Commentary

US Supreme Court's Decision on the Patent Ineligibility of Human Genes BRCA1/BRCA2 as Products of Nature

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US PATENT LAWS AND THE CONSTITUTIONAL MANDATE

The patent laws are in the U.S. Constitution dating back from 1790 to 1793 to promote, as articulated by one of the framers, Thomas Jefferson, and protect 'any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement thereof'. Although the U.S. Congress in 1952 replaced the word 'art' with the word 'process', the Congress, as well as the courts, have strived to retain the basic philosophy of the Constitutional mandate that 'ingenuity should receive a liberal encouragement'. In accordance with such constitutional mandate, and to follow the spirit of the mandate, the U.S. Supreme Court in 1980 boldly declared in the case *Diamond v. Chakrabarty* (447 U.S. 303, 1980) that 'anything under the sun that is made by man' is patent eligible under the patent laws as long as it meets the statutory requirement of novelty (35 USC section 102), non-obviousness (section 103), detailed description for enablement (section 112) and utility (section 101/112). It is noteworthy that the framers of the Constitution not only put such language in the Constitution but to emphasize the spirit of such mandate, when the first US patent was granted to Samuel Hopkins on July 31, 1790 for 14 years, President George Washington and the Attorney General Edm. Randolph signed this issued patent followed by Secretary of State Thomas Jefferson who also signed and delivered the patent to Mr. Hopkins on the 4th of August, 1790. This was thus an exciting beginning of both the promotion of the inventive spirit, legal protection of such inventions for a period of time, and the economic development in the United States. This commentary deals with a patent eligibility issue decided by the US Supreme Court on June 13, 2013 in the case *Association for Molecular Pathology, et al v. Myriad Genetics, Inc., et al* (No. 12-398), where the Supreme Court held that a naturally-occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.

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PATENT ELIGIBILITY ISSUES IN RECENT YEARS

There have been contentious court cases in recent years in the US about what is a patentable invention. Two recent patent eligibility issues involve business methods, particularly computer-related methods. The *Bilski v. Kappos* case involved a business method of hedging commodity-associated risks on price fluctuations for energy commodities such as natural gas or electricity. In 2008, the Court of Appeals for the Federal Circuit (CAFC) set forth the criteria for subject matter eligibility for patentable process claims that must be tied to a machine or apparatus or must be involved in the transformation of a material to a different state or thing. Since the *Bilski* claims did not address such issues, the CAFC decided against the patent eligibility of the *Bilski* claims. On appeal to the Supreme Court, the Court in June 2010 affirmed the CAFC decision on the patent ineligibility of the *Bilski* claims as representing abstract ideas which are not patent eligible as previously decided by the Court in the case *Diamond v. Diehr*, 450 US 175, 182, 185 (1981)

that laws of nature, natural phenomena and abstract ideas are not patent eligible under 35 USC section 101. A more recent case involving computer programming is the case *CLS Bank Int'l v. Alice Corporation Private Ltd*, involving computer programming on risk minimization for foreign currency exchange and similar monetary exchanges. Although the CAFC issued diverse opinions and split decisions, holding *Alice*'s patents on computer methods, program and storage medium as invalid, in June 2014, the US Supreme Court issued a unanimous verdict holding that the software patent claims were drawn to a patent ineligible abstract idea and were thus patent ineligible.

For patent eligibility issues involving diagnostic procedures and drug dosing, a recent relevant case is that of *Mayo Collaborative Services v. Prometheus Laboratories*. The claims in the patent applications filed by Prometheus Laboratories covered the use of thiopurine drugs to treat autoimmune diseases, and how to arrive at the optimum dosage of the drug. Since Mayo Collaborative Services and Mayo Clinic used such diagnostic tests on their own, Prometheus Laboratories sued Mayo alleging patent infringement. Although the CAFC affirmed the patent eligibility of the Prometheus patent claims as they were pertinent to the machine or transformation test, in March 2012, a unanimous Supreme Court reversed the CAFC ruling, holding that claims directed to methods of drug dosage optimization are basically a manifestation of the laws of nature and are therefore patent ineligible.

ISOLATED DNA OF HUMAN BRCA1/BRCA2 GENES, PRODUCT OF NATURE ISSUE AND PATENT ELIGIBILITY OF BRCA1/BRCA2 GENES

An interesting case involving patent eligibility of isolated and purified DNA of the human BRCA1 and BRCA2 genes, where specific mutations confer susceptibility to breast and ovarian cancers in women (and breast and prostate cancer in men, but with a lower frequency) is that of *The Association for Molecular Pathology v. Myriad Genetics, Inc*. During the period 1995 – 2000, the University of Utah Research Foundation and a company Myriad Genetics filed several patent applications to the US Patent and Trademark Office (USPTO) to cover the role of two genes BRCA1 and BRCA2 where certain mutations led to a high incidence of breast and ovarian cancers in women. Myriad Genetics quickly developed a sophisticated screening test for the detection of such mutations in the DNA isolated from the blood of women with family history of breast and/or ovarian cancers. Since Myriad Genetics owned the patents, the company was alleged to charge high fees for conducting such tests and prevent other clinicians in other parts of the United States to conduct such tests, leading to extreme frustrations among such clinicians and their vulnerable patients. A similar situation occurred in Europe where Myriad Genetics held similar patents such as EP 705 903 entitled 'Mutations of the BRCA1 gene linked to a predisposition to breast cancer and ovarian cancer' and another patent EP 705 902 on a similar topic, granted in 2001. However, in May 2004, the European Patent Office revoked a key Myriad patent EP 699 754 covering diagnosis of predisposition to breast and ovarian cancers after opposition from Institut Curie in France and many European institutions. On appeal from Myriad, and after many back and forth arguments, the revoked patent was reinstituted in a severely limited form.

In the US, frustrated with Myriad Genetics' strict enforcement of its patent rights on BRCA1 and BRCA2 genes, the Association for Molecular Pathology, the American Civil Liberties Union, the Public Patent Foundation and a group of patients and clinicians brought a lawsuit in May, 2009, in the District Court of the Southern District of New York against the USPTO alleging that the USPTO should not have issued the patents to Myriad since human genes such as BRCA1/BRCA2 are products of nature, common to mankind and should not be the products of commerce. In March 2010, Judge Robert Sweet of the District Court in Manhattan granted a Summary Judgment in favor of the plaintiffs, revoking the Myriad patents.

In June 2010, Myriad appealed the district Court ruling to the CAFC for reversal, arguing that the isolated and purified BRCA genes were not the same as they occurred in the human genome and required considerable human skill and intervention. A 3-judge CAFC panel, in July 2011, then reversed the New York District Court ruling, upholding the patent eligibility of isolated and purified BRCA genes, but not the mutations on the ground of mental exercise.

The CAFC decision was then appealed to the US Supreme Court and in March 2012, the Supreme Court vacated and remanded the *AMP v. Myriad Genetics* case, No. 11-725, to the CAFC to reconsider its decision based on the previous Supreme Court ruling on *Mayo Collaborative Services v. Prometheus Laboratories*. In August 2012, a 3-judge panel of the CAFC reaffirmed its earlier decision on the patent eligibility of isolated and purified BRCA1 and BRCA2 genes, leading the plaintiffs to appeal to the Supreme Court for a final resolution. On June 13, 2013, in a unanimous decision, the Supreme Court held that isolated BRCA1 and BRCA2 genes are naturally occurring DNA segments without any modifications and are not patent eligible. The main issues considered by the Supreme Court involved several Myriad patents and several claims such as claims 1, 2, 5, 6, and 7 of the US patent 5,747,282, claim 1 of the US patent 5,693,473 and claims 1, 6 and 7 of the US patent 5,837,492. These claims basically assert a patent on 'an isolated DNA coding for a BRCA1 polypeptide with the sequence of 1863 amino acids shown in a SEQ ID No. 2'; another claim concerns 'the isolated DNA with a nucleotide sequence shown in SEQ ID No. 1'. Another claim concerns 'an isolated DNA having at least 15 nucleotides of the DNA of claim 1', thus giving Myriad the advantage of exclusive rights to such 15 nucleotides of the BRCA genes. The Supreme Court ruled that Myriad's isolated BRCA DNA is otherwise structurally identical to the natural gene and is not markedly different from what exists in nature, making BRCA1 and BRCA2 genes as products of nature and therefore patent ineligible. The CAFC and the Supreme Court both agreed that the complementary DNA (cDNA) made from the messenger RNA (mRNA) is patent eligible.

DEFINING A PRODUCT OF NATURE: THE DEVIL IS IN THE DETAILS

The Supreme Court's verdict that BRCA1 and BRCA2 genes are not patent eligible because they are products of nature raises an interesting question: what is a product of nature? On the surface, a product of nature is something that is found in nature as is and can be isolated from nature as is. A fruit hanging from a tree is a product of nature but is the seed present inside a product of nature, or is a tiny fragment of the seed broken from it a product of nature? Thus a human cell is a product of nature because it can be isolated from the human body or various tissues as is and not being a tiny integral part of the body or tissue. A nucleus from a human cell can be isolated as is and thus is a product of nature, as are the chromosomes present in the nucleus. However, a chromosome usually harbors a few hundred genes which are integral parts of the chromosome and are not freely present in the nucleus. BRCA1 and BRCA2 genes are parts of the chromosomes and can be viewed as products of nature in the sense that human cells have produced them from parent DNA, but they have no separate existence as independent entities. As the Supreme Court pointed out in its decision, the human genome consists of approximately 22,000 genes packed into 23 pairs of chromosomes. BRCA1 and BRCA2 genes are on chromosome 17 and 13. BRCA1 gene does not exist as a continuous stretch of functional gene. It has 24 exons of varying length on chromosome 17Q21.31 while BRCA2 has a few more exons than BRCA1 spanning 84 kilobases (kb) of genomic DNA on chromosome 13Q12.3 (1, 2). BRCA1 forms a complex with mRNA-splicing machinery to regulate pre-mRNA splicing (3) and the functional gene encodes a nuclear phosphoprotein for maintenance of genomic stability through complex formation with a large number of tumor suppressors, DNA damage sensors and signal transducers with ubiquitin ligase activity (4). Mutations in BRCA1 are responsible for 40% of inherited breast cancer and about 80% of inherited breast and ovarian cancers. Chromosome 13 with the BRCA2 gene spans more than 95 mega bases with about 633 genes and 296 pseudogenes. It is thus clear that neither BRCA1 nor the BRCA2 gene exists as free genes but are split in many segments as exons surrounded by non-informational DNA sequences (introns), similar to hundreds of other genes on the chromosome, demonstrating that there are no exon-only BRCA genes on the chromosomes, as contrasted by the exon-only BRCA1/BRCA2 DNA isolated by Myriad Genetics for comparative studies between wild type and mutant genes.

Since BRCA1 and BRCA2 are distributed as tiny fragments (exons) on the two chromosomes, can they be described as genes? It is to be noted, and as pointed out by the Supreme Court in its ruling, that transcription of human genes, including BRCA1 and BRCA2 genes, from a single strand of the genes, leads to pre-RNA formation having nucleotides corresponding to both the exons and the introns in the DNA molecule. The pre-RNA is then naturally 'spliced' by the physical removal of the introns, giving rise to a strand of messenger RNA (mRNA) that contains nucleotides corresponding only to the exons from the original DNA strand. The mRNA is then translated to the BRCA1 and BRCA2 proteins, which become products of nature found within the cell. Thus technically there are no exon-only BRCA genes within the cell in its chromosomes, only their precursor exon-intron large DNA segments present as small fragments just like hundreds of other genes in the human chromosomes. This then raises an interesting question. Is a tiny fragment of the chromosome, which is a product of nature, also a product of nature? This in turn raises more interesting questions. How tiny would the fragment have to be to be considered a product of nature: a few kilo bases, a few hundred bases or just a few nucleotides such as 3 bases comprising a codon? Will any such fragments from the human chromosome, or from the BRCA genes, be considered as products of nature?

The Supreme Court's decision on the patent ineligibility of human genes such as BRCA1 or BRCA2 as products of nature does not necessarily have to be confined to human genes. As mandated by the US Constitution to encourage ingenuity and the 1980 Supreme Court decision that 'anything under the sun that is made by man' is patent eligible, the USPTO has allowed patenting of

many naturally occurring products such as antibiotics and bacterial anticancer proteins (5). The USPTO is, however, in the process of issuing fresh guidelines as of July 30, 2015, following its 2014 Interim Guidance on the patent eligibility issue involving 35 USC section 101 involving the product of nature claims following the CAFC and Supreme Court decisions. An interesting area of such patent eligibility issues is the patent eligibility of naturally occurring bacterial proteins with great potential utility never known before such as anticancer and cancer preventive activities. The University of Illinois at Chicago (UIC) holds several US patents (and many international patents) issued on a bacterial protein azurin comprising of 128 amino acids and a 28 amino acid peptide derived from azurin termed p28 (azurin amino acids 50-77 without any modifications). While both azurin and p28 have strong cancer regressing, and potential cancer preventive activity, only the peptide p28 has undergone two phase I human clinical trials. The first trial was conducted in 15 stage IV cancer patients with solid tumors that were resistant to all conventional drugs and the patients had a life expectancy of about 6 months. P28 was given as intravenous injections in 5 increasing doses to such patients. P28 demonstrated no toxicity but significant beneficial effects including both partial and complete regression of the drug-resistant tumors in some patients, significantly prolonging their lives (6). P28 is also undergoing a second phase I trial in 18 pediatric brain tumor patients in several hospitals in the US. Again, p28 appears to show acceptable toxicity and some significant beneficial effect since the trial has been on-going for more than a year and half (http://clinicaltrials.gov/ct2/show/NCT01975116; see also www.cdgti.com). Azurin, as a bacterial protein, is obviously a product of nature and its patent eligibility is now uncertain, given the Supreme Court's decision on the Myriad patents. Since BRCA1/BRCA2 genes with many exons, which comprise only fragments of the two chromosomes, are considered products of nature and therefore patent ineligible, will p28 as a fragment of azurin without any modifications be considered a product of nature and therefore patent ineligible, in spite of its potential utility as a non-toxic anticancer agent, as demonstrated by the two phase I clinical trial results? And if the 28 amino acid p28 is considered a product of nature as an unmodified fragment of the true product of nature azurin, will a fragment of p28, say p10, p5, p2 or even p1 be considered a product of nature, decimating all patents on all proteins, whether genetically engineered or not?

CONCLUDING REMARKS

The interfacing of science and law is an important subject as articulated in the past by the organization Einstein Institute for Science, Health and the Courts, and more recently by the Advanced Science & Technology Adjudication Resource Center (ASTAR, www.astarcourts.net). Thus science in the courtroom and science education to judges are an important goal of the Department of Justice. Indeed, the interrelationship between genetics and law and the challenges for lawyers and judges to effectively deal with complex scientific questions have been addressed by academic professors (7), Supreme Court judges (8), accomplished lawyers (9) and well-known bioethicists (10). The scientific and legal rationale for denying patent protection to BRCA1/BRCA2 genes could simply be the fact that such wild type genes are present in all other human beings and therefore, as we pointed out earlier (11, 12), lack utility. It's only the mutations in these genes, that are responsible for triggering breast or ovarian cancers, that merit patent protection (11, 12). It remains to be seen how the 2013 Supreme Court decision will impact innovation in life sciences and how the legal protection of such innovations, as was the goal of the framers of the US Constitution, will be addressed both by the academic/industrial sector, the judiciary and the US Congress. Most vulnerable for the current uncertainty are genetic screening and diagnostic methods as reflected in a recent CAFC decision on Sequenom Inc.'s US patent No. 6,258,540 for prenatal DNA testing to determine gender or to detect genetic defects such as Down syndrome before birth. This patent was challenged by Ariosa Diagnostics Inc. (*Ariosa Diagnostics Inc. et al v. Sequenom Inc.*, case 14-1139 at CAFC) and the CAFC considered the patent as ineligible for claiming a natural phenomenon. Similar contentious court cases have been ongoing with regard to the patenting of human embryonic stem cells where the patents held by the Wisconsin Alumni Research Foundation (WARF) have been embroiled in extended controversy (13, see also the CAFC ruling issued on June 4, 2014 in the case Consumer Watchdog v. WARF, No. 2013-1377).

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