Regulatory Insight into the European Human Pluripotent Stem Cell Registry

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ABSTRACT

The European pluripotent stem cell registry aims at listing qualified pluripotent stem cell (PSC) lines that are available globally together with relevant information for each cell line. Specific emphasis is being put on documenting ethical procurement of the cells and providing evidence of pluripotency. The report discusses the tasks and challenges for a global PSC registry as an instrument to develop collaboration, to access cells from diverse resources and banks, and to implement standards, and as a means to follow up usage of cells and support adherence to regulatory and scientific standards and transparency for stakeholders.

Funding was provided to extend scope, utility, and content of hESCreg to include all human pluripotent stem cell types.

INTRODUCTION

The European embryonic stem cell registry (hESCreg) project was originally established to provide clarity on the human embryonic stem cell (hESC) lines available for research and evidence that they had been isolated from embryos with appropriate informed consent. The technology to generate human induced pluripotent stem cell (hiPSC) lines now permits generation of many human pluripotent stem cell (hPSC) lines in many labs from many different tissue sources. Under new funding, hESCreg will now provide a source of information on both hESC and hiPSC lines that will enable comparison of data on registered lines that might not be otherwise available in the literature and also give evidence of ethical provenance of all lines.

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History and purpose

Since hESCs were first generated in 1998 [1], the ethical debate on the use of human embryos to derive these cells has been fierce [2] and resulted in a fragmented regulatory framework. In the United States, federal funding was restricted until 2009 to research on hESC lines derived before 2001, which triggered several states to expand their funding mechanisms to also include hESC research [3]. In Europe, the legal framework for research with hESC in different countries ranges from a complete ban to a permissive yet highly controlled framework [4]. The diverse regulatory landscape in Europe let the European Commission (EC) devise a funding mechanism for research with hESC, which excludes research activities intended to destroy human embryos for the procurement of hESC lines. It furthermore does not allow funding of human cloning for reproductive purposes; of research intended to modify the genetic heritage of human beings, which could make such changes heritable; and of research intended to create human embryos solely for the purpose of research or the purpose of stem cell procurement [5]. This policy was endorsed by the European Group on Ethics (EGE) in their opinion papers 16 and 22 [101], which also asks for transparency on the ethical provenance and utilization of hESC.

No global resource was available that provided comprehensive information on hESC, their source, available numbers, characteristics, use, and distribution, which made it impossible to guide funding agencies, such as the EC, on the justification for the derivation of new cell lines or the utilization of specific lines.

Table 1. The Main Content Items of hESCreg Are Shown, Comprising Ethics and Regulatory Documentation, Scientific Characterization, Provider Information, and Additional Information

Ethics and regulation	*Cell characterization*	*Provider/user*
Origin of the cell	**Donor phenotype**	**Identification of cell line generator, owner, and distributor**
Informed consent documentation	Derivation process	**Institution/country**
Evidence for regulatory compliance	Genotype	**Specific restrictions on cell availability**
Data protection measures	**Expression/marker profile**	Communication tools/feedback
Specific restrictions	**Evidence of functional pluripotency**	
	Subclones/control lines/genetic modifications	
Additional information (protocols, quality control data, applications, research projects)		

The minimal registration criteria are shown in bold.

The lack of a registry also prevented comparison of results generated with different stem cells in different laboratories and hampered regulatory harmonization and scientific standardization in the field. Moreover, the lack of a registry made it difficult for the EC to verify whether hESC lines used on European-funded projects adhere to the required scientific and ethical standards. Consequently, the EC decided in 2007 to fund the establishment of an hESCreg [6,7]. A second phase of funding was provided in 2013 to extend scope, utility, and content of hESCreg to include all hPSC types together with more comprehensive ethical and scientific information panel. The role of hESCreg to support transparency and traceability of ethical and regulatory compliance has been strongly enforced by implementing a provision of EGE opinion 22 that only lines registered in hESCreg should be eligible for use in projects funded by the EC [101].

Implementation of the European pluripotent stem cell registry

The hESCreg project has established eligibility criteria and protocols for submission and review of cell line to satisfy the need for inclusivity and transparency with respect to ethical provenance, source, and scientific validity of PSC. The minimal scientific criteria for registration include provision of evidence for pluripotency, such as expression of relevant markers and successful differentiation into cells of all three germ layers. Data on cell derivation and characterization are also requested. Supplementary data sets and details of research projects including clinical trials can additionally be uploaded. Required ethical provenance documentation includes the provision of informed consent and data protection information and evidence that appropriate informed consent procedures have been conducted and regulatory requirements were fulfilled. The uploading of original anonymized consent documents supports the identification and proper handling of sensitive ethical issues such as donor traceability and anonymity of genetic data and data access. A summary of the kinds of data obtained by hESCreg is given in Table 1.

To develop links with the scientific community, hESCreg established a committee of national representatives of leading scientists in the area of hESC research. The national representatives are instrumental in gathering information on new research and regulation in their respective countries for hESCreg. Furthermore, hESCreg is able to promote interaction between national representatives and provide information channels with the EC and inform the latter about the status of international hESC research. However, the role of hESCreg is more than provision of an information resource. It supports development of the EU-funding policy specifically by providing transparency on the number, nature, and ethics of hPSC and supports EC in administration on the screening of hESC and hiPSC for eligibility of their use in EU-funded projects and the follow-up of that use. Moreover, the collated up to date information on the status of PSC research supports the timely assessment of funding policies.

Further development and challenges

The number of hESC lines is limited due to the technically and regulatory demanding efforts required for their establishment, which also restricted the extensive proliferation of laboratories generating and working with these cells. An estimated 2000 hESC lines have been established [8], of which about 700 were registered in hESCreg by the end of the initial funding period in 2010. These cells

are principally generated in a controlled regulatory environment. This situation has dramatically changed with the advance of hiPSC in 2007 [9]. The applicability and utility of PSC has since grown rapidly together with new insights into the nature of pluripotency, improved differentiation methods, technological progress in cell cultivation, analysis, and tissue engineering. In addition, other technologies enter the field such as the generation of pluripotent stem cells by somatic cell nuclear transfer [10], which are also eligible for registration in hESCreg.

The uptake of hiPSC technology in many labs was eased by recent scientific and technical progress and a less rigidly controlled regulatory environment and less strict scientific quality assessment requirements when compared to hESC research. This situation has created new challenges for harmonization, standardization, information accessibility and transparency, which are associated with emerging ethical and regulatory demands on privacy protection. The large amount of newly available hESC and hiPSC lines and the development of large-scale banking projects demand expanded roles for centralized pluripotent stem cell registries as an instrument to support standardization efforts and facilitate search and comparison between cells. In addition, risks associated with lack of information about the cells stored in globally acting banks are mitigated, including waste of resources, ethical and regulatory uncertainties, and inadequate stem cell utilization. To prepare hESCreg for this task, several technical improvements are implemented. This includes an online registration tool and expanded options for registration of ethical, scientific, and quality data as well as uploading of documents such as protocols, and ethical and regulatory documentation. The provision of easy browsing of cell- and project-related information for registered cell lines in hESCreg also requires the development of new technical solutions such as semantic search algorithms and ontology-based data organization [11].

EBiSC: The First European Bank for Induced Pluripotent Stem Cells

The European bank for induced pluripotent stem cells (EBiSC) is a collaboration between pharmaceutical companies that are part of the European Federation of Pharmaceutical Industries and Associations (EFPIA), small and medium-sized enterprises (SMEs), and academic institutions with support from the Innovative Medicines Initiative—a public–private initiative in Europe designed to speed up the development of better and safer medicines.

The EBiSC iPS cell bank, a €35 million (44.6 million USD) project, aims to be a central storage and distribution facility for human iPS cells, to be used by researchers across academia and industry in the study of disease and the development of new treatments. For more information on EBiSC, visit http://ebisc.org/

Large banking initiatives with plans to hold tens of thousands of hiPSC lines from stratified populations for preclinical, clinical, and pharmacological research are established in several countries [12]. The European bank of induced pluripotent stem cells (EBiSC) and the StemBANCC projects are sponsored by the EC by its Innovative Medicine Initiative in order to provide well-characterized PSC resources for academia and industry. Furthermore, specialized banks to make available PSC for clinical applications include GMP-grade cells and HLA-typed cell lines with a broad immunological population coverage are under construction, for example, in Japan or the United Kingdom [13,14].

Standards on banking criteria, ethical conduct, cell-type definition, and harmonization of protocols for the generation, maintenance, and differentiation are currently being developed [15]. While this is improving the comparability of data and cells between the different banks and their inventories, there is no central registry currently available for users to search the inventory of the different banks, which would be required to find and define cell cohorts for preclinical or pharmacological studies, to compare their lines, and to build means to facilitate and promote implementation of the banking standards and regulatory guidelines. hESCreg is currently developing means to provide the functions needed for such a global registry. One of the issues related to cell comparison is the current lack of a standardized name for the cells, which causes confusion on the identity of cells and uncertainty in search results. hESCreg has developed and implemented a standardized nomenclature for hiPSC and hESC to avoid multiple naming of the same lines [16].

Not only is a common portal beneficial to provide an overview on large infrastructural projects in PSC research and promote their coordination and networking, but also it helps to improve transparency and avoid redundancy of efforts within the increasingly diversified PSC utilization, including their application in preclinical modeling, pharmacotoxicological testing, and clinical therapy. The availability of a global resource for stem cell-related preclinical model systems, their predictive utility, and their relevance for regulatory compliance will support scientists in their effort to translate research into clinical application. The sharing of the preclinical and trial data could be used as a resource for regulatory agencies to help overcome regulatory hurdles, for example, for stem cell therapies. Similarly, an information hub for clinical trials with hESC- and hiPSC-derived cells may reduce the usage of inefficient models and repetition of failed trials as well as stimulate the development of mode of action and application standards.

While the clinical application of PSC is expected to grow, the diversity of national regulatory hurdles makes it impossible for a global registry to validate cells for their eligibility for clinical use. This is rightly

the task of the responsible agencies and needs a much more detailed assessment of the available data than what a remote registry could do. However, it could serve as a tool to compare the regulatory and trial landscape, and add transparency to the cell's application. Currently, hESCreg offers providers of the cell lines to include information on whether the cells have been derived under GMP, and to upload a QC documentation as well as protocols. Moreover, information on donor traceability, HLA-type, and summary microbiological testing results as well as information about donor phenotype or diseases are registered. In addition, hESCreg maintains a list of ongoing clinical trials with PSC.

The complexity and diversity of national and international regulations relevant for the area of PSC research and application increased dramatically as diversification and application potency for these cells increased. This is not only relevant for the cell's clinical application, where Japan, for example, recently modified its laws to promote research in the field without reduced awareness toward safety [102]. Similarly, a pilot system is established in South Korea to reimburse stem cell therapies by the national insurance system, providing a significant incentive for developments in this area. Aspects of material transfer agreements, patentability, and transnational cell and data transfer are issues where fragmented regulation complicates collaboration and investments. The provision of an overview of the international and national regulatory background has already been established by hESCreg for hESC and will be further developed in other relevant areas concerning PSC such as data and material transfer and clinical trial regulation. Increasing commercialization of PSC may reduce the availability of certain cell lines, especially those obtained from patients with rare diseases, lines with valuable donor information, or lines that have been genetically modified to generate isogenic controls. As these cells are registered in hESCreg, general information on the principal availability of the lines is a required information for their validation.

Ethical aspects of PSC research and application become increasingly relevant and broad. One of the main arguments for establishment of hESCreg in 2007 was the disharmonized ethical procedure and partially unclear ethical provenance of established hESC lines. Hence, hESCreg has implemented mechanisms to provide ethical information for registered lines, including informed consent information. The demands for ethical consent have grown since then, first, because of technological developments in whole genome sequencing and the subsequent possibility for privacy breaks of anonymized data [17], and, second, by the demands put on cells and their derivatives to ensure freedom to operate. Here again, international collaboration requires the sharing of information in areas such as informed consent, handling of incidental findings, data protection, human–animal chimera usage, data, and material cross-border transfer policies and patents. Common ground in ethical procedures within the scientific community may eventually lead to harmonized ethical standards on which legal frameworks could be based. hESCreg is closely collaborating in this area with the Ethics Working Group of the International Stem Cell Forum as well as relevant banking initiatives such as EBiSC, the UK stem cell bank, and the EC, and is open to further expand its network of collaborators.

Outlook

Through the integration and coordination of scientific, ethical, and regulatory data, hESCreg is a tool for harmonization and standardization in the fast developing field of hPSC research. Its interaction with related projects, banks, other registries, and databases is required for data sharing and to make the globally spread information truly accessible. Large stem cell banking infrastructures should be linked through this network in order to make all available cells comparable to commonly used as well as to internal standards and enable the user to make the best use of the established resources.

To make registries relevant also for scientific analysis, it will be required to define cells on multiple levels, including morphology, molecular patterns, or function. The integration of all these different data and annotations in a searchable database requires new bioinformatics instruments and ontologies, which also enable direct interaction with existing resources holding, for example, annotated gene expression data [18,19].

Finally, hESCreg will now begin to establish an overview of the current ethical and legal conditions for the derivation and the use of hESC and hiPSC. This will allow users to decide whether a line is suitable for a certain application, enable sponsors to assess whether the cells used fulfill specific funding requirements and help scientists and companies to comply with the specific legal environment for operation.

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REFERENCES

Primary Literature

1. Thomson JA, J Itskovitz-Eldor, SS Shapiro, MA Waknitz, JJ Swiergiel, VS Marshall and JM Jones. (1998). Embryonic stem cell lines derived from human blastocysts. Science 282:1145–1147. Erratum in: Science 282:1827.
2. McLaren A. (2001). Ethical and social considerations of stem cell research. Nature 414:129–131.
3. Kaiser J and G Vogel. (2010). Embryonic stem cells. Controversial ruling throws U.S. research into a tailspin. Science 329:1132–1133.
4. Druml C. (2009). Stem cell research: toward greater unity in Europe? Cell 139:649–651.

5. Isasis RM and BM Konppers. (2009). *Towards Commonality? Policy Approaches to Human Embryonic Stem Cell Research in Europe*. McGill University, Montreal, Canada, pp. 29–55.
6. Hug K. (2009). Banks, repositories and registries of stem cell lines in Europe: regulatory and ethical aspects. Stem Cell Rev 5:18–35.
7. Borstlap J, A Kurtz, G Stacey, A Elstner, A Damaschun, B Arán, JC Gerlach, JC Izpisúa and A Veiga. (2008). Development of a European human embryonic stem cell registry. Regen Med 3:945–951.
8. Löser P, S Kobold, A Guhr, FJ Müller and A Kurtz. (2012). Scope and impact of international research in human pluripotent stem cells. Stem Cell Rev 8:1048–1055.
9. Takahashi K, K Okita, M Nakagawa and S Yamanaka. (2007). Induction of pluripotent stem cells from fibroblast cultures. Nat Protoc 2:3081–3089.
10. Tachibana M, P Amato, M Sparman, NM Gutierrez, R Tippner-Hedges, H Ma, E Kang, A Fulati, HS Lee, H Sritanaudomchai, K Masterson, J Larson, D Eaton, K Sadler-Fredd, D Battaglia, D Lee, D Wu, J Jensen, P Patton, S Gokhale, RL Stouffer, D Wolf and S Mitalipov. (2013). Human embryonic stem cells derived by somatic cell nuclear transfer. Cell 153:1228–1238.
11. Stachelscheid H, S Seltmann, F Lekschas, JF Fontaine, N Mah, M Neves, MA Andrade-Navarro, U Leser and A Kurtz. (2014). CellFinder: a cell data repository. Nucleic Acids Res 42:D950–D958.
12. McKernan R and FM Watt. (2013). What is the point of large-scale collections of human induced pluripotent stem cells? Nat Biotechnol 31:875–877.
13. Cyranoski D. (2012). Stem-cell pioneer banks on future therapies. Nature 488:139.
14. Taylor CJ, S Peacock, AN Chaudhry, JA Bradley and EM Bolton. (2012). Generating an iPSC bank for HLA-matched tissue transplantation based on known donor and recipient HLA types. Cell Stem Cell 11:147–152.
15. Stacey G. (2012). Banking stem cells for research and clinical applications. Prog Brain Res 200:41–58.
16. Luong MX, J Auerbach, JM Crook, L Daheron, D Hei, G Lomax, JF Loring, T Ludwig, TM Schlaeger, KP Smith, G Stacey, RH Xu and F Zeng. A call for standardized naming and reporting of human ESC and iPSC lines. Cell Stem Cell 2011;8:357–359.
17. Isasi R, PW Andrews, JM Baltz, AL Bredenoord, P Burton, IM Chiu, SC Hull, JW Jung, A Kurtz, G Lomax, T Ludwig, M McDonald, C Morris, HH Ng, H Rooke, A Sharma, GN Stacey, C Williams, F Zeng and BM Knoppers. (2014). Identifiability and privacy in pluripotent stem cell research. Cell Stem Cell 14:427–430.
18. Perez-Iratxeta C, G Palidwor, CJ Porter, NA Sanche, MR Huska, BP Suomela, EM Muro, PM Krzyzanowski, E Hughes, PA Campbell, MA Rudnicki and MA Andrade. (2005). Study of stem cell function using microarray experiments. FEBS Lett 579:1795–1801.
19. Petryszak R, T Burdett, B Fiorelli, NA Fonseca, M Gonzalez-Porta, E Hastings, W Huber, S Jupp, M Keays, N Kryvych, J McMurry, JC Marioni, J Malone, K Megy, G Rustici, AY Tang, J Taubert, E Williams, O Mannion, HE Parkinson and A Brazma. (2014). Expression Atlas update—a database of gene and transcript expression from microarray- and sequencing-based functional genomics experiments. Nucleic Acids Res 42:D926–D932.

Website

101. http://ec.europa.eu/bepa/european-group-ethics/publications/opinions/index_en.htm
102. http://dij.sagepub.com/content/early/2014/03/27/2168479014526877. Hara A, D Sato and Y Sahara. (2014) *New Governmental Regulatory System for Stem Cell-Based Therapies in Japan*. Therapeutic Innovation & Regulatory Science. Published online March 28, 2014.