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REPORT ON HUMAN EMBRYONIC STEM CELL RESEARCH

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EXECUTIVE SUMMARY

Background:

Stem cell research is one of the promising areas of biotechnology, which offers the prospect of developing new methods to repair or replace tissues or cells damaged by injuries or diseases and to treat serious chronic diseases, such as diabetes, Parkinson's, chronic heart failure as well as stroke and spinal cord injuries. Stem cell research is expected to be equally important for basic science to understand cell differentiation and growth as well as for other specific medical applications such as for the understanding of disease development and for the development of safer and more effective drugs. Scientists are intensively studying the fundamental properties of stem cells.

One of the possible sources for stem cells is human pre-implantation embryos. However, when this research involves the use of human embryos it raises the question of ethical values at stake and of the limits and conditions for such research.

The complexity of this issue with its ethical implications has been highlighted in the process of adoption of the *Sixth Framework Programme for Research (FP6)* and its implementing Specific Programmes, where the specific issue of human embryonic stem cell research was subject to debate.

In the 6th Framework Programme, Community stem cell research funding is foreseen under Priority 1 « Life Sciences, Genomics and Biotechnology for human health », section i “Application of knowledge and technologies in the fields of genomics and biotechnology for health”. In particular, “*research will focus on...development and testing of new preventive and therapeutic tools, such as somatic gene and cell therapies (in particular stem cell therapies)*”¹.

Pending the establishment of detailed implementing provisions by end 2003 at the latest, the Commission agreed however not to fund during this period research projects involving the use of human embryos and human embryonic stem cells with the exception of projects involving banked or isolated human embryonic stem cells in culture. The Commission stated its intention of presenting to Council and European Parliament a report on human embryonic stem cells, which would form the basis for discussion at an inter-institutional seminar on bioethics².

The present report is the result of this commitment, and aims to provide a description of the state of play of the scientific, ethical, legal, social and economic issues related to human stem cell research and human embryonic stem cell research.

¹ OJ L 294 of 29.10.2002, p. 10.

² See annex F.

The purpose of the report is to provide a basis for an open and informed debate at the above-mentioned inter-institutional seminar³.

Taking into account the seminar's outcome, the Commission will submit a proposal establishing further guidelines on principles for deciding on the Community funding of research projects involving the use of human embryos and human embryonic stem cells.

The content of the report

Characteristics of human stem cells

Stem cells have three characteristics that distinguish them from other types of cells:

- they are non-differentiated (unspecialised) cells,
- they can divide and multiply in their undifferentiated state for a long period.
- under certain physiological or experimental conditions, they can also give rise to more specialised differentiated cells such as nerve cells, muscle cells or insulin producing cells etc.

Stem cells are found in the early embryo, in the foetus and the umbilical cord blood, and in many tissues of the body after birth and in the adult. These stem cells are the source for tissues and organs of the foetus and for growth and repair in the new born and adult body. As development proceeds beyond the blastocyst stage (5-7 days after fertilisation), the proportion of stem cells decrease in the various tissues and their ability to differentiate into different cell types also decrease at least when they are situated in their natural environment.

Classification of human stem cells

In this report a distinction is made between three groups of stem cells, referring to their origin and method of derivation:

1. Human embryonic stem cells, which can be derived from a preimplantation embryo at the blastocyst stage.
2. Human embryonic germ cells, which can be isolated from the primordial germ cells of the foetus.
3. Human somatic stem cells, which can be isolated from adult or foetal tissues or organs or from umbilical cord blood.

Potential application of human stem cell research

Transplantation of haematopoietic stem cells (from bone marrow, peripheral blood or umbilical cord blood of a healthy donor) has been used for more than a decade to treat e.g. haematological malignancies such as leukemia or congenital immuno-deficiencies.

³ Scientific terms are explained in the glossary.

Autologous transplantation (transplantation of stem cells from the patient's own bone marrow or peripheral blood) was introduced to rescue the bone marrow of patients who had received high dose of chemotherapy. It is now increasingly being used as primary treatment of other types of cancer such as breast cancer and neuroblastoma. Autologous stem cell transplantation is also used experimentally to treat difficult auto-immune conditions and as a vehicle for gene therapy. Today, over 350 centres in Europe are performing more than 18 000 bone marrow transplants a year⁴.

Novel stem cell based therapies (often called regenerative medicine or cell based therapies) are also being investigated to develop new methods to repair or replace tissues or cells damaged by injuries or diseases and to treat serious chronic diseases, such as diabetes, Parkinson's, chronic heart failure or stroke and spinal cord injuries. Stem cell research is expected to be equally important for basic science as well as for other specific medical applications.

– **For the development of novel stem cell based therapies.** Three therapeutic concepts are currently being envisaged:

- ***Transplantation of differentiated cells derived from stem cells:*** Stem cells may be grown and directed to differentiate into specific cell types in the laboratory and then be transplanted (e.g. insulin producing cells to treat diabetes, heart muscle cells to treat heart failure or dopamine producing neurones to treat Parkinson's disease etc...) The source for the specific differentiated cell types could be embryonic or somatic stem cells, including the patient's own stem cells.
- ***Direct administration of stem cells:*** In some cases it may be possible and/or necessary to administer stem cells directly to the patient in such a way that they would colonise the correct site of the body and continuously differentiate into the desired cell type (e.g. systemic "Homing").
- ***Stimulation of endogenous stem cells:*** The possibility that self-repair could be induced or augmented by stimulating an individual's own population of stem cells for example by administering growth factors is also being explored.

These novel stem cell based therapies are still at their very early stage of development. In particular regarding the transplantation of differentiated cells derived from stem cells, several scientific and technical hurdles need to be resolved before clinical application of these therapies, including

- Understanding of the mechanisms regulating stem cell growth, fate, differentiation and dedifferentiation.
- Eliminating the risk of development of inappropriate differentiated cells and cancerous cells. The risk of tumorigenicity has in particular been highlighted concerning the use of human ES cells as these stem cells develop teratomas.
- Ensuring the function and viability of the stem cells or their derivatives during the recipient's life.

⁴ A. L. Lennard and G H Jackson, "Science, medicine and the future: Stem cell transplantation", BMJ, 2000, 321: 433-437.

- Overcoming the problem of immune rejection (which does not arise in the case where the patient's own stem cells can be used).
- **For the generation of human cells lines to be used in drug development at pre-clinical stage and in toxicology.** Normal human cell types generated from human stem cells can be genetically or pharmacologically manipulated and used for drug discovery. These cell lines may provide more clinically relevant biological systems than animal models for drug testing and are therefore expected to contribute to the development of safer and more effective drugs for human diseases and ultimately to reduce the use of animals. They also offer the possibility to develop better *in vitro* models to enhance the hazard identification of chemicals. It is possible that these applications will turn out to be the major medical impact of human ES cell research at least in a short-term perspective, as the problems of immune rejection, viability and tumorigenicity do not apply here.
- **For the understanding of human development.** Human ES cells should offer insights into developmental events that cannot be studied directly in the intact human embryo but that have important consequences in clinical areas, including birth defects, infertility, and pregnancy loss.
- **For the understanding of the basic mechanisms of cell differentiation and proliferation.** The understanding of the genes and molecules, such as growth factors and nutrients, that function during development of the embryo may be used to grow stem cells in the laboratory and direct their development into specialized cell types. Some of the most serious medical conditions, such as cancer, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapies.

The current advantages and limitations of human embryonic and somatic stem cells and the needs regarding the derivation of new human embryonic stem cell lines

In light of the current state of knowledge, human embryonic and somatic stem cells each have advantages and limitations regarding their potential uses for basic research and novel stem cell based therapies.

It is a matter of debate within the scientific community whether human embryonic stem cells have a greater potential than human somatic stem cells (isolated from foetal or adult tissue). Currently, human ES cells are of particular interest because they have the potential to differentiate into all cell types in the body (they are pluripotent). The recent reports⁵ indicating that somatic stem cells may have a greater potential for differentiation into different cell types than previously thought (for example bone marrow stem cells under certain experimental conditions may differentiate into neurones, skeletal and cardiac muscle cells), have opened up the question whether research on human embryonic stem cell is needed and ultimately whether the derivation of new human embryonic stem cell lines may be obsolete at this stage. In spite of the optimism generated by the recent research reports on the pluripotentiality of human somatic stem cells, many scientists, including those who conduct

⁵ e.g. Jiang, Yuehua et al., "Pluripotency of mesenchymal stem cells derived from adult marrow", *Nature*, 2002, 418:41-49.

somatic stem cell research, support the continuation of human embryonic stem cell research, and do not support the limitation of research to somatic stem cell research only⁶.

The conclusions of many reports⁷ have highlighted that it is too early to know what important findings will come from embryonic or somatic stem cell research and which stem cells will best meet the needs of basic research and clinical applications.

Several arguments have been put forward regarding the needs for derivation of new human embryonic stem cell lines.

In particular that human embryonic stem cell research has only just begun and scientists do not yet know if they have developed the best procedures for isolating or maintaining human ES cells in culture. It has also been reported that many of the existing embryonic stem cell lines have been patented in the US. This could create a position of dependence from private industry in other parts of the world⁸.

Governance of human stem cell research

Human embryonic stem cell research raises complex ethical questions. The question whether it is ethically defensible to do research on embryonic stem cells can be described as a conflict between different values, between different actors' rights and obligations, or between the short- and long-term interests of different groups. On the one hand, there is interest in new knowledge that can lead to treatment of hitherto incurable diseases. On the other hand, when this research involves the use of human embryos, it raises the question of ethical values at stake and of the limits and conditions for such research⁹. Opinions on the legitimacy of experiments using human embryos are divided according to the different ethical, philosophical, and religious traditions in which they are rooted. EU Member States have taken very different positions regarding the regulation of human embryonic stem cell research. It confirms that different views exist throughout the European Union concerning what is and what is not ethically defensible.

⁶ e.g. Dr. Catherine Verfaillie, University of Minnesota Medical School, stated during her presentation at the US President's Council on Bioethics meeting on 25 April 2002, <http://www.bioethics.gov/> "Embryonic stem cells in humans are very much in their infancy, the same as we are for adult stem cell biology, too, and so I don't think we are anywhere close to be able to come up with new therapies at this point in time. I would also like to reiterate that even though my laboratory and our group works on adult stem cells, we have actually actively pursued investigators in embryonic stem cell research, human embryonic stem cells, just so that within the same institution we would have laboratories that have one cell, and other laboratories that have the other cell, so we would be in a position to compare and contrast the potential of the different cell populations, and I think that it is very important".

⁷ "Stem Cells: scientific progress and future research directions", National Institute of Health (NIH), Bethesda, USA, June 2001; Swiss National Advisory Commission on Biomedical Ethics: opinion on human embryonic stem cell research, June 2002; The Health Council of the Netherlands' report on "Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells", June 2002. <http://www.gr.nl/pdf.php?ID=429>; House of Lords Select Committee UK, "Report on Stem cell research", February 2002; <http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm>; Swedish National Council of Medical Ethics: statement of opinion on embryonic stem cell research, 17.01.2002, <http://www.smer.gov.se/>.

⁸ The Health Council of the Netherlands' report on "Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells", June 2002. <http://www.gr.nl/pdf.php?ID=429>.

⁹ Annex E - Opinion No. 15 of the European Group on Ethics regarding the "Ethical aspects of human stem cell research and use". http://europa.eu.int/comm/european_group_ethics/index_en.htm.

Ethical issues at stake:

As highlighted in the opinion n° 15 of The European Group on Ethics in Sciences and New Technologies regarding « Ethical aspects of human stem cell research and use », issued 14 November 2000,¹⁰ the following fundamental ethical principles are applicable to human embryonic stem cell research:

- *The principle of respect for human dignity.*
- *The principle of individual autonomy (entailing the giving of informed consent, and respect for privacy and confidentiality of personal data).*
- *The principle of justice and of beneficence (namely with regard to the improvement and protection of health).*
- *The principle of freedom of research (which is to be balanced against other fundamental principles).*
- *The principle of proportionality (including that research methods are necessary to the aims pursued and that no alternative more acceptable methods are available).*

In addition, the EGE considers it important to take into account, based on a precautionary approach, the potential long-term consequences of stem cell research and use for individuals and the society.”

Concerning the creation of embryos for research purpose the EGE considered that “*the creation of embryos for the sole purpose of research raises serious concerns since it represents a further step in the instrumentalisation of human life*” and deemed “*the creation of embryos with gametes donated for the purpose of stem cell procurement ethically unacceptable, when spare embryos represent a ready alternative source*”.

Furthermore the EGE considered “that, at present, the creation of embryos by somatic cell nuclear transfer for research on stem cell therapy would be premature, since there is a wide field of research to be carried out with alternative sources of human stem cells (from spare embryos, foetal tissues and adult stem cells”.

Concerning the ethical acceptability of human embryonic stem cell research in the context of the Community Framework Programme, the EGE concluded that «*//... there is no argument for excluding funding of this kind of research from the Framework Programme of research of the European Union if it complies with ethical and legal requirements as defined in this programme*”.

Secondly the EGE stated, that:

“Stem cell research based on alternative sources (spare embryos, foetal tissues and adult stem cells) requires a specific Community research budget. In particular, EU funding should be devoted to testing the validity of recent discoveries about the potential of differentiation of adult stem cells. The EU should insist that the results of such research be widely disseminated and not hidden for reasons of commercial interest.”

¹⁰ Annex E - Opinion No. 15 of the European Group on Ethics regarding the “Ethical aspects of human stem cell research and use”. http://europa.eu.int/comm/european_group_ethics/index_en.htm.

The EGE identified the following principal requirements regarding human embryonic stem cell research and the procurement of embryonic stem cells from supernumerary embryos:

- Free and informed consent from the donating couple or woman.
- Approval of the research by an authority.
- No financial gain for donors.
- Anonymity of the donors and protection of the confidentiality of personal information of the donors.
- Transparency regarding research results.

Concerning clinical research the EGE stressed the importance of:

- Free and informed consent of the patient.
- Risk-benefit assessment.
- Protection of the health of persons involved in clinical trials.

Regulation of human embryonic stem cell research in EU Member States¹¹

EU Member States have taken different positions regarding the regulation of human embryonic stem cell research and new laws or regulations are being drafted or debated. Taking into account the situation, as of March 2003, the following distinctions can be made:

- **Allowing for the procurement of human embryonic stem cells from supernumerary embryos by law under certain conditions:** Finland, Greece, the Netherlands, Sweden and the United Kingdom.
- **Prohibiting the procurement of human ES cells from supernumerary embryos but allowing by law for the import and use of human embryonic stem cell lines under certain conditions:** Germany. The import and use of human ES cell lines is not explicitly prohibited in e.g. Austria, Denmark and France and authorisation is still being discussed.
- **Prohibiting the procurement of human ES cells from supernumerary embryos:** Austria, Denmark, France, Ireland and Spain. The legislation in Spain only allows the procurement of human ES cell from non-viable human embryos under certain conditions.
- **No specific legislation regarding human embryo research or human ES cell research:** Belgium, Italy, Luxembourg and Portugal.

¹¹ European Commission, DG Research, Directorate E: Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use (last update March 2003). "Survey on the National Regulations in the European Union regarding Research on Human Embryos - B. Gratton - published by the Secretariat of the EGE - European Commission - July 2002".

- **Allowing by law for the creation of human embryos for research purposes:** UK is for the moment the only Member State, which allows by law for the creation of human embryos either by fertilisation of an egg by a sperm, or by somatic cell nuclear transfer (SCNT, also called therapeutic cloning) for stem cell procurement. The bill under discussion in the Belgian Parliament would allow for the creation of human embryos for research purposes including by SCNT. The Dutch Embryo Act of 2002 includes a five-year moratorium for the creation of embryos for research purposes including by SCNT.
- **Prohibiting the creation of human embryos for research purposes and for the procurement of stem cells by law or by ratification of the Convention of the Council of Europe on Human rights and Biomedicine signed in Oviedo on 4 April 1997:** Austria, Denmark, Finland, France, Germany, Greece, Ireland, Netherlands, Portugal and Spain.

New regulations under discussion in EU Member States:

Belgium: A bill on research on human embryos *in vitro* was approved by the Belgian Senate in 2002 and it is now under discussion in the Parliament. The draft legislation proposes to authorise the procurement of embryonic stem cells from supernumerary embryos under certain conditions, and to create a “Federal Commission for scientific medical research on embryos *in vitro*”.

Denmark: A revision of the current legislation to allow for the procurement of human ES cells from supernumerary embryos is under discussion.

France: A revision of the Bioethics Law of 1994 has been approved by the Senate in January 2003 and should be discussed by the Parliament in the first semester of 2003. It proposes to allow research on supernumerary human embryos including the procurement of human ES cells for 5 years under certain conditions. A central authorizing body will be created.

Italy: a law on *in vitro* fertilisation is under discussion.

Portugal: A committee has been established in Portugal for the preparation of a law on human embryo and human ES cell research.

Spain: A revision of the current legislation is under discussion.

In 1998 the National Committee for Human Artificial Reproduction was created. In its second opinion, delivered in 2002, it advised to conduct human embryonic stem cell research using as a source supernumerary embryos, estimated in Spain to be over 30 000.

The Ethics Advisory Committee for Scientific and Technological Research was established in April 2002 and gave in February 2003 its first opinion on research on stem cells. It recommended to the government that research on both adult and embryonic stem cells should be implemented; that the legislation should be modified to allow the isolation of human embryonic stem cells from supernumerary embryos.

Sweden: A revision of the current legislation is under discussion. The Parliamentary Committee on Genetic Integrity proposed, in their report published 29 January 2003, not to implement a general prohibition against producing fertilised eggs for research purposes. It

should also be noted, however, that in the view of the Committee the creation of embryos by transfer of somatic cell nuclei (so called therapeutic cloning) should be treated in the same way and thus in principle be allowed.

Regulations in countries acceding to the EU

Cyprus, Czech Republic, Estonia, Hungary, Lithuania, Slovak Republic, Slovenia have ratified the Convention of the Council of Europe on biomedicine and human rights.

Concerning the countries acceding to the EU, no specific regulations regarding human embryonic stem cell research have at present been implemented. Estonia, Hungary, Latvia, Slovenia have implemented legislation authorising research on human embryos under certain conditions. In Lithuania, Poland and the Slovak Republic human embryo research is prohibited. No specific regulation regarding embryo research exist in Cyprus, Malta and the Czech Republic. A bill is under preparation in Czech Republic.

Governance of stem cell research in the context of FP6

As stated in the Treaty of the European Union, article 6:

“1. The Union is founded on the principles of liberty, democracy, respect for human rights and fundamental freedom, and the rule of law, principles which are common to the Member States.

2. The Union shall respect fundamental rights, as guaranteed by the European Convention for the protection of Human Rights and Fundamental Freedoms signed in Rome on 4 November 1950 and as they result from the constitutional traditions common to the Member States, as general principles of Community law.

3. The Union shall respect the national identities of its Member States.

4. The Union shall provide itself with the means necessary to attain its objectives and carry through its policies.”

In accordance with the EU Treaty, each Member State retains its full prerogative to legislate on ethical matters. At the level of the Community, ethical principles have been defined with regard to the funding of research under the research Framework Programme.

As far as FP6 is concerned, the following ethical principles have been established¹²:

- *“Fundamental ethical principles are to be respected. These include the principles reflected in the Charter of fundamental rights of the EU including the protection of human dignity and human life...”*
- *“... in accordance with Community law”*
- *“...in accordance with legislation, regulations and ethical guidelines in countries where the research will be carried out.”*

¹² OJ L 232 of 29.8.2002, p.4; OJ L 294 of 29.10.2002, p. 8.

- *“The following fields of research shall not be financed under this programme:*
 - *research activities aiming at human cloning for reproductive purposes*
 - *research activity intended to modify the genetic heritage of human beings which could make such change heritable¹³*
 - *research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer (often referred to as therapeutic cloning).*
- *... funding of research activities that are prohibited in all the Member States is in all circumstances excluded.”*
- *“In compliance with the principle of subsidiarity and the diversity of approaches existing in Europe, participants in research projects must conform to current legislation, regulations and ethical rules in the countries where the research will be carried out.*
- *In any case, national provisions apply and no research forbidden in any given Member State will be supported by Community funding in that Member State.*
- *Where appropriate, participants in research projects must seek the approval of relevant national or local ethics committees prior to the start of the RTD activities. An ethical review will be implemented systematically by the Commission for proposals dealing with ethically sensitive issues, in particular proposals involving the use of human embryos and human embryonic stem cells”.*
- *As stated in the Council minutes of 30 September 2002¹⁴ “The Council and the Commission agree that detailed implementing provisions concerning research activities involving the use of human embryos and human embryonic stem cells...shall be established by 31 December 2003. The Commission will during that period...not propose to fund such research, with the exception of banked or isolated human embryonic stem cells in culture”.*

Socio-economic aspects

While many of the demonstrations of the potential of stem cell research have arisen from academia, the development of this potential i.e. into therapeutic products requires industrial and commercial inputs. For example, industrial involvement will be needed for large scale and good manufacturing production of cell lines, to support multicentre clinical trials, marketing, distribution etc.

In 2001 about 30 public and private biotechnology firms were doing stem cell research and about a dozen are currently investigating the potential of both somatic and embryonic stem cells. Few, if any, companies are investing solely in human embryonic stem cell research.

¹³ Research relating to cancer treatment of the gonads can be financed.

¹⁴ Annex F.

Although considerable sums are available for investment in stem cell research, commercial returns on such investments are for the moment modest. This reflects the fact that most of this work is still at the basic research stage. Thus commercial interests are trying to position themselves for major profits in the future, but still face uncertain research prospects, therapeutic possibilities and the development of a regulatory environment, the latter largely influenced by ethical issues and public concerns.

INTRODUCTION

This report, prepared by the Commission services, aims to provide an overview of:

- Origin and characteristics of human stem cells and the potential application of stem cell research.
- Human embryonic stem cell research (somatic stem cell research will be addressed so far as it is relevant to the discussion on human embryonic stem cell research).
- Governance of human embryonic stem cell research including the ethical issues at stake, regulations in the EU Member States, governance of stem cell research in the context of FP6 and social scrutiny and dialogue.
- Socio-economic aspects of human embryonic stem cell research and use.

The report is complemented by a series of annexes, as follows:

- A. Biology of human development
- B. Possibilities to overcome immune rejection responses in stem cell therapy
- C. Examples of available human embryonic stem cell lines
- D. Details regarding provisions in non-EU countries relating to human embryonic stem cell research
- E. Opinion n° 15 of the European Group on Ethics regarding “Ethical aspects of human stem cell research and use” issued 14 November 2002.
- F. Statement for the minutes of the Council meeting 30 September 2002

The report takes into account:

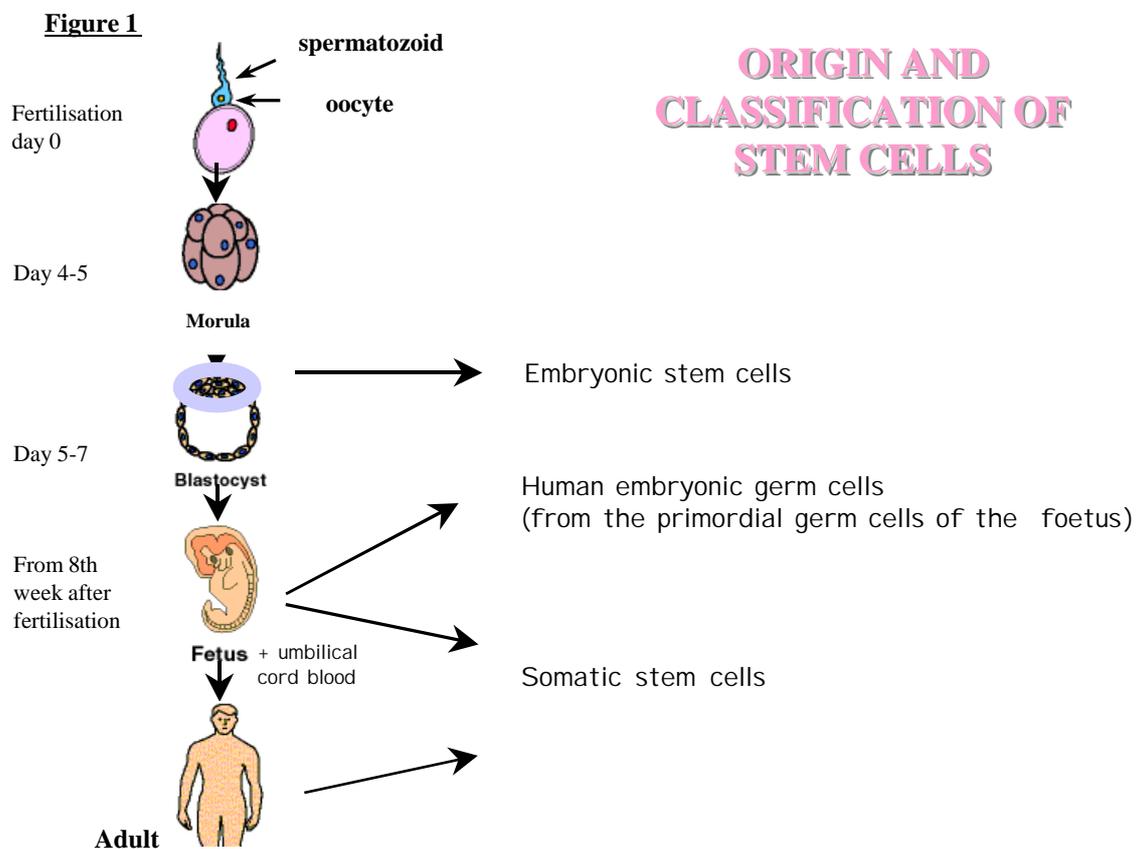
- Information collected from the survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use in EU Member States and non-EU countries. The survey was conducted by the European Commission, DG Research, Directorate E (last update March 2003);
- Opinions and reports from the European Group on Ethics in Science and New Technologies to the European Commission http://europa.eu.int/comm/european_group_ethics/index_en.htm
- Report and proceedings from the conference on “Stem cells: Therapies for the future?” organised by the European Commission, DG Research under the aegis of the European Group on Life Sciences; December 2001 <http://europa.eu.int/comm/research/quality-of-life/stemcells.html>

- Candidate Countries legislation related to ethical issues in science and research
Proceedings of the workshop of 8-10 December 2002 - Brussels - organised by the
European Commission - DG Research – Directorate C
- U. S. National Institutes of Health (NIH) documents regarding stem cells
<http://nih.gov/news/stemcell/>
- Review of recent literature;
- Presentations and communications from the scientific community.

Chapter 1: Origin and characteristics of human stem cells and potential application for stem cell research

1.1. Origin and characteristics of human stem cells¹⁵

Stem cells differ from other kind of cells in the body by their unique properties of: 1) being capable of dividing and renewing themselves for long periods, 2) being unspecialised and 3) being able to give rise to specialised cell types. They are found in the early embryo, in the foetus and the umbilical cord blood, and in some (possibly many) tissues of the body after birth and in the adult. These stem cells are the source for tissues and organs of the foetus and for growth and repair in the newborn and adult body. As development proceeds beyond the blastocyst stage (5-7 days after fertilisation), the proportion of stem cells decrease in the various tissues and their ability to differentiate into different cell types also decrease at least when they are situated in their natural environment. (See also chapter 1.2.).



¹⁵ The Health Council of the Netherlands' report on "Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells", June 2002. <http://www.gr.nl/pdf.php?ID=429>; US NIH, "Stem Cells: A primer" September 2002 <http://www.nih.gov/news/stemcell/primer.htm>.

Classification of human stem cells:

The classification of stem cells is still subject to discussion and the use of different definitions, both in the scientific literature and in public debates, often creates confusion. In this report a distinction is made between three groups of stem cells, referring to their origin and method of derivation¹⁶:

1. Human embryonic stem cells

Human embryonic stem cells derived from preimplantation embryo at the blastocyst stage (see chapter 2 for further details)

2. Human embryonic germ cells

Stem cells with embryonic characteristics have also been isolated from the primordial germ cells of the 5-10 weeks foetus. It is from these embryonic germ cells that the gametes (ova or sperm) normally develop. Research has shown that germ cell derived stem cells have the ability to differentiate into various cell types, although they are more limited in this respect than embryonic stem cells¹⁷. It should be noted that these research results have yet to be confirmed by other scientists and that the stability of these cells' genetic material is still open to discussion.

3. Human somatic stem cells

A somatic stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ, which can renew itself and can differentiate to yield the major specialised cell types of the tissue or organ. Although somatic stem cells are rare, many, if not most, tissues in the foetus and human body contain stem cells, which, in their normal location, have the potential to differentiate into a limited number of specific cell types in order to regenerate the tissue in which they normally reside. These stem cells, defined as somatic stem cells, are usually described as "multipotent". Scientists have found evidence for somatic stem cells in many more tissues than they once thought possible. Examples of the tissues reported to contain stem cells include liver, pancreas, brain, bone marrow, muscle, olfactory epithelium, fat and skin¹⁸. Some stem cells remain very active during postnatal life (e.g. haematopoietic stem cells, skin and gut stem cells), others seem relatively inactive (e.g. stem cells in the brain). It should be mentioned that recent published data have suggested that, for example cells in the liver and even the adult human brain may respond to injury by attempting repopulation¹⁹.

Possible sources for human somatic stem cells:

- **Adult tissues and organs:** Somatic stem cells can be obtained by means of invasive intervention, such as that used in connection with donation of bone marrow. Haematopoietic stem cells are routinely collected through the peripheral blood. It has

¹⁶ The Health Council of the Netherlands' report on "Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells", June 2002. <http://www.gr.nl/pdf.php?ID=429>; US NIH "Stem Cells: A primer" September 2002 <http://www.nih.gov/news/stemcell/primer.htm>.

¹⁷ Shambloott, M.J. et al. "Human embryonic germ cell derivatives express a broad range of developmentally distinct markers and proliferate extensively *in vitro*", *Proc Natl Acad Sci USA*, 2001, 98: 113-8.

¹⁸ Jiang, Y. et al., "Pluripotency of mesenchymal stem cells derived from adult marrow", *Nature*, 2002, 418 : 41-49.

¹⁹ Steindler, D.A. and Pincus D.W., "Stem cells and neurogenesis in the adult brain", *Lancet*, 2002, 359(9311):1047-1054.

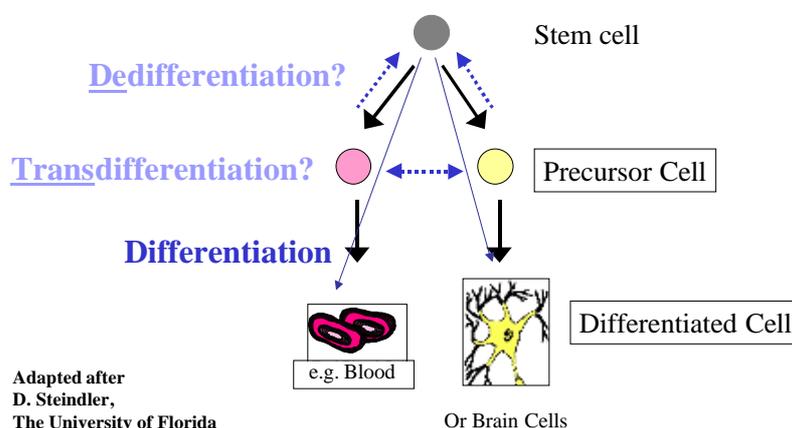
also been reported that stem cells can be obtained following autopsy, from post mortem brain tissue for example.

- **Foetal organs or tissues:** Foetal tissue or organs obtained after pregnancy termination can be used to derive stem cells, e.g. neural stem cells which can be isolated from foetal neural tissue and multiplied in culture.
- **Umbilical cord blood:** Haematopoietic stem cells can be retrieved from the umbilical cord blood at birth. Stem cells, which could give rise to other tissues, may also be present in cord blood.

1.2. Plasticity of human somatic stem cells

Figure 2

PLASTICITY OF STEM CELLS



It has recently been reported that for example:

- Brain stem cells may differentiate into blood cells²⁰
- Bone marrow stem cells in vitro may differentiate into neurons, skeletal and cardiac muscle cells and liver cells etc.²¹

This later process might be explained by the persistence of very rare pluripotent stem cells through life, which under normal conditions are “dormant”. However, other hypotheses are envisaged. The potential of a stem cell may not be defined once and forever but may depend on the cellular environment. For example a somatic stem cell might be able to make more than one tissue by one of the following ways:

²⁰ Bjornson, C et al., “Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells”, *in vivo*. *Science*, 1999, 283, 354-357.

²¹ Jiang Y, et al., “Pluripotency of mesenchymal stem cells derived from adult marrow”, *Nature*, 2002, 418:41-49; Orlic, D et al., “Bone marrow cell regenerate infarcted myocardium”, *Nature*, 2001, 410, 701-705; Petersen, B.E. et al., “Bone marrow as a potential source of hepatic oval cells. *Science*, 1999, 284, 1168-1170.

In a changed environment, the original stem cell might dedifferentiate and then be reprogrammed to generate the alternative cell types

or

The original cell might change directly into another cell type without going through a dedifferentiated intermediate stage, a process sometimes called “transdifferentiation”.

This is little short of a revolutionary concept in developmental cell biology where it has generally been considered that in mammalian cells, contrary to plants and lower micro-organisms, the process of differentiation was irreversible.

Some scientists question the plasticity of stem cells²². Current research is aimed at determining the mechanisms that underlie somatic stem cell plasticity. If such mechanisms can be identified and controlled, existing stem cells from healthy tissue might be induced to repopulate and repair a diseased tissue²³.

1.3. Potential application of human stem cell research

Transplantation of haematopoietic stem cells (from bone marrow, peripheral blood or umbilical cord blood of healthy donor) has been used for more than a decade to treat e.g. haematological malignancies such as leukemia or congenital immunodeficiencies. Autologous transplantation (transplantation of stem cells from the patient’s own bone marrow or peripheral blood) was introduced to rescue the bone marrow of patients who had received high dose of chemotherapy. It is now increasingly being used as primary treatment for other types of cancer such as breast cancer and neuroblastoma. Autologous transplantation is also used experimentally to treat difficult auto-immune conditions and as a vehicle for gene therapy. Today, over 350 centres in Europe are performing more than 18 000 bone marrow transplants a year²⁴.

Human stem cell research is expected to be of interest for several areas of science and medicine²⁵:

For the development of novel stem cell based therapies.

- Novel stem cell based therapies (often called regenerative medicine or cell based therapies) are also being investigated to develop new methods to repair or replace tissues or cells damaged by injuries or diseases and to treat serious chronic diseases, such as diabetes, Parkinson’s, chronic heart failure or stroke and spinal cord injuries. (See chapter 1.4 for further details)
- **For the generation of normal human cell lines to be used in drug development at the preclinical stage and in toxicology** Stem cells are a source for the generation of normal human cell types that can be genetically or pharmacologically manipulated

²² Wagers A.J. et al., “Little evidence for developmental plasticity of adult haematopoietic stem cells”, *Science*, 2002, 297, 2256-2259; De Witt and Knight, “Biologists question adult stem cell versatility”, *Nature*, 2002, 416, 354.

²³ US NIH, “Stem Cells: A primer”, September 2002 <http://www.nih.gov/news/stemcell/primer.htm>

²⁴ A. L Lennard and G H Jackson. “Science, medicine and the future: Stem cell transplantation”, *BMJ*, 2000, 321:433-437.

²⁵ US NIH, “Stem Cells: A primer”, September 2002 <http://www.nih.gov/news/stemcell/primer.htm>
Annex E - Opinion n° 15 of the European Group on Ethics http://europa.eu.int/comm/european_group_ethics/docs/avis15_EN.pdf

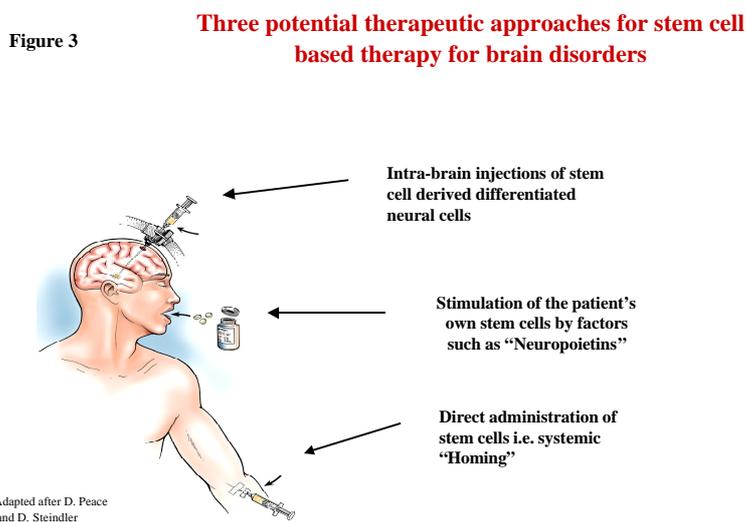
and used for drug discovery. They give scientists the ability to experimentally study - under carefully controlled conditions - the growth and development of many different human cell types that are important to diseases like cancer, diabetes, stroke, heart disease etc. These cell lines may provide more clinically relevant biological systems than animal models for drug testing and are therefore expected to contribute to the development of safer and more effective drugs for major human diseases. For example today, there exists no laboratory model for the human heart, and it is therefore very difficult (impossible) to know exactly what effect medicines have on the heart before performing human studies. The lack of availability of human cells, which express normal function, has so far been the main limiting factor for reducing animal testing in pharmaco-toxicology. It is possible that this application will turn out to be the major medical impact of human ES cell research at least in a short-term perspective. At present insufficient methods exist in some areas of *in vitro toxicology* predicting target organ toxicity. In other areas such as embryo-toxicity inter-species variation presents major obstacles and humanised systems may enhance the hazard identification of chemicals.

- **Use of stem cells in gene therapy:** Stem cells could be used as vehicles i.e. bearers of genetic information for the therapeutic delivery of genes. A problem for research on gene therapy has been to find safe delivery systems and stem cells may provide a solution here. At present, experiments are being done with gene therapy to treat diseases of the blood system. Their aim is to introduce new healthy genes in the blood-forming stem cells, which can then develop into all types of blood cells and, moreover, are able to renew themselves and thereby provide a permanent cure.
- **For understanding of human development.** Studies of human embryonic and foetal stem cells may yield a deeper understanding of evolutionary biology and the process leading from embryo to human being. Human ES cells should offer insights into developmental events that cannot be studied directly in the intact human embryo but that have important consequences in clinical areas, including birth defects, infertility, and pregnancy loss. Particularly in the early post implantation period, knowledge of normal human development is largely restricted to the description of a limited number of sectioned embryos and to analogies drawn from the experimental embryology of other species. Although the mouse is the main stay of experimental mammalian embryology, early structures including the placenta, extra-embryonic membranes, and the egg cylinder all differ substantially from the corresponding structure of the human embryo.
- **For understanding of the basic mechanisms of cell differentiation and proliferation.** A primary goal of this work is to identify how undifferentiated stem cells become differentiated into particular types of cells. Scientists know that turning genes on and off are central to this process and molecules such as growth factors and nutrients, that function during embryonic development, also play a role. This knowledge can be used to grow stem cells from various sources in the laboratory and direct their differentiation into specialized cell types. Some of the most serious medical conditions, such as cancer, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapies.

1.4. Novel stem cell based therapies

Three therapeutic concepts are currently being envisaged²⁶:

- **Transplantation of differentiated cells derived from stem cells:** Stem cells may be grown and directed to differentiate into specific cell types in the laboratory and then be transplanted e.g. insulin producing cells to treat diabetes, skeletal muscle cells for muscle diseases, dopamine producing neurons for Parkinson's disease etc. The source for the specific differentiated cell types could be embryonic or somatic stem cells including the patient's own stem cells.
- **Direct administration of stem cells:** In some cases it may be possible and/or necessary to administer stem cells directly to the patient in such a way that they would colonise the correct site of the body and continuously differentiate into the desired cell type (e.g. systemic "Homing").



- **Stimulation of endogenous stem cells:** The possibility that self-repair could be induced or augmented by stimulating an individual's own population of stem cells for example by administering growth factors is also being explored.

1.5. Scientific and technical obstacles to overcome before realising the potential clinical uses of novel human stem cell based therapy

The novel stem cell based therapies as described in chapter 1.4. are still at a an early stage of development. In particular regarding the transplantation of differentiated cells derived from stem cells several scientific and technical hurdles need to be resolved before clinical application of these therapies, including²⁷:

²⁶ "La recherche sur les cellules souches embryonnaires", Commission nationale d'éthique suisse pour la médecine humaine, Prise de position n° 3/2002; Steindler, D.A. and Pincus D.W., "Stem cells and neurogenesis in the adult brain", *Lancet*, 2002, 359(9311):1047-1054.

²⁷ US NIH, "Stem Cells: A primer", September 2002 <http://www.nih.gov/news/stemcell/primer.htm>; House of Lords Select Committee – Report on Stem cell research, February 2002

- **Differentiation, dedifferentiation and transdifferentiation:** There is still a strong need to gain a better understanding of the underlying mechanisms regulating stem cell growth, migration, fate and differentiation in order to ensure controlled and stable differentiation. If somatic stem cells are dedifferentiated to enhance their normal potential, scientists must be able to control this process.
- **Inappropriate tissue development:** One possible risk of clinical use of stem cell transplantation is that the cells will not simply grow into replacement or supportive tissue, but inappropriate differentiated tissue will develop.
- **Tumorigenicity:** The risk of tumour development does present an important risk, in particular if human ES cells are transplanted directly to the patient, as human ES cells do form teratoma.
- **Isolation and purification:** The isolation of many adult stem cells is still difficult. Purification methods need to be developed in order to avoid the transplant of inappropriate cells.
- **Immune rejection:** The human body possesses an immune system, which recognises cells that are not its own and rejects them for example following transplantation of organs, tissues or cells derived from other individuals (heterologous transplantation). Immune rejection is one of the major causes of transplant failure, and is one of the problems which will need to be overcome for stem cell-based therapy to be effective except in the case where the patient's own stem cells can be used. Different approaches are currently being envisaged to overcome immune rejection e.g. immuno-suppressive drugs, generation of immunotolerance, use of "matching tissues or by somatic cell nuclear transfer (i.e. therapeutic cloning) as described in annex B.
- **Function and viability:** The stem cells or their derivatives must function appropriately for the duration of the recipient's life and survive in the recipient after transplantation. Methods to improve and properly assess the viability and functioning of the differentiated cells need to be worked out.
- **Culture conditions:** Good manufacturing practice (GMP) needs to be defined including the establishment of germ-free culture conditions for the derivation and differentiation of specialised cell types.

1.6. Examples of novel stem cell based therapies, which are currently subject to extensive research.

Neurological diseases and disorders (see also figure 3)

Parkinson's disease (PD) is caused by a progressive degeneration and loss of dopamine (DA)-producing neurons, which leads to rigidity, hypokinesia (abnormally decreased mobility) and tremor.

Scientists are developing a number of strategies for producing dopamine neurons from human stem cells in the laboratory for transplantation into humans with Parkinson's disease including

<http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm> ; The Health Council of the Netherlands' report on "Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells", June 2002. <http://www.gr.nl/pdf.php?ID=429>.

the use of neural dopamine producing cells derived from aborted foetuses. Clinical trials in patients with Parkinson's disease have been performed on around 200 patients over the last 10 years especially in Sweden and in USA. They have shown that the transplantation of neural cells derived from the human foetus can have a therapeutic effect, with an important reduction of the symptoms of the disease in the treated patients²⁸. However, the availability of neural foetal tissue is very limited. Efforts are now being made to expand fetal neural stem cells and control their differentiation into dopaminergic neurons.

In a recent study, scientists directed mouse embryonic stem cells to differentiate into dopaminergic neurons by treatment with growth factors and by introducing the gene *Nurr1*. When transplanted into the brains of a rat model of Parkinson's disease these stem cell-derived dopaminergic neurons re-innervated the brains of the rat, released dopamine and improved motor function.²⁹

The possibility to stimulate the patient's own stem cells in the brain is also being explored. Self-repair could be induced or augmented with neuro-poiëtins - small selective growth factors that trigger repair processes by an individual's own indigenous population of stem cells³⁰.

Heart failure

When heart muscle cells (cardiomyocytes) are destroyed, e.g. after a heart attack, functional contracting heart muscle is replaced with non-functional scar tissue. It is hoped that healthy heart muscle cells generated in culture in the laboratory and then transplanted into patients could be used to treat patients with e.g. chronic heart disease.

Recent research in mice indicates that mouse cardiomyocytes derived from mouse embryonic stem cells, transplanted into a damaged heart, can generate new heart muscle cells and successfully repopulate the heart tissue. These results suggest that cardiomyocytes derived from human embryonic stem cells derived could be developed for cell transplantation therapy in humans suffering from heart failure³¹.

It has also been reported from animal studies that bone marrow stem cells³² have the potential to be used to repair the infarcted heart. The transplantation of autologous bone marrow cells (transplantation of the patient's own stem cells) into the infarcted heart has been reported in two small non randomized human studies³³.

²⁸ Bjorklund, A. and Lindvall O., "Cell replacement therapies for central nervous system disorders", *Nature Neuroscience*, 2000, 3, 537-544.

²⁹ Björklund, L. M. et al. "Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model", *Proc. Natl. Acad. Sci. USA*, 2002, 99:2344-2349; Kim J-H. et al., "Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease", *Nature*, 2002, 418: 50-56.

³⁰ Steindler, D.A. and Pincus D.W., "Stem cells and neurogenesis in the adult brain", *Lancet*, 2002, 359(9311):1047-1054.

³¹ Kehat et al., "Human embryonic stem cells can differentiate into myocytes with structural and functional properties", *J Clin Invest*, 2001, 103:407-14.

³² Orlic, D. et al. "Bone marrow cells regenerate infarcted myocardium", *Nature*, 2001, 410, 701-705. Orlic, D. et al. "Mobilized bone marrow cells repair the infarcted heart, improving function and survival", *Proc Natl Acad Sci USA* 2001, 98: 10344-9.

³³ Assmus, B. et al. "Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI)", *Circulation*, 2002, 106: R53-R61; Strauer, B.E. et al.

Diabetes

In people who suffer from type I diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's own immune system. Although diabetics can be treated with daily injections of insulin, these injections enable only intermittent glucose control. As a result, patients with diabetes suffer chronic degeneration of many organs, including the eye, kidney, nerves and blood vessels. In some cases, patients with diabetes have been treated with islet beta cell transplantation. However, poor availability of suitable sources for islet beta cell transplantation from *post mortem* donors makes this approach difficult as a treatment for the growing numbers of individuals suffering from diabetes.

Ways to overcome this problem include deriving islet cells from other sources such as:

- Human adult pancreatic duct cells that have been grown successfully *in vitro* and induced to differentiate, but the ability of these cells to restore blood glucose *in vivo* is still unproven. This promising line of research is being pursued by several laboratories.
- Fetal pancreatic stem cells and β cell precursor. The identification of endocrine precursor cells in the developing pancreas and the regulation of their differentiation by a specific cellular pathway raises the possibility to grow and differentiate endocrine precursor cells *in vitro* taken from aborted foetus or by using adult pancreatic duct cells³⁴.
- Embryonic stem cells. Research in mice has demonstrated that mouse embryonic stem cells can differentiate into insulin-producing cells and other pancreatic endocrine hormones. The cells self-assemble to form three-dimensional clusters similar in topology to normal pancreatic islets. Transplantation of these cells was found to improve the conditions of experimental animals with diabetes³⁵. New studies indicate that it is possible to direct the differentiation of human embryonic stem cells in cell culture to form insulin-producing cells.

“Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans”, *Circulation*, 2002, 106: 1913-1918.

³⁴ Serup P. et al. “Islet and stem cell transplantation for treating diabetes”, *BMJ*, 2001, 322:29-32.

³⁵ Lumelsky, N. et al. “Differentiation of embryonic stem cells to insulin - secreting structures similar to pancreas islets”, *Science*, 2001, 292: 1389-94.

Chapter 2: Human embryonic stem cell research

The first embryonic stem cells were isolated from mice in 1981 and a great deal of research has been undertaken on mouse embryonic stem cells. A new era of stem cell biology began in 1998, when the derivation of embryonic stem cells from human blastocysts was first demonstrated³⁶. Since then, several research teams have been working on the characterisation of these cells and on improving the methods for culturing them.

2.1. Origin and characteristics of human embryonic stem cells

Human embryonic stem cells can be derived from preimplantation embryo at the blastocyst stage. At this stage, which is reached after about 5 days' embryonic development, the embryo appears as a hollow ball of 50-100 cells, called the blastocyst. The blastocyst includes three structures: the outer cell layer, which will develop into the placenta; the blastocoel, which is the fluid filled cavity inside the blastocyst; and the inner cell mass, from which the human ES cells can be isolated.

The characteristics of human embryonic stem cells include:

- Potential to differentiate into the various cell types in the body (more than 200 types are known) even after prolonged culture. The human ES cells are referred to as pluripotent.
- Capacity to proliferate in their undifferentiated stage.

2.2. Possible sources for human embryonic stem cells

Human embryonic stem cells can be isolated from preimplantation embryos (blastocysts) created by different *in vitro* techniques³⁷ (i.e. embryos created outside the human body; these embryos cannot develop beyond the blastocyst stage without implantation into the uterus):

1. Supernumerary embryos:

One possible source would be to use supernumerary embryos. These are embryos, which have been created by means of *in vitro* fertilisation (IVF) for the purpose of assisted reproduction but subsequently not used. In by far the majority of cases, assisted reproduction is used in connection with fertility problems, where supernumerary embryos may be created in order to increase the success of infertility treatment. In the countries where pre-implantation diagnosis is allowed, IVF is also used in connection with this practice and human ES cells can also be derived from embryos, which are discarded following pre-implantation diagnosis. These supernumerary embryos may be donated for research by the couples concerned with their fully informed consent.

³⁶ Thomson, J.A. et al. "Embryonic stem cell lines derived from human blastocysts", *Science*, 1998, 282, 1145-1147.

³⁷ Thomson, J.A. et al. "Embryonic stem cell lines derived from human blastocysts", *Science*, 1998, 282, 1145-1147. Annex E - Opinions n°15 and 16 of the European Group on Ethics
http://europa.eu.int/comm/european_group_ethics/docs/avis15_en.pdf
http://europa.eu.int/comm/european_group_ethics/docs/avis16_en.pdf

2. Embryos created by IVF for research purposes and/or for the purpose of stem cell procurement³⁸:

Embryos created for the purpose of research may be produced with donated gametes, i. e. they are created by *in vitro* fertilisation of a human egg by human sperm.

3. Embryos created by somatic cell nuclear transfer for research purposes and/or for the purpose of stem cell procurement³⁹:

Embryos may be produced by somatic cell nuclear transfer i.e. they are created by introducing the nucleus of an adult somatic cell (e.g. a cell from the patient) into an enucleated human oocyte and then activating the egg's further development without fertilisation (often referred to as therapeutic cloning). When the blastocyst stage is reached pluripotent stem cells can be isolated and cultured. These later stem cells have the advantage of being immunologically compatible with the patient. Laboratories currently attempt to replace the nuclei of human ES cell in culture by somatic nuclei from patients' cells in order to overcome the problem of immune rejection.

4. Other possibilities:

It is also possible to obtain human ES cells by **parthenogenesis** (by stimulation *in vitro* of an egg cell to initiate the duplication of the egg's genetic information and then the division of the cell). Finally, it is speculated that ES cells may possibly be obtained by injecting stem cell or egg cytoplasm into differentiated cells transforming these cells into pluripotent stem cells (**ovoplasmic transfer**).

It is possible that new ways of deriving human ES cells could be developed in the future.

2.3. Growing human embryonic stem cells in the laboratory⁴⁰

In order to derived embryonic stem cells, the outer membrane of the blastocyst is punctured, whereupon the inner cell mass with its stem cells is collected and transferred into a laboratory culture dish that contains a nutrient broth known as culture medium. The blastocyst is thereby destroyed and cannot develop further, but the isolated human ES cells can be cultivated *in vitro* and give rise to stem cell line. The stem cell lines can be cryopreserved and stored in a cell bank. To be successful, the cultivation requires, in addition to nutrient solution, so-called "feeder" cells or support cells. Until recently fibroblasts from mice have been used for this purpose, however scientists are now able to propagate human ES cell lines using human feeder layer or even culturing human ES cells without feeder layer. This eliminates the risk that viruses or infectious agents in the mouse cells might be transmitted to the human cells.

If the stem cells are of good quality and if they show no sign of ageing, the same stem-cell line can yield unlimited amounts of stem cells. Besides their broad potential for

³⁸ In accordance with the Council decision of 30 September adopting the specific programmes implementing FP 6 the creation of embryos for research purposes and for stem cell procurement, including by means of somatic cell nuclear transfer (i.e. therapeutic cloning) are excluded from funding under the 6th Framework Programme. OJ L 294 of 29.10.2002, p. 8.

³⁹ In accordance with the Council decision of 30 September adopting the specific programmes implementing FP 6 the creation of embryos for research purposes and for stem cell procurement, including by means of somatic cell nuclear transfer (i.e. therapeutic cloning) are excluded from funding under the 6th Framework Programme. OJ L294 of 29.10.2002, p. 8.

⁴⁰ US NIH, "Stem cells: a primer", September 2002. <http://www.nih.gov/news/stemcell/primer.htm>
Swedish National Council on Medical Ethics: statement of opinion on embryonic stem cell research, 17.01.2002, <http://www.smer.gov.se>.

differentiation, embryonic stem cell lines have proved better able to survive in the laboratory than other types of stem cells. At the various points during the process of generating embryonic stem cell lines, scientists test the cells to see whether they exhibit the fundamental properties that make them, embryonic stem cells. As yet, there exists no standard battery of tests that measure the cells' fundamental properties but several kinds of tests including tests based on the presence of specific surface and gene markers for undifferentiated cells.

One can distinguish:

- **Human ES cells freshly derived** from an embryo which have not yet been subjected to any modification and which have yet to be established as stem cell lines.
- **Unmodified (undifferentiated) human ES cell lines**, which refer to cultured lines of cells, which have been propagated for an extended period originally from freshly human ES cells and which have not been modified in any other way.
- **Modified (differentiated) human ES derivatives** which refer to cultured lines of cells, derived from human ES cells or human ES cell lines, which have been modified either by genetic manipulation, or by treatment (e.g. growth factors) that causes the cells to differentiate in a particular way e.g. to differentiate into neural or muscle precursor cells (cells which are not fully differentiated, otherwise they will not multiply).

2.4. The current advantages and limitations of human embryonic stem cells and human somatic stem cells

In light of current knowledge, human embryonic and somatic stem cells each have advantages and limitations regarding potential use for basic research and stem cell based therapy.

2.4.1. Human embryonic stem cells

Advantages:

- human ES cells have the potential to generate the various cell types in the body (they are pluripotent).
- human ES cells are at present the only pluripotent stem cell that can be readily isolated and grown in culture in sufficient numbers to be useful.

Limitations:

- The most significant potential scientific limitation on the therapeutic use of human ES cells is the problem of immune rejection. Because human ES cells will not normally have been derived from the patient to be treated, they run the risk of rejection by the patient's immune system. Annex B provides an overview of the possibilities to overcome immune rejection currently under investigation e.g. immuno-suppressive drugs, generation of immuno-tolerance, use of "matching tissues" or by somatic cell nuclear transfer (i.e. therapeutic cloning).
- It has been argued that, because human ES cells have the potential to differentiate into all cell types, it might be difficult to ensure that, when used therapeutically, they do not differentiate into inappropriate cell types or generate tumors. It is clearly essential to guard against these risks in particular of tumorigenesis.

- Current methods for growing human ES cell lines in culture are adequate for research purposes, but the co-culture of human ES cells with animal materials necessary for growth and differentiation would preclude their use in therapy. Scientists are now working on generating stem cell lines, which are grown on human feeder layer or without feeder layer and in completely defined culture media.

2.4.2. *Human somatic stem cells*

Advantages:

- The potential of somatic stem cells for therapeutic application is illustrated by the use of haematopoietic stem cells to treat leukemias and other blood disorders³⁸.
- Recent studies suggesting that various somatic stem cells have much greater potential for differentiation than previously suspected have opened up the possibility that other routes to somatic stem cell therapy might be available.
- The patient's own stem cells could be expanded in culture and then reintroduced into the patient which would mean that the cells would not be rejected by the immune system. This represents a significant advantage, as immune rejection is a difficult problem.
- In the future it might be possible to stimulate proliferation and fate control of the patient's own indigenous somatic stem cell population in-situ by systemically-introduced "poietins".

Limitations:

- The isolation, growth and differentiation of adult stem cells have to date proved difficult. Stem cells generally represent a small proportion of cells in adult tissues. It should be recognised that although haematopoietic stem cells represent a small proportion of cells in the peripheral blood (i.e. haematopoietic stem cells, 1 out of 100,000 white blood cells), they are now the preferred source of autologous stem cells for transplantation in adults⁴¹.
- Where a person suffers from a genetic disorder or some types of cancers, somatic stem cells isolated from that individual will retain the damaging genetic alterations underlying the disease and so be of little therapeutic value e.g. in the case of diabetes. However, they could be corrected by gene therapy.
- It is not yet known whether somatic stem cells give rise to cells of different tissue types by transdifferentiation, or by dedifferentiation to a less differentiated stem cell, which then differentiates into the new cell types. The control and safety of dedifferentiation is a major challenge and one about which little is yet known.
- Adult stem cells may contain more DNA abnormalities caused by sunlight, toxins and errors in making more DNA copies during the course of a lifetime.

⁴¹ Lennard, A. L. and Jackson G. H., "Science, medicine and the future: Stem cell transplantation", *BMJ*, 2000, 321:433-437.

It is a matter of debate within the scientific community whether human embryonic stem cells have a greater potential than human somatic stem cells (isolated from foetal or adult tissue). The recent reports regarding the plasticity of human somatic stem cells as described earlier in chapter 1.2, have led to the question of why embryonic stem cell research is needed if somatic stem cells are available. These issues have been exhaustively considered in many national reports from advisory bodies, ethics committees, learned societies etc. and in scientific publications. The conclusions of these reports published in the recent months have highlighted that it is too early to know what findings will come from embryonic or somatic stem cell research and which stem cells will best meet the needs of basic research and clinical application⁴².

2.5. Examining the need for new human embryonic stem cell lines.

The question whether there are already enough embryonic stem cell lines that meet the criteria, which are considered ethically acceptable by Member States, is important in the debate. Although human embryonic stem cell lines have been registered, in particular at the US National Institutes of Health Human embryonic stem cell registry (see 2.6)⁴³ several arguments have been put forward regarding the needs for derivation of new human embryonic stem cell lines⁴⁴:

- Human embryonic stem cell research is so new that scientists do not yet know if they have developed the best procedures for isolating or maintaining human ES cells. It is possible that all the current cell lines are compromised, as happened with the first mouse ES cell lines.
- Many of the human embryonic stem cell lines currently available have not been sufficiently verified to see whether they exhibit the fundamental properties that make them embryonic stem cells e.g. the six human ES cell lines from the Karolinska Institute currently at the NIH registry are not available and have not yet been fully characterized⁴⁵ (see annex C for further information).
- Most currently available human ES cell lines have been cultivated in contact with mouse cells. The contact with animal cells and serum components involves an unknown risk of contamination with viruses and other infectious agents. Therefore, such cell lines or their derivatives can not be used for transplantation to humans.

⁴² “Stem Cells: scientific progress and future research directions”, National Institutes of Health (NIH), Bethesda, USA, June 2001 <http://www.nih.gov/news/stemcell/scireport.htm>; Swiss National Advisory Commission on Biomedical Ethics: opinion on human embryonic stem cell research, June 2002; The Health Council of the Netherlands’ report on “Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells”, June 2002. <http://www.gr.nl/pdf.php?ID=429>; House of Lords Select Committee UK “Report on Stem cell research”, February 2002; <http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm>; Swedish National Council of Medical Ethics: Statement of opinion on embryonic stem cell research, 17.01.2002.

⁴³ <http://escr.nih.gov/eligibilitycriteria.html>. The US National Institute of Health (NIH) has identified 78 human embryonic stem cell lines that meet the US eligibility criteria. The availability and the stage of development and characterisation of these human ES cell lines are unclear and the NIH has now indicated 9 human ES cell lines which are available for distribution to different laboratories. (James Battery, Head of NIH panel managing stem cell research). *Science* 2003 (299) 1509. The Wisconsin Alumni Research Foundation, which owns five stem cell lines, claims that it has enough to supply all scientists in the world.

⁴⁴ e.g. The Health Council of the Netherlands’ report on “Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells”, June 2002. <http://www.gr.nl/pdf.php?ID=429>.

⁴⁵ Communication from Carlstedt-Duke, Dean of Research, Karolinska Institute, Sweden.

- Currently available human ES cell lines represent only limited amount of genetic variation. It is important to notice that cell lines with a different genetic basis can have different characteristics.
- Many of the existing embryonic stem cell lines have been patented in the US. It is important not to be in a dependent position with respect to private industry.

Annex C provides examples of the currently available human ES cell lines.

2.6. Developments regarding establishment of human stem cell banks and registries.

Human stem cell banks

The need for public stem cell banks including human embryonic stem cell has been recognised at national level both in Sweden and UK.

The British Medical Research Council (MRC) in autumn 2002, in collaboration with the Biotechnology and Biological Science Research Council (BBSRC) and with the full backing of the UK Government, took the initiative to establish the first large-scale publicly funded Stem Cell Bank worldwide. The National Institute for Biological Standards and Control (NIBSC) is hosting the UK Stem Cell Bank⁴⁶, which officially started 1 January 2003.

The general aim of the UK Stem Cell Bank will be to create an independent and competent facility to store, test and release seed stocks of existing and new stem cell lines derived from adult, foetal and embryonic human tissues. There will be two primary components in this work:

- 1) To provide stocks of well-characterised stem cell lines for use in research in the UK and abroad. These will be established under well regulated, but non-GMP, conditions and made available in order to promote fundamental research.
- 2) To provide stocks of stem cell lines prepared under GMP conditions, that could be used directly for production of human therapeutic materials.

In February 2002, the Human Fertilisation and Embryology Authority (HFEA) in the UK granted the first two licences for embryo research under the 2001 Regulation to Imperial College in London and the University of Edinburgh. The protocols approved will create human embryonic stem cell lines from embryos originally created for IVF treatment but subsequently donated for research. At the time of writing this report no human ES cell lines had as yet been derived. When generated the cell lines will be placed in the UK stem cell bank. This is a requirement of HFEA research licence.

The Karolinska Institute in Stockholm is also planning to establish a Stem Cell Bank, based on the various stem cell lines established at the Institute (about 9 human ES cell lines are expected to be available within the next 12 months). These lines will be available for other scientists worldwide⁴⁷.

Human ES cell research is also ongoing at the Sahlgrenska Academy, Gothenburg University, Sweden in collaboration with Cell Therapeutics Scandinavia, AB. The two centres are active

⁴⁶ <http://www.nibsc.ac.uk/divisions/cbi/stemcell.html>

⁴⁷ Communication from Professor Carlstedt-Duke, Dean of Research, Karolinska Institute, Sweden

in generating human ES cell lines as well as in developing differentiated normal human cells. 21 human ES cell lines have so far been established. Four of these have been fully characterized and two of these four fulfil all the criteria for self-renewal and pluripotency of human ES cells. The remaining 17 cell lines have been partially characterized⁴⁸.

Extensive human ES cell research is taking place outside the EU in particular, in the USA, Australia, Israel, Singapore, Korea and China. As far as the Commission is informed it is for the moment only the UK and Sweden that are planning to establish public stem cell banks.

The stem cell bank intends not only to provide high quality starting materials to facilitate the development of stem cell therapy, but, in providing a centralised resource for researchers, it will optimise the use of existing human embryonic stem cell lines and may reduce the use of human embryos for the development of new stem cell lines by individual teams. It will also offer the opportunity to collect stem cell lines with different immuno- phenotypes. Cell lines with the best matching phenotypes can later be selected for cell or tissue transplantation.

Human embryonic stem cell registry

The US National Institutes of Health (NIH) established in autumn 2001 an Human Embryonic Stem Cell Registry which at present lists 78 human ES cell lines that meet the eligibility criteria for Federally funded research⁴⁹. The registry indicates 14 laboratories or companies across the world, which have developed human embryonic stem cell lines. The availability of these cell lines and their level of characterisation are unclear and the NIH Human Embryonic Cell Registry has recently been updated to reflect the human ES cell lines that meet the eligibility criteria for Federally funded research and which are currently available for shipping to other laboratories⁵⁰. This list includes 9 human ES cell lines:

2 human ES cell lines from BresaGen, Inc. (a US based company)

5 human ES cell lines from ES Cell International (a company based in Singapore and Australia)

1 human ES cell line from University of California at San Francisco

1 human ES cell line from Wisconsin Alumni Research Foundation

Both the European Group on Ethics in Science and New Technologies⁵¹ and the European Group on Life Sciences⁵² have highlighted the need for a European registry of stem cell lines. In particular, the EGE called in their opinion n°16 on “Ethical aspects of patenting inventions involving human stem cells” for the creation of an EU registry of unmodified human stem cell lines.

⁴⁸ Communication from Professor Hamberger, Goteborg University, Sweden.

⁴⁹ <http://escr.nih.gov/eligibilitycriteria.html>. The following eligibility criteria must be met: (i) the derivation process has been initiated before 9 August 2001; (ii) the stem cells must have been derived from an embryo that was created for reproductive purposes but the embryo was not longer needed for those purposes; (iii) informed consent must have been obtained for the donation of the embryo; (iv) no financial inducements were provided for donation of the embryo.

⁵⁰ <http://escr.nih/>

⁵¹ http://europa.eu.int/comm/european_group_ethics/docs/avis16_en.pdf

⁵² http://europa.eu.int/comm/research/life-sciences/egls/index_en.html

“Such registry, which should include information on both embryonic stem cells and embryonic germ cell lines should be publicly accessible. Its aim would be to ensure transparency and thus facilitate access by the research community to the needed biological material for further research”⁵¹

Chapter 3: Governance of human embryonic stem cell research

Human embryonic stem cell research raises complex ethical questions. It confronts scientific progress with ethical concerns and it has triggered an intense public debate on its guiding ethical principles and limitations. The question whether it is ethically defensible to do research on embryonic stem cells can be described as a conflict between different values, between different actors' rights and obligations, or between the short- and long-term interests of different groups. On the one hand, there is interest in new knowledge that can lead to treatment of hitherto incurable diseases. On the other hand, when this research involves the use of human embryos, it raises the question of ethical values at stake and of the limits and conditions for such research⁵³. Opinions on the legitimacy of experiments using human embryos are divided according to the different ethical, philosophical, and religious traditions in which they are rooted. EU Member States have taken very different positions regarding the regulation of human embryonic stem cell research. This confirms that different views exist throughout the European Union concerning what is and what is not ethically defensible.

3.1. The ethical issues at stake

The European Group on Ethics highlighted in its Opinion No.15 regarding “Ethical aspects of human stem cell research and use”, issued 14 November 2000⁵⁴, that “the fundamental ethical principles applicable to stem cell research are:

- *The principle of respect for human dignity*
- *The principle of individual autonomy (entailing the giving of informed consent, and respect for privacy and confidentiality of personal data)*
- *The principle of justice and of beneficence (namely with regard to the improvement and protection of health)*
- *The principle of freedom of research (which is to be balanced against other fundamental principles)*
- *The principle of proportionality (including that research methods are necessary to the aims pursued and that no alternative more acceptable methods are available).*

In addition, the Group considers it important to take into account, based on a precautionary approach, the potential long-term consequences of stem cell research and use for individuals and the society.”

Concerning the creation of embryos for research purpose the EGE considered that “*the creation of embryos for the sole purpose of research raises serious concerns since it represents a further step in the instrumentalisation of human life*” and deemed “*the creation*

⁵³ Annex E - Opinion No. 15 of the European Group on Ethics regarding “Ethical aspects of human stem cell research and use”; http://europa.eu.int/comm/european_group_ethics/docs/avis15_en.pdf

⁵⁴ Annex E: Opinion No. 15 of the European Group on Ethics regarding “Ethical aspects of human stem cell research and use”; http://europa.eu.int/comm/european_group_ethics/docs/avis15_en.pdf

of embryos with gametes donated for the purpose of stem cell procurement ethically unacceptable, when spare embryos⁵⁵ represent a ready alternative source”.

Furthermore the EGE considered “ *that, at present, the creation of embryos by somatic cell nuclear transfer for research on stem cell therapy would be premature, since there is a wide field of research to be carried out with alternative sources of human stem cells (from spare embryos, foetal tissues and adult stem cells)*”.

The ethical acceptability of human embryonic stem cell research in the context of Community Framework Programme for Research

The EGE noted in the same opinion that “*in some countries embryo research is forbidden. But when this research is allowed, with the purpose of improving treatment for infertility, it is hard to see any specific argument, which would prohibit extending the scope of such research in order to develop new treatments to cure severe diseases or injuries. As in the case of research on infertility, stem cell research aims to alleviate severe human suffering. In any case, the embryos that have been used for research are required to be destroyed. Consequently, there is no argument for excluding funding of this kind of research from the Framework Programme of research of the European Union if it complies with ethical and legal requirements as defined in this programme*”.

Secondly the EGE stated, that:

“Stem cell research based on alternative sources (spare embryos, foetal tissues and adult stem cells) requires a specific Community research budget. In particular, EU funding should be devoted to testing the validity of recent discoveries about the potential of differentiation of adult stem cells. The EU should insist that the results of such research be widely disseminated and not hidden for reasons of commercial interest.

At European Union level, within the Framework Programme of research, there is a specific responsibility to provide funding for stem cell research. This implies the establishment of appropriate procedures and provision of sufficient means to permit ethical assessment not only before the launching of a project but also in monitoring its implementation.”

Principal requirements regarding human embryonic stem cell research.

Concerning the use of human supernumerary embryos as a source of stem cells the EGE stressed in their opinion that “ *the derivation of stem cells from embryonic blastocysts raises the issue of the moral status of the human embryo. In the context of European pluralism, it is up to each Member State to forbid or authorise embryo research. In the latter case, respect for human dignity requires regulation of embryo research and the provision of guarantees against risks of arbitrary experimentation and instrumentalisation of human embryos*”.

The EGE also stressed regarding stem cell research and rights of women that “*Women who undergo infertility treatment are subject to high psychological and physical strain. The group stresses the necessity to ensure that the demand for spare embryos (supernumerary embryos) and oocyte donation does not increase the burden on women*”.

⁵⁵ Spare embryos: another word for supernumerary embryos.

The EGE stressed also the importance of the following requirements regarding human embryonic stem cell research and the procurement of embryonic stem cells from supernumerary embryos:

– **Free and informed consent from the donating couple or woman.**

The EGE stated: “*Free and informed consent is required not only from the donor but also from the recipient as stated in the Group's opinion on Human Tissue Banking (21/07/1998). In each case, it is necessary to inform the donor (the woman or the couple) of the possible use of the embryonal cells for the specific purpose in question before requesting consent.*” The requirements may differ on the type of information that should be provided and on the definition of which persons should give their consent (the couple or the woman). The Charter of Fundamental Rights of the European Union recognised in article 3(2) that “*In the fields of medicine and biology the following must be respected in particular – the free and informed consent of the person concerned, according to the procedures laid down by law...*”.

– **Approval of the research by an authority.**

The EGE recommended that human ES cell research should be placed, “*in the countries where it is permitted, under strict public control by a centralised authority - following, for instance, the pattern of the UK licensing body (the Human Fertilisation and Embryology Authority)*” and provided that “*authorisations given to such research are highly selective and based on a case by case approach, while ensuring maximum transparency. This must apply whether the research in question is carried out by either the public or the private sector*”.

– **No financial gain for donation**

The EGE recommended that “*The potential for coercive pressure should not be underestimated when there are financial incentives. Embryos as well as cadaveric foetal tissue must not be bought or sold, and not even offered for sale. Measures should be taken to prevent such commercialisation*”.

The Charter of Fundamental Rights of the European Union recognised in article 3(2) that “*In the fields of medicine and biology the following must be respected in particular... the prohibition on making the human body and its parts as such a source of financial gain*”.

Article 21 of the Council of Europe Convention on Human Rights and Biomedicine specifically prohibits financial gain from all or part of the human body.

– **Anonymity of the donors and protection of the confidentiality of personal information of the donors** as it applies for donation of human biological material.

The EGE recommended that “*Steps must be taken to protect and preserve the identity of both the donor and the recipient in stem cell research and use*”. As stated in the EGE's Opinion on Human Tissue Banking (21/07/1998): “*in the interests of anonymity, it is prohibited to disclose information that could identify the donor, and the recipient. In general, the donor should not know the identity of the recipient, nor should the recipient know the identity of the donor*”. In most cases the donors will not be anonymous in the sense that the embryo could be traced back to the donor of the egg and sperm. Although the identity of the donor should normally be protected through coding and other measures to ensure confidentiality, there would still be safety and quality requirements for clinical research demanding that the link to the donors not be completely removed. Anonymity will then not be possible.

– **Transparency regarding research results.**

The EGE recommended in the context of funding stem cell research within the EU Framework Programmes for Research that *“the EU should insist that the results of such research be widely disseminated and not hidden for reasons of commercial interest”*

Concerning clinical research on human stem cells the EGE stressed the importance of the following requirements:

– **Free and informed consent of the patient and the donor**

– **Risk-benefit assessment**

“Risk-benefit assessment is crucial in stem cell research, as in any research, but is more difficult as the uncertainties are considerable given the gaps in our knowledge. Attempts to minimise the risks and increase the benefits should include optimising the strategies for safety. It is not enough to test the cultured stem cells or tissues derived from them for bacteria, viruses or toxicity. Safety and security aspects are of utmost importance in the transplantation of genetically modified cells and when stem cells are derived from somatic cells. For example, the risks that transplanted stem cells cause abnormalities or induce creation of tumours or cancer have to be assessed. It is important that the potential benefits for the patients should be taken into account but not exaggerated. The grounds of a precautionary approach need to be taken into account”.

– **Protection of the health of persons involved in clinical trials**

“The possibility that irreversible and potentially harmful changes are introduced in clinical applications of stem cell research should be minimised. Techniques enhancing the possibilities of reversibility should be used whenever possible. If, for example, genetically modified cells were encapsulated when they are transplanted in order to stimulate neural cell growth, it should be possible for the procedure to be reversed if something goes wrong.”

The opinion of the EGE regarding “Ethical aspects of human stem cell research and use” dates back to 14 November 2000, but it is still considered to be relevant. Human stem cell research and in particular human embryonic stem cell research are still in an early stage of development and therefore the fundamental ethical principles at stake and the requirements for human embryonic stem cell research are still relevant.

Chapter 3.2 provides further information regarding the requirements applied in EU Member States allowing for the import and use of human embryonic stem cells and/or the procurement of human ES cells from supernumerary embryos.

3.2. Regulations in EU Member States regarding human embryonic stem cell research⁵⁶

EU Member States have already taken very different positions regarding the regulation of human ES cell research and new legislation or regulations are being drafted or debated. Table 1 attempts to provide a comprehensive overview of the situation as of March 2003.

The following distinctions can be made:

1. Allowing for the procurement of human embryonic stem cells from supernumerary embryos by law

Finland

The medical research Act of 1999 covers the preconditions and use of human embryos up to 14 days of embryonic development. The production of human embryonic stem cells from supernumerary embryos is allowed. The laboratories that do embryo research need a licence from the National Authority for Medicolegal Affairs. An ethics committee must approve research projects. The informed consent of both gamete donors is required.

Greece

The recent law 3089/2002 on medically assisted human reproduction allows for the procurement of human embryonic stem cells from supernumerary embryos. The Act requires the informed consent of both gamete donors and no financial inducement.

The Netherlands

The Embryo Act of September 2002 allows the use of supernumerary embryos for research including isolation of embryonic stem cells from such embryos. This research requires the favourable opinion of the Central committee for research involving human subjects. The informed consent of the donor is required. The research must have the aim to lead to new insights in medical science.

Sweden

The Act of 1991 on “Measures for Purposes of Research and Treatment involving Fertilised Human Ova” and the Health and Medical Care Act (18-982:763) apply. According to the Act(1991:115), *in vitro* embryo research is legally permitted until day 14 after conception, after which the embryo must be destroyed.. After some discussion there is consensus that this legislation permits human embryonic stem cell research. A revision of the law is under discussion (see chapter 3.3)

United Kingdom

The research purposes permitted by the Human Fertilisation and Embryology Act of 1990 were extended by the “Human Fertilisation and Embryology (Research Purposes) Regulation” of 2001 to permit the use of embryos in research to increase knowledge about serious diseases and their treatment. The Human Fertilisation and Embryology Authority is

⁵⁶ European Commission, DG Research, Directorate E: Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use (last update March 2003); “Survey on the National Regulations in the European Union regarding Research on Human Embryos” - B. Gratton - published by the Secretariat of the EGE - European Commission - July 2002.

responsible for licensing research involving the creation and use of human embryos. The HFEA requires the informed consent of the donors and free donation. The first two licences for stem cell research under the 2001 Regulations were issued by HFEA in February 2002.

2. Prohibition of the procurement of embryonic stem cells from human embryos but allowing by law the import and use of human embryonic stem cell lines under certain conditions.

Germany

The Embryo protection Act of 1990 forbids any research which is not for the benefit of the concerned embryo.

A new Act ensuring protection of embryos in connection with the importation and utilisation of human embryonic stem cells – Stem Cell Act – (Stammzellgesetz – StZG) was adopted on 28 June 2002.

Concerning importation and utilisation of embryonic stem cells the act specifies in section 4 , that:

(1) The importation and utilisation of embryonic stem cells shall be prohibited.
(2) Notwithstanding para 1, the importation and utilisation of embryonic stem cells for research purposes shall be permissible under the conditions stipulated in section 6 if

1. The competent agency has satisfied itself that

- a) The embryonic stem cells were derived before 1 January 2002 in the country of origin in accordance with relevant national legislation there and are kept in culture or are subsequently stored using cryopreservation methods (embryonic stem cell line)
- b) The embryos from which they were derived have been produced by medically-assisted in vitro fertilisation in order to induce pregnancy and were definitely no longer used for this purpose and that there is no evidence that this was due to reasons inherent in the embryos themselves.
- c) No compensation or other benefit in money's worth has been granted or promised for the donation of embryos for the purpose of stem cell derivation and if

2. Other legal provisions, in particular those of the German Embryo Protection Act, do not conflict with the importation or utilisation of embryonic stem cells.

(3) Approval shall be refused if the embryonic stem cells have obviously been derived in contradiction to major principles of the German legal system. Approval may not be refused by arguing that the stem cells have been derived from human embryos.

Concerning using embryonic stem cells section 5 states:

Research involving embryonic stem cells shall not be conducted unless it has been shown by giving scientific reasons that

1. Such research serves eminent research aims to generate scientific knowledge in basic research or to increase medical knowledge for the development of diagnostic, preventive or therapeutic methods to be applied to humans and that,

2. According to the state-of-the-art of science and technology,

- a) The questions to be studied in the research project concerned have been clarified as far as possible through in vitro models using animal cells or through animal experiments and
- b) The scientific knowledge to be obtained from the research project concerned cannot be expected to be gained by using cells other than embryonic stem cells.

Concerning approval section 6 states:

1) Any importation and any utilisation of embryonic stem cells shall be subject to approval by the competent agency

2) Applications for approval must be submitted in writing. In the documents accompanying the application, the applicant shall provide the following information in particular:

1. Name and official address of the person responsible for the research project concerned,
2. A description of the research project including scientific reasons showing that the research project meets the requirements set forth in section 5 above,
3. A documentation concerning the embryonic stem cells to be imported or used showing that the requirements set forth in no. 1 of para 2 of section 4 above have been complied with or equivalent evidence that
 - a) The embryonic stem cells to be imported or used are identical with those registered in a scientifically recognised, publicly accessible registry maintained by government agencies or agencies authorised by the government and that,
 - b) By way of such registration, the requirements set forth in no. 1 of para 2 of section 4 above have been complied with.

3) The competent agency shall immediately acknowledge in writing receipt of the application and the attached documents. At the same time, the agency shall request the opinion of the Central Ethics Commission on Stem Cell Research. On receipt of the opinion, the agency shall notify the applicant of the content and the date of the opinion adopted by the Central Ethics Commission on Stem Cell Research.

4) Approval shall be given if:

1. The requirements set forth in para 2 of section 4 above have been complied with,
2. The requirements set forth in section 5 above have been complied with and, accordingly, the research project is ethically acceptable, and if
3. An opinion by the Central Ethics Commission on Stem Cell Research has been submitted following a request by the competent agency to this effect.

5) If the application, complete with documentation, and the opinion of the Central Ethics Commission on Stem Cell Research have been received, the agency shall decide in writing on the application within a period of two months. In doing so, the agency shall consider the opinion adopted by the Central Ethics Commission on Stem Cell Research, the agency shall give its reasons in writing.

6) Approval can be limited in time or by imposing obligations to the extent necessary for complying with or continuing to meet the approval requirements pursuant to para 4 above. If, following approval, events occur which conflict with the granting of approval, approval can be withdrawn wholly or in part with effect in the future or be limited in time or be made dependent on the fulfilment of conditions to the extent necessary for complying with or continuing to meet the approval requirements set forth in para 4 above. Any objection to or action for rescission of withdrawal or revocation of approval shall not suspend the effect of the decision.

The first authorisation to import human embryonic stem cell lines was given in December 2002.

3. Prohibition of the procurement of embryonic stem cells from human supernumerary embryos.

Austria

The Austrian Reproductive Medicine Act of 1992 states that cells capable of development may only be used for medical assisted reproduction. According to the interpretation of the Reproductive Medicine Act the procurement of stem cells from embryonic tissues is prohibited. The use of imported human ES cells is not explicitly prohibited and discussion regarding authorisation is still ongoing.

Denmark

The Act on Medically Assisted Procreation from 1997 only allows research intending to improve *in vitro* fertilisation technique or pre-implantation diagnosis techniques. Therefore, the isolation of human ES cells from supernumerary embryos is forbidden. The importation of

human ES cells is not explicitly forbidden. However, the Danish government will give its opinion on human embryonic stem cell research in spring 2003, and has recommended that no research with human ES cell lines should be commenced until the government has presented its decision to Parliament (See also chapter 3.3)

France

Under the Bioethics Law of 1994, research on human embryos *in vitro* is forbidden except for research which does not harm the embryo. The import and use of human ES cell lines derived from supernumerary embryos is not explicitly prohibited but the authorisation is still under discussion. A revision of the Bioethics law is under discussion (see chapter 3.3)

Ireland

There is no legislation dealing with research on embryos. However, the Irish constitution of 1937 (as amended in 1983) provides that “the State acknowledges the right to life of the unborn and, with due regard to the equal right to life of the mother, guarantees in its laws to respect, and, as far as practicable, by its laws to defend and vindicate that right”.

Spain

The laws of 1988 on Assisted Reproduction Techniques and on donation and use of embryos and foetuses or their cells authorises research on *in vitro* human embryos biologically non-viable under certain conditions. There is no clear interpretation of the concept of a non-viable embryo. Concerning viable human embryos, only research for the benefit of the concerned embryos is allowed. A revision of the law is under discussion (see chapter 3.3)

4. No specific legislation regarding human embryo research

Belgium

The Royal decree of 1999 fixes the requirement for *in vitro* fertilisation centres. There is no specific legislation on research but the current practice is that research must only be performed at *in vitro* fertilisation centres following approval from the local ethics committees. A new bill is under discussion (see chapter 3.3).

Italy

Italy has not enacted legislation.

The Italian National Bioethics Committee has adopted an advice on “the therapeutic use of stem cells”. A majority of the members considered the research on human supernumerary embryos for the derivation of human ES cells as legitimate.

Luxembourg

There is no legislation covering human embryo research.

Portugal

Portugal has not enacted legislation but has ratified the Convention of the Council of Europe on Human Rights and Biomedicine signed in Oviedo on 4 April 1997, which prohibit the creation of human embryos for research purposes and has in addition the protocol on the prohibition of human cloning. The National Council of Ethics has adopted opinions covering these questions. It has taken the position that research with no benefit for the embryo concerned is not legitimated. The Ministry of Science has created in 2002 a Steering

Committee for the preparation of a law on research on human embryos including human ES cells.

5. Allowing for the creation of human embryos for stem cell procurement by law

UK is for the moment the only Member State with a specific law that permits the creation of human embryos by fertilisation of an egg with a sperm or by somatic cell nuclear transfer. The 1990 Act and the 2001 Regulation (see above) allow for the isolation of stem cells for any of the 8 research purposes set out in the law.

The Dutch Embryo Act of 2002 announces, as a general principle, the prohibition of the creation of human embryos solely for research purposes. However, this ban is not irreversible and could be lifted by Royal Decree within five years after the coming into force of the Act.

6. Prohibition of the creation of human embryos for research purposes and for the procurement of stem cells by law or by ratification of the Convention of the Council of Europe on Human rights and Biomedicine signed in Oviedo on 4 April 1997

The creation of human embryos for research purposes and for the procurement of embryonic stem cells is for the moment prohibited in Austria, Denmark, Finland, France, Germany, Greece, Ireland, Netherlands, Portugal and Spain.

REGULATIONS IN EU MEMBER STATES REGARDING HUMAN EMBRYONIC STEM CELL RESEARCH															
	AT	BE	DK	DE	ES	FI	FR	GR	IE	IT	LU	NL	PT	SE	UK
Allowing for the procurement of human embryonic stem cells from supernumerary embryos by law						X		X				X		X	X
Prohibition of the procurement of embryonic stem cells from human embryos but allowing by law for the importation of human embryonic stem cell lines				X											
Prohibition of the procurement of embryonic stem cells from human embryos	X		X		X		X		X						
No specific legislation regarding human embryo research		X								X	X		X		
Allowing for the creation of human embryos for stem cell procurement by law															X
Prohibition of the creation of human embryos for research purposes and for the procurement of stem cells by law or by ratification of the Convention of the Council of Europe on Human rights and Biomedicine signed in Oviedo on 4 April 1997	X		X	X	X	X	X	X	X			X	X		

3.3. New regulations under discussion in EU Member States⁵⁷

Belgium

A bill on research on human embryos *in vitro* was approved by the Belgian Senate in 2002 and is now under discussion in the Parliament. The draft legislation proposes to authorise the procurement of embryonic stem cells from supernumerary embryos under certain conditions and the creation of a “Federal Commission for scientific medical research on embryos *in vitro*”.

The bill also foresees to allow for the creation of human embryos for research purposes including by means of somatic cell nuclear transfer.

Article 3 proposes to allow research on human embryos *in vitro* under the following conditions:

- research for therapeutic purposes
- based on recent scientific knowledge
- carried by a registered laboratory
- embryos up to 14 days of development
- no alternative method of research as effective
- the consent of the donors

In addition the research is controlled at the local and federal levels.

Denmark

A revision of the current legislation to allow for the procurement of human ES cells from supernumerary embryos is under discussion.

France

A revision of the Bioethics Law of 1994 has been approved by the Senate in January 2003 and should be discussed by the Parliament in the first semester of 2003. It proposes to allow for research on supernumerary human embryos including the procurement of human ES cells for 5 years under certain conditions. A central authorising body will be created.

The proposed revision of the Bioethics law (as amended by the Senate in January 2003) prohibits human embryo research but includes a derogation for five years allowing for research on supernumerary human embryos including the procurement of human ES cells under the following conditions:

- the research should have the potential to lead to major therapeutic advances and only be undertaken if there is no alternative method of comparable effectiveness available;
- the embryos must derive from an *in vitro* fertilisation, in the context of a medically assisted reproduction (supernumerary embryos);
- written consent of the couple from which the embryos are issued;
- authorisation by a central body to be created.

The proposed bill will also allow the import of foetal or embryonic cells or tissues after prior authorisation by the central body.

⁵⁷ European Commission, DG Research, Directorate E: Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use (last update March 2003).

Italy

A law on *in vitro* fertilisation is under discussion. The Ministry of Health recently produced a report about the banks conserving embryos and gametes.

Portugal

A committee has been established in Portugal for the preparation of a law on human embryo and human ES cell research.

Spain

A revision of the current legislation is under discussion.

In 1998 the National Committee for Human Artificial Reproduction was created. In its second opinion, delivered in 2002, it advised to conduct human embryonic stem cell research using as a source supernumerary embryos, estimated in Spain to be over 30 000.

The Ethics Advisory Committee for Scientific and Technological Research was established in April 2002 and gave in February 2003 its first opinion on research on stem cells. It recommended to the government that research on both adult and embryonic stem cells should be implemented; that the legislation should be modified to allow the isolation of human embryonic stem cells from supernumerary embryos under the following condition: The parents' informed consent or, if this is not possible, the permission of the Centre of Assisted Reproduction in charge of keeping the embryos according to the regulation in force. The investigation must have the aim of alleviating human suffering and not just economic ends. It must be exclusively done by working groups with a proved experience in this field. The protocol of investigation must be previously evaluated by Ethics Committees and it must be under their exhaustive control. Therefore, the control and supervision of these investigations by a national committee is recommended.

Sweden

A revision of the current legislation is under discussion.

The Parliamentary Committee on Genetic Integrity proposed, in their report published 29 January 2003, not to implement a general prohibition against producing fertilised eggs for research purposes. It is the opinion of the Committee that such production must take place in order for research to be carried out on infertility and the development of the fertilised egg etc. It is not possible to set a legal limit with sufficient clarity that would delineate what, on the contrary, would be forbidden. This delineation should rather be done on a case-by-case basis within the framework of ethics review of research. It should also be noted, however, that in the view of the Committee the creation of embryos by transfer of somatic cell nuclei (so-called therapeutic cloning) should be treated in the same way and thus in principle be allowed.

3.4. Regulations in some non-EU countries regarding human embryonic stem cell research⁵⁸

Countries acceding to the EU:

Cyprus, Czech Republic, Estonia, Hungary, Lithuania, Slovak Republic, Slovenia have ratified the Convention of the Council of Europe on biomedicine and human rights⁵⁹.

No specific regulations regarding human embryonic stem cell research have a present been implemented in the countries acceding to the EU.

Cyprus:

Cyprus has ratified the Convention of the Council of Europe on biomedicine and human rights. There is no specific regulation regarding human embryo research.

Czech Republic:

Czech Republic has ratified the Convention of the Council of Europe on biomedicine and human rights. There is no specific regulation regarding human embryo research, but a law is under preparation.

Estonia

Under the Embryo Protection and Artificial Fertilisation Act of 1997 the use of supernumerary human embryos for scientific research is permitted if informed consent has been obtained.

Hungary

Under the Act of 1997 on Health Care (Chapter IX), research on human embryos is permitted if these are supernumerary embryos and not older than 14 days. This research should be approved by the Committee for Human Reproduction.

Latvia

In January 2002, Latvia has adopted a Law on Reproductive and Sexual Health. Research on human embryos may be authorised if the conditions are met: absence of alternative method, positive assessment of the scientific merit and ethical acceptability by an authorised body and informed consent of the donors.

Lithuania

The Law on biomedical research adopted in 2000, allows only observational studies of human embryos.

Malta

There is no specific regulation regarding human embryo research.

⁵⁸ European Commission, DG Research, Directorate E: Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use (last update March 2003); "Candidate Countries legislation related to ethical issues in science and research" Proceedings of the workshop of 8-10 December 2002 - Brussels - organised by the European Commission - DG Research - Unit C3 - Ethics and Science"; "Use of embryonic stem cells for therapeutic research"- Report of International Bioethics Committee – UNESCO – 6 April 2001.

⁵⁹ <http://conventions.coe.int/treaty/en/treaties/html/164.htm>

Poland

Under the Physician profession's Act of 1996, human embryos may not be used for non-therapeutic research.

Slovak Republic

The Slovak Republic's signing and ratifying the *Convention on Human Rights and Biomedicine* and the *Additional Protocol on the Prohibition of Cloning of the Human Beings*, already implemented in the national legislation, together with the older provisions contained in law No. 277/1994 on health care, especially the prohibition of the "non-therapeutic research" to be performed on human embryos and fetuses, were interpreted recently as effectively banning all human cloning (the so-called "reproductive" as well as "therapeutic").

There is a government proposal to amend the Slovak Republic's Penal Code accordingly - i.e. making human cloning a penal offence in the Slovak Republic (relevant wording being taken basically from the *Protocol*, and the legislature implementing it in the Slovak Republic).

Slovenia

The law on medically assisted reproduction prohibits the creation of embryos for research purposes and cloning of embryos and the use of *in vitro* fertilization for any purpose other than the birth of a child. The Law on Medically assisted reproduction imposes strict conditions for the use of supernumerary embryos in research. Research can be performed on embryos that are not suitable for reproduction or storage, or on those at the end of the storage period which would be destroyed. Embryos should not be older than 14 days.

The authorization of the National Medical Ethics committee should be obtained.

Other countries:

In Canada and USA there is no federal law regulating research on human embryos and/or the derivation of human embryonic stem cells. The House of Commons in Canada is discussing a draft law, which would regulate such research and allow for the procurement of human ES cells from supernumerary embryos.

On 9 August, 2001, the President of the United States announced⁶⁰ his decision to allow Federal funds to be used for research on existing human embryonic stem cell lines as long as prior to his announcement (1) the derivation process (which commences with the removal of the inner cell mass from the blastocyst) had already been initiated and (2) the embryo from which the stem cell lines was derived no longer had the possibility of development as a human being.

In addition, the President established the following criteria that must be met:

- The stem cells must have been derived from an embryo that was created for reproductive purposes;
- The embryo was no longer needed for these purposes;
- Informed consent must have been obtained for the donation of the embryo;
- No financial inducements were provided for donation.

The National Institutes of Health have implemented the above rules by setting a strategic vision for research using stem cells, including:

⁶⁰ <http://escr.nih.gov/eligibilitycriteria.html>

- Creation of the Human Embryonic Stem cells Registry, which list the human embryonic stem cells that meet the eligibility criteria,
- Promoting the number of researchers with expertise in stem cell research. The NIH recognised this as one of the key factors to allow stem cell research to move forward and is currently soliciting grant applications to support training courses to teach researchers how best to grow existing banked stem cells into useful lines.
- A number of initiatives to facilitate research on all types of stem cells. In particular, the NIH continues to support research on developing the therapeutic potential of adult stem cells.

New federal legislation is under debate in the US Congress. The State of California has passed a law, in September 2002, allowing the procurement of human embryonic stem cells from supernumerary embryos. New legislation authorising the procurement of human ES cells from supernumerary embryos is under discussion in the States of New Jersey and Massachusetts.

In Australia a new law is under discussion to allow for the derivation of human ES cells from supernumerary embryos.

Laboratories in Singapore, Taiwan, South Korea, China... are actively conducting human ES cell research. Legislation regarding this research is under discussion in some of these countries.

Annex D provides further information regarding provisions in non-EU countries relating to human embryonic stem cell research.

3.5. Governance of stem cell research in the context of FP6

As stated in the Treaty of the European Union, article 6:

“1. The Union is founded on the principles of liberty, democracy, respect for human rights and fundamental freedom, and the rule of law, principles which are common to the Member States.

2. The Union shall respect fundamental rights, as guaranteed by the European Convention for the protection of Human Rights and Fundamental Freedoms signed in Rome on 4 November 1950 and as they result from the constitutional traditions common to the Member States, as general principles of Community law.

3. The Union shall respect the national identities of its Member States.

4. The Union shall provide itself with the means necessary to attain its objectives and carry through its policies.”

In accordance with the EU Treaty, each Member State retains its full prerogative to legislate on ethical matters. At the level of the Community, ethical principles have been defined with regard to the funding of research under the research Framework Programme.

As far as FP6 is concerned, the following ethical principles have been established:

The decision No. 1513/2002/EC of the European Parliament and of the Council of 27 June 2002 concerning the sixth framework programme of the European Community for research,

technological development and demonstration activities, contributing to the creation of the European Research Area and to innovation (2002 to 2006) stipulates among others that⁶¹:

- *“Fundamental ethical principles are to be respected. These include the principles reflected in the Charter of fundamental rights of the EU including the protection of human dignity and human life...”*

The Charter of Fundamental Rights of the European Union, proclaimed in Nice, France, on 7 December 2000, explicitly prohibits eugenic practices and reproductive cloning, but does not comment explicitly on embryo research (article 3)

- ... *“in accordance with relevant international conventions and codes of conduct, e.g. ... the Convention of the Council of Europe on Human Rights and Biomedicine signed in Oviedo on 4 April 1997, and the Additional Protocol on the Prohibition of Cloning Human Beings signed in Paris on 12 January 1998”*

The Council of Europe’s Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine of 1997⁶² does not resolve the matter of the permissibility of embryo research and leaves every country responsibility for legislating on this matter, while stipulating two conditions: the prohibition of producing human embryos for research purposes and the adoption of rules designed to assure adequate protection for the embryo⁶³. An Additional Protocol to the Convention on the Prohibition of Cloning Human Beings was approved in 1998 and took effect on 3 January 2001 in thirteen Member States of the Council of Europe⁶⁴.

- *“... in accordance with Community law”*

Some EU Directives are relevant for human ES cell research. For instance, the Directive 2001/20/EC on the approximation of laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medical products for human use establishes among others that “written authorisation is required before commencing clinical trials involving medical products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms” (ref. article 9.6). The Directive 98/44 on the legal protection of biotechnological inventions, adopted on 6 July 1998, stipulates that “processes for cloning human beings” and “uses of human embryos for industrial or commercial purposes...shall be considered unpatentable”.

The draft Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells is relevant in relation to the clinical use (including clinical trial) of human ES cells and their derivatives.

- *“in accordance with legislation, regulations and ethical guidelines in countries where the research will be carried out.”*

⁶¹ OJ L232of 29.8.2002 p.4.

⁶² <http://conventions.coe.int/treaty/en/treaties/html/164.htm>

⁶³ Fifteen countries have ratified the European Convention: Cyprus, Czech Republic, Denmark, Estonia, Georgia, Greece, Hungary, Lithuania, Moldova, Portugal, Romania, San Marino, the Slovak Republic, Slovenia and Spain.

⁶⁴ Cyprus, Czech Republic, Estonia, Georgia, Greece, Hungary, Lithuania, Moldova, Portugal, Romania, the Slovak Republic, Slovenia and Spain.

These ethical principles have been further specified in the Council decision of 30 September 2002 adopting a specific programme for research, technological development and demonstration: “Integrating and strengthening the European Research Area” (2002-2006)⁶⁵.

It is stated that:

- *The following fields of research shall not be financed under this programme:*
 - *research activities aiming at human cloning for reproductive purposes*
 - *research activity intended to modify the genetic heritage of human beings which could make such change heritable⁶⁶*
 - *research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer (often referred to as therapeutic cloning).*
- *In addition, funding of research activities that are prohibited in all the Member States is in all circumstances excluded.*
- *In compliance with the principle of subsidiarity and the diversity of approaches existing in Europe, participants in research projects must conform to current legislation, regulations and ethical rules in the countries where the research will be carried out. In any case, national provisions apply and no research forbidden in any given Member State will be supported by Community funding in that Member State.*
- *Where appropriate, participants in research projects must seek the approval of the relevant national or local ethics committees prior to the start of the RTD activities.*
- *An ethical review will be implemented systematically by the Commission for proposals dealing with ethically sensitive issues, in particular proposals involving the use of human embryos and human embryonic stem cells.*

Research proposals, which raise sensitive ethical concerns, undergo an ethical review at EC level before funding. The proposals are reviewed by an independent, multidisciplinary and transnational panel, which is established by the DG Research in relation to each call for proposals. The review is conducted independently of the specific research programme and separated from the scientific evaluation. The ethical review aims to ensure that the proposers have identified all ethical issues, which the proposed research may raise, have taken the appropriate measures to fulfil all ethical and/or legal requirements at national and European level and finally have respected the ethical framework defined for the 6th Framework programme for Research.

- *Any research involving the use of human embryos and human embryonic stem cells, following the ethical review mentioned above, will be submitted to a Regulatory Committee.*
- *In specific cases, an ethical review may take place during the implementation of the project.*

⁶⁵ OJ L294 of 29.10.2002, p. 8.

⁶⁶ Research relating to cancer treatment of the gonads can be financed.

- *As stated in the Council minutes of 30 September 2002⁶⁷ “The Council and the Commission agree that detailed implementing provisions concerning research activities involving the use of human embryos and human embryonic stem cells...shall be established by 31 December 2003”.*

The Commission will during that period...not propose to fund such research, with the exception of banked or isolated human embryonic stem cells in culture.

3.6. Social scrutiny and dialogue

There are significant differences in national attitudes towards specific techniques and areas of research. In particular, human embryonic stem cell research has recently provoked intense public and political debate. As the life sciences and biotechnology develop, they contribute considerably to securing welfare on the personal and societal levels as well as to creating new opportunities for our economies. At the same time, the general public is increasingly concerned about the social and ethical consequences of these advances in knowledge and techniques as well as about the conditions forming the choices made in these fields.

The EGE stressed in its opinion regarding “Ethical aspects of human stem cell research and use” *there is a need for continuing dialogue and education to promote the participation of citizens, including patients, in scientific governance, namely in social choices created by new scientific developments”.*

The need for public dialogue on scientific advances and new technologies has also been highlighted in both the Commission’s communication on “Life Sciences and Biotechnology”, published on 27 January 2002⁶⁸ and the Commission’s action plan on “Science and Society” published in December 2001⁶⁹.

In this connection, the European Group on Life Sciences⁷⁰, set up by the European Research Commissioner Philippe Busquin, organised on 18-19 December 2001, a forum entitled “Stem cells: therapies for the future?”. The aim was to offer a platform at European level for a debate between, on one side, scientists and experts concerned with the feasibility and consequences of stem cell research and, on the other side, a wide range of representatives of society. More than 600 people participated in the event.⁷¹ Much of the public discussion that took place, both at the forum itself and by e-mail exchanges concentrated on ethical issues, particularly those relating to the use of human embryos.

As for any new potential treatment, the promises of stem cell research may create amongst patients suffering from incurable diseases and their families, high and sometimes unrealistic expectations from science and the imperative of treatment for whatever disease. Many negative research results are not published and may lead to an unbalanced presentation in the media and ultimately affect the dialogue in society. Since failure to deliver the promised cures will have very negative impact on the perception of science by the public, it is vital to communicate the state of the art and future possibilities in a most honest and realistic way. The more science is able to keep its promises, the more it will receive the public recognition necessary to reconcile the expansion of knowledge with social progress. There is a social role

⁶⁷ Annex F.

⁶⁸ <http://europa.eu.int/comm/biotechnology>

⁶⁹ <http://www.cordis.lu/science-society>

⁷⁰ <http://europa.eu.int/comm/research/quality-of-life/genetics/en/13.html>

⁷¹ <http://europa.eu.int/comm/research/quality-of-life/stemcells.html>

of the scientist and a responsibility on his/her side to communicate the advancement of science in a meaningful way.

In the Commission's Communication (COM(2003)96 final) on "Life Sciences and Biotechnology – A strategy for Europe: Progress report and future orientations" published 5 March 2003 the Commission calls for initiatives that integrate discussion platforms as a strategic element for research projects funded under FP6. The ethical and social debate should be a natural part of the research and development process, involving society as much as possible.

Chapter 4: Socio-economic aspects

Biotechnology is an area with strong potential economic growth and welfare creation. Stem cell research plays a part in its development. Although considerable sums are available for investment in stem cell research, commercial returns on such investments are for the moment modest. This reflects the fact that most of this work is still at the basic research stage. Thus commercial interests are trying to position themselves for profitability in the future, but still face uncertain research prospects, therapeutic possibilities and the development of a regulatory environment, the latter largely influenced by ethical issues and public concerns.

Regarding the exploitation of results of the stem cell research, many of the collaborations in this area with industry involve small, dedicated firms rather than large pharmaceutical companies. Small firms appear to play a key role in transferring technology from the science base into industry. A number of start-up companies have been created as spin-offs from academia in the sector.

In 2001 about 30 public and private biotechnology firms were doing stem cells research and about a dozen are currently investigating the potential of both somatic and embryonic stem cells. Few, if any, companies are investing solely in human embryonic stem cell research. According to the Gilder Biotech report June 2001 the venture capital community is at present giving preference to human somatic stem cells, which are reported to be closer to therapeutic application than human embryonic stem cells⁷².

The companies are concerned with the use of stem cells including human embryonic stem cells for:

- **Novel stem cell based therapies:** direct stem cell transplantation, transplantation of stem cell derived differentiated cells, stimulation of the body's own stem cells via e.g. growth factors or stem cells in gene therapy.
- **Drug discovery:** use of stem cells for drug screening
- **Services and technologies:** screening, isolation of stem cells, preparation and large scale culture of stem cells, storage of stem cells.

One of the current framework conditions affecting stem cell research and commercialisation of stem cells therapies is the patenting of human ES cells and their derivatives. On the one hand patent rights are necessary to protect and secure industry's huge investments to support innovative research and development. On the other hand academic research is stimulated by having free and open access to these cell lines, as they are essential starting materials for their research. Some scientists consider that human embryonic stem cell lines should not be patented at all. The debate on this issue is intense and includes the ethical dimension of this

⁷² Gilder Biotech report, The American Spectator, June 2001, "Adult cells do it better"; <http://www.gilderbiotech.com/ArticlesByScott/Op%20Ed/AdultCells.htm>

research. The European Group on Ethics⁷³ in Science and New Technologies (EGE) recommended in their opinion No.16 on patenting of human stem cells that:

Isolated stem cells, which have not been modified do not, as product, fulfil the legal requirements, especially with regards to industrial applications, to be seen as patentable. In addition, such isolated cells are so close to the human body, to the foetus or to the embryo they have been isolated from, that their patenting may be considered as a form of commercialisation of the human body.

When unmodified stem cell lines are established, they can hardly be considered as a patentable product. Such unmodified stem cell lines do not have indeed a specific use but a very large range of potential undescribed uses. Therefore, to patent such unmodified stem cell lines would also lead to too broad patents.

Therefore only stem cell lines which have been modified by in vitro treatments or genetically modified so that they have acquired characteristics for specific industrial application, fulfil the legal requirements for patentability.

As to the patentability of processes involving human stem cells, whatever their source, there is no specific ethical obstacle, in so far as they fulfil the requirements of patentability (novelty, inventive step and industrial application).

Directive 98/44 on the legal protection of biotechnological inventions, adopted on 6 July 1998, establishes that an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element. Furthermore, the directive obliges Member States to consider unpatentable inventions where their commercial exploitation would be contrary to order public or morality. The processes for cloning human beings and uses of human embryos for industrial or commercial purposes are in particular excluded from patentability.

The Commission published on 7 October 2002, the first annual report (provided for in article 16c of this Directive) on the implications of patent law for biotechnology and genetic engineering. The report raised the issue related to patentability of human stem cells and cells lines obtained from them.

In view of the preparation of future reports provided for in Article 16c of the directive the Commission has set up a group of eminent experts from science, law, and economics, and representatives from the European Patent Office (EPO) and the World Intellectual Property Organisation (WIPO). The group's mandate is to analyse important issues surrounding biotechnological inventions. It will not touch upon ethical issues, which are the mandate of the European Group on Ethics, but will focus more on legal and technical aspects and on the mutual impact of the legal framework and the research and innovation area. In this light, one of the issues identified and which will be further discussed by the expert committee will be the patentability of human stem cells and cell lines derived from them.

The "16c expert group" will meet in May 2003 to discuss patenting of products and methods involving human embryonic stem cell and human ES derivatives. The report of the 16c expert group will be published at the same time as the 2003 annual monitoring report of the Commission is delivered, towards the end of the year.

⁷³ http://europa.eu.int/comm/european_group_ethics/docs/avis16_en.pdf

While many of the demonstrations of the potential of stem cell research have arisen from academia, the development of this potential i.e. into therapeutic products requires industrial and commercial inputs. For example, industrial involvement will be needed for large scale and good manufacturing production of cell lines, to support multicentre clinical trials, marketing, distribution etc.

GLOSSARY

Adult stem cell: a stem cell derived from the tissues or organs of an organism after birth (in contrast to embryonic or foetal stem cells)

Blastocyst: a hollow ball of 50-100 cells reached after about 5 days embryonic development. The blastocyst consists of a sphere made up of an outer layer of cells (the trophoctoderm), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass)

Cell culture: growth of cells in vitro on an artificial environment

Cell line: cells of common descent continuously cultured in the laboratory is referred to as a cell line

Chromosomes: the carrier of genes, the hereditary information which resides in DNA

Clone: a cell or organism derived from and genetically identical to another cell or organism

Cloning: creating an organism that is genetically identical to another organism, or a cell that is genetically identical to another cell provided that the so-called mother and daughter cells are subsequently separated (see also reproductive and therapeutic cloning)

Cloning by somatic cell nuclear transfer: involves replacing an egg's nucleus with the nucleus of the adult cell to be cloned (or from an embryo or foetus) and then activating the egg's further development without fertilisation. The egg genetically reprogrammes the transferred nucleus, enabling it to direct development of a whole new organism (**Reproductive cloning by cell nuclear transfer**).

OR the development is stopped at the blastocyst stage and embryonic stem cells are derived from the inner cell mass. These stem cells would be differentiated into desired tissue using a cocktail of various growth and differentiation factors. The generated tissue/cells could then be transplanted into the original donor of the nucleus avoiding rejection (**Therapeutic cloning by cell nuclear transfer**).

Culture medium: the broth that covers cells in a culture dish, which contains nutrients to feed the cells as well as other growth factors that may be added to direct desired changes in the cells

Dedifferentiation: the process of inducing a specialised cell to revert towards less differentiated cell.

Differentiation: the process whereby an unspecialized cell acquires the features of a specialised cell such as a heart, liver, or muscle cell.

DNA: deoxyribonucleic acid, the genetic material; it is composed of long double stranded chains of nucleotides, the basis of genetics

Embryo: in humans, the developing organism from the time of fertilization until the end of the eighth week of gestation, when it becomes known as a foetus.

Early embryo: the term “early embryos” covers stages of the development up to the appearance of the primitive streak e. g. until 14 days after fertilisation.

Embryonic germ cell: embryonic germ cells are isolated from the primordial germ cells of the gonadal ridge of the 5-10 weeks foetus.

Embryonic stem cell line: embryonic stem cells, which have been cultured under *in vitro* conditions that allow proliferation without differentiation for months to years

Feeder layer: cells used in co-culture to maintain pluripotent stem cells

Fertilization: the process whereby male and female gametes unite

Foetus: a developing human from eight weeks after conception to birth

Foetal stem cell: a stem cell derived from foetal tissue (in biological terms « embryo » covers all stages of development up to eight weeks of pregnancy, from then on the term « foetus » is used). A distinction is drawn between the foetal germ cells, from which the gametes develop, and the remaining foetal stem cells, which are the foetal somatic cells

Gamete: the male sperm or female egg

Gene: a functional unit of heredity that is a segment of DNA located in a specific site on a chromosome. A gene directs the formation of an enzyme or other protein.

Germ cells: ova and sperm, and their precursors

Haematopoietic stem cell: a stem cell from which all red and white blood cells develop

Human embryonic stem cell: pluripotent stem cell derived from the inner cell mass of the blastocyst

Implantation: the embedding of a blastocyst in the wall of the uterus. In humans implantation takes place at day 8 after fertilization.

In vitro and in vivo: outside and inside the body; *in vitro* (literally, in glass) generally means in the laboratory

In vitro fertilization: the fertilization of an egg by a sperm outside the body

Multipotent: Multipotent stem cells are those capable to give rise to several different types of specialised cells constituting a specific tissue or organ.

Oocyte: the female egg

Plasticity: the ability of stem cells from one tissue to generate the differentiated cell types of another tissue

Pluripotent stem cell: a single pluripotent stem cell has the ability to give rise to types of cells that develop from the three germ layers (mesoderm, endoderm and ectoderm) from which all the cells of the body arise. Pluripotent stem cells have the potential to generate into every cell type in the body, but cannot develop into a embryo on their own.

Pre-implantation embryo: is an embryo in the stage prior to implantation in the wall of the uterus ; an embryo cannot develop beyond the blastocyst stage without implantation into the womb.

Primitive streak: a collection of cells which appears at about 14 days after fertilisation from which the heart, blood and the central nervous system develops

Proliferation: expansion of a population of cells by the continuous division of single cells into two identical daughter cells

Redifferentiation: the process of inducing a dedifferentiated cell to differentiate into a (different) specialised cell type

Somatic cell: cell of the body other than egg or sperm

Somatic stem cell: an undifferentiated cell found among differentiated cells in a tissue or organ, which can renew itself and can differentiate to yield the major specialised cell types of the tissue or organ.

Somatic cell nuclear transfer: the transfer of a cell nucleus to an egg (or another cell) from which the nucleus has been removed..

Supernumerary embryo or spare embryo: an embryo created by means of *in vitro* fertilisation (IVF) for the purpose of assisted reproduction but subsequently not used for it.

Totipotent: At two to three days after fertilisation, an embryo consists of identical cells, which are **totipotent**. That is to say that each could give rise to an embryo on its own producing for example identical twins or quadruplets. They are totally unspecialised and have the capacity to differentiate into any of the cells which will constitute the foetus as well as the placenta and membranes around the foetus.

Transdifferentiation: the observation that stem cells from one tissue may be able to differentiate into cells of another tissue

Undifferentiated: not having changed to become a specialized cell type

ANNEXES

ANNEX A: Biology of human development

The development of the embryo is a continual process of change, which can be described in terms of the following seven stages:

1. Day 0: Fertilisation

The female egg (“oocyte”) is fertilised by the male sperm. The egg and sperm each carry half the genes of a normal cell. The process of fertilisation consists of a number of steps, which ultimately result in a single cell, the “**zygote**”. The zygote contains all the genes necessary for the development of an individual, half derived from the mother and half from the father. A very small proportion of genes is contained in the mitochondria and is inherited exclusively from the mother.

2. Day 3-4:

Up to **the fourth cell stage** at day 3-4 all the cells are essentially identical and all are thought to have the potential, if placed in the right environment, to develop into an individual – the cells are “totipotent” (i.e. they have the capacity to develop into all type of cells needed for human development including the extra-embryonic tissues such as the placenta and the umbilical cord). Indeed, identical twins can result from the splitting of the cells at this early stage: they are genetically identical as a result of developing from the same fertilised egg (identical twins can arise later i.e. up to 14 days).

3. Days 4-5: Morula Stage

At four to five days after fertilisation (morula stage), the embryo is still made up of unspecialised embryonic cells, but these seems no longer to have the potential to give raise to an embryo on their own.

4. Days 5-7: Blastocyst stage

At day 5 after fertilisation the cells constituting the embryo start to differentiate into inner and outer cells. The **outer cells** go on to develop into non-embryonic tissues such as the placenta or umbilical cord. **The inner cell mass** will give rise to the embryo itself. If these inner cells are isolated and grown in the presence of certain chemical substances (growth factors), pluripotent embryonic stem cells (ES cells) can be derived. The ES cells, which have the potential to generate into the various cell type in the body (more than 200 types are known), are referred to as “pluripotent”.

A pre-implantation embryo is an embryo in the stage prior to implantation in the wall of the uterus; an embryo cannot develop beyond the blastocyst stage without implantation into the uterus.

5. Day 8: Implantation stage

About day 8 after fertilisation implantation of the blastocyst in the womb takes place. If implantation does not take place, the blastocyst does not develop, as it will lack specific

biochemical signals and nutrients from the mother, which are required for further development. A substantial proportion of the human embryos – many estimate it as high as 75 per cent – are naturally lost before implantation. At this stage the cells are still relatively undifferentiated and there is no trace of human structure such as a nervous system.

6. Days 14-21: Gastrula stage

At about 14 days after fertilisation, following implantation, the early embryo consists of about 2000 cells. It is only at this stage that the cells begin to become differentiated into more specialised cell types. The “primitive streak”, which gives rise to heart and blood, and from which the central nervous system develops, begins to appear at day 15. By the end of the third week of embryonic development the evolving organism consists of three different cell layers, the ectoderm, mesoderm and endoderm. Each cell layer is “programmed” to give rise to defined tissues and organs. The embryonic “outer” layer, or ectoderm, gives rise to the following tissues: central nervous system (brain and spinal cord) and peripheral nervous system; outer surface or skin of the organism; cornea and lens of the eye; epithelium that lines the mouth and nasal cavities and the anal canal; epithelium of the pineal gland, pituitary gland, and adrenal medulla; and cells of the neural crest (which gives rise to various facial structures, pigmented skin cells called melanocytes, and dorsal root ganglia, clusters of nerve cells along the spinal cord). The embryonic “middle” layer, or mesoderm, gives rise to skeletal, smooth, and cardiac muscle; structures of the urogenital systems (kidneys, ureters, gonads, and reproductive ducts); bone marrow and blood; fat; bone, and cartilage; other connective tissues; and the lining of the body cavity. The embryonic “inner” layer, or endoderm, gives rise to the epithelium of the entire digestive tract (excluding the mouth and anal canal); epithelium of the respiratory tract; structures associated with the digestive tract (liver and pancreas); thyroid, parathyroid, and thymus glands; epithelium of the reproductive ducts and glands; epithelium of the urethra and bladder.

The term “early embryo” covers stages of development up to the appearance of the primitive streak e.g. until 14 days after fertilisation.

7. Eight week after fertilisation: Foetal stage

After about seven weeks’ development, individual organs become recognisable and the embryonic stage is finished and the embryo can properly be described as a **foetus**. A distinction is drawn between the foetal germ cells from which the gametes (egg cells and sperm) develop and from which “pluripotent” embryonic germ stem cells (EG cells) can be derived during a brief period in the early foetal development and the remaining foetal tissue from which “multipotent” foetal somatic stem cells can be derived.

8. Nine months after fertilisation: birth

At around nine months, given normal gestation, the baby is born.

ANNEX B: Possibilities to overcome immune rejection responses in stem cell therapy

There are several ways of avoiding or repressing immune rejection of transplanted cells or tissues⁷⁴:

1) Use of immune-suppressant drugs

These drugs, which suppress the activity of the immune system, have been refined over many years, as part of organ transplantation research. However, they are not always effective; they must normally be taken over the lifetime of the patient; and they leave the patient open to infection.

2) Use of “matching” tissues

The magnitude of rejection is dependent on the differences between the patient's HLA system and that of the donor. For this reason, the differences should be as small as possible. Sometimes during transplantation it is possible to get a matched tissue type, usually from a near relative. This is often sought for bone marrow transplants. Finding a matching donor is unlikely to be a useful approach for most cell-based therapies. However, because stem cells can, in principle, be cultured indefinitely, it might be possible to establish stem cell banks of sufficient size to comprise stem cells with a reasonable (though never perfect) match to the majority of individuals in the population. If this proved possible, the appropriate matching stem cell from the bank could be selected and differentiated into the cell type required for therapy. Several thousand stem cell lines would be needed to obtain matches to the majority of the population comparable with those achieved with matched bone marrow transplants.

3) Generation of immunotolerance

Rejection can also be reduced by the generation of immunotolerance. Previous administration of embryonic material, or haematopoietic cells from the stem cell donor, might cause the patient's immune system to become habituated to some extent and smaller doses of immunosuppressive drugs would be required, or none at all. In addition, research is being carried out into the possibility of preventing an immune reaction by enclosing the cells to be transplanted in a capsule of inert material.

The brain is normally a privileged site for transplantation as the brain does not have an immune system, which cause rejection. However, in many pathological situations the blood brain barrier is compromised and therefore the brain may not be as immunoprivileged as previously thought, because immune cells then can enter the brain from blood.

4) Using the individual's own cells or tissues

This would be the surest means of avoiding immune rejection. Adult stem cells isolated from an individual, and then used to treat him or her, offer one possible way of achieving this,

⁷⁴ House of Lords Select Committee “Report on Stem cell research” <http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm>; The Health Council of the Netherlands' report on “Stem cells for tissue repair. Research on therapy using somatic and embryonic stem cells”, June 2002. <http://www.gr.nl/pdf.php?ID=429>.

although not in all circumstances. Alternatively somatic cell nuclear transfer (to egg cells or human ES cells in culture) could be used to generate cells or tissues that match those of the patient.

ANNEX C: Examples of available human embryonic stem cell lines

Sweden:

Karolinska Institute:

The US National Institutes of Health (NIH) register ⁷⁵ contained initially six human ES cell lines from the Karolinska Institute in Stockholm. However, these cell lines are currently not available. The six cell lines have been frozen and the work on thawing, expanding and characterising have now started. Two of these human ES cell lines have been grown on mouse feeder layer. The remaining four preparations were frozen at an earlier stage. However, these four preparations were established using human feeder cells, not mouse cells, and they are therefore very valuable for the future. It is expected that the initial NIH lines thawed should be available for others researchers within the next 12 months.

In addition to these original lines, there are at present three other stem cell lines in culture. One is fully characterised and has been expanded to such a degree that this is now being supplied to various groups for collaborative studies. The characterisation of the other two lines is expected to be completed shortly. A cell bank will be established, based on the various stem cell lines established at Karolinska Institute, and these will be available for other scientists⁷⁶.

Sahlgrenska Academy, Gothenburg University in collaboration with Cell Therapeutics Scandinavia, AB:

21 human ES cell lines have so far been established. Four of these have been fully characterized and two of these four fulfil all the criteria for self-renewal and pluripotency of human ES cells. The remaining 17 cell lines have been partially characterized⁷⁷.

Israel:

Six human embryonic stem cell lines have been established and characterised at the Rambam Medical Center, Technion- Israel Institute of Technology. Four cell lines are available and have been registered at the NIH registry. The institute has also cell lines initially produced at the Wisconsin. These cell lines are available for collaborative studies⁷⁸.

Australia:

The Australian Senate passed the Research Involving Human Embryos Bill on 5 December, 2002 allowing the destruction of human embryos for research purposes including the procurement of embryonic stem cells from supernumerary embryos. The legislation, pending the decision of State and Territory Parliaments, is expected to take effect beginning of 2003.

⁷⁵ <http://escr.nih.gov/eligibilitycriteria.html>

⁷⁶ Communication from Professor Carlstedt - Duke, Dean of Research, Karolinska Institute, Sweden

⁷⁷ Communication from Professor Hamberger, Goteborg University, Sweden.

⁷⁸ Communication from Professor Itskovitz -Eldor, Rambam Medical Centre, Israel.

Among others researchers at the Monash Institute are expecting to start deriving new human embryonic stem cell lines from supernumerary embryos however the stem cell lines will not be available until 2004⁷⁹.

⁷⁹ Communication from Professor Pera, Monash Institute, Australia.

ANNEX D: Details regarding provisions in non-EU countries relating to human embryonic stem cell research

Examples of regulatory regimes in some countries associated to the 6th Framework Programme for Research⁸⁰

Iceland

The act of 1996 on Artificial Fertilisation regulates research on human embryos. The creation of embryos for research is prohibited, as is cloning. Research on human supernumerary embryos is allowed:

- if it is part of an *in vitro* fertilisation treatment,
- if the intention is to diagnose hereditary diseases in the embryos themselves,
- if the purpose is to advance the treatment of infertility, or
- if the purpose is to improve understanding of the causes of congenital diseases and miscarriages.

Israel

The currently existing Public Health (Extra-Corporeal Fertilization) Regulations, 1997 address neither the question of the fate of frozen embryos at the end of the freezing period nor the issue of supernumerary embryos (i.e. embryos initially formed in the course and for the sake of infertility treatment and not replaced or donated for implantation for some *bona fide* reason). Likewise, the currently proposed law for the regulation of the donation of eggs for purposes of *in vitro* fertilization does not address the possibilities of embryo stem cell research. In 1999, the Israel Parliament enacted the Prohibition of genetic intervention Act 1999-5759 (human cloning and genetic modification of reproductive cells). The law prohibits specifically human reproductive cloning but does not relate to cloning for non-reproductive purposes, such as ES cell derivation

The Bioethics Advisory Committee of the Israel National Academy of Sciences and Humanities, adopted a recommendation on 8 August 2001 stating that it should be permissible to donate human supernumerary embryos no longer destined to implantation for research under certain conditions, such as:

- free and informed consent,
- no selling or buying of human embryos,
- no *in vitro* culturing of human embryos beyond 2 weeks.

⁸⁰ European Commission, DG Research, Directorate E: Survey on opinions from National Ethics Committees or similar bodies, public debate and national legislation in relation to human embryonic stem cell research and use (last update March 2003)

- separation of the medical teams involved in the IVF treatment and in the stem cell research.

The Advisory Committee also considers it ethically permissible to experiment with new technologies to produce ES cells such as nuclear transfer (so-called therapeutic cloning without reproductive purpose).

The Advisory committee also recommends that the "National Helsinki committee for genetic research in humans" of the Israel Ministry of Health examine the research protocols. In November 2002, the National Helsinki Committee has accepted in principle to authorise applications in the two above categories.

Norway

"A bill amending the Act no 56 of 5 August 1994 relating to the application of biotechnology in medicine was assented by the King/sanctioned 13 December 2002. The amendments became effective 1 January 2003 and clarify that the prohibition against research on human embryos also includes research on stem cell lines created by isolating and culturing stem cells from human embryos. The bill also laid down a ban on therapeutic cloning."

Switzerland

The Federal law on medically assisted reproduction of 18 December 1998 regulates research on embryos. Research on existing embryos is forbidden as well as creation of embryos for research purposes. The donation of embryos is forbidden by the Constitution (article 119).

At the end of May 2002, a draft of the Swiss "Federal Act on Research on Supernumerary Embryos and Embryonic Stem Cells" (EFG, Embryonenforschungsgesetz/ Embryonic Research Act) reached the pre-legislative consultation stage. The Federal Council (government) handed over a proposal for the act to parliament end of November 2002. It is the parliament's aim to enact the law before end of 2003.

This draft law proposes to allow research on "surplus" embryos from *in vitro* fertilisation for purposes of an important scientific interest in the context of reproductive medicine or developmental biology [and not "any possible purpose"] up to the 14th day after fertilisation, and the derivation of embryonic stem cells from supernumerary embryos for research purposes. The EFG draft defines an embryo as "the developing organism from the point of nuclear fusion until the completion of organ development". Interpreting the constitutional paragraph that bans "all kinds of cloning" it explicitly forbids therapeutic cloning.

Examples of regulatory regimes in third countries

Australia

A new bill was voted by the Senate in 2002, which will authorize derivation of human ES cells from supernumerary human embryos. The law may be voted by the House of Representatives in early 2003.

Canada

No legislation is currently in place. A new draft law on assisted human reproduction is now in discussion in the House of Commons and addresses the questions of research on human embryos. It proposes to prohibit the creation of embryos for research purposes but would allow research on supernumerary embryos including the procurement of human embryonic stem cell from supernumerary embryos. It also requires the informed consent of the donor of the gametes.

The Canadian Institute for Health has established guidelines concerning human stem cell research. It allows the funding of the procurement of human embryonic stem cell from supernumerary embryos.

India⁸¹

The National bioethics panel set up by the Indian Department of Biotechnology (Ministry of Science and Technology) has drafted new guidelines for human genomics research that cover the collection and use of human ES cells. The panel recommends that the embryos should not be older than 14 days, both donors should give informed consent and all projects should be approved by the National bioethics panel. The creation of embryos for research purposes should not be undertaken. In the case of commercial exploitation, a sharing of profits with the donors should be organized.

Japan

The Japanese Parliament enacted the “Human Cloning Regulation Act” on 30 November 2000. The act authorizes research on human embryos *in vitro* including the procurement of human embryonic stem cells. The detailed implementation of the act is left to the administrative guidelines.

Singapore⁸²

Singapore's Bioethics Advisory Committee has recommended a complete ban on human reproductive cloning and recommends that human stem cell research and therapeutic cloning be permitted under strict regulation.

The regulatory framework should

- require the informed voluntary consent of donors,
- prohibit the commerce and sale of donated materials, especially supernumerary embryos and
- stipulate that no one shall be under a duty to participate in any manner of research on human stem cells to which he has a conscientious objection.

The Government has announced that it will follow the recommendations of the Bioethics Advisory Committee published on 21 June 2002. It is the responsibility of the Health Minister to licence such research.

South Korea

The Government has announced that that it will approve the use of less than 14 day-old embryos for stem cell research. A new regulation will be submitted to the Korean National Assembly.

USA

Only publicly funded research is regulated. On 9 August 2001, President Bush announced that federal funds might be awarded for research using human embryonic stem cell lines that meet certain criteria⁸³. Such research is now eligible for federal funding as long as the derivation process (which begins with the destruction of the embryo) was initiated prior to 9 August 2001. These stem cells must have been derived from embryos created for reproductive

⁸¹ <http://dbtindia.nic.in/consent.html>

⁸² <http://www.bioethics-singapore.org/bac/index.jsp>

⁸³ http://grants.nih.gov/grants/stem_cells.htm

purposes and no longer needed for those purposes. In addition, informed consent must have been obtained for the donation of the embryo and the donation must not have involved financial inducements. The NIH Human Embryonic Stem Cell Registry has been created and is updated to reflect stem cell lines that meet the eligibility criteria (see also chapter 2.6). There is no federal law regulating research on human embryos and the derivation of human ES cells when such research is funded by the private sector.

However, California has passed a law, in September 2002, allowing the procurement of human embryonic stem cells from supernumerary embryos. New legislation authorising the procurement of human ES cells from supernumerary embryos is under discussion in the States of New Jersey and Massachusetts.

ANNEX E: Opinion No.15 of the European Group on Ethics regarding ethical aspects of human stem cell research and use

OPINION OF THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES

No 15

14 November 2000

ETHICAL ASPECTS OF HUMAN STEM CELL RESEARCH AND USE

Reference: Initiative of the Group

Rapporteurs: Anne McLaren and Göran Hermerén

The European Group on Ethics in Science and New Technologies (EGE),

Having regard to the Treaty on European Union as amended by the Treaty of Amsterdam, and in particular Article 6 (formerly Article F) of the common provisions, concerning the respect for fundamental rights, Article 152 (formerly Article 129) of the EC Treaty on public health, (namely paragraph 4(a) referring to substances of human origin) and Articles 163-173 (formerly Articles 130F-130P) on research and technological development;

Having regard to the European Parliament and Council Directive 65/65/CEE of 26 January 1965 and the modified Directive 75/319/CEE of 20 May 1975 concerning medicinal products;

Having regard to the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and the European Parliament and Council Directive 98/79/EC of 27 October 1998 concerning in vitro diagnostic medical devices, in particular Article 1-4 which refers to ethics and requires the respect of the principles of the Convention of the Council of Europe on Human Rights and Biomedicine, with regard to the removal, collection and use of tissues, cells and substances of human origin;

Having regard to the Council Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions and in particular Article 6, concerning certain inventions excluded from patentability, and Article 7 giving mandate to the European Group on Ethics (EGE) to evaluate "all ethical aspects of biotechnology";

Having regard to the Parliament and Council Decision of 22 December 1998 concerning the 5th Framework Programme of the European Community for research, technological development and demonstration activities (1998-2002) and in particular Article 7 requesting compliance with fundamental ethical principles;

Having regard to the Council Decision of 25 January 1999 adopting the specific programme for research, technological development and demonstration activities on quality of life and management of living resources and in particular the ethical requirements mentioned in its Annex II;

Having regard to the Charter of 28 September 2000 on Fundamental Rights of the European Union, approved by the European Council in Biarritz on October 14th 2000, in particular Article 1 on "Human dignity", Article 3 on the "Right to the integrity of the person", which refers to the principle of "free and informed consent" and prohibits "the reproductive cloning of human beings" and Article 22 on "Cultural, religious and linguistic diversity";

Having regard to the Council of Europe's Convention on Human Rights and Biomedicine, signed on 4 April 1997 in Oviedo, in particular Article 18 on embryo research, and to the additional protocol to the Convention on the prohibition of cloning human beings signed on 12 January 1998 in Paris;

Having regard to the Universal Declaration on the Human Genome and Human Rights adopted by the United Nations on 11 December 1998, in particular Article 11 which recommends to prohibit reproductive cloning of human beings, and Article 13 which refers to the responsibilities of researchers as well as of science policy makers;

Having regard to national regulations on stem cell and on embryo research and to national ethics bodies opinions, at the European Union level, concerning these subjects;

Having regard to the reports of the US National Bioethics Advisory Committee dated September 13, 1999 on the "Ethical Issues on Human Stem Cell Research", the hearings on the same subject by the US Congress, on April 2000 and the guidelines published by the Clinton administration on August 26, 2000 to be forwarded to a NIH (National Institutes of Health) scientific review in 2001;

Having regard to the Round Table organised by the Group on 26 June 2000 in Brussels with members of the European Parliament, jurists, philosophers, scientists, representatives of industries, of religions, of patients' associations, and of international organisations (Council of Europe, UNESCO, WHO);

Having regard to the Hearings of scientific experts on 6 June 2000 and on 2 October 2000, and to the Hearings of representatives of religions on 8 September 2000;

Having heard the rapporteurs Anne McLaren and Goran Hermerén;

1 - WHEREAS

SCIENTIFIC BACKGROUND

1.1. How to define stem cells?

Stem cells are cells that can divide to produce either cells like themselves (self-renewal), or cells of one or several specific differentiated types. Stem cells are not yet fully differentiated and therefore can reconstitute one or several types of tissues.

1.2. What are the different kinds of stem cells?

Different kinds of stem cells can be distinguished according to their potential to differentiate. They are progenitor, multipotent or pluripotent stem cells.

- Progenitor stem cells are those whose terminally differentiated progeny consist of a single cell type only. For instance, epidermal stem cells or spermatogonial stem cells can differentiate respectively into only keratinocytes and spermatozoa.
- Multipotent stem cells are those which can give rise to several terminally differentiated cell types constituting a specific tissue or organ. Examples are skin stem cells which give rise to epidermal cells, sebaceous glands and hair follicles or haematopoietic stem cells, which give rise to all the diverse blood cells (erythrocytes, lymphocytes, antibody-producing cells and so on), and neural stem cells, which give rise to all the cell types in the nervous system, including glia (sheath cells), and the many different types of neurons.
- Pluripotent stem cells are able to give rise to all different cell types in vitro. Nevertheless, they cannot on their own form an embryo. Pluripotent stem cells, which are isolated from primordial germ cells in the foetus, are called: embryonic germ cells ("EG cells"). Those stem cells which are isolated from the inner cell mass of a blastocyst-stage embryo are called: embryonic stem cells ("ES cells").

It should be noted that scientists do not yet all agree on the terminology concerning these types of stem cells.

1.3. What are the characteristics of the different stem cells?

Progenitor and multipotent stem cells may persist throughout life. In the foetus, these stem cells are essential to the formation of tissues and organs. In the adult, they replenish tissues whose cells have a limited life span, for instance skin stem cells, intestinal stem cells and haematopoietic stem cells. In the absence of stem cells, our various tissues would wear out and we would die. They are more abundant in the foetus than in the adult. For instance haematopoietic stem cells can be derived from adult bone marrow but they are particularly abundant in umbilical cord blood.

Pluripotent stem cells do not occur naturally in the body, which distinguishes them from progenitor and multipotent stem cells.

1.4. Where can stem cells be found?

The possible sources of stem cells include adult, foetus and embryos. Accordingly, there are:

- Adult stem cells: progenitor and multipotent stem cells are present in adults. Mammals appear to contain some 20 major types of somatic stem cells that can generate liver, pancreas, bone and cartilage but they are rather difficult to find and isolate. For instance, access to neural stem cells is limited since they are located in the brain. Haematopoietic stem cells are present in the blood, but their harvesting requires stimulatory treatment of the donor's bone marrow. By and large, adult stem cells are rare and do not have the same developmental potential as embryonic or foetal stem cells.
- Stem cells of foetal origin:
 - Haematopoietic stem cells can be retrieved from the umbilical cord blood.

- Foetal tissue obtained after pregnancy termination can be used to derive multipotent stem cells like neural stem cells which can be isolated from foetal neural tissue and multiplied in culture, though they have a limited life span. Foetal tissue can also give rise to pluripotent EG cells isolated from the primordial germ cells of the foetus.

- Stem cells of embryonic origin: Pluripotent ES cells are those which are derived from an embryo at the blastocyst stage. Embryos could be produced either by in vitro fertilisation (IVF) or by transfer of an adult nucleus to an enucleated egg cell or oocyte (somatic cell nuclear transfer – SCNT).

1.5. Human embryonic development

- At two to three days after fertilisation, an embryo consists of identical cells which are totipotent. That is to say that each could give rise to an embryo on its own producing for example identical twins or quadruplets. They are totally unspecialised and have the capacity to differentiate into any of the cells which will constitute the foetus as well as the placenta and membranes around the foetus.
- At four to five days after fertilisation (morula stage), the embryo is still made up of unspecialised embryonic cells, but these cells can no longer give rise to an embryo on their own.
- At five to seven days after fertilisation (blastocyst stage), a hollow appears in the centre of the morula, and the cells constituting the embryo start to be differentiated into inner and outer cells:

- The outer cells will constitute the tissues around the foetus, including the placenta.

- The inner cells (20 to 30 cells) will give rise to the foetus itself as well as to some of the surrounding tissues. If these inner cells are isolated and grown in the presence of certain chemical substances (growth factors), pluripotent ES cells can be derived. ES cells are pluripotent, not totipotent since they cannot develop into an embryo on their own. If they are transferred to a uterus, they would neither implant nor develop into an embryo.

HISTORICAL BACKGROUND

1.6. Research on animals

- Embryonic stem cells

Scientists have been working with mouse embryonic stem cells in vitro for more than 20 years, noting very early their remarkable capacity to divide. Some mouse ES cell lines have been cultured for more than 10 years, while retaining their ability to differentiate.

There is today some evidence from animal models that multipotent stem cells can be used for somatic therapy. Convincing evidence however has been provided up until now from ES cell-derived, and not adult derived multipotent somatic cells. For instance neural differentiated mouse ES cells when transplanted into a rat spinal cord several days after a traumatic injury can reconstitute neuronal tissue resulting in the (partial) recovery of hindlimb co-ordinated motility. Similarly, selected cardiomyocytes obtained from differentiating ES cells can be grafted into the heart of dystrophic mice to effect myocardial repair. Whether the same cellular derivatives when obtained from adult stem cells would be able to correct for the deficiencies induced in those animal models remains to be determined.

Much research on mouse ES cells has also been focused on using these cells to create transgenic animals, in particular as disease models to study human genetic disorders.

- Adult stem cells

Research is also carried out on mouse adult stem cells. While many scientists had assumed that these cells were programmed to produce specific tissues and were thus no longer able to produce other sorts of tissue, recent studies suggest that adult stem cells may be able to show more malleability than previously believed. For instance, it has been shown that mouse neural stem cells could give rise, in specific conditions of culture, to cells of other organs such as blood, muscle, intestine, liver and heart. Moreover marrow stromal cells can generate astrocytes, a non-neuronal type of cell of the central nervous system and haematopoietic stem cells can give rise to myocytes.

1.7. First grafts of human foetal cells

Stem cells in tissues such as skin or blood are able to repair the tissues throughout life. By contrast, the nervous system has a very limited capacity for self-repair because the neural stem cells in the adult brain are few in number and have a poor capacity to generate new neurons for instance to repair injury.

Based on the positive results of experimentation on rodents and primates, clinical trials in patients with Parkinson's disease have been performed on around 200 patients over the last 10 years especially in Sweden and the USA. They have shown that the transplantation of neural cells derived from the human foetus can have a therapeutic effect, with an important reduction of the symptoms of the disease in the treated patients. The clinical improvement among these patients has been observed for 6-24 months after transplantation and in some cases for 5-10 years. It has recently been shown that 10 years after the transplantation surgery, the transplanted neural cells were still alive and producing dopamine, the compound which is deficient in the brain of patients with Parkinson's disease.

However, this therapeutic approach still remains experimental. In addition, the availability of neural foetal tissue is very limited. Five to six aborted fetuses are needed to provide enough neural tissue to treat one Parkinson's patient. That is why new sources of neural cells have been explored in some countries such as the US and Sweden. The aim is to derive neural stem cells from fetuses: these stem cells could be induced to proliferate in culture, providing much greater amounts of neural tissue for transplantation.

1.8. Transplantation of human haematopoietic stem cells

The transplantation of human haematopoietic stem cells is routinely used to restore the production of blood cells in patients affected by leukaemia or aplastic anaemia after chemotherapy. There are two sources of haematopoietic stem cells:

- Adult stem cells: they can be retrieved under anaesthesia, from the bone marrow of donors, or from the patients themselves (before chemotherapy). Haematopoietic stem cells can also be retrieved directly from the blood, which requires a treatment to induce the passage of stem cells from the bone marrow into the blood circulation.
- Stem cells of foetal origin: haematopoietic stem cells can be retrieved from the umbilical cord blood at birth, though care must be taken to ensure that the baby receives enough cord blood. There are at present cord blood banks designated to facilitate haematopoietic stem cell transplantation. The systematic retrieval and cryopreservation of cord blood, at birth, has even been considered in order to have autologous stem cells available in case of later need. Stem cells of foetal origin give rise to less rejection reaction than adult stem cells.

1.9. Discoveries on human stem cells

In the late 70's, the progress of infertility treatment led to the birth of the first child by in vitro fertilisation. The formation of human embryos in vitro during the course of infertility treatment has made possible the study of human embryogenesis following fertilisation, and thus has increased our knowledge of the behaviour and characteristics of embryonic cells at a very early stage.

Since 1998, derivation and culture of embryonic and foetal human pluripotent stem cells has been performed, a process which had never been achieved before with human cells. A team at the University of Wisconsin in Madison (USA) announced in November 1998 that it had successfully isolated and cultured for several months cells from 14 human blastocysts obtained from donated surplus embryos produced by in vitro fertilisation. This team established five embryonic ES cell lines with the ability to be grown continuously without losing their capacity to differentiate into the many kinds of cells that constitute the body. At the same time, a team at the Johns Hopkins University in Baltimore (USA) reported that foetal primordial germ cells had been isolated from the gonads of foetuses obtained after pregnancy termination and cultured to make EG cells. Cell lines derived from these cells were grown for many months while maintaining the same capacity to differentiate as the ES cell lines.

In 1999, research on adult stem cells revealed that their plasticity was much higher than previously thought. Adult neural stem cells have been reported to give rise occasionally to other cell types including blood cells. A team at the University of Minnesota in Minneapolis, (USA) has shown that cells isolated from the bone marrow of adults or children were able to become neural or muscle cells. Nevertheless, bone marrow cells with such extraordinary malleability are extremely rare. In any case, these recent findings still require to be substantiated.

The future challenge is to control the differentiation of human stem cells. It has been shown in animals that by culturing stem cells in the presence of certain chemical substances referred to as "growth factors", it is possible to induce differentiation of specific cell types. Experiments on human stem cells are less advanced but finding ways to direct differentiation is presently an active focus of research.

1.10. What is the main interest of stem cell research and what are the hopes?

The main interests at present include:

- Basic developmental biology. Culturing of human stem cells offers insights that cannot be studied directly in the human embryo or understood through the use of animal models. For instance, basic research on stem cells could help to understand the causes of birth defects, infertility and pregnancy loss. It could also be useful to give a better understanding of normal and abnormal human development.
- Studies of human diseases on animal models. For example, mouse ES cells can be engineered to incorporate human mutated genes known to be associated with particular diseases and then used to make transgenic mouse strains. If such mice express the pathology of the human disease, this confirms the hypothesis that the gene is involved with the etiology of the disease. This strategy also yields an animal model of the human disease which has in most cases a much better predictability for the human situation than more conventional animal models. One of the most illustrative examples of that method is its use in order to address the potential causes of Alzheimer's disease.
- Culturing specific differentiated cell lines to be used for pharmacology studies and toxicology testing. This is the most likely immediate biomedical application, making possible the rapid screening of large numbers of chemicals. By measuring how pure populations of specific differentiated cells respond to potential drugs, it will be possible to sort out medicinal products that may be either useful or on the contrary problematic in human medicine.

- Use of stem cells in gene therapy. Stem cells could be used as vectors for the delivery of gene therapy. One current application in clinical trials is the use of haematopoietic stem cells genetically modified to make them resistant to the HIV (virus responsible for AIDS).
- Production of specific cell lines for therapeutic transplantation. If feasible, this would be the most promising therapeutic application of ES cells. Research is being actively pursued, mostly in the mouse, with the aim of directing the differentiation of pluripotent stem cells to produce pure populations of particular cell types to be used for the repair of diseased or damaged tissues. For instance, the aim would be to produce cardiac muscle cells to be used to alleviate ischaemic heart disease, pancreatic islet cells for treatment of diabetes (juvenile onset diabetes mellitus), liver cells for hepatitis, neural cells for degenerative brain diseases such as Parkinson's disease, and perhaps even cells for treating some forms of cancer. The transplantation of stem cells could also help, for example, to repair spinal cord damage which occurs frequently, mainly following trauma (for instance car accidents) and is responsible for paraplegia. Results of that kind of cell therapy on animals are promising, but are still years away from clinical application. Even more remote (possibly decades away) is the prospect of being able to grow whole organs in vitro, but if tissues for the repair of organs become available, it would greatly relieve the existing unsatisfied demand for donated organs for transplantation. In providing a potentially unlimited source of specific clinically important cells such as bone, muscle, liver or blood cells, the use of human stem cells could open the way to a new "regenerative medicine".

1.11. Why is somatic cell nuclear transfer (SCNT) considered?

Apart from its interest for basic research, SCNT is considered as a possible strategy, in "regenerative medicine", for the avoidance of immunological problems after transplantation. Neural tissues can sometimes be transplanted from one individual to another without suffering immunological rejection, but for all other tissues, stem cell therapy would need to be accompanied by long-term treatments with immunosuppressive drugs, leading to increased susceptibility to infections and even to cancer.

- One approach to avoid this immune rejection problem would involve genetic engineering of stem cells to render them non-antigenic, or immunological manipulation of the patients to render them tolerant.
- An alternative approach is based on somatic cell nuclear transfer. It consists of transferring nuclei from the patient's own body cells into donated human or even animal unfertilised eggs from which the nuclei have been removed. If these reconstructed eggs were stimulated for example with electricity to develop to the blastocyst stage, pluripotent stem cells could be derived from them to form cells genetically identical to the patient. No rejection of any transplanted cells would then occur.
- Related technology could lead to the cloning of human individuals if the reconstructed embryos were transferred to a woman's uterus. However, this is contrary to European Community law and prohibited in most European countries.

1.12. Possible origins of the embryos in countries which allow embryo research

These embryos are:

- either «spare embryos» (i.e. supernumerary embryos) created for infertility treatment to enhance the success rate of IVF, but no longer needed for this purpose. They are intended to be discarded but, instead, may be donated for research by the couples concerned,
- or research embryos, created for the sole purpose of research.

- These may either be produced with donated gametes, i.e. they are derived from the fertilisation in vitro of a human oocyte by a human sperm,
- or they may be produced by embryo splitting or nuclear transfer. In the latter case they would be derived by introducing the nucleus of an adult somatic cell into an enucleated human oocyte (sometimes misleadingly termed “embryo cloning” or “therapeutic cloning”).

LEGAL BACKGROUND

1.13. Legal situation in the Member States

At national level, stem cell research is not regulated as such.

With regard to embryonic stem cell research, it is thus necessary to refer to the general legislation on embryo research. In this respect, the situation in the Member States is diverse:

- Ireland is the only country of the EU whose Constitution affirms the right to life of the “unborn” and that this right is equal to that of the mother.

- In some Member States no legislation on embryo research exists. This is the case of Belgium and of the Netherlands, where embryo research is nevertheless carried out. In Portugal however, in the absence of legislation, no embryo research seems to be performed. This also seems to be the case in Italy although artificial reproductive techniques are widely practised.

- Where embryo research is legislated, legislation either prohibits any kind of embryo research (Austria, Germany), or authorises this research under specified conditions (Finland, Spain, Sweden, and UK). In France, where embryo research is still prohibited, the law authorises “the study of embryos without prejudicing their integrity” as well as preimplantation diagnosis.

- In some countries the Constitutional Courts have dealt with the use of human embryos (judgement of the French Constitutional Court of July 27, 1994 on Bioethics, and judgement of the Spanish Constitutional Court of July 10, 1999 on the legislation concerning assisted human reproduction techniques).

The legal situation of many countries in Europe is under development. New legislation is being drafted mainly in response to the challenge of stem cell research.

- In some countries, draft legislation is being prepared to allow research on stem cells derived from supernumerary embryos after in vitro fertilisation (The Netherlands).

- In other countries, draft legislation provides for the possibility of creating embryos by nuclear transfer, for the sole purpose of stem cell research. This is the case in Belgium, and in the UK. (In the latter case, legislation allowed creation of embryos for the purpose of research, but only in relation to the treatment of infertility, to contraception or to the avoidance of genetic disease). In France legislation is under preparation.

1.14. European legislation in the field

At the Council of Europe's level, the Convention on Human Rights and Biomedicine signed in Oviedo in 1997 in its Article 18 establishes that it is up to each country to decide whether to authorise or not embryo research. Each country is only obliged to respect two conditions: "to ensure adequate protection of the embryo", that is to say to adopt a legislation fixing the conditions and limits of such research; and to prohibit "the creation of human embryos for research purposes". The Convention is binding only for the States which have ratified it. In the European Union so far only three countries have completed the procedure and some are in the process of doing so.

At EU level, although there is no legislative competence to regulate research, some Directives allude to the issue of embryo research and use. For instance, the Directive 98/44/EC on the legal protection of biotechnological inventions (patenting on life) stipulates that "processes for cloning human beings" and "uses of human embryos for industrial or commercial purposes"... "shall be considered unpatentable". The Directive 98/79/EC on in vitro diagnostic medical devices (including the use of human tissues) provides that "the removal, collection and use of tissues, cells and substances of human origin shall be governed, in relation to ethics, by the principles laid down in the Convention of the Council of Europe for the protection of human rights and dignity of the human being with regard to the application of biology and medicine and by any Member States regulations on this matter".

At this same level, the Charter on Fundamental rights of the European Union approved by the European Council in Biarritz (France) on October 14, 2000 prohibits different kinds of practices possibly related to embryo research, namely "eugenic practices, in particular those aiming at the selection of persons " and "the reproductive cloning of human beings".

1.15. US approach related to embryo research and stem cell research

The situation in the US contrasts with that in Europe. A substantial difference is a sharp distinction between the public and the private sector. Since 1995 the US Congress has been adopting each year a provision in the Appropriation Bill to prohibit public funding for embryo research. Thus, the National Institutes of Health (NIH) cannot carry out embryo research, which, in the absence of legislation, remains free and beyond control in the private sector.

New discoveries concerning the culturing of human stem cells in 1998 have led to the reopening of the debate. The National Bioethics Advisory Committee (NBAC) issued a report on September 1999; hearings took place in 1999 and 2000 before the competent Committees of the US Congress and finally the Clinton administration proposed that, under certain conditions, the funding of research to derive and study human ES cells be permitted. New guidelines of the NIH were published in August 2000 according to which research on human ES cells can be publicly funded if two conditions are respected. First, the cells must be taken from frozen spare embryos from fertility clinics and already destined to be discarded; second, Federal funds could not be used to destroy the embryos to obtain the cells; privately funded researchers will have to pass them on to Federally supported scientists.

ETHICAL BACKGROUND

1.16. Main ethical issues with regard to stem cell research

Human stem cell research is an example of bioethical value conflicts. On the one hand, the prospect of new therapies, even in the far future, is attractive in offering an alternative to organ and tissue donation. On the other hand, when this research involves the use of human embryos, it raises the question of its ethical acceptability and of the limits and conditions for such research. Embryo research has been extensively debated in the context of research carried out to improve IVF as a treatment for infertility. Embryonic stem cell research raises the following specific additional ethical questions:

New types of research to be performed on human embryos. Up until now, research that involved destroying embryos, if allowed, was limited to research on reproduction, contraception or congenital diseases. With human stem cell research, a much wider scope of research is being considered.

The use of ES cells and stem cell lines for therapeutic purposes. Human embryos used for research were destroyed after the research was completed and therefore were never used for fertility treatment. What remained was additional knowledge. Human embryonic stem cell research is aimed at creating cell lines with appropriate characteristics, in terms of purity and specificity. There is thus continuity from the embryonic cells to the therapeutic material obtained by culture.

The creation of embryos for research purposes. This delicate issue is now raised again since there is a scientific justification of this practice, namely the possibility of producing stem cells identical to the patient's cells and thus avoiding problems of rejection in the context of the future "regenerative medicine". At the same time, creating human embryos raises new ethical concerns. The ethical acceptability of stem cell research depends not only on the objectives but also on the source of the stem cells; each source raising partly different ethical questions. Those who condemn embryo research in general will not accept this difference, but for those who accept it, this issue is of major importance.

1.17. Ethical issues in transplantation of stem cells

Clinical research and potential future applications in this field raise the same ethical issues as those dealt with in the EGE's Opinion on Human Tissue Banking (21/07/1998), concerning the respect of the donor, who should give informed consent to this use of the donated cells, the respect of the autonomy of the patients, their right to safety and to the protection of their private life and the right to a fair and equal access to new therapies.

2- OPINION

The Group submits the following Opinion:

SCOPE OF THE OPINION

2.1 Ethical issues of stem cell research and use for clinical purposes.

This Opinion reviews ethical issues raised by human stem cell research and use, in the context of the European Union research policy and European Community public health competence to improve human health and to set high standards for the safety of substances of human origin.

With regard to the specific ethical questions related to the patenting of inventions involving human stem cells, on which President Prodi requested an Opinion from the Group on 18 October 2000, this will be made public in Brussels at a later date. The following Opinion therefore excludes the patenting issue.

GENERAL APPROACH

2.2. Fundamental ethical principles at stake

The fundamental ethical principles applicable are those already recognised in former opinions of the EGE, and more specifically:

- the principle of respect for human dignity
- the principle of individual autonomy (entailing the giving of informed consent, and respect for privacy and confidentiality of personal data)
- the principle of justice and of beneficence (namely with regard to the improvement and protection of health)
- the principle of freedom of research (which is to be balanced against other fundamental principles)
- the principle of proportionality (including that research methods are necessary to the aims pursued and that no alternative more acceptable methods are available).

In addition, the Group considers it important to take into account, based on a precautionary approach, the potential long-term consequences of stem cell research and use for individuals and the society.

2.3. Pluralism and European ethics

Pluralism is characteristic of the European Union, mirroring the richness of its tradition and adding a need for mutual respect and tolerance. Respect for different philosophical, moral or legal approaches and for diverse cultures is implicit in the ethical dimension of building a democratic European society.

From a legal point of view, respect for pluralism is in line with Article 22 of the Charter on Fundamental Rights on "Cultural, religious and linguistic diversity" and with Article 6 of the Amsterdam Treaty which ensures the protection of fundamental rights at EU level, notably based on international instruments as well as common constitutional traditions, while also stressing the respect for the national identity of all Member States.

BASIC RESEARCH ON HUMAN STEM CELLS

2.4. Principal requirements according to the diverse sources of stem cells.

- The retrieval of adult stem cells requires the same conditions as those required in the case of tissue donation, based on respect for the integrity of the human body and the free and informed consent of the donor.
- The retrieval of stem cells from the umbilical cord blood after delivery requires that the donor (the woman or the couple concerned) is informed of possible uses of the cells for this specific purpose of research and that the consent of the donor is obtained.
- The retrieval of foetal tissues to derive stem cells requires, besides informed consent, that no abortion is induced for the purpose of obtaining the tissues and that the termination timing and the way it is carried out are not influenced by this retrieval.
- The derivation of stem cells from embryonic blastocysts raises the issue of the moral status of the human embryo. In the context of European pluralism, it is up to each Member State to forbid or authorise embryo research. In the latter case, respect for human dignity requires regulation of

embryo research and the provision of guarantees against risks of arbitrary experimentation and instrumentalisation of human embryos.

2.5. Ethical acceptability of the field of the research concerned.

The Group notes that in some countries embryo research is forbidden. But when this research is allowed, with the purpose of improving treatment for infertility, it is hard to see any specific argument which would prohibit extending the scope of such research in order to develop new treatments to cure severe diseases or injuries. As in the case of research on infertility, stem cell research aims to alleviate severe human suffering. In any case, the embryos that have been used for research are required to be destroyed. Consequently, there is no argument for excluding funding of this kind of research from the Framework Programme of research of the European Union if it complies with ethical and legal requirements as defined in this programme.

2.6. Public control of ES cell research.

The Group deems it essential to underline the sensitivity attached to the use of embryonic stem cells, since this use may change our vision of the respect due to the human embryo.

According to the Group, it is crucial to place ES cell research, in the countries where it is permitted, under strict public control by a centralised authority - following, for instance, the pattern of the UK licensing body (the Human Fertilisation and Embryology Authority) - and to provide that authorisations given to such research are highly selective and based on a case by case approach, while ensuring maximum transparency. This must apply whether the research in question is carried out by either the public or the private sector.

2.7. Alternative methods to the creation of embryos for the purpose of stem cell research.

The Group considers that the creation of embryos for the sole purpose of research raises serious concerns since it represents a further step in the instrumentalisation of human life.

- The Group deems the creation of embryos with gametes donated for the purpose of stem cell procurement ethically unacceptable, when spare embryos represent a ready alternative source.
- The Group takes into account interest in performing somatic cell nuclear transfer (SCNT) with the objective of studying the conditions necessary for "reprogramming" adult human cells. It is also aware that, in view of future cell therapy, the creation of embryos by this technique may be the most effective way to derive pluripotent stem cells genetically identical to the patient and consequently to obtain perfectly histocompatible tissues, with the aim of avoiding rejection after transplantation. But, these remote therapeutic perspectives must be balanced against considerations related to the risks of trivialising the use of embryos and exerting pressure on women, as sources of oocytes, and increasing the possibility of their instrumentalisation. Given current high levels of inefficiency in SCNT, the provision of cell lines would require large numbers of oocytes.
- In the opinion of the Group, in such a highly sensitive matter, the proportionality principle and a precautionary approach must be applied: it is not sufficient to consider the legitimacy of the pursued aim of alleviating human sufferings, it is also essential to consider the means employed. In particular, the hopes of regenerative medicine are still very speculative and debated among scientists. Calling for prudence, the Group considers that, at present, the creation of embryos by somatic cell nuclear transfer for research on stem cell therapy would be premature, since there is a wide field of research to be carried out with alternative sources of human stem cells (from spare embryos, foetal tissues and adult stem cells).

2.8. Stem cell research in the European Framework Programme of research

Stem cell research based on alternative sources (spare embryos, foetal tissues and adult stem cells) requires a specific Community research budget. In particular, EU funding should be devoted to testing the validity

of recent discoveries about the potential of differentiation of adult stem cells. The EU should insist that the results of such research be widely disseminated and not hidden for reasons of commercial interest.

At European Union level, within the Framework Programme of research, there is a specific responsibility to provide funding for stem cell research. This implies the establishment of appropriate procedures and provision of sufficient means to permit ethical assessment not only before the launching of a project but also in monitoring its implementation.

2.9. Stem cell research and rights of women

Women who undergo infertility treatment are subject to high psychological and physical strain. The Group stresses the necessity to ensure that the demand for spare embryos and oocyte donation does not increase the burden on women.

CLINICAL RESEARCH ON HUMAN STEM CELLS

The speed with which researchers, throughout the world, are moving to test stem cells in patients is remarkable, even if ES cell transplantation is unlikely to be attempted in the near future. Clinical trials with stem cells other than ES carried out on patients suffering from severe conditions such as Parkinson's disease, heart disease or diabetes raise the following issues:

2.10. Free and informed consent

Free and informed consent is required not only from the donor but also from the recipient as stated in the Group's opinion on Human Tissue Banking (21/07/1998). In each case, it is necessary to inform the donor (the woman or the couple) of the possible use of the embryonal cells for the specific purpose in question before requesting consent.

2.11. Risk-benefit assessment

Risk-benefit assessment is crucial in stem cell research, as in any research, but is more difficult as the uncertainties are considerable given the gaps in our knowledge. Attempts to minimise the risks and increase the benefits should include optimising the strategies for safety. It is not enough to test the cultured stem cells or tissues derived from them for bacteria, viruses or toxicity. Safety and security aspects are of utmost importance in the transplantation of genetically modified cells and when stem cells are derived from somatic cells. For example, the risks that transplanted stem cells cause abnormalities or induce creation of tumours or cancer have to be assessed. It is important that the potential benefits for the patients should be taken into account but not exaggerated. The grounds of a precautionary approach need to be taken into account.

2.12. Protection of the health of persons involved in clinical trials

The possibility that irreversible and potentially harmful changes are introduced in clinical applications of stem cell research should be minimised. Techniques enhancing the possibilities of reversibility should be used whenever possible. If, for example, genetically modified cells were encapsulated when they are transplanted in order to stimulate neural cell growth, it should be possible for the procedure to be reversed if something goes wrong.

2.13. Scientific evaluation of stem cell use for therapeutic purposes

It is urgent to outline strategies and specific requirements for the best evaluation of ethically sound and safe use of stem cells as means of therapy (gene therapy, transplantation, etc.). Such an evaluation should be done in collaboration with the European Agency for the Evaluation of Medicinal Products.

2.14. Anonymity of the donation

Steps must be taken to protect and preserve the identity of both the donor and the recipient in stem cell research and use. As stated in the EGE's Opinion on Human Tissue Banking (21/07/1998): "in the interests of anonymity, it

is prohibited to disclose information that could identify the donor, and the recipient. In general, the donor should not know the identity of the recipient, nor should the recipient know the identity of the donor".

2.15. Stem cell banks and safety

Procurement and storage of stem cells in stem cell banks leads to the collection and storage of a growing number of personal and familial data. Cell banks should be regulated at European level in order to facilitate the implementation of a precautionary approach. If unsatisfactory side effects occur, it should be possible to trace donor and recipient and to reach their medical files. Traceability must be one of the conditions required for the authorisation of cell banks at national or European level.

2.16. Stem cell banks and confidentiality

In order to reconcile the traceability requirement and the need to protect the donor's rights - medical confidentiality and privacy - cell banks must take the necessary steps to protect confidentiality of the data.

2.17. Prohibition of commerce in embryos and cadaveric foetal tissue

The potential for coercive pressure should not be underestimated when there are financial incentives. Embryos as well as cadaveric foetal tissue must not be bought or sold, and not even offered for sale. Measures should be taken to prevent such commercialisation.

2.18. Export and import of stem cell products

Stem cell imports or exports should be licensed by public authorities either at national or European level. Authorisation should be subject to ethical as well as safety rules.

2.19. Education and dialogue

There is a need for continuing dialogue and education to promote the participation of citizens, including patients, in scientific governance, namely in the social choices created by new scientific developments.

The European Group on Ethics in Science and New Technologies:

The Members

Paula Martinho da Silva

Anne McLaren

Marja Sorsa

Ina Wagner

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Gilbert Hottois

Dietmar Mieth

Octavi Quintana Trias

Stefano Rodota

Egbert Schrotten

Peter Whittaker

The Chairperson

Noëlle Lenoir

**ANNEX F: Statement for the minutes of the Council meeting 30
September 2002**



COUNCIL OF
THE EUROPEAN UNION

Brussels, 21 October 2002 (24.10)
(OR. fr)

12523/02
ADD 1 REV 1

LIMITE

PV/CONS 48
MI 186
IND 65
RECH 150

ADDENDUM TO DRAFT MINUTES ¹

Subject: 2451st meeting of the COUNCIL OF THE EUROPEAN UNION
(COMPETITIVENESS) (Internal Market, Industry and Research)
held in Brussels on 30 September 2002

¹ The information from the Council minutes which is contained in this addendum is not confidential and may therefore be released to the public.

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Items on the agenda concerning the definitive adoption of Council acts released to the public

"A" items: (list: 12355/2/02 REV 2 PTS A 45)

When definitively adopting the "A" items concerning legislative acts, the Council agreed to enter the following in the minutes:

Item 5. Directive of the European Parliament and of the Council on insurance mediation

PE-CONS 3639/02 SURE 34 CODEC 834

+ COR 1 (de,en,el,pt,sv)

The Council approved the European Parliament's amendments to the common position. The abovementioned Directive is therefore deemed to have been adopted in the form of the common position thus amended. (Legal basis: Article 47(2) and Article 55 of the Treaty establishing the European Community).

1. Joint statement by the Council and Commission

re Article 1(3), subparagraph 2

"The Council and the Commission declare that Article 1(3), subparagraph 2 aims to specify that, according to Community law, a Member State which permits third-country insurance and reinsurance intermediaries to carry on their activities in its territory from outside the Community may not provide for a regime which results in more favourable treatment for those intermediaries than that accorded to Community insurance and reinsurance intermediaries carrying on their activities in its territory under the freedom of establishment and the free provision of services in accordance with this Directive."

"B" items (Agenda: 12252/01 OJ CONS 49 MI 179 IND 61 RECH 148)

Item 3 (a) Council Decision adopting a specific programme for research, technological development and demonstration: "Integrating and strengthening the European Research Area" (2002-2006)

11385/02 RECH 139

The Council adopted the abovementioned Decision, with the Italian delegation voting against. (Legal basis: Article 166 of the Treaty establishing the European Community).

Item 3 (b) Council Decision adopting a specific programme for research, technological development and demonstration: "Structuring the European Research Area" (2002-2006)

11386/02 RECH 140

The Council adopted the abovementioned Decision (Legal basis: Article 166 of the Treaty establishing the European Community).

Item 3 (c) Council Decision adopting a specific programme of research, technological development and demonstration to be carried out by means of direct actions by the Joint Research Centre (2002-2006)

11384/02 RECH 138

The Council adopted the abovementioned Decision (Legal basis: Article 166(4) of the Treaty establishing the European Community).

Item 3 (d) Council Decision adopting a specific programme (Euratom) for research and training on nuclear energy (2002-2006)

11382/01 RECH 136 ATO 103

+ COR 1 (nl,en,sv)

The Council adopted the abovementioned Decision (Legal basis: Article 7(1) of the Treaty establishing the European Atomic Energy Community).

Item 3 (e) Council Decision adopting a specific programme for research and training to be carried out by the Joint Research Centre by means of direct actions for the European Atomic Energy Community (2002-2006)

11383/02 RECH 137 ATO 104

The Council adopted the abovementioned Decision (Legal basis: Article 7(1) of the Treaty establishing the European Atomic Energy Community).

STATEMENTS

2. Specific programmes "Integrating and strengthening the European Research Area" and "Structuring the European Research Area"

Re: Programme management

(a) The Council and the Commission state that:

The programme committee of each Specific Programme will meet in different configurations according to the nature of issues on the agenda to be discussed.

Regardless of configuration, the committee will always have the competencies of the programme committee as defined in Article 7 of the relevant specific programme decision.

The Commission services will ensure efficiency in the committees' overall work and specific support according to the configuration and agenda of each committee meeting. They will ensure that the agenda of each committee meeting in any configuration will be established in such a way and sufficiently far in advance as to enable Member States' delegations to identify the appropriate representatives for all issues on the agenda of the meeting, and to ensure the presence of appropriate specific expertise taking into account the characteristics of the specific areas involved and covering, as required, in particular:

- (i) for the Specific Programme "Integrating and Strengthening the European Research Area":
 - Life sciences, genomics and biotechnology for health;
 - Information society technologies;
 - Nanotechnologies and nanosciences, knowledge-based multifunctional materials and new production processes and devices;
 - Aeronautics and space;
 - Food quality and safety;

- Sustainable development, global change and ecosystems;
- Citizens and governance in a knowledge-based society;

(ii) for the Specific Programme "Structuring the European Research Area":

- Research and innovation;
- Human resources and mobility;
- Research infrastructures;
- Science and society.

In this context, the agenda of a given meeting should not call upon the specific expertise of more than one of the above themes.

The programme committee for each specific programme will address horizontal draft measures concerning the programme as a whole, including those issues related to overall strategy and coherence.

For the specific programme "integrating and strengthening the European Research Area" the committee will also address all horizontal draft measures under the heading "Specific activities covering a wider field of research", as well as the particular draft measures related to "Research in support of policies and anticipating scientific and technological needs", "Horizontal research activities involving SMEs", "Specific measures in support of international cooperation", and the part on "Strengthening the foundations of the European Research Area", bearing in mind the need to ensure the presence of appropriate specific expertise where relevant.

In the more specific configurations the committee of each programme will address the relevant part of the work programmes and their periodic reviews, including the use of implementation instruments, any subsequent adjustment to their use, the content of the calls for proposals as well as the draft implementing measures concerning the approval of funding of RTD actions within the relevant field.

As for themes encompassing more than one domain, the agenda should be defined in such a way as to ensure, whenever appropriate, both the overall coherence as well as the more specific articulation of themes and expertise. This should apply in particular where calls for proposals and project funding are on the agenda.

The reimbursement of one representative and one expert/adviser, from each Member State, participating in programme committee meetings will be effected from the budget of each respective specific programme in full respect of its budgetary envelope. The reimbursement of the second person (expert/adviser) will not constitute a precedent for committees operating in other fields of Community policy.

(b) The Commission states that:

In order to ensure efficiency and transparency of implementation, it will systematically make available to the Programme Committee comprehensive information covering all the proposals received for RTD actions as well as those eventually funded, regardless of their size.

The Commission will provide the information in a user-friendly form, including whenever possible in electronic form, in time for the Committee to take due account of it, at least two weeks in advance for matters for the committee's opinion and one week for matters for information.

In addition to information periodically made public through the Annual Report under Article 173 of the Treaty, as well as through the monitoring and the 5-year assessment reports, data for each priority or area will be made available during the last quarter of each year that will encompass, in a consolidated presentation, the information regularly supplied to committees on programme implementation and budget execution.

This information will cover all stages, from calls for proposals, through the evaluation of proposed RTD actions, their selection, as well as the signature of contracts and their subsequent implementation.

It will in particular include an overview of each call and for each proposal:

- summary information;
- the evaluation panels' ranking and summary reports; and
- the Commission's intentions as to proposals to be rejected or to be retained for negotiation;
- total budget and requested Community contribution.

The Commission will provide information regularly, and at least annually, on:

- the contracts signed (including partners, areas, content, resources and Member States' participation) and on their major developments, together with
- overviews of programme progress and implementation achievements, as well as
- the lists of persons having acted as evaluators over the previous period once all decisions have been made on the relevant call.

3. Specific programme "Integrating and strengthening the European Research Area"

Re: Article 3, application of ethical principles

The Council and the Commission agree that detailed implementing provisions concerning research activities involving the use of human embryos and human embryonic stem cells

which may be funded under the 6th Framework Programme shall be established by 31 December 2003. The Commission states that, during that period and pending establishment of the detailed implementing provisions, it will not propose to fund such research, with the exception of the study of banked or isolated human embryonic stem cells in culture. The Commission will monitor the scientific advances and needs as well as the evolution of international and national legislation, regulations and ethical rules regarding this issue, taking into account also the opinions of the European Group of Advisers on the Ethical Implications of Biotechnology (1991–1997) and the opinions of the European Group on Ethics in Science and New Technologies (as from 1998), and report to the European Parliament and the Council by September 2003.

The Council states that it intends to discuss this issue at a meeting in September 2003.

In the review of any subsequent proposal submitted to Council when applying Article 5 of Decision 1999/468/EC, the Commission recalls its statement concerning Article 5 of Decision 1999/468/EC, according to which the Commission, in order to find a balanced solution, will act in such a way as to avoid going against any predominant position which might emerge within the Council against the appropriateness of an implementing measure (cf. OJ C 203, 17.7.1999, p. 1).

The Council notes the intention of the Commission to submit to the Programme Committee, established under the specific research programme "Integrating and strengthening the ERA", procedural modalities concerning research involving the use of human embryos and human embryonic stem cells, in accordance with Article 6, paragraph 3, first indent.

The Council further notes the intention of the Commission to present to Council and Parliament in spring 2003 a report on human embryonic stem cell research which will form the basis for discussion at an inter-institutional seminar on bioethics.

Taking into account the seminar's outcome, the Commission will submit, based on Article 166(4) of the Treaty, a proposal establishing further guidelines on principles for deciding on the Community funding of research projects involving the use of human embryos and human embryonic stem cells.

The Council and the Commission will do their utmost, counting on the support of the European Parliament, to complete the legislative procedure as early as possible and at the latest in December 2003.

The Council and the Commission expect that the abovementioned seminar will contribute, as suggested by the European Parliament, to a Europe-wide and well-structured discussion process on the ethical issues of modern biotechnology, particularly on human embryonic stem cells, in order to enhance public understanding.

The Council and the Commission note that the ethical acceptability of various research fields is related to the diversity among Member States, and is governed by national law in accordance with the principle of subsidiarity. Moreover, the Commission notes that research using human embryos and human embryonic stem cells is allowed in several Member States, but not in others.

Re: COST

The Council and the Commission share the view of the recent report of the COST Assessment Panel that COST represents a long track record in cross-border cooperation and coordination of nationally financed RTD activities which constitutes a feature of direct relevance to building the European Research Area, while also acknowledging the scope for significant changes to the way COST is organised. Moreover, the Council notes that the Commission will not provide the administrative and scientific secretariat to any COST actions initiated during the Sixth Framework Programme. It notes also that the Commission, recognising that a new COST secretariat may not be fully operational by the end of 2002, is however prepared to continue providing the secretariat to COST actions during a transition period of a few months.

The Council and the Commission note that COST is in a process of being reformed and recognise that, following a successful outcome, and given also the recent expansion of COST and the growth in its number of Actions, a substantial grant from the Sixth Framework Programme could be justified.

The Council welcomes the Commission's intention to become a partner of COST, with a view to further developing synergy between the Framework Programme and COST. The Council invites the Commission to take appropriate steps in this respect.

4. Specific programme "Structuring the European Research Area"

Re: Human resources and mobility

The Commission states that in the implementation of the human resources and mobility actions under the present Specific Programme, family-related circumstances, such as maternity or paternity leave, will be inter alia taken into account, according to national legislations, so that potential beneficiaries will not suffer from the abovementioned circumstances.

5. Specific programme "Direct actions by the Joint Research Centre" (EC)

The Commission considers that, according to its mission and when requested, the JRC should support the European Parliament in the conception and implementation process of EU policies. Therefore the Commission welcomes the EP's intention to create an *ad hoc* committee aimed at ensuring an appropriate interface with the JRC.

The Commission wishes to confirm that the JRC multiannual work programme will be available on the JRC website: <http://www.jrc.org>.

6. Specific programme “Nuclear Energy” (Euratom)

Re: Voting rights at the consultative committee

The Council and the Commission acknowledge the unanimous agreement of the consultative committee for the fusion programme (CCFP) on the following weighted voting system, which should be applied within the Committee referred to in Article 6(2), when dealing with fusion related aspects. Accordingly, the Commission will take the appropriate steps with a view to amending the Council Decision of 16 December 1980 – as last amended by Council Decision 95/1/EC, Euratom, ECSC of 1 January 1995 – setting up the consultative committee for the fusion programme.

Germany	5
Austria	2
Belgium	2
Denmark	2
Spain	3
Finland	2
France	5
Greece	2
Ireland	2
Italy	5
Luxembourg	1
Netherlands	2
Portugal	2
United Kingdom	5
Sweden	2
Switzerland	2
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Total	44

For the adoption of an opinion, the required majority is 23 votes in favour by at least eight delegations.

7. Unilateral and bilateral statements relating to the specific programmes

(a) **Statement by Germany and Austria on Article 3 of the specific programme "Integrating and strengthening the European research area"**

"Germany and Austria emphasise that they maintain their position that, even after the end of the moratorium in December 2003, research using human embryos and human embryonic stem cells, with the exception of stem cells already held in banks or isolated in culture, should not be funded under the 6th Framework Programme. Moreover, Germany and Austria assume that, under the second specific programme, "Structuring the European Research Area", the Commission will not fund any research activities ineligible for funding on account of the statement for the minutes concerning the first specific programme "Integrating and strengthening the European Research Area"."

(b) **Statement by Ireland (bioethics)**

"Ireland, in supporting the adoption of the specific programmes to implement the Sixth Framework Programme for research, recalls its statements pertaining to research that cannot be carried out in Ireland. Ireland also recalls the Council statement and its joint statement with Italy, Germany, Portugal and Austria, pertaining to the further elaboration of detailed guidelines on ethical aspects.

Ireland welcomes

- the progress achieved to date in the elaboration of detailed implementing provisions;
- the recognition that its laws, regulations and guidelines apply in respect of any research carried out in Ireland;
- the Commission statement regarding non-funding in respect of research activities on human embryos or human embryonic stem cells under the Sixth Framework Programme;
- the Commission's intention to present a proposal in 2003, establishing further guidelines on principles for deciding on Community funding of research projects involving the use of human embryos or human embryonic stem cells. In the course of this process, Ireland which shares a number of the concerns expressed by Italy, Germany, Portugal and Austria, will continue to focus on the need to ensure utmost respect for human life and the protection of human dignity;
- the establishment of a Regulatory Committee which will consider any project proposals for research funding in ethically sensitive areas."

(c) **Statement by Italy (bioethics and funding of ITER)**

"Italy notes the Council and Commission statements on the "bioethics question" in connection with the adoption of the Specific Programmes implementing the Sixth Framework Programme for research 2002-2006. These statements represent significant progress in the endeavour to reach a joint position. In this context Italy considers that only research using

stem-cells derived from human embryos at a date preceding today or the date of the launch of the Sixth Framework Programme is admissible for Community funding.

With regard to the Specific Programme on Integrating and strengthening the European Research Area, Italy must reaffirm its vote against this. In line with the views previously expressed in the Research Council on 10 December 2001 and 3 June 2002 on respect for human dignity and protection of human life, Italy believes that research on human embryos directly or indirectly involving the destruction of the embryo should not be funded under the Sixth Framework Programme.

Regarding the EURATOM Specific Programme on Nuclear Energy, Italy takes a favourable view but points out that the funding provided for the ITER facility should not necessarily be interpreted as an endorsement of the scientific and technological choices made in the design of the facility. Italy believes that these choices should be given further scientific consideration before a final decision is taken on the feasibility of the ITER programme."

(d) Statement by Portugal (bioethics)

"Portugal congratulates the Presidency on the efforts it has made in the field of bioethics, without which it would not have been possible to launch the Sixth Framework Programme for research and technological development and the relevant specific programmes.

Portugal can give its agreement to the compromise reached, because it believes that compromise recognises the importance it attaches to issues of bioethics and research as well as the sensitivity of any future financing of research work on human embryo cells and embryonic stem cells. Portugal points out that this is a position shared by a number of other Member States and that it associates itself with many of the concerns which Italy has raised within the Council.

Portugal further stresses that research, especially through the Framework Programme, plays an important part in economic growth, employment and social cohesion, particularly in the context of a knowledge-based society and economy."

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