

OPINION NUM. 16, OF THE EUROPEAN GROUP ON ETHICAL ASPECTS OF PATENTING INVENTIONS INVOLVING HUMAN STEM CELLS, OF MAY 7th, 2002

ETHICAL ASPECTS OF PATENTING INVENTIONS INVOLVING HUMAN STEM CELLS

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

Having regard to the request of Romano Prodi, president of the European Commission, to the EGE on the ground of article 7 of the Council Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions, giving mandate to the European Group on Ethics to evaluate “all ethical aspects of biotechnology”.

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 95C (formerly article 100A) on the approximation of Law, article 152 (formerly article 129) on public health, article 157 (formerly article 130) on Industry, and article 163 (formerly article 130F) on Research and Technological Development.

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”, article 13 asserting freedom of research and article 17 which states that “intellectual property is protected”.

Having regard to the Council Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions and in particular article 5, about the patentability of elements isolated from the human body, article 6, concerning certain inventions excluded from patentability, and the above mentioned article 7 giving mandate to the European Group on Ethics (EGE) to evaluate “all ethical aspects of biotechnology”; Having regard to the proposal for a Council Regulation on the Community Patent presented by the Commission on 5 July 2000.

Having regard to the judgement of the European Court of Justice of 9 October 2001, rejecting the appeal of the Kingdom of the Netherlands for annulment of the Directive 98/44/EC as well as to the opinion of the advocate general of 14 June 2001 in this case.

Having regard to the European Patent Convention, signed in München in 1973, and establishing the European Patent Organisation, in particular article 52 on patentable inventions stipulating that discovery, as well as surgical, therapeutic or diagnostic

methods for treatment of the human or animal body, are not regarded as inventions, and article 53.a concerning the exclusion from patentability of inventions the publication or exploitation would be contrary to “order public” or morality.

Having regard to the Budapest Treaty of the WIPO on International Recognition of the deposit of micro organisms for the purposes of Patent Procedure of 28 april 1977.

Having regard to the Trade Related Aspects of Intellectual Property Rights Agreement (TRIPS) annexed to the Agreement establishing the World Trade Organisation, entered into force on 1st january 1995, and in particular article 27.2 concerning the exclusion from patentability of inventions the commercial exploitation would run counter to “order public” or morality, and article 27.3 concerning the exclusion from patentability of diagnostic, therapeutic and surgical methods.

Having regard to the Council of Europe’s Convention on Human Rights and Biomedicine, signed on 4 april 1997 in Oviedo, in particular article 15 about freedom of research, article 18.2 prohibiting the production of embryos for the sole purpose of research and article 21 stating that “*the human body and its parts shall not, as such, give rise to financial gain*”.

Having regard to the Universal Declaration on the Human Genome and Human Rights endorsed by the United Nations on 11 december 1998, in particular, article 11 which recommends to prohibit “reproductive cloning of human beings” and article 12 b) which proclaims freedom of research as “part of freedom of thought”.

Having regard to national regulations on patent and to ethics bodies opinions on stem cell research and their use.

Having regard to the previous EGE Opinion num. 3 of 30.09.1993 on the Commission proposal for a directive on biotechnological invention, Opinion num. 8 of 25.09.1996 on the patenting of inventions involving elements of human origin, Opinion num. 12 of 23.11.1998 on Human embryo research, and Opinion num. 15 of 14. 11.2000 on Human stem cell research and use.

Having regard to the Round Table organised by the Group on 20 november 2001 in Brussels with members of the European Parliament, jurists, philosophers, scientists, representatives of industries, representatives of religions, representatives of patients’ associations and other groups of interest, and of international and European organisations (UNESCO, Council of Europe, WTO, WIPO, EPO).

Having regard to the Hearings of experts on 3rd July 2001, 4th september 2001, 2nd october 2001, and 8th january 2002.

Having regard to the reports asked by the Group to Prof. Daniel Kevles (Department of History, Yale University) on “A history of patenting life in the United States with comparative attention to Canada and Europe” and to Prof. Geertrui Van Overwalle (Centre for Intellectual Property Rights, Faculty of Law, K.U. Leuven) on “Study on the patenting of inventions related to human stem cell research”.

Having heard the rapporteurs Linda Nielsen and Peter Whittaker.

1. *Whereas:*

Scientific Background

Characteristics of Stem Cells. Stem cells are cells found in all vertebrate animals, including human beings. They play roles in the processes of normal development and regeneration or repair of damaged tissues. The reason for this is their properties of dividing to give cells either identical to themselves or differentiated into particular types of cells.

Because of these properties, it is thought probable that stem cells will find use in the therapy of degenerative diseases or injuries. Other potential applications for human stem cell cultures include uses for studying fundamental processes of human development or for toxicological testing and drug design. Non-human animal stem cell lines may also be used to produce genetically modified animals. It is also possible that genetically modified non-human animal stem cell lines may be developed for human therapeutic purposes.

1.2. *Sources of Human Stem Cells.*

Different types of stem cells can be distinguished according to the sources from which they are retrieved. Thus, 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 regenerate the various tissues but they are rather difficult to find and isolate and they do not seem to 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)

One can distinguish:

Embryos created by in vitro fertilisation. They can have been created for the purpose of assisted reproduction but not used for it (the supernumerary embryos) or they can have been created specifically for the purpose of research or treatment. These embryos are viable and could lead to birth if implanted in the uterus.

Embryos created by cloning technique (by transfer of the nucleus of somatic cell into an oocyte) or created by parthenogenesis (by stimulation of an oocyte to initiate the duplication of the oocyte genetic material and then the division of the cell). Given the consensus in Europe to ban reproductive cloning, these embryos cannot be implanted in a uterus. Their capacity to lead to a birth is supposed to be either probably very reduced (in the case of the cloned embryo) or quasi-null (in the case of parthenogenesis).

— Stem cells may possibly be also obtained by injecting stem cell or egg

cytoplasm into somatic cells transforming them into stem cells (ooplasmic transfer).

— Other methods: new technical ways of deriving stem cells may be developed in the future.

1.3. *Derived Cell and Stem Cell Lines*. One should distinguish:

— Stem cells freshly derived from an organ or tissue which have not yet been subjected to any modification and which are capable of being propagated as stem cell lines,

— Unmodified stem cell lines which refer to cultured lines of cells which have been propagated originally from freshly derived stem cells and which have not been modified in any other way. When the stem cells are derived from an embryo, the undifferentiated stem cell lines which can be derived from them are pluripotent.

— Modified stem cell lines which refer to cultured lines of cells, propagated from stem cells or stem cell lines, which have been modified either by genetic manipulation, or by treatment that causes the cells to differentiate in a particular way.

Legal Background *General Background*

1.4. *What Are the Purposes of Patent Law? Patent law in general*. Patent law aims to promote technical innovation and the dissemination of its fruits. The inventor gets exclusive rights to control commercial exploitation of his invention for some years and in return, he discloses detailed description of his invention, making the new knowledge available to all. This disclosure enables others (researchers etcetera) to build on the achieved knowledge.

— European Directive

The original purpose of the 1998 EU Directive regarding legal protection of biotechnological inventions is to establish legal certainty in this area within the European Community and to help European biotechnological companies to become more efficient in promoting innovation and thus attracting investment.

In addition, the Directive includes ethical considerations which take into account specific concerns. In this aspect, the EU approach of patenting in biotechnology differs from the US legal framework in that field which does not explicitly refer to ethics.

1.5. *What is a Patent?* A patent provides the patent holder with protection, for a period of 20 years in general, against the commercial exploitation of the invention by others. A patent is not a legal title granting its holder the exclusive right to exploit his invention, nor is it a right of ownership. A patent is a legal title granting its holder the exclusive right to stop others from using or making his invention. If a third party wants to use an invention protected by patent, a licence is normally required from the owner of the patent.

The granting of a patent is not an authorisation for the use of the invention. As mentioned in recital 14 of the Directive “a patent for invention does not authorise the holder to implement that invention, but merely entitles him to prohibit third parties from exploiting it for industrial or commercial purposes”. Whether or not research, commercial use or marketing is permitted, may be dealt with by other

kinds of regulation than the patent regulation.

1.6. *What May be the Scope of a Patent?* A patent application contains a description of the invention and one or more claims. The claim(s) are an essential part of the patent as they define the scope of the rights given by the patent to the patent holder. The claim defines thus what third parties may or may not do without a licence from the patent's holder. A licence is normally based on paying a fee.

One distinguishes claim on product and claim on process or method:

— A product claim may concern a substance (like a chemical compound) or a composition of matter (like a cell line). The protection given by such patent includes the right to prevent third parties not having the owner's consent from making, selling, using or importing the said product.

— A process claim concerns the activities exercised upon for instance biological material to effect a process or a method. The protection given by such patent includes the right to prevent third parties not having the owner's consent from using the process, and using, selling or importing the product obtained by this given process. The protection does not cover the same product which would have been obtained otherwise. Thus a product claim provides stronger protection for the patent holder and more restrictions in relation to further use and research than a process claim.

1.7. *Who Grants a Patent?* Patenting facilities (National Patent Offices) are available in most countries (for

instance the USPTO* INPI** for France). The protection of the invention is limited to the state that grants the patent and the legal consequences of the patent are settled by the national courts.

In 1973, the European Patent Convention (EPC) was signed in München, creating the European Patent Organisation (EPO). At present, 20 European countries including all 15 EU Member States have signed the EPC. A patent granted by the EPO may be registered in any of the states adhering to the Convention, avoiding then for the inventor the multiplication of applications. The EPO has recently incorporated the 1998 EU Directive within its practice.

In case of dispute over a patent, only the national courts are competent and thus may adopt diverging positions on the same dispute. Therefore, the European Commission proposed to create a "Community Patent", which would be delivered by EPO, and a centralised Community tribunal in the framework of the European Court of Justice would be set up to deal with the potential disputes. This Commission Proposal is still under discussion.

1.8. *Criteria for a Patent.* A patent may be granted in all European countries, provided that the three following requirements are all met:

— Novelty. The invention must represent an advance in what is considered to be the "state of the art" in its field.

— Inventive step. The invention must not be obvious to anyone familiar with the field concerned. A simple discovery cannot constitute a patentable

* USPTO: United States Patent and Trademark Office.

** INPI: Institut National de la Propriété Industrielle.

invention. One of the main difficulties regarding patenting in biotechnology, is the ability to distinguish between a simple discovery which is not patentable and an invention as such, which is patentable. As emphasised in the EGE Opinion num. 8 of 25.09.1996 on the patenting of inventions involving elements of human origin: "The traditional distinction between discovery (not patentable) and invention (patentable) involves, in the field of biotechnology, a particular ethical dimension".

— Industrial application. The invention must be capable of industrial application. In this respect medicine and agriculture are considered to be "industry".

1.9. *Exclusions*. Traditional exclusions in Europe. In Europe patents are excluded if their publication or exploitation is in conflict with the "order public" or morality. The concept refers mainly to the respect of human dignity which is at the roots of human rights and is mentioned in the article 1 of the Charter of Fundamental Rights. The Convention of München refers to "order public" in its article 53.a and the 1998 EU Directive regarding legal protection of biotechnological inventions refers to "order public" and morality in its article 6.

Diagnostic, therapeutic and surgical methods are also traditionally excluded from patenting. This exclusion was aimed to maintain the sharing of medical knowledge and know-how for the benefit of patients. It does not concern products or drugs used for medical purposes.

Specified Exclusions. The EU Directive goes into detail to specify what is contrary to "order public" and mor-

ality in the biotechnology sector, namely article 6 states in particular that the following are considered to be unpatentable:

— Processes for cloning human beings.

— Processes for modifying the germ line genetic identity of human beings.

— Uses of human embryos for industrial or commercial purposes.

— Processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

It should be noted, as stressed in Recital 38, that this list is "to provide national courts and patent offices with a general guide to interpreting the reference to "order public" and morality... and obviously cannot presume to be exhaustive".

1.10. *Exemptions*. In Europe, there is a traditional academic exemption, mentioned in most national laws, which allows further research without paying a licence to the inventor, if this research is not commercial.

1.11. *Compulsory Licences*. As stated in most national regulations and in the above-mentioned WTO TRIPS agreements, compulsory licences may be granted if the patent protection is contrary to the common good.

1.12. *Differences between Europe and the US Concerning Patent in General*. There are four main differences between EU and US regarding law or conception of application of the law:

— *Priority of the First Inventor or the First Claimer* While disclosure or previous claim by an inventor ends any right to later patent in Europe, the

American system grants the patent right to the first inventor. After disclosure the inventor has a period of time—the so-called grace period—to claim the patent.

— *Exemption and Exclusion.* In the US, the legislation does not provide for academic exemption. But in practice, there are often agreements between patent owner and research laboratories, although it is not a right.

In the US there are no legally based exclusions regarding diagnostic and therapeutic use or ethically based exclusions.

— *Criteria of Patentability.* The criteria for patenting are traditionally interpreted in a more flexible and broader way in the US, leaving a larger place for legal interpretation and for negotiation after the patent is awarded.

In the US, the conception of what is an invention is broader.

In the US, the invention must prove to have a “utility” instead of “industrial application”, the notion of “utility” is less specific, it means it is useful. The conception of what is “useful” is broader than the more precise requirement of industrial application used in Europe.

— *Opposition to a Patent.* The possibility to oppose to a patent differs between the US and EU. In the US, only third parties whose interests are directly damaged by a patent can oppose via the US Patent Office or via a court, while in Europe, any person may oppose to a patent delivered by the European Patent Office by addressing directly the EPO, or via a court. The need to translate patent applications in different languages makes also the cost of the patent much higher in Europe than in the US.

1.13. *Patents and Transparency.* The inventor is required to publish full details of the invention in a manner sufficiently clear and complete for it to be carried out by a skilled person. When a patent has been granted patent information is provided. There are comprehensive databases with international coverage, also accessible through the Internet. Moreover, there are patent databases with national coverage and bibliographic databases covering the literature.

Patenting Biotechnological Inventions

1.14. *When were Biotechnological Inventions First Patented?* In 1980, the US Supreme Court overturned its previous case law to allow the granting of a patent on living matter, namely an oil degrading bacterium (Diamond v. Chakrabarty’s case law). But previously in the 70’s, other biotechnological inventions have also been patented with regard to methods, such as in particular methods of recombinant DNA.

Since then, there is a standing practice for patenting biotechnological inventions on living matter. Thousands of patents consist of living matter, for instance micro-organisms, genes, cell lines including human ones such as cancer cell lines, and there are recognised ways to patent such inventions.

1.15. *What is Specific to Certain Biotechnological Inventions?* As mentioned above, in the field of biotechnology, the distinction between invention and discovery may be less obvious than in other fields. Furthermore, the description of the patented

product may also be difficult. That is why, with regards to micro-organisms, it is not enough to describe the micro-organism and its industrial application, so the deposit of the micro-organism may be necessary.

Therefore, the Budapest Treaty signed in 1977 and implemented by the World Intellectual Property Organisation defines how the written description of the invention must be supplemented by the deposit of the new micro-organism in an internationally recognised depository authority. The access to the micro-organism is defined by the national law of the country where the depository authority is.

1.16. *Patents on Stem Cells*. Worldwide there have been over 2000 patent applications involving human and non human stem cells, of which one quarter refer to embryonic stem cells. Over one third of all stem cell applications and one quarter of all embryonic stem cell applications have been granted.

According to the practice in the US or in the EU, the various processes which have been considered for patenting include:

— Processes for isolation of stem cells from embryos or tissues.

— Processes for enrichment of stem cells in mixtures of cells.

— Processes for culturing of stem cells.

— Processes for genetically modifying stem cells for particular applications. For example it may be possible to modify stem cells to avoid rejection following transplantation.

— Processes for inducing stem cells to differentiate in particular ways. It will be necessary to induce stem cell cultures to differentiate into particular

types of cells (*e. g.*, neural cells, heart muscle cells) for specific regenerative therapies.

— Processes for inducing adult stem cells to undergo ‘retrodifferentiation’ or ‘transdifferentiation’. Retrodifferentiation refers to the induced reversion of adult stem cells, with limited differentiation capacity towards multipotency or pluripotency. Transdifferentiation is the induction of adult stem cells to differentiate into cells of a tissue type different from that normally associated with the particular stem cells.

— Processes to create embryos by transfer of a somatic cell nucleus to an enucleated egg (cloning technique) for derivation of stem cells. This provides the possibility for producing autologous stem cells which are less likely to be rejected.

— Processes to create non-viable “embryos” by parthenogenesis. These techniques, which may also be used to provide autologous stem cells, would eliminate the need to destroy potentially viable embryos for deriving stem cells.

— Processes for transforming somatic cells directly into stem cells, *e. g.*, by injecting them with stem cell cytoplasm or egg cytoplasm (ooplasmic transfer).

And the various products which have been considered for patenting include:

- Stem cells.
- Stem cell lines.
- Differentiated stem cells.
- Genetically modified stem cells.

1.17. *Patenting of Human Embryonic Stem Cells*. Human embryonic stem cells have so far been both isolated and cultured in the US, Australia,

India, Singapore, Israel and Sweden, and only cultured in the UK. The issue raised by the 1998 EU Directive is whether patents on human embryonic stem cells should be granted or not, and the question is still in discussion. The facts are that such patents have already been granted in the US.

One example is the US patent awarded to the Wisconsin Alumni Research Foundation (WARF), for human pluripotent stem cells derived from spare embryos created for infertility treatment. This broad patent covers both James Thomson's method of isolating human embryonic stem cells (ESC) and the five undifferentiated stem cell lines derived. That patent gives WARF control over who may work with its five stem cell lines and for what purpose. WARF decided to provide access against a nominal fee to academic researchers and access against a negotiable fee to other scientists. In return for its funding of James Thomson's research, the for-profit Geron Corporation was granted a licence agreement by WARF. Geron holds exclusive rights to develop the stem cell lines isolated at the University of Wisconsin into three specific differentiated stem cell lines for commercial purposes.

Ethical Background

1.18. *Historical Aspects of Patenting.* Since its origin at the end of the XVIII the century, modern patent law has had an ethical dimension. Its aim is indeed to define the conditions of a "social contract" between inventors and society at large. On the one hand, inventors are able to be granted financial rewards and thus to share profits

with manufacturers and industrialists. On the other hand, inventors are obliged to disclose information on useful inventions, for the benefit of the public good. That means that the purpose of a patent is to strike a balance between different interests.

The patent system aims to keep a balance between the inventor's interests and the interests of society. That is why a fair balance between both interests, meaning that the scope of the claim of the patent must be proportional to the scope of the effectively described applications of the inventions, has an ethical dimension.

1.19. *Ethical Aspects of Patenting in Biotechnology in General.* The patenting of biotechnological inventions, especially in the health sector, includes special ethical dimensions. The patenting of inventions to be used for therapeutic or diagnostic purposes may have an impact on access to health care. Concern has been expressed about the patent award by the EPO to Myriad Genetics for diagnostic tests for breast cancer and ovarian cancer. The claims include the genes BRCA1 and BRCA2. It is feared that the monopoly on the tests that this will create will result in unreasonable prices being charged with consequent reduced access to the tests. There are similar concerns expressed about the award to the Chiron Corporation of a patent granted in Europe for a combined HIV-Hepatitis C test kit. It seems probable that similar situations might arise in the stem cell area. Although patenting should encourage research, there is a fear that patenting of biotechnological inventions may entail excessive costs of research which

would also impede access to health care. Moreover, since the description of an invention is not sufficient for a researcher to reproduce or improve it, it is important to make research biological materials accessible to the researchers.

1.20. *Ethical Aspects of Patents Involving Human Stem Cells.* The patenting of inventions involving human stem cells raises specific ethical questions related to fundamental ethical principles, namely:

— The prohibition of making profits from the human body and its elements, as stated by article 3 of the Charter of Fundamental Rights, which is grounded on the principle of non-commercialisation of the human body. The donation of stem cells of human origin (adult, foetal or embryonic) must not give rise to payment of donors, apart from the justified compensation of constraints.

— The principle of free and informed consent of the donor which is also reflected in article 3 of the Charter of Fundamental Rights and in the Recital 26 of the 1998 EU Patent Directive stating “Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law”.

1.21. *Ethical Aspects of Patents Involving Human Embryonic Stem Cells.* The Group is well aware that all procedures involving directly or indirectly the human embryo are controversial in the sense that they are based on presuppositions for instance concerning the beginning of human life and

the question whether there should be an absolute or a relative protection of human life in its different stages. Political and legal decisions in these ethical matters may change the self understanding of what it means to be a human being in a given epoch and society.

The question of the dignity and the moral status of the embryo remains indeed highly controversial in a pluralistic society as the European Union. Those who are opposed to human embryo research, cannot, a fortiori, consider any patenting in that field. Among those who consider research on embryos ethically acceptable, some may feel great reluctance towards patenting the resulting inventions, while others consider patenting inventions derived from embryo research as acceptable, especially given their potential medical benefits.

Industrial and commercial exploitation of human embryos is excluded from patenting according to article 6 of the above-mentioned 1998 EU Directive. This article leaves open the question of patentability of cells obtained from donated embryos, nor does it state precisely which embryos are subjected to this exclusion. Some consider that non viable embryos, which cannot lead to a birth, such as those created by parthenogenesis, or even by somatic cell nuclear transfer (cloning), are not covered by this exclusion.

When the question is about the patentability of the process which requires the use of human oocytes to produce stem cells by any means, there is a risk that women may be submitted to undue pressure to donate oocytes.

There is at present a tendency to accept double morality where there is no coherence between different positions adopted by one country. For instance, one could expect that to consider research on human embryos to derive stem cells as unethical, might imply the prohibition of the import for research of embryonic stem cells derived from human embryos as well as of the use of potential therapeutic applications resulting from such research, which is not always the case.

Opinion

Scope of the Opinion. According to the 1998 EU Directive on the Legal Protection of Biotechnological Inventions article 7: “EGE evaluates all ethical aspects of biotechnology”.

The Group has, in its Opinion núm. 15 of 14 th november 2000 on the ethical implications of human stem cell research and its uses, made recommendations, namely:

— To set up a strict public control by centralised authorities, on human embryo research where it is allowed.

— To take measures to prevent commercialisation of human embryos or cadaveric foetal tissue; to ensure the respect of ethical principles through the control of public authorities, concerning import of human stem cells, where allowed.

This present opinion deals with the specific ethical questions related to patenting of inventions involving human stem cells. The Group is aware of the fact that patents also involve many difficult and different questions of an economic and political nature, which may influence the way of dealing with

patents, but has seen its task as providing an ethical focus on the question.

The rapid development of biotechnology, especially the promise of stem cell research, makes it appropriate to consider and clarify some questions which could not have been taken into account when the 1998 EU Directive was drafted, given the state of the art at that time.

One option would have been to forbid patenting of stem cells or stem cell lines. The consequence of such an option would be the major slowing of this research field (except in case of a very unlikely large public investment), and the EGE opinion is that it would be contrary to public (and especially patients’) interests. Moreover, the Group considers that it would be contrary to the EU choices as expressed by the 1998 EU Directive on patenting.

The Group finds that it is crucial to define the conditions required to patent, the limits of the patenting of human stem cells in relation to ethical considerations and the relevant processes securing ethical evaluation.

The Basic Ethical Dilemma

EGE recognises the importance of patents as an incentive to innovation and as a reward to the inventor for openness and publishing the results.

One ethical dilemma arises due to the fact that patents can encourage scientific progress which can be used to the benefit of better health care, and at the same time, patents can also impair access to the health care due to the need of a licence to use them and to the fees that will have to be paid to the patent holder.

It is then necessary to secure the right balance between the inventor's interests and the society's interest in the sense that one task for the community is to secure ethical principles and values in the context of possible conflicting interests of stake-holders, namely: patients and patients' associations, inventors and other researchers, donors, industry, investors, healthcare providers, and social insurance providers.

In order to be able to specify ethical limitations, a number of problems are to be considered, including:

- Content of patents (process or product).

- Various sources of stem cells.

- Methods used to derive stem cells.

- Protection of the donor.

- Possible socio-economic consequences and philosophical implications of the patent system as applied to stem cells (further research, access to health care).

Content of The patent

It is the opinion of the EGE 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 one specific use but a very

large range of potential undetermined 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).

Sources of Stem Cells

Human stem cells may be adult (from living or deceased donors), foetal or embryonic stem cells. The derivation of stem cells raises different ethical questions, depending on the source of the cells. The Group considers that applicants for a patent involving human stem cells should declare which is the source of the stem cells.

As already stressed by the Group in the Opinion núm. 15 of 14/11/2000 on the ethical aspects of human stem cell research, there are strong ethical concerns about the use of human embryos which require specific caution. These concerns are reflected in the 1998 EU Directive which states that processes which would lead to uses of human embryos for industrial or commercial purposes are contrary to "order public" and morality and not patentable.

The Group sticks to the strict application of the principle of non-

commercialisation of human embryos, which is in line with the principle of non-commercialisation of the human body.

The Group considers that patenting of inventions allowing the transformation of unmodified stem cells from human embryonic origin into genetically modified stem cell lines or specific differentiated stem cell lines for specific therapeutic or other uses, is ethically acceptable, as long as the inventions fulfil the criteria of patentability, and in respect of the above-mentioned ethical principles.

The Question of Cloning

The 1998 EU Directive states, in its article 6, section 2, that “processes for cloning human beings” shall be considered unpatentable. In recital 41 cloning is defined as “any process, including techniques of embryo splitting, designed to create a human being with the same nuclear genetic information as another living or deceased human being”. This provision raises the question of the scope of the prohibition to patent processes of cloning human beings. The Group notes that the 1998 EU Directive does not bring clarification on the specific question to apply the prohibition of patenting only to reproductive cloning or also to cloning for stem cells.

The Group recalls that:

— The process used to create embryos by somatic cell nuclear transfer is the same in both reproductive cloning and cloning for stem cells but the destiny of the cloned embryos differs.

— The prohibition to create identical human beings by cloning is shared

by all EU states, and mentioned in the Charter of Fundamental Rights and in the additional protocol to the Convention of Council of Europe and more widely shared in the world, as mentioned in the Universal Declaration on the Human Genome of UNESCO, 17.

— There is a diversity of approaches between member states concerning cloning for stem cells.

As mentioned in its Opinion núm. 15 of 14th november 2000 on Research on human stem cells, there are strong ethical concerns to be taken into account about cloning for stem cells.

Therefore, considering these ethical concerns, and particularly the risk of instrumentalisation and commercialisation of the embryo, the Group calls for a cautious approach, excluding the patentability of the process of creation of a human embryo by cloning for stem cells. The Group stresses the urgent need to engage a public debate on that issue.

Protection of the Donor

When the donated cells may become part of a patent application, donors should be informed of the possibility of patenting and they are entitled to refuse such use. Apart from justified compensation, donors ought not to get a reward which could infringe the principle of non-commercialisation of the human body. These ethical requirements should apply as far as possible to imported stem cells.

Patents and Further Research and Development

Although the appreciation of the patentability of an invention in bio-

technology as in other fields is a matter of a case by case evaluation by a patent office and eventually by a court, the Group again insists on the necessity to avoid the granting of too broad patents that would impair further research and development.

In the new area of stem cell research, the potential use is hoped to expand over time and stem cell lines may provide very important research tools. In addition to the academic exemption, it is essential to secure that patents on stem cell lines are not too broad, as this may have adverse effects on the aim to support further innovation to the benefit of health care.

It is therefore the opinion of EGE that patents shall only be granted, when the patent claim refers to a specific and a sufficiently accurately described stem cell line and its industrial application. That involves a consistent relationship between a patent claim and the description of the invention.

European Registry

The Group calls for the creation of an EU Registry of unmodified human stem cell lines, such registry which should include information on both ES (embryonic stem) and EG (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.

Patents and Access to health Care

The patent creates a control regarding commercial use. This raises ques-

tions as to the uses which are covered by the patent.

To secure that patent holders do not misuse their rights for example by charging unreasonable fees for the use of their inventions, EGE finds that the recourse to compulsory licence should be encouraged when the access to diagnosis and treatment is blocked by misuse of patent rights.

The EGE stresses the fact that it is the responsibility of the states to establish legal procedure for the delivery of compulsory licence and to examine if fair access to health care justifies such a procedure.

Ethical Evaluation of Patent Applications

According to article 7 of the 1998 Patent Directive, the European Group on Ethics is charged with the evaluation of the ethical aspects of biotechnology in general.

Besides this general evaluation, the EGE considers that there may be also a need to make ethical evaluations in the course of the examination of patent applications involving specific ethical dimensions.

It would be desirable that such ethical evaluation becomes part of the review process of national patent offices or European Institutions like EPO and those advisory panels of independent experts are set up for that purpose.

EGE proposes that, in the course of the evaluation of biopatenting required by article 16 of the 1998 EU Directive, specific attention is paid to the consequences of the patents on further research and access to health care, especially with regard to the fair

and equitable accessibility of new therapeutic and diagnostic products at high costs.

The European Group on Ethics in Science and New Technologies:

The chairperson: Noëlle Lenoir

The members:

Rafael Capurro

Anne Mc Laren

Pere Puigdomenech Rosell

Yvon Englert

Göran Hermerén

Stefano Rodota

Linda Nielsen

Peter Whittaker

Günter Virt

Inez de Beaufort

Dissident Opinion:

Profesor Günter Virt agrees in general with the above, but does not agree permitting patenting processes and products using material resulting from destroyed human embryos: "Human embryonic stem cells and also embryonic stem cell lines are excluded

from patentability because we cannot get embryonic stem cell lines without destroying an embryo and that means without use of embryos. This use as material contradicts the dignity of an embryo as a human being with the derived right to life. If the condition for patentability is the industrial and commercial use and if the use of human embryos for industrial and commercial purposes is not patentable, then every exception, which cannot exclude industrial and commercial purposes, is against the ethical sense of the directive. Patenting is an incentive. Patentability of human embryonic stem cells and stem cell lines would push research towards embryonic stem cells and thus undermine the priority of research using non embryonic stem cells. Despite the relatively clear regulations in the directive this incentive for research will lead to forms of "bypasses" which makes it impossible to guarantee an ethically tolerable situation in the field of patentability".