

Custom-Edited DNA: Legal Limits on the Patentability of CRISPR-Cas9'S Therapeutic Applications

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CUSTOM-EDITED DNA:
LEGAL LIMITS ON THE PATENTABILITY OF CRISPR-CAS9'S
THERAPEUTIC APPLICATIONS

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INTRODUCTION

Imagine a future where large corporations use CRISPR, a genetic editing tool, to modify almost every living thing.¹ Perfectly manicured lawns are comprised of genetically-modified grasses, people adore their genetically-modified pets, and parents select only the best traits to be carried by their genetically-modified children.² This is a future T. Coraghassen Boyle recently imagined in a short story in *The New Yorker*.³ In Boyle's story, genetic editing is supposed to lead to perfect happiness by removing all flaws from the natural world.⁴ The only catch is that the new, genetically perfect world feels wholly unnatural to some of the people living in it.⁵

The dystopian future envisioned in Boyle's story is fast becoming scientifically possible.⁶ (Whether it is ethically desirable is an entirely separate matter.⁷) CRISPR-Cas9, short for "Clustered Regularly Interspaced Short Palindromic Repeats" and "CRISPR-associated protein 9" is a genetic-editing technology that allows

1. This scenario comes from T. Coraghassen Boyle, *Are We Not Men?*, NEW YORKER (Nov. 7, 2016), <https://www.newyorker.com/magazine/2016/11/07/are-we-not-men> [<https://perma.cc/ZJG5-UF9P>].

2. *Id.*

3. *Id.*

4. *Id.* Boyle's description of how genetic editing could change reproduction is illustrative: What sort of child—that was the question. Previous generations had only to fret over whether the expectant mother would bear a boy or a girl or if the child would inherit Aunt Bethany's nose or Uncle Yuri's unibrow, but that wasn't the case anymore, not since CRISPR gene-editing technology had hit the ground running twenty years back. Now not only could you choose the sex of the child at conception; you could cho[o]se its other features, too, as if having a child were like going to the car dealership and picking which options to add onto the basic model. The sole function of sex these days was recreational; babies were conceived in the laboratory.

Id.

5. *Id.*

6. See, e.g., Paul Enríquez, *Genome Editing and the Jurisprudence of Scientific Empiricism*, 19 VAND. J. ENT. & TECH. L. 603 (2017) (providing—as he might put it—a sesquipedalian overview of the science behind genome editing, geared towards a legal audience).

7. See, e.g., Rebecca Cokley, *Please Don't Edit Me Out*, WASH. POST (Aug. 10, 2017), https://www.washingtonpost.com/opinions/if-we-start-editing-genes-people-like-me-might-not-exist/2017/08/10/e9adf206-7d27-11e7-a669-b400c5c7e1cc_story.html?utm_term=.22df9b9f32Dd [<https://perma.cc/CH3V-ARML>] (arguing that using genetic editing technologies to remove disabilities from the human genome is a short-sighted strategy that does not account for the valuable contributions that disabled people make to society).

scientists to edit DNA with a remarkable degree of accuracy.⁸ It is an advance on other genetic-editing technologies, which had limited programmability and, in turn, often caused off-target effects (edits to segments of DNA that the researcher was not trying to impact).⁹ Scientists continuously find new, creative uses of CRISPR-Cas9,¹⁰ and the technology is increasingly in the public eye.¹¹ The FDA recently issued a press release warning consumers that the sale of “do it yourself” CRISPR kits is against the law due to safety concerns about CRISPR-Cas9-mediated gene therapies.¹² Chinese scientists reported in October of 2016 that they had injected a lung cancer patient with cells modified by CRISPR-Cas9,¹³ scientists at Oregon Health & Science University reported in August of 2017 that they had made CRISPR-mediated repairs to non-viable human

8. See Taeyoung Koo & Jin-Soo Kim, *Therapeutic Applications of CRISPR RNA-Guided Genome Editing*, 16 BRIEFINGS FUNCTIONAL GENOMICS 38, 38, 43 (2017).

9. Samuel H. Sternberg & Jennifer A. Doudna, *Expanding the Biologist's Toolkit with CRISPR-Cas9*, 58 MOLECULAR CELL 568, 569 (2015).

10. See, e.g., Heidi Ledford, *Lights, Camera, CRISPR: Biologists Use Gene Editing to Store Movies in DNA*, NATURE (July 12, 2017), <http://www.nature.com/news/lights-camera-crispr-biologists-use-gene-editing-to-store-movies-in-dna-1.22288> [<https://perma.cc/Q9YV-SBTB>] (describing how scientists used CRISPR-Cas9 “to encode a movie into the genome of the [*E. coli* bacteria]”).

11. A Google Alert return for “CRISPR Cas9” from October 10, 2017, is instructive. It included, among many others, links to Steve Dent, *Anti-Doping Agency to Ban Gene Editing Starting in 2018*, ENGADGET (Oct. 10, 2017), <https://www.engadget.com/2017/10/10/wada-banning-sports-gene-editing-doping/> [<https://perma.cc/ZU9D-CR7B>] (describing the World Anti-Doping Agency's plan to ban “gene editing agents designed to alter genome sequences”); *Gene Drives Have the Potential to Suppress Mosquito Populations*, ECON. TIMES (Oct. 10, 2017, 10:35 AM), <https://health.economictimes.indiatimes.com/news/industry/gene-drives-have-the-potential-to-suppress-mosquito-populations/61016289> [<https://perma.cc/PUG7-B797>] (describing attempts by researchers to reduce fertility in female mosquitos using CRISPR editing); Skakel McCooey, *Yale Study Sheds New Light on Limb Regeneration*, YALE DAILY NEWS (Oct. 10, 2017), <https://yaledailynews.com/blog/2017/10/10/yale-study-sheds-new-light-on-limb-regeneration/> [<https://perma.cc/A6FR-FE8Q>] (describing a paper published by Yale researchers who used CRISPR to study limb regeneration in salamanders).

12. Press Release, Food & Drug Admin., Information About Self-Administration of Gene Therapy (Nov. 21, 2017) (available at <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm586343.htm>) [<https://perma.cc/P7BV-RKAU>].

13. See David Cyranoski, *CRISPR Gene-Editing Tested in a Person for the First Time*, NATURE (Nov. 15, 2016), <http://www.nature.com/news/crispr-gene-editing-tested-in-a-person-for-the-first-time-1.20988> [<https://perma.cc/9PAW-WZFA>]. At least 86 Chinese patients have had their genes edited by CRISPR-Cas9 so far. Preetika Rana et al., *China, Unhampered by Rules, Races Ahead in Gene-Editing Trials*, WALL STREET J. (Jan. 21, 2018, 2:19 PM), <https://www.wsj.com/articles/china-unhampered-by-rules-races-ahead-in-gene-editing-trials-1516562360?mg=prod/accounts-wsj> [<https://perma.cc/GDZ5-KK4Y>].

embryos,¹⁴ and human trials of a CRISPR-based treatment for a blood disorder will begin in Europe in 2018.¹⁵

Most of the legal scholarship on CRISPR-Cas9 has focused on the patent dispute between the University of California and The Broad Institute,¹⁶ on how the use of CRISPR should be regulated,¹⁷ or on the ethical concerns about how CRISPR should be used.¹⁸ Legal scholarship has not yet addressed the question that this Note seeks to answer: are therapeutic applications of CRISPR-Cas9 patentable? Previous articles have examined the patentability of the processes required to make CRISPR-Cas9 and transcribe it into other organisms, but have not examined the patentability of

14. Lauren Neergaard, *First Embryo Gene-Repair Holds Promise for Inherited Disease*, ASSOCIATED PRESS (Aug. 2, 2017), <https://apnews.com/fcf52fde924d430ca9441aa401c259ed/First-embryo-%20gene-repair-holds-promise-for-inherited-disease> [<https://perma.cc/S26K-4VNQ>].

15. Clara Rodríguez Fernández, *CRISPR Therapeutics Plans First CRISPR/Cas9 Clinical Trial in Europe for 2018*, LABIOTECH.EU (Dec. 13, 2017), <https://labiotech.eu/crispr-therapeutics-clinical-trials/> [<https://perma.cc/3MCR-54FQ>].

16. See Kristin Beale, *The CRISPR Patent Battle: Who Will be “Cut” out of Patent Rights to One of the Greatest Scientific Discoveries of our Generation?*, 2015 B.C. INTELL. PROP. & TECH. F. 1, <http://bciptf.org/wp-content/uploads/2016/02/KBeale-CRISPR.pdf> [<https://perma.cc/W5Z5-NY4U>]; James W. Sanner, Note, *The Struggle for CRISPR: A Billion Dollar Question in Intellectual Property*, 2016 U. ILL. J.L. TECH. & POL’Y 431 (2016). The patent dispute between the Broad Institute and the University of California began in 2013, when both entities filed for patents on CRISPR-based genetic editing systems. *Broad Inst., Inc. v. Regents of the Univ. of Cal.*, No. 106,048 (DK) (P.T.A.B. Feb. 15, 2017). The University of California, which was first to file for the patent, filed a patent interference claim, alleging that Broad’s application of CRISPR editing techniques to eukaryotic cells was an obvious application of the University’s patented process. *Id.* The Patent Trial and Appeal Board (PTAB) sided with Broad, finding that their use of CRISPR in eukaryotic cells was non-obvious, and therefore did not interfere with the University of California’s patent. *Id.* The University of California appealed this decision to the Federal Circuit, which affirmed the PTAB. *Regents of the Univ. of Cal. v. Broad Inst., Inc.*, No. 2017-1907, 2018 WL 4288968, at *1 (Fed. Cir. Sept. 10, 2018).

17. See Evita V. Grant, *FDA Regulation of Clinical Applications of CRISPR-CAS Gene Editing Technology*, 71 FOOD & DRUG L.J. 608, 609 (2016); Sarah Ashley Barnett, Comment, *Regulating Human Germline Modification in Light of CRISPR*, 51 U. RICH. L. REV. 553, 555 (2017); Teddy Ellison, Note, *Why Genetics is CRISPR Than It Used to Be: Helping the Novice Understand Germ Line Modification and its Serious Implications*, 26 S. CAL. INTERDIS. L.J. 595, 596 (2017); Adam J. Gross, Comment, *Dr. Frankenstein, Or: How I Learned to Stop Worrying and Love CRISPR-Cas9*, 56 JURIMETRICS J. 413, 414 (2016).

18. See G. Edward Powell III, *Embryos as Patients? Medical Provider Duties in the Age of CRISPR/Cas9*, 15 DUKE L. & TECH. REV. 344, 346 (2017); Natalie Ram, *Science as Speech*, 102 IOWA L. REV. 1187, 1193 (2017); Tara R. Melillo, Note, *Gene Editing and the Rise of Designer Babies*, 50 VAND. J. TRANSNAT’L L. 757, 762 (2017); Ellison, *supra* note 17.

CRISPR-Cas9 systems in the context of providing medical care by editing viral, bacterial, or human DNA.¹⁹

It is not clear that these CRISPR-Cas9 applications would qualify as patentable subject matter under the traditional tests for patentability.²⁰ This issue is further complicated because federal law prevents patents from issuing “on a claim directed to or encompassing a human organism,” and it is not obvious whether CRISPR-Cas9 systems cross that line.²¹ The legislative history of the Act suggests that Congress designed this provision to prevent “human embryos and fetuses” from being patented.²² However, the law’s authors *did* intend that “genes, stem[] cells, [and] animals with human genes” would remain patentable.²³ This suggests that researchers seeking to create scalable CRISPR-Cas9 treatments for a broad range of human ailments will have to do more than simply convince the FDA that their therapy is safe²⁴: they will also likely have to litigate the question of whether their treatment is patentable subject matter under current federal law.

This Note seeks to answer that question, and concludes that while antibacterial and antiviral CRISPR-Cas9 treatments are patentable, treatments that edit somatic or germline cells are not. Part I will provide biological context, explaining what CRISPR-Cas9 is, how it

19. See *supra* notes 16-18 and accompanying text. This Note focuses on CRISPR-Cas9’s potential as a *treatment* for human illness. CRISPR-Cas9 can also be used to *detect* illnesses. See Janice S. Chen et al., *CRISPR-Cas12a Target Binding Unleashes Indiscriminate Single-Stranded DNase Activity*, SCIENCE (Feb. 15, 2018), <http://science.sciencemag.org/content/early/2018/02/14/science.aar6245.full.pdf> [<https://perma.cc/YMC8-HUQR>] (describing a CRISPR-Cas9 variant that “enables rapid and specific detection of human papillomavirus”); Jonathan S. Gootenberg et al., *Multiplexed and Portable Nucleic Acid Detection Platform With Cas13, Cas12a, and Csm6*, SCIENCE (Feb. 15, 2018), <http://science.sciencemag.org/content/sci/early/2018/02/14/science.aaq0179.full.pdf> [<https://perma.cc/4JJK-RUK6>] (describing CRISPR-Cas9 variants that “can detect Dengue or Zika virus”).

20. See *infra* Part II.A.

21. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

22. See MANUAL OF PATENT EXAMINING PROCEDURE § 2105 (9th ed. 2015), which noted that the legislative history provides some clarity as to the meaning of the AIA. The Manual quotes a statement that observes that “[t]he U.S. Patent Office has already issued patents on genes, stems cells, animals with human genes, and a host of non-biologic products used by humans, but it has not issued patents on claims directed to human organisms, including human embryos and fetuses.” *Id.* (quoting 157 CONG. REC. E1177-04 (2011) (statement of Rep. Weldon)).

23. *Id.*

24. See Food & Drug Admin., *supra* note 12.

differs from other genetic editing technologies, and how it may be used as a treatment for human illness in the future. Part II will provide legal context, explaining the current legal landscape for patents based on human biology. Part II will also provide a background on U.S. patent law, describe the patentability of embryos, DNA, and stem cells, and summarize some of the scholarship on the patentability of CRISPR-Cas9.

Part III will attempt some line-drawing. Are CRISPR-based treatments patentable? Are they too directed at a human organism to be patented? Does the answer change depending on the therapeutic use the DNA is put to? Part III will conclude that CRISPR-Cas9 systems used to treat viral or bacterial infections are patentable because they are analogous to non-biologic drugs, but CRISPR-Cas9 systems used to alter genetic mutations or for germline therapies are not patentable because they are directed at a human organism. Part IV considers and rejects some counterarguments to the normative framework outlined in Part III.

I. SCIENTIFIC BACKGROUND

In order to be patentable, an invention must be, among other things, a “new and useful,”²⁵ “novel [],”²⁶ and “non-obvious”²⁷ thing or process.²⁸ To determine whether an invention meets these requirements, a patent examiner looks at the “prior art”²⁹—the scientific background that undergirds the patent application.³⁰ Because the scientific background is useful not just for determining whether CRISPR-Cas9 is patentable, but also for defining precisely what it is, this Part will provide a basic introduction to CRISPR-Cas9 and its therapeutic applications.

25. 35 U.S.C. § 101 (2012).

26. *Id.* § 102.

27. *Id.* § 103.

28. *Id.* § 101.

29. *See, e.g., id.* § 102.

30. In patent law, the prior art is “[k]nowledge that is publicly ... available on the date of invention[,] to a person of ordinary skill” in that field. *Prior Art*, BLACK’S LAW DICTIONARY (9th ed. 2009).

A. What is CRISPR-Cas9?

Scientists have been using genome-editing technologies since 1994.³¹ Genome-editing technologies “give scientists the ability to change an organism's DNA.”³² The three genome-editing technologies primarily in use today are zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR-Cas9.³³ Of these three, CRISPR-Cas9 has the greatest therapeutic potential because it is the most scalable—when compared to ZFNs and TALENs, CRISPR-Cas9 systems are cheap, easy to produce, efficient, and can easily be tailored to edit multiple genes at a single time.³⁴

CRISPR are short sequences of DNA that code for a guide RNA (gRNA) that is then paired with a CRISPR-associated (Cas) protein, an enzyme³⁵ that acts like a pair of molecular scissors and cleaves³⁶

31. See Philippe Rouet et al., *Introduction of Double-Strand Breaks into the Genome of Mouse Cells by Expression of a Rare-Cutting Endonuclease*, 14 *MOLECULAR & CELLULAR BIOLOGY* 8096, 8096 (1994).

32. Nat'l Inst. of Health, *What are Genome Editing and CRISPR-Cas9?*, GENETICS HOME REFERENCE (June 5, 2018), <https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting> [<https://perma.cc/V2LQ-BK9Q>].

33. Thomas Gaj et al., *Genome-Editing Technologies: Principles and Applications*, *COLD SPRING HARBOR PERSP. BIOLOGY* 1, 1 (2016), <http://cshperspectives.cshlp.org/content/8/12/a023754.full> [<https://perma.cc/4NQB-9SSZ>]. While scientists have been using genome-editing technologies for decades, these three represent a significant advance over prior technology because they can target specific sites on DNA. *Id.* at 7. “Before the emergence of [these technologies], genetically modifying mammalian cell lines was labor intensive, costly, and often times limited to laboratories with specialized expertise. However, with the advent of cost-effective and user-friendly gene-editing technologies, custom cell lines carrying nearly any genomic modification can now be generated ... simply.” *Id.*

34. *E.g.*, Jim Yeadon, *Pros and Cons of ZNFs, TALENs, and CRISPR/Cas*, JACKSON LABORATORY, <https://www.jax.org/news-and-insights/jax-blog/2014/march/pros-and-cons-of-znfs-talens-and-crispr-cas> [<https://perma.cc/BS84-WZ4U>].

35. An enzyme is a protein produced by a cell to facilitate a chemical reaction (in this case, breaking the bonds that hold the DNA molecule together). *Enzyme*, *BIOLOGY ONLINE DICTIONARY*, <https://www.biology-online.org/dictionary/Enzyme> [<https://perma.cc/A5ZD-MLXP>].

36. In genetics, “cleave” indicates a chemical reaction that cuts a larger molecule into smaller ones. *Cleavage*, *BIOLOGY ONLINE DICTIONARY*, <https://www.biology-online.org/dictionary/Cleavage> [<https://perma.cc/46LY-NN6M>].

target DNA at very specific locations in the genome.³⁷ The gRNA steers the Cas to the appropriate cutting site on the target DNA.³⁸

CRISPR-Cas9 originally evolved as an immune response in bacteria; it protected the bacteria from viral infection.³⁹ The bacteria would incorporate short sequences of DNA from viruses that had infected them into their own genetic code.⁴⁰ The bacteria could then use the incorporated viral DNA to create an “immune memory” that helped it recognize an infection from the same virus in the future.⁴¹ The incorporated viral DNA would be used as a model for a gRNA.⁴² That gRNA could then guide a Cas9 to the virus, in order to destroy it.⁴³ The gRNA would direct the Cas9 to the target site on the virus’s DNA, where the Cas9 would create a double-strand break in the viral DNA, destroying it and ending the infection.⁴⁴

CRISPR-Cas9 was first discovered in 2000 by researchers in Spain,⁴⁵ but its genetic editing potential was not publicly recognized until 2012, when scientists at the University of California, Berkeley published a paper in the journal *Science* detailing the first complete catalogue of the CRISPR-Cas9 system as found in bacteria.⁴⁶

37. See Koo & Kim, *supra* note 8, at 38. For images of Cas9 at work, see Mikihiro Shibata et al., *Real-Space and Real-Time Dynamics of CRISPR-Cas9 Visualized by High-Speed Atomic Force Microscopy*, 8 NATURE COMM. 1, 2 (2017), <https://www.nature.com/articles/s41467-20%017-01466-8.pdf> [<https://perma.cc/3C2M-2SE3>]. The full video is available in GIF format on the Twitter page of one of the paper’s authors. Hiroshi Nishimasu (@hnisimasu), TWITTER (Nov. 10, 2017, 5:32 AM), <https://twitter.com/hnisimasu/status/928933260159197184> [<https://perma.cc/3LVF-ETJV>]. An article published in *The Atlantic* includes an excellent breakdown of the video, with screen captures that show CRISPR-Cas9 creating a double-strand break in the DNA. Sarah Zhang, *An Astonishing Video Shows CRISPR Editing DNA in Real Time*, ATLANTIC (Nov. 13, 2017), <https://www.theatlantic.com/science/archive/2017/11/crispr-video-real-time/545603/> [<https://perma.cc/57VE-YLHG>].

38. Koo & Kim, *supra* note 8, at 38.

39. Sternberg & Doudna, *supra* note 9, at 568.

40. Rodolphe Barrangou, *The Roles of CRISPR—Cas Systems in Adaptive Immunity and Beyond*, 32 CURRENT OPINION IMMUNOLOGY 36, 36-37 (2015).

41. *Id.* at 36. This is similar to the way that human antibodies work. *Id.*; see also *The Defense Mechanisms of the Adaptive Immune System*, PUBMED HEALTH, <https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072581/> [<https://perma.cc/C7GE-JSM7>].

42. Barrangou, *supra* note 40, at 36-37.

43. *Id.*

44. *Id.* For images of this process, see Shibata et al., *supra* note 37, at 2-3.

45. See Francisco J.M. Mojica et al., *Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements*, 60 J. MOLECULAR EVOLUTION 174, 174 (2004).

46. Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816, 820 (2012).

CRISPR-Cas9 is incredibly useful as a genetic editing tool because it is highly accurate.⁴⁷ Because the CRISPR-Cas9 gRNA is twenty nucleotides⁴⁸ long, and each nucleotide will pair exactly with a nucleotide on the target DNA, there is less than a one in one trillion chance that the Cas9 will cleave the DNA at the wrong site.⁴⁹ Cleaving DNA at only the intended target site is critical because any off-target editing⁵⁰ risks damaging functioning DNA and creating serious, potentially lethal side-effects.⁵¹

CRISPR-Cas9's enormous therapeutic potential does not derive merely from the fact that it can damage DNA at very specific places.⁵² This capacity by itself is not unique, or even necessarily very helpful.⁵³ After all, what frequently makes carcinogens

47. See, e.g., Yeadon, *supra* note 34.

48. Koo & Kim, *supra* note 8, at 38.

49. DNA is comprised of four nucleotides: adenine, cytosine, guanine, and thymine. *Nucleotides and Bases*, GENETICS GENERATION, <http://knowgenetics.org/nucleotides-and-bases/> [<https://perma.cc/92NY-BN8N>]. Each nucleotide pairs with exactly one other nucleotide. *Id.* Thus there is a one in four chance that a single nucleotide of the gRNA will match with a nucleotide of the target DNA. See *id.* Since $(1/4)^{20} = 1/1,099,511,600,000$, there is a less than one in one trillion chance that the target DNA would contain two twenty-nucleotide sequences that are exactly the same. Of course, this assumes that DNA nucleotides are arranged randomly. In fact, scientists have found that many nucleotide sequences are repeated throughout the genome, and that these repeated sequences can serve important functions. E.g., James A. Shapiro & Richard von Sternberg, *Why Repetitive DNA is Essential to Genome Function*, 80 *BIOLOGICAL REVIEWS* 227, 243 (2005). Indeed, CRISPR's name itself reveals that nucleotide sequences are not randomly distributed: remember that CRISPR is an acronym for "clustered regularly interspaced short palindromic repeats." Koo & Kim, *supra* note 8, at 38.

50. In the genetics context, off-target editing occurs when a genetic editing technology "produce[s] unwanted DNA mutations at sites other than the desired target." Sue McGreevey, *Off-Target Gene Editing*, HARV. MED. SCH. (June 25, 2013), <https://hms.harvard.edu/news/genetics/target-gene-editing-6-25-13> [<https://perma.cc/RAP4-U9KE>].

51. See Koo & Kim, *supra* note 8, at 39, 43. Compare Kellie A. Schaefer et al., *Unexpected Mutations After CRISPR-Cas9 Editing in vivo*, 14 *NATURE METHODS* 547, 547-48 (2017) (reporting a study that purportedly showed thousands of off-target genetic mutations allegedly caused by CRISPR-Cas9 in mice treated with the technology), with Vivek Iyer et al., *No Unexpected CRISPR-Cas9 Off-Target Activity Revealed by Trio Sequencing of Gene-Edited Mice* 5 (Feb. 9, 2018) (unpublished manuscript) (available at <https://www.biorxiv.org/content/early/2018/02/09/263129.full.pdf+html>) [<https://perma.cc/4FW4-9QEJ>] (concluding that any off-target mutations in mice treated by CRISPR-Cas9 are not statistically significant from the background level of mutation found in mice untreated by CRISPR-Cas9).

52. See Koo & Kim, *supra* note 8, at 39-42. This is not to say that this aspect of CRISPR-Cas9 is not useful. The mere destruction of DNA can be very useful as a treatment for viral and bacterial infections. See *id.*; *infra* Parts I.B.1, I.B.2.

53. See Yeadon, *supra* note 34.

carcinogenic is their ability to damage DNA.⁵⁴ CRISPR-Cas9 has enormous therapeutic potential because its highly specific cutting ability targets extremely specific sequences of DNA, and can be paired with processes that insert desirable DNA at the target site, creating the potential to replace a defective gene with a functioning one.⁵⁵ This means that CRISPR-Cas9 could serve as a cure to not just infectious diseases, but also inherited ones.⁵⁶

Recent research by scientists at Stanford University indicates that CRISPR-Cas9 in its current iteration may have limited effectiveness in treating human disease.⁵⁷ The researchers discovered that because Cas9 (the cutting protein) is present in bacteria that frequently infect humans, we may have developed an immune response to it.⁵⁸ However, the scientists concede that while their study is an important reminder to be cautious with CRISPR-Cas9, it is “not a deal-breaker, even for people with immunity to [Cas9], because there are other [cutting] proteins that could be adapted to do the job.”⁵⁹ The researchers also cautioned that their results only implicate therapeutic applications of CRISPR-Cas9 where the Cas9 protein may come in contact with the human immune system.⁶⁰ Indeed, “[s]ome of the first human experiments in the U.S. ... will use the Cas9 proteins on blood cells *outside* the body, so there’s little chance the immune system will cause any trouble.”⁶¹ In the meantime, researchers can work to determine the most effective means of deploying CRISPR-Cas9 as a therapy.⁶²

54. See *Known and Probable Human Carcinogens*, AM. CANCER SOC’Y (Nov. 3, 2016), <https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html> [<https://perma.cc/4KPC-25DE>].

55. Yeadon, *supra* note 34.

56. Koo & Kim, *supra* note 8, at 40.

57. See Carsten T. Charlesworth et al., Identification of Pre-Existing Adaptive Immunity to Cas9 Proteins in Humans 2-3 (Jan. 5, 2018) (unpublished manuscript) (available at <https://www.biorxiv.org/content/biorxiv/early/2018/01/05/243345>) [<https://perma.cc/MLJ3-VZ6A>].

58. *Id.* at 5-6.

59. Faye Flam, *Scientists Don’t Fear a New Crispr Snag*, BLOOMBERG (Jan. 23, 2018, 3:27 PM), <https://www.bloomberg.com/view/articles/2018-01-23/gene-scientists-don-t-fear-the-latest-crispr-snag> [<https://perma.cc/SFL9-US4M>].

60. *Id.*; see also Charlesworth et al., *supra* note 57, at 7 (“Pre-existing adaptive immune responses may be of less concern for *ex vivo* therapies that involve the use of Cas9 to edit cells outside of direct contact with the human immune system.”).

61. Flam, *supra* note 59 (emphasis added).

62. See *id.*

B. Therapeutic Applications

CRISPR-Cas9 could be used to treat human illness and disease⁶³ in four basic ways: it has potential to (1) combat viral infections, (2) fight bacterial infections, (3) edit somatic (non-germline)⁶⁴ cells, and (4) edit germline cells.⁶⁵ Each therapeutic application could be immensely important. Using CRISPR to treat viral infections could mean a cure to HIV/AIDS.⁶⁶ Using it to treat bacterial infections could mean a solution to antibiotic-resistant tuberculosis.⁶⁷ Editing somatic cells using CRISPR could mean an end to muscular dystrophy, or a cure for cancer.⁶⁸ Editing germline cells could mean an end to infertility and a preemptive cure for all inheritable genetic diseases.⁶⁹

1. Viral Infections

Using CRISPR-Cas9 to treat viral infections such as HIV is “one of the promising new approaches in gene therapy.”⁷⁰ Researchers have used CRISPR-Cas9 to treat a variety of viruses, including HIV, HPV, herpes, and hepatitis B.⁷¹ Treatment works in one of two ways: “Cas9 can target [either] viral genes or host genes that encode essential receptors to suppress infection [by] viruses.”⁷² Human clinical trials using ZFNs, another genome-editing treatment, have proved effective at treating HIV.⁷³ Laboratory trials using CRISPR-

63. As described above, this Note focuses on the use of CRISPR-Cas9 to *treat* human illnesses, and not on its use in *detecting* human illness. See *supra* note 19.

64. For more on the difference between somatic and germline cells, see Himanshu Bhatia, *Stem Cells*, ROSWELL PARK CANCER INST., https://www.roswellpark.org/sites/default/files/Bhatia_11_8_12.pdf [<https://perma.cc/E386-RH6C>]. Essentially, somatic cells are the cells that are found in the vast majority of our organs, whereas germline cells are “the cells that are responsible for reproduction,” such as egg and sperm cells. *Id.*

65. Koo & Kim, *supra* note 8, at 39.

66. *See id.* at 39, 41.

67. *See id.* at 40; M. Doerflinger et al., *CRISPR/Cas9—The Ultimate Weapon to Battle Infectious Diseases?*, CELLULAR MICROBIOLOGY, no. 19, Feb. 2017, at 3, <https://onlinelibrary-wiley-com.proxy.wm.edu/doi/full/10.1111/cmi.12693> [<https://perma.cc/U9FD-PY6F>].

68. *See* Koo & Kim, *supra* note 8, at 40, 43.

69. *See id.* at 40.

70. *Id.* at 39.

71. *Id.* at 39, 41.

72. *Id.* at 39.

73. *Id.*

Cas9 to treat viruses have also been effective, but in some trials in which researchers targeted only one HIV gene, the virus managed to evolve into a CRISPR-Cas9-resistant mutant.⁷⁴ Researchers have suggested that the most effective CRISPR-Cas9 treatments for viral infections will target multiple genes to ensure complete removal of the virus.⁷⁵

CRISPR-Cas9 has already been used to cure HIV (although not in humans).⁷⁶ The scientists in that study used three different populations of HIV-infected lab mice, “including a ‘humanized’ [population,] where human immune cells infected with the virus were transplanted in lab mice.”⁷⁷ The CRISPR-Cas9 treatment proved effective in all three populations; the treatment removed the HIV DNA from all of the mice.⁷⁸ Buoyed by their success, the researchers hope to transition next to trials in primates, with the ultimate goal of beginning human trials by 2020.⁷⁹

Scientists at Temple University have already demonstrated that CRISPR-Cas9 can also be used to effectively cure HIV in human cells.⁸⁰ They used CRISPR-Cas9 to remove the entire HIV gene from infected human immune cells in laboratory conditions.⁸¹ It is important to note that these were not clinical trials; the tests were conducted on cell cultures (groups of cells grown outside the body) in a lab.⁸² Nonetheless, the tests are an important step forward in using CRISPR-Cas9 to treat HIV.

74. *Id.* at 40.

75. *Id.*

76. Brian Mastroianni, *Researchers Use Gene Editing to Eliminate HIV Infection in Mice*, CBS NEWS (May 3, 2017, 10:46 PM), <https://www.cbsnews.com/news/gene-editing-crispr-remove-hiv-infection-in-mice/> [<https://perma.cc/WFX8-MD3Y>].

77. *Id.*

78. *Id.*

79. See Dan Avery, *How a Transplant “Cured” This Man of HIV*, NEWNOWNEXT (Nov. 12, 2017), www.newnownext.com/how-a-transplant-cured-this-man-of-hiv/11/2017/ [<https://perma.cc/4M94-HX33>]; Mastroianni, *supra* note 76.

80. Rafal Kaminski et al., *Elimination of HIV-1 Genomes from Human T-lymphoid Cells by CRISPR/Cas9 Gene Editing*, 6 SCI. REP. 1, 10 (2016).

81. *Id.* at 2.

82. *Id.*

2. Bacterial Infections

CRISPR-Cas9 could be used to treat bacterial infections by “target[ing] bacterial genes and thereby inhibit[ing] bacterial growth.”⁸³ This is a particularly potent therapy when deployed against antibiotic-resistant bacteria, which cannot be effectively treated using standard medicines.⁸⁴ DNA encoding the CRISPR-Cas9 treatment is delivered to the bacteria through a specially engineered virus.⁸⁵ This style of treatment is especially advantageous because the CRISPR-Cas9 system is designed to target only bacterial genes.⁸⁶ Therefore, there is reduced risk that the Cas9 will damage human DNA, which does not contain the bacterial DNA sequence.⁸⁷

Researchers at Harvard University have already demonstrated that CRISPR-Cas9 can be used to kill antibiotic-resistant tuberculosis in laboratory conditions.⁸⁸ The scientists initially wanted to pair the Cas9 already present in tuberculosis cells with a custom gRNA to initiate gene knockdowns that would kill the bacteria.⁸⁹ However, they discovered that this was not an efficient treatment.⁹⁰ Instead, they used Cas9 from another bacteria, which they discovered “typically achieves 20-100 fold knockdown of [tuberculosis] gene expression.”⁹¹

Scientists in China have demonstrated another way to use CRISPR-Cas9 to *prevent* tuberculosis: editing tuberculosis resistance genes into an animal’s genome.⁹² The researchers used a

83. Koo & Kim, *supra* note 8, at 40.

84. *See id.*

85. *Id.*

86. *Id.*

87. *Id.*

88. Jeremy M. Rock et al., *Programmable Transcriptional Repression in Mycobacteria Using an Orthogonal CRISPR Interference Platform*, 2 NATURE MICROBIOLOGY 1, 4 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5302332/pdf/nihms838633.pdf> [<https://perma.cc/VWN9-UZJJ>]; *see also* Atul K. Singh et al., *Investigating Essential Gene Function in Mycobacterium tuberculosis Using an Efficient CRISPR Interference System*, 44 NUCLEIC ACIDS RES., no. 18, July 2016, at 2, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5062980/> [<https://perma.cc/X3FF-38BA>] (describing similar results).

89. Rock et al., *supra* note 88, at 2-3.

90. *Id.*

91. *Id.*

92. *Tuberculosis-Resistant Cows Developed for the First Time Using CRISPR Gene-Editing Technology*, PHYS.ORG (Jan. 31, 2017), <https://phys.org/news/2017-01-tuberculosis-resistant-cows-crispr-technology.html> [<https://perma.cc/AN5L-RY2L>].

variant of CRISPR-Cas9 called CRISPR-Cas9n to insert a tuberculosis-resistant gene into a cow's reproductive cell.⁹³ That cell was then combined with a regular cow egg, forming a fetus that was nurtured in a lab before it was inserted into a cow that then had a regular pregnancy.⁹⁴ When the genetically altered cows were later infected with tuberculosis, they showed a greater resistance to it than animals that had an unedited genome.⁹⁵ This is an example of using CRISPR-Cas9 germline editing to achieve antibiotic effects.⁹⁶

3. *Editing Somatic Cells*

Researchers have conducted numerous studies testing CRISPR-Cas9 systems designed to edit genetic diseases out of human cells.⁹⁷ Since CRISPR-Cas9 does not naturally occur in human cells, the gRNA and Cas9 either need to be delivered to the cells directly, or DNA coding for them needs to be inserted into the DNA of the cells so that the cells themselves *produce* the gRNA and the Cas9.⁹⁸ Delivering the gRNA/Cas9 complex directly to the cells has many advantages, because then the cells' defenses destroy the complex within 24 hours, which helps to limit off-target effects.⁹⁹ However, this delivery method has only limited success (because not all cells obtain the Cas9/gRNA complex), so viral delivery is widely considered to be the superior method.¹⁰⁰

Scientists at the University of California, Berkeley, announced in 2017 that they had successfully used CRISPR-Cas9 to repair the mutation that causes muscular dystrophy in mice.¹⁰¹ The scientists injected mice that had muscular dystrophy with a CRISPR-Cas9 variant called CRISPR-Gold, a new CRISPR delivery mechanism

93. *Id.*

94. *Id.*

95. *Id.*

96. *See infra* Part I.B.4.

97. Koo & Kim, *supra* note 8, at 40.

98. *Id.*

99. *Id.* The longer the complex is active in the cell, the greater the chances that it could create an off-target effect. *See id.*

100. *Id.*

101. Brett Israel, *CRISPR-Gold Fixes Duchenne Muscular Dystrophy Mutation in Mice*, BERKELEYNEWS (Oct. 3, 2017), <http://news.berkeley.edu/2017/10/03/crispr-gold-fixes-duchenne-muscular-dystrophy-mutation-in-mice/> [<https://perma.cc/DD35-88U2>].

that they had designed.¹⁰² The benefit of the CRISPR-Gold delivery mechanism is that it effectively transports the Cas9/gRNA complex into the cell intact, vitiating the need for a viral delivery mechanism.¹⁰³ Researchers found that the CRISPR-Gold treatment “led to an 18-times-higher correction rate and a two-fold increase in a strength and agility test [in treated mice when] compared to control groups.”¹⁰⁴

4. *Editing Germline Cells*

CRISPR-Cas9 could also be used to edit germline cells.¹⁰⁵ The process works in a largely similar manner to edits made to somatic cells.¹⁰⁶ The CRISPR-Cas9 complex is injected into the sperm or egg cells, or into the embryo very shortly after fertilization.¹⁰⁷ Because the injection occurs so early in the life of the organism, the hope is that the corrected DNA will spread to most or all of the cells as the newly fertilized egg begins to divide.¹⁰⁸ This treatment method can sometimes be ineffective due to “mosaicism,” when the DNA edits are present in some of the cells, but not others.¹⁰⁹ Researchers studying mice have found two to one hundred percent of cells in germline edited mice expressed the target sequence of DNA, rather than the corrected sequence that the scientists were *trying* to insert.¹¹⁰ Editing germline cells also leads to the possibility that edited DNA could be passed on to the next generation.¹¹¹ If edited DNA is expressed in cells that manufacture sperm or eggs, then the genetic edits will be passed on to future generations.¹¹²

102. *Id.*

103. *Id.* This was ground-breaking news, because all CRISPR-Cas9 treatments must be able to enter cells in order to be effective. *See generally* Koo & Kim, *supra* note 8.

104. Israel, *supra* note 101.

105. Koo & Kim, *supra* note 8, at 40. This is where moral opponents of CRISPR take their firmest stand. *See* Cokley, *supra* note 7.

106. Koo & Kim, *supra* note 8, at 40.

107. *Id.*

108. *See id.*

109. *Id.*

110. *Id.*

111. *Id.*

112. *See id.*

In a study similar to the one conducted by the Berkeley muscular dystrophy researchers, scientists at the University of Texas used CRISPR-Cas9 to cure muscular dystrophy in mice.¹¹³ These researchers, however, injected newly fertilized mouse eggs that had the muscular dystrophy genes with the CRISPR-Cas9 system.¹¹⁴ While they did see a great deal of mosaicism in the adult mice, they noted that the mice actually displayed stronger muscles than would be expected based solely on gene expression.¹¹⁵ They surmised that having even *some* properly working cells was an important treatment outcome, because those properly functioning cells could have a disproportionate positive impact on the mice.¹¹⁶

II. LEGAL LANDSCAPE

The American patent system is designed to encourage intellectual inquiry by protecting ideas and inventions.¹¹⁷ Indeed, Congress has granted patent protection to “[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof,” subject only to certain “conditions and requirements.”¹¹⁸ This Part will detail several of those requirements, focusing primarily on what is required for an invention to be patent-eligible subject matter.

A. General Requirements for Patentability

Section 101 of the Patent Act mandates that in order to qualify for patent protection, the invention first needs to be patent-eligible subject matter—something for which a patent is even allowed to issue (generally a physical object or a process).¹¹⁹ However, patents will not issue for inventions that merely describe laws of nature.¹²⁰ The

113. Chengzu Long et al., *Prevention of Muscular Dystrophy in Mice by CRISPR/Cas9-Mediated Editing of Germline DNA*, 345 *SCIENCE* 1184, 1184 (2014).

114. *Id.* at 1184-85.

115. *Id.* at 1185-87.

116. *Id.*

117. See U.S. CONST. art. I, § 8, cl. 8; Nuno Pires de Carvalho, *The Primary Function of Patents*, 2001 *J.L. TECH. & POL'Y* 25, 29 (2001).

118. 35 U.S.C. § 101 (2012).

119. See *id.*

120. See, e.g., *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 72 (2012).

Supreme Court articulated this rule in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, where it held that “[i]f a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself.”¹²¹ However, because “all inventions at some level embody, use, reflect, rest upon, or apply laws of nature,”¹²² the Court cautioned that “an *application* of a law of nature ... to a known structure or process may well be deserving of patent protection.”¹²³

In *Alice Corp. v. CLS Bank International*, the Court explained that a two-step process should be used to determine whether a patent improperly embodies a law of nature.¹²⁴ First, a court has to decide if the patent contains an abstract idea.¹²⁵ Next, it must determine whether the patent contains a sufficient “inventive concept” beyond a mere instruction to apply the rule of nature.¹²⁶ If the patent contains a sufficient inventive concept, and does not merely describe situations in which the law of nature should be applied, then patent protection is appropriate.¹²⁷

Assuming that a patent application covers appropriate subject matter, it must still meet several other requirements for patentability.¹²⁸ In order to be patentable, an invention must be useful,¹²⁹ novel,¹³⁰ non-obvious,¹³¹ and properly disclosed.¹³²

121. *Id.* at 77.

122. *Id.* at 71.

123. *Id.* (quoting *Diamond v. Diehr*, 450 U.S. 175, 187 (1981)).

124. 134 S. Ct. 2347, 2355 (2014).

125. *Id.*

126. *Id.*

127. *Id.*

128. *See, e.g.*, 35 U.S.C. § 102 (2012).

129. *Id.* § 101.

130. *Id.*

131. *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966).

132. 35 U.S.C. § 112 (2012).

B. The America Invents Act Regime

The Leahy-Smith America Invents Act (AIA) adds some additional conditions for researchers to meet in order for their invention to qualify as patent-eligible subject matter.¹³³ The AIA prevents patents from “issu[ing] on a claim directed to or encompassing a human organism.”¹³⁴ While the AIA is meant to limit patent protection for certain types of research (and, indeed, seems designed to prevent that research altogether), it is not meant to prevent patents for *all* inventions that could be consumed or used by humans.¹³⁵ Indeed, the drafters of the AIA specifically noted that patents should be allowed to issue “on genes, stem cells, animals with human genes, and a host of non-biologic products used by humans.”¹³⁶ This means that while pharmaceuticals, which at a minimum have a strong relationship with human organisms, are able to gain patent protection,¹³⁷ human embryos are not.¹³⁸

The AIA did not radically change U.S. Patent and Trademark Office (USPTO) policy on the patentability of human organisms.¹³⁹ Indeed, in a letter to Congress describing pre-AIA USPTO policy, Director of the USPTO James Rogan said that the AIA was “fully consistent with USPTO’s policy on the non-patentability of human life-forms.”¹⁴⁰ Director Rogan further elaborated on long-standing USPTO policy, saying:

The USPTO’s policy of rejecting patent application claims that encompass human life-forms, which the Weldon Amendment

133. Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

134. *Id.*

135. See MANUAL OF PATENT EXAMINING PROCEDURE, *supra* note 22, at § 2105.

136. *Id.* (quoting 157 CONG. REC. E1177-04 (2011) (statement of Rep. Weldon)).

137. *E.g.*, U.S. Patent No. 5,108,993 (issued Apr. 28, 1992) (a patent on a popular anti-HIV drug not declared invalid under long-standing USPTO policy or the AIA).

138. MANUAL OF PATENT EXAMINING PROCEDURE, *supra* note 22, at § 2105 (quoting 157 CONG. REC. E1177-04 (2011) (statement of Rep. Weldon)).

139. See 157 CONG. REC. E1177 (daily ed. June 23, 2011) (statement of Rep. Smith) (“[F]or over two decades, USPTO has had an internal policy that human beings at any stage of development are not patentable subject matter under 35 U.S.C. Section 101.”).

140. Letter from James Rogan, Dir., U.S. Patent & Trademark Office, to Ted Stevens, Chairman, Comm. on Appropriations, U.S. Senate (Nov. 20, 2003), http://www.nrlc.org/archive/Killing_Embryos/Human_Patenting/WeldonamendUSPTO.pdf [<https://perma.cc/AW7G-2M8N>].

elevates to an unequivocal congressional prohibition, applies regardless of the manner and mechanism used to bring a human organism into existence (e.g., somatic cell nuclear transfer, in vitro fertilization, parthenogenesis). If a patent examiner determines that a claim is directed to a human life-form at any stage of development, the claim is rejected as non-statutory subject matter and will not be issued in a patent as such.¹⁴¹

The policy codified in the AIA therefore was consistent with long-standing USPTO practice, and focused primarily on whole organisms, not on smaller components like stem cells or DNA.¹⁴²

C. The Law as Applied to Human Biology

USPTO policy and the proscriptions of the AIA¹⁴³ have not prevented patents from issuing on all technologies arguably targeted at human biology.¹⁴⁴ While human fetuses are consistently not patentable,¹⁴⁵ valid patents have issued on human DNA¹⁴⁶ and human stem cells.¹⁴⁷

1. Fetuses

An example of the application of the AIA policy can be found in *Ex parte Kamrava*.¹⁴⁸ In that case, the Patent Trial and Appeal Board (PTAB) affirmed the rejection of a patent application for a catheter that included “an embryo in the distal portion.”¹⁴⁹ The patent applicant argued that the catheter was patent-eligible because the patent application did not actually encompass an embryo, and the embryo did not qualify as a part of the human body because “the

141. *Id.*

142. *Id.* These, of course, may have other barriers to patentability, including other limits on patentable subject matter. *See, e.g., Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 72-73 (2012).

143. *See supra* Part II.B.

144. *See, e.g., Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595 (2013).

145. *See infra* Part II.C.1.

146. *See infra* Part II.C.2.

147. *See infra* Part II.C.3.

148. *See Ex parte Kamrava*, No. 2010-010201 (P.T.A.B. Nov. 26, 2012).

149. *Id.* at 5.

embryo in the distal portion of the catheter is a non-naturally occurring combination ... which is the product of human ingenuity.”¹⁵⁰

The PTAB ruled against the inventor on both arguments.¹⁵¹ They interpreted the patent application literally, and reasoned that if the inventor had not meant to include the embryo in the patent, she would have worded her application differently.¹⁵² Additionally, the PTAB ruled that combining the human embryo with the catheter did not make it patent-eligible, because “[t]he fact that the claims cover patent-eligible subject matter ... in combination with patent-ineligible subject matter ... does not render the claims patent-eligible.”¹⁵³ Thus, in order for an invention to be patent-eligible, no part of it may be directed at a whole human organism.¹⁵⁴

2. DNA

The Supreme Court *has*, however, allowed patents to issue on genetically modified human DNA.¹⁵⁵ In *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, the Court held that while naturally occurring DNA is a product of nature and is not patentable, DNA that does not occur naturally is patentable.¹⁵⁶ *Myriad* dealt with a company that had discovered the sequence of genes that are implicated in a patient’s risk of developing breast and ovarian cancer.¹⁵⁷ They tried to obtain a patent on the typical DNA sequence found in those genes.¹⁵⁸ If granted, the patent would have given them “the exclusive right to isolate [the relevant] genes,” a step necessary to determine a patient’s cancer risk.¹⁵⁹ The Court reasoned that

150. *Id.*

151. *Id.*

152. *Id.* (“As noted by the Examiner, if Appellant had intended not to encompass an embryo, the claims could have recited that ‘the distal portion of the catheter is adapted to receive/hold an embryo.’”).

153. *Id.* at 6.

154. *See id.*

155. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595 (2013).

156. *Id.*

157. *Id.* at 582-83.

158. *Id.* at 583-84.

159. *Id.* at 585. The property interest in the particular gene sequences would have therefore doubtless been incredibly lucrative for Myriad. *See* Matthew Herper, *Company Will Raise \$1 Billion to Create Blood Test to Detect Cancer*, FORBES (Jan. 5, 2017, 4:59 PM), <https://www.forbes.com/sites/matthewherper/2017/01/05/grail-which-aims-to-invent-blood-test-to->

because the DNA sequences were naturally occurring, Myriad could not obtain a patent on them.¹⁶⁰

The *Myriad* Court did, however, allow Myriad to obtain a patent on synthetic DNA that Myriad scientists created in a lab.¹⁶¹ Normal DNA contains both introns (regions that do not code for proteins)¹⁶² and exons (regions that do code for proteins).¹⁶³ Myriad developed complementary DNA (cDNA) that contained only exon (coding) segments.¹⁶⁴ The Court ruled that even though cDNA is based on the naturally occurring DNA sequences, because exon-only DNA strands do not occur in nature, Myriad was allowed to patent the cDNA.¹⁶⁵

The Federal Circuit recently decided *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* on a very similar basis.¹⁶⁶ In *Sequenom*, a company had found a way to isolate cell-free fetal DNA (cffDNA) from maternal blood.¹⁶⁷ When a woman is pregnant, a small amount of cffDNA from her baby is present in her bloodstream.¹⁶⁸ The company designed a test that could use cffDNA to learn about the baby's characteristics and to look for genetic abnormalities.¹⁶⁹ To test the DNA effectively, the company employed widely used techniques for isolating and amplifying DNA.¹⁷⁰ The court reasoned that Sequenom's patent failed both prongs of the *Alice* test; because cffDNA was "naturally occurring," and "the method steps were well-understood, conventional and routine," Sequenom's process did not add a sufficient "inventive concept" that would warrant patentability.¹⁷¹

detect-cancer-to-raise-1-billion/#73f2ed553792 [https://perma.cc/WBT4-CVY8].

160. *Myriad*, 569 U.S. at 591-94.

161. *Id.* at 594-95.

162. *Intron*, BIOLOGY ONLINE: DICTIONARY, <https://www.biology-online.org/dictionary/Intron> [https://perma.cc/ZBR9-C2JG] ("[An] intron ... [is a] noncoding ... sequence ... that is ... removed from the primary gene transcript and rapidly degraded during maturation of the RNA product.").

163. *Myriad*, 569 U.S. at 595; see also *Exon*, BIOLOGY ONLINE: DICTIONARY, <https://www.biology-online.org/dictionary/Exon> [https://perma.cc/3GDJ-ZCHT] ("[R]egions [of the DNA that] cod[e] for proteins and which are interrupted by the ... introns.").

164. *Myriad*, 569 U.S. at 595.

165. *Id.*

166. See 788 F.3d 1371 (Fed. Cir. 2015).

167. *Id.* at 1373.

168. *Id.*

169. *Id.*

170. *Id.*

171. *Id.* at 1376-77.

3. Stem Cells

The USPTO has extended patent protection to human stem cells for the past thirty years.¹⁷² However, the federal government has at times been openly hostile to stem cell research: from 1996 to 2009, federal funding could not be used for “research that destroyed [or] created human embryos.”¹⁷³ President Obama lifted this ban in 2009 with an executive order that allowed funding for research that used embryos, but only “if th[o]se embryos were created during *in vitro* fertilization for reproductive purposes but were no longer needed for such purposes.”¹⁷⁴

Although patents on embryonic stem cells are controversial and the subject of frequent litigation, the USPTO and the courts have consistently allowed patents on many stem cell technologies.¹⁷⁵ Indeed, researchers have noted a recent increase in patent applications on stem cell technologies that have therapeutic applications.¹⁷⁶ This is in stark contrast to the practice at the European Patent Office (EPO), which “regards patents on [stem cells] as illegal because they are patents on a human body or human body part, offend human dignity, or involve commercial or industrial uses of embryos.”¹⁷⁷ However, the willingness in America to grant patents to some stem cell therapies suggests that the door may be open to patents on some CRISPR-Cas9-based therapies, as well.¹⁷⁸

172. Sonya Davey et al., *Interfacing of Science, Medicine and Law: The Stem Cell Patent Controversy in the United States and the European Union*, 3 FRONTIERS CELL & DEVELOPMENTAL BIOLOGY, art. 71, Nov. 2015, at 3; see also Xuejun H. Parsons et al., *Patents on Technologies of Human Tissue and Organ Regeneration from Pluripotent Human Embryonic Stem Cells*, 1 RECENT PATENTS ON REGENERATIVE MED. 142, 144-45 (2011).

173. Davey et al., *supra* note 172, at 3.

174. *Id.*

175. Parsons et al., *supra* note 172, at 143.

176. *Id.*

177. *Id.*

178. The EPO, by contrast, has been hostile to many claims for CRISPR patent protection. See Kelly Servick, *Broad Institute Takes a Hit in European CRISPR Patent Struggle*, SCIENCE (Jan. 18, 2018, 3:30 PM), <http://www.sciencemag.org/news/2018/01/broad-institute-takes-hit-european-crispr-patent-struggle> [<https://perma.cc/KV22-6NP5>].

D. Scholarly Perspectives on the Patentability of CRISPR-Cas9

Although no commentator has yet written on whether therapeutic applications of CRISPR-Cas9 are eligible for patent protection, scholars have written extensively about the patentability of the CRISPR-Cas9 technology in general.¹⁷⁹ Opinion on CRISPR-Cas9's patent eligibility has been decidedly mixed, with some commentators arguing that it should not be patent eligible, and others maintaining stridently that it should.¹⁸⁰

Attorney Benjamin Tuttle contends that in light of *Myriad* and *Alice*, CRISPR-Cas9 systems are not eligible for patent protection because they “share molecular and genetic structure and function [with] the naturally-occurring molecules from which they derive.”¹⁸¹ Because they fail the first prong of the *Alice* test, Tuttle argues that CRISPR-Cas9 patents are subject to the second prong, which they also fail.¹⁸² Tuttle admits that CRISPR-Cas9 systems used to modify non-bacterial DNA qualify as an “inventive concept,” but says that policy considerations, such as the need to promote innovation, should outweigh the value of protecting the invention.¹⁸³

On the other hand, patent attorney Deborah Ku asserts that CRISPR-Cas9 technologies are patent eligible, and would survive a challenge to § 101 of the Patent Act because they satisfy the *Alice* framework.¹⁸⁴ Ku argues that the CRISPR-Cas9 system at issue in the dispute between the Broad Institute and the University of California is patentable in part because it “possesses characteristics that are markedly different from the naturally-occurring counterpart found in select bacteria.”¹⁸⁵ Ku contends that Tuttle fails to consider

179. See *supra* notes 16-18 and accompanying text.

180. Compare, e.g., Benjamin C. Tuttle, *The Failure to Preserve CRISPR-Cas9's Patentability post Myriad and Alice*, 98 J. PAT. & TRADEMARK OFF. SOC'Y 391, 392, 404-05 (2016) (arguing that CRISPR-Cas9 systems fail both steps of the *Alice* test and that policy concerns militate against patentability), with Deborah Ku, *The Patentability of the CRISPR-Cas9 Genome Editing Tool*, 16 CHI.-KENT J. INTELL. PROP. 408 (2017) (arguing that a patent on CRISPR-Cas9 should at least survive a § 101 challenge).

181. Tuttle, *supra* note 180, at 404.

182. *Id.* at 404-05.

183. *Id.* at 405.

184. Ku, *supra* note 180, at 438.

185. *Id.* at 434.

that while individual components of the CRISPR-Cas9 system might be found in nature, “the claimed system *as a whole* is not.”¹⁸⁶

Even if a court finds that the CRISPR-Cas9 system is the same as what occurs in nature, and therefore fails the first prong of the *Alice* test, Ku argues that CRISPR-Cas9 should be patent eligible because it satisfies the second prong of the test.¹⁸⁷ Ku says that the CRISPR-Cas9 system claimed in the Broad Institute and University of California patents embodies a sufficient inventive concept to satisfy the second prong of the test because “getting the naturally-found CRISPR system ... to work in [non-bacterial] cells required human intervention.”¹⁸⁸ Thus, Ku argues, CRISPR-Cas9 systems should be patentable, at least as they are defined in the patents filed by the Broad Institute and the University of California.¹⁸⁹

Under the existing regulatory regime, the extent to which the therapeutic applications of CRISPR-Cas9 are patentable remains an open question.¹⁹⁰ Inventors that attempt to patent DNA-based therapies face significant barriers to patentability, including whether their invention already occurs in nature and is therefore not patent-eligible subject matter,¹⁹¹ and whether they are so widely used that creating them required no inventive step.¹⁹² This is not to mention one of the largest barriers to patentability for CRISPR-Cas9 therapies: the AIA’s prohibition against patents “directed to or encompassing a human organism.”¹⁹³

III. ARE CRISPR-CAS9 THERAPIES PATENTABLE?

The extent to which patent law (particularly the AIA) allows patent protection to extend to therapeutic applications of CRISPR-Cas9 systems remains unclear.¹⁹⁴ CRISPR-Cas9 therapies face several

186. *Id.* at 436 (emphasis added).

187. *Id.* at 437.

188. *Id.*

189. *Id.*

190. *See supra* notes 180-89.

191. *See, e.g.,* Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 591 (2013).

192. *See, e.g.,* Alice Corp. Pty. Ltd. v. CLS Bank Int’l, 134 S. Ct. 2347, 2357 (2014).

193. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

194. *See supra* Part II.D.

hurdles to patentability: the applicant must demonstrate that the therapies (1) do not already occur in nature¹⁹⁵ or (2) embody a sufficient inventive concept,¹⁹⁶ and (3) are not “directed to or encompassing a human organism.”¹⁹⁷ As discussed below, some therapeutic applications of CRISPR-Cas9 will clear these hurdles, whereas others will not. This Part argues that therapeutic applications of CRISPR-Cas9 analogous to existing disease treatments (namely, CRISPR-Cas9 treatments of viral and bacterial infections) should be granted patent protection, whereas applications that do not have an existing therapeutic analog (somatic and germline cell editing) should not.

A. Where Patent Protection Will Apply

CRISPR-Cas9 therapies used to treat viral and bacterial infections should be granted patent protection. These therapies do not already occur in nature,¹⁹⁸ they are not yet so broadly used that they do not require an inventive concept,¹⁹⁹ and they are not “directed to or encompassing a human organism”²⁰⁰ in violation of the AIA.²⁰¹

1. Treating Viral Infections

The anti-viral applications of CRISPR-Cas9 should be granted patent protection. As explained below, anti-viral applications of CRISPR-Cas9 clear all three of the hurdles to patentability for CRISPR-Cas9 therapies. These applications do not occur in nature, the techniques for delivering the treatment are not widely used,

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

196. *Alice*, 134 S. Ct. at 2357; *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379-80 (Fed. Cir. 2015).

197. Leahy-Smith America Invents Act (AIA) § 33(a). There are, of course, other requirements for patentability, such as adequate disclosure, but these are not unique or particularly challenging in the CRISPR-Cas9 context, so they are not addressed here. *See, e.g.*, 35 U.S.C. § 112 (2012).

198. *See infra* notes 202-11 and accompanying text.

199. *See infra* notes 212-18 and accompanying text.

200. Leahy-Smith America Invents Act (AIA) § 33(a).

201. *See infra* notes 219-24 and accompanying text.

and the treatment is not “directed to or encompassing a human organism” within the meaning of the AIA.²⁰²

As a threshold matter, humans do not naturally use CRISPR-Cas9 to combat viral infection.²⁰³ As the Supreme Court’s decision in *Myriad* shows, demonstrating that an invention does not occur in nature is a low bar.²⁰⁴ A patent applicant need only show that the invention does not specifically occur in nature.²⁰⁵ In *Myriad*, even though the order of the nucleotides in the cDNA came from naturally occurring DNA, Myriad successfully patented the cDNA sequence because it excluded the introns that were present in the natural DNA sequence.²⁰⁶

Although some organisms use CRISPR-Cas9 systems as part of an immune response in nature, they are not naturally part of the human immune system.²⁰⁷ CRISPR-Cas9 evolved as an immune response in bacteria.²⁰⁸ Researchers have never recorded CRISPR-Cas9 as a natural component of the human immune system.²⁰⁹ Therefore, under the *Myriad* standard,²¹⁰ inventors should still be allowed to patent CRISPR-Cas9 systems used to treat viral infections, because the CRISPR-Cas9 system is not a natural part of the *human* immune response.²¹¹

Even assuming that a court finds that CRISPR-Cas9-based therapies are naturally occurring, the techniques used to deliver CRISPR-Cas9 systems into cells are not yet widely used,²¹² and thus require a sufficient inventive concept that satisfies the second prong of the *Alice* analysis.²¹³ Because human cells do not naturally contain Cas9 proteins, researchers cannot merely inject gRNA into virus-infected cells and expect the gRNA to kill the viruses.²¹⁴

202. Leahy-Smith America Invents Act (AIA) § 33(a); *see infra* notes 219-24 and accompanying text.

203. Sternberg & Doudna, *supra* note 9, at 568.

204. *See* Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 595 (2013).

205. *See id.*

206. *Id.*

207. Sternberg & Doudna, *supra* note 9, at 568.

208. *Id.*

209. *See id.*

210. 569 U.S. at 595.

211. *See* Sternberg & Doudna, *supra* note 9, at 568.

212. *See* Israel, *supra* note 101.

213. *See* Alice Corp. Pty. Ltd. v. CLS Bank Int’l, 134 S. Ct. 2347, 2357 (2014).

214. *See* Israel, *supra* note 101.

Instead, researchers must find a way to get the entire Cas9/gRNA complex into the cell.²¹⁵ However, this is incredibly difficult to do.²¹⁶ When the Berkeley researchers announced that they had found a way to use gold particles to transport a Cas9/gRNA complex into the cells of mice suffering from muscular dystrophy, it was groundbreaking news.²¹⁷ Because (1) this technique was developed relatively recently, (2) researchers have only published one paper describing it,²¹⁸ and (3) its efficacy has not been demonstrated for other treatments, the delivery techniques for CRISPR-Cas9 anti-viral treatments require an inventive concept that satisfies the second prong of the *Alice* analysis.

Finally, the anti-viral uses of CRISPR-Cas9 systems are not “directed to or encompassing a human organism”²¹⁹ within the meaning of the AIA. Neither the long-standing USPTO policy against issuing patents encompassing human beings, nor the AIA, have prevented patents from issuing on antiviral drugs.²²⁰ It is important to note that a CRISPR-Cas9 treatment for a viral infection is patentable only to the extent that it targets the virus’s DNA, not the patient’s.²²¹ The CRISPR-Cas9 anti-viral treatments that have been proposed edit out specific portions of the viral DNA, leaving the patient’s DNA unaltered and thus avoiding this problem.²²² Because CRISPR-Cas9 treatments do not alter the human genome in any way,²²³ they are no different—with the exception of their incredible effectiveness—than other anti-viral

215. *Id.*

216. *See id.*

217. *See id.*

218. At the time this Note was written. *See id.*

219. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

220. *See, e.g.*, U.S. Patent No. 5,108,993 (issued Apr. 28, 1992) (a patent on a popular anti-HIV drug not declared invalid under long-standing USPTO policy or the AIA).

221. *See* Kaminski et al., *supra* note 80, at 10 (“[W]e developed CRISPR/Cas9 techniques that eradicated integrated copies of HIV-1 [DNA] from human ... cells, inhibited HIV-1 infection in ... human ... cells, and suppressed viral replication *ex vivo* in ... cells of HIV-1+ patients.”).

222. *See id.*

223. *Id.*

drugs that have been granted patent protection.²²⁴ They should therefore not be treated any differently on their patent applications.

2. *Treating Bacterial Infections*

Like the anti-viral applications of CRISPR-Cas9, the anti-bacterial applications should also be granted patent protection. The analysis here is largely similar to the anti-viral application analysis.²²⁵ Although CRISPR-Cas9 systems naturally occur as an immune response in bacteria, the response is geared towards fighting viral infections, and is not directed against the bacteria itself.²²⁶ Therefore, anti-bacterial applications of CRISPR-Cas9 do not occur in nature. The techniques for delivering anti-bacterial CRISPR-Cas9 treatments are also not widely used, because they were only recently developed.²²⁷ Although some bacteria already contain Cas9 proteins that could be paired with an inserted gRNA, it is more useful to insert an entire Cas9/gRNA complex, a technique that has not yet been tested in humans.²²⁸ Finally, because the CRISPR-Cas9 treatments destroy *bacterial* DNA, and no human DNA,²²⁹ the treatments do not run afoul of the AIA.²³⁰ Anti-bacterial applications of CRISPR-Cas9 should therefore be patentable.

B. Where Patent Protection Will Not Apply

On the other hand, CRISPR-Cas9 therapies used to edit somatic and germline cells should not be granted patent protection. While these therapies satisfy both prongs of the *Alice* analysis because they do not already occur in nature²³¹ and do require an inventive

224. See, e.g., U.S. Patent No. 5,108,993 (issued Apr. 28, 1992) (a patent on a popular anti-HIV drug not declared invalid under long-standing USPTO policy or the AIA).

225. See *supra* Part III.A.1.

226. See Sternberg & Doudna, *supra* note 9, at 568-69.

227. Israel, *supra* note 101.

228. See *id.* The Berkeley muscular dystrophy researchers *did* successfully use CRISPR-Gold to insert complete Cas9/gRNA complexes into mice, and hope to begin human trials shortly. See *id.*

229. Koo & Kim, *supra* note 8, at 40.

230. See *supra* Part II.B.

231. See *infra* notes 236-39, 252-54 and accompanying text.

concept,²³² they *are* “directed to or encompassing a human organism”²³³ in violation of the AIA.²³⁴

1. *Editing Somatic Cells*

Patent protection should not be granted to CRISPR-Cas9 systems designed to edit somatic cells. These systems fail to clear the final hurdle to patentability. While somatic cell editing of this kind does not occur in nature and does use techniques that are wide-spread, it is still not patentable because it is “directed to or encompassing a human organism.”²³⁵

CRISPR-Cas9-mediated somatic cell editing does not occur in nature under the *Myriad* standard (or, for that matter, under any other rational standard).²³⁶ As discussed above in Part I.B.3, CRISPR-Cas9 evolved as an immune response in bacteria and is only present in bacteria. Although CRISPR-Cas9 does naturally occur in bacteria, editing somatic cells in humans is not its natural use.²³⁷ Inventors would have a stronger patent claim to this use than the inventors in *Myriad* had to the cDNA.²³⁸ There, the researchers were only removing certain portions of the naturally occurring DNA.²³⁹ Here, inventors are completely altering what the naturally-occurring phenomenon is used for.

Somatic-cell editing using CRISPR-Cas9 also does not employ widely-used techniques, and thus requires an inventive leap that satisfies the second prong of the *Alice* test.²⁴⁰ Because human cells do not have Cas9 proteins already in them, researchers cannot merely inject gRNA into cells that they want to edit and expect that the edits will actually occur.²⁴¹ Instead, researchers must find a way to get the entire Cas9/gRNA complex into the cell.²⁴² However, as

232. See *infra* notes 240-46, 254-56 and accompanying text.

233. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

234. See *infra* notes 240-43, 253-57 and accompanying text.

235. Leahy-Smith America Invents Act (AIA) § 33(a).

236. See *supra* Part I.B.3.

237. See Israel, *supra* note 101.

238. See *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595 (2013).

239. *Id.*

240. See *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355 (2014).

241. See Koo & Kim, *supra* note 8, at 40.

242. See *id.*

discussed above, this is incredibly difficult to do.²⁴³ The muscular dystrophy researchers who discovered CRISPR-Gold just published their discovery, and the technique has yet to be attempted in humans.²⁴⁴ Because this technique was developed relatively recently, and because researchers have only published one paper describing it, the delivery techniques for CRISPR-Cas9 somatic cell editing treatments are certainly not wide-spread, and require an inventive concept to apply.²⁴⁵ Therefore, CRISPR-Cas9 treatments that edit somatic cells clear both prongs of the *Alice* test.²⁴⁶

The stumbling block for researchers seeking to patent somatic cell-editing CRISPR-Cas9 systems is the provision of the AIA that dictates that no patent may be issued for a technology that is “directed to or encompassing a human organism.”²⁴⁷ By their very nature, CRISPR-Cas9 systems used to edit somatic cell DNA are designed to alter a human organism.²⁴⁸ Indeed, the invention of CRISPR-Gold as a delivery mechanism, which solves the problem of how to efficiently deliver the Cas9/gRNA complex into somatic cells,²⁴⁹ only complicates the AIA issue. Whereas before scientists would have injected the Cas9/gRNA complex directly into the cells they wished to affect, now they simply have to inject the solution containing the Cas9/gRNA complexes into the body of the patient, potentially impacting any cell containing the target DNA.²⁵⁰ An invention that has the potential to fundamentally alter the DNA in every cell in the body is clearly “directed to ... a human organism,”²⁵¹ and should not receive patent protection under the AIA.

2. *Editing Germline Cells*

CRISPR-Cas9 systems designed to edit germline cells should also not be granted patent protection. The analysis here is very similar

243. See Israel, *supra* note 101.

244. *Id.*

245. *See id.*

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

247. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

248. Israel, *supra* note 101.

249. *Id.*

250. *See id.*

251. Leahy-Smith America Invents Act (AIA) § 33(a).

to the somatic cell system analysis above: systems designed to edit germline cells clear the first two hurdles to patentability, but stumble upon the third. CRISPR-Cas9 does not naturally edit germline cells in nature.²⁵² It does not even naturally occur in humans, and in the bacteria where it does naturally appear, it is used solely for the purpose of destroying viral DNA.²⁵³ Germline editing systems therefore exceed the *Myriad* standard.²⁵⁴ Germline editing using CRISPR-Cas9 also does not use techniques that are widely employed, and thus require an inventive concept.²⁵⁵ There is (as of yet) no wide-spread genetic editing of any kind of human germline cells.²⁵⁶

The argument is even stronger for CRISPR-Cas9-mediated editing of germline cells than it is for somatic cells that the technique is “directed to or encompassing a human organism.”²⁵⁷ The benefit of germline editing (from a research and treatment perspective) is that if scientists can overcome issues with mosaicism, the altered DNA will be expressed in every cell of the adult body.²⁵⁸ An invention designed to fundamentally alter the DNA in every cell in the body is clearly “directed to ... a human organism.”²⁵⁹ The altered DNA also has the potential to be passed on to the offspring of edited individuals, ensuring that the offspring will have edited DNA fully incorporated into their genome.²⁶⁰ Moreover, serious ethical concerns will likely prevent the USPTO from issuing patents on any technology that could so fundamentally alter a person’s genetic code.²⁶¹ For these reasons, CRISPR-Cas9 systems designed to edit germline cells should also be unpatentable.

252. Sternberg & Doudna, *supra* note 9, at 568.

253. *Id.*

254. See *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595 (2013).

255. See, e.g., Rana et al., *supra* note 13 (noting the only known CRISPR-Cas9 therapy currently being used in humans is a treatment for cancer patients).

256. See Neergaard, *supra* note 14.

257. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

258. Koo & Kim, *supra* note 8, at 40.

259. Leahy-Smith America Invents Act (AIA) § 33(a).

260. Koo & Kim, *supra* note 8, at 40.

261. See Letter from James Rogan, Dir., U.S. Patent & Trademark Office, to Ted Stevens, Chairman, Comm. on Appropriations, U.S. Senate, *supra* note 140.

IV. COUNTERARGUMENTS

This Part addresses counterarguments to the normative framework outlined in Part III. It considers and rejects arguments that CRISPR-Cas9 should not be patentable at all;²⁶² that patents have been granted on some CRISPR-Cas9-based therapies, and therefore all therapies should be patentable;²⁶³ and that certain somatic cell editing should be patentable.²⁶⁴

A. CRISPR-Cas9 Should Not Be Patentable at All

As noted above, some scholars have argued that CRISPR-Cas9 should be considered unpatentable altogether.²⁶⁵ Benjamin Tuttle believes that *Myriad* and *Alice* foreclose patentability for all CRISPR-Cas9 systems, because they “share molecular and genetic structure and function to the naturally-occurring molecules from which they derive.”²⁶⁶ Tuttle argues that the systems thus fail the first prong of the *Alice* test, and are subject to the second prong, which he claims they also fail.²⁶⁷ Tuttle admits that CRISPR-Cas9 systems used to modify non-bacterial DNA may qualify as an “inventive concept,” but argues that policy considerations should outweigh the value of protecting the invention.²⁶⁸ In the context of the subset of CRISPR-Cas9 systems that could be used as therapies for human illness, Deborah Ku may actually support Tuttle.²⁶⁹ She writes that patent protection applies when “the claimed CRISPR system is not used as an immune system, but as a genome editing tool. Hence its function is different [than it would be in nature].”²⁷⁰

Tuttle’s paper was written in the context of the patent dispute between The Broad Institute and the University of California, and

262. *Infra* Part IV.A.

263. *Infra* Part IV.B.

264. *Infra* Part IV.C.

265. Tuttle, *supra* note 180, at 392; *supra* notes 181-83 and accompanying text.

266. Tuttle, *supra* note 180, at 404.

267. *Id.* at 404-05.

268. *Id.* at 405.

269. See Ku, *supra* note 180, at 435.

270. *Id.*

does not directly deal with therapeutic applications of CRISPR-Cas9.²⁷¹ Taken in the context of therapeutic applications, however, his arguments about the patentability of CRISPR-Cas9 carry significantly less weight. His arguments fail to account for the magnitude of the inventive leap when a genetic system used as part of an immune response in bacteria is repurposed as a medical treatment in humans.²⁷²

As Ku wrote in her paper, even assuming that CRISPR-Cas9 systems fail the first prong of the *Alice* test, they do not fail the second.²⁷³ The human intervention required to transform a bacterial immune response into a genetic-editing technology that can be used in human cells is an inventive leap large enough to satisfy the second prong of the *Alice* test.²⁷⁴ This is a massive step forward that reflects the culmination of the policy goals that Tuttle expresses,²⁷⁵ and far outweighs any reasons not to grant patent protection to CRISPR-Cas9 therapies in some instances.

B. Patents Have Issued on Some CRISPR-Cas9-Based Therapies

In contrast, those arguing in favor of granting patents on all CRISPR-Cas9-based therapies might observe that patents already have issued on CRISPR-Cas9 systems used to edit human immune cells,²⁷⁶ and patents should therefore be issued on all CRISPR-based therapies. However, this position fails to account for the fact that while patents are given a presumption of validity,²⁷⁷ “the ultimate question of patent validity is one of law,” to be determined by a court.²⁷⁸ Until a court has determined the validity of these

271. *Id.* at 436; Tuttle, *supra* note 180, at 404-05.

272. *See* Koo & Kim, *supra* note 8, at 40.

273. Ku, *supra* note 180, at 437.

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

275. Tuttle, *supra* note 180, at 405.

276. *Two Issued U.S. Patents Granted to Collectis for CRISPR Use in T-Cells*, BUS. WIRE (Feb. 13, 2018, 12:01 AM), <https://www.businesswire.com/news/home/20180212006461/en/Issued-U.S.-Patents-Granted-Collectis-CRISPR-T-Cells> [<https://perma.cc/DFA9-L759>] (describing patents that issued on CRISPR-Cas9-based technologies used to edit human T-cells).

277. 35 U.S.C. § 282(a) (2012).

278. *Microsoft Corp. v. i4i P'ship*, 564 U.S. 91, 96 (2011) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

patents, there is no reason to believe that patents on CRISPR-Cas9 therapies are per se valid.

C. Some Somatic Cell Editing Should Be Patentable

In a similar vein, CRISPR-Cas9 therapies that edit certain somatic cells arguably should be patentable. For example, CRISPR-Cas9 therapies could be used to knock out the genes that cause unrestricted growth in tumor cells.²⁷⁹ Such unrestricted growth is not normally present in the human genome,²⁸⁰—the argument goes—so destroying the genes that cause it using CRISPR-Cas9 is a treatment that is not “directed to or encompassing a human organism.”²⁸¹

What this argument fails to account for is that tumor cells are created when human DNA is mutated so that the factors that normally restrict cell growth are no longer active.²⁸² The cancer cells still have human DNA, and even if that particular expression of DNA is not the default in humans, it does still naturally occur in them.²⁸³ Any attempt to edit out the mutation is thus an attempt to edit human DNA in a live patient, and is therefore “directed to ... a human organism.”²⁸⁴

CONCLUSION

In his short story, Boyle paints a dark and concerning picture of a CRISPR-mediated future, made all the more worrisome because, as discussed above,²⁸⁵ many of the steps that he describes have already been taken:

When the CRISPR technology first came to light, governments and scientists everywhere assured the public that it would be

279. See Ingrid Lobo, *Chromosome Abnormalities and Cancer Cytogenetics*, NATURE EDUC. (2008), <https://www.nature.com/scitable/topicpage/chromosome-abnormalities-and-cancer-cytogenetics-879> [<https://perma.cc/4VBC-CPQB>].

280. *Id.*

281. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

282. Lobo, *supra* note 279.

283. *Id.*

284. Leahy-Smith America Invents Act (AIA) § 33(a).

285. See *supra* Part I.B.

employed only selectively, to fight disease and to rectify congenital deformities, editing out the mutated BRCA1 gene that predisposes women to breast cancer, for instance, or eliminating the ability of the *Anopheles* mosquito to carry the parasite that transmits malaria. Who could argue with that? Genome-editing kits (“Knock Out Any Gene!”) were sold to home hobbyists, who could create their own anomalous forms of yeast and bacteria in their kitchens, and it was revolutionary—and, beyond that, fun. Fun to tinker. Fun to create.... The Chinese were the first to renounce any sort of regulatory control and upgrade the human genome, and, as if they weren’t brilliant enough already, they became still more brilliant as the first edited children began to appear, and of course we had to keep up.²⁸⁶

Fortunately, safeguards in intellectual property laws will likely mean that CRISPR-Cas9 therapies are only patentable under the *Myriad* standard and the AIA when they do not lead to upgrading the human genome.²⁸⁷ DNA in somatic or germline cells is incorporated into the body, and, in the case of the germline cells (or an organ donor who gives an organ containing DNA edited by CRISPR), could even be passed on to another person.²⁸⁸ CRISPR-Cas9 systems in somatic or germline cells should not be patentable under the AIA, because they are “directed to ... a human organism.”²⁸⁹

However, CRISPR-centered treatments for viral and bacterial infections *should* be patentable.²⁹⁰ Like pharmaceuticals, they should not lose their patent protection simply because they entered the human body.²⁹¹ Because they do not occur in nature and represent an inventive leap, antiviral and antibacterial CRISPR-Cas9 treatments satisfy the *Myriad* and *Alice* standards.²⁹² Likewise, the genetic editing techniques used to treat viral and bacterial infections will not run afoul of the AIA, because, like current pharmaceuticals, they are directed at foreign organisms that inhabit humans, and not the “human organism” itself.²⁹³ This is no small

286. Boyle, *supra* note 1.

287. *See supra* Part III.A.

288. *See supra* Parts I.B.3, I.B.4.

289. Leahy-Smith America Invents Act (AIA) § 33(a); *see also supra* Part III.B.

290. *See supra* Part III.A.

291. *See supra* Part II.A.

292. *See supra* Part III.A.

293. *See supra* Part II.

step forward. Currently, there are no cures for viral infections, including those that are highly lethal (such as HIV/AIDs), and those that are incredibly common (the flu).²⁹⁴ Additionally, the rapid evolution of bacteria means that antibiotic-resistant strands of highly dangerous illnesses like tuberculosis will soon be entirely unsusceptible to traditionally effective antibiotics, requiring a new kind of treatment entirely.²⁹⁵

The patent system as it exists now will help to ensure that some of the therapeutic applications of CRISPR-Cas9 receive protection, while others, too clearly “directed to ... a human organism” will remain unprotected.²⁹⁶ This outcome should help prevent some of the ethical concerns that Boyle highlights about CRISPR-Cas9 therapies from becoming a reality.²⁹⁷

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294. *See supra* Part I.B.1.

295. *See supra* Part I.B.2.

296. Leahy-Smith America Invents Act (AIA), Pub. L. No. 112-29, § 33(a), 125 Stat. 340 (2011).

297. *See* Boyle, *supra* note 1.

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