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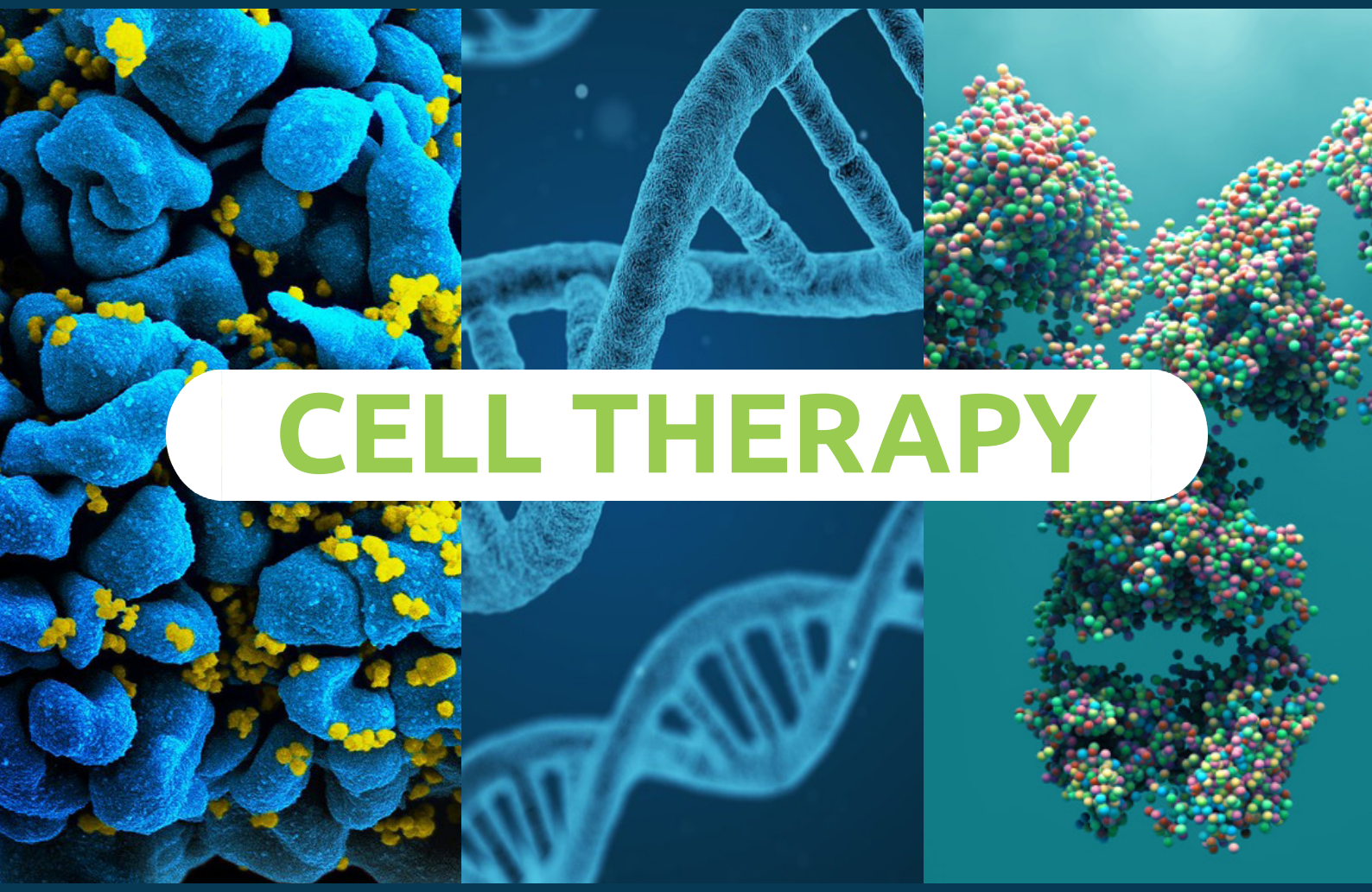

CELL THERAPY

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INTRODUCTION

MabDesign's Immunowatch is a one-of-a-kind information monitoring newsletter in the field of biologics. Its aim is to provide members of our association with the most recent and pertinent data gathered or generated through the key expertise of MabDesign and its collaborators in scientific research, business intelligence, market analysis and intellectual property.

Each edition will focus on trending type of biologics. Its general format includes market study research, financial and economic data, invited contributions from scientific teams working in the industry or in academia and a section dedicated to intellectual property. The content of each edition is decided by an editorial composed of two field experts. Decision concerning the theme and conception of each newsletter is done in-house by the permanent members of our editorial team.

Finally, we would like to acknowledge the support of the Ambition Recherche & Développement (ARD) Biomédicaments 2020 Phase II programme, funded by the Centre Val de Loire region during the initial phases of launching this newsletter.

BIOPHARMACEUTICALS
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Introduction

Cell therapy refers to the transfer of autologous or allogeneic cellular material into a patient for medical purposes. It is a promising, rapidly advancing field with the potential to transform medicine across disease areas with significant therapeutic need. For example, since the discovery of stem cells over half a century ago, more than 5000 US clinical trials have utilised stem cells. Currently, most cell therapies are in early stages of development (phase 1/2), with several exceptions being either a current best practice in specific settings (e.g., bone marrow/stem cell transplants, hepatocyte transplantation, skin equivalents), or approved for specific indications, such as PROVENGE® (sipuleucel-T), LAVIV® (azficel-T), MACI® (autologous cultured chondrocytes on porcine collagen), and KYMRIAH™ (tisagenlecleucel) among others.

Cell therapy combines stem cell- and non–stem cell-based unicellular or multicellular therapies. It typically employs autologous or allogeneic cells; might involve genetic engineering or manipulations in formulation; and can be administered topically or as injectables, infusions, bioscaffolds, or scaffold-free systems. Cell therapy spans multiple therapeutic areas, such as regenerative medicine, immunotherapy, and cancer therapy.

Treatment using cell-based therapies relates to a global market size estimated to expand from USD 9.5 billion in 2021 to USD 23.0 billion in 2028. It is also one that involves significant investment and, therefore, can be expected to have concomitantly significant costs to patients and their insurers. Accordingly, patent exclusivity will be important to defray high development and regulatory compliance costs. The nature of such therapies, and recent patent law trends regarding natural products and methods relating to the practice of medicine, suggest these therapies may not be given the type of robust patent protection conventionally available for small-molecule drugs.

About Regimbeau

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REGIMBEAU, a French IP law firm, has been assisting companies and private and public project developers to protect, enhance, and defend their innovations and creations (patents, trademarks, designs) for more than 85 years. Fifteen partners head a team of more than 200 people whose skills are put into practice in every strategic aspect of Intellectual Property – business intelligence and information search, license agreements, IP portfolio audits, partnership negotiations, acquisition of industrial property rights, litigation. A dedicated team of technical and legal experts, with hands-on experience in tackling issues and challenges of innovation in immunology, can assist you in protecting your inventions with your best interest in mind. More info on our specific webpage.

Different types of cell therapies

Cell therapies come in all sizes and shapes and can be classified in various overlapping categories.

A first, commonly-used classification is based on the origin of the cells used. For example, these therapies may use cells taken from and administered to the same individual (autologous). In this case, the cells are isolated and/or derived from a patient, concentrated, modified, or otherwise manipulated and then returned to the patient. Examples of current technologies using autologous cells include haematopoietic stem cells (HSC) isolated from bone marrow or umbilical cord blood. Other, more nascent sources of autologous cells include adult stem cells or progenitor cells isolated from tissues; these include e.g., skin stem cells and mesenchymal stem cells (MSC) derived from adult tissue or stimulated to differentiate from embryonic stem cells. A variety of immune cells, such as tumour infiltrating lymphocytes (TILs), viral reconstitution T cells, dendritic cells, γδT cells, regulatory T cells (Treg) and macrophages are also somatic cells that are being developed as cell therapies.

Another broad area corresponds to cells derived from a donor who is different from the ultimate patient benefiting from the treatment (allogeneic). Such cells have the advantage of being capable of mass production and being available off-the-shelf and, to some extent, standardised with regard to biochemical, metabolic, and antigenic properties. Disadvantages include the possibility that for any particular patient, immunological rejection may be triggered. These cells include cells having the broadest applicability, such as human embryonic stem cells and induced pluripotent cells (iPS), which can be generated by introducing four well-defined genes (Oct3/4, Sox2, c-Myc, and Klf4) into cells from appropriate tissues. Human embryonic stem cells have the broadest potential applicability because they are the most pluripotent, but their use can raise ethical issues, whereas iPSCs although less robust but also less ethically challenging.

Cell therapies can also be classified by the therapeutic indication they aim to address, e.g., neurological, cardiovascular, ophthalmological. On a more general level, they can be classified as being directed to regenerative medicine, immune system disorders, cancer therapies, or others.

In particular, many stem cell-based therapies are currently used in regenerative settings, either as investigational or established treatments with the rationale of repopulating damaged cells or resetting tissue homeostasis. In regenerative medicine, adipose stem cells (ASCs) are considered the most promising among cell therapies. HSCs have been widely used for treating haematopoietic disorders such as those resulting from myeloablative treatment. On the other hand, the clinical application of embryonic stem cells (ESCs) or iPS seems to be more distant, due to preparation and standardisation obstacles and lack of therapeutic evidence.

Most commonly, cell-based therapies are classified by cell types and the modifications involved. For example, the EU regulatory classification of cell-based therapies discriminates between minimally manipulated cells for homologous use (transplants or transfusions) and those regulated as medicines which are required to demonstrate quality, safety and efficacy standards to obtain a marketing authorisation before becoming commercially available (referred to as Advanced Therapy Medicinal Products; ATMPs) which are further subdivided into somatic cell, gene therapy and tissue engineered products. In this regard, CAR-T cells therapy is particularly promising; questions regarding patent protection and freedom to operate of this specific technology were previously discussed[1] and will not be addressed herein.

Patent protection prospects

The patentability of pluripotent stem cells has given rise to a number of fundamental questions, both legal and ethical, to which answers have been given on a country-by-country basis. Specifically, attitudes towards the patentability of hESC research findings are undergoing dynamic adjustment based on benefit weighing and the general evolution of jurisprudence. This question is particularly pregnant in Europe and the US wherein more than 35 % of all patent applications with stem cell technology are filed.

[1] Gillet & Bouquin (2020) Disruptive CAR-T therapy is driving a new wave of patenting challenges. Immunowatch n° 2, p. 37.
[2] 447 U.S. 303 (1980)

Patentability of hESCs in the U.S.

US law poses no morality-based barrier to patenting human stem cells. In the US, patent eligible subject matter is "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." (35 USC §101).

Until recently, this section has been interpreted broadly by the courts, including in Diamond v. Chakrabarty[2], when the Supreme Court stated that "everything under the sun made by man" should be patent-eligible. The important companion case to Chakrabarty is In re Bergy, wherein the United States Court of Customs and Patent Appeals (CCPA) opined that the biologically pure culture was not a product of nature and that patentability was not affected by the microorganism being alive.

Stem cells were protected under this pretence for about thirty years. The patentability of hESC-related findings suffered not much resistance in the United States. For instance, the Wisconsin Alumni Research Foundation (WARF) held a series of fundamental patents, including patents covering hESCs. Both inventions were patented in the United States. In reexamination proceedings, USPTO concluded that the previously existing technologies were too unpredictable to allow other scientists to culture hESCs and accepted the non-obviousness of the WARF patents. This case shows the American attitude toward the patentability of hESCs-related findings.

This situation changed with the passage of "America Invents Act" ("AIA") into law. The AIA provides that "no patent may issue on a claim directed to or encompassing a human organism"[3]. The legislative history of AIA clarifies that under this act, stem cells are patent eligible but patent claims directed to or encompassing a human organism, including human embryos are prohibited. However, the AIA does not define "human organism". There is unfortunately no way of predicting how the courts will interpret these words. In particular, if, in the future, courts construes "human stem cells" as being a kind of "human organism", stem cells would be patent ineligible.

New court decisions in the last ten years have however seriously restricted the scope of patent eligibility in the U.S.

In Association for Molecular Pathology v. Myriad Genetics, Inc. (2013)[4], hereafter referred to as the Myriad decision, the Supreme Court ruled that DNA isolated from nature was patent ineligible, while at the same time deciding that cDNA was patent eligible. The court's rationale, though, was particularly worrisome with regard to patenting natural products. This rationale was that "mere" isolation of a portion of human DNA (a "gene") from a chromosome was not enough to render the isolated DNA patent eligible. There has to be "something more", in accordance with another Supreme Court decision, this time involving diagnostic method claims, Mayo Collaborative Services v. Prometheus Laboratories[5], which has been interpreted to mean a structural difference.

This strongly suggests that all products — nucleic acids, proteins, cells, etc. — which are not significantly different from a product of nature might be patent-ineligible. For example, it is because the claimed clone did not present any difference with the organism that they were derived from that the Federal Circuit found that claims directed to Dolly the sheep were not patent eligible[6]. Genetically engineered or otherwise modified cells likely remain patent eligible under Myriad. However, other types of cells used in cell-based therapies (e.g., hematopoietic cells, embryonic and adult stem cells, and products of such cells such as dermal sheets used to treat burn victims) are clearly at risk with regard to whether patent protection is or will be available.

On the other hand, process patents are less likely to be patent-ineligible laws of nature. In Rapid Litigation Management v. Cellzdirect, Inc., the claims were directed to a method of preparation of hepatocytes. The court reasoned that these claims differed from patent-ineligible law of nature claims because they did more than just observe the law of nature — they are directed to a new method of better preserving hepatocyte cells. In addition, the steps of that method were not "routine or conventional" in relation to the prior art. In its holding, the court repeatedly emphasized that these claims were eligible because they claimed a

[3]AIA, Pub. L. 112-29, sec. 33(a), 125 Stat. 284
[4]Association for Molecular Pathologists v. Myriad Genetics, 133 S. Ct. 2107 (2013)
[5]Mayo Collaborative Services v. Prometheus Laboratories Inc., 132 S. Ct. 1289(2012).
[6]In re Roslin Institute, 750 F.3d 1333 (Fed. Cir. 2014)

method or process, and the result may have been different if the claims only covered the frozen hepatocyte product.

Over the last five years, the United States has significantly narrowed the scope of patent-eligible subject matter in the field of biotechnology. Subject matter that was previously considered patentable may now be rejected as unpatentable. Even though the Supreme Court has not classified stem cells as patent-ineligible subject matter, the worry that stem cells may be so classified is on many investors' minds.

Patentability of hESCs in Europe

Nothing is ever simple in Europe. When considering patent law, three overlapping layers of jurisdiction coexist and must be taken into account. A first level is provided by the European Patent Convention ("EPC"), an international treaty signed in 1973. The EPC created the European Patent Office ("EPO") and also created the substantive law as to what is patentable in the member states. The provisions of the EPC are interpreted by the Boards of Appeal, the judicial instances of the EPO. It is important to note that the EPC is distinct from the EU. Indeed, a second level of jurisdiction relevant for patentability of stem cells is constituted by the European Union ("EU"). The EU is an important source of legislation in Europe, both direct (directives and regulations) and indirect, through the case law of the Court of Justice of the European Union ("CJEU"). Finally, national patent laws and their interpretation by the national patent organisations and national courts add another layer of complexity. Notably, national patent laws must be compatible with the EPC whilst respecting the EU legislation.

The discussion of the legal protection of biotech inventions, including stem cells, originated in the EU. The result was eventually the Directive 98/44/EC of 6 July 1198, widely known as the Biotech Directive. This directive defines the legal basis for protection of all biotechnological inventions, including stem cells. Firstly, the recitals state that a mere discovery cannot be patented. Secondly, however, articles 3 and 5 open the doors for patenting isolated biological matter or human body elements, even if their structure is identical to a structure occurring in nature. The principles of patenting stem cells and gene sequences are regulated in Article 6 of the Biotech Directive. This article prohibits patenting inventions that use the human embryo for industrial or commercial purposes, as their commercial exploitations would be contrary to ordre public or morality.

The EPO, which as previously noted is separate from the EU, was under no obligation to make any legislative adaptation of its own. Yet the EPO's Administrative Council nevertheless decided in 1999 to adapt the Implementing Regulations to the EPC (the EPC Rules), in view of the large overlap between EU member states and EPC contracting states. It thus incorporated the criteria and definitions set out in the Biotech Directive into the European Patent Convention (EPC) Implementing Regulations (Rules 26 to 29) and Guidelines for Examination (Part G, II.5.2). According to Rule 28(c) of the EPC Implementing Regulations (corresponding to Article 6(2)(c) of the Biotech Directive), European patents cannot be granted to inventions that use human embryos for industrial or commercial purposes. This provision must be read in conjunction with Article 53 (a) of the EPC which states that, if the commercial exploitation of the invention is contrary to ordre public or morality, it is excluded from patenting. In other words, the prohibition of inventions using human embryos for industrial or commercial purpose is based on morality which strongly suggested that it would be a blanket interdiction.

Decision G 2/06 (November 2008) of the Enlarged Board of Appeal of the EPO was based on an application relating to a cell culture comprising primate embryonic stem (ES) cells. The board held that subject matter relating to products (i.e., stem cells) which on the filing date can be exclusively prepared by methods necessarily involving the destruction of human embryos from which said products are derived is not patentable under the EPC. Technical developments after the filing date are irrelevant. Importantly, this applies even if the destructive method is not explicitly part of the claims. In other words, the application must be taken as a whole for this assessment

A few years after G 2/06, a similar case was heard by the CJUE. The patent at stake was directed

to methods maintaining hESCs in culture in an undifferentiated state, as well as a cell culture comprising hESCs. In this case (C-34/10; Oliver Brüstle v Greenpeace e.V.), the Luxembourg judges had to consider for the first time the term 'uses of human embryos for industrial or commercial purposes' within the meaning of Article 6(2)(c) of the Biotech Directive.

The CJUE decided that according to the Biotech Directive, inventions are excluded from patentability where the technical teaching that is the subject-matter of the application 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. Therefore, it is not possible to isolate the subject-matter of the patent from the prior destruction of the embryo, even if the link between both is not immediate. The decision of the CJEU appears to be in line with G 2/06, as it confirms that an invention is excluded from patentability where the technical teaching which is the subject matter of the patent application requires the prior destruction of human embryos or their use as a base material.

In the same decision, the Court had to interpret the term 'embryo', since it is nowhere defined in the Biotech Directive. The CJUE opined that the term 'embryo' had to be widely interpreted. This term should encompass all stages of human development after fertilisation of a human egg, as well as cells "capable of commencing the process of development of a human being".

This immediately provoked an outcry. It was argued that such a broad definition would permanently stifle European stem cell research, since it is well known that the possibility of obtaining a patent in a technical area has a significant impact on whether and how research organisations move into an area. Moreover, the decision was criticised on scientific grounds as seemingly including pseudo-fertilised eggs, or parthenotes, in the definition of 'embryo, when, in reality, these cells do not develop in the same way as normal embryos; nor are they developmentally viable if made without nuclear transplant.

This last point was corrected in a later decision (C-364/13; International Stem Cell Corporation v. Comptroller General of Patents) wherein, contrary to the previous decision, the court held that an unfertilised human egg whose division and further development has been stimulated by parental genesis does not constitute a 'human embryo' within the meaning of the Biotech Directive. In light of current scientific knowledge, it does not, in itself, have the inherent capacity to develop into a human being. Consequently, the term 'embryo' covers only cells that have the capacity to develop into a human being and parthenotes-based inventions may be patentable in Europe.

A question immediately arising from the decisions relates to the "relevant" date of the invention. Both G 2/06 and Brüstle (in combination with ISCC) prohibit patenting inventions involving the destruction of an embryo. To establish whether cells are obtained by the destructive use of a human embryo, one has to take into consideration not only the teaching of the application, but also «the state of the art at the filing date». It is therefore necessary to determine the point in time when new technology for obtaining hESC lines without destroying embryos rendered such practices more flexible.

In T 1441/13 the Board of Appeal concluded that at the 2001 filing date of the patent in suit, the known and practised method for achieving cultures of human ES cells (i.e., the starting material of the claimed method) necessarily included preceding steps that involved the destruction of human embryos. Another source of pluripotent cells was not specified in the application. According to the evidence before the board, the first public disclosure of a method by which human embryonic stem cells could be obtained without destroying a human embryo was published in January 2008.

This date was further pushed back in time in T 385/14. The claimed method involved using an in vitro differentiated cardiomyocyte with the proviso that this cell was not derived from a human embryonic stem cell. The board, referring explicitly to Brüstle and ISCC, found that, at the priority date (May 2004), it was possible to derive hESCs from parthenotes since a protocol had already

been made available by the publication of a patent application[7] on 5 June 2003.

Another important question raised by G 2/06 and Brüstle (in combination with ISCC) relates to the identity of the person 'destroying the embryo'. In particular, one could ask whether the exemption would apply only when the embryo was destroyed (so to speak) by the person seeking or owning a patent.

However, in T 2221/10, the competent EPO board of appeal answered negatively to that question. This case was based on an application relating to methods for maintaining hESCs in culture in an undifferentiated state by the addition of certain human foreskin cells, as well as a cell culture comprising hESCs. The claim thus did not require the destruction of a human embryo. The board considered that if such hESCs were derived from human embryos that had been destroyed, it was irrelevant how early in the performance of the invention such destruction occurred. The board thus held that Article 53(a) and Rule 28(c) EPC do not merely exclude the patentability of biotechnological inventions that make use of human embryonic stem cells obtained by de novo destruction of human embryos, but also apply to inventions which employ publicly available cell lines which were initially derived by a process resulting in the destruction of human embryos.

The law that governs the patentability of stem cell technologies in Europe is thus complex, at least insofar as the stem cells are embryonic in origin. It has a convoluted genesis and is overlaid with case law from the CJEU, the EPO, and national courts, not all of which have historically taken the same approach, although the CJEU and EPO now appear to be aligning.

Patentability of hESCs in China

As in Europe, some inventions in China's patent law are exempted from patentability on ordre public and morality grounds. In China, ethical concerns about embryos mainly emerge in areas of human cloning and the destruction of human genetic consistency. Hence, ethical and moral restrictions placed on human embryos in China have restrained the regulation and practice of hESCs patentability.

Article 5(1) of China's Patent Law (CPL) provides that "[n]o patent shall be granted for an invention that contravenes any law or social morality or that is detrimental to public interests."

Whether an invention contravenes social morality is subject to preliminary examination under China's Patent Law. Article 5(1) also provides a basis for rejecting a Chinese patent application during substantive examination, and for invalidating a Chinese patent claim. Therefore, passing the preliminary examination or even obtaining an issued patent is no guarantee that China National Intellectual Property Administration (CNIPA) will not come back to reject a patent application or invalidate an issued patent for contravention of social morality.

This provision was originally interpreted very strictly, so that both "utilisation of human embryos for industrial or commercial purposes" and utilisation of human embryos for the purpose of treatment or diagnosis and are beneficial to human embryos were considered to be patent-ineligible. Over time these restrictions relaxed. In particular, in 2015, it was determined that human cells without developmental totipotency were not embryos and, as such, were not excluded from patentability.

In addition to the CPL and Implementing Regulations thereof, the Guidelines for Patent Examination (GPE) are crucial in the practice of patent review as a specific standard for patent applications and requests in accordance with the other two regulations. The GPE were reviewed in 2020, with in particular the introduction of a specific provision forbidding patentability of inventions directed to the use of embryos for commercial or industrial purposes. On the other hand, hESCs are now explicitly defined as not reflecting a stage of human development. This means that there exists no blanket prohibition of patenting hESCs and methods for preparing them.

Unlike in the United States, where patent eligibility or the lack thereof is frequently the subject of heated legal battles and often subject to judicially crafted tests, China's primary approach to this issue has been administrative. Even though the GPE supposedly only binds patent examiners, it is unlikely that Chinese courts will take a different position from that of the GPE.

[7] WO 2003/046141

Conclusion

Cell-based therapy is a rapidly-growing field of clinical research, sustained by substantial global investment. Strong patent protection is essential for investors. However, recent legislative and jurisprudential developments have converged towards limitations of patent eligibility of cell-based therapy-related inventions, notably hESCs, around the world.

In the US, the AIA and recent Supreme Court decisions have casted doubt on the patentability of hESCSs and other cell products identical to natural products. In Europe, the Biotech Directive and its application by courts of both the EU and the EPO has excluded patentability for hESCs on a morality basis. In China, strict interpretation of the morality clause led to severe restrictions on human cell patentability; however, CNIPA has since re-adjusted its construction of the provision, reaching a position more akin to Europe.

While many worry that unduly restrictive patents will hinder innovation, the long-term effect is not clear cut. However, the harmonisation of the concept of patentability-excluded subject-matter in relation to cell therapy in the major markets may bring a level of stability most welcome by investors.

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