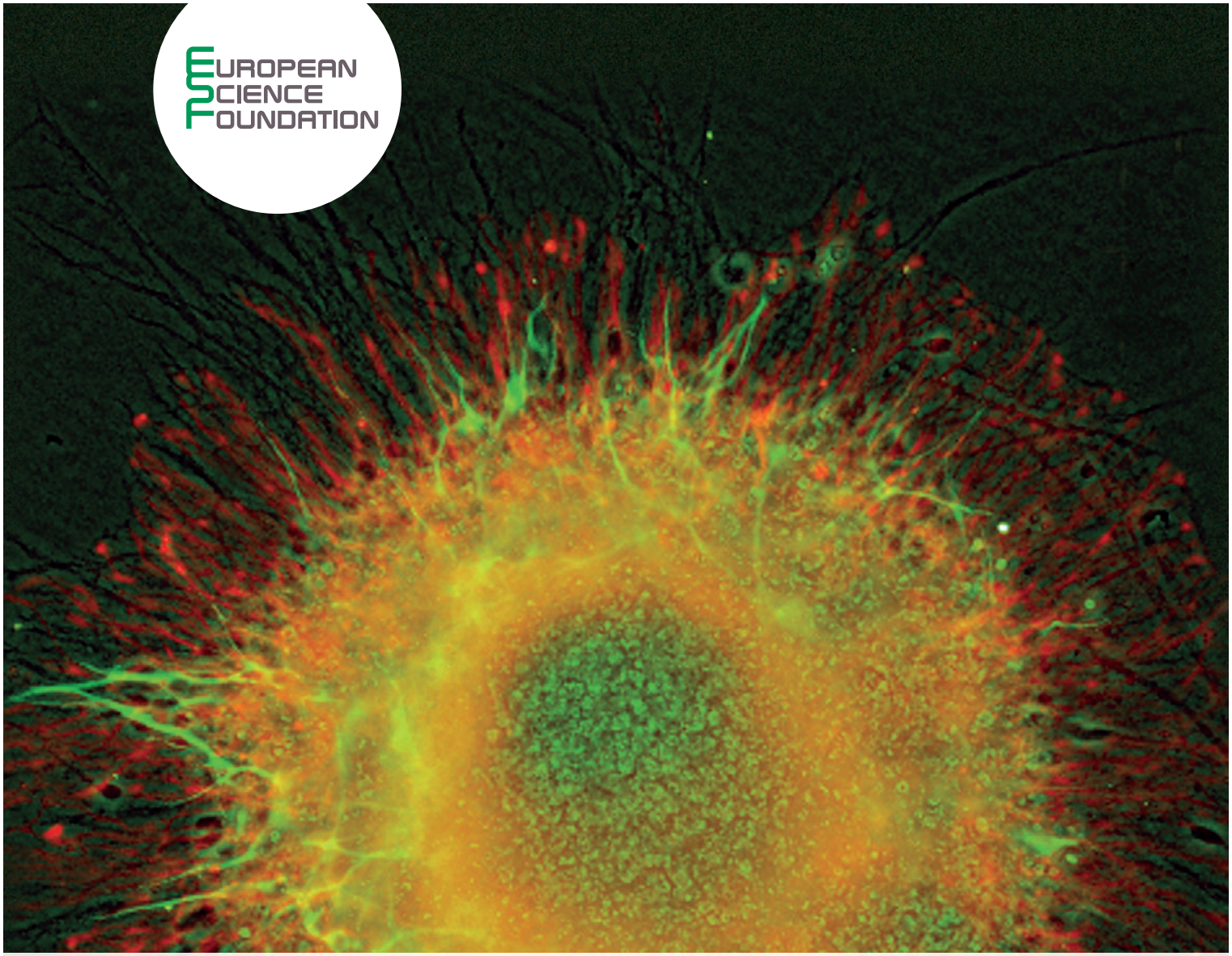
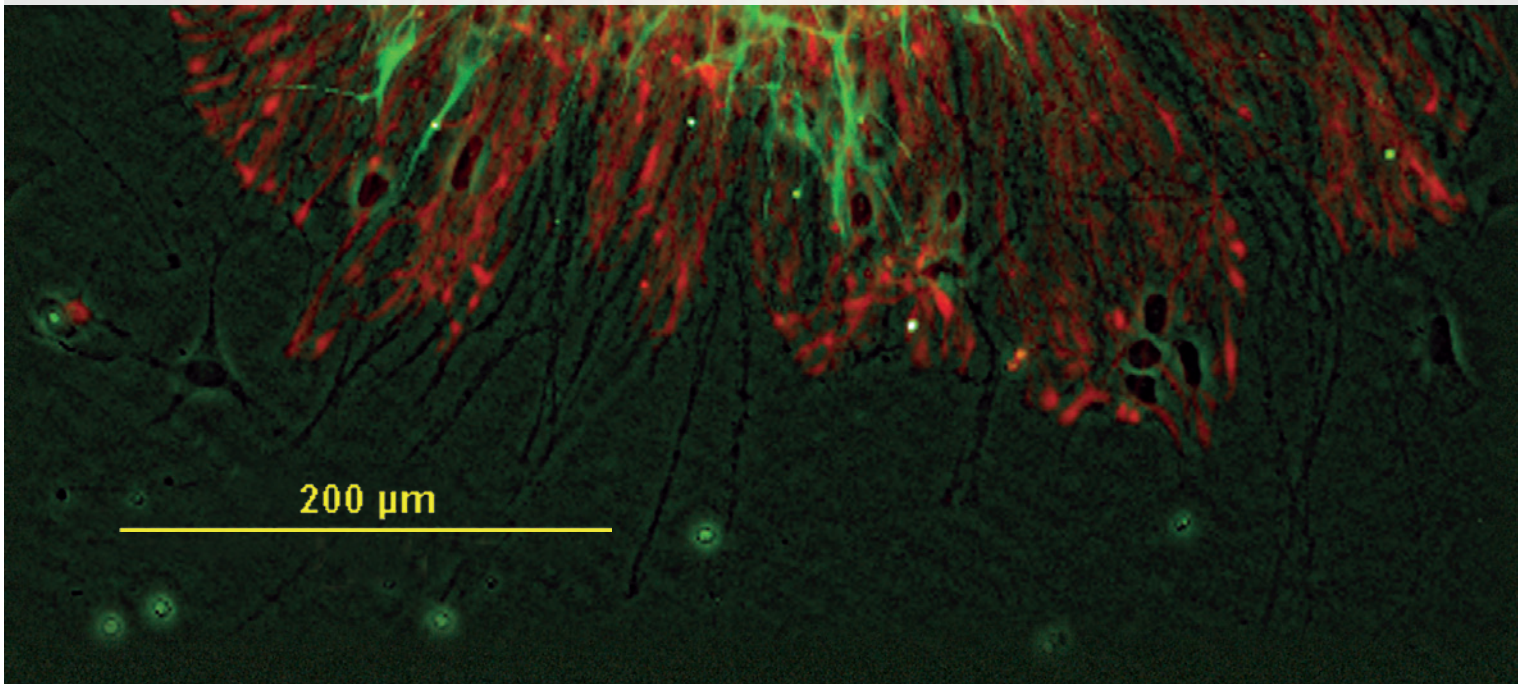


Human Stem Cell Research and Regenerative Medicine

Focus on European policy and scientific contributions



European Science Foundation (ESF)

The European Science Foundation (ESF) was established in 1974 to provide a common platform for its Member Organisations to advance European research collaboration and explore new directions for research. It is an independent organisation, owned by 67 Member Organisations, which are research funding organisations, research performing organisations and academies from 29 countries. ESF promotes collaboration in research itself, in funding of research and in science policy activities at the European level. Currently ESF is reducing its research programmes while developing new activities to serve the science community, including peer review and evaluation services.

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Authorship, Contributors and Acknowledgements

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Cover picture:
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 courtesy of Dr Katja Puttonen, University of Eastern Finland (FI).
Original magnification ×200.

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Contents

Foreword

Stem cell research is a field that has generated much activity in laboratories, media offices and higher courts. Parallel to the potential new treatments for incurable diseases and opportunities for bioentrepreneurs, heated ethical and legal debates have arisen around the world.

The European Science Foundation (ESF) has been an active player in policy in this field over the last decade, as reflected by reports published in 2001, 2002 and 2010. As science continues to advance, so do legislation and funding decisions. At the national level, policy developments are taking place almost daily. At the European Union (EU) level, current discussions between different Committees and Directorate Generals within the European Parliament and the European Commission are now focused on whether human stem cell research and innovation should continue to be funded through the Horizon 2020 programme for research and innovation, and on how decisions can be tied in with the positions and recent rulings of the European Patent Office (EPO) and the European Court of Justice (ECJ).

Encouraged by the European Commission Directorate for Research and Innovation's Health Directorate and with the support of ESF Member Organisations, this new report has been produced in order to provide a constructive contribution to the on-going debate and providing evidence that may help inform future decisions. The information presented consists of an update on the current legal landscape across 30 European countries, supplemented by a selection of ESF activities focusing on stem cell research and relevant European outputs from basic and clinical research in different healthcare fields.

This compilation of information illustrates Europe's valuable track record in the area of stem cell research and highlights the need to continue to fund this research so that its full potential can be realised.

Professor Stig Slørdahl
Chair, ESF Scientific Review Group for the Biomedical Sciences

Mr Martin Hynes
ESF Chief Executive

Executive Summary

In recent years, international research on regenerative medicine and stem cells has yielded some promising results and even greater expectations in society. Europe is currently witnessing developments and debates that will impact regulation and public funding of stem cell research and innovation for years to come. In the light of these changes and the international collaborations emerging, key questions arise: How do current policy and regulatory frameworks differ across Europe? Is there a need for pan-European alignment of regulations and funds? Should the European Union continue to sponsor human stem cell research, particularly under Horizon 2020?

This European Science Foundation (ESF) report presents a comparative overview of the legislative framework on human stem cell research across 30 countries, a brief compilation of ESF collaborative research funding opportunities, and a collection of relevant European outputs in this field. Overall, countries' positions on human stem cell research can be grouped in five broad categories: very permissive, permissive with restrictions, restrictive by default, very restrictive, and unlegislated. Sixty-three percent of the countries studied fall into the first two categories. Legal sources of human embryonic stem cells (hESCs) vary across Europe, with very few countries authorising the creation of embryos exclusively for research purposes. Most nations only allow for the derivation of hESCs from surplus *in vitro* fertilisation (IVF) embryos. Few countries ban the derivation of these cells altogether, and yet some permit cell line imports under strict conditions. In addition, the brief selection of promising results in terms of scientific production and clinical trials highlights the achievements of a vibrant community of scientists and innovators.

The evidence contained in this report suggests that Europe has a substantial track record and an unprecedented opportunity to leverage on the benefits of the investments and efforts made to date. For this to happen, sustained public endorsement and funding need to continue, so that further research is carried out and public-private partnerships develop to bring safe and innovative therapies to the market for the potential benefit of millions of patients worldwide. This report may help to inform future policy and funding decisions across Europe and thus contribute to ensuring this continent's scientific leadership, social welfare and economic growth.

Introduction

The use of stem cells has developed under much expectation and even controversy worldwide, particularly there where human embryonic stem cells (hESCs) are concerned. The enormous potential of regenerative medicine for restoring tissue or organ function and benefitting mankind has been acknowledged by society with world-class distinctions such as the 2012 Nobel Prize in Medicine and Physiology awarded to John Gurdon and Shinya Yamanaka.

In Europe, research and innovation in regenerative medicine are supported by legislation such as the so-called Biopatent Directive[1]. 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.

Furthermore, although the EPO excludes any invention based on the destruction of human embryos from patenting, in practice it does allow the patentability of hESC-derived inventions if the cell lines already existed at the time of filing. Interestingly, not all EU countries are bound to abide by this rule, as the EPO only affects countries that are signatories of the European Patent Convention[2].

Many other types of innovations around stem cell research continue to emerge in Europe. Consumables, procedures and devices needed to carry out stem cell research, as well as molecules and media used in *in vitro* cell or tissue culture protocols, can all be patented. Also, recent research on adult stem cells such as mesenchymal stem cells (MSCs) or induced pluripotent stem cells (iPSCs) is associated to less ethical and legal constraints than hESC research[A] and thus continues to make progress.

The ESF and the European Medical Research Councils (EMRC) have long supported human stem cell research and regenerative medicine issuing Science Policy Briefings on these topics in 2001[3], 2002[3] and 2010[4]. Throughout 2012, ESF and EMRC continued to actively engage in advocacy and policy making, liaising with key networks of scientists and politicians, contributing to a dedicated workshop at the European Parliament[5] and publishing an editorial in a relevant policy journal[6].

The aim of the present ESF report is to constructively contribute to the ongoing debate and to provide evidence that will help inform future policy and funding decisions impacting human stem cell research in Europe. To do this, and building on the information provided in the aforementioned ESF reports, we have conducted a review of the evolving policy and regulatory stem cell research landscape across 30 European countries. In addition, the added value that this field may bring to novel diagnostic and therapeutic options is showcased through a brief compilation of ESF-sponsored workshops and collaborative research and networking activities, supplemented by a selection of successful frontier research projects and advanced European clinical trials.

In Europe, EU legislation and recommendations impacting the use of stem cells are found in a vast array of reports, resolutions, directives and regulations. These documents frequently address related topics such as tissue research, transplants,

A. For the various definitions, see "Types of stem cells and their current uses: short summary": http://www.eurostemcell.org/files/SC_types_overview_table_FINAL_Aug2012_0.pdf

advanced therapies, biobanks and data protection. At the national level, positions vary widely from one country to another. Amidst lively debates and constant discoveries worldwide, the different bodies of the EU are discussing how to best integrate and update legislation that would apply to all European countries alike. Yet binding legal decisions and their ramifications for funding continue to ensue, both at the national and European level. The challenge is that some of the latest decisions and positions at the European level may not fully align, as explained below.

Chronologically, the European Directive on the legal protection of biotechnological inventions[1] and the European Patent Convention[2] started by stating that essential biological processes for the production of plants and animals are not patentable. In 2011, when studying the Brüstle case, the ECJ ruled that it was illegal to patent stem cell discoveries[7]. These legally binding decisions constituted, in turn, the basis of a 2012 resolution by the European Parliament[8] 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.

Consequently, 2012 witnessed a major revision to the complex regulatory framework in place, articulated around the Clinical Trials Directive[9], the Medicinal Products Directive[10] and the Medical Devices Directive[11]. Stem cell research is mainly affected by the so-called Human Tissues and Cells Directive (2004/23/EC)[12], two technical directives from 2006, the Biopatent Directive (98/44/EC)[1] and additional extensive legislation on medicinal products for human and veterinary use. The main hurdles to boosting true pan-European research and innovation come from the heterogeneous implementation of this legislation across the EU, with stances ranging from very permissive to very restrictive (see Table 1 and Figure 1).

For researchers working in Europe, the two main consequences of a final restrictive policy outcome would be legal and financial. Legally, Article 6 of the Biopatent Directive[1] remains somewhat unclear on whether certain inventions are currently patentable or not. As mentioned earlier, this article states that "uses of human embryos for industrial or commercial purposes" are not allowed, but there is no legal definition of either "embryo" or "industrial or commercial purposes", thus leading to diverse potential interpretations. Furthermore, ECJ Advocate General Yves Bot argued in 2011 that hESCs were not to be considered an embryo *per se*, because they lack the capacity to become a human being by themselves. Yet procedures involving hESCs known as pluripotent cells were not allowed to be patented. All this controversy led to the 2011 ruling of the ECJ[7], which is now legally binding for all EU Member States.

The other key issue at stake is European funding for stem cell research, as this strongly depends on the final decision regarding the European Commission's next main funding programme for research and innovation, Horizon 2020[13]. Within EU political structures, the main stakeholders shaping stem cell legislation and funding and their positions as of early 2013 can be summarised as follows:

- Within the European Commission, two Directorate Generals: DG SANCO (Health and Consumers) and DG Research and Innovation. While DG SANCO seems to focus on ensuring safety and is not likely to propose any new legislation on stem cells, DG Research and Innovation advocates for continued funding of stem cell research under Horizon 2020.
- Within the European Parliament, namely JURI (Legal Affairs) and ITRE (Industry, Energy and Research) Committees. While JURI voted against funding research that is not patentable, ITRE voted for maintaining future funding as it comes under Framework Programme 7 [B].

Even if public opinion across countries remains divided, there is currently a risk that European research projects involving hESCs may no longer receive EU funding in the future. This could jeopardise not only the fate of international research projects and clinical trials already underway, but also funding decisions for many years to come. Other types of stem cell research may continue to advance, nonetheless.

B. On 18 September 2012, JURI called for the exclusion of research with human embryos and hESCs from research funding under Horizon 2020. By contrast, on 28 November 2012, ITRE adopted its negotiated position containing an amendment to maintain EU funding for embryonic stem cell research. This ITRE resolution states that no projects using hESCs are to be funded unless they are approved under the law of the member state concerned, that no activity can be funded that is forbidden in all member states and that no activity can be funded in a member state where such activity is forbidden.

Policy and Regulatory Framework

Legislative and governance frameworks for stem cell research in 30 European countries have been assessed after compiling public information and feedback provided voluntarily by officials from each country (see Table 1).

Governance players with regulatory and advisory roles vary somewhat from country to country, with diverse ministries, governmental agencies and advisory committees playing different roles in each country.

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), as summarised in Figure 1:

- *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.

These data suggest that the landscape for hESC research is rather permissive in 19 countries, which account for 63% of the nations studied. Within this situation, some countries are at the boundary between the two categories, so this classification is only intended to be used as a guideline.

Some countries have either very restrictive or unregulated frameworks, probably related to complex ramifications of their own historical and cultural heritage.

Paradoxically, some of the greatest challenges in hESC research may arise in countries with no legislation in place, due to diverse interpretations of what can and what cannot be done. This ill-defined situation could lead to a complete ban in practice, or it might dissuade innovators and venture capitalists from investing in an uncertain commercial environment, to the potential detriment of patients worldwide.

Beyond research *per se*, innovation policies and regulations are restrictive throughout Europe: the ECJ, for instance, deems that patents based on the destruction of human embryos are illegal.

In sum, this variety in legal settings and regulatory and advisory players across Europe offers the opportunity to test different policy and research approaches. The absence of a single "consolidated market", however, may also hamper international

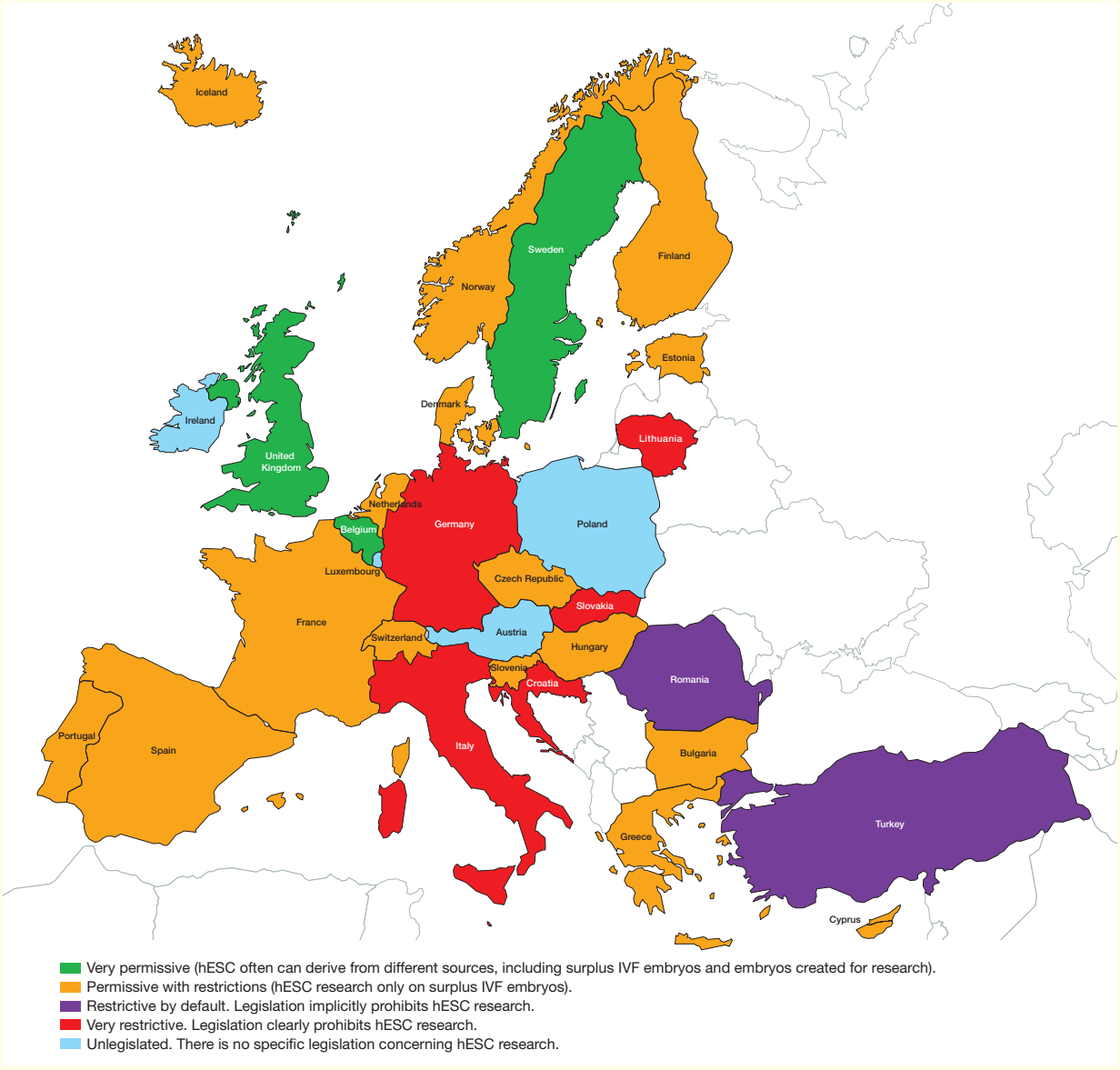

Figure 1. National positions on human embryonic stem cell research policy and regulatory framework in Europe.

collaborations and innovation in Europe. It seems reasonable to infer that continued support of stem cell research will yield more data and enable future advances that will help clarify the safest and most suitable indication for each type of stem cell therapy.

ESF-Funded Scientific Activities in Stem Cell Research and Regenerative Medicine

In response to bottom-up requests from scientists and opt-in decisions from their home institutions (ESF Member Organisations), ESF has funded and managed several European Collaborative Research programmes (EUROCORES), Research Networking Programmes and Exploratory Workshops in the fields of regenerative medicine and human stem cell research. These are summarised in Box 1.

Box 1. ESF-funded scientific activities in the fields of stem cell research and regenerative medicine

Research Networking Programme 'Regenerative Medicine', REMEDIC (2008-2013)

Chair: Professor Reinhold Erben, University of Veterinary Medicine, Vienna (AT)

Programme supported by 17 national funding organisations in 14 countries

Total networking and dissemination budget over 5 years: 470 k€

http://www.esf.org/remedic

REMEDIC aimed at creating a network to facilitate the transfer of knowledge among basic researchers, clinicians and industrial partners, to gather information on regulations, standards and patents in regenerative medicine, and to map research and development resources.

The first European Interdisciplinary Summit on Cell-Based Advanced Medicinal Products was held in Vienna on 2-3 May 2013. The meeting provided a forum for discussion of the challenges involved in the development, application and marketing of these therapies, with special emphasis on regulatory issues and safety models. The following topics were covered: ethics and economy, treatment algorithms and reimbursement, manufacturing challenges, non-clinical models, safety models, EU funding, interdisciplinarity and education, clinical studies and quality assurance, and a Roadmap 2020 for cell-based advanced medicinal products.
http://www.esf-remedic2013.org

EUROCORES Programme 'Development of a Stem Cell Tool Box', EuroSTELLS (2005-2008) (EC contract number: ERAS-CT-2003-980409)

Project Leaders: Professor Cesare Galli, Department of Veterinary Medical Sciences, University of Bologna, Cremona (IT), Professor Elaine Dzierzak, Erasmus University Medical Center, Rotterdam (NL) and Professor Stefan Krauss, The National Hospital (Rikshospitalet), University of Oslo (NO)

This large consortium featured three collaborative research projects, consisting of 21 individual research projects in 10 countries

Budget for research: 3.2 M€ including ca. 385 k€ for networking and dissemination activities over 3 years

EuroSTELLS was designed to generate fundamental knowledge on stem cell biology by setting up the bases for comparative analyses of stem cells of different origins and future clinical applications. In addition, it provided financial support to the International Society for Stem Cell Research

(ISSCR: www.isscr.org) Task Force to prepare their *Guidelines for the Clinical Translation of Stem Cells*[C] published in 2008, which served as the basis for the *US National Institutes of Health Guidelines on Human Stem Cell Research*[D] in 2009. More information about this programme is available at http://www.esf.org/coordinating-research/eurocores/completed-programmes/eurostells.html

Exploratory Workshop 'Around Mesenchymal Stem Cells (MSCs): Dissection and Exploitation of Secretory Activity of MSC for Regenerative Medicine and Anticancer Therapies'. Bologna (IT), 11-13 April 2012

Convenors: Professor Nicola Baldini, Department of Biomedical and Neuromotion Sciences, University of Bologna and Professor Massimo Dominici, Department of Oncology, Hematology and Respiratory Diseases, University of Modena and Reggio Emilia (IT)

This Exploratory Workshop attracted 20 participants from 13 countries

Budget: ca. 15 k€

The aim of the workshop was to explore emerging research fields with potential impact on new developments in MSC biology and its clinical applications and to establish collaborative research in the emerging field of cell-free therapy for regenerative medicine and anticancer strategies based on the paracrine activity of MSCs. Soluble factors, exosomes, microvesicles, apoptotic bodies and MSC-secreted proteins (e.g. inflammatory cytokines and growth factors) reduce inflammation and cell death, activate intrinsic stem cells and promote regeneration. The workshop focused on defining potential clinical applications of cell-free therapies, discussing their main advantages and limitations and identifying current knowledge gaps. More information can be found at http://www.esf.org/coordinating-research/exploratory-workshops/biomedical-sciences-med.html?year=2012&domain=EMRC

C. http://www.isscr.org/home/publications/ClinTransGuide
D. http://stemcells.nih.gov/policy/pages/2009guidelines.aspx

Success Stories in Frontier Research

Europe plays a leading role in frontier research on stem cells. A selection of some promising results and potential applications in healthcare is featured in Box 2.

Box 2. **Examples of promising results and potential clinical applications of frontier research on stem cells in Europe**

EYES Transplantation of photoreceptor nervous cells and adult human retinal stem cells in animals is a promising tool for restoring vision in people with degenerative eye diseases that cause blindness[14,15].

LIVER Functional hepatocytes derived from human stem cell populations can help repair liver damage[16,17]. A better understanding of how hepatic parenchyma develops may help provide novel therapeutic options[18].

BRAIN Neurons derived from hESCs integrate efficiently into brain circuits *in vivo*[19]. Neural stem cells can be stimulated by proteins from neighbouring blood vessels, and this could help the brain repair itself after injury or disease, as in cases of stroke, traumatic brain injury and dementia[20]. Both neural crest stem cells and MSCs from bone marrow may be interesting tools for cellular therapies to replace neurons in various neurological diseases[21].

ONCOLOGY MSCs derived from adipose tissue and bone marrow are being used to modulate tumour cell behaviour[22-24].

NEUROLOGY Neural progenitors derived from human-induced pluripotent stem cells offer hope for personalised regenerative cell therapy in amyotrophic lateral sclerosis[25].

DENTISTRY Stem cells from human dental pulp hint at osteogenic potential[26].

STEM CELL-BASED, TISSUE-ENGINEERED ORGANS The first pediatric, tissue-engineered trachea transplant was successfully carried out in a child with congenital trachea stenosis. Two years later, the child had a functional airway and was able to return to school[27].

EARS Human embryonic and fetal stem cells can differentiate into auditory neurons that improve auditory-evoked response thresholds. This achievement is a step forward in the development of cell-based therapies for deafness[28,29].

ENDOCRINOLOGY Pancreatic progenitor cells have been derived from hESCs, shedding light on possible new treatments for diabetes[30]. Functional thyroid cells have been obtained from embryonic stem cells, advancing potential options to treat conditions such as hypothyroidism[31].

DERMATOLOGY Studying different stem cells in the skin has increased knowledge of how skin cancers develop and how the epidermis may be repaired[32,33].

TRAUMA AND ORTHOPEDIC SURGERY Bone marrow mesenchymal and hematopoietic stem cells are being studied to develop better repair strategies for the osteoarticular system[34].

Advanced Clinical Trials

European academia and industry are conducting clinical trials with human stem cells that have produced promising results. Data from 514 clinical trials on stem cells registered in the EU Clinical Trials Register as of 4 October 2013 were examined.

Of the 514 trials analysed, only 25 were found to be ongoing 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). Some of the trials were being coordinated by more than one country. 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 and inflammatory bowel disease.

European industry is also pioneering valuable efforts. Two companies based in Belgium[35,36] are leading phase III clinical trials in congestive heart failure and Crohn's disease.

Interestingly, of all the clinical trials investigating MSCs, the two trials that were completed illustrate two extremes of the sponsorship spectrum. One was an investigator-driven, phase II study on coronary artery disease coordinated by Denmark[37], and the other was a phase III, industry-sponsored study on a potential treatment for graft-versus-host disease that was coordinated by Italy, the UK and Spain[38].

Conclusions

Europe plays a leading role in regenerative medicine research, with most countries featuring legislative frameworks that are globally favourable to human stem cell research. This study shows that very few countries authorise the creation of embryos exclusively for research purposes, while the majority only allow for the derivation of hESCs from IVF embryos. In addition, promising results from clinical trials hint at the potential of this field and underpin the achievements of a vibrant community of scientists and innovators.

Europe remains an attractive place to work on research and innovation in stem cells, and continues to seek to bring advanced therapies to patients in need. These healthcare advances are likely to ensue if public funding and endorsement continue, particularly at pan-European scale. International partnerships are a way for scientists to collaborate and compete, share expertise and resources, optimise infrastructures, and thus contribute to Europe's knowledge economy and benefit humans worldwide.

National and EU leaders now have an unparalleled opportunity to support research and innovation with adequate policies and funds. This will help unravel the true benefits and risks of this emerging field and, by doing so, potentially contribute to the provision of innovative healthcare products and services, ensuring social welfare and the creation of new jobs.

In a globalised world, patients and researchers travel across national boundaries in pursuit of favourable environments that enable new solutions. The biomedical research and entrepreneurial community should maintain an active role in communicating to the rest of society the progress being made in human stem cell research, while highlighting opportunities and risks with equal objectivity. Research transparency, integrity and safety must continue to stand at the heart of any future developments in this field.

Annexes

Websites of Interest

- Europe's hub for stem cell research, regenerative medicine and ethics, EuroStemCell: http://www.eurostemcell.org/
- International Database on the Legal and Socio-Ethical Issues in Stem Cell Research, StemGen: http://www.stemgen.org/
- EU Clinical Trials Register: www.clinicaltrialsregister.eu

Abbreviations

ECJ: European Court of Justice
EMRC: European Medical Research Councils
EPO: European Patent Office
ESF: European Science Foundation
EU: European Union
hESC: human embryonic stem cell
IVF: *in vitro* fertilisation
MSC: mesenchymal stem cell
SCNT: somatic cell nuclear transfer

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Table 1. Human stem cell policy and regulatory framework in 30 European countries.

Country	Main Legislative Framework	Governance Bodies (Regulators and Advisors)
AUSTRIA	No specific legislation on hESC research **2004** Reproductive Medicine Act	Ministry of Justice http://www.bmj.gv.at Ministry of Science and Research http://www.bmwf.gv.at Austrian Bioethics Commission, Federal Chancellery http://www.bka.gv.at/site/3575/default.aspx
BELGIUM	**2003** Law on *in vitro* embryo research **2007** Law on medically assisted reproduction and the use of surplus embryos and gametes **2008** Law on the procurement and use of human body material intended for human medical applications or for scientific research purposes	Advisory Committee on Bioethics, Federal Service of Health, Food Chain Safety and Environment http://www.health.belgium.be/eportal/Healthcare/Consultativebodies/Commitees/Bioethics/index.htm?fodnlang=en Federal Agency for Medicines and Healthcare Products http://www.fagg-afmps.be/en
BULGARIA	**1987** Regulation for the artificial reproduction of women **2000** Law on drugs and pharmacies in human medicine **2003** Law on the transplantation of organs, tissues and cells **2003** Law on blood, blood donation and blood transfusion **2004** Health Act **2007** Law on assisted reproduction	Bulgarian Central Ethics Commission (CEC), Ministry of Health http://www.mh.government.bg/Articles.aspx?lang=bg-BG&pageid=380 Commission on Ethics in Drug Trials, Ministry of Health Specialised Committee for Approval of Conducting Clinical Trials, Ministry of Health Bulgarian Drug Agency Commission on Research Ethics, Ministry of Education and Sciences Executive Agency for Transplantation, Ministry of Health
CROATIA	**2009** Act on medical fertilisation	Ministry of Health Ministry of Science, Education and Sports
CYPRUS	**2001-2010** Laws on medicinal products for human use **2001** Law 31 (Oviedo Convention research on pharmaceuticals, medical devices, medical radiation and imaging, surgical procedures, medical records, and biological samples, as well as epidemiological and psychological investigations) **2005** Operational guidelines that include research on pharmaceuticals, medical devices, and biological samples	National Bioethics Committee http://www.bioethics.gov.cy/law/cnbc/cnbc.nsf/DMLindex_en/DMLindex_en?OpenDocument
CZECH REPUBLIC	**2006** Act on human embryonic stem cells	Central Ethics Committee, Ministry of Health www.mzcr.cz Bioethical Commission, Research and Development Council. http://www.vyzkum.cz Ministry of Education, Youth and Sport http://www.msmt.cz/research-and-development-1

	Types of Stem Cell Research Authorised	Status
	No legislation on stem cell research. *De facto*, hESC research is prohibited. Embryos and gametes cannot be donated for purposes other than medically assisted reproduction in the frame of stable heterosexual relationships. Procurement of hESCs and therapeutic and reproductive cloning are prohibited. Regarding public funding for research, adult stem cells are prioritised over hESCs. However, the Austrian Bioethics Commission advocates hESC derivation from surplus embryos (majority position with dissenting opinion).	**UNLEGISLATED**
	hESC research is allowed, but cannot be patented nor have commercial applications. Embryos can come from surplus IVF embryos or, under certain conditions, be created for research.	**VERY PERMISSIVE**
	hESC research is not directly regulated but falls within the Health Act, whereby surplus IVF embryos can be used for research purposes, subject to the informed consent of the donor(s). Reproductive cloning of humans is prohibited.	**PERMISSIVE WITH RESTRICTIONS**
	hESC research and reproductive cloning are prohibited.	**VERY RESTRICTIVE**
	hESC research using IVF embryos is allowed if adequate protection of the embryo is ensured. Cloning is prohibited.	**PERMISSIVE WITH RESTRICTIONS**
	hESC research is allowed with IVF embryos or imported cells, under informed consent and providing that the embryo is not older than 7 days. Reproductive cloning is prohibited.	**PERMISSIVE WITH RESTRICTIONS**

Country	Main Legislative Framework	Governance Bodies (Regulators and Advisors)
DENMARK	**1992** Act on a scientific ethical committee system and the handling of biomedical research projects **1997** Act on medically assisted procreation (artificial fertilisation) **2003** Act on a scientific ethical committee system and the handling of biomedical research projects **2011** Act on research ethics review of health research projects	National Committee on Health Research Ethics, part of a national system of health committees http://www.cvk.sum.dk/cvk/home/english.aspx Danish Ministry of Health http://www.sum.dk/English.aspx Council of Ethics http://www.etiskraad.dk/en.aspx
ESTONIA	**2003** Act on artificial insemination and embryo protection	Estonian Council of Bioethics, Ministry of Social Affairs http://www.eetikakeskus.ut.ee/260565
FINLAND	**1999** Act on medical research **2001** Act on the medical use of human organs, tissues and cells	National Supervisory Authority for Welfare and Health http://www.valvira.fi/en Finnish Medicines Agency http://www.fimea.fi/frontpage National Committee on Medical Research Ethics http://www.tukija.fi/en National Advisory Board on Social Welfare and Health Care Ethics www.etene.fi Board for Gene Technology, Ministry of Social Affairs and Health http://www.geenitekniikanlautakunta.fi/en
FRANCE	**2004** Law on bioethics, revised in 2013	Biomedicine Agency http://www.agence-biomedecine.fr/Site-pour-le-grand-public National Consultative Committee on Ethics http://www.ccne-ethique.fr
GERMANY	**1949** Basic Law of the Federal Republic of Germany **1990** Act on the protection of embryos **2002** Act ensuring the protection of embryos in connection with the importation and use of human embryonic stem cells **2008** Act ensuring the protection of embryos in connection with the importation and use of human embryonic stem cells	Central Ethics Committee for Stem Cell Research http://www.rki.de/EN/Content/Institute/DepartmentsUnits/StemCell/StemCell_node.html German Ethics Council http://www.ethikrat.org/about-us/our-mandate?set_language=en
GREECE	**2002** Law on medically assisted human reproduction **2005** Law on medically assisted reproduction	National Transplantation Organisation www.eom.gr National Authority on Medically Assisted Reproduction www.iya.gr Hellenic Republic National Bioethics Commission www.bioethics.gr

	Types of Stem Cell Research Authorised	Status
	hESC research is allowed but only if the surplus IVF embryo is used within 14 days of fertilisation and under informed consent. Reproductive cloning is prohibited.	PERMISSIVE WITH RESTRICTIONS
	The 2003 Act deals with IVF embryos and their use in research, but there is no specific reference to hESC research. Reproductive cloning (by SCNT), is explicitly prohibited. There are no specific laws regulating biobanks.	PERMISSIVE WITH RESTRICTIONS
	hESC research is allowed with IVF embryos up to 14 days after fertilisation. Cloning is prohibited. SCNT is allowed by default, since under this legislation "embryo" is defined as a living group of cells resulting from fertilisation.	PERMISSIVE WITH RESTRICTIONS
	hESC research using IVF embryos of up to 8 days is allowed, providing that the medical rationale is well founded, no other means are suitable to research the issue and informed consent is obtained. hESC imports are authorised. Cloning is prohibited.	PERMISSIVE WITH RESTRICTIONS
	After December 2001, hESCs cannot be created or derived. Cloning is prohibited. hESC research is allowed only if imported cell lines produced before May 1, 2007 are used and only if proven vital for the development of new medical and scientific knowledge.	VERY RESTRICTIVE
	hESC research using IVF embryos or aborted foetuses is allowed. Reproductive cloning is prohibited. The creation of human embryos for research only is prohibited.	PERMISSIVE WITH RESTRICTIONS

Country	Main Legislative Framework	Governance Bodies (Regulators and Advisors)
HUNGARY	**1978** Criminal Act modified in 1998 – articles on violation of regulations of research on embryos and gametes **1992** Act on the protection of the foetus' life **1997** Healthcare Act Chapter IX (Articles 165-187) **1998** Ministerial order on extraordinary procedures of human reproduction, the treatment of embryos, gametes and their storage. **2002** Law on biomedical research on human subjects **2008** Act on the protection of human genetic data and the regulation of human genetic studies, research and biobanks	Stem Cell Committee, Health Science Council http://www.ett.hu Human Reproduction Commission (HRB), Health Science Council Scientific and Research Ethics Commission (TUKEB), Health Science Council
ICELAND	**1996** Act on artificial fertilisation and use of human gametes and embryos for stem cell research **2000** Biobanks Act **2008** Regulation on scientific research in the biomedical field	National Bioethics Committee, Ministry of Welfare http://www.visindasidanefnd.is http://eng.velferdarraduneyti.is
IRELAND	No specific legislation dealing with stem cell research or research on embryos produced during IVF	Commission on Assisted Human Reproduction, Department of Health http://www.dohc.ie/issues/nacb
ITALY	**2004** Law on medically assisted reproduction	National Bioethics Committee http://www.palazzochigi.it/bioetica
LITHUANIA	**1996** Law on donation and transplantation of human tissues, cells and organs **2000-2007** Law on ethics of biomedical research	Lithuanian Bioethics Committee http://bioetika.sam.lt
LUXEMBOURG	No specific legislation	National Ethics Commission (CNE) http://www.cne.public.lu National Committee of Research Ethics (CNER), Ministry of Health http://www.cner.lu
THE NETHERLANDS	**1999-2006** Act on medical research involving human subjects **2002** Embryo Act **2006** Regulation on stem cell transplantation	Health Council of the Netherlands http://www.gr.nl Central Committee on Research Involving Human Subjects (CCMO) www.ccmo-online.nl

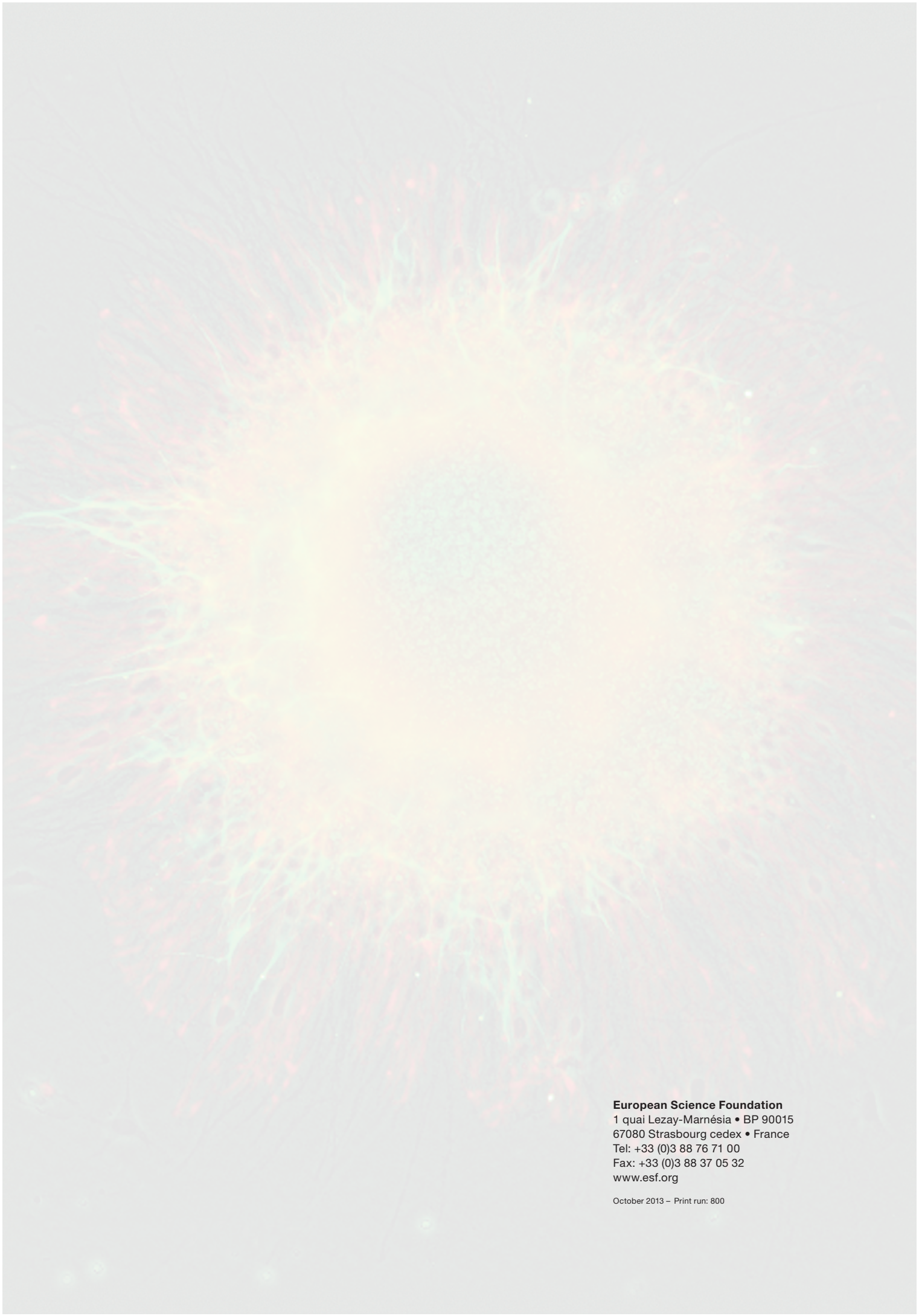
	Types of Stem Cell Research Authorised	Status
	hESC research using IVF embryos of up to 14 days is allowed. Embryos cannot be created for research purposes. Reproductive cloning is prohibited. Therapeutic cloning is prohibited but sex selection of the human embryo is allowed to avoid an inheritable disease.	PERMISSIVE WITH RESTRICTIONS
	Research on IVF embryos is permitted if it is part of IVF treatment or if it is aimed at diagnosing hereditary diseases of embryos, advancing treatment for infertility or enhancing understanding of causes of congenital diseases and miscarriages. The informed consent of gamete donors is required. Human embryos can only be stored for up to 10 years and for implantation purposes only. It is forbidden to produce embryos for research purposes only, to cultivate embryos beyond 14 days outside the body, or to perform cloning. Creation of stem cell lines (even through SCNT) is allowed if well justified.	PERMISSIVE WITH RESTRICTIONS
	No legislation on stem cell research	UNLEGISLATED
	hESC research is prohibited unless it is specifically aimed at improving the therapeutic and medical condition of the embryo concerned. Derivation of embryonic stem cell lines is prohibited. Embryonic cell import is allowed for research.	VERY RESTRICTIVE
	hESC research is restricted to clinical observations (non-interventional trials). Other uses and the import and export of tissues of a human embryo, stem cells of a human embryo and lines thereof are prohibited.	VERY RESTRICTIVE
	No legislation on stem cell research	UNLEGISLATED
	hESC research using IVF embryos or embryos created for research is authorised if legally approved and only if the embryo is used within 14 days of fertilisation. Research is prohibited if its purpose is the birth of genetically identical individuals, germ line genetic modification, the combination of human and animal gametes aiming at the creation of multicellular hybrids, the creation and/or implantation of chimera, the implantation of human embryos into an animal and the implantation of animal embryos into a human. Embryo sex selection is prohibited unless there is risk of serious sex-linked hereditary disease. No distinction is made between research and treatment in the field of (stem) cell therapy.	PERMISSIVE WITH RESTRICTIONS

Country	Main Legislative Framework	Governance Bodies (Regulators and Advisors)
NORWAY	**1996** Act on organ donation **2003** Act on biobank for therapeutic purposes **2003** Biotechnology Act **2005** Regulations on the withdrawal, testing, processing, storage, and distribution of human blood and blood components, and on the handling of health data in blood donor registers **2008** Health Research Act **2008** Regulations on quality and safety requirements for the handling of human cells and tissues	Norwegian Biotechnology Advisory Board http://www.bion.no/english National Committee for Medical and Health Research Ethics, Ministry of Health and Care Services http://www.etikkom.no/
POLAND	No specific laws on embryonic research	Commission of Bioethics at Wroclaw Medical University http://www.bioetyka.am.wroc.pl/ang/index.html
PORTUGAL	**2006** Law on medically assisted procreation	National Council for Medically Assisted Reproduction (CNPMA) http://www.cnpma.org.pt National Council for Ethics in Life Sciences (CNECV) http://www.cnecv.pt/pareceres.php
ROMANIA	**1998** Law on the removal and transplantation of human tissue and organs **2004** Law on good conduct in scientific research, technological development and innovation **2011** Law related to the ratification of the convention on human rights and biomedicine and the additional protocol on prohibition of human cloning.	Bioethics Commission, Ministry of Health National Ethics Council for Scientific Research, Technological Development and Innovation, Ministry of Education and Research http://www.ancs.ro/ro/categorie/966/despre-ancs-organizare-organe-consultative-3-consiliul-national-de-etica
SLOVAKIA	**1994** Law on healthcare	National Ethics Committee, Ministry of Health http://www.health.gov.sk/Index.aspx
SLOVENIA	**2000** Law on biomedically assisted fertilisation **2007** Act on quality and safety of human tissues and cells, for the purposes for medical treatment	National Medical Ethics Committee http://www.kme-nmec.si
SPAIN	**2006** Law on techniques for human assisted reproduction **2006** Law on quality and safety norms for donation, obtention, evaluation, processing and distribution of human cells and tissues **2006** Law on imports and exports of biological samples **2006** Law on human assisted reproductive technology **2007** Law on biomedical research **2010** Law regulating the Guarantees Commission for the donation and use of human cells and tissues and the registry of research projects	National Commission on Assisted Human Reproduction, Ministry of Health, Social Services and Equality http://www.cnrha.mspsi.es/home.htm National Bioethics Committee, Ministry of Health, Social Services and Equality http://www.comitedebioetica.es Guarantees Commission for the Donation and Use of Human Cells and Tissues Ministry of Economy and Competitiveness

	Types of Stem Cell Research Authorised	Status
	hESC research using IVF embryos or aborted foetuses is allowed. Cloning is prohibited.	PERMISSIVE WITH RESTRICTIONS
	No legislation on stem cell research. *De facto*, embryonic research is prohibited, although not explicitly formulated as such because laws are old. Legally, human embryos are considered "conceived children" and thus cannot be involved in experimentation. hESC research is considered by the Polish Parliament as "inconsistent with Polish law". Human embryos may not be used for non-therapeutic research.	UNLEGISLATED
	hESC research is only allowed with IVF embryos. The creation of embryos for research is prohibited.	PERMISSIVE WITH RESTRICTIONS
	Stem cell research is allowed under official approvals, but there is no regulation on IVF, research on embryos, or embryonic stem cells. There is no specific law on human genetics. Cloning is prohibited.	RESTRICTIVE BY DEFAULT
	hESC research is prohibited if it is not for the benefit of a specific embryo. Cloning is prohibited.	VERY RESTRICTIVE
	hESC research is allowed if IVF embryos up to 14 days post-fertilisation are used and if informed consent and official approval are obtained. The creation of embryos for research and cloning is prohibited.	PERMISSIVE WITH RESTRICTIONS
	hESC research is allowed but with restrictions. Human cloning by SCNT is allowed for therapeutic and research purposes only. The creation of embryos exclusively for research and reproductive cloning is prohibited.	PERMISSIVE WITH RESTRICTIONS

Country	Main Legislative Framework	Governance Bodies (Regulators and Advisors)
SWEDEN	**2002** Law on biobanks in medical care **2003** Law on ethical reviews of research on humans **2006** Law on genetic integrity	National Council on Medical Ethics http://www.smer.se National Board of Health and Welfare www.socialstyrelsen.se Swedish Gene Technology Advisory Board www.genteknik.se/sv/in-english
SWITZERLAND	**2003** Federal Act on research involving embryonic stem cells	National Advisory Commission on Biomedical Ethics http://www.bag.admin.ch/nek-cne/index.html?lang=en
TURKEY	**1979** Law on organ transplantation **2005** Regulation on cord blood banks **2006** Circular on stem cell and guidelines for non-embryonic clinical therapeutic stem cell research, Ministry of Health **2008** Directive on the coordination of the centres for embryonic stem cell research **2011** Regulation on clinical research and trials **2012** Regulation on the transplantation of organ and tissues	Ministry of Health http://www.ttb.org.tr/mevzuat/index.php?option=com_content&task=view&id=387&Itemid=35
UNITED KINGDOM	**1990** Human Fertilisation and Embryology Act, amended in 2009 **2001** Human Reproductive Cloning Act **2004** Human Tissue Act	Human Fertilisation and Embryology Authority (HFEA) http://www.hfea.gov.uk Human Tissue Authority (HTA) http://www.hta.gov.uk Medicines and Healthcare products Regulatory Agency (MHRA) http://www.mhra.gov.uk Health Research Authority (HRA) www.hra.nhs.uk Emerging Science and Bioethics Advisory Committee (ESBAC), Department of Health https://www.gov.uk/government/policy-advisory-groups/emerging-science-and-bioethics-advisory-committee

	Types of Stem Cell Research Authorised	Status
	hESC research is allowed if IVF embryos of up to 14 days post-fertilisation are used or after SCNT. Therapeutic cloning is allowed if hereditary genetic traits remain unchanged. Reproductive cloning is banned.	**VERY PERMISSIVE**
	hESC research is allowed with IVF embryos up to 7 days post-fertilisation, under strict conditions and with informed consent, or with cells imported specifically for research purposes. Cloning is prohibited. The creation of embryos for research is prohibited.	**PERMISSIVE WITH RESTRICTIONS**
	hESC research is prohibited. Cloning is prohibited. Only non-embryonic, hematopoietic stem cell research is allowed by law, under informed consent and if officially approved.	**RESTRICTIVE BY DEFAULT**
	hESC research is allowed, subject to a licence from the Human Fertilisation and Embryology Authority (HFEA). Licensed research can only take place on IVF embryos up to 14 days after creation or the appearance of the primitive streak, whichever is the earlier. Research needs to prove necessary and aligned with the purposes of the laws, which include increasing knowledge about serious medical conditions, developing treatments for serious medical conditions, advancing the treatment of infertility, increasing knowledge about the causes of miscarriage, developing more effective contraception techniques, developing methods for detecting genetic or mitochondrial abnormalities in pre-implantation embryos, and increasing knowledge of embryonic development. Reproductive cloning is prohibited. Permitted sources of hESC lines include surplus IVF embryos, embryos created by IVF specifically for research purposes, embryos created by SCNT, “admixed embryos” including hybrids (created from human and animal gametes), “cytoplasmic hybrids” (created by SCNT using human nuclei and animal oocytes), transgenic human embryos (created by introducing animal DNA into a human cell), chimeric human embryos (created by introducing one or more animal cells into a human embryo), or any other embryos that contain both human and animal DNA, but in which animal DNA is not predominant.	**VERY PERMISSIVE**



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