PERSPECTIVES

STEM CELLS — SCIENCE & SOCIETY

US policies on human embryonic stem cells

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Abstract | The United States is a federal union with separate state jurisdictions. In part owing to the sometimes heated debate about public support for human embryonic stem-cell (ESC) research, there has been restricted federal support and little central regulation of this research to date. Instead, guidelines developed by scientific organizations have set principles for oversight and good practice for this research. These guidelines are functioning well, have influenced developing state regulations and, one hopes, will affect any future federal regulation.

In the decade since human embryonic stem-cell (ESC, see Glossary) lines were first established[1,2], research on this topic has proceeded actively in the United States, despite major restrictions on federal funding and an almost complete absence of federal regulation. Human ESCs are derived from cells of early human embryos (FIG. 1) and have the capacity to develop into most different cell types and tissues (see Glossary for further definitions of relevant terms). This potential raises hopes for their future use in regenerative medicine. However, their derivation from embryos raises issues for some people concerning the ethical basis of human ESC research. Owing to both its promise and the ethical debates, human ESC research has been subject to controversy, both in the United States and elsewhere, and ethical, policy and political discussions continue to this day.

These constraints have meant that the principal source of funding for biomedical research in the United States, the National Institutes of Health (NIH), which would otherwise have had a key role in funding and regulating human ESC research, has had a much smaller part in these processes. Instead, scientific organizations have developed guidelines to oversee this research and some individual states have introduced their own legislation and funding for human ESC research, which has led to a patchwork of rules and procedures.

Recent publications reporting the reprogramming of somatic cells to pluripotent cells by the introduction of exogenous genes[3–5] have introduced both new promise in research and additional debate about how research should proceed. As the Bush administration enters its final months of government, this seems an opportune time to review the status of the science, its funding and its regulation. There is strong, though not universal, support for human ESC research in the American public and it seems likely that the next administration and Congress will be more supportive of the promise of human ESC research. Any move to expand federal funding and oversight will necessitate the revision of policies and regulations, taking into account the background of existing procedures.

US federal policies

Although there are virtually no federal laws that specifically regulate human ESC research, local Institutional Review Boards (IRBs) operating under the Common Rule, a federal policy regarding the protection of human subjects, govern federally supported research that involves human subjects (BOX 1). Many IRBs voluntarily apply the Common Rule to all human subjects research, even if it is privately funded. IRBs review and approve human subjects research protocols, including issues of informed consent and reimbursement. Therefore, donations of oocytes (eggs) and embryos for human ESC research are reviewed by IRBs. Similarly, introduction of any cells into human patients requires IRB review and approval. Furthermore, the Food and Drug Administration (FDA) regulates human clinical trials and the introduction of all cells, tissues and devices into patients, and has indicated its intention to include human ESCs and their progeny under these regulations (BOX 1).

However, none of these regulations adequately addresses specific issues pertaining to human ESCs, such as their immortality and pluripotency, their potential use in animal transplantation experiments, in therapy and in commercial development. Given the sensitivity of the ethical debates surrounding the use of human embryos and other reproductive materials (for example, eggs and sperm), there is a clear need to monitor the derivation and use of human ESCs. However, the federal government has not enacted regulations that specifically cover human ESC research. A brief historical review

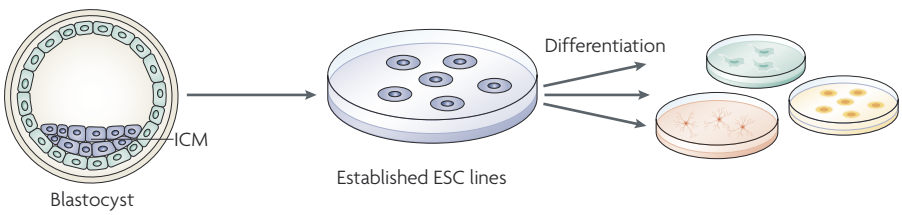

Figure 1 | **Derivation of human embryonic stem cells.** Embryonic stem cells (ESCs) are derived from the inner cell mass (ICM) of an early embryo (blastocyst). ESCs proliferate continuously when cultured under appropriate conditions. The potential to differentiate ESCs into most different cell types *in vitro* raises great hopes for their future use in regenerative medicine.

shows why this is so. This past history will also affect future initiatives.

A historical perspective. In 1994, an NIH advisory panel, acting under the NIH Revitalization Act (1993), recommended funding for the derivation of human ESCs from surplus embryos in *in vitro* fertilization (IVF) clinics. This recommendation came even before the isolation of human ESCs. Once human ESC isolation had occurred, President Clinton established a National Bioethics Advisory Commission (NBAC), which recommended in 1999 that federal funds be made available for the derivation and use of human ESCs, and outlined a national system of review and oversight of human ESC research[6]. However, the use of NIH or other federal funding to create or destroy human embryos is prevented by the so-called Dickey–Wicker amendment, a congressional amendment that was first introduced in 1996 and has been renewed annually as a rider to the appropriations (budgetary) bill for the Department of Health and Human Services. This amendment effectively precludes the use of any federal funds to generate human ESCs from embryos. The NIH therefore developed draft regulations that would allow the funding of research with existing human ESC lines, but not their derivation. Those draft regulations were issued in August 2000, the final year of the Clinton administration, but the NIH could not fund any research before the new administration halted the process in early 2001.

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After review and consultation, President Bush announced on 9 August 2001 that the NIH would be allowed to fund research only on human ESC lines that had been established before that date. He announced that there were “more than 60” of such cell lines, and directed the NIH to establish an ESC register. Funding would be restricted to experiments that used these approved cell lines. This initially seemed to provide a boost to human ESC research, but it soon became clear that many of the cell lines were either unavailable or unsuitable, and there is now general agreement that only 20 or so ‘presidential’ lines are eligible for NIH funding (BOX 1). Furthermore, these lines are inadequate in many ways (for example, they were derived with outdated procedures, are contaminated by co-culture with mouse cells and bovine serum products and have probably deteriorated during maintenance), and these inadequacies will compromise their use in therapy.

Later lines made with improved procedures are thought to be superior, but are ineligible for federal funding under the Bush policy. Several attempts have been made to expand the number of human ESC lines that are eligible for federal support: most recently a bill that was passed in 2007 by both houses of Congress expanded support to all ‘ethically derived’ human ESC lines. However, the bill was vetoed by President Bush, and Congress could not override the veto. A revised version of the bill (the Stem Cell Research Enhancement Act) is now working its way through Congress, but seems unlikely to be enacted during the remainder of the Bush administration.

Current federal policies. Because of the history summarized above, the NIH can currently fund and regulate only a fraction of useful human ESC research[7]. This research does not include the sensitive topics of the derivation of any new lines from embryos or the use of any of the many newer lines that have been derived using non-federal funds. As in any new field, the first round of research materials are usually replaced by improved versions as scientists learn to tackle the new area effectively. However, under the Bush policies, NIH-funded researchers are restricted to working on the older presidential human ESC lines, which are generally agreed to be deficient. Furthermore, NIH policy specifies that research with non-approved lines cannot be “directly or indirectly” supported by federal funds (BOX 1). This means that research using non-presidential lines cannot be conducted using personnel, reagents, equipment or even laboratory space that are even partially supported by federal funds, without complex cost allocations. This means that, even if a scientist obtains non-federal support to conduct human ESC research on state-of-the-art, newly derived human ESC lines, that research must be conducted with personnel, equipment and supplies seperate from those supported by federal funds. This inevitably increases the costs of the research, because additional (and often duplicated) laboratory space and equipment are required, and significant opportunity costs are expended on monitoring compliance.

These rules also block any researchers without non-federal support from human ESC research using the best lines. This is a major impediment to the advance of the field, as the NIH provides the principal

Box 1 | **Guidelines and regulations relevant to human embryonic stem cell research**

National Research Council and Institute of Medicine of the National Academies, USA
Original guidelines (2005)[9] and subsequent amendments[10,11] are available for download at http://dels.nas.edu/bls/stemcells/reports.shtml
The National Academies of Science also maintains links to sources of information about stem cells at http://dels.nas.edu/bls/stemcells/introduction.shtml

International Society for Stem Cell Research (ISSCR) guidelines
Conduct of human embryonic stem cell research guidelines are available for download at http://www.isscr.org/guidelines/index.htm
The ISSCR also maintains links to sources of information about stem cells at http://www.isscr.org/public/index.htm

Stem cell information from the National Institutes of Health (NIH)
Information about the eligibility of stem cells for federal funding and the registry of approved lines can be found at http://stemcells.nih.gov/

National Institutes of Health, Office of Human Subjects Research
http://ohsr.od.nih.gov/guidelines/45cfr46.html

US Department of Health and Human Services
The Basic Health and Human Services (HHS) Policy for Protection of Human Research Subjects is available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.110

US Food and Drug Administration (FDA)
The FDA oversees the introduction of all cells, tissues and devices into human patients. Information about the work of the FDA can be found at the web sites below.
- http://www.fda.gov/cber/gene.htm
- http://www.fda.gov/cber/tiss.htm
- http://www.fda.gov/cber/devices.htm
- http://www.fda.gov/cber/genetherapy/clone.htm

funding of biomedical research in the United States. Passage of the Stem Cell Research Enhancement Act would remove these significant restrictions to the benefit of research, without crossing any new ethical boundaries. Unfortunately, the Bush administration seems steadfastly resistant to expanding support for human ESC research, and progress will have to await a new administration.

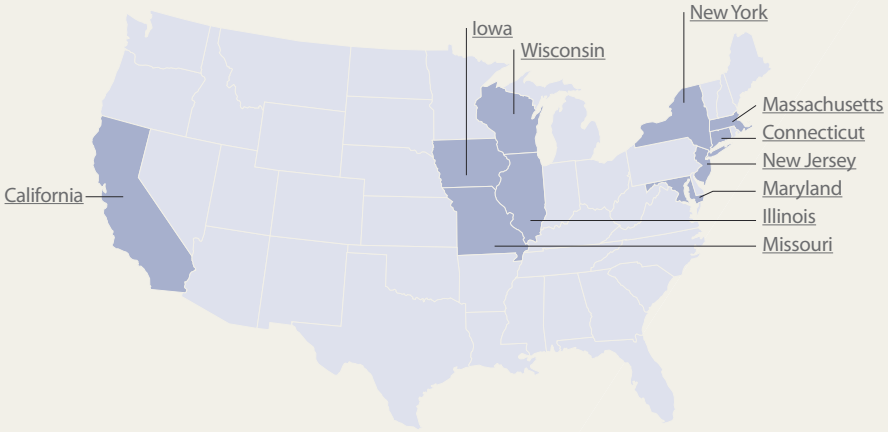
The polarization of the political debate has also ensured that no federal legislation to regulate human ESC research or IVF has been passed by Congress. That includes a failure to ban or restrict human reproductive cloning, although most people on both sides of the debate agree that this should not be allowed. The FDA has stated that attempts to perform reproductive cloning would be a form of cell-based therapy that is subject to FDA regulations, and that it would not currently approve any such procedure. Therefore, reproductive cloning could be subject to criminal and financial penalties for violating FDA regulations. Professional groups, including the American Society for Reproductive Medicine (ASRM), the National Academies of Science (NAS) and the International Society for Stem Cell Research (ISSCR), have gone on record to oppose any attempts to reproductively clone humans.

Guidelines for human ESC research

The vacuum in federal leadership in the face of a promising and rapidly advancing field of research that, at the same time, raises ethical and policy issues, meant that human ESC research proceeded with essentially no guidelines for appropriate conduct and procedures. Individual states were introducing either diverse regulatory systems or none at all, and research funded by private sources was underway with almost no oversight. This was felt to be highly undesirable, both from a policy perspective and also in terms of the future directions of the science. Scientific progress relies on the sharing of cell lines, which were being derived with differing and sometimes inadequate attention to ethical procedures. This concern has recently surfaced anew with an ironic twist; it seems that several of the NIH-approved presidential lines were derived with informed consent procedures that fall short of current ethical standards[8].

Because of these concerns about the absence of federal government regulations, responsible scientists desired guidelines for the appropriate conduct of human ESC research. Accordingly, in 2004, the National Research Council and the Institute of Medicine of the NAS convened a committee to develop guidelines for human ESC research, and in 2006, the ISSCR did the same. These two committees published their sets of guidelines in April 2005 (REFS 9–12) and December 2006 (REFS 13,14), respectively, and these have since served as the basis for the oversight of human ESC research. Although the NAS guidelines were developed specifically for the United States, they incorporated many features from existing legislation in other countries, particularly the United Kingdom and Canada. Similarly, the ISSCR guidelines, although intended to be applicable in many countries, adopted many features of the NAS guidelines, as did many US states in writing their own regulations. There has been a continuing effort to seek concordance among different sets of guidelines and, although they necessarily differ in some details because of their differing contexts, there is good agreement on the major principles that underlie their rules.

Box 2 | **Policies in individual states**



States currently endorsing and providing support for human ESC research
The links below direct to web sites of state-specific regulations (see figure).

California. Two sets of standards, one covering research supported by the California Institute for Regenerative Medicine (CIRM) and the other covering research funded from other sources. CIRM regulations can be found at http://www.cirm.ca.gov/reg/default.asp

Connecticut. http://www.ct.gov/dph/cwp/view.asp?a=3142&q=389702&dphNav_GID=1825

Illinois. http://www.illinois.gov/gov/execorder.cfm?eorder=46

Iowa. http://coolice.legis.state.ia.us/Cool-ICE/default.asp?category=billinfo&service=billbook&GA=82&hbill=SF162

Maryland. http://www.mscrf.org/content/aboutus/actof2006.cfm

Massachusetts. http://www.mass.gov/legis/laws/seslaw05/sl050027.htm

Missouri. http://www.sos.mo.gov/elections/2006petitions/ppStemCell.asp

New Jersey. http://www.state.nj.us/scitech/stemcell/

New York. http://stemcell.ny.gov/

Wisconsin. http://www.wisgov.state.wi.us/journal_media_detail.asp?locid=19&prid=1943 and http://www.stemcells.wisc.edu/

For more information on individual state regulations, see:

Interstate Alliance on Stem Cell Research. This site has a listing of state stem-cell programmes with links to individual state regulations. It also has available for download a useful summary table of state policies compiled by S. Stayn, who has also published on the issue of the need for conformity among guidelines and individual state regulations[16,17]. The web site can be found at http://www.iascr.org/states.shtml

National Conference of State Legislatures. This site has a listing of state stem-cell programmes with links to individual state regulations, and also lists states that have enacted prohibitions on certain types of research. The web site can be found at http://www.ncsl.org/programs/health/genetics/embfet.htm

See online for an interactive version of this box.

Glossary

Chimaera
An organism that is composed of cells from at least two genetically different sources. The cells could be from the same or separate species.

Cybrid
A cell with a nucleus from one cell and cytoplasm from another. For example, it is possible to reprogramme a somatic cell nucleus by inserting it into the cytoplasm of an oocyte or another pluripotent cell.

Embryonic stem cell
(ESC). A primitive (undifferentiated) cell that is derived from early embryos. These are usually derived from the blastocyst (50–250-cell stage), but are sometimes derived from the morula (16–32-cell stage). ESCs have the potential to become a wide range of specialized cell types.

Induced pluripotent stem (iPS) cell
A cell that has been derived from a somatic cell by reprogramming the nucleus to induce pluripotency, using exogenous genes or other factors.

Nuclear transfer
(NT). Replacing the nucleus of a cell with the nucleus of another cell.

Pluripotency
The capacity of a cell to develop into cells of all three germ layers (endoderm, ectoderm and mesoderm) and most cells and tissues of an embryo.

Reproductive cloning
The generation of viable organisms from cloned pluripotent cells.

Reprogramming
The alteration of the epigenetic programme of a nucleus or cell to change its differentiation capacity. For example, a differentiated cell of limited potential is reprogrammed by nuclear transfer (NT) or by the introduction of exogenous genes (currently using retroviruses but alternative methods are being researched).

Retroviruses
RNA viruses that are used as carriers or vectors to introduce genes into the genomes of cells. Retroviruses are used in basic research and have been used in gene therapy, in which they have been reported to induce cancer in a limited number of patients.

Somatic cell
Any cell other than a germ cell or a germ-cell precursor.

Stem cell
A cell that has the ability to divide extensively *in vivo* or in culture and to give rise to specialized cells.

Both the NAS and ISSCR guidelines prohibit human reproductive cloning and the *in vitro* culture of human embryos beyond 14 days or beyond the development of the embryonic axis. Both lay out clear rules regarding the acquisition of eggs, embryos and other cell types for generating human ESC lines, including the necessity for appropriately detailed and informed consent, and both require review and approval by an IRB or equivalent panel. Both sets of guidelines allow the derivation of human ESC lines from excess embryos from IVF clinics, from embryos created explicitly for human ESC research, from oocytes into which the nuclei of other cells have been introduced by nuclear transfer (NT) or from single cells obtained from embryos (for example, during pre-implantation genetic diagnosis). It is of interest that both the NAS and ISSCR guidelines include, among their informed consent items, the possibility of interspecies mixing. The background section of the NAS guidelines explicitly mentions the possible use of cybrids, in which human somatic cell nuclei are introduced into enucleated animal oocytes to induce reprogramming. Such procedures were recently approved in the United Kingdom, but only after considerable debate about intermixing of species (see the article by Lovell-Badge in this issue).

Both the NAS and ISSCR guidelines allow reimbursements of 'reasonable costs' that have been incurred during the donation of oocytes, embryos or other materials, but preclude the payment of 'valuable consideration' (payments beyond reimbursement for expenses) for such donations. The precise definitions of reasonable costs and valuable consideration differ slightly and are undergoing continual review by both the NAS and the ISSCR, and by states that have adopted similar rules (see below). Nonetheless, both sets of guidelines adhere to the principle that 'undue inducements' to donate and the commodification of reproductive materials should both be avoided. The appropriate recompense for donations, especially of oocytes, is a complex issue with sound arguments on all sides and a full discussion is beyond the space available here. Interested readers should refer to the specific guidelines in which the issues are discussed extensively (BOX 1).

Both the NAS and ISSCR guidelines make detailed recommendations about the distribution, sharing and banking of human ESC lines, which will be essential as the research proceeds. The guidelines do not address clinical trials — as mentioned, clinical trials in the United States fall under FDA regulations and local IRB oversight.

> "…the NAS and ISSCR guidelines […] lay out clear rules regarding the acquisition of eggs, embryos and other cell types for generating human ESC lines…"

Oversight committees. The NAS and ISSCR guidelines require the review of all human ESC research by a qualified panel that includes scientists, ethicists and representatives of the public (this panel is commonly called an Embryonic Stem Cell Research Oversight (ESCRO or SCRO) committee). These committees must document the provenance of any human ESC lines to be used, review and approve the research proposed and keep a record of human ESC research underway at each institution. The ESCRO committee is also responsible for coordinating other necessary reviews, for example, by IRBs for studies in which the derivation of human ESC lines or other human subjects research are involved, or by animal research oversight committees if the introduction of human ESCs or their descendants into animals is proposed.

The issues associated with the introduction of human ESCs and other stem cells into animals (chimaera research) have raised their own set of controversies about the mixing of species. Many concerns about research using chimaeras are a consequence of the failure to understand the necessity for such experiments in preclinical testing of human ESCs and their descendants, *en route* to therapeutic applications. In addition, most chimaera experiments (which are routine in biological research) have no particular ethical concerns beyond those that concern animal welfare, and such concerns are already well regulated by animal research oversight committees. There are a few potential concerns regarding the introduction of neural progenitors (either human ESC-derived or from other sources) into animals, as these might incorporate into and affect the brain, or the introduction of cells that might contribute to the germ line and gametes (sperm and eggs). The NAS and ISSCR guidelines provide advice to ESCRO committees as to which experiments need special monitoring. As research proceeds with appropriate oversight, it will become clear which, if indeed any, of these experiments actually present any concerns.

As the guidelines were developed, it was noted that stem cells of other types (for example, neural stem cells) present some of the same issues as human ESCs when introduced into animals. With the development of induced pluripotent stem (iPS) cells by the reprogramming of somatic nuclei to induce pluripotency[3,4,5] (the ability to differentiate into multiple cell types, including neural

cells and gametes), it has become clear that other cells also need to be reviewed by ESCRO committees for some experiments, especially those that involve introduction into animals. Both the NAS and ISSCR are currently reviewing their guidelines in recognition of the issues raised by these new cells. It is worth noting that iPS cells might have much of the same potential as human ESCs for the generation of many differentiated cells for use in regenerative medicine, and some have suggested that they obviate the need for continued human ESC research. This is far from the truth. iPS cells need much further validation, including extensive comparisons with human ESCs to determine their full potential. Furthermore, current protocols for deriving iPS cells use retroviruses, and the introduction of such viruses has been known to cause cancer in gene therapy trials[15]. Clearly, further research will be required to develop either iPS or human ESCs to realize their full potential for therapeutic applications and it is incorrect to suggest that further research on either one is unnecessary.

The ESCRO committee system is working well — most institutions that conduct human ESC research in the United States have either established such committees or have access to ESCRO committees that are shared with other institutions. The distributed style of oversight conforms with the mechanisms that are used in the United States for the local review of human and animal research. The ability of scientists working with their own professional organizations to oversee human ESC research in the absence of central government regulation has been well received, and forms the template on which certain individual states have established their own regulatory and funding policies.

Stem-cell research in individual states

Although most states do not have regulations that govern human ESC research, some do prohibit certain experiments with human embryos or fetuses, which effectively precludes human ESC derivation. Around a dozen states explicitly endorse human ESC research, including derivation, although there are differences in the details of what is approved where. Several states also provide funding for human ESC and other stem-cell research (BOX 2 collects current information along with references and web sites for up-to-date information). Where detailed regulations have been promulgated, they closely follow the principles of the NAS guidelines, although there are, of course, differences in detail, and the scene is constantly changing[16,17].

Within the various states, the ESCRO committee system operates uniformly, although there are variations in response to individual state laws. The diversity of state regulations has the obvious potential to interfere with interstate collaborations, particularly if the regulations are notably divergent in different jurisdictions. This issue also applies to international collaborations. The NAS and ISSCR guidelines were written taking this potential for discordancy among regulations into consideration and, in general, the same has been true of individual states. There are ongoing efforts to coordinate guidelines and regulations among states, such as the Interstate Alliance on Stem Cell Research (IASCR), and both the IASCR and the National Conference of State Legislatures have web sites with useful information about the regulations in different states.

Conclusions and perspectives

Human ESC research is proceeding actively in the United States, despite rather limited federal support under the current administration. In the absence of specific federal regulations, scientific organizations have developed guidelines for the responsible conduct of the research and these are operating well. Individual states that have endorsed, and in some cases, funded, human ESC research, have adapted the guidelines and developed their own regulations. As science develops, one hopes with greater federal support in the future, it will be important for the rules and regulations in different jurisdictions to be written so as to enhance, rather than inhibit, collaboration and exchange among scientists in different states and countries. The template of the existing guidelines and the ESCRO committee mechanism is already serving as a good base for developing state regulations. It seems probable that the next Congress and presidential administration will modify or remove the restrictions on federal funding of human ESC lines that were developed before August 2001. This in itself would provide a considerable boost to human stem-cell research in the United States.

The prospects for federal funding of the derivation of new human ESC lines from embryos seem much slimmer. However, the rapidly advancing development of iPS cells, which lack the ethical complications of derivation from embryos[18], seems certain to provide pluripotent stem cells for research purposes. Development of either human ESCs or iPS cells for therapy requires additional research to overcome existing technical hurdles and one hopes that the public policy, ethical and federal funding issues that have slowed this research during the past decade will become less of an impediment in the future.

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1. Thomson, J. A. *et al.* Embryonic stem cell lines derived from human blastocysts. *Science* **282**, 1145–1147 (1998).
2. Shamblott, M. J. *et al.* Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proc. Natl Acad. Sci. USA* **95**, 13726–13731 (1998).
3. Takahashi, K. & Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663–676 (2006).
4. Takahashi, K. *et al.* Induction of pluripotent stem cells from adult fibroblasts by defined factors. *Cell* **131**, 1–12 (2007).
5. Yu, J. *et al.* Induced pluripotent stem cell lines derived from human somatic cells. *Science* **318**, 1917–1920 (2007).
6. National Bioethics Advisory Commission. Ethical Issues in Human Stem Cell Research. I. Report and recommendations. *National Bioethics Advisory Commission* [online], http://www.bioethics.gov/reports/past_commissions/index.html (1999).
7. National Institutes of Health. Notice NOT-OD-01–059: funding of research using specified existing human embryonic stem cells. *National Institutes of Health* [online], http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-059.html (2001).
8. Streiffer, R. Informed consent and federal funding for stem cell research. *Hastings Cent. Rep.* **38**, 40–47 (2008).
9. National Research Council and Institute of Medicine. Guidelines for Human Embryonic Stem Cell Research. *National Academies of Science* [online], http://dels.nas.edu/bls/stemcells/reports.shtml (2005).
10. National Research Council and Institute of Medicine. 2007 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research. *National Academies of Science* [online], http://dels.nas.edu/bls/stemcells/reports.shtml (2007).
11. National Research Council and Institute of Medicine. 2008 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research. *National Academies of Science* [online], http://dels.nas.edu/bls/stemcells/reports.shtml (2008).
12. Moreno, J. D. & Hynes, R. O. Guidelines for human embryonic stem cell research. *Nature Biotech.* **23**, 793–794 (2005).
13. International Society for Stem Cell Research. Guidelines for the Conduct of Human Embryonic Stem Cell Research, version 1. *International Society for Stem Cell Research* [online], http://www.isscr.org/guidelines/index.htm (2006).
14. Daley, G. Q. *et al.* The ISSCR guidelines for human embryonic stem cell research. *Science* **315**, 603–604 (2007).
15. Hacein-Bey-Abina, S. *et al.* Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. *J. Clin. Invest.* **118**, 3132–3142 (2008).
16. Stayn, S. Navigating emerging legal requirements in human embryonic stem cell research. *Med. Res. Law Policy Rep.* **5**, 297–301 (2006).
17. Stayn, S. A guide to state laws on hESC research and a call for interstate dialogue. *Med. Res. Law Policy Rep.* **5**, 718–725 (2006).
18. Nishikawa, S.-I. *et al.* The promise of human induced pluripotent stem cells for research and therapy. *Nature Rev. Mol. Cell Biol.* **9**, 725–729 (2008).

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FURTHER INFORMATION
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