



Stem Cell Banks, Libraries and Registries

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Globally, stem cell science continues to progress at an astounding rate. Countries differ in their regulatory approaches to the science, yet it remains an international endeavor. Research teams are composed of scientists from around the globe, and there is a growing need to have access to cell lines that have been created in other parts of the world.

As countries place restrictions on which cell lines may be used for research and under what conditions they may be used, it is increasingly important for scientists to have access to a registry of detailed information about existing cell lines. This information may have a scientific purpose: Is the cell line an appropriate tool for a particular research protocol in that it manifests, for example, a specific disease condition? Or, this information may have a gatekeeping or regulatory purpose: Was the cell line derived under conditions that meet regulatory standards such as with specific written consent?

Several countries, states, and institutions are beginning to house and catalogue stem cell lines to address these questions. These initiatives sometimes differ in both nature and purpose. Facilities that physically house samples are commonly known as banks. Perhaps the best known stem cell bank is the UK Stem Cell Bank (UKSCB), which houses research- and clinical-grade stem cell lines. In the United States the National Stem Cell Bank is hosted by WiCell, a non-profit foundation in Madison Wisconsin, which holds the National Institutes of Health (NIH) stem

cell lines. Recently WiCell founded the International Stem Cell Bank (ISCB) to hold a broader spectrum of stem cell lines including the induced pluripotent stem cell lines (iPS) derived at the University of Wisconsin in 2007. Stem cell registries, on the other hand, do not store cell lines. Instead, registries catalogue stem cell lines and provide certain subsets of information about each line, including provenance, subculture, disease characteristics, derivation, ethics approval, storage facility and contact information.

Stem cell libraries collect detailed scientific information about specific cell lines that comes from research on those lines. Information in these libraries is constantly being added to and updated as research progresses and can be thought of as akin to information collected in the human genome project. For example, in June 2007, McMaster University announced that it would develop Canada's first human embryonic stem cell (hES) library, envisioned as the first facility in the world to focus on understanding the role played by each gene in hES cells.¹ Smaller scale projects also exist, such as the Stem Cell Database run as a joint project between laboratories at Princeton University and the University of Pennsylvania.²

Although all stem cell registries catalogue stem cell lines, they may differ in two major respects. First, they may differ in purpose. Certain registries are created for *regulatory* purposes and contain information relevant to regulatory standards, such as whether or not proper research ethics board (REB) or stem cell research oversight (SCRO) committee approval was obtained. Regulatory registries

1 McMaster University, "Donation will create Canada's first human embryonic stem cell library" Daily News, 27 June 2007, available at <http://dailynews.mcmaster.ca/story.cfm?id=4793>

2 Stem Cell Database, <http://stemcell.mssm.edu/v2/>

may create distinctions between lines according to their designated use (clinical vs. research) or their ability to be supported by government funds according to specific government criteria. Other registries may be created for *research* purposes that are specific to an organization, such as the International Stem Cell Forum (ISCF). Such research registries may or may not make the information they hold publicly available. A second major difference between stem cell registries is the scope of information kept about each cell line. What follows is a description of some of the major existing and proposed stem cell registries and their defining characteristics.

At present, there are five registries that catalogue stem cell lines available for research and commercial purposes. These include the UKSCB's registry [www.ukstemcellbank.org.uk], ISCF's International Stem Cell Characterisation Initiative (ISCI) registry [www.stemcellforum.org/isci_project.cfm], the United States' NIH Human Pluripotent Stem Cell Registry [<http://stemcells.nih.gov/research/registry/>], the European Union Human Embryonic Stem Cell Registry (hESCReg) [www.hescreg.eu], and the International Stem Cell Registry [www.umassmed.edu/Content.aspx?id=48096] launched by the government of Massachusetts. There are many more proposed stem cell registries. An established registry, the ISCI registry is an international research initiative aimed at characterizing "as many human embryonic stem cell (hES) isolates as possible." The ISCI data sets may be browsed online, and participating laboratories' contact information is linked with the stem cell data. In contrast, the NIH and UK registries are national initiatives that consolidate existing hES lines and make them available for purchase and distribution. The NIH registry currently registers approximately 38 cell lines available for distribution. The UKSCB registry currently lists over 100 hES lines that have been approved by the Steering committee for use/import into the United Kingdom. Researchers wishing to use/import these cell lines must apply to the Steering Committee for approval of their project.

Both the NIH and UKSCB registries are components of national regulatory structures for stem cell research. The NIH registry is a commercially focused, mandatory requirement for federally-funded stem cell research. The NIH registry

currently lists international stem cell lines that meet its eligibility criteria and registers lines in Sweden, Singapore, and Israel in addition to those in the United States. The UKSCB registry requires the registration and banking of a stem cell line as a precondition for obtaining a Human Fertilisation and Embryology Authority (HFEA) license. However, the registry also catalogs stem cell lines from other countries, including the United States and Australia.

While the central focus of existing and proposed stem cell registries is on hES lines, the NIH was directed under President G. W. Bush to expand its registry to pluripotent cells. The UKSCB registry also catalogues adult stem cell lines. There are not, at this time, separate registries for non-embryonic stem cell lines. There are several differences between the above-referenced established stem cell registries, including registration and eligibility criteria. These are illustrated in Appendix A.

Regulatory Stem Cell Registries

*The United Kingdom Stem Cell Bank and Registry*³

Under the Human Fertilisation and Embryology Act, 1990, all hES cell lines created in the United Kingdom using donated oocytes must be created pursuant to a license granted by the HFEA. It is a condition of HFEA licenses that a sample of all hES lines derived in the United Kingdom be deposited in the UKSCB. Perhaps the best known stem cell bank in the world, the UKSCB was created in 2003 to act as curator for ethically-sourced, quality-controlled human stem cell lines from all sources, including adult and fetal stem cell lines. Stem cell lines are divided according to their potential use into research-grade and clinical grade lines. The bank stores and maintains detailed information about the stem cell lines. To register a cell line with the UKSCB, a long list of information must be submitted, ranging from details on the license holder and provider of the stem cell line to morphological characteristics in the culture of the cell line. The UKSCB has a Code of Practice that lays out detailed criteria on issues related to ethics and consent.⁴ Although primarily a United Kingdom repository, the UKSCB will register hES lines from international sources.

3 Medical Research Council, "Using the UK Stem Cell Bank." http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Stemcellbank/Usingthestemcellbank/index.htm#P19_725

4 UK Steering Committee for the Stem Cell Bank, "Code of Practice for the Use of Human Stem Cell Lines," Version 2 (March 2005), available at <http://www.ukstemcellbank.org.uk/documents/Code%20of%20Practice%20for%20the%20Use%20of%20Human%20Stem%20Cell%20Lines.pdf>

The National Institutes of Health (NIH) Pluripotent Stem Cell Registry

To date, the NIH has kept a registry of stem cell lines that are eligible for US federal funding, providing investigators with a unique NIH code for each stem cell line and contact information to facilitate their acquisition of stem cell lines. From August 9, 2001 to March 9, 2009, only hES lines derived before August 9, 2001 were eligible for federal funding in the United States. Although President G. W. Bush stated there were approximately 60 lines available at the time of the registry's creation, there are, in fact, only 21 lines available for federal funding, of which only a smaller subset are suitable for research leading to potential treatments in humans. The NIH maintains relatively detailed derivation, investigator contact, and characteristic information on all the cell lines in the Registry. In keeping with his opposition to using human embryos for research, in June 2007, President Bush made an executive order changing the name of the NIH Embryonic Stem Cell Registry to the Pluripotent Stem Cell Registry. This renaming signals a change from a purely hES registry to a broader registry, including all types of ethically produced human pluripotent cells. The stem cell lines in the registry are housed in the National Stem Cell Bank by WiCell, a non-profit foundation associated with the University of Wisconsin.⁵

On March 9, 2009 by executive order, President B. Obama revoked the funding restrictions put in place by past president G.W. Bush. The executive order entitled "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells" permits the NIH to "support and conduct responsible scientifically worthy human stem cell research, including human embryonic stem cell research to the extent permitted by law."⁶ While this will enable hundreds of stem cell lines previously derived to be eligible for federal research dollars, it does not enable federal funding for the derivation of hES. This is due to the annual passage by Congress of the Dickey-Wicker amendment which bans the use of federal funds in research that creates human embryos for research or involves the destruction of human embryos.

Research Stem Cell Registries

International Stem Cell Forum (ISCF)

The ISCF was founded in 2003 by an international group of 21 funders of stem cell research to encourage international scientific and funding collaboration. Its stated aims include the promotion of global good practice and the acceleration of scientific advance in the field. To that end the ISCF has established a set of global criteria for the derivation, characterization, and maintenance of hES lines, called the International Stem Cell Initiative (ISCI).⁷ In June 2007 the ISCF launched an electronic registry to record quality hES cell lines. The registry contains detailed information on subculture protocols, media, and feeder cells, with more limited information on provision of the embryos.⁸ Thus far, only laboratories that have participated in the characterization study may register their cell lines. The ISCF has approved funding for a second phase of the ISCI that will focus on comparing the how hES culture in different media and on any genetic changes that accumulate in hES as they live in cell lines. ISCI also includes provision for collecting data on new hES lines and incorporating these data into the ISCI registry. The Canadian Institutes of Health Research has established an ethics working party to provide the ISCF with legal and ethical advice.

The European Commission Human Embryonic Stem Cell Registry (hESCreg)

In March 2007 the European Commission proposed the creation of a registry for hES lines available in Europe and funded by the European Union's (EU) Research Framework Programme (a European-wide funding initiative). The European hES cell registry is jointly operated by the Centre of Regenerative Medicine in Barcelona and the Berlin-Brandenburg Centre for Regenerative Therapies in Berlin. One of the central organizations in the hESCreg is the Banco Nacional de Lineas Celulares (the Spanish National Stem Cell Bank). One of the first national stem cell banks, formed in 2003, the bank holds both adult and embryonic stem cell lines. The 10 EU countries that currently allow hES research are eligible to register cell lines and must provide a limited

5 WiCell and the National Stem Cell Bank, <http://www.wicell.org>

6 President B. Obama, Executive Order 13505, "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells," http://www.whitehouse.gov/the_press_office/Removing-barriers-to-responsible-scientific-research-involving-human-stem-cells/

7 International Stem Cell Forum, http://www.stemcellforum.org/about_the_iscf.cfm

8 International Stem Cell Forum Stem Cell Registry, http://www.stemcellforum.org/jisci_project/the_registry.cfm

data set on each line, including news on clinical trials, information on hES projects from EU-funded projects, cell line origin and derivation methodology, and different parameters used for characterization. An independent ethics advisory board provides ethical guidance on the information provided and other issues, such as data protection. As of November 2008 there were 300 cell lines in the database that may be freely searched.⁹

American University Initiatives

The US National Academies of Science (NAS) published ethical guidelines for hES research in 2005. These guidelines recommend that all hES research be subject to oversight by an embryonic stem cell research oversight (ESCRO) committee. The NAS recommended that ESCRO committees “maintain registries of hES research conducted at the institution and hES cell lines derived or imported by institutional investigators” and “include on their registry a list of cell lines that have been imported from other institutions or jurisdictions and information on the specific guidelines, regulations, or statutes under which the derivation of the imported cell lines was conducted.”¹⁰ As a result of these recommendations, a number of institutions have proposed establishing internal and external registries, including the University of California, San Francisco and The Harvard Stem Cell Institute. Few registries, however, are currently operational.

The Tri-Institutional Stem Cell Initiative

In May 2005, the Starr Foundation announced that it would donate \$50 million over three years to Rockefeller University, Weill Medical College of Cornell University, and Memorial Sloan-Kettering Cancer Center to be used in part to create a registry of stem cell lines being used on the three campuses. That registry is currently available as an intranet site for faculty and staff. It is unclear whether or not it will become publicly available in the future. The information collected includes details on provenance (where available), gamete donor consent, payment, prior assurance of consent and if there is consent information on file, restrictions, IRB information, and whether or not it is an NIH registry line. As of July 2007, there were 24 lines in the registry.¹¹

The International Stem Cell Registry

In September 2008, the Government of Massachusetts launched a searchable database of hES lines and other pluripotent stem cell lines. Called the International Stem Cell Registry, the registry currently includes profiles of over 190 hES and induced pluripotent stem (iPS) cell lines. The profiles contain data on the derivation, availability and characteristics of each line. In addition, a key unique feature of the registry is a searchable database of publications related to the properties and applications of each cell line. The registry purports to include cell lines from non-profit institutions, academic centers, research enterprises, stem cell banks and industry based in the United States and abroad.

Proposed Stem Cell Registries

At present, proposed stem cell registries include a database by the International Society for Stem Cell Research (ISSCR) for published stem cell lines and a national registry for Canadian hES lines from the Canadian Institutes of Health Research (CIHR).

The Canadian Institute of Health Research (CIHR) Embryonic Stem Cell Registry

In 2006, the CIHR proposed the creation of a national electronic registry for all Canadian hES lines created using CIHR federal funding. As with the UK Stem Cell Bank, participation in the Canadian Stem Cell Registry is to be a prerequisite for CIHR funding of hES research protocols. All hES lines created using CIHR funds are to be made available by the researcher to other researchers, subject to “reasonable cost-recovery charges” as a means of minimizing the need to generate large numbers of cell lines and, therefore, the need for donation of large numbers of embryos. Registration criteria are outlined in the Guidelines for Human Pluripotent Stem Cell Research and include information related to derivation and consent.¹² In 2008 the Stem Cell Oversight Committee of Canada recommended that the registry be expanded to house any hES lines derived by institutions receiving funds from the Canadian research agencies, not just those receiving CIHR funding.

9 European Human Embryonic Stem Cell Registry, <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/07/437>

10 National Academies of Science, “2007 Amendments to the National Academies’ Guidelines for Human Embryonic Stem Cell Research,” http://books.nap.edu/openbook.php?record_id=11871&page=8

11 Phone interview with Kathleen Pickering of Weill Medical College.

12 Canadian Institutes of Health Research, “Updated Guidelines for Human Pluripotent Stem Cell Research,” June 29, 2007, available at <http://www.cihr-irsc.gc.ca/e/34460.html>

The table in Appendix A provides examples of the type of eligibility criteria for inclusion in stem cell banks, and some of the information that can be found in different registries.

References

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Appendix A: Eligibility and Registration Criteria of Stem Cell Banks

Registry	Eligibility Criteria	Registration Criteria
U.K. Stem Cell Bank	<p>It is a condition of an HFEA license that a sample of all human embryonic stem cell lines derived in the UK must be deposited in the UK Stem Cell Bank.</p> <p>The Stem Cell Steering Committee will accept stem cell deposits that are:</p> <ol style="list-style-type: none"> (1) Ethically sourced (2) With fully informed donor consent <p>Cell lines present a valuable resource for the biomedical research community</p>	<ol style="list-style-type: none"> (1) Name(s) of cell line(s) / Number of cell lines (2) Name and title of PI; Name of owner of the cell line (s) (3) Country of origin (4) Origin of cell line(s): embryonic, fetal, adult (5) Grade of cell line: clinical/therapeutic/research (6) Restrictions placed on the use of the cell line by the donor (7) Listed in the registrar of Steering Committee Approved Stem Cell Lines? (8) Listed in the NIH registry? (9) Contact information for PI; provider of stem cell line; person with authority to sign Materials Transfer Agreement; HFEA license holder (10) Information on consent for lines that are not embryonic or produced in the UK (11) Description and characterization of the tissue of origin: fresh or cryopreserved; date of donation; date used or thawed (12) Information of the derivation of the stem cell line (13) Details: the morphological characteristics in culture of the cell line; differentiation characteristics and functional analysis of the cell line; determination of pluripotency; markers used to characterize cell line and result; clonal analysis performed
International Stem Cell Forum	<p>Invitation to research groups to participate in ISCI project</p> <p>Voluntary participation of 17 laboratories in ISCF member countries</p>	<ol style="list-style-type: none"> (1) Participating laboratory (2) Contact name / information (3) Cell line name (4) Cell line derivation: embryo (fresh/frozen); was the embryo used known to carry any mutation; if so please provide details; Whole embryo or isolated inner cell mass (by Mechanical dissociation; by immunosurgery); if immunosurgery, what antibody and complement was used; media used; feeder cell used; time to first passage; subculture methods used to first passage (5) Subsequent cell line maintenance: subculture protocol used media used; feeder cells used; population doubling time, if known; karyotype of cells; alteration over time in (Culture conditions, cell characteristics, karyotype, differentiation, other) (6) Any other comments/information
U.S. National Institutes of Health	<p>Mandatory for those providers applying for NIH funding, stem cell lines must meet the following criteria:</p> <ol style="list-style-type: none"> (1) the derivation process (which commences with the removal of the inner cell mass for the blastocyst) had already been initiated before August 9, 2001 (2) the embryo from which the stem cell lines was derived no longer had the possibility of development as a human being (3) the stem cells must have been derived from an embryo that was created for reproductive purposes (4) the embryo was no longer needed for those purposes (5) informed consent must have been obtained for the donation of the embryo (6) no financial inducements were provided for donation of the embryo 	<ol style="list-style-type: none"> (1) Product Description (2) Cell Line Provider (3) Contact Information (4) NIH Code (5) Provider's Code (6) Date Frozen (7) Culture Method (8) Cryopreservation Method (9) Embryo: Source; Category; IVF Status (10) Characteristics: Passage #; Mouse feeder cells used in isolation; karyotype; Stem cell immunomarkers; gender; Frozen/thawed (short-term / long-term); Pluripotent (11) Commercialization: Available; Price (In U.S. / Outside U.S.); # Shipped