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Patentable parthenotes? Advocate General says yes

In the latest development to the patentability of human stem cells, the AG has recommended that stem cells derived from parthenogenically activated oocytes should not be excluded from patentability any longer. The AG drew the distinction between totipotent and pluripotent cells, noting that cells that do not have the capacity to develop into a human being should not be excluded from patentability.

Good news could be on the horizon for stem cell patenting in Europe, following the Advocate General's (AG) opinion in the most recent stem cell case to be considered by the CJEU (C-364/13). The AG has recommended that unfertilized human ova that have been stimulated to develop by parthenogenesis are excluded from the definition of "human embryo" and are therefore back in the realm of patentable subject matter. If the CJEU follows this recommendation, it would refine the position established in the Brüstle decision in 2011 (C 34/10).

Background

International Stem Cell Corporation (ISC) applied to the UK Intellectual Property Office (UK IPO) for two patents (GB0621068.6 and GB0621069.4) for inventions that related to stem cells derived from parthenogenetically activated oocytes. These applications claimed methods of producing pluripotent human stem cell lines from parthenogenetically-activated oocytes, stem cell lines produced according to the claimed methods and methods of producing synthetic cornea or corneal tissue involving the isolation of pluripotent stem cells from parthenogenetically-activated oocytes.

The UK IPO refused these applications on the grounds that the inventions covered uses of human embryos as defined by the Court of Justice in *Brüstle*. At first reading, the IPO's decision to refuse ISC's applications seems clear-cut. The *Brüstle* decision on the meaning of a "human embryo" in the sense of Article 6(2)(c) of EU Directive 98/44/EC on the legal protection of biotechnological inventions (the Biotech Directive) appears to exclude parthenogenetically-activated oocytes, otherwise known as parthenotes, from patentability. However, an inconsistency in the technical reasoning regarding the nature of parthenotes makes this exclusion less clear. ISC appealed the IPO's refusals to the High Court, which in turn asked the CJEU for clarification as to whether parthenotes should be considered to be human embryos.

Technical background

Human development typically starts with the fertilisation of a human ovum. Over the next five days, the cells in the fertilized ovum, or zygote, divide rapidly and then begin to differentiate into different types of cells. By day five, a structure called a blastocyst has formed. The blastocyst contains different types of cells, some of which will go on to form the body of the embryo and some of which will go on to form other structures such as the placenta, referred to as extra-embryonic tissues. Both are essential for development of the blastocyst into a human being.

Embryonic stem cells are commonly derived from human embryos in these early stages of development. These stem cells can be divided into different categories, depending on their potential to develop and change into different types of cells. "Totipotent" cells are capable of developing into all human cell types, while "pluripotent" cells can only develop into the cell types that make up the body, and not into extra-embryonic tissues. Therefore, pluripotent cells cannot develop into a human being.

At the time of the present referral it was agreed by all parties that, according to current scientific knowledge, a human parthenote cannot develop past the blastocyst stage. A parthenote has not been fertilized and so only contains maternal DNA. Consequently, a parthenote cannot develop all extra-embryonic tissues, and so cannot develop into a human being. It is generally accepted that mammalian parthenotes are not able to develop to full term without further intervention.

The technical evidence presented in the *Brüstle* case was different. In that decision, the CJEU did not make any technical distinction between (i) fertilised ova, (ii) non-fertilised ova subjected to somatic-cell nuclear transfer and (iii) parthenotes. In fact, the court commented that parthenotes "are, as is apparent from the written observations presented to the Court, capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do so". It was against this background that the CJEU decided that parthenotes were within the definition of "human embryos".

What did the CJEU mean by "capable of commencing" in *Brüstle*?

In *Brüstle*, the CJEU held that the definition of a human embryo must be understood in a wide sense, so any inventions that do not respect human dignity are excluded from patentability. Consequently, the CJEU defined a human embryo as "any human ovum after fertilisation, any non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted, and any non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis". The decision was informed by technical submissions from both sides about the developmental potential of cells derived from human embryos at various stages in their development, and was intended to exclude from patentability any cells that are "capable of commencing the process of development of a human being".

The crux of the new referral was therefore the meaning of the term "capable of commencing the process of development of a human being". Does this mean that the first developmental steps mimic the development of a fertilized ovum, i.e. cell division and differentiation similar to that of a fertilised ovum, or is the outcome more significant, i.e. must the cells possess the capacity to develop into a human being?

The UK High Court favoured the latter interpretation, and so referred the following question to the CJEU:

> "Are unfertilised human ova whose division and further development have been stimulated by parthenogenesis, and which, in contrast to fertilised ova, contain only pluripotent cells and are incapable of developing into human beings, included in the term "human embryos" in Article 6(2)(c) of Directive 98/44 on the Legal Protection of Biotechnological Inventions?".

Crucially, this question is limited to those parthenotes that are incapable of developing into human beings.

Future-proofing the definition

In revisiting the issues of the patentability of stem cells, the AG has answered a slightly different question than that referred in *Brüstle*. The need for a further referral to clarify the patentability of human embryonic stem cells highlights the difficulty in making decisions in technical fields that are changing at such a rapid pace. On reflection, three years down the line, it might be said that the CJEU erred in excluding parthenotes from patentability and including them in the same category as fertilised ova and non-fertilised ova subjected to somatic-cell nuclear transfer. Both of these have a full complement of maternal and paternal DNA, and are capable of developing into a human being. A parthenote, we now know, is not.

How then, to future-proof the definition? Are we likely to find ourselves in another three years' time in a position where it is technically possible to coax a parthenote to develop into a human being?

The AG clearly had this in mind, and therefore answered the referred question with a caveat: a parthenote is not a human embryo but only as long as it is not capable of developing into a human being and has not been genetically manipulated to acquire such a capacity.

The AG's opinion brings us firmly back to the fundamental reasons for the Biotech Directive: the need to respect human dignity and exclude human beings, at any stage of development, from patentability. However, where there is no capacity to develop into a human being, there is no justification for a centralised exclusion from patentability across the whole of Europe. It remains to be seen whether the court agrees with the AG's opinion, and whether the AG's suggested caveat on genetic manipulation goes far enough.

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