THE STRUGGLE FOR CRISPR: A BILLION DOLLAR QUESTION IN INTELLECTUAL PROPERTY

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I. INTRODUCTION

In the past fifty years, colossal advances in genetic technology have revolutionized and redefined the way research is done in the biotechnology sector.[1] The ability to manipulate nucleic acid sequences, and thus to dictate the structure and function of the end products encoded by those sequences, has enormously shifted the landscape of agribusiness, medicine, and research science.[2] While various robust genetic tools have existed for decades, perhaps no single discovery promises to revolutionize the field like CRISPR. CRISPR, short for "Clustered Regularly Interspaced Short Palindromic Repeats" allows the user to effectively "copy and paste" desired genetic content within targeted regions of an organism's genome.[3] The potential to exploit this technology is staggering; already, researchers have implemented the technology in livestock and plants, while development of targeted gene therapies for humans are proposed and in development.[4] Tied to this enormous utility is an enormous economic impact: at least one estimate of the genome editing market predicts a value in excess of $3.5 billion by 2019.[5]

With such revolutionary and important technology, it should come as no surprise that the intellectual property rights to this technology are a premium commodity. Two competing patent claims have appeared in the three years since the discovery was initially disclosed. A research team led by Dr. Jennifer Doudna, working at University of California-Berkeley, and Dr. Emmanuel Charpentier, at the Helmholtz Centre for Infection Research (Germany), ostensibly has the earliest claim to the CRISPR-Cas9[6] technology.[7] On the other side, Dr. Feng Zhang of the Massachusetts Institute of Technology and the associated Broad Institute have already obtained twenty patent grants for

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1. *See, e.g.*, Asude Alpman Durmaz et al., *Evolution of Genetic Techniques: Past, Present, and Beyond*, BIOMED RES INT'L (Dec. 5, 2014) (recounting the history of genetic techniques).

2. *See, e.g.*, Heidi Ledford, *CRISPR, the Disruptor*, NATURE (June 3, 2015), http://www.nature.com/news/crispr-the-disruptor-1.17673 (describing CRISPR as "the biggest game changer to hit biology since [polymerase chain reaction]").

3. Andrew Pollack, *Jennifer Doudna, a Pioneer Who Helped Simplify Genome Editing*, N.Y. TIMES (May 11, 2015), http://www.nytimes.com/2015/05/12/science/jennifer-doudna-crispr-cas9-genetic-engineering.html?_r=0.

4. *See* Ledford, *supra* note 2 (discussing the genetic engineering of smaller pigs, introduction of disease-resistance in rice and wheat, and development of gene therapies and disease treatments for humans); *see also* Sarah Zhang, *An Arcane Patent Law May Decide CRISPR's Big Legal Fight*, WIRED (Jan 5, 2016, 7:00 AM), http://www.wired.com/2016/01/crispr-patent-dispute-gets-really-arcane/ ("The money is getting as real as the lab results. The gene-editing company Editas, which licenses the Broad [Institute]'s patent, filed for a $100 million IPO [on January 4, 2016].").

5. *See Genome Editing/Genome Engineering Market Worth 5.54 Billion USD by 2021*, MARKETSANDMARKETS, http://www.marketsandmarkets.com/PressReleases/genome-editing-engineering.asp [hereinafter *Genome Market*] (discussing a forthcoming report entitled "Genome Editing/Genome Engineering Market by Technology (CRISPR, TALEN, ZFN), Applications (Cell Line Engineering, Animal Genetic Engineering, Plant Genetic Engineering), End User (Biotechnology & Pharmaceutical Companies, CROs—Global Forecast to 2021").

6. "Cas9" stands for "CRISPR-associated protein 9," which is one of the many components of the system referred to briefly as "CRISPR." Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCI. 816, 816 (2012). It occurs naturally in a number of bacterial species, most notably *Streptococcus pyogenes*, where it is used to detect and cleave foreign DNA strands. *Id.*

7. Pollack, *supra* note 3.

applications of the CRISPR-Cas9 system in eukaryotic organisms.[8] This dispute has given rise to attempts to reopen the prosecution of Zhang's patent in order to conduct an interference proceeding, which will pit the University of California against the Broad Institute in an attempt to demonstrate that Doudna and Charpentier are entitled to priority (and thus, to the right of patent) based on an earlier date of invention.[9] Interference proceedings are a dying phenomenon, gutted and largely removed from the patent system by the Leahy-Smith America Invents Act (AIA) in 2011.[10] These proceedings are still available, however, for any patent filed prior to March 16, 2013—the effective date of the AIA.[11] In this Note, I will present a historical background of the patent system's interference proceedings, and predict each party's chance of success. I will provide an explanation of the function of CRISPR, and describe the history of the technology and of biotechnology in general within the patent system. I will describe the recently declared interference proceeding involving the Zhang patent and Doudna/Charpentier application, and will recommend a standard for obviousness and novelty for patent cases seeking to differentiate between technologies that utilize prokaryotic and eukaryotic cell types. I will recommend that the Patent Trial and Appeal Board find that the original Zhang patent be found obvious in light of even the pre-amendment Doudna/Charpentier application, which I also recommend be accorded the presumption of first inventorship and ultimately receive a favorable judgment in the proceeding.

II. BACKGROUND

A. Genetics, Cell Biology, and CRISPR-Cas9: A Primer

Genetics itself is not by any means a novel concept. The idea of manipulating nucleic acid sequences to modulate the form and function of an organism (or parts of an organism) has been an elementary component of bioscience research and innovation for decades.[12] In most forms of life, the primary genetic material is deoxyribonucleic acid (DNA) composed of nucleotide bases A, T, C, and G.[13] CRISPR-Cas9 is a gene-editing system originally found in bacteria that confers variable and responsive adaptive immunity to bacteria being invaded by foreign DNA.[14] The system incorporates an endonuclease enzyme (Cas9) capable of introducing double-

8. *Information About Licensing CRISPR Genome Editing Systems*, BROAD INST., https://www.broadinstitute.org/partnerships/office-strategic-alliances-and-partnering/information-about-licensing-crispr-cas9-syste (last visited Oct. 15, 2016).

9. Pollack, *supra* note 3.

10. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011); 35 U.S.C. § 321 (2012) (codifying AIA's post-grant review procedures).

11. MPEP § 2159 (9th ed. Rev. 7, Nov. 2015).

12. *See, e.g.*, Durmaz et al., *supra* note 1 (recounting the history of genetic techniques).

13. *The Genetic Basics: What Are Genes and What Do They Do?*, NAT'L INST. HEALTH, https://history.nih.gov/exhibits/genetics/sect1a.htm (last visited Oct. 15, 2016).

14. Jinek et al., *supra* note 6.

stranded breaks in a target DNA sequence.[15] When a genetic target of interest is identified by the scientist, a twenty nucleotide ribonucleic acid (RNA) sequence, variably referred to in the profession as either a "guide" RNA (gRNA) or CRISPR RNA (crRNA), is designed that is identical to a DNA sequence that is unique within the genome.[16] Briefly, the gRNA sequence acts as a scaffold that, in complex with the Cas9 enzyme, activates the enzyme's DNA cleavage function, and simultaneously dictates the region of DNA to which the gRNA will anneal.[17] Once the double-strand break has been introduced at the desired DNA location, the scientist has a decision to make about how she would like the process to proceed. Most organisms will repair double-stranded breaks using a process called Non-Homologous End Joining (NHEJ).[18] This results in an efficient and rapid repair of the break, but is prone to introduce insertions of a few nucleotides, or deletions of a few nucleotides.[19] This can result in "knockouts" of the targeted gene resulting from the mutation.[20] A scientist wishing to exercise more precise control over the modification to the target gene might choose to use Homology Directed Repair (HDR) instead.[21] This method is considerably more complicated and less efficient than NHEJ, but can produce insertions or deletions of a desired DNA fragment or can result in modification of a specific nucleotide, rather than relying on the far more random and unpredictable NHEJ.[22] The HDR method requires synthesis and introduction of DNA regions that are homologous to the target region and to the desired region the scientist wishes to modify.[23] The cellular machinery effectively uses these synthetic, homologous DNA fragments as a template when repairing the double-stranded break introduced by Cas9, and thus, whatever sequence is included in the synthetic template will be copied into the host cell genome.[24]

The Doudna patent and published paper recite CRISPR-Cas9 applications in prokaryotic cells, while the Zhang patent and publication(s) apply that same technology in eukaryotic cells.[25] Prokaryotic cells and eukaryotic cells are more similar than they are different; prokaryotic cells are even thought to be the evolutionary "progenitors" of eukaryotic cells.[26] Both prokaryotic and eukaryotic cells utilize DNA as their primary information-coding material, but substantial differences exist at the level of gene expression.[27]

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15. *Id.*
16. *CRISPR/Cas9 Guide*, ADDGENE, https://www.addgene.org/CRISPR/guide/ (last visited Oct. 15, 2016).
17. *Id.*
18. *Id.*
19. *Id.*
20. *Id.*
21. *Id.*
22. *Id.*
23. *Id.*
24. *Id.*
25. *See infra* Section II.D.
26. Tibor Vellai & Gabor Vida, *The Origin of Eukaryotes: The Difference Between Prokaryotic and Eukaryotic Cells*, 266 PROC.: BIOLOGICAL SCI. 1571 (1999).
27. *Id.*

In order for the CRISPR-Cas9 system to function in a desired cell, the scientist must introduce the DNA coding for those components into that cell.[28] Between prokaryotic and eukaryotic cells, this is accomplished through two different, but related, laboratory techniques. In prokaryotic cells, this process is called transformation, and typically involves creation of a circular DNA construct called a plasmid that encodes the sequence of whatever the scientist wishes to introduce into the cell.[29] Some prokaryotic cells are naturally receptive to plasmid uptake; such cells are referred to as "competent."[30] Otherwise, the scientist must induce the desired cell to become competent, which is usually accomplished chemically, or via administration of a controlled electric shock (electroporation).[31] Once the plasmid has been taken up by the cells, prokaryotic cells effectively treat plasmids as though they were part of the cells' normal chromosomal DNA for purposes of replication, expression, etc.[32] In eukaryotes, the process of introducing plasmid DNA is called transfection.[33] As with some prokaryotes, eukaryotic cells must be primed for transfection through the creation of pores in the cell membrane that permit plasmid uptake.[34] In some higher eukaryotic organisms, this can even take the form of microinjection via needle that punches directly through the cell membrane.[35] Once uptaken, the plasmid DNA is replicated along with the host chromosomes, and transcribed into mRNA by host machinery.[36]

B. The Patent System and Interference Proceedings

The history of technological advancement in the United States is replete with examples of inventors arguing amongst themselves about who invented what, and who has what rights to what things. Until recently, the United States patent system "enjoyed" the unique distinction of giving priority to an inventor who was the first to invent the subject of a patent, unlike the majority of countries, which have long chosen to bestow priority upon the first inventor to

28. *See generally, e.g.*, HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY § 8.5 (4th ed. 2000) (describing methods of creating transgenic animals by introducing foreign DNA material into cells of varying type).

29. *Plasmid/Plasmids*, SCITABLE, http://www.nature.com/scitable/definition/plasmid-plasmids-28 (last visited Oct. 15, 2016).

30. *See, e.g.*, Joshua Chang Mell & Rosemary J. Redfield, *Natural Competence and the Evolution of DNA Uptake Specificity*, 196 J. BACTERIOLOGY 1471, 1471 (2014) (describing natural competence in cells).

31. *See* Melina Fan, *Save Time and Money by Making Your Own Competent Cells*, ADDGENE (Jan. 28, 2014, 10:10 AM), http://blog.addgene.org/save-time-and-money-by-making-your-own-competent-cells (providing methods for electroporation and chemical competency).

32. *See* Gloria del Solar et. al., *Replication and Control of Circular Bacterial Plasmids*, 62 MICROBIOL. MOL. BIOL. REV. 434 (1998) (describing bacterial control and methods of replication of plasmid DNA).

33. *Transfection*, PROMEGA, https://www.promega.com/resources/product-guides-and-selectors/protocols-and-applications-guide/transfection/ (last visited Oct. 15, 2016).

34. *Id.*

35. *Id.* For example, microinjection is useful in *C. elegans*, a nematode worm. Thomas C. Evans, *Transformation and Microinjection*, WORMBOOK (Apr. 6, 2006), http://www.wormbook.org/chapters/www_transformationmicroinjection/transformationmicroinjection.html. The plasmid solution is injected directly into the gonad of the hermaphrodite worm, where the DNA is uptaken by developing egg cells and expressed in subsequent generations. *Id.*

36. *Transfection*, *supra* note 33.

file a patent application.[37] Unsurprisingly, the question of who *truly* crafted the invention first has given rise to no small amount of disagreement. Traditionally, the question of priority in the patent system has fallen to the determination of the United States Patent and Trademark Office (USPTO),[38] and not to the courts.[39] This process is called an interference proceeding, which is governed by 35 U.S.C. § 135.[40] Interference proceedings can be initiated by any patent applicant who believes that another application claims the same invention.[41] An interference proceeding is then conducted before the USPTO Patent Trial and Appeal Board (PTAB) (formerly the USPTO Board of Patent Appeals and Interferences (BPAI)), which conducts limited discovery and an oral hearing.[42] Per 35 U.S.C. § 102(g)(1), a party is not entitled to a patent if another inventor involved in an interference proceeding shows that her invention preceded that of the other party in the proceeding.[43] In order to demonstrate entitlement to priority, a party must show that it was either the first to conceive of the invention and the first to reduce that invention to practice, or the first to conceive of the invention and the last to reduce to practice, provided that the time between conception and reduction to practice was spent working on perfecting the invention with reasonable diligence.[44]

Patent law in the United States imposes a requirement that the claimed invention not be "obvious" in light of prior art in the relevant field.[45] In making a determination of obviousness, the proper inquiry is to ask whether the invention, in light of the relevant prior art from the same field as the invention, would have been obvious to a person of ordinary skill in the art at the time the invention was conceived.[46] In 2004, the USPTO modified its regulations for interference proceedings, making explicit that an obviousness

37. George E. Frost, *The 1967 Patent Law Debate—First-to-Invent vs. First-to-File*, 1967 DUKE L.J. 923, 923–25 (1967).

38. 35 U.S.C. § 135 (2012); 37 C.F.R. § 41.202 (2015).

39. This is not true, however, for appeals of USPTO rulings that result from an interference proceeding. Biogen Idec MA, Inc. v. Japanese Found. for Cancer Research, 38 F. Supp. 3d 162, 168 (D. Mass. 2014). Appeals from such rulings are within the sole jurisdiction of the United States Court of Appeals for the Federal Circuit. *Id.*

40. 35 U.S.C. § 135.

41. *See* MPEP § 2304 (9th ed. Rev. 7, Nov. 2015) ("The suggestion for an interference may come from an applicant or from an examiner."); *see also* 37 C.F.R. § 41.202 (2015) (outlining requirements for suggesting an interference to the USPTO).

42. Generally, an interference proceeding is divided into an interlocutory phase, wherein the parties produce briefs and file motions, and a testimonial phase, wherein parties again can produce briefs and conduct oral argument. *See* MPEP § 2301 (outlining the procedure of an interference proceeding).

43. 35 U.S.C. § 102(g)(1), *repealed by* Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 285–87 (2011). Section 102(g) was removed when the AIA took effect, being rendered irrelevant by the elimination of interference proceedings. 125 Stat. at 285–87.

44. *See* 35 U.S.C. § 102(g)(2), *repealed by* Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284, 285–87 (2011) ("In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.").

45. *Id.* § 103.

46. *Id.*; *see also* Graham v. John Deere Co., 383 U.S. 1 (1966) (holding that three conditions must be filled in order to render an invention obvious: (1) the scope and content of the prior art must be determined; (2) differences between that prior art and the claims of the patent are to be discerned; and (3) the level of ordinary skill in the relevant art must be determined).

inquiry was a component thereof.[47] The regulation articulates that "[a]n interference exists if the subject matter of a claim of one party would, if prior art, have anticipated *or rendered obvious* the subject matter of a claim of the opposing party and vice versa."[48] For this reason, the question of obviousness will inevitably bear on each party's likelihood of success at the first phase of the interference proceeding at issue.

C. Patentable Subject Matter

Under 35 U.S.C. § 101, the United States affords patent protection to "any new and useful process, machine, manufacture, or composition of matter . . . ."[49] Research in the biological sciences has often found itself without a clear fit within this set of categories when patents are sought. A biologist might prevail by suggesting that her invention is a "composition of matter," which "includes all composite articles, whether they be results of chemical union, or of mechanical mixture . . . ."[50] Or she might instead describe her invention as a manufacture, which is defined as "the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or by machinery."[51] In either case, the biologist will have to get around another obstacle: the rule that "laws of nature, physical phenomena, and abstract ideas" are generally excluded from patentability.[52] CRISPR itself exists in nature; it was discovered in bacteria, which performed the process as a means of viral immunity.[53] Accordingly, an attempt to patent CRISPR itself would likely fail under the standard set forth in *Association for Molecular Pathology v. Myriad Genetics*, which found isolated DNA to be unpatentable subject matter because it was indistinguishable from something found in nature.[54] The patents directed at CRISPR avoid this pitfall because, despite CRISPR itself being an arguable product of nature, the claims are directed at methodologies for introducing the CRISPR-Cas9 system into cells and using it to accomplish gene-editing tasks beyond the cells' normal natural function.[55]

D. The Patents at Issue

The interference declared in January 2016 names a number of patents belonging to the same family as the original Zhang '359 patent, and just the

47. *See* MPEP § 2301.03 ("An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa.").

48. *Id.* (emphasis added).

49. 35 U.S.C. § 101.

50. Shell Dev. Co. v. Watson, 149 F. Supp. 279, 280 (D.D.C. 1957).

51. Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980) (quoting American Fruit Growers, Inc. v. Brogdex Co., 283 U.S. 1, 11 (1931)).

52. *Id.* at 309.

53. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116 (2013).

54. *Id.*

55. *Id.* at 2118.

single patent application of the Doudna/Charpentier group (the "'859 patent application").[56] This Note will focus on the original Zhang patent and the '859 application. Keeping in mind that the pre-AIA statutory scheme (with its first-to-invent rules) applies here, Doudna and Charpentier's '859 application was the first of the two to be filed.[57] Although their filing was provisional, it established a priority date of May 25, 2012.[58] Zhang filed for his patent (the "'359 patent") several months later on December 12, 2012, also in a provisional application.[59] The '859 application and Zhang's application (which would eventually issue as the '359 patent) were each formally filed non-provisionally on March 15, 2013, and October 15, 2013, respectively.[60] Despite the later priority date, Zhang's application received examination (and was granted) before the '859 application because he requested "fast track" examination via the USPTO's "Track One" prioritized examination program.[61] This process involves the filing of a "Petition to Make Special" with the USPTO, which must indicate a desire by the patentee to take advantage of accelerated examination.[62] When such a petition is granted, the examination time from approval to final determination (issuance or rejection) is reduced to one year.[63] When Zhang filed his non-provisional, full application for the '359 patent on October 15, 2013, he also filed a Petition to Make Special Under Accelerated Examination Program.[64] On November 7, 2013, the USPTO granted Zhang's request.[65] Zhang's '359 patent issued less than a year later on April 15, 2014.[66]

Initially, the two applications could be ostensibly distinguished, in that the '859 application contained language that could be interpreted as limiting the claims to prokaryotic cells.[67] Zhang's '359 patent, on the other hand,

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56. Declaration of Interference, *In re* U.S. Patent Application No. 13/842,859 (2016).

57. U.S. Patent Application No. 13/842,859 (filed May 25, 2012) [hereinafter '859 Patent Application].

58. *Id.*

59. U.S. Patent No. 8,697,359 (filed Dec. 12, 2012) [hereinafter '359 Patent].

60. *Id.*; '859 Patent Application, *supra* note 57. Perhaps, however, Doudna should have waited just one day—until March 16, 2013—to file her patent application. That date was the effective date for the AIA, which would have put her patent application under the "first-to-file" system, and we would not be having this discussion today. *See* MPEP § 2159.01 (9th ed. Rev. 7, Nov. 2015) (stating that changes in the AIA do not apply to any applications filed before March 16, 2013).

61. The "Track One" program allows an applicant to pay a higher fee in order to obtain "prioritized examination" for a plant or utility patent application. *USPTO's Prioritized Patent Examination Program*, USPTO, http://www.uspto.gov/patent/initiatives/usptos-prioritized-patent-examination-program (last visited Oct. 9, 2016). This effectively allows an applicant to jump the line of patent applications, which is ordinarily processed in filing date order. *Id.*

62. *See* 37 C.F.R. § 1.102 (2015) (describing acceptable criteria on which the USPTO may decide to expedite a patent application); *see also* MPEP § 708.02(a) (describing requirements for eligibility for a Petition to Make Special Under Accelerated Examination).

63. USPTO, *supra* note 61.

64. Petition to Make Special Under Accelerated Examination Program, *In re* Patent Application of Feng Zhang et al. Application Serial No. 14/054,414 (2013).

65. Decision Approving Petition to Make Special, *In re* Patent Application of Feng Zhang et al. Application Serial No. 14/054,414 (2013).

66. Issue Notification, *In re* Patent Application of Feng Zhang et al. Application Serial No. 14/054,414 (2014).

67. '859 Patent Application, *supra* note 57 ("The present disclosure provides genetically modified cells that produce Cas9; and Cas9 transgenic non-human multi-cellular organisms.").

claims (among others) a method of performing CRISPR-Cas9 genetic modification in eukaryotic cell types.[68] Zhang's receipt of the patent grant prompted the University of California to amend the claims of the '859 patent application and to file paperwork in an attempt to provoke an interference proceeding to determine novelty.[69] Notably, the amended claims removed any reference suggesting that they are limited to a particular type of cell (i.e., the claims are not solely directed at performing CRISPR-Cas9 genetic modification methods in prokaryotic cells, like bacteria).[70] This opened the door to the University of California's objection that, because the subject material of the two patents are the same, an interference proceeding should be initiated to determine which party is entitled to the patent on the CRISPR-Cas9 technology.[71]

III. ANALYSIS

A. The U.S. Patent and Trademark Office Will Conduct an Interference Proceeding

In making an assessment of whether to open an interference proceeding in response to a properly pleaded petition, the Patent Trial and Appeal Board carefully assesses whether the claims set forth are allowable, and makes sure that the opposing patents do not contain "patentably distinct" claims.[72] The ultimate decision on whether to declare the interference proceeding is discretionary, regardless of the showing of the parties.[73] Here, the amended claims of the '859 patent application removed the limitation that would render the claims "separately patentable" from those of Zhang's '359 patent.[74] The University of California (on behalf of the Doudna/Charpentier group) thus seemingly satisfies the relevant prong of the "two part" test articulated in 37 C.F.R. § 1.601(i) by showing that each claimed invention would render obvious the other.[75] This Note will discuss issues related to obviousness analyses in the context of biotechnology in significantly more depth in later sections.

On December 21, 2015, Michelle K. Joike, the examiner tasked with the

68. '359 Patent, *supra* note 59.

69. *See* Suggestion of Interference Pursuant to 37 C.F.R. § 41.202, *In re* Patent Application of Jennifer Doudna et al. Application Serial No. 13/842,859 (2015) [hereinafter Suggestion of Interference] (requesting an interference proceeding concerning claims 165–247 of the '859 patent application, which were filed along with this request as an amendment to the original application).

70. *Id.*

71. *Id.*

72. 37 C.F.R. § 1.601 (2015); Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wash., 334 F.3d 1264, 1270 (Fed Cir. 2003).

73. *See Eli Lilly*, 334 F.3d at 1267 ("Congress has expressly indicated its preference that declaration of an interference . . . be discretionary."). This decision is, however, reviewable for abuse of discretion. *Id.* at 1266.

74. Suggestion of Interference, *supra* note 69; '359 Patent, *supra* note 59; '859 Patent Application, *supra* note 57.

75. 37 U.S.C. § 1.601(i) (2012); *see also* MPEP § 2159 (9th ed. Rev. 7, Nov. 2015) (clarifying the reciprocal obviousness prong of the "two part" test).

'859 patent application, released an Initial Interference Memo, which formally recommended that the PTAB initiate an interference proceeding.[76] While the PTAB is not required to follow the recommendation of the examiner in this memorandum, it is rare that the PTAB chooses otherwise.[77] Indeed, on January 11, 2016, the PTAB declared that an interference proceeding would be initiated between MIT's Broad Institute and the University of California.[78] In March of 2016, the judges in the interference proceeding ruled that the panel would consider motions from the University of California directed at establishing earlier invention by the Doudna/Charpentier group.[79] If the panel agrees with the University of California on this point, the Broad Institute's only hope in prevailing is to demonstrate a non-obvious improvement over what would be the '859 application's prior art.[80] The panel also agreed to permit the Broad Institute to file a motion asserting that the '859 application's claims are impermissibly broad, and thus invalid.[81] A holding in favor of the Broad Institute on such a motion would gut the '859 application, and the proceeding would end in favor of the Broad Institute (and the Zhang patent).[82] Clearly, the stage is set for a tense fight with high stakes, but a final answer on these motions will not arrive until November at the earliest, with the panel setting oral arguments for November 17, 2016.[83]

B. Doudna and Charpentier Will Likely Prevail

The peculiarities of the patent application filing timeline in this case present a somewhat unusual set of circumstances. Typically in interference proceedings, there is a presumption that the first party to file a patent application is the true inventor.[84] This can be parsed into two scenarios. Where the junior (later in time) patent filer applies before the senior patent filer receives his patent grant, the junior filer has the burden of establishing by a preponderance of the evidence that she was in fact the true inventor.[85] If the junior filer applies after the senior filer has received his patent grant (or has disclosed the contents of the application to the public), the junior filer must

76. Jacob S. Sherkow, *The CRISPR Patent Interference Showdown Is on: How Did We Get Here and What Comes Next?*, STANFORD L. SCH.: L. & BIOSCIENCES BLOG (Dec. 29, 2015), https://law.stanford.edu/2015/12/29/the-crispr-patent-interference-showdown-is-on-how-did-we-get-here-and-what-comes-next/.

77. *Id.*

78. The Broad Inst., Inc. v. Bd. of Regents of the Univ. of Cal., No. 106,048 (P.T.A.B. Jan. 11, 2016).

79. Order Authorizing Motions and Setting Times Under 37 C.F.R. § 121, No. 106,048 (P.T.A.B. Mar. 17, 2016) [hereinafter March 17th Order].

80. Sharon Begley, *In the CRISPR Patent Fight, the Broad Institute Gains Edge in Early Rulings*, STAT (Mar. 18, 2016), https://www.statnews.com/2016/03/18/crispr-patent-dispute/.

81. *See* March 17th Order, *supra* note 79, at 6 ("Broad requests authorization for a motion to argue that UC's claims are unpatentable under 35 U.S.C. § 112, first paragraph, for lack of written description . . . . Authorization for this motion is GRANTED.").

82. Begley, *supra* note 80.

83. *See* Order—Schedule 37 C.F.R. § 41.104(a), No. 106,048 (P.T.A.B. Mar. 30, 2016) (noting that the oral argument would "default" to November 17, 2016, but that the date may be changed by order "provided in due course").

84. 37 C.F.R. § 41.207(a) (2015).

85. *Id.* § 41.207(a)(2).

establish her true inventorship by clear and convincing evidence.[86] In the case of the Doudna/Charpentier and Zhang applications, the scenario is unusual: the junior filer received his patent grant before the senior filer. This situation is only possible as a result of the Zhang patent receiving expedited processing under the "Track One" program at the USPTO.[87] The USPTO has not issued any regulations clarifying the applicability of the standard presumptions in this scenario, nor has any case law emerged on this point. In the next Section, I recommend that the presumption of true ownership remain with the first filer as a matter of policy.

During the pending interference proceeding, the PTAB will almost certainly be confronted with the issue of priority. As a reminder, prior to the institution of the AIA, the United States' first-to-invent patent system determined priority not by filing date, but by the date of invention.[88] During an interference proceeding, a finding that a party is entitled to priority may well decide the proceeding outright, provided an interference is demonstrated to in fact exist.[89] A would-be patentee who finds herself in a struggle to establish priority is not without statutory recourse, however.[90] In a process commonly known as "swearing behind" the invention, a patent applicant can submit an affidavit averring to the applicant's "invention of the subject matter . . . prior to the effective date" of another reference.[91] In this case, ostensibly both parties would need to avail themselves of this strategy as, depending on the effective date of either patent, each could be an anticipatory (novelty-defeating) reference to the other.

C. Zhang's Eukaryote-Based Patent Is Obvious in Light of the Pre-Amendment '859 Patent Application and Academic Paper

As discussed above, the question of obviousness depends on the prior art, and whether the invention in question would be obvious to a person of ordinary skill in the art given those prior art references.[92] In an interference proceeding, a party may choose to mount an attack on the substance of the opposing party's patent.[93] The party seeking to provoke an interference proceeding must (as discussed above) make out a prima facie priority case in order for the interference to be declared.[94] Once initiated, an interference proceeding is

86. *Id.*

87. USPTO, *supra* note 61.

88. *See, e.g.*, Gene Quinn, *A Brave New Patent World—First to File Becomes Law*, IPWATCHDOG (Mar. 16, 2013), http://www.ipwatchdog.com/2013/03/16/a-brave-new-patent-world-first-to-file-becomes-law/id= 37601/ (discussing the transition to first-to-file patent law in the United States).

89. Sherkow, *supra* note 76 ("Rule 131 [37 C.F.R. § 1.131] statements may decide the interference proceeding outright . . . the three judge panel may decide . . . that there is an interference in-fact and Doudna wins because she has priority . . . .").

90. 37 C.F.R. § 1.131.

91. *Id.*

92. 35 U.S.C. § 103 (2012).

93. *See* Sherkow, *supra* note 76 (describing the briefings and motions available to parties during the initial phases of the interference).

94. *See* 37 C.F.R. § 41.202 (describing what an applicant must provide and allege in order to suggest an interference); MPEP § 2304.02 (9th ed. Rev. 7, Nov. 2015) (same).

conducted in a similar manner to a "miniature" court proceeding, with discovery, oral hearings, and the opportunity for parties to file substantive motions.[95] This interlocutory phase can be used to try to persuade the panel to consider "the patentability of the inventions at-issue."[96] Here, it is likely that the Doudna/Charpentier group would make such an assertion of un-patentability against Zhang's '859 patent based on their own prior disclosures and the '859 patent application, and indeed, Zhang and the Broad Institute have already done so.[97]

1. Obvious to Try: KSR *and* Kubin

The "obvious to try" doctrine, reaffirmed by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, and embraced by the Federal Circuit in *In re Kubin*, will likely be informative.[98] The Supreme Court articulated two situations where "obvious to try" can be equated with general obviousness. The first consideration requires that there be some design need or market pressure to solve a problem, and the second consideration is whether there are a finite and predictable number of solutions available to address that problem in light of the prior art.[99] Here, the design need and market pressure may be said to be analogous to those that face the pharmaceutical and biotechnology industries on a regular basis—there is a drive to develop gene therapies for diseases that cannot be readily addressed by conventional means.[100] To the second consideration, the answer is fairly clear. Eukaryotic cells, including human cells, are by far the best model for research in human disease, and establishing functional methods in those cell types is certainly one of very few options. One might argue that the "predictability" prong is a stumbling block here; after all, biotechnology and chemistry are said to be the "unpredictable arts" for a reason.[101] However, the scientific obstacle here between operation in prokaryotic cells and eukaryotic cells is relatively slim; the CRISPR-Cas9 system does not rely on any endogenous prokaryotic components that cannot be readily transfected into CRISPR-Cas9, but harnesses the processes of non-homologous end joining and homology-directed repair common among both classes of organisms.[102] The most unpredictable required step, then, would be testing transfection of eukaryotic cells to create transgenic cells expressing the

95. *Id.*
96. *Id.*
97. *See supra* Section III.A.
98. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398 (2007); *In re* Kubin, 561 F.3d 1351 (Fed. Cir. 2009).
99. *See KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under [35 U.S.C. § 103].").
100. *See, e.g.*, Jack McCain, *The Future of Gene Therapy*, 2 BIOTECH. HEALTHCARE 52, 52 (2005) (describing the advances in gene therapy research pushing forward and characterizing gene therapy treatments as likely to "become a staple of 21st century medicine").
101. *KSR*, 550 U.S. at 422.
102. *CRISPR/Cas9 Genome Editing: Transfection Methods*, MIRUS, https://www.mirusbio.com/applications/crispr-cas-transfection (last visited Oct. 9, 2016).

CRISPR-Cas9 genes.[103] No step of this process is so unusual or outside the realm of believability. The question is whether the person of ordinary skill in the art would have a reasonable expectation of success, underlining the importance of making the proper determination of exactly what qualifications that person of ordinary skill possesses.[104]

The Federal Circuit, sitting after the Supreme Court's decision in *KSR*, adopted and endorsed the "obvious to try" approach in *In re Kubin*.[105] *Kubin* concerned a patent application for DNA sequences encoding the protein Natural Killer Cell Activation Inducing Ligand (NAIL), a cell surface receptor expressed on natural killer cells (and also known as CD244).[106] The patent claims were directed at a genus of polynucleotide sequences that binds to the NAIL receptor ligand (CD48) and "is at least 80% identical" to a substantial portion of the NAIL binding region's amino acid sequence.[107] The Federal Circuit (handling this appeal from an appeal of a BPAI determination) affirmed the BPAI's finding of obviousness based on the Valiante, Sambrook, and Mathew references.[108] Those references cumulatively disclosed the gene sequence and isolation of the NAIL protein, and the court found that the subsequent isolation by the patentee was done "using conventional techniques."[109] Additionally, the court used the *Kubin* case as an opportunity to modify its biotechnological obviousness jurisprudence, noting that "under *KSR*, it's now apparent 'obvious to try' may be an appropriate test . . . ."[110] The court affirmed the BPAI's determination of obviousness, explaining that the patentee in *Kubin* was not, in the process of developing the claimed invention, "throwing metaphorical darts at a board filled with combinatorial prior art possibilities," but rather was pursuing "known options" from a "finite number of . . . predictable solutions."[111]

In re Kubin thus provides two possibilities for where the "obvious to try" doctrine is clearly inapposite.[112] One is the metaphorical dart throwing discussed above. The other situation is where a patentee is exploring a new, seemingly promising area of technology, where "the prior art gave only

103. A majority of methods for performing CRISPR/Cas9 experiments in eukaryotes require transfection using a synthetic plasmid encoding Cas9. *Id.* Transfection is the procedure by which foreign DNA is introduced into a eukaryotic cell. *Id.* A plasmid is a circular structure composed of DNA containing, at the discretion of the designer, genes that encode desirable enzymes or other proteins, selective markers (so that the success of the procedure can be verified and populations of cells controlled), and other components as the particular application requires. *What Is a Plasmid?*, ADDGENE, https://www.addgene.org/mol-bio-reference/plasmid-background/ (last visited Oct. 15, 2016).

104. *KSR*, 550 U.S. at 421.

105. *In re* Kubin, 561 F.3d 1351 (Fed. Cir. 2009).

106. *Id.* at 1352; *CD244 Molecule [Homo Sapiens (Human)]*, NAT'L CTR. BIOTECH. INFO., http://www.ncbi.nlm.nih.gov/gene/51744 (last updated Oct. 9, 2016).

107. *In re Kubin*, 561 F.3d at 1353.

108. *Id.* at 1353–56.

109. *Id.* at 1356.

110. *Id.* at 1358 (quoting *Ex parte* Kubin, No. 2007-0819, 83 U.S.P.Q.2d 1410, 1414 (B.P.A.I. May 31, 2007)).

111. *Id.* at 1359–60.

112. *Id.* at 1355–60.

general guidance" about the invention or how it could be achieved.[113] As we look to assess whether the Zhang patent fits into either of these categories, it is fairly clear that Zhang was not engaged in "dart throwing" where he attempted near-random variations on prior art protocols.[114] A more substantial question exists as to whether Zhang's work with CRISPR-Cas9 in eukaryotes is an exploration of new technology in a novel area. This Note will go on to recommend that the PTAB find that applying technology developed from prokaryotes to eukaryotic systems be considered presumptively not new.

2. Obvious to Try in the Biological Sciences

While the threshold past which an invention may have been "obvious to try" in biotechnology is unclear, the Federal Circuit's application of the principles articulated in *KSR* has suggested that obviousness may be surprisingly easy to find.[115] In *Syngenta Seeds, Inc. v. Monsanto Co.*, the Federal Circuit held that Syngenta's claims covering corn plants that expressed an insecticide[116] were invalid as obvious.[117] The court focused on one prior art reference, a published patent application ("Barton"), which disclosed a method for "improving Bt expression in plant genes."[118] The Barton patent application further taught that Bt corn expression was optimal where codons[119] were optimized for high G+C nucleotide content.[120] Syngenta's patented Bt corn claimed a G+C content in relevant regions of greater than 60%.[121] Finding that a person of skill in the relevant art would have found it obvious, based on the Barton reference, to attempt to create a Bt corn gene with G+C content greater than 60%, the Federal Circuit invalidated Syngenta's claims.[122] The *Syngenta* decision, handed down two years prior to the decision in *Kubin*, seems to be an early signal of the move towards "obvious to try."[123] The effect of the ruling was that if a person of skill in the art would consider, based on even a single prior art reference, attempting to test the teachings therein, the result may be considered obvious.

The Federal Circuit handed down a similar ruling in *Pfizer v. Apotex*.[124] In *Pfizer*, Apotex sought to invalidate Pfizer's patent covering amlodipine

113. *Id.* (quoting *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)).

114. *Id.*

115. *See, e.g.*, Syngenta Seeds, Inc. v. Monsanto Co., 231 Fed. Appx. 954, 958 (Fed. Cir. 2007) (applying the "obvious to try" standard); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007) (same).

116. So called "Bt" corn, because the gene for the insecticide originated in the bacterium *Bacillus thuringiensis*. Ric Bessin, *Bt-Corn, What It Is and How It Works*, U. KY. C. AGRIC., FOOD & ENV'T, https://entomology.ca.uky.edu/ef130 (last visited Oct. 9, 2016).

117. *Syngenta*, 231 Fed. Appx. at 959.

118. *Id.* at 957.

119. A codon is a three-nucleotide sequence that functions during gene expression by coding for one of twenty amino acids, as a starter sequence for translation of a protein, or as a stop signal to terminate translation. *Codon*, SCITABLE, http://www.nature.com/scitable/definition/codon-155 (last visited Oct. 9, 2016).

120. *Syngenta*, 231 Fed. Appx. at 957.

121. *Id.* at 956 ("Those claims require that the DNA sequence have a sufficient number of particular codons . . . so that the sequence contains at least about 60 percent G+C nucleotides.").

122. *Id.* at 958.

123. *Id.*; *In re* Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

124. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007).

besylate, known as the drug Norvasc.[125] A single prior art reference, the '909 patent, disclosed a genus of "pharmaceutically-acceptable anions" for amlodipine, including the acid-addition salts (maleates).[126] Finding that the '909 patent reference did not exclude amlodipine besylate or the use of benzene sulphonate as an anion, and that the only limitation so placed was that the anion be "pharmaceutically acceptable," the court held that the '909 patent claims "literally encompass" amlodipine besylate.[127] Rejecting Pfizer's arguments that the success of the besylate salt was unexpected, the court held that a person of reasonable skill in the art would have found it obvious to apply the teachings of the '909 patent, rendering the Pfizer patent invalid.[128] The *Pfizer* case is thus perhaps best described as facilitating obviousness findings even in the face of unobvious or unexpected beneficial properties, which to date had enjoyed somewhat more substantial deference.[129]

3. Institut Pasteur*: Looking at a Similar Case for Obviousness Analysis*

One previous USPTO administrative proceeding has considered a similar issue, culminating in an appeal to the Federal Circuit.[130] The case, *Institut Pasteur v. Focarino*, did not concern competing patent applicants, but was another form of administrative review called *inter partes* reexamination (which, as a result of the AIA, is no longer used).[131] An *inter partes* reexamination proceeding permitted any third party to petition for a reexamination proceeding before the USPTO.[132] A panel of patent examiners conducted the proceeding, which included opportunities for third parties to participate.[133] Not every challenge to a patent could serve as the premise for an *inter partes* reexamination petition: the bases of novelty and obviousness were the only grounds, and within those, only patents and printed publications could be presented as prior art references.[134] In the *Pasteur* case, third party Precision Biosciences, Inc. filed a request for *inter partes* reexamination for three patents, the '545, '252, and '605 patents.[135] All three patents were directed at group I intron-encoded endonucleases (GIIE endonucleases), originally isolated by the Institut Pasteur in eukaryotes (yeast, specifically) and

125. *Id.*
126. *Id.* at 1361.
127. *Id.*
128. *Id.* at 1372 ("[W]e hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results, this secondary consideration does not overcome the strong showing of obviousness in this case.").
129. *See, e.g.*, *In re* Papesch, 315 F.2d 381 (C.C.P.A. 1963) (describing the importance of considering the pharmacological properties of a claimed compound even though it may appear structurally obvious in light of a prior reference).
130. Institut Pasteur v. Focarino, 738 F.3d 1337, 1338 (Fed. Cir. 2013).
131. *See* MPEP § 2609 (9th ed. Rev. 7, Nov. 2015) (describing *inter partes* reexamination proceedings and the criteria for implementation thereof).
132. *Id.*
133. *Id.*
134. *Id.*
135. *Institut Pasteur*, 738 F.3d at 1339.

useful in mammalian genetics as high-specificity DNA cleavage enzymes.[136] Precision Biosciences asserted that certain claims of the '545, '252, and '605 patents were invalid as obvious under 35 U.S.C. § 103.[137] The patent examiner tasked with reexamination (and, on review, the BPAI[138]) agreed with Precision, finding a number of claims invalid as "obvious to one skilled in the art" as of the priority date of the patents (May 12, 1992).[139]

The examiner and BPAI based their findings on two printed publication references published in scientific journals, which were referred to as the Bell-Pedersen and Quirk references.[140] Those references disclosed the use of the same class of enzymes (GIIE endonucleases) in prokaryotic cells.[141] The BPAI considered, in the context of the prior art, that there was "reason to substitute the [nonchromosomal prokaryotic] DNA described in Quirk and Bell-Pedersen with chromosomal DNA of a eukaryotic cell."[142] Relying on two additional references (Frey and Dujon), the BPAI additionally found that "one of ordinary skill in the art [had] a reasonable expectation that the teachings of Quirk and Bell-Pedersen could be successfully applied to [chromosomal DNA] in yeast cells."[143] Accordingly, the BPAI held that the application of GIIE endonucleases for use in eukaryotic (mammalian or otherwise) cells was obvious, and that the Pasteur patent claims directed at such were invalid as obvious.[144] Institut Pasteur appealed to the Federal Circuit, which agreed with the BPAI's framing of the issue, but not with the BPAI's conclusion:

> [T]he key issue in making [an obviousness] determination is whether the relevant skilled artisan—after reading Quirk's and Bell-Pedersen's disclosure that a GIIE endonuclease can promote targeted gene transfer into *non-chromosomal* DNA in *prokaryotic* cells—would have expected that a GIIE endonuclease would successfully promote targeted gene transfer into the chromosomal

136. *Id.* ("GIIE endonucleases can cleave DNA in the chromosomes of eukaryotic (nucleus-possessing) cells, and second . . . eukaryotic cells can successfully repair such cleavages by initiating a process known as homologous recombination.").

137. *Id.*

138. *Id.* at 1338 (showing that these proceedings were conducted prior to the switch to the PTAB name).

139. *Id.* at 1341–43; Precision BioSciences, Inc. v. Institut Pasteur, No. 11-010572, 2012 WL 1050568 (B.P.A.I. Mar. 14, 2012); Precision BioSciences, Inc. v. Institut Pasteur, No. 11-010715, 2012 WL 1050569 (B.P.A.I. Mar. 14, 2012); Precision BioSciences, Inc. v. Institut Pasteur, No. 11-011261, 2012 WL 1050570 (B.P.A.I. Mar. 14, 2012); Precision BioSciences, Inc. v. Institut Pasteur, No. 11-012285, 2012 WL 1050572 (B.P.A.I. Mar. 14, 2012).

140. *Institut Pasteur*, 738 F.3d at 1342; Deborah Bell-Pedersen et al., *Intron Mobility in Phage T4 Is Dependent upon a Distinctive Class of Endonucleases and Independent of DNA Sequences Encoding the Intron Core: Mechanistic and Evolutionary Implications*, 18 NUCLEIC ACID RES. 3763 (1990) (the "Bell-Pedersen reference"); Susan M. Quirk et al., *Intron Mobility in the T-Even Phages: High Frequency Inheritance of Group I Introns Promoted by Intron Open Reading Frames*, 56 CELL 455 (1989) (the "Quirk reference").

141. *Institut Pasteur*, 738 F.3d at 1342; Bell-Pedersen et al., *supra* note 140, at 3763; Quirk et al., *supra* note 140, at 455.

142. *Institut Pasteur*, 738 F.3d at 1342 (quoting Precision BioSciences, Inc. v. Institut Pasteur, No. 11-010715, 2012 WL 1050569, at *6 (B.P.A.I. Mar. 14, 2012)).

143. *Id.*

144. *Id.*

> DNA of eukaryotic cells, and thus had good reason to pursue that possibility.[145]

Applying *KSR*, the Federal Circuit found that the BPAI improperly characterized the prior art[146] and "failed to give proper consideration to at least two categories of evidence—(1) teachings in the prior art that targeting a cell's chromosomal DNA could be toxic to the cell and (2) industry praise and licensing of Pasteur's invention—that are important to the obviousness evaluation."[147]

First, the Federal Circuit determined that the BPAI's assessments of the prior art references Frey and Dujon were incorrect.[148] While the BPAI determined that the two references taught that yeast chromosomal DNA could be cleaved by the GIIE endonucleases *in vivo*, the Federal Circuit found that neither reference disclosed such a method or use of the claimed endonucleases inside a living yeast cell.[149] Additionally, the references were imprecise about the type of DNA subject to GIIE endonucleolytic activity: "the reference is silent about what type of DNA is cleaved."[150] From a cell biology perspective, the significance of this is that a person skilled in the art would not commonly think to apply a technique used *in vitro* in an *in vivo* fashion, in many circumstances; nor would a researcher assume that an enzyme with demonstrated nuclease activity towards an extra-chromosomal fragment would be equally effective against chromosomal DNA.[151] Therefore, the Federal Circuit concluded, one skilled in the art would not have had a reasonable expectation that the teachings of the Bell-Pedersen and Quirk references would successfully be applicable to yeast (or higher eukaryotic) cells, particularly for the purpose of chromosomal DNA cleavage.[152]

The Federal Circuit's second category is encompassed by the general group of "secondary indicia" used in the *KSR* framework as part of a prima facie finding of obviousness.[153] There are a number of secondary considerations (or as the given court may say, secondary factors, secondary indicia, etc.) that have long been part of the courts' obviousness analysis, though they have historically been afforded less import than in the post-*KSR* world.[154] Such considerations have included commercial success, long felt but unsolved needs, failure of others, professional attitudes towards the invention,

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145. *Id.* at 1344.

146. A fundamental part of the *KSR* obviousness assessment incorporates the Graham requirement that "the scope and content of the prior art [be] . . . determined; differences between the prior art and the claims are . . . ascertained; and the level of ordinary skill in the pertinent art resolved." KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 399 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966)).

147. *Institut Pasteur*, 738 F.3d at 1344.

148. *Id.* at 1344–45.

149. *Id.* ("In fact, neither reference discloses a GIIE endonuclease cleaving yeast chromosomes *while those chromosomes are in yeast cells*." (emphasis added)).

150. *Id.* at 1345.

151. *See, e.g.*, Leslie A. Pray, *Restriction Enzymes*, SCITABLE (2008), http://www.nature.com/scitable/topicpage/restriction-enzymes-545 (describing restriction enzymes and their utility).

152. *Id.*

153. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 420 (2007).

154. *Id.*

the extent to which the prior art "teaches away" from the patented invention, licensing of the invention, and others.[155] In *Pasteur*, the court focused on the "teaching away," licensing of the patented technology, and the professional and industry attitudes towards the invention.[156] The court found that the BPAI "ignored" another prior art reference that specifically contemplated the cytotoxic effects of targeting chromosomal DNA with a GIIE endonuclease *in vivo*.[157] Additionally, the BPAI did not discuss or account for the licensing activities of Pasteur's competitors or customers.[158] The patents had been licensed to Cellectis S.A., which presented evidence of numerous sublicense agreements.[159] Finding this evidence to be "probative and cogent evidence" of non-obviousness, the court found this too to be error on the part of the BPAI.[160]

Lastly, the court found that the BPAI erred in ignoring the attitudes of the professionals and relevant industry to which the invention pertained.[161]

The lesson of *Pasteur*, as applied to the current dispute over CRISPR, is that the obviousness analysis is often more nuanced than it appears at first blush. Numerous secondary factors will be relevant to the final determination of obviousness, particularly in light of the extensive licensing agreements and ever-growing patent families involved.[162] A finding that research in prokaryotic organisms renders obvious the application of similar research in eukaryotes would be of no small impact. Such a finding would entirely gut Zhang's patent and damage the foundation of numerous other patents in the same family. It would also dramatically increase the value of the '859 patent application, assuming it is granted. While the applications of the CRISPR-Cas9 technology are many, the most lucrative emerging uses are in eukaryotic cells.[163] Because the Doudna/Charpentier group's '859 application claims were amended to eliminate any reference to specific cell types (prokaryotic or otherwise), the reach of her patent, should it be granted, would almost certainly encompass at least the claims of the '359 patent.[164]

While a finding that the '359 patent is invalid based on obviousness in this case would certainly have a strong impact on the parties, the impact on other research spanning the prokaryote-eukaryote bridge is less clear. As with other questions of the "uncertain sciences," a bright-line obviousness rule

155. *See* Natalie A. Thomas, Note, *Secondary Considerations in Nonobviousness Analysis: The Use of Objective Indicia Following* KSR v. Teleflex, 86 N.Y.U. L. REV. 2070 (2011) (describing secondary considerations used by the courts and assessing their relative importance); Graham v. John Deere Co., 383 U.S. 1 (1966).

156. Institut Pasteur v. Focarino, 738 F.3d 1337, 1345–46 (Fed. Cir. 2013).

157. *Id.*

158. *Id.*

159. *Id.*

160. *Id.* at 1346 (quoting Stratoflex, Inc. v. Aeroquip Corp., 713 F.3d 1530 (1983)).

161. *Id.*

162. *Id.* at 1344.

163. *See* Paul BG van Erp et al., *The History and Market Impact of CRISPR RNA-Guided Nucleases*, 12 CURR. OP. IN VIROLOGY 85, 87–90 (2015) (describing and listing CRISPR investments in agribusiness, pharmaceuticals, and others).

164. Suggestion of Interference, *supra* note 69.

would be inappropriate. Rather, an assessment of a given piece of technology as a whole is necessary, and a careful consideration of whom exactly is the "person of ordinary skill in the art" is critical, because that portion of the inquiry may be determinative.[165] Several factors may be used in making a determination of the qualifications and characteristics of the person of ordinary skill in the art, including: "(1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field."[166] A person of reasonable skill in the art who holds, for example, a PhD in cell biology, is unlikely to attempt to apply a technique directed towards an exclusively prokaryotic cell system in eukaryotes where the level of difference is too great.[167] But perhaps this is where structuring it as a rebuttable presumption would make the most sense by placing the burden on the scientists who seek a patent on a technique in eukaryotes to show why the technique applied in prokaryotic cells does not create an obviousness issue. Effectively shifting the standard in this way moves some of the need for scientific expertise away from the bench. In the next Part, I will recommend a minimum level for a person of ordinary skill in the art for this assessment.

IV. RECOMMENDATIONS

A. The Doudna/Charpentier Patent Is Entitled to the Presumption of First Inventorship

The assertions set forth by the Doudna/Charpentier/University of California patent call into serious question the claims of the Zhang/Broad Institute patent, raising issues of priority and substantive patentability. Under the reciprocal obviousness threshold assessment, the claims of the Doudna and Zhang patents each would seemingly render the other obvious.[168] Accordingly, the USPTO has declared an interference proceeding.[169]

The presumption of priority should be vested in the Doudna/Charpentier patent. As discussed above, the statutory presumption of priority assumes that the inventor who was first to file enjoys a presumption of true first inventorship.[170] Here, regardless of the fact that Zhang's patent was granted first, the fact remains that both his provisional and substantially complete

165. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 420 (2007).

166. *See* Daiichi Sankyo Co., Ltd. v. Apotex, Inc. 501 F.3d 1254, 1256 (Fed. Cir. 2007) (quoting Envtl. Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed. Cir. 1983)).

167. An example of such a technique might be a technique directed at optimizing a specific bacterial DNA polymerase, which differ in significant ways from eukaryotic DNA polymerases and are highly unlikely to be useful in eukaryotic systems. *See, e.g.*, GEOFFREY M. COOPER, THE CELL: A MOLECULAR APPROACH (2d ed., online version, 2000), https://www.ncbi.nlm.nih.gov/books/NBK9940/ (describing the differences between prokaryotic and eukaryotic DNA replication and discussing polymerase diversity).

168. *See* MPEP § 2301.03 (9th ed. Rev. 7, Nov. 2015) (noting instances when a party's subject matter can be an interfering subject matter that renders other party's subject matter obvious).

169. *Id.*

170. 37 C.F.R. § 41.207(a) (2015).

patent applications were filed after the respective dates for the Doudna/Charpentier patent application.[171] There is no reason for the USPTO to make an exception to the general statutory presumption of priority simply because Zhang was able to avail himself of the "Track One" fast-track procedure; nothing about that procedure bears on a finding of priority. The presumption, then, should (1) presume that Doudna/Charpentier are the first inventors, and (2) require Zhang to establish by a preponderance of the evidence that in fact he is entitled to priority.[172] In an interference proceeding, the party with the ostensibly senior filing is named the "senior party," while the later filer is the "junior party."[173] Because Doudna/Charpentier were the first to file, the Broad Institute bears the burden of proving Zhang's first inventorship.[174]

It is unlikely that Zhang will be able to make such a showing. The Doudna/Charpentier group contends that it established date of conception and constructive reduction to practice, at the latest, when the Doudna lab published the first CRIPSR article in 2012.[175] The ultimate determination of date of conception (and, potentially, that of reduction to practice) will likely be settled by comparing laboratory notebooks.[176] Zhang and the Broad Institute at the Massachusetts Institute of Technology have submitted to the USPTO notebooks from the Zhang lab that they claim establishes a date of conception back to 2011.[177] Presumably, the Doudna lab will submit similar evidence to counter Zhang's claim.

B. The PTAB Should Find Zhang's Patent Claims to Be Obvious

The United States Patent and Trademark Office should decide that the application of CRISPR-Cas9 technology in eukaryotic cells, as claimed by the Zhang patent, is obvious in light of the Doudna/Charpentier application and its associated disclosures.[178] In making this determination, the USPTO should apply the Supreme Court's "obvious to try" assessment,[179] which will demonstrate that a person of skill in the relevant art, with the '859 application in hand, would have considered it obvious to attempt to apply the CRISPR-Cas9 system to eukaryotic cells. Additionally, doing so would be a logical response to a market need for technological advancement in eukaryotic

171. *See supra* Section II.D.
172. 37 C.F.R. § 41.207(a).
173. *Id.* § 41.201.
174. *Id.* § 41.207(a)(2).
175. Jinek et al., *supra* note 6.
176. *See* Antonio Regalado, *CRISPR Patent Fight Now a Winner-Take-All Match*, MIT TECH. REV. (Apr. 15, 2015), https://www.technologyreview.com/s/536736/crispr-patent-fight-now-a-winner-take-all-match/ (describing the importance of lab notebooks in corroborating invention details).
177. *Id.*
178. *See* '359 Patent, *supra* note 59 (listing claims to applications of the CRISPR-Cas9 system in eukaryotic cells); *see also* '859 Patent Application, *supra* note 57 (showing the Doudna patent application); *see also* Suggestion of Interference, *supra* note 69 (listing amended claims without language limiting the application of CRISPR-Cas9 in the Doudna patent to any particular cell type).
179. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417–18 (2007).

genetics, and could be done with relatively predictable results.[180] This is not mere speculation: at least one reputable expert in the field, using only the Doudna group's 2012 publication and their patent application, was able to conduct CRISPR-Cas9 experiments in eukaryotic cells.[181]

C. The Person of Skill in the Art Should Be, at Minimum, a Bioscience Graduate Student

A determination of the qualifications of the relevant person of ordinary skill in the art will be critical in making a determination of obviousness, particularly where emerging, novel technology is concerned.[182] Traditionally, courts have taken the phrase to require the creation of a hypothetical person with some skill in the area of technology relevant to the invention.[183] The importance of this inquiry is clear: a person having a Bachelor's degree in genetics is more likely to grasp the nuance and importance of this discovery than one with only one such class on her transcript, and a person with a PhD and laboratory experience is likelier still to understand the implications of the technology. What may thus be obvious to a given hypothetical person skilled in the art depends substantially on what that person knows. This Note recommends that the person of ordinary skill in the art be, at minimum, a post-graduate student in genetics or related biological sciences who is familiar with prokaryotic and eukaryotic cellular biology and laboratory protocol. Usually, this would be satisfied by a graduate student in the relevant biological science, or a PhD holder therein.[184] This selection comports with the need to examine the prior art from the perspective of a person who would understand the technological background of prokaryotic enzyme systems and genetic manipulation techniques, which necessarily requires an understanding of both prokaryotic cell biology and knowledge of (in this case) the involved mechanisms of DNA double-strand break repair.[185] A person of such a background would certainly also understand the extent and degrees of similarity between relevant cellular processes and components in prokaryotic

180. *Id.* at 421.

181. Alex Lash, *Doudna, Berkeley Gain Expert's Backing in CRISPR Patent Fight*, XCONOMY (Apr. 15, 2015), http://www.xconomy.com/san-francisco/2015/04/15/doudna-berkeley-gain-experts-backing-in-crispr-patent-fight/.

182. 35 U.S.C. § 103 (2012) (defining a person of ordinary skill in the art to be a hypothetical person who is presumed to have known the relevant art at the time of the invention).

183. There is a fair question of whether, in a scenario like the one here, a singular "person of ordinary skill" is sufficient to make a fair determination of obviousness, given that multiple scientists were involved in the process of discovery. At least one commentator has asked whether this should motivate courts to consider the "nuances of teamwork" and consider the "overall broader depth of knowledge" that reflect the reality of multiple-inventor cases. Dennis Crouch, *Person(s) Skilled in the Art: Should the Now Established Model of Team-Based Inventing Impact the Obviousness Analysis?*, PATENTLY-O (May 17, 2011), http://patentlyo.com/patent/2011/05/persons-skilled-in-the-art-should-the-now-established-model-of-team-based-inventing-impact-the-obviousness-analysis.html; *see also* Jinek et al., *supra* note 6 (listing authors of the initial Doudna paper); '359 Patent, *supra* note 59 (showing multiple listed "inventors").

184. *See, e.g.*, *PhD in Biochemistry and Molecular Genetics*, U. ILL. CHI. (UIC), http://catalog.uic.edu/gcat/colleges-schools/medicine/bcmg/phd/ (last visited Oct. 15, 2016) (listing admission requirements to UIC's PhD program in Biochemistry and Molecular Genetics).

185. *See supra* Section II.A.

and eukaryotic cells, and would understand the ramifications of implementing the CRISPR-Cas9 system successfully in those cells. Together with the discussion of "obvious to try" above, from the perspective of this hypothetical person of ordinary skill in the art, it would have been obvious to apply the CRISPR-Cas9 system to eukaryotic cells.

Perhaps more difficult to predict is the application of the secondary factors per *KSR*.[186] There are certainly numerous considerations here. The Zhang patents were extensively licensed, served as the basis for extensive additional scientific research on the CRISPR system, and enjoyed massive commercial success (in various licensed embodiments).[187] But this Note recommends that even such compelling secondary considerations should not trump the "obvious to try" determination per *Kubin*.[188] There is a solid policy reason for this recommendation that transcends the weary and nearly dead venue of an interference proceeding. Should the "obvious to try" test be satisfied, allowing commercial success to overcome such a determination would be tantamount to encouraging opportunistic variation on patented technology so long as it could be commercially exploited. This could have a chilling effect on innovation and would significantly harm fundamental research efforts.

D. The Rebuttable Presumption Concept

Courts (and the PTAB) should consider implementing a rule that applies a rebuttable presumption of obviousness against the patentee of a biological technique in eukaryotic cells where there is prior art applying that technique in prokaryotes. While such a specific rule is perhaps an aberration, patent law in the biological sciences is admittedly an "uncertain," as described extensively above.[189] The advantages of such a rule would be to place the burden on the new patentee to demonstrate why, scientifically, his invention was more than merely "obvious to try," which will so often be satisfied prima facie in such cases. Another strong advantage could be that basic researchers will be incentivized to disclose their findings with respect to prokaryotic systems without fear of losing first bite at the apple for the oftentimes more lucrative eukaryotic applications.

V. CONCLUSION

The odyssey of the CRISPR-Cas9 system is a cautionary tale in the world of biotech intellectual property. The intensifying patent battle has caused uncertainty as to licensing and has stifled the ability of would-be developers to utilize the system in research. While Zhang's work with the CRISPR system is

186. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406–07 (2007).

187. *See, e.g.*, *Genome Market*, *supra* note 5 (noting size and significant growth of global genome editing market).

188. *In re* Kubin, 561 F.3d 1351, 1358–59 (Fed. Cir. 2009).

189. *See supra* Section II.C; Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966).

undoubtedly an important advance on the technology developed by Doudna and Charpentier, it does not represent an advance that takes it outside of 35 U.S.C. § 103's obviousness determination, because a person of ordinary skill in the art would have had a reasonable expectation of success in adapting the technology. Accordingly, the interference panel should rule in favor of the University of California with respect to their motion to award priority to the Doudna group, and should likewise determine that Zhang's claims do not represent a non-obvious patentable advance over the subject matter of the Doudna patent.

While this Note recommends that the dispute be resolved in favor of Doudna/Charpentier, the disciplines of research science fundamentally depend on collaboration and incremental advances in technology that can be applied and improved upon by others in the field.[190] This notion is embedded in the foundation of modern research science, and anytime acrimonious legal disputes arise between ostensible academic peers, it could threaten the integrity and efficacy of collaborative research and might be seen as a betrayal of trust. With a piece of technology that promises such dramatic and exciting applications as does CRISPR, it is important to reconcile these concerns and balance economic exploitation with the goals of academic research. Whatever the outcome of the interference proceeding, and inevitable subsequent appeal to the Federal Circuit, the question of obviousness as between techniques applicable to one cell type or another will fundamentally depend on the exact nature of the technology in question. But as a matter of policy, a presumption that a technique developed for use in prokaryotic cells would be "obvious to try" in eukaryotic cells, rebuttable by the would-be patentee, makes sense in light of the current obviousness standards and as a matter of science and policy.

190. *See generally, e.g.*, Herbert L. DuPont, *Importance of Collaborative Research to Improve World Health*, 163 J. INFECTIOUS DISEASES 946 (1991) (describing how it is critical for researchers to work together to efficiently solve global health concerns).