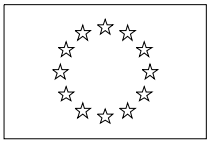

OPINION OF THE EUROPEAN GROUP ON ETHICS
IN SCIENCE AND NEW TECHNOLOGIES
TO THE EUROPEAN COMMISSION

No 15 **14 November 2000**

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ETHICAL ASPECTS OF HUMAN STEM CELL RESEARCH AND USE

Reference: Initiative of the Group
Rapporteurs: Anne McLaren and Göran Hermerén

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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 multipoten 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.

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- **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 cells 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 foetuses 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 foetuses: 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").

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 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.

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