

European Scientific, Ethical, and Legal Issues on Human Stem Cell Research and Regenerative Medicine

OUTI HOVATTA, MIODRAG STOJKOVIC, MARIA NOGUEIRA, ISABEL VARELA-NIETO

INTRODUCTION

In 2002, the European Science Foundation (ESF) published a Science Policy Briefing entitled Human Stem Cell Research: Scientific Uncertainties and Ethical Dilemmas. Since then there have been significant advances in the field of research, notably the emergence of regenerative medicine (RM) which promises to be a fascinating development, opening the possibility of repairing or replacing tissue or organ function lost due to age, disease, damage, or congenital defects using human stem cells (hSCs)—an approach that also raises ethical issues.

The increase in chronic diseases and population ageing has led to an increasing demand for transplantation of organs such as liver, heart, lung, and kidney. There are currently 56,000 patients waiting for a suitable organ donor in the European Union (EU). Less invasive treatments, such as enabling regeneration of damaged heart tissue with hSCs, would help alleviate this problem.

The European Medical Research Councils at the ESF established a High-Level Expert Group which made specific recommendations intended to stimulate continuing efforts by relevant stakeholders to ensure that SC research is developed into RM applications and other benefits for patients, when ensuring that research is conducted in accordance with accepted principles of ethics. With this article, the ESF aims to summarize the current scientific and ethical issues that surround hSC research in RM, review the current legislation landscape in Europe, and set out the position of the ESF on future priorities in this area. The new updated Science Policy Briefing “Human Stem Cell Research and Regenerative Medicine: a European Perspective on Scientific, Ethical and Legal Issues” has now been published by the ESF (ESF Science Policy Briefing 38. 16 pp, ISBN 978-2-918428-12-1) and is available at: ww.esf.org/publications/science-policy-briefings.

Embryonic, induced pluripotent stem (iPS) cells, fetal, adult- and tissue-derived stem cells are all the focus of active research in European countries and elsewhere. All these different types of SCs have their own characteristics and are important in research, representing potential sources of cells for clinical use. At this stage it would be premature to consider limiting any potential avenues of research.

In August 2009, there were approximately 650 hESC lines worldwide and many of these (252 European and 349 non-European) are registered in the European Human Embryonic Stem Cell Registry (www.hescereg.eu) funded by the European Commission.

The International Stem Cell Forum (ISCF), a 21-member organization (academies, research institutes and councils, foundations) has managed extensive projects such as the International Stem Cell Initiatives (ISCI) involving several European laboratories. ISCI1 aims to extensively characterize a larger number of hESC lines worldwide, whereas ISCI2, which addressed the culture conditions, is completed; ISCI3, exploring the genetic stability of hESCs, is underway. hESCs also provide methods to evaluate disease mechanisms and high-throughput screening of new compounds for drug development.

The use of somatic cell nuclear transfer (SCNT) to obtain patient-specific SC lines has been superseded in European laboratories by the introduction of the new promising alternative of reprogramming somatic cells to pluripotency using defined factors (iPS cells). There is now intensive research worldwide to develop methods for inducing pluripotency to achieve safe iPS cells for cell transplantation in clinical trials. iPS cells already represent a unique route for drug development and for studying inherited or environment- and age-related human diseases.

The EU Tissues and Cells Directive (EUTCD, http://ec.europa.eu/health/ph_threats/human_substance/legal_tissues_cells_en.htm) regulates the quality of all cells used in human therapy including hSCs and requires Good Manufacturing Practice-based production systems for clinical applications. Additional requirements in terms of quality of procedures and cleanliness of products exist in the case of hSCs.

Adult- and tissue-derived stem cells are already being used clinically, for example, hematopoietic SCs for bone marrow transplants since 1968. However, SCs derived from adult tissues such as the skin, adipose tissue, and bone marrow are still at an early-stage of evaluation in clinical trials. Mesenchymal stem cells (MSCs) are the most popular type of adult SCs for these clinical applications and the type of adult SC that is expected to reach clinics next. The websites of the European Community EudraCT (<https://eudract.emea.europa.eu/>) and of the US National Institutes of Health (www.ClinicalTrials.gov) provide information on the 107 current clinical trials based on the use of MSCs. Eight of these trials are in phase III as of April 2010, but only one (just completed) testing the use of MSCs in graft-versus-host-disease involved European clinical centers, in Italy, U.K., and Spain. However, European involvement is much higher in phase I/II clinical trials, most of these being investigator-driven (not industry-driven) trials: 25 of the 82 current phase I/II trials using MSCs are based in 12 different European countries (Belgium, Denmark, Italy, Germany, the Netherlands, Norway, Spain, U.K., France, Finland, Ireland, Slovenia). Therapeutic indications of ongoing clinical trials using adipose-derived SCs include steroid-refractory graft-versus-host disease, periodontitis, severe chronic myocardial ischemia, distal tibia fracture, osteoarthritis, decompensated liver cirrhosis, multiple sclerosis, tumor-induced osteomalacia, vascular diseases, diabetes, fistulising Crohn's disease, and several others.

The ESF Forward Look Investigator-Driven Clinical Trials (<http://www.esf.org/idct>) makes recommendations on the conduct of clinical trials, most of these being applicable to the hSC research field, such as the need for harmonizing the mission and role of ethics committees and increasing the ethical standards of clinical trials, and the need for fully exploiting the knowledge produced by new medical breakthroughs.

Safety aspects, such as tumor formation, immunogenicity, epigenetic status, and stability, are the major current issues facing the clinical use of all types of hSCs worldwide.

Ethical and legal issues are crucial in Europe. In most European countries ethical approval and informed written consent of the patient are required for all use of human cells and tissues. Consent is the central focus of legislation relating to access to identifiable patient data and use of identifiable tissue for research (<http://www.wma.net/en/30publications/10policies/b3/index.html>). All donors must be fully informed in writing, in particular, about the aims of the research and any potential commercial interest.

Advanced Therapies refers to Regulation European Commission (EC) No 1394/2007 on Advanced Therapy Medicinal Products that will bring gene, cellular, and tissue-based therapies together within a single, integrated European regulatory framework. This regulation was formally adopted by the EU Council and entered into force on December 30, 2007. The implementation plan has been agreed with the European Medicines Agency.

Patenting hESCs at the European Patent Office (EPO) has proved to be a difficult process as national states implement different policies on the topic of human embryonic stem cells (hESC) research. The European Patent Convention (EPC) regulates the granting of patents (examination, issuance) but the legal effects (validity, infringement) of a patent fall under national jurisdiction. The EPC prohibits hESC patentability on ethical grounds for inventions whose “exploitation or publication would be contrary to ordre public or morality.” Furthermore, the EPC does not allow patenting on “uses of human embryos for industrial or commercial purposes” (EPC: “Under Article 53.(a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following: [...] (c) uses of human embryos for industrial or commercial purposes.”) [4–6]. Nonetheless, the current EPO approach to patenting hESCs in Europe requires a revision to adapt to the fast development of SC technologies, an issue that European leaders should address quickly.

Legislation Across Europe

One of the recommendations from the previous 2001 and 2002 editions of the ESF Science Policy Briefing Human Stem Cell Research: Scientific Uncertainties and Ethical Dilemmas was to update the table of regulations on the use of

hSCs in the 30 ESF membership countries (see Annex 1 of the ESF Science Policy Briefing 38, data from <http://www.hescreg.eu/index.php?id¼8> and <http://www.isscr.org/public/regions/region.cfm?RegionID¼1>). In summary, 25 countries have adopted legislation which explicitly prohibits human reproductive cloning (excluding Poland, Lithuania, Ireland, Croatia, and Luxembourg). Seven countries allow hESC research and the derivation of new hESC lines from supernumerary in vitro fertilization embryos by law (Belgium, Sweden, U.K., Spain, Finland, the Czech Republic and Portugal). The same countries allow SCNT by law except Finland and the Czech Republic who neither prohibit nor allow it. Three countries have adopted legislation to allow the creation of embryos for research purposes under strict conditions (Belgium, Sweden, U.K.). Currently, 17 countries allow the procurement of SCs from supernumerary embryos and six countries have not adopted legislation regarding hSC research (Bulgaria, Croatia, Cyprus, Luxembourg, Romania, and Turkey). This ever expanding field needs constant updating of legislation and new thinking on the ethical questions that arise. For instance, there are different ethical aspects to be considered in iPS cell research compared with hESC research.

Seven Statements and Recommendations Were Made by the ESF Working Group

1. Continued research on all types of SCs derived from embryos, fetal tissues, and adults remains necessary as it is too early to predict their value in a specific field. Research using embryonic and iPS cells are required, as the knowledge derived from both is complementary and for the moment the benefits and risks are not sufficiently known.
2. Although clinical research is clearly important, basic research remains essential to understand cellular differentiation and function.
3. The lack of common criteria and universal standards for the preparation of SCs has greatly hampered further progress. Furthermore, functional characterization of SCs is limited by the available methods for in vitro differentiation. There is an urgent need for a comprehensive understanding of SC identity and characteristics.
4. Progress toward therapies would be faster if researchers across Europe were given equitable research opportunities provided that balanced facts about the risks and benefits of research are understood. If therapies become available, all patients across Europe should have equitable access to such therapies.
5. In view of safety concerns relating to SCs in clinical applications, chemically defined animal substance-free products and standard operational procedures (SOPs) should be further developed and implemented. Aspects including proof of functionality, safety, quality control, storage, and banking need to be addressed before therapy enters the market.

6. More studies about the immunogenicity, epigenetic status and stability of SCs, and the immune response of the human organism are needed.

7. Public funding, including at the European level, is necessary to support the translation and implementation of SCbased products into the market.

FUTURE OF STEM CELL RESEARCH IN EUROPE

SC research in Europe has proceeded at a rapid pace over the past decade with a high level of science being maintained in a field that has become globally competitive. Provided that adequate funding is maintained and unresolved issues surrounding patents are addressed, there is hope that new treatments for many severe diseases could emerge. SCs offer the opportunity for the revolutionary therapy and medical challenge of the 21st century, a challenge that needs to be met by the EU based on ethical principles that may differ between European countries, on respect for human rights both within and outside EU frontiers, and on the intellectual integrity that has built the identity and democracy of today's Europe.