which all government decisions are made should be public. However, it appears that CIRM has persuaded the legislature that requiring full transparency would undermine the effectiveness of the program. In the meantime, the agency has hired a consultant to help build the peer review and grants management structure, modeled after that used by NIH.

Finally, because the realm of stem cell expertise is small globally and even smaller in California, the ICOC had to go outside the state to find scientists qualified to review the science without conflict (because they cannot be recipients of any awards, which is also true of ICOC members). CIRM currently is advertising for program and review officers, and blood stem cell expert Stuart Orkin of Harvard University has agreed to chair the Peer Review Working Group, which includes 15 non-California scientists and seven patient advocates.

Hall says that peer reviewers will assign scores to proposals, just as NIH does, to grants recommended for funding and to worthy grants that are not recommended for funding. Final funding decisions will then be made by the ICOC at open meetings, allowing a patient advocate, for example, to make a case for a project that was not recommended for funding.

Hall recognizes that this process resembles that used by NIH (a two-tiered system of review—peer review followed by review and approval by an advisory council). A slight variation is the weight given to the voices of patient advocates, who are involved in decisionmaking "every step of the way." A more significant deviation from the NIH model is the fact that the ICOC must make its decisions in public, which requires that CIRM take special precautions to protect confidential information. Hall says the ICOC model for decisionmaking is closer to that developed by the Department of Defense's Congressionally Directed Medical Research Programs. Although these programs focus on basic and clinical research and training, they have developed a reputation for consumer participation in priority setting and peer review. Levey says that the patient advocates are very conscious of putting quality first and that there is no concern on the part of the scientists about consumer involvement. In fact, they welcome it.

The system has only recently been tested, with a first round of training grants approved by the ICOC in September 2005. Despite its inability to sell bonds because of the pending lawsuits, CIRM still plans to award 170 three-year fellowships at 16 institutions in November worth \$40 million. Robert Klein is raising interim “bridge” funds from private sources to cover these initial awards.

Hall says that the funding mechanisms will mimic those traditionally offered by NIH: training grants and fellowships, seed grants, R01-like awards, center grants, and program project awards. He is comfortable with and confident in these mechanisms. From 1994 to 1997, Hall was Director of the National Institute of Neurological Disorders and Stroke at NIH, where he presided over a major reorganization of intramural and extramural research programs. At the time Hall was director, the agency had an annual budget of \$780 million and employed more than 700 scientists and administrators. Before going to NIH, Hall was Chair of the Department of Physiology at the University of California-San Francisco and head of the Biomedical Sciences Graduate Program. After leaving NIH, Hall took over as Executive Vice Chancellor at the University of California-San Francisco where he oversaw the development of the new Mission Bay Campus. He is well known for his administrative skills as well as his scientific expertise, and many feel he is exactly the right person to jumpstart a new research agency.

Intellectual Property Issues

Intellectual property protection is essential to pharmaceutical and biotechnology firms that must invest hundreds of millions of dollars in R&D to bring a drug to market. To provide an incentive and to recoup the necessary investment in drug development, companies require a period of exclusive sale of the product.

The federal government, whose investments support the vast majority of fundamental biomedical research in the United States, has adopted policies over the past 25 years intended to promote the commercialization of research conducted in universities as a means of speeding the development of benefits to the public good. In particular, the Patent and Trademark Amendments of 1980 (PL 96-517, also known as

The California Council on Science and Technology reported in August 2005 that many of the promises made during the campaign were “based on unrealistic assumptions about the potential economic impact of CIRM’s research program.”

the Bayh-Dole Act) cede to universities the right to claim intellectual property protection for discoveries that result from federally funded research and permit universities and faculty inventors to benefit financially from licensing and royalty payments.

One of the key provisions of Proposition 71 was that the state would benefit from royalties and patents that were issued from discoveries made with Proposition 71 funds. Specifically, Proposition 71 stated that the ICOC set intellectual property standards that:

...balance the opportunity of the state of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements.⁶

The promotional materials for Proposition 71 recognized the need to sell the concepts of local advantage and short-term payoffs. Supporters pointed to a commissioned financial analysis that said California could recoup \$537 million to \$1.1 billion if it were to get a cut of the licenses and royalties that companies would need to pay to use any Proposition 71-funded discovery in further research or drug production. This analysis assumes either that private investors or companies would agree to pay money in addition to what they traditionally pay research institutes to license technologies—or that the research institutes would be willing to take less. SCA 13 also sets forth an objective for California to recover its CIRM expenditures through royalties.

There are several problems with this approach.⁷

⁶ Health & Safety Code §125290.30(h)s.

⁷ For an extensive discussion of these issues see *The Politics and Economics of Implementing State-Sponsored Embryonic Stem-Cell Research*, by Roger G. Noll, Stanford University. Available at siepr.stanford.edu/papers/pdf/04-28.

First, even the most successful research universities do not bring in significant levels of licensing and royalty income. In 2000, the University of California system spent \$2 billion on research and received \$74 million in licensing income.⁸ Thus, it is unreasonable to expect that CIRM would recover \$300 million a year from such revenues.

Second, it is bad science policy to restrict the sale of intellectual property rights based on geography. Science is fluid and global.

Third, it is hard to imagine what the incentives would be for universities and companies to invest time and resources in research for which they have no chance of collecting licensing or royalty fees. It could, in fact, discourage researchers from accepting CIRM funds in favor of funds from other sources that do not have such restrictions.

Fourth, the policy of the state holding the property rights runs counter to the spirit of Bayh-Dole. Some experts argue that the easiest course would be for California to adopt the same approach as the federal government, which has an established model that has worked well. Moreover, scientists and research institutions are familiar with the Bayh-Dole requirements and would be likely to resist a new policy.

CIRM is in the process of discussing with state officials and the legislature how best to handle this contentious issue. The ICOC voted to establish a task force of ICOC members to work with the legislature on an intellectual property policy, specifically one including the goal of advancing access to therapies for low-income Californians. In addition, a task force of the California Council on Science and Technology—a group of science and technology experts in academia and industry—was asked by the state legislature to make recommendations for handling the rights to any discoveries that result from research funded through Proposition 71. The Council issued its interim report in August 2005, stating that many of the promises made during the campaign were “based on unrealistic assumptions about the potential economic impact of CIRM’s research program.”⁹ It recommended that the California policy be consistent with the Bayh-Dole Act, that it create incentives for commerce, and that it encourage timely publication of results to diffuse results widely.

More specifically, the Council recommended that California permit grantees to own patent rights from CIRM-funded research because 25 years of federal policy allowing such ownership has been shown to spur innovation and technology transfer.

Access to Care

What might be the most problematic expectation of CIRM is Ortiz’s demand that the results of stem cell research be “accessible and affordable to low-income residents,” including those eligible for state- and county-funded healthcare programs. Access and affordability are worthwhile goals, certainly. But medical researchers cannot possibly know in advance, before they have conducted their experiments and before they calculate the costs of research and clinical developments, whether the results of their efforts will be affordable.

According to Hall, this concept goes beyond the institute’s mandate, in the same way that, for example, Congress would never expect NIH to ensure that the results of its research were available to the nation’s poor. The means for reducing health disparities and uneven access to care will not be found in research, although it can play an important role in identifying and addressing such needs. The latest wording being discussed is that CIRM will “seek to” ensure affordability. However, even that language worries Hall, because it “presents another target for litigation.”¹⁰ The litigation could come from many directions, not just from those who want to promote Ortiz’s goal. For example, anti-trust laws might prohibit Californians from receiving a unique price break on drugs that could result from stem cell research.

In media interviews, Robert Klein has suggested that one approach could be to designate a percentage of the licensing and royalty fees on Proposition 71 intellectual property to be put aside to reimburse Medi-Cal for therapies provided to Californians who can least afford them.

⁸ See www.technologyreview.com/articles/01/scorecard0901.asp.

⁹ California Council on Science and Technology, Intellectual Property Study Group. *Policy Framework for Intellectual Property Derived from Stem Cell Research in California: Interim Report to the California Legislature, Governor of the State of California, California Institute for Regenerative Medicine*, August 2005. Available at <http://www.ccst.us/ccst/pubs/IP/IP%20Interim.pdf>.

¹⁰ See C. Holden, “Stem Cells: California Institute: Most Systems Go,” *Science*, 2005;309(5732):241.

VII. Lessons Learned

It is probably too soon to form any useful conclusions about whether the California stem cell initiative is the right way, or even a good way, to support research that the federal government will not. And it is not clear whether other states can, or even should, pursue the California model. David Jensen, journalist and publisher of the *California Stem Cell Report*, notes that “working in its favor was the presidential election and a host of other California ballot measures. So much was going on politically that forces that would naturally oppose creation of the agency just did not focus on it effectively.” Jensen adds that it is not entirely clear that a similar measure could be successful in another state: “Timing is everything in politics along with luck.”

But some lessons can be seen in the experience to date of the California stem cell initiative.

First, the passing of Proposition 71 did not insulate embryonic stem cell research from political risk. Even after California voters gave the go-ahead to Proposition 71, opponents in Sacramento and around the state found ways to challenge its very existence as well as its policies and nascent procedures.

Second, an initiative that promises success and preaches optimism can have far-ranging impact. Zach Hall says he is reminded every day that “a message of hope” is what propels him and supporters of the initiative to keep at it, despite the daily challenges of bureaucracies and politics.

This optimism is contagious, even if premature. As reported in *Science*, for example, Stanford University’s three-year-old stem cell center plans to hire several new scientists. The University of California-San Francisco, which distributes a number of cell lines, is planning to establish an embryo bank to supply excess embryos, eggs, and sperm from fertility clinics to California researchers. In southern California, the University of California-San Diego, the Burnham Institute, the Salk Institute, and the Scripps Research Institute have formed the La Jolla Stem Cell Initiative to compete for CIRM funds. Thus, the mere endorsement of this research, even prior to the handing out of any money,

has catalyzed an intensive redirection of talent and resources toward building the infrastructure that will be necessary to conduct the research.

Third, there are dangers in overselling the potential benefits of such an investment. **High expectations that cannot be met, either in the form of cures or intellectual property revenues, will result in heightened scrutiny and dwindling political support.** This requires educating policymakers and the public about what they can reasonably expect. In addition, tying complex social goals, such as affordable healthcare, to a research program imposes an unreachable standard.

Fourth, there are advantages and disadvantages to creating a new research infrastructure from the ground up rather than using existing infrastructure and institutions. One advantage is that the program is relatively free from the political and administrative constraints of entrenched bureaucracies. On the other hand, CIRM has had to re-create an administrative infrastructure that in essence replicates that which is already in place in California agencies and academic institutions or in the federal research environment, but is inaccessible because of the requirement for CIRM’s independence. Like any start-up, it has had to bid out several contracts to get essential work done while hiring occurs. This has led to the criticism that CIRM has a high burn rate, an unfair analysis given its mandate to achieve certain goals within a short period with no in-place administrative structure to manage daily operations.

On the other hand, once established, CIRM will be able to leverage existing infrastructure as it makes awards to California researchers and institutions. Jensen doubts that the measure would have passed if the recipient institutions—University of California schools, for example—had been named at the outset. “It would have brought out the usual enemies of the University of California, complaints about its lack of transparency, its past failures, for example, oversight of the Livermore Lab, and so forth,” said Jensen. “What helped to make Proposition 71 attractive is that the new agency carried no baggage.”

Alta Charo, Associate Dean of the University of Wisconsin Law and Medical Schools and a member of an ICOC working group, said it is an open question which approach may be best for a state considering a similar program. She wondered if it is better to have explicit up-front terms about how the money can be used—only for salaries and laboratories, for example, and not for bricks and mortar—or whether it is better to be vague and open-ended on the front end, allowing public discussion about how to spend the money. She noted that the characteristics of the state are probably the most important indicator of which approach will work. That is, can the governor work with the legislature? Is there a level of trust between the legislative and executive branches? How are public academic research institutions perceived and brought into discussions on matters concerning contentious public policies?

Levey's advice to other states is to establish their programs as incubators and set them loose. He feels that this approach would fast track the research and produce results in less time. He describes the early months of CIRM as "exceedingly tedious and slow." Although excited about the program, Levey is frustrated by the "inch-by-inch" approach that has been taken. Yet he realizes it is a major investment by the state and that oversight and governance issues have to be satisfactorily resolved.

Earlier in this paper, we posed three questions. We can now try to answer them.

The historical contract between the federal government and the public in terms of funding important public health research has been under strain for many years.

The national paralysis over supporting embryonic stem cell research with federal funds forged a new landscape for biomedical research. Multiple states are rushing to fill the void left by insufficient federal support. The ongoing question is whether this trend will continue. As emerging technologies create conflict and controversy, will the states be increasingly well-situated to take charge? As more states develop the infrastructure needed to fund research and promote technology transfer, the answer might be yes.

As for the second set of questions—about whether this new configuration for advancing science has opened up new opportunities and strategies for pursuing cutting-edge research—the answer is more equivocal. **In many ways, CIRM is relying on a model that works—that is, the model used by NIH and other federal funding agencies.** Absent the federal infrastructure and oversight system, CIRM chose, probably wisely, to re-create the federal infrastructure on a smaller scale, even hiring ex-federal scientists and administrators to do the job. In an area of high risk, such as state-supported stem cell research, there appears to be no need to experiment with entirely new funding or disbursement models.

Third, does this new model of public financing of research create an opportunity to move quickly in critical areas of research considered too controversial for risk-averse politicians and federal bureaucrats? **The California initiative has provided an opportunity to move quicker, if not quickly.** However, establishing the infrastructure takes time, and CIRM has done much to lay the foundation in a short time period. Every step it takes brings new research findings closer to realization. Thus, one could describe the progress of Proposition 71 as "slowly winding up."

Finally, **the true measure of whether Proposition 71 is a success will be in the science conducted and the results translated, not in how well CIRM operates administratively.** There will continue to be conflict between those who expect efficiency and streamlining as a measure of wise public investment and those who understand that science is imprecise and unpredictable, that it cannot aim for efficiency as a goal. And one can expect that other measures of success, such as patents, royalties, and revenue streams will continue to create conflicts between those who want to fill state coffers and those who want to spur commercialization.

To be sure, California's stem cell initiative is a new and different blending of science and government, business, and politics. The combinations are threatening to some of those who are invested in the status quo, even if they support the goals of the agency in principle.

As emerging technologies create conflict and controversy, will the states be increasingly well-situated to take charge?

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