Cell Stem Cell
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Harmonizing Standards and Coding for hESC Research

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DOI 10.1016/j.stem.2008.02.002

The regulation of human embryonic stem cell (hESC) research has emerged as an important international policy issue. Many governments around the world have sought to advance the field through the development of regulatory frameworks to guide research activities (Knowles, 2004), providing an opportunity to ensure public confidence and enable a more permissive policy context. However, proliferation of these frameworks has raised concerns among scientists that "piecemeal" regulation may hinder the development of new therapies. We propose that developing reciprocal policy agreements between jurisdictions and agreeing on a global coding information system will maximize the potential benefit for researchers.

Researchers' concerns regarding the lack of cohesion across the increasing number of regulatory frameworks span a spectrum of policies ranging from ethical standards for creating and obtaining embryos to licensing, patent, and other intellectual property rules for the use of stem cell lines and cell-based products. In contrast, regulations may be viewed as a means of enhancing public confidence and enabling a permissive policy context for the science. Surveys in the UK, such as the consultation on public attitude to embryo research, reveal that the existence of strong regulation gives people confidence in new techniques being permitted. We recognize the fundamental importance of maintaining ethical standards for creating and obtaining embryos for hESC research, and both the Human Fertilisation and Embryology Authority (HFEA) and the California Institute for Regenerative Medicine (CIRM) organizational mandates include the development of regulations for the safe and ethical procurement of material for hESC research. Recently, both organizations have been involved in deliberations concerning the procurement of gametes and embryos for research. We have emerged from these discussions confident that policies can assure the ethical conduct of research while advancing international exchange and collaboration toward the development of new therapies. This sense of optimism is grounded in our experience from state, regional, national, and international policy deliberations involving extensive consultation with scientists, policy makers, interest groups, and the public. In addition, the comparability of HFEA and CIRM regulations leads us to believe that most jurisdictional policies, while not identical, are often, through discussion and understanding, compatible. This compatibility arises from the common approach utilized to address core ethical concerns. Rather than hinder research, we believe this compatibility can be capitalized on to promote exchange and collaboration. Toward this end, we suggest that efforts be made internationally to develop clarity through consensus standards for coding stem cell lines according to policy criteria. We suggest an international committee made up of scientists, regulators, and stem cell banks be convened to address this issue. We recognize that jurisdiction policies span a range of governance levels and that peer-based self regulation has a vital role. We recommend engaging this full scope of governance into the forum.

The specific areas that coding should address will be considered later in this discussion, but we acknowledge explicitly that such coding should allow for the transparency of difference rather that requiring absolute consensus from the start. Thereafter, a longer-term agreement on standards should be an ambition.

International guidelines and regulations tend to focus on a set of core concerns related to the creation and use of embryos for research purposes (Greely, 2006). Some jurisdictions have permissive policies allowing the creation of embryos for research purposes. A larger number of jurisdictions permit the derivation of stem cell lines from "excess" or "surplus" embryos originally created for assisted reproduction. Others do not allow the derivation of cell lines but permit the importation and use of hESC lines (Okie, 2005). Some nations have no regulatory systems specific to hESC research. Increasingly, jurisdictions are putting such frameworks in place, conscious of the need to ensure standards and public confidence.

Fundamental ethical requirements include review and approval of projects by an independent panel, and voluntary and informed consent from participants (Lomax et al., 2007). Oversight mechanisms vary and include bodies at the institutional, regional, national, or international level or by some coordinated combination of these elements.

While there is consensus with regard to the fundamental requirements for review and consent, policies for material procurement is one area of variation. In particular, policies regarding payments or reimbursements to oocyte donors are often inconsistent. CIRM has adopted a "nothing gained, nothing lost principle" in which donors can receive reimbursement for expenses incurred. The UK has an equivalent standard with regard to reimbursement and also permits a policy that allows In vitro fertilization (IVF) services to be provided at a reduced cost if oocytes are donated for research. This "egg sharing" policy takes into account the costs of stimulation and drugs used in any cycle of donation. The International Society for Stem Cell Research (ISSCR) has adopted a flexible policy allowing payments so long as they do not constitute undue inducement to participate (Daley et al., 2007). Variation regarding benefits or reimbursement for gametes and embryos is important because of the

Table 1. Examples of Questions for hESC Lines	
Source of hESCs	Were hESCs derived from embryos created solely for research purposes?
	Were hESCs derived from embryos originally created for reproductive purposes?
Review and consent	Was derivation of hESC reviewed and overseen by a body independent of the investigator?
	Was voluntary and informed consent obtained?
Reimbursement or payment polices	Were donors reimbursed for gametes or in excess of direct expenses?
	Were donors provided with any other compensation for gametes?
	Were donors incentivized to take part in research or donate gametes?

implications for the use of the resulting hESC lines. For example, the CIRM regulations and the U.S. National Academies' Guidelines adopt an "acceptably derived" standard for hESC lines (National Research Council, 2005). This standard requires consent and oversight and sets limits on payments to donors. One implication of the "acceptably derived" standard is that hESC lines from paid gamete donors are not be available for CIRM-funded research.

Thus, the core concerns related to the ethical conduct of hESC research center around three general issues: (1) source of hESCs, (2) review and consent procedures, and (3) reimbursement polices. Within each of these categories there is variation among jurisdictional policies. Some commentators may perceive this variation as a potential impediment to collaborative research and will advocate for consistent standards in which the sharing of stem cell lines derived from different standards could not transgress any jurisdiction's rules. We would recommend otherwise. Considering societal differences over the application of embryo research, we believe variation is healthy because it serves to enable the advancement of promising scientific inquiry in a manner consistent with the norms and values of the respective jurisdictions.

We believe an appropriate response is the development of standards for the documentation of hESC sources, review, and consent procedures and remuneration policies. Perhaps the most logical mechanism is documentation protocols for hESC banks. Documentation of cell line characteristics is a central function of banks. The primary aim of the UK Stem Cell Bank, for example, is to provide access for researchers to ethically sourced stem cell lines that have been subjected to characterization and quality control in order to guarantee their authenticity, purity, and performance in stem cell research (Healy et al., 2005). To date, banking protocols have focused largely on characterizing the technical and physical qualities of cell lines. Similar documentation is warranted with regard to ethical criteria.

The challenge in any registry system is to develop a discrete coding scheme that addresses variables of concern. For two of the core categories described previously, sources of hESC and payment policies for gamete donors, we believe the universe of possibilities is limited, thus making discrete coding feasible. We hesitate to make specific recommendations, recognizing any proposed scheme should benefit from input from a broad constituency. Rather, we pose key questions relevant to policy considerations that such a scheme should answer (Table 1).

In contrast, the review, oversight, and consent category may prove more challenging. Evaluating such information for a hESC cell line is laborious. In a recent CIRM evaluation involving 21 research institutions, verification of appropriate consent for imported cell lines was identified as the major regulatory challenge. Further, there are normative differences between jurisdictions on how reviews are performed. The HFEA requires peer review of any embryo research and places consenting processes as an essential element within that review. A local ethics committee scrutinizes consent processes even before an application for state license is made. It may be possible to include in any coding system a question on whether such independent scrutiny was required of the project prior to its commencement, including approval of the ethical soundness of the consent process.

A more fundamental solution to the difference in standards between jurisdiction and the potential inconsistencies managed by scientists working across borders may lie in reciprocal policy agreements. For example, the CIRM regulations explicitly allow all stem cell lines derived under HFEA license or in accordance with the Canadian Institutes of Health Research Guidelines to be used in CIRM-funded research. Recognizing reciprocal standards as a matter of policy serves to enhance efficiency by eliminating the need for investigators to conduct independent reviews. Documenting compliance with a jurisdictional standard for hESC line derivation within a coding scheme could advance the ethical conduct of research, improve efficiency, and promote exchange and collaboration critical to advancing the field (Taylor, 2007).

In summary, we believe that most jurisdictional policies regarding the ethical conduct of hESC research are capable of compatibility. This compatibility can be capitalized on to advance international exchange and collaboration by addressing a limited set of information needs and by formally recognizing reciprocal policy arrangements. We recommend the international science community join with representatives of the regulatory bodies to establish a forum to first set the principle issues for coding and agree on a global coding and information system. Second, we encourage policy makers to consider utilizing reciprocal agreements to support exchanges of hESC lines and cell-based products. Finally, we suggest that the international forum work toward a long-term objective of consensus between jurisdictions on the standards themselves.

ACKNOWLEDGMENTS

The opinions expressed in this article do not necessarily reflect the views or policies of the HFEA or the CIRM.

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