



MEDICAL RESEARCH LAW & POLICY



REPORT

Reproduced with permission from Medical Research Law & Policy Report, 8 MRLR 253, 04/01/2009. Copyright © 2009 by The Bureau of National Affairs, Inc. (800-372-1033) <http://www.bna.com>

Stem Cell Research

On March 9, President Obama issued Executive Order 13505, rescinding the restrictive policy of the Bush administration on federal funding of human embryonic stem cell (“hESC”) research. President Bush’s policy, announced in August 2001 and spelled out in Executive Order 13454 issued in June 2007, allowed funding of hESC research by federal agencies such as the National Institutes of Health only with respect to a limited number of specified hESC lines already in existence. Executive Order 13505 lifts the Bush administration’s funding restriction, and announces that it will be the policy of the Obama administration to “expand NIH support for the exploration of human stem cell research.” The new policy represents a major change in the way hESC research will be funded and conducted in the United States. This article is a compilation of essays by BNA editorial advisory board members on the effects the new policy will have on various activities related to this promising but controversial field of study.

The Implications of Obama’s Executive Order on the Study of Embryonic Stem Cells

Administrative Implications for Research Institutions

By **Robert J. Kenney Jr., Esq.**
Hogan & Hartson LLP
Washington

President Obama’s order states that NIH may support and conduct “responsible, scientifically worthy human stem cell research, including human embryonic stem cell research, to the extent permitted

by law.” It directs the secretary of health and human services, through NIH, to issue new guidance on human stem cell research, based on “other widely recognized guidelines on human stem cell research, including provisions establishing appropriate safeguards.” The NIH guidance is to be issued within 120 days from the date of the order, or by July 7. The “widely recognized guidelines” to which the order refers almost surely include those published by the Institute of Medicine of the

National Academies and the International Society for Stem Cell Research.

It may be assumed that federal funding for hESC research will not actually become available until the NIH guidance on human stem cell research has been issued this summer. If grant applications for hESC research are not even invited or accepted until after that guidance is in place, the release of NIH hESC research funding may not occur until the end of 2009 or later. The NIH's acting deputy director has publicly stated that he anticipates that some of the new \$10 billion in NIH grant funding included in the federal government's stimulus legislation will be available for use under the new NIH hESC guidelines. In any case, there is little question that the president's executive order in fairly short order will result in very significant NIH support for hESC research. NIH is highly motivated to make that happen, as is the Obama administration.

Another consequence of the executive order, although less significant in the long run, will be felt immediately and will be warmly welcomed by research institutions engaged in hESC research. Since President Bush's stem cell policy was first announced, many research institutions have gone to enormous trouble and expense to segregate their hESC research activities (funded by nonfederal sources) from their federally funded research activities. They have done so out of a concern that any intermingling of federally funded research activity with their (nonfederally funded) hESC research might be viewed as a form of partial federal funding of hESC research, in violation of the Bush administration's policy. At some institutions, equipment purchased under federal grants has been specially marked to ensure that it is never used in hESC research, even though, in general, federal rules would clearly permit the institutions to use the equipment on nonfederal projects. A few institutions have gone so far as to create virtual hESC research institutes, walled off physically, administratively, and financially from other institutional research activity, including most importantly federal activity. Needless to say, these "firewalls" have resulted in a great amount of needless expense and inconvenience, and have adversely affected the quality of both the federal research and the hESC research. There appears to be no good reason now not to dismantle the firewalls that the Bush administration policy caused so many institutions to set up.

It is important to keep in mind, however, that the executive order authorizes federal support of hESC research only "to the extent permitted by law." The so-called Dickey-Wicker Amendment,¹ an annually enacted appropriations rider that prohibits HHS funding of research in which human embryos are created or destroyed, is still law. Most hESC research is performed using existing hESC lines, and does not involve the creation or destruction of human embryos. For hESC research that is covered by the Dickey-Wicker amendment, however, some of the kinds of firewalls described above might still be necessary. This may be a short-term issue, because there appears to be considerable support in Congress for enacting legislation that would do away with the Dickey-Wicker limitation.

¹ Omnibus Appropriations Act, 2009, Pub. L. No. 111-8, § 509, 123 Stat. 524 (2009).

The Propriety of Executive Branch Rulemaking Through Executive Orders²

By Robert Charrow, Esq.
Greenberg Traurig LLP
Washington

The hESC see-saw, where one administration through an executive order curtails funding for stem cell research and another administration's order rescinds that order, illustrates both the power and peril of issuing policy statements through executive orders.

That battle on what has been a politically contentious subject also brings to the fore a fundamental, yet unresolved, legal issue, namely, the propriety of Executive Branch lawmaking through executive orders, directives, and policy statements,³ and whether there is even such a thing as "presidential rulemaking." A strong argument can be made that Bush's policy statement and subsequent executive order were unconstitutional and that Obama's hESC order is valid to the extent that it rescinds the infirm EO, but invalid to the extent it requires the secretary to issue guidance in a manner inconsistent with the notice-and-comment requirements of the Administrative Procedure Act.

The authority to make laws rests exclusively with Congress. Congress can and has in various statutes delegated that authority, subject to certain constraints, to the heads of various agencies. However, an agency can issue a legislative rule only to the extent authorized by Congress. *See Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208 (1988); *United States v. Storer Broadcasting Co.*, 351 U.S. 192 (1952). Absent such congressional authorization, agencies lack rulemaking authority. With respect to domestic authority, the president, like agency heads, lacks independent rulemaking authority. Congress has rarely, if ever, delegated rulemaking authority to the president and absent such authority, the president is powerless to act.⁴

Thus, in *Youngstown Sheet & Tube Co. v. Sawyer*, 343 U.S. 579 (1952), the Supreme Court overturned President Truman's attempt through an executive order to seize most steel mills in the United States. In so holding, the court reasoned that since the seizure was not authorized by statute, it necessarily presupposed lawmaking by the president, but the president has no inde-

² The views expressed in this section are those of author and do not necessarily represent the views of Greenberg Traurig LLP or any of its clients.

³ There was a somewhat similar back-and-forth with regard to research involving fetal tissue from abortions. On April 15, 1988, the assistant secretary of health imposed a funding moratorium on such research. The moratorium, which many viewed as extralegal, was repealed by the National Institutes of Health Revitalization Act of 1993.

⁴ Nor can a president derive any solace from the Administrative Procedure Act ("APA") which regularized the processes by which executive branch agencies issue rules and adjudicate claims but does not authorize rulemaking. The courts have consistently held that while the Executive Office of the President may be an "agency" within the APA (*see* 5 U.S.C. § 551(1)), the Office of the President is not. *See Judicial Watch Inc. v. Dep't of Justice*, 365 F.3d 1108 n.1 (D.C. Cir. 2004); *In Re Cheney*, 334 F.3d 1096, 1113 n.1 (D.C. Cir. 2003) (Randolph, J., dissenting). Although this implies that none of the APA's restrictions, *e.g.*, notice and comment, would apply to the president, it also suggests that Congress has elected not to delegate rulemaking authority to the president.

pendent authority to make laws. Under *Youngstown*, President Bush's original policy statement and subsequent executive order were likely unconstitutional. The president has been given no statutory authority to tinker with federal funding of research and the constitution provides no help. Bush's executive order was, therefore, likely invalid although the issue is complex and open to significant debate.⁵ Given the apparent infirmity of Bush's executive order, it is somewhat surprising that no university or other research institution challenged the president's action. One has to wonder whether the research community has become too docile.

In contrast, Obama's recent executive order would be valid, but only to the extent it rescinded a previously invalid order. Obama's executive order appears to go beyond rescinding a prior unlawful order and as a result, it too may be constitutionally infirm. Specifically, the order directs the HHS secretary to issue "guidance" that is consistent with the order. However, to the extent that the guidance is really law, *e.g.*, limits agency discretion, it can only be issued as a "rule" following notice and comment rulemaking.⁶

Congressional Activity on hESC Research

By Robert E. Wanerman, Esq.
Epstein Becker & Green PC
Washington

Despite the executive order lifting federal restrictions on hESC research, it is still unclear whether any federal funds can be appropriated to support that research.

The problem lies in the language of the Dickey-Wicker Amendment, which has been a part of all federal appropriations bills since 1996, and most recently was incorporated into the Omnibus Appropriations Act of 2009, which was signed into law just three days after the executive order was signed by President Obama. This amendment prohibits the use of federal funds to either create a human embryo for research purposes or to conduct research in which a human embryo is "destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero." A human embryo is defined broadly as "any organism not protected as a human subject under 45 CFR 46 [the Common Rule] . . . that is derived by fertilization, parthenogenesis, cloning, or other means from one or more human gametes or human diploid cells."⁷

A question left unresolved by the language of the Dickey-Wicker Amendment is whether federal funds can be used to fund research using stem cell lines derived from research using private funds. Although toward the end of the Clinton administration the HHS general counsel informed the director of NIH that federal funds could be used for this research, no funds

⁵ See Morton Rosenberg, *Beyond the Limits of Executive Power: Presidential Control of Agency Rulemaking Under Executive Order 12,291*, 80 MICH. L. REV. 193 (1981-1982) (providing an excellent and detailed discussion of the limits of the President's Article II powers in the context of rulemaking).

⁶ See 36 Fed. Reg. 2532 (Feb. 5, 1971) (imposing rulemaking requirements on all HHS legislative rules even if exempt under the APA); *Humana of South Carolina v. Mathews*, 419 F. Supp. 253, 260 (D.D.C. 1976).

⁷ Pub. L. No. 111-8, Title 5, § 509.

were ever allocated or awarded based on this interpretation before the 2001 executive order took effect.

The Obama administration has not yet taken a position on the Dickey-Wicker ban, and has indicated that only Congress can reverse it. Two versions of a bill that would accomplish this recently were reintroduced in the House by Reps. Diana DeGette (D-Colo.) and Michael N. Castle (R-Del.).⁸ A companion bill was introduced in the Senate by Sen. Tom Harkin (D-Iowa).⁹ Previous versions of the bills were vetoed twice during the Bush administration. The bills would authorize federal support of research using hESC, subject to the following guidelines:

- the stem cells must have been derived from embryos donated from *in vitro* fertilization clinics, and must be in excess of the clinical needs for any fertility treatment;
- there must be a determination in consultation with the individuals seeking fertility treatment that the embryos would never be implanted; and
- the individuals donating the embryos must give their informed consent without any inducements to make the donation.

In addition, both versions of the bill would obligate the director of NIH to publish guidelines on research involving hESCs. Both H.R. 872 and the Senate bill would mandate that all research conducted or supported by NIH comply with the published guidelines, although NIH could determine the extent to which any guidelines apply to research using hESCs derived before the effective date of the guidelines.

IRBs and hESC Research: Guidance Missing in Action

By T. Howard Stone, J.D., LL.M.
Center for Biomedical Research
University of Texas Health Center
Tyler, Texas

President Obama's executive order included a directive to the HHS secretary, through the director of the NIH leadership, to review NIH and other "widely recognized guidelines on human stem cell research" and to issue new NIH guidelines by July 7. Many members of the scientific community, as well as many patient advocacy groups, applauded the executive order as a critical step in facilitating what had been considered a stymied, poorly coordinated march toward improving our understanding of pernicious conditions such as diabetes, Alzheimer's disease, and Parkinson disease.

The loosening of federal restrictions and the prospect of additional federal funding for hESC research undoubtedly will increase the pace and volume of hESC research activity at research institutions across the United States, particularly for institutions whose traditional source of research funding largely has been provided by the federal government through NIH. This in turn will increase the pace and volume of review of hESC research by these institutions' institutional review boards ("IRBs"), presenting these boards with a set of challenges involving human subject protections and other ethical issues that they may or may not be sufficiently prepared to consider and address, includ-

⁸ H.R. 872 and 873, 111th Cong., 1st Sess.

⁹ S. 487, 111th Cong., 1st Sess.

ing, for example, informed consent, gamete and embryo procurement processes, risks to donors, risks to potential recipients of interventions involving the use of cell line products, use of personal information and protection of confidentiality, and profound moral and community ambivalence towards the use of embryos for research purposes. Remarkably for what apparently has been such an overtly contentious research issue, there is a dearth of federal regulatory guidance with regard to these and other issues that currently exists to which IRBs may refer in the review of hESC research. Chief among these are *Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles* (HHS Office for Human Research Protections, 2002; NIH, 2002) and the more generalized *Guidance on Research Involving Coded Private Information or Biological Specimens* (OHRP, 2008). These guidance documents serve primarily to establish parameters for determining when research involving hESC or biological specimens is considered human subject research, and thus subject to 45 C.F.R. Part 46. Neither of these documents provides specific guidance on the challenges and ethical issues noted earlier.

For IRBs of institutions at which hESC research may be conducted with federal support, the prospect of revisiting and perhaps improving upon existing NIH guidelines that serve as a framework against which review of hESC research is undertaken therefore may be a welcome relief from what is widely acknowledged as a near-void of federal regulatory guidance for hESC research. Such relief may be short-lived, however. While the lack of more precise or meaningful U.S. regulatory guidance has been addressed to some degree by non-regulatory guidance on hESC research provided by, for example, the National Academy of Sciences (e.g., *Guidelines for Human Embryonic Stem Cell Research*) and the International Society for Stem Cell Research (e.g., *Guidelines for the Conduct of Human Embryonic Stem Cell Research*)—it is not altogether clear that IRBs have found such guidance compelling or even useful, particularly since these guidelines were developed for and focus more upon non-IRB oversight and review mechanisms, and even carefully stipulate that such review is in addition to—not a replacement for—IRB review.

Absent regulatory guidance specific to IRB review of hESC research, many IRBs understandably will resort to the broad regulatory framework with which they already are familiar. Sometimes to the dismay or frustration of investigators, research sponsors, and even research institutions, this regulatory framework accords IRBs with considerable and sometimes unassailable discretion in their review of human subject research. As provided for under 45 C.F.R. § 46.109(a) and without exception, “an IRB shall review and have authority to approve, require modification in (to secure approval), or disapprove all research activities covered by this policy.” Such discretion is not totally unfettered however. Under 45 C.F.R. § 46.109(d), IRBs must notify investigators of their decision to approve or disapprove of proposed research, and for disapprovals, provide a statement of their reasons and provide investigators “an opportunity to respond in person or in writing.” And while institutions may in accordance with 45 C.F.R. § 46.112 subject proposed research to further review by institutional officials, institutional officials “may not ap-

prove the research if it has not been approved by an IRB.” Few institutional mechanisms appear to attract the annoyance of investigators as does IRB review and oversight of their research activities.

The combination of increased federal support for hESC research, unique ethical challenges implicated by hESC research, abbreviated related federal regulatory guidance, and statutorily expansive IRB discretion in the review of human subject research may—in both anticipated and unforeseen ways—lead IRBs to impose their own limitations on hESC research. One possibility is that proposed hESC research inadvertently may be deemed human subject research based upon a loose or misunderstood interpretation of federal guidance, leading to the imposition of conditions for IRB approval of hESC research that otherwise might have been characterized as exempt research. For example, OHRP’s 2002 guidance document on hESC research provides that human cell lines for which the “identity of the donor(s) cannot readily be ascertained by the investigator” are not considered human subject research and are not governed by HHS regulations at 45 C.F.R. Part 46 or Food and Drug Administration regulations at 21 C.F.R. Parts 50 and 56; however, this guidance does not explain what would constitute a subject’s identity that cannot readily be ascertained. Instead, reference must be made to OHRP’s 2008 guidance document on coded private information or biological specimen research, which actually does provide some examples of how investigators may satisfy the requirement that identifiable information not be readily ascertained for purposes of establishing whether research involving biological specimens is or is not human subject research and subject to HHS regulations. The consistency with which IRBs consult or cross-reference these guidance materials in their review of hESC research is anyone’s guess.

Another possibility is that, lacking appropriate scientific expertise, an IRB may disapprove of what otherwise may constitute approvable hESC research without securing relevant expertise for the purpose of assisting the IRB with its review of hESC research. Such an arrangement is provided for under 45 C.F.R. § 46.107(f), but for some institutions obtaining such expertise (other than members of the research team whose proposed hESC research is before the IRB and for whom providing such expertise to the IRB would raise the obvious potential conflict-of-interest issue) may be difficult or impractical given the highly specialized nature of hESC research or the small cadre of hESC experts readily available for IRB consultation. In such circumstances, IRB review may be delayed until appropriate expertise is secured, potential conflict-of-interest issues are resolved, or review may need to be deferred to outside review. Moreover, for hESC research involving human subjects (identifiable donors or recipients of interventions derived from cell line products) investigators may fail to consider and develop meaningful informed consent processes that adequately address the unique informational needs of human subjects, such as the prospect that cell lines established from donors’ embryos will contain donors’ DNA. Finally, moral and community ambivalence about the use of human embryos for research purposes understandably may permeate IRB deliberations and review of proposed hESC research. All research institutions should be aware of as well as sensitive to their communities’ perspectives about research, especially research that has attracted

such a divergence in opinion as has hESC research. Federal regulations at 45 C.F.R. § 46.107(d) provide for community participation in IRB review of research, even if such participation may not be as meaningful as may have been intended. Nonetheless, for IRBs of research institutions in communities in which concern or ambivalence toward hESC research is most pronounced, some pressure to carefully limit or even restrict hESC research may be inevitable and may lead the IRB or the institution to forego hESC research. To what extent this actually takes place would be an interesting research exercise in itself.

The Opportunity to Harmonize Human Subject Protection Regulations That Relate to hESC Research

By Carol A. Pratt, Ph.D., J.D.
K&L Gates LLP
Portland, Ore.

The anticipated expansion of research involving hESCs, in combination with the Obama administration's interest in and support of hESC research, may provide a catalyst to plug some gaps in the patchwork of federal regulations that apply to in vitro research involving human specimens generally and hESC research in particular. The gaps are the result of inconsistencies in two sets of federal regulations protecting human subjects in research.

The two sets of federal requirements are the HHS regulations at 45 C.F.R. Part 46, known as the "Common Rule," and FDA's regulations at 21 C.F.R. Parts 50 and 56. Generally, both sets of regulations require studies that involve "human subjects" to be reviewed and approved by an IRB. However, the two sets of regulations differ in two aspects that have a significant effect on in vitro research involving the derivation or use of hESCs.

The first major difference in the two sets of federal regulations is how they define "human subject." The Common Rule defines human subject broadly to include "identifiable private information," which includes individually identifiable human tissue or cells. In contrast, FDA defines human subject narrowly to mean a living individual, not specimens.¹⁰ Thus, in vitro hESC research could be subject to the Common Rule but generally would not be subject to FDA's human subject protection regulations.

The second major difference in the two sets of federal regulations limits the scope of in vitro hESC research that is subject to the Common Rule. As a threshold matter, the Common Rule applies generally only to federally funded research. While an institution that receives federal funding for research may elect under its assurance with OHRP to apply the Common Rule to all human subject research regardless of funding source, it is only required for research that is supported in whole or in part by federal funding. As a result of President Obama's stem cell executive order, federal funding for in vitro hESC research will increase, and this research will be subject to IRB oversight under the Common Rule if it involves identifiable tissue or cells.

¹⁰ An exception is the use of biological specimens to test in vitro diagnostic devices. 21 C.F.R. § 812.3(p).

The differences between the Common Rule and its counterpart FDA regulations create an uneven regulatory terrain for in vitro hESC research. While this has obvious ethical implications, it also is problematic given that the eventual goal of most hESC research, regardless of whether it was federally funded or conducted by private companies, is to obtain FDA approval of stem cell products for use as therapeutic agents. In order to be approved as a drug or a biologic, hESCs must be tested in humans and must comply with FDA's regulations on human cells, tissues, and cellular or tissue-based products ("HCT/Ps").¹¹ FDA requires that HCT/Ps retain sufficient information about the donor to allow a donor eligibility determination, which means that in vitro hESC research would need to be conducted on identifiable human embryonic tissue/cells. If federally funded, such research would be subject to IRB oversight under the Common Rule.

It would seem logical and prudent for all to make in vitro hESC research, regardless of funding source, subject to the same regulatory oversight and requirements. This could be achieved by expanding FDA's definition of human subject to be consistent with the Common Rule's definition. Whether the stem cell executive order is a catalyst for harmonizing the Common Rule and FDA regulations remains to be seen.

Implications for NIH Policies Governing Research Institutions and Investigators

By LaDale K. George, Esq.
Neal, Gerber & Eisenberg LLP
Chicago

The Obama administration's executive order revoking restrictions on federal funding of hESC research will alter the definition and conduct of this field of study, and requires NIH to issue new guidance to direct compliance of research institutions and investigators.

Since Aug. 9, 2001, federal funding for hESC research had been restricted by the criteria established by the Bush administration. The former president restricted federal funding to hESC research being conducted using stem cell lines that already were in the derivation process (the inner cell mass removal stage) and the source embryo was determined no longer to have the ability to develop into a human being. The qualifying criteria also required the source embryo to have been created for reproductive purposes and no longer to be needed for that purpose, as well as that the donor of the source embryo provide informed consent and receive no financial inducement for making the donation.

The Bush administration executive order of June 20, 2007, contained a specific definition of "human embryo" to mean any organism "derived from fertilization, parthenogenesis, cloning, or other means from one or more human gametes or human diploid cells" that is not protected by existing human subject protection regulations governing research. These policies limited the availability of federal funding for hESC research to only 21 independent, fully developed stem cell lines available for widespread distribution to researchers.

¹¹ 21 C.F.R. Part 1271.

Obama's executive order expressly states that the previous presidential statement "shall have no further effect" and that Bush's supplemental executive order on hESC research "is revoked." This action opens the door for the Obama administration to issue a new policy definition of "human embryo" and criteria for hESC research. This new policy also will need to address the informed consent and financial involvement of the donor of the source embryo.

The guidance document adopted by NIH on April 10, 2002, and issued by OHRP, titled *Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles*, sought to inform investigators and institutions, including their IRBs, on whether hESC research fell within the authority of the human subject protection regulations promulgated by OHRP and/or FDA. The guidance indicated that the disclosure of identifiable private information of the source embryo of the hESC, or the interaction or intervention of a hESC test article in a human being, would subject the research to federal oversight and would require the research institution to have appropriate policies to protect the hESC source and the research subject.

In addition, NIH Sept. 18, 2007, issued the "Plan for Implementation of Executive Order 13435" to guide the agency and research community on the supplemental hESC policy of the Bush administration executive order. The plan sought to expand the discussion of federal funding of stem cell lines beyond hESC to include "pluripotent" stem cells. This expansion, however, did not expand the sources of hESC.

For research institutions and investigators, NIH guidance usually translates into the need to develop site-specific policies. Whether these policies are directed at the conduct of research or the application and use of research funding, the research institutions and investigators generally are obligated to comply. For hESC-specific policies, research institutions and investigators will need to wait for NIH to complete its review and be in a position to react to any new guidance. Certainly any new guidance will require the research institution to review its policies on the definition and criteria for conducting hESC research, as well as the administration of the institution's human subject protection program.

Whether the new policy will be broader or narrower, in certain aspects, is yet to be seen. However, the language used in the president's remarks accompanying the new executive order clearly indicates that the new administration sees great potential in the advancement of hESC research through federal support. The president states that there "is no finish line in the work of science. The race is always with us . . . using every resource at our disposal, with renewed determination to lead the world in the discoveries of this new century; we rededicate ourselves to this work."

The Stem Cell Patent Landscape Has Not Changed

By Kevin E. Noonan, Ph.D., Esq.
McDonnell Boehnen Hulbert & Berghoff LLP
Chicago

The change in availability of federal government funds for stem cell research should not affect, or be af-

ected by, the patent landscape. Although restrictions on the uses of stem cells by academic and federally funded researchers have been slightly relaxed recently, the Wisconsin Alumni Research Foundation ("WARF") controls the three dominating patents for human embryonic stem cells: U.S. Patent Nos. 5,843,780; 6,200,806; and 7,029,913. These patents were challenged in re-examination proceedings by the Public Patent Foundation and the Foundation for Taxpayer and Consumer Rights, a California taxpayer group, but all three survived re-examination with minimal restrictions to the scope of their claims. Re-examination certificates were issued by the U.S. Patent and Trademark Office on June 26, 2008, for the '780 and '806 patents; these decisions cannot be appealed. Last July, the challengers filed an appeal to the Board of Patent Appeals and Interferences over the favorable determination of the *inter partes* re-examination of the '913 patent.

WARF has been extremely active in supporting stem cell research by academic scientists, starting with a program administered through NIH in the wake of the Bush administration ban limiting federal funding to certain approved stem cell lines. WARF initially charged research institutions \$5,000 for access to these lines (in aliquots of about 6 million cells); this fee also included a three-day training session on how to grow the cells (which are notoriously difficult to maintain in culture). In January 2007, WARF reduced the fee for academic researchers to \$500 as part of an initiative to make these cells even more accessible. This policy change also permitted easier, cost-free transfer of stem cells between academic researchers. To date, WARF, through its stem cell licensing arm WiCell, has sent human embryonic stem cells to more than 563 researchers in 25 countries and 40 states, and fulfilled 914 licenses with academic researchers, according to its Web site (<http://www.wicell.org>).

Licensing to commercial entities, and particularly to the California Institute for Regenerative Medicine ("CIRM"), has carried a higher price tag, and it ostensibly was these practices that provoked the re-examination efforts. These commercial licenses ranged from about \$75,000 to a reported \$400,000. Nonetheless, WiCell states on its Web site that it has licensed 25 commercial entities, most notably Geron, which has an exclusive license for cardiomyocytes, neural stem cells, and pancreatic islet cells. Regarding CIRM, the January 2007 policy changes to WARF's licensing practices now permit CIRM to provide stem cell research grants without a license from WiCell, based on its status as a not-for-profit organization. Moreover, CIRM will not be required to remit to WARF or WiCell any portion of any payment that CIRM receives from its grantees.

As a further part of its January 2007 revisions to its licensing policies, WARF now permits academic and other researchers to be supported by industry grant monies without the granting company obtaining a commercial license, regardless of whether intellectual property rights are granted to the funding company. Transfer of research into company laboratories and commercialization activities still requires a commercial license, however.

Perhaps more daunting than the WARF/WiCell licensing requirements may be patent activities by others. While federally funded projects were limited under the Bush ban, a variety of private entities, here and abroad, and groups funded by foreign and U.S. state

governments, were active. At present, there are 143 granted U.S. patents relating in some way to human embryonic stem cells, and over a thousand published applications. Whether these patents result in a stem cell patent thicket remains to be seen, but their existence raises the possibility that private companies may face greater challenges in bringing stem cell-derived therapies to market than have been encountered to date.

The Effect on State Stem Cell Activity

**By Wendy L. Krasner, Esq.
Manatt Phelps & Phillips LLP
Washington**

The issuance of the president's executive order also has rekindled debate about the role of the states in embryonic stem cell research. Since President George W. Bush limited federal funding in 2001, according to a list compiled by the National Conference of State Legislatures ("NCSL"), eight states—California, Connecticut, Illinois, Iowa, Maryland, Massachusetts, New Jersey, and New York—had passed programs authorizing spending on such research.

As with most health care issues today, the effects of the executive order are very complex. On the one hand, it could be expected that the expanded scope of permissible research with federal funds would further jumpstart ongoing state activities. On the other hand, cash-strapped states may be reassessing whether these programs can now be viewed as ready targets no longer in need of state commitments. Further, other states that previously did not engage in this space are now considering the imposition of state restrictions similar to the ones in effect under Bush.

The dilemmas now facing states already active in this arena are well illustrated in California, which has been on the leading edge of stem cell research since the passage in 2004 of Proposition 71, a \$3 billion bond issue. While the California Institute for Regenerative Medicine ("CIRM") first had to fight off legal challenges, it now has awarded almost \$700 million in grants for research, training, and construction of laboratories. Indeed, during the federal hiatus, it emerged as the largest funder in the world of stem cell research. Thus it would appear that California has the infrastructure—scientists and laboratories—to put federal funds to use.

However, arguably the new order has removed the original reason for state initiatives. New Jersey and Massachusetts already have had to reduce overall life sciences spending, and the California program may run out of money by the end of 2009 because the state is not in a position to issue bonds at a reasonable rate. Other nonfinancial considerations involve how the California leaders will adjust to NIH now taking on the leadership role they have had, and what changes in direction are prudent as they focus on how to augment and complement the NIH efforts. The Dickey-Wicker Amendment still prohibits the use of federal funds to develop new stem cell lines from embryos (although experiments can be funded once the cell lines are established). States need to determine where they can add the most value and concentrate their efforts accordingly.

Beyond the ongoing need to create new lines, some believe robust state efforts will continue because the mere fact that the restrictions were lifted does not mean that there will be sufficient federal money for stem cell research. In addition, the funds are likely to be directed

to basic research at a time when CIRM reportedly is shifting its longer-term focus toward translating basic discoveries into therapies that will help humans. Some stakeholders in turn see the eventual focus on testing therapies in human patients as a way of securing an influx of private funds back to the states.

The adjustments may go both ways, of course. CIRM of necessity had to develop regulations to cover ethical standards for stem cell research and intellectual property policy. NIH may benefit from this work done by using California's ethical rules as the basis for regulations that the president has directed it to draft by July 7. In other words, both NIH and the states may have to adjust their roles in response to the order.

At the same time, the order is prompting strong debate in states less receptive to stem cell research. According to the NCSL, research already is directly restricted in several states, including Arkansas, Indiana, Louisiana, Missouri, North Dakota, and South Dakota. Moreover, other states are seeking to clamp down on allowing any stem cell research in their states. For example, in direct response to the issuance of the order, Georgia is considering legislation to limit and even criminalize some stem cell research.

It remains to be determined whether the states that soldiered on during the Bush years will be best positioned to benefit from the order. There will be new and perhaps unexpected challenges that will necessitate back-and-forth adjustments between federal and state initiatives as the constantly changing stem cell research dynamics evolve.

Implications for Creation of Tissue Repositories Needed to Support Clinical and Translational Research and Personalized Medicine

**By Bernadette Broccolo, Esq.
and Amy Kearbey, Esq.
McDermott Will & Emery LLP
Chicago**

Human embryonic tissue is a remarkably rich and powerful source of the tissue needed to support leading-edge genomics research because it can be used to generate many different human cell types. The Bush administration executive order created a disincentive to harness this valuable resource by making it impossible to tap it for use in federally funded research. The new executive order thus should generate an increased appetite for undertaking the harnessing effort, which in turn will generate a renewed focus on transferring the approximately 500,000 frozen embryos now stored at in vitro fertilization ("IVF") clinics throughout the country to the tissue repositories now being created through collaborations among academic medical centers, research institutions, and others across the country. Accordingly, the availability of federal funding for hESC research should significantly fuel the creation of the large-scale, sophisticated tissue repositories that the federal government, the provider community, and industry all have recognized as the cornerstone for clinical and translational research and the development of personalized medicine solutions.

Mastery of the science involved in using human embryonic tissue for hESC research certainly is an essen-

tial ingredient for the success of these efforts to transform the delivery of medical care. Also essential will be the ability to identify and manage the many complex legal and regulatory feasibility issues involved in creating a powerful tissue repository that can be lawfully accessed and used once created. A fundamental consideration is whether the individuals involved gave adequate and timely consent to use of the tissue for research and development. The consent requirement is addressed in both state and federal case law and in statutes such as the federal Common Rule that governs federally funded human subject research,¹² the Health Insurance Portability and Accountability Act (“HIPAA”),¹³ and the Uniform Anatomical Gift Act that has been adopted by many states, yet in many respects these sources are unclear and conflicting.¹⁴ A 2008 study found that 41 percent of patients with stored frozen embryos who were certain that they did not want a baby were very likely to choose to donate embryos for research purposes.¹⁵ However, not everyone may share that sentiment and some may be unwilling to give consent to use for these purposes. Further, even when an individual gives written consent at the time the embryonic tissue is obtained, wording the consent in a way that both preserves maximum flexibility for future research and adequately informs the individual presents a meaningful challenge. Limiting the extent to which identifying information is associated with the tissue can be an effective means of avoiding the complexities of these consent issues. As a practical matter, however, inclusion of annotations with the tissue that contain individually identifiable information protected under HIPAA and state privacy laws may be essential for the compliant transfer of the embryos to the repository and for the meaningful use of the tissue in research.

Other important legal and regulatory feasibility issues arise from FDA’s tissue regulations,¹⁶ import/export controls,¹⁷ and intellectual property principles relating to protection and ownership of the repository and its component parts. Careful consideration of all these issues at the outset of the repository initiative is of paramount importance.

Alternatives to Human Embryonic Stem Cells and Their Effect on the Ethical Debate

By Edward B. Goldman, J.D.
University of Michigan
Ann Arbor, Mich.

In 1998 Dr. James Thomson of the University of Wisconsin first reported a way to isolate human embryonic stem cells. His technique involved use of the inner cell mass of an embryo thereby destroying the embryo.

¹² 45 C.F.R. § 46.101 *et seq.*

¹³ 42 U.S.C. §§ 1320d-1320d-8; 45 C.F.R. Parts 160, 162, 164.

¹⁴ See, e.g., M.G.L. Ch. 113, §§ 7-13.

¹⁵ Anne Drapkin Lyerly et al., *Fertility patients’ views about frozen embryo disposition: results of a multi-institutional U.S. survey*, FERTILITY AND STERILITY (in press).

¹⁶ See 21 C.F.R. Parts 1270 and 1271.

¹⁷ International transactions involving human tissue may be subject to a variety of requirements promulgated by federal agencies, including Customs and Border Protection, the Centers for Disease Control and Prevention, FDA, and the Commerce Department’s Bureau of Industry and Security.

What he created was pluripotent cells that could give rise to all the cell types in the human body. The hope is that these cells can be researched so that we can learn how to create specialized cells to treat a wide variety of diseases.

Recently new research has focused on creating of pluripotent cells that are derived from adult cells so that an embryo need not be destroyed. The term used to describe this is “induced pluripotent stem cells” (“iPS cells”). The techniques used vary but the current thought is to use adult skin cells and to “reprogram” them with a vector derived from the Epstein-Barr virus first removing the viral mechanism so that the resultant cell line is less likely to form cancers.¹⁸

Two papers in the March 2009 issue of the journal *Nature* reported on creation of cell lines from adult skin cells reprogrammed to act like embryonic cells. These cell lines are derived from adult cells so although they act like embryonic cells their creation does not involve destruction of an embryo.¹⁹

Initial work using the Epstein-Barr virus to reprogram the adult cells into pluripotency could make the cell line unstable and cause a higher risk of a cancerous cell growth. The most current work is reported to avoid these risks. That work was carried out by Thomson, among others, who said he is hopeful but reports there is still much work to be done. The new lines need to be monitored to see if this process could lead to mutations or other problems. Most importantly, each new approach needs to be compared to all other approaches and to true embryonic cell lines to see if there are differences. And the scientists must show that the new lines are truly pluripotent. So, the initial questions are still around safety, efficacy, and if this approach is as scientifically useful as cell lines derived from embryos.

Currently the research is interesting. It allows for scientists to study the “basic biology of reprogramming” without use of viruses.²⁰ See:

Reverse engineering adult cells to act like embryonic cells looks promising as a way to obtain pluripotent cell lines. It is not yet known if induced pluripotent stem cells are as good as hESCs. Nor has safety been established. Further, if the adult lines have reduced pluripotency that would show up as a long-term problem. If the adult lines form tumors when implanted we will have new ethical challenges. At the moment induced pluripotent stem cell lines are the subject of ongoing scientific discovery and debate and their potential is exciting. But the debate over use of about-to-be-discarded embryos is not concluded.

¹⁸ See Amabile, G., and Meissner, A., *Induced pluripotent stem cells: current progress and potential for regenerative medicine*, TRENDS IN MOLECULAR MEDICINE, vol. 15, no. 2, pp. 59-68, Jan. 21, 2009.

¹⁹ See http://blogs.nature.com/reports/theniche/2009/03/human_ips_cells_without_geneti.html.

²⁰ See Smith, A., *quoted in THE SCIENTIST: Newsblog: “Piggybacking to pluripotency,”* <http://www.the-scientist.com/blog/print/55486>.

The Effect on Federal Funding of Other Controversial Research²¹

By John E. Steiner Jr., Esq., CHC, CCEP
UK HealthCare
University of Kentucky
Lexington, Ky.

President Obama's executive order is a watershed event in many respects, as described in this compilation article.

Predictably, there is healthy speculation on the implications of that decision for other types of research. For example, there are strong views as to whether federally funded human "cloning" will be approved in the near future. Fundamentally, the executive order signals the political recognition that medical knowledge and advances are difficult to restrict. As the country has witnessed over the past decade, private funding often sustains public dialogue over the merits of federal funding for certain types of research for the benefit of people.

With respect to human "cloning," there are two clear issues: definitions and funding sources. The debate is whether somatic cell nuclear transfer will be federally funded. That technique involves the scientific produc-

tion of embryos that, in turn, produce stem cells used for research. Embryos developed in this manner are not intended for implantation. Thus, the core issue is whether embryo creation, using this technique, should be labeled as "cloning."

The semantic point, of course, is that "cloning" can connote different things to different people. Most scientists do not view somatic cell nuclear transfer as cloning because the embryos that are created are not likely to be viable fetuses, even if they were implanted. On the other hand, conservative religious groups may label the technique as human cloning.

This summer, NIH will provide recommendations to the HHS secretary for guidelines for hESC research that are consistent with the executive order.

One guidepost for consideration of those recommendations and, presumably, the debate over possible federal funding of somatic cell nuclear transfer is the following language from Obama's order:

Section 2: *Research* The Secretary of Health and Human Services (Secretary), through the Director of NIH, may support and conduct *responsible, scientifically worthy* human stem cell research, including human embryonic stem cell research, to the extent permitted by law. (emphasis added)

There are numerous resources and opinions available to help frame the debate over human cloning. Section 2 of Executive Order 13505 provides guidance for furthering policy discussion of that topic and other emerging scientific research techniques.

²¹ The thoughts and views expressed in this article are solely those of the author.