Intellectual property strategy for regenerative medicine: is it time to 'regenerate'?

"...the environment relating to regenerative medicine is now on the move. Therefore, it is time to 'regenerate' our intellectual property strategy..."

Keywords: cellular medicine • data/market exclusivity • induced pluripotent stem cell (iPSC) • intellectual property • market approval • Mayo • myriad • natural products • *ordre public* (public order) • patent • patent eligibility • priority • regenerative medicine • stem cell

Introduction: is it time to 'regenerate'?

Regenerative medicine, including stem cell technology, cellular medicine and the like, is a promising and progressing technology in the field of medicine for near future, and thus is presently under developments from a variety of points of view.

For example, after Shinya Yamanaka won a Nobel Prize in Medicine and Physiology in 2012 for the discovery that mature cells can be reprogrammed to become pluripotent [1] or induced pluripotent stem cells, the Japanese government has been continuously emphasizing the importance of research and development of regenerative medicine, and has revised the Pharmaceutical Affairs Act in 2013 in order to facilitate market approvals for medicines relating to regenerative medicine. The amendment to the law will come into effect on 25 November, 2014. In parallel, the Japan Patent Office announced that the scope of patent term extension should be extended to cover patents relating to regenerative medicine in February 2014 [2]. The patent term extension system is to extend patent life for a certain period of time (typically a maximum of 5 years), thereby enhancing protection of an intellectual property related thereto. Of course, the USA and Europe also take own their special steps towards regenerative medicine from different point of view [3,4].

As such, the environment relating to regenerative medicine is now on the move. Therefore, it is time to 'regenerate' our intellectual property strategy and, to that end,

this editorial will focus on and summarize the recent developments in this field and will propose future prospective.

Patents & data exclusivity

Intellectual property rights relating to regenerative medicine products are mainly protected by patents. Regenerative medicine products are also protected by data/market exclusivity where clinical data has exclusivity and generic drug makers cannot utilize such clinical data of an innovator for market approval. Additionally, regulatory implementation is an important aspect of intellectual property as the data related thereto is protected by data protection/exclusivity and/or a re-examination system by preventing other parties from entering into the market. In this regard, in Japan, the Pharmaceutical Affairs Act was recently amended to include a special section directed to the protection of regenerative medicine products. The USA also enacted similar legislation in July 2013 (US FDA Safety and Innovation Act [5]). Recently, the FDA US Center for Biologics Evaluation and Research held a public workshop dealing with cellular therapies and regenerative medicine products on 31 March 2014 [6]. Regarding data exclusivity, if there is an orphan drug designation, then there will be a special treatment for data exclusivity [7].

The European Medicines Agency (EMA) classifies regenerative medicine/cellular medicine products as 'advanced therapies' [8,9], and has established a body called 'the Committee for Advanced Therapies' (CAT)

Takeshi S Komatani

SHUSAKU YAMAMOTO, Grand Front
Osaka Tower C, 3-1 Ofuka-cho, Kita-ku,
Osaka, 530-0011, Japan
tskomatani@shupat.gr.jp

**FUTURE
SCIENCE** part of

fsg

specifically responsible therefore [10]. As the data exclusivity is associated with clinical data, there is less room to create a distinguished strategy. On the other hand, patents may be well created by preparing a good strategy/portfolio in advance

Ordre public: in order?

Regenerative medicine is closely or even directly related to human life *per se* and, as such, there are a number of restrictions and limitations – particularly *ordre public* (public order) or ethical issues.

“Patent eligibility ... when you prepare patent strategy to cover regenerative medicine products, you must consider the ‘difference’ between your regenerative medicine products and the natural products, and such ‘difference’ is associated with significant utility.”

In the European Patent Convention (EPC), there is an article that actively includes certain subject matter relating to regenerative medicine [11], it reads “(a) inventions the commercial exploitation of which would be contrary to ‘*ordre public*’ or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation...”. Furthermore, the EPC Implementing Regulations possess specific sections that could be restrictions to some regenerative medicine products [12]. In this regard, the CJEU renders a negative decision regarding the patent eligibility of human embryonic stem cells in 2011 [13]. (This decision held “... any human ovum after fertilisation, ... constitute a ‘human embryo’; ...excludes ... from patentability where the technical teaching ... requires the prior destruction of human embryos ... whatever the stage at which that takes place...”. This case is now in further progress – the CJEU is now considering a related question in *ISCC v. UKIPO* that may provide a way forward). Currently, according to the EPC rule and its implementation, there are a number of detailed regulations, and one must take care a number of items (see Box 1, Rule Art. 28 and 29)

With respect to induced pluripotent stem cells, EPO generally allows patent and such an artificial stem cell is one of the important factors to secure patent protection in EPC. As such, special care must be paid in order to appropriately protect biological materials directly related to stem cells or tissues and the like having pluripotency in the EPC member countries.

In the USA, the Leahy–Smith America Invents Act, which has recently been enacted to amend the Patent Act also has a particular section relating to prohibition of patent protection of certain inventions relating to human organism [14], it held that “[Notwithstanding]

any other provision of law, no patent may issue on a claim directed to or encompassing a human organism” [15], and the United States Patent and Trademark Office (USPTO) has interpreted this to be a ban on human organisms, including human embryos and fetuses [16].

In Japan, the Examination Guidelines have not yet set out sections relating to regenerative medicine [17]. In practice, the Japan Patent Office applies requirements of *ordre public* and/or industrial applicability to inventions relating to regenerative medicine, and limits the allowable subject matter based on its own policy.

Patent eligibility: new issue?

Patent eligibility is a requirement that deals with whether the subject matter at issue is susceptible of patent protection. This became an important issue for regenerative medicine products and stem cell technology after the Myriad decision [18] and Prometheus decision [19] by the Supreme Court of the United States (SCOTUS).

Distinguishing from ‘natural’ products is the key word. In the guidance recently published by the USPTO [20] based on the SCOTUS decisions, it turned out that the guidance deal with not only DNA sequences but also other ‘natural’ products. In the guidance, three questions must be addressed:

- Question 1: Is the claimed invention directed to one of the four statutory patent-eligible subject matter categories: process, machine, manufacture, or composition of matter?
- Question 2: Does the claim recite or involve one or more judicial exceptions?
- Question 3: Does the claim as a whole recite something significantly different than the judicial exception(s)?

Question 2, may be problematic for regenerative medicine. It is explained that “[Judicial] exceptions include abstract ideas, laws of nature/natural principles, natural phenomena, and natural products.” Regenerative medicine products should ideally be as identical as possible to a human body portion of a patient, in other words, as identical as possible to ‘natural products.’ In this regard, Question 3 will give you a hint as to how to protect your regenerative medicine products. The key phrase is “significantly different.” It seems that this came from the Chakrabarty decision in 1980 [21]. The decision held “[the] patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature’s handiwork, but his own; accordingly it is patentable...”. Therefore, when you prepare patent

Box 1. The European Patent Convention Implementing Regulations, Rule Art. 28 and 29.

- Rule 28 defines unpatentable subject matter regarding cloning, germ line, embryos and modification without medical benefit; Rule 28(c) prohibits European patents which concern 'uses of human embryos for industrial or commercial purposes'. In this regard, the Enlarged Board of Appeal held that this forbids the patenting of any invention that necessarily involved the destruction of a human embryo, even if the destruction is not part of the claimed invention (e.g., if the invention uses human embryonic stem cells that, at the filing date, could only have been produced by the destruction of human embryos) [G 2/06]. Currently, the European Patent Office (EPO) considers that this even applies to inventions that could be implemented using human embryonic stem cell lines, if the production of the cell lines involved the destruction of human embryos [C-34/10]. Current EPO practice is that techniques to provide human embryonic stem cells without destroying human embryos have been available since 10 January 2008 [24], which disclosed the single blastomere biopsy technique). As such, inventions that are applied to human embryos that are beneficial to the embryo or resulting person are not forbidden.
- Secondly, Rule 29(1) prohibits the patenting of 'the human body, at the various stages of its formation and development'. The EPO interprets this to forbid the patenting of totipotent stem cells that have the capacity to develop into a human being. Claims to, or involving, pluripotent or multipotent stem cells, which do not have the capacity to develop into a human being, are patentable provided that the cells can be obtained without the prior destruction of a human embryo.

strategy to cover regenerative medicine products, you must consider the 'difference' between your regenerative medicine products and the natural products, and such 'difference' is associated with 'significant utility.' Of course, it must be noted that the subject guidance used this phrase without actual case law.

In any event, one should be well prepared to create a patent portfolio in advance that is 'adaptable' in response to any (potential) changes in the patent law and practice and/or 'resistant' to any challenges for invalidation/rejection, as new technical matter or information cannot be added to patent applications after having been filed with the patent office.

International protection: patent point of view

In order to appropriately secure patent protection international considerations should be considered. Patents have 20–25 years life. As developments expected in the regenerative medicine in the next decades are enormous, such 20–25 years are expected to have significant meaning to protect regenerative/cellular medicine products. As the market will likely go global, one should take a look at the world from the patent point of view: international and domestic strategies are both sides of the coin.

General conventions & domestic legislations

Patents need to be well prepared for global/whole strategy even before research and development has actually started, because once research and development has started, some information will be in the public domain, which would prevent you from protecting intellectual property rights owing to lack of novelty. On the other hand, one cannot realistically prepare a patent application before starting research. Otherwise,

one will have no results on which to base the application. As such, realistically, one should prepare and file a patent application before publication, which is likely at an early stage of research and development.

There are a couple of treaties and conventions that govern intellectual property rights from an international point of view, such as the Paris Convention [22] the Patent Cooperation Treaty (PCT) [23], and the like. The Paris Convention is important as it defines 'priority' right for a patent applicant to allow 1 year priority to file a patent application outside your country.

Priority may not be 'priority'

However, when considering an international/global patent portfolio, priority under the Paris Convention should always be carefully treated.

When contemplating filing a patent application directed to pharmaceutical or biological inventions including various countries (hereinafter 'later application') claiming priority to a basic patent application within 1 year, it is important to note that such a later application may add some additional information such as experimental data *vis-à-vis* the basic patent application. However, in most jurisdictions, such added information *per se* cannot enjoy priority right (i.e., such newly added information shall be treated as being filed on the later date). Therefore, if there is some intervening disclosure relating to the invention between the filing of the basic patent application and the later patent application, the later patent application relying on the added information shall be rejected owing to the intervening disclosure. As such, when formulating intellectual property strategy in the field of pharmaceutical or biological inventions from a global point of view, it is advisable that the practitioner should consider as to how and when experimental data should be added

or disclosed, especially prior to actually filing a basic patent application in his/her own country.

Proper strategy

Turning to the patent applications, it is noted that not only applications of cells or tissues derived therefrom, but also other ‘peripheral’ products/processes involving regenerative medicine technology, including apparatus, devices, culture media and reagents for stem cells, biological markers, clinical test system and the like, should also be considered. This is especially important in this field, in view of the facts that cells or tissues *per se* sometimes cannot be protected or are difficult to protect in some of the countries you wish to protect. On the other hand most ‘peripheral’ products/processes can be protected without difficulty as the other subject matter, and as such there is much room to maneuver patent strategy for such peripheral products/processes. It may be worthwhile to think and simulate what can be protected by patents over the world. It would be essential to prepare a well ‘equipped’ patent strategy in advance of the actual research and development to appropriately protect your valuable regenerative medicine products.

References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- 1 The Nobel Prize in Physiology or Medicine 2012. www.nobelprize.org/nobel_prizes/medicine/laureates/2012/yamanaka-facts.html
- 2 The Japan Patent Office. Summary of the 2nd meeting of the working group on the Patent Term Extension of Regenerative Medicine etc. 2014. www.jpo.go.jp/shiryou/toushin/shingikai/saisei-wg02_gijiyousi.htm
- 3 Decision of the European Court of Justice (Grand Chamber), Case C – 34/10, Oliver Brüstle v. Greenpeace eV, judgment of 18 October 2011.
- 4 USPTO. USPTO’s memorandum and guidance for determining subject matter eligibility of claims reciting or involving laws of nature, natural phenomena, and natural products. www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf
- 5 Alliance Regenerative Medicine. Sweeping FDA reforms successfully enacted. www.alliancerm.org/what-pdufa-means-to-regenerative-medicine
- 6 US FDA. Public Workshop: Synergizing efforts in standards development for cellular therapies and regenerative medicine products. www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm364114.htm
- 7 FDA. Small business assistance: frequently asked questions for new drug product exclusivity. www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm
- 8 European Medicines Agency. Advanced therapies. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0
- 9 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
- 10 European Medicines Agency. Committee for Advanced Therapies (CAT). www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp
- 11 European Patent Convention (EPC) Art. 53. www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar53.html#REF
- 12 EPC_Article 53(a), Implementing Regulations, Rule 28 (Exceptions to patentability) and Rule 29 (the human body and its elements).
- 13 Oliver Brüstle v. Greenpeace eV Decision of the European Court of Justice (Grand Chamber), Case C 34/10, judgment of 18 October 2011.
- 14 AIA The Leahy–Smith America Invents Act (AIA), Pub.L. 112-29, sec. 33(a), 125 Stat. 284.
- 15 USPTO’s Memorandum. Claims Directed to or Encompassing a Human Organism.

Disclaimer

This review describes the opinions and observations of the author as a Japanese patent attorney and does not necessarily represent the viewpoints of the author’s employers or author’s firm. By its nature, the subject article provides the author’s general opinion, and necessarily limited discussion of various topics; it does not purport to give specific legal advice or a substitute for legal counsel. As legal advice must be tailored to the specific circumstances of each case, nothing provided herein should be used as a substitute for advice of competent counsel. The author and the author’s firm assume no liability for the use or interpretation of information contained herein. The author and the author’s firm expressly disclaim all liability in respect of anything done or omitted to be done wholly or partly in reliance of this material.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

- www.uspto.gov/aia_implementation/human-organism-memo.pdf
- 16 Manual of Patent Examining Procedure 2105.
www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar53.html
 - 17 Provisional English translation of Examination Guidelines for Patent and Utility Model in Japan.
www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/1312-002_e.htm
 - 18 *Association for Molecular Pathology v. Myriad Genetics*, 569 U.S. 12–398 (2013).
 - **This decision deals with the patent eligibility of a naturally occurring gene, which results in drastic changes in patent examination standard.**
 - 19 *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* 132 S. Ct 1289 (2012).
 - **This decision is related to patent eligibility of a method of treatment and diagnosis based on the measurement of a certain marker from the human body. The decision held that the subject method only adds conventional and routine steps to natural phenomenon or laws of nature. This results in drastic changes in patent examination standard.**
 - 20 USPTO's Memorandum and Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, and Natural Products.
www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf
 - **This guidance is published based on the Myriad and Mayo decisions, which may affect the patent practice in any chemical and biological entities.**
 - 21 *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
 - **This decision is related to a genetically modified microorganism, which opened the way to secure patent protection regarding biotechnological inventions.**
 - 22 Paris Convention for the Protection of Industrial Property of March 20, 1883, as revised at Brussels on December 14, 1900, at Washington on June 2, 1911, at The Hague on November 6, 1925, at London on June 2, 1934, at Lisbon on October 31, 1958, and at Stockholm on July 14, 1967, and as amended on September 28, 1979.
 - 23 Patent Cooperation Treaty. Done at Washington on June 19, 1970, amended on September 28, 1979, modified on February 3, 1984, and on October 3, 2001.
 - 24 Chung Y, Klimanskaya I, Becker S *et al.* Human embryonic stem cell lines generated without embryo destruction. *Cell Stem Cell* 2(2), 113–117 (2008).