# Patent border wars: defining the boundary between scientific discoveries and patentable inventions

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**Drawing an appropriate boundary between unpatentable natural phenomena and patentable inventions is crucial in preventing the patent laws from unduly restricting access to fundamental scientific discoveries. Some would argue that, particularly in the U.S., patents are being issued that purport to claim a novel product or process but that, in effect, encompass any practical application of a fundamental biological principle. Examples include gene patents, which Congress is considering banning, and patents relating to biological correlations and pathways, such as the patents at issue in the headline-grabbing *LabCorp v. Metabolite* and *Ariad v. Eli Lilly* litigations. In view of the mounting concern, it seems likely that Congress and/or the courts will address the issue, and perhaps substantially shift the boundary.**

## Introduction

The range of potentially patentable subject matter is vast, particularly in the U.S., where essentially any non-naturally occurring product or process is eligible for patent protection.[*] U.S. law does allow the government to block the patenting of an invention in certain rare situations, in which publication of a description of the invention would endanger national security [1]. But the purpose of this provision is to prevent the dissemination of information, not to deny the inventor patent protection *per se*, and the inventor is entitled to government compensation for any losses that result from an inability to patent the invention [2]. The law also limits the ability of patent owners to enforce certain disfavored classes of patents, such as patents that claim medical procedures [3] or business methods [4]. But the U.S. has declined to enact any subject matter specific limitation on patentable subject matter; even attempts to ban the patenting of genetically engineered mammals (including human beings) and human cloning have failed to win Congressional approval[†] [5,6].

In contrast, other countries explicitly rule out the possibility of patenting certain types of subject matter, often on moral grounds. For example, under the European Patent Convention surgical, therapeutic and diagnostic procedures are not considered patentable [7], and the European Union (EU) classifies as unpatentable certain inventions involving human cloning, germ line modification and embryonic stem cells [8]. For a time, the European Patent Office even refused to issue patents that claim human genes, a longstanding practice in the U.S., but the moratorium was lifted in 1999 in line with the directive of the European Commission for harmonizing biotechnology patents in the EU [9]. Until 2005, Indian law did not allow product patents on substances capable of use as a medicine, drug or food, but this policy was terminated to comply with international treaty obligations [10].

## A dichotomy between unpatentable 'laws of nature and natural phenomena' and patentable inventions

Prior to 1980 there was considerable uncertainty in the U.S. as to the extent to which patent protection would be available for biotechnology-related innovations. In particular, it was unclear whether living organisms were patentable subject matter. Some feared that even inventions based on the constituent parts of living organisms, such as recombinant biomolecules and biotechnological processes, would be found ineligible for patent protection. However, these concerns were largely dispelled by the landmark decision of *Diamond v. Chakrabarty*, wherein the Supreme Court held that a genetically engineered microorganism can be patented [11]. Subsequent decisions by the courts and U.S. Patent and Trademark Office (USPTO) have expanded upon that principle, establishing that genetically modified plants and non-human mammals are also eligible for patent protection, as are genetic sequences and other biotechnology-based inventions [12,13].

In an oft-quoted passage from *Chakrabarty*, the Court stressed that Congress intended the realm of potentially patentable subject matter to encompass 'anything under the sun that is made by man' [11]. This language, expansive as it is, nonetheless evokes the key caveat under U.S. law, that to be patentable an invention must be of human origin. By contrast, the Court has repeatedly emphasized that 'laws of nature, natural phenomena and abstract ideas' are not patentable [11]. Although the discovery of a previously unrecognized principle of nature might

[*] Of course, in order to be patentable the product or process must satisfy various patentability requirements, such as novelty and nonobviousness, and satisfy some minimal threshold of practical utility (35 U.S.C. §§ 101 *et seq.*).

[†] The U.S. Patent and Trademark Office (USPTO) has implemented a policy of refusing to grant patent claims that would encompass a human being, though neither Congress nor the courts have provided any explicit support for the practice. Section 2105 of the USPTO Manual of Patent Examining Procedure (MPEP), available at http://www.uspto.gov/web/offices/pac/mpep/mpep.htm (last visited Sept. 1, 2007). See also http://www.patentlyo.com/patent/2005/02/uspto_still_no_.html (last visited Sept. 1, 2007).

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warrant a Nobel Prize, in and of itself it will not provide the basis for a patent. The Court has characterized fundamental scientific discoveries, such as 'E = $mc^2$' and the law of gravity, as 'manifestations of . . . nature, free to all men and reserved exclusively to none' [11].

Of course, because only products and processes can be patented, it would be impossible to literally patent the bare recitation of law of nature, such as E = $mc^2$. However, the practical exploitation of a law of nature in the guise of a new product or process is patentable, regardless of whether the invention was only made possible by the discovery of the underlying natural phenomenon. For example, Chakrabarty's invention was a genetically-modified bacterium capable of degrading crude oil. Although the existence of genes encoding the requisite metabolic processes and the ability of bacteria to take up and express foreign DNA might be characterized as natural phenomena, Chakrabarty's creative integration and practical utilization of the discoveries transformed these phenomena into patentable technology.

Although the 'made by man' requirement is easy to state as an abstract concept, in practice it is often difficult to draw the line to between an unpatentable scientific discovery and a manmade invention. For example, should one be able to patent an obvious practical application of a newly discovered natural phenomenon? Perhaps not, because on more than one occasion the Supreme Court has indicated that some significant additional inventive contribution is necessary to 'transform an unpatentable principle into a patentable process' [14]. What about a product or process claimed in such broad terms as to effectively encompass any practical application of a newly discovered natural phenomenon? Again, arguably no, based on a Supreme Court decision that invalidated a patent claiming a computer program because it effectively pre-empted any 'substantial practical application' of the underlying algorithm [15]. Nonetheless, many would argue that in practice the lower courts and USPTO have been overly permissive in allowing patents that claim obvious applications of newly discovered scientific principles, or that effectively cover any practical use of the discovery, and that these patents have a negative impact on biomedical research and ultimately on public health.[‡]

## Gene patents

So-called 'gene patents' increasingly have become the subject of public criticism [13,16] (see also http://www.whoownsyourbody.org/). Whereas naturally-occurring genes as they exist in the body are considered unpatentable 'products of nature,' various forms of human intervention, such as purifying a genetic sequence from its native environment, converting an mRNA to its corresponding cDNA, or chemically synthesizing a gene, are considered sufficient to confer patentability upon isolated or recombinant polynucleotides [13]. Patent law generally treats isolated polynucleotides in the same manner as it would any other newly invented molecular compound [13]. The principle that purification of a naturally-occurring biological material from its native environment can render the purified product patentable has a long history. For example, in 1873 Louis Pasteur received a patent that claimed 'yeast, free from organic germs of disease, as an article of manufacture' [17]. Since then, the courts have upheld the validity of claims directed to purified adrenalin and prostaglandin, noting that the isolated forms of these molecules do not exist in nature and have substantial therapeutic utility [18]. Purified native proteins are also routinely patented.[§]

Despite the established precedent that allows the patenting of purified natural products, some argue that genes should be treated differently. For example, Affymetrix, a leading supplier of DNA hybridization array technology, has argued before the courts that 'isolated, purified and synthesized' cDNA molecules should be classified as unpatentable 'products of nature,' because the mere removal of DNA from its native environment and excision of noncoding regions does not result in any substantial functional difference from naturally occurring DNA or RNA [19]. Likewise, the Deputy Director of the World Intellectual Property Organization has argued that 'isolated, purified and synthesized human genes are not statutory patentable subject matter because, when isolated from the human body, they maintain identical or very similar characteristics to those found in nature . . . [and] because they realize exactly the same function that genes inserted in their natural environment perform' [20].

It is not surprising that a DNA chip company like Affymetrix would oppose patents that claim naturally occurring genetic sequences, because these are the raw materials for the manufacture and use of their products. A single microarray might contain thousands of polynucleotides, each corresponding to a distinct genetic sequence, and it has been suggested that a thicket of gene patents might impede the development of this important technology [21]. However, Affymetrix has been a successful provider of hybridization array technology for more than a decade and appears to have never been sued for infringing a gene patent [22]. More generally, the hypothetical threat of a gene patent thicket does not appear to have manifested itself in actual patent enforcement against the makers and users of hybridization arrays [22]. Although this does not mean that gene patents will never be asserted against the providers or users of hybridization array technology, or that a perceived threat of lawsuit has not restricted the development of certain applications of the technology, it does suggest that perhaps the extent of problem has been overstated.

Congress is now considering a bill intended to ban altogether the patenting of genes, entitled the Genomic Research and Accessibility Act of 2007 (GRAA) [23]. In fact, the language of the proposed legislation appears to go farther than that by rendering unpatentable all 'nucleotide

[‡] Sarnoff, J.D. (2006) Shaking the Foundations of Patentable Subject Matter, or Taking Exclusions for Science, Nature, and Ideas, Principles of Invention, and *Parker v. Flook* Seriously, Presented at the Oracle International Corp.-George Washington University Law School 2006 Symposium *What's Ahead on Highway 101* (manuscript on file with author).

[§] See, for example, *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir 1991) (alleging infringement of U.S. Patent No. 4,677,195, which claims purified erythropoietin) and *Scripps Clinic and Research Inst. v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991) (alleging infringement of U.S. Reissue Patent No. 32,011, which claims purified Factor VIII:C).

sequences, their properties and correlations, and their naturally occurring products'. The GRAA provides no definitions for the terms used, but assuming 'nucleotide sequence' refers to polynucleotides, it would seem to encompass any invention that comprises DNA, RNA, and perhaps even synthetic variants such as peptide nucleic acids (PNAs). If taken literally, the bill would apparently ban the patenting of any DNA-based invention, which includes synthetic genetic sequences that do not occur in nature, and technologies that employ DNA in nongenetic applications, such as aptamers, DNA computers, and DNA used as a structural molecule in nanotechnology applications. Not only would the prohibition be sweeping, extending well beyond genes *per se*, it would also be unprecedented; as noted above, U.S. law currently contains no subject-matter-specific bar to patentability. At this time, the bill has reportedly garnered little support and much criticism, and passage appears to be unlikely [24]. However, this is not the first attempt in recent years to limit the patentability of genetic sequences and likely will not be the last [25].

### Patents that claim fundamental biological phenomena

Although gene patenting has been the focus of much of the debate over the appropriate definition of patentable subject matter, gene patents are merely one example of a more general phenomenon: an apparent increase in the rate at which patents that broadly cover the use of fundamental biological relationships, correlations, and pathways are being issued by the USPTO and asserted in court. Some patents that broadly claim the practical exploitation of a fundamental scientific discovery are shown in Table 1.

For example, the discovery of a correlation between certain mutations in the BRCA1 (breast cancer 1, early onset) gene and a susceptibility to cancer resulted in several patents [26] that purportedly encompass any practical diagnostic procedure for detecting these mutations [27]. Although these patents have never been successfully asserted in court, the owner of the patents, Myriad, has been accused of using the threat of patent litigation to restrict access to the tests, which raises the cost and prevents other laboratories from developing improved testing procedures [27,28].

Myriad's BRCA1 patents are often categorized as gene patents, but many of the most problematic patents directed at fundamental biological principles do not claim genes or their direct function. For example, consider the case of *Metabolite v. LabCorp* [29]. The patent at issue in *Metabolite* arose out of the discovery by university researchers of a correlation between the level of total homocysteine in a human body and the existence of a vitamin B deficiency. Based on this discovery, the university secured a patent that effectively claimed any method for detecting a vitamin B deficiency that involves the steps of: (i) assaying the body fluid of a patient for total homocysteine; and (ii) correlating an observation of elevated total homocysteine with the existence of a vitamin B deficiency [30]. Significantly, the patent purports to encompass the use of any methodology for assaying for total homocysteine, even assay technology developed after the university applied for the patent. The university licensed the patent to Metabolite, which then sued LabCorp for performing total homocysteine tests and promoting the test as a means for doctors to diagnose vitamin B deficiency. The Court of Appeals of the Federal Circuit, the highest patent specific appellate court in the U.S., found that the patent was infringed by doctors who ordered homocysteine assays for their patients and used the results to diagnose for vitamin B deficiency [29]. Although the doctors were the direct infringers, LabCorp was held liable for indirectly infringing the patent by performing the test and 'inducing' doctors to use the test to diagnose vitamin B deficiency. The court ordered LabCorp to stop performing any tests for total homocysteine. Note that LabCorp does not appear to have ever enforced its patents directly against physicians, and that commercial total homocyteine testing is still available in the U.S. from other providers [see, e.g., the Diazyme Laboratories website, http://www.diazyme.com/products.php (last visited Sept. 1, 2007)], thus attenuating the negative impact of the decision on U.S. patients.

The patent at issue in *Metabolite* appears to cross the line into unpatentable subject matter by effectively foreclosing any practical use of a natural phenomenon. Although the patent does require an assaying step, once the existence of such a correlation was discovered it seems obvious that a health care provider would need to assess the total homocysteine of a patient to apply the discovery to patient care. In the words of the Supreme Court, the mere inclusion of an assay step arguably constitutes insufficient 'post-solution activity' to transform the discovery into a

**Table 1. Examples of patents that broadly claim the practical exploitation of a fundamental scientific discovery**

| U.S. Patent No. | Claimed subject matter | Corresponding patent litigation |
|---|---|---|
| 6,432,644 | Methods of detecting mutation in KCNE1 gene linked with long QT syndrome | *DNA Sciences, Inc. v. Genedx, Inc.*, Civ. No. 02–5578 (N.D. Cal.) |
| 5,753,441 | Methods of detecting mutations in BRCA1 gene linked with cancer | *Myriad v. Oncormed*, Civ. No. 98–35 (D. Utah) |
| 4,940,658 | Method of correlating elevated total homocysteine with vitamin B deficiency | *Metabolite Laboratories., Inc. v. Laboratory Corp. of America*, 370 F.3d 1354 (Fed. Cir. 2004) |
| 6,420,139 | Method of using a correlation between vaccination schedule and risk of developing an immune disorder in vaccination protocols | *Classen Immunotherapies v. Biogen IDEC*, 381 F. Supp. 2d 452 (D. Md. 2005) |
| 6,410,516 | Method of repressing NF-κB activity | *Ariad Pharmaceuticals v. Eli Lilly*, 2007 WL 2011279 (D. Mass. 2007) |
| 5,324,668 | Method of correlating a woman's maternal serum level of free β human chorionic gonadotropin and gestational age with the woman's risk of carrying a fetus with Down syndrome | *JN MacRi Technologies, LLC et al.*, Civ. No. 04–953 (E.D.N.Y.) |
| 5,843,780 | Purified preparation of primate embryonic stem cells | Not applicable |

Abbreviations: Civ. No., Civil Number; D., District; E.D.N.Y., Eastern District of New York; Fed. Cir., United States Court of Appeals for the Federal Circuit; F.Supp., Federal Supplement; KCNE1, potassium voltage-gated channel, Isk-related family, member 1; LLC, Limited Liability Company; N.D., Northern District.

patentable invention [14]. Also troubling is the fact that the patent was found to be infringed based primarily on an infringing doctor's mental correlation of homocysteine and vitamin B levels.

Although the Supreme Court rarely decides patent cases, it agreed to hear an appeal of *Metabolite* to specifically address a single question: whether the patent violated the Court's prohibition against patenting 'laws of nature, natural phenomena, and abstract ideas' [31]. Ultimately, after the parties had fully briefed and argued the case, the Supreme Court changed its mind and 'decided not to decide' the case after all, so the decision by the Federal Circuit still stands. A majority of the justices ruled that the earlier decision by the Court to hear the case had been a mistake, essentially because the issue of patentable subject matter had not been directly addressed in the lower courts, and because the Supreme Court normally does not decide issues that were not already argued in the lower court [32]. Nevertheless, a vocal minority of three justices would have decided the case and invalidated the patent claim [32]. These dissenting justices voiced strong concerns regarding the policy implications of such patents, and seemed eager to decide the case in a manner that would restrict the patentability of processes that in effect embody a law of nature.

### The prospect of future Supreme Court intervention

Although in principle Congress could intervene to limit the scope of patentable subject matter by statute, this seems unlikely, at least in the short term. For example, patent reform legislation currently being considered by Congress would not address the issue [24]. This leaves the Supreme Court in the best position to reverse the trend in the USPTO and lower courts towards an overly expansive interpretation of the scope of patentable subject matter. The decision by the Supreme Court to at least consider the issue in *LabCorp v. Metabolite*, and the three dissenting justices expressed desire to rein in the scope of patentable subject matter, particularly with regard to biological discoveries, suggest that the Court might be poised to do just that. At the very least, the Court could provide some needed clarification in this highly controversial area of law. Two cases currently working their way through the lower courts, *Classen v. Biogen* [33] and *Ariad v. Eli Lilly* [34], might serve as appropriate vehicles for the Supreme Court to address this important issue should it so choose.

*Classen* involves four patents, all based on the discovery that variations in vaccination schedule can affect the risk of developing chronic immune-mediated disorders. The patents, issued to a Dr Classen, broadly claim methods for determining vaccination protocols based on comparing the incidence of immune disorders between two or more groups of subjects immunized under different schedules [35]. Note the similarity to *Metabolite*: in both cases the patents at issue purport to effectively encompass any practical exploitation of a newly discovered but naturally existing biological correlation. A district court concluded that the correlation between vaccination schedule and risk of developing an immune disorder is a natural phenomenon, and that the claims amounted to an 'indirect attempt to patent the idea that there is a relationship between vaccine schedules and chronic immune mediated disorders' [36]. The court ruled that the patents were invalid for effectively encompassing an unpatentable natural phenomenon, but Classen has appealed, and perhaps ultimately the Supreme Court will have an opportunity to decide the case.

*Ariad* has garnered much more public attention than *Classen* but raises similar policy issues. The patent at issue in *Ariad* arose out of the discovery by prominent university researchers of the transcription factor NF-κB (nuclear factor-kappa B), and the crucial role the NF-κB pathway plays in regulating gene expression in a variety of contexts. The discovery resulted in a patent that broadly claims methods of inhibiting NF-κB-mediated intracellular signaling by reducing NF-κB activity [37]. The patent was ultimately licensed to Ariad, a private company that proceeded to assert the patent against several pharmaceutical companies, notably Eli Lilly and Amgen, based on the sale of drugs whose mechanism of action purportedly involves an inhibition of NF-κB activity. Significantly, there is no indication that the discovery of the NF-κB pathway played any direct role in the development of these drugs. Last year, a jury found that the use of Eli Lilly's drugs raloxifene (Evista®), a selective estrogen receptor, and drotrecogin alfa (Xigris®), used for the treatment of sepsis, both infringe the patent and awarded Ariad $65 million in back royalties and 2.3% royalty on future U.S. sales [34,38].

Subsequent to the jury's decision, Eli Lilly asked the district judge hearing the case to invalidate the patent for impermissibly claiming a principle of nature. As with the patents at issue in *Metabolite* and *Classen*, Ariad's patent seems to broadly cover any practical application of the discovery of the ubiquitous NF-κB pathway, including the use of drugs that inadvertently affect that pathway but which were developed without any specific intent to affect NF-κB. However, in this case the judge rejected the argument and found that Lilly had not provided sufficient evidence to prove that Ariad's patent claimed an unpatentable natural phenomenon [34]. Part of Eli Lilly's problem might have stemmed from its difficulty in overcoming a fairly strong presumption under U.S. law in favor of validity in cases where the USPTO has examined and allowed the challenged patent to issue. This story is far from over, however, because unless the parties settle it seems inevitable that Eli Lilly will appeal the court's decision to the Federal Circuit, and perhaps eventually even to the Supreme Court.

### Conclusions

Although it has been suggested that a more restrictive interpretation of the patentable subject matter doctrine might hurt the biotechnology industry, these sorts of patents tend to come out of universities, not private companies. This should come as no surprise, because basic research tends to lead to fundamental scientific discoveries, and in recent years universities have become increasingly aggressive in seeking and enforcing patents [39]. For example, Myriad's earliest BRCA patents [27], and the patents at issue in *Metabolite* and *Ariad* all trace their origin to university research, as do the University of Wisconsin's controversial patents that claim cultured

embryonic stem cells [40]. By contrast, established biotechnology and pharmaceutical companies are more likely to find themselves on the receiving end of an infringement suit, as exemplified by the cases discussed above that were brought against Amgen, Eli Lilly, Biogen and LabCorp.

On the whole, the advance of biotechnology would probably be better served by a patent law that more effectively limits the patenting of basic scientific discoveries. The patented university discoveries described in this article, that is, mutations in the BRCA genes, cultured embryonic stem cells, NF-κB and the correlation between homocysteine and vitamin B, would all surely have been discovered with or without the incentive of a patent. This sort of basic research is typically funded by grants, and the promise of publication and recognition should be enough incentive for university researchers to make and disclose these types of discoveries. By contrast, these patents can serve as a hindrance and disincentive to the follow-on research and commercial development activities required to transform fundamental discoveries into potentially life-saving technologies.

Although the attempt to ban gene patents embodied in the GRAA is clearly intended to address some of the important policy concerns discussed in this article, the proposed legislation is highly problematic. As noted above, although the language is vague, the bill would appear to eliminate patent protection for any invention involving DNA, and perhaps polynucleotides in general. Synthetic genetic constructs and nongenetic applications of DNA are clearly the product of human invention, not natural phenomena. To institute a blanket prohibition on patenting such inventions would be a substantial and unwarranted blow not only to biotechnology, but other technology sectors that also employ DNA and other polynucleotides, such as nanotechnology. At the same time, the legislation fails to address the more general problem of patents that broadly claim obvious applications of newly discovered biological principles, the vast majority of which do not directly involve polynucleotides or their 'properties and correlations.'

Furthermore, gene patents are asserted in court only infrequently, and there is little evidence to demonstrate that they have substantially impeded the progress of biomedical research, or the availability of the resulting cures [22,27,28]. Nevertheless, if some legal reform is deemed necessary to address a perceived problem of gene patents, there are alternative approaches that would be preferable to the GRAA. For example, instead of banning DNA patents, a more reasonable solution might be to limit the enforceability of gene patents in the context of research and genetic testing. In fact, this was the approach embodied in the Genomic Research and Diagnostic Accessibility Act of 2002, a bill introduced in Congress that was never enacted into law [25]. Alternatively, Congress should consider legislation that would comprehensively address the more general problem of patents that broadly claim fundamental scientific discoveries, rather than focusing narrowly on genes and DNA.

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