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Ongoing dynamics in the regulatory landscape of human embryonic stem cell research

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Summary

The international situation regarding the specific nature of regulation on human embryonic stem cell research is still quite complex due to pluralistic historical, cultural and ethical opinions that dominate in respective countries. By establishing the Human European Stem Cell Registry (hESCreg, www.hescreg.eu) in 2007, the EU initiated the first steps towards comparison and science-driven harmonization of hESC legislation. The hESCreg consortium currently includes representatives from 15 countries (including European and non-European countries), who act as National Contacts for hESCreg and regularly update the registry with information on stem cells as well as legislative and ethical discussions in the field of stem cell research. Several of these countries have experienced recent legislative changes; these were implemented in China, Finland, the Netherlands, Norway, the United Kingdom, and the USA. Others expect regulatory changes in the near future, such as in Australia, India, and Turkey. Whilst many countries have introduced legislation to liberalize embryonic stem cell research, others hold to stricter regulations on embryo-derived stem cells (e.g. Turkey, Germany, Hungary, and Italy). In this article we summarize and complete the information on the current status of international hESC regulation provided in our recent report.
Keywords: stem cells, human embryonic stem cells, law, regulatory, legislation, pluripotency

Introduction

The young field of stem cell research leads to a change of paradigm in the modern medicinal world from a symptomatic to a causal treatment of previously untreatable diseases such as Parkinson's disease, Diabetes mellitus, and heart failure. In 1998, the first human embryonic stem cell (hESC) lines were established in the USA [1]. It was in 2002 that the combination of somatic cell nuclear transfer (SCNT), ES cell derivation, and gene therapy in a mouse model provided indications for autologous treatment of immune deficiencies in the near future [2]. The reprogramming of adult somatic cells into pluripotent cells was achieved by 2006 [3], marking a milestone with fundamental implications on developmental dynamics, which also challenged the categorization of cells by potency. The first human-induced pluripotent stem cells (hiPSC) via transference of pluripotence-associated genes were produced in Japan [4]. Although hiPSC have already had a great impact on the development of therapeutic strategies, hESC remain the benchmark for characterization of pluripotency. A unifying problem for the research on hESC or hiPSC is the lack of standardized methods and criteria to characterize pluripotency, which are essential for comparing scientific results and controlling the risks in future clinical and diagnostic applications. A harmonized regulatory landscape of stem cell research would promote an environment for the efficient development of internationally accepted standards for pluripotent cells characterization and their donation, handling, and application.

In order to reach this goal it is necessary to make regulations and their current changes known and transparent to the stem cell research community, regulators, and stakeholders. hESCreg provides an efficient tool and central platform for the registration and documentation of human embryonic stem cell (hESC) lines being derived and available to the European Union and beyond [5, 6, 7, 8]. Currently, the registry holds information on more than 700 hESC-lines and several hiPSC-lines (see figure 1). hESCreg is coordinated by the Berlin-Brandenburg Center for Regenerative Therapies (BCRT) and the Center for Regenerative Medicine Barcelona, with the UK Stem Cell Bank as a lead partner. Community representatives from more than 15 countries act as National Contacts for hESCreg. These are Australia, Belgium, the Czech Republic, China, Denmark, Finland, France, India, Israel, the Netherlands, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the USA.

	Regulatory Positions on Human Embryonic Stem Cell Research	List of Countries
•	• hESC research permitted • derivation of new hESC lines from supernumary IVF embryos permitted • SCNT permitted	Australia, Belgium, China[1], Finland[2], Norway, Spain[1,3], Sweden, the Netherlands, UK[1,2], USA[4]
•	• hESC research permitted • the derivation of new hESC lines from supernumary IVF embryos permitted • SCNT prohibited	Czech Republic, Denmark, France, Israel, Portugal[3], Switzerland, India
•	• hESC research permitted only with imported hESC lines • derivation of new hESC lines from supernumary IVF embryos prohibited • SCNT prohibited	Germany, Italy, Hungary, Turkey

Table 1. Regulatory Variations for Embryonic Stem Cell Research in National Contact countries of hESCreg. Whilst certain countries enable specific legislation on hESC research there may be an effective ban on such research in others. The three different colored sections in the table resemble the three different positions on hESC research in Europe and beyond. For a geographical overview please see figure 1.
1 creation of interspecies embryos allowed,
2 law open to interpretation as regards SCNT,
3 compensation for embryo or cell donation,
4 not with federal funding as outlined in Dickey-Wicker.

Relevant legislation and its practical interpretation in selected countries

The following section describes the legal situation in countries where a) hESCreg has a National Contact representative, and b) which have been selected due to recent or upcoming changes in their hESC-specific legislation: Australia, China, India, Finland, the Netherlands, Norway, Turkey, UK, and the USA (see also figure 1 and table 1).

Information on hESC legislation in other National Contact countries of hESCreg, such as Belgium, the Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Portugal, Spain, Sweden, and Switzerland can be found in another of our recent publications [6]. In both articles we focus on regulatory issues such as pre-implantation genetic diagnosis (PGD), procurement of embryos for research, research on and derivation of hESC lines from a) supernumerary embryos coming from in-vitro fertilization (IVF) programs and that are no longer intended for clinical use, and b) embryos created for research, i.e. human embryos created by IVF with donated gametes and not intended to induce pregnancy, creation of embryos by SCNT, and the creation of interspecies embryos including cytoplasmic hybrid embryos and hiPSC.

The legislative bases for human embryo and hESC research in **Australia** are the Act on Prohibition of Human Cloning for Reproduction (2002), and the Act on Research Involving Human Embryos (2002), both being amended in December 2006 and effective from June 2007 on. They allow the creation of IVF and SCNT embryos as well as the derivation of hESC lines from these sources as well as research on hESC lines. PGD is allowed. Further regulatory changes are already expected in 2010.

In **China** the guidelines on human embryonic stem cell research from 2003, which were amended in March 2009, now allow the creation of supernumerary IVF and SCNT embryos for research. Moreover, PGD is permitted and the use of surplus PGD embryos and interspecies embryos are allowed.

Finland experienced the last amendment of the Medical Research Act 488 from 1999 in November 2009. The production of embryos for research purposes is prohibited. The legislative text is open to interpretation whether the creation of SCNT embryos is permitted or not, since the definition of an embryo refers to a "living group of cells resulting from fertilization". The creation of an IVF embryo is not regulated in the law but the research on surplus IVF embryos is allowed. Regulation of the research on PGD embryos as well as the derivation of hESC lines from supernumerary PGD or IVF embryos is open to interpretation of the legislative text.

In **India** the DBT-ICMR guidelines regulate issues on stem cell research but have not become law yet. The creation of embryos by SCNT is allowed, this issue falls under "restricted areas of research" of the DBT-ICMR guidelines. The derivation of hESC lines from supernumerary IVF embryos is allowed, as is the research on embryos and hESC lines.

The Netherlands' Embryo Act from 2002 was amended in 2007. The creation of embryos solely for research purposes is not allowed. The creation of IVF embryos for research purposes is not allowed. The derivation of hESC lines from supernumerary IVF and SCNT embryos for research is allowed if no other source than embryonic stem cells can be used as an alternative. PGD is allowed. Both, hESC line derivation and PGD must be applied at and approved by the CCMO (Central Committee for Research Invol-

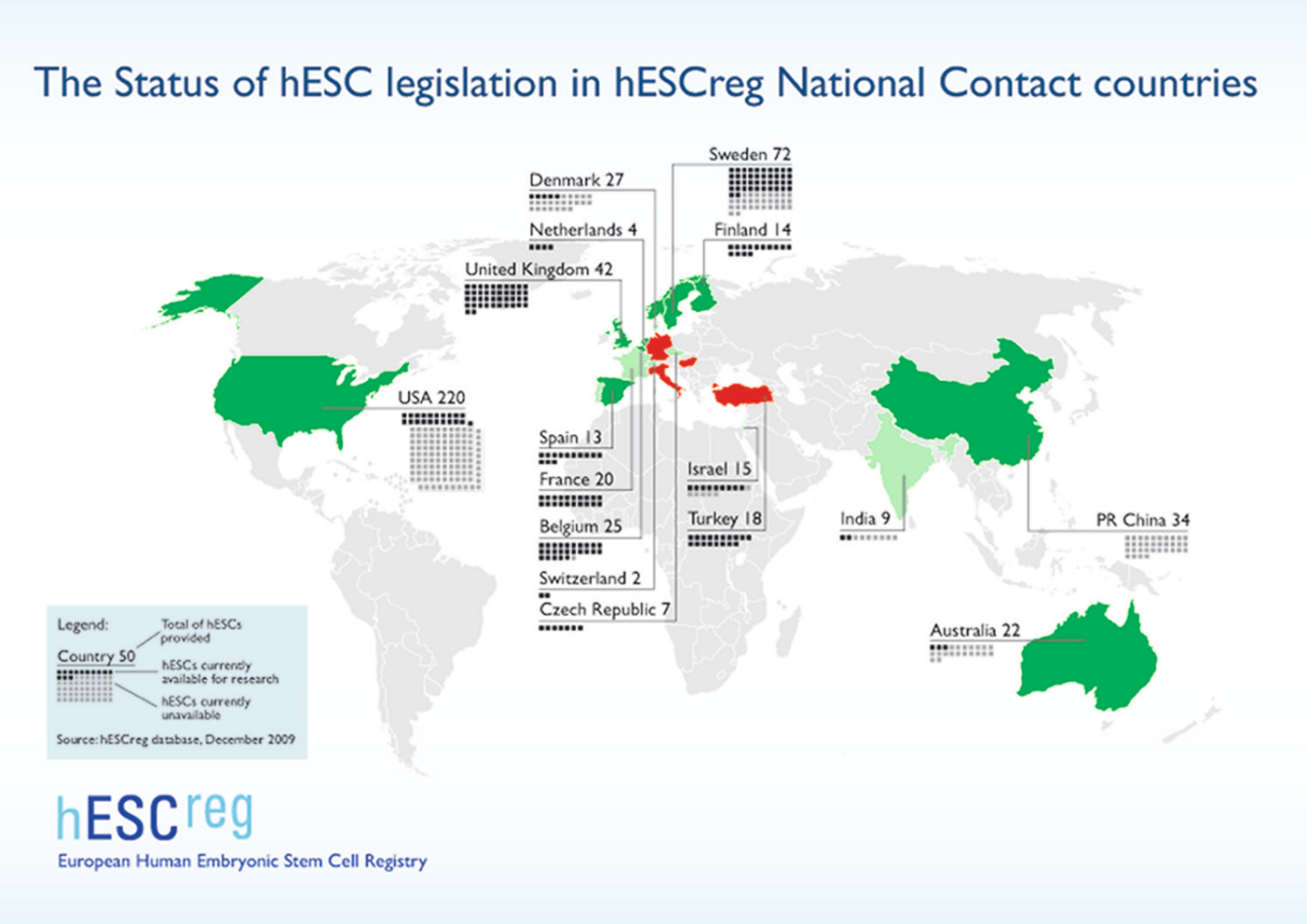

Figure 1. The Status of hESC Research Legislation in National Contact countries of hESCreg. The three different colors resemble the three different positions on hESC research: For a detailed overview please refer to table 1. Dark green: hESC research and derivation of hESC lines from supernumerary IVF embryos permitted, SCNT permitted, Light green: hESC research and derivation of hESC lines from supernumerary IVF embryos permitted, SCNT prohibited, Red: hESC research permitted only with imported hESC lines, hESC derivation and SCNT prohibited. Number of hESC provided = number of hESC lines derived in the respective country.

ving Human Subjects). There are no further changes expected before 2012.

The **Norwegian** Biotechnology Act from 2007 was revised in 2008. It does not allow the creation of IVF embryos for research purposes. Research on supernumerary IVF embryos and PGD embryos is allowed. The derivation of hESC from supernumerary IVF embryos and SCNT for medical and biological research is allowed.

In **Turkey** the act "By-law on centers for in vitro fertilization and embryo transfer" concerning research on human embryos from 1987 was amended in 2005. IVF and PDG are legal in the country. hESC research is not regulated by a specific law. However, the Ministry of Health announced a 2005 memorandum stating that until specific guidelines are established, hESC derivation and research should not be performed in the country. Research with imported hESC lines may be performed. A new act is expected to be announced in 2010. For that, it is expected that hESC derivation for research purposes and hESC research will be regulated and allowed in certain qualified institutions and under certain conditions (such as lines with genetic diseases).

In the **United Kingdom** the Human Fertilisation and Embryology Act, which became law in 1990, was amended at the end of 2008 and legalizes the creation of embryos (including artificial techniques as SCNT) and the creation of interspecies embryos for research. The derivation of hESC lines from supernumerary IVF, SCNT and interspecies embryos are allowed. The definition of an embryo now includes embryos created by cloning and other processes.

In the **USA** there are different legal situations with respect to embryo and hESC research. The federal law concerning human embryo and embryonic stem cell (hESC) research is the Dickey-Wicker Amendment of 1995, which was again amended in 2009. The research on hESC lines and the derivation of hESC lines from IVF embryos, from embryos created by SCNT and from human admixed embryos is allowed but not for those projects with federal funding as outlined in the Dickey-Wicker Amendment. NIH-funded research is allowed with NIH-approved cell lines only. The NIH reviews information on informed consent and derivation for each line it registers. Non-federally funded research is reviewed by institutional review boards (IRB/SCRO). Creation of embryos for research must follow an IRB-approved protocol (45 CFR 46.107). In addition, IRB/SCRO committees tend to follow national guidelines such as those established by the National Academies of Science and the ISSCR.

Conclusion

Novel legislation and legislative changes need to take into account scientific progress and must be flexible enough to accommodate novel research results and the subsequent changes in the foundations of ethical views. It is unlikely that there will be a single universally accepted view on the ethical, legal, and moral status of the embryo as such, nor on the use of hESC lines derived thereof [5, 6]. But the recent advances in reprogramming show an enormous dynamic and developmental potential of almost any cell and thus question the basis for defining the embryo only as inherently totipotent. Totipotency is probably not inherent to cells derived from embryos and may become inducible by technical means from any differentiated adult cell, for example through the generation of sperm and oocytes from hiPSC. These questions are not yet or only partially reflected in legislative texts. Japan, for example, has prohibited the use of hiPSC for the creation of human gametes, embryos, and their implantation into animal or human wombs [9, 10]. It is therefore expected that the legislative and regulatory landscape will continue to change and that the pressure for international harmonization and transparency will increase.

An essential requirement is therefore the transparent information of what can be done with hiPSC and hESC. One of the tasks of the hESCreg is the reflection of international pluralism by providing information on each registered cell including its source and characteristics, as well as the ethical provenance [6, 7, 8]. This will be one aspect for safeguarding high standards in relation to ethical concerns and transparency in research. Consequently, the European Commission might use hESCreg as a central reference for all funding decisions on proposed hESC research projects within the Seventh EU Framework Programme.

Furthermore, hESCreg is also involved in providing information to the public about this highly sensitive field of research and its legal framework. By providing transparency an increased acceptance of this work is expected. Future tasks of the registry will include the establishment of a pluripotent stem cell registry at the international level, the inclusion of all types of pluripotent stem cells (hiPSC and others), the integration of a knowledge-service tool, the inclusion of banking service tools, the provision of an open and standardized common forum for exchange, and last but not least the development of guidelines for standards, governance, and ethical procurement of pluripotent stem cells.

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Текущая динамика правового регулирования исследований эмбриональных стволовых клеток человека

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Резюме

Специфика межнациональных особенностей основ правового регулирования в области научных исследований эмбриональных стволовых клеток человека (ЭСКЧ) все еще остается весьма сложным вопросом из-за множества исторических, культурных и этических мнений, которые преобладают в тех или иных странах. Путем учреждения Европейского Регистра стволовых клеток человека (ЕРСК, hESCreg, www.hesc-reg.eu), Европейский Союз в 2007 г. инициировал первую концепцию, касающуюся сравнений и научно обоснованной гармонизации законодательства в области ЭСКЧ. Консорциум ЕРСК в настоящее время включает в себя представителей 15 стран (в том числе европейских и неевропейских государств), которые действуют в качестве национальных контактных организаций, и регулярно обновляют Регистр информацией о стволовых клетках, а также о законодательных и этических дискуссиях в области исследований стволовых клеток. Некоторые из этих стран недавно испытали серьезные изменения законодательства, которые вступили в силу в Китае, Финляндии, Норвегии, Великобритании и США. В других странах ожидаются изменения правил в близком будущем, как, например, в Австралии, Индии и Турции. В то время как многие страны ввели законоположения, направленные на либерализацию исследований ЭСК, некоторые государства придерживаются более строгих правил, касающихся ЭСК (например, Турция, Германия. Венгрия и Италия). В данной статье обобщена и собрана информация о нынешнем состоянии международных правил ЕРСК, которая представлена нами в настоящем докладе.

Ключевые слова: эмбриональные стволовые клетки, человек, исследование, законодательство, Европейский регистр