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RESEARCH ARTICLE

PATENTING GENOMICS INNOVATIONS:POST-*MYRIAD* CHALLENGES AND POSSIBILITIES

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Abstract

Patenting gene and its nucleotide sequence has been a controversial subject since the release of working draft of the Human Genome Project. A number of US Supreme Court judgments pronounced in the recent past and accordingly revised patent examination strategies of the United States Patent and Trademark Office (USPTO)created a huge confusion in the field of biotechnology.

The present article explores the volatile nature of judicial decision-making in modern biotechnology arena and attempts to analyze and gauge the practical impact of the landmark judgment of *Association for Molecular Pathology v. Myriad genetics Inc.* The present article also reveals how the *Myriad* judgment changed the USPTO's long-standing practice of granting patents on isolated DNA molecules and set a new patent-eligibility standard for genes and DNA related innovations.

The present article also endeavors to investigate the challenges and possibilities of patenting isolated proteins, sequence homology and protein three-dimensional structure based innovations in post-*Myriad* US patent regime.

Introduction:-

After the release of working draft of the Human Genome Project, the US Patent and Trademark Office (USPTO) received a number of letters from stakeholders including the then NHGRI[1] director Francis Collins arguing a revision of its acceptability norms for gene and DNA sequence related patent applications. In 2001, USPTO issued a guideline raising the bar on patent-eligibility standard for DNA related patent applications stating that identification of gene sequence alone is not patentable, but that discoveries directed to genes isolated from their natural environment might be patentable if they possessed "specific, substantial and credible utility".[2]USPTO specifically clarified in its revised guidelines that even if a gene was discovered from its natural source but "isolated" and "purified" from other molecules naturally associated with it would be patent-eligible as long as the requirements of title 35 of the US code were met. And in such cases questions whether the gene is an invention or discovery will not

[1] The National Human Genome Research Institute (NHGRI) is a division of the National Institute of Health (NIH) originally established as the National Centre for Human Genome Research (NCHGR) in 1989 to carry out the International Human Genome Project (HGP).
[2] Federal Register, Pub. L. No. 4, 66 1092–99 (2001)

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arise even if the isolated gene in question has a nucleotide sequence similar to its natural counterpart.[3]However, USPTO has always been of the opinion that purified state of synthetic gene is different from those of the naturally occurring compounds. Hence, there is no objection in granting patents for such genes as 'composition of matter' or 'a matter of manufacture'.[4]Patent applications directed to isolated gene never faced unavoidable challenge at the USPTO, however, the scenario dramatically changed in 2013 when the US Supreme Court invalidated three disputed patents of Myriad Genetics Inc. related to BRCA gene. The *Myriad* judgment has not only set a new interpretation standard for§101 but also created an uncertain environment for future patent applications related to genes and DNA molecules. The present article investigates the adverse effect of *Myriad* judgment caused to gene or DNA based future patent applications and possibilities of patenting other genomics innovations in post-*Myriad* American patent regime.

Landmark Court Decisions And Changing Patent-Eligibility Jurisprudence in Modern Biotechnology Arena:-

2.1 The Us Supreme Court Judgment On Gene Patenting And Legal Uncertainty

In patent ecosystem, it is a well-observed phenomenon that even a brilliant discovery or a breakthrough innovation does not by itself is patent-eligible unless they meet the statutory requirements[5]. This fact becomes more prominent when the real world experience of genomic technology is brought to Courts in the form of actual cases. In 2013, a landmark judgment of the US Supreme Court completely changed the scenario of gene patenting in America. The US Supreme Court's ruling on *Association for Molecular Pathology* v. *Myriad genetics, Inc.* altered the USPTO's thirty years old practice of granting patents on isolated genes and DNA molecules[6]. In *Myriad* case, the observation of the US Supreme Court was completely different from the observation once had in *Parke-Davis & Co.* v. *H. K. Mulford Co.*, an age-old landmark case on adrenaline patent dispute. It was then noted by the Supreme Court that compounds "'isolated' from nature are patentable even if it were merely an extracted product without change; there is no rule that such products are not patentable."Surprisingly, the US Supreme Court completely undermined the long history of natural product patenting and relied heavily on the *Mayo v Prometheus*, a process-patent litigation, to decide *Myriad's* disputed patents directed to genomic DNA. The controversial patent dispute between Mayo Collaborative Services and Prometheus Laboratories was related to diagnostic test and method of determining appropriate dose of thiopurine metabolite for the treatment of patients suffering from autoimmune diseases. The US Supreme court held in that patent dispute that giving drugs to patient, measuring metabolites for that drug etc. as claimed in US patent No. 6,355,623 and 6,680,302,were not allowable as they were close to *natural law* exception of the US patent statute. Though the *Prometheus* patent dispute was not entirely relevant for *Myriad'*s human gene patenting issue, however, it influenced the US Supreme Court to a large extend which led to rejection of nine claims directed to genomic DNA of three disputed patents.[7]The Court clarified its position stating that "a naturally occurring DNA segment is a 'product of nature' and not patent eligible merely because it has been isolated". The Supreme Court's decision in *Myriad* is not only an unexpected departure from a long-standing affirmation of isolated DNA patenting but also raises obvious questions regarding the volatile nature of judicial decision-making in the modern biotechnology arena.

In *Myriad* litigation, the US Supreme court set a new paten-eligibility standard applicable for all future patent applications related to gene or DNA sequence. The "new and useful…composition of matter"–requirements as set forth in §101 or claiming naturally occurring phenomena (*natural law*[8] *exception*) will be judged based on the

[3]*Id.*

[4]*See infra* 16.

[5]Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127.

[6] The Federal Circuit pointed out in *Myriad* Case that the USPTO has issued patents directed to DNA for almost thirty years. The FC also pointed out that 2,645 patents claiming "isolated DNA" has already been issued by the USPTO.

[7] Claims 1,2,5,6 and 7 of US patent No. US 5,747,282; Claim 1 of US patent No. US 5,693,473 directed to BRCA-1 gene and Claims 1, 6 and 7 of US patent No. US 5,837,492 directed to BRCA-2 gene.

[8] As described in MPEP §2106, in addition to the terms laws of nature, physical phenomena, and abstract ideas, judicial exceptions have been described using various other terms, including natural phenomena, products of nature, natural products, naturally occurring things, scientific principles, system that depends on human intelligence alone, disembodied concept, mental process and disembodied mathematical algorithms and formulas, for example. The exceptions reflect the judicial view that these fundamental tools of scientific and technological work are not patentable.

primary enquiry–whether the claimed invention is meant for creating "incentives that lead to creation, invention, and discovery or impeding the flow of information that might permit, indeed spur, invention". [9]In this regard, the US Supreme Court observed that a delicate balance is required to be maintained in order to arrive at a rational conclusion. The Court further clarifies that the synthetic DNA fragments e.g. exons-only DNA fragment or cDNA is patent-eligible like before[10], even if the nucleic acid sequence of the synthetic DNA molecule is similar to that of the naturally occurring gene codes for the same protein.

Challenges and Possibilities In Genomics Innovations:-

Though the magnitude of *Myriad* judgment is huge, however, it is not a blanket prohibition for patenting all DNA/gene sequence of human origin or any other origin, but for those DNA/genes that are *merely* "isolated" from natural environment and do not show *markedly different* characteristics (as established in *Diamond v. Chakrabarty*case) in terms of modification in the nucleic acid chain.

Immediately after the *Myriad* judgment, USPTO again changed its examination strategy towards gene-related innovations. According to a memorandum[11] issued by the USPTO on 13thJune2013, patent examiners were instructed to reject all product claims directed to naturally occurring DNA molecule whether it was isolated or not.

3.1 Nucleotide sequence-based innovations

DNA sequence information represented by A, T, G, and C alone is not a patent-eligible subject matter under the US patents law as it is nothing more than a typical nucleic acid sequence information.[12] However, according to *Myriad* interpretation standard of §101, *markedly different* DNA fragment or gene described by nucleic acid sequence in the form of A, T, G and C is patent-eligible provided they meet the utility requirements as set forth in the current US patent statute.

Similarly, ESTs[13] are also patent-eligible under the current US patents law if they meet the criteria of utility, novelty and non-obviousness. Moreover, the *Myriad* judgment further strengthened the patent-eligibility of EST as the Supreme Court has completely acknowledged patent eligibility of cDNA.[14]

A reasonably favorable environment is also expected for nucleotide homology-based innovations. There is no specific rule in the United States for DNA sequence homology based patent applications. Therefore, it is most likely that USPTO will continue to assess such patent applications based on their own technical merits. According to general practice, the USPTO accepts homologous DNA sequences (both nature and the degree of homology) of genes or fragments thereof as a patent-eligible subject matter as long as they satisfy other criteria, e.g. sufficiency of disclosure, credible utility etc. The USPTO has a coherent approach for sequence homology related broad claims. Claims reciting whole nucleotide genus is also allowable in a single patent application on the condition that the representative nucleotide species are adequately described in the specification. Though protection of whole nucleotide genus sometimes leads to cross-species patent coverage because of the fact that some homology/percent identity claims encompasses a large number of macromolecule variants which may belong to entirely different species[15] or orthologs, however, USPTO does not raise any unavoidable objection in accepting them. Additionally, DNA homologs are not considered to be non-patentable *merely* because of the reason that the function and utility of the claimed DNA homologs have asserted through bioinformatics method analyzing sequence homology with prior-art nucleic acid sequence found in public databases.[16]

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[9]*12-398 Association for molecular pathology v. Myriad genetics, Inc. (06/13/2013), (us 2013).*
[10]*Id.*
[11]MEMORANDUM from Deputy Commissioner for Patents Examination Policy to Patent Examining Corps, Supreme Court Decision in Association for Molecular Pathology v. Myriad Genetics, Inc. (USPTO Jun. 13, 2013).
[12] S*upra note* 2
[13] Expressed Sequence Tags (ESTs) are small chain of nucleic acids, generally 200-800 base pair (bp) in length, generated from randomly selected cDNA clones. ESTs are extremely useful for purpose of gene identification and verification of gene prediction. --- *John Parkinson (ed.). Expressed sequence Tags (ESTs): Generation and analysis, vol.533, Humana Press 2009.*
[14]*Supra note 9.*
[15]Letter from Eli Lilly and Co. to USPTO, COMMENTS OF ELI LILLY AND COMPANY ON THE REVISED INTERIM WRITTEN DESCRIPTION GUIDELINES 132 (USPTO).
[16]*supra* note2, at 1096

3.2 Amino acid sequence-based innovations

USPTO has a non-stringent practice regarding the acceptability of protein homology-based claims. Amino acid sequence disclosed for a single species is considered to be a *representative of the genus* because all member amino acid sequence have at least certain degree of percent identity with the parent genus and therefore obtaining patents on this subject matter does not involve major challenges as long as the description of representative amino acids fulfills enablement requirements stipulated in §112 of U.S.C. 35.

According to recent USPTO guideline[17] issued on March, 2014, claims directed to proteins are close to judicial exceptions i.e. natural phenomena or natural product. Therefore, proteins are not patent-eligible under §101 unless they are *significantly different*[18] from the judicial exception regardless of the use of words like, "isolated", "recombinant", or "synthetic" etc. in claims reciting a protein. Similar to DNA sequence, amino acid sequence of a protein or peptide alone is not patent-eligible unless it is *markedly different* (in terms of addition, deletion or substitution of amino acid(s)) from the naturally occurring protein molecule[19].

In advent of major breakthroughs in bio techniques, functional genomics products, e.g. therapeutic proteins produced by recombinant DNA (rDNA) technology have been successfully used worldwide including in the USA to treat a wide range of diseases for which there was no cure using pharmaceutical drugs.[20] Proteins/peptides are considered to be potential drug candidate for various practical reasons which include target specificity, non-interference with other biological processes of the human body etc. Because of these useful characteristics, researcher's principle objective always focused on producing synthetic protein/peptide molecules that are structurally (both in terms of amino acid sequence information and three-dimensional conformation) similar to those found in human body[21]for example, Humulin®.[22]Although these man-made variants of structurally resembling molecules are often confused with the molecules found in nature and contested during prosecution ,however, patenting these therapeutic macromolecules should not face any additional challenge in post-*Myriad* US patent regime because of the fact that the Court's observations on isolated genomic DNA will certainly have some limits and will not necessarily be applicable for isolated proteins or peptides and encoding amino acid sequence thereof. Any adverse impact to isolated protein patenting can also be ruled out in view of the *Prometheus* judgment. In *Mayo Collaborative Services v. Prometheus Labs, Inc.*, the Court stated that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract idea," and "too broad an interpretation of this exclusion principle could eviscerate patent law".[23]In addition to that, in *Myriad*, the Court had no observation regarding patent-eligibility of isolated proteins and USPTO has no specific guidelines in this regard either. Hence, it can be said that isolated proteins/peptides of natural origin or their recombinant variants are still patent-eligible under §101 of the US patent law.

3.3 Structural Genomics Innovations

Besides patenting isolated therapeutic proteins and amino acid sequence based innovations, it is also evident that trends of protecting structural genomics innovations have been increased significantly around the world. Three-dimensional structural information of protein is always proved to be crucial; naturally, protection of this spatial information has great value for bio technology industry. According to a report on the comparative study[24] conducted

[17]MEMORANDUM from Deputy Commissioner for Patents Examination Policy to Patent Examining Corps., 2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural Principles, Natural Phenomena, And / Or Natural Products (USPTO Mar. 4, 2014).

[18]*Id.*

[19] USPTO, *supra* note 17.

[20]Tom Strachan and Andrew Read, Human Molecular Genetics (New York : Garland Science/Taylor & Francis Group, c2011., 4th ed. 2011).

[21]*Id.*

[22]Humulin® is a polypeptide hormone manufactured by Eli Lilly &Co. from a non-disease-causing laboratory strain of *Escherichia coli* bacteria, is the world's first recombinant DNA drug approved by the FDA. Structurally, this rDNA originated insulin is indistinguishable from pancreatic human insulin designed to save millions of lives around the world suffering from diabetes.

[23]10-1150 Mayo collaborative services v. Prometheus laboratories, Inc. (03/20/2012), (US 2012).

[24] Trilateral Co-operation between EPO, JPO and USPTO was set up in 1983 with the objectives including improvement of the quality of patent examination process, improving quality of incoming applications, solving

by trilateral patent offices, inventions that claim protein three-dimensional structural coordinates fall under the category of "information contents" which is further interpreted as nothing more than "mere presentation of information or abstract ideas". Therefore, innovations related to this technological field are not patent-eligible under §101.

However, protein three-dimensional structures represented by spatial arrangements of atoms or structural coordinate data are considered to have technical effect as long as they are used in an *in silico* or bioinformatics screening method to generate chemical compounds. In 1999, USPTO granted a patent in this area for the first time for an invention directed to the use of structural coordinates of interleukin-1β converting enzyme (ICE) and mutants thereof to screen and design potential drug candidate. Since then a number of patents have been granted by the USPTO, e.g. patent No. US6,490,588 and US6,329,184 to name a few for inventions directed to protein three-dimensional structure and their use in structure-based-drug-design (SBDD).

The patent-eligibility standard has certainly been raised for gene-related innovations in light of a number of Supreme Court judgments[25] and revised USPTO guidelines; however, there has been no sign of increase in the number of rejection of patent applications from 2012 until now. Patent prosecution history of post *Myriad* era suggests that USPTO has been issued patents for genomics innovations after a thorough patent-eligibility assessment under § 101; naturally, that process led to a substantial increase in the issuance of office action until grant.

Conclusion:-

It was initially estimated that the material consequence of the Supreme Court judgment in *Myriad* patent litigation would be far-reaching. However, it seems that the practical impact of this judgment to gene related future patent applications will not be severe as anticipated. The trend of filing patent applications at the USPTO and issued patents in the area of gene or DNA related innovation is still maintaining its usual momentum. Most importantly, no significant irregularity in this regard has been noticed in post-*Myriad* patent regime.

However, in light of revised patent practice of the USPTO, chances of obtaining patents is certainly higher for those genomics innovations that are more restricted to non-naturally-occurring nucleotides, such as cDNA or nucleotides of man-made variants. On the other hand, isolated proteins and its recombinant variants including their encoding amino acid sequences should not face any additional challenge at the USPTO as the breadth of *Myriad* judgment is limited to isolated genomic DNA or genes of human origin. Inventions directed to sequence homology or percent identity is likely to be assessed based on their individual technical merit and scope of the invention, like before. Whereas, other genomics innovations, e.g. innovations directed to protein 3D structures and their applications in drug discovery (SBDD) are less susceptible to any direct impact of *Myriad* judgment. Though spatial information of protein itself is far beyond any patent protection, however, protection for the use of such structural information in the production of useful products will continue to be allowable under the useful and credible utility doctrines until any specific guidelines in this regard is issued by the USPTO in contrary to present examination practice.

Finally, it can be said that the Supreme Court decisions and USPTO guidelines issued in various occasions since 2012 certainly elevated the standard of subject matter eligibility of biotechnology innovations. However, the overall patent granting scenario in biotechnology domain has not been changed significantly in post-*Myriad* era except the fact that there has been an increase in the number of office action till the grant of each biotechnology patent application.

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common problems related to IPR protection, harmonization in practice between three patent offices etc. -- *Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims (2002).*

[25]Supreme Court's ruling on diagnostic method claims (Mayo Collaborative Services v. Prometheus Laboratories, Inc., 566 U.S. ___, 132 S.Ct. 1289 (2012); Supreme Court's rejection of patents directed to isolated genomic DNA segments (Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. ___, 133 S.Ct. 2107 (2013)) and Supreme Court's observation on abstract idea in Alice Corp. v. CLS Bank Int'l, 134 S.Ct. 2347 (2014).