The CRISPR Patent Battle: Who Will be "Cut" Out of Patent Rights to One of the Greatest Scientific Discoveries of Our Generation?

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ABSTRACT

At the center of the United States patent system lies an intricate balance between creating monetary incentives that lead to creation, invention, and discovery, and impeding the flow of the very information that might permit invention. [1] One such invention, that of a novel gene-editing technology called CRISPR-Cas9, has been called one of the "greatest scientific discoveries in the last century." [2] In simplest terms, the ability to edit genes (the basis of hereditary traits in living organisms made up of DNA) allows scientists to target a specific mutated gene sequence that leads to disease, cut that region out, and, if necessary, replace that sequence with a "healthy" version. CRISPR-Cas9 has already been applied in experiments to rid mice of Muscular dystrophy [3], block cells from HIV infection [4], and cure mice of rare liver disease. [5]

I. Introduction

CRISPR-Cas9 is a naturally occurring process that bacterial cells use to fight viral infection. [6] Scientists have been able to adapt and control this system for use in animal and human cells, which renders the CRISPR-Cas9 system patentable. [7] So, who owns the patent rights to a technology predicted to be worth billions? [8] The result will be determined in an epic patent interference battle raging between Dr. Jennifer Doudna of University of California Berkeley, and Dr. Feng Zhang of The Broad Institute and MIT. Although the United States Patent and Trademark Office (USPTO) awarded Zhang the first patent rights to CRISPR-Cas9, Doudna has filed an interference claim against Zhang in a "winner takes all" patent contest. To further complicate an already intense patent conflict, in September of 2015 Zhang announced his discovery of a "newer and more improved" version of CRISPR, called CRISPR-Cpf1. [9] How might this new version affect the ongoing patent battle, and is this new version original enough to warrant its own patent? Those are questions that remain to be answered while the CRISPR-Cas9 patent battle continues on.

II. CRISPR-Cas 9: Why is this technology such a big deal?

CRISPR-Cas9 is a naturally-occurring process that functions as a bacterial immune system to resist infection by viruses. [10] When viruses attack bacteria, they inject their unique DNA into the cell, causing the bacteria to use its own cellular machinery to copy and propagate the viral DNA instead of its own. The tricked bacteria create copies of the virus which escape the host and spread to infect new bacteria. To fight the spread of infection bacteria cells utilize special DNA cutting enzymes called Cas (CRISPR-associated) enzymes. [11] Cas enzymes

recognize foreign DNA sequences and cut them up into small DNA fragments rendering them inactive. To prevent infections by the same virus in the future, these small viral DNA fragments are then incorporated and stored in the bacteria's genome. These storage regions are called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) sequences. [12] If the bacteria is ever subsequently invaded by a viral DNA sequence that has been stored in the CRISPR "catalog", the cell will transcribe this sequence, which will then bind with Cas enzymes like Cas9, forming a viral "inactivation" complex. [13] This CRISPR-Cas9 complex (Abbreviated CRISPR) then floats around the cell looking for the viral DNA that matches in sequence. Once CRISPR finds the viral DNA match, Cas9 will bind to the viral DNA and "chop" up the sequence, preventing the virus from replicating further. [14] Essentially, Cas9 cuts the DNA like scissors, and CRISPR tells it where to cut.

The really exciting part is that scientists have been able to "hijack" the bacteria's CRISPR system to create a new gene-editing tool that works in animal, plant, and human cells. Scientists have already used CRISPR to modify crops, eradicate viruses, and screen humans for cancer genes. [15] Essentially, CRISPR can be programmed to recognize and target *any* DNA sequence. One very controversial application of CRISPR was a demonstration that the technology works in human reproductive cells. [16] Scientists from China were able to use CRISPR in non-viable fertilized embryos obtained from fertility clinics to edit the gene responsible for β–thalassaemia, a potentially fatal blood disorder. [17] This proof of principle experiment shows that scientists could theoretically modify genes in viable embryos before they are born, potentially eradicating genetically inherited diseases like Down Syndrome, Cystic Fibrosis, Huntington's Disease, certain cancers, and many others. If CRISPR can target any DNA sequence in embryos, it could also be used to target and modify genes that determine eye color, muscle development, or even

intelligence. [18] The manipulation of the DNA of future generations of humans is an area with deep philosophical and ethical concerns, and the potential for CRISPR to create "designer babies" puts the technology squarely at the center of the ethical debate. [19] The US currently does not have a ban on human reproductive cell modification, instead strict regulations implemented by the National Institute of Health are in place, however, the experiments with CRISPR in reproductive cells has led many scientists (including Doudna) to call for a moratorium on such work due to safety, efficacy and ethical issues. [20] In the meantime CRISPR is securing itself as the most widely used gene-editing technology in science to date, with 545 research papers published using this system in 2015 alone. [21] As the application of CRISPR technology rapidly moves forward, there is a clear and present need for the areas of science, law, and policy to converge in order to ensure that CRISPR can be used in the most efficient, ethical, and safe way possible.

III. Patentability of CRISPR.

As CRISPR occurs as a natural biological process, it cannot itself be patented. [22] The U.S. Supreme Court, interpreting 35 USC 101, held that laws of nature, natural phenomena, and abstract ideas are not patentable. [23] In Association for Molecular Pathology v. Myriad Genetics, (hereinafter, "*Myriad*"), Myriad identified mutated DNA sequences in patients that increase the chance of developing breast or ovarian cancer (BRCA 1 and BRCA 2) and used these sequences to develop genetic screening tests for patients. USPTO granted Myriad patent rights to BRCA 1 and 2. If valid, these patents would grant Myriad exclusive rights to the generation and use of BRCA-based medical tests. Petitioners from the Association for Molecular Pathology filed suit, seeking declaration that Myriad's patents were invalid because they covered

products of nature. [24] The Supreme Court agreed, stating that although Myriad found an important and useful set of genes, the sequences existed in nature before they were discovered. Myriad did not alter or create the DNA, and the Court held that unaltered genes are not patent eligible. [25] The Court warned that granting such patents might tie up the use of such naturally occurring phenomena like DNA. [26] Patent rights over natural DNA sequences like the BRCA genes might prevent other scientists from studying those genes and potentially developing better tests or treatments for breast and ovarian cancer, inhibiting future innovations premised upon these sequences. [27] This type of patent would be at odds with the very point of patents, which exist to promote innovation. [28]

Unlike the BRCA genes in *Myriad*, CRIPSR is patentable because scientists were able to alter, control and modify CRISPR to function in animal and human cells, a cellular system in which CRISPR does not naturally function. [29] Once Doudna learned how CRISPR functioned in bacterial cells, she isolated the CRISPR components from these cells and figured out how to direct CRISPR to act upon specific sequences that were of scientific interest (like regions of DNA with a mutated sequence). This ability to direct the natural components of CRISPR is a step beyond its natural design of targeting invasive viral sequences. Scientists could now "manually" navigate CRISPR to a mutated sequence of their choosing, direct CRISPR to cut out that sequence, and have CRISPR replace the cut out sequence with a non-mutated sequence in its place. [30]

Zhang's group showed that CRISPR could function not only in prokaryotic cells (like bacteria) but also in animal and human cells. [31] This meant that scientists could use CRISPR in a non-endogenous system to potentially treat human disease. These modifications to CRISPR are what lead to the generation of a powerful and novel gene-editing tool, making CRISPR worthy

of a valid and very lucrative patent.

IV. The Current CRISPR Patent Battle.

So far, the CRISPR patent battle has been nothing short of complex. As it stands, Doudna filed a patent regarding her work showing that she could isolate and control CRISPR activity with a priority date of May 25, 2012. [32] Zhang filed several patents regarding his work showing that CRISPR could be used in animal and human cells, with a priority date of December 12, 2012. [33] However, Zhang paid an additional fee to accelerate his patent application process. [34] Patent applications are typically examined by USPTO in the order of their effective filing date. [35] However, applicants may petition to the USPTO for their patent application to be "made special", which, if granted, accelerates the total length of examination time to as little as six months after filing. [36] In order for a patent application to be made special, a statement must be made that the claimed subject matter is directed to environmental quality, the development of conservation of energy resources, or countering terrorism. [37] CRISPR does not obviously fall into those categories, however USPTO has created additional categories of subject matter that it considers for special status. [38] These include, (1) applications relating to safety of research in the field of recombinant DNA (2) applications relating to HIV/AIDS and cancer (3) applications involving superconductivity materials and (4) applications filed by small entities that relate to biotechnology. [39] CRISPR would fall into the category of (1) applications relating to the safety of research in the field of recombinant DNA technology, and potentially (2) applications relating to HIV and cancer given the applications of CRISPR thus far.

This means that even though Zhang filed his patents after Doudna, he was issued his patents by USPTO first since they were examined first. On April 14, 2014 Zhang was officially

issued 10 different patents for CRISPR. [40] Specifically, these patents give Zhang control over commercial use of CRISPR technology in eukaryotic cells (human and animal cells, not bacterial cells). That means that Zhang wins control over the technology that will work in pigs, monkeys, mice and humans, most of the models that advance the study of human disease therapeutics, and therefore where most of the profitable use of CRISPR technology would be generated. Some say that Zhang's patents were most likely granted first due to this "fast track" method, without which the USPTO would have flagged the patent for being similar to Doudna's earlier patent application. [41] Zhang claims that USPTO was correct in granting his patents valid first, despite Doudna filing first, because his research showed CRISPR could work outside of bacterial cells, directly in animal and human cells, and that Doudna's patent application was only speculative on this scientific application. [42]

Although Zhang was awarded these CRISPR patents in animal and human cells, Doudna's patent may still be granted, but with significant revisions to the scope of scientific application. For example, her patent might only grant her the rights to CRISPR in bacterial cells, which although useful for mechanistic studies, is not the system in which the majority of CRISPR technology will be used in human disease studies.

V. Patent interference: The winner takes all.

A. Determining priority of invention: conception and reduction to practice

After the news of Zhang's patent award, Doudna filed a patent interference claim (also known as a priority contest) against Zhang stating that Zhang's patent should be ruled invalid after review of her patent application due to her being "first-to-invent" CRISPR. [43] Since both Doudna and Zhang filed their patents before March 16 2013, the first-to-invent rule will still be

applicable to their case. [1] An interference proceeding based on first-to-invent can be initiated when a dispute arises between pending applications; between pending applications and issued patents (like in Doudna/Zhang case); or between issued patents. [44] Interference proceedings afford the party claiming to be the first inventor an opportunity to contest priority and assert its right to patent the invention by filing an application for interference within one year of the issuance of the contested patent. [45]

The Patent Trial and Appeals Board (PTAB) will then determine questions of priority of inventions under 35 U.S.C. § 135(a) with the authority to determine whether Zhang's patent should be deemed invalid. An interference is deemed to exist if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious subject matter of a claim of the opposing party. [46] Doudna filed her interference claim immediately after Zhang had been granted patents to CRISPR. If Doudna were to win the interference, the results for Zhang could be devastating. An adverse ruling on an existing patent results in the cancellation of the involved claims of the patent and awards the prevailing party with the claim in dispute. [47] Essentially, this is a "winner takes all" patent contest.

Invention consists of two distinct acts: conception and reduction to practice of the invention. [48] Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." [49] Actual reduction to practice requires that the claimed invention works for its

[1] On September 16, 2011 Congress signed into law the America Invents Act, which switched the US patent system from a first-to-invent to a first-to-file system. This means that after March 16, 2013 an inventor who files a patent application first is awarded the patent even if another independent inventor for the same invention was first to invent. *See* Wendell Ray Guffey, Kimberly Schreiber, *America Invents Act: The Switch to A First-to-File Patent System*, 68 J. Mo. B. 156 (2012).

intended purpose. [50]

In *Cooper v Goldfarb*, a patent interference was issued to resolve priority of invention of materials used in blood vessel grafting. [51] PTAB awarded priority of invention to the "junior party", the party that had a pending patent (like Doudna) after the "senior party", the party that was granted the first patent (like Zhang), failed to establish reduction to practice first. [52] Both parties were working on experiments involving artificial vascular grafts using flexible membrane tubing, called PTFE tubing. The issue presented in the interference regarded which of the parties was the first to recognize the importance of the PTFE tubing fibril length and reduce it to invention by practice by performing a successful experiment using the claimed structure. [53] Cooper began research in 1972, and claimed he discovered that the length of fibrils was important in vascular grafting, and in 1973 several experiments were conducted in dogs to test this theory. [54] After two of the grafts proved successful in these dog trials, he filed a patent on April 2 of 1974. [55] He claimed conception and reduction to practice as of May 1, 1973 based on statements recorded in his lab notebook. Goldfarb began research in Feb of 1973 using the PTFE vascular grafts provided by Cooper. [56] He claims however, that he was the one to identify the importance of the fibril length in making PTFE vascular grafts successful after conducting experiments in twenty-one different dogs, and that he informed engineers of the necessary fibril length in June of 1973 after he microscopically measured them all. [57] He then filed a patent in October of 1974, claiming reduction to practice as of June 30, 1973. [58]

Goldfarb (junior party) then filed a patent interference claim against Cooper (senior party) claiming he was first-to-invent. The Board found that although Cooper mentioned experiments in his notebook before Goldfarb, these experiments were failures that did not show the importance of the PTFE fibril length. They also fail to specify a fibril length, like the experiments conducted

by Goldfarb. [59] They awarded priority to Goldfarb stating that Cooper's experiments did not reduce the invention to practice. [60] Cooper appealed to the United States Court of Appeals, Federal Circuit, but the Court also ruled in favor of Goldfarb regarding first-to-invent, but recommended that PTAB review whether Goldfarb's efforts inure benefit to Cooper, since Goldfarb did get the original grafts from Cooper. [61] This is an example of a patent case that took more than ten years to settle, which is suggestive of the time it might take to decide the ultimate CRISPR patent interference battle.

B. Who was the first to conceive of CRISPR?

Doudna and Zhang are in a similar situation, because Doudna is challenging Zhang's patent by claiming priority based on first-to-invent. Doudna first published her research findings focusing on the capability of CRISPR to cut and splice genes with better efficiency than any other previous gene-editing technology in the August 2012 issue of the top-tier science publication journal *Science*. [62] This publication was the first to show the fundamental experiment (proof of principle) that CRISPR machinery could be controlled and directed by scientists, one of the aspects mentioned earlier that makes CRISPR patentable. These experiments successfully showed that Doudna was able to conceive of and show that CRISPR could be hijacked from bacterial cells and directed to cut at specific, targeted regions in genes.

Zhang's defense is that he has proof that he independently conceived the idea of using CRISPR for gene-editing, and performed all original proof of principle experiments a full year before Doudna. [63] As evidence, he is presenting copies of all the laboratory notebooks from his lab for the years of 2011-2015. [64] It is possible that Zhang's motivation for waiting to publish these results was a desire to demonstrate that CRISPR worked in animal and human cells

because such results would be more impactful. PTAB will ultimately have to determine the authenticity of these claims after hearing testimony to these facts and decide who conceived the idea of CRISPR first.

C. Who was the first to reduce CRISPR to practice?

Zhang further contends that his paper, published in *Science* four months after Doudna's paper, established that CRISPR could work in animal and human cells, which is the accurate reduction to practice exemplifying the intended use of CRISPR. His experiments demonstrated that CRISPR can be used for gene-editing in mice, monkeys, and humans, the systems in which CRISPR would be most valuable to disease research. [65]

Some academics have commented that Doudna's experiments, "take place in a test tube" and "simply highlight the potential that genome-editing might be possible". [66] If PTAB were to make this distinction given the evidence, Zhang could satisfy the requirement of reduction to practice requiring that the claimed invention works for its intended purpose. The intended purpose of CRISPR is to work in animal and human cells, and without this experiment all Doudna is showing is that CRISPR can be controlled, but not in the system that is most relevant.

Doudna's defense, identified in her interference claim, includes specific experiments from her research and published work that indicate that she did, in fact, show that CRISPR works in animal and human (eukaryotic) cells, despite Zhang's claim to the contrary. [67] In her brief to PTAB, she argues that:

> The Zhang Declaration was accompanied by several exhibits, including excerpts from laboratory notebooks and a manuscript. Dr. Zhang asserted that the exhibits were evidence that patents

> had been actually reduced to practice before applicants constructively reduced their invention to practice. Dr. Zhang is wrong. Dr. Zhang's attempts to demonstrate…teach, suggest, describe, or enable CRISPR methods of using the same in eukaryotic cells also are incorrect. [68]

Doudna's brief goes on to point out 10 different examples, including photos of Zhang's own lab notebooks, that she argues shows that what he is claiming is not accurate. [69] It appears that PTAB will have to spend a lot of time sifting through evidence presented in notebook documentation and carefully determining the scientific implications of each experiment. This could explain why some patent attorneys predict that it could be another 2-3 years before a clear winner of the CRISPR patent is announced. [70]

So which party should win? The one that first published the proof of principle experiments, or the one that demonstrated that the technology could work in the most efficient system? The CRISPR patent comes down to not only who filed or invented first, but also to the scope of each patent. Even if Doudna filed first, would the patent she might be awarded cover CRISPR technology in bacterial cells only? Or are her experiments sufficient to show reduction to practice, providing experimental evidence that CRISPR could work in animal and human cells as well as providing the first proof of principle experiment? Or will Zhang's lab notebooks from 2011 be ruled as sufficient evidence that he was in fact the one to conceptualize and reduce CRISPR to practice? If Zhang's notebooks do show that he independently conducted these initial experiments, he would have a strong claim for winning the interference battle (and keeping his awarded patents) by satisfying both conception and reduction to practice requirements for first-to-invent. Ultimately, whoever wins patent rights to CRISPR in animal and human cells is the

one who is going to reap the most financial reward from companies and laboratories wanting to use CRISPR technology. However, regardless of who wins the patent rights to the original CRISPR system, there is a new aspect that even further complicates matters, Zhang's new discovery of a "better and more efficient" version of CRISPR that utilizes different "cutting" enzymes.

VII. Zhang's "new and improved" CRISPR system: Another level of complexity in the CRISPR patent conundrum.

Zhang recently published in the October 2015 issue of *Cell* experiments showing his use of a new cutting enzyme that works with CRISPR better than Cas9. [71] His new system, CRISPR-Cpf1 has been shown to be more efficient, easier to use in animal and human cells, and less prone to the editing errors that can occur with CRISPR-Cas9 targeting. [72] A big question now becomes whether the use of a new cutting enzyme, which is in the same class of enzymes as Cas9, is novel enough to warrant its own patent, and if so, whether this new patent will render the CRISPR-Cas9 patent less significant.

Should Doudna be awarded exclusive rights to CRISPR technology, she could theoretically seek to invalidate any CRISPR-Cpf1 patent that Zhang files based on the concept of obviousness. Under the U.S. Patent Act, an invention cannot be patented if "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. [73] In addition, the party seeking to invalidate a patent based on obviousness must demonstrate with clear and convincing evidence that someone with skills in that area would have been motivated to combine teaching of the prior art in order to achieve the claimed invention with a reasonable expectation of success in

doing so. [74] An obviousness determination is made by analyzing a range of factual circumstances: scope and content of prior art, differences between claims and prior art, the level of ordinary skill in pertinent art, and secondary considerations such as commercial success. [75]

In *Proctor & Gamble Co. v Teva Pharmaceuticals, Inc.* (*P&G)* the Federal Circuit had to determine whether chemical modifications to a drug compound to generate a new drug substance were obvious thereby invalidating any patents on the new substance. [76] P&G owned the '406 patent, which related to the intermittent dosing methods for treating osteoporosis with compounds called bisphosphonates (inhibit bone resorption). [77] This patent mentions 36 different bisphosphonates for use in the claimed method, including the compound 2-pyr EHDP. Later, P&G chemically modified 2-pyr EHDP to generate the drug risedronate, which is the active ingredient in P&G's osteoporosis drug Actonel. [78] They subsequently secured the '122 patent for risedronate. [79] Teva Pharmaceuticals (Teva) notified P&G of their plans to market a generic version of risedronate, which prompted P&G to file a patent infringement suit against Teva. Teva's defense was that the '122 patent was invalid due to obviousness of the previous patent '406 because the chemical process done to improve '406 patented material and create risedronate was obvious. Teva argued that this process rendered the '122 patent not a special enough innovation to warrant patent protection, and therefor they should be able to market a generic version of risedronate. [80] The Court upheld the lower court ruling in favor of P&G that found the '122 patent to be valid, and non-obvious. [81] Specifically, they ruled that a skilled person in the field would not have identified 2-pyr EHDP as a lead compound in osteoporosis treatment, nor have modified the compound to generate risedronate specifically. [82] An expert on bisphosphonates testified that each bisphosphonate is unique and should be treated and evaluated differently. [83] Therefore, the modification that was made was not routine, but

additional and unique experimental work. Furthermore, the court ruled that P&G also introduced unexpected results which showed that risedronate was extremely potent at low doses and lacked the toxicity of similar bisphosphonates, making this compound modification a novel drug which satisfied a long-felt but unmet need in the osteoporosis drug field. [84]

Similar arguments could eventually surface between Doudna and Zhang depending on the results of the CRISPR patent interference case. Should Doudna ultimately be awarded the CRISPR patent, she could claim that CRISPR-Cpf1 was an obvious iteration of CRISPR, given the existence of Cas-9, and therefore not worthy of its own patent. She would have to show that Zhang's identification of CRISPR-Cpf1 was within the skillset of a person having ordinary skill in the art of CRISPR technology, and that this discovery was only made possible by combining teaching of the prior art (CRISPR-Cas9) with knowing to a reasonable extent that success would result. Meaning, anyone with experience in the CRISPR field could have reasonably used the current CRISPR system to identify Cpf1 and know to a substantial certainty that it would perform similarly as a gene-editing tool. Zhang identified Cpf1 by doing a sequence search of enzymes that might be similar to Cas9, using the Cas9 amino acid sequence as the basis for his comparative search. [85] Any skilled scientist would be able to perform such a search, even outside of the field of CRISPR specifically. Also, such a search would not be possible without the original identification of Cas9. Additionally, Zhang is still pairing Cpf1 with CRISPR, a central component of the CRISPR-Cas9 patent.

Zhang could argue that even if he did find Cpf1 based on the Cas9 sequence, the naturally occurring sequence of Cas9 itself is not patentable. [86] Such a limitation would prevent scientists from making any improvements or novel innovations in the CRISPR field. Furthermore, Zhang would be able to produce evidence that each cutting enzyme is unique,

similar to the bisphosphonates in *P&G*, requiring their own isolation and experimentation. Zhang could also produce evidence of unexpected results. [87] Cpf1 has been shown to cut more efficiently than Cas9, and in different regions of the genome. [88] Essentially, Cpf1 and Cas9 are two different kinds of DNA scissors. Cas9 acts like straight edge scissors, cutting both strands of the DNA double helix in the same place, leaving blunt, exposed ends (exposed ends of DNA can undergo mutation). Cpf1 acts like saw-tooth edged scissors, cutting DNA and leaving offset ends, which reduce the chances of mutation and makes pasting in healthy DNA sequences easier. [89] This use of Cpf1 now opens up new editing sites within the genome. Cpf1 also is less prone to editing errors than Cas9 (cutting in the wrong spots, a phenomenon called "off target effects"), which is a worry with all gene-editing technology. [90] This decrease in error could be ruled to satisfy a long-felt, unmet need in the field of gene-editing technology, making CRISPR-Cpf1 worthy of a valid patent.

VIII. Does Cpf1 render the CRISPR patent less potent: What does this mean for the winner of the battle?

If Zhang is awarded a separate patent for Cpf1, this could mean that laboratories and start up companies could make the switch from using CRISPR-Cas9 to CRISPR-Cpf1 in order to avoid possible infringement of the CRISPR patent, essentially continuing advancement in the scientific application of this technology while Doudna and Zhang spend years battling over CRISPR-Cas9 patent rights. As it stands currently, both Doudna and Zhang have granted non-exclusive CRISPR licenses to academic institutions and start up companies. Zhang has licensed use of CRISPR to the biotech company Editas Medicine, which has raised $120M to research developing CRISPR-Cas9 into a therapeutic agent. [91] Since Zhang works for The Broad

Institute, an academic non-profit organization, several academic use licenses have also been granted to teaching laboratories around the country. [92] Meanwhile, Doudna's biotech company, Intellia Therapeutics, has raised more than $70M for development of CRISPR as a therapeutic tool. [93]

It is unclear how the current patent battle will affect CRISPR as it is being used in academic laboratories and startup companies moving forward, but awarding Zhang a CRISPR-Cpf1 patent might allow scientists to move forward with important gene-editing research without worrying about any future CRISPR infringement claims being filed against them. Granting such a patent might also encourage other scientists to search for even better/more accurate versions of CRISPR, research that might have previously been hindered due to the complex legal landscape of the CRISPR patent. These potentially hindering aspects of the CRISPR patent battle raise many issues about the function and efficiency of the US patent system. Although the patent system may act to promote and encourage inventors to advance scientific progress by ensuring that they have exclusive rights to their inventions, individual patents like CRISPR do not always contribute to that progress. If Doudna were awarded a broad CRISPR patent, which includes all work stemming from CRISPR, potentially including CRISPR-Cpf1, then advancement in improvements to this groundbreaking system could be significantly slowed as researchers worry more about patent infringement and less about how beneficial improving CRISPR could be for biotechnology research.

IX. Conclusion

So who will walk away with the patent rights to the greatest discovery of our generation? That is a question that could unfortunately take several more years to be answered. Even once settled, it is still uncertain what the scope of the patent awarded will be,

and how new technology that will continue to evolve in this field will affect the financial worth of the original patent. Will Doudna win the patent interference battle and subsequently be granted patent rights to CRISPR in all cell types or just bacteria? Will Zhang emerge victorious and not only have patent rights to CRISPR, but also secure new patents for his new and improved version, CRISPR-Cpf1? Regardless of who wins the CRISPR patent battle, it is clear that CRISPR has attracted a lot of attention and money to the exciting and controversial field of gene-editing. Future questions are bound to extend beyond that of who gets the patent, as the application of CRISPR, and CRISPR-Cpf1 rapidly moves forward into grey areas of ethical research. How will law, policy, and science come together to ensure that CRISPR is used ethically and safely? Perhaps Doudna and Zhang will have to put aside their patent battle differences in the future to serve as scientific experts in gene-editing as these important questions begin to be addressed and policies and regulations are molded.

ENDNOTES

[1]. *See Mayo Collaborative Serv. v. Prometheus Lab, Inc*., 132 S. Ct. 1289 (2012).

[2]. *See* Regalado, A. *Who Owns the Biggest Biotech Discovery of the Century?* MIT Technology Review, 2014.

[3]. *See* Xu, L, et al., *CRISPR-mediated Genome Editing Restores Dystrophin Expression and Function in mdx Mice*. Mol. Ther, 2015.

[4]. *See* Hou, P, et al., *Genome Editing of CXCR4 by CRISPR/cas9 Confers Cells Resistant to HIV-1 infection*, Sci. Rep., 2015.

[5]. *See* Yin, H, et al., *Genome Editing with Cas9 in Adult Mice Corrects a Disease Mutation and Phenotype.* Nat Biotechnol, 2014.

[6]. *See* Liang, Q, et al., *The Molecular Mechanism of CRISPR/Cas9 System and its Application in Gene Therapy of Human Diseases,* 2015.

[7]. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013).

[8]. *See* Terry, M. *Despite Patent Battle Worth Billions, CRISPR Raises $64 Million in Series A&B Rounds,* 2015, *available at* http://www.biospace.com/News/despite-patent-battle-worth-billions-crispr-raises/374403.

[9]. *See* Zetsche, B, et al. *Cpf1 is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, Oct 2015.

[10]. *See* Zhao, Y, et al., *Developing CRISPR/Cas 9 Technologies for Research and Medicine, MOJ* Cell Science and Report (2014).

[11]. *See Id.*

[12]. *Id.*

[13]. *Id.*

[14]. *Id.*

[15]. For CRISPR application in plants *See* Schaeffer SM, et al., *CRISPR/Cas9-mediated Genome Editing and Gene Replacement in Plants: Transitioning from Lab to Field.* Plant Sci. Review, 2015; for CRISPR use in eradicating viruses *see* Ebina, H. et al., *Harnessing the CRISPR/Cas9 System to Disrupt Latent HIV-1 Provirus.* Sci Rep 2015; for CRISPR use in screening for cancer genes *see* Shalem, O. et al., *Genome-scale CRISPR-Cas9 Knockout Screening in Human Cells.* Science, 2014.

[16]. *See* Cyranoski, D. *Chinese Scientists Genetically Modify Human Embryos: Rumors of Germline Modification Prove True – and Look to Reignite an Ethical Debate,* Nature News, April 2015, *available at* http://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378.

[17]. *See Id.*

[18]. *Id.*

[19]. *See* Gallager, J. *"Designer babies" Debate Should Start, Scientists Say,* BBC Health News, Jan 2015, *available at* http://www.bbc.com/news/health-30742774.

[20]. *See* Berry, K. *Ethics for CRISPR and the Big Leap Forward, available at* http://blogs.law.harvard.edu/billofhealth/2015/04/24/ethics-for-crispr-and-the-big-leap-forward/.

[21]. National Center for Biotechnology Information, available at http://www.ncbi.nlm.nih.gov/pubmed.

[22]. *See Diamond v Diehr*, 450 U.S. 175 101 (1981).

[23]. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 133 S. Ct. 2107, 2116 (2013).

[24]. *Id*. at 2109.

[25]. *Id.* at 2110.

[26]. *Id*. at 2116.

[27]. *Id.*

[28]. *Id.*

[29]. *See* Cong, L et al. *Multiplex Genome Engineering Using CRISPR/Cas Systems,* Feb. 2013.

[30]. *See* Jinek, M, et al. *A Programmable Duel-RNA-guided DNA Endonuclease in Adaptive Bacterial Immunity.* Science, Aug. 2012.

[31]. *See* Cong, L et al. *Multiplex Genome Engineering Using CRISPR/Cas Systems,* Feb. 2013.

[32]. U.S. Patent No. 842,859 (filed May 2012).

[33]. U.S. Patent No. 8, 697, 359 (filed December 2012).

[34]. Broad Institute, *Information about licensing of CRISPR-Cas9 systems, available at* https://www.broadinstitute.org/partnerships/office-strategic-alliances-and-partnering/information-about-licensing-crispr-cas9-syste.

[35]. *Id.*

[36]. Manual of Patent Examining Procedure (MPEP), §708.02., Petition to Make Special. [R-07.2015].

[37]. MPEP §37 C.F.R. 1.102 (c)(2). Advancement of Examination.

[38]. MPEP §708.02

[39]. *Id.*

[40]. U.S. Patent No. 8, 697, 359 (issued April 2014).

[41]. *See* Rood, J. *Who Owns CRISPR?* The Scientist Blog, *available at* http://www.the-scientist.com/?articles.view/articleNo/42595/title/Who-Owns-CRISPR-/.

[42]. *See Id.*

[43]. U.S. Patent No. 842,859 (filed May 2012).

[44]. *Patent Law Fundamentals* §16:13 (2d ed.).

[45]. 35 U.S.C.A. § 135(b); 37 C.F.R. § 1.205.

[46]. 37 C.F.R. 41.203(a).

[47]. 35 U.S.C. s 135(a) (1988).

[48]. Garascia, C. *Evidence of Conceptio in U.S. Patent Interference Practice: Proving Who is the First and True Inventor.* 73 U. Det. Mercy L. Rev. 717 (1996).

[49]. *Robinson On Patents* 532 (1890).

[50]. *See Great Northern Corporation v. Davis Core & Pad Co*., 782 F.2d 159, 166 (Fed. Cir. 1986).

[51]. *See Cooper v Goldfarb*, 154 F.3d 1321 (Fed. Cir. 1998).

[52]. *Id.* at 1323.

[53]. *Id.* at 1324.

[54]. *Id.*

[55]. *Id.* at 1325.

[56]. *Id.*

[57]. *Cooper v Goldfarb*, 154 F.3d at 1326.

[58]. *Id.*

[59]. *Id.* at 1328.

[60]. *Id.* at 1330.

[61]. *Id.* at 1333.

[62]. *See* Jinek, M, et al., *A Programmable Duel-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity,* Aug. 2012.

[63]. *See* Regalado, A. *Who Owns the Biggest Biotech Discovery of the Century?* MIT Technology Review, 2014.

[64]. *Id.*

[65]. *See* Cong, L et al. *Multiplex Genome Engineering Using CRISPR/Cas Systems,* Feb. 2013.

[66]. Connor, S. *Crispr: Scientists' Hopes to Win Nobel Prize for Gene-editing Technique at Risk over Patent Dispute, available at* http://www.independent.co.uk/news/science/crispr-scientists-hopes-to-win-nobel-prize-for-gene-editing-technique-at-risk-over-patent-dispute-a6677436.html.

[67]. *See* Doudna's Suggestion of Interference Pursuant to 37 C.F.R §41.202 Claim, Application Serial No. 13/842,859, *available at* http://www.technologyreview.com/sites/default/files/docs/interference.pdf.

[68]. *Id.*

[69]. *Id.*

[70]. *See* MIT Technology Review. *CRISPR Patent Fight Now a Winner-Take-All Match.*

[71].*See* Zetsche, B et al. *Cpf1 is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System,* Oct 2015.

[72]. *Id.*

[73]. 35 U.S.C. § 103 (a).

[74]. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed.Cir.2007).

[75]. *See Graham v. John Deere Co.*, 86 S.Ct. 684 (1966).

[76] *See Proctor & Gamble Co. v Teva Pharmaceuticals USA, Inc*., 566 F.3d 989 (Fed. Cir. 2009).

[77]. U.S. Patent No. 4,461,406 (June 1985).

[78]. *See Proctor & Gamble v Teva*, 566 F.3d at 992.

[79]. U.S. Patent No. 5,583,122 (December 1985).

[80] *See Proctor & Gamble v Teva*, 566 F.3d at 992.

[81]. *Id.* at 993.

[82]. *Id.*

[83]. *Id.* at 995.

[84]. *Id.* at 997.

[85]. *See* Zetsche, B et al. *Cpf1 is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, Oct. 2015.

[86]. *See Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 133 S. Ct. 2107, 2116 (2013).

[87]. *See Proctor & Gamble v Teva*, 566 F.3d at 997.

[88]. *See* Zetsche, B et al. *Cpf1 is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, Oct. 2015.

[89]. Sharon Begley, *Genome-editing Find May Improve System's Precision,* Boston Globe. 2015, *available at* https://www.bostonglobe.com/business/2015/09/25/crispr-genome-editing-discovery-may-upend-high-stakes-patent-dispute/9WQTAQe2xuphAuMtindB4K/story.html.

[90]. *See* Zetsche, B et al. *Cpf1 is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, Oct. 2015.

[91]. Fidler, B. *CRISPR Race Heats Up As Gates, Crossovers Put $120M into Editas,* 2015*, available at* http://www.xconomy.com/boston/2015/08/10/crispr-race-heats-up-as-gates-crossovers-put-120m-into-editas/2/.

[92]. *Information about licensing of CRISPR-Cas9 systems,* Broad Institute, *available at* https://www.broadinstitute.org/partnerships/office-strategic-alliances-and-partnering/information-about-licensing-crispr-cas9-syste.

[93]. McClune, C. *Intellia Therapeutics Closes $70M in Series B Funding to Develop CRISPR/Cas9 Therapies,* 2015, *available at* http://synbiobeta.com/intellia-therapeutics-closes-70m-in-series-b-funding-to-develop-crisprcas9-therapies/.

