A patent perspective on US stem cell research

Albert Wai-Kit Chan, Alice Yuen-Ting Wong & Hon-Man Lee

What are the implications of recent US Supreme Court decisions on the patent eligibility of stem cells?

Research into stem cells has developed greatly since the first proof, more than 50 years ago, of their existence[1]. Stem cells are regarded as promising agents in personalized medicine owing to their self-renewing and pluripotent properties. Human embryonic stem cells (ESCs), adult stem cells and induced pluripotent stem cells (iPSCs) have been extensively studied for their potential uses in personalized medicine, and stem cell technology has been extended successfully from the laboratory to clinic—as in the generation, for example, of an artificial trachea from epithelial cells and chondrocytes derived from a patient's own mesenchyme stem cells[1], and of retinal-pigmented epithelium cells derived from human ESCs for the treatment of age-related macular degeneration[2].

As estimated on ClinicalTrials.gov, a US government website providing information of clinical studies worldwide, there have been more than 4,490 clinical trials employing stem cells. Thirty-four trials were found to include the term 'embryonic', suggesting that ESCs are rarely used for direct treatment of patients. By contrast, adult stem cells have been proven useful in treating patients with a wide range of diseases, including cancers, autoimmune diseases and neurodegenerative diseases, as well as wounds and injuries. Moreover, with reports of the creation of human stem cells from somatic cells[3] and the absence of ethical concern over the use of adult stem cells and iPSCs, these cells are likely to be frequently engaged in future therapeutics.

Albert Wai-Kit Chan and Hon-Man Lee are at the Law Offices of Albert Wai-Kit Chan, PLLC, Whitestone, New York, USA. Alice Yuen-Ting Wong is at Albert Wai-Kit Chan Intellectual Property Limited, Hong Kong, SAR, China.
e-mail: akitchan@aol.com, wonga@kitchanip.com, leehm@kitchanlaw.com

Table 1 Analysis of the three individual steps of Prometheus's claim

Individual steps	Court's opinion
The administering step	Simply tells doctors to treat patients with certain diseases with thiopurine drugs, which has long been practiced in the field
The determining step	Determines current level of the metabolite where methods for measuring the metabolite are known in the field
The wherein clauses	Suggest the doctors reconsider the drug dosage in light of a law of nature

But despite the optimistic outlook for stem cell research, the risk involved is still extremely high owing to the costs and time for research and development[4]. It is therefore essential for researchers to have an articulated intellectual property strategy for the protection of their inventions as well as to attract financial support for R&D.

The United States has long been an active region for stem cell research and patenting[5]. In this article, we analyze two recent US Supreme Court decisions and discuss the possible impact, from a stem cell perspective, of the cases on patenting biotechnological or pharmaceutical inventions. We then suggest a course for applying for patents in light of the recent case law. The two fundamental questions involved are: how and when is a process applying law(s) of nature patentable, and how and when is a product of nature patentable?

Mayo v. Prometheus

Mayo v. Prometheus[6] concerned patents owned by Prometheus Laboratories concerning the use of thiopurine drugs in the treatment of autoimmune diseases. At the time of invention, it was already known that blood levels of 6-thioguanine and its nucleotides (6-TG) and 6-methylmercaptopurine (6-MMP) correlated with the likelihood that a particular dosage of a thiopurine drug could cause harm or prove ineffective. However, the precise correlations between the metabolite levels and likely harm or ineffectiveness are not known. The patents at issue set forth method claims that embody the findings that identified these correlations with some precision[6].

On 20 March 2012, the Supreme Court ruled that the claims simply recited a natural law that is patent-ineligible subject matter under 35 USC §101, thereby rendering the patent invalid[6]. But although laws of nature are patent ineligible, a process applying laws of nature may be patentable[7], provided it contains "inventive concept" to ensure that the process amounts to significantly more than a patent upon the natural law itself[8]. The court viewed Prometheus's patents as setting forth a law of nature—namely the correlation between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm. Although it requires human action—the administration of a thiopurine drug—to trigger a manifestation of this correlation in a particular person, the relation itself exists in principle apart from any human action[6]. Hence, the question before the court became: did the patent claims add enough to their statements of the natural correlations for the claimed method to qualify as a patent-eligible process that applies the natural law[6]?

The answer from the court was no. After analyzing the individual steps of the claim (**Table 1**), the court concluded that "the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field. … upholding the patents would risk disproportionately tying up the use of the underlying

Table 2 Myriad's claims challenged by the Association for Molecular Pathology

Claims	Subject matter in the claims	US patent no.
Gene of *BRCA*	Isolated genes of *BRCA1*	5,747,282
	Isolated cDNA of *BRCA1*	
	Isolated DNA having at least 15 nucleotides of gene of *BRCA1*	
Method of analyzing or comparing *BRCA* sequence	Method of detecting the cancer-prone mutations in the genes by analyzing the nucleotide sequence of *BRCA1* from a human sample	5,709,999
	Method for screening a tumor sample bearing the cancer-prone mutations by comparing the nucleotide sequences of *BRCA1* of the tumor and nontumor samples	5,710,001
Method for screening potential cancer therapeutics	Method for screening compounds as potential therapeutics of breast cancer	5,747,282

natural laws, inhibiting their use in the making of further discoveries"[6]. The court reasoned that the steps in the claim do not add anything specific to the laws of nature and do not lead to an inventive application of them; that is, the steps are not sufficient to transform the claimed method to a patent-eligible process.

In light of *Mayo*, the US Patent and Trademark Office (USPTO) issued a memorandum on 3 July 2013 to provide guidelines to patent examiners on the determination of subject-matter eligibility of process claims involving laws of nature[8]. The memo instructs that a claim focusing on use of a natural principle must also include additional elements or steps to show that the inventor has practically applied, or added something significant to, the natural principle itself. The additional steps must be sufficient to ensure that the claim amounts to significantly more than the natural principle itself by including one or more elements or steps that limit the scope of the claim and do more than generally describe the natural principle with generalized instructions to 'apply it'. The additional elements or steps must narrow the scope of the claim such that others are not foreclosed from using the natural principle (a basic tool of scientific and technological work) for future innovation. Elements or steps that are well understood, purely conventional and routinely taken by others to apply the natural principle, or that only limit the use to a particular technological environment (field of use), would not be sufficiently specific. Patentable claims are those that confine their reach to particular patent-eligible applications of those natural laws[8].

Association for Molecular Pathology v. USPTO and Myriad Genetics

Association for Molecular Pathology v. USPTO and Myriad Genetics is a case of significant impact because it touches on the USPTO's 30-year practice of granting gene patents. It was estimated that the USPTO had issued patents covering more than 40,000 genes by 2005 (ref. 9).

On 12 May 2009, 20 entities, including the Association for Molecular Pathology, filed a lawsuit against the USPTO and Myriad Genetics challenging the validity of 15 claims in seven Myriad patents related to *BRCA1* and *BRCA2*, two human genes that were found to be associated with increased risk of breast and ovarian cancers[10] (**Table 2**). The plaintiffs claimed that the human genes were materials found in nature and thus not a patentable subject matter under 35 USC §101. They also contended that the method claims have no transformative steps and therefore only cover abstract and mental steps. The district court invalidated the claims and ruled that isolated DNA containing naturally occurring sequences is not patentable subject matter.

The case was appealed and heard twice by the US Court of Appeals for the Federal Circuit[11,12], which held that the isolated DNA claims are patent eligible, with each of the three judges on the Federal Circuit panel writing separately on the case (**Table 3**). The three method claims were analyzed in a similar fashion as in *Mayo*, with consideration on whether transformative steps are provided to turn the processes from abstract ideas to patentable subject matter. The court decided that the "analyzing" or "comparing" claims are patent ineligible because they claim only abstract processes. Nonetheless, the Federal Circuit overturned the district court's decision and ruled that the "screening" claim is patent eligible because there is a transformative step involved. **Table 3** summarizes the key opinions on the patent eligibility of Myriad's claims from various judges and courts.

A petition for certiorari was filed with respect to the Federal Circuit's second decision, and the US Supreme Court revisited the case on patent eligibility of the isolated DNA and cDNA claims. The Supreme Court unanimously ruled on 13 June 2013 that an isolated DNA with identical sequence to natural DNA is not a patentable subject matter[13]. The court held that even though the company had found an important and useful gene, separating that gene from its surrounding genetic material is not an act of invention, and extensive effort alone was not sufficient to satisfy the demands of 35 USC §101. On the other hand, cDNA is patent eligible because it is not naturally occurring. However, a short strand of cDNA that is indistinguishable from natural DNA may not be patentable[13].

The USPTO acknowledged in a memo to its patent examiners that *Myriad* would significantly change the examination policy regarding nucleic acid–related technology[14]. Claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, are not patentable[13]. On 4 March 2014, the USPTO issued an examination guideline[15] on patenting natural matters including laws of nature/natural principles, natural phenomena and natural products. Echoing the previously issued memos in light of *Mayo* and *Myriad*[8,14], the new guideline instructs that claimed natural matters must be "significantly" or "markedly" different from what exists in nature to be patent eligible. Under the guideline, a claimed natural product must possess a structural difference to be "markedly" different, whereas a functional difference does not necessarily lead to a marked difference. Patent-eligible applications or uses of natural matters must be significantly limited and do more than general instructions to apply or use the natural matters.

On 9 May 2014, the USPTO held a forum to collect public feedback on the guideline and interpretation of the Supreme Court precedents[16]. Various public parties profoundly expressed their dissent over the guideline and contended that the USPTO has misinterpreted or overlooked some of the precedent cases[17]. The USPTO indicated that the office is "open to hearing alternative interpretations and considering examples"[16].

Impact of *Mayo* and *Myriad*

The full impact of *Mayo* and *Myriad* on biotech and pharma patenting is not yet known, as much depends on subsequent measures taken by the USPTO and Congress. Nevertheless, it is beneficial for inventors to recognize the issues of patent eligibility in question and the rationale behind the rulings.

First, whether an isolation of subject matter is a patent-ineligible discovery or patent-eligible invention is essentially determined by whether the isolated product is identical to the naturally occurring product. The Supreme Court held that Myriad did not create or alter any of the genetic information encoded in the *BRCA1* and *BRCA2* genes. The isolated DNA has a sequence identical to that of the naturally occurring DNA and thus not a "new

Table 3 Summary of opinions on Myriad's claims from various authorities

		Federal Circuit				
Claims	**District Court**	**Judge Lourie**	**Judge Moore**	**Judge Bryson**	**US Supreme Court**	**Government**
Isolated DNA	Patent ineligible • Isolated DNAs are products of nature and are not "markedly different" from the native DNA.	Patent eligible • Isolated DNAs are different from natural products in "name, character and use" with new chemical composition. • They are the product of human manipulation and ingenuity.	Patent eligible • The chemical differences between isolated DNA molecules and the genomic DNA are insufficient to hold the isolated DNA a patentable subject matter. • However, the truncations of native DNA are not naturally produced without the intervention of man. • Also considers the USPTO's practice and interest of patent holder.	Patent ineligible • The cleaving of the chemical bonds during isolation does not turn the genes into "different materials." • Function of the isolated DNA is not attributable to the nature of the isolation process or to the difference in chemical composition. • Asserts no deference to USPTO's practice should be given.	Patent ineligible • A naturally occurring segment of DNA is not patent eligible by virtue of its isolation from the human genome. • Myriad's claims do not express in terms of the chemical composition nor rely on the chemical changes resulted from the isolation process.	Patent ineligible • Isolated and unmodified genomic DNA exists because of evolution, not humans.
cDNA	Patent ineligible • cDNA and short nucleotides without introns are not "markedly different" from native DNA. • Use of these DNA molecules as primers for probing or sequencing is the characteristic defined by the nucleotide sequence, which is naturally occurring.	Patent eligible • cDNA is especially distinctive, lacking noncoding introns. • They are results of human intervention.	Patent eligible • cDNA sequences do not exist in nature and have a distinctive character and use, with markedly different chemical characteristics from native DNA.	Patent eligible • cDNA cannot be isolated from nature but is created in laboratory. They have distinct structure and utility.	Patent eligible • cDNA is something new that is unquestionably created by the lab technician and not a product of nature, except those very short series of DNA that have no intervening introns to remove when creating cDNA.	Patent eligible • cDNA is DNA engineered by humans.
Short nucleotides as small as 15-mer		/	Patent eligible • 15-mer nucleotide has a variety of applications and uses in isolation that are new and distinct as compared to the sequence in our body.	Unpatentable • The claim is too broad as it encompasses each *BRCA 1* exon and covers portions of the cDNA of more than 4% of human genes and portions of DNA of nearly all human genes.	/	/
Method of analyzing or comparing *BRCA* sequences	Patent ineligible • The method merely covers abstract mental processes independent of any physical transformations. • The isolation and sequencing of DNA do not satisfy the machine-or-transformation test described in *In re Bilski*[22].	Patent ineligible • Only abstract mental processes are claimed. • Indistinguishable from the invalidated Mayo claim discussed above.			/	/
Method for screening potential cancer therapeutics	Patent ineligible • It claims a basic scientific principle, and the transformative steps amounted to only preparatory data gathering. • The administration of the test compound and creation of the transformed eukaryotic cell do not satisfy the machine-or-transformation test described in *In re Bilski*[22].	Patent eligible • The claim does not merely apply the law of nature and includes more than the abstract mental step of comparing the growth rate of two host cells. • The transformed cells arose from human effort by inserting a foreign gene into the cells.			/	Patent eligible

composition of matter" under §101. Human effort in discovering and isolating the DNA is insufficient to turn the isolated DNA into a patent-eligible subject matter under §101. By contrast, cDNA is patent eligible because it is not naturally occurring but created in the lab (except those very short fragments of DNA that have sequences identical to those of the naturally occurring DNA)[13].

Applying this reasoning to determine the patentability of stem cells isolated from a human body, one has to consider whether the isolated stem cells are fundamentally identical to the natural cells in our body. For instance, do the isolated embryonic and adult stem cells have more pluripotency and/or a higher rate of regeneration than the stem cells of the body? Do the isolated stem cells have a distinct structure (e.g., genomic or proteomic profile) from the natural stem cells? Or do the isolated stem cells have any features that are not found in the stem cells of the body? One may argue that the isolation of stem cells has opened up the potential for *in vitro* use of the stem cells. However, in view of *Myriad*, it may not be persuasive, as the possible new uses of the isolated DNA and cDNA were not considered to be as crucial as their intrinsic properties[13]. Conversely, iPSCs induced from somatic cells or ESCs derived by somatic cell nuclear transfer are more inclined to be patentable subject matter because they are not naturally occurring and are products resulting from human intervention.

It should be noted that 35 USC §101 is not the exclusive criterion for determining patentability. An isolated product that qualifies as patentable subject matter under §101 must also fulfill other statutory requirements such as novelty and nonobviousness, and the patent application needs to fulfill the enablement and written description requirements. In other words, the applicant must demonstrate a novel and nonobvious invention with clear and sufficient support in the patent application.

Second, the patent eligibility of a process applying abstract mental processes or laws of nature lies in whether the physical steps in the claims add enough to transform the abstract mental processes or laws of nature into an inventive application of these processes and laws. As instructed in the USPTO's memo[8], the fundamental inquiry for determining the patent eligibility of a process claim involving a natural principle (i.e., a law of nature, a natural phenomenon or a natural correlation) is: is the claim merely a description of and general instruction to apply the natural principle, or is it a practical application of a natural principle that amounts to more than the natural principle itself?

The following must be satisfied for a process claim to be patent eligible: (i) the claim is not merely a generalized statement or instruction to apply the natural principle; (ii) the claim contains at least one additional element or step that imposes a meaningful limit on the scope of the claim such that it does not seek a monopolized use of the natural principle; (iii) additional elements or steps inserted into the claim are not well-understood, routine, conventional activities previously engaged in by the researchers in the field and are not those that must be taken by one practicing the natural principle; and (iv) steps, such as data gathering and storage, that are merely nominally, insignificantly or tangentially related to the application of the natural principle are not sufficient.

In *Mayo*, the method claim includes steps of 'administering' and 'determining', and there are steps of extracting and sequencing DNA for the 'comparing' or 'analyzing' claims in *Myriad*. However, these steps were deemed insufficient to render the claims patentable because these are conventional steps specified at a high level of generality[6,12]. Conversely, for the 'screening' claim in *Myriad*, the Federal Circuit recognized the step of inserting a foreign gene into cells as transformative, as the step results in artificial cells with enhanced function and utility. The claim is thus not purely covering an abstract mental step of comparing the growth rate of two host cells and is patent-eligible[12].

Applying the above principles to inventions involving the uses of stem cells, the following methods may risk rejection under §101: (i) a method of determining whether a cell is pluripotent or differentiated by detecting the expression of specific, naturally occurring protein marker(s) on the cells, and (ii) a method of evaluating a treatment for neurodegenerative diseases by comparing the number of neurons in a subject receiving the treatment and a subject receiving no treatment. Method (i) is likely to be rejected because it merely recites the natural phenomenon wherein pluripotent or differentiated cells express particular protein(s). To render method (i) patent eligible, one needs to further limit the scope of the claim; for example, by reciting a step of using a particular antibody (especially one that is not known in the field) for detecting the protein marker. Method (ii) is likely to be rejected because it simply recites a natural correlation, wherein an effective treatment of a neurodegenerative disease would increase the number of neurons in a subject, without providing any practical application of the correlation. To survive the §101 test, one needs to further limit the scope of the claim by including additional steps, such as cell-viability assays that are not routinely used in the field. The key is to avoid simply reciting or generally applying the natural principle. A claim merely reciting a general concept or natural principle would effectively monopolize the concept or principle and thus would not be patent eligible. Patent-eligible method claims must include physical or nonconventional steps that impose limits on the natural principle so as not to cover all substantial applications of it.

Beyond the rulings

The court in *Mayo* and *Myriad* expressed its concerns about the impact of the rulings on various aspects of society, such as incentives for research entities, the loss of patent rights of current patent holders and the benefit to patients[18]. Judge Stephen Breyer takes the view that patent protection is a double-edged sword and that a balance is needed between providing "incentives that lead to creations, invention and discovery" and "impeding the flow of information that might permit, indeed spur, invention"[6].

It has been estimated that the USPTO has granted patents covering 41% of genes in the human genome[19]. Worries over a too-broad product or method claim that will deter scientific development or jeopardize public welfare continue to persist. After *Mayo* and *Myriad*, a broad claim that monopolizes the use of a product or method, or restricts others from further developing the product or method, may not be patentable. In the stem cell area, claims encompassing general stem cell lines or routine culture methods that cover virtually all human stem cells may no longer be patentable[20].

In view of these rulings, we suggest the following to inventors to facilitate patent procurement and enforcement: first, discriminate the difference(s) between the isolated and natural forms of a natural product and stress the distinctive features of the isolated product. Demonstrate useful application(s) of the isolated product with sufficient experimental support in the application. Second, avoid simply applying the natural principle in a process claim and avoid high levels of generality and well-understood, routine and conventional steps or elements in the process claim. Finally, limit the scope of a process claim that applies natural principle so that it does not seem to preempt the use of the principle or block every substantial practical application of the principle. Try to insert 'man-made ingredients' such as a machine or other specific reagents into the claim. Features that merely cover essential steps for applying the natural principle are too general and insufficient to limit the scope of the claim.

Conclusions

Changes in US patent policy in relation to biotech inventions are on the horizon. The USPTO may revisit the guideline on examining natural matters, and is expected to release a study on "effective ways to provide independent, confirming genetic diagnostic test activity"[21] that would touch on whether providing secondary genetic diagnostic tests would infringe gene or diagnostic method patents. Inventors are advised to revisit their patenting strategy and portfolio regularly to seek sufficient protection for their inventions.

ACKNOWLEDGMENTS

We thank N. Yi-Chen Su for insights into and comments on this article.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.2945).

1. Armstrong, L. *et al. Stem Cells* **30**, 2–9 (2012).
2. Schwartz, S.D. *et al. Lancet* **379**, 713–720 (2012).
3. Tachibana, M. *et al. Cell* **153**, 1228–1238 (2013).
4. Burrone, E. Patents at the core: the biotech business (2006). http://www.wipo.int/sme/en/documents/patents_biotech_fulltext.html
5. Bergman, K. & Graff, G.D. *Nat. Biotechnol.* **25**, 419–424 (2007).
6. *Mayo v. Prometheus*, 566 US 132 (2012).
7. *Parker v. Flook*, 437 US 584 (1978).
8. Hirshfeld, A.H. *2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature* (USPTO memorandum, 3 July 2012). http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf
9. Rogers, E.J. *J. Pat. Trademark Off. Soc.* **19**, 93 (2011).
10. *Ass'n v. USPTO*, 702 F. Supp. 2d 181 (S.D.N.Y., 2010).
11. *Ass'n v. USPTO*, 653 F. 3d 1329 (2011).
12. *Ass'n v. USPTO*, 689 F. 3d 1303 (2012).
13. *Ass'n v. Myriad*, 569 US 12–398 (2013).
14. Hirshfeld, A.H. *Supreme Court Decision in* Association for Molecular Pathology v. Myriad Genetics, Inc. (USPTO memorandum, 13 June 2013). http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf
15. Hirshfeld, A.H. 2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, and/or Natural Products (USPTO memorandum, 4 March, 2014). http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf
16. Zuhn, D.L. USPTO Holds Forum on Subject Matter Eligibility—Part I (Patent Docs, 12 May 2014). http://www.patentdocs.org/2014/05/uspto-holds-forum-on-subject-matter-eligibility-part-i.html
17. Zuhn, D.L. USPTO Holds Forum on Subject Matter Eligibility—Part III (Patent Docs, 15 May 2014). http://www.patentdocs.org/2014/05/uspto-holds-forum-on-subject-matter-eligibility-part-iii.html
18. Offit, K. *et al. J. Clin. Oncol.* **31**, 2743–2748 (2013).
19. Rosenfeld, J.A. & Mason, *C.E. Genome Med.* **5**, 27 (2013).
20. Thomson, J.A. US Patent No. 6,200,806 (2001).
21. Section 27 of Leahy-Smith America Invents Act. Public Law 112-29 (2011).
22. *In re Bilski*, 545 F.3d 943 (2008).