Human stem cells patents-Emerging issues and challenges in Europe, United States, China, and Japan

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Abstract

Stem cell technology is undergoing a rapid development for its high potential in versatile therapeutic applications. Patent protection is a vital factor affecting the development and commercial success of life sciences inventions; yet human stem cells-based inventions have been encountering significant restrictions particularly in the perspective of patentable subject matters. This article looks into the patentability limits and unique challenges for human stem cells-based patents in four regions: Europe, the United States, China and Japan. We will also provide suggestions for addressing the emerging issues in each region.

Introduction

Stem cell technology is an eye-catching and fast-growing research area with huge therapeutic potential. Human stem cells in particular are the focus of much interest in research, and much hope and hype surrounds their clinical therapy potential. However, ethical considerations and regulatory restrictions over human stem cells have framed the development of regenerative medicine and drug discovery. While the legal protection of life sciences inventions via patents has been recognized for years, it continuously raises challenges worldwide. It is especially true regarding patents based on human stem cells, particularly human Embryonic Stem Cells (hESCs). For instance, the recent Courts' decisions regarding the restriction of patents based on hESCs in Europe and the exclusion of natural products in the United States have undoubtedly hampered the patent protection for many human stem cells products. On the other hand, methods for the treatment or diagnosis of diseases practiced on human are generally not patentable in most major jurisdictions. While it is difficult to have a clear idea of how the patentability limits are affecting the human stem cells markets, it is obvious that developers of stem cells-based products or processes, whether they be academics or companies, have to adapt their research and commercial strategies to the scopes of patentability. Looking into the context of in-force patent laws, rules, regulations and relevant court decisions, this paper looks into the emerging issues in the patentability of inventions based on human stem cells in four regions: Europe, the United States (U.S.), China and Japan which have the majority of patents applications (World Intellectual Property Organization, 2015, p. 23). However, this article does not cover the patentability of human stem cells under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement (World Trade Organization, 1994),

even though the U.S., China, Japan, all Member States of the European Union (EU) as well as the EU itself are contracting parties to the TRIPS agreement. It should be noted that, despite each region has its unique patent system imposing various patentability requirements, most countries build their patentability framework around five limbs of patentability; namely patentable subject matter, novelty, inventiveness, written description and enablement. This article does not only discuss these requirements and their standard in each of the four jurisdictions as far as stem cells are concerned. More importantly, the authors aim to provide an overview of the patent framework and exclusions of patentability in the four jurisdictions, and highlight the unique challenges for human stem cells-based patents in each region. We will also provide suggestions for overcoming these obstacles and adapting the changing landscape. Last but not least, specific aspects of the four patent systems are compared to provide a glimpse of global protection for stem cell inventions.

I - Europe

A) Background

In Europe, patent law is relatively uniform although in addition to each State, two different organizations are regulating the field: the European Patent Organization (EPO) and the European Union (EU).

The European Patent Organization covers 28 Member States of the EU and 10 non-EU countries.[1] It is based on the European Patent Convention (EPC), a multilateral Treaty signed in Munich on October 5, 1973. The EPO is mainly in charge of granting European patents. Its organizational structure notably includes 28 independent Technical Boards of Appeal that can refer to the Enlarged Board of Appeal to ensure a uniform application of the law. A European patent confers protection in all the contracting States that have been designated by the applicant as long as it has been validated by their national patent offices.

The European Union regulates stem cells patents on the basis of the Directive on the legal protection of biotechnological inventions of July 6, 1998 (European Parliament and Council, 1998). The Directive harmonizes national patent laws: it has been transposed in every EU Member States and it is applied by their national patent offices. Contrary to the EPO that has been established to regulate patents only, the EU competency goes beyond patentability. Thus, it has not had a specific court for patents disputes and these matters have fallen under the remit of the general Court of Justice of the European Union. However, in 2012, the Member States of the EU (except Spain, Poland and Croatia) decided to establish an enhanced cooperation and to adopt the so-called “patent package”. It includes a regulation creating a European patent with unitary effect (hereafter the “unitary patent”) (European Parliament and Council, 2012), a regulation on the language regime applicable to the unitary patent (European Council, 2012) as well as an agreement between the EU countries to set up a specialized Unified Patent Court (European Council, 2013). This “patent package” will enter into force once ratified by any thirteen Member States including France, Germany and the United Kingdom (UK).[2] However, following the UK’s vote to exit the EU, a minima new delay could be expected for such entry into force (Grubb *et al.,*

2016; Jaeger, 2017). Besides already existing national patents (regulated by national laws that have been harmonized by the European Directive 98/44/EC) and the classical European patents (regulated by the EPC), the unitary patent will be a third option. Granted by the EPO under the provisions of the EPC, a unitary patent will be a European patent to which a unitary effect for the territories of the participating States will be given, at the patentee's request, after grant.

Finally, it should be highlighted that even though the EPO and the EU are two distinct organizations, the contracting States of the former decided to incorporate the Directive 98/44/EC as secondary legislation into the Implementing Regulations to the EPC. This directive is used as a supplementary means of interpretation of the EPC since 1999. Thus, there is a trend for a global "uniformization" of European patents laws in the field of biotechnological inventions although a European patent relied on the EPC framework and a national patent relied on both the Directive 98/44/EC and on national law implementing it. While the articulation between the different kinds of patents, notably with the future unitary patent, and patent laws in Europe are raising lots of concern (Kaesling, 2013; Kaisi, 2014; Mahne, 2012; Pila and Wadlow, 2014; Plomer, 2015), what is going beyond the patentability of inventions based on human stem cells is not considered in this article.

In Europe, there are four basic criteria for patentability.[3] First, there must be an invention belonging to any field of technology that is both a technical and concrete character. Second, the invention must be susceptible of industrial application, i.e. it can be made or used in any kind of industry as any physical activity of "technical character". Third, it must be new, not forming part of the state of the art. In the absence of grace period[4], the invention must not have been made available to the public before the date of filing of the patent application. Fourth, it must involve an inventive step, such that it is not obvious to a person skilled in the art. Finally, the "sufficient disclosure" requirement implies that the full scope of a claim must be adequately enabled by disclosing methods of practicing the invention in the specification (Marty *et al.,* 2014). It should be highlighted there is not a clear distinction between "enablement" and "clear written description" but both account for patentability in Europe (Schuster, 2007).

B) The exclusions of patentability

In Europe two types of exclusions could be distinguished: "moral exclusions" and "ineligible subject matters".

Moral exclusions

European patent law provides "moral exceptions" (Min, 2012) from patentability; that is, patents are not granted where the commercial exploitation of the inventions is contrary to *ordre public* or morality, beyond the straightforward prohibition by law or regulation.[5]

Regarding the exclusions specific to the patentability of biotechnological inventions, the wording of the EPC and of the Directive 98/44/EC is the same. On one hand, "the human body, at the various stages of its formation and development, and

the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions."[6] However, it is specified, "an element isolated from the human body or otherwise produced by means of a technical process,[7] including the sequence or partial sequence of a gene,[8] may constitute a patentable invention, even if the structure of that element is identical to that of a natural element."[9] Similarly, a microbiological or other technical process, or a product obtained by means of such process can be patented.[10] On the other hand, European patent law provides a non-exhaustive list of inventions of which the commercial exploitation is contrary to "*ordre public*" or morality: processes for cloning human beings; processes for modifying the germ line genetic identity of human beings; and uses of human embryos for industrial or commercial purposes.[11]

Ineligible subject matters

Article 52 (2) of the EPC provides general exclusions that are not specific to biotechnological inventions: (a) discoveries, scientific theories and mathematical methods; (b) aesthetic creations; (c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers; (d) presentations of information. Moreover, and apart from plant or animal varieties that are not covered in this article, European patent law also excludes "methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body"; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.[12]

C) Main challenges for stem cells patents

Exclusion of the uses of human embryos for industrial or commercial purposes

In Europe, the main challenge to stem cells patents is related to embryonic stem cells and to the moral exclusions provided both by the Directive 98/44/EC and the EPC, especially the uses of human embryos for industrial or commercial purposes. Interpreted by the EPO and the European Court of Justice of the European Union, such disposal has been aligned to exclude from patentability inventions using human embryonic stem cells (hESCs) obtained either by *de novo* destruction of human embryos, or from publicly available hESC lines initially derived by a process destroying the human embryo (Mahalatchimy *et al*., 2015a; Mahalatchimy *et al*., 2015b). First, on November 25, 2008 in the *Wisconsin Alumni Research Foundation* case, the enlarged board of the European Patent Office decided that European patents with "claims directed to products which-as described in the application could be prepared, at the filing date, exclusively by a method which necessarily involved the destruction of human embryos" are prohibited.[13] Second, the Court of Justice of the European Union has gone a step further in the exclusion with the *Brüstle v Greenpeace eV* (hereafter the *Brüstle*) case.[14] On the hand, it has provided a wide definition of the human embryo: any human ovum after fertilization, and any non-fertilized human ovum into which the cell nucleus from a mature human cell has been transplanted or whose division and further development have been stimulated by parthenogenesis. However, the European Court of Justice of the European Union

recently came back to its definition of the human embryo to allow the patentability of inventions using embryonic stem cells made from 'parthenotes' egg (Baeyens and Goffin, 2015; Bonadio and Rovati, 2015; Kirwin, 2015; Mansnérus, 2015; Stazi, 2015). Henceforth, "an unfertilized human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo', (…) if, in the light of current scientific knowledge, it does not, in itself, have the inherent capacity of developing into a human being, this being a matter for the national court to determine."[15] (Faeh, 2015; Ribbons and Lynch, 2014)

On the other hand, the *Brüstle* case has given an extensive interpretation of the patent's exclusion for uses of human embryos for commercial or industrial purposes: an invention is excluded from patentability where it involved the prior destruction of human embryos or their use as base material. It occurs whatever the stage at which such destruction takes place and even if the claim does not refer to the use of human embryos. The *Brüstle* case has been widely commented both by scientists (Wilmut, 2011; Koch *et al*, 2011; Vrtovec and Scott, 2011) and lawyers (Bonadio, 2012; Davies and Denoon, 2011; Plomer, 2012). Third, on February 4, 2014 in the *Technion Research and Development Foundation* Case, the European Patent Office followed the *Brüstle* case excluding from patentability inventions using hESCs obtained by destruction of human embryos, whenever such destruction takes place.

Exclusion of surgery, therapy and diagnostic methods

Even though methods for the treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body are excluded from patentability in accordance with the EPC, such exclusion has been limited (Ventose, 2010). First, it does not cover products used in such methods (European Patent Office, 2015). Second, clarifications have been provided regarding the interpretations to be given to "treatments by surgery" and "treatment and diagnostic methods".

For surgery, the EPO clarified that "treatments by surgery" are not confined to surgical methods pursuing a therapeutic purpose.[16] Consequently, beyond surgical treatment for therapeutic purposes, methods of treatment by surgery for embryo transfer or for cosmetic purposes are also excluded from patentability.

As for treatment and diagnostic methods, exclusions are generally limited to those that are carried out on living human (or animal) bodies. Thus, where these treatment or diagnostic methods are carried out on dead bodies, they are not excluded from patentability. Similarly, they are not excluded from patentability if they are carried out *in vitro*, i.e. on tissues or fluids that have been removed from living bodies, as long as they are not returned to the same body.[17]

Further, as in China and Japan, the aim of the methods is determining to their patent eligibility. Methods of treatment of living human beings or animals such as pure cosmetic treatment of a human by administration of a chemical product [18] or methods of measuring or recording characteristics of the human or animal body are patentable, where they are of a technical and not essentially biological character.[19]

Perspectives

European patent law excludes from patentability products and processes based on hESCs obtained by the destruction of human embryos, whenever such destruction takes place. According to the interpretation of the European Courts, this exclusion is not restricted to *de novo* destruction of human embryos and covers the use of publicly available hESC lines initially derived by a process destroying human embryos (Mahalatchimy *et al*., 2015a). This wide interpretation and the extensive definition given to the "human embryo" imply that no patent could be obtained on inventions based on human hESCs in Europe. However, several elements are limiting or could limit such broad exclusion.

First, divergences have appeared in the national implementations of the *Brüstle* case regarding the proofs of hESCs via methods that do not involve the destruction of human embryos (Mahalatchimy, 2014). The EPO and the UK patent office have considered the inventor should prove that hESCs have been obtained by other methods than the destruction of human embryos.[20] On opposite, the German Federal Court has considered it is not required to be proved.[21] Consequently, a general claim of non-destruction of human embryos would be sufficient to obtain a patent for an invention based on hESCs as long as other criteria are satisfied. On the basis of such wide interpretation, it may be easier to obtain a patent for an invention based on hESCs than in other countries having a stricter interpretation of the *Brüstle* case as long as the Court of Justice of the European Union has not clarified such question.

Second, the *International Stem Cell Corporation case law*[22] of the Court of Justice of the European Union which is generally seen as a clarification of European patent law on ESCs (Moore and Wells, 2015) is nevertheless questionable (Norberg and Minseen, 2016): should it be considered as an exception to the *Brüstle* case or as an opening to a wider reversal of jurisprudence of the Court of Justice of the European Union? Indeed, parthenotes are not considered anymore to be human embryos and consequently not excluded as long as they do not have the inherent capacity of developing into a human being. However, one can expect other techniques (that were previously interpreted as given rise to human embryos in the *Brüstle* case) could be claimed as not having the inherent capacity of developing into a human being. For instance, it could be considered that hESCs obtained by somatic cell nuclear transfer would need to be implanted in utero (although it is forbidden in accordance with the prohibition of human cloning) to have the capacity to develop into a human being. The same could be claimed for induced pluripotent stem cells (iPSCs) even though they have not been mentioned in these cases of the European Courts and they have not been included in the wide definition of human embryos. It seems the *International Stem Cell Corporation case law* should be seen as a clarification that narrows the extent of the exclusion from patentability of the uses of human embryos for industrial or commercial purposes. Indeed, the European Commission has been recommended to take no further action for clarification following the recent jurisprudence by most of the members of the Expert Group on the development and implications of patent law in the field of biotechnology and genetic engineering (Expert Group on the development and implications of patent law

in the field of biotechnology and genetic engineering of the European Commission, 2016).

Beyond hESCs, patents could be obtained on products and manufacturing methods based on allogeneic stem cells. However, for autologous cell-based regenerative therapies that are based on the patient's own cells (the donor of the cells is also the recipient of the final product made from these cells), it is not the product that is manufactured at the industrial scale (the product is patient specific as autologous); it can only be the manufacturing process industrially applicable.

Moreover, treatment processes that generally occur by surgery in the field of cell therapy are excluded from patentability under the exclusion of surgery, therapy and diagnostic methods. Consequently, treatment methods based on stem cells would not be patentable.

Thus, although European patent law is relatively uniform, national divergences remain in the interpretation of the most recent jurisprudence on stem cells and new issues need to be solved regarding the future unitary patent, especially on the implementation of the moral exclusions by both the Court of Justice of the European Union and Unified Patent Court (Aerts, 2014; McMahon, 2017).

Inventiveness

The inventive step criterion might be a hurdle in stem cell patenting. Inventions are opposed to mere discoveries that are not patentable. Indeed discoveries as such have no technical effect and are therefore not inventions in accordance with European patent laws.[23] Moreover, it should be noted that in Europe, secondary indicators such as an unexpected technical effect or a long-felt need may be regarded as indications of inventiveness. However, commercial success alone is not to be regarded as an indication of inventive step, except when coupled with evidence of a long-felt want provided that "the success derives from the technical features of the invention and not from other influences (e.g. selling techniques or advertising)".[24] The author will discuss this requirement in details in the following U.S. session for its seemingly higher standard than the other three regions.

II - United States

A) Background

The United States Patent and Trademark Office (USPTO) is responsible for examining and granting patents under the U.S. Patent Law (Title 35 of United States Code, 35 U.S.C.) and Rules (Title 37 of Code of Federal Regulations, 37 C.F.R.). A utility patent is granted for any "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof".[25]

An invention must be useful[26], new[27] and non-obvious[28] to be patentable in the United States. Moreover, the invention must have a specific and substantial utility that one skilled in the art would find credible.[29] Further, the statute mandates that an invention shall be fully described and enabled by the specification;[30] and that the specification must disclose the best mode of making and practicing the invention as the inventors contemplate, although it is not necessary to point out the best mode

embodiment.[31,32] Notably, the written description requirement is separate and distinct from the enablement requirement. The former requires that an invention shall be adequately described to show possession of the invention whereas the enablement requirement is satisfied where a person skilled in the art can make and use the claimed invention without undue experimentation. More specifically, the specification should disclose at least one method for making and using the claimed invention.[33] Unlike the mainstream absolute novelty standard, the U.S. offers a one-year grace period for inventors to file a patent application after disclosure of the invention.[34]

B) The exclusions of patentability

One notable feature which imparts a significant difference between U.S. and the other three regions is that U.S. patent law does not impose any moral consideration in determining whether a subject matter should be excluded from patent protection. Laws of nature, natural phenomena and abstract ideas have been historically excluded from the U.S. patent protection (Lesser, 2016).[35] Living organisms including animals, plants and microorganisms are all patent-eligible[36] but patents directed to or encompassing a human organism including a human embryo and a fetus are prohibited.[37]

The U.S. has issued a wide range of stem cell patents from products (e.g. hESCs, iPSCs and regenerated tissues) to methods (e.g. manufacturing processes and therapeutic applications). However, the patent eligibility landscape changed dramatically in the past few years in light of several Supreme Court decisions *Mayo* in 2012,[38] *Myriad* in 2013[39]and *Alice* in 2014.[40] *Mayo* and *Myriad* respectively touched on claims involving the natural correlation between metabolite levels and drug effectiveness/toxicity and claims for human genes. They have significantly expanded the scope of exclusion to many biotech and pharmaceutical inventions.

Very briefly, *Mayo* invalidated diagnostic claims that determine whether a particular dosage of a drug is ineffective or harmful to a subject based on the level of metabolites in the subject's blood.[41] Two physical steps were recited in the claim, namely a step of administering the drug to a subject and a step of determining the level of a specific metabolite in the subject. However, the Court regarded these steps as "well-understood, routine and conventional" activities which researchers are already engaged in the field to apply the natural correlation and hence the claim as a whole does not amount to "significantly more" than the natural law itself (Dutra, 2012; Chan *et al.*, 2014; Selness, 2017).

Myriad held that an isolated nucleic acid having sequence identical to a breast cancer-susceptible gene BRCA is not patent-eligible because it is a product of nature; whereas a complementary DNA (cDNA) having non-coding introns of the gene removed is eligible because the cDNA is not naturally-occurring and distinct from the natural gene.[42] Following the precedent ruling in *Charkrabarty* that upheld the patentability of a genetically engineered microorganism,[43] the Court looked for "markedly different characteristics from any found in nature" of the isolated gene to determine patent eligibility. The Court noted: "separating [the] gene from its surrounding genetic material is not an act of invention".[44] (Chan *et al.*, 2014) Even if

the claimed DNA molecules are somehow different from the genes in the genome in terms of chemical structure, the Court gave no deference to that because the claims were not relying on the chemical aspect of the DNA but the genetic information of the DNA that was neither created nor altered by the patentee. On the face of *Myriad*, isolated products such as chemicals, genes, proteins and even cells have to be different from the natural substances to a certain extent to be patent-eligible (Wong and Chan, 2014; Chan *et al.*, 2014).

Alice concerns abstract ideas and adopted the *Mayo* framework, ruled that "[t]he mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into patent-eligible invention", and that claims directed to an abstract idea is ineligible when the computer or software feature adds nothing more than generic or conventional functions to the invention.[45] *Alice* has a dramatic impact on inventions related to software or business methods (Stern, 2014; Jesse, 2014; Ford, 2016).

New criteria for eligibility

Evolving with the development of Court cases, the USPTO successively issued four guidelines during 2012-2014 for Examiners on how to apply *Mayo*, *Myriad*, *Alice* and other precedent cases to examine eligibility of claims related to natural phenomenon, laws of nature or abstract ideas. The in-effect guideline was released on December 16, 2014 (United States Patent and Trademark Office, 2014a), and supplemented by two updates (United States Patent and Trademark Office, 2015; United States Patent and Trademark Office, 2016a).

For natural products, eligibility is determined principally on whether the claimed product possesses any structural, functional and/or other properties that represent "markedly different characteristics" from the natural counterparts. Importantly, neither innate characteristics of the natural product nor characteristics resulted irrespective of inventor's intervention qualify as "markedly different characteristics" (United States Patent and Trademark Office, 2016a).[46,47] A combination of natural products is examined as a whole rather than as individual components (United States Patent and Trademark Office, 2014a).

While for claim which sets forth or describes an exception (in contrast to "is based on" or "involves" an exception), the claims must contain additional elements that "add significantly more" to the exception such that it is "more than a drafting effort designed to monopolize the exception" (United States Patent and Trademark Office, 2014a). General applications of natural products or natural laws employing well-understood, routine and conventional activities known in the field are not patent-eligible (United States Patent and Trademark Office, 2014a). For example, a process claim is eligible if it is focused on a process of practically applying the product for treating a particular disease that does not seek to tie up the natural product (United States Patent and Trademark Office, 2014b).

Most patents invalidated after *Mayo*, *Myriad* and *Alice* have been business method or software-related inventions. Among these patents, *Ariosa* is a notable case in which the decision has sparked intense debates and worries in the field of biotechnology, and more specifically molecular diagnosis. In *Ariosa*, the Federal

Circuit upheld the invalidation of a patent for a method of detecting cell-free fetal DNA (cffDNA) in maternal serum or plasma under the *Mayo* framework.[48] Despite the Court acknowledged that the discovery of the presence of cffDNA in maternal plasma or serum was new and useful, it recognized that the steps of amplifying and detecting cffDNA with methods such as Polymerase Chain Reaction (PCR) are well-understood, routine and conventional activities in 1997; and the claimed method amounts to a general instruction to doctors to apply routine and conventional techniques to detect cffDNA and hence is not eligible for patent. The Court also noted that "preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility", meaning that a claim is not eligible merely for not blocking all other alternative uses of the natural product or law. In March 2016, Sequenom filed a Petition for Writ of Certiorari in the Supreme Court to challenge the Federal Court's decision in *Ariosa*; however, the highest Court declined to review and thus the *Ariosa* decision is finalized (Selness, 2017). [49]

The disfavorable disposition was slightly relieved in *Rapid Litigation Management*,[50] in which the Federal Circuit, for the first time since the decisions in *Mayo* and *Alice*, upheld a patent that was drawn to a law of nature. In *Rapid Litigation Management*, the inventors of the concerned patent developed an improved method of preserving hepatocytes upon repeated steps of freezing and thawing. The claims at issue were drawn to a method of preparing multi-cryopreserved hepatocytes of which the resulting hepatocytes are capable of being frozen and thawed at least two times and exhibit 70% viability after the final thaw. The Federal Court found the claims patent-eligible because they were not directed to the ability of hepatocytes to survive multiple freeze-thaw cycles but a new and useful laboratory technique for preserving hepatocytes, noting that the inventors "employed their natural discovery to create a new and improved way of preserving hepatocyte cells for later use".[51] Although individual steps of freezing and thawing were well known, the Court recognized that at the time of the invention, it was believed that a single round of freezing severely damaged hepatocyte cells and resulted in lower cell viability and therefore the prior art actually taught away from multiple freeze-thaw cycles. As such, the Court concluded that the claimed method which "[r]epeating a step that the art taught should be performed only once can hardly be considered routine or conventional".[52]

Specifically, the Court looked into whether the end result of the method was directed to a patent-ineligible concept. The Court said no because the end result was "not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles"; rather, the claims recited a number of steps that manipulate the hepatocytes in accordance with their ability to survive multiple freeze-thaw cycles to achieve the "desired preparation".[53] (Sanzo, 2017; United States Patent and Trademark Office, 2016b)

<u>More §101 rejections</u>

Impacts of *Myriad* and *Mayo* to the biotech and pharmaceutical industries are far-reaching and tremendous. At the USPTO in the service responsible for biotechnology and organic chemistry (i.e., Patent Technology Centre 1600), it was estimated that the

percentage of Office Actions with a U.S.C. §101 rejection regarding ineligible subject matters in May 2015 increased by nearly two folds than two months before the March 2012 *Mayo* decision (11.86% vs 6.81%) (Sachs, 2015). Patent Technology Centre 1630 designated for molecular biology and nucleic acids related inventions was profoundly affected, having the §101 rejection rate boosted from 16.8% to 52.3% (Sachs, 2015).

The total rejection rate in Technology Centre 1600 was rising from 10.4% before *Alice* to 13.1% in December 2015, followed by a notable drop to 10.9% in July 2016 and 10.0% in May 2016 (Sachs, 2016). While it is too early to conclude that the situation becomes less adverse to the patentees, it may signal that the stringent situation has started to relax while uncertainties remain (Leung, 2015).

C) Main challenges for stem cells patents

Major hurdles in stem cell patenting are the expanded scope of ineligible subject matters and obviousness rejections.

Patent eligibility

Product claims

Usefulness of patents is limited if the patented inventions cannot be commercialized. The applicant has to resolve the dilemma: non-native features would weigh toward the eligibility of stem cells already existing in nature, however stem cells for medicinal uses should be native enough to be as safe and effective as the natural stem cells.

Myriad held that purification or isolation is not an act of invention. Stem cells, be they ESCs or adult stem cells, or produced by a new, ground-breaking method, are not patentable absent any distinctive structural, functional or other properties from the natural cells in our body.[54] iPSCs obtained using exogenous genes are more likely to survive for their artificial nature; however, iPSCs that are produced otherwise may be ineligible if the cells are indistinguishable from a naturally-occurring stem cells except the production method. On the opposite, regenerated tissues and organs would typically be patentable because they are usually not exactly the same as the actual tissues and organs (Tran, 2015).

Intrinsic properties of stem cells add no weight to the eligibility, hence stem cells identified by natural biomarkers are likely to be construed as a product of nature and deemed not patentable. In contrast, new traits resulted from inventor's efforts such as extended lifespan, higher self-renewal ability and expression of new biomarkers may open up patentability for isolated stem cells. For example, U.S. Patent 9,175,264 claims an isolated population of human postnatal deciduous dental pulp multipotent stem cells expanded *ex vivo*. This application was initially rejected under U.S.C. §101 because the Examiner opined that the claimed cell is a product of nature; but was later allowed after the applicant limited the cell to express CD146 that is absent in the natural counterpart. [55]

Lastly, it is worth noting that a product-by-process claim is examined based on the product itself not the manufacturing process, hence stem cells pursued under a

product-by-process claim still need to abide on the "markedly different characteristics" requirement for natural products (United States Patent and Trademark Office, 2014a).

Method claims

Method claims may be more favorable given the unclear prospect of stem cell patents. The USPTO's records indicate that methods for stem cell production, maintenance or differentiation remain patentable post-*Mayo* and post-*Myriad*.

Methods of producing iPSCs by reprograming somatic cells are likely patentable (e.g. U.S. Patent 9,234,179), but differentiation methods that make no difference from the natural differentiation processes could be unpatentable. As discussed, under the "significantly more" requirement, applications of a natural phenomenon must possess additional features that transform the claims into some eligible processes that amount to more than the natural phenomenon itself. Thus, for a method of differentiating stem cells using components of a signaling pathway (e.g. basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF) for neural differentiation) reciting no additional feature that amounts to "significantly more", the examiner may regard the method as a general application of the natural phenomenon and hence unpatentable (Morad, 2012).

Methods of identifying or selecting stem cells based on the detection of natural biomarkers may be rejected if the claims only recite routine and conventional techniques to detect the biomarkers (Chan *et al.*, 2014). As implied in *Ariosa*, patentability is not justified albeit the inventor newly discovered the presence of biomarkers in these cells. Diagnostic methods hinging on the detection of natural biomarkers may be likewise rejected if specified at a high level of generality. As exemplified by the USPTO, a diagnostic method relying on the detection of a natural human biomarker in a plasma sample by an antibody is patent eligible if the antibody has not been routinely or conventionally used for detecting human proteins (United States Patent and Trademark Office, 2016c). Notably, the Office suggests that it is feasible to limit the claim to the detection of a biomarker without reciting any step of diagnosis of the disease or analysis of the results such that the claim would not be regarded as ineligible for describing a natural correlation between the presence of the biomarker and the presence of the disease (United States Patent and Trademark Office, 2016c); yet, the author takes the position that this is contradictory to *Ariosa* which ruled that methods of detecting cffDNA in maternal serum are not eligible. On the other hand, as learnt from *Rapid Litigation Management*, for claims which are based on a natural law or natural phenomenon, it may be useful to focus on the end result of the claims and emphasize that the claims are directed to the manipulation of something (e.g. a pool of mesenchymal stem cells) to achieve a desired end result (e.g. exhibits specific therapeutic functions) to argue that the claims are not directed to a patent-ineligible concept.

When it comes to methods for treatment or screening compounds using natural stem cells, they are eligible if the methods *per se* are specific enough such that they do not preempt the use of the natural cells. The USPTO exemplified that using a

natural purified amazonic acid compound for treating breast or colon cancer (United States Patent and Trademark Office, 2014a) and that using an antibody against tumor necrosis factor (TNF) for treating julitis are both patent eligible.[56] As an analogy, a method of treating leukemia by administering an effective amount of natural hematopoietic stem cells to a leukemia patient is likely patentable.

Perspectives

Many practitioners have urged the Congress to make clear whether the ruling of *Myriad* applies beyond nucleic acids, and at what extent should *Mayo* be applied to the field of diagnostics. The USPTO is continuously seeking public comment to its latest update in May 2016 (United States Patent and Trademark Office, 2016d) and may issue new update that may better sort out how *Myriad* and *Mayo* are applied to various disciplines. The Office held two roundtables in late 2016 to solicit public views respectively on its subject matter eligibility guidances and larger questions concerning the legal contours of eligible subject matter in the U.S. patent system (United States Patent and Trademark Office, 2016e, 2017a, 2017b). The life science industry and also supporters from computer-related industry are calling for new legislation to replace the *Mayo/Alice* test with a technological or useful art test, and to clearly define exceptions to eligibility or clearly separating eligibility from other patentability requirements (United States Patent and Trademark Office, 2017c).

While law and policy could change depending on the subsequent measures of the USPTO and Congress, it is beneficial to pursue both product claims (stem cells) and method claims (producing processes and applications), although the former are likely rejected for their native nature. Inventors may concentrate on non-§101 rejections such as obviousness and enablement while postponing the subject matter arguments to buy time to get a clearer picture from additional guidance or court decisions (Gaudry *et al.*, 2015). Inventors may also look into the prosecution history of patented applications to learn what is eligible and *vice versa*, and the rationale behind so as to enhance their chance to survive under §101.

Notably, patent eligibility could highly depend on how the claim is structured (Smith, 2014). Inventors should examine and describe in the application any distinctive features between the isolated stem cells and their natural forms, and include these characteristics in the claims when necessary. It is also useful to emphasize the association of human effort with these characteristics. Inventors may also concurrently pursue cultural media or system, compositions or treatment kits comprising stem cells and non-natural components and so on for multiple levels of protection.

While for applications of stem cells or natural principles, the fact that the inventor discovers a new and useful natural product or law does not weigh toward patent eligibility of their uses. Although the framework of *Mayo* and *Alice* appears not to have been changed or reshaped by *Sequenom* and *Rapid Litigation Management*, the two cases did provide additional guidance on eligible subject matters concerning natural matters in the field of life sciences. The general advice is, method claims should not merely read on the natural products or laws and should be scrutinized on

any preemptive effect for the natural matters; and specific and inventive steps should be added to the claims to reduce the level of generality of the methods. It is undisputed that simply using the word "apply" does not avail, the standard of "significantly more" is general yet unclear. It is not easy to interpret whether the additional step would be treated as a "well-understood, routine and conventional activity practiced in the field", or an element capable of transforming the natural matter into something eligible. Importantly, the USPTO noted that a technique that is known (or even has been used by a few scientists) "does not necessarily show that an element is well-understood, routine and conventional activity" practiced in the field; rather, the evaluation turns on whether the *use* of that particular known technique was a well-understood, routine and conventional activity previously engaged in by scientists in the relevant field (United States Patent and Trademark Office, 2016a). Hence, applicants may argue that the recited step was not a technique prevalently used in the field at the time the application was filed to overcome the rejection.

Obviousness

Obviousness is a big challenge to stem cell patenting common in the four regions. The four regions share a similar framework in determining obviousness but the U.S. appears to adopt a higher standard than the other three regions. The authors chose to use the U.S. system to illustrate this topic for two reasons: 1) the readers may be more benefited if we discuss the topic at a higher standard; 2) the U.S. has a large volume of case law and administrative decisions touching upon this topic including some useful examples in the areas of stem cells.

The U.S. in general adopts a similar approach for determining obviousness as in other jurisdictions, i.e., determining the scope and content of the prior art, ascertaining the difference between the invention and the prior art, and resolving the level of ordinary skill in the art (the "Graham" factors).[57]

"Teaching, suggestion, or motivation" test (the "TSM test") has long been the standard for obviousness determination, under which a claim would only be proved obvious if some motivation or suggestion to combine the prior art teachings could be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art (Davidson and Myles, 2008).[58] However in 2007, *KSR* held that precise teachings in the prior art are not required to prove obviousness; rather, an invention is obvious if one skilled in the art has good reasons to combine the prior art elements to arrive at the claimed invention with an anticipated success.[59] Since then, more rationales can be used to prove obviousness thus significantly lowering the obviousness threshold. The USPTO has provided a non-exhaustive list of rationales for supporting an obviousness conclusion (Dorsey, 2008),[60] the examples include "combining prior art elements according to known methods to yield predictable results", "obvious to try - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success" and the TSM test (United States Patent and Trademark Office, 2010).

As compared to the TSM test, the "obvious to try" rationale is more subjective, thus leaving uncertainty in winning the obviousness battle. Seemingly, an invention

that is “obvious to try” with a “reasonable expectation of success” would be deemed obvious and hence not patentable. Nonetheless, the examiner must provide articulated reasoning to support the obviousness conclusion; mere conclusion statements are not acceptable.[61]

One of the feasible approaches to overcome an obviousness rejection is to carefully study the entirety of the prior art and the examiner’s rationale, and rebut by pointing out the insufficiency of the examiner’s reasoning. For example, one may refute that teaching away exists in the prior art, the examiner failed to address every claimed element with sound reasons, or the conclusions are hindsight bias. Another approach is to identify all possible differences between the claim and the prior art to locate any feature unique to the invention but absent in the references, or any unexpected effect achieved by the claimed invention to show that the combination of the prior art elements would not be able to arrive at the claimed invention (Davidson and Myles, 2008).

Declaration under 37 C.F.R. §1.132 could be an effective tool to traverse the obviousness rejection by virtue of objective expert’s opinion and/or evidence (Messinger and Horn, 2010). The declaration can be, for example, an expert’s opinion on the inoperability of references or their combination, or an expert’s justification of the level of ordinary skill in the art at the time of invention. Secondary considerations such as lacking a solution for a long-felt need and failure of others, unpredictable results and commercial success can also be testified using a declaration.[62] For example, direct comparative results of the claimed invention and the closest prior art may be presented to show unpredictable results of the invention, while series of patents and publications attempted to solve the same problem but unsuccessful may be used to show a long-felt but unsolved need.

The power of substantiated expert’s opinions and objective evidence on addressing obviousness may be illustrated by the reexamination proceeding of U.S. Patent No 7,029,913 (here after the ‘913 patent’). Claiming an *in vitro* culture of hESCs and granted to Dr. James Thomson, the ‘913 patent’ was challenged in 2006. One of the debates is whether the claimed hESCs would have been obvious in view of several references which teach, among other things, the isolation or derivation of ESCs from mouse and the culture of these murine ESCs using feeder cell layers. The proceeding took more than 6.5 years for the appellant Board to affirm the patentability after minor claim amendment.[63] During the reopened prosecution, the patentee submitted a declaration from an expert in the field of mouse embryogenesis and stem cells, along with scientific publications, to testify that the prior art method of isolating stem cells without feeder cells was not enabled to produce hESCs, and that no one could derive stem cells from rats till 27 years after the first isolation of murine ESCs despite mice and rats are closely related. One of the strong proof of non-obviousness is a research paper which reported the failure to isolate a replicating *in vitro* cell culture of pluripotent hESCs following the same prior art method. The declaration also pointed out that the invention was widely recognized as a breakthrough and highly praised by scientists in the field. The Board finally concluded that the above

presented strong evidences of non-obviousness and thereby affirmed the patentability of the claims.

Lastly, while the '913 patent' concerns a post-grant proceeding, it is very important that a §1.132 declaration be timely submitted before the final Office Action for consideration in the prosecution and appeal procedures, and be justly supported more than an attorney's assertion.

In sum, the laws governing the subject matter eligibility are evolving and clearly unsettled, the actual impacts to the stem cell landscape remain to be seen but applications directed to natural stem cells and their applications have been rejected. Case law implicates that the claim language could be determining to patent eligibility. Stakeholders are advised to learn from court cases and seek advice from practitioners with biotech expertise to overcome the high patentability hurdles.

III - China

A) Background

The State Intellectual Property Office of China (SIPO) is the administrative agency overseeing patents under the Patent Law and its implementing regulations. In addition to design patents that are not used in the case of stem cells, two types of patents, namely an invention patent and a utility model, are available (Zhang and Yu, 2008; Chen, 2010).

An invention patent protects new technical solutions for a product, a process or their improvement; while a utility model is exclusive to products, protecting the shape, structure or their combination of a product.[64] Hence, both types of patents may protect a device. A utility model is significantly different from an invention patent in that the former is generally not examined for inventiveness[65] and only grants a 10-year patent term as compared to 20 years by an invention patent.[66] Invention patent is more preferable for protecting stem cell inventions than utility model, hence the following sections refer to invention patents unless specified otherwise.

China adopts the common patentability requirements of novelty, inventiveness and industrial applicability,[67] and likewise requires an enabling description that clearly and fully describes the invention.[68] Further, direct and original sources of genetic resources on which the invention relies upon must be identified.[69] Embracing the absolute novelty standard, a six-month grace period for public disclosure is possible only for three very limited circumstances: (1) The invention is exhibited for the first time at an international exhibition sponsored or recognized by the Chinese Government; (2) The invention is published for the first time at a specified academic or technological conference; and (3) The contents are divulged by others without the consent of the applicant.[70]

B) The exclusions of patentability

Similar to Europe and Japan, China denies patents on moral grounds and precludes patents on therapeutic and diagnostic methods.

<u>Moral exclusion</u>

The moral exception under Article 5 of the Patent Law forbids patents on inventions that violate the laws or social ethics, or harm the public interest. Also, inventions that are accomplished relying on genetic resources obtained or used in violation of laws and administrative regulations are also prohibited.[71]

The authority made clear that any industrial or commercial use of human embryos is contrary to social ethics and should not be patented, thus hESCs and their production methods are not patentable.[72,73] Furthermore, human body at various forms and developmental stages including germ cells, fertilized eggs, embryos and individuals are also prohibited from patenting for moral reasons.[74]

Ineligible subject matters

Article 25 of the Patent Law explicitly excludes patents for six subject matters: 1) scientific discoveries; 2) rules and methods for mental activities; 3) methods for the diagnosis or treatment of diseases; 4) animal or plant varieties; 5) substances obtained by means of nuclear transformation; and 6) designs that are mainly used for marking the pattern, color or the combination of the two of prints.[75] (Chen, 2002)

Animal varieties are interpreted to exclude human but include whole animals, animal ESCs, germ cells, fertilized eggs and embryos, thus all of the above cannot be patented.[76, 77] Notwithstanding, methods for producing an animal or plant variety are allowed,[78] and natural genes and microorganisms in their isolated forms are patent eligible.[79]

Methods for the treatment or diagnosis of diseases practiced on living human or animals are strictly prohibited, nonetheless devices for practicing the treatment or diagnosis, or materials used in these methods are patentable.[80] Similar to the European framework, treatment and diagnostic methods that are practiced on dead bodies are patentable. [81] (Chen, 2002)

As for diagnostic methods, even if the tested item is a sample isolated from a living subject, the method is not patentable if it has the immediate intention of obtaining diagnostic results for a disease or a health condition of the same subject.[82] For instance, tests based on genetic screenings or prognosis of disease susceptibility are interpreted to be diagnostic methods and hence patent ineligible.[83]

Treatment methods encompass methods for the prevention of disease and for immunization. Notably, although surgical methods practiced on living human or animals that are not for therapeutic purposes are not forbidden under Article 25, they could not be used (or used for production) industrially and hence are not patentable for lacking industrial applicability.[84]

C) Main challenges for stem cells patents

The SIPO has granted patents on stem cells and methods for producing stem cells that do not involve human embryos or hESCs. The major barriers in stem cell patenting are the moral exclusion and the treatment exclusion.

Moral exclusion

The scope of moral exclusion is largely unclear because terminologies including "social ethics", "human embryo" and "industrial or commercial use" are not explicitly defined. Claims can be rejected for moral reasons even if they are not directed to human embryos or hESCs. We may infer from Chinese application no. 03816184.2 how SIPO exercises the moral provision to exclude patents that may involve an industrial or commercial use of human embryos.

Directed to a production of glial cells using undifferentiated primate pluripotent stem (pPS) cells, CN application no. 03816184.2 was rejected for violating social ethics and lacking industrial applicability in 2011. Upon reexamination, the Patent Reexamination Board reversed all the rejections.[85] (Tao and Duan, 2013)

This application claimed an *in vitro* system for producing glial cells that comprises an established cell lineage of undifferentiated pPS cells and a population of cells differentiated from the pPS cell lineage. The claims also covered, among other related inventions, the population of cells differentiated from the pPS cell lineage, and producing methods and uses of the glial cells.

Despite all the claims were limited to established cell linages of either primate pluripotent stem cells or hESCs, the Examiner opined that these established cell lineages have to be obtained from human embryos (given that pPS cells could include hESCs), therefore the claims are directed to the industrial or commercial use of human embryos which is prohibited by the Patent Law. Further, the Examiner rejected all the claims for lacking industrial applicability because, in the case where the claimed pluripotent stem cells are derived from non-embryonic tissues, human or animal bone marrow or other tissues must first be obtained using non-therapeutic surgical methods. Thus, the invention pertains to non-therapeutic surgical methods applied on living human and cannot be used industrially, and hence should be rejected.

During prosecution, the applicant set forth the followings to address the objections: the invention relies upon established cell lineages of hESCs that are readily available before the filing date of the application; the acquisition of established hESCs lineages does not necessarily violate social ethics; and the use of established hESCs lineages is not an industrial or commercial use of human embryos. The applicant further amended the description to delete descriptions involving acquisition of hESCs; however the case was finally rejected.

Upon appeal, the claims were amended to explicitly exclude pPS cells or hESCs that are directly disaggregated from human embryos or blastocysts. The applicant further provided evidence showing that the initial cell lineages derived from human embryos have been widely employed and patented, and cell lineages H1 and H7 used in the examples were commercially available before the priority date, therefore the invention does not require the use of human embryos.[86]

In May 2012, the Board ruled in favor of the applicant, concluding that the invention does not violate the moral provision. The Board reasoned that the description and claims have already precluded the direct use or disaggregation of human embryos and blastocysts, and that hESCs lineages are available in public depositories, thus apparently the invention uses established and commercialized cell

lineages and does not pertain to an industrial or commercial use of human embryos. In response to the Examiner's proposition that the established cell lineages H1 and H7 must be obtained through the destruction of human embryos, the Board enjoined that it is inappropriate to incessantly trace the acquisition of the established cell lineages to their initial origin (*i.e.*, human embryos), given that cell lineages H1 and H7 have been publicly available and can be indefinitely proliferated *in vitro* and obtained with known techniques.[87]

While for industrial applicability, the Board noted that none of the claims are directed to the isolation of pluripotent stem cells from non-embryonic tissues, and that the claims are limited to established lineages of pPS cells or hESCs, hence non-therapeutic surgical methods for the isolation of the pluripotent stem cells are not compulsory for practicing the invention, hence reversed the rejection for lacking industrial applicability.[88]

Perspectives

In practice, the examiners tended to strictly adopt the moral exclusion to exclude inventions which read on hESCs (e.g. hESCs *per se* and preparing methods thereof), and also inventions which are not direct to but related to hESCs. However, it appears that China has loosened its restrictions as indicated by a plurality of the Board's decisions in upholding patents over hESCs downstream technology (Peng, 2016). Although these Board's decisions are not binding, they illustrate that an invention which does not indispensably use human embryos could traverse the moral exclusion. Inventions in which the devastation or use of human embryos or fertilized eggs is not requisite, such as those on somatic cell nuclear transfer (SCNT) (e.g. CN1280412C and CN1209457C) and iPSC (e.g. CN103429732B) would have a higher chance of success. It is thus advised to explicitly exclude the use of human embryos in the claims and the description, and to make necessary clarification to avoid rejections on moral grounds. All class of inventions including stem cells and differentiated cells, and manufacturing methods and uses of these cells should be put on guard.

<u>Exclusion of therapeutic methods</u>

Patents on pharmaceutical compositions made of stem cells and their manufacturing methods are patentable but therapeutic methods using stem cells are prohibited. As in Japan, applicant may pursue Swiss-type claims in the format of "use of a composition in the preparation of a medicament (or kit) for treating a disease" to protect medicinal uses of stem cell products (Chen and Feng, 2002).

In short, morality is the biggest consideration in granting a patent to stem cell inventions and claims that read on hESCs are likely rejected. While SIPO has started to relax its rules and allowed patenting inventions which involve yet not directed to hESCs, it is essential to show with objective evidence why the claimed invention is free of ethical issues to have a higher chance of success.

<u>Inventiveness</u>

China also takes into account secondary considerations for justifying the inventiveness of an invention. Provided by the patent examination guideline, China considers long-felt but unsolved needs, unexpected results and commercial success.[89]

IV - Japan

A) Background

The Japanese Patent office (JPO) examines patents under the Patent Act and Utility Model Act. Inventions that can be protected by a patent, as defined, are "highly advanced creation[s] of technical ideas utilizing the laws of nature".[90] (Borowski, 1999; Kariyawasam *et al.*, 2015) Generally, subject matters eligible for a patent can be a product, a device or a process. In contrast, a utility model is designed to protect a device that is related to the shape or structure of an article or the combination of articles which is industrially applicable;[91] it does not go through the substantive examination as a patent does and confers a 10-year patent right.[92]

Sharing similar rules as other jurisdictions, novelty, inventiveness, industrial applicability,[93] and a sufficient and enabling description[94] are the basic patentability requirements in Japan.

Japan provides a six-month grace period which is stricter than the U.S. but more lenient than China. Inventions that were tested,[95] were disclosed through presentations in printed publications or electric telecommunication line,[96] or disclosed against the will of the person having the right to obtain a patent[97] are eligible for the grace period if the application is a direct national application, or is an international patent application under the Patent Corporation Treaty (PCT) designating Japan. Notably, the international filing date would be interpreted as the filing date for cutting off the six-month grace period for PCT application.[98] Except for third-party disclosures, a proof document to identify the relevant disclosure has to be submitted within 30 days from the filing date of the application. [99,100]

B) The exclusions of patentability

Moral exclusion

Codified at Article 32 of the Patent Act, Japan has an explicit moral provision that excludes inventions liable to injure public order, morality or public health from patent protection.[101] (Borowski, 1999) One example of such inventions is human produced through genetic manipulation.[102] However, whether a human body of various stages of its development is interpreted to be a human is not specified in the Patent Act and Examination Guidelines. Although the Patent Act and Examination Guideline do not specify that inventions involving human embryos are not patentable, applications involving a step of destroying human embryos have been rejected under Article 32 (Sugimura and Chen, 2013).

Ineligible subject matters

A statutory invention must be a creation of a technical idea utilizing a law of nature. Thus, laws of nature, discoveries *per se* (e.g. natural products and phenomenon), inventions contrary to the laws of nature, and inventions that are not using the laws of nature (e.g. economic laws, mathematical methods and mental

activities) are not regarded as an invention.[103] However, natural products and microorganisms that are artificially isolated from their surroundings are patentable. [104]

Similar to Europe and China, Japan interprets methods for surgery, treatment, or diagnosis practiced on humans are incapable of industrial application and therefore could not be patented (Sato, 2011).[105] However, patents are possible if these methods are applied on animals and explicitly exclude human. Materials that are used in these methods, and products of these methods are patentable.[106]

Notably, any method that processes or analyzes a sample taken from a human body is not patentable unless the sample is not supposed to be returned to the same body. [107] While for diagnostic methods, Japan adopts a similar approach as China, defining that any method for the judgment of physical or mental conditions of a human body is a diagnostic method and hence not patentable. [108] Further, methods designed for the purpose of prescription, treatment or surgery plans are regarded as diagnosis of human and hence disallowed. [109]

Thus, in a general sense, methods for extracting or analyzing a sample, or gathering data from a human body which are not for judging physical or mental conditions, or for the planning of drug prescription, treatment or surgery are patent eligible. The Examination Guideline sets forth some examples of medical activity that are patent eligible.[110] For example, methods of determining susceptibility to a disease by determining and comparing the gene sequence with a standard can be patented. [111]

There are certain exceptions to methods involving a "sample extracted from a human body and presumed to be returned to the same body". Specifically to the stem cell area, methods for manufacturing a medicinal product or material using raw materials from a human body is patent eligible. [112] Thus, method for preparing a cell or artificial skin sheet is patentable even if these articles are intended to be returned to the same person. Methods for differentiating or purifying a cell using raw materials from a human body, or analyzing medicinal products or materials using raw materials from a human body are also eligible. [113]

C) Main challenges for stem cells patents

Japan appears to be less restrictive than Europe and China in granting stem cell patents despite Japan has comparable stances on moral violation and industrial applicability of medicinal activity in its patent framework. Japan has issued patents on stem cell lines, manufacturing methods, uses of stem cells for drug production and so on, and is the pioneer granting patents on iPSC (Simon *et al.,* 2010).

Moral exclusion

Although the JPO sets no explicit rule on human embryos and hESCs, it is likely that inventions relied on human embryos will be rejected. Therefore, it is advised to take an approach similar to that proposed for the Chinese landscape; that is to preclude the possibility of destruction of human embryos for practicing the invention (*supra*).

Following the JPO guidance which exemplifies that methods of differentiating stem cells are patentable, methods for producing stem cells based on established

embryonic stem cells lines are likely allowed (Sugimura and Chen, 2013). For example, JP 5,862,061 claims a method of culturing hESCs, and JP 5,841,926 was granted on a method of producing ESCs using blastomere and compositions comprising the ESCs, of which the description specifies that the cells can be derived without embryo destruction.

Exclusion of therapeutic and diagnostic methods

Treatment methods are generally not patentable. While methods for manufacturing medicinal products (e.g. vaccine or cells) or artificial substitutes using raw materials collected from a human body is patentable, uses of these medicinal products on human are likely regarded as treatment methods and hence not patentable. Testing or assaying methods should devoid of any step pertaining an evaluation or determination of a physical or mental condition of a human, such that the method would not be interpreted as a diagnosis practiced on human. Methods for the collection of data and/or comparison of data with a control do not correspond to a diagnostic method and hence is likely patentable.

Devices for practicing a treatment or diagnosis, as well as methods for controlling the operation of these devices are largely patentable as long as the function of the medical device itself is represented as a method.[114] JPO specifies that a method for controlling the operation of a medical device is not a method of surgery, treatment or diagnosis of human,[115] given that the method does not involve a step with an action of a physician on the human body or a step with an influence on the human body by the device (e.g. incision and excision of patient's body by an irradiated device).[116] Thus, it may be feasible to redraft the forbidden therapeutic or diagnostic claims to methods for controlling the operation of the therapeutic or diagnostic devices or systems without any steps involving a physician's action on the human body or steps affecting the human body by the device. For instance, "a method for irradiating X-rays onto the human body by changing the tube voltage and the tube current of the X-ray generator each time the generator rotates one lap inside the gantry" is considered to be a method of surgery, therapy or diagnosis of human while "a method for controlling the X-ray generator by control means of the X-ray device; wherein the control means change the tube voltage and the tube current of the said X-ray generator each time the generator rotates one lap inside the gantry" would be patent eligible.[117]

In short, Japan is more liberal than Europe and China in granting stem cell patents provided that the claimed invention does not involve the destruction of human embryos. The Japanese Examination Guidelines helpfully provide a lot of examples of eligible and ineligible claims, stakeholders are advised to read through these examples and craft the claims accordingly.

Inventiveness

As in the other three regions, secondary considerations can be used in Japan for justifying the inventiveness of an invention. For example, commercial success and long-felt need may be considered provided that these are contributed by the technical

features of the claimed inventions and supported by the applicant's arguments and evidences.[118]

V – Discussion

Patent systems in each jurisdiction are standalone yet have similarities. Coherent with the above discussion, the most notable difference in the landscape of stem cell patents is that the U.S. neither establishes a moral exclusion nor excludes inventions that involve the destruction of human embryos. Furthermore, despite patentability requirements in the four regions are similar in the broadest sense, they are subject to disparate interpretations and standards. That is why it is not uncommon that an invention is awarded a patent in one region but not in another one.

Seeking patent protection for the same invention in multiple jurisdictions is commonplace. Very often, patent applications filed in different jurisdictions share the same or substantially the same disclosure while claims could be tailor-made in order to comply with the local rules and meet the interests of the stakeholders. Hence, to set up a favourable global and regional strategy for patent protection, it would be advantageous to look into the aspect of patent procurement in each of the jurisdictions of interest, and to deal with issues that may disfavour patent protection at the very beginning. The aspect of patent enforcement should not be overlooked but goes beyond the scope of this chapter.

Focusing on patent procurement, the following section will highlight the main similarities and differences in patentability issues between the four regions that may be worthy of attention. While a side-by-side comparison and analysis are not feasible due to limited space here, we summarize a few general and specific aspects of the four systems for a quick and easier comparison (Table 1- Comparison of stem cell patent systems).

A) The unique territorial patent system in Europe

Europe is a region that includes both national patent laws and European patent laws, whereas the U.S., China and Japan are sovereign countries that have a single national patent law. The co-existence of national and European patent law systems brings inherent complexity which should not be overlooked.

As discussed, there are several possibilities to obtain patents in Europe: a European patent at the EPO, national patents at each national patent offices, and in the future a European patent with unitary effect in all the Member States of the European Union at the EPO. It is especially complex in the evolving scientific and technical field of stem cells as inferred from the definition of human embryos by the Court of Justice of the European Union. Although the EPO and the EU have been generally successful in providing a quite uniform patent law that overpasses national heterogeneities, small national divergences with potentially high consequences can always appear as it has been shown by the different national implementations of the *Brüstle* case, especially on whether or not it should be proved that hESCs have been obtained without previous destruction of human embryos (Mahalatchimy, 2014).

B) Utility vs industrially applicability

Among the five general criteria for patentability, the utility or industrially applicability requirement appears to be most distinctive.

Different from the industrially applicability requirement of Europe, China and Japan, the U.S. does not specify that an invention must be susceptible of industrial application. Rather, it requires the invention must have a specific and substantial utility. While the utility requirement is not usually an issue for stem cells patents in the U.S., it is totally different for the industrial application criterion which precludes certain types of methods that are not industrially applicable from patentability. As discussed, therapeutic, diagnostic and surgery methods practiced on human are mostly not patentable in Europe, China and Japan.

C) Moral exclusion

Absent a moral exclusion, the U.S. appears to be the most liberal among the four regions in granting human stem cell patents while Europe is the strictest. Europe appears as the region that places the strongest emphasis on moral exclusion as evidenced by the extensive coverage and specific examples of the moral exclusions in the patent law and rules. Firstly, Europe is the region where a definition of the human embryo has been provided in the field of patents. Secondly, Europe has explicitly defined that uses of human embryos for industrial or commercial purposes fall within the moral exclusion and provided the most extensive interpretation of the exclusion: to cover the destruction of human embryos whenever it takes place, not only *de novo* destruction.

China is the closest to Europe (Farrand, 2016) but more lenient regarding the interpretation of the uses of human embryos for commercial or industrial purposes. Although the decisions of the Chinese Patent Reexamination Board are not necessarily binding, the Board considers the exclusion is limited to the *de novo* destruction of human embryo. Thus, the use of hESC from publicly available cells lines deposited in biobanks does not prevent the grant of patent. It also provides a clearer answer than the European Courts as it specified that it is inappropriate to incessantly trace the acquisition of the established cell lines to their initial origin as long as they are publicly available. While the European courts adopted the opposite view, they did not clarify whether the non-destruction of human embryos should be proved in the claims and by whom. Japan has placed a moral exclusion in the patent law but does not specify whether the involvement of human embryos would render an invention injuring the public order, morality or public health. It has consequently been considered as an attractive country with more liberal policy to stem cell patents (Kariyawasam et al., 2015). On the face, stem cell products are largely patent eligible in China and Japan provided that the *de novo* destruction of human embryos is excluded from the claimed invention in view of the description.

D) Limited eligibility for natural products, laws and phenomenon in the U.S.

The recent changes in the interpretation of patent eligibility in the U.S. has imposed a unique and huge challenge to the stem cell arena. As discussed, a natural

product be it synthetic or isolated from natural sources, is not patentable absent any "markedly different characteristics" from the naturally-occurring product. Hence, a purified population of stem cells may be patent eligible in the other three regions but not in the U.S. if it is essentially the same as the cells in the human body. Diagnostic methods using stem cells albeit are not excluded for lacking industrial applicability, the prospect of getting a patent is unclear unless more solid criteria of the "significantly more" standard are provided. Finally, as the U.S. has significantly narrowed the scope of eligible subject matter, one can foresee the convergence of consequences of different US and EU laws regarding stem cell patent eligibility. (Davey et al, 2015).

E) Patent - A double-edged sword?

Undoubtedly patents are awards granted by the government to innovators for their intelligent efforts by conferring them an exclusive right in their innovation; however, in essence, the primary objective of the patent system is to promote innovation and economic development through encouragement of information exchange among the community.

On the one hand, patent protects the interests of the innovators, allowing them to generate revenue and gain capital to foster their research and business. Market exclusivity including patent right and data exclusivity are particularly important to the pharmaceutical and medical devices industries to offset the huge yet disproportionate risks and investment in the development of drugs, diagnostic kits or medical devices. Such risks and difficulty for finding investment are particularly true in the field of stem cells patent. Monopoly status, even if it only lasts for a limited period of time, is crucial for the industries and venture capitalists to invest into the development and commercialization of innovations. First and foremost, patents help to minimise the risk of infringement. Secondly, patents can effectively suppress competition and permit firms to earn revenue as a return on their investment. This second point as well as the public impact as a result of the suppression of competition by patents can be illustrated by the well-known story of Myriad. Before the Supreme Court decision which invalidated Myriad's claims over the natural BRCA genes, genetic tests for breast cancer which based on the evaluation of BRCA1 and BRCA2 genes costed about $3,000-4,000 in the U.S. (Cartwright-Smith, 2014). Holding the patents which claimed the natural sequence of BRCA genes, Myriad was the sole company that could administer the BRCA1/2 tests. Laboratories which provided BRCA tests were forced to terminate their services after Myriad alleged them for patent infringement, thereby barring patients from obtaining a second diagnostic opinion from an independent laboratory. The cost of the BRCA tests soon fell to around $1,000-2,300 after the Supreme Court decision (Cartwright-Smith, 2014).

As for academia, patent protection also plays a significant role insofar as commercialization is concerned. No matter the technology is to be licensed to a third party or commercialized by the researchers (e.g. in the form of spin-off), patents could provide some level of comfort to the potential licensees and investors in favour of the deal. Capital investment and revenue generated from royalties and licensing fees

received by the universities or companies can be used in subsequent research and thereby promote innovation. It also gives renown to academia and may facilitate the publications of papers; the latter being the main way of assessment for research and consequently proof of its good quality.

On the other hand, although patent information is in open access, the public is prohibited by law from engaging the patented products or methods in research without the consent of the right holders. Nonetheless, in addition to anti-competition or similar laws, patent system itself does provide certain filtering mechanisms to prevent overly broad patents. The first filtering mechanism is the exclusion of patentability of common goods. Scientific discoveries, natural phenomenon and natural products *per se* are generally barred from patent protection in most if not all jurisdictions, but applications of these natural matters are still patentable provided that they meet other patentability requirements. While preclusion of patentability is an effective means to prevent the preemption of uses of natural goods, it is noteworthy that decisions of *Mayo* and *Myriad* have been heavily criticized by the industries and the patent practitioners for hindering the development of biotechnology especially the diagnostic field since these decisions have effectively excluded many biotech and diagnostic inventions from patent protection. The second filtering mechanism is imposing restrictions on patent rights. Patent law precludes certain activities from patent infringement and thereby waives one's liability of patent infringement as a result of these exempted activities. Examples include prior use defense, research exemption and regulatory review exemption (so-called the "Bolar exemption" which is an exemption of patent infringement for use of patented products in experiments for the purpose of obtaining regulatory approval for drugs, this is established to enhance public access to generic drugs) (Misati and Adachi, 2010; Kappos and Rea, 2012).

Therefore, patents can be seen as a double-edge sword which simultaneously promotes innovations and suppresses competitions. Availability of new information and the incentives given by patent may promote research, yet existing patent rights may discourage people from developing basic research into commercial embodiments that are practical and beneficial to the community. Doubts as to whether a patent system promotes or suppresses innovation and of what magnitude always exist.

Particularly to the arena of stem cells, any monopoly over the use of natural human stem cells likely inhibits the research and development of stem cells-based technologies. Yet, the first filtering mechanism may operate to prevent a party from tying up the natural stem cells at some level, for example stem cells obtained directly through the destruction of the human embryo (e.g. in China, Europe and Japan) and stem cells isolated from natural sources (in the U.S.). While for patented technologies, the research exemption does leave room for research using stem cells technologies covered by patents, although the permissible scope may be narrowly limited to non-commercial research.

While the authors do not have an affirmative answer as to whether patents promote research of stem cells or not, we believe that patent itself is a very useful tool to promote the exchange of information. Free flow of information is essential to enrich our knowledge, invoke our creativity and prompt the emergence of ground-

breaking or disruptive technologies. Indeed, issues of patent infringement may arise when a research involving the use of patented technology matures to some sort of commercial activity; however, negotiations or collaborations between the owners/ exclusive licensees of the patented technology and innovators of the follow-on inventions are often possible to allow commercialization of the follow-on inventions without patent infringement. It should be highlighted that patent policy is more than the issue of free market and academic freedom. As with other areas of law, public policy reasons always play a role in formulating patent laws and rules. It is for the executive branch and the legislature to strike a balance between the general public and individual rights and liberties and adjust the laws and policies to achieve the best overall interest.

VI - Conclusion

Definitely, human stem cells have a great potential in the fields of regenerative medicine and personal medicine. Stem cell technologies must be timely and comprehensively protected by all means of intellectual property particularly patents. Even though the field of human stem cells have been the object of clarifications by Courts or guidelines in each region, the complexity and uncertainties remain (Schwartz and Minssen, 2015). How the *ISSC* case on the destruction of human embryos is applied in Europe? How *Myriad* and *Mayo* on natural genes and diagnostic methods are applied in the U.S.? Will the non-binding decisions of the Chinese Patent Reexamination Board upholding the patentability of invention that uses hESC from publicly available cells lines deposited in biobanks be followed in the process of patent examination and various patent proceedings? Will Japan provide more explanation and examples on its moral exclusion? All these uncertainties, among other challenges such as the regulatory requirements, could be of utmost importance to the commercialization and success of stem cell inventions. Practitioners should closely follow the development in the patent landscape from patent law to court decisions with a comparative view, and researchers and the industry should adjust their strategy to strive for success through the challenges.

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[1] Albania, Switzerland, Iceland, Lichtenstein, Monaco, Former Yugoslav Republic of Macedonia, Norway, San Marino, Serbia, Turkey.

[2] As of December 16, 2017, it has been signed by 25 Member States, including France only among the three required countries. European Council: http://www.consilium.europa.eu/en/documents-publications/agreements-conventions/agreement/?aid=2013001 (Last Accessed December 16, 2017).

[3] Article 52(1) of the European Patent Convention.

[4] The grace period is a period of time priori to the patent application filing during which the inventions can be divulgated without impeding the invention to be considered new or inventive.

[5] Article 53 (a) of the European Patent Convention and Article 6(1) of Directive 98/44/EC.

[6] Article 5. 1 Directive 98/44/EC and Rule 29 (1) EPC.

[7] This is to be understood regarding the distinction between a mere discovery (such as the finding of a previously unrecognized substance occurring in nature) that is not

patentable and an invention (such as a substance found in nature that is shown to produce a technical effect) that is patentable.

[8] Regarding sequences and partial sequences of genes, the industrial application requirement has specific form: "The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application." Article 5. 3 Directive 98/44/EC and Rule 29 (3) EPC. Both the Court of Justice of the European Union (ECJ, gr. ch., July 6, 2010, Monsanto Technology LLC v. Cefetra BV and a., C-428/08, Rec. I-06765) and the EPO (Board of Appeal of the EPO, *The University of Utah Research Foundation v. Institut Curie*, *Assistance Publique-Hôpitaux de Paris, Institut Gustave Roussy-IGR, Vereniging van Stichtingen Klinische Genetica, et al., De Staat der Nederlanden, Greenpeace e.V.*, November 13, T 0666/05 (2008)) have specified the patent protection is limited to the function for which the sequences and partial sequences of genes have been patented.

[9] Article 5. 2 Directive 98/44/EC and Rule 29 (2) EPC.

[10] Rule 27 EPC; Article 4.3 Directive 98/44/EC.

[11] The list also includes "processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes." Rule 28 of the implementing regulations to the European Patent Convention and Article 6(2) of Directive 98/44/EC.

[12] Article 53 (c) of the European Patent Convention and Recital (35) of Directive 98/44/EC.

[13] Enlarged Board of Appeal of the EPO, *Wisconsin Alumni Research Foundation (WARF)*, November 25, G02/06 (2008).

[14] Court of Justice of the European Union, Grand Chamber*, Brüstle v Greenpeace eV*, October 18, C-34/10 (2011).

[15] Court of Justice of the European Union, Grand Chamber, *International Stem Cell Corporation v Comptroller General of Patents, Designs and Trade Marks*, 18 December 2014, Case C- 364/13 (2014).

[16] European Patent Office, Enlarged Board of Appeal,Enlarged Board of Appeal of the EPO, *Medi-Physics Inc.*, February 15, 2010, G 1/07.

[17] *Ibid.*[18] European Patent Office, Technical board of appeal, March 27, 1986, *E.I. du Pont de Nemours and Company*, T 0144/83.

[19] *Ibid.*

[20] European Patent Office, Board of Appeal, T2221/10 Technion Research and Development Foundation Ltd, February 4, 2014; UK Intellectual Property Office, International Stem Cell Corporation, August 16, 2012, BL O/316/12.

[21] German Federal Court, BGH, Urteil vom November 27, 2012, Az. X ZR 58/07, (German Federal Court case law, 2012; http://openjur.de/u/596870.html).

[22] Court of Justice of the European Union (2014), Grand Chamber, *International Stem Cell Corporation v Comptroller General of Patents, Designs and Trade Marks*, 18 December 2014, Case C- 364/13, *op. cit.*

[23] Article 52 (1) (a) EPC; recitals (13), (16), (34) of Directive 98/44/EC. The criterion of inventiveness has been detailed by the EPO with clarifications regarding the state of the art, the non-evident concept and the definition of the person skilled in the art notably; the obviousness being included within the inventive step criterion. EPO, Part G Chapter VII, Guidelines for examination.

[24] EPO, Part G Chapter VII, 10.3, Guidelines for Examination.

[25] 35 U.S.C. §101.
[26] *Ibid.*
[27] 35 U.S.C. §102.
[28] 35 U.S.C. §103.
[29] Manual of Patent Examining Procedure (MPEP) §2107, Revision 9 (July 2015).
[30] 35 U.S.C. §112.
[31] *Ibid.*
[32] Manual of Patent Examining Procedure (MPEP) §2165.01, Revision 9 (July 2015).
[33] Manual of Patent Examining Procedure (MPEP) §2164.01(b), Revision 9 (July 2015).
[34] *Ibid. 33.*
[35] *Diamond v. Chakrabarty*, 447 U.S. 303, 100 S. Ct. 2204 (1980).
[36] Manual of Patent Examining Procedure (MPEP) §2105, Part II, Revision 9 (July 2015).
[37] Manual of Patent Examining Procedure (MPEP) §2105, Part III, Revision 9 (July 2015).
[38] *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. ___, 132 S. Ct. 1289 (2012).
[39] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. ___, 133 S. Ct. 2107 (2013).
[40] *Alice Corp. v. CLS Bank Int'l,* 573 U.S. __, 134 S. Ct. 2347 (2014).
[41] *Ibid.38*
[42] *Ibid. 39*
[43] *Ibid. 35*
[44] *Ibid.39*
[45] *Ibid. 40*
[46] *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 68 S. Ct. 440 (1948).
[47] *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333 (Fed. Cir. 2014).
[48] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015).
[49] *Ariosa Diagnostics, Inc. v. Sequenom, Inc*., 788 F.3d 1371 (Fed. Cir. 2015)., cert. denied, 579 U.S. __ (U.S. June 27, 2016).
[50] *Rapid Litigation Management v. CellzDirect*, 827 F.3d 1042 (Fed. Cir. 2016).
[51] *Ibid.*
[52] *Ibid.*
[53] *Ibid.*
[54] *Ibid.39*
[55] Prosecution history of US Patent 9,175,264, retrieved from Public Patent Application Information Retrieval (PAIR) System of the USPTO.
[56] "Julitis" is a hypothetic autoimmune disease given by the USPTO (United States Patent and Trademark Office, 2016c).
[57] Manual of Patent Examining Procedure (MPEP) §2141, Revision 9 (July 2015).
[58] *KSR Int'l Co. v. Teleflex Inc.* 550 U.S. 398 (2007).
[59] *Ibid.*
[60] Manual of Patent Examining Procedure (MPEP) §2143, Revision 9 (July 2015).
[61] Manual of Patent Examining Procedure (MPEP) §2142, Revision 9 (July 2015).
[62] Manual of Patent Examining Procedure (MPEP) §716, Revision 9 (July 2015).
[63] *The Foundation For Taxpayer & Consumer Rights v. Wisconsin Alumni Research Foundation*, Appeal 2012-011693, Decision on Appeal (January 22, 2013).

http://e-foia.uspto.gov/Foia/RetrievePdf?system=BPAI&flNm=fd2012011693-01-22-2013-1.

[64] Patent Law of the People's Republic of China, Article 2.
[65] Guidelines for Patent Examination (2010), Section I, Chapter II.
[66] Patent Law of the People's Republic of China, Article 42.
[67] Patent Law of the People's Republic of China, Article 22.
[68] Patent Law of the People's Republic of China, Article 26.
[69] *Ibid.*
[70] Patent Law of the People's Republic of China, Article 24.
[71] Patent Law of the People's Republic of China, Article 5.
[72] Guidelines for Patent Examination (2010), Section I, Chapter I, Section 3.1.2.
[73] Guidelines for Patent Examination (2010), Section II, Chapter X, Section 9.1.1.1.
[74] *Ibid.*
[75] Patent Law of the People's Republic of China, Article 25.
[76] Guidelines for Patent Examination (2010), Section I, Chapter I, Section 4.4.
[77] Guidelines for Patent Examination (2010), Section II, Chapter X, Section 9.1.2. However, animal somatic cells, animal organs and tissues are still eligible.
[78] *Ibid. 75, 76*.
[79] *Ibid. 76.*
[80] Guidelines for Patent Examination (2010), Section I, Chapter I, Section 4.3.
[81] *Ibid.*
[82] *Ibid.*
[83] *Ibid.*
[84] *Ibid.*
[85] Patent Reexamination No. 1F123416, Decision on Reexamination 42698 (May 29, 2012).
[86] *Ibid.*
[87] *Ibid.*
[88] *Ibid.*
[89] Guidelines for Patent Examination (2010), Section II, Chapter 4, Section 5.
[90] Patent Act of Japan, Article 2(1).
[91] Utility Model Act of Japan, Article 1.
[92] Japanese Patent Office, FAQs on Utility Model https://www.jpo.go.jp/english/faqs/utility-model.html (Last Accessed December 16, 2017).
[93] Patent Act of Japan, Article 29.
[94] Patent Act of Japan, Article 36(4)(i).
[95] Patent Act of Japan, Article 30(2).
[96] *Ibid.*
[97] Patent Act of Japan, Article 30(1).
[98] Examination Guidelines for Patent and Utility Model in Japan. Part III, Chapter 2, Section 5.
[99] *Ibid.*
[100] Patent Act of Japan, Article 30(4).
[101] Patent Act of Japan, Article 32.
[102] Examination Guidelines for Patent and Utility Model in Japan. Part III, Chapter 5.
[103] Examination Guidelines for Patent and Utility Model in Japan. Part III, Chapter 1, Section 2.
[104] *Ibid.*

[105] Examination Guidelines for Patent and Utility Model in Japan. Part III, Chapter 1, Section 3.1.1.
[106] *Ibid.*
[107] *Ibid.*
[108] *Ibid.*
[109] *Ibid.*
[110] Examination Guidelines for Patent and Utility Model in Japan. Part III, Chapter 1, Section 3.2.
[111] *Ibid.*
[112] *Ibid.*
[113] *Ibid.*
[114] *Ibid.*
[115] *Ibid.*
[116] *Ibid.*
[117] Examination Handbook for Patent and Utility Model in Japan. Annex A, Case Examples 3. Eligibility for Patent and Industrial Applicability (Main Paragraph of Article 29(1).
[118] Examination Guidelines for Patent and Utility Model in Japan. Part III, Chapter 2, Section 2.