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SHEDDING LIGHT ON THE OBVIOUSNESS OF GENE PATENTS

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I. INTRODUCTION

Gene therapies have been heralded as medicinal "forever fix[es]"[1]—robust tools to remedy the most resilient hereditary diseases and imperfections. Nearly 50,000 gene sequences, many with potential for use in gene therapy treatments, have been patented in the United States as of 2016.[2] And yet, geneticists face significant challenges in protecting their innovations via patent. To date, most legal discussion on the protection of gene therapies has centered on the question of whether extracted strands of human deoxyribonucleic acid ("DNA" or "biological code") are sufficiently "man-made" to avoid 35 U.S.C. § 101's prohibition of patents on "naturally occurring phenomena."[3]

The United States Supreme Court formally addressed this issue in *Association for Molecular Pathology v. Myriad Genetics*. The Court invalidated several claims of a patent that disclosed a method to screen a patient for two genes known to increase the risk of breast and ovarian cancer.[4] Even if the isolation processes were "groundbreaking, innovative, or even brilliant . . . [f]inding the location of the BRCA1 and BRCA2 genes does not render the genes patent eligible 'new . . . composition[s] of matter.'"[5] The Court held that isolated human DNA is a "naturally occurring phenomenon" and ineligible for patent protection.[6] Conversely, it upheld claims for synthetic cDNA strands—lab-made DNA with small structural differences—finding

1. Ricki Lewis, *Gene Therapy and September Scenes*, DNA SCI. BLOG (Sep. 02, 2017, 10:00am), http://blogs.plos.org/dnascience/2017/09/14/gene-therapy-and-september-scenes/.

2. Robert Cook-Deegan, *Gene Patents*, THE HASTINGS CTR. (Sep. 02, 2017, 10:33am), http://www.thehastingscenter.org/briefingbook/gene-patents/.

3. 35 U.S.C. § 101 (2012); *see, e.g.*, *Nicolle-Wagner v. Deukmejian*, 230 Cal. App. 3d 652 (Cal. Ct. App. 1991), *reh'g denied and opinion modified* (June 13, 1991).

4. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013); *see also* Lara Cartright-Smith, *Patenting Genes: What Does* Association for Molecular Pathology v. Myriad Genetics *Mean for Genetic Testing and Research?*, 129 PUB. HEALTH REP. 289, 290 (2014).

5. *Myriad*, 569 U.S. at 591.

6. *Id.*

them sufficiently synthetic to be patentable under 35 U.S.C. § 101.[7] However, in a footnote the Court also mentioned that it "express[ed] no opinion whether cDNA satisfies the other statutory requirements of patentability."[8] This reservation has been interpreted by some members of the genetics community as a "whisper" from the Court that even synthetic gene patents could soon face patentability issues under the novel and non-obvious requirements.[9]

This Note will answer the salient question of how those man-made genetic sequences which survived *Myriad* might interact with traditional patent validity challenges. Specifically, it will discuss how obviousness challenges under 35 U.S.C. § 103—by far the most popular invalidity defense among infringement defendants[10]—apply to the invention of new "functional uses" of gene therapies; namely the product of taking existing cDNA sequences and adapting them for different medical applications within the human body by altering viral delivery mechanisms, viral concentrations, and minor structural changes to existing cDNA. By focusing on the optogenetic subset of gene therapy, this Note will argue that under current obviousness case law[11], novel functional uses of patented cDNA sequences will be vulnerable to *prima facie* obviousness challenges from pharmaceutical competitors if the sequences ever become commercially-viable medical treatments.

II. OPTOGENETICS: THE BIOMEDICAL SCIENCE GOING VIRAL

In optogenetics, researchers design cDNA strands which, once integrated into a host cell, instruct that cell to create light-sensitive pore-like proteins (called "channelrhodopsins") on the surface of its cellu-

7. *Id.*

8. *Id.* at 2120.

9. Robin Feldman, *Gene Patenting After the U.S. Supreme Court Decision – Does* Myriad *Matter?*, 26 STAN.L.& POL'Y REV. 16, 21 (2014).

10. *See* Michael Furrow, *Pharmaceutical Patent Life-Cycle Management After* KSR v. Teleflex, 63 FOOD & DRUG L.J. 275, 284 (2008) (discussing vulnerability of patents to obviousness challenges).

11. Most obviousness issues with gene-based patents arise as part of the initial patent prosecution with the United States Patent and Trademark Office ("USPTO") — an insufficient body of jurisprudence to map out how actual obviousness challenges brought by sophisticated parties will pan out. As the Supreme Court has pointed out, there is a "notorious difference between the standards applied by the Patent Office [and those applied] by the courts." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 18 (1966). This Note will thus examine controlling case law in the field of obviousness to predict how currently established standards are likely to interact with the particular nature of innovating in the functional use space for genetics.

lar membrane.[12] When a small amount of light strikes one of these proteins, it opens and allows the free flow of ions across the membrane of the cell.[13] This is particularly relevant for treatments targeting nerve and muscle cells, which rely on the flow of ions to communicate and to contract, respectively. For example, paralyzed muscle cells that have been modified to express channelrhodopsins can be instructed to contract by applying a weak laser to the surface of the skin over the injured muscle, effectively restoring some level of motor control.[14] Optogenetics has also shown promise in treating central nervous disorders such as Alzheimer's Disease and stroke by modifying specific cells in the brain and spinal cord and using precise lasers to turn them "on" or "off."[15] Finding these treatments remains a complex and often cumbersome process; while one team of researchers design the cDNA to code for different channelrhodopsins, others must determine how to subsequently express that cDNA in different cell types and effectively use the channelrhodopsins for targeted therapies.[16]

Suppose a new channelrhodopsin called "Chrimson"[17] is patented that is specifically sensitive to red light over other colors or wavelengths. A geneticist wants to find a way to use Chrimson in a human's sciatic nerve in order to stimulate paralyzed gastrocnemius (calf) muscles. If an existing publication in *Nature* teaches that a similar protein expresses poorly in mice without a certain mouse DNA fragment incorporated into the encoding gene, our pioneering scientist may attempt to fuse the DNA coding for Chrimson with several

12. Hiromu Yawo et al., *General Description: Future Prospects of Optogenetics*, in OPTOGENETICS: LIGHT-SENSING PROTEINS AND THEIR APPLICATIONS 111, 113–14 (Hiromu Yawo et al. eds, 2015).

13. *See id.* at 114.

14. *See, e.g.*, Benjamin Maimon et al., *Transdermal Optogenetic Peripheral Nerve Stimulation*, 14 J. NEURAL ENG'G. 21, 46 (2017) (disclosing a method to stimulate and contract otherwise paralyzed gastrocnemius muscle in C51 mice via laser pointer). This particular application is seeing a recent influx of study as a promising form of non-invasive treatment options for neural disorders.

15. See Aravanis et al., *An Optical Neural Interface:* In Vivo *Control of Rodent Motor Cortex with Integrated Fiberoptic and Optogenetic Technology*, 4 J. NEURAL ENG'G. 143 (2007); Shah et al., *Optogenetic Neuronal Stimulation of the Lateral Cerebellar Nucleus Promotes Persistent Functional Recovery After Stroke*, 7 NATURE SCI. REP. 46612 (2017).

16. *See, e.g.*, Karl Llewellyn, *Orderly Recruitment of Motor Units Under Optical Control* In Vivo, 16 NATURE MED. 1161 (2010) (disclosing the first application of channelrhodopsin-2 to control skeletal muscle by expression of the gene in the peripheral nervous system); G. Nagel et al., *Channelrhodopsin-2, A Directly Light-Gated Cation-Selective Membrane Channel*, 100 PROC. NAT. ACAD. SCI. 13940, 13940–13945 (2003) (disclosing creation and optical characteristics of channelrhodopsin-2); Chris Towne et al., *Optogenetic Control of Targeted Peripheral Axons in Freely Moving Animals*, 8 PLOS ONE 72691 (2013) (building upon Llewellyn, disclosing the first recorded method to deliver channelrhodopsin-2 and stimulate skeletal muscle in fully awake mice).

17. Channelrhodopsins are often playfully named with an extra "h". *See, e.g.*, U.S. Patent Application No. 14/357,635 (filed Nov. 12, 2012).

strands of native human DNA. There would likely be no direct human analog to the mouse gene that facilitated expression, so our scientist would make many varied but informed attempts at incorporating human (and possibly mouse) DNA fragments into the genetic code in the hopes that one such effort would facilitate the expression of Chrimson in the sciatic nerve. The changes do not necessarily need to be structural—adaptation of existing genes often also involves changing the viral delivery mechanism, the genetic promoter which accompanies the cDNA, the dosage, and the actual site of injection.[18]

Celebrated neuroscientist Ed Boyden describes the process as requiring "serendipity"—but that such "serendipity can be optimized to some degree . . . if one is aware of the complex properties of the brain throughout the entire process of invention, from concept generation all the way to final testing."[19] In other words, optogenetics is sufficiently demanding that skill and expertise of neuronal function are required on the part of the researcher to move the craft beyond an exercise in pure luck. Unfortunately for would-be patentees, lower courts have found (and the Supreme Court affirmed in *Myriad*) that the abstract level of "difficulty" experienced during the invention process is irrelevant for patent protection.[20] Furthermore, patent law has traditionally assumed invalidity on a patent disclosing the adaptation of existing materials—in this case, the cDNA—to a novel use.[21] What protection then, does this leave this particular school of genetic inventors?

III. "OBVIOUS IN LIGHT OF"—THE STATE OF § 103

Under 35 U.S.C. § 103,[22] an invention does not warrant patent protection if it would have been obvious to a person of ordinary skill in the art at the time of invention. In *KSR International Co. v. Teleflex Inc.*, Justice Kennedy wrote for a unanimous Court to broaden previous interpretations of the statute, declaring that "a person of ordinary

18. *See, e.g.*, Maimon et al., *supra* note 14 (altering each of the described factors to adapt Chrimson for use in mouse sciatic nerve).

19. Edward Boyden, *A History of Optogenetics: The Development of Tools for Controlling Brain Circuits with Light*. 3 F1000 BIO. REP. 11, 91 (2011).

20. *Stewart v. Mahoney*, 23 F.Cas. 68 (C.C.D. Mass. 1879) ("The amount of labor or thought necessary to produce an invention is not material."); *Myriad*, *supra* note 5, at 579.

21. *See, e.g.*, *Layne-New York Co., Inc. v. Allied Asphalt Co., Inc.*, 501 F.2d 405, *certiorari denied* 421 U.S. 914 (holding that a new use for an old process is not patentable); *Application of Noel F. Albertson*, 332 F.2d 379 (C.C.P.A. 1964) (holding that the use of an unobvious starting material cannot render a process unobvious).

22. "A patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103 (2012).

skill is also a person of ordinary creativity, not an automaton."[23] The Court consequently reversed decades of jurisprudence from the Court of Appeals for the Federal Circuit ("CAFC"), which had strictly required some type of teaching, suggestion, or motivation to invalidate a patent as obvious. Instead, these indicia became merely a "helpful insight."[24] Second, the Court remarked that "the [CAFC] erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was *obvious to try*."[25]

If our modified treatment for Chrimson from before—we'll call it Chrimson-X—actually functions to express the desired protein in the calf muscle, it would pass the subject matter check of *Myriad* because the sequence is not a direct product of nature. Further, a patent for Chrimson-X would likely survive the pre-*KSR* obviousness test because fusing Chrimson with any particular strand of human DNA is not obvious in the abstract if there are many possible ways to modify Chrimson for expression in human sciatic nerve.[26]

After *KSR*, however, even though Chrimson-X could be non-obvious in the abstract, it would be easy to for the scientist's rival to argue that the *Nature* publication renders such work *obvious to try* because the only difference between Chrimson and Chrimson-X is the adaptation of the methods disclosed in the *Nature* article to human genes, and such an option was *at least* one of the many open to the scientist in his efforts to adapt Chrimson to human use. By introducing the "obvious to try" standard, the Court held inventions resulting from "choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success" to be unpatentable under 35 U.S.C. § 103.[27]

A. In re Kubin

With this in mind, the CAFC did carve out narrow exceptions to the "obvious to try" standard in *In re Kubin*.[28] The first is a quantity-based escape hatch to an obviousness invalidation and applies when an inventor merely "throws metaphorical darts at a board filled with combinatorial prior art possibilities."[29] The exact contours of this metaphorical dart board were not and have not yet been defined by the CAFC, but sparse district court applications of the rule show the pos-

23. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007).
24. *Id.*
25. *Id.* (emphasis added).
26. *See, e.g.*, *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1325 (Fed. Cir. 1999).
27. USPTO, *Manual of Patent Examining Procedure*, R-08, 2143 (2012).
28. *See In re Kubin*, 561 F.3d 1351, 1352 (Fed. Cir. 2009).
29. *Id.* at 1359.

sibility of favorable treatment for gene therapies. In *Johnson & Johnson v. CIBA* for example, the United States District Court for the Middle District of Florida used the exception to uphold a patent for silicone hydrogel contact lenses where the prior art contained at least one hundred references that could have been combined to create the claimed invention.[30]

The second exception occurs when the process that was "obvious to try" was to explore a sufficiently broad new technology. This is *Kubin*'s quality-based escape hatch. If the prior art gives only "general guidance as to the particular form of the claimed invention or how to achieve it," then any given process might be obvious to try, but not yield the "reasonable expectation of success" prescribed under *KSR*.[31] Courts have been hesitant to apply this test directly, and almost all citations to this half of *Kubin* have been used to reject, not uphold claims for obviousness.[32]

Our Chrimson-X example would thus be unlikely to find support against an obviousness challenge from the second exception in *Kubin*, but could arguably survive under the first. After all, new genetic engineering tools such as CRISPR allow for thousands of possibly meaningful substitutions in genetic code in modifying existing genes.[33] Any number of substitutions can be banded together for some cumulative effect, compounding the "combinatorial" nature of the prior art. On the other hand, the CAFC may consider the skill of a geneticist of ordinary skill in the art as knowing, as Boyden suggests, which exact substitutions are likely to yield successful modifications to existing code.

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30. *Johnson & Johnson Vision Care, Inc. v. CIBA Vision Corp.*, 616 F. Supp. 2d 1250 (M.D. Fla. 2009).

31. *Kubin*, 561 F.3d at 1355.

32. Ultimately, these two tests are narrow exceptions to the broader rule. The CAFC reiterated in its holding that it "could not, in the face of KSR, cling to formalistic rules for obviousness, customize its legal tests for specific scientific fields in ways that deem entire classes of prior art teachings irrelevant, or discount the significant abilities of artisans of ordinary skill in an advanced area of art." *Id*. at 1360. The presumption for new functional uses of existing genes will be against patent validity unless the CAFC chooses to use *Kubin* and its progeny to provide subject-matter specific exceptions to the "obvious to try" test introduced in *KSR*. *See, e.g.*, *Oatey Co. v. IPS Corp*., 665 F. Supp. 2d 830 (N.D. Ohio 2009) (holding the claims of an electromagnetic motor sufficiently specific to invalidate claims for a washing machine); *Howmedica Osteonics Corp. v. Zimmer, Inc*., 640 F. App'x 951 (Fed. Cir. 2016) (emphasizing the "reasonable expectation for success" standard in invalidating the claims of an ultra-high molecular weight polyethylene in light of prior art).

33. *See* Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCI. 819–823 (2013).

B. A Question of Approval

One potential drawback of a higher obviousness standard for gene therapies is that it discourages commercial investment in potential treatments or products. This relationship is already a well-documented phenomenon in traditional medicine.[34] Pharmaceutical companies will not pursue research and approval for otherwise effective and beneficial drugs if they fear that they will not be able to get the patent protection needed to recuperate costs.[35] Firms must invest hundreds of millions of dollars in research, prototyping, and multi-stage clinical trials for novel treatments. Once these clinical trials are completed, competitors (absent patent protection) can often duplicate a drug—called a 'generic' in the pharmaceutical market—at an exceedingly low per-unit cost, rendering the investment pointless.[36]

This may have foreboding consequences for the prospect of delivering functional uses of synthetic genes to human patients. On August 30th 2017, the first direct-administered gene therapy was approved by the FDA for use in the United States.[37] Marketed as "Kymriah," the therapy instructs a patient's body to produce modified immune cells that target and kill leukemia cells.[38] Kymriah is not the first therapy to earn regulatory approval—in October 2012, the European Commission approved Glybera, a gene therapy for the treatment of hereditary lipoprotein lipase deficiency.[39] In both cases, the therapy was protected by a valid patent throughout clinical testing.[40] If low patentability would discourage pharmaceutical companies, which may already be taking major risks by seeking approval for a gene therapy, there are simply few, if any, parties that would be able to afford the

34. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV., 503 (2009) (Roin points out that this phenomenon "acts to deter innovation when development and commercialization costs are high").

35. *Id.* at 545.

36. *Id.* at 510.

37. *FDA Approval Brings First Gene Therapy to United States*, FDA NEWS RELEASE (Aug. 30, 2017) https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm.

38. *See id.*

39. *European Medicines Agency Recommends First Gene Therapy for Approval*, EUROPEAN MEDS. AGENCY (July 20, 2012), http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/07/news_detail_001574.jsp&mid=WC0b01ac058004d5c1.

40. Even with patent protection, Glybera was marred by exceptionally high costs (pricing to patients at around $ 1.2 million US) and was later pulled from European markets. Because the effects of gene therapies can be long lasting if not permanent, clinical trials for efficacy and safety must necessarily be longer than for traditional drugs, driving up the cost of development. *See* US Patent No. 7,741,465 (filed July 2, 1993) (disclosing claims for Kymriah); WO Patent No. 2,011,031,467 (disclosing claims for Glybera). *See also* U.S. Patent No. 5,658,785 (filed June 6, 1994) (issued Aug 19, 1997) (patent for adenoassociated virus (AAV) later granted FDA approval).

bill. Therefore, while commentators have often pointed out that low levels of patentability for genetic tools and therapies have, to date, worked to encourage research in the genetics space,[41] such a trend will most likely lead only to commercialization of *diagnostic* products such as those in *Myriad* because they do not require direct human treatment and therefore bypass FDA or other regulatory approval.[42]

IV. CONCLUSION

The adaptation of existing strands of cDNA to new areas of the body is a difficult process requiring both awareness of the complex properties of the human body as well as a moderate dose of serendipity. Under current obviousness law, there exist narrow exceptions that might allow patent validity for new functional uses of existing genes, but the presumption under current CAFC jurisprudence points towards a finding of obviousness. This presents a dilemma between balancing patent protection to not paralyze the academic researchers in large part driving modern genetic innovation and to award sufficient incentives to corporate actors capable of funding studies for the regulatory approval of genetic treatments. Without adequate protection, novel genetic therapies relying on the invention of a new functional use for a known protein or cDNA strand may never see the light of day.

41. Larry Greenemeier, *Case Studies Reveal that Patents Can Hinder Genetic Research and Patient Care,* SCI. AM. (September 14, 2017, 8:10pm), https://www.scientificamerican.com/article/gene-patent/.

42. *See* J.R. Johnson, *Approval Summary for Erlotinib for Treatment of Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer*, 11 CLINICAL CANCER RES., 6414, 6420 (2005). *But see* N.S. Que-Gewirth & B.A. Sullenger, *Gene Therapy Progress and Prospects: RNA Aptamers.* 14(4) J. GENE THERAPY 283, 287 (2007) (disclosing the FDA approval of RNA aptamer treatments in 2006).