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Stem Cell Research in California: The Intersection of Science, Politics, Culture, and Law

Zach W. Hall*

In November 2004 the voters of California passed Proposition 71 (the California Stem Cell Research and Cures Bond Act), which authorized the expenditure of $3 billion for stem cell research raised through the issuance of state bonds.[1] The passage of Proposition 71 marked a new phase in American biomedical research. For the first time, a state undertook to finance, through bonds, a large-scale biomedical research project in a new and untested area.

Alive with scientific and medical possibility, stem cell research is nevertheless a new field whose effective application to human disease remains to be demonstrated. The most promising facet of the new technology involves human embryonic stem cells, whose use in the United States is embroiled in ethical and political controversy rooted in the sensitive issue of abortion.[2] Because of the controversy, the federal government has declined to support this research except on a limited basis,[3] leaving California and other states to fill the gap. Large, state-supported biomedical research projects offer an opportunity to develop new structures for funding biomedical science, but they also pose new challenges as inexperienced state governments struggle to establish

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1. California Stem Cell Research and Cures Bond Act of 2004, CAL. HEALTH & SAFETY CODE § 125291.30 (West 2004).

2. *See generally* D.C. Wertz, *Embryo and Stem Cell Research in the United States: History and Politics*, 9 GENE THERAPY 674 (2002).

3. Press Release, White House Fact Sheet: Embryonic Stem Cell Research (Aug. 9, 2001), http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html; *see also* Exec. Order No. 13,435, 72 Fed. Reg. 34,591 (June 22, 2007).

funding agencies and mechanisms. In addition, the consequences of substituting a patchwork of state programs for strong central support from the federal government pose special problems for science administration.

Stem cell research in the United States touches the separate worlds of science, politics, ethics, law, and culture and brings them into an unusual juxtaposition, sometimes productively and sometimes not. The California Institute for Regenerative Medicine ("CIRM") established by Proposition 71,[4] now in its fourth year, has been involved in each of these realms.[5] In view of the growing involvement of states in biomedical research, this article attempts to examine the California experience and determine what lessons can be learned. Part I provides an overview of the science and importance of stem cell research; Part II discusses the development of current federal policies for oversight and funding of stem cell research; Part III discusses California's Proposition 71; and Part IV concludes with lessons from the California experience.

I. THE IMPORTANCE OF STEM CELLS AND STEM CELL RESEARCH

A. THE UNDERLYING SCIENCE

A brief summary of the early stages of human embryonic development is helpful in understanding the basis of stem cell research. Fertilization of a mammalian oocyte, or egg, by a sperm results in successive rounds of cell division to produce a ball of about sixteen cells called the morula. At this stage each of the roughly sixteen daughter cells, if separated from the others, can undergo successive divisions to form a new morula. Further cell divisions in the morula result in a more complicated structure, the blastocyst, a hollow sphere of

4. Proposition 71 enacted an amendment to the California Constitution creating CIRM, amended a section of the California Government Code, and added sections to the Health and Safety Code. *See* CAL. CONST. art. XXXV, § 1; CAL. GOV'T CODE § 20069 (West 2004); California Stem Cell Research and Cures Act, CAL. HEALTH & SAFETY CODE §§ 125290.10–125291.85 (West 2004).

5. *See generally* California Institute of Regenerative Medicine, http://www.cirm.ca.gov (last visited Sept. 27, 2008).

trophoblastic cells surrounding a fluid-filled cavity. Inside this liquid-filled cavity is a clump of 60–200 cells, attached to the wall on one side, which constitutes the inner cell mass. The trophoblasts are responsible for subsequent attachment of the embryo to the uterine wall and the formation of the placenta; the inner cell mass differentiates and forms the more than 200 different kinds of cells that make up the tissues of the body.[6]

The inner cell mass can be removed from the blastocyst and cultured as embryonic stem cells.[7] It should be noted that in the absence of trophoblasts and uterine implantation, the cultured stem cells are unable to form an organized embryo. Instead, the cells divide robustly in culture to reproduce themselves and, under appropriate conditions, differentiate into the various cells of the body, such as nerve, muscle, skin, and blood. The remarkable ability to self-renew through cell division, both in the embryo (*in vivo*) and in culture (*in vitro*), and the ability under appropriate conditions to produce any cell in the body, are the two defining features of embryonic stem cells and form the basis of their wide-ranging scientific and medical potential.[8]

During normal embryonic development, embryonic stem cells evolve along well-defined pathways to produce fully differentiated cells. Differentiation is normally a one-way process; as cells become specialized, biochemical modification of the DNA, and of the proteins associated with it, alter the pattern of gene expression in a way that is appropriate for the differentiated cell.[9] Muscle, skin, or thyroid cells, for example, each produce proteins that are specific for their respective functions. These cells remain specialized and do not normally replicate. The differentiaton of stem cells into fully specialized cells does not occur in a single step, but along a pathway of intermediate cell types. At each stage in the pathway, the capacity to self-renew and the potential to differentiate into other cells of the intermediates becomes more restricted.[10] Some of the later stage intermediates, called progenitor cells or

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6. *See* BRUCE M. CARLSON, HUMAN EMBRYOLOGY AND DEVELOPMENTAL BIOLOGY 43–44 (Inta Ozols & Joanie Milnes eds., 3d ed. 2004); KEITH L. MOORE & T.V. N. PERSAUD, THE DEVELOPING HUMAN: CLINICALLY ORIENTED EMBRYOLOGY 36–41 (7th ed. 2003).

7. M.J. Evans & M.H. Kaufman, *Establishment in Culture of Pluripotential Cells from Mouse Embryos*, 292 NATURE 154, 154–55 (1981); Gail R. Martin, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells*, 78 PROC. NAT'L ACAD. SCI. 7634, 7634–37 (1981).

8. National Institutes of Health, *Stem Cell Information*, http://stemcells.nih.gov/info/basics (last visited Oct. 14, 2008).

9. Rudolf Jaenisch & Richard Young, *Stem Cells, the Molecular Circuitry of Pluripotency and Nuclear Reprogramming*, 132 CELL 567, 567 (2008).

10. National Institutes of Health, *supra* note 8.

adult stem cells, remain in adult tissues in specialized sites called niches, where they can be activated to divide and produce the various cells of the tissue in which they reside, but not other cells.[11] The adult stem cells in the bone marrow, for example, are responsible for maintaining circulating blood cells; it is these cells that replenish blood-forming capacity after a bone marrow or stem cell transplant.[12] Consequently, adult stem cells may offer therapeutic possibilities in specific situations. In contrast to embryonic stem cells, however, the therapeutic potential of adult stem cells is limited because of their small numbers, the difficulty of isolating and growing them, and the limited kinds of cells that they can produce.[13]

B. STEM CELLS AS THERAPEUTIC AGENTS AND SCIENTIFIC TOOLS

The unlimited capacity of embryonic stem cells to self-renew in culture to produce large numbers of cells, and their ability to differentiate into more specialized cells of various types are the bases of their potential use in cell replacement therapies. In such therapies, specialized cells made *in vitro* from stem cells are introduced into the body to replace damaged or diseased cells. Cell replacement therapy has potential applicability to a wide variety of ailments including diabetes, neurodegenerative disease, brain and spinal cord injury, and cardiovascular disease.[14] Stem cell implantation can also be used as a means of delivering enzymes, growth factors, and other cellular products to discrete locations in the body.[15] This can be accomplished by genetic manipulation of stem cells in culture to produce specific factors followed by injection of these stem cells into the needed sites, such as the brain, muscles, or joints.[16]

Most of the human embryonic stem cell lines now available

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11. David T. Scadden, *The Stem-Cell Niche as an Entity of Action*, 441 NATURE 1075, 1075–76 (2006).

12. David Bryder et al., *Hematopoietic Stem Cells: The Paradigmatic Tissue-Specific Stem Cell*, 169 AM. J. OF PATHOLOGY 338, 338 (2006).

13. Calvin B. Harley & Mahendra S. Rao, *Human Embryonic vs. Adult Stem Cells for Transplantation Therapies*, *in* HUMAN EMBRYONIC STEM CELLS 239, 239–43 (Arlene Y. Chiu & Mahendra S. Rao eds., 2003).

14. *See generally* National Institutes of Health, *supra* note 8.

15. *Id.*

16. Rahul Jandial et al., *Genetic Modification of Neural Stem Cells*, 16 MOLECULAR THERAPY 450, 450–53 (2008).

were derived from excess embryos made for *in vitro* fertilization ("IVF") and donated by couples for research and therapeutic purposes.[17] To fully realize the potential of human embryonic stem cells, it would be advantageous to have cell lines, which are cells maintained in culture that are derived from a single source, from a variety of individuals of different genotypes. Human stem cell lines from those with an inherited disease would be particularly valuable for scientific purposes, as they could be used to investigate disease mechanisms and to identify new therapeutic targets for drug therapy.

To more easily obtain human embryonic stem cell lines of particular genetic backgrounds, scientists have explored various ways of using adult cells to make cell lines with the properties of embryonic stem cells.[18] In animals, such cells have been made by transferring the nucleus of an adult cell into an unfertilized oocyte whose own nucleus has been removed. The cytoplasm in the oocyte effectively "reprograms" the adult DNA to erase the biochemical modifications that accompanied cell differentiation.[19] The oocyte, containing the new DNA, is then induced to divide and form a blastocyst, whose genetic makeup is now identical, excluding the mitochondria, to the individual who donated the adult cell.[20] The inner cell mass of the blastocyst can then be isolated and stem cell lines can be made using conventional means.

Recently, scientists have been able to use gene transfer techniques to "reprogram" adult skin cells in both animals and humans, converting them into cells resembling embryonic stem cells.[21] These induced pluripotent stem cells ("iPSCs") are currently being intensively investigated as they offer great promise both for scientific investigation and possibly therapy, and they avoid many of the ethical issues associated with nuclear transfer into oocytes. Umbilical cord blood and the

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17. James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCI. MAG. 1145, 1145 (1998).

18. Megan J. Munsie et al., *Isolation of Pluripotent Embryonic Stem Cells from Reprogrammed Adult Mouse Somatic Cell Nuclei*, 10 CURRENT BIOLOGY 989, 989–91 (2000).

19. *Id.* at 989.

20. *Id.*

21. *See* Rudolf Jaenisch & Richard Young, *Stem Cells, the Molecular Circuitry of Pluripotency and Nuclear Reprogramming*, 132 CELL 567, 567 (2008); Nimet Maherali et al., *Directly Reprogrammed Fibroblasts Show Global Epigenetic Remodeling and Widespread Tissue Contribution*, 1 CELL STEM CELL 55, 55–68 (2007); Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 1, 1–9 (2007); Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663, 663–73 (2006); Marius Wernig et al., In-Vitro *Reprogramming of Fibroblasts into a Pluripotent ES-Cell-Like State,* 448 NATURE 318, 318–23 (2007).

amniotic fluid surrounding the embryo may also contain cells that can be used for scientific or therapeutic purposes.[22]

II. FEDERAL SUPPORT FOR STEM CELL RESEARCH

The political and ethical issues that make stem cell research controversial have their roots in abortion politics, which for religious and other reasons has played a distinctive and important role in American cultural and political life. Because of the unwillingness of the federal government to engage these issues, research on human embryos in the United States has languished over the past thirty years.[23] Most of the work done has occurred with private funding, both commercial and philanthropic, largely out of the public eye.[24] With the legalization of abortion following *Roe v. Wade* in 1973,[25] human fetal tissue was available for research for the first time, the ethical dimensions of which were addressed by the Belmont Report on Protection of Human Subjects of Biomedical and Behavioral Research.[26] The Report, published in 1979, concluded that research on human fetal tissue was important for human health, but that the human fetuses, like other human subjects, had rights that deserved protection.[27] To ensure this protection, the Belmont Report required that each proposal for federally-supported research on fetuses be approved by an Ethics Advisory Board.[28] Before the Board approved and finalized any proposals, it was disbanded and not re-established.[29] Human fetal tissue research was thus left in

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22. Ravindra Majeti et al., *Identification of a Hierarchy of Multipotent Hematopoietic Progenitors in Human Cord Blood*, 1 CELL STEM CELL 635, 635–44 (2007); *see generally* David T. Harris & Ian Rogers, *Umbilical Cord Blood: A Unique Source of Pluripotential Stem Cells for Regenerative Medicine,* 2 CURRENT STEM CELL RES. & THERAPY 301 (2007).

23. STEPHEN S. HALL, MERCHANTS OF IMMORTALITY: CHASING THE DREAM OF HUMAN LIFE EXTENSION 97–122 (2003).

24. *See id.*

25. 410 U.S. 113 (1973).

26. *See* Hall, *supra* note 23, at 98–122.

27. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, 44 Fed. Reg. 23,192–97 (Apr. 18, 1979).

28. *Id.* at 23,194–97.

29. According to Albert Jonsen, the Board was "summarily disbanded" by Patricia Harris, Secretary of Health, Education & Welfare in the Carter

a catch-22 situation, requiring approval by a body that did not exist. This difficulty has not been resolved by subsequent administrations.

The political and ethical issues were further clouded by the success of IVF. The first successful IVF procedure, resulting in the birth of a healthy baby, was carried out in the United Kingdom in July 1978[30] with little public fanfare and under no regulatory authority. Within a few years IVF technology was used successfully in other countries. As this procedure grew into a world-wide industry, more than 100,000 procedures were performed each year in the United States alone.[31] With the success of IVF and its increasingly widespread use, the British government in 1990 established the Human Fertilisation and Embryology Authority as a regulatory agency to oversee all clinical and scientific use of human embryos.[32] The United States government, however, was caught between a constituency of childless couples who embraced the new technology and those who viewed all manipulation of the human embryo as suspect and immoral, and simply avoided the issue. Thus, the IVF industry, and now stem cell research, has developed in the United States without federal regulation.

The malaise and inaction of the federal government was overtaken by new scientific discoveries. In 1982, Martin Evans in the United Kingdom and Gail Martin in the United States independently discovered mouse embryonic stem cells;[33] in 1996, Ian Wilmut in the United Kingdom extended IVF technology by using nuclear transfer techniques to clone Dolly;[34] and in 1998, Jamie Thompson isolated the first human embryonic stem cells.[35] Thompson's work was supported by private, non-federal funds.

These and other developments prompted two U.S. Congressmen, Representatives Roger Wicker of Mississippi and

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administration. Hall, *supra* note 23, at 101.

30. Robert G. Edwards et al., *Establishing Full-Term Human Pregnancies Using Cleaving Embryos Grown* In-Vitro, 87 BRIT. J. OBSTETRICS & GYNAECOLOGY 737, 750 (1980).

31. The Centers for Disease Control collects IVF information each year and publishes this data. For 2005, over 134,000 cycles of IVF were reported by participating fertility clinics, resulting in 38,910 live births. Department of Health and Human Services, Centers for Disease Control and Prevention, 2005 Assisted Reproductive Technology Report, http://www.cdc.gov/art/ART2005/section1.htm (last visited Oct. 2, 2008).

32. Human Fertilisation and Embryology Act, 1990, c. 37, §5, sched. 1 (Eng.).

33. Evans, *supra* note 7; Martin, *supra* note 7.

34. I. Wilmut et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, 385 NATURE 810, 810–12 (1997).

35. Thomson, *supra* note 17, at 1145–47.

Jay Dickey of Arkansas, to add an amendment to the 1996 National Institutes of Health (NIH) appropriations bill that prohibited federal funding for work "in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero."[36] This prohibition, now known as the Dickey Amendment, was continued in subsequent NIH budgets by inclusion in the Department of Health and Human Services appropriations bill.[37] This was the beginning of federal human stem cell research policy, one that effectively removed the United States government from any role in funding or regulating the field.

In August 2001, in a dramatic, televised address to the nation, President George W. Bush declared that federal funds could be used for experiments on human stem cell lines, as long as the lines were derived prior to the date of the President's address.[38] Thus federal funds could not be used to derive new lines, but could be used for lines that had already been derived using non-federal funds. To qualify for federal support, the lines had to be derived from unused blastocysts made for reproductive purposes.[39] At the time, the President stated that there were more than sixty such lines that qualified for federal approval;[40] subsequently, most have proved useless. At present only twenty-one federally-approved lines exist,[41] and only a handful are easily available; all were made with mouse feeder cells, raising the prospect that they have mouse antigens, and many have chromosomal rearrangements that are characteristic of tumor cells,[42] thus making them unsuitable for therapeutic uses.

President Bush deserves credit for permitting, for the first

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36. Pub. L. No. 106-554 § 510(a)(2), 114 Stat. 2763A-71 (2000).

37. Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, Pub. L. No. 107–116, § 510, 115 Stat. 2177, 2219 (2002).

38. Press Release, White House Fact Sheet, *supra* note 3.

39. *Id.*

40. *Id.*

41. National Institutes of Health, *Stem Cell Information*, http://stemcells.nih.gov/staticresources/research/registry/PDFs/EligibilityCriteria.pdf (last visited Oct. 3, 2008) (indicating the twenty-one federally approved stem-cell lines that exist as of May 4, 2007).

42. Anirban Maitra et al., *Genomic Alterations in Cultured Human Embryonic Stem Cells*, 37 NATURE GENETICS 1099, 1099–1102 (2005).

time, federal funds to be used for human embryonic stem cell research. But the severe limitations of the presidential policy have significantly truncated the development of this field in the United States, as acknowledged by Elias A. Zerhouni, the Director of NIH.[43] Most seriously, the lack of federal support has discouraged bright and ambitious young scientists from entering what many see as an exciting new frontier in biomedical research.[44]

III. CALIFORNIA'S STEM CELL INITIATIVE: PROPOSITION 71

A. THE INITIATIVE CAMPAIGN

California's answer to the federal restriction was Proposition 71, the California Stem Cell Research and Cures Bond Act.[45] As early as 2002, California state legislators, led by State Senator Deborah Ortiz, introduced legislation to fund stem cell research in California.[46] When the legislation failed to pass, Ortiz suggested that funding be obtained through an initiative, whereby voters pass judgment directly on legislative issues and bond measures. Following a suggestion by Peter Van Etten, then CEO of the Juvenile Diabetes Research Foundation, Ortiz teamed with others, including a charismatic real estate development expert named Robert Klein, to mount a proposition campaign. Klein rapidly became the dominant force, writing the proposition, directing the campaign, and raising more than $26 million to support it. Klein, who has a son with Type I diabetes, had become involved with patient advocacy through the Juvenile Diabetes Research Foundation.[47] For the ballot campaign a coalition was organized that included scientists, business leaders, politicians, and most importantly, a group of patient advocates, including Michael J. Fox and Christopher Reeve.[48] The campaign was

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43. Mary Ann Akers, *Going Against Bush, NIH Director Urges Expanded Stem Cell Research*, WASH. POST, Oct. 17, 2007, at A15.

44. For example, on a trip in 2006, I met several young graduate students from California who had come to the United Kingdom to pursue graduate training in human embryonic stem cell research because adequate training was unavailable in the United States.

45. California Stem Cell Research and Cures Bond Act of 2004, CAL. HEALTH & SAFETY CODE §§ 125290.10– 125291.85 (West 2004).

46. S. 1272, 2001-2002 Leg., Reg. Sess. (Cal. 2002), *available at* http://www.leginfo.ca.gov/pub/01-02/bill/sen/sb_1251-1300/sb_1272_bill_20020115_introduced.pdf.

47. CHRISTOPHER THOMAS SCOTT, STEM CELL NOW: FROM THE EXPERIMENT THAT SHOOK THE WORLD TO THE NEW POLITICS OF LIFE 171 (2006).

48. *Id.* at 172–73.

waged as a full-scale political operation, including television advertisements, focus groups to sample public opinion, and an economic analysis that predicted a positive economic impact for the state from stem cell research.[49] The campaign aggressively promoted the potential cures that might result. For example, a video of spinal cord-injured rats walking after treatment with fetal stem cells was shown in support of the campaign.[50]

On November 4, 2004, Proposition 71 passed with fifty-nine percent of the vote[51] at a time of fiscal difficulty for the State of California. Post-election demographic analysis indicated that the Proposition received strong support across ethnic, gender, class, and geographical lines.[52]

The long and detailed ballot initiative, which included an amendment to the California Constitution, authorized the issuance of bonds totaling $295 million per year for ten years to support stem cell research at California institutions, prohibited funding for "reproductive cloning" to produce human beings, and established the California Institute for Regenerative Medicine ("CIRM"), its oversight board, the Independent Citizens Oversight Committee ("ICOC"), and three advisory working groups to implement the provisions of the measure.[53] Significantly, the Proposition also prohibited any modification of its terms by the legislature for three years and then only by a seventy percent margin in each house and with the consent of the governor.[54] This strong barrier to modification has

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49. LAURENCE BAKER & BRUCE DEAL, ECONOMIC IMPACT ANALYSIS: PROPOSITION 71, CALIFORNIA STEM CELL RESEARCH AND CURES INITIATIVE 26–39 (2004).

50. Terri Somers, *Proposition 71 Opens Tap for Stem-Cell Studies,* SAN DIEGO UNION-TRIB., Oct. 8, 2004, at A1; s*ee also* SCOTT, *supra* note 48, at 184.

51. Carl T. Hall, *Proposition 71: State Voters Strongly Backing Cell Research*, S.F. CHRON., Nov. 3, 2004, at B4.

52. MARK BALDASSARE ET AL., MAKING HEALTH POLICY AT THE BALLOT BOX: CALIFORNIANS AND THE NOVEMBER 2004 ELECTION 14–15 (2005).

53. Proposition 71, Text of Proposed Laws, http://www.cirm.ca.gov/pdf/prop71.pdf (last visited Oct. 6, 2008); *see also* California Stem Cell Research and Cures Bond Act of 2004, CAL. HEALTH & SAFETY CODE §§ 125290.10– 125291.85 (West 2004).

54. Proposition 71, Text of Proposed Laws, http://www.cirm.ca.gov/pdf/prop71.pdf (last visited Oct. 6, 2008); *see also* LAURENCE BAKER & BRUCE DEAL, *ANALYSIS OF THE FINANCIAL IMPACT ON THE CALIFORNIA STATE BUDGET OF THE PROPOSED CALIFORNIA INSTITUTE OF REGENERATIVE MEDICINE (2003)*, *available at* http://www.etopiamedia.net/empnn/pdfs/baker2003.pdf, for an economic analysis of the Act on the state budget.

protected the stem cell research project in California from political interference, but has also made it difficult to modify the many detailed terms in the Proposition.

Proposition 71 has several notable features. First, the idea of funding scientific research through the issuance of general obligation bonds is novel. This financial mechanism provides stable long-term support, free from the vagaries of year-by-year political appropriations. Viewed in these terms, the development of intellectual and scientific capital is treated, like schools, highways, and water systems, as a long-term investment in the state's infrastructure. This model of research financing has attracted attention both internationally and nationally. Texas, for example, recently voted in favor of a $3 billion bond issue for cancer research.[55] Second, in comparison to the NIH model, the Proposition gives considerable power to the ICOC relative to the CIRM, most notably in the executive responsibilities that are conveyed to the ICOC Chair.[56] Third, as discussed below, Proposition 71 gives patient advocates on the ICOC a powerful decision making role.

B. IMPLEMENTATION: STRUCTURE OF THE ICOC AND CIRM

The ICOC, whose composition is specified by the Proposition, consists of twenty-seven individuals, thirteen of whom are high-level administrators (e.g., deans, chancellors) of research institutions, four are from the private sector, and ten are patient advocates, plus a chair and vice-chair.[57] The chair and vice-chair, Robert Klein and Ed Penhoet,[58] respectively, are nominated by state officials and elected by the board. All but five of the members are appointed by state officials within specific categories (i.e., by disease or type of institution). All members serve fixed terms of at least six years. Surprisingly, there are no positions explicitly assigned to scientists, clinicians, bioethicists, or representatives of the public, and there are no provisions for removing ICOC members for

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55. H.R.J. Res. 90, 80th Leg., Reg. Sess. (Tex. 2007), *available at* http://www.legis.state.tx.us/tlodocs/80R/billtext/pdf/HJ00090F.pdf.

56. Transcript of Regular Meeting Before the Independent Citizens' Oversight Committee to the California Institute for Regenerative Medicine Organized Pursuant to the California Stem Cell Research and Cures Act at 139–73 (2006), *available at* http://www.cirm.ca.gov/transcripts/pdf/2006/06-02-06.pdf.

57. California Institute of Regenerative Medicine, Independent Citizens Oversight Committee List of the California Institute for Regenerative Medicine, http://www.cirm.ca.gov/faq/pdf/Members.pdf (last visited Oct. 3, 2008).

58. *Id.*

cause.[59]

The initiative limits CIRM, which is responsible for administering the grants, to a staff of fifty, and its budget for the life of the enterprise is limited to six percent of the $3 billion in total bond proceeds.[60] The current CIRM president is Dr. Alan Trounson, a prominent reproductive biologist from Australia.[61]

Further, Proposition 71 provides for the establishment of three advisory working groups. The Grant Working Group is devoted to research grant evaluation and is composed of scientists from outside California and patient advocates from the ICOC. The Ethics Working Group develops recommendations for medical and ethical standards and is composed of ethicists, scientists, and patient advocates from the ICOC. The Facilities Working Group provides recommendations for facilities funding and is composed of real estate experts and patient advocates from the ICOC.[62] The Proposition allows up to ten percent of the $3 billion to be spent for the construction of new research facilities of non-profit institutions.[63] All final decisions on funding and policy are made by the ICOC. CIRM staff do not make recommendations on ethical matters or funding decisions, but they are responsible for overseeing the process. Patient advocates are the only representatives from the ICOC who are on the working groups. Because there are only ten, all serve on one or two working groups; some are on all three, requiring a tremendous commitment of time and effort. Each working group has either a co-chair or vice-chair who is a patient advocate.

The prominent role of the patient advocates in guiding the stem cell project is unusual and reflects, in part, the influential role that they played during the campaign, which was supported by over seventy disease groups, including the Christopher Reeve Paralysis Foundation, Parkinson's Action

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59. California Stem Cell Research and Cures Act, CAL. HEALTH & SAFETY CODE §§ 125290.20 (West 2004).

60. *Id.* §§ 125290.45, 125290.70.

61. California Institute of Regenerative Medicine, Leadership, http://www.cirm.ca.gov/info/leadership.asp (last visited Oct. 3, 2008).

62. California Stem Cell Research and Cures Act, CAL. HEALTH & SAFETY CODE § 125290.50 (West 2004).

63. *Id.* § 125290.70(a)(4).

Network, Project ALS and the Juvenile Diabetes Foundation among others. The role of the patient advocates in the project is critical, as they focus attention on the ultimate goal, which is to treat disease. Their expectations and mode of operation, however, have sometimes been at odds with the scientific and academic members of the ICOC. As addressed below, bridging this gap has been one of the important issues that the ICOC has dealt with.

C. INITIAL CHALLENGES

At its inception, CIRM and its oversight board, the ICOC, faced at least four major challenges. First, the defining scientific mission of CIRM was formidable: to develop disease therapies based on a new and untested technology at the frontier of modern science.[64] Human embryonic stem cells were first described only ten years ago,[65] and even now there is much that scientists do not understand about them. Moreover, to bring any therapy to the stage of clinical use is a long and expensive process with a high rate of attrition.[66] To achieve its goals, CIRM developed a comprehensive plan, the Scientific Strategic Plan, to guide its efforts over the life of the project.[67] During the first two years, CIRM implemented this plan by awarding more than $200 million in funds for research and education. Because of these grants, research on human embryonic stem cells is now underway in more than 100 laboratories in non-profit research institutions throughout California.[68]

Second, CIRM had to establish a new granting agency in its early years. CIRM developed policies to ensure that the research it funds is carried out according to the highest medical and ethical standards, that awards are made based on merit and without bias, and that both financial accountability and a financial return to the state, where appropriate, exist. After

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64. Arlene Y. Chiu & Zach W. Hall, *Stem Cell Research: The California Experience*, 26 J. NEUROSCI. 6661, 6662 (2006).

65. *See generally* Thomson et al., *supra* note 17 (discussing the possibility of human stem cells lines in 1998).

66. Joseph A. DiMasi, *Risks in New Drug Development: Approval Success Rates for Investigational Drugs,* 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 297, 297 (2001); Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180–83 (2003).

67. California Institute of Regenerative Medicine, CIRM, http://www.cirm.ca.gov/meetings/pdf/2006/12/120706_item_7.pdf (last visited Oct. 10, 2008).

68. California Institute of Regenerative Medicine, CIRM: Approved CIRM Grants as of June 2008, http://www.cirm.ca.gov/info/grants.asp (last visited Oct. 3, 2008).

extensive discussion and public input, CIRM adopted appropriate policies and procedures in these areas.[69]

Third, CIRM was a new state government agency, which had to be established from the ground up. Rigorous conflict-of-interest policies were established, and, in accordance with the California Administrative Procedure Act,[70] all of the proposed policies were examined by the state with a formal period of public comment and response until they became formal regulations with the power and effect of state law.

Fourth, litigation that was almost immediately brought against CIRM complicated its ability to accomplish other goals during the first two years.[71] Although the lawsuits were based on constitutional grounds, the organizations that brought suit represented or were funded by the religious right.[72] The suits were eventually found to be completely without merit,[73] but during the litigation and appeals — lasting about eighteen months — CIRM was unable to raise bond money, leaving both operating and grant funds severely limited. Short-term loans totaling $45 million from philanthropic individuals and foundations, plus a loan of $150 million from the state,[74] allowed CIRM to fund the grants described above. In October 2007, the state issued the first tranche of bonds, worth $250 million, for stem cell research.[75]

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69. *See* California Institute of Regenerative Medicine, CIRM Policies, http://www.cirm.ca.gov/policy/policy.asp (last visited May 12, 2008); *see also* California Institute of Regenerative Medicine, Adopted CIRM Regulations, http://www.cirm.ca.gov/reg/default.asp (last visited Oct. 3, 2008).

70. California Administrative Procedure Act, CAL. GOV'T CODE §§ 11340–11365 (2007).

71. Cal. Family Bioethics Council v. Cal. Inst. for Regenerative Medicine, 55 Cal. Rptr. 3d 272, 312 (Cal. Ct. App. 2007); s*ee* Doe v. Klein II, No. 5:2005-cv-00438-RSWL-SGL (C.D. Cal. 2005), *aff'd*, 254 Fed.Appx. 626 (9th Cir. 2007).

72. *See Stem-cell Institute Gets $5 Million Gift*, SACRAMENTO BUS. J., June 7, 2005, *available at* http://eastbay.bizjournals.com/sacramento/stories/2005/06/06/daily15.html.

73. *Cal. Family Bioethics Council*, 55 Cal. Rptr. at 312 (affirming the lower court decision finding no constitutional issue or legal infirmity with Proposition 71); *Doe*, 254 Fed.Appx. at 629 (granting defendant's motion to dismiss for improper venue), *cert. denied*, 128 S.Ct. 1751 (2008).

74. CAL. INST. FOR REGENERATIVE MED., CAL. INST. FOR REGENERATIVE MED. ANN. REP. 2007 at 5, *available at* http://www.cirm.ca.gov/press/pdf/annual_rpt.pdf.

75. *Id.* at 30.

IV. LESSONS FROM THE CALIFORNIA EXPERIENCE

One striking aspect of the California stem cell project has been the strong degree of public interest that it evoked. The fascination of the public with CIRM is partially grounded in the deep hopes that stem cell research inspires and the belief that California is in the vanguard in bringing this important new scientific area to therapeutic fruition. The project also attracted the intense attention of the press, state politicians, and public interest representatives, particularly in its early years.[76] Although not elected or accountable in any real sense, these public interest representatives receive attention, sometimes an excessive amount, from the press. Fortunately, most are responsible and well-meaning critics who support stem cell research, but also want the agency to represent the highest standards of accountability, transparency, and responsibility to the public.

Critics outside of the courtroom have been mostly from the left, focusing on issues of transparency, conflict-of-interest, egg donation, and access for all Californians to stem cell therapies developed by CIRM funding. Many of these issues have revealed a deep gulf between scientific and political cultures at the state level. For example, politicians sometimes do not understand the advantages of confidential peer review, which Proposition 71 protects, and to which CIRM has adhered. Likewise, scientists are unaccustomed to the strong "sunshine laws" of California that require all meetings of state bodies, with certain narrow exceptions written into Proposition 71, to be public meetings and that the public be allowed input before decisions are reached. The extensive involvement of the public in all aspects of the development of CIRM policies, scientific and otherwise, has been time-consuming and often tedious, but has been necessary to gain public confidence. The public's participation in CIRM's decision-making process strengthened the decisions. As a public agency, CIRM must be accountable to the public and to the legislature, and must work to earn the confidence of both.

A striking and related feature of the CIRM experience is the powerful role of patient advocates. The increased role of the public and particularly of patient advocates in making decisions about scientific policy and direction is not unique to California. "Advocates want a say in the way biomedical

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76. In July 2005, the first six months after the creation of CIRM, a count of news stories covering CIRM conducted by Edelman (a public relations firm) totaled 2,481 (921 from January 1-April 6, 2005; 1,560 from April 7-July 22, 2005). Email from N. Pagano, former Communications Officer, CIRM to Dr. Zach Hall, former president of CIRM (Apr. 14, 2008) (on file with the author).

research is conducted."[77] The inclusion of patient advocates brings a sense of urgency and zeal to biomedical research that makes its relevance clear, and it is an important component of earning public support. Patient advocates also bring an intimate knowledge of disease and its effects on patients and their families that scientists often lack, and they keep the scientific community focused on the aim of curing disease.

The perspectives of science and patient advocacy, although in many ways complementary, are often not aligned. Scientists are generally focused on questions of mechanism and understanding, whereas patients are focused on immediate cures. Both aims are necessary for success and, in a cooperative way, both can be achieved.

A third feature of the California experience is the conflict of interest issue, arising from the composition of the ICOC. The largest group on the board consists of leaders of research institutions that are grantees of CIRM. The resulting conflict of interest is easily managed when the ICOC considers grants to individual researchers, as members simply abstain from discussing and voting on grants to their institution. On other issues, such as an appropriate level of indirect cost returns, all of the institutional leaders have a large financial stake in the outcome. The issue arises again in considering funding for facilities, as each of the institutions competes against others for limited funds. CIRM lawyers have determined that in this situation, all institutional leaders have a conflict of interest for each application, because the success of one diminishes the chances of success for others.[78] The final decision awarding $271 million for facilities, the largest single expenditure to date by CIRM, was decided by only seven members out of the 29 positions on the ICOC, the only ones who as patient advocates or members of the private sector had no institutional conflict of interest.[79] A poor understanding of conflict of interest issues and difficulty in separating the respective roles of being a member of the ICOC and of being an institutional leader has

77. REBECCA DRESSER, WHEN SCIENCE OFFERS SALVATION: PATIENT ADVOCACY AND RESEARCH ETHICS 23 (2001).

78. California Stem Cell Report, Zipped Lips and CIRM's $263 Million, http://californiastemcellreport.blogspot.com/2008/01/zipped-lips-and-cirms-263-million.html (last visited Oct. 14, 2008).

79. John M. Simpson, *Stem Cell Agency's Conflicted Board,* http://www.consumerwatchdog.org/patients/articles/?Story Id+20122 (last visited Oct. 10, 2008).

also recently created significant legal and political problems for the ICOC.[80]

For the expanding role of patient advocates and public members in the scientific enterprise to be successful, recognition of the distinct perspectives of constituents and a continuing effort to build trust and understanding are necessary. Time, energy, and a willingness to change one's point of view are also necessary. As not all members of the various communities are equally suited to or interested in this task, it becomes important that those who are appointed to decision-making positions have, in addition to other qualifications, respect for, and the ability to work with, members of the other constituencies.

Having a broader range of ideas among those involved in making decisions requires developing new structures and procedures. The most successful structures will be those that include all parties in the deliberations and that respect the areas of expertise of each. Patient advocates best represent the needs of the patient community; scientists are best-equipped to determine directions of scientific strategy; ethicists clarify the moral and ethical questions; and representatives of the public recognize the responsibilities to the larger community. As the group of decision-makers broadens, the extent to which values are shared about how decisions are made will diminish. This requires a more conscious attempt to think about both conflicts of interest and how decisions can be made not only effectively, but also fairly and without bias.

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80. *See California Against Cronyism*, 453 NATURE 1, 1 (2008); Editorial, *Piecemeal Reform Won't Do for Stem Cell Institute*, SACRAMENTO BEE, Mar. 11, 2008, at B6; Op-Ed., *Stem Cell Housecleaning: Grants are Great, but the California Institute Created to Fund Research Needs to Put its Business in Order*, L.A. TIMES, Dec. 12, 2007, at A30; Terri Somers, *Elimination of Conflicts of Interest at Stem Cell Institute Target of Bill*, SAN DIEGO UNION-TRIB., Feb. 23, 2008, http://www.signonsandiego.com/uniontrib/20080223/news_1b23stems.html.