MOLECULES OR CARRIERS OF BIOLOGICAL INFORMATION: A CHEMIST'S PERSPECTIVE ON THE PATENTABILITY OF ISOLATED GENES

*Guyan Liang**

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* Adjunct Associate Professor at the Department of Chemistry and Biochemistry, The University of North Carolina at Greensboro; Lead Research Investigator at Molecular Innovation Technology, Sanofi-aventis Pharmaceuticals; e-mail: guyan.liang@verizon.net, phone: (908) 938-4619, address: 62 Briarwood Drive East, Warren, NJ 07059.

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I. INTRODUCTION

The intense debate over the validity of gene patents has a widespread impact on biomedical research and public healthcare. By 2004, about 20 percent of known human genes, 4,382 out of 23,688 identified at the time, had been explicitly claimed in issued patents.[1] In 2009, the U.S. Patent and Trademark Office (USPTO) had granted 50,000 patents containing at least one DNA-related claim, with some claiming isolated genes and others claiming therapeutic products, such as insulin, growth hormones, growth factors, antibodies, and other therapeutic biologics.[2] Although patents claiming therapeutic products have been a subject of litigation, there has been relatively little media attention or public controversy.[3]

In contrast, patents claiming isolated genes, modified or unmodified, are more controversial and have attracted more public attention.[4] To scientists in the field of biotechnology, being able to patent isolated genes is a form of societal recognition and financial reward for their achievement, which is part of the purpose of our patent laws.[5] However, due to special properties of genes and their relationship to human life, both legal professionals and public opinions are divided on the issue regarding whether isolated genes are patentable.[6] The recent rulings in *AMP v. Myriad*[7] regarding BRCA1 and BRCA2 genes

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[1] Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCIENCE 239, 239 (2005).

[2] *See* Subhashini Chandrasekharan & Robert Cook-Deegan, *Gene Patents and Personalized Medicine—What Lies Ahead?*, 1 GENOME MED. 92, 92 (2009) (defining gene patents and explaining their therapeutic uses).

[3] *Id.*; *see* Rebecca S. Eisenberg, Commentary, *Why the Gene Patenting Controversy Persists*, 77 ACAD. MED. 1381, 1381 (2002).

[4] *See* Jensen, *supra* note 1, at 239; Eisenberg, *supra* note 3, at 1381–83.

[5] Mark A. Chavez, *Gene Patenting: Do the Ends Justify the Means?* 7 COMPUTER L. REV. & TECH. J. 255, 255–57 (2003).

[6] *See* Jordan Paradise et al., Response, *Problems in Patenting Human Genes*, 308 SCIENCE 1868, 1869–70 (2005) (explaining that gene patents are used to patent genetic information, not chemical compounds); Christopher M. Holman, *Trends in Human Gene Patent Litigation*, 322 SCIENCE 198, 198–99 (2008) (discussing the legitimacy of fears that gene patents pose a public health risk through an analysis of empirical research); Kenneth G. Chahine, Commentary, *Anchoring Gene Patent Eligibility to its Constitutional Mooring*, 28 NATURE BIOTECHNOLOGY 1251, 1251–53 (2010) (listing five criteria that courts, legislatures, and businesses should use when confronted with a question of subject matter eligibility for gene patents); Brendan Borrell, *Lawsuit Rekindles Gene-Patent Debate*, 463 NATURE 413, 413 (2010).

[7] 702 F. Supp. 2d 181 (S.D.N.Y. 2010), *rev'd in part*, 653 F.3d 1329 (Fed. Cir.

brought gene patents to the forefront of the debate over the scope of intellectual property protection.[8]

The present article attempts to analyze the patentability of isolated genes from a chemist's point of view by focusing on three highly contested issues. First, is an isolated gene, such as BRCA1 and BRCA2 in Myriad's patents, a biomacromolecule or a physical carrier of biological information? Second, are utilities of an isolated gene uniquely linked to its DNA sequence? Finally, is an isolated gene markedly different from its parental chromosome? As will be discussed in section IV, isolated genes function more like biomacromolecules than carriers of biological information. Their utilities are more dependent on their unique structures than their DNA sequences (section V). An isolated gene can have markedly different characteristics from its parental chromosome (section VI).

II. HISTORICAL DEBATE AND PUBLIC POLICY CONSIDERATIONS FOR GENE PATENTS

There has been a long debate surrounding the validity of gene patents with various studies, articles, position papers, and legal arguments pointing in different directions.[9] Patents for isolated genes have been issued worldwide for many years.[10] However,

2011). This article focuses on the rationale of Judge Sweet's decision in the district court. It must be noted that, after the submission but prior to the publication of this article, the Federal Circuit partially reversed Judge Sweet's decision. Thereafter, the Supreme Court released its opinion in *Mayo v. Prometheus*. Mayo Collaborative Servs. v. Prometheus Labs., Inc., (U.S. Mar. 20, 2012), available at http://www.supremecourt.gov/opinions/11pdf/10-1150.pdf. On March 26, 2012, the Supreme Court granted the certiorari for *AMP v. Myriad*, vacated the judgment, and remanded for further consideration in light of *Mayo v. Prometheus*, http://www.supremecourt.gov/Search.aspx?FileName=/docketfiles/11-725.htm.

[8] *See id.* at 204–09.

[9] *Compare* Jon F. Merz et al., Commentary, *Diagnostic Testing Fails the Test*, 415 NATURE 577, 579 (2002) (highlighting concerns regarding the patenting of "biotechnology discoveries"), *and* Mildred K. Cho et al., Special Article, *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. MOLECULAR DIAGNOSTICS 3, 3 (2003) ("We conclude that patents and licenses have had a significant effect on the ability of clinical laboratories to develop and provide genetic tests."), *with* Robert Cook-Deegan et al., Commentary, *The Dangers of Diagnostic Monopolies*, 458 NATURE 405, 405–06 (2009) ("We propose that patient rights should trump patent rights if a company engages in practices that undermine the purpose of patents in the first place.").

[10] H. Phoebe Chan, *International Patent Behavior of Nine Major Agricultural Biotechnology Firms*, 9 J. AGROBIOTECHNOLOGY MGMT. & ECON. 59, 59 (2006),

there is still a fierce legal debate involving interested parties such as patients, clinicians, scientists, business investors, legal scholars, practicing lawyers, legislators, patent agencies, and people from whom genes were extracted.[11] Critics describe gene patents, especially those covering human genes, as a "land grab" for intellectual property.[12] It has been suggested that the current USPTO practice for gene patents hinders scientific research, increases the cost of innovations relying on genomic information, slows the development of new medications, and discourages investment in downstream businesses.[13]

In contrast, the supporting argument for gene patents is that the very nature of patent laws is to grant a period of exclusive right in exchange for public disclosure of the invention.[14] Strong protection for intellectual properties, including gene patents, is a cornerstone for modern societies, like the United States, which increasingly rely on scientific and technological innovations for economic growth.[15] For example, the rapid development of the biotech industry was largely attributed to the effective patent protection for biotechnological innovations, including isolated

available at http://agbioforum.org/v9n1/v9n1a07-chan.pdf.

[11] Matthew M. Karlan, Note, *Patent Policy, Natural Products, and the Gene Patent Debate: Seeking the Proper Judicial Mode of Analysis*, 67 N.Y.U. ANN. SURV. AM. L. 95, 95–97 (2011); Jensen, *supra* note 1, at 239.

[12] Jensen, *supra* note 1, at 239.

[13] *See* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698, 698–701 (1998) (explaining that high transaction costs, difficulty in comparing patent values, and overestimation of worth will impede scientific progress); Timothy Caulfield et al., *Patenting Human Genetic Material: Refocusing the Debate*, 1 NATURE REVIEWS 227, 227–31 (2000) (stating that limited monopolies granted by patents restrain progress, prevent research, and raise the costs of provisioning genetic technology); Lori B. Andrews, *Genes and Patent Policy: Rethinking Intellectual Property Rights*, 3 NATURE REVIEWS 803, 803–08 (2002) (opining that gene patents hamper research, undermine the scientific method, and impede invention and healthcare); Sandy M. Thomas et al., *Shares in the Human Genome-The Future of Patenting DNA*, 20 NATURE BIOTECHNOLOGY 1185, 1185–88 (2002) (explaining how gene patents limit access to healthcare services by increasing costs of genetic testing).

[14] *See* Mike Stott & Jill Valentine, *Impact of Gene Patenting on R&D and Commerce*, 21 NAT. BIOTECHNOLOGY 729, 729–31 (2003) (discussing U.S. innovations compared to the rest of the world); *see also* John J. Doll, *The Patenting of DNA*, 280 SCI. 689, 689–90 (1998) ("A strong U.S. patent system is critical for the continued development and dissemenation to the public of information on DNA sequence elements.").

[15] *See* Doll, *supra* note 14, at 689–90 (discussing how patents provide incentive for more research and development).

genes.[16]

The USPTO determined that an isolated gene is patentable subject matter.[17] The USPTO Patent Examination Guideline states: "[A]n excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature." [18] Applicants are entitled to a patent if the isolated gene satisfies other requirements of the patent law, such as novelty,[19] non-obviousness,[20] utility,[21] and enablement.[22] This position is evidenced by the fact that USPTO granted Myriad a long list of patents for its applications claiming BRCA1 and BRCA2 genes, and their use as medical diagnostic tools for breast and ovarian cancers.[23]

The standard for patent examination at the USPTO is dynamic and evolving. In 1999, the USPTO announced higher thresholds for utility and written description requirements of patent claims pertaining to DNA sequences.[24] The recent Supreme Court decision in, *KSR International v. Teleflex Inc.*[25] raised the standard for the obviousness test.[26] The Supreme Court in *Bilski* further clarified the standard for patent eligibility, although it

[16] *See id.* at 690 (discussing gene patents and their relationship to the rapid surge in the field of biotechnology).

[17] Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001).

[18] *Id.*

[19] 35 U.S.C.A. § 102 (West, Westlaw through P.L. 112-89 (excluding P.L. 112-55, 112-74, 112-78, 112-81) approved 1/3/12).

[20] 35 U.S.C.A. § 103 (West, Westlaw through P.L. 112-89 (excluding P.L. 112-55, 112-74, 112-78, 112-81) approved 1/3/12).

[21] 35 U.S.C. § 101 (2006).

[22] 35 U.S.C.A. § 112 (West, Westlaw through P.L. 112-89 (excluding P.L. 112-55, 112-74, 112-78, 112-81) approved 1/3/12).

[23] U.S. Patent No. 5,693,473 (filed June 7, 1995); U.S. Patent No. 5,709,999 (filed June 7, 1995); U.S. Patent No. 5,624,819 (filed June 7, 1995); U.S. Patent No. 5,747,282 (filed June 7, 1995); U.S. Patent No. 5,753,441 (filed Jan. 5, 1996); U.S. Patent No. 5,710,001 (filed June 7, 1995); U.S. Patent No. 5,837,492 (filed Apr. 29, 1996); U.S. Patent No. 5,989,885 (filed June 13, 1997); U.S. Patent No. 6,033,857 (filed Mar. 20, 1998).

[24] Utility Examination Guidelines, 66 Fed. Reg. 1092–99 (Jan. 5, 2001); Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, 66 FED. REG. 1099, 1100–01, 1104–05 (Jan. 5, 2001).

[25] 550 U.S. 398, 418–21 (2007).

[26] *Id.* at 419–21, 427 (holding that the obviousness test "must not be confined within a test or formulation too constrained to serve its purpose," commonly referred to as the teaching-suggestion-motivation test).

was not directed to gene patents.[27] The majority in *Bilski* held that business method is not categorically unpatentable and that the machine-or-transformation test, while a useful tool, is not the sole test for determining the patent eligibility of a process claim.[28]

AMP v. Myriad is the first trial on the patent eligibility of isolated genes.[29] The frequency for gene patents to trigger litigation is about the same as for other patents, even if gene patents are more controversial and attract more media attention.[30] Professor Christopher Holman, in his "Trends in Human Gene Patent Litigation," reported a systematic study of litigation involving gene patents between 1987 and 2008.[31] Based on his findings, only one to two percent of gene patents actually triggered litigation, which is about the same litigation frequency as for other patents.[32] Additionally, among 31 gene patent litigations identified by Holman, 16 were litigations regarding claims to therapeutic proteins, seven were regarding claims to research tools, only six involved diagnostic testing using human genes.[33] What is more striking is that all six cases pertaining to diagnostic testing settled at an early stage of litigation, whereas seven cases pertaining to therapeutic proteins reached the end of their trials.[34] A precedent-setting case directly on point concerning patent eligibility of isolated genes did not exist before

[27] Bilski v. Kappos, 561 U.S. ____, 130 S.Ct. 3218, 3227–28 (2010).

[28] *Id.* at 3227–29.

[29] *See* Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181, 231 (S.D.N.Y. 2010), *rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011). It must be noted that, after the submission but prior to the publication of this article, the Supreme Court released its opinion in *Mayo v. Prometheus*. The unanimous court overturned the Federal Circuit's decision that diagnostic method claims are eligible for patenting under 35 U.S.C. **§** 101. However, the court also stated that "too broad an interpretation of this exclusionary principle could eviscerate patent law" and that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." The impact of this decision on the patentability of isolated genes remains to be seen. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. ____, 132 S.Ct. 1289, 1289 (2012).

[30] *See* Chandrasekharan, *supra* note 2, at 92; *see also* Holman, *supra* note 6, at 198 (providing statistical figures on gene-related patents and patent disputes).

[31] *See* Holman, *supra* note 6, at 198 (explaining the general parameters of the study).

[32] *Id.*

[33] Holman, *supra* note 6, at 198.

[34] *Id.* at 198–99.

AMP v. Myriad.[35]

Legal scholars have also debated the validity and scope of the natural products doctrine on which gene patents hinge heavily. Pursuant to § 101 of the patent code, "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[36] The Supreme Court, in *Bilski,* stated that 35 U.S.C §101 was intended to define a broad and flexible domain for patentable subject matters to be adaptable to advances in new technology.[37] Notwithstanding such intention, "[t]his is not to suggest that § 101 has no limits or that it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not patentable."[38] Products produced "with markedly different characteristics of any found in nature" especially where such products have a likelihood of significant utility, were distinguished from the three exceptions specifically enumerated by the Supreme Court.[39]

Case law for the products of nature doctrine, however, is not consistent. The Supreme Court, in *Funk Brothers Seed Co. v. Kalo Inoculant Co.,*[40] stated that natural laws are "free to all men and reserved exclusively to none" and that the discoverer of an "unknown phenomenon of nature has no claim to a monopoly of it."[41] The court further stated that invention from such a discovery "must come from the application of the law of nature to a new and useful end."[42] Thirty years later, the Supreme Court, in *Parker v. Flook,*[43] held that although "a phenomenon of nature or mathematical formula may be well known, an inventive application of the principle may be patented."[44] In the 2010 decision of *Prometheus v. Mayo,*[45] the Federal Circuit stated that

[35] *See id.*

[36] 35 U.S.C. § 101 (2006).

[37] Bilski v. Kappos, 561 U.S. ——, 130 S.Ct. 3218, 3225 (2010) (interpreting congressional statutory intent as favoring patent rights for the purpose of promoting inventions and entrepreneurship).

[38] Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).

[39] *Id.* at 310, 319.

[40] 333 U.S. 127 (1948).

[41] *Id.* at 130.

[42] *Id.*

[43] 437 U.S. 584 (1978).

[44] *Id.* at 594.

[45] 628 F.3d 1347 (Fed. Cir. 2010), *cert. granted*, Mayo Collaborative Servs. v.

"transformative steps utilizing natural processes are not unpatentable subject matter" and that this holding was consistent with *Bilski*.[46]

According to some commentators, the natural products doctrine is like a "legal house of cards" that was created based on how judges perceived the invention without direct support from either the Constitution or the Patent Act.[47] The objective of the doctrine was "to prevent patents being given on fundamental discoveries [of a natural law], that might stymie [future] innovation."[48] As will be discussed in later sections, however, isolated genes may not be as fundamental to life sciences as was led to believe.[49] First, patents of an isolated gene only claim the gene outside of its natural environment, not the one existing in its natural cellular system, such as the section of DNA embedded in its parental chromosome with exactly the same sequence.[50] Additionally, it is possible to design a new sequence of nonnatural nucleotides around the claimed gene to serve the same purpose.[51]

III. AMP V. MYRIAD BROUGHT GENE PATENTS TO THE FOREFRONT OF THE DEBATE

Myriad Genetics (Myriad), and the litigation challenging the validity of its patents claiming BRCA1 and BRCA2 genes, brought the gene patent debate to the forefront of intellectual property protection. Because the litigation challenged the validity of claims for isolated DNA sequences, the trial court's ruling and the appellate court's decision have had a widespread impact on thousands patents with similar claims, which consequently will affect biomedical research, public healthcare, and business models of the biotech industry.

Myriad is a privately funded biotechnology company based in

Prometheus Labs., Inc., No. 10-1150, 2011 WL 973139 (U.S. June 20, 2011).

[46] *Id.* at 1356, 1349–50.

[47] Chahine, *supra* note 6, at 1252.

[48] *Id.*

[49] *See infra* part V.

[50] *See* Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181, 231 (S.D.N.Y. 2010), *rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011).

[51] Irene Lee & Anthony J. Berdis, *Non-Natural Nucleotides as Probes for the Mechanism and Fidelity of DNA Polymerases*, 1804 BIOCHIMICA ET BIOPHYSICA ACTA 1064, 1078 (2010).

Salt Lake City, Utah.[52] On August 1994 and December 1995, scientists in Myriad, collaborating with external researchers, successfully sequenced two genes correlated with elevated risk of breast cancer, Breast Cancer Susceptibility Genes 1 and 2 (BRCA1 and BRCA2).[53] Myriad filed patent applications for isolated BRCA1 and BRCA2 genes, as well as the method of using them as medical diagnostic tools.[54] A long list of patents was subsequently granted by the USPTO; seven of them were challenged in *AMP v. Myriad*.[55]

BRCA1 and BRCA2 genes, claimed by Myriad, are highly correlated with the risk of breast cancer and ovarian cancer.[56] Information about these two genes and their mutations is an important factor for patients and their clinicians to consider in deciding treatment options, such as prophylactic surgery, hormonal therapy, chemotherapy, and other measures.[57] Consequently, these two genes, their related mutants, and the method of detecting them are of significant commercial value.

"Myriad offers multiple forms of BRCA1/2 testing to the general public."[58] According to Myriad, its Comprehensive BRACAnalysis and BRACAnalysis Rearrangement Test (BART) "can detect virtually all large rearrangement mutations in the BRCA1 and BRCA2 genes."[59] Those tests are available to clinicians and patients at a cost of about three-thousand dollars per test.[60] Currently, insurance companies cover over 90 percent of the costs for tests performed by Myriad.[61] Some insurance policies, however, do not cover those tests. As a result, some patients were not able to access the test for BRCA1 and BRCA2 mutations, as claimed by Association for Molecular Pathology

[52] *About Myriad*, MYRIAD, http://www.myriad.com/about/ (last visited Jan. 2, 2012).

[53] *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 201–02.

[54] U.S. Patent No. 5,693,473 (filed June 7, 1995); U.S. Patent No. 5,709,999 (filed June 7, 1995); U.S. Patent No. 5,747,282 (filed June 7, 1995); U.S. Patent No. 5,753,441 (filed Jan. 5, 1996); U.S. Patent No. 5,710,001 (filed June 7, 1995); U.S. Patent No. 5,837,492 (filed Apr. 29, 1996); U.S. Patent No. 6,033,857 (filed Mar. 20, 1998).

[55] *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 211–12.

[56] *Id.* at 232.

[57] *See id.* at 203 (explaining the gravity of the decisions a patient must make when diagnosed with breast cancer).

[58] *Id.* at 203.

[59] *Id.*

[60] Borrell, *supra* note 6, at 413.

[61] *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 204.

(AMP) and other plaintiffs.[62]

Myriad has judicially enforced its patent right against commercial infringers of its patents.[63] According to Myriad, it allows research scientists to use BRCA1/BRCA2 genes freely, which resulted in over 5600 publications by over 18000 scientists.[64] However, Myriad does not extend a free license to entities that test BRCA1/BRCA2 genes and their mutations commercially. For example, Genetic Diagnostic Laboratory at the University of Pennsylvania and Yale DNA Diagnostic Lab offered BRCA1/BRCA2 testing services at one time.[65] After receiving Myriad's cease and desist letters, however, they both stopped the testing service.[66]

AMP, joined by several other organizations and individuals, filed a lawsuit in the U.S. District Court for the Southern District of New York (SDNY) against the USPTO and Myriad.[67] AMP alleged that the USPTO's practice of granting patents on isolated DNA sequences was wrong, because isolated genes are products of nature.[68] More specifically, AMP alleged that Myriad's patents were invalid because BRCA1 and BRCA2 genes are not markedly different from their parental chromosomes, therefore, are products of nature and not patentable subject matter.[69] Both parties filed motion for summary judgment.[70] On March 29, 2010, Judge Sweet of the SDNY ruled that Myriad's patents for BRCA1 and BRCA2 genes were invalid.[71] In his opinion, Judge Sweet

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62 *Id.* at 189.

63 *Id.* at 205–06.

64 *Id.* at 210.

65 *Id.* at 204.

66 *Id.* at 187, 204–05. For example, "[Dr. Haig Kazazian] is the Seymour Gray Professor of Molecular Medicine in Genetics in the Department of Genetics at the University of Pennsylvania School of Medicine," and "Dr. Ganguly is an Associate Professor in the Department of Genetics at the Hospital of the University of Pennsylvania." *Id.* "Drs. Kazazian and Ganguly ceased their *BRCA1/2* testing in response to cease-and-desist letters from Myriad relating to the patents-in-suit." *Id.*

67 *Id.* at 186.

68 *See id.* at 185 (arguing that the isolation of a particular DNA sequence from the greater genetic code does not constitute a change from DNA's status as an inherently natural phenomenon sufficient enough to warrant the imposition of patent rights on that isolated sequence).

69 *See id.* (furthering the position that isolated sections of DNA are not materially different from the same isolated sections of DNA as contained within their decidedly non-patentable, chromosomal form).

70 *Id.* at 184–85.

71 *Id.* at 238.

stated that those patents were improperly granted because "DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature" and because "DNA's existence in an 'isolated' form alters neither this fundamental quality of DNA as it exists in the body nor the information it encodes."[72] Consequently, Myriad's motion for summary judgment was denied, and AMP's motion for summary judgment was granted.[73]

Judge Sweet supported his ruling with three pivotal notions. The first notion was that both isolated genes (DNAs) and their parental chromosomes were physical carriers of biological information because information encoded in DNA was not about its own molecular structure incidental to its biological function, but rather reflected its primary biological function: directing the synthesis of proteins.[74] Judge Sweet declared that "DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature—those that define the construction of the human body."[75] In Judge Sweet's opinion, DNA was not patentable because proteins were "biological molecules of enormous importance" that "catalyze[d] biochemical reactions" and constituted "major structural materials of the animal body."[76]

The second notion from Judge Sweet was that DNAs, including isolated genes and their sequences, were too unique and fundamental in nature to be designed around.[77] Judge Sweet reasoned that the "utility of the isolated DNA as a primer or probe is primarily a function of the nucleotide sequence identity between native and isolated *BRCA1/2* DNA"[78] and that "a different nucleotide sequence would not have the same utility because it would be unable to hybridize to the proper location in

[72] *Id.* at 185.

[73] *Id. But see* Ass'n for Molecular Pathology v. USPTO, 653 F.3d 1329 (Fed. Cir. 2011) (reversing judgment that the claimed genes are patent-ineligible, and affirming the District Court's decision that Myriad's methods to analyzing and comparing DNA are patent-ineligible).

[74] *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 228.

[75] *Id.*

[76] *Id.* (quoting *In re O'Farrell*, 853 F.2d 894, 895–96 (Fed. Cir. 1988)).

[77] *See id.* at 231 (noting that the uniqueness and fundamental nature of DNA and isolated genes is derived from their ability to "target and interact with other DNA molecules").

[78] *Id.*

the *BRCA1* gene."[79]

The third notion promoted by Judge Sweet was that isolated genes, such as BRCA1 and BRCA2, were not patentable subject matter under 35 U.S.C. § 101 because "none of the structural and functional differences cited by Myriad between native *BRCA1/2* DNA and the isolated *BRCA1/2* DNA claimed in the patents-in-suit render the claimed DNA 'markedly different.'"[80] This notion, however, is incorrect, because an issued patent is presumably valid and AMP had the burden to prove otherwise.[81] The Federal Circuit, in *Pfizer v. Apotex,*[82] stated that "by statute a patent is valid upon issuance" and that "the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence"[83] and "that burden of proof never shifts to the patentee to prove validity."[84] "The presumption [of validity] remains intact and [the burden of proof remains] on the challenger throughout the litigation, and the clear and convincing standard does not change."[85]

The rest of the present article will rebut these three notions. Section **IV** will demonstrate that not only physical carriers of biological information may still be patentable but also isolated genes, unlike their parental chromosomes, are no longer physical carriers of biological information. Section V will discuss that properties of an isolated gene are not uniquely linked to its DNA sequence and it is possible to design a different molecule around the original DNA sequence to bind the same DNA template. Section VI will illustrate, through several examples, that isolated genes can have totally different structures and properties from their parental chromosomes when chemical bonds are severed during the isolation process.

IV. ISOLATED GENES: BIOMACROMOLECULES OR PHYSICAL CARRIERS OF BIOLOGICAL INFORMATION?

Judge Sweet did not specifically demonstrate that BRCA1 or

[79] *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 231.
[80] *Id.* at 229.
[81] Pfizer, Inc., v. Apotex, Inc., 480 F.3d 1348, 1359 (Fed. Cir. 2007).
[82] *Id.*
[83] *Id.* at 1359.
[84] *Id.* (citing Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1375 (Fed. Cir. 1986)).
[85] *Id.* at 1359–1360 (quoting *Hybritech*, 802 F.2d at 1375).

BRCA2 genes existed in nature, but rather categorically concluded that all genes isolated from nature were products of nature.[86] He reasoned that a gene is a physical carrier of biological information, and an isolated gene carries the same biological information as the same DNA sequence embedded in its parental chromosome existing in nature.[87] Because natural chromosomes are products of nature, all isolated genes are also products of nature.[88] Judge Sweet stated that the "information encoded in DNA is not information about its own molecular structure incidental to its biological function," but rather "reflects its primary biological function: directing the synthesis of other molecules in the body, namely, proteins."[89] Judge Sweet further reasoned that DNA's nucleotide sequence is vitally important "to both its natural biological function as well as the utility associated with DNA in its isolated form."[90] Therefore, Judge Sweet concluded: "The preservation of this defining characteristic of DNA in its native and isolated forms mandates the conclusion that the challenged composition claims are directed to unpatentable products of nature."[91]

However, as will be discussed in more detail in this section, Judge Sweet's analysis overlooked the fact that a DNA is also a biomacromolecule, in addition to being a physical carrier of biological information.[92] A DNA sequence is simply a shorthand notation of its molecular structure.[93] Each unique DNA sequence represents a molecule with its unique structure and properties: physical, chemical, and biological.[94] While being a carrier of biological information is the main task of DNA in a cellular environment, intermolecular interactions, which are closely related with molecular structures, are more important for isolated genes *ex vivo*, especially for the purpose of medical

[86] *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 229.

[87] *Id.* at 228–29.

[88] *See id.* (noting that "products of nature" tend to carry similarly embedded biological information).

[89] *Id.* at 228.

[90] *Id.* at 229.

[91] *Id.*

[92] DAVID L. NELSON & MICHAEL M. COX, PRINCIPLES OF BIOCHEMISTRY 273 (Jane O'Neill ed., 4th ed. 2005).

[93] BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 199 (Marjorie Anderson & Sherry Granum eds., 5th ed. 2008).

[94] *See id.* ("[O]rganisms differ from one another because their respective DNA molecules have different nucleotide sequences . . . .").

diagnostic testing.[95] This section will proceed in three subsections: subsection A will introduce the shorthand notation of the DNA sequence; subsection B will prove that a carrier of biological information is not necessarily unpatentable; and subsection C will prove that utilities of isolated genes are more related with their molecular structures than being carriers of biological information.

A. A DNA Sequence Is a Shorthand Notation of Its Molecular Structure

Both isolated genes and naturally existing chromosomes are biomacromolecules.[96] Although their sizes vary dramatically, they are all composed of nucleotides.[97] Different genes and chromosomes are formed by connecting nucleotides in different sequences through a special chemical bond—a phosphodiester bond.[98] However, at the very basic level, all genes and chromosomes are biomacromolecules made of carbon, oxygen, nitrogen, phosphorus, and hydrogen atoms.[99] The reason genes and chromosomes can perform their genetic function in the cellular environment is that they are chemical compounds with well-defined structures and physical-chemical properties, and they have highly specialized intermolecular interaction patterns at the atomic level.[100]

Both genes and chromosomes are polymers of nucleotides, four different types of which exist naturally, as shown in figure 1.[101] Each nucleotide in the figure consists of three components: phosphate on the left, deoxyribose ring in the middle, and the base ring on the right. The third and fifth carbons of each deoxyribose ring form phosphodiester bonds with adjacent phosphate groups so that the polynucleotide backbone is formed

[95] *See* NELSON, *supra* note 92, at 273, 319, 321 (describing the use of DNA in detecting viral infections before patients become symptomatic and its use in the prenatal detection of genetic disorders).

[96] *See id.* at 273 (describing the makeup of genes and their function); ALBERTS, *supra* note 93, at 202 (describing chromosomes and DNA in eucaryotes).

[97] *See* ALBERTS, *supra* note 93, at 61, 197, 202, 204 (explaining the composition of isolated genes, chromosomes, and the nature of nucleotides).

[98] *See id.* at 199.

[99] NELSON, *supra* note 92, at 273–74, 279.

[100] *See id.* at 923–24 (explaining the structure of genes and chromosomes).

[101] *See* ALBERTS, *supra* note 93, at 61, 202 (explaining that nucleotides are the subunits of DNA and chromosomes).

with alternating phosphate and deoxyribose groups.[102]

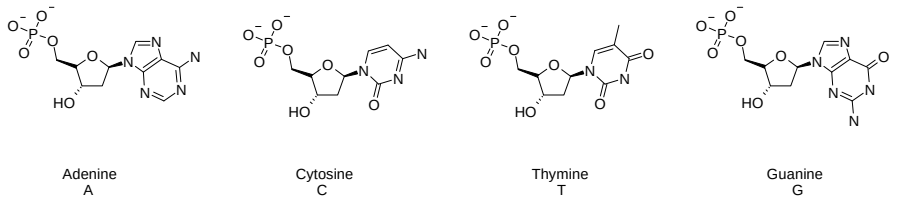

Figure 1. Four naturally-existing nucleotides found in chromosomes and genes.

A DNA sequence is a shorthand notation of its molecular structure. For example, "ATCG" is a convenient way to describe the molecule shown in figure 2. Each unique gene sequence represents a molecule with a unique structure.[103] Whereas the backbone of polynucleotide is formed with phosphate groups and the deoxyribose rings, which are conserved among all DNAs, each of the four bases is unique in structure and properties.[104] If one cites a polynucleotide "ATCG", the composition of matter in question is really about the structure associated with "ATCG", as shown in figure 2, and its unique properties. For example, the four different aromatic base rings have different intermolecular interaction patterns, which determine how this molecule interacts with others.[105] Additionally, those components must be connected by chemical bonds in a well-defined manner.[106] Any modification to any component or to any chemical bond can significantly change the structure of the molecule and its properties.[107] Therefore, a DNA is not just a sequence but rather a well-defined molecule, a biomacromolecule.

[102] *Id.* at 62.

[103] *See id.* (describing gene differentiation of heredity and evolution through hydrogen-bonding of different nucleic acid molecules).

[104] *See* NELSON, *supra* note 92, at 274, 276–77 (diagramming the different structures of the purine and pyrimidine bases of nucleic acids).

[105] *Id.* at 279; ALBERTS, *supra* note 93, at 62.

[106] NELSON, *supra* note 92, at 279; ALBERTS, *supra* note 93, at 62.

[107] *See* ALBERTS, *supra* note 93, at 62 (describing gene differentiation of heredity and evolution through hydrogen-bonding of different nucleic acid molecules); NELSON, *supra* note 92, at 274 (diagramming the different nucleotides created with the same base).

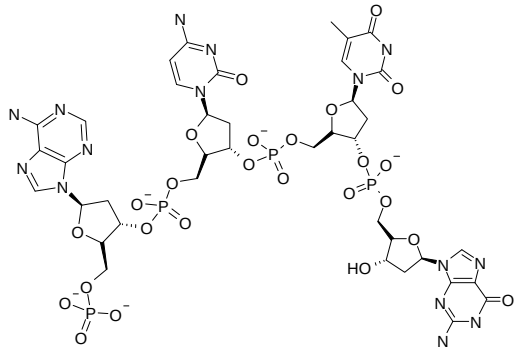

Figure 2. Molecular structure of the polynucleotide "ATCG"

B. Carriers of Biologic Information Are Not Necessarily Unpatentable

As well accepted in molecular biology, DNA plays an important role in a cellular environment as a carrier of biological information through DNA replication and protein production.[108] During the replication process, a DNA double helix separates itself into two single-stranded DNA chains, each of which is used as a template to build a complete DNA double helix identical to the original one.[109] This DNA replication process is critically important in biology because it ensures that genetic information is accurately transferred from one generation to the next.[110]

DNA also controls another important biological function, protein production, through a two-step process.[111] At the first step, genetic information stored in DNA is transferred to messenger RNA (mRNA), which is used as a template for protein production at the second step.[112] Just as the name implied, mRNA serves as a messenger and uses the genetic information copied from DNA to control the production of all proteins in our bodies, such as protein receptors and enzymes.[113]

However, the working mechanism behind being a carrier of genetic information is DNA's unique structure and structure-

[108] *See* ALBERTS, *supra* note 93, at 61 (explaining how nucleotides, which make up RNA and DNA, store biological information and are essential to the formation of nucleic acids).

[109] *See id.* at 200 (describing the process of DNA replication).

[110] *Id.*

[111] *See id.* at 202–04 (describing the function of DNA in protein production).

[112] *Id.* at 4.

[113] *See id.* (regarding mRNA's function as an intermediary, controlling the synthesis of proteins during the process of translation).

related properties.[114] The unique intermolecular interaction between nucleotides controls the stability of a DNA double helix.[115] The unique intermolecular interaction between nucleotides and DNA polymerases controls the highly accurate DNA replication process.[116] The unique intermolecular interaction between nucleotides and RNA polymerases ensures the transfer of genetic information from DNAs to mRNAs.[117] The unique intermolecular interaction between mRNAs and ribosomes decides how proteins are made according to the genetic information stored in mRNA.[118]

Carrying biological information is not unique to DNA. Many other molecules, both small molecules and macromolecules, are capable of carrying biological information.[119] One example is mRNA as discussed in the previous paragraph. Another example is various hormones in our bodies.[120] A hormone is a chemical compound released by a cell or a gland in one part of the organism that sends out messages affecting cells in other parts of the organism.[121] For example, thyroid hormones, produced by the thyroid gland, are primarily responsible for regulating general metabolism;[122] insulin produced in the pancreas regulates carbohydrate and fat metabolism; and adrenaline triggers the fight-ready-response in our bodies, such as increasing heart rate, constricting blood vessels, increasing blood pressure, and dilating air passages.[123]

Similar to DNA, underlining the function of each hormone is its unique structure and its structure-dependent interactions with its partners.[124] For example, adrenaline has a unique

[114] *See id.* at 197–99 (describing DNA as two strands of polyneucleotides wound into the double helix shape).

[115] *See id.* (explaining the complementarity of both shapes and hydrogen-bonding features between the two nucleobases within a pair.).

[116] *Id.* at 268–70.

[117] *Id.* at 335–37.

[118] *Id.* at 335–36.

[119] *See id.* at 335–36, 884 (providing proteins and nucleic acids as examples of macromolecules).

[120] *See id.* at 882.

[121] *Id.*

[122] *Id.* at 890.

[123] *Id.* at 1444; *see also* WILLIAM H. FRISHMAN ET AL., CURRENT CARDIOVASCULAR DRUGS 152 (4th ed. 2005); Stephen L. Aronoff et al., *Glucose Metabolism and Regulation: Beyond Insulin and Glucagon*, 17 DIABETES SPECTRUM 183, 185 (2004).

[124] *See* ALBERTS, *supra* note 93, at 882–83, 903–04 (highlighting the

structure-dependent interaction with ß-adrenergic receptor because the receptor specifically recognizes both hydrophobic and hydrogen-bonding features, as well as the shape of adrenaline.[125] Once adrenaline binds in the binding pocket of the receptor, the receptor changes its conformation, which triggers a cascade of downstream biological responses, including restriction of blood vessels and increased heart rate.[126] In this case, the biological information being carried is increasing blood pressure and the initial carrier of the biological information is adrenaline. Once adrenaline interacts with ß-adrenergic receptor, the biological information is transferred to the receptor, which carries the information further downstream and eventually increases blood pressure if all carriers along the pathway have done their jobs faithfully.[127]

Referring to a molecule as a carrier of biological information is just a convenient way to illustrate a complex biological system and its working mechanism. In fact, anything that has any impact on biological functions is a carrier of biological information.[128] In order for a substance to have an impact on biological functions, it must interact with the biological system and transfer its biological information to the system.[129] Those interactions, at the microscopic level, are intermolecular interactions, which trigger a cascade of downstream reactions through various biological pathways.[130] For example, all drugs, regardless if they are small molecules or macromolecules, are carriers of biological information.[131] Those drug molecules enter

differences between endocrine and neuronal methods for long range signaling and that receptor structures vary based on these methods).

[125] *See id.* at 903–04 (explaining how adrenaline activates nine G protein coupled receptors that function to translate the adrenaline's signals).

[126] *Id.* at 905, 07; *see also* M.T. Piascik, *The Pharmacology of Adrenergic Receptors*, ADRENERGIC PHARMACOLOGY, http://www.uky.edu/~mtp/OBI836AR.html (last visited Jan. 8, 2012).

[127] *See* Piascik, *supra* note 126.

[128] ALBERTS, *supra* note 93, at 2–5.

[129] *Id.* at 415–17.

[130] *See id.* at 45–46, 48 (stating that, at the most basic level, electrons control how atoms interact, which in turn determines interactions between molecules and, therefore, more complicated biological functions).

[131] *See* Richard Steane, *Production of Penicillin in Industrial Fermenters (Bioreactors)*, BIOTOPICS, http://www.biotopics.co.uk/microbes/penici.html (last visited Mar. 12, 2012) (explaining that penicillin is a drug known to prevent cell wall production and carries some biological information with similarities to the bacterial cell walls it is designed to attack.)

our bodies and interact with their specific drug targets, such as a protein receptor or an enzyme.[132] Through their specific intermolecular interaction, the biological functions of those drug targets are changed.[133] Therefore, the biological information carried by the drug is delivered to the drug target.

Being a carrier of biological information does not render a molecule unpatentable, but rather demonstrates the utility of the molecule. All drugs are carriers of biological information because they interact with biological systems and trigger biological responses.[134] They are patentable if they are novel, useful, and nonobvious.[135] For example, 100 years ago, the Honorable Learned Hand held, in *Parke-Davis & Co. v. H.K. Mulford Co.,*[136] that adrenaline was patentable.[137] Judge Sweet, in *AMP v. Myriad,* tried to distinguish *Parke-Davis* from *Myriad* reasoning that the holding for *Parke-Davis* was based on § 102, where the holding for *Myriad* was based on § 101.[138] However, this argument is not convincing because the requirement of § 101 is a threshold question for patentable subject matter.[139] If a patent claim fails § 101 test, it is the end of the discussion and one needs to go no further.[140] By upholding the validity of the patent in *Parke-Davis,* the Honorable Learned Hand must have concluded that adrenaline was patentable subject matter. Thus, carriers of biological information are not necessarily unpatentable.

C. Isolated Genes Are Not Carriers of Biological Information

When a novel isolated gene is discovered and claimed, the composition of matter is not the genetic information hidden in the sequence, but rather its novel structure and unique properties represented by the structure.[141] Natural chromosomes

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132 THOMAS NOGRADY & DONALD F. WEAVER, MEDICINAL CHEMISTRY: A MOLECULAR AND BIOCHEMICAL APPROACH 68 (3d ed. 2005).

133 *See id.* at 67 (explaining the process of a drug binding to a receptor site and changing the molecular function thereby triggering a secondary response).

134 *See id.* (explaining that the activity of drugs is initiated by their atomic-level interaction with a receptor).

135 35 U.S.C. § 103 (2006).

136 189 F. 95 (C.C.S.D.N.Y. 1911), *rev'd in pt.* 196 F. 496 (2d Cir. 1912).

137 *Id.* at 114–15.

138 Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181, 225 (S.D.N.Y. 2010), *rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011).

139 35 U.S.C. § 101 (2006).

140 *See id.*

141 *See* Richard M. Lebovitz, *Gene Patents: "What God Hath Wrought!",* 4 J.

play an important role in carrying genetic information from one generation to the next and in producing specific proteins based on genetic information carried.[142] An isolated gene, however, has different utilities. For example, when Myriad claimed isolated BRCA1 and BRCA2 genes, the compositions of matter were not the biological information carried by those DNAs (isolated genes not in a cellular environment), but rather the unique utility of those isolated genes in detecting certain DNA sequences hidden in biological samples (natural chromosomes in a cellular environment) that have high correlation with breast cancer and ovarian cancer.[143]

This unique utility can be exemplified by numerous well-known molecular biology techniques, most of which rely on molecular structures and structural properties of isolated genes.[144] For example, polymerase chain reaction (PCR), for which Kary Mullis was awarded the Noble Prize in Chemistry 1993,[145] heavily relies on molecular interactions during its operation.[146] PCR can be used to detect and amplify isolated DNA sequences, such as BRCA1 and BRCA2.[147] PCR uses a DNA template containing the DNA sequence being amplified and two primers marking the starting points of the sense strand and the anti-sense strand of the DNA template.[148]

PHIL. SCI. & L. 1, 11–12 (2004). ("When a gene is patented as a chemical structure . . . it is called a composition of matter since it covers the gene as a compound.").

142 *See* ALBERTS, *supra* note 93, at 195, 199 (discussing the role of natural chromosomes in cellular reproduction and protein synthesis.).

143 *Myriad*, 702 F. Supp. 2d at 211–14.

144 *See id.* at 196–97 (examining some of the uses of isolated DNA).

145 Kary B. Mullis, *Polymerase Chain Reaction (Nobel Lecture)*, 106 ANGEWANDTE CHEMIE INT. ED. ENG. 1209 (1994).

146 *See* Randall K. Saiki et al., *Enzymatic Amplification of β-Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia*, 230 SCIENCE 1350, 1350–54 (1985) (discussing molecular interatctions during polymerase chain reactions); Kary B. Mullis & Fred A. Faloona, *Specific Synthesis of DNA* in Vitro *via a Polymerase-Catalyzed Chain Reaction*, 155 METHODS IN ENZYMOLOGY 335, 345–50 (1987) (describing the process of in vitro PCR).

147 *See* Patricia Hartge et al., *Breast Cancer Risk In Ashkenazi BRCA1/2 Mutation Carriers: Effects of Reproductive History,* 13 EPIDEMIOLOGY 255, 256 (2002) (explaining how detecting BRCA1/2 gene can estimate age-specific risk for carriers and non-carriers).

148 *See* Julia Khandurina et al., *Integrated System for Rapid PCR-Based DNA Analysis in Microfluidic Devices*, 72 ANALYTICAL CHEMISTRY 2995, 2295–96, 2998 (2000) (discussing successful DNA amplification for PCR).

A primer must be carefully designed to have a proper melting temperature to ensure proper annealing to the DNA template at a temperature range that is preferred, or at least tolerable, by the DNA polymerase being used.[149] The melting temperature of the primer is determined by the binding free energy between the primer and the DNA template, which includes the interaction energies of all atomic pairs between them.[150] It is fair to conclude that the fundamental driving force behind the PCR technique is not the genetic coding, but rather the sophisticated handling of molecular structures and binding affinities at the atomic level.[151] PCR and PCR-related technologies can only operate on isolated genes not on a whole chromosome, even if the whole chromosome contains a DNA section with the same sequence.[152]

TaqMan® is another popular molecular biology technique that heavily relies on structural features and molecular interactions rather than genetic coding.[153] First developed in 1991,[154]

[149] Arun Apte & Saurabha Daniel. *PCR Primer Design*, in PCR PRIMER: A LABORATORY MANUAL 61–62 (Carl W. Dieffenbach & Gabriela S. Dveksler eds., 2d ed. 2003).

[150] *See* Alejandro Panjkovich & Francisco Melo, *Comparison of Different Melting Temperature Calculation Methods for Short DNA Sequences*, 21 BIOINFORMATICS 711, 711 (2005) (discussing that different nucleotide DNA sequences play a major role in the experimental value of T_mS).

[151] *See* H.R. Garner, *Automating the PCR Process*, *in* POLYMERASE CHAIN REACTION 182, 182 (Kary B. Mullis, Francois Ferré & Richard A. Gibbs eds. 1994) (explaining that new techniques must be developed to increase the rate samples are processed before PCR is a reasonable method of analysis for human DNA).

[152] *See id.* at 185–86, 190 (explaining the process of preparing DNA templates and the use of multiple separate gel electrophoresis as a detection method for PCR products); Richard H. Tullis, *Ultrasensitive Nonradioactive Detection of PCR Reactions: An Overview*, *in* POLYMERASE CHAIN REACTION 123, 123–29 (Kary B. Mullis, Francois Ferré & Richard A. Gibbs eds.1994) (explaining methods of detection of pieces of amplified DNA strands); Margaret Hunt, *Real Time PCR*, MICROBIOLOGY AND IMMUNOLOGY ON-LINE: UNIVERSITY OF SOUTH CAROLINA SCHOOL OF MEDICINE (July 1, 2010), http://pathmicro.med.sc.edu/pcr/realtime-home.htm ("Polymerase chain reaction . . . is a method that allows exponential amplification of short DNA sequences (usually 100 to 600 bases) within a longer double stranded DNA molecule."); *How do we Sequence DNA?*, THE UNIV. OF MICHIGAN DNA SEQUENCING CORE, http://seqcore.brcf.med.umich.edu/doc/educ/dnapr/sequencing.html ("The human genome is 3 *billion* bases long, arranged on 23 pair of chromosomes. . . . To [sequence DNA], we break the entire genome up into manageable pieces and sequence them.").

[153] *See* Pamela M. Holland et al., *Detection of Specific Polymerase Chain Reaction Product by Utilizing the 5' → 3' Exonuclease Activity of* Thermus aquaticus *DNA Polymerase*, 88 PROC. NAT'L ACAD. SCI. U.S. 7276, 7276, 7279

TaqMan® uses a tailored molecular probe that can specifically bind to the gene sequence being detected.[155] A fluorophore is attached to one end of the probe, and a quencher is attached to another end.[156] The probe is often a polynucleotide containing 20 to 30 bases, which can specifically recognize the structure of the DNA sequence being detected, such as BRCA1 and BRCA2.[157] Without binding to the DNA sequence, this probe does not emit fluorescence because the quencher and the fluorophore are constrained to close proximity by the probe.[158] However, once the probe binds to the DNA sequence being detected, the fluorophore is separated from the quencher by the exonuclease activity of the Taq-polymerase.[159] Without the quencher nearby, the fluorophore emits fluorescence that signals the existence of the particular DNA sequence.[160]

The entire operation of the TaqMan® technology heavily depends on the structural properties that have little to do with being a carrier of biological information.[161] The binding of the probe to the DNA sequence is a pure intermolecular interaction.[162] Its specificity and stability depend on both hydrophobic interactions and hydrogen-bonding interactions between the two molecules.[163] It can only operate on isolated genes and does not work for a whole chromosome containing the same sequence segment.[164] The cleaving of the fluorophore by the

(1991) (describing Taq DNA polymerase specificity).

154 *Id.* at 7276.

155 *See* Deepti Parashar et al., *Applications of Real-Time PCR Technology to Mycobacterial Research*, 124 INDIAN J. MED. RES. 385, 387 (2006) (explaining how Taq polymerase binds and separates with a specific gene site).

156 *Id.* at 389 fig. 4.

157 *See* ASHRAF F. FOUAD, ENDODONTIC MICROBIOLOGY 76 (2009) (explaining the increased specificity as well as length of the TaqMan probe).

158 *See id.* ("Free molecular beacons acquire a hairpin structure when in solution, and the stem keeps the arm in close proximity. This results in efficient quenching of the fluorescent dye.").

159 *Id.*

160 *Id.*

161 *See* Parashar, *supra* note 155, at 387, 389 (explaining how TaqMan hybridizes to internal structures during operation).

162 *Id.*

163 *See* M. Sundaralingam & P.K. Ponnuswamy, *Stability of DNA Duplexes with Watson-Crick Base Pairs: A Predicted Model*, 43 BIOCHEMISTRY 16467, 16468 (2004) (examining the factors which affect stability of DNA binding.).

164 *See* Garner, *supra* note 151, at 185–86, 190 (explaining the process of preparing DNA templates and the use of multiple separate gel electrophoresis as a detection method for PCR products); Tullis, *supra* note 152, at 123–29

Taq-polymerase breaks a chemical bond within the probe, which is a well-defined chemical reaction.[165] Neither the binding of the probe nor the cleaving of the fluorophore occurs in a natural biological system or has anything to do with carrying or passing biological information.[166]

In summary, an isolated gene is a chemical compound in nature. Its utilities are more related with its molecular structure than being a carrier of biological information. Isolated BRCA1 and BRCA2 genes are tool compounds in molecular biology research, whereas their parental chromosomes are carriers of biological information in human body. They have different structures, different properties, and different utilities. Isolated genes are not products of nature even if their parental chromosomes are.

V. A DNA SEQUENCE CAN BE "DESIGNED AROUND"

Judge Sweet opined that the utility of an isolated gene is primarily the function of its DNA sequence, and a different DNA sequence would not have the same utility.[167] This opinion echoed the argument, best articulated by Professor Jordan Paradise in 2005 that properties of DNA are uniquely linked to its sequence and cannot be designed around.[168] This is one of the strongest arguments distinguishing genes from other chemical compounds and disfavoring patenting isolated genes.[169] According to this argument, people can design a new molecule around an ordinary chemical compound to carry out the same function, such as

(explaining methods of detection of pieces of amplified DNA strands); Hunt, *supra* note 152 ("Polymerase chain reaction . . . is a method that allows exponential amplification of short DNA sequences (usually 100 to 600 bases) within a longer double stranded DNA molecule."); THE UNIV. OF MICHIGAN DNA SEQUENCING CORE, *supra* note 152 ("The human genome is 3 *billion* bases long, arranged on 23 pair of chromosomes. . . To [sequence DNA], we break up the entire genome up into manageable pieces and sequence them.").

165 *See* Parashar, *supra* note 155, at 387 fig. 2.

166 *See* D.H. Kim & J.U. Kang, *Review: Upconversion Microscopy for Biological Applications*, *in* 1 MICROSCOPY: SCIENCE, TECHNOLOGY, APPLICATIONS AND EDUCATION 571, 575–76 (A. Méndez-Vilas & J. Diaz eds., 2010) (explaining upconversion luminescence).

167 Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181, 231 (S.D.N.Y. 2010), *rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011).

168 Paradise, *supra* note 6, at 1869–70.

169 *See* Allen K. Yu, *Within Subject Matter Eligibility–A Disease and a Cure*, 84 S. CAL. L. REV. 387, 410–12 (2011) (explaining the differences of genetic materials and why patenting them is unfavorable).

designing a new drug molecule around a patent-protected drug to attack the same drug target and cure the same disease.[170] However, "one cannot design around a human nucleotide sequence if one wants to study, diagnose, or treat the genetic disease at issue."[171]

While this statement was correct for a long time and is still recognized by many molecular biology textbooks,[172] some very recent scientific discoveries prove the contrary.[173] As will be discussed in this section, just like any other chemical compound, a gene sequence can also be designed around.

In order to illustrate the uniqueness of DNA sequences and possible strategies to design around a DNA sequence, one needs to understand the structural foundation of Watson-Crick base pairs. The two strands of a DNA double helix are anti-parallel and complementary to each other.[174] The complementarities of the two strands are reflected in both the shape and hydrogen-bonding features.[175] The highly specific binding of DNA is due to the fact that only two pairs of mutually recognizing bases exist in natural DNA, where adenine (A) is only recognized by thymine (T) and guanine (G) is only recognized by cytosine (C).[176] This pairwise recognition is commonly referred to as Watson-Crick base pairs, which is the predominant stabilizing force for DNA structures.[177]

As shown in figure 3, adenine has a double-ring base and thymine has a single-ring base, which creates shape complementarities.[178] In an ideal situation, a hydrogen-bond donor (atoms colored in blue) prefers to interact with a hydrogen-bond acceptor (atoms colored in red).[179] As shown in figure 3,

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[170] *See* Paradise, *supra* note 6, at 1869–70 ("[T]raditional composition of matter patents cover a chemical composition with a particular function, such as a drug, which can be designed around.").

[171] *Id.* at 1870.

[172] *See* ALBERTS, *supra* note 93, at 196–200 (explaining the building blocks of DNA and sequencing).

[173] *See* Lee *supra* note 52 at 1064 (exhibiting a way of replicating DNA using nonnatural building blocks).

[174] *See* ALBERTS, *supra* note 93, at 199 (explaining the basic structure of DNA).

[175] *See id.* at 197–98 (explaining how the opposing strands of DNA complement each other).

[176] *Id.* at 197.

[177] Lee, *supra* note 52, at 1064–65.

[178] *See* ALBERTS, *supra* note 93, at 198 fig. 4-4.

[179] *See id.* at 197, 198 fig. 4-4 ("*Hydrogen bonds* between the base portions of

between the two single-ring-base nucleotides, cytosine and thymine, which complement to adenine in shape, only thymine can have an ideal hydrogen-bonding interaction with adenine.[180] Therefore, only thymine can be recognized by adenine.[181] The same exercise can be done for guanine to explain why it only recognizes cytosine.[182]

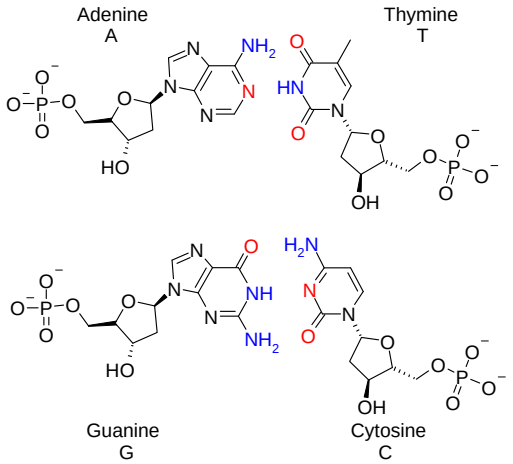

Figure 3. Natural Watson-Crick base pairs. Hydrogen-bonding interactions within each pair of natural nucleotides stabilize the double helix folding of DNAs. Atoms colored in red are hydrogen-bond acceptors and atoms colored in blue are hydrogen-bond donors. A hydrogen-bond acceptor of one nucleotide prefers to interact with a hydrogen-bond donor of another nucleotide. This figure appears in color in the online version of this article.

This highly specific pairwise recognition is best reflected in DNA replication process. At each cell division, one strand of DNA serves as a template to make another strand, with which it forms a complete DNA double helix.[183] This highly precise and efficient replication process, catalyzed by DNA polymerases, allows a cell to pass on the identical genetic information to its daughter cells.[184]

To "design around" a DNA sequence, the newly proposed compound must satisfy the structural requirement of Watson-Crick base pairs. One of the most obvious and toughest tests is whether the newly introduced compound is similar enough to the

the nucleotides holds the two chains together.")

[180] *Id.* at 197, 198 fig. 4-4.

[181] *Id.*

[182] *Id.*

[183] *Id.* at 200.

[184] *Id.* at 266.

original DNA to be recognized by DNA polymerases in places reserved for natural nucleotides, building blocks of natural DNA.[185] DNA polymerases are fascinating enzymes, which display incredible selectivity as they have an error rate of one out of a million.[186] It is a high standard to design nonnatural nucleotides to compete against natural nucleotides that evolved from billion years of biological evolution. From the time the first DNA structures were discovered until recently, this task was believed impossible.[187] However, the foundation of this dogma has recently been challenged by findings that designed nonnatural nucleotides can be effectively and specifically recognized by DNA polymerases in places that were exclusively reserved for the four natural nucleotides.[188] Several studies have demonstrated that nonnatural nucleotides can be used to "design around" natural nucleotides.[189] This newly formed polynucleotide using nonnatural building blocks can recognize the same DNA sequence as efficiently and selectively as the original natural polynucleotide.[190]

Joseph Piccirilli and coworkers were among the first groups that published their findings of nonnatural polynucleotides.[191] As shown in figure 4, they followed a seemingly straightforward strategy by constructing nonnatural base pairs that are

185 *See* Lee, *supra* note 52, at 1064 ("The ability of DNA polymerases to efficiently and accurately replicate genetic material represents one of the most fundamental yet complex biological processes found in nature. The central dogma of DNA polymerization is that the efficiency and fidelity of this biological process is dependent upon proper hydrogen-bonding interactions between an incoming nucleotide and its templating partner.").

186 Myron F. Goodman & D. Kuchnir Fygenson, *DNA Polymerase Fidelity: From Genetics Toward a Biochemical Understanding*, 148 GENETICS 1475, 1479 (1998) (providing an example of polymerases providing base substitution error of less than one out of one million).

187 *See* Lee, *supra* note 52, at 1064–65 (explaining the *dogma* of DNA polymerization is that the process is dependent on the natural nucleotides).

188 *Id.*

189 *See id.* at 1065–74, 1078 (examining instances where nonnatural base pairs can be used and their benefit).

190 *See id.* at 1065 (describing how the effects of both natural and nonnatural nucleotides are similar).

191 *See* Joseph A. Piccirilli et al., *Enzymic Incorporation of a New Base Pair into DNA and RNA Extends the Genetic Alphabet*, 343 NATURE 33, 33–34 (1990) ("A new Watson-Crick base pair, with a hydrogen bonding pattern different from . . . [natural] base pairs, is incorporated into duplex DNA and RNA by DNA and RNA polymerases and expands the genetic alphabet from 4 to 6 letters.").

geometrically identical to the original natural base pairs but with different spatial arrangement of hydrogen-bonding features.[192] This strategy was implemented using the *E. coli* Klenow fragment and became one of the first examples of a nonnatural polynucleotide constructed by DNA polymerase based on a natural DNA template.[193]

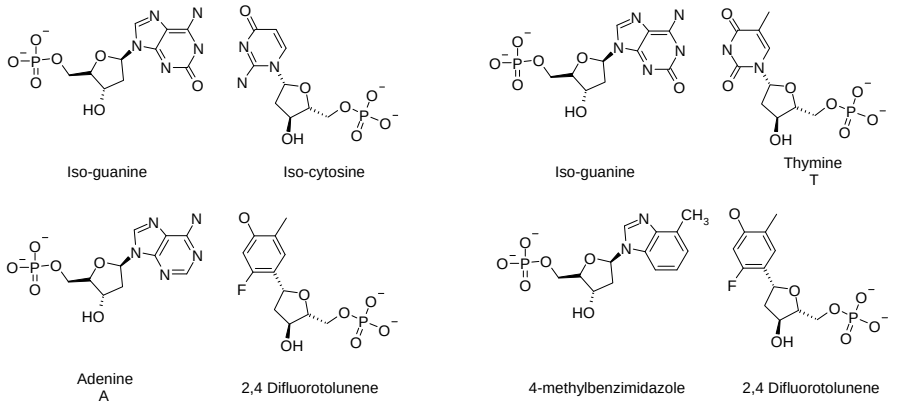

Figure 4. Examples of nonnatural nucleotides and their pairwise recognition discovered by Joseph Piccirilli and coworkers (See footnote 193).

Masahide Ishikawa and coworkers developed an alternative strategy using positive/negative reinforcement to generate novel nonnatural nucleotide base pairs.[194] The "[p]ositive reinforcement [was gained] through Watson-Crick hydrogen-bonding interactions . . . to optimize enthalpic contributions . . . ."[195] The negative reinforcement was achieved by introducing specific bulky groups to hinder mispairing sterically.[196] Their work also demonstrated that nonnatural nucleotides could be recognized and incorporated by DNA polymerases selectively and efficiently.[197]

Eric Kool and coworkers explored another approach to incorporate nonnatural nucleotides during DNA replication, where the classic hydrogen-bonding functional groups were completely devoid and the sole recognition was derived from

192 *Id.* at 33 fig. 1.

193 Lee, *supra* note 52, at 1065–68.

194 *Id.* at 1067 (citing Masahide Ishikawa et al., *Chemical Synthesis of Novel Base Pairs and Their Enzymatic Incorporation into DNA*, 42 NUCLEIC ACIDS SYMP. SER. 125 (1999)).

195 *Id.*

196 *Id.*

197 *Id.* at 1067–68.

shape and hydrophobic interactions.[198] They concluded "that hydrogen bonding interactions between the incoming nucleotide and the templating nucleobase are not needed for polymerization but are required for optimal efficiency."[199]

In summary, utilities of an isolated gene are not uniquely linked to its nucleotide sequence but rather derived from its chemical structure. Just like one can design a new molecule around a patent-protected drug to attack the same drug target, one can design a new nucleotide sequence around a patent-protected DNA sequence to serve exactly the same purpose. DNA sequences are not too unique and fundamental for life to be patented. Just like any other chemical compound, an isolated gene is patentable if it satisfies other requirements of patent law, such as novelty, utility, and non-obviousness.

VI. AN ISOLATED GENE CAN HAVE "MARKEDLY DIFFERENT CHARACTERISTICS" FROM ITS PARENTAL CHROMOSOME

Isolated genes do not exist in natural biological organisms.[200] The closest naturally existing matter to an isolated gene is its parental chromosome containing a segment of the same DNA sequence.[201] To prove BRCA1 and BRCA2 are products of nature because their parental chromosomes are products of nature, AMP must prove that BRCA1 and BRCA2 are not "markedly different" from their parental chromosomes.[202] As will be discussed in section VI.A, AMP failed to prove specifically that BRCA1 and BRCA2 are not "markedly different" from their parental chromosomes. Judge Sweet's opinion tried to conclude generally that all isolated genes (DNAs) are not markedly different from their parental chromosomes.[203] However, Judge Sweet's conclusion is not correct scientifically. As will be demonstrated in

198 *Id.* at 1068 (citing Sean Moran, Rex X.-F. Ren & Eric T. Kool, *A Thymidine Triphosphate Shape Analog Lacking Watson-Crick Pairing Ability is Replicated with High Sequence Selectivity*, 94 PROC. NAT'L ACAD. SCI. 10506 (1997).

199 *Id.*

200 *See* Ass'n for Molecular Pathology v. USPTO, 653 F.3d 1329, 1368 (Fed. Cir. 2011) (Moore, J., concurring in part).

201 *Id.*

202 *See* Diamond v. Chakrabarty, 447 U.S. 303, 310 (1980) (patentee showed the product to have "markedly different characteristics" from anything naturally occurring and the court found it to be patentable subject matter).

203 Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181, 232 (S.D.N.Y. 2010), *rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011).

three examples (subsections B, C, and D), when a biomacromolecule, such as DNA, is severed from its parental molecule, it may gain markedly different characteristics.

A. AMP Must Prove That Isolated Genes Are Not "Markedly Different"

The District of Columbia Federal District Court, in *Shell Development v. Watson,*[204] construed the composition of matter under the patent statute to include "all compositions of two or more substances and . . . all composite articles, whether they be results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids."[205] After analyzing the legislative history, the Supreme Court, in *Diamond v. Chakrabarty,*[206] stated that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'"[207] Although "[t]he laws of nature, physical phenomena, and abstract ideas have been held not patentable," [208] a composition is patentable subject matter under § 101 if it has "markedly different characteristics from any found in nature."[209]

Patents at issue in *AMP v. Myriad* were granted by the USPTO[210] and presumed valid.[211] AMP had the burden of proving their invalidity by clear and convincing evidence under *Pfizer v. Apotex*.[212] Based on the holding of *Diamond v. Chakrabarty*, to prove Myriad's claims are invalid under § 101, AMP must at least prove that BRCA1 and BRCA2 do not have "markedly

[204] 149 F. Supp. 279 (D.D.C. 1957).

[205] *Id.* at 280.

[206] 447 U.S. 303 (1980).

[207] *Diamond*, 447 U.S. at 309 (quoting S. REP. NO. 1979, at 5 (1952), H.R. REP. NO. 1923, at 6 (1952)).

[208] *Id.* at 309.

[209] *Id.* at 310.

[210] Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181, 211–12 (S.D.N.Y. 2010), *rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011); U.S. Patent No. 5,693,473 (filed June 7, 1995); U.S. Patent No. 5,709,999 (filed June 7, 1995); U.S. Patent No. 5,747,282 (filed June 7, 1995); U.S. Patent No. 5,753,441 (filed Jan. 5, 1996); U.S. Patent No. 5,710,001 (filed June 7, 1995); U.S. Patent No. 5,837,492 (filed Apr. 29, 1996); U.S. Patent No. 6,033,857 (filed Mar. 20, 1998).

[211] *See* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359–60 (Fed. Cir. 2007) (asserting that decisions of the USPTO are presumed valid under 35 U.S.C. § 282).

[212] *See id.* ("Since we must presume a patent valid, the patent challenger bears the burden of proving the factual elements of invalidity by clear and convincing evidence.").

different characteristics from any found in nature."[213] AMP did not satisfy its burden of proving that BRCA1 and BRCA2 did not have "markedly different characteristics" from their parental chromosomes or any other things found in nature. Judge Sweet erred by shifting the burden of proof and holding that BRCA1 and BRCA2 were not patentable under § 101 because "[n]one of Myriad's arguments establish the distinctive nature of the claimed DNA."[214]

Without specifically proving BRCA1 and BRCA2 are not markedly different from their parental chromosomes, Judge Sweet generally concluded that an isolated DNA was not markedly different from the native DNA segment embedded in its parental chromosome with the same nucleotide sequence.[215] This conclusion, however, overlooked the fact that DNA is a biomacromolecule with properties much beyond its DNA sequence. To compare the difference or similarity between any two molecules, one must compare their structures and properties.[216] As demonstrated in following examples, by severing chemical bonds, just like what happens when a gene is isolated from its parental chromosome, a biomacromolecule can change its structure and properties significantly.

B. Example: Inactive Prethrombin-2 Versus Active Thrombin

By simply breaking one chemical bond, a chemical reaction can significantly change a molecule's structure and biological properties.[217] This can be demonstrated through a comparative study of prethrombin-2 and thrombin. Thrombosis is a biological process controlling blood coagulation (clotting).[218] It is vitally important that blood can clot when it needs to and does not clot under normal circumstances. Thrombin, a trypsin-like serine protease, is at the center of the sophisticated blood coagulation cascade.[219] Prothrombin, the precursor protein of thrombin, is

[213] *Diamond*, 447 U.S. at 310 (explaining the requisite basis to satisfy 35 U.S.C. § 101).

[214] *Myriad*, 702 F.Supp.2d at 229.

[215] *Id.*

[216] Paul G. Seybold, Michael May & Ujjvala A. Bagal, *Molecular Structure-Property Relationships*, 64 J. OF CHEMICAL EDUC. 575, 575.

[217] *See id.* at 575 tbl. 1 (examining the physical properties of isomers).

[218] *Definition of Thrombosis*, MEDICINENET.COM, http://www.medterms.com/script/main/art.asp?articlekey=25023 (last visited Fed. 26, 2012).

[219] *See* Earl W. Davie et al., *The Coagulation Cascade: Initiation,*

secreted into blood circulation and remains there.[220] Because prothrombin is not biologically active, it does not cause unwanted blood clotting during normal blood circulation.[221]

At the onset of a triggering event, such as an injury, prothrombin can be converted to thrombin through different pathways, one of which is shown in figure 5.[222] At the first step of the activation process, the peptide bond at the R271 position is cleaved and the pro-domain of Gla/K1/K2 is removed.[223] The product of this step is Prethrombin-2 which does not have blood clotting activity either.[224] At the second step of the activation process, the peptide bond at the R320 position is cleaved.[225] Due to the cleavage of this single chemical bond, prethrombin-2 is converted to thrombin, which is fully active and triggers the downstream coagulation response.[226] Even if prethrombin-2 and thrombin have an identical sequence, their biological functions are totally different.[227]

Maintenance, and Regulation, 30 BIOCHEMISTRY 10363, 10364 (1991).

[220] *Definition of Prothrombin*, MEDICINENET.COM, http://www.medterms.com/script/main/art.asp?articlekey=5089 (last visited Feb. 26, 2012).

[221] Davie, *supra* note 219, at 10363, 10365–67.

[222] *Id.* at 10364 fig. 1.

[223] Zhiwei Chen et al., *Crystal Structure of Prethrombin-1*, 107 PROC. NATL. ACAD. SCI. 19278, 19278 fig. 1 (2010).

[224] *Id.* at 19278–79.

[225] *Id.* at 19278.

[226] *Id.*

[227] *See* Rainer Friedrich et al., *Staphylocoagulase is a Prototype for the Mechanism of Cofactor-Induced Zymogen Activation*, 425 NATURE 535, 535–39 (2003) (analyising the structure of Thrombin and Prethrombin-2); *see also* Philip D. Martin et al., *New Insights into the Regulation of the Blood Clotting Cascade Derived from the X-Ray Crystal Structure of Bovine Meizothrombin Des F1 in Complex with PPACK*, 5 STRUCTURE 1681, 1681–93 (1997) (comparing the structures and functions of Thrombin and Prethrombin-2).

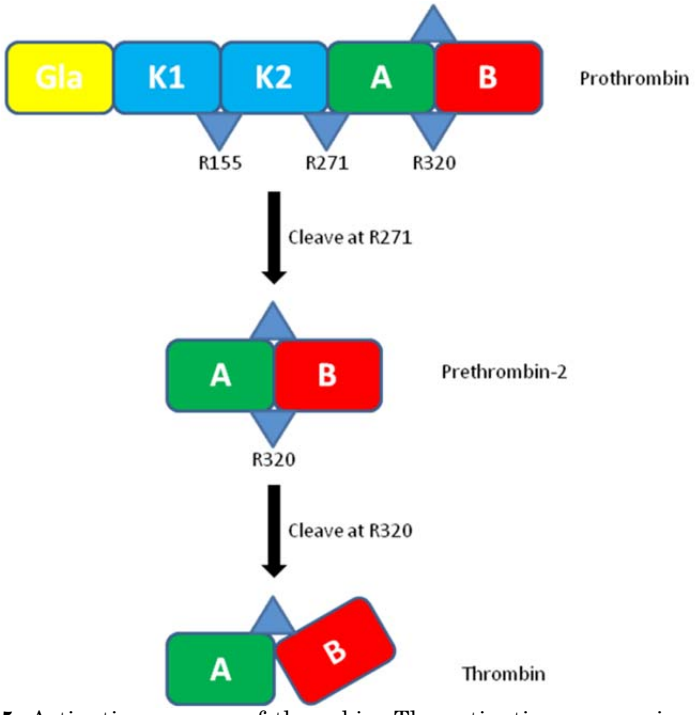

Figure 5. Activation process of thrombin. The activation process involved two steps: cleaving the peptide bond at the arginine 271 (R271) position to convert prothrombin to prethrombin-2 and cleaving the peptide bond at the arginine 320 (R320) position to convert prethrombin-2 to thrombin. This figure appears in color in the online version of this article.

This dramatic difference in biological function is supported by the comparison of their X-ray structures solved by protein crystallography.[228] Figure 6 is a stereo view of superimposed structures of thrombin and prethrombin-2, in which the thrombin is colored green and the prethrombin-2 is colored red. The yellow-colored space is the catalytic site where protein substrates comes in, interacts with thrombin, and undergoes hydrolysis reaction. The product of this hydrolysis reaction triggers the downstream coagulation activities.[229]

[228] Chen, *supra* note 223, at 19278.
[229] Davie, *supra* note 219, at 10366.

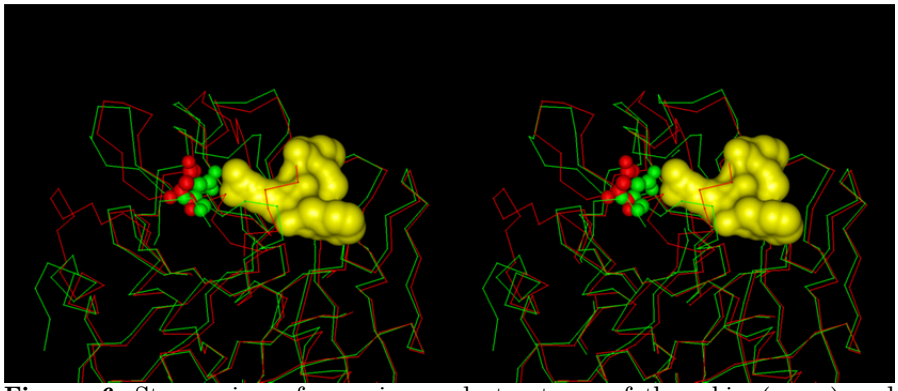

Figure 6. Stereo view of superimposed structures of thrombin (green) and prethrombin-2 (red). The space around the catalytic binding site, which is the space accessible by protein substrates, is colored in yellow. Only alpha carbons are shown in a trace-line view except Aspartic acid 189 (D189) which is shown in a space-filled all-atom view. (Note to readers: one can see a 3-D picture by pretending to watch something infinitely far away so that the left eye sees the left picture and the right eye sees the right picture). This figure appears in color in the online version of this article.

Several residues, from thrombin and prethrombin-2, play an important role to carry out this hydrolysis reaction.[230] One of them is aspartic acid 189 (D189).[231] D189 carries a strong negative charge and can form an H-bonding interaction with the positively charged arginine residue of the substrate.[232] Due to this interaction, the substrate can be recognized, recruited, and bound in the catalytic pocket, which is a prerequisite for the hydrolysis reaction. For this to happen, D189 must have a direct access to the substrate-binding pocket.[233]

As shown in figure 6, D189 of prethrombin-2 (the red-colored residue) is about five Å away from the substrate-binding pocket (the space colored in yellow) and is hidden behind other atoms. As a result, it cannot form the critical hydrogen-bonding

[230] *See id.* at 10364 fig 1 (pictorially explaining the "coagulation cascade"); Michael G. Malkowski et al.,, *The Co-Crystal Structure of Unliganded Bovine α-Thrombin and Prethrombin-2: Movement of the Tyr-Pro-Pro-Trp Segment and Active Site Residues Upon Ligand Binding*, 6 PROTEIN SCI. 1438, 1438 (1997) (examining the coagulation process).

[231] *Clotting Factors (Serine Proteinase)*, SBI: STRUCTURAL BIONFORMATICS, http://sbi.imim.es/web/files/projects/master/2010/Coagulation_serine_proteases/Thr_Thrombin.html *(last visited* Feb. 26, 2012).

[232] Michael J. Page et al., *Engineering the Primary Substrate Specificity of* Streptomyces griseus *Trypsin*, 42 BIOCHEMISTRY 9060, 9064 (2003).

[233] *See id.* (describing the process of D189 binding).

interaction with the substrate.[234] After severing a single peptide bond at the R320 position, D189 moves into the substrate binding pocket and avails itself for hydrogen-bonding interaction with substrates, as shown in the green-colored position in figure 6, which activates the enzyme biologically.[235]

As we have seen, breaking a single chemical bond, such as the peptide bond at R320 position for thrombin, can dramatically change the structure and properties of a protein. The cleavage of this chemical bond triggered a folding change in the most important area of the protein, the catalytic center. Before this change, the protein was biologically inactive. After the change, the protein gained full activity of its biological function. Breaking a single chemical bond can transform a protein to a totally different composition of matter.

C. Example: Harmless Amyloid Precursor Protein Versus Aβ That Causes Alzheimer's Disease

By simply breaking two peptide bonds, amyloid precursor protein (APP) is converted to amyloid beta (Aβ), as shown in figure 7, which has different physical, chemical, and biological properties.[236] APP is a transmembrane protein consisting of 695 to 770 amino acids.[237] APP has a stable 3-D folding and its structure has been determined by X-ray crystallography.[238] APP is believed to contribute to nervous signal transductions and can pass through the blood-brain barrier (BBB) relatively easily to enter and exit the central nervous system (CNS).[239] APP can be converted to Aβ by cleaving two peptide bonds sequentially, as shown in figure 7.[240] Aβ is a group of polypeptides consisting of

[234] *See id.* at 9064–65 (describing D189's preference due to hydrogen bonding).

[235] *See id.* at 9064–65; Davie, *supra* note 219, at 10363–70 (describing substrate binding).

[236] *See* Paul M. Gorman & Avijit Chakrabartty, *Alzheimer β-Amyloid Peptides: Structures of Amyloid Fibrils and Alternate Aggregation Products*, 60 BIOPOLYMERS 381, 384 (2001) (Descrbing how APP is converted into Aβ); S. Zhang et al., *The Alzheimer's Peptide A β Adopts a Collapsed Coil Structure in Water*, 130 J. OF STRUCTURAL BIOLOGY 130, 130 ("Aβ is derived from a type I transmembrane polypeptide known as the amyloid precursor protein.").

[237] Gorman, *supra* note 236, at 384; Zhang, *supra* note 236, at 130.

[238] *See* Gorman, *supra* note 236, at 385; Zhang *supra* note 236, at 131.

[239] *See* Gorman, *supra* note 236, at 381–84 (examining the history of APP).

[240] Gorman, *supra* note 236, at 385; Zhang *supra* note 236, at 130 (explaining APP can be converted to Aβ by cleaving).

approximately 36 to 43 amino acids.[241] They do not have a stable 3-D folding and cannot pass through the BBB easily.[242] If one has abnormally elevated β-secretase and γ-secretase activities in the CNS, more than normal amount of Aβ can be generated in the brain.[243] Because Aβ cannot pass the BBB to exit the CNS, it accumulates and precipitates inside the brain to form Aβ plaques, which cause Alzheimer's disease.[244]

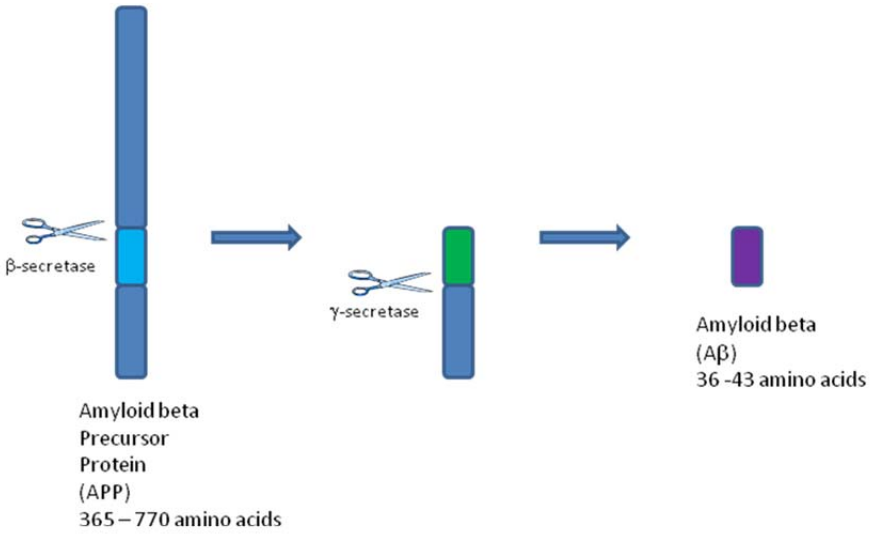

Figure 7. Two peptide bonds of amyloid precursor protein (APP) are cleaved by β-secretase and γ-secretase to form amyloid beta (Aβ). This figure appears in color in the online version of this article.

Aβ, severed from APP, is a different chemical substance from either APP or the polypeptide segment embedded in APP with the same sequence.[245] When embedded within APP, the polypeptide segment identical in sequence to Aβ can adopt a stable 3-D fold, pass the BBB, and carry out other biological

[241] Gorman, *supra* note 236, at 384 (explaining that Aβ is a polypeptide); Zhang, *supra* note 236, at 130.

[242] *See* Gorman, *supra* note 236, at 381 (explaining that the molecule is insoluble); Zhang, *supra* note 236, at 131 (explaining that these molecules adopt a beta-sheet folding pattern).

[243] *See* Gorman, *supra* note 236, at 385 (explaining how Aβ levels in the body can rise); Zhang, *supra* note 236, at 130 (showing that APP releases Aβ).

[244] Arvi Rauk, *The Chemistry of Alzheimer's Disease*, 38 CHEMICAL SOC. REVIEWS 2698, 2698 (2009); Carlos Morgan et al., *Structure and Function of Amyloid in Alzheimer's Disease*, 74 PROGRESS NEUROBIOLOLGY 323, 325 (2004).

[245] Rauk, *supra* note 244, at 2699; Morgan, *supra* note 244, at 326.

functions as part of APP.[246] However, the isolated Aβ does not have a stable 3-D fold, does not pass the BBB, and precipitates to amyloid plaques in the brain.[247] Isolated Aβ has "markedly different characteristics" from the polypeptide segment embedded in APP even if they have exactly the same sequence.

D. Example: Double-Stranded DNA Versus Severed Single-Stranded DNA

Similar to polypeptides, after being severed from its parental chromosome, an isolated gene can also have a different structure and different properties. DNAs in their natural state exist in double-stranded DNA helixes.[248] The location and orientation of each base ring are stabilized by hydrogen-bonding interactions with the base ring of its counterpart to form a twisted "rope ladder"-like structure.[249] However, when a section of a single-stranded DNA, such as an isolated gene, is severed from its natural environment, this stabilizing hydrogen-bonding network does not exist anymore.[250] As a result, a single-stranded DNA exhibits a different 3-D fold, as evidenced by the study of Kyle Brown and coworkers.[251]

Kyle Brown used nuclear magnetic resonance spectroscopy (NMR) measuring 3-D structures of DNAs based on nuclear Overhauser effect.[252] Structures of both double-stranded and single-stranded DNAs were resolved.[253] As shown in Figure 8, all base rings in the double-stranded DNA (left and middle pictures) stayed in a perfect "rope ladder"-like conformation with all the base rings parallel to one another. However, as shown in the right picture of figure 8, the single-stranded DNA did not have

[246] *See* Rauk, *supra* note 244, at 2700 (explaining the solubility of APP while embedded with Aβ); Morgan, *supra* note 244, at 331 (explaining the structure of the polypeptide).

[247] *See* Rauk, *supra* note 244, at 2701; Morgan, *supra* note 244, at 324–25 (showing the difficulty of the ability to prove similar folding and explaining the plaque deposits in the brain).

[248] Barry W. Duceman, *DNA Analysis: Scientific and Legal Aspects*, 2 ALB. L.J. SCI. & TECH. 53, 57 (1992).

[249] *Id.*

[250] *See* Kyle L. Brown et al., Structural Perturbations Induced by the α-Anomer of the Aflatoxin B_1 Formamidopyrimidine Adduct in Duplex and Single-Strand DNA, 131 J. AM. CHEMISTRY SOC'Y 16096, 16105 (2009).

[251] *See id.* at 16104 (examining the difference in structures of DNA).

[252] *See id.* at 16098–100 (explaining how the experiment was conducted).

[253] *See id.* at 16100–03 (noting the structures of both types of DNA).

this "rope ladder"-like structure with all base rings adapting their independent orientations.[254] This experiment demonstrates that an isolated gene, which is a severed single-stranded DNA, can have a structure different from its parental chromosome and different from the same DNA segment embedded within its parental chromosome.

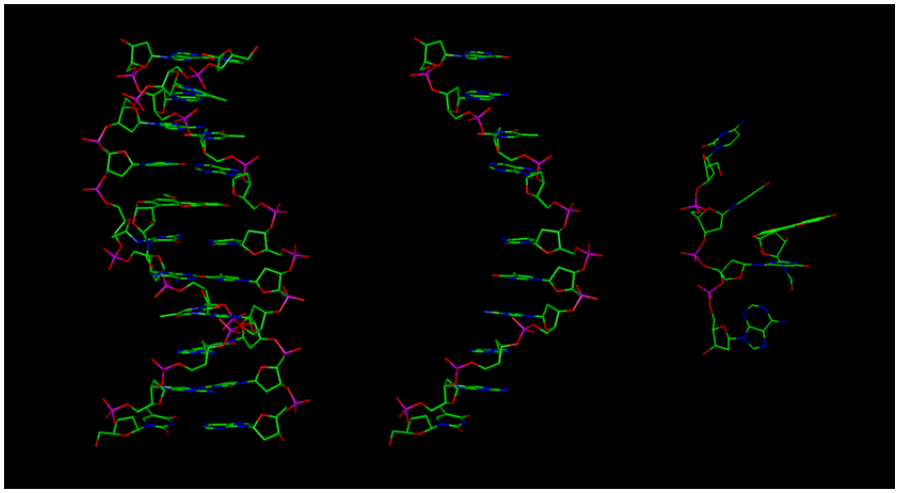

Figure 8. NMR structures of DNA (left: double-stranded DNA; middle: one strand of the double-stranded DNA from the left; right: single-stranded DNA). All the base rings (the rings with blue-colored nitrogen atoms) in the double-stranded DNA (the left and middle pictures) are parallel to one another in a perfect ladder-like conformation, whereas base rings of the single-stranded DNA (the right picture) do not have such uniformed orientation. This figure appears in color in the online version of this article.

An isolated gene can also have different properties from its parental chromosome and be used in many molecular biology applications, which are not suitable for its parental chromosome.[255] For example, an isolated gene can be used as an injectable vector in gene therapy, which is a promising treatment for many hard-to-treat diseases.[256] Isolated genes can be used as

[254] *Id.* at 16104.

[255] *See* Ass'n for Molecular Pathology v. USPTO ("Myriad"), 653 F.3d 1329, 1362 (Fed. Cir. 2011) (Moore, J., concurring in part) ("[A] fragment of a DNA sequence has different properties than the parent molecule from which it is derived.").

[256] *See* Erlinda M. Gordon & Frederick L. Hall, The 'Timely' Development of Rexin-G: First Targeted Injectable Gene Vector (Review), 35 INT'L J. ONCOLOGY 229, 231 (2009) (explaining the use in gene therapy); Bruce C. Trapnell, Adenoviral vectors for Gene Transfer, 12 ADVANCED DRUG DELIVERY REVIEWS 185, 194–96 (1993) (explaining the potential benefits of gene therapy).

a genetic vector in plant breeding and selection, which has a significant scientific value in both basic research and agricultural applications.[257] Isolated genes can also be used in vaccine research and development.[258] Protection against infections of herpes simplex virus, influenza virus, and vesicular stomatitis virus has been demonstrated using this technology.[259] Those broad applications are all based on the special characteristics of isolated genes, not their parental chromosomes existing in nature.

In summary, as shown in the examples cited above, severing a section of a biomacromolecule can significantly change its structure and properties. It is wrong to assume that isolated genes are never "markedly different" from their parental chromosomes just because they share a section of identical sequence. It is wrong to conclude categorically that isolated genes are products of nature simply because their parental chromosomes are products of nature. BRCA1 and BRCA2 are patentable unless AMP carries its burden of proving that those two isolated genes are not "markedly different" from anything found in nature, which AMP failed to do.

VII. CONCLUSION

Isolated genes are patentable subject matter because they are not necessarily products of nature. BRCA1 and BRCA2 genes and their utilities claimed in Myriad's patents are more attributable to their molecular properties than being physical carriers of biological information. Severing a gene from its parental chromosome can transform it to a new chemical substance with totally different structure and properties. Utilities of an isolated gene are more dependent on its molecular structure than its DNA sequence. Just like any other chemical compound, an

257 *See* Charles H. Shaw, *Ti-Plasmid—Derived Plant Gene Vectors*, 1 OXFORD SURVEYS PLANT MOLECULAR & CELL BIOLOGY 211, 212 (1984) (explaining the development of controlled expression in plant cells); Richard Walden et al., The Use of Gene Vectors in Plant Molecular Biology, 1 METHODS MOLECULAR CELLULAR BIOLOGY 175, 179 (1990) (showing how isolated DNA can be used to turn a single cell into an entire plant); Jeffrey W. Davies & John Stanley, Geminivirus Genes and Vectors, 5 TRENDS IN GENETICS 77, 80 (1989) (stating the application of isolated genes and gene vectors in plant molecular biology).

258 Bernard Moss, *Vaccinia Virus Vectors*, 10 BELTSVILLE SYMP. IN AGRIC. RES. 317, 317 (1986).

259 *Id.* at 320–22.

isolated gene can be designed around using nonnatural nucleotides to perform the same function. Just like any other chemical compound, they are patentable if they are useful, novel, and not obvious to one skilled in the art as specified in the patent law. Judge Sweet erred in *AMP v. Myriad* by holding that isolated genes like BRCA1 and BRCA2 were not patentable subject matter.