Ethics assessment in different fields

Stem cell research

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Annex 2.c.7
Ethical Assessment of Research and Innovation: A Comparative Analysis of Practices and Institutions in the EU and selected other countries
Deliverable 1.1

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Contents

1 Introduction[1]

The possibility of repairing or replacing tissue or organ function lost due to age, disease, damage or congenital defects, using human stem cells (hSCs), raises deep ethical issues, often evoking strong emotions.

Even with increased support for research projects in transplantation, there remains an enormous need for Regenerative Medicine (RM) therapies[2]. In the last decade, research in these areas has been translated into early clinical trials with mixed results, raising hope amongst patients.

There are many different sources of hSCs, each having their own advantages and disadvantages. The various types of hSCs are based upon a taxonomy devised by Professor Austin Smith, as published in Nature in 2006[3].

One significant factor that has influenced the course of hSCs research is the ethics surrounding their use.

The value of hSCs research for RM is significant and its value is not only restricted to its direct application towards cell-based therapies, but also in areas such as the development of hSC-based models of disease and drug discovery and development. Significant advances have been made since 2002, including, for example, understanding how Mesenchymal Stem Cells (MSCs) impair autoimmunity. As a result, allogeneic MSCs can be explored in a variety of clinical settings, although much remains to be learnt about how to control and direct hSCs fate and function in a patient.

2 Sources of the stem cell tissues

2.1 Sources of Stem Cells

2.1.1 Foetal stem cells

Foetal SCs can be derived from umbilical cord blood after delivery or from foetal tissues after termination of pregnancy or spontaneous abortion. For cell therapy purposes, there are two types of foetal SCs that are currently of particular medical interest: cord blood SCs and foetal brain tissue.

2.1.2 Cord blood SCs.

Cord blood SCs are gaining increased popularity as a cell source in blood cell transplantations. Their particular features (cord blood-derived cells produce fewer cytokines and contain fewer

[1] European Science Foundation (ESF), "Human Stem Cell Research and Regenerative Medicine. A European Perspective on Scientific, Ethical and Legal Issues", 2010. http://www.esf.org/fileadmin/Public_documents/Publications/SPB38_HumanStemCellResearch.pdf
[2] Regenerative Medicine, *Nature (Insight Supplement),* Vol. 453, No. 7193, 2008, pp. 301-351.
[3] Smith, A., "A glossary for stem cell biology", *Nature,* Vol. 441, No. 7097, 2006, p. 1060.

natural killer cells) allow a more permissive donor-host tissue mismatch and a smaller number of cells to be used. So cord blood is now routinely used for allogeneic transplantation.[4]

Most of these transplantations use cord blood from non-profit public cord banks, but a number of private cord banking services have also been established to provide patient-specific cord blood for future use.

2.1.3 Foetal brain tissue

Foetal brain tissue obtained from aborted foetuses has been used in the treatment of Parkinson's disease as it contains neural progenitor cells. In 2000, Björklund reported that more than 200 patients have already been treated in the US and in Sweden[5]. However, the results obtained to date make it difficult to draw conclusions about the efficacy of these transplantations. These treatments pose particular problems like obtaining enough brain tissue to transplant a sufficient number of cells into one patient and difficulties to meet the standard safety requirements.

2.1.4 Human embryonic stem cells

Derived from early embryos (not only from the inner cell mass, but also from the morula, blastomere or from arrested embryos), hESC lines have the potential to form any cell or tissue in the body, making them a possible source for cell transplantation and tissue engineering.

Since the establishment of the first hESC line in 1998 till 2010, 311 hESC lines are registered in the European Human Embryonic Stem Cell Registry funded by the European Commission (EC), a comprehensive collection of information on hESC lines that have been derived in Europe or are being used in projects based in the EU (www.hescreg.eu). This was made possible with the derivation of new hESC lines through the legalised access in certain countries to donated surplus eggs following in vitro fertilisation (IVF) treatment.

In recent years, some countries have funded projects that have helped to develop well-characterised hESC lines. Such projects include the International Stem Cell Initiative 1(ISCI1, ISCI2, ISCI3), European Human Embryonic Stem Cell Registry (hESCreg), European Bank for induced pluripotent Stem Cells (EBiSC), which use common criteria and unified protocols.

However, using hESCs for therapy, as opposed to their use for generating fundamental knowledge or identifying targets for drug development, is a much greater challenge for many reasons, including the unpredictability of their self-renewal and differentiation, immunological rejection (as the hESCs are heterologous, i.e. not from the patient) and the potentially long-term follow up of treatment, as the cellular transplants may survive for many years. However, the results from pre-clinical studies using hESC-derived cells to treat animal models of human diseases have been promising, demonstrating functional improvement (for instance, Parkinson´s disease and diabetes)[6,7]. Nevertheless, moving into a clinical setting with human patients is a challenge, with immune rejection being a particular issue.

[4] Sullivan, M.J., " Banking on cord blood stem cells", *Nat.Rev. Cancer*. Vol. 8, No.7, 2008, pp. 555-563.
[5] Björklund, A., O. Lindvall, "Cell replacement therapies for central nervous system disorders", *Nat. Neurosci,* Vol. 3, No. 6, 2000, pp. 537-544.
[6] Barnabe-Heider, F., J. Frisen, "Stem cells for spinal cold repair", *Cell Stem Cell*. Vol. 3, No.1, 2008, pp. 16-24.

2.2 Sources of human embryonic stem cell-like cells

2.2.1 Derivation of hESCs by somatic cell nuclear transfer (SCNT)

This process involves the replacement of the genetic material of an oocyte with the genetic material from an adult cell. This procedure has the potential to overcome rejection by establishing patient-specific hESC lines. Attempts have been made in some of the European countries that allow this procedure (which are Belgium, Portugal, Spain, Sweden and UK), but derivation of hESC lines from the few embryos established by SCNT in human has not been successful to date. One of the drawbacks is the difficulty in obtaining enough donated oocytes for this purpose.[8]

2.2.2 Induced pluripotent stem cells – iPS cells

One promising alternative to obtaining patient-specific pluripotent cell lines is by reprogramming somatic cells. Yamanaka and Takahashi were able to reprogram mouse skin cells into SC-like cells, so-called "induced pluripotent stem cells" (iPS cells) by transferring four key pluripotency genes (Oct-3/4, Sox2, Klf4 and c-Myc) using retroviruses[9]. By altering the expression of these genes, skin cells simply dedifferentiated into pluripotent cells, demonstrating many of the properties of hESCs. This remarkable discovery has opened up a new approach to generating patient-specific cells, and since then researchers have been investigating how to improve the technique through a reduction in the number of genes required or using alternative gene delivery systems. Recently, researchers succeeded in using just one gene (Oct-4)31, eliminating the need for the other three genes that were previously required, two of which are known to be potent oncogenes[10].

The use of iPS cells in the treatment of various human diseases would address the immunological and important ethical challenges that face the use of hESCs. However, there is an immediate need to improve methods to robustly develop these cells before clinical trials can even be considered. At this stage, it is not possible to say whether generating safe iPS cells for cell transplantation in clinical trials will be successful but at the moment these cells represent a unique route for drug development and for studying inherited or environment or age-related human diseases[11].

2.2.3 Adult- and tissue-derived stem cells; Mesenchymal stem cells (MSCs)

Adult SCs are undifferentiated cells found in a tissue or organ that can differentiate to produce the major specialised cell types of that tissue or organ. Examples include hematopoietic SCs

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[7] Soria, B., F.J. Bedoya, J.R. Tejedo, A. Hmadcha, R. Ruiz-Salmerón, S. Lim, F. Martin, "Cell therapy for diabetesmellitus: an opportunity for stem cells?", *Cells Tissues Organs,* Vol. 188, No.1-2, 2008, pp. 70-77.
[8] Li, J., X. Liu, H. Wang, S. Zhang, F. Liu, X. Wang, Y. Wang, "Human embryos derived by somatic cell nuclear transfer using an alternative enucleation approach", *Cloning Stem Cells,* Vol. 11, No. 1, 2009, pp. 39-50.
[9] Takahashi, K., S. Yamanaka, "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors", *Cell,* Vol. 126, No. 4, 2006, pp. 663-676.
[10] Kim, J.B., V. Sebastiano, G. Wu, M.J. Araúzo-Bravo, P. Sasse, L. Gentile, K. Ko, D. Ruau, M. Ehrich, D. van den Boom, J. Meyer, K. Hübner, C. Bernemann, C. Ortmeier, M. Zenke, B.K. Fleischmann, H. Zaehres, H.R. Schöler, "Oct4-induced pluripotency in adult neural stem cells", *Cell,* Vol. 136, No. 3, 2009, pp. 411-419.
[11] Gunaseeli, I., M.X. Doss, C. Antzelevitch, J. Hescheler, A. Sachinidis, "Induced pluripotent stem cells as a model for accelerated patient- and disease-specific drug discovery", *Curr. Med. Chem,* Vol. 17, No. 8, 2010, pp. 759-766.

(HSCs) that give rise to the many types of blood cells, including red blood cells, macrophages and platelets. The first example of adult SC-based therapy occurred in 1968 with the successful completion of the first bone marrow transplant. Since then, the landscape of SC research and its impact on the treatment options for human diseases has expanded considerably.

They offer unprecedented potential for the treatment of many diseases and disorders such as Crohn's disease, graft-versus-host disease, bone and cartilage lesions and degeneration, tissue and organ regeneration, as well as Parkinson's disease, Duchenne muscular dystrophy and heart disease.

Adult SCs may be derived from adult tissues such as the skin, adipose tissue and bone marrow.

Mesenchymal stem cells (MSCs) represent the most popular type of adult SCs. So far, few reports on side effects of clinically applied MSCs have been published, but MSCs undergo mutations during culture, and tumorigenicity is a possible risk[12].

Adult SCs have other advantages: they do not evoke the same ethical concerns as using ESCs and are not rejected by the patient's immune system if originating from an autologous source. When it is not possible to obtain autologous SCs of sufficiently good quality for expansion, the use of allogeneic cells may be required, as in organ transplantation, thus raising issues of immunosuppressive therapy. The emerging field of iPS cells, as pluripotent cells, may replace tissue-derived stem cells in the future in many situations.

3 Values and principles

To obtain embryonic stem cells, the early embryo has to be destroyed. This means destroying a potential human life. But embryonic stem cell research could lead to the discovery of new medical treatments that would alleviate the suffering of many people. Embryonic stem cell research faces two, deeply rooted, moral traditions in our culture: the pursuit of beneficence and respect for human dignity. [13]

The bioequivalence of iPS and embryonic stem cells has yet to be conclusively proven, and embryonic stem cells remain the most realistic source of hope for patients with diseases that cannot be treated with adult stem cells and for which iPS cell therapy has not been sufficiently investigated. There seems to be sufficient argument in favour of continuing research on all types of stem cells and therefore it is necessary to deal with the ethical issues arising.

The need to develop clinical studies that respond to treatment of diseases raises issues related to the principles of autonomy and justice, as well as related to freedom and solidarity values.

[12] Røsland, G.V., A. Svendsen, A. Torsvik, E. Sobala, E. McCormack, H. Immervoll, J. Mysliwietz, J.C. Tonn, R. Goldbrunner, P.E. Lønning, R. Bjerkvig, C. Schichor, "Long-term cultures of bone marrow-derived human mesenchymal stem cells frequently undergo spontaneous malignant transformation", *Cancer Res,* Vol. 69, No.13, 2009, pp. 5331-5339.
[13] http://www.eurostemcell.org/factsheet/embyronic-stem-cell-research-ethical-dilemma

International interdisciplinary projects may play an important role to facilitate consensus on some issues. But the obvious conclusion is that it will take a long time to achieve harmonisation between different traditions.

3.1 Therapeutic value

Stem cell research holds the promise of treating many serious and disabling diseases and disorders by replacing damaged, lost or diseased cells through regeneration. It can be considered part of a new field of activity that emerged in the early 1990s, rapidly developing over the last decade, and commonly referred to as either tissue engineering or RM. (While RM includes tissue engineering, it also includes targeted treatments such as gene and small-compound therapies.)

Even with increased support for research projects in transplantation, there remains an enormous need for RM therapies. The RM is presented as a less invasive alternative to alleviate the absence of the required number of donations for transplantation.

Among the numerous potential applications for RM using hSCs are, for example, heart muscle repair following a myocardial infarction, treatment of neurodegenerative disorders including Parkinson's disease, enhancement of wound repair of the skin, and replacement of damaged bone and cartilage.[14]

Using human stem cells (hSCs) for therapeutic purposes raises deep ethical issues ranging from the need to ensure good manufacturing practice (GMP)[15] and to develop clinical trials following recommendations regarding the conduct of investigator-driven clinical trials[16]. Most of these recommendations are applicable to the field of hSCs research. However, iPS cell replacement therapy raises new ethical concerns. How should potential risks and benefits be assessed and weighed up against each other? When is it appropriate to move from animal testing to human testing? What are the appropriate procedures for obtaining informed consent?[17]

In this sense, the mission and role of ethics committees should be harmonised and the ethical standards of clinical trials should be increased.

[14] Regenerative Medicine. Nature (Insight Supplement), op. cit., 2008, pp. 302-305.
[15] European Parliament and of the Council, Directive 2004/23/EC of the 31.03.2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, 2004. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32004L0023
[16] European Parliament and of the Council, Directive 2001/20/EC of the 4.04.2001 on Clinical Trials on Medicinal Products for human use, 2001.
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF
[17] Fung, R.K., I.H. Kerridge, "Uncertain translation, uncertain benefit and uncertain risk: ethical challenges facing first-in-human trials of induced pluripotent stem (iPS) cells", *Bioethics,* Vol. 27, No. 2, 2013, pp. 89-96.

3.2 Ethical and legal issues

3.2.1 Moral status of embryos

While embryonic stem cell research has promised much, it has faced a series of scientific, practical, legal and moral barriers. Embryonic stem cell research poses a moral dilemma. It forces us to choose between two moral principles: the duty to prevent or alleviate suffering and the duty to respect the value of human life. For example, the creation of an embryonic stem cell line requires the destruction of the embryo, which has provoked strong moral objections based on firmly held positions regarding moral status and human dignity. [18] Further barriers have included the legal restrictions placed on access to embryos left over from IVF technology in many countries, the technical difficulties of achieving adequate efficiency in somatic cell nuclear transfer and the scarcity of donor oocytes. [19]

In light of this, the discovery of iPS cells in 2006 created great excitement within the scientific community. And from a socio-moral perspective, iPS cell technology circumvents the moral objections against embryo destruction involved in the production of embryonic stem cell lines.

3.2.2 Risk assessment in clinical research

Many researchers stress the need to address the long-term safety, tolerability and efficacy of cell-based treatments in general, and in particular their carcinogenic risk and about the probability of teratomas. An article published by Fung in relation to Parkinson´s disease therapies points to the difficulties of assessing the risk in clinical trials of iPS cell replacement therapy: "It is arguable that the risk-benefit ratio of cell replacement trials is unlikely to be particularly favourable, and that it would be difficult to justify the serious and potentially irreversible risks associated with iPS cell transplantation." [20]

For instance, in the case of embryonic stem cell based therapies, contamination of iPS cell grafts may lead to teratoma formation in the host brain.[21] All of these risks are outlined in the International Society for Stem Cell Research (ISSCR)'s Guidelines for the Clinical Translation of Stem Cells and are posited as justification for requiring all the more stringent pre-clinical evidence before first-in-human trials should be allowed to proceed.[22]

Given the difficulties of risk assessment, the question is whether the development of clinical trials should be blocked if it can ensure the safety of patients and how does one weigh up the

[18] Hotta, Y., "Ethical Issues of the Research on Human Embryonic Stem Cells", *J Int Bioethique,* Vol. 19*,* 2008, pp. 77–85.
[19] ESHRE Task Force on Ethics and Law, "ESHRE Task Force on Ethics and Law 12: Oocyte Donation for Non-reproductive Purposes", *Hum Reprod,* Vol. 22*,* 2007, pp. 1210–1213.
[20] Fung, op. cit., 2013, p. 92.
[21] Dawson, L., A.S. Bateman-House, D. Mueller- Agnew, H. Bok, D.W. Brock, A. Chakravarti, M. Greene, P.A. King, S.J. O'Brien, D.H. Sachs, K.E. Schill, A. Siegel, D. Solter, S.M. Suter, C.M. Verfaillie, L.B. Walters, J.D. Gearhart, R.R. Faden, "Safety Issues in Cell-based Intervention Trials", *Fertil Steril,* Vol. 80*,* 2003, pp. 1077–1085.
[22] International Society for Stem Cell Research (ISSCR), "Guidelines for the Clinical Translation of Stem Cells", 2008. http://www.isscr.org/docs/guidelines/isscrglclinicaltrans.pdf

need to ensure the safety of research participants in first-in-human trials against the potential benefits of expedited access to cell replacement therapy for the broader patient community.[23]

3.2.3 Advanced clinical trials

European academia and industry are conducting clinical trials with human stem cells that have produced promising results. In October 2013, 514 clinical trials on stem cells were registered in the EU Clinical Trials Register. Of the 514 trials analysed, only 25 were found to be on-going and involving MSCs but not blood cells. In this subset, the vast majority of trials were coordinated by Spain (n=20), followed by Germany (2), the Netherlands (2), Italy (2), the Czech Republic (1), Denmark (1), the UK (1), Belgium (1), Austria (1) and Hungary (1). Conditions being studied ranged from lower limb and central nervous system ischemia, to therapies for wounds, bones or muscles, incontinence, amyotrophic lateral sclerosis, bronchopleural fistula, inflammatory bowel disease and phase III clinical trials in congestive heart failure and Crohn's disease. [24]

3.2.4 iPS cell therapy

While these questions are worthy of consideration, there are other important ethical issues raised by the clinical testing of iPS cell therapy which have received much less attention. Some of these issues have been identified by Zarzeczny and colleagues, including:

- Preventing the 'misuse' of iPS cells to derive gametes for reproductive purposes;
- Safeguarding the privacy and informed consent of cell donors;
- Minimising, in the clinical setting, the safety risks to patients which arise not only from the intrinsic properties of immortal cell lines but also from epigenetic changes acquired during the derivation process; [25]
- The relative unreliability of available animal models;
- The vulnerability of the target patient group, and
- The intense public scrutiny that surrounds stem cell research.

3.2.5 Cloning

Research using human stem cells to grow new tissues (in order to repair or replace those damaged by disease) holds potential promise. Some of this research may involve nuclear fusion of an adult individual's cell with an enucleated egg, a first step toward potential human cloning. The possible benefits of research using nuclear fusion to produce tissues for the treatment of disease are recognised, provided that there would be no attempt to reproduce an

[23] Fung, op. cit., 2013, p. 93.
[24] European Science Foundation (ESF), Human Stem Cell Research and Regenerative Medicine Focus on European policy and scientific contributions. 2013. http://www.esf.org/fileadmin/Public_documents/Publications/HumanStemCellResearch.pdf
[25] Zarzeczny, A., C. Scott, I. Hyun, J. Bennett, J. Chandler, S. Chargé, H. Heine, K. Kato, R. Lovell-Badge, K. McNagny, D. Pei, J. Rossant, A. Surani, P.L. Taylor, U. Ogbogu, and T. Caulfield,"iPS Cells: Mapping the Policy Issues", *Cell, Vol. 139,* 2009, pp. 1032–1037.

entire human being. At the present time, “reproductive human cloning" is unsafe and should not be attempted.[26]

3.3 Other issues

3.3.1 Stem cell tourism

In 2010 and 2011 especially, many articles on stem-cell tourism were published.[27] The vast majority have been critical of attempts to exploit the hope of desperate patients and their relatives. Both stem-cell tourism and the marketing practices of the clinics have been criticised, as well as the prices some patients have faced. In these practices there is more than minimal risk of harm involved. In this regards, the ISSCR published guidelines and a handbook for patients.[28]

3.3.2 Biobanking and data protection

Biobanks and registries containing information about these samples are essential resources for research and therapy. They are also connected with questions about how to deal with conflicting demands of traceability (to promote safety) and anonymity (to protect privacy), as well as with the conditions under which donors may withdraw their consent. Biobanks cannot guarantee that donors of cells and tissues can never be re-identified. But they are able to protect confidentiality. Forms of broad consent, anonymity and traceability of samples are familiar ethical issues in this context. These aspects should be considered in the informed consent process.

3.3.3 Use of animals in research

According to the Declaration of Helsinki, adequate animal experimentation should be conducted prior to launching first-in-human trials in order to collect pre-clinical evidence of safety and efficacy. Currently, therefore, the desire to reduce the risks to human participants of first-in-human studies of iPS cell therapy appears to demand extensive use of animals in research. [29]

3.3.4 Chimeras

Recently, the generation of human-animal chimeras for research purposes has been largely superseded by iPS cell research.

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[26] Wertz, D.C., J.C. Fletcher, K. Berg,“Review of Ethical Issues in Medical Genetic”. Report of consultants to WHO. Human Genetics Programme. Management of Noncommunicable Diseases. 2003. WO/HGN/ETH/00.4. http://www.who.int/genomics/publications/en/ethical_issuesin_medgenetics%20report.pdf

[27] Murdoch, C.E., C.T. Scott, “Stem cell tourism and the power of hope”, *Am J Bioeth*, Vol. 10, No. 5, 2010, pp. 16-23.

[28] International Society for Stem Cell Research (ISSCR), “Patient Handbook on Stem Cell Therapies”, Appendix I of the Guidelines for the Clinical Translation of Stem Cells, 2008. http://www.closerlookatstemcells.org/Patient/ISSCRPatientHandbook.pdf [Accessed 10 Jul 2014].

[29] Fung, op.cit., 2013, p.94.

4 Ethical assessment

4.1 Role of the Research Ethics Committees (RECs)

The guide emphasises the role of the Research Ethics Committees (RECs). RECs should ensure that informed consent documents accurately portray these uncertainties and potential risks, and clearly explain the experimental nature of the clinical study (in order to avoid therapeutic misconception).[30]

4.2 Informed consent

Stem cell research presents two critical moments: on the one hand, obtaining biological samples (blood, tissues, oocytes ...) and on the other, participation in clinical research.

4.3 Obtaining biological samples.

Scientists and clinicians conducting human stem cell research must ensure that human biological materials are procured in a manner according to globally accepted principles of research ethics. In the case of donation for allogeneic use, the donor should give written informed consent that covers, where applicable, the following issues:

- That cells and/or cell lines may be subject to storage. Use of the sample and/or line for a specific project and its subsequent destruction or indefinite maintenance of the line;
- That the donor may (or may not) be approached in the future to seek additional consent for new uses or to request additional material (blood or other clinical samples) or information;
- That the donor will be screened for infectious and possibly genetic diseases;
- That the donated cells may be subject to genetic modification by the investigator;
- That with the exception of directed altruistic donation, the donation is made without restrictions regarding the choice of the recipient of the transplanted cells;
- Disclosure of medical and other relevant information that will be retained, and the specific steps that will be taken to protect donor privacy and confidentiality of retained information, including the date at which donor information will be destroyed, if applicable;
- Explanation of what types of genomic analyses (if any) will be performed and how genomic information will be handled; and
- Disclosure that any resulting cells, lines or other stem cell-derived products may have commercial potential, and whether any commercial and intellectual property rights will reside with the institution conducing the research.
- Women should be informed about the unpleasant and risk of the ovarian stimulation procedures when doctors seek to obtain oocytes.

4.4 Participation in clinical research

The ISSCR guidelines recommend that special emphasis be placed on the unique risks of stem-cell-based clinical research during the informed consent process. These risks include

[30] ISSCR, op. cit., 2008. Recommendation 28, p. 14.

sensitivities surrounding the source of cellular products, tumour formation, immunological reactions, unexpected behaviour of the cells, and unknown long-term health effects.

Research volunteers must be informed and educated about the realistic potential for therapeutic benefit as they may have recourse to reasonable therapeutic alternatives and because they may harbour misconceptions about the potential for therapeutic efficacy.

Moreover, the ISSCR guidelines recommend that research subjects' comprehension of relevant information—especially of the risks and uncertainties—be evaluated at the time of obtaining consent. For patients contemplating participation in stem-cell-based clinical research, the ISSCR provides information for patients in the appendices of the guidelines to assist their decision-making.

In Recommendation 28, ISSCR guidelines point out the aspects to be considered in the informed consent process for clinical trials involving highly innovative interventions.

- Patients need to be informed when novel stem cell-derived products have never been tested before in humans and that researchers do not know whether they will work as hoped.
- Cell-based interventions, unlike many pharmacological products or even many implantable medical devices, may not leave the body and may continue to generate adverse effects for the lifetime of the patient. The possible irreversibility of a cellular transplant should be explained clearly.
- Subjects should be informed about the source of the cells so that their values are respected.

5 Benefits

5.1 Promising results in frontier research

Examples of promising results and potential clinical applications of frontier research on stem cells in Europe can be consulted in European Science Foundation (ESF).[31]

5.2 Patents

In Europe, research and innovation in regenerative medicine are supported by legislation such as the so-called Biopatent Directive.[32] It is the use of hESCs that has sparked the most controversy: although Article 6(2)(c) of the directive excludes "uses of human embryos for industrial or commercial purposes" from patentability, the term "embryo" is not defined and hence there are many interpretations across Europe. In 2011, from the Brüstle case, the European Court of Justice (ECJ) ruled that it was illegal to patent stem cell discoveries.[33] These legally binding decisions constituted, in turn, the basis of a 2012 resolution by the

[31] ESF, op. cit., 2013, p. 12.
[32] European Parliament and of the Council, Directive 98/44/EC of the 6.07.1998 on the legal protection of biotechnological inventions.
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31998L0044
33 Court of Justice of the European Union. Judgment in Case C-34/10, Oliver Brüstle v Greenpeace e.V. 2011 Ruling. http://curia.europa.eu/juris/liste. jsf?language=en&num=C-34/10

European Parliament[34] affecting animal and plant breeding which further supported this ruling. The implications were that it would not make sense to invest in something that could not be patented and thus would not contribute to innovation in Europe. Additionally, this resolution invited the European Commission to align other EU policies with this position.

6 Legislation across Europe

In 2013, the European Science Foundation (ESF) checked the status of the legal regulation and governance frameworks for stem cell research in 30 European countries.[35]

Only three countries authorise the creation of human embryos for research. Most of the others allow for the derivation of cells solely from surplus IVF embryos (see below). Other nations ban the derivation of hESCs altogether, although some permit cell line imports under strict conditions. There are also nuances in the definition of human embryo and the timeline of its legally authorised uses across countries. Overall, the results of the survey suggest that in terms of hESC research policy, countries can be grouped under five broad categories (each with its nuances):

- Very permissive (allowing even the creation of embryos for research purposes): Belgium, Sweden, UK.
- Permissive with restrictions (allowing research only on surplus IVF embryos and prohibiting the creation of embryos solely for research purposes): Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, The Netherlands, Norway, Portugal, Slovenia, Spain, Switzerland. Bulgaria could be added to this list since there is no specific hESC legislation but de facto, under other existing laws, hESC research in surplus IVF embryos is allowed.
- Restrictive by default (where legislation is not explicit but national practices are quite restrictive in practice): Romania, Turkey.
- Very restrictive (where legislation explicitly bans research on hESCs): Croatia, Germany, Italy, Lithuania, Slovakia.
- Unlegislated (where there is no legislation on hESCs): Austria, Ireland, Luxembourg, Poland.

More details (main legislative framework, governance bodies, types of stem cell research authorised) can be found in the report produced by the European Science Foundation (ESF), entitled Human Stem Cell Research and Regenerative Medicine Focus on European policy and scientific contributions and published in 2013. [36]

[34] European Parliament, RSP 2012/2623/ of the 10.05. 2012 on patenting essential biological processes.
[35] European Science Foundation (ESF), Human Stem Cell Research and Regenerative Medicine Focus 0n European policy and scientific contributions. 2013.
http://www.esf.org/fileadmin/Public_documents/Publications/HumanStemCellResearch.pdf.
[36] ESF, op. cit., 2013, p. 13.

There has been criticism that the lack of a single "consolidated market" may also hamper international collaborations and innovation in Europe.[37]

7 Institutionalisation

- Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. ETS No: 164, 1997. http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm
- Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research. ETS No: 195, 2005. http://conventions.coe.int/Treaty/EN/Treaties/Html/195.htm
- Council of Europe, Explanatory Report to the Convention on Human Rights and Biomedicine. Council of Europe, Strasbourg, 1997. http://conventions.coe.int/Treaty/EN/Reports/Html/164.htm
- Council of Europe, Steering Committee on Bioethics (CDBI/INF), Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes. Strasbourg, 27.XI.2008 http://conventions.coe.int/Treaty/EN/Treaties/Html/203.htm
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