PART II. PATENTS ON HUMAN STEM CELLS

Part II describes the current patent practice with regard to human stem cell technology and offers an in depth examination of some prototype patents.
Much of the progress made to date in stem cell technology was dependent on animal models and understandings gained from mouse models and mouse stem cell research. However, this part will mainly focus on the patent practice and patent framework for human stem cell technology.

CHAPTER 1. INTRODUCTION

A. Patent claims

A minimum degree of clarity about claim drafting is necessary in order to obtain a sound foundation for understanding some of the problematic issues surrounding patents on human stem cells discussed in this report.

Patent applications usually contain a request for the grant of the patent, a description of the invention, one or more claims, drawings referred to in the description or the claims and, last but not least, an abstract [51]. The claims are at the centre or the heart of the patent, since they define the exact scope of the exclusive right provided by the patent. Article 84 EPC explicitly stipulates in this regard that the claims "shall define the matter for which protection is sought" and they shall be clear and concise and be supported by the description [52].
Thus, claims are very important since they are the basis of the interpretation of patent protection. It is from the claims that third parties are able to know what they may do and what they may not do [53].

In view of the crucial importance of claims, the present study carefully examines and cites claims of various patents, to gain a better understanding of the exact scope of the patent. In order to avoid some common misconceptions with regard to this difficult matter, we start by explaining some basics notions on patent claims.

1. Product and process claims

[51] With regard to European patents this is clearly stipulated in article 78 EPC.

[52] Rule 29 (1) of the Implementing Regulations to the EPC further emphasises that the claims "shall define the matter for which protection is sought in terms of the technical features of the invention" and specifies that, wherever appropriate claims shall contain: (a) a statement indicating the designation of the subject-matter of the invention and those technical features which are necessary for the definition of the claimed subject-matter but which, in combination, are part of the prior art; (b) a characterising portion - preceded by the expression "characterised in that" or "characterised by" - stating the technical features which, in combination with the features stated in sub-paragraph (a), it is desired to protect.

[53] World Intellectual Property Organisation (WIPO), *Introduction to Intellectual Property*, London-the Hague-Boston, Kluwer Law International, 1997, 129. Cf. CORNISH, W.R., *Intellectual Property*, London, Sweet & Maxwell, 1996, p. 140, n° 4-37.

In modern patent systems a basic distinction is made between, on the one hand, product or substance claims, and on the other hand, process, method or use claims. The EPC employs the same standard divisio.
The EPC clarifies in this respect, that the first basic kind of claim ('product claim') includes a substance or compositions (e.g. chemical compound or a mixture of compounds) as well as any physical entity (e.g. object, article, apparatus, machine, or system of co-operating apparatus) which is produced by man's technical skill. Examples are: "a steering mechanism incorporating an automatic feedback circuit..."; "a woven garment comprising..."; "an insecticide consisting of X, Y, Z"; or "a communication system comprising a plurality of transmitting and receiving stations" [54].
The second basic kind of claim ('process claim') is applicable to all kinds of activities in which the use of some material product for effecting the process is implied; the activity may be exercised upon material products, upon energy, upon other processes (as in control processes) or upon living things [55].

Product claims are infringed primarily by making, selling or using the things claimed. In the case of process claims, infringement consists primarily of performing the activity. The basic distinction which is to be watched is the following: a claim to a product, a thing, gives a monopoly over it whatever it is to be used for; a claim to a method is restricted to that method alone. Product claims are correspondingly broad. It has to be admitted, that claims are sometimes drawn in a way that it is difficult to decide which kind of claim they are [56].

If the subject matter of the European patent is a process, the protection conferred by the patent shall extend to the products directly obtained by such process (article 64 (2)) EPC).

2. Independent and dependent claims

All patents and patent applications contain one or more claims directed to the essential features of the invention. The major claim, the so-called 'independent' claim, is drafted to avoid prior art known at the time of the drafting of the patent application [57].
In many cases such independent claim is followed by one or more claims of narrower scope concerning 'particular embodiments' of that invention. The succeeding claims are more narrowly, with the aim to withstand any anticipation by more relevant prior art which might be produced by a patent office during examination (or by third parties during any opposition or invalidation proceedings) [58]. The narrower claims following

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[54] *Guidelines for substantive examination of the European Patent Office*, Part C, Chapter III, 3.1. (Also see http://www.european-patent-office.org/legal/gui_lines/e/c_iii_3.htm).

[55] *Guidelines for substantive examination of the European Patent Office*, Part C, Chapter III, 3.1. (Also see http://www.european-patent-office.org/legal/gui_lines/e/c_iii_3.htm).

[56] CORNISH, 1996, p. 144, n° 4-46.

[57] World Intellectual Property Organisation (WIPO), *Introduction to Intellectual Property*, London-the Hague-Boston, Kluwer Law International, 1997, 131. Cf. *Guidelines for substantive examination of the European Patent Office*, Part C, Chapter III, 3.4.

[58] World Intellectual Property Organisation (WIPO), *Introduction to Intellectual Property*, London-the Hague-Boston, Kluwer Law International, 1997, 131. Cf. *Guidelines for substantive examination of the European Patent Office*, Part C, Chapter III, 3.4.

the broad claim usually refer back to one or more of the preceding claims. Therefore, they are usually called 'dependent' claims [59].

According to the EPC a European patent application may contain two or more independent claims in the same category (product, process, apparatus or use) where it is not appropriate, having regard to the subject matter of the application, to cover this subject matter by a single claim [60]. It is further emphasised that any claim stating the essential features of an invention may be followed by one or more claims concerning particular embodiments of that invention [61] [62].

It is emphasised that when claims apparently have a similar scope, an EPO examiner should not allow an unnecessary proliferation of independent claims, he should not adopt an over-academic or rigid approach to the presence of a number of claims which are differently worded but apparently of similar effect [63].

3. Broad and narrow claims

It appears to be generally accepted that claims should be as broad as possible. Claims must be wide enough to cover substitutes or alternatives, while still achieving the same result [64]. Broad claims are undoubtedly advantageous for the patent holder.

Especially in novel technologies, like biotechnology, broad claiming is common practice. Lately, however, many concerns have been raised with regard to the breadth of biotech claims. The question arises where the delicate boarder line lies between broad claiming and *unduly* broad claiming. In many cases, that boarder line is very thin, "wafer-thin".
It is generally understood that an unduly broad claim exists when the protection which is claimed is not in conformity with what has been made public to the man skilled in the art, in other words, when the patent claims are not in agreement with the patent description.
The dilemma can be illustrated with an example from the chemical field. If the patentee is restricted to claims upon the substances that he has used in his experiments, a third party is free to take up the nearest imitation. If, however, the patentee is given a claim to the whole family of compounds, his monopoly may appear *unduly* wide. The breadth of claim issue has been the subject of many debates in academic and patent office circles for many years. Authorities in various countries have reacted with greater or less caution in seeking some compromise [65].

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[59] Cf. *Guidelines for substantive examination of the European Patent Office*, Part C, Chapter III, 3.5 ("A claim which includes all the features of any other claim is commonly termed a 'dependent claim'").

[60] See Rule 29 (2) Implementing Regulations to the EPC.

[61] See Rule 29 (3) Implementing Regulations to the EPC.

[62] The term 'particular embodiment' should be construed broadly as meaning any more specific disclosure of the invention than that set out in the main claim or claims. See *Guidelines for substantive examination of the European Patent Office*, Part C, Chapter III, 3.4. (Also see http://www.european-patent-office.org/legal/gui_lines/e/c_iii_3.htm).

[63] *Guidelines for substantive examination of the European Patent Office*, Part C, Chapter III, 3.2. (Also see http://www.european-patent-office.org/legal/gui_lines/e/c_iii_3.htm).

[64] World Intellectual Property Organisation (WIPO), *Introduction to Intellectual Property*, London-the Hague-Boston, Kluwer Law International, 1997, 129.

[65] CORNISH, 1996, p. 146, n° 4-50.

4. Claims and description

Claims are intended to determine the scope of the patent. Article 69 EPC explicitly stipulates in this respect that "the extent of the protection conferred by a European patent or a European patent application shall be determined by the terms of the claims. Nevertheless, the description and drawings shall be used to interpret the claims".
The claims thus are drafted in the light of the much more detailed text of the description. The description should disclose the invention in a manner sufficiently clear and complete for the invention to be evaluated and to be carried out by a person skilled in the art. This is of fundamental importance, since one of the main functions of the description is to provide new technical information to third parties [66].

The claims may not be significantly broader or different from that which has been described [67]. The description of the invention must include details of the substitutes or alternatives so that the broad claim can be supported by the description.

B. Patents on human cells

For a long time it is has been common practice to file patent applications for biological material which is removed from the human body. As a matter of routine, numerous patents have been granted for human somatic cells, both in the U.S. and in Europe, during the past years. Apparently, such applications have "run through the mill of patent grant procedure without causing a great stir" [68].

1. Examples

In the framework of the current study, an extensive patent search on human cells was not carried out. However, by way of example, some patents dealing with human cell research will be discussed in more depth.

A somewhat older patent application which gained attention, was U.K. patent *application* 1.300.391, based on an invention of Arie Zuckermann and filed on 22 August 1969. The invention related to a method for producing a human embryo liver cell line which comprises disaggregating human embryo liver, suspending the cells in a growth medium, replacing this with fresh medium if it becomes acid, and allowing a confluent sheet of spindle-shaped cells of the cell line to form.
The patent claims included a human embryo cell (claim 1), a cell culture system (claim 2, 4, 5, 15), a virus culture system (claim 3, 16), a virus cultivation process (claim 6, 7, 8, 9), a virus (claim 10) and a vaccine (claim 12-14).
Claim 1 reads as follows:

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[66] Ibidem, 129. Rule 29 (6) Implementing Regulations to the EPC further stipulates that claims shall not, except where absolutely necessary, rely, in respect of the technical features of the invention, on references to the description or drawings. In particular, they shall not rely on such references as: "as described in part ... of the description", or "as illustrated in figure ... of the drawings".

[67] Ibidem, 129.

[68] MOUFANG, R., 'Patenting of Human Genes, Cells and Parts of the Body? – The Ethical Dimensions of Patent Law', 25, *International Review of Industrial Property and Copyright Law (IIC)*, 1994, (487), 509. Similarly, DOLDER, 'Schranken der Patentierbarkeit biotechnologischer Erfindungen nach dem Europäischen Patentübereinkommen', *Mitteilungen der deutschen Patentanwälte*, 1984, (1), 5 ff., footnote 35 ff; PAVER, *Patent World*, 1992, Issue n° 3, (9), 15.

"A human embryo liver cell line having the characteristics of cells deposited with the ATCC under number CL99"

Claim 2 runs as follows:

"A cell culture system comprising cells derived from the human embryo liver cell line designated by ATCC number CL 99 in a nutrient culture medium therefor".

A somewhat similar patent is the Belgian patent 752.908 granted [69] by the Belgian Patent Office to the WELLCOME FOUNDATION in London on July 2 1970 relating to the culture of human liver cells [70]. The claims relate to human heteroploid epithelial cell lines (claim 1 ff.), culture methods (claim 4 ff.), cell cultures derived from human heteroploid epithelial cell lines (claim 10 ff.), methods for culturing viruses (claim 15 ff.), virus cultures (claim 17) and methods for the preparation of a vaccin (claim 20 ff.).

Claim 1 reads as follows:

"Lignée de cellules épithéliales hétéroploïdes de foie humain, comme la lignée WRL 68, caractérisée par la formation d'îlots ou de grumeaux distincts lors de la culture sur un milieu de croissance, par une morphologie d'étroitement semblable à celle des hépatocytes de foie human et un délai de reproduction n'excédant pas 24 heures, par un accroissement de la production de glycobène lors d'une culture dans un milieu à 1% de glucose et par son aptitude à entretenir des virus".

Claim 10 runs as follows:

"Culture de cellules d'une lignée de cellules épithéliales hétéroploïdes de foie humain, caractérisée en ce qu'elle comprend une lignée de cellules suivant l'une quelconque des revendications 1 à 3 en association avec un milieu de culture nutritif"

An example of a European patent is EP 96 839, entitled "Method for producing human antibody" which was granted on January 1989 25 to Asahi Kasei Kogyo Kabushiki Kaisha, Osaka. The invention relates to a method of effectively producing antibodies by creating antibody-producing hybrid cell lines utilising an established B cell line as a parent cell lines and fusing these B cells to normal, human antibody-producing cells. A preferred established B cell line for use in this invention consists of B cells characterised by the presence of immunoglobulin at their cell surface. There is only one claim.

The only claim runs as follows:

"Method for producing human antibody by using an antibody producing hybrid cell line created from the fusion of

- a mutant B cell line (which is deficient in hypoxanthine/guanine phosphoribosyl transferase) with
- an antibody-producing human cell, characterised in that
- the mutant B cell line ATCC CRL 8118, which produces lgM type antibody and is not derived from myeloma cells or
- a mutant of ATCC CRL 8118 offering the same relevant effect has been used for the fusion with a normal human lgG type antibody-producing cell".

Another example is European patent 113 769 entitled "Mutation assays involving blood cells that metabolise toxic substances". The inventors were Charles Crespi and

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[69] According to article 2 of the (former) Belgian Patent Act of 1854, the Belgian Patent Office could not develop a policy of its own, as the Belgian patent system was merely a registration system without any prior examination of the patentability of the inventions. See VAN OVERWALLE, G. 'The Legal Protection of Biological Material in Belgium', *International Review of Industrial Property and Copyright Law,* 2000, (259), 267-268.

[70] French *"Cultures de cellules épithéliales"*. See VAN OVERWALLE, G. 'The Legal Protection of Biological Material in Belgium', *International Review of Industrial Property and Copyright Law,* 2000, (259), 268.

William Thilly and the patent was delivered to Massachusetts Institute of Technology on February 15 1989. The patented invention relates to a line of human blood cells which have high levels of oxidative activity (such as oxygenase, oxidase, peroxidase, and hydroxylase activity). Such cells grow in suspension culture, and are useful to determine the mutagenicity of xenobiotic substances that are metabolised into toxic or mutagenic substances. Mutation assays using these cells, and other cells with similar characteristics, are also disclosed.
The claims relate to a human lymphoblastoid cell line (claim 1) and a method for determining mutagenicity of a substance (claims 3-8).

Claim 1 reads as follows:

"A human lymphoblastoid cell line characterised in that the cell line is capable of continuous reproduction in suspension culture, and can be mutated in a statistically significant degree in the absence of exogenous oxidative enzyme activity (for example oxygenase activity, oxidase activity, peroxidase activity or hydroxylase activity) when contacted with a chemical (for example dimethyl nitrosamine or a polynuclear aryl hydrocarbon; e.g. aflatoxin B, benzo(α)-pyrene, or 2-acetoaminofluorene) in non-oxidised form requiring oxidative activation in order to become capable of causing genetic change".

Claim 2 runs as follows:

"The human cell line identified by AHH-1; ATCC accession number CRL 8146"

Another example is European patent 143 809, entitled "Method for obtaining human hepatocytes cultures, cultures obtained thereby and biological and biochemical applications thereof". The patent was granted to the *Institut national de la santé et de la recherche médicale (INSERM)* on January 18 1989. The patented invention discloses a method for culturing human hepatocytes is disclosed. The method comprises associating a culture of human hepatocytes including a medium with cells of hepatic origin, these cells being different from the hepatocytes and being of the type insuring in vivo specific cellular interactions with the hepatocytes. The culture obtained maintains hepatocyte functions at a high level for an extended period of time.
The patent claims include a culture method for human hepatocytes (claims 1-13), human hepatocyte co-cultures (claims 14-18) and biological and biochemical uses of the co-cultures (claim 19).

Claim 1 reads as follows:

"Culture method for human hepatocytes, characterised in that there are associated, with a culture of human hepatocytes, cells of hepatic origin, different from the hepatocytes, originating from lines obtained from animals ensuring in vivo specific cellular interactions with the hepatocytes"

Claim 14 runs as follows:

"Human hepatocyte co-cultures, characterised in that they comprise in association human hepatocytes and cells of hepatic origin as defined in any one of claims 1 to 4, 12 or 13"

One of the patents that gained enormous international attention was U.S. patent 4.438.032 entitled "Unique T-Lymphocyte Line and Products Derived Therefrom" which was based on the work of David W. Golde and Shirley Quan and was delivered to the Regents of the University of California on March 20 1984. The patented invention was based on the use of T-lymphocyte cells from John Moore.
The claims include a method for producing in an excretory protein produced by a T-lymphocyte (claim 1 ff.), a method for cloning DNA (claim 8 ff.), a protein composition (claim 14 ff.), a single cell suspension (claim 16), a genetic library comprising DNA fragments (claim 19) and a method for stimulating the proliferation of human bone marrow cells (claim 20 ff.).

Claim 1 runs as follows:

"A method for producing in isolatable amounts an excretory protein produced by a T-lymphocyte, said method comprising: cultivating as a single cell suspension the Mo cell line in a nutrient medium, whereby said excretory proteins are produced and excreted into said nutrient medium"

Claim 16 reads as follows:

"A single cell suspension of the Mo celline in a nutrient medium"

Claim 20 reads as follows:

"A method for stimulating the proliferation of human bone marrow cells, which comprises contacting said bone marrow cells an amount sufficient to cause proliferation of a composition according to claim 4"

This patent was the start of a long and heated dispute, which finally lead to Supreme Court decision on 9 July 1990 [71]. The main issue at stake was the right of property in human tissue and the question of proper informed consent procedures. Less consideration was given to the patent issue and to the question of whether or not patent protection can be granted for an invention based on the use of biological material from human origin. Apparently the latter was considered possible.

2. IPC Classification

Also witness of the patent practice of patenting human cells, is the fact that relevant categories have been adopted into the International Patent Classification [72].

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[71] California Supreme Court, *Moore v. University of California*, 9 July 1990, 15 *United States Patent Quarterly (USPQ)*, 1753. There is a vast amount of literature on this case, see for example BIAGI, K.G., 'Moore v. Regents of the University of California: Patients, Property Rights, and Public Policy', *Saint Louis University Law Journal*, vol. 35, 1991, 433-462; BERGMAN, H.R., 'Case Comment : Moore v. Regents of the University of California', *American Journal of Law & Medicine*, vol. XVIII, 1992, 127-145; HEYER, C., 'Moore v. Regents of University of California: the Right of Property in Human Tissue and its Effect on Medical Research', *Rutgers Computer & Technology Law Journal*, vol. 16, 1990, 629; POTTS, J.A., 'Moore v. Regents of the University of California. The Problem of Expanded Disclosure and Limited Property Rights', *Northwestern University Law Review*, vol. 86, 453-496 and the references cited there.

[72] WIPO, *International Patent Classification* (Sixth Edition), *Guide, Official Catchword Index:*

C	Chemistry, Metallurgy
C 12	Biochemistry; Beer; Spirits; Wine; Vinegar; Microbiology; Enzymology; Mutation Or Genetic Engineering
C 12 N	Micro-Organisms or Enzymes; Compositions Thereof (Biocides, Pest Repellants or Attractants, or Plant Growth Regulators Containing Micro-Organisms, Viruses, Microbial Fungi, Enzymes, Fermentates, or Substances Produced by, or Extracted from Micro-Organisms or Animal Material; Food Compositions, Medicinal Preparations; Chemical Aspects of, or Use of Materials for, Bandages, Dressings, Absorbent Pads or Surgical Articles; Fertilisers); Propagating, Preserving, or Maintaining Micro-Organisms (Preservation of Living Parts of Humans or Animals); Mutation or Genetic Engineering; Culture Media (Microbiological Testing Media)
C 12 N 5/00	Undifferentiated human, animal or plant cells, e.g. cell lines; Tissues; Cultivation or maintenance thereof; Culture media therefor (plant reproduction by tissue culture techniques
C 12 N 5/08	. Human cells or tissues
C 12 N 5/10	. Cells modified by introduction of foreign genetic material, e.g. virus transformed cells
C 12 N 5/12	.. Fused cells, e.g. hybridomas
C 12 N 5/22	... Human cells
C 12 N 5/24	.... on of the fusion partners being a B lymphocyte
C 12 N 5/26	... Cells resulting from interspecies fusion
C 12 N 5/28	.... one of the fusion partners being a human cells

C. Patents on human stem cells

To obtain relevant and detailed information on the current situation with regard to patenting in the field of human stem cell research, a thorough examination of both European and US patent databases was conducted.

1. Statistical data

a. Patent applications and granted patents

The extensive patent search carried out in the framework of this report proved that about 2.029 patents were applied for or granted for stem cells [73] and that 512 patents were applied for or granted for embryonic stem cells [74] world-wide on October 22 2001. However, the figures of 2.029 and 512 have to be put in perspective, since they refer to the total amount of patents applied for or granted in different *jurisdictions*, not to the total amount of patent *families*. A patent family includes all patents relating the same invention and claiming the same priority. So, the amount of patent families relating to stem cells and embryonic stem cells would considerably be lower than the amount of patents, so a good much below 2.029 and 512, respectively.

An analysis of the list of results for embryonic stem cells showed that the first patents related to embryonic stem cells date from 1987. A steady increase can be noticed starting 1993 and 1994 [75].

b. Granted patents

Further documentary research identified 727 granted patents for stem cells [76] and 134 granted patents for embryonic stem cells [77] in Europe and in the United States in the autumn of 2001. Here again, it has to be recalled that the figures of 727 and 134 reflect the total amount of patents granted in Europe and in the United States, and not the patent families. The amount of patent families, and thus inventions, will be significantly lower.

2. Prototype patents

Various problems arose in interpreting and refining the research results. The major problem was that the patents on stem cells and embryonic stem cells, included inventions both relating to cells from human and animal origin. It was difficult to search for only human stem cell patents, since including the word 'human' in the

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[73] A search was carried out on October 22 2001 in the DELPHION database looking for 'stem cell' in European and US patent applications and granted patents (full text), Japanese patents (abstract) and WIPO PCT publications (full text).

[74] A search was carried out October 22 2001 in the DELPHION database looking for 'embryonic stem cell' in European and US patent applications and granted patents (full text), Japanese patents (abstract) and WIPO PCT publications (full text).

[75] See Appendix 1. 'Snapshot of the result set for query on 'embryonic stem cells' (DELPHION), October 22 2001.

[76] A search was carried out on October 22 2001 in the DELPHION database looking for 'stem cell' in European and US patent granted patents (full text).

[77] A search was carried out on November 19 2001 in the DELPHION database looking for 'embryonic stem cell' in European and US patent granted patents (full text). The query result is attached as Appendix 2. A snapshot ranged in order of year of issuance is attached as Appendix 3.

query might exclude patents relating to 'animal' or 'mammal' and enclosing 'human' stem cell research as well.

Instead of further attempting to draw up a detailed and correct statistical list of patents granted for human (embryonic) stem cells in Europe and in the United States, we decided to examine some pioneer patents relating to human stem cells, in order to gain some insight in the patent practice in the field of human stem cell research.

CHAPTER 2. PATENTS ON PLURIPOTENT HUMAN STEM CELLS

Extensive patent searches led to a wide range of patents and patent applications in the field of human stem cell research. The multitude of patents has been divided in two major categories - pluripotent and multipotent human stem cell patents (Chapter 3 and 4) – and various subcategories, consistent with the subdivisions made in Part I.

A. Human embryonic stem cells

The wide variety of patents and patent applications relating to embryonic stem cell research, can be divided in three categories:
- patents describing manipulation of embryonic stem cells from non-human origin, claiming human embryonic stem cells,
- patents describing manipulation of embryonic stem cells from non-human origin, in which a 'non-human' disclaimer was absent, and
- patents describing and claiming manipulation of human embryonic stem cells.

A few pioneer patents have been selected in each of these categories for further discussion.

1. Patents describing manipulation of embryonic stem cells from non-human origin, claiming human embryonic stem cells

US patent 6.200.806, entitled "Primate embryonic stem cells", March 13 2001

A key example of a patent which has been granted for human embryonic stem cell technology, wherein the manipulation of embryonic stem cells of non-human nature was described, but human embryonic stem cells were claimed, is US patent 6.200.806 entitled 'Primate embryonic stem cells'. The patent related to an invention from James THOMSON from Madison and was delivered to the Wisconsin University of Madison on March 13 2001 [78]. (It should be noticed, however, that the patent was first applied for in 1995, thus mainly relying on scientific results prior to that date [79].)

[78] The full text of US patent 6.200.806 entitled 'Primate embryonic stem cells' is enclosed as Appendix 4.

[79] US patent 6.200.806 B1 is a division of application n° 08/591.246, filed on January 18 1996 [now US patent 5.843.780, issued on December 1 1998] and a continuation-in-part of application n° 08/376.347, filed on January 20 1995 [Priority number: US1995000376327], now abandoned. In theory, because humans are primates, the first patent issued on December 1 1998 covered human cells as well. But the Wisconsin University applied for a second patent to make its claim on human cells explicit. See STOLBERG, S.G., 'Patent Laws May Determine the Shape of Stem Cell Research', *New York Times*, August 17 2001 (see www.nytimes.com/2001/08/17/health/genetics).

The starting point from this invention is the idea that because humans are primates, and the development is remarkably similar among primates, primate embryonic stem cell lines will provide a faithful model for understanding the differentiation of primate tissues in general and human tissues in particular [80].
At the time no primate ES cell line was known to exist, apart from embryo-derived cells lines that had convincingly demonstrated to differentiate from rodents (mouse, rat, hamster) and possibly a rabbit. Published reports of embryo-derived cell lines from domestic species had failed to conclusively demonstrate differentiation of derivatives [81].

The patented invention relates to the purified preparation of pluripotent primate embryonic stem cells. For the isolation, two primate species, the common marmoset (*Callithrix jacchus*) and the rhesus monkey (*Macaca mulatta*) were used as exemplary species [82]. Research led to the development of primate embryonic stem cell lines which are true, pluripotent embryonic stem cell lines in that they (1) are capable of indefinite proliferation in vitro in an undifferentiated state, (2) are capable of differentiation to derivatives of all three embryonic germ layers (endoderm, mesoderm and ectoderm) even after prolonged culture – for at least one year and (3) maintain a normal karyotype throughout prolonged culture [83]. It is a feature of the primate embryonic stem cell lines that the cells can differentiate to trophoblast in vitro and express chorionic gonadotropin.
The embryonic stem cells are fully pluripotent in that the cells have the ability to develop into any cell derived from the three main germ cell layers including bone, cartilage, smooth muscle, striated muscle, and hematopoietic cells (mesoderm); liver, primitive gut and respiratory epithelium (endoderm); neurons, glial cells, hair follicles and tooth buds (ectoderm) or an embryo itself [84].

The patented invention also comprises a method of isolating a primate embryonic stem cell line. The method includes the steps of isolating a primate blastocyst, isolating cells from the inner cellular mass (ICM) of the blastocyst, plating the ICM cells on a fribroblast layer (wherein ICM-derived cell masses are formed), removing an ICM-derived cell mass and dissociating the mass into dissociated cells, replating the dissociated cells on embryonic feeder cells and selecting colonies with compact morphology containing cells with a high nucleus/cytoplasm ratio and prominent nucleoli. The cells of the selected colonies are then cultured [85].
Using the techniques described, the inventor derived three independent embryonic stem cell lines from two rhesus monkey blastocysts (one cell line remaining undifferentiated and continuing proliferating after continuous culture for over one year) [86] and isolated 7 putative marmoset embryonic stem cell lines, each of which have been cultured for over 6 months [87].

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[80] See the description of US patent 6.200.806 B1, column 2, column 6, column 18 (lines 48-53).
[81] See the description of US patent 6.200.806 B1, column 7.
[82] See the description of US patent 6.200.806 B1, column 6. (Detailed description of the preferred embodiments).
[83] See US patent 6.200.806 B1, column 4.
[84] See US patent 6.200.806 B1, column 11.
[85] See US patent 6.200.806 B1, column 4.
[86] See US patent 6.200.806 B1, column 14
[87] See US patent 6.200.806 B1, column 17.

The claims of the patented invention relate to a purified preparation of pluripotent *human* embryonic stem cells (claim 1 ff.), a method of isolating a pluripotent *human* embryonic stem cell lines (claim 9 ff.) and a cell line (claim 11).

Claim 1 reads as follows:

"A purified preparation of pluripotent human embryonic stem cells which
(i) will proliferate an in vitro culture for over one year,
(ii) maintains a karyotype in which the chromosomes are euploid an not altered through prolonged culture,
(iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and
(iv) is inhibited from differentiation when cultured on a fibroblast feeder layer".

Claim 9 runs as follows:

"A method of isolating a pluripotent human embryonic stem cell line, comprising the steps of:
(a) isolating the human blastocyst;
(b) isolating cells from the inner cell mass of the blastocyst of (a);
(c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed;
(d) dissociating the mass into dissociated cells;
(e) replating the dissociated cells on embryonic feeders cells;
(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and
(g) culturing the cells of the selected colonies to thereby obtain an isolated pluripotent human embryonic stem cell line".

Claim 11 reads:

"A cell line developed by the method of claim 9".

The extension of the invention results with regard to *common marmoset and rhesus monkey* embryonic cell lines to claims on *human* embryonic stem cells is striking. The extension is argued by the fact that it is demonstrated that it is possible to isolate embryonic stem cell lines from a representative species of both the Old World (rhesus monkey) and the New World (common marmoset) using similar conditions, which leads to believe that the techniques described may be used successfully in deriving embryonic stem cell lines in other higher primates as well. Given the close evolutionary distance between rhesus macaques and humans, and the fact that feeder-dependant human embryonic stem cell lines can be grown in conditions similar to those that support primate embryonic stem cell lines, the same growth conditions will allow the isolation and growth of human embryonic stem cells.

It is worthwhile noticing that the NIH has limited authority over the patenting and licensing activities of their contractors and grantees. Quite recently, the NIH emphasised that with regard to the stem cell patents and patent applications, it would be appropriate to address questions to the owners and licensees of this technology as to what conditions they may apply to those who desire to use the intellectual property[88].

A European patent *application* for the same subject matter was filed on January 19 1996 [89]. The application was published together with the search report on May 2

[88] FREIRE, M., Statement of National Institutes of Health, Before Senate Appropriations Subcommittee on Labour, Health and Human Services, Education and Related Agencies, August 1 2001 (See www.nih.gov/news/stemcell/080101freire.htm).

[89] Application number: EP19960000903521. Cf. WO 09622362, filed on January 19 1996

1997 as EP 770.125. Similar claims as in the US patent were put forward [90]. Contrary to the US patent, the European counterpart has not been granted yet.

2. Patents describing manipulation of embryonic stem cells from non-human origin, in which a 'non-human' disclaimer was absent

EP 695 351 entitled "Isolation, selection and propagation of animal transgenic stem cells", December 8 1999

An example of a patent which has been granted for embryonic stem cell technology from non-human origin in which a 'non-human' disclaimer has been omitted is European patent 695 351 (EP 695 351) entitled "Isolation, selection and propagation of animal transgenic stem cells". This patent relates to an invention from Austin SMITH of the AFRC Centre for Genome Research of the University of Edinburgh and Peter MOUNTFORD from Stem Cell Sciences in Melbourne (UK). The patent was granted to the University of Edinburgh on December 8 1999 [91]. It should be noticed, however, that the patent stems from an application filed in April 1994, with a priority date in April 1993 [92], thus mainly relying on scientific results prior to that date.

At the time of the invention stem cells, which had been isolated from tissue samples, consisted of mixed cell types and could mostly not be grown readily in culture. When attempts were made to culture stem cells, the cells grew at different rates and the stem cells rapidly became overgrown by non-stem cell types.
Exceptions were two embryonic stem cells from two specific strains of mice, which could be cultured *in vitro*. However, there had developed a pressing need to isolate and maintain *in vitro* embryonic stem cells from other murine strains and more especially from other species including laboratory animals (e.g. rats, rabbits and guinea pigs), domesticated animals (e.g. sheep, goats, horses, cattle, pigs, birds, fish, etc.) and primates [93].

The patented invention relates to a technique by which the aforementioned problems of low degree of heterogeneity and overgrowth in culture by non-pluripotent cells, can be overcome. The invention concerns animal cells with unlimited capacity for differentiation into cells with specialised functions and into cells which foreign genetic material can be introduced [94].

The claims of the patented invention relate to a method of isolating and/or enriching and/or selectively propagating desired animal stem cells (claim 1 ff.), an animal cell capable of being cultured form a mixture of cells including desired stem cells and cells other than the desired stem cells (claim 37 ff.), a vector for use in genetically modifying cells (claim 39 ff.) and a method of preparing a transgenic animal (claims 47 & 48).

Claim 1 reads as follows:

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[90] See the claims in WO 09622362.
[91] The full text of EP 695 361 is attached as Appendix 5.
[92] Priority number: GB 9308271.7, 21 April 1993.
[93] See the description of EP 695 351, p. 2, [0001] to [0007].
[94] See the description of EP 695.351. Also see SOLTER, D. and GEARHART, J., 'Putting Stem Cells to Work', 283, *Science*, 5 March 1999, 1468-1470 (Especially the figure on p. 1469 is clarifying).

> "A method of to isolating and/or enriching and/or selectively propagating desired animal stem cells, which comprises maintaining a source of said cells under culture conditions conducive to cell survival, characterised in that the source of cells includes cells containing a selectable marker which is capable of differential expression in (a) desired stem cells of said source and (b) cells of said source other than the desired stem cells, whereby differential expression of said selectable marker results in preferential isolation and/or survival and/or division of the desired stem cells containing the said selectable marker"
>
> Claim 2 (a so-called dependent claim) reads:
>
> "A method according to Claim 1 wherein the desired stem cells are selected from unipotential stem cells, pluripotential stem cells, embryonic stem cells, gonadal stem cells, somatic/progenitor cells, heamatopoietic stem cells, epidermal stem cells or neuronal stem cells"
>
> Claim 37 runs as follows:
>
> "An animal cell capable of being cultured form a mixture of cells including desired stem cells and cells other than the desired stem cells, characterised in that all cells in the said mixture of cells contain a selectable marker and in that in the said mixture of cells, under appropriate selective culture conditions, differential expression of the selectable marker in (a) the desired stem cells and (b) cells other than the desired stem cells enables selective survival or growth of the desired stem cells to occur, so as to enable isolation and/or enrichment and/or propagation of desired stem cells.
>
> Claim 47 reads as follows:
>
> "A method of preparing a transgenic animal comprising obtaining a desired stem cell according to the method of any of claims 1-36, excising the selectable marker from the desired stem cell and generating the transgenic animal therefrom"
>
> Claim 48 runs:
>
> "A method of preparing a transgenic animal, said animal comprising a selectable marker capable of differential expression in (a) desired stem cells and (b) cells other than desired stem cells, the method comprising: providing a blastocyst; providing animal cells according to any of claims 37-38, introducing the animal cells into the blastocyst, transferring the blastocyst to a recipient and allowing an embryo to develop to a chimaeric animal to enable germline transmission of the selectable marker".

The original patent application also included claims on a transgenic animal [95]. However, those claims have not been retained in the finally issued patent.

3. Patents describing and claiming manipulation of human embryonic stem cells

US patent 6.280.718 entitled "Hematopoietic differentiation of human pluripotent embryonic stem cells", August 28 2001

A typical example of a patent describing and claiming manipulation of human embryonic stem cells is US patent 6.280.718, entitled "Hematopoietic differentiation of human pluripotent embryonic stem cells". The use of human embryonic stem cells to create blood-related stem cells and the use of those blood-related stem cells for various purposes has been described by James THOMSON and Dan KAUFMAN, both of Madison. The patent was granted to the Wisconsin Alumni Research Foundation

[95] Claim 40 from the patent application read "A transgenic animal which comprises a source of cells suitable for the isolation and/or propagation of stem cells by a method according to any claims 1 to 37" and claim 41 read "A transgenic animal generated using a cell obtained by a method claimed in any of the claims 1 to 37" (PCT International Application, WO 94/24274 – International filing date: 21 April 1994).

from Madison on August 28 2001 [96]. It should be noticed, however, that the patent was applied for in 1999 [97], thus mainly relying on scientific results prior to that date.

At the time of the invention, hematopoietic stem cell populations had been isolated directly from bone marrow and there had been some attempts to direct murine embryonic stem cell populations towards hematopoietic stem cells. However, applying these teachings to primates had been proven difficult. A need existed for techniques causing human embryonic stem cell cultures to differentiate to desired hematopoietic colonies and to develop improved uses for hematopoietic cells [98].

In one aspect the invention provides a method for obtaining human hematopoietic cells. One exposes a human embryonic stem cell culture to mammalian hematopoietic stromal cells, so as to thereby create human hematopoietic cells [99]. In another aspect the invention provides a human hematopoietic cell which was derived from human embryonic stem cell culture in vitro [100].
The method of the patented invention comprised various steps. The starting point of the majority of the experiments were the previously described human embryonic cell lines H1, albeit some of the studies were done with other cell lines with similar results. These cells were removed from frozen (liquid nitrogen) stocks of cells derived from the original isolated and propagated cell line and then grown in well culture dishes. The dish was first coated with a gelatine solution for one or more days in a 37°C/5%C02 incubator. After the one or more days, the gelation solution was removed and the wells of the plate were coated with irraditated mouse embryonic fibroblast (MEF) cells, which were derived from day 12-13 mouse embryos. After some more manipulations, the human embryonic stem cells were harvested. To promote hematopoietic differentiation the cells were then plated in well plates coated with mammalian stromal cells, which were originally obtained from the yolk sac of mice at embryonic day 12. After 3-7 days from further plating, the embryonic cells began to visually appear differentiated in that they did not have the same uniform appearance as the undifferentiated embryonic stem cells maintained in the original (MEF) feeder cells. The colonies of embryonic cells began to form multiple different cell types. Some of those colonies had regions that appeared to consist of cells with a cobblestone morphology indicative of colonies of early hematopoietic progenitor cells[101].

The claims of the patented invention relate to a method for obtaining human hematopoietic cells (claim 1 ff.) and a method of transplanting human cells into a human recipient host (claim 6 ff.).

Claim 1 reads as follows:

"A method for obtaining human hematopoietic cells, comprising exposing a human pluripotent embryonic stem cell culture to mammalian hematopoietic stromal cells, wherein at least some of the human hematopoietic cells that are so produced will form hematopoietic cell colony forming units if placed in methylcellulose culture"

Claim 6 runs as follows:

"A method of transplanting human cells into a human recipient host, comprising:

[96] The full text of US patent 6.280.718 is attached as Appendix 6.
[97] Priority number: US 09/435.578, November 8 1999.
[98] US patent 6.280.718, column 1.
[99] US patent 6.280.718, column 2.
[100] US patent 6.280.718, column 2.
[101] US patent 6.280.718, column 4-5.

> obtaining human hematopoietic cells which have been derived in vitro from a human pluripotent embryonic stem cell culture;
> obtaining a selected human cell other than hematopoietic cells, the selected non-hematopoietic cell having major histocompatibility complex compatibility to the human hematopoietic cells; and
> transplanting both the human hematopoietic cells and selected human non-hematopoietic cell into the human host".

A European patent for the same subject matter was filed on August 25 2000 [102]. Contrary to the US patent, the European counterpart has not been granted yet.

B. Human embryonic germ cells

US patent 6.090.622 entitled "Human Embryonic Pluripotent Germ Cells", July 18 2000

A classic example of a patent which has been granted for human embryonic germ cells, is US patent 6.090.622 entitled 'Human Embryonic Pluripotent Germ Cells'. The inventors were John GEARHART and Michael SHAMBLOTT, both of Baltimore and the patent was delivered to the Johns Hopkins School of Medecine in Baltimore on July 18 2000 [103]. The patent for this invention was filed in 1997 [104].

The patented invention relates to methods and compositions for the production of human pluripotent embryonic germ (hEG) cells or cell lines. The human embryonic germ cells are derived from embryonic germ cells isolated from gonadal tissues, genital ridges, mesenteries or embryonic yolk sacs of human embryos (respectively 8 and 11- week last menstrual period aborted human foetal material) and cultured under conditions which allow long term cell culture (more than 30 days). The resulting human embryonic germ cells resemble embryonic stem cells in morphology, biochemical histotype and in pluripotency [105].

The main claim relates to human pluripotential embryonic germ cells, exhibiting dependence on a ligand which binds to a receptor which can heterodimerise with glycoprotein 130 and dependence on a growth factor (claim 1). No claims are enclosed referring to the methods used, or to the applications which are envisaged (e.g. construction of early development and human pluripotent embryonic germ cell DNA libraries or production of differentiated cells for replacement, repair or augmentation of damaged, non-functional, or impaired cells or tissues).

> Claim 1 reads as follows:
> "Human pluripotential embryonic germ cells, wherein the cells exhibit the following culture characteristics during maintenance:
> (a) dependence on a ligand which binds to a receptor which can heterodimerize with glycoprotein 130 (gp 130); and
> (b) dependence on a growth factor".

[102] Application number EP200000957842. Cf. WO 20000US23469 - WO 0134776, filing date: 17.05.2001 (The EPO acted as international searching authority in the framework of this PCT-filing).
[103] The full text of US patent 6.090.622 is attached as Appendix 7.
[104] US1997000829372, filed March 31 1997.
[105] US patent 6.090.622, column 2 and column 4.

US patent 6.245.566 entitled "Human Embryonic Germ Cell Line and Methods of Use", June 12 2001

A continuation of US patent 6.090.622 is US patent 6.245.566 entitled 'Human Embryonic Germ Cell Line and Methods of Use', based on the work of John GEARHART and Michael SHAMBLOTT and delivered to the Johns Hopkins School of Medicine in Baltimore on June 12 2001 [106].

The claims in the latter patent are directed towards a method for producing human pluripotent embryonic germ cells (claim 1 and claim 28) and a method of maintaining a culture of human pluripotent embryonic germ cells in a substantially undifferentiated stated (claim 22 and 35).

> Claim 1 reads as follows:
> "A method for producing human pluripotent embryonic germ (hEG) cells, comprising culturing human primordial germ cells in a specific culture medium, comprising:
> (a) a ligand which binds to a receptor which can associate with glycoprotein 130 (gp 130); and
> (b) a growth factor;
> until cells with the morphology of human pluripotent embryonic germ cells are observed, and wherein the cells exhibit the following culture characteristics during maintenance:
> (i) dependence on a ligand that binds to a receptor, which can associate with gp 130; and
> (ii) dependence on a growth factor"

For the US patent 6.245.566 a European patent was filed on March 31 1998 [107]. The patent has not been granted yet.

CHAPTER 3. PATENTS ON MULTIPOTENT HUMAN STEM CELLS

A. Human foetal stem cells

PCT patent application (WO 01/66698 A1) entitled "Human cord blood as a source of neural tissue for repair of the brain and spinal cord", March 7 2001

An international patent *application* which gained much public attention is a patent applied for by CRYO-CELL International from Clearwater (U.S.) on 7 March 2001, entitled "Human cord blood as a source of neural tissue for repair of the brain and spinal cord" [108]. The invention relates to the use of umbilical cord blood cells from a donor or patient to provide neural cells which may be used in transplantation. The isolated cells according to the present invention may be used to effect autologous and allogeneic transplantation and repair of neural tissue, in particular, tissue of the brain and spinal cord and to treat neurodegenerative diseases of the brain and spinal cord.

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[106] The full text of US patent 6.245.566 is attached as Appendix 8.

[107] Application number: EP1998000915243. Publication number: EP 1.023.085.

[108] International application number: WO 01/66698 A1. The current PCT application relates to a US priority patent from 9 March 2000 (US 60/188.069) and from 16 February 2001 (US 60/269.238). The front page and the claims of this PCT patent are attached as Appendix 9.

The claims relate to neural cells (claim 1 ff.), a method of producing neural cells from umbilical cord blood (claim 4 ff.), a method of producing a sample of enriched neural cells from a sample of mononuclear cells obtained from umbilical cord blood (claim 15 ff.), a method of treating a patient (claim 24 ff.), a composition comprising umbilical cord blood (claim 31 ff.), a method of producing a pharmaceutical composition comprising a sample of mononuclear cells (claim 37 ff.).

> Claim 1 reads as follows:
> "Neural cells obtained by exposing pluripotent stem or progenitor cells obtained from umbilical cord blood to an amount of a differentiation agent effective for changing the phenotype of said stem or progenitor cells to a neural phenotype".
> Claim 4 reads as follows:
> "A method of producing neural cells from umbilical cord blood comprising: a. obtaining a sample of mononuclear cells from said umbilical cord blood; and (b) growing sad mononuclear cells from step a in a culture medium containing an effective amount of a differentiation agent for a period sufficient to change the phenotype of said stem or progenitor cells to neural".
> Claim 24 runs as follows:
> "Method of treating a patient with a neurodegenerative disease comprising administering an effective number of neural cells according to any of claims 1-20 said patient"

B. Human adult stem cells

US patent 6.265.175 entitled "Method for production of neuroblasts", July 24 2001

A key example of a patent which has been granted for adult stem cells, is US patent 6.265.175 entitled "Method for production of neuroblasts" which was based on the work of Fred GAGE and Jasodhara RAY, both of San Diego and delivered to the Regents of the University of California on July 24 2001 [109]. It should be noted, however, that the patent was applied for in 1997 [110], thus mainly relying on scientific results prior to that date.

Prior to the date of the patented invention, various researchers succeeded in isolating and immortalising progenitor cells from different regions of the brain and different stages of development. There was a need, however, for a long-term *in vitro* culture system which would allow large-scale production and maintenance of a neuronal cell population which will proliferate and can be passaged and subcultured over time [111].
The inventors developed an *in vitro* method and a culture system for the generation of continuous, neuronal cell cultures from different regions of the brain, from both foetal and adult tissue, which are capable of proliferation. These cells, termed neuroblasts, can be produced by utilising methodology which comprises culturing a neuronal cell in a serum-free media supplemented with at least one trophic factor using a vessel which allows attachment of the cell [112].
It is underlined that the neuronal cell of the invention, which is utilised for production of a neuroblast, can be derived from any foetal or adult neural tissue, including tissue from the hippocampus, cerebellum, spinal cord, cortex, striatum, basal forebrain, ventral mensencephalon and the locus ceruleus.

[109] The full text of US patent 6.265.175 is attached as Appendix 10.
[110] Application number: 08/884.427, filed June 27, 1997. Continuation in part of application number 08/001.543, January 6 1993, now abandoned.
[111] US patent 6.265.175.
[112] US patent 6.265.175.

The claims of the patented invention mainly relate to a method for identifying a composition which stimulates or inhibits neuroblast proliferation or differentiation (claim 1 and 2), the neuroblast potentially being genetically modified (claim 3 and 4).

Claim 1 reads as follows:

"a method for identifying a composition which stimulates or inhibits neuroblast proliferation or differentiation, comprising
(a) incubating components comprising a neuroblast and a composition to be tested for the ability to stimulate or inhibit proliference or differentiation of the neuroblast, wherein the incubating is carried out under conditions and for a time sufficient to allow the composition to be tested to bind to the neuroblast and to allow the neuroblast to be cultured in the absence of oncogenic transformation and in a vessel in a serum-free basal media supplemented with about 1ng/ml to 100ng/ml of basic fibroblast growth factor, wherein a surface in the vessel allows attachment of the cells and wherein the neuroblast proliferates for greater than seven days, and thereby can result in a long term continuously proliferating neuroblast culture, and
(b) detecting an effect of the composition of the proliferation or differentiation of the neuroblast, thereby identifying a composition that stimulates or inhibits neuroblast proliferation or differentiation".

Claim 2 (a so-called 'dependent' claim) runs as follows:

"The method of claim 1, wherein the neuroblast is derived from neural tissue selected from the group consisting of hippocampus, cerebellum, spinal cord, cortex, striatum, basal forebrain, ventral mesencephalon and locus ceruleus".

Claim 3 (also a dependent claim) reads:

"The method of claim 1, wherein the neuroblast is genetically modified to contain an exogenous gene which encodes a neuronal receptor".

Claim 4:

"The method of claim 3, wherein the receptor is selected from the group consisting of receptors which bind adrenaline, noradrenaline, glutamate, serotonin, dopamine, GABA and acetylcholine".

The development of primary neuronal cultures maintained as cell lines permits investigation of fundamental questions regarding the biochemical and cellular properties of these cells and the dynamics of interaction between their cellular and chemical environment [113]. Neuroblasts of the patented invention are also useful as a screening tool for neuropharmacological compounds which affect a biological function of the neuroblast.

The present invention also provides a method of treating a subject with a neuronal cell disorder, which comprises administering to the subject a therapeutically effective amount of the neuroblast of the invention. This method of treating entails intracerebral grafting of neuroblasts to the region of the CNS having the disorder. Administration of the neuroblasts of the invention into selected regions of the recipient subject's brain, may be made by drilling a hole and piercing the dura to permit the needle of a micrisyringe to be inserted. The neuroblast can alternatively be injected intrathecally into the spinal cord region.

The neuroblast used for treatment of a neuronal disorder may optionnally contain an exogenous gene. For example, neuroblasts to be grafted into a subject with a disorder of the basal ganglia, such as Parkinson's disease, can be modified to contain an exogenous gene encoding L-DOPA, the percursor to dopamine.

[113] US patent 6.265.175.

Quite recently, GAGE and his team succeeded in isolating clonogenic human central nervous system stem cells (hCNS-SC) from fresh human foetal brain tissue [114].

CHAPTER 4. CONCLUSIONS

The in depth examination of various prototypes of patents leads to the following conclusions.

A. Subject matter

Careful examination of the various prototype patents, reveals that patent protection has been granted for inventions and applications in the whole spectrum of human stem cell research. Patents were issued for inventions in the field of pluripotent embryonic stem cells, pluripotent embryonic germ cells, multipotent adult stem cells, as well as multipotent foetal stem cells.

B. Patent claims

1. Product and process claims

Two basic kinds of claims appear in the prototype patents: process claims and product claims. In the first category, claims can be distinguished on:

- stem cells:
  - e.g. human pluripotential embryonic germ cells (US patent 6.090.622),
  - a purified preparation of pluripotent human embryonic stem cells (US patent 6.200.806)
- stem cell lines:
  - e.g. a [human] cell line (US patent 6.200.806)
- differentiated stem cells:
  - e.g. neural cells (WO 01/66698 A1)
- genetically modified stem cells:
  - e.g. an animal [human] cell capable of being cultured to form a mixture of cells including desired stem cells and cells other than the desired stem cells (EP 695 351)

In the second category, process claims can be distinguished on:

- isolation methods, selection methods:
  - e.g. a method of isolating a pluripotent human embryonic stem cell line (US patent 6.200.806),
  - a method of isolating and/or enriching and/or selectively propagating desired animal stem cells (EP 695 351),
  - a method for obtaining human hematopoietic cells (US patent 6.280.718),
  - a method for producing human pluripotent embryonic germ cells (US patent 6.245.566)
- cultivation methods:

[114] See UCHIDA, N., BUCK, D.W., HE, D., REITSMA, M.J., MASEK, M., PHAN, T.V., TSUKAMOTO, A.S., GAGE, F.H. and WEISSMAN, I.L., 'Direct Isolation of Human Central Nervous System Stem Cells', 97, *PNAS*, December 19 2000, 14720-14725.

  - e.g. a method of maintaining a culture of human pluripotent embryonic germ cells in a substantially undifferentiated stated (US patent 6.245.566),
  - a method for identifying a composition which stimulates or inhibits neuroblast proliferation or differentiation (US patent 6.265.175)
- cloning methods:
  - e.g. a method of preparing a transgenic [human] animal (EP 695 351)
  - a method of transplanting human cells into a human recipient host (US 6.280.718)
- treating methods:
  - method of treating a patient (WO 01/66698 A1 – CryoCell) [115]

In most prototype patents, product and process claims from different types were included.

An issue that remains unclear is the difference between a claim on a 'cell' and a claim on a 'cell line'. According to Webster's a 'cell' is "a small usually microscopic mass of protoplasm bounded externally by a semipermeable membrane, usually including one or more nuclei and various other organelles with their products, capable alone or interacting with other cells of performing all the fundamental functions of life, and forming the smallest structural unit of living matter capable of functioning independently" [116] and a 'cell lineage' is "the developmental history of a cell from the first cleavage division until its ultimate fate is determined" [117]. According to *Molecular Cell Biology* the term 'cell line' is used for *continuously* growing cells to distinguish them from cultured cell strains with a *finite* life-span [118].
So, from a scientific point of view, there seems to be a difference between cells and cell lines. What are the implications of this difference with regard to patenting? Do claims on 'cells' refer to something else than claims on 'cell lines'? If not, why are the two terms used at the same time? If yes, do they have a different patent scope?

2. Broad claiming

Various patents could be discerned where the claimed subject matter was not in agreement with the patent description. It occurred that patents describing manipulation of embryonic stem cells from non-human origin, claimed – directly or indirectly - human embryonic stem cells.

The key example of a patent describing manipulation of embryonic stem cells from non-human origin and *directly* claiming human embryonic stem cells is U.S. patent

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[115] This claim has been included in a patent *application*. It is not sure whether it will be retained, especially in the light of article 52 (4) EPC. This provision stipulates that "Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods".

[116] MERRIAM-WEBSTER, *Merriam-Webster's Collegiate Dictionary*, http://www.m-w.com/cgi-bin/dictionary (Neither the word 'cell lineage', nor 'cell line' could be found in this edition).

[117] MERRIAM WEBSTER, Webster's Third New International Dictionary (Unabridged), Springfield, Merriam, 1976.

[118] LODSICH et al, *Molecular Cell Biology*, p. 196.

6.200.806 entitled 'Primate embryonic stem cells' [119], where the invention results with regard to common marmoset and rhesus monkey embryonic cell lines were extended to claims on human embryonic stem cells. The extension was argued by the fact that it is demonstrated that it is possible to isolate embryonic stem cell lines from a representative species of both the Old World (rhesus monkey) and the New World (common marmoset) using similar conditions, which leads to believe that the techniques described may be used successfully in deriving embryonic stem cell lines in other higher primates as well.

The model example of a patent describing manipulation of embryonic stem cells from non-human origin and *indirectly* claiming human embryonic stem cells is EP 695 351 entitled "Isolation, selection and propagation of animal transgenic stem cells" [120].

Can the claims in those two cases be considered *unduly* broad? To which extent can the expansion of research results be justified? Given the heated discussions with regard to too broad claims in gene patenting, guidance would be welcomed on this point.

C. Differing granting policy between the U.S. and Europe

1. Current policy

The USPTO appears to be welcoming patents relating to human stem cell research. Over the last years, the USPTO has been granting product patents for human pluripotent embryonic stem cells as well as for human pluripotential embryonic germ cells. The USPTO has also granted protection for process patents for methods for the isolation of pluripotent human embryonic stem cells, as well as for methods for producing human pluripotent embryonic germ cells.

Ever since the Edinburgh patent, which was granted on December 8 1999, the EPO seems rather reluctant with regard to patents for inventions related to human stem cell research [121]. As far as we could see, various patent applications have been submitted, but hardly any – if none – patent on human stem cell research has been granted since then. Going through the prototype patents, resulted in the following examples of granted US patents, for which a European patent is pending:

- US patent 6.200.806 entitled "Primate embryonic stem cells" was granted on March 13 2001; a European patent application was filed on January 19 1996 and published - together with the search report - on May 2 1997 as EP 770.125. Similar claims as in the US patent were put forward.
- US patent 6.280.718 entitled "Hematopoietic differentiation of human pluripotent embryonic stem cells" was delivered on August 28 2001; a European patent application was filed on August 25 2000 (Application number EP200000957842.).

[119] Invention from James Thomson from Madison, patent delivered to the Wisconsin University of Madison on March 13 2001. Supra.

[120] Invention from Austin Smith of the AFRC Centre for Genome Research of the University of Edinburgh and Peter Mountford from Stem Cell Sciences in Melbourne (UK), patent delivered to the University of Edinburgh on December 8 1999. Supra.

[121] More details on the EPO position in the Edinburgh case can be found, supra.

- US patent 6.245.566 entitled "Human Embryonic Germ Cell Line and Methods of Use", was issued June 12 2001; a European patent was filed on March 31 1998 (Application number: EP1998000915243).

2. Future policy. The effect of Bush's decision of August 9 2001

On August 9 2001 President Bush announced that federal funds may only be awarded for research using human embryonic stem cell lines that meet certain criteria [122]. The President decided that federal funds will only be used for research on existing stem cell lines that were derived (1) with the informed consent of the donors, (2) from excess embryos created solely for reproductive purposes and (3) without any financial inducements to the donors [123]. No federal funds will be used for (1) the derivation or use of stem cell lines derived from newly destroyed embryos, (2) the creation of any human embryos for research purposes or (3) the cloning of human embryos for any purpose [124].

In order to ensure that federal funds are used to support only stem cell research that meets the criteria outlined by the President, the Secretary of Health and Human Services, Tommy G. Thompson, requested the NIH to examine the derivation of all existing stem cell lines and create a registry of those lines that satisfied this criteria. After several weeks of preparation, the NIH named the 10 laboratories throughout the world that owned 64 embryonic stem cell lines which meet the President's criteria for federally funded research [125].
Research is now eligible for federal funding as long as the derivation process (which begins with the destruction of the embryo) was initiated prior to 9:00 p.m. EDT on August 9, 2001.
The President's decision relates only to the use of *federal* funds for research on existing stem cell lines. The President's decision was did not relate to *privately* funded research.

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[122] Bush literally said: "As a result of private research, more than 60 genetically diverse stem cell lines already exist and I have concluded that we should allow federal funds to be used for research on these existing stem cell lines where the life and death decision has already been made. This allows us to explore the promise and potential of stem cell research without crossing a fundamental moral line by providing taxpayer funding that would sanction or encourage further destruction of human embryos that have at least the potential for life", WHITE HOUSE, Fact Sheet, Embryonic Stem Cell Research, 9 August 2001 (see www.whitehouse.gov/news/releases/2001/08/20010809-1.html).

[123] WHITE HOUSE, Fact Sheet, Embryonic Stem Cell Research, 9 August 2001 (see www.wwhitehouse.gov/news/releases/2001/08/20010809-1.html).

[124] Ibidem.

[125] The following entities reported to the NIH that they have derived human embryonic stem cells that meet the President's criteria (Name - Number of existing stem cell lines reported to NIH): BresaGen, Inc., Athens, Georgia – 4; CyThera, Inc., San Diego, California – 9; Karolinska Institute, Stockholm, Sweden – 5; Monash University, Melbourne, Australia – 6; National Center for Biological Sciences, Bangalore, India - 3; Reliance Life Sciences, Mumbai, India – 7; Technion-Israel Institute of Technology, Haifa, Israel – 4; University of California, San Francisco, California – 2; Göteborg University, Göteborg, Sweden – 19; Wisconsin Alumni Research Foundation, Madison, Wisconsin – 5. (NIH, Update on Existing Human Embryonic Stem Cells, 27 August 2001 (see www.nih.gov/news/stemcell/08270list.htm). Also see Statement by Tommy G. Thompson, Secretary of Health and Human Services Regarding Stem Cell Lines, 27 August 2001 (see www.hhs.gov/news/press/2001pres/20010827a.html). Also see http://escr.nih.gov.

It remains to be seen, to which extent the President's new policy will affect basic human stem cell research in the public and the private sector and possible subsequent patenting.