EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

SCIENCE POLICY BRIEFING • May 2010 38

Human Stem Cell Research and Regenerative Medicine

A European Perspective on Scientific, Ethical and Legal Issues

Contents

Foreword

In 2002 the European Science Foundation (ESF) published a Science Policy Briefing (SPB) entitled *Human Stem Cell Research: Scientific Uncertainties and Ethical Dilemmas*[1]. Since then there have been many significant advances in the field of research, although progress has perhaps been slower than was originally predicted. During this time, we have witnessed the emergence of regenerative medicine (RM), which promises to be one of the most fascinating and controversial scientific developments of the 21st century.

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. Clearly, as stated in 2002, scientific research in this field must be undertaken with a simultaneous consideration of the ethical issues involved. Thus, the purpose of this policy briefing is to examine the key scientific questions in hSC research in the field of RM, examine the current ethical concerns, particularly as we advance towards clinical application, and finally analyse how the legislative landscape has altered in Europe within the previous seven years.

The European Medical Research Councils (EMRC) at the ESF established a High-Level Expert Group, partly comprised of members of the previous 2002 Expert Group but also drawing in other leading researchers, to reflect the rapidly changing scope of the field. Based on a dedicated workshop and remote correspondence, these members made specific recommendations, intended to stimulate continuing efforts by relevant stakeholders to ensure that stem cell research is developed into RM applications and other benefits for patients, while at the same time ensuring that the research is conducted in accordance with accepted principles of research ethics. These recommendations are summarised at the end of this report. The draft SPB was presented to the EMRC Standing Committee which reviewed the report in the wider context of medical research priorities and the divergent legislation regarding stem cell research across our Member Organisations. Finally, we would like to acknowledge and thank the High-Level Expert Group for their excellent work.

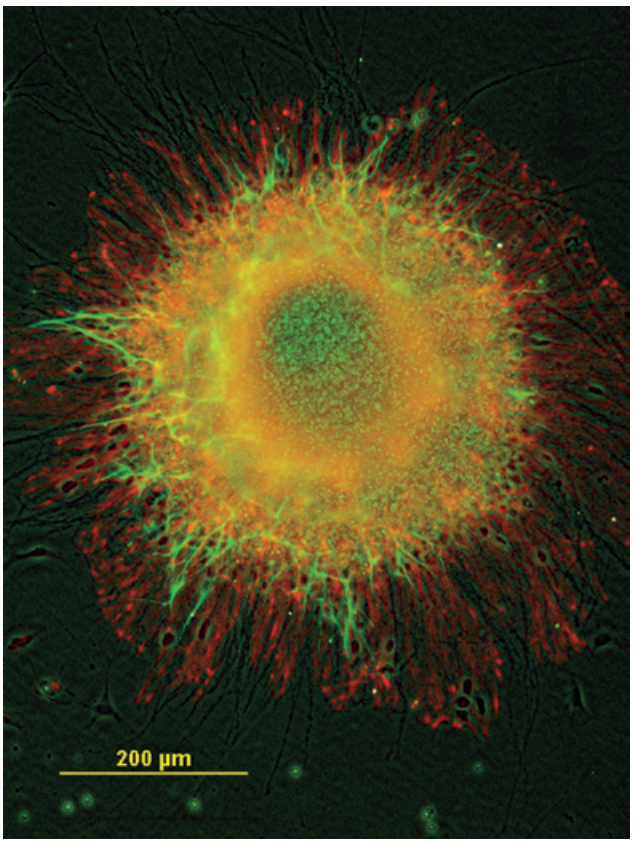

Figure 1. A sphere formed by neural progenitor cells differentiated from the human embryonic stem cell line HS360 in four-week serum-free culture in N2B27 medium. Green immuno-reaction for the marker Map-2, and red for Nestin.
Photo by Katja Puttonen, University of Kuopio, Finland. Original magnification ×200.

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Introduction

Stem cell (SC) 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.)

Transplantation remains today the only possible therapy for certain terminal organ insufficiencies (liver, heart, lung, kidney). The increase in chronic diseases and population ageing has led to an increasing demand for transplantation, but at the same time the number of potential donors is decreasing. For many patients, organ transplantation represents the only life-saving treatment available. There are currently 56 000 patients waiting for a suitable organ donor in the European Union (EU).

On 8 December 2008, the European Commission (EC) adopted a proposal for a Directive of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation (http://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_directive_en.pdf) and a ten-point Action Plan for closer co-operation between Member States on organ donation and transplantation (http://ec.europa.eu/health/ph_threats/human_substance/oc_organs/docs/organs_action_en.pdf). The Directive and Action Plan address three key challenges: (1) improving the quality and safety of organs across Europe, (2) increasing organ availability and (3) making transplant systems more efficient and accessible.

Even with increased support for research projects in transplantation, there remains an enormous need for RM therapies. This is evident, to take only one example, from the high number of heart transplantations, 3 500, that are undertaken worldwide each year. The number is limited by the lack of appropriate donors and the intensive treatment regimens that are not easy to administer to the elderly people who most urgently need transplants. Less invasive treatments, such as enabling regeneration of damaged heart tissue with SCs, would clearly help to alleviate this kind of problem.

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[2]. In the last decade, research in these areas has been translated into early clinical trials with mixed results, raising hope amongst patients. It is notable that the first clinical trials using therapy based on human embryonic stem cells (hESC) were approved by the Food and Drug Administration (FDA) in the US in January 2009 for patients with acute spinal cord injury (SCI)[a], even though there have been some drawbacks with this project more recently. However, it is perhaps in the area of bone and cartilage repair where successful translation is likely to be achieved first, due in part to the accessibility of the tissues, their reduced complexity in comparison to myocardial or neuronal tissues and a high level of concurrent work on new biomaterials for tissue repair.

There are many different sources of SC, each having their own advantages and disadvantages. The various types of SC can be seen in the glossary in Table 1, which is based upon that devised by Professor Austin Smith, as published in *Nature* in 2006[3].

One significant factor that has influenced the course of hSC research is the ethics surrounding their use[4]. It was as a consequence of the strong debate about hSC ethics – reflected in the first SPB published by the ESF on this topic in 2001 – that stimulated concerted efforts on the part of some national governments to find alternative methods using adult SCs, as their use is considered more acceptable by the general public. In the US for example, the National Institutes of Health (NIH) spent US$3.5 billion on SC research in the period 2005-2008, of which US$260 million was dedicated to hESC research[b]. This has yielded the remarkable result of so-called induced pluripotent stem cells (iPS cells) – the reprogramming of adult human cells into ES-like cells. The International Society for Stem Cell Research (ISSCR) published in December 2008 its "Guidelines for the Clinical Translation of Stem Cells" (http://www.isscr.org/clinical_trans/index.cfm) partly supported by the EUROCORES Programme EuroSTELLS, supported by the EC, Sixth Framework Programme, under contract no. ERAS-CT-2003-980409. These served as a basis for the publication of the NIH "Guidelines for Human Stem Cell Research" released on July 7 2009 (accessible at http://stemcells.nih.gov/policy/2009guidelines.htm) that have given a new impulse to SC research in the US.

The value of SC 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. While significant advances have been made since 2002, including, for example, understanding how mesenchymal stem cells (MSCs) impair autoimmunity, with the result that allogeneic MSCs can be explored in a variety of clinical settings, much remains to be learnt about how to control and direct SC fate and function in a patient.

With this paper, the ESF aims to summarise 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.

Foetal stem cells

With improved molecular characterisation of various cell types, we are obtaining a richer picture of the different stem and progenitor cell types residing in the embryo.

a. www.geron.com

b. www.nih.gov/news/fundingresearchareas.htm (accessed Apr-19, 2010)

For cell therapy purposes, foetal SCs can be derived from umbilical cord blood after delivery, or from foetal tissues after termination of pregnancy or spontaneous abortion. There are two types of foetal SCs that are currently of particular medical interest: cord blood SCs and foetal brain tissue. Cord blood SCs are gaining increased popularity as a cell source in blood cell transplantations, as cord blood-derived cells produce fewer cytokines and contain fewer natural killer cells, thus causing less severe graft-versus-host disease following transplantation. Furthermore, cord blood SCs have a higher proliferative potential. These features allow a more permissive donor-host tissue mismatch and smaller number of cells to be used, and cord blood is now routinely used for allogeneic transplantation[5]. 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 (see also 'Private companies and personal cell banks' below). Foetal brain tissue obtained from aborted foetuses has been used in the treatment of Parkinson's disease as it contains neural progenitor cells. More than 200 patients have already been treated in the US and in Sweden[6]. In these treatments, several foetuses are needed to transplant a sufficient number of cells into one patient. Results of the transplantations are mixed, and different transplantation strategies, such as unilateral versus bilateral implantation, graft size and preparation of donor cells prior to transplantation, make it difficult to yet draw firm conclusions about the efficacy of the transplantations[7,8]. The feasibility of using homologous foetal SCs in perinatology for tissue engineering in a foetus with a congenital birth defect has been proposed[9]. Foetal SCs can also be used in the fields of hepatic cell transplantation[10] and heart valve tissue re-engineering[11].

Safety issues are important when foetal cells are used. If rejection and viability of transplanted cells do not seem to be a problem in the central nervous system, concerns have been raised regarding potential host-to-graft disease propagation. Two subjects with Parkinson's disease who had long-term survival of transplanted foetal mesencephalic dopaminergic neurons for 11 and 16 years, respectively, presented evidence for Lewy bodies in their grafted neurons. However, the majority of grafted cells were functionally unimpaired after a decade, and recipients still experienced long-term symptomatic relief[12]. Non-proven treatments can be dangerous as shown by the case of an Israeli boy who developed multiple tumours of the central nervous system after receiving an inappropriate treatment for his ataxia telangiectasia syndrome in Moscow. He was given foetal brain cells, which resulted in a severe complication[13].

Table 1: Glossary with definitions and abbreviations for stem cells and regenerative medicine

Term	Abbreviation	Definition
Regenerative medicine	RM	Reconstruction of functionally impaired, diseased or injured tissue by activation of endogenous repair systems or by implantation of exogenous cells or combination products.
Tissue engineering		An interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function.
Stem cell	SC	A cell that can continuously produce unaltered daughters and also has the ability to produce daughter cells that have different, more restricted properties.
Embryonic stem cell	ESC	Pluripotent SC lines derived from early embryos before formation of the tissue germ layers.
Foetal stem cell	Foetal SC	Found in blood from the umbilical cord, in the placenta or isolated from aborted foetus.
Adult stem cell	Adult SC	May be derived from umbilical cord blood or adult tissues, among which bone marrow and fat are mostly used.
Tissue stem cell		A cell derived from, or resident in, a foetal or adult tissue, with potency mostly limited to that tissue. These cells sustain turnover and repair throughout life in some tissues.
Induced pluripotent stem cell	iPS cell	An adult somatic cell which is reprogrammed to become pluripotent and behave like ESCs typically, by inducing a "forced" expression of certain genes (including the master transcriptional regulators Oct-4 and Sox2).
Mesenchymal stem cell	MSC	An adult multipotent cell derived from a well-characterised population that can form fat cells, cartilage, bone, tendon and ligaments, muscle cells, skin cells and even nerve cells.

Other abbreviations used for stem cells

Term	Abbreviation
Human embryonic stem cell	hESC
Human stem cell	hSC

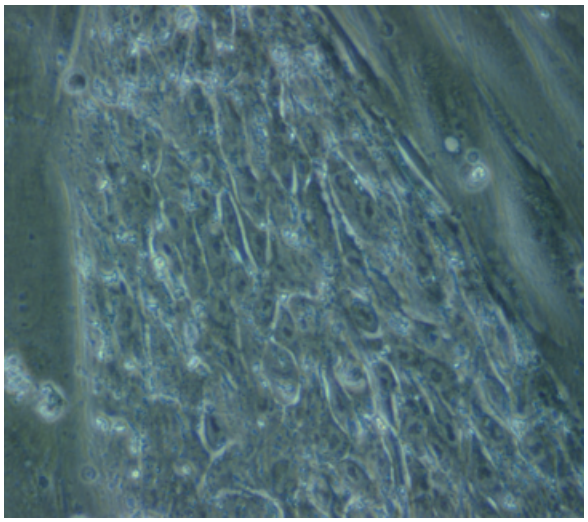

Figure 2. Non-differentiated human embryonic stem cells growing on a feeder cell layer formed by human skin fibroblasts.
Photo by Outi Hovatta, Karolinska Institutet, Sweden. Original magnification ×400.

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 (Figures 1 and 2). Since the establishment of the first hESC line in 1998[14], a much better understanding of how tissues are generated and maintained has been gained. 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 August 2009, it was estimated that 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 funded by the European Commission (EC), which is not a cell bank but serves as a comprehensive collection of information on hESC lines that have been derived in Europe or are being used in projects based in the EU[c]. One long-term goal of the European hESC registry website is to provide a platform to compare clinical research results using hESCs across Europe in a standardised way.

One notable project during the last five years has been a common effort to characterise hESC lines, managed by the International Stem Cell Forum (ISCF), a 21-member organisation (academies, research institutes and councils, foundations, etc.) established to encourage international collaboration and funding support for SC research. Known as the International Stem Cell Initiative 1 (ISCI1), 58 hESC lines from 18 laboratories worldwide were characterised and shown to have similar expression patterns for several hESC markers[15], but there were also many differences between the lines[16]. A second study, ISCI2, which addressed the culture conditions, is completed. ISCI3 is underway to explore the genetic stability of hESCs, as they have a tendency to undergo genetic alterations during long-term culture.

Many other studies have contributed vast knowledge of basic biological characteristics of hESCs, their self-renewal, growth control and optimal culture conditions. Differentiation protocols have been published for many cell types including neurons, cardiac muscle cells and β-cells of pancreatic islets. Basic knowledge about SC biology may also teach us about the body's natural healing capacity and the involvement of an endogenous pool of SCs that is recruited upon tissue damage[17,18]. hESCs may also provide us with good culture systems to evaluate disease mechanisms[19, 20, 21, 22], as well as to screen – in a high-throughput manner – new compounds for drug development[23,24] which is the current goal of many biotechnology companies. The UK, for example, has set up a public-private consortium "Stem Cells for Safer Medicine" with the long-term objective of developing a bank of human cell lines derived from hESCs to be used in early drug discovery[d].

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. The first targets have been disorders with relatively local cell degeneration: SCI[25], diabetes[26] and Parkinson's disease. The latter has been one of the first targets of a new approach, i.e. the generation of iPS cells (see below)[27]. Treatments of more general disorders will take a longer time to achieve. In, for instance, amyotrophic lateral sclerosis, cell therapy using different types of SCs, both pluripotent and tissue-derived SCs as the cell source, has been extensively studied[28]. Nevertheless, moving into a clinical setting with human patients is a challenge, with immune rejection being a particular issue.

In summary, understanding the fundamental mechanisms of self-renewal, pluripotency and differentiation and creating a reliable characterisation process is critical if hESCs are to be used as therapeutic tools in RM. Even though other methods are being developed to generate hESC lines, including induced (non-embryonic) pluripotent SCs, at this stage it would be premature to consider limiting any potential avenues of research.

c. www.hescreg.eu

d. www.sc4sm.org

Other sources of human embryonic stem cell-like cells

Derivation of hESCs by somatic cell nuclear transfer (SCNT)

One possible solution to overcome rejection would be establishing patient-specific hESC lines by a process called somatic cell nuclear transfer (SCNT). This involves the replacement of the genetic material of an oocyte with the genetic material from an adult cell. 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 have not been successful to date[29]. One of the drawbacks is the difficulty in obtaining enough donated oocytes for this purpose.

Reprogramming somatic cells by defined factors (induced pluripotent stem cells – iPS cells)

One promising alternative to obtaining patient-specific pluripotent cell lines is by reprogramming somatic cells, which marked a major breakthrough in the field of SC research (Figure 3). 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[30]. By altering the expression of these genes, skin cells simply dedifferentiated into pluripotent cells, demonstrating many of the properties of hESCs; in essence 'turning back the clock' on the adult skin cells. 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. Although the virus itself which is used to carry the gene may integrate into the genomic DNA, thus ruling out the use of viral vectors in a clinical setting, the results marked another step towards the virus-free generation of iPS cells. The feasibility of deriving human iPS cells free of reprogramming factors by using excisable lentiviruses has been demonstrated. For obvious safety reasons, these human iPS cells represent a more suitable source of cells for modelling human disease[32].

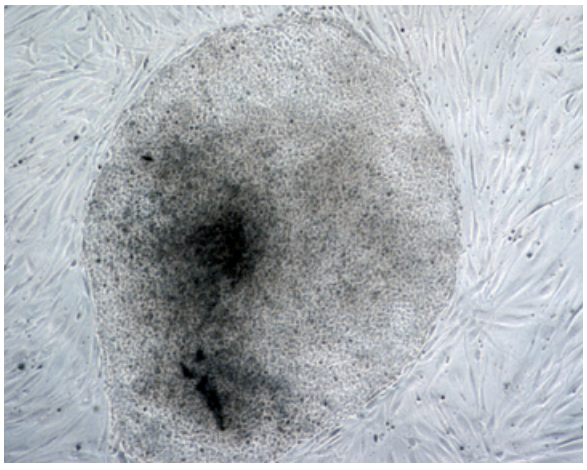

Figure 3. A round colony of tightly growing human induced pluripotent stem cells on human fibroblast feeder layer. The cells have been formed from the parental skin fibroblast line.
Photo by Outi Hovatta, Karolinska Institutet, Sweden. Original magnification ×100.

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/age-related human diseases[33].

Adult- and tissue-derived stem cells

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 (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. Adult SCs 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 or 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. They can be easily isolated from various tissues (e.g. bone marrow, adipose and hepatic tissues, umbilical cord blood) and expanded *in vitro*. So far few reports on side effects of clinically applied MSCs have been published, but MSCs undergo mutations during culture[34] and tumorigenicity is a possible risk. Some of the preliminary observations have appeared promising even though the beneficial effects of MSC applications were in some studies probably not associated with cell replacement and MSC differentiation, but with the MSC secretory function that provides indirect trophic effects of the cell therapy[35]. The mech-

anisms of action are still largely unknown, and much research remains to be done.

Adult SCs 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. However for certain applications such as neurodegenerative diseases, it may not be possible to obtain autologous SCs of sufficiently good quality for expansion. In such cases, therefore, 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.

Germinal stem cells have been identified in human testes[36] but their culture, propagation and maturation *in vitro* are still at an early basic research stage. This research may add to current standard protocols for sperm preservation purposes. Mature sperm and oocytes have been obtained from mouse ESCs[37, 38]. Whilst obtaining gametes capable of fertilisation from human SCs is likely to be some way in the future, ongoing research suggests that this could be possible. For instance, human early meiotic germ cells have been differentiated from hESCs[39].

Towards clinical application

Various applications of stem cells in regenerative medicine

SCs could be applied in RM in various ways, from understanding fundamental aspects of SC biology, identifying new compounds for drug development, and perhaps most appealing for the general public, used as cell-based therapies for many injuries, disorders and diseases.

GMP compliance – regional/national (EU Tissues and Cells Directive)

The EU Tissues and Cells Directive (EUTCD)[e] regulates the quality of all cells used in human therapy and requires good manufacturing practice (GMP)-based production systems, which include quality. Regarding hSCs, the quality of the procedures and cleanliness of the products have been regulated in this manner, and there are additional requirements for hSC-derived cells. If culture constituents contain animal-derived components (e.g. mouse feeder cells or foetal bovine serum), cells can absorb animal proteins which are immunogenic and may promote the rejection of cells after transplantation[40]. Such substances may also contain infectious agents which are difficult to remove after having been introduced exogenously[40]. Hence, xeno-free culture systems would be optimal in human cell transplantation[40]. Six clinical grade hESC lines have so far been derived[41], but the derivation system is not xeno-component free. Xeno-free culture media, feeder cells and feeder-free matrices that have been developed are under investigation.

Clinical proof of concept

The current clinical status is that while adult SCs of the hematopoietic system – HSCs – are commonly used for bone marrow transplants, other adult SCs are still at an early stage of evaluation in clinical trials. The websites of the European Community EudraCT (https://eudract.emea.europa.eu/) and of the US NIH (www.ClinicalTrials.gov) provide information on the 107 current clinical trials based on the use of MSCs, the type of adult SC that is expected to reach clinics next. 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, UK 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 out 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, UK, 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 ischaemia, distal tibia fracture, osteoarthritis, decompensated liver cirrhosis, multiple sclerosis, tumour-induced osteomalacia, vascular diseases, diabetes, fistulising Crohn's disease, and several others.

The ESF Forward Look *Investigator-Driven Clinical Trials* published in March 2009 (available at http://www.esf.org/idct) made the following recommendations regarding the conduct of investigator-driven clinical trials, most of them being applicable to the field of hSC research:

- Knowledge produced by new biomedical breakthroughs should be fully exploited. This will require the creation of sufficient infrastructure for translational studies (including tissue and sample banks) and harmonisation of regulations for sample storage, sample shipment and use of biobanks;
- All regulators should use a broad risk-based categorisation of studies, with cell therapy being categorised as high risk (level D in the proposed categorisation);
- All procedures and requirements should be adapted to the appropriate level of risk and include the risk-based approach in the EU Clinical Trials Directive on Medicinal Products (2001/20/EC of 4 April 2001)[f];
- The mission and role of ethics committees should be harmonised and the ethical standards of clinical trials should be increased;
- Procedures for submission of clinical trial authorisations to the competent authorities should be streamlined across Europe, ideally with only one centralised application;

e. The EUTCD is made up of three Directives, the parent Directive (2004/23/EC), which provides the framework legislation, and two technical Directives (2006/17/EC and 2006/86/EC), which provide the detailed requirements of the EUTCD. Available from: http://www.hta.gov.uk/guidance/licensing_guidance/expected_standards_directions.cfm. See also: http://ec.europa.eu/health/ph_threats/human_substance/legal_tissues_cells_en.htm (accessed Apr-19, 2010)

f. Available from: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-1/index_en.htm (accessed Apr-19, 2010)

- Innovative clinical trials should be strongly encouraged. Specific financial support for GMP production of the necessary products should also be part of the financial support, independent of industry;
- Support should be given to academic institutions acting as sponsors. Regulatory requirements should be adapted to reflect the risk associated with the study, not its commercial or non-commercial objective;
- Funding agencies should allow universities, hospitals and learned societies to conduct solid, multinational, large-scale investigator-driven clinical studies based on the correctly powered scale. For smaller scale proof-of-concept studies the funding and structure of organisation of the trials should be adapted appropriately; and
- Funds should be made available not only for clinical trials but also for novel add-on biological studies. Funding streams for clinical trials should cover all types, not just medicines.

Various treatment strategies – autologous versus heterologous

For cell therapy, choices have to be made regarding cell type and preparative culture before the therapy begins. Each of the different SCs described above have their own advantages and disadvantages in terms of mechanism of action and regulation. The most obvious and easiest option to implement would be the use of autologous adult SCs, as these can be harvested from bone marrow or adipose tissue. However, these may have a variable capacity to repair tissue, which might be influenced by the patient's age and/or gender, the nature of the disease or concomitant medical treatments.

Another way to obtain autologous SCs is by the generation of iPS cells. The potential risk of inappropriate behaviour such as tumour formation needs to be investigated thoroughly before therapy based on iPS cells can be considered for clinical trials.

The use of heterologous SCs would offer a logistically simpler method that could provide, in effect, an "off the shelf" product consisting of banked adult SCs or hESCs. These cells can be much better characterised or even (genetically) modified before application but might pose a risk of rejection.

The choice of preparative culture is dependent on the proposed application and on the cell type being used. If adult SCs are used, it appears feasible to skip the need for long-term culture and instead prepare and possibly select cells in the operation room. The cells can then immediately be applied without the need for second surgery. As the risk of cell transformation during culture is excluded, this method is much simpler in terms of regulatory approval and can often be registered as a "medical device" instead of "Advanced Therapy Medicinal Products" (ATMPs) (see 'Transplants' below). On the other hand if a culture procedure is used, more extensive characterisation of the product can be done before application, leading to a better controlled procedure. Regardless of which option is chosen, the clinical outcome and therapeutic index (efficacy/toxicity) will mostly determine which approach is to be preferred for a specific clinical application.

Safety studies including long-term studies in animals – teratoma formation

The major current issue facing the use of hSCs in therapy is that of safety, including questions regarding the epigenetic status and stability of these cells. A critical issue is the risk of teratoma (tumour) formation after transplantation of undifferentiated hESCs/iPS cells, which have the ability to form inappropriate tissues. A so-called anti-apoptotic gene, termed survivin, contributes to teratoma formation by hESCs[42]. In a previous study, rats grafted with hESCs that had been predifferentiated *in vitro* for 16 days developed severe teratomas, whereas most rats grafted with hESCs predifferentiated for 20 days or longer remained healthy until the end of the experiment[43]. This illustrates the need to develop efficient differentiation protocols based on the generation of fully differentiated or committed precursor cells. Several strategies can also be used to avoid the transplantation of undifferentiated hESCs, such as sorting pluripotent cells using GMP-grade flow cytometry, or using 'suicide genes'.

It is also important to note that not only undifferentiated hESCs could provoke tumour or cancer formation. A case report shows that even four years after transplantation of a mix of foetal neural stem cells, a brain tumour appeared[44]. The theory that tumour cells may be damaged versions of normal adult SCs has been intensively studied. Researchers are still debating which cell becomes a tumour cell and tumour SC, but one finding[45] suggests it is the immature adult SC, at least for certain types of leukemia. Mice whose adult SCs - both progenitor and immature – contained a gene that causes leukemia were bred. While the results were not conclusive in proving that SCs cause leukemia, they showed that low doses of cancer genes can transform a SC from something that protects life to something that might threaten it. hESCs may also inherently harbour features of neoplastic progression[46]. This highlights the importance of long-term studies to assess clinical treatments.

The immunogenicity of hESCs is another challenge. Although autologous tissue-derived cells are ideal in this respect, there are many situations where this is just not feasible. Although hESCs have been shown to be less susceptible to immune rejection than adult cells, this 'immune privileged' status has been questioned[47] and hESCs or their derivatives may be rejected by the patient's immune system. This could be overcome with an immunosuppressive regimen, which carries an inherent risk, well known in the field of organ transplantation. Other possible options include modulation of the immune response, an exciting topic of current research[48], or the generation of patient-specific hESC lines[49]. Matching the most suitable existing hESC line for each recipient may reduce the need of immunosuppression. Regarding iPS cells, another possibility exists. HLA homozygous donor-derived iPS cells would provide unprecedented cell banking for RM. A calculation has predicted that 50 unique iPS cell lines, which are homozygous for the three major HLA loci, would cover 90% of the Japanese population with a perfect match[50].

Ethical and legal issues

Research (social justice, changes to legislation, human-animal interaction)

Most scientists are overwhelmed when they review all relevant regulations and guidelines covering the removal, storage, use and disposal of secretions, organs and tissues for research applications. In general terms, there are a number of key issues that must be addressed when sourcing human tissues for research use, whether this is from approved Research Tissue Banks or when establishing a prospective collection. These cover organs unsuitable for transplantation; samples collected specifically for research, for example blood, other body fluids or small biopsies; and *post mortem* material or so-called "surplus tissue" left over from clinical and diagnostic procedures. The challenge is to be able to work within the regulations and guidelines at a practical level in order to be able to obtain the specific human tissue for research.

In most European countries ethical approval and informed written consent of the patient are required[g]. Consent is the central focus of legislation relating to access to identifiable patient data and use of identifiable tissue for research. All donors must be fully informed in writing in particular about the aims of the research and any potential commercial interest. When sourcing tissues from Research Tissue Banks one has to be sure that the banks are properly licensed, that they have certified systems to provide safe tissues with reliable quality and that the initial informed consent is respected. The banks' premises, facilities and equipment must be suitable for the storage of human tissues.

Generation of human-animal chimeras for research purposes has a long history in science and has been a subject of considerable ethical discussions. Teams in the UK obtained permission from the Human Fertilisation and Embryology Authority (HFEA) to create animal-human hybrid embryos using SCNT. Following the approval of the Human Fertilisation and Embryology Act in October 2008, this technique is now legal in the UK subject to license by the HFEA[h]. The Human Fertilisation and Embryology Act regulates the creation of a number of types of animal-human hybrids, including "true" hybrids, transgenic human embryos and chimeric human embryos. The licences so far issued in the UK are for the creation of animal-human hybrids which combine an animal oocyte with genetic material from a human adult cell which would result in a cell with animal mitochondria but human nuclear genes[51]. What happens to such mitochondria and how such cells function remains to be seen. Evidence suggests that animal-human hybrids do not express the genes required for pluripotency[51] but further research remains to be done. It is clear however, that while such hybrids provide valuable insights into the fundamental aspects of SC development and may provide models for studying disease development, such embryos could not under current conditions be used for therapeutic purposes. More recently, this animal-human hybrid approach has been largely superseded by iPS cell research.

Although technically challenging at the moment, germ cell differentiation from hESC/iPS cells could offer an unprecedented system to understand the pathologies of infertility and develop new drugs to overcome those. This issue also needs to be discussed from world-level ethical points.

Private companies and personal cell banks

There is increasing interest among private companies to create personal cell banks where parents can pay for their child's umbilical cord blood to be stored for potential future therapeutic use. Though the use of autologous SCs procured from umbilical cord blood has immunological advantages, it is far from clear whether treatments will be available in the future based on SCs derived from cord blood. Parents or grandparents may be lured into buying access to personal cord blood banking for their child or grandchild by attractive advertising and marketing methods of private companies. If treatments on the basis of cord blood SCs become available there is an issue of social justice and social equality with regard to personal cord blood banking. Given that such banking is expensive, only a small proportion of the population may be able to buy access to a personal cord blood bank. Quite apart from these ethical issues, the quality of cord blood conservation needs to be guaranteed.

Transplants (ATMPs)

"Advanced Therapies" refers to Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products (ATMPs)[i] that will, for the first time, bring all advanced therapies (gene, cellular and tissue-based) together within a single, integrated European regulatory framework, thereby ensuring consistency across Member States. The definition of an ATMP is a "medicinal product for human use that is a gene therapy medicinal product, a somatic cell therapy medicinal product or a tissue engineered product". The Regulation sets out specific technical requirements for these innovative therapies and establishes new standards for clinical trials in the development of advanced medicinal products. Following the opinion of the European Parliament on 25 April 2007, the Council of Ministers approved the Regulation on advanced therapies in first-reading on 31 May 2007. The Regulation was translated into all EU official languages and on 30 October 2007 the Advanced Therapy Regulation was formally adopted by the EU Council. The Regulation was published in the EU Official Journal on 10 December 2007 and entered into force on 30 December 2007. Soon after the publication of the Regulation, DG Enterprise and Industry made public its priorities for the implementation of the Advanced Therapies Regulation. The implementation plan has been developed and agreed

g. http://www.wma.net/en/30publications/10policies/b3/index.html (accessed Apr-19, 2010)
h. http://www.opsi.gov.uk/acts/acts2008/pdf/ukpga_20080022_en.pdf (accessed Apr-19, 2010)
i. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:EN:PDF (accessed Apr-19, 2010)

with the European Medicines Agency, the EU pharmaceutical regulatory resource that provides guidance for newly licensed formulations for human and veterinary use, and whose approval is required for market licensing of medicinal products. This public consultation document presents preliminary proposals to replace the existing Part IV of the Annex I to Directive 2001/83/EC. Detailed information can be found under:
http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/docs/consultation-paper-nr_2008-04-08.pdf

It remains to be clarified whether SC therapies fit into the definition of ATMPs and of "investigational medicinal products" as described in the EU Clinical Trials Directive on Medicinal Products: "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form"[j].

Patent situation in Europe

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 hESC research.

A patent is a temporary right "to exclude others from making, using, offering for sale, or selling" the invention which fulfills specific patentability requirements[52] in the specified jurisdiction in return for a disclosure of the invention. However, having a patent does not give one the right to use the invention, but only to exclude all others from the use of the patented invention. A patent owner is still subject to national laws (such as cloning, embryo research laws, environmental laws, marketing regulations, earlier dominating patents, and so forth).

The European Patent Convention (EPC) regulates the granting of patents[53] (examination, issuance) but the legal effects (validity, infringement) of a patent fall under national jurisdiction.[54] The EPO issues a bundle of national patents[55] resulting from a joint application.

In general, the EPC is not clear on the issue of patentability of hESC technology. Although hESC inventions may fulfill the standard patentability requirements, the EPC prohibits patentability on ethical grounds for inventions whose "exploitation or publication would be contrary to *ordre public* or morality."[56] The EPO guidelines suggest that the goal of this morality clause is to "deny protection to inventions likely to induce riot or public disorder, or to lead to criminal or other generally offensive behavior."[57,58] Furthermore, the EPC does not allow patenting on "uses of human embryos for industrial or commercial purposes"[59].

The past few years of the EPO's rulings[60] have failed to provide any clear-cut answer to the patentability of hESCs, which resulted in many hopes being pinned on the so-called WARF[61] appeal before the Enlarged Board of Appeal (EBA, the Supreme Court of the EPO). On 25 November 2008, the EBA delivered a long-awaited WARF ruling[62] and affirmed that the EPO will not grant a patent if the invention relies exclusively on a method which necessitates the "destruction of a human embryo" from which the said products are derived. The WARF decision confirms that this ban stands "even if the said method is not part of the claims". The EBA stated that "what needs to be looked at is not just the explicit wording of the claims but the technical teaching of the application as a whole as to how the invention is to be performed". It further adds that, "to restrict the application of Rule 28(c)… to what an applicant chooses explicitly to put in his claim would have the undesirable consequence of making avoidance of the patenting prohibition merely a matter of clever and skilful drafting of such claim."[63] According to the EBA, the WARF decision does not concern the general question of hSC patentability. In addition, the EBA rejected the request for a preliminary ruling on the matter by the European Court of Justice (ECJ) due to lack of any legal and institutional link between the EPO and the EU.[64]

With the carefully worded WARF decision, the EBA has in effect postponed the patent morality issue for another few years. It is interesting to see how practices of the national patent offices will change in view of the importance of the WARF decision. The UK Intellectual Property Office (IPO) has already altered its patenting practice[65] placing it in line with the EPO. This supersedes the UK IPO's previous practice notice and signals a significant shift in policy. How this will affect British patent policy on hESCs remains to be seen. In addition, the pending Brüstle appeal of a German patent (DE 19756864; European Patent EP 1040185) before the German Federal Supreme Court led the Court to refer a number of controversial questions to the ECJ in late 2009. The ECJ is now asked to rule on the "interpretation of 'human embryo' in the sense of Article 6 of the Biotech Directive; whether a stem cell derived from a blastocyst has lost its ability to develop into a human still an embryo? If so, is a blastocyst a human embryo? If so, is purely therapeutic use of stem cells a 'commercial or industrial purpose' in the sense of Article 6?"[k] How the ECJ addresses these queries has the potential to shed light on the issue of patenting biotech applications claiming the use of hESCs.

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

In line with one of the recommendations from the previous editions of the ESF Science Policy Briefing *Human Stem Cell Research: Scientific Uncertainties and Ethical Dilemmas*, the table of regulations on the use of hSCs in

j. Available from: http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-1/index_en.htm (accessed Apr-19, 2010)

k. Directive 98/44/EC of the European Parliament and of the Council on the Legal Protection of Biotechnological Inventions (entered into force on 6 July 1998); The IPKat, Bundesgerichtshof refers human stem cell patent case to ECJ (Nov. 2009): http://ipkitten.blogspot.com/2009/11/bundesgerichtshof-refers-human-stem.html (accessed Apr-19, 2010).

ESF membership countries was updated (see Annex 1), with information on 30 countries included[l,m]. In summary, 25 countries have adopted legislation which explicitly prohibits human reproductive cloning (excluding Poland, Lithuania and Ireland as well as Croatia and Luxembourg). Seven countries allow hESC research and the derivation of new hESC lines from supernumerary IVF embryos by law (Belgium, Sweden, UK, 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 (data not shown in Annex 1). Three countries have adopted legislation to allow the creation of embryos for research purposes under strict conditions (Belgium, Sweden, UK). 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 to hESC research.

Access to therapies

Differing legislation may lead to differences and imbalanced access in Europe to treatments deriving from hESC research. Patients may travel from one country to another where they may have access to a treatment that is forbidden in their own, leading to what could be considered as an unequal distribution of the benefits and the burdens of SC research. It could be seen as an issue that some countries bear all the burdens of SC research while patients and inhabitants of other countries, where such research is not allowed, benefit from the treatments. This does not mean that patients should be denied treatment, but that access to objective information regarding SC treatment should be made widely available for all European citizens.

l. http://www.hescreg.eu/index.php?id=8 (accessed Apr-19, 2010)
m. http://www.isscr.org/public/regions/region.cfm?RegionID=1 (accessed Apr-19, 2010)

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[66].

While the media has tended to make promises to the public – including patients – European scientists have continued to tread a careful path and act responsibly, while making impressive scientific advances. As research proceeds, it is clear that tissue-derived SCs, hESCs and iPS cells should be studied in parallel. Well-controlled clinical trials are being carried out where appropriate. As knowledge increases about the safety and function of different cell types, the promise of the field will hopefully start to meet people's expectations. Legislation relating to the safe use of SCs has been successfully implemented, and provided that adequate funding is maintained and unresolved issues surrounding patents are addressed, then 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.

Statements and recommendations

- Continued research on all types of SCs derived from embryos, foetal tissues and adults remains necessary as it is too early to predict their value in a specific field. Research using embryonic and iPS cells is required, as the knowledge derived from both is complementary and for the moment the benefits and risks are not sufficiently known;
- While clinical research is clearly important, basic research remains essential to understand cellular differentiation and function;
- The lack of common criteria and universal standards for the preparation of SCs has greatly hampered further progress. Furthermore, functional characterisation 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;
- 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;
- 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;
- More studies and information about the immunogenicity, epigenetic status and stability of SCs and the immune response of the human organism are needed; and
- Public funding, including at the European level, is necessary to support the translation and implementation of SC-based products into the market.

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Acknowledgement:
We are extremely grateful to **Dr Laurence Lwoff**, Head of the Bioethics Division at the Council of Europe (Strasbourg, France) who carefully and critically reviewed this document on all ethical aspects.
The initiative for and the development of this Science Policy Briefing have been coordinated by **Dr Fiona Kernan**, former Science Officer, **Dr Maria Manuela Nogueira**, Science Officer, and **Dr Carole Moquin-Pattey**, former Head of the Medical Sciences Unit, European Science Foundation, France.

Annex 1: Human stem cell regulations and legislation in Europe (May 2010)

Country	Reproductive cloning prevented by national law	Research authorised by national law on				Prohibition of human embryonic stem cell (hESC) research	No specific legislation regarding hESC research	Ministry or official body in charge
		Stem cells*	Human embryos		Aborted foetuses			
			Procurement of stem cells from super-numerary embryos	Creation of human embryos for research purposes**				
Austria [1,2]	●	●						Federal Chancellery
Belgium	●		●	●				Public Health & Research (W) Justice & Health (F)
Bulgaria [3,4]	●						●	Health
Croatia [3,4]							●	N/A
Cyprus [3,4]	●						●	Independent Body
Czech Republic [3,4]	●		●					Health
Denmark [3]	●		●					Science Technology and Innovation
Estonia [3,4]	●		●					Social Affairs
Finland	●		●		●			Social Affairs and Health
France	●		●		●			Health
Germany	●	●						Federal Ministry of Health
Greece [3,4]	●		●					Development and Health
Hungary [3,4]	●		●		●			Health
Iceland [3,4]	●		●					Health and Social Security
Ireland		●						Department of Health and Children
Italy	●	●			●			Health
Lithuania [1,3,4]						●		Health
Luxembourg [6]							●	Health
The Netherlands	●		●		●			Health, Welfare and Sports
Norway [3]	●		●		●			Health and Care Services
Poland [1]						●		Health and Social Affairs & National Education and Science
Portugal [3,4]	●		●					Health
Romania [3,4]	●						●	Health
Slovakia [1,3,4]	●				●	●		Health
Slovenia [3,4,7]	●		●		●			Health
Spain [3,4]	●		●		●			Health & Science and Innovation
Sweden [8]	●		●	●	●			Health and Social Affairs & Education
Switzerland [3,4]	●		●					Federal Office of Public Health
Turkey [3,9]	●						●	Health
United Kingdom	●		●	●	●			Department of Health

* Prohibiting the procurement of stem cells from supernumerary embryos but allowing the import and use of stem cell lines.
** SCNT is not considered in this table: Belgium, Sweden, UK, Spain and Portugal allow SCNT by law, while Finland and the Czech Republic neither prohibit nor allow it by law.
1. Countries that voted against the Council Decision on hESC research during FP7 (www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/intm/90654.pdf)
2. AT: The Austrian Bioethics Commission published an opinion on 16 March 2009 which recommends allowing hESC derivation from supernumerary IVF embryos.
3. Countries who have signed and ratified the 1997 Convention of the Council of Europe on Human Rights and Biomedicine CETS 164 (http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=8&DF=4/16/2009&CL=ENG)
4. Countries who have ratified the 1998 Protocol on the Prohibition of Cloning in Human Beings CETS 168 (http://conventions.coe.int/Treaty/en/Treaties/Html/168.htm)

Specific national committee(s)	Competences of the committee members	Committee website(s)
Bioethics Commission	Medical experts (reproductive medicine, gynaecology, psychiatry, oncology, pathology), legal experts, sociologists and experts in philosophy, theology and microbiology.	www.bka.gv.at/DesktopDefault.aspx?TabID=3575&Alias=english
Advisory Committee on Bioethics [5]	Biologists, ethicists, lawyers, philosophers, physicians and theologians.	https://portal.health.fgov.be/portal/page?_pageid=56,512676&_dad=portal&_schema=PORTAL
Central Ethical Committee [5]	Medical doctors, pharmacist, pharmacologist and laywer.	Not available
N/A	N/A	N/A
National Bioethics Committee	Biologist, geneticist, medical doctor, psychologist and sociologist.	www.bioethics.gov.cy
(a) Bioethical Commission of the R & D Council and (b) Ethical Committee of the Ministry of Health [5]	Bioethicist, biologist, biotechnologist, ethicists, geneticist, immunologist, medical scientist, molecular biologists, philosophers, physiologist, sociologist and theologian.	www.vyzkum.cz/FrontClanek.aspx?idsekce=15908
Council of Ethics [5]	Bishop, former politician, journalist, lawyer, lay persons, scientists, teacher, theologian and vicar.	www.etiskraad.dk/sw293.asp
Council on Bioethics	Ethicists, lawyers, medical doctors and ministry representatives.	http://eetika.ut.struktuur.ee/260565
Sub-committee on Medical Research Ethics of the National Advisory Board on Health Care Ethics [5]	Ethicists, medical doctors, lawyers and lay persons.	www.etene.org/e/index.shtml
Biomedicine Agency [5]	Lay persons, philosophers, theologians, scientists and medical doctors.	www.agence-biomedecine.fr
(a) German National Ethics Council (Deutscher Ethikrat) and (b) Central Ethics Commission for Stem Cell Research [5]	(a) Scientists, politicians, lawyers, lay persons, philosophers, medical experts, bishop and theologians and (b) biologists, ethicists, medical experts and theologians.	www.nationalerethikrat.de www.rki.de/cln_049/nn_216782/EN/Content/Institute/DepartmentsUnits/StemCell/StemCell__node.html?__nnn=true
National Bioethics Commission	Lawyers, philosophers, scientists and theologians.	www.bioethics.gr/index.php?category_id=3
Health and Scientific Council/National Scientific and Ethical Committees [5]	Bioethicist, biologist, geneticist, lawyer, lay person, medical doctors, nurse and priest.	www.ett.hu (in Hungarian only)
National Bioethics Committee	Lawyers, medical doctors, philosophers, scientists and theologians.	www.visindasidanefnd.is
Irish Council for Bioethics [5]	Ethicists, lawyers, scientists, philosophers and physicians.	www.bioethics.ie/
National Bioethics Committee [5]	Ethicists, lawyers, medical doctors, scientists, pharmacologists and patient representative.	www.palazzochigi.it/bioetica/eng
Bioethics Committee	Ethicist, geneticist, lawyer, medical doctors, philosophers, psychologists, psychiatrist and priest.	http://bioetika.sam.lt/index.php?-1876243809
(a) National Consultative Bioethics Commission for Health and Life Sciences and (b) Committee for Research Ethics (Ministry of Health)	Government representative (Social Security), lawyers, medical doctors, social workers, teachers and theologians.	www.cne.public.lu/
Central Committee on Research Involving Human Subjects [5]	Ethicists, medical doctors, nurses, scientists and pharmacologists.	www.ccmo-online.nl
National Committee for Medical and Health Research Ethics [5]	Ethicists, lawyer, lay persons, pharmacist, philosopher and psychologist.	www.etikkom.no/In-English/
N/A	N/A	N/A
(a) National Committee for Reproductive Medicine and (b) National Council of Ethics for the Life Sciences [5]	(a) Biologists and medical doctors and (b) geneticists, legal experts, medical doctors, philosophers and theologians.	www.cnecv.gov.pt/cnecv/en/
Bioethics Commission of Health and Family	N/A	N/A
National Ethics Committee	Geneticist, medical doctor, ministry representative (Health), priest, sociologist and theologian.	www.health.gov.sk
(a) National Committee for Medically Assisted Reproduction and (b) National Medical Ethics Committee	(a) Ethicist, lawyer, medical doctor, ombudsman representative and psychologist and (b) ethicist, lay person, lawyer, physicians, psychologist, sociologist and theologian.	Not available
(a) National Commission on Human Reproduction and (b) Observatory of Law and Ethics	Scientists, lawyers, psychologists and government representatives (Health).	Not available
National Council on Medical Ethics	Ethicists, lawyer, medical doctors, politicians and ministry representative (Health and Social Affairs).	www.smer.se
National Advisory Commission on Biomedical Ethics [5]	Ethicists, lawyers, lay persons, medical doctors and scientists.	www.swissethics.ch www.bag.admin.ch/nek-cne/
Ethics Council [5]	Medical doctors, a pharmacist, and ministry representatives (Health).	Not available
(a) Human Fertilisation and Embryology Authority and (b) Human Genetics Commission [5]	Ethicists, journalist, lawyers, lay person, medical doctors and scientists.	www.hfea.gov.uk www.hgc.gov.uk

5. Apart from national committee(s), whether existing or not, there are local and/or regional ethical committees.
6. LU: A new law is under preparation. Opinion against human reproductive cloning has been given in 2004. Opinion for the authorisation of research on stem cells obtained from supernumerary embryos and of creation of embryos for therapeutic purposes has been given in 2003.
7. SI: Research on supernumerary embryos from IVF procedures (and thus the procurement of hESC) is allowed with zygotes or embryos until 14 days of development.
8. SE: Tissue from aborted fetuses may be used for medical purposes only.
9. TK: hESC research has been suspended at all levels by the Turkish Ministry of Health and legislation regarding hESC research is under preparation.

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ISBN: 978-2-918428-12-1

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Print run: 1000 – May 2010