GENE PATENTS, PATENTING LIFE AND THE IMPACT OF COURT RULINGS ON US STEM CELL PATENTS AND RESEARCH

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ABSTRACT
In June 2013, the US Supreme Court ruled that naturally occurring genes were unpatentable in the case *Association for Molecular Pathology v. Myriad Genetics*. Up until this decision, Myriad Genetics was the only company in the US that could legally conduct diagnostic testing for *BRCA 1* and *2*, genes that are linked to familial breast and ovarian cancer. The court case and rulings garnered discussion in public about patenting biological materials. This paper describes the progression of the Myriad Genetics case, similar US rulings and biological intellectual property policies. In addition, it discusses the impact of the case on biological patents – specifically those for human embryonic stem cells.

KEYWORDS: AMP, BRCA, genes, Myriad Genetics, patents, USPTO

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PERSPECTIVES

On June 13, 2013, the US Supreme Court ruled that naturally occurring genes were unpatentable in the court case *Association for Molecular Pathology (AMP) v. Myriad Genetics* [1,2]. In 1998 [3] and 2000 [4], Myriad Genetics was granted patents for two genes, *BRCA1* and *BRCA2*, which are implicated in hereditary breast and ovarian cancer. Prior to this ruling, Myriad was the only company in the USA that could legally conduct diagnostic testing for these genes. Myriad chose not to license the patents and harshly pursued anyone infringing on them. The patenting of the *BRCA* genes launched a raucous debate about the ability to patent life: how do we distinguish between what is simply discovered and what is truly "made by man" [2,5]?

Here, we will describe the progression of the *AMP v. Myriad Genetics* case, as well as compare the legal and scientific rationale for and against gene patents with that of stem cell patents, especially focusing on human embryonic stem cell (hESC) patents. We will also compare US rulings and policies on similar technologies and elaborate on the problems associated with resolving highly scientific disputes in the courts. Finally, we will discuss potential changes to the intellectual property landscape as a result of this ruling.

GENES, CELLS AND ORGANISMS: A HISTORY OF US LIFE SCIENCE PATENTING

Patents for science and biology have a long history in the US courts, beginning early in the 20th century (Table 1). In 1911, the Supreme Court ruled in *Parke-Davis v. Mulford* that pure adrenaline could be patented because, in its concentrated form, it was distinct from its natural form in glands [6]. Several years later, the Supreme Court clarified this ruling in *American Fruit Growers v. Brogdex* [7]. In this 1931 decision, the Court deemed that oranges that had been treated with borax to prevent pests were not patentable because they were not "markedly different" from oranges existing in nature, setting this requirement for future life technologies. Finally, the Patent Act of 1952 codified the requirement for all patents to be nonobvious to those doing similar work [8].

More significant to biotechnology are the series of rulings over the past 30 years. In 1980, the landmark case *Diamond v. Chakrabarty* guaranteed the ability to patent some forms of life [5]. Researchers fought to patent a bacterium that had been genetically modified to digest oil, and ultimately, the court ruled that "anything under the sun made by man" was patentable. This was later upheld in the 1991 court decision of *Animal Legal Defense Fund v. Quigg,* which tried unsuccessfully to overturn the US Patent and Trademark Office (USPTO) guidelines for the patenting of "non-naturally occurring, non-human multicellular organisms" [8,11]. Finally, in 1995, the Biotechnology Process Patent Act (PL 104-41) established the official standards of USPTO for biological patents [16]. These decisions led to the patenting of transgenic mice strains (1988; the "oncomouse" [10]), hESCs (2001 by Wisconsin Alumni Research Fund [WARF] [12]), and other living organisms or their components, including genes [3,4].

Overall, there are four broad categories that are eligible for patents: process (an act or series of acts or steps), machine, manufacture (an article produced from raw or prepared materials by giving them new forms) and a composition of matter. Many biotechnological patents, such as gene or DNA patents, include claims for both a composition of matter, the gene itself and a process, such as a diagnostic test. Furthermore, to obtain a patent, a biotechnology invention must meet the same criteria as other patents: it must be novel, be nonobvious to researchers in the field and have utility [8]. Three judicially recognized exceptions are laws of nature, physical phenomena and abstract ideas.

Recently, several biological patents have been challenged in court because they do not meet the USPTO patent criteria. Typically, a patent that involves a "law of nature" must show some manipulation or transformation beyond isolation to be patent eligible. In the 2012 Supreme Court case *Mayo Collaborative Services v. Prometheus Laboratories* [15], Mayo challenged a Prometheus patent for a diagnostic test that measured metabolites in the blood [17]. The test determined the dosing efficacy of a class of drugs, thiopurines, which can be toxic when given in excess. The Supreme Court ruled in favor of Mayo, stating that the diagnostic test was merely an application of a law of nature; the test did not transform the metabolites into something new [17]. On similar legal grounds, gene patents were recently challenged in *AMP v. Myriad Genetics* [1].

The first gene patent was granted in 1982 for a gene fragment for the hormone endorphin [9]. Since then, patents have been granted for a variety of forms of DNA, including cDNA, genes (although naturally occurring genes are no longer eligible) and diagnostics associated with genes. In 2003, the Weldon Amendment prohibited patents for entire genomes or human organisms [8]. USPTO previously allowed gene patents, stating that "an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state and processed through purifying steps that separate the gene from other molecules naturally associated with it" [8]. Before the *AMP v. Myriad Genetics* 2013 ruling, it was estimated that approximately 20% of human genes had US patents associated with them [18]. However, fewer gene patent applications have been submitted in recent years, most likely due to the fact that most genes are now in the public domain as a result of the Human Genome Project. With the 2013 Supreme Court decision, most of these patents for naturally occurring genes will be invalidated.

In addition to patents for genes, patents for cells have been granted and challenged. In stem cell research, the most controversial patents are the hESC patents held by WARF. In 2001, WARF was granted a patent for the creation of hESC lines [14] and in 2006, was granted a second patent for its stem cell culture formula involving leukemia inhibitory factor [12]. These patents allow WARF to charge a royalty for use of the lines it developed, as well as prohibit the creation, use or selling of hESCs without a license. Several researchers opposed these patents, arguing that hESC patents did not fulfill the nonobvious requirement. They alleged that the procedure was based on protocols previously used to

isolate embryonic stem cells from other animal species such as the mouse [19,20]. Furthermore, other researchers were pursuing hESC isolation at the time of Thomson's discovery in 1998 [21] and published their similar findings [22] shortly after Thomson. Researchers also believed that the patenting of hESCs hindered research and development in this area, as WARF gained a monopoly on the lines and the process to create them. As a result, in 2006, the Foundation for Taxpayer and Consumer Rights and the Public Patent Foundation asked USPTO to revoke the patents [23]. While USPTO ultimately validated the patents, WARF, responding to the challenges, amended some of its claims and relaxed its licensing procedures [24].

Although WARF obtained patents for hESCs in the USA, it was unable to obtain similar patents in the EU because the technology violated public morality, as described in the European Biotechnology Directive [25]. Specifically addressed in the 2011 EU Court of Justice case *Brüstle v. Greenpeace* [26], the European Biotechnology Directive deems technologies that require the destruction of a human embryo unpatentable [25]. This policy is in contrast to gene patents, which are currently allowed in the EU, but not the USA [25,27].

GENES IN THE COURT: AMP V. MYRIAD GENETICS

The *BRCA 1* and *2* genes were discovered in 1994 and 1995, respectively [28]. From the beginning, scientists knew these genes were important in understanding and diagnosing a familial type of breast and ovarian cancer. Soon after their discovery, Myriad Genetics filed and received patents for the two genes (Box 1). The patents covered three areas: the isolation of the genes or composition; the process of detecting the mutation in *BRCA*, which causes cancer; and the drug screening method to determine which therapeutics are most effective for certain types of cancer. Using these patents, Myriad Genetics dominated the market for *BRCA1/2* genetic mutation testing, forcing out competitors who tried to enter the market by aggressively defending their patents [2].

The American Civil Liberties Union and AMP challenged Myriad's gene patents in 2009 [1,2]. The lawsuit was a result of Myriad's strict enforcement of their patents, which limited genetic testing services and discouraged academic research. In addition, AMP argued that gene patents interfered with the practice of medicine and the ability of doctors to make treatment decisions.

In the US District Court, Judge Robert Sweet invalidated the *BRCA* patents on several accounts, asserting that the process of isolating DNA does not fundamentally change the nature of DNA or the information it encodes [1,28]. This ruling was challenged and reversed 2-1 in the Federal Appeals Court, where two of the judges stated that DNA isolated from the body is "markedly different" than DNA found in the body. AMP appealed this ruling to the US Supreme Court. In 2012, the Supreme Court heard the case *Mayo Collaborative Services v. Prometheus Laboratories* [15] and overturned a patent involving a diagnostic test of blood metabolites to determine the effectiveness of drug dosages because the patents' claims were a "law of nature" [17]. As a result, the Supreme Court returned *AMP v. Myriad Genetics* to the Federal Appeals Court, who determined that, despite the Mayo ruling, all of the Myriad patents remained valid [1,28]. Furthermore, in light of this decision, USPTO established new guidelines for evaluating process claims that involved laws of nature [8].

The US Supreme Court selected the case again for its 2013 docket. The court looked specifically at one of Myriad Genetics' claims—the patentability of human genes. On April 15, the court heard arguments in the case that included the US Justice Department (represented by the US Solicitor General Donald Verrilli), who testified in support of neither party [29]. During the oral arguments, many of the court's questions revolved around the central idea of "why the gene is or is not a product of nature." Gregory Castanias (counsel for Myriad Genetics) claimed that the *BRCA 1* and *2* genes were invented because

scientists determined the beginning and end of the genetic sequence. On the contrary, Christopher Hansen (counsel for AMP) argued that though important, the discovery of the *BRCA* genes was simply that—a discovery—as opposed to a patentable invention.

The patentability of cDNA was also discussed in the hearing [29]. Hansen opposed cDNA patents, emphasizing that these fragments of DNA did exist in nature and were therefore, like genes, unpatentable. Castanias and Verrilli (US Solicitor General and "a friend of the court"), both asserted that cDNA was a manmade creation. The final question by Sotomayor to Hansen foreshadowed the court's ruling: "Is there some value to us striking down isolated DNA [patents] and upholding the cDNA [patents]?" [29].

In the end, as expected based on oral arguments, the court ruled that naturally occurring genes are not patentable. But the court left open the patentability of cDNA. Since cDNA is created in a laboratory environment through the conversion of mRNA to DNA, it was not considered a "law of nature." What is unclear is whether cDNA would pass the "nonobvious" criterion, since scientists would be producing the cDNA from a known genetic sequence using established techniques. The court's ruling attempted to strike a balance between the economic incentives provided by patents and the dispersion of knowledge for research purposes. Scientists and doctors supporting the plaintiffs and AMP celebrated the victory, calling it a "great decision" [2]. Supporters of Myriad and the gene patent, including executives from WARF and the Biotechnology Industry Organization, called the ruling "troublesome" and a "departure from decades of judicial and Patent and Trademark Office precedent" [2].

From Genes to Stem Cells

The US Supreme Court ruling to prohibit patenting naturally occurring genes may or may not affect the patentability of other biological "inventions" such as stem cells. Much will depend on how the patents were written. If they include the isolation techniques, culturing conditions and applications using the cells—especially if they alter the cells' structures in the process—they will have a better chance of being upheld, as opposed to patents for the cell itself. But, ultimately, the courts—when new cases are brought up for review—will determine how to interpret the *AMP v. Myriad Genetics* ruling [2,30]. This could potentially result in more cases at the Supreme Court level to clarify patent policy on other aspects of biotechnology.

The courts could view genes and stem cells similarly because they are both derived from larger tissues, but most likely they will be viewed similarly to cDNA. Genes were determined to be "products of nature" because their isolation did not require significant manipulation [1]. The starting product was structurally similar to and encoded the same information as the final product. In contrast, the courts saw cDNA as distinctly created by man. Since stem cells are often manipulated through cell culturing, it is likely they would be classified similarly to cDNA, but this might depend heavily on the wording of specific patents.

Still left to be determined is whether cDNA or stem cells can be classified as "nonobvious." If, indeed, the technologies are defined as obvious, their patents would be invalidated. For hESCs, the initial cells were isolated from a blastocyst, but required strict and specific culture conditions for growth. These cultured cells are functionally identical to the isolated cells, which could affect their patent eligibility. However, the patents from WARF include the cells as well as the procedures to culture and differentiate them. The scope of the patents makes them less likely to be completely nullified as a "law of nature," although part of the patents could be struck down if determined to be "obvious." The interpretations of the *AMP v. Myriad Genetics* still leave the results of a challenge uncertain.

Patents related to induced pluripotent stem cells, on the other hand, have a stronger argument. Patent holders and scientists can prove that these cells are not found in nature but created in a laboratory—an argument used successfully for cDNA patents. To generate induced pluripotent stem cells, isolated somatic cells are returned to a pluripotent state by turning on specific genes.

It seems that the easiest way to avoid having a patent challenged is to not be overly harsh or strict as to how it is enforced. Both patents for the *BRCA* genes held by Myriad genetics and the hESC patents held by WARF were contested because of harsh licensing procedures. Scientists and patient advocates perceived these practices as stifling innovation and hindering the progression of research [2,20]. But, ultimately, judicial rulings are focused not on how strictly a patent is enforced but on the type of claimed invention.

The two patent cases are significantly different in both how they were challenged as well as why. While the AMP challenge proceeded in the federal court system, the challengers for the hESC patents have focused on USPTO. Asking USPTO to re-examine a patent is a far less costly option, but it limits the ability of the challenger to question the patent holder or their submissions [12]. The two sets of patents were also initially challenged for different reasons. The *AMP v. Myriad Genetics* cases concentrated on whether the patents were for products of nature, while the hESC patent challenges have focused on the nonobvious clause. USPTO requires that an invention be sufficiently different from what has been used or described before and not "obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains" [8]. Several prominent scientists from around the world have supported the assertion that hESCs were indeed an extension of previous work [19]. It has also been contended that the group only isolated them first because it had access to substantial financial resources. Nevertheless, to date, none of the USPTO reviews have successfully invalidated WARF's hESC patents or claims. However, as a result of the *AMP v. Myriad Genetics* ruling, Foundation for Taxpayer and Consumer Rights and Public Patent Foundation decided to challenge the WARF patents in court on the grounds that hESCs, like genes, are products of nature [31].

Whether the recent *AMP v. Myriad Genetics* court decision will impact the USPTO view of hESC patents remains to be determined, but several scientists and policy scholars have already begun speculating on whether they will be overturned [2]. WARF's managing director has argued that, unlike genes, hESCs are not naturally occurring, and if WARF's patent is overturned, so will other biological patents such as human insulin and cell receptors.

CONCLUSIONS

Since the *Diamond v. Chakrabarty* decision in 1980 [5], the patenting of life in the USA continued to trudge forward. But this was not without debate on the moral and ethical implications of these patents. Many workshops, publications and books have been written over the past 20 years looking at different perspectives, including those in science, industry and religion [32-34]. Discussions predominately focused on the commoditization of human life, such as whether these entities should be subject to ownership. Many scholars are staunchly opposed to profiting from these types of patents. They argue that the patenting of genes, cells or organisms devalues life and diminishes the respect that all forms of life deserve. Others maintain that if a biological entity has commercial value and can benefit society, it should be patentable [34].

However, the ethical and moral debate has never impeded the ability to patent biotechnological inventions in the USA. No legislation, with the exception of the Weldon Amendment, has been passed to limit patents on genes or cells. Furthermore, patent examiners purely evaluate the patent to see if it fits

within a patentable category and meets the major criteria for patent eligibility. They are not tasked with evaluating the patent's morality. In addition, the USPTO guidelines for patentability of biological material have not adapted in the face of growing scientific knowledge or as a result of moral arguments. Thus, the majority of the legal opposition has focused on whether the material that is being patented meets the criteria for patentability.

By contrast, the EU Biotechnology Directive explicitly states that "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" [35]. Often referred to as the "morality clause," this policy allows for the review and sometimes rejection of biological patents for ethical and moral reasons. However, genes and DNA sequences can be patented in the EU when isolated from the body. The EU drew a line at the patenting of hESCs. The EU Biotechnology Directive prohibits the patenting of "human embryos for industrial or commercial purposes." In *Brüstle v. Greenpeace* [26], this part of the Directive was used to outlaw the patenting of products and technologies using hESCs if human embryos are destroyed at any point in the development of the hESC line or the technology itself [35]. In the USA, however, the patenting of hESC lines and products is permitted, despite these types of moral arguments.

However, the addition of a morality clause to patent regulations could create unintended consequences. A morality clause would most likely become political in the current partisan climate in Washington. Patents to technologies related to controversial areas such as birth control or assisted suicide could be revoked in one presidential administration and granted in others. In the USA, politics has affected the ability to conduct human embryonic and hESC research with federal funding for decades [36]. Federal funding has largely been influenced by the political party leading the executive branch. Adding an ethical component to patent law may make patenting biotechnology challenging if each change in administration or leadership in Congress shifts the moral compass. However, with the current patenting system and lack of outcry for change, the inclusion of a "morality clause" in the USPTO guidelines is unlikely to occur anytime soon.

An additional issue is that the US patenting system is set up in such a way that there is little opportunity to challenge a patent until after it has been granted [12]. Challenges occur usually in one of two ways: asking for USPTO to review a patent or a business impacted by the patent could ask the courts to invalidate it.

The first course gives the challenger limited ability to present evidence and question the patent holder. The court system, however, is expensive. In addition, the rulings are limited to the patentability of the item in question. Courts often refrain from making broader statements or delineating guidelines for what is and is not considered patentable. Neither avenue of contestation reviews whether the innovation should be patented from a moral or ethical standpoint.

Utilizing the courts to develop and clarify patent policies for biotechnology is common in the USA. However, this practice is also limited by the ability of judges to understand the technology and its impact. In fact, in the *AMP v. Myriad Genetics* case, all three Appeals Court judges interpreted the product of nature doctrine differently to support their opinions [27]. And, by their own admission, the US Supreme Court justices were not experts in any scientific field [31]. They relied heavily on materials such as amicus briefs submitted to the court, especially a detailed genetics background from Eric Lander, founding director of the Broad Institute and chair of the President's Council of Advisors for Science and Technology [31]. However, this material was not available to the lower courts when making their decisions.

During *AMP v. Myriad Genetics*, the justices and attorneys used several different analogies to put the scientific arguments into a context that was understandable and relatable. As a comparison to gene isolation, the justices used an analogy of an explorer discovering a new plant in the Amazon and subsequently taking an extract from that plant [29]. Castanias compared the isolation of a gene to making a bat out of a piece of wood; in both, the "inventor" must decide where the gene/bat begins and ends. Analogies helped to make the science easier to comprehend, but none fully explained the scientific principles that were being argued.

Unfortunately, the broadness of the *Diamond v Chakrabarty* ruling [5]—"anything under the sun made by man can be patented"—left much to interpretation and has resulted in patent challenges in court, despite the fact that these venues may not be the most appropriate for ruling on scientific material. These major scientific decisions should be revisited outside of a courtroom. While the recent change to US patent policy—the 2011 Leahy-Smith America Invents Act—did make changes to patent law, it only altered the patenting procedure from first to invent to first to file [8,37]. The new law left the scope of what is patentable unaddressed. Congress, with experts at USPTO and in consultation with scientific and legal scholars, should now discuss and evaluate biological patents and, ultimately, make the decision on patents instead of the courts.

Scientific discoveries are progressing, leading to innovation and new technologies. Inventors deserve patent protection, but the rights of patients and ethical considerations should be addressed before blindly granting patents. Furthermore, the complexity of biotechnology might reduce the need for patents in the future, as it would be difficult for potential copiers to infringe upon these patents. Patents are valid for only 20 years, and half of this time has already passed on several hESC patents, with currently no treatment available using hESCs that has successfully completed all phases of clinical trials. Inventors may file for patent extensions if they meet certain criteria, for instance to account for time that the product was patented, under regulatory review and not being marketed [8].

FUTURE PERSPECTIVE

While the Supreme Court ruling only applies to naturally occurring gene patents, it could still impact other areas of biotechnology and the overall patenting process. In light of the decision, USPTO revisited the guidelines for patent eligibility when the claims involve a "law of nature." Since the ruling in *AMP v. Myriad Genetics* only applies to naturally occurring gene patents, other existing biotechnology patents will most likely be challenged separately—and a challenge for hESCs is already underway. Changes in the US system are unlikely to include a "morality clause" to determine what should and should not be patented, but could include changes in reviews of application and licensing regulations. In addition, universities will be more engaged in the future by increasing patent applications, as well as making sure that their researchers are not infringing on existing patents.

There do not appear to be any major shifts in the patentability of biotechnology after the *AMP v. Myriad Genetics* ruling. Although USPTO revisited the guidelines for patenting products of nature, the ability to patent biotechnology itself does not seem to be in real peril [38]. In fact, the Supreme Court decided the case fairly narrowly—only addressing naturally occurring genes. Other forms of DNA patents seem unaffected by the ruling. Because cDNA patents remain patentable, it is likely that hESCs and other stems cells, which require manipulation beyond their isolation, will likely not be revoked on these grounds. However, they, like cDNA, may be challenged successfully in the future based on other requirements such as the nonobvious criterion.

Patent policy for biotechnologies has predominately been created as a result of court decisions in the USA, although the Weldon Amendment did outlaw the patenting of human organisms. It is doubtful this will change in the near future. Moreover, the USA has no clause that prohibits patenting of biotechnology for ethical reasons, meaning that these considerations are not usually taken into account. With the development of new technologies, especially those that involve parts of the human body, asking the question whether this should be patentable on moral grounds becomes quite important, but this question is unlikely to be addressed through legislation or court rulings anytime soon.

The area that has seen change recently and could see additional changes in the future is related to overall patent guidelines. Today, approximately half a million patents are filed every year in the USA, and this number is growing [8]. Patent officers are overwhelmed, and it now takes over two years from filing a patent to approval. The new guidelines —switching from first to invent to first to file—make the US system similar to other patent offices, including the European Patent Office. But this change does not address other problems with the system, such as the ability to review patents before they are granted and improving ways to challenge existing patents [12].

Currently, there is no outside review of patents before they are implemented. Patents are only challenged after they are granted through the Board of Patent Appeals at USPTO or in the courts [8]. This is typically a long, drawn-out process. In the case of biotechnology patents, the median length from challenge to resolution is 6.5 years, which favors the patent holder [12]. A public comment time either before the patent is granted or before it is enforceable would allow stakeholders and peers to review applications and challenge them at lower cost and risk. In the case of hESC patents, this could have saved years of challenges by addressing the issue from the beginning of whether they were “obvious.”

Furthermore, overly strict enforcement will lead to more patent challenges through the courts and USPTO system. Licensing oversight is an area that the US Congress could get involved with in the near future, instead of changing patent procedures [27]. A prominent concern about patents is that there is a “tragedy of the anticommons,” or when people “underuse resources because too many owners block them” [39]. In biotechnology, it has been alluded to that the large number of patents and diverse set of owners make it hard for scientists to conduct research and develop new technologies – using the Myriad and hESC patents as examples. Aside from these examples, however, research on patenting has not found convincing evidence that overproliferation of patents is stifling innovation [16,40]. Instead of limiting the patentability of biotechnology, policymakers could focus patent licensing to minimize restrictive practices that interfere with research and development.

In addition, with the vast number of new patents each year, scientists and universities will become more aware of patents related to research [41]. For the most part, patent holders are open to licensing their technologies to university researchers at little to no cost. But these agreements must still be arranged; scientists cannot freely use these technologies without consequence. There are a few exceptions to this rule. Scientists can begin to use a patented material or process, without infringement, to prepare products for market ahead of patent expiration. This is termed the “Hatch-Waxman” exemption in the USA. For instance, drug companies can use this exemption to begin early production of generic drugs prior to patent expiration, so the drugs are ready for market as soon as the patent expires [42]. The exemptions also allow the use of patented products for nonprofit purposes for the sake of curiosity and discovery, as in the common law research exemption. This exemption prevents people who may be tinkering around in their basement from being slapped with an expensive infringement lawsuit. However, this policy has been broadly interpreted by the courts and typically excludes research at universities where future commercial development is possible [43].

Universities in the USA should become proactive in pursuing patenting opportunities for their scientists as well as ensuring that research does not infringe on existing patents. However, it has been suggested that in seeking patents and creating their own sets of complex material transfer agreements, universities have been more a part of the problem with the patent landscape than an aid to help promote free exchanges of research ideas [44]. Establishing a transparent, universal process for the sharing of materials and ideas may be a good first step to promote the progression of research and prevent costly infringement lawsuits.

Furthermore, patent descriptions should become more detailed to ensure "inventions" meet patent requirements. Patents are often written broadly to encompass many possible forms and applications of an invention and prevent the patenting of similar technologies by outside entities. However, broadly written patents have been successfully challenged in the courts recently and have left the patent holder at risk of losing their intellectual property rights [23,45]. Without the inclusion of specific details in the process, it can be difficult to distinguish between what a scientist has actually invented and what he/she discovered. Instead, scientists should work to include the innovative details in the patent [38]. This inclusion will make it more difficult for the patent to be challenged in court on the basis of not meeting the patent requirements of novelty and nonobviousness. However, adding specific details to patents makes it easier for similar patents to be written that do not infringe, and broad patents are favored by industry. Certainly a balance must be struck between the two, but as patents continue to be filed, the ability to write broad patents that successfully meet patent requirements becomes more difficult.

Finally, the recent court cases that have been decided in the USA and EU make it difficult to get universal patent protection for a biotechnological invention. In the EU, naturally occurring genes can be patented while hESCs and their products cannot. The exact opposite is true in the USA. This discrepancy in the patent eligibility confounds efforts being made globally to harmonize patent laws [8]. One of the goals of the America Invents Act was to reshape US patent law to be more in line with that of European nations, thus the change from first to invent to first to file [8]. In addition, the absence of a worldwide set of guidelines or regulations for biotechnology patents and the uncertainty of what court challenges could arise may make some researchers and investors shy away from research and commercialization in this field. This could have vast implications on the development of new medical diagnostics and therapeutics.

The future ability to patent biotechnological inventions is murky. There is no doubt that with the advancement of scientific research, biotechnology patents will continue to be filed. Because many of these types of patents will involve "laws of nature," it is inevitable that several will be challenged in court. Moving forward, scientists must be aware of the broad patent landscape and push for new patent and licensing guidelines. This could keep patents out of court, make the patenting process more seamless and help to spur innovation.

EXECUTIVE SUMMARY

HISTORY OF LIFE SCIENCE PATENTS: GENES, CELLS AND ORGANISMS

- The scope and patentability of biological materials have been determined by the courts over the past century.
- In the landmark case *Diamond v. Chakrabarty*, the court ruled that "anything under the sun made by man" was patentable. This ruling guides most biotechnology patent policies.

ASSOCIATION FOR MOLECULAR PATHOLOGY V. MYRIAD GENETICS: GENES IN THE COURT

- The **ASSOCIATION FOR MOLECULAR PATHOLOGY** sued Myriad Genetics due to overly strict enforcement.
- The US Supreme Court ruled in June 2013 that naturally occurring genes were unpatentable because they were considered laws of nature.

FROM GENES TO STEM CELLS

- The US Supreme Court ruling to prohibit patenting naturally occurring genes may or may not affect the patentability of other biological "inventions" such as stem cells.
- As a result of the *Association for Molecular Pathology v. Myriad Genetics* ruling, the Wisconsin Alumni Research Fund patents are being challenged on the grounds that human embryonic stem cells, like genes, are laws of nature.

CONCLUSION

- US patent policy does not include what should be patented from a moral perspective.
- USPTO offers limited opportunities to challenge patents – all occur after the patent is granted.
- Courts are inappropriate places to determine patent policy for complex biological inventions.

FUTURE PERSPECTIVE

- Biological patents will be challenged, and a few which involve products of nature may be narrowed or dismissed.
- It is unlikely the US Congress will visit the ethics and morality of biological patents, but changes to the USPTO review process and patent licensing regulations are possible.
- Universities will continue to push for research patents from their scientists and patent scope will become more limited to avoid court challenges and patents.

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Table 1: Timeline of US Life Science Patents and Patent Laws		
Year	Court case	Ref.
1911	*Parke-Davis v. Mulford*: pure adrenaline is deemed patentable because it is distinct from adrenaline found in gland tissue	6
1936	*American Fruit Growers v. Brogdex:* product/material must be markedly different to product of nature to be patent eligible	7
1952	Patent Act of 1952: "nonobviousness" a requirement for patentability	8
1980	*Diamond v. Chakrabarty*: "Anything under the sun made by man" can be patented	5
1982	First gene/DNA patent granted: the hormone endorphin	9
1988	First animal patented: the "Oncomouse"	10
1991	*Animal Legal Defense Fund v. Quigg:* validated patents of organisms not existing in nature	11
1998	*BRCA1* gene patents issued to Myriad Genetics	3
2000	*BRCA2* gene patents issued to Myriad Genetics	4
2001	hESC patents issued to WARF	12-14
2003	Weldon Amendment: patenting human organisms is illegal	8
2006	WARF patents challenged. In 2010, USTPO validated WARF's patents, although some had their scope narrowed.	12
2009	*AMP v. Myriad Genetics:* challenge of *BRCA1/2* gene patents	1
2011	US Patent Reform Act/Leahy-Smith America Invents Act: changed inventor from first to invent to first to file	8
2012	*Mayo Collaborative Services v. Prometheus Laboratories:* diagnostic tests to determine drug dosing deemed unpatentable	15
2013	Supreme Court rules on *AMP v. Myriad Genetics case:* naturally occurring genes are not patentable, but cDNA created in a laboratory is	1

AMP: Association for Molecular Pathology; hESC: human embryonic stem cell; USPTO: US Patent and Trademark Office; WARF: Wisconsin Alumni Research Fund.

Box 1: Timeline of Myriad Genetics Court Case	
1998	**November 17: *BRCA2* Patent US5837492 issued to Myriad Genetics (UT, USA).** The gene was isolated in 1995, and the patent for it was filed in 1996.
2000	**December 19: *BRCA1* Patent US6162897 issued to Myriad Genetics.** The gene was isolated in 1994, and the patent for it was filed in 1995. This patent covers three areas: the isolation of the gene itself (composition), the process of detecting the mutation (method) and the drug screening method to determine which therapeutics work best for certain mutations (drug screening).
2009	**May 12: AMP filed a lawsuit against the US Patent and Trademark Office and Myriad Genetics stating the patents for *BRCA1* and *BRCA2* were invalid.** The lawsuit was a result of Myriad's strict enforcement of the patents discouraging genetic testing services and academic research. In addition, AMP believed gene patents interfered with the practice of medicine and the ability of doctors to make treatment decisions.
2010	**March 29: The US District Court rules that Myriad's patents were invalid.** Judge Sweet ruled against all three claims: composition, method and drug screening. The isolation of the gene involved a law of nature, therefore making it unpatentable. The comparison of the DNA sequences in the method consisted of abstract mental processes, not a methodology, and was therefore unpatentable. Finally, the drug screening involved cell growth rates, which the judge decided was a basic scientific principle and not eligible to be patented either.
2011	**July 29: The US Appeals Court reversed District Court ruling and held that genes were eligible for patents.** The Appeals court overturned two of the rulings specifically on composition and drug screening. It determined that the gene was not found isolated in nature and was therefore patentable. For the drug screening, the court believed that since the cells were transfected with the mutation, it was patentable. The judges did uphold the district court's determination that the method was unpatentable. **December 7: The ACLU filed petition for a US Supreme Court review of the case.**
2012	**March 26: The US Supreme Court vacated previous judgments and sent the case to the Appeals Court for review in light of recent Supreme Court ruling on *Mayo Collaborative Services v. Prometheus Laboratories*.** **August 16: The US Appeal Court ruled that the Myriad Patents were legal.** This was as similar of a decision as that in 2011. **November 30: The US Supreme Court granted a petition to review the case.**
2013	**April 15: The US Supreme Court heard the arguments.** **June 13: The US Supreme Court ruled that *BRCA* genes were unpatentable.** The court ruled that naturally occurring genes were products of nature and therefore unpatentable.
Data taken from [1,3,4]. *ACLU: American Civil Liberties Union; AMP: Association for Molecular Pathology*	