### Title
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# The New Federalism: State Policies Regarding Embryonic Stem Cell Research

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> "It is one of the happy incidents of the federal system that a single courageous state may, if its citizens choose, serve as a laboratory; and try novel social and economic experiments without risk to the rest of the country."
>
> New State Ice Co. v Liebmann, 285 U.S. 262 (1932) (Brandeis, J., dissenting).

## Introduction

American policy regarding the experimental use of human embryonic stem cells was forged in the period 2001–2006. This article will focus on that period, as the directions chosen in that period greatly influenced the policy course for the foreseeable future. This article will also include an update of more recent events at its conclusion, but the decisions made during President George W. Bush's first term and during the first several years of the California Institute for Regenerative Medicine formed the federal-state stem cell policy conflict that continues today.

A comparison of two events of 2005 may provide some perspective on those policy choices. The University of California opened a new campus in Merced (UCM) in 2005. A scientist who planned to do human embryonic stem cell (ESC) research at UCM would have needed to organize the new laboratory facilities into two physically and functionally separate suites of laboratories. No scientific rationale compelled the scientist to keep separate rooms, perhaps even in separate buildings with distinct support infrastructures, along with a separate set of account ledgers about the funding source of each experiment, the time allocation for each employee, and the use of all materials. These separations existed solely because of federal funding policies—not to serve any scientific purpose. One set of facilities would hopefully be used for the experiments that the taxpayers of California were funding, while those same experiments might be strictly prohibited in the laboratory funded by those same taxpayers via their federal taxes.

A scientist at Tulane University, which was under re-construction after the devastation of Hurricane Katrina in August of 2005, who wanted to do similar ESC experiments would have faced a different problem. Construction of separate laboratories would not be sufficient as a local statute at that time stated, "The use of a human ovum fertilized in vitro is solely

for the support and contribution of the complete development of human in utero implantation. No in vitro fertilized human ovum will be farmed or cultured solely for research purposes or any other purposes." (1) In other words, no Louisiana scientist was allowed to establish new human embryonic stem cell lines in order to obtain cells that might provide insights into the nature and treatment of human disease. Perhaps that same Louisiana scientist could have used stem cell lines established by a California colleague, although even the legality of use of embryo derived cell lines established outside of Louisiana had not been clearly established. A possible prison sentence and a fine in the millions of dollars discouraged the testing of limits.

The stem cell research policy in the United States is a "Tale of Two Laboratories" both in the practical sense of how the research is organized and in the policy sense. There is federal policy and then there is a collection of divergent state policies. Instead of a simple bifurcation of policy between what is funded by federal grants and what is funded by anything else, there are layers of policy derived from policy promulgated by President George W. Bush. Although Bush outlined the policy in an August 9, 2001 speech (2), the policy was not formalized into an Executive Order until 2007. The Bush "compromise" limited federal funding for human embryonic stem cell research to the cell lines already in existence at that point in time. Much of the public criticism of this policy focused on the small number (less than two dozen) and limited biological utility of the "eligible" cell lines.

The public debate focused on the limitations imposed by the Bush stem cell policy but a second important aspect of the federal policy is what it did not do. The Bush policies did not prohibit any experiment of any sort; it simply stated what is eligible for federal funding. This is a policy consistent with precedent. Since the construction of our national research enterprise during and after World War II, funding limitations govern what can be done scientifically. For example, research in which human embryos are either created or destroyed has been precluded from federal funding since 1995 by an annually renewed amendment to the NIH appropriation known as the Dickey-Wicker Amendment (3). Because of Dickey-Wicker, scientists have needed to use non-Federal funds to establish cell lines from embryos before using their NIH funds to study these cells. This approach was validated in the 2011 decision by the U.S. Court of Appeals for the District of Columbia Circuit in the case of *Sherley v. Sebelius*, 644 F.3d 388 (D.C. Cir. 2011). The Bush policy was different from prior limitations by its explicit extension to cell lines derived from embryos and in the possibility of extending that limitation to indirect support. Still, there was nothing in federal law or regulation to prevent an investigator from using non-federal funding to do any ESC laboratory experiment, even controversial ones involving nuclear transfer or animal-human chimeras, so long as the experiment was demonstrably free of federal funding. This situation created something of a policy vacuum, as attempts to further limit federal involvement (e.g., anti-cloning legislation) or to remove the August 2001 limitation on stem cell lines either failed to muster support in both houses of Congress in the former instance or were the subject of Presidential veto in the latter case. In the face of limited policy guidance from Washington, and with strong and well-organized constituencies at the local levels active on the issue, the various states were quickly drawn into the stem cell legislative arena. First among these was California.

## The Origins of the California Experiment

The State of California stands in the forefront of stem cell policy, both in creating a highly structured policy alternative and in the amount of funding dedicated to this area of research. California filled the policy vacuum via a ballot initiative formally called the Stem Cell Research and Cures Act but popularly known as “Prop 71” (for Proposition 71, its identification on the ballot) that was passed by California voters in November 2004 (4). This measure dedicated $3 billion for stem cell research. In order to accomplish this task, the measure also created an entirely new state agency that has broad policy implications.

The greenhouse in which the Prop 71 effort was nurtured and brought to fruition is the patient advocacy community. Patient groups rely on the dedication of volunteers, family members, and patients to make the case to policy makers to improve the future for those afflicted with a disease. These advocates are effective because of their authenticity and passion, and no group is more passionate or dedicated than the parents of children with debilitating diseases. The origins of Prop 71 are to be found among a group of wealthy and politically sophisticated Californians who are parents of children with Type I diabetes. Stem cells hold much promise for diabetes research, and diabetes groups such as the Juvenile Diabetes Research Foundation (JDRF) were among the first to put resources into stem cell research in the hopes of developing new ways to grow insulin-producing pancreas cells to replace cells lost to disease in these patients. The catalyst that mobilized diabetes activists on national political issues was federal legislation (S.1899) proposed by then Senator Sam Brownback (R-KS) in 2002 that would have created criminal penalties for attempting human cloning, but which made no distinction between reproductive cloning and “therapeutic” or research cloning (5). Similar legislation proposed by Representative David Weldon (R-FL) passed the House of Representatives in 2002 and President Bush had indicated support for it; therefore, the Senate was the last line of defense for the opponents of such legislation. “Therapeutic” cloning, technically called somatic cell nuclear transfer (SCNT), is a procedure that could theoretically result in stem cells of the same genetic constitution as an individual patient. This experimental procedure is a frequent point of conflict between stem cell advocates who want all therapy options available and stem cell critics who find many procedures involving human ova to be highly objectionable.

A group of Hollywood-based patient activists, including film producer Janet Zucker, film director Jerry Zucker, movie executive Lucy Fisher, and film producer Douglas Wick formed a national advocacy outlet called CuresNow (6). As parents of children with Type I diabetes, they passionately believed that stem cells offered hope for cures for their children and that the nation was missing a crucial opportunity. They raised money for television advertising and CuresNow was among those organizations that distributed and publicized a letter signed by forty Nobel Laureates opposing S.1899. The Brownback legislation never came to a vote in the Senate and powerful advocates for stem cell research such as Senators Orrin Hatch (R-UT), Arlen Specter (at that time R-PA), and Tom Harkin (at that time D-IA) took up the cause of promoting stem cell research. Stem cell policy and politics took center stage, along with climate change, as the premier science policy issues of the day.

Scientific groups engaged in extensive Washington lobbying, with concerted efforts on stem cells by groups such as Research!America (a science advocacy group well connected on Capitol Hill), the Federation of American Societies for Experimental Biology (a consortium of scientific professional societies representing over 125,000 biomedical investigators), and the Coalition for the Advancement of Medical Research (a coalition organized by the American Society for Cell Biology and dedicated solely to this issue.) These efforts were almost always done in collaboration with patient advocacy groups such as the JDRF or the National Health Council (an umbrella organization of patient advocacy groups), cementing the patient-scientist partnership. The results of the Washington efforts were notable as the debate gradually shifted from preventing draconian limitations as embodied in the Brownback and Weldon proposals to reversing the limits imposed by the President. By approving H.R. 810 in 2006—a straight forward removal of the August 2001 limit—Congress finally moved decisively in the direction of expanded stem cell research. However, President George W. Bush's prompt veto and Congress' failure to override the veto left the federal policy situation unchanged.

The Washington D.C. events of 2001–2003 had important lessons for stem cell partisans, and the CuresNow team incorporated what had been learned into the California Prop 71 effort that followed. First of all, it was increasingly clear that stem cells were a potent political issue. Polls consistently showed that most Americans, regardless of religious affiliation or political inclinations, favored investing in stem cell research (7). There was even a suggestion in the October 25, 2004 Newsweek magazine cover featuring activists Christopher and Dana Reeve that stem cells might become the central issue of the 2004 presidential contest. Although stem cells did not eclipse security issues as a presidential campaign issue, stem cells had emerged as an issue of consequence in electoral politics. The combination of patient advocates and scientists was seen as an effective instrument in pushing this issue.

It had also become clear that during a George W. Bush presidency neither new federal legislation nor new federal policy was likely to further the cause of ESC research. Therefore, while advocacy in Washington continued at a high level, attention began to focus on those states where politics and science might work together to actually advance the ESC program with new funds. California, home to many research universities and institutes and with a liberal voting record, was an obvious target.

The founders of CuresNow joined forces in early 2003 with other wealthy activist parents of diabetic children, one of whom was real estate developer Robert Klein II. This collection of diabetes activists made the crucial decision that the California initiative process provided the best opportunity to bypass the impasses at both federal and state levels. They used their considerable financial resources to organize a comprehensive effort. They brought in lawyers, pollsters, public relations specialists and scientists as advisors and looked in detail how a ballot proposition might be constructed that could actually achieve victory and make a real impact on stem cell research. The organizational and political effort involved was vividly described in Connie Bruck's reporting in The New Yorker (8). Dr. Shane Smith, a young biologist who had recently completed his doctoral studies at UCLA served as the campaign's Scientific Director and he forged links with prominent biologists who became

effective and credible spokespersons for Prop 71. Importantly, the Prop 71 proponents reached out to many patient groups expanding well beyond the diabetes orientation of the original organizers.

The dimensions of Prop 71 were decided on the basis of scientific rationale and practical politics. The scientific leaders who were consulted emphasized that the need for parallel facilities required a significant sized program in order to have a major impact. Polling suggested that anything beyond $3 billion would be seen as disproportionately large and expensive.

On the surface, 2004 seemed a dubious choice as a time to mount such an effort. The state was in a severe fiscal crisis that cost Democratic Governor Gray Davis his job in the recall election of October 2003. Adding $3 billion of debt for stem cell research was going to be a difficult sell to an electorate worried that huge state deficits would necessitate additional taxation. Furthermore, many stem cell advocates were hopeful that a Democratic challenger to President Bush would be successful and stem cell research might be supported at the federal level. The proponents of Prop 71 pressed ahead, astutely deciding that Californians would want to take the lead on this issue no matter what happened in the national election. As it happened, 2004 was a perfect time to present this initiative. California was not a “battleground” state with Massachusetts Senator John Kerry easily ahead in polls there, resulting in a quiet electoral campaign in California with little national advertising and campaigning primarily focused on fundraising. Senator Barbara Boxer was also a comfortable favorite for re-election, so voter attention could be focused on the ballot issues rather than the candidates. The advocates for Prop 71 proved to be very adroit at raising campaign funds while the opposition was disorganized and poorly funded. The proponents of the initiative had a mammoth edge in resources (9). The pro-71 forces raised and spent about $37.5 million while the opposition was only able to gather less than $600,000. Over sixty individuals or groups contributed more than $25,000 each and at least ten donors each gave more than the total amount available to the opposition. The pro-71 campaign had television advertising and high level endorsements while the anti-71 viewpoint was nearly invisible. In a very large state like California where media access is a central part of political strategy, a funding advantage of these dimensions is usually impossible to overcome.

The campaign in favor of Prop 71 used a broad range of arguments to attract voters. It promised cures to a wide range of dreadful diseases; it envisioned a dynamic growing California that led the nation in research prowess and made its citizens proud; it claimed that the investments would be paid back from economic growth, savings in health care costs, and the state’s share of intellectual property; and it pointed to support from patients, scientists, and politicians. Both Senators Boxer and Dianne Feinstein endorsed the effort as did Democratic Lieutenant Governor Cruz Bustamonte. Republican Governor Arnold Schwarzenegger also endorsed the measure, albeit late in the campaign at a time when its passage already seemed assured. No statewide official opposed it and the opposition lacked any spokesperson with statewide recognition. Despite the large price tag which was expected to be the most difficult argument for the proponents to make, the issue of the cost never gathered traction.

November 2, 2004 was the first test of the appeal of stem cell research at the ballot box and it was a striking victory for Prop 71, the Stem Cell Research and Cures Act (10). It garnered more than 7 million favorable votes for a 2.1 million vote margin (59% to 41%). It ran ahead of Senator Kerry (54% to 44% for President Bush) and almost as well as the popular Senator Barbara Boxer. It is notable that some traditionally conservative areas swung in favor of Prop 71. San Diego County was carried by President Bush 53% to 46% for Senator Kerry but Prop 71 won with 58% of the vote; Riverside County went for Bush with 58% of the vote and for Prop 71 with 54%; and even the bedrock conservative Orange County endorsed Prop 71 with 52% of the vote while choosing Bush over Kerry 60% to 39%. Clearly, stem cells had proven their ballot appeal, crossing partisan lines and appealing well beyond its core of activists. Now the challenge would be one of implementation.

## Proposition 71 In Action

The measure that the voters of California passed in 2004 was much more than a generous financial support of stem cell research. It was a major departure, perhaps even a paradigm shift, in how a publicly funded medical research program can be organized. The largest and most important precedent prior to Prop 71 is the world's biggest medical research program, the more than $30 billion U.S. National Institutes of Health (NIH)(11). To briefly summarize the NIH model, the NIH is part of the Department of Health & Human Services, so the policies of the Executive branch apply to the way in which NIH meets its research mission. Congress determines the annual NIH budget and the funding for the various Institutes and Centers within the NIH. Congress also determines the distribution of funding among these entities as its way of implementing national research priorities. Scientific priorities are determined by individual institutes with extensive consultation from advisory bodies of scientific experts along with some input from patient advocates. Individual applications for research support are subject to peer review by scientific panels with expertise in the discipline. Occasionally Congress seeks to influence these decisions by ruling out funding for an area of research or even for a specific grant proposal.

Thus, NIH is governed by two very different mechanisms – scientific peer review and political (i.e., Congressional and Executive) prioritization. The California formula is quite different, undoubtedly in response to the various political pressures that are brought to bear on NIH, the most obvious of which is the restrictions on stem cell research.

Prop 71 was structured as both a bond proposal and an amendment to the California State Constitution. This structure provides considerable legal protection for its unique approach to science. Prop 71 amended the California Constitution to "establish a right to conduct stem cell research which includes research involving adult stem cells, cord blood stem cells, pluripotent stem cells, and/or progenitor cells." The right to do stem cell research (including SCNT) and the prohibition on reproductive cloning were made law in California in 2002. but the incorporation of these matters into the state constitution would put them out of easy reach of legislative change and manipulation. The measure authorized $3 billion in bonds to fund stem cell research and facilities in California. In contrast to federal programs, the amount of money available for this program is known in advance over a significant time frame thus allowing multi-year commitments without necessarily cutting into new grants.

Long range planning is possible for California while this has never been a feature of the federal biomedical research program.

Prop 71 amended the state constitution to create a new state agency, the California Institute for Regenerative Medicine (CIRM)(12). This agency is authorized to make grants and loans for stem cell research and facilities and to establish related regulatory standards and oversight bodies. Detailed statutory language sets out the mission and governance of CIRM, including funding priorities. The measure specifically prohibits modification by initiative or legislation for three years to make sure that the priorities remained intact. In contrast to the federal approach and its emphasis on what cannot be funded, Prop 71 specifically states its funding priorities and what should be supported.

An important and interesting aspect of Prop 71 is its governance. The measure created an "Independent Citizens Oversight Committee" (ICOC) to govern CIRM. The ICOC is charged with creating the processes and standards for spending the bond proceeds, choosing the expert advisory groups, and making the final decisions as to what proposals to fund. The membership of this twenty-nine-member governing body is described in detail in the Proposition and creates a board where the coalition of patient advocates and scientists that nurtured this effort reap the reward of choosing its directions and overseeing its operations. In sharp contrast to NIH, where the oversight is provided by political bodies (the Department of HHS and Congress), CIRM is firmly in the hands of the scientists and patients. ICOC actions must adhere to California public agency rules and regulations such as open meeting laws and processes for rule making, but the ICOC does not need to get permission from the Legislature or the Governor to implement any assigned task or to expend funds. This governance structure reflects a deep distrust of government interference, fearing that a more traditional structure would be susceptible to political whims and pressures. Allowing the patient advocates and the scientific community to lead the program was seen as a means of protecting its goals. The most significant influence of the state government is in choosing the membership of the ICOC, but even that responsibility is carefully defined and constrained in the measure.

The CIRM structure merits close examination as it was both a new direction in science policy and an important influence on subsequent state programs in Connecticut, Maryland, New York, and elsewhere. The twenty-nine members of the California ICOC are chosen by designated state constitutional officers with the exception of the Chancellors of the five University of California campuses with medical schools (San Francisco, Los Angeles, Davis, San Diego and Irvine). These Chancellors choose an Executive Officer from each of their campuses for eight-year terms. Four representatives of other California universities are to be named for six-year terms by statewide elected officials (i.e., the Governor, Lt. Governor, Treasurer and Controller) acting independently. Criteria for choosing the institutions besides the University of California are specifically delineated and include the size of the research portfolio and the number of research or clinical faculty who are members of the National Academy of Sciences.

These criteria guaranteed that the institutions represented are among the other important research universities in California and not parochial institutions that may have strong

opposition to stem cell research primarily because of their religious orientations. The Bush administration's appointment of several individuals who had strong religious affiliations to scientific or medical advisory bodies caused the Prop 71 drafters to fear what might be done through an appointment process where a politician had sole discretion for choosing candidates. Thus, highly restrictive language that really allowed only the remaining campuses of the University of California and three other institutions to qualify was included in Prop 71. Given these criteria, representatives of UC Berkeley, Stanford University, the University of Southern California, and the California Institute of Technology were predictably named. These nine research university representatives on CIRM have typically been the dean of the medical school or a campus wide research official.

The same four statewide elected officials that appoint representatives from California universities also get to appoint four representatives of nonprofit research institutes to six-year terms. These representatives have come from institutions such as the Salk Institute, the Burnham Institute, Cedars-Sinai Medical Center, and the City of Hope. Thus, a total of thirteen of the twenty-nine ICOC positions are reserved for leaders of the academic scientific community, although none for stem cell scientists per se. The four elected officials also choose representatives of four California commercial entities involved in the life sciences, although companies actually doing stem cell research are excluded. These representatives have generally been from biotechnology-pharmaceutical firms or from healthcare investment companies.

A central feature of the ICOC is that twelve members, including the Chair and Vice-Chair, must come from various disease advocacy organizations. Once again, the role of elected officials is to choose from a list specified in the initiative to include spinal cord injury, Alzheimer's disease, types I and II diabetes, multiple sclerosis or amyotrophic lateral sclerosis, heart disease, cancer, Parkinson's disease, mental health, and HIV/AIDS. Ten disease advocate representatives are appointed for eight-year terms by specified California officials (the Governor, Lieutenant Governor, Treasurer, Controller, the Speaker of the Assembly and the President pro Tempore of the Senate). The Chair and Vice Chair are elected by the ICOC from candidates nominated by each constitutional officer, and serve six-year terms. Several of the disease advocates are also academics, thus reinforcing the ruling alliance. CIRM operations are run by a small professional staff headed by a President, currently stem cell scientist and biotechnology entrepreneur, C. Randal Mills.

The ICOC appoints several "working groups" for advice on scientific, ethical, and facilities issues. Each of these working groups includes a specified number of ICOC members, the ICOC Chair, and external experts. The Scientific and Medical Research Funding Group handles the core responsibility of scientific peer review. Using eminent external experts from outside California to imbue the process with credibility, this group does the crucial job of sorting through the applications to find those that are scientifically most meritorious and hold the most promise for medical application. Final approval authority rests with the ICOC. Like NIH Councils, the ICOC will make sure that the funding is not too narrowly focused and that the mission of CIRM is reflected in what is funded. The eleven-member Scientific and Medical Facilities Working Group makes recommendations to the ICOC on grant or loan proposals involving buildings, building leases and capital equipment. In these areas, the

California approach is similar to the NIH or to other granting agencies. The ICOC also developed detailed conflict of interest and intellectual property policies. These were areas ripe for contention and it took considerable effort to hammer out a workable set of regulations that are designed to promote the scientific progress and promoting commercialization of significant developments. Nevertheless, the most embarrassing area for CIRM has been conflict of interest. The governance structure has been criticized as inherently flawed, as scientists on the governing board review each other's institutions, although they are excluded from voting on applications from their own institution (13). The most acute case of apparent conflict of interest was when a former President of CIRM took a seat on the Board of Directors of a biotechnology firm that had been the recipient of funding from CIRM (14).

Probably the most interesting departure from other granting agency approaches is the ethical framework for research on human embryonic stem cells that was developed as state regulations through The Scientific and Medical Accountability Standards Working Group. A group of ICOC patient advocate members and external ethicists and scientists wrestled with the problem of devising a set of standards to govern complex and potentially contentious areas such as oocyte donation, informed consent procedures for blastocyst donation, the role of the IRBs, the use of human stem cells in animals, and stem cell clinical trials policy. The starting point for their work was the useful and influential set of ethical guidelines promulgated by the National Academy of Sciences (15) which served as the CIRM interim guidelines until CIRM finalized its own standards. The CIRM Standards working group consulted widely in creating its standards, both within its formal meeting structure and through meetings sponsored by interested parties such as the University of California. A set of regulations was issued by CIRM that are now California state policy and serve as a detailed and comprehensive manual for human stem cell research (16). Institutions that seek funding through the CIRM mechanism must adhere to those regulations. The central oversight responsibility is devolved upon the institution where the research takes place. As suggested initially by the National Academy, a standing oversight committee (Stem Cell Research Oversight (SCRO)) must exist in any applicant institutions. Each institutional SCRO reviews human stem cell proposals and determines if they meet the CIRM standards, if the experiment is scientifically worthwhile, and if the experiments pose ethical problems. The high visibility of this area of research generates passionate opposition. Furthermore, just as the SCRO processes were being worked out the public scandals of fraudulent experimentation and fabricated claims arose in the Korean stem cell program. It became clear that it was in everyone's best interest to have ESC research programs thoroughly scrutinized before and during their performance. It has been reported that Harvard stem cell scientist Douglas Melton's proposal to do somatic cell nuclear transfer was reviewed by eight separate committees (17). The California model is no less thorough and the CIRM standards, along with other obligatory oversight reviews such as IRB for human subject protection, constitute a multi-layered oversight process that has been consistently implemented throughout the state. Most ESC experiments were not eligible for federal support until 2009 when the NIH developed a thorough review process to allow for the use of NIH funds for additional human embryo derived stem cell lines (discussed below).

In summary, the passage of Prop 71 by the California electorate resulted in a novel governmental agency dedicated to stem cell research. Unlike other public agencies, CIRM operates on the basis of only one detailed piece of legislation, the Stem Cell Research and Cures Act of 2004. It differs from almost any other governmental granting agency as its governance is firmly in the hands of the patient advocates and their scientific allies. The governing board of the CIRM was cleverly named the Independent Citizens Oversight Committee, and it is a citizen governance board in the sense that most ICOC members are not professional politicians (the current Vice-Chair of the ICOC, former State Senator Art Torres, is a notable exception). But the reality is that the electorate chose to trust a mechanism of letting those with a stake in the success of medical research, the patients and the academic leaders, run the research program in a way that is well insulated from political pressure. There have been some tensions between the patient advocates and the scientists on the ICOC such as the issue of how to proceed with funding for facilities (18), but, in general, the alliance has remained intact and effective in guiding the California stem cell program. The concept of peer review as the centerpiece of science policy is not new with Prop 71. It has been a key feature of American science since Vannevar Bush's contributions during and after World War II (19). Episodes of governmental intrusion into scientific issues during the G.W. Bush Administration made this new formulation of peer review look attractive and California voters vigorously endorsed this experiment.

## Stem cells and the California courts

CIRM is an innovative means to manage a public medical research program, and its innovative nature soon became the target of litigation. Shortly after its victory at the polls, Prop 71 was challenged in the courts. Several different suits were filed by organizations involved in "right to life" politics basing their objections on issues ranging from legal technicalities to claims to act in defense of unborn lives. The various actions were eventually consolidated into one suit known as *People's Advocate v. Indep. Citizens' Oversight Comm.*, 2006 WL 1417983 (Cal. Super. Ct., May, 12, 2006). The argument that became the centerpiece of the litigation was not the liberation of frozen embryos or any other headline grabber. Instead, the fate of CIRM hinged on whether or not it was a legitimate state agency subject to state oversight.

The argument that the Stem Cell Research and Cures Act was unconstitutional faced a formidable challenge, since the Proposition itself was an amendment to the California Constitution. Furthermore, the courts in California have been very reluctant to overturn referenda approved by the voters. The opponents tried to prove that CIRM and its governing body were acting in a manner substantially different than any other state agency, as illustrated by the fact that CIRM had its appropriation for ten years while all other state agencies were funded annually by the Legislature.

On May 12, 2006, Alameda County Superior Court Judge Bonnie Lewman Sabraw ruled that Prop 71 was constitutional in its entirety (20). The Judge pointed out the many ways in which CIRM and its officers functioned much like any other state agency and the strict adherence of CIRM and the ICOC to open meeting requirements, audit policy, and other requirements. Judge Sabraw's ruling was affirmed by the California Court of Appeal in *Cal.*

*Family Bioethics Council v. Cal. Inst. for Regenerative Med.*, 147 Cal. App. 4th 1319 (Cal. Ct. App. 2007) and with the refusal of the State Supreme Court to hear a further appeal, the matter was finally settled in favor of CIRM.

Frustration levels rose among scientists and patients during the year and a half that elapsed between the approval of Prop 71 at the polls and the court decision. The bonds could not be sold until the legality of the program was established, so CIRM proceeded on a small budget that precluded funding any research. However, this was not entirely wasted time. This new agency had much to do, and this period allowed it to organize itself in a thoughtful and considered way. A headquarters was established in San Francisco, a staff including the President was hired, the working groups were appointed, hearings were held all across the state on important issues related to stem cell policy, and essential policies were hammered out. It is hard to imagine how CIRM would have developed its intellectual property policy, its conflict of interest policy, its grants program, and its ethical standards if it had to start issuing grants nearly immediately as originally planned. It was also a period of intense planning among potential recipient institutions. New faculty were recruited, space was reconfigured, collaborations were developed and donors were cultivated. Major gifts were obtained by several institutions and the vision of California as the center of the stem cell scientific universe was beginning to become real. Upon Judge Sabraw's ruling that Prop. 71 was constitutional, Governor Schwarzenegger moved to get the entire CIRM program in high gear without having to wait for the appeals process to be completed. The Governor arranged for $150 million of state funds to be loaned to CIRM so that almost half its planned first year program could be implemented and California was back on track as the place to be doing human embryonic stem cell research in the United States.

## Other states join the stem cell revolution

Several other states besides California moved to develop state sanctioned or state supported stem cell research programs (21). Between 2002 and 2006 five states passed legislation in support of stem cell research led by New Jersey, the first state to provide legal safeguards for embryonic stem cell research. New Jersey and California were followed in rapid succession by Massachusetts, Connecticut, Maryland, and Missouri. All designed their programs along similar lines. The foundational concepts of the legislation in each of these states is a prohibition on reproductive cloning along with a guaranteed right to do stem cell research, including somatic cell nuclear transfer. Varying amounts of funding in several different configurations are then dedicated to these research efforts. In general, states have opted either for a peer review process of investigator- initiated applications (California, Connecticut, Maryland, New York, and Illinois) or allocations made directly to state institutions (New Jersey and Massachusetts).

Several characteristics are in common among the permissive stem cell states besides coastal geography. All these states have large research universities and active biotechnology industries and would expect to benefit economically from the successful growth of this technology. New Jersey has the added incentives of being the center of the pharmaceutical industry in the United States and its universities are often in competition with neighboring

New York for scientific talent. Funding dedicated to an area of research that would not be otherwise available was seen as a real competitive advantage.

There are also some political features in common among these states. At the time of legislative passage, the legislatures in all these states were controlled by the Democratic Party and all except New Jersey had Republican governors. This could be taken as a measure of the bi-partisan support for stem cell research, although the level of gubernatorial enthusiasm was quite variable. Governor Jodie Rell was an advocate for the Connecticut measure, while in neighboring Massachusetts the legislation was passed over the veto of then Governor Mitt Romney who objected to the provisions protecting SCNT.

State funding of embryonic stem cell research has been at varying levels using a variety of mechanisms. Even before the passage of Prop 71 in California, New Jersey enacted supportive stem cell legislation, but major funding for the New Jersey program was only decided upon in 2006 (22). Although the format of the New Jersey legislation follows the familiar pattern of linking prohibition of reproductive cloning with legalization of embryonic stem cell research including SCNT, the funding was handled in a manner distinct from the other supportive states. Recognizing the need for facilities imposed in part by the federal restrictions on funding, the New Jersey approach dedicated $270 million in bond funding to the creation of new stem cell research facilities at the Stem Cell Institute at Rutgers University ($150 million), the New Jersey Institute of Technology ($50 million), a consortium of programs centered at Rutgers-Camden ($50 million), and $10 million each for two smaller projects including a cord blood stem cell program. An investigator-initiated grants program of $5 million was undertaken in 2005. The focus on facilities in New Jersey, while not unique (California also dedicated a major portion of its funds to facilities), was designed to provide a strong foundation for building a long lived program in that state. However, that plan suffered a major setback on November 6, 2007 when Public Question No. 2, a ballot proposition for $450 million in bonds for stem cell research, was defeated by a little more than 73,000 votes out of 1.3 million votes cast (23). This was a low turnout off-year election and much of the interest focused on Question No. 2, a plan devised by Governor James McGreevey before he resigned and subsequently advocated by Governor Corzine. It turned out to be an ill-timed effort in a state with a burgeoning state debt problem. The rough and tumble of New Jersey politics as applied to stem cell politics was well summarized in a perceptive and thorough analysis by Meredith Wadman for Nature magazine (24). In contrast to California, where stem cell proponents had a huge funding advantage, the opposition to New Jersey’s bond proposal was well financed and had an effective media campaign while Governor Corzine was dependent on his personal financial contributions and a few other major donors to fund a very modest media effort. The opposition resources came from New Jersey Right to Life and from unnamed donors to Americans for Prosperity, a political action committee identified with the publicity shy but politically active Koch brothers of Koch Industries (25). Although the New Jersey proponents of stem cell research pledged another electoral effort following their narrow defeat, none has yet materialized. As of this writing, the New Jersey 2007 campaign is the sole instance of a state stem cell program being defeated at the ballot box.

Massachusetts, like the 2006 New Jersey program, focused on making the state a receptive environment for academic and biotechnology investigators. The initial legislation in Massachusetts did not include new funding, but instead was designed to clarify the legality of stem cell research as Massachusetts law had been quite murky prior to the passage of S.B. 2039. Private funding sources flocked to support stem cell research at Harvard University and the General Court of the Commonwealth of Massachusetts (the state legislature) moved in 2006 to support its public university with a $2.5 million allocation to the University of Massachusetts in Worcester, once again overriding the veto of Governor Romney (26).

Connecticut and Maryland adopted the California approach of creating a peer review process to allocate state stem cell funding. Connecticut's program started in June 2005 with the passage of Public Act 05-149, "An Act Permitting Stem Cell Research and Banning the Cloning of Human Being" (27). The Connecticut stem cell research program is administered by the Connecticut State Department of Public Health via two committees, an Advisory Committee (chaired by the Commissioner of the Connecticut Department of Public Health) and a Peer Review Committee. The Advisory Committee is similar to California's ICOC and consists of scientists, ethicists, and public members appointed by elected officials. The Committee is to provide broad oversight of the program, to encourage and integrate philanthropic support for the program, and to promote the development of a biotechnology industry in the state. A Peer Review Committee of five eminent out-of-state stem cell scientists reviews scientific proposals. The program was initiated with a $20 million allocation and $10 million per year from tobacco settlement funds guaranteed through the year 2015.

Maryland entered the stem cell club with its Maryland Stem Cell Research Act of 2006 (S.B. 144)(28). Once again, this legislation linked prohibition of reproductive cloning with a guaranteed right to do stem cell research including somatic cell nuclear transfer. The initial funding was for $15 million and eighty-nine letters of intent were received from Maryland scientists, indicating a robust demand for research support. The Maryland structure is similar to the California and Connecticut models, featuring an independent state commission within the Maryland Technology Development Commission and peer review of investigator initiated scientific proposals. The Maryland Stem Cell Research Commission once again features the alliance of scientists and patient advocates that was pioneered in California. The fifteen-person Commission has designated slots for scientists, patient advocates, biotechnology experts, and ethicists, with appointment power given to the Governor, various other elected state officials, and the state's two research universities. The ethics category includes an unusual and potentially controversial provision. Along with two bioethicists to be chosen by the University of Maryland and Johns Hopkins University, are "Two individuals with expertise in the field of biomedical ethics as it relates to religion, appointed by the Governor." It is undeniable that many of the ethical issues regarding stem cells are rooted in religious thought, but to entrust oversight of a state program to a commission that includes those with a required expertise in religious ethics treads very close to violating the "establishment" clause of the US Constitution. This concern was the basis for some distress within scientific circles although thus far the Maryland program has not been challenged in the courts.

Another California-style ESC program started in New York in fiscal year 2008. A new state agency, the Empire State Stem Cell Board, administers this important program which both mimics and competes with the California effort. It started with an appropriation of $100 million for its first year and is guaranteed at least $50 million annually for ten years. Reproductive cloning is to be prohibited without other research restrictions (29). The Empire State Stem Cell Board did stray from the usual patterns by becoming the first state to authorize monetary compensation from public funds for the donation of human oocytes donated solely for research purposes (30). The lack of voluntary altruistic donors of human eggs for research studies when young women are routinely well compensated for their donation for clinical purposes has prompted much discussion of the practicalities of SCNT and other studies using oocytes. New York is unique in addressing this issue via compensation of donors. California tried to go this route and passed legislation in 2013 to compensate human oocyte donors, but Governor Brown vetoed it (31).

There are several states that have supported stem cell research without benefit of legislation through initiatives by the state's governor. For example, in Illinois then Governor Rod Blagojevich bypassed an impasse in the state legislature by issuing Executive Order Number 6 on July 12, 2005 creating an Illinois Regenerative Institute for Stem Cell Research (32). Wisconsin Governor Jim Doyle was an ardent and outspoken advocate for stem cell research, pointing with pride that human embryonic stem cells were first identified at the University of Wisconsin. However, the Wisconsin legislature was much less enthusiastic and at times overtly hostile towards stem cell research. Legislation prohibiting SCNT was passed by the Legislature in 2005 but vetoed by the Governor. Since gubernatorial programs may not last beyond the term of the governor and these states lack permanent legislation, they will not be further considered here.

Missouri was the second state after California to directly test the use of embryonic stem cells at the polls. The election battle of November 2006 over the "Missouri Stem Cell Research and Cures Initiative" was widely seen as an important test of the breadth of appeal of stem cells. Could the formula that was successful in liberal coastal California also work in mid-western and southern border swing state Missouri? The device used, an initiative known as Amendment 2, is a straightforward legal protection for stem cell research (33). Consistent with the other states that support stem cell research, the initiative includes prohibitions on reproductive cloning, creation of blastocysts solely for research, and the sale of human embryos or eggs for research. There are also oversight and informed consent requirements. However, Amendment 2 does not allocate nor require any state appropriation for research.

Amendment 2 seemed to be a reprise of the California story, as scientists, patient advocates, and philanthropists rallied to it. However, several key differences are worth noting. The opposition to Amendment 2 in Missouri was well funded and ran a vigorous media campaign, focusing mostly on the fact that techniques such as SCNT are a potential step towards human cloning. Perhaps most importantly, Missouri in 2006 was the site of a hard fought and highly competitive U.S. Senate contest between Democrat Claire McCaskill and incumbent Republican Senator Jim Talent. Stem cell policy became a prominent part of the senatorial campaign making Amendment 2 a much more partisan issue than was Prop 71 in California. The end results were narrow victories for both McCaskill and Amendment 2 as

both won by about 50,000 votes out of 2.1 million cast (34). Some commentators felt that the association of stem cell research with partisan politics cost more votes for Amendment 2 than it gained for McCaskill (35). Even if that interpretation is correct, stem cell research again proved that is has appeal for voters even under adverse circumstances. However, Missouri stem cell policy remains the subject of continuing political and legal wrangling. The Missouri campaign is among the many stem cell topics thoughtfully analyzed in “Sin No More,” (36) by John Dombrink and Daniel Hillyard, a book about crime, law, and morality in American society. These authors pay close attention to the differences and similarities of stem cell politics to other morality-based political issues such as abortion.

Iowa joined the pro-stem cell states in 2007 when the state legislature repealed restrictive legislation (37). This simple expedient allowed scientists in Iowa to access philanthropic, federal, and state funding sources for research. Reproductive cloning remained off limits.

Finally, several states have attempted to ride the popularity of the stem cell issue while avoiding the contentious issues surrounding embryos and fetuses. Approaches that have been used include funding limited to adult stem cell research such as Virginia’s Christopher Reeve Stem Cell Research Fund. Another approach was the promotion of cord blood banks and registries (Florida, Tennessee, and Virginia). State policies regarding adult or cord blood stem cells will not be further considered here as they do not carve out any new policy directions nor do they encounter any conflicts with federal policy.

## States restricting stem cell research – the cloning issue

A number of states have approved legislation restricting some aspects of stem cell research (21). These restrictions fall into three major groups:

- States with legislation prohibiting human reproductive cloning
- States with legislation regarding cloning that includes research
- States with legislation regarding research on embryos or fetuses that may affect the performance of stem cell research.

Cloning is a pervasive and potent issue in stem cell policy development. It can be argued that cloning is an irrelevant issue, as human reproductive cloning is scientifically distant at best. There is no significant group pushing for reproductive cloning for medical or other reasons. The scientific community has universally condemned it (38). The rare advocates of cloning are at the fringes of medical science and are highly unlikely to be able to accomplish this very technically challenging feat. Perhaps most importantly, the U.S. Food and Drug Administration (FDA) asserted regulatory authority over human reproductive cloning and is in a position to make it impossible (39). Yet the debate about cloning continues. It is possible that the specter of asexually produced cloned humans is sufficiently appalling that policy makers feel compelled to legislate against it no matter how unlikely it may be. Alternatively, cloning may be seen as a weak link in the argument for embryonic stem cell research and a convenient way to prevent the further development of ESC technology. “Loan to clone” was an effective campaign tagline in the defeat of bond funding in New Jersey in

2007. Whatever the motivations, cloning remains one of the most contentious aspects of stem cell policy.

One group of states prohibited human reproductive cloning without otherwise limiting stem cell research. This group includes California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York, Missouri, and Rhode Island. The latter passed legislation to prohibit reproductive cloning without venturing further into the stem cell issues while all the rest are states that have encouraged embryonic stem cell research. Attempts at reproductive cloning are subject to a range of civil and/or criminal penalties.

Another group of states banned human cloning with a comprehensive ban on SCNT technology by a prohibition on the creation of cloned embryos. This is the same approach advocated in legislation passed in 2003 and 2004 in the U.S. House of Representatives but which has died in the U.S. Senate (5). These states include Arkansas, Arizona (public funds only), Indiana, Louisiana (public funds only), Montana, North Dakota, and Virginia. The language of the Virginia legislation intended to prohibit reproductive cloning is ambiguous as to what constitutes a ‘human being’ and probably excludes SCNT with human cells as well. The penalties for violating these laws are generally quite severe, often up to ten years in prison and large fines. From a policy perspective, this is an unusual and perhaps even radical approach to science policy. Instead of dealing with an undesirable outcome (cloned people), this approach criminalizes certain laboratory procedures even if they are not designed to promote that outcome. Instead of the regulatory approach of the FDA which has been a central feature of new biotherapies such as gene therapy, we have criminalization of an entire area of investigation before the field has even developed. There is no obvious parallel to this approach in other areas of American science. Could physics have developed in this country if experiments with high energy particles were prohibited out of concern that new weapons might be developed?

During his 2006 State of the Union, President Bush urged Congress to pass legislation prohibiting the creation of human-animal hybrids (40). However, Congress failed to respond until then Senator Sam Brownback (R-KS) proposed the Human-Animal Hybrid Prohibition Act of 2009 (S. 1435). The bill never made it out of the Senate Judiciary Committee (41). Despite the lack of federal legislation on this issue, Arizona, Lousiana, and Ohio enacted their own state legislation. Similar bills were also introduced in Georgia and Mississippi but went nowhere.

## States restricting various aspects of stem cell research other than cloning

Cloning may dominate the debate, but there are other policy issues of importance relating to stem cells and these have played out in various ways among the states (21). One approach which is consistent with many aspects of American science policy is to restrict the use of public funds while leaving private funding unaffected. For example, Nebraska and Indiana prohibit the use of state money for human cloning including research using cloning technology. Arizona and Lousiana also banned the use of state money for SCNT and went a step further by denying a state tax credit to firms doing stem cell research.

The most common area for state legislation has been restrictions on the sale or transfer of embryos, fetuses, or their products for research. As of 2015, twenty-five states had some sort of regulation banning the sale for research of either embryos, fetuses, or both. (21) As voluntary and altruistic donation of human derived materials is the norm in stem cell research, such restrictions would seem to be reasonable public policy that should not be a significant deterrent to embryonic stem cell research. However, recent incidents indicate that some anti-abortion activists see the donation of fetal materials for medical research as a means of targeting abortion providers (42).

There are several states that have developed highly restrictive policies that would preclude many types of experiments that are central to current stem cell research. These statutes fall into two general types: (1) the laws that are aimed at discouraging the research use of abortions, and (2) laws designed to preclude the research use of pre-implantation embryos. The anti-abortion-type restriction is the law in sixteen states, including some states that are otherwise supportive of research. These laws might possibly impede studies of fetal stem cells depending on the exact wording and enforcement in each state. To the degree that such laws preclude fetal stem cells as objects of study, stem cell research will be set back.

The situation with regard to embryos is much more complicated with a variety of approaches in use. Most states have regulations of embryos on the books, but not all of them will significantly affect stem cell research. Many of these laws are aimed at IVF practices or “designer baby” research and will not affect stem cell research under current circumstances. Then there are the states discussed above that aim their restrictions at cloning by prohibiting research on cloned embryos (as distinguished from the prohibitions on actual reproductive cloning.) Laws against doing research on cloned embryos clearly preclude SCNT from being done in laboratories in those states, although all other elements of stem cell research appear safe.

This leaves several states with criminal penalties for stem cell research activities that would be permitted in other states – Louisiana, South Dakota, North Dakota, Ohio, and Oklahoma. Louisiana legislation is complex with laws being superseded by similar legislation at various times. The legislation of 1986 focused on IVF embryos stating, “The use of a human ovum fertilized in vitro is solely for the support and contribution of the complete development of human in utero implantation. No in vitro fertilized human ovum will be farmed or cultured solely for research purposes or any other purposes.” (43). The legislation goes on to define a human embryo as, “…an in vitro fertilized human ovum, with certain rights granted by law, composed of one or more living human cells and human genetic material so unified and organized that it will develop in utero into an unborn child.” This legislation leaves no room for stem cell research or even research on birth defects or better methods of IVF. However, other legislation (44) placed this research into a broader context of prohibition of non-consented human experimentation, which specifically prohibits, “…the conduct, on a human embryo or fetus in utero, of any experimentation or study except to preserve the life or improve the health of the human embryo or fetus.” With a penalty of “not less than five years and not more than twenty years” at hard labor, Louisiana is not a hospitable place for stem cell investigators.

South Dakota is similarly comprehensive in its approach, prohibiting any and all research on a living fetus or embryo (45). The legislation that would affect stem cell research simply states, “Research that destroys human embryo prohibited—Violation as misdemeanor. No person may knowingly conduct nontherapeutic research that destroys a human embryo. A violation of this section is a Class 1 misdemeanor.” Later in the same section an embryo is defined as “…a living organism of the species Homo sapiens at the earliest stages of development (including the single-celled stage) that is not located in a woman’s body.” Class 1 misdemeanors in South Dakota are punishable by one year imprisonment and/or a $2000 fine. (46). These few words effectively place scientists at South Dakota academic institutions or commercial ventures outside the stem cell world.

North Dakota legislation states “A person may not use a fetus or fetal organs or tissue resulting from an induced abortion in animal or human research, experimentation, or study, or for animal or human transplantation except for diagnostic or remedial procedures, the purpose of which is to determine the life or health of the fetus or to preserve the life or health of the fetus or mother, or pathological study.” (47). Again, this clearly leaves no room for stem cell research. A violation of this section constitutes a Class C felony, which is punishable by five years of imprisonment and/or up to $5000 in fines (48).

Ohio prohibits any “experiment upon … the product of human conception which is aborted.” (49). While there is one exception for autopsies, this clearly falls outside of stem cell research. Violators of this statute are subject to being charged with a first degree misdemeanor, which carries with it a penalty of 180 days in jail and/or up to $1000 in fines. (50).

Lastly, Oklahoma laws state “No person shall experiment upon a child or an unborn child resulting from an abortion or which is intended to be aborted unless the experimentation is therapeutic to the child or unborn child. No person shall experiment upon the remains of a child or an unborn child resulting from an abortion.” (51). Violations of this law constitute a felony, which is punishable by with up to two years of imprisonment and/or up to $1000 in fines (52).

## Developments since the 2008 election

The election of President Obama was the most important event in the stem cell world in 2008, but it was not the only victory for stem cell advocates. Once again, permissive stem cell legislation was victorious at the ballot box with the passage of the Michigan Stem Cell Amendment, Proposal 2 by a margin of 53% to 47% (53). This legislation was similar to the approaches in other mid-western states such as Iowa and Missouri in that it stated the legality of stem cell research, allowed access to federal and state funding while not appropriating any funds, and continued the ban on reproductive cloning. The Michigan result showed that stem cells continued to resonate with the voters if the issues were well defined and the financial burdens small.

Nationally, the election of President Obama allowed an opportunity for the reversal of the restrictions of the previous administration. As Congress twice had passed legislation with

strong bi-partisan support to remove the Bush limitations on the use of stem cell lines, it must have been tempting to try to use a legislative solution to this problem. However, the legislative agenda of the early days of the Obama Administration was focused on economic recovery issues and waiting for federal stem cell legislation would have excluded this line of investigation from the new increases in the NIH budget. On March 11, 2009, President Obama issued Executive Order 13505 (54) which revoked the Bush policy that started on August 9, 2001 and instead instructed NIH to develop procedures to accept other ethically derived embryonic cell lines into a national registry eligible for federal research funds. NIH has established clear guidelines (55) using the commonly identified criteria for ethical derivation. The NIH Registry (56) of March, 2016, listed 362 cell lines eligible for federal funding (as compared to twenty-one during the Bush Administration) and another forty-one lines were pending review. This is generally perceived in the scientific community as a reasonable sampling of the genetic diversity of our species. Notably, sixty-five lines were rejected in this process, indicating the stringent ethical criteria used for inclusion. During the Obama Administration, stem cell research grants were awarded, ESC research began in several laboratories at the NIH itself, and a national ESC program began to grow.

The national stem cell program was surprisingly diverted on August 23, 2010 by an injunction issued by Judge Royce Lamberth of the U.S. District Court for the District of Columbia. (57). Judge Lamberth found a conflict between the Obama Executive Order and the Congressional intent in the “Dickey-Wicker” Amendment and issued an injunction staying the NIH from any new support of embryonic stem cell research. On appeal, however, the U.S. Court of Appeals for the District of Columbia Circuit vacated the lower courts decision (58). The U.S. Supreme Court denied certiorari, thus validating President Obama’s stem cell policies.

## Current Federal Legislation on Stem Cell Research

Today, fetal and embryonic stem cell research is regulated on the federal level through a patchwork of various regulations and statutes. A few months after the first basic regulations of governing the protection of human subjects involved in research were published in 1974, the National Research Act was signed into law. This Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was tasked with “investigat[ing] and study[ing] the nature and extent of research involving the living human fetus and to recommend to the Secretary the circumstances (if any) under which such research should be conducted or supported by the Department [of Health Education and Welfare].” The Commission issued its report a year later (59), which led to the adoption of several regulations that same year. The regulations—which are still applicable today—apply to “all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services.” 45 C.F.R. § 46.201.

These regulations focus on research with pregnant women that might affect the health of the fetus but also include a prohibition on inducements, monetary or otherwise, that might offered to terminate pregnancy. Researchers must not take part in the decision making of the pregnancy (i.e., timing, method, procedure), nor can they have any part in determining the

viability of a neonate. 45 C.F.R. §46.201. Despite the establishment of firm regulations enabling fetal research, political turbulence resulted in a moratorium on ESC research from 1988 to 1993.

Following the conclusion of the moratorium on fetal research, President Clinton signed into law the National Institutes of Health Revitalization Act of 1993. This Act largely restated several aspects already contained in the laws and regulations at the time. Notably, however, the Act created more robust requirements on informed consent. First, the women providing human tissue must provide a written and signed statement affirming that: she is donating tissue for the research of "therapeutic purposes"; the donation is made without any restrictions on potential recipients of the tissue; and she had not been informed the identity of any potential recipients. 42 U.S.C. § 289g-1(b). Second, the physician must provide a separate written and signed statement affirming that: in the case of induced abortions, consent for the abortion was obtained prior to obtaining consent for tissue donation, the physician did not alter the abortion process, and the abortion was performed in accordance with state law; the tissue is being provided for research of "therapeutic purposes"; full disclosure has been provided to the donor regarding the physician's interest, if any, and medical and privacy risks. Lastly, the recipient must provide a written and signed statement declaring: the recipient is aware the tissue is human fetal tissue, how it was obtained, and that it was donated for research purposes; the recipient has provided such information to others with research responsibilities; the recipient will require recipients to provide written acknowledgment of receipt of such information; the recipient had no part in any decisions relating to the termination of the pregnancy.

Aside from increased requirements on informed consent, the Act required that all research on human fetal tissue be in accordance with applicable state and local laws. Also, the Act continued to prohibit the exchange of "valuable consideration" for human fetal tissue; however, it allowed for "reasonable payments" associated with the processing of such tissue, such as transportation, implantation, and storage." 45 U.S.C. § 289g-2(e)(3). Finally, the Act implemented criminal penalties for violations of the Act, thus allowing fines of up to $500,000 and/or up to ten years in prison." 45 U.S.C. § 289g-2(d).

The Fetus Farming Prohibition Act of 2006 provided two additional provisions to the existing regulations at the time. First, it made it unlawful for any person or entity involved in interstate commerce to "solicit or knowingly acquire, receive, or accept a donation of human fetal tissue knowing that a human pregnancy was deliberately initiated to provide such tissue." 45 U.S.C. § 289g-2(c)(1). It also made it unlawful to "knowingly acquire, receive, or accept tissue or cells obtained from a human embryo or fetus that was gestated in the uterus of a nonhuman animal." 45 U.S.C. § 289g-2(c)(2).

The federal legal provisions regarding human fetuses and fetal cells make it clear that stem cell research using donated fetal cells is legal, so long as stringent donation procedures are followed. This does not preclude controversy, as anything that touches on abortion is likely to generate heated debate, but the pathway for American scientists to use fetal stem cells is clear.

## Lessons to be learned from America's patchwork stem cell policy

Stem cell policy is one area where Justice Brandeis's vision of the states as laboratories of social policy experimentation has come true. In the absence of a comprehensive national level stem cell policy, many states stepped in with experimental solutions that are diverse and sometimes diametrically opposed. There is an aphorism in laboratory science that not all experiments are successful but all experiments teach. In this case, the state variations on stem cell policy may be able to teach us much about the most desirable components of a future national policy.

The states that forged their own policies to promote stem cell research chose to include several features that may be of importance in the future. These state programs all function within well-defined limits and with considerable oversight. This shows that research can be conducted in areas complicated by religious and ethical concerns but policy makers (legislatures or electorates) feel comfortable venturing into these difficult areas when unambiguous ethical guidelines are established. Thus, the stem cell research states have clearly stated that reproductive cloning is unacceptable, that embryos should not be bought and sold, that donations of gametes or embryos must be made with fully informed consent and that oversight mechanisms should be in place to provide assurance that the program is delivering what it promised. One result is the flowering of SCRO (Stem Cell Research Oversight) committees as recommended by the National Academies of Science. This kind of regulatory oversight is familiar to academic settings with standing committees examining research on many issues such as human subject protection, animal use, biohazards, radiation exposure, and financial conflict of interest. Adding another oversight group to monitor embryonic stem cell research is likely to be more immediate and effective than is the distant and often unrealistic threat of police enforcement of criminal penalties for the performance of various types of experiments.

A second innovation of the states that have chosen to support stem cell research is a new paradigm for the administration of medical research funds. Instead of the federal model of a government agency controlled by the political process supplemented by advisory scientific expertise, the model used in California (and also Connecticut, Maryland, and New York) creates new administrative bodies that are heavily weighted towards scientists and patient advocates. There are some obvious advantages to this approach, as legislative bodies generally lack the expertise to allocate funding to the various research subspecialties but must respond to the pressure from constituents (primarily the patient advocates) to devote more resources to specific problems. Handing this responsibility to a coalition of scientists and patients would solve the dilemma for legislatures. On the other hand, it can be argued that this approach is an abdication of responsibility by the political sector. This is an important experiment and its results should be monitored carefully.

There are also lessons to be learned from the states that chose to restrict embryonic stem cell research. The restrictive states are obviously concerned with high profile issues such as abortion, cloning, commerce in embryos and donor consent. Although abortion is too large and divisive a political subject to solve solely for the sake of stem cell policy, the other issues are addressable. Convincing safeguards are necessary, especially regarding cloning,

that will satisfy concerned opponents while not hindering important scientific directions. That formula has yet to be found, but it is worth the search. One candidate policy is the familiar federal policy of prohibiting nothing but selectively funding only the most broadly acceptable research. One could envision compromises that would not criminalize SCNT but might leave that one type of experiment to private sources for funding. As it stands, a number states with great research universities are excluded from the forefront of the stem cell research arena because of the cloning issue and the chief victim is scientific progress.

Several states chose to prohibit a specific kind of experiment, i.e., research using “cloned” human embryos or SCNT. The unanswered question is how these states will deal with changes in technology that make such a specific prohibition obsolete by finding some alternative to SCNT? Induced pluripotent stem cells (iPS) derived from adult cells can obviate some of the controversy, but one could also use these cells to make gametes with all the attendant ethical issues that might entail. And how will a law enforcement agency distinguish between cloned embryos and other genetic manipulations of embryos? How we will deal with new “gene editing” techniques when they are combined with stem cell studies? Similarly, how will states that have banned any research that results in destruction of an embryo deal with alternatives such as the use of single blastomeres that do not necessarily result in the death of the embryo? The rapid rate of evolution of this technology is a strong argument for regulatory approaches that can adapt to changes in the scientific issues rather than legislative ones that prohibit specific experiments.

Even if American stem cell policy is fragmented and variable by state, one can ask if the collection of state experiments constitute an adequate collective stem cell research program? Are the investments being made in six to ten states sufficient? This has been addressed by some stem cell advocates and not surprisingly they concluded that even the major investments in California and other states are insufficient (60). But they only way to know if the stem cell program is sufficient is the way we know in other fields of medical research. When one has a national grants program it is a straight forward exercise to see how many good applications go unfunded. This measure cannot yet be applied to embryonic stem cell research in this country, although the large application numbers in the states that have initiated programs indicates that there are lots of good ideas in this exciting new field and that the scientific opportunities apparently exceed the resources. The states can experiment and point the way. Ultimately, the United States needs and deserves a coherent national stem cell program and policy.

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