ALLEA Statement on Patenting of Inventions Involving Human Embryonic Pluripotent Stem Cells in Europe [1]

ALLEA draws attention to the fact that European researchers in the field of human embryonic stem cells find themselves in a regulatory dilemma, and, potentially, at a competitive disadvantage, due to the inconsistencies in the application of moral approaches between European legislators and the institutions called upon to enforce the regulatory framework. This dilemma results partly from a decision handed down by the Enlarged Board of Appeal of the European Patent Office in 2008 that restricts patenting on a wide range of results from research into pluripotent human embryonic stem cells. In December 2009, the Federal Supreme Court of Germany referred a number of essential issues to be answered by the Court of the European Union, all also related to the decision of the EBA. This statement explains the situation, urges that the position be clarified as soon as possible, and makes recommendations aimed at strengthening support for R&D capacities in this field in Europe.

I. Introduction (1): Opportunities and obstacles in research on pluripotent human stem cells

Since the late 1990s, technologies that are based on stem cell research have often been discussed in a very controversial manner. On the one hand, there were great hopes in the area of regenerative medicine: human embryonic pluripotent stem cells (i.e.: cells which can develop into tissues of all organs, but which do not have the potential to develop into entire human body), have been viewed as a promising source for generating and regenerating cells of such organs as the liver and pancreas, [2] of heart muscle tissue, [3] and, for instance, for the repair of damaged neural brain cells of patients suffering of Parkinson's, multiple sclerosis or Alzheimer's [4]. On the other hand, stem cell research has been facing severe ethical concerns because embryos had to be used (i.e. destroyed) in order to generate human embryonic pluripotent stem cells.

In the meantime, scientists have succeeded in generating so-called pluripotent human stem cells and stem cell lines by reprogramming adult fibroblast cultures, using pluripotency associated genes (iPS) [5]. Even though iPS can be generated without destroying human embryos, iPS, because of the existing safety risks [6], are not used at present in clinical trials for therapeutic purposes [7]. Their use is limited to pre-clinical toxicology and safety tests, as well as for drug discovery purposes [8]. Thus, for the time being, research into human pluripotent embryonic stem cells and innovative use of them remains essential for the development of therapeutics.

II. Introduction (2): European and national legislation on research into human embryonic stem cells

Research into human embryonic stem cells is well developed in Europe. Many European countries, such as Belgium, the Czech Republic, the Netherlands, Spain, Sweden and the United Kingdom allow research involving human embryos under stringent conditions. Others, like Poland, allow such research by refraining from adopting any specific rules. Legal instruments of the European Union such as the Directive 2004/23/EC on the *Setting Standards of Quality and Safety for the Donation, Testing, Processing, Preservation, Storage and Distribution of Human Tissues and Cells*, and the Regulation (EC) No.1394/2007 on *Advanced Therapy, Medical Products* and Amending Directive 2001/83/EC and Regulation (EC) No.26/2004 are explicitly applicable to human embryonic stem cells: They allow controlled use of human embryonic stem cells but at the same time leave it, under certain circumstances, to the national legislator to prohibit the use of such cells.

The EU-Directive 98/44/EC on the *Legal Protection of Biotechnological Inventions* does not contain any provision, which would directly relate to human embryonic stem cells. However, Article 5.1 excludes from patent

protection the human body, at various stages of its formation and development, and the simple discovery of its elements. Moreover, the Directive excludes from patent protection also inventions, the exploitation of which is contrary to *ordre public* or morality, and indicates that this includes, in particular, the use of human embryos for industrial or commercial purposes (Article 6.1, 6.2c). At the same time the Directive states that an element isolated from the human body or otherwise produced by means of a technical process, can be patented, provided that the regular patentability requirements are met (Article 5.2).

III. Contradictions arising from the decision of the Enlarged Board of Appeal of the European Patent Office (25/11/2008)

The present statement focuses exclusively on an inconsistency in law, which results from a decision handed down by the *Enlarged Board of Appeal* (EBA) of the European Patent Office of November 25, 2008[9]. According to the EBA inventions involving pluripotent embryonic stem cell lines of human origin, i.e. originally generated from a human embryo and involving its destruction, cannot be patented. This prohibition applies even where the respective stem cell lines have been generated in full compliance with the regulatory rules controlling research in human embryos that apply at national levels (as in Sweden and the UK; and in Australia, Israel and the USA). Nor does it matter, according to the EBA, that the exercise of the invention itself does not depend on any subsequent, repeated use of human embryos.

The Board based its decision on Rule 28.c of the Implementing Regulations to the European Patent Convention (EPC), which entirely corresponds to Article 6.2c of the EU Directive 98/44/EC on the *Legal Protection of Biotechnological Inventions*. According to the Directive, the use of human embryos for industrial or commercial purposes is excluded from patent protection, as an explicit category of inventions, the commercial exploitation of which would be contrary to *ordre public* or morality.

The Board reached that conclusion despite the provision of Article 5.2 of the Directive, which allows, in principle, the patenting of "an element isolated from the human body or otherwise produced by means of a technical process,... even if the structure of that element is identical to that of a natural product."

The Board noted that neither the EU legislator nor the EPC legislator have chosen to define the term "embryo". Yet both must have been aware of such definitions in some national laws, in view of the purpose of the respective provision to protect human dignity and prevent the commercialization of embryos. The Board therefore presumed that the meaning of "embryo" should not be in any way restrictive, because it would have the effect of undermining the intention of the legislature. Restrictive interpretation would leave the question of what is an embryo to be determined in the context of each particular application.

The Board also emphasized that Rule 28.c does not mention claims, but refers to "invention" in the context of its exploitation; accordingly, what needs to be looked at is not just the explicit wording of the claims but the technical teaching of the application as a whole as to how the invention is to be performed.Before human embryonic cultures can be used they have to be made. Since the only disclosed teaching of how to perform the invention involves making human embryonic stem cell cultures through the destruction of human embryos, the resulting "invention" would be excluded from patenting. A contrary view would restrict the application of Rule 28.c EPC to what applicants choose explicitly to put in their claims. However the Board argued that avoiding the patenting prohibition would become merely a matter of skilful drafting of such a claim.. Hence, the Board explicitly added that "making the claimed product remains commercial or industrial exploitation of the invention even where there is an intention to use that product for further research."

It reiterated that "this use involving destruction (of human embryos) is thus an integral and essential part of the industrial or commercial exploitation of the claimed invention and thus violates the prohibition of Rule 28.c EPC."

The Enlarged Board of Appeal also explicitly refused as "neither necessary nor indeed appropriate to discuss... whether the standard of ordre public or morality should be a European one or not, whether it matters if research in certain European countries involving the destruction of human embryos to obtain stem cells is permitted, whether the benefits of the invention for humanity should be balanced against the prejudice to the embryo...".

Ultimately, the Board held that the provisions of Rule 28.c EPC, i.e. Article 6.2c of the Directive are

clear in that respect and do not leave any room for interpretation.

As a consequence of this decision inventions involving pluripotent embryonic stem cells of human origin are not eligible for patent protection under the EPC, notwithstanding the fact that the stem cells have been generated in full compliance with the applicable regulatory provisions (as, e.g., in Belgium, Netherlands, Sweden and the UK, and likewise in Australia, Israel, New Zealand or the United States). This exclusion from patent protection applies also where the exercise of the disclosed and claimed invention, i.e. the technical teaching for solving a technical problem, can be commercialised subsequently as drugs under the EU regulatory laws. Examples would be liver or pancreatic lineages, or early cardiogenic precursors that were technically (in the laboratory) generated from pluripotent human embryonic stem cell lines.

It is to be feared that without patents as a necessary incentive for investments in developing therapeutics based on human pluripotent embryonic stem cells, such developments will take place outside Europe. Such developments may even be based on research results of European scientists and researchers, who may have applied and may have been granted patents, e.g. in the US, China, etc., and licensed them outside of Europe. Europe may, eventually, become just a market for those therapeutics, since their marketing is, in principle, allowed, but be prevented from enjoying the economic benefits of the research undertaken.

ALLEA is aware of the fact that the legal uncertainty surrounding stem cell research and the exploitation of its results in Europe has already resulted in a significant move of researchers and research projects in this area (particularly in industry) to Asia and the Americas. ALLEA expresses its concerns that a continued lack of clarity on the issue of patenting risks putting research in Europe at a competitive disadvantage.

IV. Referral of the German Federal Supreme Court

ALLEA is aware of the fact that the Court of Justice of the European Union is at present hearing a case [10] based on a referral of the German Federal Supreme Court of November 12, 2009. In that case the validity of a German Patent11 is in dispute, which relates to "neuronal precursors, methods of production and use for therapy of neural defects", issued by the German Patent Office in April 1999, claiming, *inter alia*, "isolated, purified precursor cells from embryonic stem cells with neural or glial characteristics." In its referral the German Federal Supreme Court asked the Court in Luxembourg to provide an interpretation of Articles 5 and 6, especially Articles 6.2c of the EU Directive with regard to the patentability of inventions involving human pluripotent embryonic stem cells, which function, i.e. can be performed without any use or re-use of human embryos.

V. Recommendations

ALLEA expresses the hope that the **Court of Justice of the European Union** will clarify matters in line with its established case law, namely "...that Article 5.2 of the Directive thus seeks to grant specific rights as regards the patentability of elements of the human body. Even though it provides merely for the possibility that a patent be granted, it obliges the Member States, as is apparent from the 17th to 20th recitals in the preamble to the Directive, "**to provide that their national law does not preclude the patentability of elements isolated from the human body, in order to encourage research aimed at obtaining and isolating such elements valuable to medicinal production.**" [12].

ALLEA also hopes that it be clarified that the Directive **concerns only the grant of patents**, and that the scope of the Directive "does not therefore extend to activities before and after the grant, whether they involve research or the use of the patented product" [13] and that, finally, "the grant of a patent does not preclude legal limitations or prohibitions applying to research into patentable products or the exploitation of patented products, as the 14th Recital of thePreamble to the Directive points out. The purpose of the Directive is not to replace the restrictive provisions which guarantee, outside the scope of the Directive, compliance with certain ethical rules which include the right to self-determination by informed consent." [14]

ALLEA is confident that a **balanced solution** can be found: such a solution should ensure that inventions involving pluripotent stem cells of human embryonic origin, that are generated in compliance with the competent regulatory provisions, but not involving use of human embryos, and whose products, in compliance with the EU legislation and the legislation of the respective EU Member States, can be commercialised as therapeutics or diagnostics, will enjoy the same incentives by

the patent system as other inventions, particularly those in the area of pharmaceuticals.

ALLEA draws attention to the ethical guidelines offered by the European Group on Ethics in Science and New Technologies to the European Commission in its Opinion No. 16 of 7 May 2002 on *Ethical Aspects of Patenting Inventions Involving Human Stem Cells*.

ALLEA is also aware that excluding from patent protection inventions, the final products of which can be commercialized in one or more of the EU Member States, potentially violates obligations which Member States entered into in international legal instruments, such as the TRIPS Agreement. In fact, the same Directive that had been used by the EBA as a mainstay of their argument explicitly emphasizes in its Article 1.2 and Recital 36 that it does not interfere with the obligations which the Member States entered into under the TRIPS Agreement.

As a case in point, ALLEA wishes to refer to a number of patent applications pending in the European Patent Office which are related to inventions involving pluripotent human embryonic stem cells. ALLEA *expresses its hope and is confident* that, taking cue from the current referral by the German Supreme Court and the subsequent reactions of the Court in Luxembourg, the competent institutions of the European Union will undertake all the necessary steps that the principles of the judgment of the Court of Justice of the European Union will, eventually, control also patent applications pending in the European Patent Office, and that the current regulatory dilemma be resolved as soon as possible.

Drafted by Standing Committee on Intellectual Property Rights

Professor William Cornish
British Academy
Professor Carine Doutrelepont
Royal Academy of Sciences, Letters and Fine Arts of Belgium
Professor Sir Roger Elliott
Royal Society, United Kingdom (chair until 2009)
Professor Stanislaw Soltysinski
Polish Academy of Arts and Sciences
Professor Are Stenvik
Norwegian Academy of Arts and Sciences
Professor Joseph Straus
Union of German Academies of Sciences (Chair)
Professor Ünal Tekinalp
Turkish Academy of Sciences
Professor Tomasz Twardowski
Polish Academy of Sciences
Professor Feer Verkade
Royal Netherlands Academy of Arts and Sciences
Professor Sylvester Vizi
Hungarian Academy of Sciences
Professor Alain Strowel, Brussels (guest)
Rüdiger Klein (ex officio, ALLEA)

Footnotes

[1] **ALLEA emphasizes that this statement does not address the regulatory solutions concerning embryo research in European countries, nor does it address embryo research as such; it focuses exclusively on a regulatory dilemma and the resulting effects on research efforts based in Europe.**

[2] Cf., e.g., Zaret/Grompe, Generation and Regeneration of Cells of the Liver and Pancreas, 2008 Science 1490.

[3] Cf., e.g., Chien/Domian/Parker, Cardiogenesis and the Complex Biology of Regenerative Cardiovascular Medicine, 2008 Science 1494.

[4] Brüstle/Jones/Learish/Karram/Choudhary/Wiestler/Duncan/McKay, Embryonic Stem Cell-Derived Glial Precursors: A Source of Myelinating Transplants, 1999 Science 754.

[5] Cf. only Takahashi/Yamanaka, Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors, 2006 Cell 663.

[6] Cf. Holden/Vogel, A Seizemic Shift for Stem Cell Research, 2008 Science 561; Wobus, The Janus Face of Pluripotent Stem Cells – Connection Between Pluripotency and Tumourigenicity, 2010 Bioassays 993.

[7] Cf. Alper, Geron Gets Green Light for Human Trial of ES Cell-Derived Product, 2009 Nature Biotechnology 213.

[8] Webb, Burgeoning Stem Cell Product Market Lures Major Suppliers,, 2010 Nature Biotechnology 535.

[9] OJ EPO 2009, 306 – Use of Embryos/WARF.

[10] Case No. C-34/10.

[11] DE 19756864 – Inventor and patentee Professor Brüstle.

[12] Judgment of 16 June 2005, Case No. -45603, Commission of the European Communities v. Italian Republic, No. 70.

[13] Judgment of 9 October 2001, Case No. -377/98, Kingdom of the Netherlands, supported by Italian Republic; and see Kingdom of Norway v. European Parliament and Council of the European Union, supported by Commission of the European Communities, No. 79.

[14] Ibidem No. 80.