Commentary

Patenting human genes and mutations: A personal perspective

Received: June 20, 2013

Ananda Mohan Chakrabarty
is a distinguished university professor at the University of Illinois at Chicago. In 1980 Dr. Chakrabarty's genetically modified *Pseudomonas* bacteria became the first genetically-engineered organism to gain a US patent, as a result of the Supreme Court decision in *Diamond vs. Chakrabarty*. He is the co-founder of two companies, CDG Therapeutics Inc. in Chicago and Amrita Therapeutics in India, that are developing protein/peptide anticancer agents from microbial sources.

Journal of Commercial Biotechnology (2013) 19(3), 3–5. doi: 10.5912/jcb.602
Keywords: Patent; human gene; mutation

I AM THE BENEFICIARY of a June 16, 1980 US Supreme Court decision in *Diamond v. Chakrabarty (447 U.S. 303, 1980*) that granted patent protection of a genetically-modified life form — in this case an oil-digesting bacterium harboring multiple hydrocarbon-degradative plasmids. It is generally accepted that this 5-4 decision significantly encouraged the development of commercial biotechnology in the United States, as demonstrated by a thriving economy, by allowing patent protection to inventions related to live microorganisms, plants, animals, cells, genes, etc, including patenting of human embryonic stem cells and human genes isolated and purified from the chromosome with demonstrated utility. 33 years later, on June 13, 2013, a very different U.S. Supreme Court in a unanimous decision held that a) isolation and purification of a naturally occurring DNA segment is not eligible for patent protection because the 'invention' is fundamentally a product of nature and b) complementary DNA (cDNA) is eligible for patent protection because it is not naturally occurring. This decision reversed a 2-1 decision by the Court of Appeals for the Federal Circuit (CAFC) that two human genes BRCA1 and BRCA2, where certain mutations and gene rearrangements promote the onset of breast and ovarian cancers, are eligible for patent protection, but deciphering the mutations was a mental exercise and therefore ineligible for patenting. The Supreme Court did not address the issue of patenting of mutations in these genes.

In contemplating these rulings, it is important to understand what the patent laws in the US represent. The patent laws are in the US Constitution (35 USC section 101) framed in 1790 with basically two goals: (i) to promote the progress of 'any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement thereof ' and (ii) to ensure that 'ingenuity should receive a liberal encouragement', as articulated by Thomas Jefferson. Indeed, the first US patent was issued on July 31, 1790, to Samuel Hopkins of the City of Philadelphia and the patent was signed by President George Washington, Secretary of State Thomas Jefferson and the Attorney General of the United States Edm. Randolph to signify and demonstrate the deep commitment of the newly-independent country to encourage innovations in science and technology, and the protection of such innovations. Further, in 1980 when the U.S. Supreme Court found my engineered life forms to be patentable, it declared boldly that 'anything under the sun that is made by man' is patent eligible in the United States (447 US 303, 1980), provided such invention meets the statutory requirements of novelty (35 USC section 102), non-obviousness (section 103), detailed description for enablement (section 112) and utility (section 101 and 112), and according to the 2001 January affirmation of the US Patent & Trademark Office (US PTO), the utility should be specific, substantial and credible.

The fact that the early patents, including the first patent granted on July 31, 1790, were signed by the President of the United States, the Secretary of State and the Attorney General, demonstrates the deep commitment the framers of the US Constitution had in promoting and protecting through the patent system innovations in new and useful process, machine, manufacture or composition of matter. The two key words were that such innovations must be new and useful. While the Supreme Court dealt with the novelty issue in *Association for Molecular Pathology, et al., v. Myriad Genetics, Inc., et al* (No. 12-398), finding that simple isolation and purification of the BRCA genes from their neighboring sequences on the two chromosomes did not constitute patent-eligible

Correspondence: Ananda Mohan Chakrabarty, University of Illinois at Chicago, US. E-mail: pseudomo@uic.edu

invention, it did not address the issue of the utility of such genes. Since thousands of isolated and purified genes from various sources have been patented, it is hard to revoke all such patents by simply saying that such procedures do not involve any inventive steps. Much efforts over the years were spent just to localize the two genes that were believed to be tumor suppressor genes and where specific mutations led to a loss of this tumor suppressing activity of breast and ovarian cancer. A much better scientific rationale would have been to reject patent eligibility because of a lack of demonstrated utility of the isolated and purified BRCA1 and BRCA2 genes, as we have argued recently (1, 2). Myriad Genetics' patent claims on these two genes center on the use of such genes as wild type reference genes against which mutant genes from various sources can be compared to locate the mutations. While locating and identifying the mutations, which are central to the determination of cancer susceptibility, are the essence of seeking patent protection, it is hard to see how a reference gene can have such protection. A simple example will illustrate this. Imagine that an agricultural biotechnology company developed a new variety of roses by introducing a bacterial gene that improves both color and the fragrance of the rose, and that they seek patent not only for the genetically modified rose but also for patent protection of garden-variety roses against which the genetically modified rose was compared to determine its improved color and fragrance. It would obviously be unacceptable to allow patenting of the reference garden variety roses along with the genetically modified roses, indicating why a reference wild type BRCA gene should not be patent eligible. On the other hand, isolation and purification of a gene such as the human insulin gene, which was patented in the 1980s, is of great utility since such a gene can be expressed in *Escherichia coli* under appropriate promoters to bulk-produce human insulin for the treatment of diabetes. Bacterial expression of a purified human gene, which can be expressed to produce a product of great medical importance that was not previously available, makes an exceptionally strong case for patent eligibility of such a gene.

An important question not addressed by the Court was the question of the patent eligibility of BRCA1 and BRCA2 gene mutations. The importance of these mutations is that women with family history of breast or ovarian cancer can seek genetic testing to identify if they have mutations in these genes, and if they test positive for the mutations, they can take measures to prevent the onset of breast cancer. Thus a combination of isolation, purification and sequence comparison of BRCA1 and BRCA2 genes for the delineation of cancer-inducing mutations should be patent eligible, even though the CAFC ruled against the patent eligibility of such mutations as sheer mental exercises. It is important to note that there is Supreme Court precedent for allowing patentability of mental exercises when such exercises are tied to a useful invention, as follows from *Diamond v. Diehr, 450 US 175 (1981*), holding that application of the Arrhenius equation to a process of the determination of optimum curing of rubber as patent eligible under 35 USC 101.

The immediate impact of the Supreme Court decision on *AMP et al., v. Myriad Genetics*, *Inc. et al.,* coupled to the Court's March, 2012 unanimous decision on *Mayo Collaborative Services v. Prometheus Laboratories* denying patent protection of diagnostic dosing of drugs, will likely be in the arena of diagnostic test development and personalized medicine. A significant segment of biotechnology industry that relies on deciphering genetic changes and modifications in the DNA isolated from the chromosomes and not involving cDNA will be affected. An interesting outcome of this decision may also involve patent eligibility considerations of many natural products such as antibiotics or drugs developed from medicinal plants with great usefulness in combating disease. Since such patented products simply represent isolation and purification of the same naturally-occurring product, will their patent protection be in jeopardy because of this ruling?

Finally, the question of the patent eligibility of BRCA1 and BRCA2 mutations aside, an important question is what does a woman, particularly a young woman of child-bearing age but with a family history of breast or ovarian cancer, do when tested positive for mutations in these genes? One option is to remain vigilant, looking for early signs of cancer (2). An increasingly common, but a dreaded and traumatic option, is to surgically remove the breasts and the ovary. Unfortunately, current anticancer drugs have not only significant toxicity but they are also amenable to resistance development and have limited cancer preventive ability. What is sorely needed is a drug that not only exhibits very little toxicity but should have cancer therapeutic activity to interfere in multiple pathways through which cancer cells grow so as to minimize resistance development. Ideally, if such a drug exhibits cancer preventive activity, then the drug can be taken on a long term basis to evaluate its ability to prevent the onset of breast/ovarian cancer in vulnerable women. While no such drug currently exists because of the pharmaceutical industry's dependence on rationally-designed small molecule compounds, there appears to be on the horizon the emergence of protein/peptide drugs with low toxicity and both cancer therapeutic and preventive activities (1, 3). These protein/peptide drugs are of bacterial origin and certain pathogenic bacteria have been known for over hundred years to combat cancers. Some accelerated efforts to develop the new kinds of drugs with no toxicity but significant therapeutic and

cancer preventive activity are urgently needed now to help eradicate cancer in our lifetime.

REFERENCES

1. Fialho, A.M. and Chakrabarty, A.M. (2012) Patent controversies and court cases: cancer diagnosis, therapy and prevention. *Cancer Biol. Therap.* 13: 1229-1234.
2. Chakrabarty, A.M. (2013) Patenting of genes and mutations: recent US Supreme Court cases. Science in the Courtroom, 1: 000-000 (in press).
3. Chakrabarty, A.M. (2012) Bacterial proteins: a new class of cancer therapeutics. *J. Comm. Biotechnol.* 18: 4-10.