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# Human Embryonic Stem Cell Registries: Value, Challenges and Opportunities

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## ABSTRACT

The accelerating pace of human embryonic stem cell (hESC) research has created an urgent need for the development of hESC registries, information repositories intended to gather, organize and disseminate hESC information. Although of enormous value to this evolving field, registries face significant challenges to their development. These challenges include addressing the legal and ethical issues surrounding hESC derivation as well as complex intellectual property concerns. In addition to these issues, registries must develop tools to efficiently gather, validate and present many different types of hESC information from a variety of sources. Given the pace and regulatory complexities of this field, it is important that registries develop cooperative mechanisms to avoid duplication and more efficiently support hESC research. J. Cell. Biochem. 105: 625–632, 2008. 

**KEY WORDS:** HUMAN EMBRYONIC STEM CELLS; REGISTRIES; hESC

The biology and applications of human embryonic stem cells (hESC) are rapidly evolving. These pluripotent cells provide novel dimensions to understanding development, differentiation and tissue remodeling. hESCs offer options for treatment of acquired and inherited diseases that resist traditional strategies for drug design and discovery. The accrual of insight into the properties and therapeutic potential of hESCs, by investigators in academia and in the private sector, necessitates organizing and integrating current knowledge of hESCs in a manner that is comprehensive and readily accessible.

This review focuses on the need for, and challenges to, the development of comprehensive hESC registries. Registries are defined here as repositories of information intended to assist researchers by providing extensive and up to date information on hESCs. As such, registries must be aware of, and constantly adapt to, the volume of research findings and the complexity of issues in a rapidly expanding field. This review provides a perspective of current issues in hESC research and the status of hESC registries worldwide.

Embryonic stem (ES) cells are a collection of cells found only in very early development. These pluripotent, undifferentiated cells have the potential to be the precursors to every cell type in the human body. The vast majority of cells in the body (somatic cells) fall into specific classes or types, such as muscle, bone and neurons, each of which have unique characteristics and functions. However, these cells are not interchangeable (a muscle cell cannot become a neuron) and most of these cells have lost the ability to divide and create new cells. ES cells differ from all other cells in two important ways. First, they can be induced to change, or differentiate, into virtually any cell type. Second, unlike somatic cells which have finite lifespans, ES cells can proliferate indefinitely in culture. These two unique characteristics give ES cells enormous potential to medicine and science.

hESCs have the capacity to repair damaged organs and replace cells that do not function properly. Since they grow indefinitely, the large numbers of cells necessary to repair or replace these tissues can be produced. Therefore, ES cells can be a renewable source of replacement cells used to treat medical problems that include Parkinson's and Alzheimer's disease, diabetes, strokes, burns, spinal cord damage, and heart disease. However, there are many challenges yet to be surmounted before achieving this goal [Puceat and Ballis, 2007; Klimanskaya et al., 2008]. In addition to their promise for regenerative medicine, hESCs are beginning to play an important role in drug discovery and screening by their ability to produce unlimited quantities of specific cell types for target validation and toxicity testing [Cezar, 2007].

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## CURRENT CHALLENGES IN hESC RESEARCH

### hESC DERIVATION: ISSUES AND ALTERNATIVES

hESCs are derived by microsurgical removal of cells from the inner cell mass of a blastocyst stage embryo. The ethical and moral concerns surrounding the resulting destruction of the embryo has made the derivation and use of hESCs highly controversial [de Wert and Mummery, 2003].

In addition, the pace and direction of hESC research has been shaped in part by the ethical and intellectual property issues surrounding their derivation, as well as concerns about immune rejection in hESC therapy. This has resulted in the exploration of numerous alternatives to the "standard" derivation of hESCs, some of which also address the issue of immune compatibility, as they allow derivation from the cells of a specific individual. The alternatives include:

*Adult stem cells*: The human body has a relatively small number of lineage committed cells. These adult stem cells are capable of differentiating into a defined range of cell types. For example, hematopoietic stem cells are capable of changing into a number of different types of specialized blood cells. However, adult stem cells have limitations. First, they are limited in the number of types of cells into which they can change (i.e., blood stem cells cannot form bone). Second, unlike ES cells, adult stem cells do not appear to have the same capacity to grow and divide indefinitely. Third, they are difficult to isolate as well as grow in the laboratory. For these reasons, although adult stem cells such as bone marrow cells are in clinical use today, adult stem cells are not viewed at this time as a comprehensive alternative to embryonic stem cells.

*ES cells from single blastomeres*: This technique, developed by the biotechnology company Advanced Cell Technology, bypasses the ethical issue of embryo destruction by creating ES cells from a single blastomere that is removed from the embryo [Klimanskaya et al., 2006] utilizing a technique that was originally developed for pre-implantation genetic diagnosis (PGD). This procedure maintains the viability of the embryo. However, it has not been determined if embryonic stem cell lines derived from a single blastomere that does not compromise the embryo can be investigated with NIH funding.

*Somatic Cell Nuclear Transfer (SCNT)*: First dramatically demonstrated in 1996 by the creation of Dolly the sheep [Campbell et al., 1996], SCNT is a method whereby embryos are made by the insertion of a somatic cell nucleus into an enucleated egg [Wilmut et al., 2002]. SCNT is currently in use for reproductive cloning of animals. Although hESC lines have yet to be developed using this technique, recent publications have demonstrated production of primate ES cells [Byrne et al., 2007] and human blastocysts [French et al., 2008] by SCNT. However, the inefficiency of the technique and difficulties in obtaining human eggs are significant challenges to the widespread use of SCNT for the production of hESC.

*Induced pluripotent stem (iPS) cells*: Recent publications from Japan and Wisconsin describe the derivation of ES-like iPS cells from adult mouse and human cells [Takahashi et al., 2007; Yu et al., 2007; Nakagawa et al., 2008]. These researchers introduced specific sets of genes encoding transcription factors expressed in undifferentiated ES cells to reprogram the adult cells. While the initial studies indicate that these cells share characteristics of "true" ES cells, more detailed work is needed to determine how closely they resemble ES cells. In addition, the reintroduction of these genes can have numerous adverse consequences. For example, the retroviral vectors and introduced genes can promote oncogenesis and may also interfere with the physiological balance between growth and differentiation. These challenges will need to be addressed if iPS technology is to move toward clinical application. It is realistic to anticipate that refinements of reprogramming strategies which do not require retroviruses will be compatible with clinical applications. Registries need to be responsive to the excitement surrounding this new technology and some registries plan to or are in the process of listing these cell lines. Due to the potential for rapid development of vast numbers of iPS cell lines, registries will need to develop mechanisms to prioritize the listing of these lines.

### TECHNICAL CHALLENGES

There are several key characteristics of a viable hESC line. These properties include karyotype stability, retention of an undifferentiated state through repeated cell division cycles and prolonged culture, competency for lineage commitment and the ability for reproducible terminal differentiation into a variety of cell types. However, there are frequent reports of heterogeneity between lines and within the same lines in different laboratories. Differences between lines can be attributed to causes that include embryo quality and stage, and variations in the method and reagents (such as feeder cells) used in the derivation. Genetic variation, medical history of donors and even the maternal diet can influence the phenotype of cell lines [Martin et al., 2005]. Characteristics of the same cell line can vary significantly depending upon the culture conditions used [Allegrucci and Young, 2007]. All of these variations can influence the ability of the ES cells to differentiate. Furthermore, approaches and reagents used to induce differentiation have varying degrees of success. Thus, a challenge of hESC research is to obtain comprehensive knowledge of the cell lines and the consequences of disparate technical tools utilized for isolation, maintenance, propagation and differentiation. It has been suggested that a standard set of characterization tests be used to ensure consistency of the hESC lines [Loring and Rao, 2006; Adewumi et al., 2007]. In addition to standardization, there is a need for venues in which detailed methodology can be presented, which rarely occurs in published manuscripts, as well as presentation of negative results. These results, while often not of sufficient impact to warrant publication, are valuable in defining the properties and or quality of a particular line or method.

### INTELLECTUAL PROPERTY ISSUES

Based on the original hESC derivation [Thomson et al., 1998], the Wisconsin Alumni Research Foundation (WARF) and James Thomson of the University of Wisconsin were awarded a very broad patent (# 6,200,806) on the isolation of hESC on March 13,

2001. The patent claims are sufficiently broad-based that any use of hESCs for any purpose may fall under the WARF patent. This patent has been challenged by two groups, the Foundation for Taxpayer and Consumer Rights and the Public Patent Foundation on the basis that the discovery was not unique. Although many researchers are of the opinion that the WARF patents stifle hESC research and innovation, in 2008 the United States Patent and Trademark Office upheld the claims of the WARF hESC patents.

Currently, WiCell Research Institute Inc. (a subsidiary of WARF) requires a licensing agreement, or Memorandum of Understanding (MOU) acknowledging WARF's patent rights, for the distribution of any hESC lines in the US regardless of their source or NIH approval status. In addition, any University receiving hESC for research are expected to sign a MOU with WiCell. As WARF patents are not recognized outside the United States, US investigators may be at a disadvantage in pursuing commercial applications of hESCs. In addition to the WARF patents, the increased patent protection for stem cells and related technologies in the US has raised concerns about the emergence of a patent thicket in which overlapping claims block therapeutic applications of hESCs and the pathways to market—both by causing uncertainty about freedom to operate (FTO) and by imposing multiple transaction costs [Saha et al., 2007].

### hESC REGULATORY MAZE

The regulatory environment surrounding hESC research is complex in the US and globally. Various governments around the world and individual US states have their own legislations, which range from permissive to an outright ban on hESC research. Current US government policy prohibits the use of federal funds (which may comprise at least 80% of biomedical research dollars) for hESC research except for research done using the 78 lines developed prior to 2001 (http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html). Unfortunately, the majority of these lines have proven to be unsuitable for research, leaving 22 lines that are generally utilized. As a result, many states are also providing state funds to fuel research on hESC lines not approved for NIH funding. In an effort to simplify the complex patchwork of guidelines within the US and around the world, several groups have produced, or are in the process of developing, guidelines for hESC research that would provide standards for the derivation, procurement, banking, distribution and applications of hESC and create universally accepted documents such as informed consent forms and material transfer agreements (Table I). In addition, groups such as the Interstate Alliance on Stem Cell Research (IASCR) are working to facilitate collaborative hESC research across state lines within the US, whereas others have focused on facilitating collaborations across international borders. It has been suggested that the solution to the lack of cohesion across regulatory frameworks may reside in reciprocal policy agreements. For example, the California Institute for Regenerative Medicine regulations allow funding for hESC research that utilizes cell lines that were derived in the UK under the Human Fertilization and Embryology Authority license or in accordance with the Canadian Institutes of Health Research Guidelines [Lomax and McNab, 2008]. Despite these efforts, the various guidelines shown in Table I each have their own set of rules regarding provenance of hESC lines, such as the specifics of informed consent and donor reimbursement. The acquisition of detailed provenance information which will identify cell lines that adhere to specific derivation guidelines is becoming increasingly important as researchers apply for funding from various agencies.

## WHY IS THERE A NEED FOR COMPREHENSIVE REGISTRIES?

The challenges outlined above have created an atmosphere for hESC research in the US that has resulted in the concentration of effort on a limited number of hESC lines. An analysis of published studies using the 18 hESC lines listed in the National Stem Cell Bank, which are likely the most widely utilized hESC lines over the past 10 years, suggests that research on human ES cells is dominated by the use of only two lines, H1 (WA01) and H9 (WA09) (Fig. 1).

Although only 22 hESC lines have approval for NIH funding and are in wide distribution, it was reported that over 400 different hESC lines have been derived worldwide as of 2006 [Guhr et al., 2006]. This number has certainly increased, but there is no accurate accounting of the actual number in existence. In addition, most of the existing lines are unpublished and there is little or no information about their quality, characteristics or derivation. The available lines have been derived by many laboratories, both academic and commercial, in numerous countries throughout the world.

A comprehensive hESC registry, which would provide one stop shopping for thorough, up to date information about hESC lines worldwide, is needed. Such a registry would serve as a repository of all vital aspects of hESC lines that would include:

TABLE I. hESC Research Guidelines

| Title | Source organization | Date of first publication |
|---|---|---|
| Guidelines for Human Embryonic Stem Cells Research http://books.nap.edu/catalog.php?record_id=11278 | National Academy of Sciences (US) | 2005 |
| Amendments to the National Academies' Guidelines http://books.nap.edu/catalog.php?record_id=11871 | National Academy of Sciences (US) | 2007 |
| The CIRM Medical and Ethical Standards Regulations http://www.cirm.ca.gov/reg/pdf/reg100010_compregs.pdf | California Institute for Regenerative Medicine | 2006 |
| The Code of Practice http://cop.hfea.gov.uk/cop/ | Human Fertilization and Embryology Authority (UK) | 1991 |
| The ISSCR Guidelines for Human Embryonic Stem Cells Research http://www.isscr.org/guidelines/isscrhescguidelines2006.pdf | International Society for Stem Cell Research | 2006 |
| Guidelines for Human Pluripotent Stem Cell Research http://www.cihr-irsc.gc.ca/e/34460.html | The Canadian Institutes of Health | 2006 |

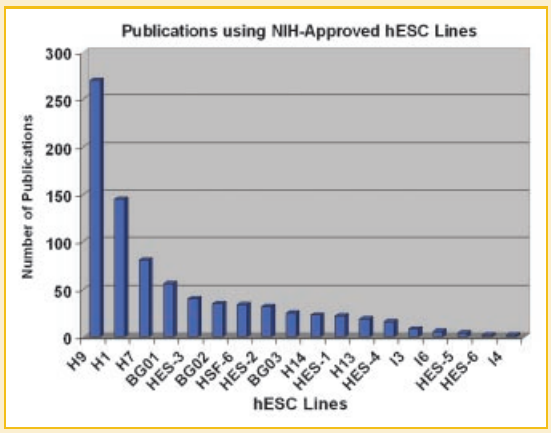


Fig. 1. Cell line publications. Graph representing the number of published studies found in which each of the 18 NIH-approved lines were used. Publications range from 1998 through early 2008.

- Information on the provenance of hESC lines.
- Intellectual property information.
- Availability.
- Published (and unpublished) characterization data.
- Methodologies for each cell line.

Furthermore, such a registry would host an online forum for ethical and methodological discussions, and establish a strong outreach program to educate the general public about the potential benefits of hESC research. The value of a comprehensive hESC registry is significant and includes the optimization of information-gathering and experimental design processes, facilitation of R&D initiatives, and the winning of public support and research funding. Figure 2 depicts how registries can function to gather and disseminate hESC information.

## CHALLENGES TO ACHIEVING A COMPREHENSIVE REGISTRY

There are several obstacles to establishing and maintaining a comprehensive hESC databank or registry. General challenges include efficient initial data collection and subsequent maintenance of the databank to ensure that the information remains current. These functions in existing registries are performed by site curators or steering committees, which depend on data submission from stem cell banks and research communities (Table II). Difficulties in gathering information for every cell line derived to date include the availability of published data and provenance information. Although more than 400 cell lines have been derived, characterization of only 43% of these cell lines have been published in peer-reviewed journals [Guhr et al., 2006]. This is partly due to lack of a cost effective approach for characterization, and the length of time required for characterization. Provenance data such as donor information have not been made available to the public due to their confidential nature. Conflicting reports about certain aspects of ES cells exist [for e.g., see: Buzzard et al., 2004; Draper et al., 2004; Rosler et al., 2004] and may be attributed in part to a lack of consistency in characterizing hESC lines.

## EXISTING REGISTRIES

Although a comprehensive hESC registry does not currently exist, several independent registries provide some of the relevant information mentioned above. There are four types of registries (Table II): (1) registries that are associated with an hESC bank and contain information only for banked cell lines, (2) independent registries that aim to provide information for all cell lines, (3) registries that present characterization information of specific cell

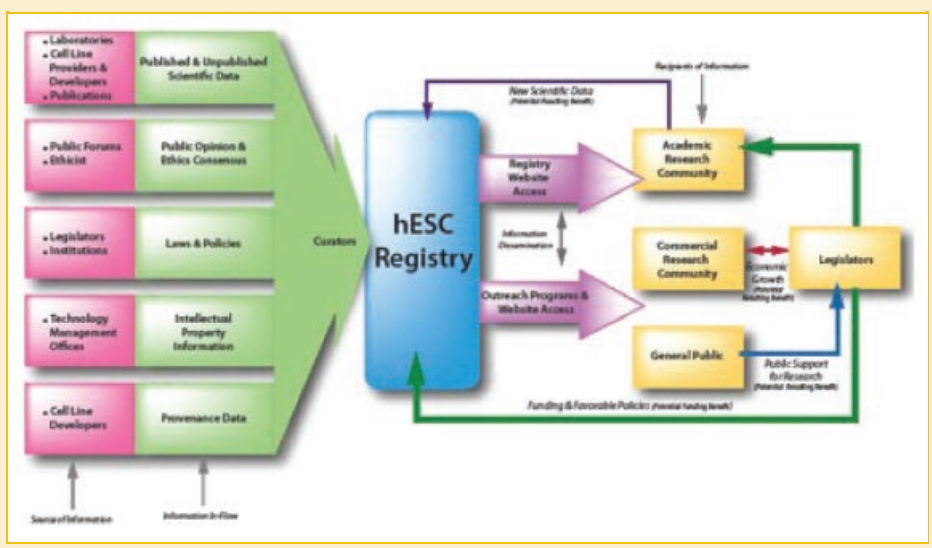


Fig. 2. Information flow through hESC registries. This diagram describes how hESC registries can serve as hubs for the efficient gathering of information from multiple sources, the dissemination of this information to a variety of audiences and the potential benefits that result from these activities.

TABLE II. General Information on Existing Registries

| | NIH registry | Stem cell community | International stem cell forum (ISCF) | European hESC registry (hESCreg) | International stem cell registry at Umass |
|---|---|---|---|---|---|
| Address | stemcells.nih.gov/research/registry/ | stemcellcommunity.org | www.stemcellforum.org | www.hescreg.eu | www.umassmed. edu/iscr |
| Year launched | 2001 | 2005 | 2006 | 2008 | 2008 |
| hESC Bank or Affiliation | National Stem Cell Bank at WiCell, NIH Stem Cell Unit | Scripps Research Institute | UK Stem Cell Bank collected and prepared antibodies for distribution to participating labs | Collaborations between UK Stem Cell Bank, Barcelona Stem Cell Bank and Berlin-Brandenburg Center for Regenerative Therapies | Umass hESC Bank |
| Location of Registry | Bethesda, Maryland | La Jolla, California | | Berlin, Germany | Worcester, Massachusetts |
| Data Gathering Method | Data submitted by developers and SCU | Site curator and graduate students | 17 Labs worldwide | Steering committee as bridge to research communities | 2 Curators and support staff |
| Funding Source | NIH | Donations | ISCF membership comprises 21 medical research funders | 6th Framework Programme for Research and Technological Development of the European Commission | Massachusetts Life Sciences Center |

lines, and (4) registries that are associated with an hESC bank and aim to include information on all cell lines.

As seen in Table II, an example of the first type of registry is the NIH hESC Registry, which is associated with the National Stem Cell Bank and is limited to listing hESC lines that are eligible for federal funding. The second type of registry that is not officially associated with a stem cell bank includes the Stem Cell Community. The International stem cell forum (ISCF) represents the third registry type, providing detailed characterization data for a set of cell lines. The fourth type is represented by the International Stem Cell Registry (ISCR) at the University of Massachusetts Medical School (Umass), which is affiliated with the hESC Bank at Umass and will contain data derived from new findings produced by the bank, as well as existing research publications and unpublished data on all cell lines. The registries listed in Tables II and III have been chosen for this review due to their information content and the number of cell lines listed. These registries were developed at different times, and with different goals, funding sources and methods for data accrual.

## NIH hESC REGISTRY

Published in 2001, the NIH Registry lists the 78 derivations of stem cell lines that according to President Bush's moratorium meet the criteria for federal funding. The purpose of the Registry is to provide investigators with a unique NIH Code for each cell line that must be used when applying for NIH funding and contact information for providers of approved stem cell lines. Only 22 of the 78 eligible cell lines are suitable for research and available for distribution, 15 of which are currently banked and distributed by the National Stem Cell Bank at WiCell. The NIH registry is a pdf file providing basic information for 28 cell lines (a small subset of the total number of existing cell lines) as submitted by their developers. The basic information includes passage number, karyotype and status for stem cell immuno markers. In addition, the NIH Stem Cell Unit (SCU) associated with the Registry has performed characterization studies on 19 cell lines and provides data such as HLA typing, microbiological testing, growth curves and subcloning analyses. The key advantage of performing these assays in a single laboratory is that it allows a direct side-by-side comparison of these cell lines. The primary aim of the SCU is to establish standards for all aspects of the culture process, as well as quality control and monitoring. The NIH Stem Cell website contains a comprehensive primer on stem cell research and related issues, as well as an extensive list of links to other stem cell resources.

## STEM CELL COMMUNITY REGISTRY

This stem cell database was funded by donations and developed in 2005 by the Burnham Institute. It currently lists 260 cell lines and provides basic, limited information for each line. In addition, seven spreadsheets from published and unpublished analyses of gene expression in stem cells have been gathered. This database can be searched for multiple stem cell characteristics and cell lines.

## INTERNATIONAL STEM CELL FORUM (ISCF)

In 2006 the ISCF, funded by 21 international medical research agencies, published results of the International Stem Cell

TABLE III. Strengths and Limitations of Existing Registries

| | NIH hESC registry | Stem cell community | International stem cell forum | hESCreg | ISCR at Umass |
|---|---|---|---|---|---|
| Number of cell lines | 28 | 260 | 59 | 234 | 120 |
| NIH approval | ✓ | ✓ | | | ✓ |
| Provider information | ✓ | ✓ | | ✓ | ✓ |
| Availability | ✓ | ✓ | | ✓ | ✓ |
| Embryo IVF status | ✓ | ✓ | ✓ | ✓ | ✓ |
| Derivation method | | | Detailed information | Detailed information | Links to details |
| Feeder cells | ✓ | ✓ | Detailed information | Detailed information | Detailed information |
| Culture methods | ✓ | | Detailed information | Detailed information | Links to details |
| Passage No. | ✓ | ✓ | ✓ | ✓ | |
| Karyotype | ✓ | ✓ | ✓ | ✓ | ✓ |
| Gender | ✓ | ✓ | ✓ | | ✓ |
| Freeze/thaw testing/method | ✓ | ✓ | | Detailed information | |
| HLA typing | ✓ | | | ✓ | ✓ |
| Microbiological testing | ✓ | | ✓ | ✓ | |
| Genotype | ✓ | | | | ✓ |
| Cell growth | ✓ | | ✓ | | ✓ |
| Subcloning | ✓ | | | ✓ | ✓ |
| Transgenic cell lines | | | | | ✓ |
| Directed differentiation | | | | | ✓ |
| Differentiation (EB/teratoma) | | | Detailed information | Detailed information | Links to details |
| Expression of markers | RT-PCR, IF, FACS | Unspecified assays | RT-PCR, IF | Northern, RT-PCR, IF, FACS, ELISA, Array | RT-PCR, IF, FACS |
| Search features | Browse by cell line | Detailed search | Browse by lab or search by cell line | Detailed search; browse by cell line | Browse by cell line; basic search; literature search |
| Strengths of registry and website | Extensive stem cell primer and links to related resources<br>Side-by-side characterization of cell lines by Stem Cell Unit | Currently lists the most cell lines<br>Limited published and unpublished gene expression data | Raw data and analyzed data<br>Imprinting data<br>Side-by-side characterization of cell lines by 20 labs using uniform methods and common pool of antibodies | Rating of cell lines about information available in registry<br>Side-by-side display of four cell lines<br>Rapid accrual of cell lines that depends on data submission by research groups and banks | Provenance information<br>Searchable listing of publications for individual cell lines<br>Most data have links to sources |
| Challenges | Restricted to 28 approved cell lines | Limited data per cell line | Restricted to 59 cell lines | Amount of registry information per cell line is mostly determined by willingness of cell banks and research groups to provide data | Data accrual for unpublished cell lines |

Not all information is provided for each cell line. This summary is current as of July 17, 2008.

Characterization Initiative, which characterized 59 hESC lines from 17 laboratories worldwide using specified protocols and a common pool of antibodies [Adewumi et al., 2007]. The Initiative was formed to systematically study hESCs in an effort to establish an international set of standards for characterization. Cells and embryoid bodies were cultured under specified conditions and surface antigen and gene expression patterns were established by FACS analysis, immunofluorescence (IF) microscopy and Taqman low-density array (LDA) based assays. Additional data include microbiological status (mycoplasma contamination), imprinting data and assessment of xenograft tumors. Information regarding origins (e.g., embryo status, derivation method), karyotype and culture conditions were also gathered from each participating laboratory. The ISCF study results are organized in two ways: as several files of analyzed data for each cell line or as aggregated data for all cell lines. Individual cell lines can be accessed using a keyword search feature or by browsing the list of cell lines or participating laboratories.

### EUROPEAN hESC REGISTRY (hESCreg)

hESCreg was launched in January 2008 and is funded by the 6th Framework Programme for Research and Technological Development of the European Commission, with an envisaged duration of 3 years. hESCreg is intended to provide information of hESC lines derived and used in the European Union. The Steering Committee of hESCreg, composed of national contacts from the European Union, Switzerland and Israel, provides updates to the registry on scientific and legal developments in their countries as well as on the cell lines that are available. In addition to basic information, hESCreg currently provides results for over 234 cell lines from expression assays such as FACS, RT-PCR, IF, ELISA and arrays. Each listed cell line has a rating that is based on registered information such as hESC line availability, expression of four markers, expression of ISCI core set of markers (Nanog, TDGF, Pou5F1, GABRB3, GDF3, and DNMT3B), culture conditions, provenance documents and legislative information. In addition, hESCreg aims to increase the transparency of human stem cell research and to standardize hESC research by providing links to other repositories, cell banks, regulatory bodies, and, notably, specific research projects. The registry depends on data submission from stem cell banks and research projects. Thus the amount of information and the rate of its accrual are not directly determined by the registry.

### INTERNATIONAL STEM CELL REGISTRY (ISCR) At Umass

The ISCR at Umass was established in 2008 and is funded by the Massachusetts Life Sciences Center. The mission of ISCR at Umass is to provide a searchable, comprehensive database that includes published and validated unpublished information on all hESC lines as well as other pluripotent stem cell lines. For each cell line in the registry, two registry curators gather data from multiple sources, such as publications, online resources (i.e., the NIH SCU, ISCF, etc.) and unpublished data from investigators. In addition, the ISCR at Umass also provides information about the provenance of many of the lines listed in the registry. This information can include a blank consent form and/or a letter that is intended to serve as documentation of provenance from the institution where each cell line was derived. These letters give assurance that the cell lines were derived under a protocol and using a consent form reviewed by an Institutional Review Board, informed consent was obtained for the donation of embryos and there were no financial inducements for the donations. The ISCR at Umass features a searchable hESC literature database that is indexed by cell line and displays search results as links to published studies via PubMed. Links to the data sources are also provided for most of the registered information. The ISCR at Umass currently lists 120 hES and iPS cell lines.

## OPPORTUNITIES FOR hESC REGISTRIES THROUGH COLLABORATIONS

There is often overlap in the goals and information provided by different existing and proposed registries (Table III). In addition to the overlap between some registries, other organizations have expressed the intent to establish specialized registries that focus on a specific set of information. For example, the International Society for Stem Cell Research (ISSCR) is in the process of creating a registry that will provide information on the provenance of hESC lines (personal communication with Heather Rooke and Patrick Taylor, project leads). The existence of multiple registries reduces their effectiveness as useful tools because investigators would need to identify and visit several online resources for hESC information.

There currently exists an urgent need for an integrated approach that supports efficient information exchange within the hESC research community, and now is the optimal time for the registries to work together to organize a concerted effort that will benefit all. Several possibilities exist to collaborate and minimize costly duplication, including one suggested by ISSCR's president, Dr. George Daley. A recent editorial states that Dr. Daley hopes to coordinate with hESCreg so that these databases are complementary and interlinked [Editorial, 2008]. Establishment of a clearinghouse for hESC data was discussed recently at a workshop hosted by the Berkeley Stem Cell Center. The workshop was titled "Institutional Landscape in Stem Cell Research & Development" and addressed a proposal for the sharing of information regarding the technical, proprietary, and ethical characteristics of stem cell research tools developed at public institutions, while also fostering collective licensing approaches [Saha et al., 2007]. Maximal effectiveness will require a global approach toward collaborations among all registries and databases containing hESC information, perhaps through the formation of a comprehensive registry that is "complementary and interlinked." To facilitate discussion of collaborative efforts, the stem cell program at the University of Massachusetts Medical School invited representatives from existing and proposed registries for a workshop in June 2008 and a consensus statement as a platform for collaboration is being developed. We are confident that these discussions will lead to a roadmap for cooperation among registries.

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## REFERENCES

Adewumi O, Aflatoonian B, Ahrlund-Richter L, Amit M, Andrews PW, Beighton G, Bello PA, Benvenisty N, Berry LS, Bevan S, Blum B, Brooking J, Chen KG, Choo AB, Churchill GA, Corbel M, Damjanov I, Draper JS, Dvorak P, Emanuelsson K, Fleck RA, Ford A, Gertow K, Gertsenstein M, Gokhale PJ, Hamilton RS, Hampl A, Healy LE, Hovatta O, Hyllner J, Imreh MP, Itskovitz-Eldor J, Jackson J, Johnson JL, Jones M, Kee K, King BL, Knowles BB, Lako M, Lebrin F, Mallon BS, Manning D, Mayshar Y, McKay RD, Michalska AE, Mikkola M, Mileikovsky M, Minger SL, Moore HD, Mummery CL, Nagy A, Nakatsuji N, O'Brien CM, Oh SK, Olsson C, Otonkoski T, Park KY, Passier R, Patel H, Patel M, Pedersen R, Pera MF, Piekarczyk MS, Pera RA, Reubinoff BE, Robins AJ, Rossant J, Rugg-Gunn P, Schulz TC, Semb H, Sherrer ES, Siemen H, Stacey GN, Stojkovic M, Suemori H, Szatkiewicz J, Turetsky T, Tuuri T, van den Brink S, Vintersten K, Vuoristo S, Ward D, Weaver TA, Young LA, Zhang W. 2007. Characterization of human embryonic stem cell lines by the International Stem Cell Initiative. Nat Biotechnol 25:803–816.

Allegrucci C, Young LE. 2007. Differences between human embryonic stem cell lines. Hum Reprod Update 13:103–120.

Buzzard JJ, Gough NM, Crook JM, Colman A. 2004. Karyotype of human ES cells during extended culture. Nat Biotechnol 22:381–382; author reply 382.

Byrne JA, Pedersen DA, Clepper LL, Nelson M, Sanger WG, Gokhale S, Wolf DP, Mitalipov SM. 2007. Producing primate embryonic stem cells by somatic cell nuclear transfer. Nature 450:497–502.

Campbell KH, McWhir J, Ritchie WA, Wilmut I. 1996. Sheep cloned by nuclear transfer from a cultured cell line. Nature 380:64–66.

Cezar GG. 2007. Can human embryonic stem cells contribute to the discovery of safer and more effective drugs? Curr Opin Chem Biol 11:405–409.

de Wert G, Mummery C. 2003. Human embryonic stem cells: Research, ethics and policy. Hum Reprod 18:672–682.

Draper JS, Smith K, Gokhale P, Moore HD, Maltby E, Johnson J, Meisner L, Zwaka TP, Thomson JA, Andrews PW. 2004. Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells. Nat Biotechnol 22:53–54.

Editorial. 2008. Registries and banks. Nat Cell Biol 10:111.

French AJ, Adams CA, Anderson LS, Kitchen JR, Hughes MR, Wood SH. 2008. Development of human cloned blastocysts following somatic cell nuclear transfer with adult fibroblasts. Stem Cells 26:485–493.

Guhr A, Kurtz A, Friedgen K, Loser P. 2006. Current state of human embryonic stem cell research: An overview of cell lines and their use in experimental work. Stem Cells 24:2187–2191.

Klimanskaya I, Chung Y, Becker S, Lu SJ, Lanza R. 2006. Human embryonic stem cell lines derived from single blastomeres. Nature 444:481–485.

Klimanskaya I, Rosenthal N, Lanza R. 2008. Derive and conquer: Sourcing and differentiating stem cells for therapeutic applications. Nat Rev Drug Discov 7:131–142.

Lomax G, McNab A. 2008. Harmonizing standards and coding for hESC research. Cell Stem Cell 2:201–202.

Loring JF, Rao MS. 2006. Establishing standards for the characterization of human embryonic stem cell lines. Stem Cells 24:145–150.

Martin DI, Ward R, Suter CM. 2005. Germline epimutation: A basis for epigenetic disease in humans. Ann NY Acad Sci 1054:68–77.

Nakagawa M, Koyanagi M, Tanabe K, Takahashi K, Ichisaka T, Aoi T, Okita K, Mochiduki Y, Takizawa N, Yamanaka S. 2008. Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. Nat Biotechnol 26:101–106.

Puceat M, Ballis A. 2007. Embryonic stem cells: From bench to bedside. Clin Pharmacol Ther 82:337–339.

Rosler ES, Fisk GJ, Ares X, Irving J, Miura T, Rao MS, Carpenter MK. 2004. Long-term culture of human embryonic stem cells in feeder-free conditions. Dev Dyn 229:259–274.

Saha K, Graff G, Winickoff D. 2007. Enabling stem cell research and development. eScholarship Repository. Berkeley: University of California. http://repositories.cdlib.org/csls/fwp/48

Takahashi K, Okita K, Nakagawa M, Yamanaka S. 2007. Induction of pluripotent stem cells from fibroblast cultures. Nat Protoc 2:3081–3089.

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. 1998. Embryonic stem cell lines derived from human blastocysts. Science 282:1145–1147.

Wilmut I, Beaujean N, de Sousa PA, Dinnyes A, King TJ, Paterson LA, Wells DN, Young LE. 2002. Somatic cell nuclear transfer. Nature 419:583–586.

Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin II, Thomson JA. 2007. Induced pluripotent stem cell lines derived from human somatic cells. Science 318:1917–1920.