

Patenting embryonic stem cells – influence of recent jurisprudence on (Belgian) stem cell research

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Table of contents

Acknowledgements	i
Table of contents.....	ii
List of abbreviations	v
List of patent cases and decisions	vi
Abstract	vii
Samenvatting.....	viii
Part 1: Introduction.....	1
1.1 Stem cells and their therapeutic value.....	1
1.1.1 Stem cells.....	1
1.1.2 Stem cell potency	1
1.1.3 Human embryonic stem cells	2
1.1.4 Value of hESCs in therapy and drug development.....	3
1.1.5 Induced pluripotent stem cells.....	5
1.2 The ethical aspects of human embryonic stem cells.....	5
1.2.1 The principal objections	5
1.2.2 An embryo-saving alternative	6
1.3 The legal aspects of human embryonic stem cells.....	6
1.3.1 Statutory law on embryonic stem cell research.....	6
1.3.2 Intersection between patent law and morality.....	8
1.4 Essential aspects of (biotechnology) patenting	9
1.4.1 Patent protection: different criteria and purposes.....	9
1.4.2 From filing an application to the grant of a patent	10
1.4.3 Importance of patent protection in the biotech industry	10
1.4.4 Importance of patent protection in academic institutions	11
1.5 Patenting human embryonic stem cells in Europe.....	11
1.5.1 Filing routes and decision-making organs on patent law.....	11
1.5.2 The legal framework.....	12
1.5.3 The WARF case	15
1.5.4 The Brüstle case in the EU.....	16
1.5.5 The Brüstle case at the EPO.....	19
1.6 Human embryonic stem cells: changes in EPO's practice?	20
1.6.1 EPO's previous practice	20
1.6.2 EPO's current practice	21

1.6.3	EPO's emerging practice.....	21
Part 2:	Aim of the study	22
Part 3:	Results and analysis.....	23
3.1	Impact of the CJEU judgment on (Belgian) stem cell research	23
3.1.1	Questioning and evaluation	23
3.1.2	The view from academic institutions	24
3.1.3	The view from a translational research expert	25
3.1.4	The view from stem cell companies.....	26
3.1.5	The view from research funding agencies.....	27
3.2	Statistical data	30
3.2.1	A hitch in the evolution of embryonic stem cell patenting	30
3.2.2	Embryonic stem cell patenting in Europe <i>versus</i> the U.S.....	35
3.2.3	Embryonic <i>versus</i> induced pluripotent stem cell patenting.....	36
3.2.4	Who files embryonic stem cell patent applications?	38
3.2.5	Pluripotent stem cell research in an academic setting	38
3.3	The Brüstle patents and the patentability of their subject matter	39
3.3.1	A matter of policy	39
3.3.2	The German patent held by Brüstle	39
3.3.3	The European patent held by Brüstle.....	40
3.4	European patent applications and the impact of the Brüstle cases	41
3.4.1	Positioning pending patent applications.....	41
3.4.2	Influence of the CJEU judgment on European patent applications	42
3.4.3	Influence of the Brüstle cases on patent application EP 2327762.....	47
Part 4:	Discussion	49
4.1	Impact of CJEU ruling C-34/10 on (Belgian) stem cell research	49
4.2	Impact of CJEU ruling C-34/10 on European patent applications.....	50
4.3	Implications of a stringent outcome in the Brüstle v. Geron case	51
4.4	General conclusion	51
Part 5:	Discussie	53
5.1	Impact van HvJ EU Arrest C-34/10 op stamcelonderzoek (in België).....	53
5.2	Impact van HvJ EU Arrest C-34/10 op Europese octrooiaanvragen.....	54
5.3	Implicaties van een streng besluit in de zaak Brüstle v. Geron.....	55
5.4	Algemene conclusie.....	56
Part 6:	Materials and methods	58

6.1	Materials.....	58
6.2	Methods	58
6.2.1	Identifying the actors in the area of stem cell research.....	58
6.2.2	Searching patent applications and consulting information thereof (Espacenet)	59
6.2.3	Taking interviews.....	59
6.2.4	Classification searching (Espacenet)	60
6.2.5	Field Combination searching (PATENTSCOPE)	60
6.2.6	Searching in Thomson Innovation Patent Database	61
6.2.7	Searching in PubMed.....	62
6.2.8	Consulting information from a patent examination (European Patent Register).....	62
	References.....	63
	Attachments	69
	Attachment I.....	69
	Attachment II.....	70
	Attachment III.....	72
	Attachment IV	73
	Attachment V	74
	Attachment VI	75
	Attachment VII	81
	Attachment VIII	87

List of abbreviations

BGH	Bundesgerichtshof
BPatG	Bundespatentgericht
CJEU	Court of Justice of the European Union
DIE	Dienst voor de Intellectuele Eigendom
DPMA	Deutsches Patent- und Markenamt
EBoA	Enlarged Board of Appeal
EPC	European Patent Convention
EPO	European Patent Office
EU	European Union
hESC	human Embryonic Stem Cell
NIH	National Institutes of Health
PCT	Patent Cooperation Treaty
PGD	Pre-implantation Genetic Diagnosis
SBB	Single Blastomere Biopsy
TBoA	Technical Board of Appeal
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UK	United Kingdom
UKIPO	United Kingdom Intellectual Property Office
ULB	Université Libre de Bruxelles
U.S.	United States
USPTO	United States Patent and Trademark Office
UT	University of Twente
VUB	Vrije Universiteit Brussel
WARF	Wisconsin Alumni Research Foundation
WIPO	World Intellectual Property Organization

List of patent cases and decisions

Brüstle v. Greenpeace case	Decision of the German Patent Court	3 Ni 42/04
	(05.12.2006)	
	Decision of the CJEU	C-34/10
	(18.10.2011)	
	Decision of the German Federal Court of Justice	X ZR 58/07
	(27.11.2012)	
Brüstle v. Geron case	Decision of the EPO Opposition Division	
	(11.04.2013)	
WARF case	Decision of the Enlarged Board of Appeal	G 2/06
	(25.11.2008)	

Abstract

The use of human embryonic stem cells used to require the destruction of a human embryo in order to obtain these stem cells. This traditional requirement has been – worldwide – an ethical and legal sticky point through 15 years by now. Several European countries have yet acquired a favorable regulatory framework for the conduct of embryonic stem cell research; however, the patentability of human embryonic stem cell-based inventions is a crucial factor in determining whether the many potential therapies will move from academic laboratories via the industry to the patient. In late 2011, the Court of Justice of the European Union ruled that procedures relating to human embryonic stem cells or human embryonic stem cell lines are excluded from patentability if they involved the destruction of human embryos. This European Union ruling consequently has affected the practice of the European Patent Office and, needless to say, has caused a lot of confusion in the scientific community. In this thesis, we evaluate the impact of current patent debate on the universities, companies, suppliers and public funding authorities that are engaged in stem cell research. Therefore, interviews were taken of the actors in both the Benelux and the United Kingdom. We also performed several database searches in order to map the influence of the European Union ruling on the filing and examination of European patent applications and, subsequently, we compared the obtained results with the patenting of human embryonic stem cell-based inventions in the United States and the patenting of induced pluripotent stem cell-based inventions in Europe. We conclude that there have been a lot of misconceptions about the influence of the Court's recent decision and that a vocal minority is awaiting the European Patent Office to take a conclusive position in this matter. Moreover, it is of great importance that human embryonic stem cell research is to be continued, irrespective of induced pluripotent stem cell research.

Samenvatting

Het gebruik van humane embryonale stamcellen vereiste aanvankelijk de destructie van een humaan embryo ter verkrijging van de stamcellen. Dit traditioneel gevolg vormt – vanuit een globaal perspectief – alreeds gedurende 15 jaar een twistpunt op zowel ethisch als wettelijk vlak. Verschillende Europese landen hebben tot dusver toch een gunstig regelgevingskader samengesteld waarbij de uitvoering van embryonaal stamcelonderzoek mogelijk is, hoewel de octrooieerbaarheid van uitvindingen op basis van humane embryonale stamcellen een cruciale rol speelt in de bepaling of de vele potentiële therapieën zich een weg zullen banen van de academische laboratoria via de industrie naar de patiënt. Eind 2011 heeft het Hof van Justitie van de Europese Unie bepaald dat procedures gebruikmakende van humane embryonale stamcellen of humane embryonale stamcellijnen niet octrooieerbaar zijn indien deze de vernietiging van humane embryo's teweegbrengen. Deze uitspraak heeft vervolgens een invloed uitgeoefend op het beleid van het Europees Octrooibureau en, vanzelfsprekend, heel wat verwarring veroorzaakt in de wetenschappelijke wereld. In deze scriptie evalueren we de invloed van het huidig debat rond humane embryonale stamcel octrooien op de academische instellingen, bedrijven, leveranciers en publieke overheden die betrokken zijn in stamcelonderzoek. Daarvoor hebben we interviews afgelegd van de actoren in de Benelux en het Verenigd Koninkrijk. We hebben alsook verschillende database searches uitgevoerd zodat we de invloed van de uitspraak in de Europese Unie op het indienen en behandelen van Europese octrooiaanvragen in kaart kunnen brengen. Vervolgens vergeleken we de verkregen resultaten met de data voor het octrooieren van uitvindingen gebruikmakend van humane embryonale stamcellen in de Verenigde Staten en het octrooieren van uitvindingen gebruikmakend van geïnduceerde pluripotente stamcellen in Europa. We kunnen besluiten dat er heel wat misopvattingen bestaan over de impact van de recente beslissing en dat een luidruchtige minderheid wacht op het definitief standpunt van het Europees Octrooibureau in deze materie. Daarenboven is het van therapeutisch belang om het humaan embryonaal stamcelonderzoek verder uit te voeren, ongeacht het bestaan van de relatief onbetwiste geïnduceerde pluripotente stamcellen.

PART 1: INTRODUCTION

1.1 Stem cells and their therapeutic value

1.1.1 Stem cells

Stem cells are undifferentiated or 'mother' cells found in the human body, which have the potential to develop into many different cell types that carry out different functions (Bosch, 2008). Most cells in the human body are differentiated. That means that they are built to function in a particular organ system and carry out a specific function. These differentiated cells result from the process of cell division, a process that begins with undifferentiated stem cells. One of the main characteristics of stem cells is their ability to self-renew or multiply while maintaining the potential to develop into other types of cells. As such, stem cells can become cells of the blood, heart, skin, muscles, brain, *etc.* There are various sources of stem cells but all stem cell types have the same capability to develop into differentiated cell types.

1.1.2 Stem cell potency

The essential role of stem cells appears from their presence in presumably all multicellular organisms, throughout every stage of life (Bosch, 2008). However, not all stem cells have the same differentiation potential. A stem cell's potency ranges from totipotent to unipotent, which denotes, respectively, the power of a single cell to construct a complete organism (e.g. a zygote) and the power of a cell to yield merely one cell type (e.g. a myoepithelial stem cell) (Van Keymeulen *et al*, 2011). Between these extremes a stem cell might be pluripotent or multipotent: the term "pluripotency" refers to the capacity of a cell to develop into all cell types excluding those that constitute extra-embryonic tissue, whereas multipotent cells are solely able to differentiate into a closely related family of cells (e.g. hematopoietic stem cell). Human stem cells are classified consistent with their developmental potential and residency. Although four broad types of stem cell sources may be recognized (stem cells from embryos, fetuses, umbilical cords or adults – see Attachment I), the most commonly used classification primarily distinguishes between embryonic and adult stem cells, i.e. tissue-specific stem cells derived from a fetus or postnatal individual (Table 1.) (Can, 2008). Totipotent cells, strictly speaking, are not considered to be fully "stem cells" since they lose self-renewal capacity as these cells undergo cleavage divisions (Bongso & Lee, 2005). Yet they are relevant in this thesis because totipotent cells form the basis for the development of an entire human being.

Table 1. Overview of the features that typify human totipotent, embryonic and adult stem cells

Stem cells	Stem cell source	Cell potency				Main advantages	Main disadvantages
		Toti-	Pluri-	Multi-	Uni-		
Fertilized egg, Early blastomere	From zygote to the morula (see Figure 1.)	▪				Human embryo research*	- controversial
Embryonic stem cell (ESC)	Inner cell mass of the blastocyst (see Figure 1.)		▪			Unlimited capacity for proliferation	- controversial - immunogenicity - development of teratoma (tumour)
Adult or tissue-specific stem cell	Fetal, juvenile and adult tissues			▪	▪	Autologous or allogeneic cell-based treatments	- lower proliferative capacity than ESC - difficult to obtain from some tissues

*Research on early human embryos is of great importance in the fields of developmental biology and reproductive medicine.

1.1.3 Human embryonic stem cells

Embryonic stem cells are characterized by pluripotency and can be harvested from the inner cell mass of the blastocyst (Figure 1.). The blastocyst is an embryo which has not yet been implanted into the uterine wall and becomes generated at day 5 after human fertilization. At this developmental stage, the very first cell lineage decision is realized by separating the cells that will give rise to the future embryo (inner cell mass) from the cells that are destined to form the placenta (outer cell mass) (Niakan *et al*, 2012). More specifically the epiblast of the inner cell mass, i.e. the inner cell mass cells adjacent to the outer cell mass, will differentiate into the embryo proper once the blastocyst is attached to the uterine wall. Thus, the epiblast contains the founder population of pluripotent cells for the formation of all three germ layers during the following stage of development. The stem cells in each of these germ layers, characterized by multipotency, are committed to differentiate into unipotent stem cells and hundreds different types of cells in the human body (Figure 2.) (Sell, 2004).

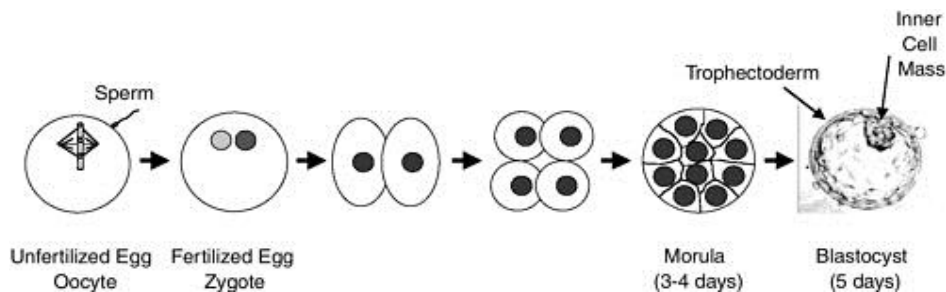


Figure 1. Human pre-implantation embryo development. The human pre-implantation embryo sprouts from the fusion of a human egg and sperm, whereupon it cleaves approximately once a day up to the morula stage. The morula is followed by the blastocyst stage which is morphologically distinguishable by the appearance of the inner cell mass (embryoblast), the outer cell mass (trophectoderm) and the blastocyst cavity (National Research Council, 2005).

Human embryonic stem cells (hESCs) were first isolated and short-term cultured by Dr. Ariff Bongso's group in 1994 (Bongso *et al*, 1994). Four years later, the first hESC line was established by Dr. James Thomson's group at the University of Wisconsin–Madison (Thomson, 1998). In both research groups, spare blastocyst-stage embryos donated by couples undergoing *in vitro* fertilization were used as the stem cell source. An inner cell mass isolation from supernumerary embryos is currently the most common way to derive hESCs, although several other methods enabling the preparation of pluripotent stem cells have been set up in the last decade (see Attachment II). The pluripotent inner cell mass comprises a clump of 30-50 cells which can be propagated in highly specific culture conditions. In view of their envisaged therapeutic applications, these conditions include a xenogeneic-free and feeder-free culture system that preserves the ability of human embryo-derived stem cells to produce embryonic stem cell progeny whilst their tendency to differentiate is being suppressed (Ilic *et al*, 2012; Tannenbaum *et al*, 2012).

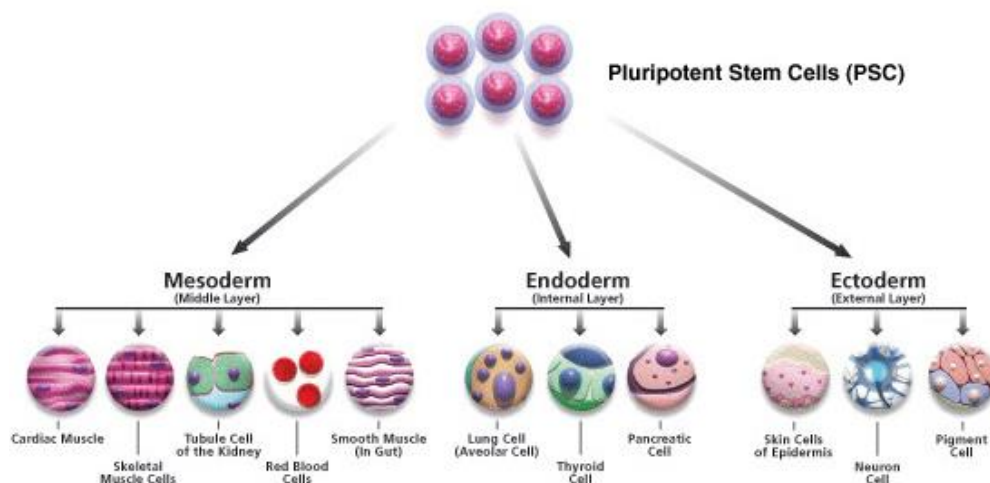


Figure 2. Pluripotent stem cells give rise to the three germ layers (mesoderm, endoderm, ectoderm) during mammalian embryogenesis. The more than 200 different cell types that are present in the human body are derived from these primary layers. As an illustration, the mesoderm aids in the production of cardiac muscle, skeletal muscle, smooth muscle, red blood cells and kidneys; the endoderm constitutes tissues within the lung, thyroid and pancreas; the ectoderm aids in the construction of melanocytes, epidermis and neuronal cells (Sigma-Aldrich, 2013).

1.1.4 Value of hESCs in therapy and drug development

The miniscule clump of cells from which mammalian organisms originate, is thought to be able to offer a similar contribution to medicine as human genetic engineering. Where gene

therapy purposes to regain normal cellular function by modifying the genetic content of a patient, cell therapy endeavors to repair diseased or damaged tissue by the introduction of new cells. Gene therapy and embryonic stem cell therapy are particularly interesting to treat genetic diseases for which experts have found no cure so far. Both approaches may be considered complementary depending on the degree of tissue degradation, however, converging the two technologies in a novel treatment strategy called stem cell-based gene therapy might be the most promising (Yates & Daley, 2006; Uzzaman *et al*, 2009; Zhao *et al*, 2012; Beutner *et al*, 2013). The theory is substantiated by the fact that cell-based gene delivery provides unique advantages over direct gene transfer (NIH, 2009a) and genetically engineered human embryonic stem cells could overcome the safety issues surrounding hESCs for their use as human therapeutic agent (Strulovici *et al*, 2007). It is indeed evidenced by transplanted cells differentiated from mouse embryonic stem cells that those cells entail the risk to create teratomas, i.e. tumours containing a mixture of cell types, when even small numbers of undifferentiated cells are present within the transplant (Bjorklund *et al*, 2002; Robinson *et al*, 2005). Another concern involves the immunologic rejection of hESC-derived cells because such transplanted cells are potentially recognized as foreign by the recipient. Although adult stem cells deliver a source of non-tumorigenic and autologous starting material, the use of human embryonic stem cells holds the promise of long-term maintenance and expansion taking into account their infinite lifespan as well as their greater capacity to self-renew (NIH, 2009a). For example, the combination of hESC and gene therapy may initiate long-term expression of the therapeutic gene needed to correct chronic diseases such as Parkinson's disease, traumatic spinal cord injury, diabetes, osteogenesis imperfecta, liver or heart failure, *etc.*, in a controlled fashion (Strulovici *et al*, 2007). Regardless of the original source of stem cells, the future of regenerative medicine lies in manufacturing "off-the-shelf", allogeneic treatments which are suitable for any patient with a specific illness (Moran *et al*, 2012).

Human embryonic stem cell lines, which have been derived from an embryo carrying one or more affected alleles, could also produce an *in vitro* model of the disease for the purpose of better understanding its underlying mechanisms (Pickering *et al*, 2005; Ben-Yosef *et al*, 2008; Niclis *et al*, 2009). Any pure population of human cell types can be generated at the desired amount through directing the stem cells along a given cell lineage (Murry & Keller, 2008). Subsequently these physiological models provide an invaluable resource for drug discovery

and toxicity screening. Since derivatives of disease-specific hESC approximate more to the human biological system than animal testing does, it is clear that such approach might offer safer and more effective results during the development of new pharmaceuticals (Gauthier *et al*, 2011; Zuba-Surma *et al*, 2012).

1.1.5 Induced pluripotent stem cells

At the end of 2007, the first reports on the creation of human induced pluripotent stem cells were published (Yu *et al*, 2007; Takahashi *et al*, 2007). This work received renewed interest in response to the ethical controversy by which human embryonic stem cell research was persistently hampered (see section 1.2.1), but represents a continuation of earlier results (Takahashi & Yamanaka, 2006). The concept of "induced pluripotency" includes the application of adult somatic cells (e.g. a skin cell) whereby the embryonic state is artificially induced by introducing transcription factors reactivating crucial stem cell genes. As such adult cells are dedifferentiated and become phenotypically embryonic stem cell-like. While it is as yet unclear whether induced pluripotent stem cells are as versatile as embryonic stem cells, the important difference is that the starting material does not originate from embryos.

1.2 The ethical aspects of human embryonic stem cells

1.2.1 The principal objections

Ethical considerations raised by the implementation of human embryonic stem cell research encompass the use of a human embryo, the creation of a human embryo for the purpose of isolating stem cells, high payments for oocyte donation, cryopreserving human embryos, the potential misapplication for reproductive cloning, *etc.*

Opponents of human embryonic stem cell research likewise express a moral objection to the classical approach of isolating hESCs given that this procedure requires the destruction of a human embryo. Killing an early human embryo is considered impermissible in view of its moral status and this outweighs the benefits for a living person from being treated by the application of human embryo-derived stem cells. This puts investigators in front of an ethical dilemma between discontinuing the development of a young embryo in order to save a person's life or the other way around (Hug, 2006). The human embryo is considered to have the same moral status as an individual human being. Proponents of the sanctity of life doctrine consider that human life is inviolable from conception to natural death. Thus, while

human embryonic stem cells *per se* may not be sacred, destroying an early stage human embryo in order to harvest those stem cells is considered equivalent to committing murder (Hyun, 2010). Any stage of human development holds full moral rights which cannot be violated under any circumstances, not even when embryos left over from fertility treatments which would be discarded anyway, irrespective of whether such stem cells or stem cell derivatives may be used to save mature human life. Albeit one may look upon a 5 days old embryo solely as an unconscious developing embryo, followers of the full moral status view are convinced that human beings for whom each is assigned the intrinsic value of human life come into existence immediately after fertilization (Holm, 2003). It is noted in this regard that also some proponents of embryonic research *per se* have moral objections against legally protecting procedures using human embryos or human embryonic stem cells, as it is considered to represent the commodification of human life.

1.2.2 An embryo-saving alternative

Single blastomere biopsy (SBB) starts from an earlier stage of human embryo development (morula) than applied in the traditional way of deriving hESCs (blastocyst). The morula stage appears approximately 3 days after fertilization and allows the extraction of one blastomere without being interrupted for further development. Embryonic stem cells are then obtained by bathing the individual blastomere in nutrients that are naturally found in human embryos (Chung *et al*, 2008). Although SBB does not imply the killing of embryos, nor does it interfere with the embryo's developmental potential, yet some people query the invasiveness of such biopsies. In point of fact, the procedure of SBB is similar to that one used in pre-implantation genetic diagnosis (PGD) by fertility clinics. Because these methods both aspirate blastomeres out of the morula stage, the moral debate of destroying embryos is simply shifted to the moral debate of PGD practice (De Melo-Martin *et al*, 2006). The invasive technology has been morally objected to reasoning that the embryo is possibly harmed, embryo loss is at risk and the long-term health implications have been poorly studied (Yu *et al*, 2009).

1.3 The legal aspects of human embryonic stem cells

1.3.1 Statutory law on embryonic stem cell research

All prohibitive, restrictive and permissive stem cell policies worldwide have been determined on the basis of ethical and scientific deliberations. Countries that acknowledge the full moral

status of a human embryo impose the prohibition of research using embryos or cell products derived from embryos, whereas the majority of countries occupy an intermediate position in the stem cell dilemma by authorizing limited embryonic stem cell research (The Hinxton Group, 2006). Belgium, the United Kingdom, Sweden, Israel, Australia, Japan, China (People's Republic), California (U.S.), Illinois (U.S.) and Iowa (U.S.) are examples of the few countries or states having a permissive stem cell policy. As an illustration, the table in Attachment III gives an overview of the bulk of European countries' national legislation concerning human embryonic stem cell research.

Authorizing limited embryonic stem cell research can be rather permissive or restrictive. For instance, the stem cell policy that is currently in force in the Netherlands, Denmark, Canada, Virginia (U.S.), Indiana (U.S.), Brazil, Russia, India and China (Hong Kong) emanates from the moral distinction between IVF embryos and "research embryos". The former embryos were originally generated in view of an *in vitro* fertilization treatment and thus primarily intended for reproductive purposes. The latter includes embryos which are manufactured via somatic cell nuclear transfer (SCNT). It is believed that using already existing IVF embryos is morally more acceptable than using embryos created especially for research purposes (Hug, 2005). The main argument in defense of this allegation is based on the "nothing is lost" principle. Seeing that spare IVF embryos will have no chance of being implanted into the mother's womb and develop into a human being, nothing will be lost if one applies them to harvest pluripotent stem cells (Outka, 2002).

More restrictive stem cell policies, such as the policy in Germany, Austria, Ireland, Italy and Oklahoma (U.S.), have been influenced by the moral difference between employing already existing hESC lines and deriving human embryonic stem cells in order to establish a stem cell line (Moran *et al*, 2012). The rationale behind this discrepancy rests on the fact that the embryo, from which cell lines were produced before the stem cell debate was emerged, or from which cell lines are allowed to be established under permissive stem cell policies, will never regain viability. As inner cell mass isolation necessitates the sacrifice of a human embryo, it would, however, be ethically unacceptable to approve further acts of embryo destruction. This perception has led to the moral permissibility of utilizing publicly available hESC lines, whilst deriving hESCs from embryos is regarded as an immoral practice (Green, 2001). Thus, the governments only tolerate the import and application of hESC lines in existence, typically created before a certain date.

1.3.2 Intersection between patent law and morality

As a large part of research is funded or co-funded by industry, which needs to see a return on investment, the development of human embryonic stem cells into clinical therapy will also depend on the availability of patent protection on this technology.

The ethical issues on patenting human-derived biotech inventions as well as the patenting of morally controversial subject matter are two discussions based on a moral component which need to be distinguished. By now, different political systems have enacted measures to deal with the concerns that are associated with biotechnology patenting (Bahadur & Morrison, 2010). As an example, the European Union (EU) directive on the legal protection of biotechnological inventions permits that "*an element isolated from the human body [...] may constitute a patentable invention*" (Directive 98/44/EC, Art. 5 (2)) or the Supreme Court of the United States (U.S.) decided, in the context of the landmark case *Diamond v. Chakrabarty*, that patentable subject matter embraces "*anything under the sun made by man*" (US Supreme Court, 1980).

Over the centuries and from a global perspective, morality has been playing an inferior role in patent law (Lenk *et al*, 2007). Nevertheless, the extent to which inventions with a morally fraught nature are patentable remains a challenging question. Europe and the U.S. provide contrasting examples of approaches towards the patenting of morally controversial subject matter (Bagley, 2007). While both the EU biotechnology directive and the European Patent Convention encompasses a morality clause (see section 1.5.2), the patent law of the U.S. was formulated without any notice regarding the patentability of biotech inventions in terms of ethics or morality. The latter approach, also defined as the "patent first, ask questions later" approach, originated from the reasoning that patent law and morality should be kept strictly separate since both aspects represent another value, respectively, an economic and cultural value (Bagley, 2003). As such, in contrast to the situation in Europe, there are fewer restrictions on U.S. patenting procedures relating to human embryonic stem cells, whereas ethically undesirable outcomes become moderated by legal provisions outside the scope of U.S. patent law. In the United States, the cultural value of safeguarding human embryos is maintained by financially supporting solely those stem cell lines that were produced according to the ethical standards set forth by the National Institute for Health (NIH, 2009b). The diversity of approaches towards the patentability of human embryonic stem cells is widespread around the world and is at all times shaped by localized cultural norms and

political structures. For example, the Canadian Patent Office has excluded the patentability of fertilized eggs and totipotent cells since these are regarded as "higher life forms", but allows any subject matter that is connected with the cells or cell products (e.g. pluripotent cells) to be patented (Hagen, 2008). Not unlike European patent law, Japanese patent law contains a morality exception (Linehan, 2012). The Japanese Patent Office has recognized that the morality clause is invoked when inventions involve the destruction of a human embryo, although methods or products developed on the basis of existing hESC lines are eligible for protection. Australia's patent act, likewise effective in a country that executes a permissive stem cell policy, describes one bright line exclusion, i.e. "*human beings, and the biological processes for their generation, are not patentable inventions*" (Australian Patent Act, Section 18 (2)). Yet, this patent act dates from 1990, it is mentioned that "*Australia's IP position will no doubt change as the technology evolves*" (Australian Law Reform Commission, 2004) and interested eyes are attentive for decisive legislative action (Aoun, 2011).

1.4 Essential aspects of (biotechnology) patenting

1.4.1 Patent protection: different criteria and purposes

An invention is likely to be protected under patent law on the four fundamental conditions that the technology is not already part of the state of the art, involves an inventive step or is non-obvious, is susceptible of industrial application or utility, and can be produced by a person that is skilled in the art (WIPO, 2004). The patent protection system is designed as an incentive mechanism for research progress and innovation. This purpose is pursued, on the one hand, by publicly disclosing detailed information on each legally protected invention so that a valuable source of technical knowledge is composed for researchers, inventors and innovators (Thumm, 2003). On the other hand, the grant of a patent appropriates the inventor or owner of the patented invention the statutory right to exclude others from commercially exploiting his proprietary technology. This defensive right is valid in those countries that are designated in the patent document for the duration of generally twenty years and empowers the patent holder to derive material benefits as a reward for intellectual effort and experimentation (WIPO, 2004).

1.4.2 From filing an application to the grant of a patent

In order to obtain patent protection on an invention, a patent application drafted thereon and filed with a national or regional patent office will in most cases be carefully examined for patentability. The length of time between filing and granting can reach up to several years. However, both in Europe and now recently also in the U.S., the date of first filing is extremely important in view of evaluating the patentability requirements "novelty" and "inventive step". The date of first filing, termed the priority date, will furthermore be recognized for a subsequent application in another country provided that the application is filed within one year after priority filing and that both countries are contracting parties of the Paris Convention (Paris Convention 1979, Art. 4). The right of priority is applicable regardless of whether the first patent application was filed on a national, regional (e.g. EPO, USPTO) or international (PCT) level. While the applicant may seek patent protection in as many countries as desired (or economically feasible), it should be taken into account that there exist some differences from one region or country to the other with regard to the procedural and substantive requirements (e.g. what is considered patentable subject matter?). The part of a patent application that is most important in this regard are the "claims", defining the scope of protection by the essential features of the invention, and thus indicating how broad or narrow the exclusionary power of the patent owner is.

1.4.3 Importance of patent protection in the biotech industry

Irrespective of the ongoing debate on what types of inventions in the field of biotechnology are eligible for patent protection, the business strategy of biotechnology firms relies heavily on intellectual property rights. In view of the R&D intensity as well as the capital intensity of a biotechnology firm, its patent portfolio and proprietary technical information are typically the most valuable asset. Small and medium-sized biotechnology enterprises frequently arise on the basis of potentially exploitable patents acquired from public research organizations or universities. Other biotechnology enterprises work towards the patent as a final product and collect revenues from either selling or licensing patents to companies that accommodate the resources required to market an invention (Burrone, 2006). Unlike trade secret protection, patents secure the substantial investment and high risks involved in the long product development life cycle by prohibiting competitors from mimicking or independently launching the knowledge-based innovation. Hence such a property right greatly reduces the

hazard for all sizes of enterprises within the life sciences and biotechnology sector to end up fruitlessly. *Vice versa*, investors in biotechnology research will decide whether or not the firm's intellectual property strategy is sufficiently solid for financial support by carrying out a patent due diligence investigation (Gogoris & Clarke, 2001).

1.4.4 Importance of patent protection in academic institutions

Biotechnological inventions *in se* will never constitute innovation as long as these inventions are not converted into practice. Beyond the main goal of academic scientific research, which comprises the publication of novel findings, technology transfer processes have adopted an increasingly important role in maximizing the flow-through of academic knowledge towards our society. By transferring the authorization of patent rights, granting licenses or setting up spin-off companies, it is ensured that the know-how of universities is much more accessible for exploitation. Many academic institutions and government funded research organizations established their own technology transfer office. As a first step, these offices determine the potential commercial interest of research results. Subsequently an appropriate valorization strategy will be discussed and conducted. If the regulatory framework assigns the ownership of publicly funded research patents to the university itself, which is for example the case in Belgium, technology transfer through patents and licensing is moreover reciprocal (Verspagen, 2006). Both the society and university receive additional value considering that the net revenues earned via patent valorization are largely invested in the further acquisition of academic knowledge.

1.5 Patenting human embryonic stem cells in Europe

1.5.1 Filing routes and decision-making organs on patent law

European biotech patent law, including statutory law and case law, operates at three distinct levels: the national level, the European Union (EU) level and the European level. Even though preparations are being made with the prospect of a unitary patent (De Girolamo, 2012), patent protection in European countries can at this time be obtained via either, or both, a national and European patent application. One may prefer the national route if protection is sought in a single or a few countries and potentially brings about a national patent that is conferred by the relevant national patent office. Whenever a third party attacks the validity of the national patent, it is the task of the *National Court* to assess whether the patent falls

within the legal framework. Applicants typically prefer the European route if patent protection is required in many European countries. A single European patent application and examination procedure may lead to protection in up to thirty-eight European countries. Once the patent is awarded by the European Patent Office (EPO), the European patent must be confirmed in each designated country of interest, after which it will be subject to national legislation and practices. The validity of the European patent might be scrutinized at both the European level, before the *Opposition Division of the EPO*, and at the national level, before the National Court. Opposition proceedings at the European Patent Office are particularly interesting from a third party perspective since decisions by the opposition division affect all countries where the European patent is to be enforced (Mejer & Van Pottelsberghe, 2009). Nonetheless, as in any judicial systems of first instance, decisions of the opposition division are appealable and can be challenged before the *Board of Appeal of the EPO*. Judgments on patent validity taken by a national court are only applicable to the country where the court resides. In exceptional cases, the *Court of Justice of the European Union (CJEU)* can be called upon, when national courts need further interpretation on statutory EU patent law to make its decision.

An important aside to mention is that the European Patent Office is not a European Union institution but runs independently of the European Union, as the signatory member states do not completely overlap (see Attachment IV and V). Although the EPO and EU have certain provisions and multiple member states in common, the EPO is not legally bound by decisions of the Court of Justice of the European Union.

1.5.2 The legal framework

Table 2. European patent law with reference to human embryos or human embryonic stem cells: for whom is it relevant?

	EPO (*)	EU (**)
A. Substantive patent law		
European Patent Convention (the 14 th edition) – Article 53(a)	▪	
Implementing Regulations to the European Patent Convention – Rule 28(c)	▪	
EU Directive (98/44/EC) on the legal protection of biotechnological inventions – Article 6(1), Article 6(2)(c), Recital 42		▪
National patent act	▪	▪
B. Case law		
Decision of the EPO's Board of Appeal in the WARF case (G 2/06)	▪	
Decision of the European Court of Justice in the Brüstle case (C-34/10)		▪
National jurisprudential decisions	▪	▪

*thirty-eight contracting states of the European Patent Office (EPO); ** twenty-eight member states of the European Union (EU)

Table 2 summarizes the legal framework upon which the patenting of inventions with regard to human embryos or human embryo-derived stem cells relies. First, the European Patent Convention (EPC), setting out uniform patent legislation for all contracting states of the EPO, comprises the internationally accepted component of patent law that tolerates inventions to be excluded from patentability on grounds of "ordre public" or morality (cf. TRIPS agreement Annex 1C, Art. 27). The morality clause is indicated under Article 53 (a) of the EPC and a list of exclusions in the area of biotechnological inventions is enumerated under Rule 28 of the EPC Implementing Regulations (Table 3). The first half-sentence of Art.53 (a) explicitly forbids the grant of a patent on an invention whereby its commercial exploitation would be contrary to the public order or morality. According to EPO's Board of Appeal, the "*ordre public*" remains in its entirety so long as the environment, the physical integrity of individuals and the public security is protected, whereas "*morality*" is related to the culture-specific beliefs with which behaviour is defined as right or wrong (TBoA, 1995). The following half-sentence of Art.53 (a) implies that the commercial exploitation of an invention shall not be deemed to be contrary to one of the key concepts solely because it is forbidden by law or regulation, as well as implies that if the commercial exploitation of an invention is not prohibited by law or regulation, it might be so contrary (Sterckx, 2008). Hence, Art.53 (a) raises questions about the justification of commercially developing an invention and is, neither concerned with the morality of patenting a particular invention, nor with the morality of that invention *per se* (TBoA, 2004). Within the scope of Art.53 (a), Rule 28 (c) excludes the industrial or commercial use of human embryos from patentability. Second, the European Union directive on the legal protection of biotechnological inventions contains morality provisions under Article 6 which are virtually identical to those included in the EPC. The EPO replicated these provisions from the EU biotechnology directive – though the EPC had already a morality clause beforehand – because the morality clause in Article 6 (1) was complemented by the addition of four non-exhaustive exclusions under Article 6 (2) (cf. Rule 28 EPC; Table 3). Even though the EU has no authority over the EPO, the EU biotechnology directive was introduced to balance the technical and ethical concerns over biotechnology patenting, to harmonize legislation for EU member states in the field of biotechnology and to indirectly steer the granting policy of the EPO (Van Overwalle, 2010). As a matter of fact, EU member states, which are at the same time also contracting states of the EPO, are obliged to translate any EU directive into national law. Third, national patent acts in European

countries usually describe the morality exception as a consequence of the EU biotechnology directive, however, interpretations vary among the member states.

Table 3. Exceptions to patentability in the European Patent Convention and its Implementing Regulations.

European Patent Convention (14 th edition) Article 53	Implementing Regulations to the EPC Rule 28
<p>European patents shall <u>not</u> be granted in respect of:</p> <ul style="list-style-type: none"> (a) inventions the commercial exploitation of which would be contrary to "ordre public" or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States; (b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision shall not apply to microbiological processes or the products thereof; (c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods. 	<p>Under Article 53 (a), European patents shall not be granted in respect of biotechnological inventions which, in particular, concern the following:</p> <ul style="list-style-type: none"> (a) processes for cloning human beings; (b) processes for modifying the germ line genetic identity of human beings; (c) uses of human embryos for industrial or commercial purposes; (d) 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 is clear from statutory patent law that the use of human embryos for industrial or commercial purposes must be excluded from patentability, unless therapeutic or diagnostic purposes are applied to the human embryo itself and are useful to it (Directive 98/44/EC, Recital 42). Though, the inextricable link between human embryos and human embryonic stem cells has entangled the patentability of human embryonic stem cell inventions in the morality clause. Case law of the Board of Appeal indicates that the EPO will no longer issue stem cell patents which, at the time of invention, necessitate the destruction of a human embryo and invoked Art.53 (a) EPC in the rejection of the WARF patent application (see section 1.5.3). Case law of the Court of Justice of the European Union ruled in the *Brüstle v. Greenpeace* case, on the basis of morality provisions, that inventions regarding human embryo-derived stem cells are not patentable – irrespective of the point in time at which the

human embryo was destroyed (see section 1.5.4). Nevertheless, case law of the German Federal Court of Justice opens up new perspectives for (national) human embryonic stem cell patents (see section 1.5.4) and case law of the EPO Board of Appeal is most probably expected in the *Brüstle v. Geron* case, which may quench the patent debate surrounding embryonic stem cells (see section 1.5.5).

1.5.3 The WARF case

On May 2, 1997 the technology transfer office of the University of Wisconsin-Madison (also known as the Wisconsin Alumni Research Foundation, abbreviated WARF) filed a European patent application (EP 0770125), in which they broadly claimed cultures of human embryonic stem cells and a method for maintaining the human embryonic stem cell cultures. As an illustration, one of the relevant claims in the WARF patent application reads as follows:

"A cell culture comprising primate embryonic stem cells
which (i) are capable of proliferation *in vitro* culture for one year, [...]"

The patent application was refused by EPO examiners in 2004 because the disclosed cultures of human embryonic stem cells are inseparable from the methods that generate them and thus from the use of a human embryo as starting material, which violates Art.53 (a) in conjunction with R.28 (c) EPC. A couple of months later, WARF lodged an appeal against the refusal of the EPO Examining Division to the Technical Board of Appeal of the EPO, who in turn referred questions to the Enlarged Board of Appeal of the EPO (Sterckx, 2008). Eventually, the latter ruled in a final **decision G 2/06** on November 25, 2008 that inventions (here: hESC cultures) which, at the time of filing the application, can only be obtained by destroying human embryos are not patentable under R.28 (c) EPC (EBoA, 2008). This is equally valid if the method has not been cited in the claims, but is irrelevant if, after the time of filing the application, the claimed products can be obtained without sacrificing human embryos (e.g. products based on publicly available hESC lines). Nevertheless, the Enlarged Board of Appeal emphasized that this decision is not concerned with the patentability of human embryonic stem cell inventions in general. More specifically, although the European ruling unambiguously extends the exclusion on patents claiming the use of human embryos to patents claiming human embryonic stem cells on the grounds that their isolation involves the destruction of a human embryo, the Enlarged Board still left open the question of whether the morality provisions extend to downstream derivative products (Nayanah, 2009).

1.5.4 The Brüstle case in the EU

The patent (DE 19756864) held by Brüstle **December 19, 1997 (priority date)**

Prof. Dr. Oliver Brüstle is the proprietor of a German patent in which improved methods of generating neural precursor cells from embryonic stem cells, the cell cultures produced by these methods and the use of the derivative products for the treatment of neural disorders are claimed. The national patent was granted in 1999 and has not been contested before the German Patent and Trademark Office (DPMA) during the three-month opposition period after the publication of the grant of the patent. However, in 2004, Greenpeace filed a nullity action against the patent before the German Patent Court (Rimmer & MacLennan, 2012). According to Greenpeace, Brüstle's patent claims insofar as concerning precursor cells developed from human embryo-derived stem cells are non-patentable under, primarily, Article 6 (2) (c) of the EU biotechnology directive and, later, Section 2 (2) (3) of the German Patent Act. Two years later, the German Patent Court ruled in favor of Greenpeace (BPatG, 2006). Brüstle subsequently appealed the decision to the Bundesgerichtshof and requested the patent to be upheld in an amended form. Surely, in view of the already available hESC lines, the patented methodology could be exploited without the direct use and destruction of human embryos. Given that this patent case relies on the interpretation of Article 6 (2) (c) in EU Directive 98/44/EC, the Bundesgerichtshof referred a number of questions to the Court of Justice of the European Union (BGH, 2009):

1. What is meant by the term "human embryos" [...]?
2. What is meant by the expression "uses of human embryos for industrial or commercial purposes" [...]?
3. Is technical teaching to be considered unpatentable [...] even if the use of human embryos does not form part of the technical teaching claimed with the patent [...]?

As much as the morality clause included in the EU biotechnology directive is ambiguous, the path to the Court of Justice of the European Union (CJEU) is not straightforward and involves several steps between the national court referring questions and the CJEU ruling a judgment.

Decision of the Court of Justice of the European Union **October 18, 2011**

Advocate General Yves Bot was appointed to provide the Court of Justice of the European Union with legal advice on the Brüstle v. Greenpeace case, after which the EU Court largely

followed the conclusions which have been outlined in his preliminary ruling (Bot, 2011). In doing so, the CJEU declared by the controversial **decision C-34/10** that Article 6 (2) (c) of the EU biotechnology directive must be interpreted as meaning that (CJEU, 2011):

1. The concept of human embryo comprises any human ovum after fertilization, any non-fertilized human ovum into which the cell nucleus from a mature human cell has been transplanted and any non-fertilized human ovum whose division and further development have been stimulated by parthenogenesis. *It is for the referring court to ascertain, in the light of scientific developments, whether a stem cell obtained from a human embryo at the blastocyst stage constitutes a "human embryo".*
2. The concept of "uses of human embryos for industrial or commercial purposes" covers also uses for purposes of scientific research, *only use for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it are not excluded from patentability.*
3. An invention is excluded from patentability where a technical teaching requires the prior destruction of human embryos *or their use as base material, whatever the stage at which that takes place and even if the description of the technical teaching claimed does not refer to the use of human embryos.*

In summary, the national court is commissioned to define whether stem cells collected from human embryos are considered patentable or not, however, the answer to the last question referred by the Bundesgerichtshof makes it impossible to either isolate embryonic stem cells or use embryonic stem cell lines in view of the fact that CJEU decision C-34/10 prohibits any destruction of the human embryo, even if such embryo destruction was carried out already several years ago. This signifies that inventions involving downstream derivative products of human embryonic stem cell lines or procedures with regard to human embryo-derived stem cells need to be rejected as non-patentable subject matter. This landmark decision is valid for all EU national governments and provoked huge dismay in the scientific community (Abbott, 2011). Though, a fully consideration of the judgment (cf. Recital 36 and Recital 37 of CJEU judgment C-34/10) divulges that entities "*capable of commencing the process of development of a human being*" are integrated within the concept of "human embryo", the latter of which is unachievable without significant intervention when applying hESCs *in vitro* (Hitchcock, 2012).

The Bundesgerichtshof (German Federal Court of Justice) recently decided to uphold the German patent in an amended form, i.e. in the version of auxiliary request I¹ which has been presented by Brüstle during the appeal process (BGH, 2012). This version includes the original patent text whereby the claims concerning embryonic stem cells were complemented with, either a reference to embryonic stem cell lines instead of embryonic stem cells, either the introduction of a disclaimer. The latter eliminates the fact that the disclosed embryonic stem cells have been obtained through destruction of a human embryo. According to the Bundesgerichtshof, auxiliary request I contains patentable subject matter since the claims are excluded under Section 2 (2) (3) of the German Patent Act only if the derivative products or manufacturing methods would be based on stem cells capable of evolving into a human being and the claims explicitly reject human embryo destruction (De Clercq & Partners, 2013). In addition, the Brüstle patent denotes the use of embryonic germ cells as a non-destructive way to apply embryonic stem cells, which makes the disclosure of the introduced disclaimer comprehensible for a person skilled in the art. In other words, the Bundesgerichtshof allows claims pertaining to human embryonic stem cells provided that the technical teaching of the patent pinpoints a method for obtaining these stem cells, apart from killing human embryos.

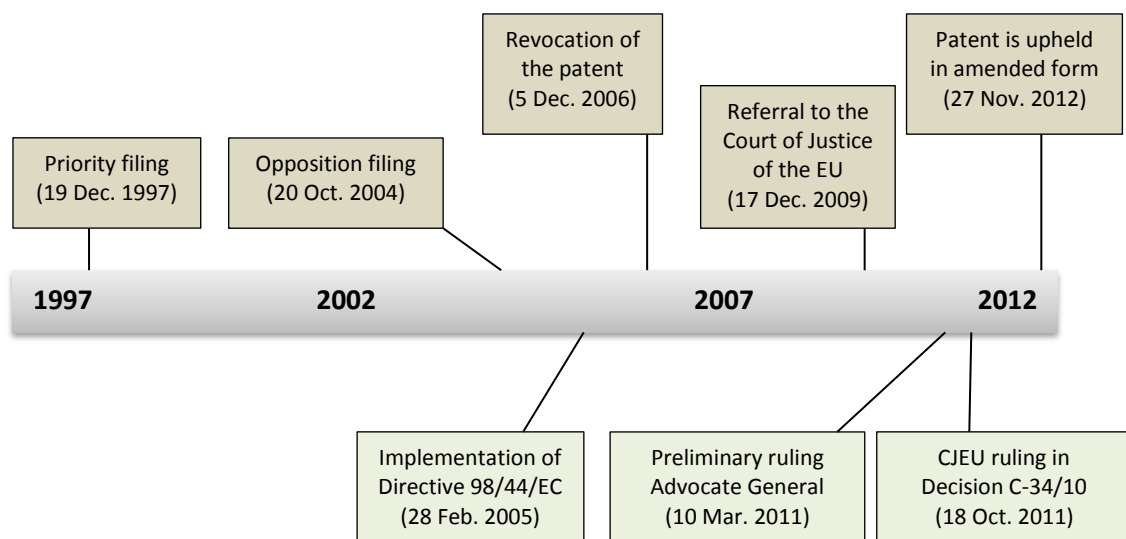


Figure 3. Timeline for the German patent held by Brüstle

¹ An appellant can advocate a main request which includes the appellant’s preferred options (i.c. patent without disclaimer) and also a first auxiliary request, second auxiliary request, etc. which includes the appellant’s less preferred options (i.c. the first auxiliary request encompasses the patent text with disclaimer)

1.5.5 The Brüstle case at the EPO

The patent (EP 1040185) held by Brüstle

December 19, 1997 (priority date)

Prof. Dr. Oliver Brüstle is likewise the proprietor of a European patent which is equivalent to the German patent above and hence concerns the same invention. The European patent was granted on February 22, 2006 and a notice of opposition was filed on November 21, 2006 by Geron Corporation since patent validity can be challenged before the European Patent Office within a nine-month opposition period. In accordance with the European Patent Convention, it is possible to apply for opposition in the case that the claimed subject matter of the patent opposed is not patentable (either because the subject matter does not exhibit novelty or an inventive step, either because the subject matter is excluded from patentability), in the case that the specification of the patent opposed does not sufficiently disclose the invention for a person skilled in the art or in the case that the claimed subject matter of the patent opposed extends beyond the content of the patent application as originally filed (EPC 2000, Art. 138). The opposition of Geron Corporation against the European Brüstle patent is based on all three grounds (Geron, 2006).

Decision of the Opposition Division of the EPO

April 11, 2013

The EPO Opposition Division has lately decided to annul the European patent held by Brüstle for other reasons than designating the commercial exploitation of hESC-based inventions as contrary to the public order or morality (Art.53 (a)). It was concluded at the oral proceedings that the disclaimer, which was introduced to comply with the morality clause, does not meet the patentability requirement "enablement". Although the Brüstle patent denotes the use of embryonic germ cells as a non-destructive way to use embryonic stem cells, the specification of the patent merely refers to a publication about the establishment of embryonic germ cells (Shamblott *et al*, 1998). As such, the alternative procedure, avoiding embryo destruction and strengthening the disclaimer, is not revealed in a manner sufficiently clear and complete to be carried out by a person that is skilled in the art (EPC 2000, Art. 83). Another reason for revoking the patent dealt with the permissibility of introducing the disclaimer in view of the Enlarged Board of Appeal decision G 1/03 (EBoA, 2004), whereby it is stated that subject matter that is not disclosed in the original patent application may not be introduced under the enablement criterion (EPC 2000, Art. 123). The written decision is currently still awaited.

The decision of the EPO Opposition Division in the Brüstle case is currently open to appeal. It is presumed that the case will appear before the Boards of Appeal of the EPO within the next couple of years so as to resolve the enablement issues and subsequently the morality issues. Most striking is that, as regards the issues relating to enablement, the disclaimer in question has been successfully introduced in the equivalent German patent and, as regards the issues relating to morality, the Boards of Appeal have the options to follow the restrictive approach of the CJEU or the lenient approach of the Bundesgerichtshof. Meanwhile, EPO examiners consider patent applications on the basis of hESCs, which have been harvested by applying the technique Single Blastomere Biopsy (see section 1.3.2) as patentable (see section 1.6.3).

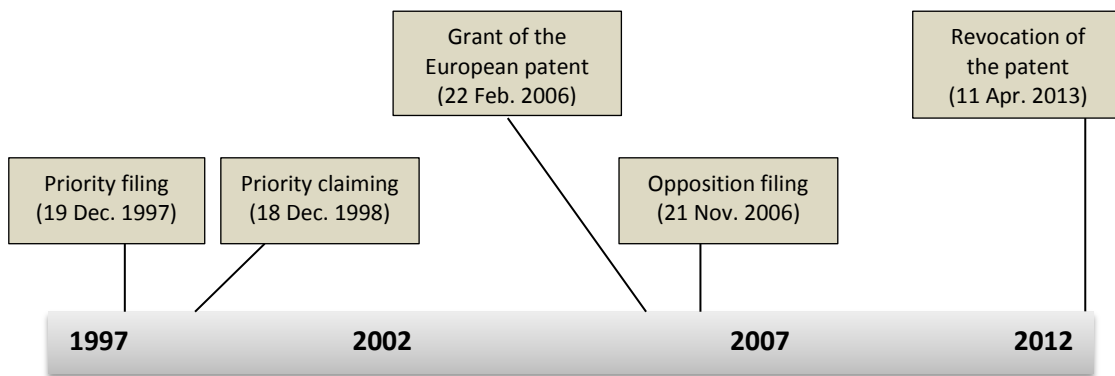


Figure 4. Timeline for the European patent held by Brüstle

1.6 Human embryonic stem cells: changes in EPO’s practice?

1.6.1 EPO’s previous practice

On account of decision G 2/06, the European Patent Office adopted the practice of allowing patent claims with reference to human embryonic stem cells in those applications that were filed from 9 May 2003 onwards. This is the date when human embryonic stem cell lines are considered publicly available and is in line with the Enlarged Board of Appeal decision above since, in the case of filing an application after the cut-off date, the claimed products could be obtained without sacrificing human embryos – at least not in a direct way. Patents or patent applications that had been filed before 9 May 2003 required an amendment or disclaimer by stating that the human embryonic stem cell-based product or the method developed on the basis of human embryonic stem cells was not obtained through human embryo destructions.

1.6.2 EPO's current practice

On account of decision C-34/10, the cut-off date of May 2003 was expelled and the granting policy has been converted to a more restrictive approach. Even though the EPO is not legally bound by the CJEU, mutual consideration is indispensable to avoid severe disharmony within the European patent system. The Guidelines for Examination of the EPO have been adjusted with respect to Rule 28 (c) EPC and are in force since 1 June 2012. These include following (Guidelines for Examination 2012, Part G – Chapter II, 5.3 (iii)):

"(iii) Uses of human embryos for industrial or commercial purposes

*A claim directed to a product, which at the filing date of the application could be exclusively obtained by a method which necessarily involved the destruction of human embryos from which the said product is derived is excluded from patentability under Rule 28(c), even if said method is not part of the claim (see G 2/06). **The point in time at which such destruction takes place is irrelevant.***

When examining subject-matter relating to human embryonic stem cells under Art. 53(a) and Rule 28(c), the following has to be taken into account:

(a) the entire teaching of the application, not only the claim category and wording, and

(b) the relevant disclosure in the description in order to establish whether product such as stem cell cultures are obtained exclusively by the use, involving the destruction, of a human embryo or not. For this purpose, the disclosure of the description has to be considered in view of the state of the art at the date of filing.

The exclusion of the uses of human embryos for industrial or commercial purposes does not affect inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it (EU Dir. 98/44/EC, rec. 42)."

(The marked part is new vis-à-vis the previous Guidelines for Examination)

1.6.3 EPO's emerging practice

10 January 2008, the date on which the technique described in 1.2.2 was reported, holds the potential to stipulate a new and presumably definitive cut-off date taking into consideration the inextricably intertwined human embryo-derived stem cells and morality clause (De Clercq & Partners, 2012). The single blastomere biopsy (SBB) process provides a method of collecting – naturally occurring – pluripotent stem cells from a human embryo whilst the embryo remains intact. As such, if priority is claimed after 10 January 2008, the subject matter is eligible for patent protection.

PART 2: AIM OF THE STUDY

The controversial patent held by Brüstle was challenged both at national and European level. We purpose to outline what impact the various jurisprudential decisions in the Brüstle cases have had and may have on European stem cell research. Patenting embryonic stem cells at the European patent Office (EPO) previously relied on EPO's Board of Appeal decision in the WARF case, which is dated around 2008 and stipulated that biotechnological inventions are excluded from patentability only if the invention necessarily involved the destruction of a human embryo at the time of filing a patent application. The decision of the Court of Justice of the European Union (CJEU) in the Brüstle v. Greenpeace case, however, is dated around 2011 and goes far beyond the former practice of the EPO by judging that biotechnological inventions are non-patentable if the invention was obtained via human embryo destruction at any point in time. This ruling, referred to as decision C-34/10, needed to be implemented at the EPO and triggered great concerns towards the scope of patent protection available for human embryonic stem cell inventions. The patentee himself (O. Brüstle) stated: *"With this unfortunate decision, the fruits of years of translational research by European scientists will be wiped away and left to the non-European countries. European researchers may conduct basic research, which is then implemented elsewhere in medical procedures, which will eventually be re-imported to Europe. How do I explain that to the young scientists in my lab?"* Nevertheless, little data have so far been collected on the actual consequences that are stemming from CJEU's recent decision and for this reason we will firstly describe what influence this judgment has had on the stem cell research projects carried out in the Benelux and the United Kingdom. The different aspects to be studied encompass whether or not the research plans have been changed due to decision C-34/10, whether or not difficulties have been encountered in search of financial support and whether or not – or in what way – have inventions with respect to human embryonic stem cells become legally protected. Secondly, we will point out the implications in the event that a prospective decision of the EPO Boards of Appeal in the Brüstle v. Geron case favors the stringent ruling of the CJEU despite the fact that the ruling of the Bundesgerichtshof in the Brüstle v. Greenpeace case is more indulgent.

PART 3: RESULTS AND ANALYSIS

3.1 Impact of the CJEU judgment on (Belgian) stem cell research

3.1.1 Questioning and evaluation

By taking an interview of universities, companies, suppliers and public authorities that are all involved in the field of stem cell research, we pursued to achieve a complete overview of the impact that is attributable to CJEU judgment C-34/10 on the stem cell projects carried out in the Benelux. We received sufficient feedback of the academic institutions; however, in order to enhance the participation of stem cell companies, we also made contact with enterprises in the United Kingdom and thereby got the opportunity to interview a translational research expert. The Belgian Office for Intellectual Property (DIE) was not surveyed in the category of public authorities because this patent office does not carry out a substantive examination of the patent application's content.

The survey intended for the universities, companies and suppliers include questions relating to their past and future research plans regarding pluripotent stem cells, their experiences in attracting financial support, and their perspectives in terms of intellectual property strategy. For example, it was evaluated whether they anticipated decision C-34/10 when filing patent applications. Academic institutions were interrogated both at the level of the Technology Transfer Office and at the level of the research group, while life science supplier companies were specifically approached as the CJEU stated in its judgment that "uses of human embryos for industrial or commercial purposes covers also uses for purposes of scientific research". The survey that is composed for authorities whose mission is to fund scientific research, queries their stance towards a hESC-based funding request and the involvement of economic valorization, in particular the intellectual property aspects.

Table 4. Proportion of actors involved in the field of stem cell research that participated in the survey.

	Universities	Companies	Suppliers	Authorities	In total	Useful
Contacts	17	43	10	10	80	N/A
Responses	10	22	6	5	44	N/A
Interviews in	7	6	1	2	16	12
Belgium	5	3	0	2	10	8
The Netherlands	2	1	0	0	3	2
G.D. Luxembourg	0	0	0	0	0	0
United Kingdom	N/A	2	N/A	N/A	2	2
Germany	N/A	N/A	1	N/A	1	0

Table 4 displays the actors in the four different categories that participated in the survey and eventually we applied the results of two stem cell companies, four academic institutions and two public funding agencies in Belgium; one stem cell company and one academic institution in the Netherlands; one stem cell company and one innovation centre in the United Kingdom and thus, the proportion companies v. research institutions v. academic institutions is 4:1:5.

3.1.2 The view from academic institutions

It is understood that the conduct of pluripotent stem cell research in an academic setting has suffered no consequences as a result of decision C-34/10. In the opinion of some technology transfer representatives, research strategies using embryonic stem cells are out-of-date with the advent of "induced pluripotency". However, this statement was clearly not supported by research scientists, albeit a research group may prefer induced pluripotent stem cells rather than embryonic stem cells because of reasons of accessibility. Investigators in the hESC field do have encountered an influence of the CJEU judgment when applying for financial support. One research project, which depends on the use of hESCs, was refused funding from a public authority for lack of economic valorization, while another research group is considering filing a proposal on the basis of utilizing human induced pluripotent stem cells in order to acquire financial support and subsequently hand over the research results to an interested company.

"Our request to fund the hESC project has been deferred as no industrial partner could have been found to collaborate with bearing in mind the non-patentability. The only option left is to present a similar project for non-economic purposes, by which is meant that the project should be tailored to the treatment of an orphan disease." (Research Scientist at VUB, Belgium)

Although patent protection is not the primary goal that is imposed by academic institutions, several patent applications concerning human embryonic stem cells are pending at the EPO and were for the most part filed in advance to the CJEU judgment ruled on October 18, 2011.

"For the time being, we are lucky to have incorporated the reference to human induced pluripotent stem cells in every patent application with regard to hESCs, however, I am not convinced that new hurdles won't come up for these induced pluripotent stem cells." (Technology Transfer Representative at ULB, Belgium)

Two examples came forward demonstrating that university patenting has been subjected to decision C-34/10, *inter alia* a technology transfer representative chose earlier in consultation

with a patent attorney not to submit the patent application as only limited protection could have been provided for the hESC-based invention. In addition, a well-known researcher said:

"We are currently seeking patent protection for an invention that is appropriate for human embryonic stem cells as well. It remains unclear if we will take up the latter into the claim part, but discussions are continuing on how to avoid being in conflict with the CJEU ruling." (Research Scientist at UT, the Netherlands)

Remarkably, though, one research scientist who happens to be also a member of the Belgian Federal Commission for Medical and Scientific Research on Embryos *in vitro* notified that the question has been raised whether the use of hESCs in view of commercial purposes is legal according to the Belgian law on research on embryos *in vitro*². The answer is currently still in consideration.

3.1.3 The view from a translational research expert

The UK Cell Therapy Catapult Centre is a recently established organisation which is aimed at setting up stem cell companies with a focus on translational research. The research projects have not yet been commenced, but plans are underway to develop clinical applications using human embryonic stem cells, induced pluripotent stem cells or specific adult stem cell types.

"Nowadays there is sufficient know-how on human embryonic stem cells and it is important to proceed with the knowledge obtained. Human induced pluripotent stem cells are still in the early research stage and will not be employed in clinical trials at short notice." (CEO at Cell Therapy Catapult Centre, the United Kingdom)

The organisation itself has not applied for hESC patent applications hitherto – collaborative entities may well have done so –, though the interest is high as patents are beneficial to attract investors.

"We will choose the best strategy to obtain intellectual property rights for those hESC-based inventions, either via patent protection or trade secret protection. At this moment we are not looking for ways to get around the Court's judgment, we are just awaiting the decision of the EPO Opposition Division in the Brüstle case." (CEO at Cell Therapy Catapult Centre, the United Kingdom)

² Belgian Act of 11 May 2003

3.1.4 The view from stem cell companies

Solely a few companies have been and are working on human embryonic stem cells. What is striking is that the UK stem cell companies, relatively, seem to have the most experience and interest in the performance of hESC research, although this does not apply for all companies.

"There is confusion on what is going to happen. The situation keeps on changing, both in the United States of America and in Europe. We sold our hESC technology a couple of years ago and, in my estimation, the stem cell industry will ultimately not utilize those cells for therapeutic applications. Induced pluripotent stem cells hold much more potential." (CEO at a biotechnology SME, the United Kingdom)

Up to the present time, companies in the Benelux have not yet shown interest in conducting human embryonic stem cell-based experiments, except for one company in the Netherlands that is operating purely on this stem cell source. The latter is known as "Pluriomics" and was launched as a spin-off company from the Leiden University shortly before judgment C-34/10.

"We are confident that the human embryonic stem cells offer an advantage over the human embryonic-like stem cells when developing toxicity tests on the basis of pluripotent cells. The use of induced pluripotent stem cells could nevertheless constitute added value in the field of personalized medicine. The Court's decision has forced us not to change course in one of our research plans, but to adjust our intellectual property strategy. Herewith we speak of a modified ratio of different types of intellectual property rights." (CEO at Pluriomics, the Netherlands)

Pluriomics was able to receive funding from the Seventh Framework Programme (FP7) of the European Commission, from several organisations which support the creation of marketable inventions and from private investment, whereas the Belgian companies surveyed have thus far not requested financial support for a hESC-based project. One of these companies, which does not make use of human stem cells of any kind, was still confronted with the effects of the CJEU judgment by claiming an invention that is applicable to a wide variety of stem cells.

"The patent attorney argued that the scope of the claims with reference to stem cells needed to be narrowed by excluding those stem cells brought forth through embryo destruction. We lost six to nine months negotiating the specific wording of these patent claims because we are seeking patent protection for an invention by which any stem cell could achieve something, we are not specifically targeting the invention's application using human embryonic stem cells."

(Director of Regulatory Affairs at Cardio3 Biosciences S.A., Belgium)

Another company, being a pharmaceutical company, has not been affected by the judgment in question, but determined beforehand to work with human induced pluripotent stem cells for reasons of corporate social responsibility.

3.1.5 The view from research funding agencies

The public agencies who participated in the survey offer different types of research funding in Flanders. The Flemish government agency for Innovation by Science and Technology (IWT) was established to foster innovative projects in the Flemish Community and thereby, among other things, hands out research grants to individual investigators, universities, enterprises, the non-profit sector, *etc.* The Federal Fund for Scientific Research, inclusive of the Research Foundation Flanders (FWO), was set up to encourage groundbreaking fundamental research. Both funding bodies impose specific requirements according to their mission and depending on the type of fellowship. In contrast to the FWO, the IWT representative said the following:

"Patentability is first and foremost a determinative factor during the assessment of a business project proposal. Its role is considered as well when candidates are applying for an IWT doctoral scholarship, but comes in the second place after the factor of applicability. I am not fully aware of what types and numbers of funding requests regarding human embryonic stem cells have been submitted, however, no relevant R&D projects have been proposed to us before or after the decision."

3.1.6 Funding requests and funding approvals

As the criteria applied by the IWT predominantly involve an economic aspect and the criteria applied by the FWO are focused on the scientific excellence of the project, we first compare the number of hESC-based funding requests that have been yearly submitted to each agency since 1998. Figure 5 and Figure 6 display data for the year in which a hESC-based project was planned to receive financial aid on the condition that its funding request, submitted either in the same year or preceding year, had been approved. The numbers of FWO funding requests seem to have adopted an increasing tendency since 2011, while there is no obvious trend to be noticed regarding the IWT funding requests. As expected from a young scientific research field, the first decade is characterized by a total number of FWO funding requests exceeding the total number of IWT funding requests, although both totalities remain on the low side. If

we look at the different types of research funding, Figure 5 reveals that funding applications were essentially filed in order to carry out a doctoral research project and demonstrates no numbers for funding requests in view of either R&D projects or strategic basic research with economic purposes. One IWT postdoctoral scholarship, whereby the economic valorization is gaining importance, was approved for a hESC-based research project and started off in 2010.

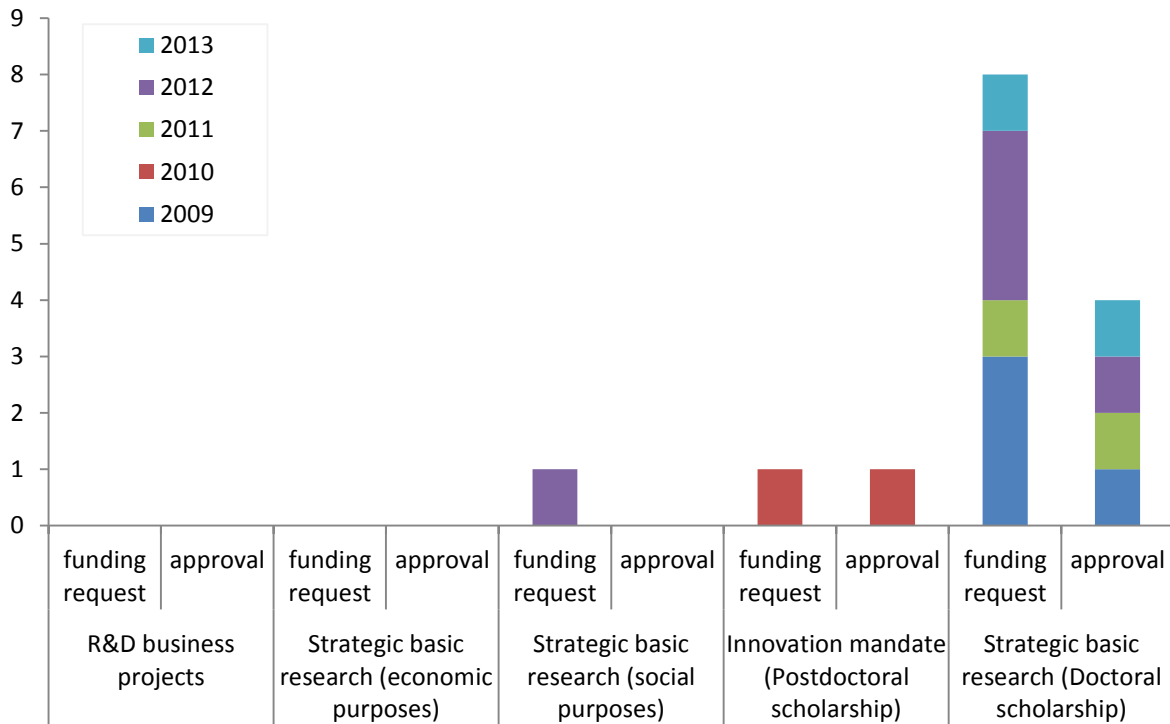


Figure 5. Bar graph showing the numbers of (approved) funding requests: filed with the aim of implementing a human embryonic stem cell-based project and managed by the Flemish government agency for Innovation by Science and Technology (IWT). Data are shown for five relevant types of fellowships that are offered by the IWT and represent the years in which a hESC-based project was scheduled to receive financial support. Funding applications have been predominantly submitted and approved in order to conduct doctoral research projects.

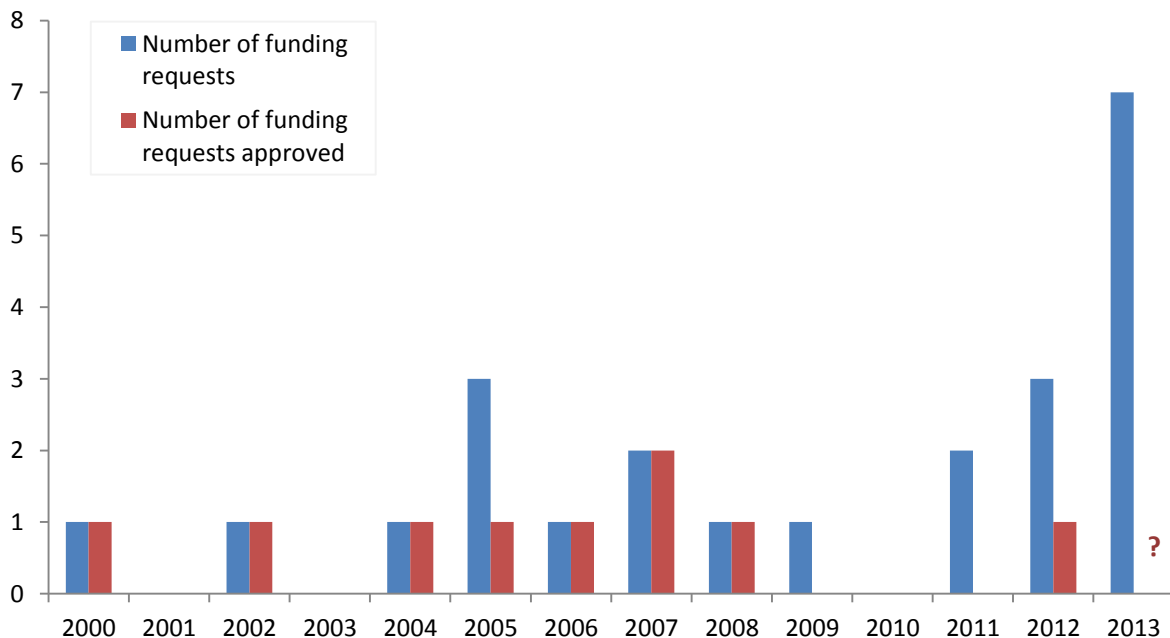


Figure 6. Bar graph showing the numbers of (approved) funding requests: filed with the aim of implementing a scientific hESC-based project and managed by Research Foundation Flanders (FWO). The data represent the years in which a hESC-based project was scheduled to receive financial support and include requests for a pre- or postdoctoral mandate and for a collective research project. Data exclude the predoctoral mandates of 2013.

3.2 Statistical data

3.2.1 A hitch in the evolution of embryonic stem cell patenting

Figure 7 presents the evolution of international patent application (PCT) filings and European patent application (EPO) filings concerning embryonic stem cells or embryonic germ cells based on the year in which these applications were published. The former type of patent application is filed in view of a preliminary examination on patentability and depends on the requirements of the Patent Cooperation Treaty (PCT), i.e. an international patent law treaty. The two different curves describe how the evolution proceeds from the year in which the WARF patent application, disputed before EPO's Enlarged Board of Appeal, was published. Yet, it needs to be taken into account that every patent application becomes published at 18 months from filing. In this way Figure 7 must be interpreted in parallel with Table 5 in order to read the different tendencies for patent application filings. It also follows that results are shown for patent applications which are filed in between 1 July 1995 and 28 November 2011 (the latter represents the date being 18 months before the evolution curves were extracted).

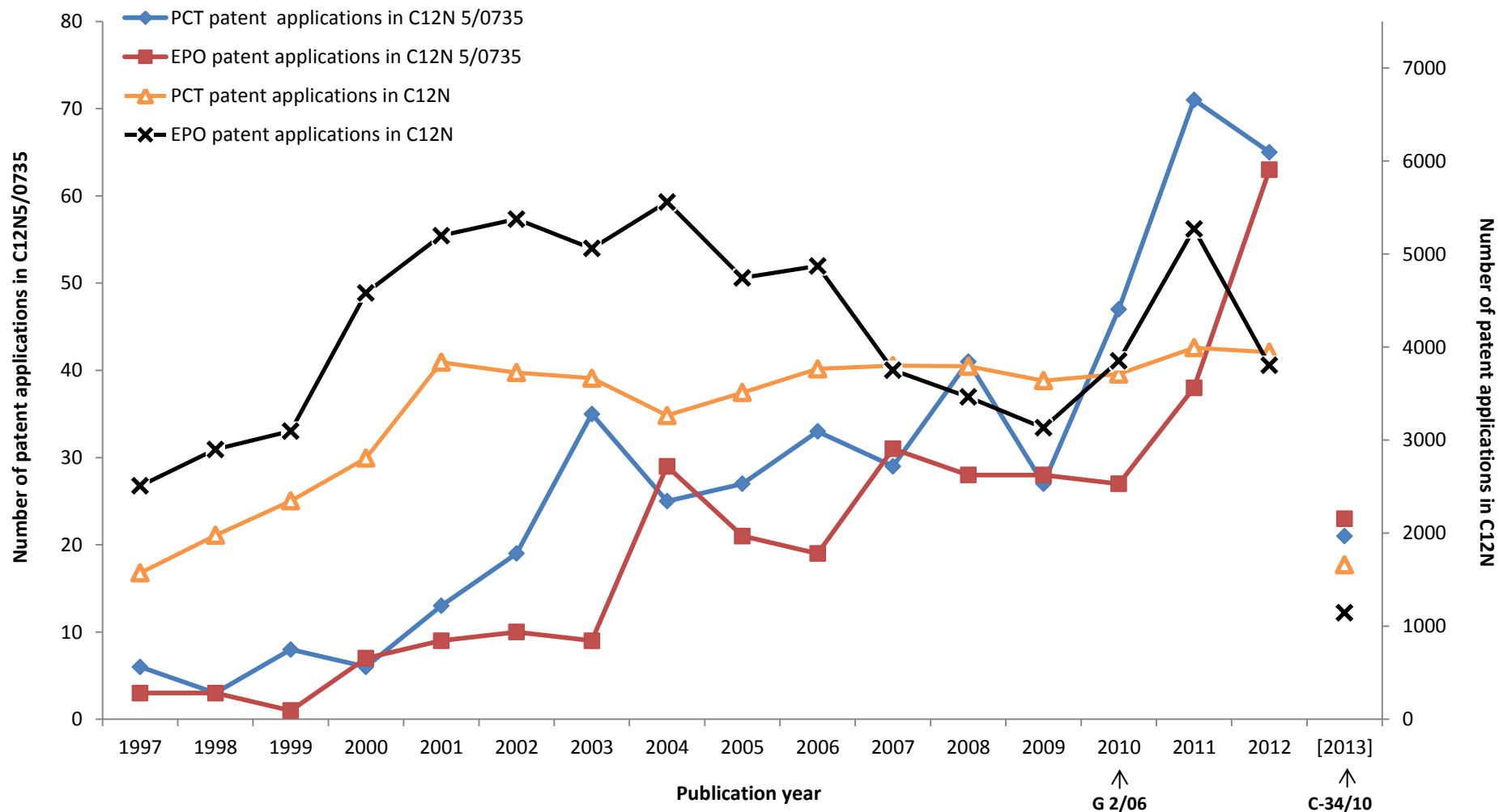


Figure 7. Evolution per publication year of the PCT patent applications and EPO patent applications in subclass C12N 5/0735 (Embryonic stem cells, Embryonic germ cells) as well as of the PCT patent applications and EPO patent applications in class C12N of the International Patent Classification. There is an exponential increase to be noticed for both PCT patent applications and EPO patent applications related to embryonic cells since 2009 and 2010, respectively. G 2/06 represents the Enlarged Board decision in the WARF case, C-34/10 represents the CJEU decision in the Brüstle case. Data are incomplete for publication year 2013 as these were obtained on 28 May 2013.

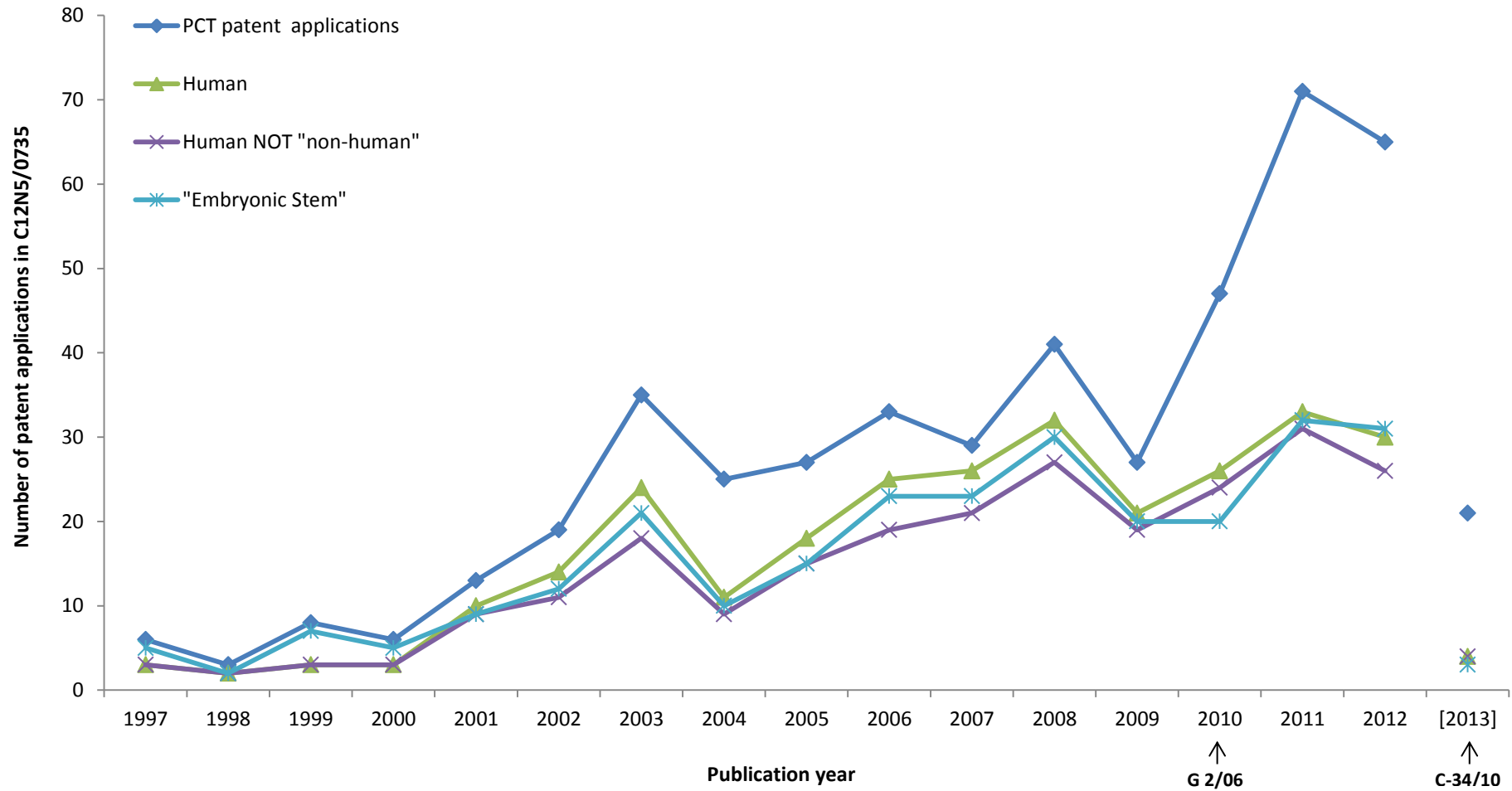


Figure 8. Evolution per publication year of the PCT patent applications in subclass C12N 5/0735 (Embryonic stem cells, Embryonic germ cells) in combination with the evolutionary character of embracing the term human, human exclusive of "non-human" or "embryonic stem" in the claim part of these patent applications. Recording the term "human" in the claims of an international patent application was frequently applied over the entire evolution. G 2/06 represents the Enlarged Board decision in the WARF case, C-34/10 represents the CJEU decision in the Brüstle case. Data are incomplete for publication year 2013 as these were obtained on 28 May 2013.

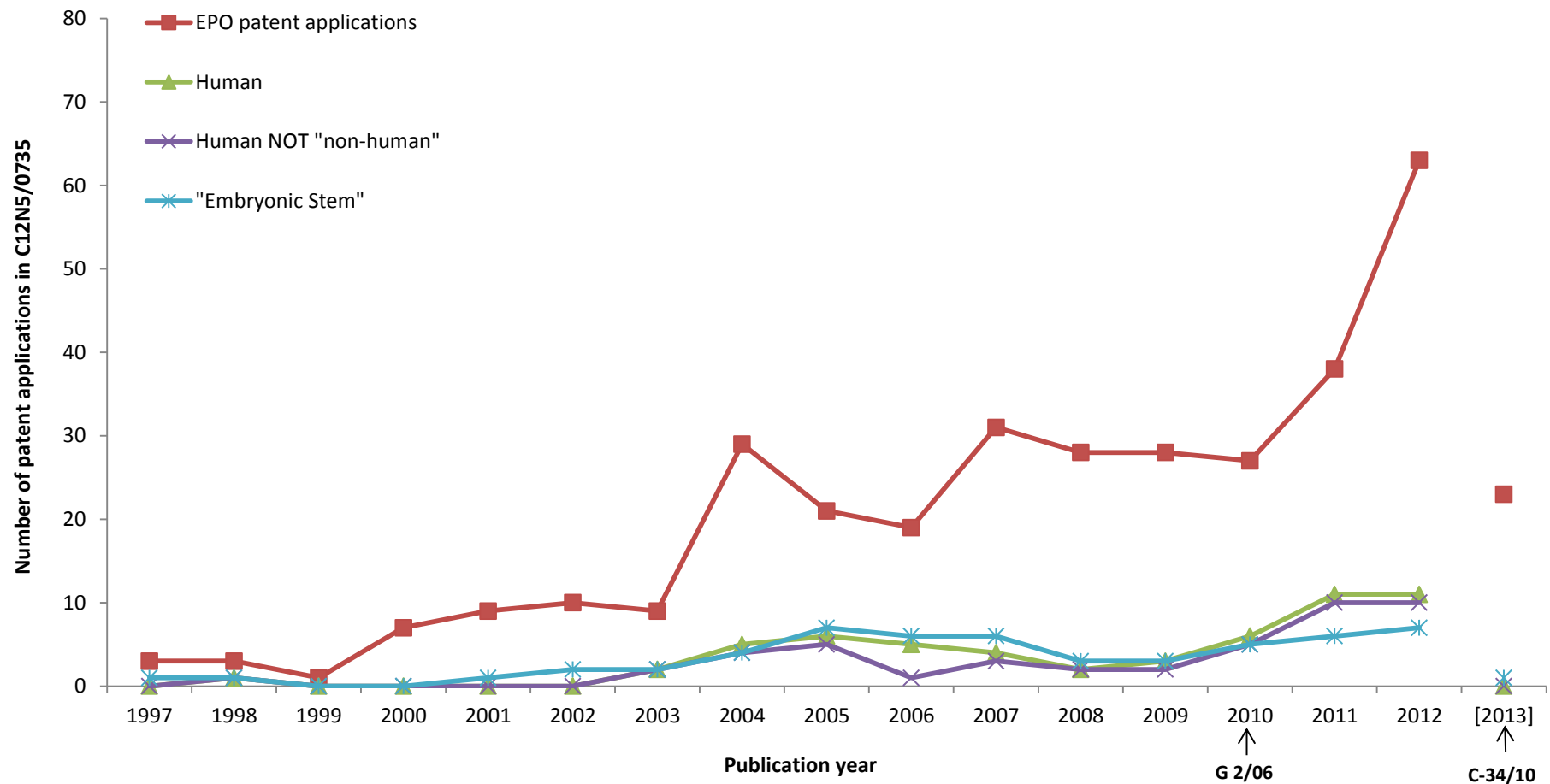


Figure 9. Evolution per publication year of the EPO patent applications in subclass C12N 5/0735 (Embryonic stem cells, Embryonic germ cells) in combination with the evolutionary character of embracing the term human, human exclusive of "non-human" or "embryonic stem" in the claim part of these patent applications. Recording the term "human" in the claims of a European patent application was not frequently applied over the evolution. G 2/06 represents the Enlarged Board decision in the WARF case, C-34/10 represents the CJEU decision in the Brüstle case. Data are incomplete for publication year 2013 as these were obtained on 28 May 2013.

Table 5. Representation of the corresponding publication and filing year for a patent application.

Publication year	Filing year	Publication year	Filing year
1996	1 July 1994 – 30 June 1995	2005	1 July 2003 – 30 June 2004
1997	1 July 1995 – 30 June 1996	2006	1 July 2004 – 30 June 2005
1998	1 July 1996 – 30 June 1997	2007	1 July 2005 – 30 June 2006
1999	1 July 1997 – 30 June 1998	2008	1 July 2006 – 30 June 2007
2000	1 July 1998 – 30 June 1999	2009	1 July 2007 – 30 June 2008
2001	1 July 1999 – 30 June 2000	2010	1 July 2008 – 30 June 2009 *
2002	1 July 2000 – 30 June 2001	2011	1 July 2009 – 30 June 2010
2003	1 July 2001 – 30 June 2002	2012	1 July 2010 – 30 June 2011
2004	1 July 2002 – 30 June 2003	2013	1 July 2011 – 30 June 2012 **

*Year in which EPO's Enlarged Board of Appeal ruled its decision in the WARF case (G2/06)

**Year in which the European Court of Justice ruled its decision in the Brüstle case (C-34/10)

It can be derived from Figure 7 and Table 5 that the European patent application filings with respect to embryonic cells have been stabilized during those three years before and the year wherein the EPO's Enlarged Board of Appeal ruled its decision in the WARF case. This lenient ruling may have triggered off an exponential increase in both the European and PCT patent application filings, though the reference curves in C12N do not provide a confirmation. The then awaited CJEU judgment in C-34/10 has clearly not been influencing the patent filings. Although data is incomplete for publication year 2013, it is expected that the decision of the CJEU, at least, caused a hitch in the evolution of embryonic stem cell patenting. At this time, the last data point represents the number of patent applications filed in between 1 July 2011 and 28 November 2011 and hence, when that number is extrapolated to a full year of filing, it is potentially the beginning of an exponential decay in European patent application filings. From Figure 8 and Table 5, it follows that recording the term "human" in the claims of a PCT patent application regarding embryonic cells was frequently applied in earlier times and has not obviously been subjected to jurisprudential decisions in European cases. This in contrast with recording the term "human" in the claims of a European patent application with regard to embryonic cells (see Figure 9). It is notable from Figure 9 that claiming cells specifically for a "human" source was not frequently applied over the entire evolution of patent application filings at the EPO. This phenomenon even reaches its highest data point in publication years 2011 and 2012. The European patent applications which have been published and were filed between 1 July 2011 and 28 November 2011 does not include the claim term "human" at all.

3.2.2 Embryonic stem cell patenting in Europe *versus* the U.S.

Because patent law in the U.S. does not comprise an explicit morality clause and, moreover, the United States Patent and Trademark Office (USPTO) has adopted a less restrictive stance towards the patentability of human embryonic stem cell-based inventions, we juxtapose the number of patent families regarding embryonic stem cells as well as the number of granted patents thereof at the USPTO and at the EPO. As can be seen in Figure 10, this comparison is solely based on patent families that include a PCT patent application in order to assess the extent of granting either U.S. patents or European patents for an embryonic stem cell-based invention in equal proportion. Figure 10 reveals that presently 76% of the PCT patent families have already entered into the U.S. national phase, whereby 15% were issued as U.S. patents. At the side of the EPO, 60% of the patent families in question are registered in the European national phase, whereby 7% embryonic stem cell patents were granted. Among the twenty-eight European patents, none of them have been issued after the CJEU judgment in C-34/10.

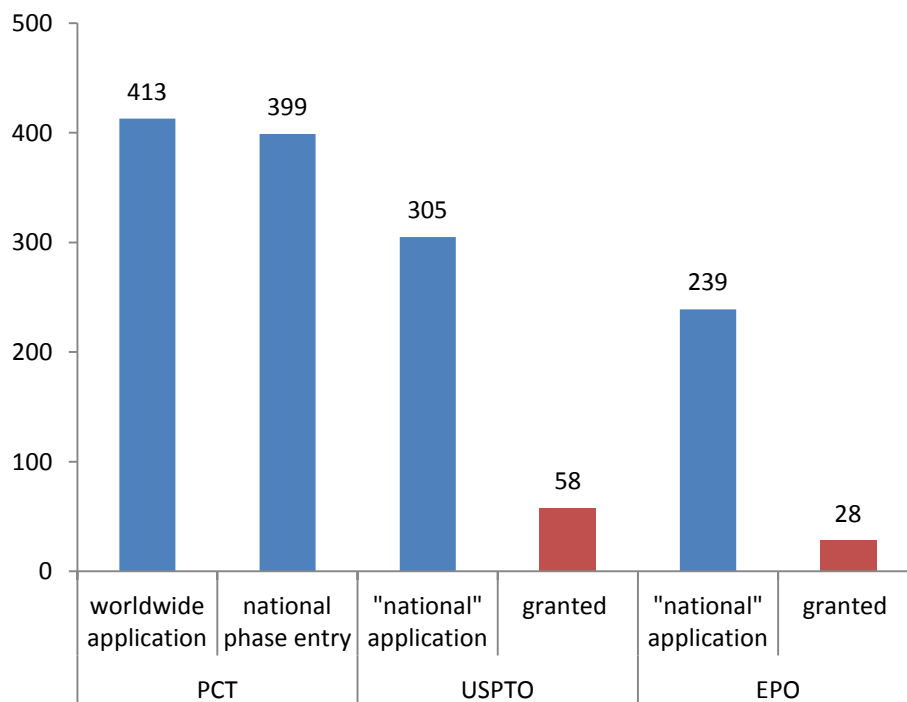


Figure 10. Bar graph which shows the number of patent families with a PCT patent application and the numbers of PCT patent families with a U.S. patent (application) or European patent (application) in Class C12N 5/0606 (Pluripotent embryonic cells) of the Cooperative Patent Classification. Twice as much patents concerning pluripotent embryonic cells were granted at the United States Patent and Trademark Office (USPTO) in comparison with those granted at the European Patent Office (EPO). There is no vast difference between the number of U.S. patent families and the number of EPO patent families.

3.2.3 Embryonic *versus* induced pluripotent stem cell patenting

As human induced pluripotent stem cells are patentable at the EPO, we weigh the number of patent applications and grants relating to embryonic stem cells against the number of patent applications and grants relating to induced pluripotent cells (Figure 12). Therefore, we rely on the same strategy departing from patent families with a PCT patent application as explained in section 3.2.2 and hence we simultaneously refer to an analogue comparison at the USPTO. As shown in Figure 11, the number of EPO patent applications concerning induced pluripotent cells does not significantly differ with the number of such U.S. patent applications, let alone exceeds it. It is, nevertheless, generally considered that the USPTO achieves faster patent grants.

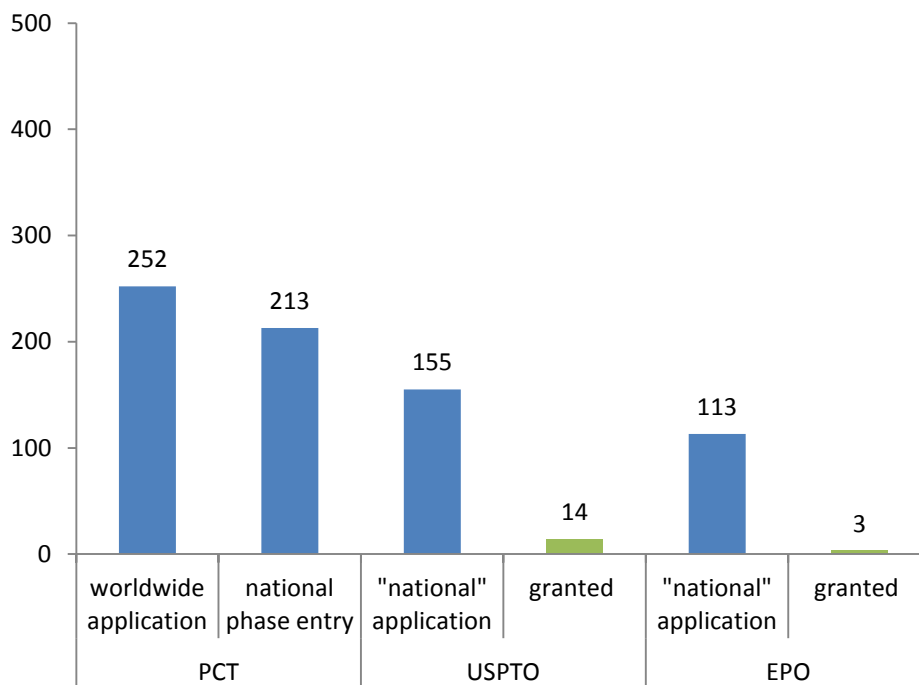


Figure 11. Bar graph which shows the number of patent families with a PCT patent application and the numbers of PCT patent families with a U.S. patent (application) or European patent (application) in Class C12N 5/0696 (Artificially induced pluripotent cells) of the Cooperative Patent Classification. The difference between the number of patent applications and grants relating to induced pluripotent cells at the U.S. Patent and Trademark Office (USPTO) and at the European Patent Office (EPO) is not significant.

Even though "induced pluripotency" is a recently established method of use, it is remarkable that the number of EPO patent applications which are specifically categorized in patent class "Artificially induced pluripotent cells" already accounts for practically half of the EPO patent applications which are specifically categorized in patent class "Pluripotent embryonic cells".

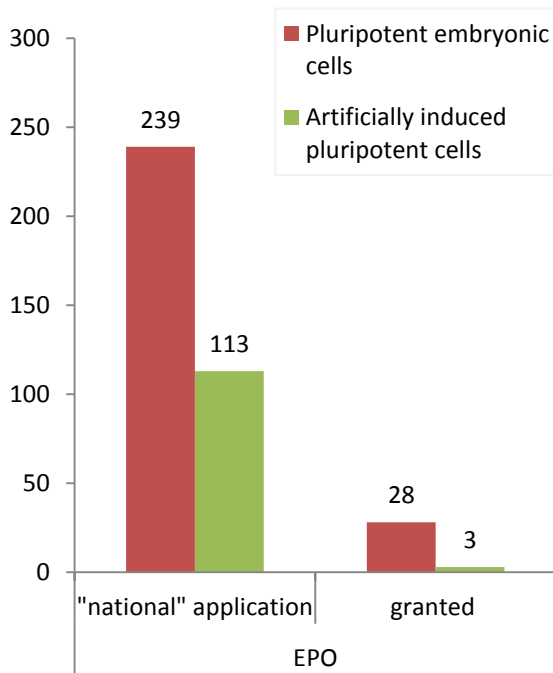


Figure 12. Numbers of EPO patent application filings and numbers of European patent grants with regard to pluripotent embryonic cells (Class C12N 5/0606 of the Cooperative Patent Classification) and artificially induced pluripotent cells (Class C12N 5/0696 of the Cooperative Patent Classification). The four numbers are obtained solely from patent families that include an international patent application. Although induced pluripotent stem cells involve a relatively new source of pluripotent stem cells, the EPO patent applications specifically categorized in class "Artificially induced pluripotent cells" already accounts for almost half of the EPO patent applications which are specifically categorized in the class "Pluripotent embryonic cells".

Figure 13 presents the evolution of European patent application filings regarding embryonic cells or induced pluripotent cells consistent with the Cooperative Patent Classification (CPC).

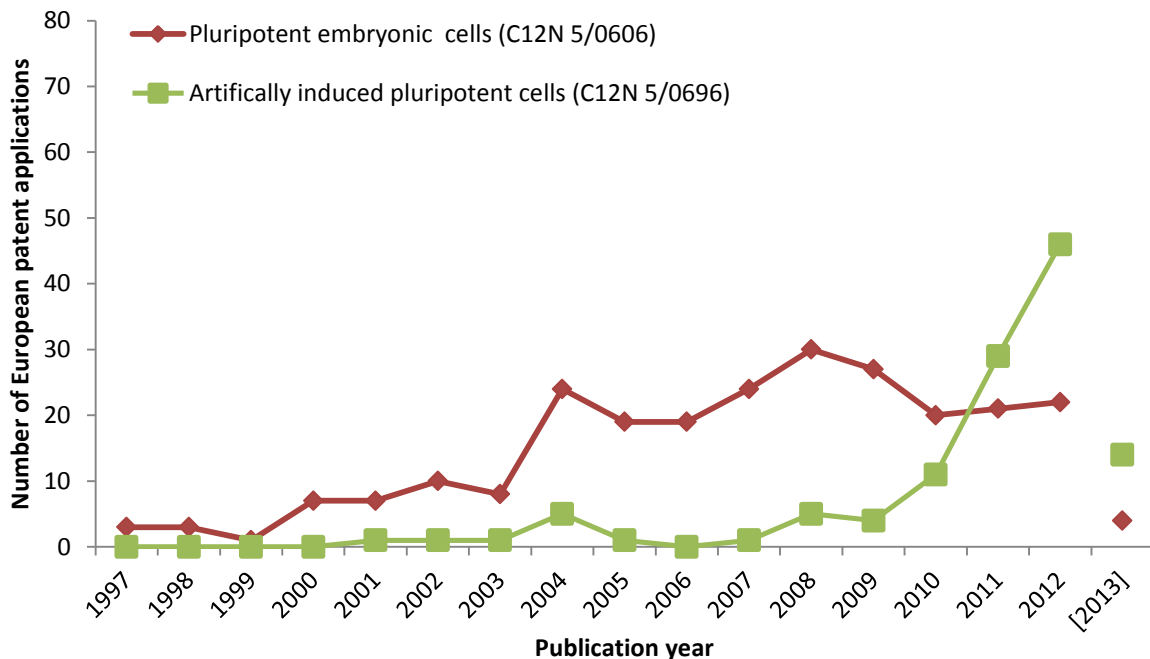


Figure 13. Evolution per publication year of the EPO patent applications in CPC Class C12N 5/0606 (Pluripotent embryonic cells) and CPC Class C12N 5/0696 (Artificially induced pluripotent cells). Patent application filings concerning induced pluripotent cells are exponentially increasing since 2009. Although results are incomplete for publication year 2013 as these were obtained on 29 May 2013, its current data point in line with the green curve exceeds its data point in line with the red curve with a surplus of ten European patent application filings.

At present, we need to be careful in interpreting results that are collected on the basis of the CPC system seeing that this classification system is still in its infancy (in force since 1 January 2013). The CPC system has replaced the former European Classification (ECLA) system and it is envisaged to also replace the International Patent Classification (IPC) system, on which the evolution curves in section 3.1.6 are based. Though, the CPC system is the only classification providing a specific class for patent application filings in relation to induced pluripotent cells.

3.2.4 Who files embryonic stem cell patent applications?

We grouped the EPO patent applications as a result in section 3.2.2 per patent applicant (see Table 6). Stem cell companies file twice as much as compared to publicly funded institutions.

Table 6. Types and rates of applicants as regards embryonic stem cell patents

European applications in patent class "Pluripotent embryonic cells" (C12N 5/0606)	in %
From universities	19
From public research organisations	12
From enterprises	66
From individual patent applicants	3

3.2.5 Pluripotent stem cell research in an academic setting

For the purpose of mapping the research scientist’s interest in pluripotent stem cell sources, we set out the evolution of publications with reference to pluripotent stem cells in Figure 14.

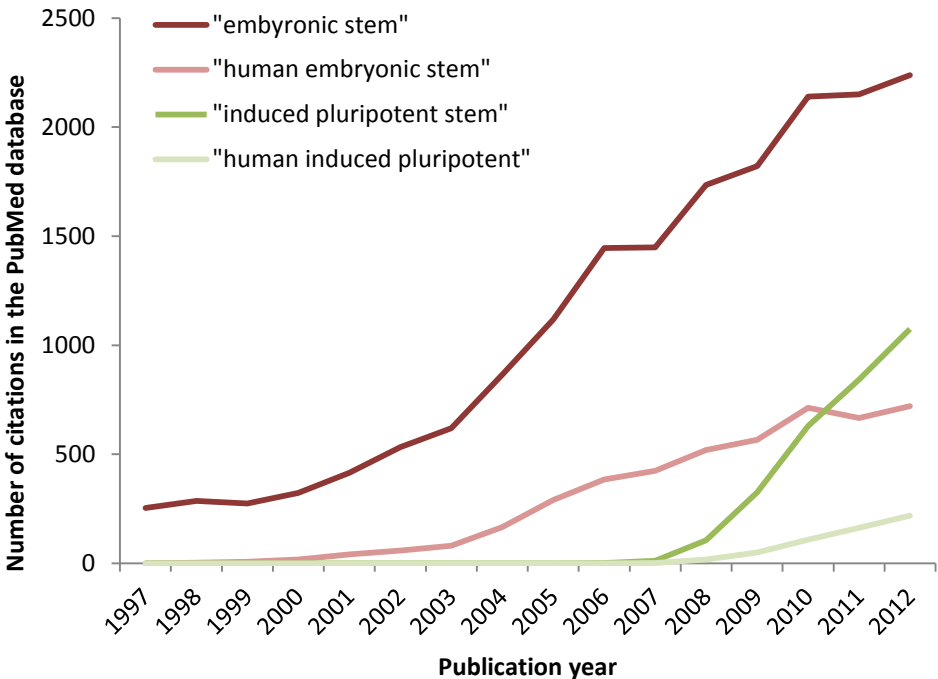


Figure 14. Evolution between 1997 and 2012 of the PubMed citations comprising one of four different phrases referring to a pluripotent stem cell source in title or abstract. Conducting induced pluripotent stem cell research has increased rapidly immediately after its introduction in 2006.

3.3 The Brüstle patents and the patentability of their subject matter

3.3.1 A matter of policy

Whether the claimed subject matter disclosed in the controversial patents held by O. Brüstle effectively meets the requirements of either the national legislation (i.c. German Patent Act) or international treaty (i.c. European Patent Convention) is determined as a matter of policy. Both the German patent and European patent were opposed for the reason that the subject matter is regarded as non-patentable by the opponent. The opposition proceedings against the European patent are additionally based on grounds of insufficient disclosure and added matter. Before we discuss the influence of the Brüstle case in the EU and the Brüstle case at the EPO on the examination of European patent applications, we will primarily review the claims of Brüstle which have been disputed in the context of "exceptions from patentability".

3.3.2 The German patent held by Brüstle

Title: NEURAL PRECURSOR CELLS, METHOD FOR THE PRODUCTION AND USE THEREOF IN NEURAL DEFECT THERAY (DE19756864)	
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Priority date: 19.12.1997	The date of grant of the patent: 29.04.1999
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Granted claims (English translation):

The granted claims all require the proliferation and cultivation of embryonic stem cells, e.g.

Claim 1 Isolated, purified precursor cells with neuronal or glial properties from embryonic stem cells, comprising at most about 15% primitive embryonic and non-neutral [meant is: non-neural] cells, obtainable by the following steps [...]

Opposition under Section 2 (2) (3) of the German Patent Act on October 20, 2004:

"The Plaintiff has requested to declare invalid the patent in suit, insofar as claims 1, 12, and 16 comprise precursor cells that are obtained from human embryonic stem cells. Furthermore, he has requested to declare invalid the scope of claim 8, indirectly referring back to claim 1, insofar as the former comprises human cells. The Plaintiff has reasoned that the technical teaching of the patent in suit was to this extent excluded from patentability pursuant to Section 2 of the German Patent Act."

(Source: Annex to a letter dated 11.03.2013 in view of European opposition proceedings)

Requests of the Defendant and Appellant (O. Brüstle):

- The **Main Request** includes a full dismissal of the revocation of the patent.
- According to **Auxiliary Request I**, the claims are to be amended as follows:
 - In claims 1, 12, and 16 in the paragraphs beginning with "a)" and "a')", respectively, after "ES cells": "from cell lines" is to be inserted,
 - To the end of claim 1:
", wherein no isolated purified precursor cells from human embryonic stem cells are encompassed during the generation of which embryos have been destroyed" is to be additionally appended,
 - To the end of claims 12 and 16, respectively:
", wherein no human embryonic stem cells are used during the generation of which embryos have been destroyed" is to be additionally appended

Final status: Patent upheld in amended form (cf. Auxiliary Request I)

3.3.3 The European patent held by Brüstle

Title: NEURAL PRECURSOR CELLS, METHOD FOR THE PRODUCTION AND USE THEREOF IN NEURAL DEFECT THERAY (EP1040185)	
Priority date: 19.12.1997	The date of grant of the patent: 22.02.2006

Granted claims (English translation):

The granted claims all require the proliferation and cultivation of embryonic stem cells. After an objection under Art. 53(a) EPC by the EPO Examining Division on December 27, 2001, a disclaimer (cf. underlined part) was introduced in independent claims 1, 3, 15 and 18, e.g.

Claim 1 Non-tumorigenic cell composition obtained from mammalian embryonic stem cells, containing

- a) at least 85% isolated neural precursor cells with the ability to differentiate into neuronal or glial cells, and
- b) no more than 15% primitive embryonic and non-neural cells, obtainable by the steps of [...]

with the proviso that the method does not include the destruction of human embryos.

Opposition under Art. 53(a) and R. 28(c) EPC on November 21, 2006:

"Rule 28(c) EPC prohibits the patenting of uses of human embryos for industrial or commercial purposes. In an attempt to comply with this provision, all four independent claims of the patent contain a disclaimer that the method comprising the steps recited in each claim does not include the destruction of human embryos. This disclaimer is intended to exclude methods in which the human ES cells referred to in the claims are produced by upstream steps involving the destruction of human embryos. A final decision as to whether the disclaimer in the granted claims meets the requirements of Art. 53(a) and R.28 (c) EPC and, if not, what disclaimer would be allowable, cannot be reached until the questions regarding the interpretation of Art. 53(a) and R.28 (c) EPC pending before the Enlarged Board of Appeal in G2/06 have been answered. [...]

In the event that the Enlarged Board decides that the exclusion in R.28(c) EPC should be interpreted broadly, the patent should be revoked for failure to meet the requirements of Art. 53(a) EPC [...]. In the event that the Enlarged Board interprets the exclusion in R.28(c) EPC more narrowly, it will need to be considered whether the granted claims meet the requirements of this more limited exclusion." (Notice of opposition)

Oral proceedings were held on April 11, 2013.

Current status: Patent is revoked on other grounds of opposition (Art. 83 and Art. 123 EPC)

3.4 European patent applications and the impact of the Brüstle cases

3.4.1 Positioning pending patent applications

The examination of a large amount of stem cell patent applications is still pending at the EPO. In section 2.4.2, we illustrate two patent applications for which an objection under Article 53(a) and Rule 28 (c) EPC was recently made by the EPO Examining Division and in this manner we notify that the impact of CJEU decision C-34/10 extends beyond claiming an invention that is essentially based on human embryonic stem cells (see Example 1 and Example 2). Remedial action has been required to align the pending claims, which imply human embryo destruction at any point in time, with the revised Guidelines for Examination of the EPO (June 2012). Therefore, European patent attorneys introduced a disclaimer (see Example 2, Example 3 and Example 4), rejected parts of the original claim (see Example 4) or amended the claim formulation (see Example 5), whether or not subsequent to an objection

by the EPO Examining Division. In section 2.4.3, we exemplify that examination processes are greatly delayed by both the CJEU ruling in the *Brüstle v. Greenpeace* case and the decision of the EPO Examining Division in the *Brüstle v. Geron* case on the basis of letters communicated between a patent attorney, representing a patent applicant, and the EPO Examining Division.

3.4.2 Influence of the CJEU judgment on European patent applications

Example 1. IMPROVED MODALITIES FOR THE TREATMENT OF DEGENERATIVE DISEASES OF THE RETINA (EP2479262)	
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Priority date: 24.01.2005	Entry into the European phase: 23.08.2007
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Original claims:

All claims are based on the first independent claim which refers to pluripotent stem cells, i.e.

Claim 1 Isolated retinal pigment epithelium (RPE) cells generated from mammalian pluripotent stem cells, optionally human pluripotent stem cells, which are [...]

Objection under Art. 53(a) and R. 28(c) EPC on March 14, 2013:

"Although it is true that the human pluripotent stem cells in claim 1 are only an optional cell source, they are still embraced by claim 1 and thus claim 1 embraces cells that at the time of filing could exclusively be obtained by the destruction of a human embryo. The applicant is therefore requested to amend the claims and the description accordingly."

(Communication from the Examining Division)

Claim amendments: Reply to the communication from the Examining Division is awaited

Current status: Examination is in progress

Example 2. IMPROVED CRYOPRESERVATION OF ADIPOSE TISSUE FOR THE ISOLATION OF MESENCHYMAL STEM CELLS (EP2278873)	
--	--

Priority date: 19.03.2008	Entry into the European phase: 15.10.2010
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Original claims:

All three independent claims (i.e. claim 1, 4 and 7) contain a reference to adipose tissue, e.g.

Claim 4 A method for the cryopreservation of adipose tissue, comprising the steps [...]

Objection under Art. 53(a) and R. 28(c) EPC on February 11, 2013:

"As mentioned in the International Preliminary Examination Report, the EPO excludes from patentability the use of human embryos for industrial or commercial purposes (see Art. 53(a) and R. 28(c) EPC). As human embryos, at a certain stage of development, may contain adipose tissue, in order to fulfill the requirements of Art. 53(a) and R. 28(c), the claims should exclude the possibility that the adipose tissue be obtained from a human embryo." (Communication from the Examining Division)

Amended claim:

Claim 4 A method for the cryopreservation of adipose tissue, comprising the steps [...]
wherein said adipose tissue is not obtained from a human embryo.

Current status: Examination is in progress

Example 3. PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF HEART DISEASES (EP2432482)	
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Priority date: 20.05.2009	Entry into the European phase: 16.12.2011
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Original claims:

Five dependent claims (i.e. claim 11, 12, 13, 14 and 18) cover a wide range of stem cells, e.g.

Claim 11 A pharmaceutical composition according to any of the preceding claims, wherein said cells committed to the generation of heart tissue are stem cells.

Notification under Art. 53(a) and R. 28(c) EPC on March 16, 2011:

"The general reference to stem cells in claims 11-14 and 18 also includes human embryonic stem cells, which, according to the provisions of the EPO would offend against Art. 53 (a) EPC would offend against Art 53(a) EPC – Contrary to "ordre public" or morality. A clear reference to "non-embryonic" stem cells would be appropriate to overcome this problem possibly arising at a later stage. "

(Copy of the international preliminary examination report)

Observation by the European patent attorney on July 12, 2012:

"In the International Preliminary Examination Report, the Examiner has raised a concern that the scope of claims 11-14 and 18 encompasses the use of human embryonic stem cells, and as such, are in contravention of Art. 53(a) EPC. New claims 6 and 7 (previous claims 11 and 12) have now been amended to recite a disclaimer against the destruction of human embryonic stem cells [meant is: human embryos]. We trust that new claims 6, 7, 8 and 10 (previous claims 11, 12, 13 and 18) are now allowable. Previous claim 14 has been deleted." (Amendments received before examination)

Amended claims (renumbered):

A disclaimer (cf. underlined part) was introduced in dependent claims 6, 7, 8 and 10, e.g.

Claim 6 A pharmaceutical composition according to any of the preceding claims, wherein said cells committed to the generation of heart tissue are stem cells provided their production implies no human embryo destruction.

Current status: Examination is in progress

Example 4. GENES WITH ES CELL-SPECIFIC EXPRESSION (EP2354227)	
Priority date: 31.05.2001	Entry into the European phase: 19.12.2003

Original claims:

Independent claims 1, 6, 14 and dependent claims 2, 7-9, 11 refer to an embryonic stem (ES) cell, e.g.

Claim 1 A probe when used for determining if a cell is an ES cell, comprising a DNA of the following [...]

Objection under Art. 53(a) and R. 28(c) EP on October 4, 2012:

"Claims 1-2, 6-9, 11, 14 explicitly refer to a use of human ES cells. Thus, while a part of the invention as claimed may be implemented with other cells than hESC (such as non-human embryonic stem cells or mouse ES cells), the use of hESC is an avowed method of implementation (see [...]).

What could be considered allowable: Methods of use of [...] but limited to a mouse ES cell (claim 3). The use of a general disclaimer such as non-human is not advisable because the

human [...] sequences would only be useful as probes for human cells and not for any other non-human cells." (Communication from the Examining Division)

Amendments in the claims:

- Original claim rejection:
parts (a) and (b) of previous claim 1 have been deleted from new claim 7; previous claim 2 has been deleted; parts (Ia), (Ib), (IIa) and (IIb) of previous claim 6 have been deleted from new claim 9; previous claim 7 has been deleted
- All references to ES cells have been amended to clarify that they are concerned with "non-human" ES cells.

Current status: Examination is in progress

Example 5. SERUM FREE CULTIVATION OF PRIMATE EMBRYONIC STEM CELLS (EP1261691)	
Priority date: 09.03.2000	Entry into the European phase: 23.09.2002

Original claims:

Independent claims 1, 10, 11 and dependent claims 2-9 refer to embryonic stem cells, e.g.

- Claim 1 A method of culturing primate embryonic stem cells, comprising: culturing the stem cells in a culture free of mammalian fetal serum and in the presence of [...]"
- Claim 7 The method of any one of claims 3 to 6, wherein the primate embryonic stem cells are human embryonic stem cells.
- Claim 11 A culture of primate embryonic stem cells which culture comprises: primate embryonic stem cells; and a culture system for culturing primate embryonic stem cells according to claim 10.

Objections under Art.53(a) and R.28(c) EPC:

- Office Action on account of EPO decision G 2/06 on December 14, 2009:
"With regard to the human embryonic stem (hES) cells, the one and only source indicated in the description is a human embryo, from which the ES cells can be obtained by the method disclosed in Thomson *et al.*, Science (1998) 282: 1145-1147. No alternative source of hES cells appears to be indicated. Even if at the time of the filing several usable

cell lines of hES cells were contemplated, which appears to be unlikely considering the filing date of the present application, this does not appear to be mentioned in the application, nor appears to be disclosed therein a reference to any further specific cell lines. Instead, the application only discloses that hES cells are obtainable directly from embryos (via the method of Thomson *et al.*)

Therefore, the subject-matter of claims 1 to 9, and 11 falls within the remit of G2/06 and is not allowable under Article 53 (a) and Rule 28(c) EPC."

(Communication from the Examining Division)

- Reply of the applicant:

A discussion followed with regard to the date on which human embryonic stem cell lines became publicly available

- Office Action on account of CJEU decision C-34/10 on September 13, 2012:

"Claim 7, and [...] explicitly refer to hESCs. Thus, while a part of the invention as claimed may be implemented with cells other than hESCs (such as non-human embryonic stem cells), the use of hESCs is an avowed method of implementation (see [...]). Irrespective of the question whether the public availability of hESC lines can be considered to be sufficiently established at the filing date of the application, such hESC lines were necessarily produced by the destructive use of human embryos, namely by derivation from the inner cell mass of the blastocyst whereby the blastocyst is necessarily destroyed. Taking into account the above-mentioned principles, the implementation of the invention as of the filing date thus requires the use of human embryos for industrial or commercial purposes within the meaning of Rule 28(c) EPC.

As a consequence, based on the presently submitted documents, the Examining Division is of the opinion that the invention is excluded from patentability under Article (a) and Rule 28(c) EPC." (Communication from the Examining Division)

Amended claims (renumbered):

Claim 1 ~~A method of~~ A culture system for culturing primate embryonic stem cells, comprising: [...]

Claim 3 ~~The method of~~ The culture system of claim 1 or 2, wherein the primate embryonic stem cells are human embryonic stem cells.

Current status: Grant of patent is intended

3.4.3 Influence of the Brüstle cases on patent application EP 2327762

Casus: STEM CELLS (EP2327762)	
Priority date: 05.06.2002	Entry into the European phase: 23.12.2004

Original claims:

Independent claim 1 and dependent claims 3 and 4 refer to pluripotent stem cells, e.g.

Claim 3 The method of claim 1, wherein said pluripotent stem cells comprise embryonic stem cells.

Claim 4 The method of claim 3, wherein said embryonic stem cells comprise human embryonic stem cells.

Communication from the Examining Division on January 25, 2012:

"The Applicant will be aware that the European Court of Justice ruled that stem cells extracted from human embryos cannot be patented if the embryos are destroyed in the process. The Court [...] said it is not possible to ignore the origin of this pluripotent cell. Since a pluripotent stem cell that is derived by removal from the blastocyst will destroy the embryo, any claims to or essentially involving the use of such cells will fall under the exceptions of Rule 28(c) EPC. The Applicant may file new claims which take in to account the above comments."

Applicant requested for extension of time limit to the Examining Division on July 26, 2012:

"Given that a change of practice which could impact on the present application is being discussed at the EPO, we request an extension of time until the full details regarding the implementation of Decision C-34/10 have been published."

(No reply)

Objection under Art. 53(a) and R. 28(c) EPC on October 29, 2012:

"Claim 3 [sic] explicitly refers to hESC. Thus, while a part of the invention as claimed may be implemented with cells other cells than hES (such as non-human embryonic stem cells), the use of hES is an avowed method of implementation (see [...]). The implementation of the invention thus requires a use of human embryos within the meaning of R. 28(c) EPC." (Communication from the Examining Division)

Applicant requested for extension of time limit to Examining Division on February 19, 2013:

"With reference to the Communication of 29 October 2012, I request an extension of two months of the time for filing a response."

Grant of extension of time limit on February 25, 2013:

"With reference to your request, the time limit for replying to the communication [...] dated 29.10.2012 has been extended by 2 months to a total of 6 months from the date of the above-mentioned communication." (Communication from the Examining Division)

Applicant requested for extension of time limit to the Examining Division on May 3, 2013:

"The recent Decision of the Court of Justice of the EU in Case 34/10 has impacted significantly on the practice of the EPO [...]. In particular, the EPO's Opposition Board recently revoked EP1040185, but the Minutes of the Proceedings and the Decision of the EPO's Opposition Board have not yet published. We kindly request an extension of time to give the applicant the opportunity to review this Decision and to assess its potential impact on the prosecution of the present case."

Refusal of request for extension of time limit:

"Your request dated 03.05.2013 for an extension of the time limit has been refused for the reason below: The reasons given in the request are not sufficient, see [...]. A separate communication will be issued concerning the legal consequence that will ensue."
(Communication from the Examining Division)

Current status: Examination is in progress

PART 4: DISCUSSION

4.1 Impact of CJEU ruling C-34/10 on (Belgian) stem cell research

Our small-scale survey study reveals that the use of stem cells derived from human embryos is mainly practiced in academic scientific research and barely applied in stem cell companies. In this observation, CJEU ruling C-34/10 does not play a role as a causative factor, but rather represents an extension of the issues that have hampered the progress of human embryonic stem cell research. That is why the Belgian and Dutch companies' interest in embryonic stem cells has generally been lagging and academic scientists have expressed their frustrations at the non-scientific problems surrounding this research field. Acquiring financial support for the performance of basic or translational research using a human embryonic stem cell-based strategy has not been problematic, however, from the moment that an economic purpose is mentioned, those chances become strongly reduced. The interest of UK stem cell companies in human embryonic stem cells, for some time, had taken another dimension considering the UK's leading position in regenerative medicine. This can be illustrated by the United Kingdom Intellectual Property Office which, following the Board of Appeal decision in the WARF case, emphasised their liberal approach towards the patentability of human embryonic stem cells and depended on the guideline saying "*on balance the commercial exploitation of inventions concerning human embryonic stem cells would not be contrary to public policy or morality in the United Kingdom*", though the office had to reconsider their practice in view of the CJEU decision (UKIPO, 2009). While the influence of judgment C-34/10 cannot be supported with numerous examples of failed R&D projects, because few R&D attempts have so far been carried out in this relatively new scientific field, we have now come to a point that human embryonic stem cell-based applications are ready to be commercially developed (cf. Pluriomics was launched in 2011) and scrutinized in clinical trials (cf. Advanced Cell Technology published preliminary clinical trial results in 2012). This statement was echoed by the CEO at Cell Therapy Catapult Centre, who has adopted a wait-and-see attitude in view of the hESC patentability in Europe and compares the current challenges surrounding hESC-based therapies with the difficulties monoclonal antibody-based therapies had been going through at the start of his career; the therapeutic use of monoclonal antibodies was not approved for the period of 10 years after the first reliable antibody was developed and subsequently another 15 years was required to exploit the antibodies into the successful

class of drugs which they represent now. Yet, since the introduction of induced pluripotent stem cell research, opinions on whether this type of stem cell holds much more potentiality as compared to naturally occurring pluripotent stem cells are divided. Although induced pluripotent stem cells do not comprise the non-scientific problems embryonic stem cells have, those artificial pluripotent cells are still in their infancy.

4.2 Impact of CJEU ruling C-34/10 on European patent applications

As the Enlarged Board of Appeal of the EPO concluded that the decision in the WARF case "*is not concerned with the patentability in general of inventions relating to human stem cells or human stem cell cultures*", the question whether human embryonic stem cell inventions are patentable still remains open (EBoA, 2008). The answer thereto is expected to be given in the Brüstle case at the EPO and, thereby, CJEU decision C-34/10 might impose severe restrictions on the scope of patent protection for downstream derivative products or procedures with regard to human embryo-derived stem cells. At this time, the broad interpretation of Article 6 (2)(c) in EU directive 98/44/EC of the CJEU is taken over by EPO patent attorneys and EPO examiners for the interpretation of Article 53 (a) and Rule 28 (c) EPC, which has resulted in far-reaching objections to any claim that insinuates the destruction of a human embryo and in numerous claim amendments. Furthermore, we have seen that stem cell patent applications at the EPO are delayed in proceeding to the grant of a patent and become temporized in anticipation of the final outcome in the Brüstle v. Geron case. It is far too early to draw conclusions in terms of European patent filings in the year in which the EU Court delivered its judgment, however, current public information reveals that decision C-34/10 will be responsible for another hitch in the evolution of embryonic stem cell patenting and, although the actual judgment was not a direct cause, the whole patent discussion regarding human embryonic stem cell inventions can be held in connection with the exponential increase in European patent filings pertaining to induced pluripotent stem cells. Indeed inventions on the basis of artificial pluripotent cells have provided and still provide more legal certainty. Nonetheless, it is said by EPO examiners that the method called "single blastomere biopsy" may resolve some non-scientific problems (see section 1.5.5) of human embryonic stem cells. Seeing that this technique enables the isolation of stem cells from a human embryo whilst the embryo remains viable, claims involving stem cells or tissue would no longer be objected under Article 53 (a) and Rule 28 (c) EPC for the

sole reason that a human embryo could have been destroyed so as to obtain the claimed product or method.

4.3 Implications of a stringent outcome in the *Brüstle v. Geron* case

The fruits of years of translational research by European scientists will effectively be wiped away and left to the non-European countries if the final outcome in the *Brüstle v. Geron* case leads to an exclusion from patentability of human embryonic stem cell inventions by arguing that the use of human embryonic stem cells is still inextricably linked with the use of human embryos, whether or not the viability of the embryo is maintained. Although this is rather a worst-case scenario as case law of the EPO Boards of Appeal indicates that any exceptions to patentability must be narrowly construed, the Boards of Appeal will evaluate the policy that has been proposed by EPO examiners once the decision of the EPO Opposition Division in the *Brüstle v. Geron* case is appealed. An inability to patent human embryonic stem cells is a reason not to financially support embryonic stem cell research and hence could threaten the lead and competitiveness of Europe in the sector of regenerative medicine.

For the time being, there is not a significant difference between Europe and the U.S. in terms of patent filings or patent grants relating to embryonic stem cells, however, this observation is probably due to an unfavorable regulatory framework which has hobbled, for a long time, hESC research in the United States. Though, the outlook brightens for U.S. researchers as the regulatory climate has been changing under the leadership of President Obama and a recent ruling of the U.S. Supreme Court ensures continued government funding for hESC research (Wadman, 2013).

4.4 General conclusion

There have been a lot of misconceptions about the influence of CJEU's recent decision in the *Brüstle v. Greenpeace* case. Its consequences turn out to be not as dramatic as was primarily feared; the CJEU ruling in C-34/10 does not equal the end of the conduct of embryonic stem cell research in Europe, nor has it caused a flight of research or scientists from Europe. It did, however, brought about hurdles in acquiring public funding for hESC-based projects with an economic purpose, modifications in the ratio of patent *v.* trade secret protection, and delays in either the filing or examination process of stem cell patent applications at the EPO. These effects merely represent the present level of uncertainty for patenting embryonic stem cells

in Europe and send out a negative message that impedes the development and marketing of potentially life-saving therapies, but therefore are not necessarily definite; as Europe used to attract companies because of the strong regulatory framework (cf. Pfizer Neusentis Unit, UK, 2008) and is currently struggling with patenting issues, the United States offers an attractive environment for the commercialization of cell therapies whilst they have only recently been tackling its restrictive regulatory framework. This is understood by researchers who have set their hopes on potential appeal proceedings in the *Brüstle v. Geron* case, whereby it is likely that the Boards of Appeal of the EPO will take a position towards the patentability of human embryonic stem cells in Europe. If the policy that has been proposed by EPO examiners then gets an approval, it follows that hESC-related patent applications which are filed onwards of 10 January 2008 at the EPO are not excluded from patentability. However, it remains to be seen whether the new EPO policy, if approved by the Boards of Appeal, will also not be objected to by certain organizations, leading again to referrals to the Enlarged Board of Appeal or even questions to the CJEU.

Moreover, it is concluded that the conduct of induced pluripotent stem cell research cannot be continued at the expense of human embryonic stem cell research. Both stem cell sources are of great importance to clarify all the mechanisms behind the character of "pluripotency" and each one holds the potential to be used in clinical applications. It is not yet known which one will eventually be the most effective stem cell source for clinical use, nevertheless, they should be explored complementary rather than substitutive and a cell therapy in the benefit of patients with life-threatening diseases should not be driven by politics and public opinion. A recent statement that is written in view of the next Framework Programme (Horizon 2020) of the European Commission has now been signed by 19 organisations and urges to provide further funding for all types of stem cell research in order to enable scientists to understand the massive potential of stem cells (Wellcome Trust, 2012). This includes EU funding for research projects on the basis of e.g. human embryonic stem cells, induced pluripotent stem cells, adult stem cells or trans-differentiated cells. The preliminary agreement maintains the status quo³ for financing hESC research in Horizon 2020 (Moran, 2013).

³ The "triple-lock", which was negotiated for the Seventh Framework Programme (FP7), states that EU-funded embryonic stem cell research must conform with the laws of the country in which it is undertaken; that the research is subject to ethical review; and that EU money cannot be used for the derivation of new human embryonic stem cell lines, or any research involving the destruction of human embryos.

PART 5: DISCUSSIE

5.1 Impact van HvJ EU Arrest C-34/10 op stamcelonderzoek (in België)

Uit ons kleinschalig onderzoek blijkt dat humane embryonale stamcellen voornamelijk gebruikt worden voor academisch wetenschappelijk onderzoek en amper onderzocht worden in een industriële omgeving. In deze vaststelling speelt het Arrest in zaak C-34/10 van het Hof van Justitie van de Europese Unie (HvJEU) geen oorzakelijke rol, maar vormt het eerder een verlenging van de kwesties die de vooruitgang van humaan embryonaal stamcelonderzoek bemoeilijkt hebben. Om die reden hebben Belgische en Nederlandse bedrijven tot nog toe weinig interesse getoond in dit onderzoeksgebied en academische onderzoekers hebben hun frustraties geuit over de niet-wetenschappelijke problemen die dit onderzoeksgebied met zich meebrengt. Het aanvragen van subsidies voor fundamenteel of translationeel onderzoek gebruikmakende van humane embryonale stamcellen is niet problematisch, maar van zodra er een economisch doeleinde vermeld wordt, is de kans om publieke financiering te verkrijgen erg klein. De interesse van de bedrijven die gevestigd zijn in het Verenigd Koninkrijk heeft voor enige tijd een andere dimensie aangenomen omwille van de leiderspositie van het Verenigd Koninkrijk in de regeneratieve geneeskunde. Dit kan geïllustreerd worden aan de hand van het voormalig beleid in het nationaal octrooibureau van het Verenigd Koninkrijk waarbij, na de beslissing van de Grote Kamer van Beroep van het Europees Octrooibureau in de zaak WARF, de nadruk gelegd werd op hun liberale visie ten opzichte van de octrooieerbaarheid van humane embryonale stamcellen en berustten toen op volgende richtlijn "*on balance the commercial exploitation of inventions concerning human embryonic stem cells would not be contrary to public policy or morality in the United Kingdom*", maar het bureau moest dit beleid herzien na uitspraak van Arrest C-34/10 (UKIPO, 2009). Terwijl de invloed van Arrest C-34/10 niet onderbouwd kan worden met talrijke voorbeelden van O&O-projecten die werden stopgezet aangezien tot nog toe weinig O&O-projecten zijn opgestart in dit relatief nieuw onderzoeksgebied, zijn we op een punt gekomen waarop er voldoende kennis vergaard is om toepassingen gebruikmakende van humane embryonale stamcellen te ontwikkelen (cf. Pluriomics is opgericht in 2011) en deze te bestuderen in klinisch onderzoek (cf. Advanced Cell Technology publiceerde voorlopige resultaten van hun klinische proeven in 2012). Deze stelling werd bevestigd door de CEO van Cell Therapy Catapult Centre, die eveneens een afwachtende houding heeft aangenomen

aangaande de octrooieerbaarheid van humane embryonale stamcellen in Europa en vergelijkt huidige uitdagingen rond hESC-gebaseerde therapieën met de moeilijkheden waarmee monoclonaal antilichaam-gebaseerde therapieën geconfronteerd zijn bij het begin van zijn professionele carrière; het therapeutisch gebruik van monoclonale antilichamen werd niet goedgekeurd gedurende een periode van 10 jaar nadat de eerste betrouwbare bron van antilichamen was ontwikkeld en vervolgens heeft nog 15 jaar geduurd voor de exploitatie van de antilichamen resulteerde in de succesvolle klasse van medicijnen die ze dezer dagen voorstellen. Doch, sinds het geïnduceerd pluripotent stamcelonderzoek geïntroduceerd werd, zijn de meningen aangaande het potentieel van deze artificiële cellen ten aanzien van natuurlijk voorkomende pluripotente stamcellen sterk verdeeld. Hoewel geïnduceerde pluripotente stamcellen geen niet-wetenschappelijke problemen met zich meedragen zoals embryonale stamcellen, staan deze artificiële pluripotente cellen nog steeds in hun kinderschoenen.

5.2 Impact van HvJ EU Arrest C-34/10 op Europese octrooiaanvragen

Vermits de Grote Kamer van Beroep van het Europees Octrooibureau geconcludeerd heeft dat hun beslissing in de zaak WARF "*is not concerned with the patentability in general of inventions relating to human stem cells or human stem cell cultures*", de vraag of humane embryonale stamcellen al dan niet octrooieerbaar zijn in Europa staat nog steeds open (EBoA, 2008). Het antwoord daarop wordt hoogst waarschijnlijk gegeven in de zaak Brüstle in het Europees Octrooibureau en daarbij kan Arrest C-34/10 beperkingen opleggen aangaande de mate waarin uitvindingen voor producten of procedures gebruikmakende van human embryonale stamcellijnen octrooieerbaar zijn. Momenteel wordt de brede interpretatie van Art. 6(2)(c) in de EU-Biotechnologierichtlijn van het HvJ EU overgenomen door octrooigemachtigden en examinatoren van het Europees Octrooibureau ter interpretatie van Art. 53(a) en R.28(c) EPC, wat geleid heeft tot verregaande bezwaren tegen elke claim dat de destructie van een humaan embryo insinueert alsook in talrijke wijzigingen van de claims. Bovendien stellen we vast dat octrooiaanvragen met betrekking tot stamcellen sterk vertraagd worden in hun behandeling in het Europees Octrooibureau en worden tevens op de lange baan geschoven in afwachting van de finale uitkomst in de zaak Brüstle v. Geron. Het is nog veel te vroeg om besluiten te trekken betreffende het indienen van Europese octrooiaanvragen in het jaar waarin Arrest C-34/10 is uitgesproken, maar,

huidige publieke informatie onthult dat het Arrest verantwoordelijk zal zijn voor een hapering in de evolutie van octrooiaanvragen met betrekking tot embryonale stamcellen en, hoewel de eigenlijke uitspraak geen oorzaak is, de volledige discussie rond het octrooieren van humane embryonale stamcellen kan in verband gebracht worden met de exponentiële stijging in Europese octrooiaanvragen met betrekking tot geïnduceerde pluripotente stamcellen. Uitvindingen op basis van artificiële pluripotente stamcellen bieden immers meer rechtszekerheid. Echter examinatoren van het Europees Octrooibureau hebben aangegeven dat de methode genaamd "single blastomere biopsy" heel wat niet-wetenschappelijke problemen van de hESCs zou kunnen oplossen (zie sectie 1.5.5). Aangezien deze methode het mogelijk maakt om stamcellen te isoleren uit humane embryo's waarbij het embryo levensvatbaar blijft, zouden er geen bezwaren meer kunnen gemaakt worden onder Art. 53 (a) en R. 28(c) EPC tegen claims die betrekking hebben op stamcellen of weefsel met het argument dat een humaan embryo kan vernietigd worden om het product of de procedure waarop aanspraak gemaakt wordt in de octrooiaanvraag te kunnen verkrijgen.

5.3 Implicaties van een streng besluit in de zaak Brüstle v. Geron

De vruchten van jarenlang translationeel onderzoek uitgevoerd door Europese onderzoekers zullen tenietgedaan worden of overgelaten worden aan niet-Europese landen indien de finale uitkomst in de zaak Brüstle v. Geron leidt tot een uitsluiting van de octrooieerbaarheid van humane embryonale stamcellen. Bijvoorbeeld door te stellen dat het gebruik van deze stamcellen onlosmakelijk verbonden is met het gebruik van humane embryo's, ongeacht of de levensvatbaarheid van het embryo wordt behouden. Hoewel dit eerder een pessimistisch scenario is omdat jurisprudentiële beslissingen van de Grote Kamer van het Europees Octrooibureau erop wijzen dat Art. 53(a) EPC eng moet worden geïnterpreteerd (EPO, 2010), zal de Grote Kamer het beleid dat voorgesteld wordt door examinatoren van het Europees Octrooibureau evalueren van zodra Brüstle in beroep gaat op de beslissing van de Oppositie-Divisie van het Europees Octrooibureau. Indien octrooieren van uitvindingen gebaseerd op humane embryonale stamcellen onmogelijk wordt, is dit een reden om niet te investeren in embryonaal stamcelonderzoek en kan dit de leiderspositie en het concurrentievermogen van Europa in de regeneratieve geneeskunde in het gedrang brengen.

Voorlopig is er geen significant verschil tussen Europa en de Verenigde Staten (VS) op vlak van het aantal octrooiaanvragen ingediend of het aantal octrooien toegekend met betrekking tot embryonale stamcellen. Deze waarneming is hoogst waarschijnlijk te wijten aan het ongunstig regelgevingskader in de VS dat, voor een lange periode, de uitvoering van embryonaal stamcelonderzoek gehinderd heeft. Doch, de vooruitzichten fleuren op voor onderzoekers in de VS aangezien het regelgevingskader aan het veranderen is onder de autoriteit van President Obama en een recente uitspraak van het Federaal Hooggerechtshof in de VS garandeert een verderzetting van de publieke financiering voor dit onderzoeksveld (Wadman, 2013).

5.4 Algemene conclusie

Er bestaan heel wat misopvattingen over de invloed van HvJ EU Arrest C-34/10 in de zaak *Brüstle v. Greenpeace*. Diens gevolgen blijken niet zo dramatisch als eerst werd gevreesd; Arrest C-34/10 betekent niet het einde van embryonaal stamcelonderzoek in Europa, noch heeft het een vlucht veroorzaakt van onderzoek of wetenschappers uit Europa. De uitspraak veroorzaakte evenwel moeilijkheden bij het verkrijgen van publieke financiële steun voor onderzoeksprojecten op basis van humane embryonale stamcellen met een economisch doeleinde, het heeft een wijziging teweeggebracht in de verhouding octrooibeschermt v. geheimhouding, alsook zorgde het Arrest voor heel wat vertraging voor het indienen en de behandeling van octrooiaanvragen bij het Europees Octrooibureau. Deze effecten geven het huidige niveau van rechtsonzekerheid weer, hetgeen de ontwikkeling en het vermarkten van potentieel levensreddende therapieën hindert, maar zijn daarom niet noodzakelijk definitief; zoals Europa aanvankelijk bedrijven aantrok omwille van het aantrekkelijk regelgevingskader (cf. Pfizer Neusentis Unit, Verenigd Koninkrijk, 2008) en momenteel worstelt met kwesties bij het octrooieren, zo biedt de VS een aantrekkelijke omgeving voor het commercialiseren van stamceltherapieën terwijl ze pas recent gestart zijn met het aanpassen van hun restrictief regelgevingskader. Dit wordt begrepen door onderzoekers die rekenen op een potentiële hoger beroepsprocedure in de zaak *Brüstle v. Geron*, waarbij het waarschijnlijk is dat de Grote Kamer van het Europees Octrooibureau een standpunt zal innemen ten opzichte van de octrooieerbaarheid van humane embryonale stamcellen in Europa. Indien het beleid dat wordt voorgesteld door examinatoren van het Europees Octrooibureau wordt goedgekeurd, zullen octrooiaanvragen met betrekking tot humane embryonale stamcellen

die ingediend zijn na 10 januari 2008 in aanmerking komen voor octrooibeschermtng. Doch, het valt af te wachten of dit beleid, indien het goedgekeurd wordt door de Grote Kamer, niet opnieuw wordt aangevochten door bepaalde organisaties, zodat de zaak opnieuw wordt doorverwezen naar de Grote Kamer van het Europees Octrooibureau of zodat er opnieuw vragen zullen gesteld worden aan het Hof van Justitie van de Europese Unie.

Daarenboven kan er geconcludeerd worden dat de uitvoering van geïnduceerd pluripotent stamcelonderzoek niet ten koste mag gaan van embryonaal stamcelonderzoek. Beide types van stamcellen zijn van groots belang voor de opheldering van de cel mechanismen die de eigenschap "pluripotentie" bepalen en elk type stamcel heeft het potentieel om gebruikt te worden in therapeutische toepassingen. Het is echter nog niet bekend welke bron daarvoor het meest geschikt is en daarom is het nodig om beide stamcel types eerder complementair te onderzoeken dan elkaar vervangend, zodat, in het voordeel van de patiënt met een levensbedreigende ziekte, de meest effectieve therapie kan ontwikkeld worden zonder dat deze keuze gedreven is door een politiek beleid of publieke opinie. Een verklaring dat recent geschreven werd met het oog op het volgende Framework Programme (Horizon 2020) van de Europese Commissie werd momenteel reeds ondertekend door 19 organisaties en verzoekt verder EU financiering te voorzien voor alle soorten stamcelonderzoek, opdat de onderzoeker alleen op deze manier het vermoedelijke potentieel van stamcellen zal kunnen begrijpen (Wellcome Trust, 2012). Dit omvat een vraag naar EU financiering voor projecten gebruikmakende humane embryonale stamcellen, geïnduceerde pluripotente stamcellen, adulte stamcellen of cellen verkregen via transdifferentiatie. Een voorlopige overeenkomst garandeert het behoud van de status quo voor de financiering van humaan embryonaal stamcelonderzoek in Horizon 2020 (Moran, 2013).

PART 6: MATERIALS AND METHODS

6.1 Materials

- Questionnaire for stem cell companies (see Attachment VI)
- Questionnaire for academic institutions (see Attachment VII)
- Questionnaire for public authorities (see Attachment VIII)
- Espacenet (free online access)
<http://worldwide.espacenet.com/>

The Espacenet database includes a full-text collection of (inter)national published patent applications. This patent database is administered by the European Patent Organisation.

- PATENTSCOPE (free online access)
<http://patentscope.wipo.int/search/en/search.jsf>

Database PATENTSCOPE includes a full-text collection of (inter)national published patent applications and is administered by the World Intellectual Property Organization (WIPO).

- Thomson Innovation Patent Database (requires membership)
<https://www.thomsoninnovation.com/login>
- PubMed (free online access)
<http://www.ncbi.nlm.nih.gov/pubmed>

The PubMed database comprises more than 22 million citations for biomedical literature (source: journals, online books) and is directed by the National Institutes of Health (NIH).

- European Patent Register (free online access)
<https://register.epo.org/espacenet/regviewer>

The European Patent Register is an initiative of the European Patent Organisation, which contains all information on European patent applications as they pass through the grant procedure, including oppositions, patent attorney *versus* EPO correspondence and more.

6.2 Methods

6.2.1 Identifying the actors in the area of stem cell research

We identified the actors involved in stem cell research in four different categories: academic institutions, stem cell companies, life science supplier companies and public authorities that are commissioned to financially aid scientific research. The geographical boundaries are set based on the union of three neighbouring countries in which our mother country, Belgium, is

included (Benelux). Additionally, stem cell companies were identified in the United Kingdom.

1. The academic institutions and public authorities of interest were identified on the basis of all publicly available information on internet.
2. Stem cell companies and life science supplier companies were identified by means of an internet search engine (e.g. Google) or a list or database that compiles the profiles of the biotechnology companies being located in a fixed region (e.g. the Life Sciences Database of FlandersBio, Dutch life sciences companies in Life Sciences Health, Members list of the Luxembourg BioHealth Cluster, *etc.*).
3. Multinational companies in the life sciences sector (e.g. large pharmaceutical companies or parent supplier companies delivering products to the Benelux) were contacted as well.
4. Stem cell companies, life science supplier companies and academic institutions that are occupied with patenting were identified through PATENTSCOPE or Espacenet (see 5.2.2).

6.2.2 Searching patent applications and consulting information thereof (Espacenet)

1. Go to Espacenet: <http://worldwide.espacenet.com/>
2. Select "Advanced Search"
3. Enter the name of a person or organisation in the field "Applicant(s)" or "Inventor(s)"
4. Optionally: enter English keywords in the field "Title or abstract"
5. Hit the search button
6. Select a patent application of interest from the results list
7. Specific patent application information can be obtained through the list of options on the left-hand side of the web page, e.g. bibliographic data, description, claims, *etc.*
8. If the patent application concerns a European filing, its legal status can be consulted via the link "EP register" on top of the web page

6.2.3 Taking interviews

Interviews of the companies, suppliers, universities and public authorities were taken by way of either a face-to-face-interview or a telephone interview using a homemade questionnaire. The results presented by means of bar graphs in section 3.1.6 were collected by applying the digital archive of the research funding agency and selected on the basis of following criteria:

Terms enclosed in the title of the funding request,

Inclusive of

"humane embryonale stamcellen"

"humane ESC's"

"embryonale stamcellen"

"pluripotente stamcellen"

Exclusive of

"menselijke stamcellen"

"geïnduceerde pluripotente stamcellen"

"stamcel- en gentherapie"

6.2.4 Classification searching (Espacenet)

1. Go to Espacenet: <http://worldwide.espacenet.com/>
2. Select "Classification Search"
3. Enter key concepts in the field "Search for"
Example: embryonic stem
4. Hit the search button
5. A list of related classes in the Cooperative Patent Classification is shown
6. Click on the CPC patent class which is most related to the key concepts
Example: C12N 5/00 Undifferentiated human, animal or plant cells, e.g. cell lines; [...]
7. Define the CPC subclass according to the description shown in addition
Example: C12N 5/0735 {Pluripotent embryonic cells, e.g. embryonic stem cells}
8. The concordance table of CPC and IPC patent classes can be found at:
<http://www.cooperativepatentclassification.org/cpcConcordances/CPCtoIPCpdf.pdf>

6.2.5 Field Combination searching (PATENTSCOPE)

The results presented by means of line graphs in section 3.2.1 were collected following:

1. Go to the PATENTSCOPE Search Service:
<http://patentscope.wipo.int/search/en/structuredSearch.jsf>
2. Specify "Office" by ticking off "European Patent Office"
3. Select the search fields of interest using the arrow of the pull-down menu
4. Make sure that the Boolean operator is AND in the AND/OR boxes

5. Enter search terms in the field for "Publication Date" AND "International Class"
Example: 1997 AND C12N5/0735
6. Identify the terms for your claim search
7. Make use of the distinct types of terms: a Single Term is a single word such as "human", whereas a Phrase is a group of words surrounded by double quotes such as "embryonic stem". The use of Phrases is applied in order to search for multiple words in exact order.
8. Boolean operators (e.g. AND, NOT) allow multiple terms to be combined in a search field
Example: human NOT "non-human"
9. Enter search terms in the field for "Publication Date" AND "International Class" AND "English Claims"
Example: 1997 AND C12N5/0735 AND human NOT "non-human"
10. Repeat the same protocol after ticking off "PCT" to specify "Office" (Step 2.)
11. A wildcard "*" is required to extract the PCT patent applications in IPC class C12N5/0735 i.e. C12N5/073*
12. The Query Syntax supported in PATENTSCOPE can be found at:
<http://patentscope.wipo.int/search/en/help/querySyntaxHelp.jsf>

6.2.6 Searching in Thomson Innovation Patent Database

The results presented by Figure 10, Figure 11, Figure 12 and Table 6 were collected on the basis of following selection criteria:

- Class of interest in the Cooperative Patent Classification (CPC)
- Patent family
- PCT patent application
- National phase entry
- National phase entry into the U.S. or national phase entry into Europe
- Granted patent

The results presented in Figure 13 were collected on the basis of following selection criteria:

- Class of interest in the Cooperative Patent Classification (CPC)
- Patent family
- European patent application
- First published patent application

6.2.7 Searching in PubMed

The results presented in Figure 14 were collected following:

1. Go to the PubMed database: <http://www.ncbi.nlm.nih.gov/pubmed>
2. Identify the query for your search according to:
 - Generic syntax: Term [Search Field Tag] Operator
 - Enclose a phrase in double quotes such as "embryonic stem"
 - Combine search terms by using Boolean operators (e.g. AND)
 - Apply following Search Field Descriptions and Tags:
Title/Abstract words [TIAB], Publication date [DP]
3. Enter the query in the search box
Example: "human embryonic stem" [TIAB] AND 2006 [DP]
4. Hit the search button
5. An overview of the PubMed syntax can be found at:
http://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.PubMed_Quick_Start

6.2.8 Consulting information from a patent examination (European Patent Register)

The results presented in section 3.3 and 3.4 were collected following:

1. Go to the European Patent Register: <https://register.epo.org/espacenet/regviewer>
2. Select "Smart Search"
3. Enter the patent classification code or publication number of interest in the search field
(enter the characters without space)
4. Hit the search button
5. Select a patent application of interest from the results list
6. Select "All Documents" on the left-hand side of the web page
7. Documents concerning the patent examination process or patent opposition process can be gathered using the arrow of the pull-down menu "All Documents"
8. Tick off the document of interest
9. Download the document via "Selected documents" on top of the web page

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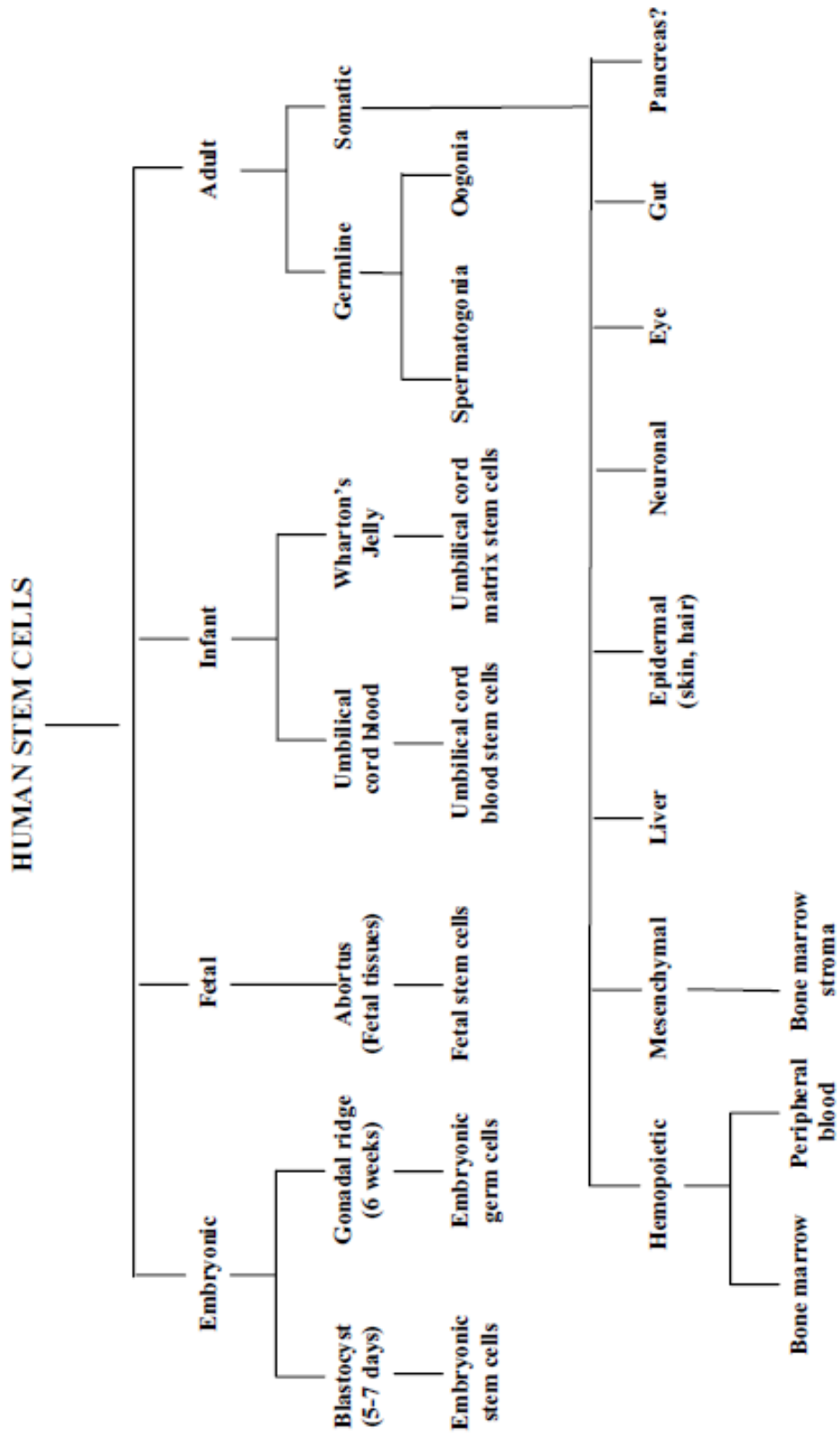
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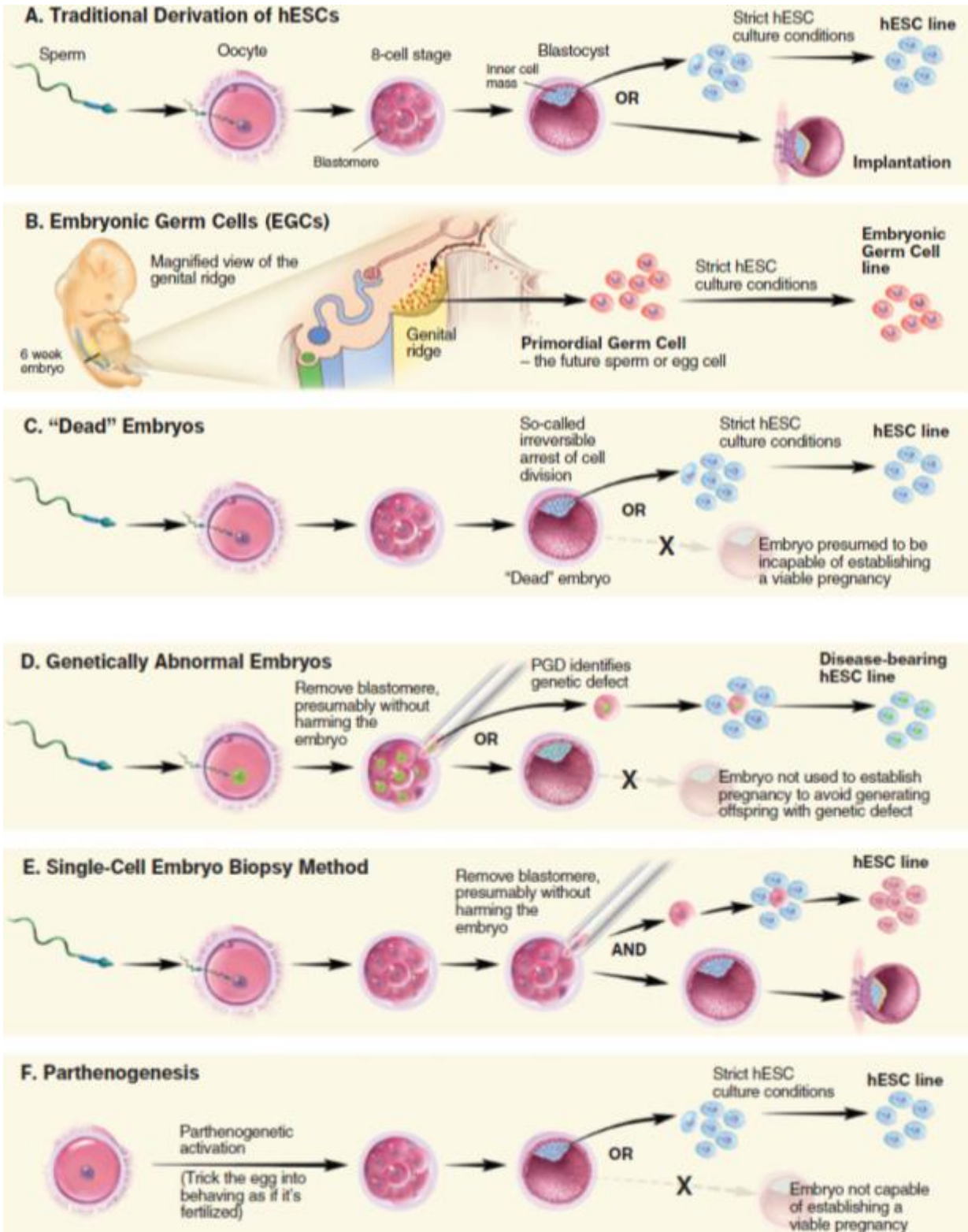
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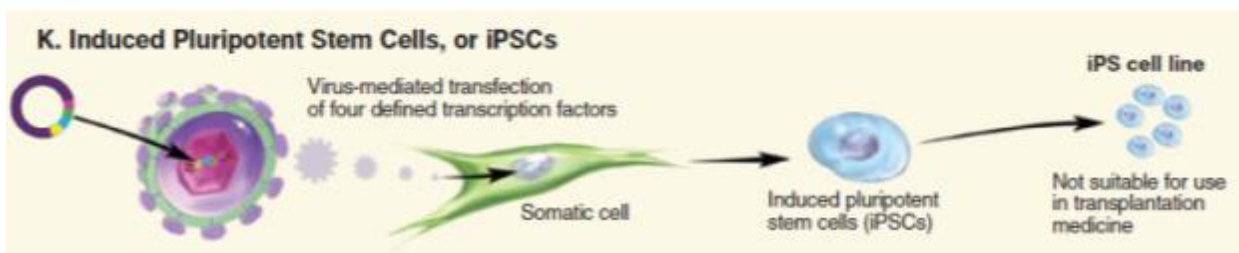
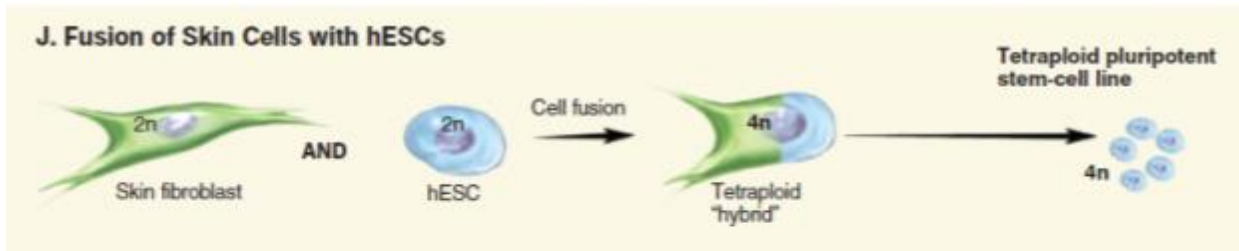
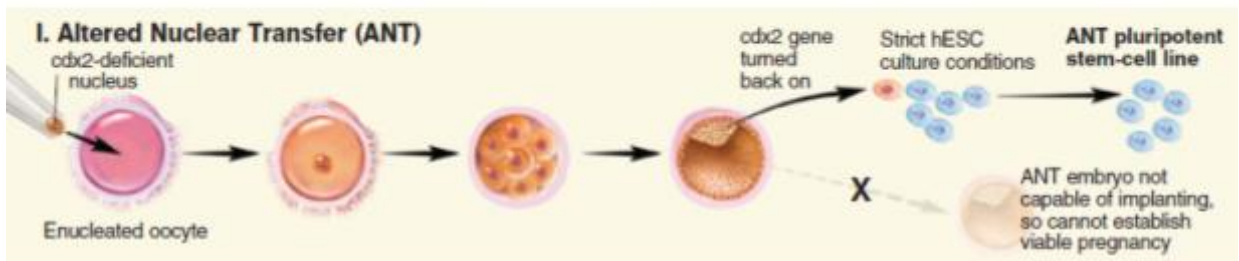
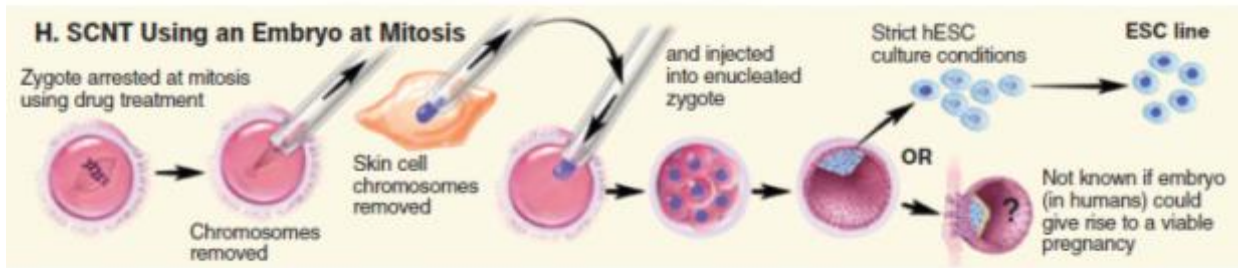
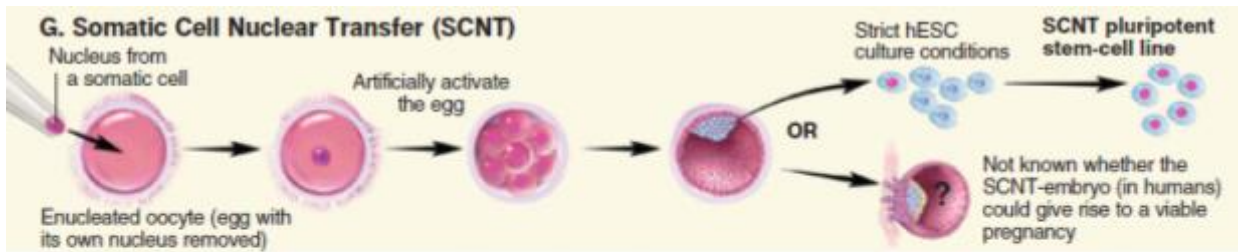
Attachment I



(Bongso & Lee, 2005)

Attachment II





(Battey *et al*, 2010)

Attachment III

Country	Reproductive cloning prevented by national law	Research authorised by national law on				Prohibition of human embryonic stem cell (hESC) research	No specific legislation regarding hESC research
		Stem cells*	Human embryos		Aborted foetuses		
			Procurement of stem cells from super-numerary embryos	Creation of human embryos for research purposes**			
Austria ^{1,2}	•	•					
Belgium	•		•	•			
Bulgaria ^{3,4}	•						•
Croatia ^{3,4}							•
Cyprus ^{3,4}	•						•
Czech Republic ^{3,4}	•		•				
Denmark ³	•		•				
Estonia ^{3,4}	•		•				
Finland	•		•		•		
France	•		•		•		
Germany	•	•					
Greece ^{3,4}	•		•				
Hungary ^{3,4}	•		•		•		
Iceland ^{3,4}	•		•				
Ireland		•					
Italy	•	•			•		
Lithuania ^{1,3,4}						•	
Luxembourg ⁶							•
The Netherlands	•		•		•		
Norway ³	•		•		•		
Poland ¹						•	
Portugal ^{3,4}	•		•				
Romania ^{3,4}	•						•
Slovakia ^{1,3,4}	•				•	•	
Slovenia ^{3,4,7}	•		•		•		
Spain ^{3,4}	•		•		•		
Sweden ⁸	•		•	•	•		
Switzerland ^{3,4}	•		•				
Turkey ^{3,9}	•						•
United Kingdom	•		•	•	•		

* Prohibiting the procurement of stem cells from supernumerary embryos but allowing the import and use of stem cell lines.

** SCNT is not considered in this table: Belgium, Sweden, UK, Spain and Portugal allow SCNT by law, while Finland and the Czech Republic neither prohibit nor allow it by law.

1. Countries that voted against the Council Decision on hESC research during FP7 (www.consilium.europa.eu/ueDocs/cms_Data/docs/pressData/en/intm/90654.pdf)

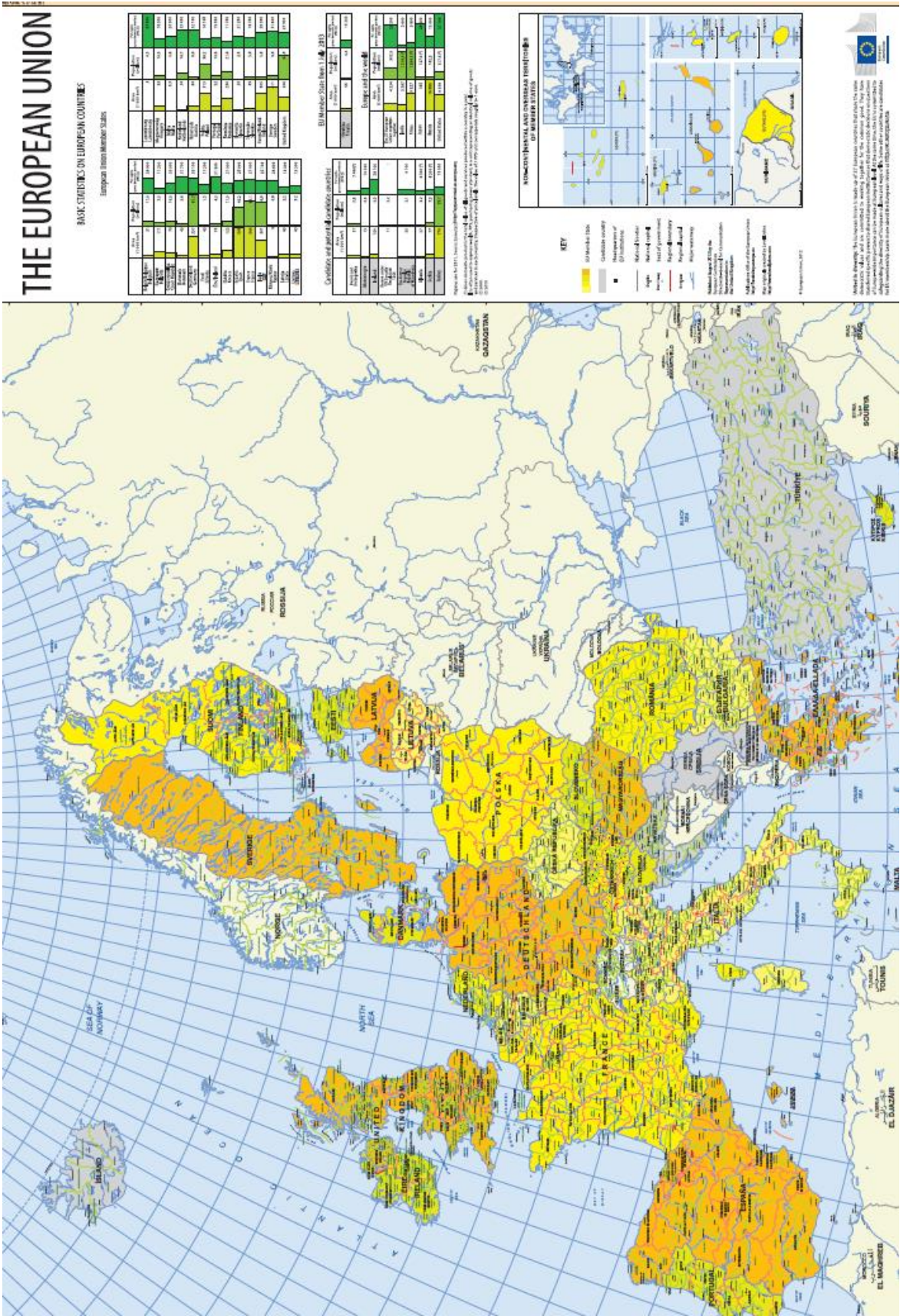
2. AT: The Austrian Bioethics Commission published an opinion on 16 March 2009 which recommends allowing hESC derivation from supernumerary IVF embryos.

3. Countries who have signed and ratified the 1997 Convention of the Council of Europe on Human Rights and Biomedicine CETS 164 (<http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=8&DF=4/16/2009&CL=ENG>)

4. Countries who have ratified the 1998 Protocol on the Prohibition of Cloning in Human Beings CETS 168 (<http://conventions.coe.int/Treaty/en/Treaties/html/168.htm>)

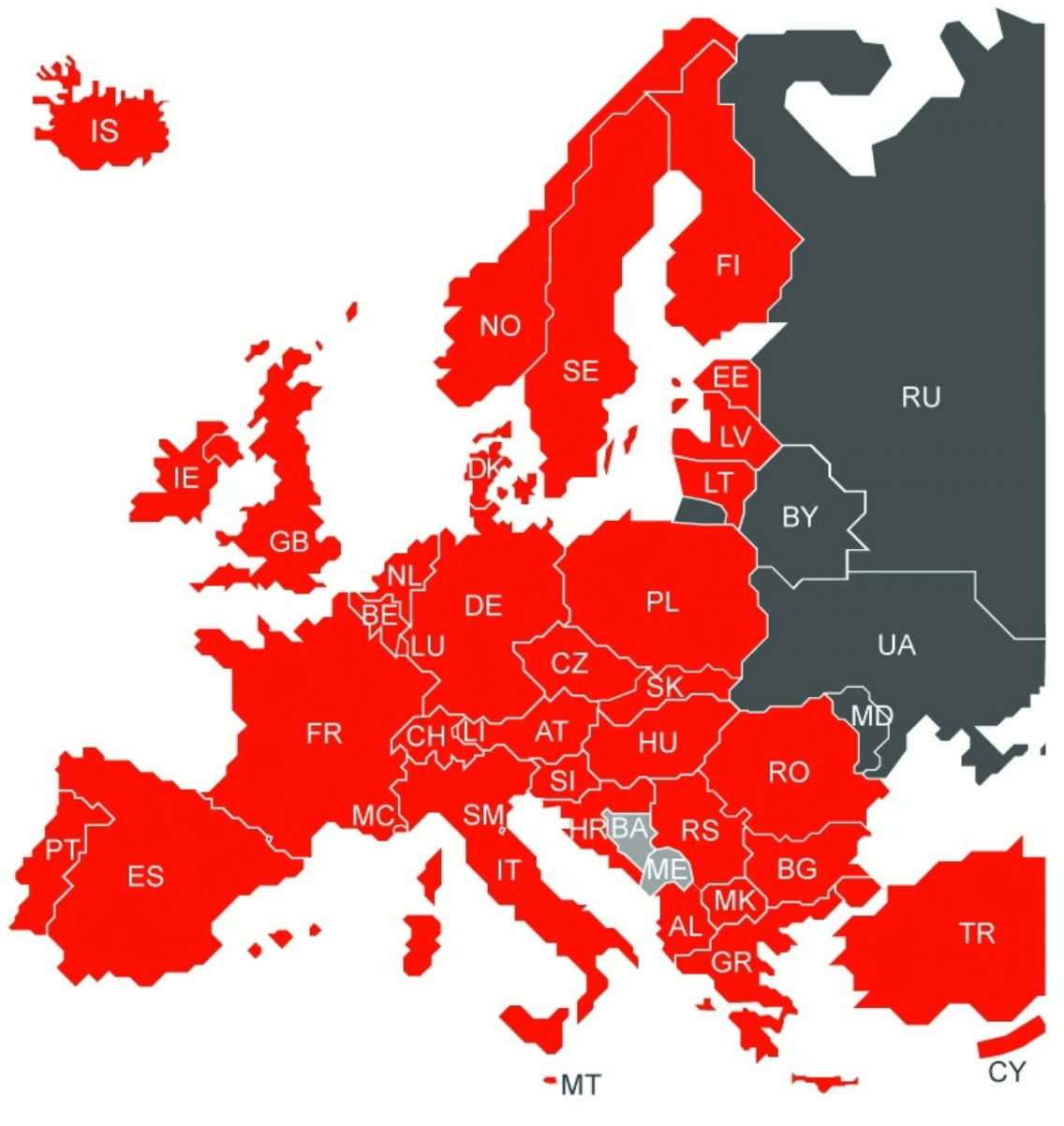
(Moran *et al*, 2012)

Attachment IV



(Lovell, 2013)

Attachment V



(EPO, 2013)

Attachment VI

VRAGENLIJST.....(naam bedrijf / anoniem)

DEEL A. Kennis m.b.t. wet- en regelgeving

Vraag 1. Bent u op de hoogte van de nieuwe richtlijnen omtrent het octrooieren van humane embryo's en het gebruik ervan voor industriële of commerciële doeleinden, die het Europees Octrooibureau (EPO) in voege gebracht heeft sinds 1 juni 2012? **JA / NEE**

Vraag 2. Is de omstreden beslissing van het Europees Hof van Justitie in de zaak Brüstle v. Greenpeace (C-34/10) – een beslissing aangaande de octrooieerbaarheid van uitvindingen met betrekking tot humane embryonale stamcellen – u bekend? **JA / NEE**

Vraag 3. Kent u de Belgische embryowet (mei 2003) die afbakent welke toepassingen met menselijke embryo's aanvaardbaar zijn en die, wat betreft dit onderwerp, tevens één van de meest progressieve wetten is in Europa? **JA / NEE**

DEEL B. Onderzoek en financiering

Vraag 4. Heeft het bedrijf in het verleden al onderzoek uitgevoerd op menselijke embryonale stamcellen? Wat was de reden indien deze toepassing is beëindigd?

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Vraag 5. Voert het bedrijf momenteel onderzoek uit op menselijke embryonale stamcellen?

JA / NEE

Vraag 6. Plannen jullie een toepassing met menselijke embryonale stamcellen mogelijk in de toekomst? Welke hindernissen spelen een rol om deze overweging niet te maken?

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Vraag 7. Ervaart het bedrijf moeilijkheden bij het aantrekken van financiering omwille van onderzoeksprojecten die betrekking hebben op het gebruik van menselijke embryo's?

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Vraag 8. In hoeverre speelt de octrooieerbaarheid van humane embryonale stamcellen een rol bij het verwerven van geldmiddelen?

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Vraag 9. Wat is de verhouding openbare -/privé financiering voor dergelijke onderzoeken?

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DEEL C. Octrooieren

Vraag 10. Heeft het bedrijf al een octrooiaanvraag ingediend welke betrekking hebben op humane embryonale stamcellen (hESC)? **JA:** ga naar vraag 11 / **NEE:** ga naar vraag 25

Vraag 11. Koos het bedrijf voor internationale, Europese en / of nationale octrooiaanvragen?

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Vraag 12. Wat is de status van de lopende octrooiaanvragen?

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Vraag 13. Zijn er octrooiaanvragen lopende, waarvan nog geen publicatie bestaat (aanvraag ingediend na X-X-2011)? **JA / NEE**

Vraag 14. Hebben de octrooiaanvragen betrekking op een methode (vb. hESC cultiveren, inductie van differentiatie, ...) of een product (vb. genetisch gemodificeerde stamcellen, ...)?

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Vraag 15. Wat zijn uw algemene bevindingen over het verloop van de behandeling van de octrooiaanvra(a)g(en)? [Indien de aanvraag zich in een prille fase bevindt, ga naar vraag 21]

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Vraag 16. Bemerkt men hierbij vertragingen door het Europees Octrooibureau (EPO)?

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Vraag 17. Heeft het bedrijf al één of meerdere octrooiaanvragen met betrekking tot hESC teruggetrokken? **JA / NEE**

Zo ja, met welke reden?

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Vraag 18. Ondervond/ondervindt men belemmeringen rond de standaardvoorwaarden voor octrooierbaarheid, i.e. nieuw, inventief, industrieel toepasbaar, “sufficiency of disclosure”?

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Vraag 19. Welke gegevens aangaande het gebruik van menselijke embryonale stamcellen hebben mogelijk een **negatieve invloed** op het toekennen van het octrooi (vb. ‘filing date’)?

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Vraag 20. Welke gegevens aangaande het gebruik van menselijke embryonale stamcellen hebben mogelijk een **positieve invloed** op het toekennen van het octrooi (vb. 'filing date', de commerciële exploitatie vereist geen hESC, een technisch hulpmiddel voor hESC-gebruik)?

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Vraag 21. Op welke manieren tracht het bedrijf te anticiperen op beslissing C-34/10 van het Europees Hof van Justitie en de nieuwe richtlijnen van het EPO aangaande het gebruik van humane embryo's (vb. methoden beschrijven die een vernietiging van het embryo uitsluiten)?

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Vraag 22. Bezit het bedrijf licentie(s) of aast het bedrijf naar een licentie dat de productie of het gebruik van menselijke embryonale stamcellen mogelijk maakt? **JA / NEE**

Zo ja, welke licentie(s)?

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Vraag 23. Opteert het bedrijf daarnaast voor andere vormen van intellectuele eigendom, in het bijzonder geheimhouding, ter bescherming van de biotechnologische uitvindingen inzake menselijke embryonale stamcellen? **JA / NEE**

Zo ja, met welke reden?

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Vraag 24. Zijn er verder bijzonderheden die vermeldenswaardig zijn in de patentdiscussie over humane embryonale stamcellen?

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Hartelijk dank voor uw medewerking.

Vraag 25. Heeft men destijds een octrooigemachtigde geconsulteerd naar aanleiding van een potentiële octrooiaanvraag met inbegrip van hESC?

JA: ga verder naar vraag 26 / **NEE:** ga verder naar vraag 27

Vraag 26. Waarom is er uiteindelijk geen octrooiaanvraag ingediend?

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Vraag 27. Is er een octrooiaanvraag met betrekking tot hESC in aanmaak? **JA / NEE**

Vraag 28. Bezit het bedrijf licentie(s) of aast het bedrijf naar een licentie dat de productie of het gebruik van menselijke embryonale stamcellen mogelijk maakt? **JA / NEE**

Zo ja, welke licentie(s)?

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Vraag 29. Verkiest het bedrijf andere vormen van intellectuele eigendom, in het bijzonder geheimhouding, ter bescherming van de biotechnologische uitvindingen met betrekking tot menselijke embryonale stamcellen? **JA / NEE**

Zo ja, met welke reden?

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Vraag 30. Werkt het bedrijf samen met een buitenlands bedrijf voor onderzoek op hESC (via uitbesteding, uitwisseling van resultaten, ...)? **JA / NEE**

Hartelijk dank voor uw medewerking.

Attachment VII

VRAGENLIJST.....(naam universiteit)

DEEL A. Kennis m.b.t. wet- en regelgeving

Vraag 1. Bent u op de hoogte van de nieuwe richtlijnen omtrent het octrooieren van humane embryo's en het gebruik ervan voor industriële of commerciële doeleinden, die het Europees Octrooibureau (EPO) in voege gebracht heeft sinds 1 juni 2012? JA / NEE

Vraag 2. Is de omstreden beslissing van het Europees Hof van Justitie in de zaak Brüstle v. Greenpeace (C-34/10) – een beslissing aangaande de octrooieerbaarheid van uitvindingen met betrekking tot humane embryonale stamcellen – u bekend? JA / NEE

Vraag 3. Kent u de Belgische embryowet (mei 2003), die afbakt welke toepassingen met menselijke embryo's aanvaardbaar zijn en die, wat betreft dit onderwerp, tevens één van de meest progressieve wetten is in Europa? JA / NEE

DEEL B. Onderzoek en financiering

Vraag 4. Heeft de vakgroep in het verleden onderzoek uitgevoerd op menselijke embryonale stamcellen? Wat was de reden indien deze toepassing is beëindigd?
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Vraag 5. Voert de vakgroep momenteel onderzoek uit op humane embryonale stamcellen? JA / NEE

Vraag 6. Plannen jullie een toepassing met menselijke embryonale stamcellen mogelijk in de toekomst? Welke hindernissen spelen een rol om deze overweging niet te maken?
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Vraag 7. Ervaart de vakgroep moeilijkheden bij het aantrekken van financiering omwille van onderzoeksprojecten die betrekking hebben op het gebruik van menselijke embryo's?

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Vraag 8. In hoeverre speelt de octrooieerbaarheid van humane embryonale stamcellen een rol bij het verwerven van geldmiddelen?

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Vraag 9. Wat is de verhouding openbare -/privé financiering voor dergelijke onderzoeken?

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DEEL C. Octrooieren

Vraag 10. Heeft de vakgroep al een octrooiaanvraag ingediend met inbegrip van humane embryonale stamcellen (hESC)? **JA:** ga naar vraag 11 / **NEE:** ga naar vraag 25

Vraag 11. Koos men voor internationale, Europese en / of nationale octrooiaanvragen?

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Vraag 12. Wat is de status van de lopende octrooiaanvragen?

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Vraag 13. Zijn er octrooiaanvragen lopende, waarvan nog geen publicatie bestaat (aanvraag ingediend na X-X-2011)? **JA / NEE**

Vraag 14. Hebben de octrooiaanvragen betrekking op een methode (vb. hESC cultiveren, inductie van differentiatie, ...) of een product (vb. genetisch gemodificeerde stamcellen, ...)?

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Vraag 15. Wat zijn uw algemene bevindingen over het verloop van de behandeling van de octrooiaanvra(a)g(en)? [Indien de aanvraag zich in een prille fase bevindt, ga naar vraag 21]

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Vraag 16. Bemerkt men hierbij vertragingen door het Europees Octrooibureau (EPO)?

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Vraag 17. Heeft de vakgroep al één of meerdere octrooiaanvragen met betrekking tot hESC teruggetrokken? **JA / NEE**

Zo ja, met welke reden?

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Vraag 18. Ondervond/ondervindt men belemmeringen rond de standaardvoorwaarden voor octrooieerbaarheid, i.e. nieuw, inventief, industrieel toepasbaar, 'sufficiency of disclosure'?

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Vraag 19. Welke gegevens aangaande het gebruik van menselijke embryonale stamcellen hebben mogelijk een **negatieve invloed** op het toekennen van het octrooi (vb. 'filing date')?

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Vraag 20. Welke gegevens aangaande het gebruik van menselijke embryonale stamcellen hebben mogelijk een **positieve invloed** op het toekennen van het octrooi (vb. ‘filing date’, een therapeutisch of diagnostisch doeleinde, een technisch hulpmiddel voor hESC-gebruik)?

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Vraag 21. Op welke manieren tracht de vakgroep te anticiperen op beslissing C-34/10 van het Europees Hof van Justitie en de nieuwe richtlijnen van het EPO aangaande het gebruik van humane embryo’s (vb. methoden beschrijven die vernietiging van het embryo uitsluiten)?

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Vraag 22. Bezit de universiteit licentie(s) of aast de universiteit naar een licentie dat de productie of het gebruik van menselijke embryonale stamcellen mogelijk maakt? **JA / NEE**
Zo ja, welke licentie(s)?

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Vraag 23. Opteert de vakgroep daarnaast voor andere vormen van intellectuele eigendom, in het bijzonder geheimhouding, ter bescherming van de universitaire kennis inzake humane embryonale stamcellen? **JA / NEE**

Zo ja, met welke reden?
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Vraag 24. Zijn er verder bijzonderheden die vermeldenswaardig zijn in de patentdiscussie over humane embryonale stamcellen?

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Hartelijk dank voor uw medewerking.

Vraag 25. Heeft men destijds een octrooigemachtigde geconsulteerd naar aanleiding van een potentiële octrooiaanvraag met inbegrip van hESC?

JA: ga verder naar vraag 26 / **NEE:** ga verder naar vraag 27

Vraag 26. Waarom is er uiteindelijk geen octrooiaanvraag ingediend?

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Vraag 27. Is er een octrooiaanvraag met betrekking tot hESC in aanmaak? **JA / NEE**

Vraag 28. Bezit de universiteit licentie(s) of aast de universiteit naar een licentie dat de productie of het gebruik van menselijke embryonale stamcellen mogelijk maakt? **JA / NEE**

Zo ja, welke licentie(s)?

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Vraag 29. Verkiest de vakgroep andere vormen van intellectuele eigendom, in het bijzonder geheimhouding, ter bescherming van de universitaire kennis met betrekking tot menselijke embryonale stamcellen? **JA / NEE**

Zo ja, met welke reden?

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Hartelijk dank voor uw medewerking.

Attachment VIII

VRAGENLIJST.....(naam overheidsorganisatie)

Vraag 1. Welke trend heeft het aantal subsidieaanvragen voor wetenschappelijk onderzoek met betrekking tot menselijke embryonale stamcellen (hESC) gevolgd tussen 1997 en 2012?

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Vraag 2. Indien de overheidsinstantie subsidies mag verlenen aan zowel ondernemingen als onderzoeksinstituten (universiteiten, hogescholen, ...), worden onderzoeksvorstellen ten aanzien van hESC gelijkmatig voorgelegd door beide partijen? **JA / NEE**

Zo nee, wat is een mogelijke verklaring?

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Vraag 3. In welke verhouding wordt financiële steun voor hESC-onderzoek toegewezen aan ondernemingen versus onderzoeksinstituten?

Vraag 4. Hoe verhoudt het aantal gesubsidieerde projecten zich, ruw geschat, ten opzichte van het totaal aantal subsidieaanvragen betreffende hESC-onderzoek?

Vraag 5. Werd de verlening van overheidsfinanciering voor onderzoeksprojecten aangaande het gebruik van humane embryo's destijds aan welbepaalde tendensen onderworpen (vb. in respons op de Belgische embryowet of op beslissing C-34/10 van het Hof van Justitie van de Europese Unie - zie inleiding)?

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Vraag 6. Neemt de overheidsorganisatie het aspect van octrooieerbaarheid in acht alvorens men subsidie toekent? **JA / NEE**

Zo ja, hoe zwaar weegt deze factor door?

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Vraag 7. Evalueert men projectvoorstellen die betrekking hebben op menselijke embryonale stamcellen op vlak van kennisvalorisatie? **JA / NEE**

Zo ja, welke indicatoren past men hoofdzakelijk toe?

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Vraag 8. In casu onderzoeksvorstellen wat betreft humane embryonale stamcellen, is een octrooi(aanvraag) of licentie in portefeuille een vereiste voor een hoog valorisatiepotentieel?

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Vraag 9. Welke onderzoekprojecten met toepassing van hESC subsidieert men momenteel?

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Vraag 10. Zijn er verder bijzonderheden die vermeldenswaardig zijn voor het subsidiëren of valoriseren van wetenschappelijke onderzoekstudies inzake hESC?

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Hartelijk dank voor uw medewerking.