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The Patentability of the Crispr-Cas9 Genome Editing Tool

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ABSTRACT

The biotechnology sector is rapidly changing with the increase in technological advancements.[1] *The laws governing patent protection, specifically the laws governing patent eligibility, have also changed to adapt to these innovations.*[2] *This paper focuses on the CRISPR-Cas9 technology, a genome editing tool that is changing the field of genetic engineering.*[3] *As of November 2016, the U.S. Patent and Trademark Office has issued 42 patents on the CRISPR-Cas9 technology.*[4] *This paper addresses the issue of whether patents claiming the core CRISPR-Cas9 technology can survive a 35 U.S.C. §101 ("§101") subject matter eligibility challenge. The paper concludes that the CRISPR-Cas9 technology is patentable subject matter under §101. In reaching this conclusion, the paper will do the following: explain the CRISPR-Cas9 technology, compare it to genome editing tools that utilize ZFNs and TALENs, examine relevant §101 Supreme Court and Federal Circuit decisions, introduce the current Alice framework, and apply it to a hypothetical §101 invalidity dispute.*

1. *Timeline of Medical Biology*, AMGEN, http://www.biotechnology.amgen.com/timeline.html (last visited Jan. 20, 2017).

2. Arti K. Rai & Jacob S. Sherkow, *The Changing Life Science Patent Landscape*, 34 NATURE BIOTECH. 292, 292-94 (2016).

3. Ekaterina Pak, *CRISPR: A Game-changing Genetic Engineering Technique*, SITN BLOG (July 31, 2014), http://sitn.hms.harvard.edu/flash/2014/crispr-a-game-changing-genetic-engineering-technique.

4. Lee McGuire, *For Journalists: Statements and Background on the CRISPR Patent Interference Process*, BROAD INSTITUTE (Dec. 6, 2016), https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-interfer.

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CRISPR, a genome editing technology, has been hailed as "the biggest biotech discovery of the century."[5] CRISPR is not the first or the only genome editing tool available to researchers.[6] However, it has generated a substantial amount of excitement and concern among not only scientists, but those outside of the scientific community as well.[7] CRISPR has been used in mice to treat sickle cell anemia, a debilitating blood disorder caused by a

5. Antonio Regalado, *Who Owns the Biggest Biotech Discovery of the Century?*, MIT TECH. REV. (Dec. 4, 2014), https://www.technologyreview.com/s/532796/who-owns-the-biggest-biotech-discovery-of-the-century.

6. *See Gene Editing*, HORIZON, https://www.horizondiscovery.com/gene-editing (last visited Jan. 20, 2017); Hyongbum Kim & Jin-Soo Kim, *A Guide to Genome Engineering with Programmable Nucleases*, 15 NAT. REV. GENET. 321 (2014).

7. *See* Bruce Booth, *Riding the Gene Editing Wave: Reflections on CRISPR/Cas9's Impressive Trajectory*, FORBES (May 31, 2016), http://www.forbes.com/sites/brucebooth/2016/05/31/riding-the-gene-editing-wave-reflections-on-crisprs-impressive-trajectory/#184c8697141c.

single nucleotide change (i.e. A to T) in the DNA.[8] CRISPR screening technologies have also been implemented to identify human host proteins that are vital to Zika and dengue viral replication.[9] Even more, CRISPR was used on a human for the first time this year.[10] Chinese scientists are currently conducting human trials with CRISPR on patients suffering from a specific form of lung cancer.[11] This genome editing tool is reshaping the way scientists conduct research, and is predicted to revolutionize not only the fields of medicine, biology, and agriculture, but much like cars, the way humans live.[12]

A. The CRISPR-Cas9 System: A Closer Look

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats, and is used to refer to the entire CRISPR/CRISPR-associated (Cas) system.[13] The CRISPR-Cas9 system (hereinafter "CRISPR"), as previously mentioned, is a genome editing tool.[14] In order to understand how CRISPR can be used to manipulate genes, it is necessary to understand the general overview of the central dogma of molecular biology.[15] Each gene provides instructions for building a particular protein.[16] This information is stored in the DNA.[17] Characteristics such as eye color, hair color, and physical features are all manifested through the proteins our bodies make.[18] Therefore, a cell makes a particular protein from the information stored in

8. S*ee generally* Heidi Ledford, *CRISPR Deployed to Combat Sickle-cell Anaemia*, NATURE (Oct. 12, 2016), http://www.nature.com/news/crispr-deployed-to-combat-sickle-cell-anaemia-1.20782.

9. Jim Fessenden, *Scientists Use CRISPR to Discover Zika and Dengue Weaknesses*, PHYS.ORG (June 21, 2016), https://phys.org/news/2016-06-scientists-crispr-zika-dengue-weaknesses.html.

10. Timothy J. Seppala, *China Completes First Human Trial with CRISPR-edited Genes*, ENGADGET (Nov. 15, 2016), https://www.engadget.com/2016/11/15/china-completes-first-human-trial-with-crispr-edited-genes/.

11. *PD-1 Knockout Engineered T Cells for Metastatic Non-small Cell Lung Cancer*, CLINICALTRIALS.GOV (Nov. 2016), https://clinicaltrials.gov/ct2/show/NCT02793856.

12. *See* Maywa Montenegro, *CRISPR is Coming to Agriculture- with Big Implications for Food, Farmers, Consumers and Nature*, ENSIA (Jan. 28, 2016), https://ensia.com/voices/crispr-is-coming-to-agriculture-with-big-implications-for-food-farmers-consumers-and-nature/.

13. Martin Jinek et al., *A Programmable Dual-RNA-guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCI. 816 (2012).

14. Regalado, *supra* note 5.

15. *See Central Dogma (DNA to RNA to Protein)*, KHANACADEMY, https://www.khanacademy.org/science/biology/gene-expression-central-dogma/ (last visited Dec. 23, 2016).

16. *See Intro to Gene Expression (Central Dogma)*, KHANACADEMY, https://www.khanacademy.org/science/biology/gene-expression-central-dogma/central-dogma-transcription/a/intro-to-gene-expression-central-dogma (last visited Dec. 23, 2016).

17. *Id.*

18. *Id.*

our DNA through a process known as gene expression.[19] The cell will find the appropriate gene and create a copy of the gene (i.e. the instruction set) through a process known as transcription.[20] This copy is called messenger RNA (mRNA). mRNA is then read and "decoded" to build a protein through a process called translation.[21]

CRISPR, in the simplest terms, can be described as an RNA-guided nuclease system. RNA, a chemical cousin of DNA, can recognize and bind to a matching DNA sequence.[22] A nuclease is a type of enzyme that can cut DNA.[23] Therefore, CRISPR is a 2-part system that consists of a Cas9 nuclease, which acts as a pair of "molecular scissors,"[24] and a guide RNA (gRNA), which leads the Cas9 nuclease to the target DNA sequence.[25] The gRNA, which consists of roughly 20 nucleotides (bases), can be programmed to match with specific sequences in the DNA.[26] Researchers studying a specific genetic disorder can design a gRNA[27] or simply order it online.[28]

Once in the cell, the gRNA and Cas9 bind together to form a Cas9-gRNA complex.[29] This Cas9-gRNA complex then searches through the entire genome to find the exact portion of the DNA that matches with the 20

19. *Id.*

20. *Id.*

21. *Id.*

22. Jekaterina Aleksejeva, *RNA Facts—the Ultimate Guide to the Chemical Cousin of DNA*, LEXOGEN (July 6, 2016), https://www.lexogen.com/rna-facts-the-ultimate-guide-to-the-chemical-cousin-of-dna/.

23. *CRISPR Systems in Prokaryotic Immunity*, DOUDNA LAB (2012), http://rna.berkeley.edu/crispr.html (last visited Jan. 26, 2017); *s*). *ee also Why is Everyone Talking About CRISPR-Cas9 Technology?*, DNA-SCISSORS (June 6, 2016), https://dnascissors.wordpress.com; Peter Cavanagh & Anthony Garrity, *The Answer*, CRISPR/CAS9 BLOG, https://sites.tufts.edu/crispr/answer/ (last visited Jan. 26, 2017).

24. Guy Riddihough, *CRISPR Cas9 Molecular Scissors*, 351 SCI. 827, 827 (2016), http://science.sciencemag.org/content/351/6275/827.1; Ellen Jorgensen, *What You Need to Know About CRISPR*, TEDSUMMIT (Oct. 24, 2016), https://www.ted.com/talks/ellen_jorgensen_what_you_need_to_know_about_crispr.

25. *Id. See also* Cavanagh & Garrity, *supra* note 23.

26. Jorgensen, *supra* note 24; *CRISPR Systems in Prokaryotic Immunity*, *supra* note 23.

27. Kenian Chen et al., *CRISPR Explorer: A Fast and Intuitive Tool for Designing Guide RNA for Genome Editing*, 3 J. BIOLOGICAL METHODS e56 (2016).

28. John Doench, *How to Design Your gRNA for CRISPR Genome Editing*, ADDGENE (Feb. 16, 2016), https://innovativegenomics.org/blog/how-to-make-a-guide-rna-for-cas9/. *See* Jacob Corn, *How to Make a Guide RNA for a Cas9 Knockout*, INNOVATIVE GENOMICS INITIATIVE (Aug. 12, 2014), https://innovativegenomics.org/blog/how-to-make-a-guide-rna-for-cas9/.

29. Jeffry D. Sander & J. Keith Joung, *CRISPR-Cas Systems for Editing, Regulating, and Targeting Genomes*, 32 NATURE BIOTECH. 347, 349 fig.2b (2014).

nucleotides of the gRNA.[30] When CRISPR finds this region, the gRNA will insert itself between the two strands of the DNA and latch onto the corresponding DNA sequence.[31] This will trigger the Cas9 enzyme to cut the DNA, introducing a double stranded break (DSB).[32] This break is important because DNA needs to be stable.[33] At this point, one of two main repair pathways can be used to fix the break.[34] The cell can repair the DSB on its own through a process known as "non-homologous end joining" (NHEJ), or through a process known as homologous recombination (HR).[35]

With NHEJ, the broken ends of the DNA are rapidly joined together.[36] NHEJ, however, is an error-prone repair process that results in the insertion or deletion of one or more bases at the site of repair.[37] Adding or removing a base (i.e. nucleotide) results in a frameshift mutation because it causes a shift in the codon reading frame.[38] Codons, each consisting of 3 nucleotides, code for amino acids.[39] Amino Acids are the building blocks of proteins.[40] Frameshift mutations can introduce premature stop codons and result in many amino acid changes that prevent the protein from properly

30. *Id*.; CRISPR/Cas9 Guide, ADDGENE, https://www.addgene.org/crispr/guide (last visited Jan. 28, 2017); Jennifer Doudna, *Genome Engineering with CRISPR-Cas9: Birth of a Breakthrough Technology*, IBIOLOGY (Mar. 23, 2015), https://www.ibiology.org/ibiomagazine/jennifer-doudna-genome-engineering-with-crispr-cas9-birth-of-a-breakthrough-technology.html. *See also* Jorgensen, *supra* note 24.

31. Sander & Joung, *supra* note 29, at 349 fig.2b; CRISPR/Cas9 Guide, *supra* note 30; Doudna, *supra* note 30. *See also* Jorgensen, *supra* note 24.

32. Sander & Joung, *supra* note 29 at 351, fig.4.

33. Doudna, *supra* note 30; Jorgensen, *supra* note 24; *see also* A. J. Davis & D. J. Chen, *DNA Double Strand Break Repair Via Non-homologous End-joining*, 2 TRANS. CANCER RES. 130, 132 (2013).

34. D. Akcay et al., *The Past, Present and Future of Gene Correction Therapy*, 3 ACTA MEDICA 51, 54-55 (2014).

35. *Id*.

36. *Id*. at 55.

37. *Id*. at 54-55.

38. *Id*.

39. *Central Dogma and the Genetic Code*, KHANACADEMY, https://www.khanacademy.org/science/biology/gene-expression-central-dogma/central-dogma-transcription/a/the-genetic-code-discovery-and-properties (last visited Jan. 27, 2017).

40. *Id*.

functioning.[41] Hence, the NHEJ process can be used to inactivate a gene (i.e. "knock out" a gene).[42]

DSBs can also be repaired through the HR process if an identical sequence homology is present in the cell.[43] Unlike NHEJ, HR repairs the DSB by using an undamaged identical DNA template.[44] Researchers can use an artificial DNA sequence to trigger HR, and "knock in" or even "knock out" genes at target locations.[45] This process introduces three components into the cell: the gRNA, Cas9, and a piece of DNA (donor DNA).[46] When the Cas9 enzyme makes a DSB in the DNA, the cell will look for a related DNA sequence to use as a template to repair the DNA.[47] Humans inherit two sets of chromosomes from each parent.[48] When a DSB occurs in diploid organisms such as humans, the sister chromatid is usually used as a template in the HR process to repair the DNA.[49] However, researchers can trick the cell into using a foreign donor DNA to mend the break.[50] In this case, the donor DNA is designed such that the specific elements to be added are in the middle, and the ends consist of arms (homology arms) that are homologous to the corresponding end regions of the DSB.[51] Hence, when the Cas9

41. *What Kinds of Gene Mutations are Possible?* G1 10ENETICS HOME REF., https://ghr.nlm.nih.gov/primer/mutationsanddisorders/possiblemutations (last visited Feb. 14, 2017); *see also* Abby Dernburg, *Lecture 4: Classification of Mutations by Their Effects on the DNA Molecule*, http://mcb.berkeley.edu/courses/mcb142/lecture%20topics/Dernburg/Lecture6_Chapter8_screenviewing.pdf (last visited Dec. 23, 2016).

42. What Kinds of Gene Mutations are Possible?, *supra* note 41. *See also* Dernburg, *supra* note 41.

43. Akcay, *supra* note 34, at 54.

44. *Id*.

45. Ignazio Maggio & Manuel A. F. V. Goncalves, *Genome Editing at the Crossroads of Delivery, Specificity, and Fidelity*, 33 TRENDS BIOTECH. 280, 280-81 (2015). *See also* Akcay, *supra* note 34, at 54.

46. *Id*. at 280; *Generating a Knock-out Using CRISPR/Cas9*, ADDGENE, https://www.addgene.org/crispr/guide/#ko-generation (last visited Feb. 14, 2017).

47. Martin Jinek et al., *RNA-programmed Genome Editing in Human Cells*, 2 eLIFE e00471 (2013), http://dx.doi.org/10.7554/eLife.00471. *See also* Jorgensen, *supra* note 24; Jennifer Doudna, *How CRISPR Lets Us Edit Our DNA*, TED (Sept. 2015), https://www.ted.com/talks/jennifer_doudna_we_can_now_edit_our_dna_but_let_s_do_it_wisely.

48. April Klazema, *Haploid vs Diploid Cells: How to Know the Difference*, UDEMYBLOG (June 13, 2014), https://blog.udemy.com/haploid-vs-diploid.

49. Tamara Goldfarb & Michael Lichten, *Frequent and Efficient Use of the Sister Chromatid for DNA Double-Strand Break Repair during Budding Yeast Meiosis*, 8 PLOS BIO. e1000520 (2010), 10.1371/journal.pbio.1000520; *see also* Jorgensen, *supra* note 24; Doudna, *supra* note 30.

50. *The Basics of CRISPR/Cas9*, GENOME EDITING UIC, https://sites.google.com/site/genomeedits/basics (last visited Feb 15, 2017); *see also* Jorgensen, *supra* note 24; Doudna, *supra* note 30.

51. Akcay, *supra* note 34 at 54fig1; *s. ee also* Chari Cortez, *CRISPR 101: Homology Directed Repair*, ADDGENE BLOG, http://blog.addgene.org/crispr-101-homology-directed-repair (last visited Feb 15, 2017).

enzyme makes the cut, the cell proceeds to incorporate it into the gap through HR instead of NHEJ.[52]

This idea of using donor DNA to introduce desired genes into our cells opens endless possibilities because HR is considered to be a more accurate and precise repair pathway than NHEJ.[53] With HR, researchers are theoretically able to turn on and off genes at targeted locations without disrupting untargeted parts of the genome.[54] There are currently over 10,000 human diseases caused by a mutation in a single gene.[55] Single gene disorders, also known as monogenic diseases, include Huntington's disease, Cystic Fibrosis, Sickle cell anemia, Tay sachs disease, and Thalassaemia.[56] Beyond single gene disorders, researchers believe CRISPR will one day be used to cure complicated genetic disorders, and even prevent disorders such as Down syndrome before a child is born.[57]

B. CRISPR, ZFNs, and TALENs

CRISPR is the latest genome editing tool to enter the biotech field, but it is not the only tool that can make DSBs.[58] The CRISPR system, as previously mentioned, relies on a programmable RNA-guided nuclease to target specific DNA sequences.[59] Currently, researchers are using the Cas9 enzyme to cleave DNA.[60] However, it is only a matter of time before a more efficient RNA-guided nuclease is discovered.[61] For instance, the Cpf1 enzyme was recently found to be easier to use and produce less errors in comparison to the Cas9 enzyme.[62]

52. *Id*.

53. Cortez, *supra* note 51.

54. Jelor Gallego, *Modified CRISPR Can Now Turn Gene Expression On and Off*, FUTURISM (Mar. 17, 2016), https://futurism.com/modified-crispr-can-now-turn-gene-expression-off.

55. *Genes and Human Disease*, WORLD HEALTH ORG., http://www.who.int/genomics/public/geneticdiseases/en/index2.html (last visited Dec. 23, 2016).

56. *Id*.

57. *CRISPR . . . Changing the World*, GENOME COMPILER (Nov. 12, 2013), http://www.genomecompiler.com/crispr-changing-the-world.

58. Akcay, *supra* note 34, at 60-61.

59. Jinek, *supra* note 13, at 816.

60. *Id*.

61. Mike Williams, *Rice Lab Offers New Strategies, Tools for Genome Editing*, RICE (Feb. 8, 2016), http://news.rice.edu/2016/02/08/rice-lab-offers-new-strategies-tools-for-genome-editing.

62. Bernd Zetsche et al., *Cpfl is a Single RNA-guided Endonuclease of a Class 2 CRISPR-Cas System*, 163 CELL 759 (2015).

Researchers have been, and are still using other technologies that utilize programmable nucleases to modify eukaryotic genomes.[63] Technologies based on artificial enzymes known as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have also been used by researchers for years.[64] Researchers have been using technologies based on ZFNs and TALENs to study how our genes work in mice, rats, and in various cell lines similar to those in humans.[65] ZFNs, which have been in use since the mid-1990s, was tested for the first time by U.S. researchers in 2014 on 12 HIV patients.[66] ZFN-based technology was used to modify the gene encoding CCR5, the "Trojan horse" used by HIV to infect the human immune system.[67] Similarly, in 2015, TALEN-based technology was used for the first time in a human by British researchers.[68] It was successfully used to treat a baby diagnosed with acute lymphoblastic leukemia.[69] Technologies utilizing ZFNs, TALENs, and CRISPR largely make up the genome editing market today.[70] It is currently a $2.84 billion-dollar industry that is projected to nearly double in revenue by 2021.[71]

C. Why is CRISPR Special?

The two major repair pathways NHEJ and HR are not new.[72] Researchers have been studying these pathways for years by implementing them in fruit flies and lab animals.[73] Gene editing tools that make DSBs are not new.[74] Moreover, tools utilizing programmable nucleases to target specific DNA sequences are not new.[75] Technologies based on ZFNs and

63. Akcay, *supra* note 34, at 60-61.

64. Akcay, *supra* note 34, at 55-57.

65. *Id*.

66. Sara Reardon, *Gene-editing Method Tackles HIV in First Clinical Test*, NATURE (Mar. 5, 2014), http://www.nature.com/news/gene-editing-method-tackles-hiv-in-first-clinical-test-1.14813.

67. *Id*.

68. Sara Reardon, Leukemia Success Heralds Wave of Gene-editing Therapies, NATURE (Nov. 10, 2014), http://www.nature.com/news/leukaemia-success-heralds-wave-of-gene-editing-therapies-1.18737.

69. *Id*.

70. RnR Market Research, *Genome Editing Market (CRISPR, TALEN, ZFN) to See 14.3% CAGR to 2021*, PR NEWSWIRE (Oct. 13, 2016), http://www.prnewswire.com/news-releases/genome-editing-market-crispr-talen-zfn-to-see-143-cagr-to-2021-596898941.html.

71. *Id*.

72. Akcay, *supra* note 34, at 53-55.

73. *Id.* at 56.

74. *Id.* at 53.

75. *Id.* at 60-61.

TALENs are still being used even with the rise of CRISPR.[76] Further, genome editing technology has successfully been used in humans to treat genetic conditions.[77] At this point, it is only logical to ask why CRISPR is considered to be "revolution"[78] if it is not doing something new.

First, CRISPR is relatively simpler to use in comparison to the other options.[79] ZFN and TALEN based technology rely on proteins for DNA recognition.[80] This means that every time a researcher wants to target a different segment of the DNA, a new protein needs to be engineered.[81] Unlike ZFNs and TALENs, CRISPR relies on RNA and complementary base pairing for DNA recognition.[82] A researcher using CRISPR need only synthesize a 20-nucleotide strand of gRNA, which is simple compared to the amount of work that goes into ZFN and TALEN based technology.[83] ZFN and TALEN are difficult to engineer, require sophisticated protein engineering, and involve a certain degree of trial and error (depending on how complex the sequence is).[84] Today, do-it-yourself (DIY) bacterial CRISPR kits are available for sale on the market.[85] These DIY kits give people outside of the scientific community a chance to use CRISPR to modify genes of a strain of bacteria.[86]

Second, CRISPR is a much cheaper alternative to ZFNs and TALENs due to its simplicity.[87] ZFN enzymes cost anywhere from $4,000 to $7,000 a piece.[88] TALEN plasmids, on the other hand, cost only $65 a piece, with the

76. *Id*.

77. Reardon, *supra* note 68.

78. Jennifer Doudna, *Genome-editing Revolution: My Whirlwind Year with CRISPR*, NATURE (Dec. 22, 2015), http://www.nature.com/news/genome-editing-revolution-my-whirlwind-year-with-crispr-1.19063; Brad Plumer & Janvier Zarracina, *Guide to CRISPR Gene Editing Revolution*, GENETIC LITERACY PROJECT (Jan. 3, 2017), https://www.geneticliteracyproject.org/2017/01/03/guide-crispr-gene-editing-revolution; Bruce Booth, *CRISPR/Cas9 Already is a Revolution in Molecular Biology*, MEDCITYNEWS (June 9, 2016), http://medcitynews.com/2016/06/crispr-cas9-revolution.

79. Paul BG van Erp et al., *The History and Market Impact of CRISPR RNA-guided nucleases*, 12 CURRENT OPINION IN VIROLOGY, 85, 85-90 (2015).

80. *Id*. at 86.

81. *Id*.

82. *Id*.

83. *Id*.

84. *Id*.

85. Andrew Tarantola, *I Played God with the Odin's DIY CRISPR Kit*, ENGADGET (June 30, 2016), https://www.engadget.com/2016/06/30/i-played-god-with-the-odins-diy-crispr-kit.

86. *Id*.

87. van Erp et al., *supra* note 79, at 87.

88. Brian Wang, *Disruptive CRISPR Gene Therapy is 150 Times Cheaper Than Zinc Fingers and CRISPR is Faster and More Precise*, NEXT BIG FUTURE (June 9, 2015), http://www.nextbigfuture.com/2015/06/disruptive-crispr-gene-therapy-is-150.html; *see* Heidi Ledford,

popular Golden Gate TALEN Kit priced at $425.[89] For research labs across the world, purchasing just one customized mouse or rat model could cost up to $20,000.[90] CRISPR on the other hand, can cost as little as $30.[91] This is because researchers generally only need to purchase the RNA segment.[92] CRISPR gives more labs the ability to design CRISPR systems on their own because it does not require complex engineering like ZFNs and TALENs do.[93]

Third, CRISPR is much more efficient than ZFNs and TALENs.[94] Efficiency rates for CRISPR in eukaryotic cells was higher than the rates reported for ZFNs and TALENs.[95] Unlike ZFNs and TALENs, CRISPR allows researchers to modify several genes at once by introducing multiple gRNAs.[96] Before CRISPR, it could take anywhere from 6 to 12 or more months to genetically engineer mice to carry mutations in several genes.[97] Today, labs using CRISPR can implement the same process and generate the same results within one month.[98] CRISPR has also changed the way whole genomes are screened.[99] One research lab used CRISPR with nearly 65,000 different gRNAs to target 18,000 genes.[100] Because of its efficiency, cost, and ease of use, CRISPR has changed the way scientific research is conducted.[101] It is predicted that every research lab in the future will be using CRISPR.[102]

CRISPR, the Disruptor, NATURE (June 3, 2015), http://www.nature.com/news/crispr-the-disruptor-1.17673.

89. Wang, *supra* note 88.

90. Jon Cohen, *'Any Idiot Can Do It.' Genome Editor CRISPR Could Put Mutant Mice in Everyone's Reach*, SCI. MAG. (Nov. 3, 2016, 10:00 AM), http://www.sciencemag.org/news/2016/11/any-idiot-can-do-it-genome-editor-crispr-could-put-mutant-mice-everyones-reach.

91. Wang, *supra* note 88.

92. *Id*.

93. *Id*.

94. Monya Baker, *Gene Editing at CRISPR Speed*, 32 NATURE BIOTECH. 309, 309-12 (2014).

95. *Id*.

96. Haoyi Wang et al., *One-Step Generation of Mice Carrying Mutations in Multiple Genes by CRISPR/Cas-mediated Genome Engineering*, 153 CELL 910, 910-18 (2013).

97. *Id*. at 914.

98. *Id*.

99. Baker, *supra* note 94, at 310.

100. *Id*.

101. Aileen Christensen, *The "Miracle Method": How CRISPR is Changing Biological Research*, ELSEVIER (Jan. 13, 2017), https://www.elsevier.com/connect/the-miracle-method-how-crispr-is-changing-biological-research; *s. ee also* Jorgensen, *supra* note 24; Doudna, *supra* note 30.

102. Cohen, *supra* note 90.

CRISPR however, is not perfect.[103] It is known in the scientific community to have problems with cutting DNA at off-target sites.[104] One researcher found as many as five mismatches when using CRISPR to cut specific target locations.[105] Additionally, using CRISPR-induced HR to integrate donor DNA has not been a simple feat.[106] Despite the attachment of homology arms at either side of the donor DNA, most cells usually repair the DSB on its own through the NHEJ process.[107] Some cells repair through HR, by using the other chromatid as a template instead of the donor DNA.[108] Hence, inducing HR in these types of cell lines can be difficult.[109] Researchers are trying to find ways to use CRISPR-induced HR to successfully manipulate target cells.[110] Despite the numerous scientific articles published on CRISPR, there is still so much researchers do not know about CRISPR.[111] Researchers will most likely begin their projects by using CRISPR in order to screen target sequences because of the previously-mentioned reasons.[112] However, after screening, researchers will most likely utilize TALENs or ZFNs to build their projects.[113] In comparison to CRISPR, TALENs and ZFNs not only have better specificity, but also have the capacity to recognize longer DNA sequences.[114]

103. Baker, *supra* note 94, at 310.

104. *Id*.

105. *Id*.

106. Lin et al., *Enhanced Homology-Directed Human Genome Engineering by Controlled Timing of CRISPR/Cas9 Delivery*, eLIFE, Dec. 2014, at 1, 1, *available at* http://dx.doi.org/10.7554/eLife.04766.

107. *CRISPR Frequently Asked Questions*, IDT, https://www.idtdna.com/pages/docs/default-source/synthetic-biology/crispr_faq_043015.pdf?sfvrsn=2 (last visited May 13, 2017); *see also* Yoshimi et al., *ssODN-Mediated Knock-In with CRISPR-Cas for Large Genomic Regions in Zygotes*, NATURE COMMC'NS, Jan. 20, 2016 at 1, 2, *available at* doi:10.1038/ncomms10431.

108. *See CRISPR Frequently Asked Questions*, *supra* note 107; Lin et al., *supra* note 106, at 1.

109. *PITCh-ing an Alternative Knock-In Strategy for TALENs and CRISPR/Cas9*, GEN (Dec. 4, 2014), http://www.genengnews.com/gen-news-highlights/pitch-ing-an-alternative-knock-in-strategy-for-talens-and-crisprcas9/81250665.

110. *Harvard, MGH Team Creates CRISPR/Cas9 Variant That Eliminates Off-Target Effects*, GENOMEWEB (Jan.6, 2016), https://www.genomeweb.com/gene-silencinggene-editing/harvard-mgh-team-creates-crisprcas9-variant-eliminates-target-effects; Sandeep Ravindran, *Eliminating CRISPR-Cas9's Off-target Effects*, BIOTECHNIQUES (Jan. 13, 2016), http://www.biotechniques.com/news/Eliminating-CRISPR-Cas9s-Off-target-Effects/biotechniques-362580.html#.WKP11_JfbIU.

111. *Probing How CRISPR-Cas9 Works: Study Examines DNA Targeting Dynamics in Live Cells*, PHYS.ORG (Aug. 26, 2016), https://phys.org/news/2016-08-probing-crispr-cas9-dna-dynamics-cells.html.

112. Baker, *supra* note 94, at 310-11.

113. Sarah Zhang, *Everything You Need to Know About CRISPR, the New Tool That Edits DNA*, GIZMODO (May 5, 2015), http://gizmodo.com/everything-you-need-to-know-about-crispr-the-new-tool-1702114381.

114. *Id*.

D. CRISPR: Naturally-Occurring vs. Modified CRISPR Systems

CRISPR, that is the functions of CRISPR, is not new to the scientific community.[115] CRISPR is a naturally-occurring adaptive immune system of select bacteria and archaea.[116] CRISPR was initially discovered in 1987 by researchers who were studying the bacteria *E.coli*.[117] It was not until 2007 when scientists were able to prove the function of CRISPR by experimenting on *S. thermophilus*, a bacterial strain used to convert milk into yogurt.[118] There are actually three types of CRISPR systems that have been identified, of which the type II system is the most studied.[119] The type II CRISPR system, the simplest of the three systems, is the basis for the CRISPR genome editing tool used by researchers today.[120]

In bacterium such as *Escherichia coli*, the type II CRISPR system includes CRISPR arrays of short palindromic repeats known as CRISPR repeats.[121] These CRISPR repeats are separated by spacers, which contain unique sequences known as protospacer sequences.[122] Each time the bacterium is invaded by a foreign DNA, the type II CRISPR system incorporates fragments of the invading DNA into these spacers.[123] Hence, the CRISPR array grows with every new protospacer sequence that is inserted.[124] The CRISPR arrays is transcribed into a precursor CRISPR RNA known as pre-crRNA.[125] The pre-crRNA is processed into mature short CRISPR RNAs (crRNAs).[126] Each crRNA has "protospacer" regions, which contain complementary sequences that match to a specific sequence in the

115. Jinek et al., *supra* note 13, at 816.

116. *Id*.; Carl Zimmer, *Breakthrough DNA Editor Born of Bacteria*, QUANTA MAG. (Feb. 6, 2015), https://www.quantamagazine.org/20150206-crispr-dna-editor-bacteria.

117. Zimmer, *supra* note 116.

118. *Id*.

119. Jinek, *supra* note 13, at 816; Krzysztof Chylinski et al., *Classification and Evolution of Type II CRISPR-Cas Systems*, 42 NUCLEIC ACIDS RES. 6091, 6091-105 (2014).

120. Chylinksi et al., *supra* note 119, at 6091

121. Devashish Rath et al., *The CRISPR-Cas Immune System: Biology, Mechanisms and Applications*, 117 BIOCHIMIE 119, 119-20 (2015).

122. *Id*.; Sander & Joung, *supra* note 29, at 349 Figure 3.

123. Rath et al., *supra* note 121, at 119-20; Sander & Joung, *supra* note 29, at 349fig 3.; Zhang, *supra* note 113.

124. Rath et al., *supra* note 121, at 119-20; Sander & Joung, *supra* note 29, at 349fig 3; Zhang, *supra* note 113.

125. Rath et al., *supra* note 121, at 119-20; Sander & Joung, *supra* note 29, at 349fig 3; Zhang, *supra* note 113.

126. Eric S. Lander, *The Heroes of CRISPR*, 164 CELL 18, 18-28 (2016). S*ee also* Rath et al., *supra* note 121, at 119-20; Sander & Joung, *supra* note 29, at 349fig 3; Zhang, *supra* note 113.

virus DNA.[127] Each crRNA hybridizes with an additional RNA known as a trans-activating CRISPR RNA (tracrRNA).[128] These 2 types of RNA (crRNA and tracrRNA) then form a complex with a Cas9 nuclease.[129] This complex actively searches the cell for DNA that matches its protospacer sequences.[130] Therefore, when the same virus attacks again, the complex is able to use the crRNA and tracrRNA to recognize the virus, and latch onto a specific site of the invading viral DNA.[131] After the matching protospacer sequence of the complex binds with the corresponding target site of the DNA, Cas9 will disable the virus by cutting the viral DNA.[132] The type II CRISPR system not only allows the bacterium to remember, record, and deactivate its foreign invaders, but also allows it to pass all its stored information onto the next generation.[133]

The CRISPR system is the adaptive and inheritable immune system of certain bacteria and archaea, which are prokaryotes.[134] Prokaryotes are simple single-celled organisms that lack a nucleus.[135] Instead, prokaryotic cells have DNA in the form of a single circular chromosome.[136] The CRISPR system does not exist naturally in eukaryotic cells.[137] Animals and plants are eukaryotes.[138] Eukaryotic cells have many features such as membrane-bound organelles, which are not found in prokaryotic cells.[139] However, the most important distinction between prokaryotic and eukaryotic cells is that eukaryotic cells have a membrane-bound nucleus, which stores the cell's genetic information.[140] The genetic information of eukaryotic cells, DNA, is organized in chromosomes, of which humans have 46.[141]

127. Sander & Joung, *supra* note 29, at 348.

128. Sander & Joung, *supra* note 29, at 348-49. Lander *supra* note 126, at 19 Figure 1.

129. Sander & Joung, *supra* note 29, at 348-49. Lander *supra* note 126, at 19, Figure 1.

130. Sander & Joung, *supra* note 29, at 348-49. Lander *supra* note 126, at 19, Figure 1.

131. Sander & Joung, *supra* note 29, at 348-49. Lander *supra* note 126, at 19, Figure 1; s*ee* Jorgensen, *supra* note 24; Doudna, *supra* note 30.

132. Sander & Joung, *supra* note 29, at 348-49. Lander *supra* note 126, at 19, Figure 1; s*ee* Jorgensen, *supra* note 24; Doudna, *supra* note 30.

133. Sander & Joung, *supra* note 29, at 348-49. Lander *supra* note 126, at 19, Figure 1; s*ee* Jorgensen, *supra* note 24; Doudna, *supra* note 30.

134. Zimmer, *supra* note 116.

135. *Biology-Structure of a Cell*, KHANACADEMY, https://www.khanacademy.org/science/biology/structure-of-a-cell/prokaryotic-and-eukaryotic-cells/a/prokaryotic-cells (last visited Dec. 23, 2016).

136. *Id*.

137. Zimmer, *supra* note 116.

138. KHANACADEMY, *supra* note 135.

139. *Id*.

140. *Id*.

141. *Id*.

In 2012, researchers successfully adapted the type II CRISPR system to eukaryotic cells.[142] Although the basic function of the naturally-occurring type II CRISPR system is mirrored in the engineered CRISPR system, there is a notable distinction between the two.[143] As previously mentioned, the naturally-occurring CRISPR system involves a dual-RNA structure, which consists of crRNA and tracrRNA.[144] Researchers from the Doudna and Charpentier labs of the University of California, Berkeley ("UCB") modified the CRISPR system so that Cas9 can be used with a single RNA structure instead of the dual-RNA structure found in nature.[145] A single RNA-guided Cas9 complex would allow researchers to program a single RNA to target and cut specific sites in the human DNA.[146] To create a single RNA structure, UCB scientists connected the tracrRNA and crRNA together to create a tracrRNA-crRNA chimera.[147] The majority of the engineered CRISPR systems today utilize a guide RNA ("gRNA") that is a chimeric RNA— a fusion between a CRNA and part of the tracrRNA.[148]

The CRISPR genome editing technology has been used to produce some of the most exciting advancements for geneticists in recent years.[149] The potential uses of CRISPR for the advancement of human health is both exciting and daunting.[150] The financial stake in this technology is enormous.[151] Numerous life science companies are offering CRISPR-related products.[152] CRISPR's potential for the growth of the therapeutics market has also attracted much interest from investors.[153] All this excitement in the scientific community however, cannot escape the concern surrounding the intellectual property (IP) of the CRISPR technology.[154]

142. Jinek, *supra* note 13, at 816.
143. Sander & Joung, *supra* note 29, at 349 Figure 3.
144. *Id*.
145. Jinek, *supra* note 13, at 817-20.
146. *Id*. at 820.
147. *Id*.
148. Sander & Joung, *supra* note 29, at 349.
149. *See* Ledford, *supra* note 8; Fessenden, *supra* note 9; CLINICALTRIALS.GOV, *supra* note 11.
150. Ledford, *supra* note 88.
151. RnR Market Research, *supra* note 70.
152. *Id*.
153. *Id*.
154. Tony Fong, *As CRISPR-Cas Technology Sets to Take Off, Uncertainty Swirls Around IP Landscape*, GENOMEWEB (June 18, 2014), https://www.genomeweb.com/rnai/crispr-cas9-technology-sets-take-uncertainty-swirls-around-ip-landscape.

II. CRISPR: RELEVANT §101 CASE LAW

CRISPR has been the subject of an intense patent dispute between Feng Zhang of the Broad Institute and MIT ("Broad") and Jennifer Doudna of the University of California, Berkeley ("UCB") as to who invented the technology first.[155] There is also another ownership dispute between Broad and Rockefeller University as to who the inventors are of several other CRISPR patents.[156] The United States Patent and Trademark Office ("USPTO") has issued 28 patents on the CRISPR technology as of 2016.[157] Outside of the U.S., there is a patent dispute over Zhang's European CRISPR patents.[158] These aggressive ownership disputes illustrate the role patents have in not only protecting an inventor's work, but also in commercializing technology.

The inventorship disputes surrounding CRISPR raise other patent-related concerns such as patent validity.[159] Because the USPTO has issued patents as to CRISPR, it is hypothesized that invalidity disputes as to several CRISPR patents will find their way to federal court. CRISPR has garnered a lot of interest by scientists, research institutions, and companies—many who would clearly benefit from using the technology unencumbered. Invalidity disputes concerning the CRISPR patents will most likely be raised under 35 U.S.C. §102 ("§102") for lack of novelty or under 35 U.S.C. §103 ("§103") for obviousness.[160] However, this paper will only evaluate the CRISPR technology under a hypothetical 35 U.S.C. §101 dispute challenging patent-eligible subject matter.

Currently, there is no dispute in federal court challenging the eligibility of the CRISPR patents under 35 U.S.C. §101 (hereinafter "§101"). However,

155. Heidi Ledford, *Bitter Fight Over CRISPR Patent Heats Up*, NATURE (Jan. 12, 2016), http://www.nature.com/news/bitter-fight-over-crispr-patent-heats-up-1.17961.

156. Kerry Grens, *That Other CRISPR Patent Dispute*, THE SCIENTIST (Aug. 31, 2016), http://www.the-scientist.com/?articles.view/articleNo/46921/title/That-Other-CRISPR-Patent-Dispute.

157. Jacob S. Sherkow, *Who Owns Gene Editing? Patents in the Time of CRISPR*, BIOCHEMICAL SOC'Y 26, 26-29 (2016), http://www.biochemist.org/bio/03803/0026/038030026.pdf.

158. *Id*.

159. Jennifer K. Wagner, *The Patent Dispute Over Gene Editing Technologies*, GENOMICS L. REP. (Feb. 4, 2016), http://www.genomicslawreport.com/index.php/2016/02/04/the-patent-dispute-over-gene-editing-technologies-the-broad-institute-inc-vs-the-regents-of-the-university-of-california; s*ee* Kristin Beale, *The CRISPR Patent Battle: Who Will be "Cut" Out of Patent Rights to One of the Greatest Scientific Discoveries of Our Generation*, B.C. INTELL. PROP. & TECH. F. (2015), http://bcipt.org; Benjamin C. Tuttle, *The Failure to Preserve CRISPR-Cas9's Patentability Post Myriad and Alice*, 98 J. PAT. & TRADEMARK OFF. SOC'Y 391, 404 (2016).

160. This is hypothesized based on the current interference proceeding between Broad and UCB; s*ee* Isobel Finnie & Catherine Williamson, *CRISPR Patent Wars*, GEN (Feb. 6, 2017), http://www.genengnews.com/gen-exclusives/crispr-patent-wars/77900842.

recent Supreme Court decisions on §101 have affected the landscape for life science patents.[161] By evaluating the CRISPR technology under a hypothetical §101 dispute in federal court, this paper intends illustrate how the modern §101 framework is applied to life science inventions.

A. Patents: The Basics

A patent is a property right the government grants to an inventor for a limited period of time—generally, 20 years from the effective filing date of the patent application.[162] A patent does not grant an inventor the exclusive right to make, use, offer for sale, sell, or import the invention.[163] Rather, a patent grants an inventor the right to exclude others from "making, using, offering for sale, or selling" the invention in the U.S. or "importing" the invention into the country.[164] A patent's "claims" establish the scope of the invention, and define the exclusive right granted to the inventor.[165] Hence, when a patent dispute is in court because of issues such as invalidity or infringement, it is the claims that are litigated—the claims are at stake.[166]

The power to grant patents is found in the United States Constitution in Art. I, Sec. 8, Clause 8, also known as the Intellectual Property Clause. This clause grants Congress the power "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."[167] Pursuant to this authority, Congress enacted the U.S. Patent Act ("Patent Act").[168] The Patent Act, which is found in Title 35 of the United States Code, authorizes the USPTO to establish patent rules not inconsistent with the law.[169] The USPTO examines patent applications and issues patents.[170]

161. Alice Corp. v. CLS Bank Int'l, 134 S. Ct. 2347, 2355 (2014); Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116 (2013); Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 71 (2012).

162. *General Information Concerning Patents*, USPTO (Oct. 2015), https://www.uspto.gov/patents-getting-started/general-information-concerning-patents (last visited Feb. 14, 2017).

163. *Id*.

164. 35 U.S.C. §154(a)(1) (2017).

165. USPTO, *supra* note 162.

166. *Id*.

167. U.S. CONST. art. I, §8, cl. 8

168. USPTO, *supra* note 162.

169. *Id*.

170. *Id*.

The 5 primary requirements for patentability are as follows: patentable subject matter, utility, novelty, non-obviousness, and enablement.[171] These requirements are all found in 35 U.S.C. §§101, 102, 103, and 112. After a patent has been issued, its validity can be challenged (on any of the grounds previously mentioned) in special proceedings at the USPTO or in federal court.[172] It is worth briefly mentioning that there are two different standards that govern patent claims.[173] Prior to issuance, the claims in a patent application are examined by the USPTO under a broadest reasonable interpretation (BRI) standard.[174] In contrast, patent claims at dispute in federal court are construed in accordance to a plain meaning standard.[175]

B. Subject Matter Eligibility Under 35 U.S.C. §101

35 U.S.C. §101 ("§101") states that anyone who "invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[176] Hence, only inventions that fall within the patent eligible categories: "process, machine, manufacture, or composition of matter" are eligible for patent protection.[177] The Supreme Court, traditionally, has interpreted §101 to also include "implicit exception[s]" to 3 broad principles: laws of nature, natural phenomena, and abstract idea.[178] Inventions directed to one of these judicially recognized exceptions (referred to as "judicial exceptions") have long been held by courts as patent ineligible.[179] The discovery of a law of nature, physical phenomena, or abstract idea itself is not patentable because these are "manifestations of nature which are free to all men and reversed exclusively to none."[180] Hence, the discovery of a new mineral or plant found

171. *Patent*, LEGAL INFO. INST., https://www.law.cornell.edu/wex/patent (last visited on Dec. 23, 2016).

172. MPEP §1216 ("Judicial Review") (9th ed., rev. 7 Nov. 2015) (hereinafter "MPEP").

173. MPEP §2111 ("Claim Interpretation; Broadest Reasonable Interpretation").

174. *Id*.; *see also* Fanelli Haag, *Practical Implications of the Two Claim Construction Standards in the Post-AIA World*, LEXOLOGY, July 16, 2015, http://www.lexology.com/library/detail.aspx?g=260f7965-7f9c-463d-859f-7d5c6b6a7575.

175. *Id*. (this is also known as the *Phillips* standard.).

176. 35 U.S.C. § 101 (2012).

177. *Id*.

178. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116 (2013) (quoting Mayo Collaborative Servs. v. Prometheus Labs, Inc., 566 U.S. 66, 70-71 (2012)).

179. *Id*.

180. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (quoting Funk Brothers Seed. Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)).

in nature is not patentable.[181] This also explains why celebrated discoveries such as Einstein's formula $E=mc^2$ and Newton's law of gravity were not patentable.[182]

The patent system exists to award inventive activity and encourage innovation.[183] Hence, patents are not meant to give a select few the power to monopolize knowledge belonging in the public domain. On the other hand, too narrow of an interpretation of §101 could impede innovation.[184] In recognizing the dangers of interpreting the judicial exceptions too broadly, the Supreme Court has long acknowledged that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas."[185] Thus, the Supreme Court has held that the mere recitation of a judicial exception does not make a claim ineligible for patenting.[186] Rather, it is the application of the judicial exception that needs to be examined.[187]

C. Pre-Alice: Relevant Supreme Court Decisions

Before applying the modern framework to a hypothetical §101 subject matter eligibility CRISPR dispute, it is helpful to review several relevant Supreme Court decisions. Prior to *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*,[188] (hereinafter "*Alice*") the Supreme Court had issued several subject matter eligibility decisions pertinent to the life sciences field. In *Diamond v. Chakrabarty* (hereinafter "*Chakrabarty*"), the Supreme Court held that living organisms are patentable subject matter under §101.[189] In *Chakrabarty*, a super oil-eating bacterium was at issue.[190] Four strains of oil-eating bacteria that exist in nature, each possess the ability to digest different components of the oil.[191] These bacteria have plasmids, which are rings of

181. *Id*.
182. *Id*.
183. U.S. CONST. art. I, § 8, cl. 8.
184. Marshall Phelps, *Do Patents Really Promote Innovation? A Response to the Economist*, FORBES, Sept. 16, 2015, http://www.forbes.com/sites/marshallphelps/2015/09/16/do-patents-really-promote-innovation-a-response-to-the-economist/3/#62d9e6db32b5. *See*; *see also* E. Richard Gold et al., *Are Patents Impeding Medical Care and Innovation?*, 7 PLOS MED e1000208 (2010).
185. Mayo Collaborative Servs., v. Prometheus Labs, Inc., 566 U.S. 66, 71. (2012).
186. *Id.* at 71-72.
187. *Id.*
188. Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347 (2014).
189. Diamond v. Chakrabarty, 447 U.S. 303 (1980).
190. *Id.* at 305.
191. *This Week in Science History- the First Genetic Patent*, NAKED SCIENTIST, Mar. 30, 2009, http://www.thenakedscientists.com/articles/interviews/week-science-history-first-genetic-patent.

DNA that code for the proteins that eat the oil.[192] Dr. Chakrabarty combined the four plasmids into a single bacterium, effectively creating a new species of bacteria.[193] In a 5-4 decision, the Supreme Court held that a live, human-made microorganism was patentable subject matter under §101 because the oil-eating property of the genetically modified bacterium was not possessed by any naturally occurring bacteria.[194]

The *Chakrabarty* decision laid the foundation for allowing the patenting of genetically modified living organisms such as transgenic mice.[195] It is important to note that patent claims directed to human organisms, such as embryos and fetuses, have never been patent eligible subject matter.[196] In *Mayo Collaborative Servs. v. Prometheus Labs., Inc* (hereinafter "*Mayo*"), the Supreme Court laid out the inventive concept requirement seen in the second step of the *Alice* framework.[197] The invention at issue in *Mayo* was a personalized medicine dosing process.[198] Researchers discovered natural correlations between specific metabolite levels in the body and a dosage range for the drug thiopurine.[199] The invention identified methods reciting steps such as "administering" a drug to a patient, "determining" the level of metabolite in the patient, and adjusting the dosage based on the correlation discovered by the researchers.[200] In a 9-0 decision, the Supreme Court held that the dosing process was not patentable subject matter under §101 because the correlation claimed was a law of nature.[201] Further, the Court held that the additional steps, "when viewed as a whole," were not enough to transform the judicial exception into a patentable application of it.[202]

192. *Id.*

193. *Id.*

194. *Id.; Diamond*, 447 U.S. at 309-10.

195. *This Week in Science History- the First Genetic Patent*, *supra* note 191.

196. Leahy-Smith America Invents Act, Pub. L. No. 112-29, §33(a), 125 Stat. 284, 340 (2011) ("Notwithstanding any other provision of the law, no patent may issue on a claim directed to or encompassing a human organism.")*; see also* Memorandum from Robert W. Bahr to Patent Examining Corps (Sept. 20, 2011), (available at https://www.uspto.gov/sites/default/files/aia_implementation/human-organism-memo.pdf).

197. Alice Corp. Pty. Ltd., v. CLS Bank Int'l, 134 S. Ct. 2347, 2357-58 (2014).

198. Mayo Collaborative Servs., v. Prometheus Labs, Inc., 566 U.S. 66, 72 (2012); *see also* Dennis Crouch, *Mayo v. Prometheus: Natural Process + Known Elements = Normally No Patent*, PATENTLYO, Mar. 20, 2012, http://patentlyo.com/patent/2012/03/mayo-v-prometheus-natural-process-known-elements-normally-no-patent.html; Judith Kim & Scott Schaller, *After Alice: The Two-step Rule*, LSIPR NEWSLETTER, 2015, at 10-13, http://www.skgf.com/uploads/1378/doc/LSIPR_Jan15_AfterALice.pdf.

199. *Id.*

200. *Mayo Collaborative Servs.*, 566 U.S. at 71-72.

201. *Id.* at 92.

202. *Id.* at 80.

In *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.* (hereinafter "*Myriad*"), the Supreme Court held that a "naturally-occurring DNA segment" is not patent eligible merely because its covalent bonds were severed in order to isolate the DNA segment.[203] Rather, an isolated segment of naturally occurring DNA is a patent ineligible product of nature.[204] The Court also held that complementary DNA (cDNA) is patent eligible subject matter.[205] The Court reasoned that cDNA, a synthetic version of DNA created from mRNA, "contains only the exons that occur in DNA, omitting the intervening introns."[206] Exons are the expressed sequences of DNA that code for protein whereas intron are non-expressing sequences of DNA that do not code.[207] The rationale behind the *Myriad* decision is based on the fact that DNA stores genetic information.[208] Although isolated DNA and naturally occurring DNA have chemical differences due to the breaking of the covalent bonds, the genetic information stored in the isolated DNA is the same when compared to its naturally occurring state.[209] The breaking of covalent bonds "does not change the information-transmitting quality."[210] However, cDNA is created in a lab by removing introns from naturally occurring genomic DNA through known lab procedures.[211] Hence, because cDNA is not naturally occurring in its natural environment (human cells), it is patent eligible.[212] This decision has sparked much debate in the scientific community as many scientists believe that the difference between cDNA and naturally occurring genomic DNA (gDNA) are trivial.[213]

Lastly, it is worth pointing out *In re Roslin Inst. (Edinburgh)*, hereinafter "*Roslin*."[214] This decision from the U.S. Court of Appeals for the

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

204. *Id.* at 2111.

205. *Id.*

206. *Id.* at 2109.

207. *Id.*

208. Jason Rantanen, *Myriad: Isolated DNA Out, cDNA In*, PATENTLYO, June 13, 2013, http://patentlyo.com/patent/2013/06/myriad-isolated-dna-out-cdna-in.html.

209. *Id.*

210. *Ass'n for Molecular Pathology*, 133 S. Ct. at 2115.

211. *Id.*

212. *Id.*

213. Noam Prywes, *The Supreme Court's Sketchy Science*, SLATE, June 2013, http://www.slate.com/articles/health_and_science/science/2013/06/supreme_court_patent_case_science_the_justices_misunderstand_molecular_biology.html; Megan Krench, *New Supreme Court Decision Rules that cDNA is Patentable*, SCIENTIFIC AMERICAN, July 9, 2013, https://blogs.scientificamerican.com/guest-blog/new-supreme-court-decision-rules-that-cdna-is-patentablewhat-it-means-for-research-and-genetic-testing; *see also* Rantanen, *supra* note 208.

214. In re Roslin Inst. (Edinburgh), 750 F.3d 1333, 1337 (Fed. Cir. 2014).

Federal Circuit (hereinafter "Federal Circuit") was issued one month before the Supreme Court's *Alice* decision.[215] In *Roslin*, the Federal Circuit held that Dolly the cloned sheep, effectively any genetic clone, is not patentable subject matter under §101.[216] Dolly was cloned from an adult somatic cell.[217] The method of cloning mammals by using somatic cells was patented, and not at issue in this case.[218] At issue, rather, was whether the products of the cloning method could be patented.[219] The *Roslin* court compared the claimed clones to the isolated DNA in *Myriad* and reasoned that no genetic information (of the clones) was created or altered.[220] The court also pointed out that "the genetic structure of the DNA used to make [the] clones" was not created or altered in any way.[221] In rejecting the patent claims, the Federal Circuit reasoned that Dolly, the claimed subject matter, did not possess markedly different characteristics from her donor parent.[222] Dolly was an "exact genetic replica" of her donor parent, and therefore patent ineligible.[223]

D. The Modern Approach on §101 Analysis: Alice

At the outset of every §101 subject matter eligibility inquiry, it is necessary to ask if the invention falls within one of the 4 patent-eligible categories.[224] If the invention does not have any claims directed to either a process, machine, manufacture, or composition of matter, the inquiry goes no further.[225] The invention is not eligible for patent protection.[226] In *Alice*, the Supreme Court articulated a 2-part framework for distinguishing patents that claim a patent-ineligible judicial exception from those that claim a

215. *Id.* at 1333.

216. *Id.* at 1337.

217. Gene Quinn, *Dolly the Cloned Sheep Not Patentable in the U.S.*, IPWATCHDOG, May 8, 2014, http://www.ipwatchdog.com/2014/05/08/dolly-the-cloned-sheep-not-patentable-in-the-u-s/id=49471.

218. *Id.*

219. In re Roslin Inst. (Edinburgh), 750 F.3d at 1333.

220. *Id*. at 1337.

221. *Id.*

222. *Id.* at 1337-39.

223. Quinn, *supra* note 217.

224. Alice Corp. Pty. Ltd., v. CLS Bank Int'l, 134 S. Ct. 2347, 2355 (2014).

225. *See Id.;* 2014 Interim Eligibility Guidance Quick Reference Sheet, USPTO Examination Guidance and Training Materials (Dec. 2014), https://www.uspto.gov/patents/law/exam/2014_eligibility_qrs.pdf.

226. *See Alice Corp. Pty. Ltd.,* 134 S. Ct. at 2355; 2014 *see* Interim Eligibility Guidance Quick Reference Sheet, *supra* note 225.

patent-eligible application of the exceptions.[227] The *Alice* decision focused on the judicial exception of abstract ideas in the context of computer-related inventions.[228] However, its framework was derived in large part from *Mayo*, where the Supreme Court held methods of administering a drug based on specific levels of a metabolite to be patent ineligible.[229]

The first step of the *Alice* framework is to determine "whether the claims at issue are directed to a patent-ineligible concept."[230] It is well established that products of nature, as opposed to those of human intervention, fall within the judicial exceptions.[231] Therefore, inventions that encompass a product derived from natural sources (known as "nature-based products") are analyzed more closely under this first step.[232] Nature-based products, like CRISPR, must possess "markedly different characteristics" from any found in nature in order to be patent eligible.[233] The nature-based product limitation is compared to its naturally-occurring counterpart found in its natural state.[234] Types of characteristics to consider when determining "markedly different characteristics" include, but are not limited to the following: biological functions or activities, chemical and physical properties, phenotype, and structure and form.[235] If the nature-based product limitation has markedly different characteristics, the patent claim at issue is patent eligible under §101.[236] The eligibility inquiry stops here.[237]

If, however, the answer is no (there are no markedly different characteristics), the eligibility inquiry continues onto the second step.[238] The second step of the *Alice* framework is to determine whether the claim recites any "additional elements [that] 'transform the nature of the claim' into a patent-eligible application."[239] There needs to be an inventive concept

227. *See Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355; *see* 2014 Interim Eligibility Guidance Quick Reference Sheet, *supra* note 225.

228. *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2357.

229. *Mayo Collaborative Servs.*, 566 U.S. at 71-72.

230. *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355.

231. 2014 Interim Eligibility Guidance Quick Reference Sheet, *supra* note 225.

232. *Id.*; *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355.

233. 2014 Interim Eligibility Guidance Quick Reference Sheet, *supra* note 225.

234. *Id.*

235. Analyzing Nature-based Products Slides, USPTO Training Materials on Subject Matter Eligibility, 1-39, 9 (Feb. 2015), *available at* https://www.uspto.gov/sites/default/files/documents/101%20JE%20training%20Nature-Based%20Products%20Module.pdf

236. 2014 Interim Eligibility Guidance Quick Reference Sheet, *supra* note 225.

237. *Id.*

238. *Id.*

239. *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2357 (quoting *Mayo Collaborative Servs.*, 566 U.S. at 78).

sufficient to guarantee that the claim "amounts to significantly more" than the judicial exception itself.[240] In determining if there is an inventive concept, all the claim elements, must be considered "both individually and in combination[.]"[241] If there is an inventive concept, the claims at issue are patent eligible under §101.[242] If the patent claims instead recite additional elements that involve "well-understood, routine, conventional activity," the claims are patent ineligible.[243]

E. Post-Alice Decisions: Applying Alice

Since the Supreme Court's *Alice* decision in 2014, the Federal Circuit has issued several §101 subject matter eligibility decisions, of which two are relevant to the life sciences field.[244] These decisions provide some guidance on how the *Alice* framework is being applied to life science inventions in federal court. First, the Federal Circuit held in *Rapid Litig. Mgmt. v. CellzDirect, Inc*. ("*CellzDirect*") that an improved process of cryopreserving hepatocyte cells was patent eligible under §101.[245] Hepatocytes, a type of liver cell, are preserved for future use in a process known as cryopreservation.[246] Here the inventors discovered that "some fraction of hepatocytes are capable of surviving multiple freeze-thaw cycles."[247] Instead of using frozen cells once, scientists could refreeze the cells and use them again.[248] The patent claimed an improved process which recited steps such as "subjecting" previously frozen cells to a known technique to separate viable and non-viable cells, "recovering" the viable cells, and "refreezing" these cells.[249] The claims specified that this preparation could be used immediately after thawing, exhibiting 70% viability.[250]

In applying the first step of the Alice framework, the Federal Circuit held that the claims were not directed to a patent ineligible judicial

240. *Id.*
241. *Id.* at 2357 n.3.
242. *Id.* at 2355.
243. *Id.* at 2359. (quoting *Mayo Collaborative Servs.*, 566 U.S. at 73).
244. Rapid Litig. Mgmt v. CellzDirect, Inc., 827 F.3d 1042 (2016); Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (2015).
245. 827 F.3d at 1050-51.
246. *Id.* at 1045.
247. *Id.*
248. *Id.*
249. *Id.*
250. *Id.*

exception.[251] The court reasoned that the inventors did not patent their natural discovery, but instead used it "to create a new and improved way of preserving hepatocyte cells for later use."[252] The Federal Circuit emphasized that in asking if a claim is "directed to" a judicial exception, "merely identify[ing] a patent-ineligible concept" "is not enough."[253] Rather, "the end result of the process," as a whole must be an ineligible judicial exception.[254] The end result here was more than an "observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles"—it was an improved process "of producing a desired preparation."[255] Because the patent claims were not directed to a judicial exception, the eligibility inquiry did not move on to the second step.[256]

Second, the Supreme Court denied a petition for writ of certiorari in *Sequenom, Inc. v. Ariosa Diagnostics, Inc.*[257] (hereinafter "*Sequenom*"), leaving the Federal Circuit decision in place.[258] In *Sequenom*, the Federal Circuit held a fetal DNA diagnostic method to be patent ineligible subject matter under §101.[259] Scientists discovered the presence of cell-free fetal DNA (cffDNA) in the bloodstream of pregnant women.[260] The idea was that fetal DNA could be accessed separately from the maternal DNA by linking it to the paternal DNA portion of the cffDNA.[261] This discovery made it possible to create a non-invasive prenatal test to screen for genetic defects in the fetus.[262] The patent claimed a method, which recited two steps: "amplifying" a sample of cffDNA taken from a pregnant woman, and "detecting" the paternally-inherited portion of DNA in the cffDNA.[263]

In applying the first step of the *Alice* framework, the Federal Circuit held that the claimed method was directed to a patent ineligible natural

251. *Id.* at 1049-51.

252. *Id.* at 1048; *see also* Memorandum on Recent Subject Matter Eligibility Rulings from Robert W. Bahr to Patent Examining Corps (July 14, 2016), *available at* https://www.uspto.gov/sites/default/files/documents/memo_rlm-sequenom.pdf.

253. *Rapid Litig. Mgmt.*, 827 F.3d at 1050.

254. *Id.* at 1048.

255. *Id.*

256. *Id.* at 1048-49.

257. Sequenom, Inc. v. Ariosa Diagnostics, Inc., 2016 U.S. LEXIS 4087 (June 27, 2016).

258. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (2015).

259. *Id.* at 1376.

260. *Id.*

261. Dennis Crouch, *Federal Circuit Reluctantly Affirms Ariosa v. Sequenom and Denies En Banc Rehearing*, PATENTLYO (Dec. 3, 2015), http://patentlyo.com/patent/2015/12/reluctantly-sequenom-rehearing.html.

262. *Id.*

263. *Ariosa Diagnostics, Inc.*, 788 F.3d at 1373-74.

phenomena.[264] In applying the second step, the court held that the method did not recite an inventive concept that transformed the judicial exception (presence of cffDNA in maternal bloodstream) into a patent eligible application of the exception.[265] The court compared the invention to *Mayo* and reasoned that the additional "amplifying" and "detecting" steps were "well-understood, routine, and conventional activity" at the time the patent application was filed.[266] This decision was not unexpected.[267] However, it was not well-received by the life sciences field,[268] especially after the court acknowledged that the discovery "may have been a significant contribution to the medical field."[269] Many in the life sciences field believe that under the Intellectual Property Clause and patent laws, new and useful discoveries should be eligible for patent protection.[270]

III. CRISPR: HYPOTHETICAL §101 PATENT INVALIDITY DISPUTE

As previously mentioned, there are 28 U.S. patents on the CRISPR technology as of February 2016.[271] These patents all claim different aspects and variations of the CRISPR technology.[272] Instead of applying the §101 framework to each of the patents, it would be in the best interest of this paper's purpose to focus on the patent claims that cover the core CRISPR technology. This paper will apply the §101 analysis to the single count in the current USPTO patent interference proceeding between Doudna (UCB) and Zhang (Broad).[273] The one count in dispute is as follows:[274]

> A method, in a eukaryotic cell, of cleaving or editing a target DNA molecule or modulating transcription of at least one gene encoded thereon, the method comprising:

264. *Id.* at 1376.

265. *Id.* at 1377-79. *See also* Memorandum on Recent Subject Matter Eligibility Rulings from Robert W. Bahr to Patent Examining Corps, *supra* note 252.

266. *Ariosa Diagnostics, Inc.*, 788 F.3d at 1337.

267. Crouch, *supra* note 261.

268. *Id.*

269. *Ariosa Diagnostics, Inc.*, 788 F.3d at 1379-80.

270. Crouch, *supra* note 261.

271. *CRISPR Patents and Licensing Information*, BROAD INST., https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-patents-and-licensing-information (last visited Feb. 14, 2017).

272. Knut J Egelie et al., *The Emerging Patent Landscape of CRISPR-Cas Gene Editing Technology*, 34 NATURE BIOTECH. 1025, 1025-31 (2016).

273. USPTO Patent Interference No. 106048 (public interference documents can be accessed at https://acts.uspto.gov/ifiling/PublicView.jsp).

274. Notice to Declare Interference, 1-17 (Jan. 11, 2016) for USPTO Patent Interference No. 106048.

> contacting, in a eukaryotic cell, a target DNA molecule having a target sequence with an engineered and/or non-naturally-occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system comprising:
>
> a) a DNA-targeting RNA comprising
>
> i) a targeter-RNA or guide sequence that hybridizes with the target sequence, and
>
> ii) an activator-RNA or tracr sequence that hybridizes with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment, and
>
> b) a Cas9 protein,
>
> wherein the DNA-targeting RNA forms a complex with the Cas9 protein, thereby targeting the Cas9 protein to the target DNA molecule, whereby said target DNA molecule is cleaved or edited or transcription of at least one gene encoded by the target DNA molecule is modulated.[275]

A count is a best described as a "hypothetical patent claim" that covers the overlapping invention.[276] In the CRISPR interference proceeding, a 3-judge panel compared UCB's pending patent application (No. 13/842,859) to the Broad's 12 U.S. patents and found that they overlapped as to the one count mentioned above.[277] At issue is a DNA-editing method.[278] The method recites one step of "contacting" a target DNA molecule in a eukaryotic cell with a Type II CRISPR system.[279] The claimed CRISPR system is described as essentially having two components: a guide RNA (the "DNA-targeting RNA") made up of a targeter and an activator RNA, and a Cas9 protein.[280] The guide RNA (gRNA) is described as forming a complex with the Cas9 protein to cut the target DNA molecule.[281]

275. *Id*. at 10-11.
276. Sherkow, *supra* note 157 at 27.
277. Notice to Declare Interference, *supra* note 274, at 3-9.
278. *Id*.
279. *Id*. at 10.
280. *Id*. at 11.
281. *Id*.

A. CRISPR: Applying the §101 Alice Framework

Before applying the *Alice* framework, the patent claim in dispute needs to fall within one of the four subject matter eligible categories. Here, a process claim is in dispute. The first step in *Alice* asks whether the claim at issue is directed to a patent-ineligible judicial exception. Per the USPTO training materials, process claims are not subject to the markedly different characteristics analysis used for nature-based products unless the process claim is "drafted in such a way that there is no difference in substance from a product claim to a nature-based product."[282] Here, the only method step is arguably the "contacting" step. The rest of the claim is directed to a nature-based product limitation because the type II CRISPR system is a naturally occurring phenomena in select prokaryotes. Hence, this CRISPR system described in the patent claim needs to be examined under the "markedly different characteristics" analysis.[283]

The claimed CRISPR system possesses characteristics that are markedly different from the naturally-occurring counterpart found in select bacteria. Under the analysis, markedly different characteristics based on properties such as structure and function need to be identified. First, the structure of the "DNA-targeting RNA"[284] in the claimed CRISPR system is different from the structure found in nature. In the naturally-occurring CRISPR system, the "DNA-targeting RNA"[285] is a dual RNA structure comprising of crRNA, which is the targeter RNA, and tracrRNA, which is the activator RNA. The "DNA-targeting RNA" found in the claimed CRISPR system is a single RNA structure. This single RNA structure (gRNA), is a fusion of the crRNA and tracrRNA, which is naturally found in the CRISPR system of select prokaryotes.[286] Researchers implementing the type II CRISPR system design gRNA using segments of crRNA and tracrRNA.[287] However, even though the naturally-occurring components are the same, the amount of each component used is different.[288] The claimed

282. Analyzing Nature-based Products Slides, *supra* note 235 at 6.

283. It is important to note that the USPTO guidance and training materials are used by examiners at the USPTO when examining claims during patent prosecution. In a subject matter eligibility dispute at federal court, a judge may or may not refer to the USPTO's guidance and training materials.

284. Notice to Declare Interference, *supra* note 274, at 11.

285. *Id*.

286. Jinek, *supra* note 13, at 819-20.

287. *Id*.; Patrick D. Hsu, *DNA Targeting Specificity of RNA-guided Cas9 Nucleases*, 31 NATURE BIOTECH. 827, 827-32 (2016).

288. Jinek, *supra* note 13, at 819-20; Hsu, *supra* note 287, at 827-32.

CRISPR system is used in different eukaryotic cell lines.[289] Based on the cell line and need, truncated versions of crRNA and tracrRNA can be used.[290]

The rationale in *Myriad* seems to emphasis the importance of structural differences over chemical differences in determining whether a nature-based product is markedly different from its naturally-occurring counterpart.[291] In *Myriad*, the Supreme Court held that "Myriad did not create or alter either the genetic information encoded in the BRCA1 and BRCA2 genes or the genetic structure of the DNA."[292] Similar to the cDNA of *Myriad*, which was held to be patent eligible because of the removal of naturally present introns[293], the fusion of crRNA and tracrRNA here into a single RNA structure is a notable structural difference.

Second, the function of the claimed CRISPR system is different from the function of its naturally-occurring counterpart. The CRISPR system of bacteria such as *Streptococcus pyogenes*, acts as an immune system to help the bacteria defend against foreign invaders, such as viruses.[294] The type II CRISPR system incorporates segments of the invading virus DNA into its protospacer regions.[295] Further, naturally-occurring CRISPR of some bacteria wait until the foreign invader starts replicates before attacking.[296] In contrast, the claimed CRISPR system is not used as an immune system, but as a genome editing tool. Hence its function is different.

Also, instead of inserting a piece of foreign DNA into its system to defend against future attacks, the claimed CRISPR system is inserted into eukaryotic cells in order to recognize and cut target DNA sequences. Further, the purpose of modifying the dual RNA structure to a single RNA structure is to deliver foreign DNA (i.e. specific sequences of DNA) to specific target sites in the genome.[297] Programming a single RNA structure to target different DNA sequences is a markedly different characteristic consistent with the rationale of *Myriad* and *Roslin*. In *Roslin*, the Federal Circuit held that the clones did not have "markedly different characteristics from the donor animals" because the genetic information of the clones remained

289. Jinek, *supra* note 13, at 819-20; Hsu, *supra* note 287, at 827-32.
290. Jinek, *supra* note 13, at 819-20; Hsu, *supra* note 287, at 827-32.
291. Rantanen, *supra* note 208. *See* Krench, *supra* note 213.
292. *Ass'n for Molecular Pathology* 133 S. Ct. at 2109-10.
293. *Id*.
294. Zimmer, *supra* note 116.
295. Sander & Joung, *supra* note 29, at 349-50.
296. *A Newly Discovered Form of Immunity Helps Explain Viruses*, PHYS.ORG (Feb. 4, 2016), https://phys.org/news/2016-02-newly-immunity-bacteria-viruses.html#nRlv.
297. Jinek, *supra* note 13 at 819-21.

unchanged.[298] Unlike the clones in *Roslin*, the genetic information of the "DNA-targeting RNA"[299] in the claimed CRISPR system is different from its naturally-occurring counterpart because each "DNA-targeting RNA"[300] can incorporate different DNA sequences to target a specific sequence in the genome.

A narrow interpretation of recent case law has led some to conclude that the claimed CRISPR system does not possess markedly different characteristics from its naturally-occurring counterpart.[301] In *The Failure to Preserve CRISPR-Cas9's Patentability Post Myriad and Alice*, Tuttle points to the fact that the same Cas9 nuclease, crRNA, and tracrRNA found in nature are used in the engineered CRISPR system.[302] Further, Tuttle points out that in order to cut at target DNA sites, the "DNA-targeting RNA"[303] needs to incorporate a matching sequence that is identical to its naturally-occurring counterpart.[304] He elaborates that if this does not occur, the targeter RNA of the "DNA-targeting RNA"[305] will not recognize and bind to its target DNA sequence.[306] Although these are all valid points to be made, the Federal Circuit emphasized in the recent *CellzDirect* decision that the patent claim as a whole, that is, "the end result of the process," needs to be directed to a judicial exception in the first *Alice* step.[307] Although the type II CRISPR system itself is a natural phenomenon, and the individual components of the claimed CRISPR system can be found in nature, the claimed system as a whole is not naturally found in prokaryotes or eukaryotes. A court that finds the patent claim at issue to not be directed to a patent ineligible judicial exception will stop the eligibility inquiry here, and hold that the claim covering the CRISPR system is patent eligible subject matter under §101.[308]

If a court instead finds that the claimed CRISPR system contains no markedly different characteristics from its naturally-occurring counterpart, the eligibility inquiry will continue onto the second step under *Alice*. The

298. *In re Roslin Inst. (Edinburgh)*, 750 F.3d at 1339.

299. Notice to Declare Interference, *supra* note 274 at 11.

300. *Id*.

301. Tuttle, *supra* note 159 at 404 ("Given the recent case law, an application of the markedly-different analysis to each CRISPR component would likely lead a court to conclude that the claimed products-of-nature are not patent eligible.").

302. *Id*. at 404-05.

303. Notice to Declare Interference, *supra* note 274 at 11.

304. Tuttle, *supra* note 159, at 404.

305. Notice to Declare Interference, *supra* note 274 at 11.

306. Tuttle, *supra* note 159, at 404.

307. Rapid Litig. Mgmt. v. CellzDirect, Inc, 827 F.3d 1042, 1048 (2016).

308. *Id*. at 1047.

second step asks whether the patent claim recites additional elements that transform the judicial exception into a patent-eligible application of the exception (here, nature-based product).[309] In short, under this second step, there needs to be an inventive concept.[310] If a court did not find the patent claim covering the CRISPR system to be patent eligible under the first step of *Alice*, they will most certainly find it to eligible under the second step. First the patent claim at issue takes the naturally-occurring type II CRISPR system and implements it in a eukaryotic cell. Eukaryotic cells do not naturally have a CRISPR system.[311] Scientific literature from the Doudna (UCB) and Zhang (Broad) labs (as well as earlier scientists) illustrate that getting the naturally-found CRISPR system (dual RNA structure) to work in eukaryotic cells required human intervention.[312] Both the Doudna and Zhang publications illustrate the experiments both labs conducted in order to get the naturally-occurring CRISPR system (dual RNA structure) and claimed CRISPR system (single RNA structure) to properly function in eukaryotic cells.[313]

Second, scientists connected crRNA and tracrRNA to form a single RNA structure to use the claimed CRISPR system as a genome editing tool in eukaryotic cells.[314] This is similar to the improved process of preserving hepatocyte cells in *CellzDirect*. In *CellzDirect*, scientists discovered that a fraction of frozen hepatocyte cells could be reused again. [315] They subsequently patented an application of that discovery—an improved method of preserving hepatocytes for later use.[316] The Federal Circuit held that the scientists did not patent the discovery, but rather "as the first party with knowledge of the cells' ability, they were 'in an excellent position to claim applications of that knowledge.'"[317] In the same way, scientists at UCB and Broad discovered the function and mechanisms of the type II CRISPR system as an adaptive immune system. Instead of patenting this discovery, scientists patented applications of this discovery by claiming a genome editing tool. Hence, the patent claim at issue is arguably different from the

309. *Id*.
310. *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355.
311. Jinek, *supra* note 13, at 819.
312. *Id*.; Le Cong et al., *Multiplex Genome Engineering Using CRISPR/Cas Systems*, 339 SCI. 819-23 (2013).
313. *Id*.
314. *Id*.
315. Rapid Litig. Mgmt. v. CellzDirect, Inc., 827 F.3d 1042, 1048-49 (2016).
316. *Id*.
317. *Id*. at 1048.

personalized dosing process of *Mayo* as well as the prenatal genetic screening process of *Sequenom*. Unlike *Mayo* and *Sequenom*, the scientists here did not stop after discovering the natural phenomena, but worked to invent a patent eligible application of the phenomena. Further, the Supreme Court emphasized in *Alice* that the claim elements in the second step of the analysis need to be considered "both individually and in combination" as a whole.[318] Therefore, a court could reasonably conclude that the patent claim at issue, when considered as a whole, is a patent-eligible application of a judicial exception. Hence, the single count of the interference proceeding would be patent eligible subject matter under §101.

CONCLUSION AND CONSIDERATIONS BEYOND §101

Under modern patent law, the count ("hypothetical patent claim")[319] currently at the center of the USPTO interference proceeding would most likely be held as patent eligible subject matter. Many people question the ethical and moral implications of the patented CRISPR technology.[320] However, the current §101 framework does not take moral and ethical values into consideration. Others like Tuttle are concerned that these patents will impede rather than promote downstream research and innovation.[321] However, the hypothetical §101 invalidity dispute illustrates that under the modern *Alice* framework, the CRISPR-Cas9 technology of the Doudna/Zhang interference qualifies as patentable subject matter. Preemption concerns can be addressed outside the scope of §101 by raising §102 (novelty) and §103 (obviousness) issues. Hence, §101 will likely not be an issue in future invalidity challenges. Rather, it is highly probable that invalidity challenges as to §103 (obviousness) will be made in federal court.[322]

318. *Alice Corp. Pty. Ltd.*, 134 S. Ct. at 2355 n.3.

319. Sherkow, *supra* note 157, at 27.

320. Rob Stein, *Breaking Taboo, Swedish Scientist Seeks to Edit DNA of Healthy Human Embryos*, NPR (Sept. 22, 2016), http://www.npr.org/sections/health-shots/2016/09/22/494591738/breaking-taboo-swedish-scientist-seeks-to-edit-dna-of-healthy-human-embryos. *See* Robert Sanders, *CRISPR Inventor Calls for Pause in Editing Heritable Genes*, BERKELEY NEWS (Dec. 1, 2015), http://news.berkeley.edu/2015/12/01/crispr-inventor-calls-for-pause-in-editing-heritable-genes/.

321. Tuttle, *supra* note 159 at 404. *See* Shobita Parthasarathy, *CRISPR Dispute Raises Bigger Patent Issues That We're Not Talking About*, THE CONVERSATION (Apr. 4, 2016), http://theconversation.com/crispr-dispute-raises-bigger-patent-issues-that-were-not-talking-about-56715.

322. This prediction is based on the current interference proceeding between UCB and Broad because the question in the interference proceeding is whether it was obvious to implement CRISPR in eukaryotes based on Doudna's (UCB) disclosure of CRISPR in prokaryotes.

Further, it is important to note that the count only claims a CRISPR system that utilizes the Cas9 nuclease. Since the introduction of the CRISPR-Cas9 technology in 2012, scientists have worked to find a better alternative to Cas9.[323] In 2015, Zhang discovered Cpf1, a smaller and potentially more efficient nuclease than Cas9.[324] Researchers from UCB recently discovered CasX and CasY—two nucleases which are much smaller and potentially more useful than Cas9.[325] Further, researchers last year discovered a new CRISPR system, C2c2, which potentially allows researchers to edit RNA instead of DNA.[326] The CRISPR-Cas9 technology allows researchers to edit DNA and make permanent changes to a cell's genome.[327] C2c2, on the other hand, will allow researchers to target RNA and make temporary changes to a cell's genome.[328] Some of these researchers have filed patent applications over their improved CRISPR systems.[329] The outcome of the current interference proceeding will impact the scope of patent protection available to alternative genome editing tools based on the CRISPR-Cas9 technology.[330] Hence, future invalidity disputes over genome editing patents will most likely focus on §102 (novelty) and §103 (obviousness) issues rather than §101 issues.

323. Kristen V. Brown, *Why the Patent Battle Over CRISPR Matters (and Why It Doesn't)*, GIZMODO (Jan. 9, 2017), http://gizmodo.com/will-the-battle-over-the-biotech-discovery-of-the-centu-1790981150.

324. Mary Gearing, *Cpf1: A New Tool for CRISPR Genome Editing*, ADDGENE (Oct. 14, 2015), http://blog.addgene.org/cpf1-a-new-tool-for-crispr-genome-editing.

325. Kerry Grens, *New CRISPR-Cas Enzymes Discovered*, THE SCIENTIST (Dec. 22, 2016), http://www.the-scientist.com/?articles.view/articleNo/47845/title/New-CRISPR-Cas-Enzymes-Discovered/.

326. *Researchers Unlock New CRISPR System for Targeting RNA*, PHYS.ORG (June 2, 2016), https://phys.org/news/2016-06-crispr-rna.html. *See* Omar O. Abudayyeh et al., *C2c2 is a Single-component Programmable RNA-guided RNA-targeting CRISPR Effector*, 353 SCI.aaf5573 (2016), *available at* doi:10.1126/science.aaf5573.

327. Jinek, *supra* note 13, at 816.

328. *Researchers Unlock New CRISPR System for Targeting RNA*, *supra* note 326.

329. Lee McGuire, *What is the Key Issue with Respect to the CRISPR-Cas9 Patents?*, BROAD INST., https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-interfer (last visited Feb. 14, 2017).

330. Egelie et al., *supra* note 272 at 1029-30.