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Stem Cell Research: Toward Greater Unity in Europe?

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There are four major positions on human embryonic stem cell research in the different member states of the European Union, ranging from permissive to very restrictive. This reflects the diversity of research systems within Europe and poses a challenge to developing a common European research policy.

"Pluralism is characteristic of the European Union, mirroring the richness of its tradition and adding a need for mutual respect and tolerance." This statement—by the European Group on Ethics in Science and New Technologies to the European Commission—is particularly pertinent to research on human embryonic stem cells (hESCs) within Europe (http://ec.europa.eu/european_group_ethics/index_en.htm).

Pluralism in the EU

In 2000, the European Union (EU) decided to unify research efforts across Europe and created the European Research Area with the goal of developing a genuine common research policy for all of Europe. However, hESC research provides an ideal example of the challenges to developing such a research policy and the ambivalence of plurality. Looking at the 27 member states of the EU (EU27), we can see a multitude of opinions at the level of both national legislations and bioethics committees.

The European Group on Ethics, which advises the president of the European Commission about the ethical implications of biotechnology, has issued several opinions on hESC research within the past decade. In an early document, it stated that it would be inappropriate for the EU to impose "one exclusive moral code." However, the EU's goal with the creation of a European Research Area was to develop the "most competitive and dynamic knowledge based economy in the world" (March 2000, Lisbon Strategy). This achievement has been hindered by diverging research regulations in the single EU member states. Within the European Research Programs, known as Framework 6 (FP6) and FP7, EU funding of research involving human embryos and hESCs is permitted provided the national laws of the single member states allow it. However, EU funds, which come from the single member states and originate from national taxes, are also used for funding hESC research in EU-wide projects, even if such research is not permitted by a single member state that is part of the project.

The multitude of national laws and bioethics rules across the EU27 on research using human embryos and hESCs can be classified roughly into four major positions: a permissive position, a permissive position with restrictions, a restrictive position, and a position with no specific legislation or only indirect legislation (http://ec.europa.eu/european_group_ethics/index_en.htm) (Table 1). The permissive position is the case for Belgium, Sweden, Spain, and the United Kingdom (UK). In these countries, specific legislation covers the procurement of hESCs and their use for research; the creation of human embryos for research purposes is allowed and therapeutic cloning as well. Spain, where legislation pertaining to hESC research is most recent, allows for somatic cell nuclear transfer to obtain hESCs.

In the permissive position with restrictions, specific legislation allows the derivation of new hESC lines from human embryos created by assisted reproduction technology or in vitro fertilization for the purposes of pregnancy, but only when they can no longer be used for that purpose. This is the situation in the Czech Republic, Denmark, Finland, France, Greece, the Netherlands, and Portugal. France is currently revising its Bioethics Law and will consider the issue of hESC research and the human embryo along with other issues of bioethical relevance to public discourse (http://www.ccne-ethique.fr/docs/avis105anglais.pdf).

Germany and Italy have a restrictive position, where scientists working in these countries are not allowed to derive new

Table 1. Legislation Governing hESC Research in EU Member States

Permissive Position	Permissive Position with Restrictions	Restrictive Position	No Specific Legislation	No Specific Legislation[a]
Belgium	Czech Republic	Germany	Bulgaria	Austria
Spain	Denmark	Italy	Cyprus	Lithuania
Sweden	Finland		Estonia	Malta
UK	France		Ireland	Poland
	Greece		Hungary	Slovakia
	Netherlands		Latvia	
	Portugal		Luxemburg	
			Romania	
			Slovenia	

[a]Voted against hESC research during Council decision on EU funding for European Research Framework.

hESC lines but can import them from other countries. A particularly interesting system exists in Germany, where research is only permitted using imported hESC lines created before May 1, 2007 ("Stichtag") (the original date was January 1, 2002, but this was changed as the older hESC lines were of poor quality). In Italy, the legislation covers assisted reproductive technology and the production of new hESCs, but research involving the destruction of the human embryo is not allowed, and there is no legal provision regarding the use of imported hESCs or existing hESCs. This has lead to the recent action by three leading Italian scientists, who have appealed against the Italian government's decision to arbitrarily exclude hESCs from a recent call for grant proposals. They perceive the exclusion of their research as an open violation of their fundamental and constitutional right to freedom of research.

The remaining countries with no specific legislation are Bulgaria, Cyprus, Estonia, Ireland, Luxemburg, Latvia, and Romania. Hungary and Slovenia are countries with only indirect legislation covering human embryo research. An especially curious situation can be seen in those countries (Austria, Lithuania, Malta, Poland, and Slovakia) that do not have specific regulations but nonetheless voted against hESC research during the Council decision for the European Research Framework. (The European Research Programs have to be adopted by the European Commission and subsequently must be approved by a joint decision of the European Parliament and Council.)

Stem cell research is a typical example of a bioethical value conflict, the main focus of conflict being the diverging opinions about the moral status of the human embryo. The different legal systems show astonishing solutions exemplified by Italian or German laws, which allow the intentional importing of hESC lines for research from abroad but do not permit scientists to develop them in the country itself.

Diversity in Many Layers

One of the problems with comparing the different systems of hESC research in Europe is that there is not just "one" research law in the respective countries that either permits or prohibits hESC research, but rather there is a multitude of different laws. There are sometimes not even laws specifically directed at stem cell research per se, but rather the laws cover in vitro fertilization and other issues and so have to be interpreted in order to judge if stem cell research is allowed or not. In Austria, for instance, there is currently no explicit regulation covering hESCs. There is a law for in vitro fertilization (the Austrian Reproductive Medicines Act), which regulates medically assisted reproduction. Although deriving hESCs from fertilized eggs is prohibited, research using pluripotent embryonic stem cells is not, as long as these cells are imported from abroad. Another challenging issue to be overcome when aiming to harmonize hESC research across Europe is the definition of an embryo, which varies widely depending on the European country. In the Austrian Reproductive Medicines Act, the word "embryo" is not even mentioned, only the term "viable cells." In many European countries, the legal term "embryo" is not identical to the medical term.

Comparing and assessing hESC research across Europe is further complicated by ethical issues. There is a "multilayered" system with a legal framework specifically covering stem cell research, indirect legislation, no legislation, and at the next level the opinions of national bioethics committees. Bioethics committees (which advise the government or parliament) are constituted in different ways in the different EU member states. Some of them have members that are appointed ad personam without appropriate professional expertise in ethics, which reflects a pluralistic and multidisciplinary society. These committees may be prone to politicize the bioethics debate and have been the subject of some criticism (Plomer, 2008).

As stated above, there is currently no explicit regulation covering hESC research in Austria; therefore the Austrian National Bioethics Commission started discussion of the issue after its formation in October 2007. In March 2009, the majority of the Commission's members voted in favor of hESC research (http://www.bundeskanzleramt.at/DocView.axd?CobId=36660). The Commission recommended the creation of a suitable legal framework to provide clear legal safeguards including the procurement of hESCs from fertilized eggs or surplus embryos, which are no longer needed for medically assisted reproduction, provided the voluntary consent of those persons from whom the gametes were harvested is obtained. Additionally, methods for producing viable embryonic cells other than by fertilization—for example, somatic cell nuclear transfer or the formation of cybrids (by transferring the nucleus of an adult human cell into an enucleated animal cell egg)—should also be permissible provided that implantation into a woman's body is prohibited. All female members of the Commission supported this vote. Whether this opinion of the national Austrian Bioethics Commission will find its way into national legislation remains to be demonstrated.

From Bench to Bedside

The supporting argument most often used by opponents of hESC research is that stem cell research should not be pursued as it has not yet been shown to have clinical value. But opponents do not want to take into account that this field of research is still relatively new, dating from 1998 when James Thomson first derived and cultured hESCs. Even the field of pharmaceutical research registers an average period of 24 years between the first description in a journal and the publication of the first article showing clinical application (Contopoulos-Ioannidis et al., 2008).

Earlier this year, the US Food and Drug Administration (FDA) granted permission to Geron Corporation (http://www.geron.com), a California biotechnology company, to conduct clinical trials with their product GRNOPC1 (a biopharmaceutical developed from hESCs) in patients with new spinal cord injuries. In August 2009, however, the FDA put the trial on hold before it was initiated due to reports of microscopic cysts forming in the regenerating injury site in animal studies and requested further information. Introducing products derived from hESCs into clinical trials could change the discussion of the legitimacy of hESC research.

Even traditionally Catholic countries like Ireland are taking into account the therapeutic promise of stem cell research. The Irish Council for Bioethics has discussed the moral dilemma for Irish citizens if hESC research is banned in Ireland but stem cell therapies become available abroad. They posed the question of whether it is morally consistent for a government to pro-

vide treatments derived from hESCs if the research is not permitted in the country (http://www.bioethics.ie/uploads/docs/StemCell.pdf). When realistic therapeutic opportunities appear, state prohibitions that impede the development of promising therapies without sufficient legal argument would need to be justified with respect to Article 8 of the European Convention on Human Rights.

A further paradox can be seen in the laws governing hESC research in European countries that either did or did not sign the 1997 Oviedo Convention on Human Rights (http://www.coe.int/t/dg3/healthbioethic/Activities/01_Oviedo%20Convention/). This is another European instrument with the goal of achieving greater "unity" among the EU member states. Article 18.1 of the Convention permits (provided the legislation within the member state allows it) research on human embryos in vitro, and Article 18.2 forbids the creation of human embryos for research. Among the countries that have not signed the Convention, there are two distinct groups: those who have not signed and ratified it because the Convention is too liberal (Germany, Ireland), and those where the Convention seems to be too strict for their research policies (Belgium, UK). The principal features of the Convention where EU member states do not agree are not only the protection of the human embryo but also the inclusion in clinical research trials of persons who are not able to consent (e.g., mentally ill or critically ill patients). Currently the Convention is ratified and in force in 22 European countries, many of them from the former Eastern block.

Human embryonic stem cell research can be considered as the symbol of the dilemma of societies regarding the advancement of science. No other issue has such potential for establishing gaps within a society. Stem cell research is a synonym for a wide range of other issues that span from the beginning of life (abortion, prenatal diagnosis, preimplantation genetic diagnosis, assisted reproduction) to end of life issues (withholding and withdrawing of therapies, euthanasia, and organ transplantation). The ferocity with which these debates are conducted may seem like a holy war, but hESC research can also be seen as the center of a crisis of public trust. Societal trust and confidence in scientific research are decreasing. One reason is the progressive complexity of the different research disciplines in the life sciences, which even scientists from other research fields have difficulties assessing. What we do not understand and what is not clear keeps us at a distance and thus provides grounds for distrust. Other reasons include the Vioxx and Paroxetine drug scandals, which were fundamental violations of public trust. Obviously, these occurrences confirm the views of supporters of the "slippery slope" argument, who seem to be prevailing over supporters of the rational argument that in general legislation is adequate enough to prevent abuse.

Stem cell research is not the only issue in Europe where a diverging ethical and legal basis makes international cooperation difficult. Another example is clinical research and the comparatively uncontroversial field of research ethics committees or institutional review boards (IRBs). The rules of such IRBs are implemented in a very heterogeneous way across Europe. Industry has driven the legislation on clinical drug trials that was finally implemented in the EU Clinical Trials Directive of 2001 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm), with national legislations being implemented in 2004 (Druml et al., 2006). As the EU does not provide "one single opinion" about clinical research ethics with regard to European-wide multicenter clinical trials, the EU member states each had to establish a system to obtain a single opinion from their own ethics committees for each multicenter clinical trial testing a medicinal product in their country.

The number of research ethics committees within the different EU member states varies greatly and is not related to the amount of research conducted per country. Furthermore, the composition of ethics committees varies greatly with little guidance on selection of members. There are no requirements for initial and ongoing training of the members and no quotas for gender representation. As a result, the situation and quality differ widely and there is a multitude of different combinations of interactions between local and multicenter ethics committees. This poses a burden for industry and much more so for academic researchers and disfavors investigator-initiated clinical trials as single investigators do not have the resources that industry does for exploring the many different legal and administrative systems of ethical review within the different EU member states. The goal of the European Clinical Trials Directive was to enhance the competitiveness of European clinical research, especially in comparison with clinical research in the United States. However, ethical issues are dealt with at the EU member states' own discretion, resulting in systems that differ greatly throughout Europe (Druml et al., 2009).

Exchange, collaboration, and networking are the basis of biomedical research worldwide. European programs, international journals, the worldwide web, and the mobility of all researchers are a fundamental guarantee of knowledge exchange. Today, new scientific results spread worldwide within hours of being announced. Within the framework of European research, hESC research is financed with the money of all EU member states and therefore must remain permissible. The principle should apply that participation in foreign research projects that are permissible under the respective local law must not lead to criminal liability in the country of the researcher, as is the case in some European countries. Given the heterogeneity of laws governing stem cell research and reproductive medicine across Europe, harmonization is not to be expected any time soon, and the legal problems facing international collaborations across Europe will continue. The big challenge for Europe is to respect diversity while unifying the different systems in order to foster advances in European research for the benefit of all.

REFERENCES

Contopoulos-Ioannidis, D.G., Alexiou, G.A., Gouvias, T.C., and Ioannidis, J.P. (2008). Medicine. Life cycle of translational research for medical interventions. Science *321*, 1298–1299.

Druml, C., Singer, E.A., and Wolzt, M. (2006). Report of the 1st meeting of the "Vienna Initiative to save European Academic Research (VISEAR)". Wien Klin Wochenschr. *118* (Supplement), 1–12.

Druml, C., Wolzt, M., Pleiner, J., and Singer, E.A. (2009). Research Ethics Committees in Europe – trials and tribulations. Intensive Care Med. *35*, 1636–1640.

Plomer, A. (2008). The European Group on Ethics: Law; politics and the limits of moral integration in Europe. Eur. Law J. *14*, 39–859.