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Genome Editing and the Jurisprudence of Scientific Empiricism

Paul Enriquez

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Genome Editing and the Jurisprudence of Scientific Empiricism

Paul Enríquez*

ABSTRACT

Humankind has reached, in tow by the hand of a scientific breakthrough called CRISPR, the Rubicon of precise genetic manipulation first envisioned over fifty years ago. Despite CRISPR's renown in science and its power to transform the world, it remains virtually unaddressed in legal scholarship. In the absence of on-point law, the scientific community has attempted to reach some consensus to preempt antagonistic regulation and prescribe subjective standards of use under the guise of a priori scientific empiricism. Significant and complex legal issues concerning this technology are emerging, and the void in legal scholarship is no longer tolerable.

This Article shrinks the scholarly gap, and it is the first to introduce CRISPR to legal literature. By providing a resource for jurists, scholars, and practitioners, it challenges conventional notions concerning the false dichotomy frequently associated with mutually exclusive normative roles for science and law. The Article makes two independent contributions. First, it lays a robust and comprehensive epistemic foundation of genome editing suitable for legal audiences. This element is descriptive, but essential because a detailed and coherent understanding of the nuts and bolts of the science is requisite for a discussion of law and policy. Second, it advocates for a jurisprudence of scientific empiricism, namely, a normative legal framework that consolidates empiricism and technological—e.g., genome editing—applications into a uniform doctrinal structure unencumbered by common substantive impediments to constructive debate. These impediments consist of impractical and often

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sensationalist claims about issues raised by technological advances and are collectively characterized as “deceptive simplicity.” The proposed paradigm, which lays a blueprint for the legal community to combat the deleterious effects of scientific illiteracy, flows from the Supreme Court’s recent decision in Association for Molecular Pathology v. Myriad Genetics and is broadly adaptable to addressing questions of science in law.

Applying this framework, the Article reconsiders Buck v. Bell and argues that, contrary to long-held views, Buck is not a direct product of false science, but of unbridled deceptive simplicity. Lastly, the Article sets the stage for a series of forthcoming works that will analyze genome editing from regulatory, constitutional, international, egalitarian, ethical, and policy standpoints, which highlight pivotal synergistic roles for law, science, and public policy in the development of this remarkable nascent biotechnology.

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I. INTRODUCTION

The most significant technological breakthrough of this generation, namely, a genome editing tool called “CRISPR,” has inconspicuously arrived. Only on rare occasions does a technology with such far-reaching implications lightly knock to announce its arrival while holding the power to forever change the world and humankind.

The world has heard that sporadic light knock before. Nearly eight decades ago, scientific inquiry conceptualized nuclear fission¹ as a theoretical explanation for the recondite empirical evidence that ²³⁹U, an isotope of uranium produced by the neutronic irradiation of ²³⁸U, could have its nucleus split into highly radioactive fragments.² That theory was ultimately supported by experimental observations showing the enormous release of ionization energy resulting from nuclear fragmentation,³ thereby confirming a decades-old relationship between mass and energy— $E = mc^2$ —first formulated by Albert Einstein.⁴ With remarkable speed, the newfangled knowledge covertly

1. Lise Meitner & O.R. Frisch, *Disintegration of Uranium by Neutrons: A New Type of Nuclear Reaction*, 143 NATURE 239, 239 (1939).

2. Von O. Hahn & F. Strassmann, *Über den Nachweis und das Verhalten der bei der Bestrahlung des Urans Mittels Neutronen Entstehenden Erdalkalimetalle* [Concerning the Existence of Alkaline Earth Metals Resulting from Neutron Irradiation of Uranium], 27 DIE NATURWISSENSCHAFTEN 11 (1939), translated in Hans G. Graetzer, *Discovery of Nuclear Fission*, 32 AM. J. PHYSICS 9, 10 (1964).

3. O.R. Frisch, *Physical Evidence for the Division of Heavy Nuclei Under Neutron Bombardment*, 143 NATURE 276, 276 (1939).

4. A. Einstein, *Ist die Trägheit Eines Körpers von Seinem Energieinhalt abhängig?* [Does the Inertia of a Body Depend upon its Energy-Content?], 18 ANNALEN DER PHYSIK 639 (1905), translated in THE COLLECTED PAPERS OF ALBERT EINSTEIN, VOL. 2, THE SWISS YEARS: WRITINGS, 1900–1909, at 172 (Anna Beck trans., Princeton University Press 1989), <http://einsteinpapers.press.princeton.edu/vol2-trans/1?ajax> [https://perma.cc/K6TE-UP3M].

served as the basis for the Manhattan Project, the research program that ultimately developed the atomic bomb through nuclear fission.⁵

The scientific breakthrough *modus operandi* is, to a certain extent, wholly universal. The genesis of modern computing had its principles neatly packaged in a seminal paper authored by the mathematician Alan Turing.⁶ The revolutionary notion that a machine could imitate computations performed by humans spawned the first “Turing-complete,” programmable, general-purpose, Electronic Numerical Integrator and Computer (ENIAC).⁷ Unpredictably, the technology evolved into personal computers and smartphones, and enabled the ensuing development of the Internet.⁸ Other fundamental discoveries over the past few centuries—in mathematics, physics, chemistry, and biology—have facilitated our ability to harness the power of natural phenomena in space travel, wireless communications, medicine, and a myriad other applications.

The technological breakthrough of this generation, unlike many of its predecessors, holds the power to alter humankind from

5. For a historical account of the origins and development of the US atomic bomb program of World War II, see generally F.G. GOSLING, *THE MANHATTAN PROJECT: MAKING THE ATOMIC BOMB* (U.S. Dep’t of Energy ed. 1999).

6. A.M. Turing, *On Computable Numbers, with an Application to the Entscheidungsproblem*, 42 *PROC. LONDON MATHEMATICAL SOC’Y* 230, 230 (1937).

7. Electronic Numerical Integrator and Computer, U.S. Patent No. 3,120,606 (filed June 26, 1947) (issued Feb. 4, 1964). To this day, debate exists concerning whether the first modern computer was the Atanasoff-Berry Computer (ABC) or the ENIAC. See generally ALICE ROWE BURKS, *WHO INVENTED THE COMPUTER?: THE LEGAL BATTLE THAT CHANGED COMPUTING HISTORY* 247–68 (2003). *Honeywell Inc. v. Sperry Rand Corp.*, No. 4-67 Civ. 138, 1973 WL 903, at *7, *30–38, *90 (D. Minn. Oct. 19, 1973), invalidated the ENIAC patent on grounds that the ABC constituted prior art, which rendered the patent invalid and unenforceable. However, the ABC was neither programmable nor Turing-complete. *Atanasoff-Berry Computer*, *COMPUTER HIST. MUSEUM*, <http://www.computerhistory.org/revolution/birth-of-the-computer/4/99> [<https://perma.cc/MPU6-S6PX>] (last visited Feb. 23, 2017). Indeed, the ABC may be considered the first electronic computer, while the ENIAC was the first general-purpose, programmable, electronic computer. BURKS, *supra*, at 247–49, 330–31. It is somewhat settled that ENIAC was the first Turing-complete, large-scale, electronic, programmable digital computer. See Michael R. Williams, *A Preview of Things to Come: Some Remarks on the First Generation of Computers*, in *THE FIRST COMPUTERS: HISTORY AND ARCHITECTURES* 3 (Raúl Rojas & Ulf Hashagen eds., 2000). Thus, the debate focuses on whether ENIAC’s programmable and Turing-complete features qualify it as the direct precursor to modern computers. Ultimately, some dismiss the importance of whether the ABC, ENIAC, or other machines of the time constituted the “first” computer. *Id.* Others argue that the invention of the modern computer has ambiguous origins and involves contributions from scientists in at least three different countries. See Raúl Rojas, *Who Invented the Computer? The Debate from the Viewpoint of Computer Architecture*, in *MATHEMATICS OF COMPUTATION 1943-1993: A HALF-CENTURY OF COMPUTATIONAL MATHEMATICS*, 48 *PROC. SYMPOSIA APPLIED MATHEMATICS* 361, 364–65 (Walter Gautschi ed., 1993).

8. See BARRY M. LEINER ET AL., *BRIEF HISTORY OF THE INTERNET* 1 (2012), http://www.internetsociety.org/sites/default/files/Brief_History_of_the_Internet.pdf [<https://perma.cc/ZL6B-37EP>] (chronicling the origins and evolution of the Internet).

within. A quantum leap in genome editing⁹ capabilities has led us to the Rubicon of precise, endogenous, genetic manipulation—one originally envisioned decades ago, yet methodologically beyond reach for prior generations of scientists. The protagonist of this genome editing revolution is an atomic, programmable, macromolecular machine comprising a pair of precision scalpels that shear DNA molecules and has been colloquially baptized as “CRISPR,” an acronym for the system of Clustered, Regularly Interspaced, Short Palindromic Repeats (CRISPR) and CRISPR-associated (Cas) proteins.¹⁰

In the last four years, CRISPR systems—and CRISPR-Cas9 in particular—have been adapted in laboratories across the globe at an exponential rate. Astoundingly, more than 2,500 scientific publications¹¹ feature theory, empirical observations, and descriptions of applications for this budding biotechnology. Stratospheric expectations for CRISPR systems have already attracted more than \$1 billion in venture capital¹² in a brief period of time. One of a few CRISPR-based companies became the first to file the requisite paperwork for an initial public offering with the Securities and

9. See definition *infra* Part II; see also *infra* notes 53–55 and accompanying text.

10. See discussion *infra* Section III.D.

11. A search on the PubMed scientific database using the “CRISPR” acronym filtered by title and abstract returned 2,565 hits as of February 10, 2016. PubMed.gov Search Results for CRISPR, PUBMED.GOV, [http://www.ncbi.nlm.nih.gov/pubmed/?term=CRISPR\[Title%2FAbstract\]](http://www.ncbi.nlm.nih.gov/pubmed/?term=CRISPR[Title%2FAbstract]) [https://perma.cc/7PC2-BNN8] (last visited Feb. 10, 2016) (search for CRISPR filtered by title and abstract by using the language “CRISPR[Title/Abstract]”). Note that the search does not include papers that refer to CRISPR in the body of the paper, which may return more hits.

12. See, e.g., John Carroll, *Bayer Bets \$335M on CRISPR Therapeutics and the Future of Gene Editing*, FIERCEBIOTECH (Dec. 21, 2015), <http://www.fiercebiotech.com/story/bayer-bets-335m-crispr-therapeutics-and-future-gene-editing/2015-12-21> [https://perma.cc/LU94-5MUF]; Caroline Chen, *Gene-Editing Drugmaker Backed by Google, Gates Files for IPO*, BLOOMBERG BUS. (Jan. 4, 2016), <http://www.bloomberg.com/news/articles/2016-01-05/gene-editing-drugmaker-backed-by-google-gates-files-for-ipo> [https://perma.cc/S47Q-8EK8]; Matthew Herper, *Bill Gates and 13 Other Investors Pour \$120 Million into Revolutionary Gene-Editing Startup*, FORBES (Aug. 10, 2015), <http://www.forbes.com/sites/matthewherper/2015/08/10/bill-gates-and-13-other-investors-pour-120-million-into-revolutionary-gene-editing-startup/#12f70a01664c> [https://perma.cc/W7HL-7C5A]; Alex Lash, *CRISPR Cash: Intellia the Latest Gene-Editing Firm to Nab Big Money*, XCONOMY (Sept. 1, 2015), <http://www.xconomy.com/boston/2015/09/01/crispr-cash-intellia-the-latest-gene-editing-firm-to-nab-big-money/> [https://perma.cc/8CZ9-FBK5]; *Vertex and CRISPR Therapeutics Establish Collaboration to Use CRISPR-Cas9 Gene Editing Technology to Discover and Develop New Treatments for Genetic Diseases*, BUS. WIRE (Oct. 26, 2015), <http://www.businesswire.com/news/home/20151026005392/en/Vertex-CRISPR-Therapeutics-Establish-Collaboration-CRISPR-Cas9-Gene> [https://perma.cc/4HYM-SE7F].

Exchange Commission (SEC) recently,¹³ and rumors abound that other firms will follow suit in the near future.¹⁴

Despite its renown¹⁵ in select scientific niches, CRISPR continues to be an arcane secret in the legal realm. Whereas scientific scholarship has produced thousands of publications on CRISPR,¹⁶ legal scholarship concerning this transformative biotechnology is virtually nonexistent.¹⁷ The gap is striking, notably on account of an ongoing, high-stakes, intellectual property battle over patent rights to CRISPR systems with multi-billion-dollar ramifications.¹⁸

The neglect of CRISPR in legal scholarship poses grave uncertainty regarding how the law will treat this emerging technology going forward. Legal scholars have either largely ignored this field or kept a distance from it, presumably due, in part, to the challenges that complex scientific principles often pose to non-scientists in the legal

13. Editas Medicine, Inc., *Form S-1 Registration Statement Under the Securities Act of 1933*, U.S. SEC. & EXCHANGE COMMISSION (Jan. 4, 2016), <http://www.sec.gov/Archives/edgar/data/1650664/000104746916009534/a2226902zs-1.htm> [<https://perma.cc/4F4E-TNRU>].

14. See, e.g., Chen, *supra* note 12. Between the time this Article was accepted for publication and its printing, other companies have filed for initial public offerings with the SEC. For instance, CRISPR Therapeutics AG filed for an initial public offering with the SEC on September 9, 2016. CRISPR Therapeutics AG, *Form S-1 Registration Statement Under the Securities Act of 1933*, U.S. SEC. & EXCHANGE COMMISSION (Sept. 9, 2016), <http://www.nasdaq.com/markets/ipos/filing.ashx?filingid=11077159> [<https://perma.cc/KM9L-9YEH>].

15. CRISPR earned the 2015 “Breakthrough of the Year” accolade awarded by the prominent *Science* journal. Marcia McNutt, *Breakthrough to Genome Editing*, 350 *SCIENCE* 1445, 1456 (2015).

16. See *supra* note 11 and accompanying text.

17. An unfiltered search on the Westlaw database using the “CRISPR” acronym at the time this Article was completed in late 2015 returned zero hits for all primary—statutory and case law—sources, and only one hit for all legal scholarship journals. Westlaw Search for CRISPR, WESTLAW (search for all documents containing “CRISPR”) (last visited Feb. 1, 2016). The sole mention of CRISPR in all of legal scholarship was relegated to one sentence without explanation of what CRISPR is or even what it means. See Girard Kelly, Note, *Choosing the Genetics of Our Children: Options for Framing Public Policy*, 30 *SANTA CLARA HIGH TECH. L.J.* 303, 312 (2014).

18. A patent interference proceeding is underway, which challenges priority and validity of the first CRISPR patent. See *Engineering and Optimization of Systems, Methods and Compositions for Sequence Manipulation with Functional Domains*, U.S. Patent No. 8,993,233 (filed Dec. 12, 2013) (issued Mar. 31, 2015). In early 2016, the U.S. Patent and Trademark Office agreed to allow the interference proceedings to determine whether the Broad Institute of MIT and Harvard—on one side—or the University of California, Berkeley, the University of Vienna, and Emmanuelle Charpentier—on the opposite side—were first to invent CRISPR under US Patent Law. See Heidi Ledford, *Bitter Fight over CRISPR Patent Heats up*, 529 *NATURE* 265, 265 (2016), http://www.nature.com/polopoly_fs/1.17961!/menu/main/topColumns/topLeftColumn/pdf/nature.2016.17961.pdf [<https://perma.cc/6MGY-TLNA>].

and legislative arenas.¹⁹ A recent concurring opinion by the late Justice Antonin Scalia famously illustrated the degree of scientific antipathy among some members of the legal community.²⁰ Exercising great candor,²¹ Scalia conceded his lack of knowledge of relevant scientific details in a case before him.²² At the same time, he disturbingly remarked he did not even believe in scientific facts that have been well established for decades.²³

19. Consider, for example, the questions and commentary by Justices of the Supreme Court during oral argument in a recent case involving complex concepts in genetics and molecular biology. See *generally* Transcript of Oral Argument, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 12-398), http://www.supremecourt.gov/oral_arguments/argument_transcripts/12-398-amc7.pdf [<https://perma.cc/8STG-PXJF>].

"I thought that maybe the cDNA was kind of an economy class gene, was—it wasn't. . . . That may be incorrect for the record, but that was my present understanding." *Id.* at 20:6 (Kennedy, J.).

I just didn't understand, because I thought the . . . chromosome has the BRCA gene in the middle of it and it's attached to two ends. But also in the body, perhaps because cells die, there is isolated DNA. . . . I probably misread it.

There's a better chance that I've misread it.

Id. at 38:2 (Breyer, J.) (BRCA appears without emphasis in the original transcript, though proper scientific nomenclature requires the gene to be italicized).

My understanding is that here, . . . what's involved, is snipping. You've got the thing there and you snip—snip off the top and you snip off the bottom and there you've got it. . . . I still don't understand what—in what sense it's different than just snipping along—along the line.

Id. at 41:8, 42:22 (Roberts, C.J.).

To get back to your baseball bat example, which at least I—I can understand better than perhaps some of this biochemistry, I suppose that in . . . all of that time possibly someplace a branch has fallen off a tree and it's fallen into the ocean and it's been manipulated by the waves, and then something's been washed up on the shore, and what do you know, it's a baseball bat.

Id. at 48:4 (Alito, J.).

"[I]f I've read it correctly, that when you have an R—the messenger RNA does not have the same base pairs. There's a U or something instead of an A or whatever it is." *Id.* at 18:5 (Breyer, J.).

20. See *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2120 (2013) (Scalia, J., concurring in part and concurring in the judgment) ("I join the judgment of the Court . . . except Part I-A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief.").

21. To some extent, Scalia's admission is commendable from the perspective that a person in a position of great power should not be afraid to admit knowledge gaps. After all, no human holds absolute knowledge in any area. On the other hand, it is worrisome that a powerful person may be called to decide pivotal questions with broad societal implications when that person makes no effort whatsoever to close self-perceived knowledge gaps. Expressing disbelief in science is not sufficient. Those with power to delineate the contours of what constitutes the rule of law ought to educate themselves about matters before them.

22. *Myriad*, 133 S. Ct. at 2120.

23. See *id.*

That kind of scientific aversion has corrosive effects. It ultimately hinders the sort of interdisciplinary dialogue and insight required to fully understand and address significant problems in an increasingly interconnected world.²⁴ In the near future, law- and policy-makers will be confronted with many questions related to CRISPR, and the legal community must proactively take steps to familiarize itself with this new technology. Given the rapid expansion of CRISPR-based applications, the void in legal scholarship concerning the technology is becoming increasingly problematic.

As a testament to this growing problem, Judge David Neuberger, President of the UK Supreme Court, recently published a commentary in *Nature* calling attention to the scientific community and arguing that scientific primers would be “hugely beneficial” for the legal community.²⁵ Such primers, he contended, would save money and time, help assess the reliability of expert witnesses, and increase the proportion of cases that are settled without trial.²⁶ Specifically, he singled out genetic engineering as an area in which a primer would be useful to jurists given that legal controversies in the field are likely to recur.²⁷

In the absence of on-point law, some in the scientific community are campaigning, in arguably self-serving ways,²⁸ for a

24. Paul Enríquez, *Deconstructing Transnationalism: Conceptualizing Metanationalism as a Putative Model of Evolving Jurisprudence*, 43 VAND. J. TRANSNAT'L L. 1265, 1269, 1336 (2010).

25. David Neuberger, *Stop Needless Dispute of Science in the Courts*, 531 NATURE 9, 9 (2016).

26. *Id.*

27. *Id.*

28. See Edward Lanphier et al., *Don't Edit the Human Germ Line*, 519 NATURE 410, 410 (2015) (advocating for a complete ban of germline genome editing). Notably, this commentary co-authored by Edward Lanphier, President and Chief Executive Officer of Sangamo BioSciences, highlights a meaningful need to elaborate on issues concerning competing financial interests. Sangamo BioSciences currently controls a vast intellectual property portfolio comprising twenty issued U.S. patents encompassing the foundational technology of design, selection, and application of an older generation of genome editing tools consisting of Zinc Finger proteins, nucleases, and transcription factors. See Sangamo BioSciences, Inc., *Form 10-K Annual Report Under the Securities Act of 1933*, U.S. SEC. & EXCHANGE COMMISSION (Dec. 31, 2014), https://www.sec.gov/Archives/edgar/data/1001233/000156459015000950/sgmo-10k_20141231.htm [<https://perma.cc/N68E-4X64>]. As of February 4, 2015, Sangamo has compiled “133 families of internally generated U.S. patent filings, including 120 U.S. and 437 foreign issued patents.” *Id.* A few things are worth pointing out.

First, CRISPR-based biotechnologies may pose an economic threat to Sangamo's monopoly over genome editing using older Zinc Finger-based technologies. Although Sangamo has recently hopped on the CRISPR wagon, see, e.g., Screening Assays for Therapeutics for Parkinson's Disease, U.S. Patent Application No. 14/647,732 (filed Dec. 2, 2013), it lacks the commanding foundational intellectual property it enjoys in the Zinc Finger field. Second, many of Sangamo's gene editing biotechnologies, some of which are currently in clinical trials, see *infra* notes 179–

consensus to preempt antagonistic regulation and prescribe subjective standards of use under the misguided auspices of *a priori* scientific empiricism. This must give us pause. Einstein memorably remarked, “[T]he man of science is a poor philosopher.”²⁹ Most scientists—by training—are unfamiliar with intricate legal principles, constitutional doctrine, regulatory processes, and policy making; likewise, most lawyers are oblivious to scientific theory, physico-chemical laws, and cellular and macromolecular processes. Given these vastly different realms of knowledge, it is understandable that many scientists and lawyers often pursue insularism by academic discipline. Surely, there is comfort in academic seclusion, but isolation is often dangerous to learning and the pursuit of knowledge. “People do not learn very much when they are surrounded only by the likes of themselves.”³⁰ Interdisciplinary colloquy, therefore, is the most sensible approach to bridge the current chasm between science and law surrounding this momentous biotechnology.

Broadly speaking, this Article seeks to shrink the scholarly gap vis-à-vis genome editing and CRISPR-based technologies in legal literature. It is the first of a series of forthcoming articles³¹ that, collectively, propose a normative structural legal framework; namely, they conceptualize a jurisprudence of scientific empiricism that is broadly adaptable to addressing questions of science in law. The scientific empiricism referred to in this Article specifically concerns the natural sciences—e.g., physics, chemistry, biology—and not the

81, are based on somatic cell, rather than germ cell, therapeutics. Correcting genomes in the germline is arguably more effective than that in somatic cells, given that germ cells are totipotent and give rise to all cell types. Accordingly, CRISPR-Cas9 germline editing could in theory, if proven safe, obviate resorting to a number of Sangamo’s therapeutic tools, which would dilapidate more than a decade of capital investments in research and development. Third, Lanphier and colleagues’ efforts to distinguish somatic and germline editing along with claims that germline therapeutic benefits are tenuous, and philosophically and ethically unjustifiable, see Lanphier et al., *supra*, at 411, inordinately approach the logical fallacy of a distinction without a difference, particularly given the commentary’s moral-arbiter tone. The authors avoid acknowledging that, as with any incipient biotechnology including Sangamo’s own Zinc Finger Nucleases at one time, safety and ethical concerns are always part of the calculus behind a cost-benefit analysis for clinical applications of a technology in its early developmental stages. For a more detailed discussion of Zinc Finger Nucleases and other older genome editing technologies based on protein-DNA interactions, see discussion *infra* Section III.C.

29. Albert Einstein, *Physics and Reality*, 221 J. FRANKLIN INST. 349, 349 (Jean Piccard trans., 1936). Whether his assessment is correct is, of course, beyond the scope of this Article.

30. Regents of the Univ. of Cal. v. Bakke, 438 U.S. 265, 312 n.48 (1978) (citing William G. Bowen, *Admissions and the Relevance of Race*, PRINCETON ALUMNI WKLY., Sept. 26, 1977, at 9).

31. See, e.g., Paul Enriquez, *CRISPR GMOs*, 18 N.C. J.L. & TECH. (forthcoming 2017), available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2928557 [https://perma.cc/B6X9-WR8S].

social sciences—e.g., sociology, psychology, economics, political science, etc. This distinction is mainly due to discrete research methodologies and analytical tools endogenous to each discipline.³² The paradigm proposed here originates from the Supreme Court's recent decision in *Association for Molecular Pathology v. Myriad Genetics*, which this Article will refer to as *Myriad*.³³

This Article introduces CRISPR and the next generation of genome editing tools to legal scholarship. By providing a resource for jurists, scholars, and practitioners alike, it challenges conventional views regarding the false dichotomy frequently associated with mutually exclusive normative roles for science and law—the proximate cause driving laissez-faire attitudes³⁴ of deference to elude questions of “law in science and science in law.”³⁵

32. In particular, this point revolves around the fact that, whereas the natural sciences rely extensively on quantitative methods, the social sciences depend, to a great extent, on qualitative research. The proposed framework in this Article is exclusively concerned with scientific empirical data that is reproducible and quantifiable. Hence, for example, a jurisprudence of scientific empiricism would seek to answer whether genome editing may lawfully be used to correct a genetic mutation associated with a monogenic disease as a consequence of a clinical trial, given the existence of empirical data demonstrating that such genetic corrections are feasible and reproducible (or not) under controlled experiments. The approach, however, would not apply to deciding the legal status by studying the decision making processes and attitudes toward genome editing of the patients undergoing treatment under the clinical trial. The primary empirical data acquired from social scientists in the former scenario would largely depend on interviews and other qualitative research that may be considered ontologically subjective.

It bears to note that, although the notion of a jurisprudence of scientific empiricism has not previously been proposed as articulated in this Article, in the past, scholars have discussed—amid great controversy—using empirical evidence from the *social sciences* to instruct legal analysis. See, e.g., ANGELO N. ANCHETA, *SCIENTIFIC EVIDENCE AND EQUAL PROTECTION OF THE LAW* (2006); Joshua B. Fischman, *Reuniting 'Is' and 'Ought' in Empirical Legal Scholarship*, 162 U. PA. L. REV. 117 (2013); Tracey L. Meares, *Three Objections to the Use of Empiricism in Criminal Law and Procedure—and Three Answers*, 2002 U. ILL. L. REV. 851 (2002); Craig Allen Nard, *Empirical Legal Scholarship: Reestablishing a Dialogue Between the Academy and Profession*, 30 WAKE FOREST L. REV. 347 (1995); Steven R. Schlesinger & Janet Lesse, *Justice Harry Blackmun and Empirical Jurisprudence*, 29 AM. U. L. REV. 405 (1980); J. Alexander Tanford, *The Limits of a Scientific Jurisprudence: The Supreme Court and Psychology*, 66 IND. L.J. 137 (1990); Timothy Zick, *Constitutional Empiricism: Quasi-Neutral Principles and Constitutional Truths*, 82 N.C. L. REV. 115 (2003).

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

34. See, e.g., *Craig v. Boren*, 429 U.S. 190, 204 (1976) (“There is no reason to belabor this line of analysis. It is unrealistic to expect either members of the judiciary or state officials to be well versed in the rigors of experimental or statistical technique.”); ROBIN FELDMAN, *THE ROLE OF SCIENCE IN LAW* 37–48 (2009) (discussing lawyers’ proclivities to defer to scientific expertise).

35. This Article adopts this phrase from the title of an article penned by Oliver W. Holmes, Jr. over a century ago. See Oliver Wendell Holmes, *Law in Science and Science in Law*, 12 HARV. L. REV. 443, 444 (1899). Ironically, the same Holmes authored the infamous *Buck v. Bell* decision upholding the constitutionality of sexual sterilization for the mentally disabled relying on dubious science. See discussion *infra* Section V.C.

Although legal scholars need not become “amateur scientists,”³⁶ this Article insists that law- and policy-makers must become engaged and proactively strive to grasp the core elements of significant technologies like CRISPR, which hold the power to transform the world. The Article’s overarching goals are to (1) ignite a measured and scholarly conversation about the current and prospective uses of select biotechnologies, stripped of illusory conjectures, and (2) provide the legal community with a primer on genome editing to facilitate an interdisciplinary exchange of ideas. There is much the legal community can contribute to this field.

In furtherance of these goals, the Article makes two independent but synergistic contributions. First, it provides a robust and comprehensive epistemic foundation of the history and current state of the scientific literature in the field of genome editing. It is descriptive and technical, but is intended to be suitable for both legal and scientific audiences. This work is precisely the type of primer for which Judge David Neuberger recently advocated.³⁷ Notably, it faithfully tracks and explains primary scientific sources, something generally absent from legal scholarship construing scientific themes. This prologue is essential because, without a detailed explanation and coherent understanding of the nuts and bolts of genome editing, the audience may extrapolate unfounded notions of the immediate, short-term, and long-term prospects and limitations of the technology.³⁸ Simply put, a solid foundation of key genome editing scientific principles offers the structural scaffolding—an insurance policy, so to speak—for a fruitful dialogue grounded in reason rather than baseless conjecture.

The second contribution propounds positive claims for prospective applications of genome editing that are firmly grounded in empirical evidence.³⁹ One substantial predicament about powerful technologies is that they are often prone to manipulation by speculative agents who—knowingly or not—spread misinformation and oversell what is technologically feasible. By anchoring prospective technological applications in a jurisprudence of scientific empiricism, this Article advocates for a normative approach that consolidates genome editing applications into a uniform doctrinal

36. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 601 (1993) (Rehnquist, C.J., concurring in part and dissenting in part).

37. *See* Neuberger, *supra* note 25, at 9.

38. *See* discussion *infra* Parts IV and V.

39. A revolution is well underway in genome editing science with the potential to fundamentally reshape the way we approach agriculture, synthetic biology, ecosystems, bioterrorism, gene therapy, and biomedicine through law and policy. *See* discussion *infra* Part IV.

structure unencumbered by common substantive impediments to constructive debate. These impediments consist of impractical and often sensationalist claims about issues raised by technological advances and are collectively characterized as “deceptive simplicity.”⁴⁰ This approach aims to cultivate and expand *Myriad*’s roots of scientific empiricism and is broadly applicable to other fields of law in which scientific inquiry may play important or dispositive roles.

The synergism between these two contributions underscores the importance of interdisciplinary efforts to prevent, mitigate, and resolve future “global problems”⁴¹ raised by technological progress. In essence, a jurisprudence of scientific empiricism is based on the notion that “[c]ritical thinking . . . cannot possibly be restricted to the examination of the concepts of [one’s] own specific field.”⁴²

This Article is divided into four sections. Part II begins by proposing a genome editing definition,⁴³ a necessity for any applicable regulatory or statutory scheme.⁴⁴ It introduces the reader to the manipulation of genetic material, explains how this concept of biotechnology is well rooted in popular and scientific history, and describes the discovery of two critical elements that facilitated genome editing.

Part III rummages through the genome editing toolbox and examines the development of modern, cost-effective, powerful, programmable tools that are democratizing researchers’ access to genome editing technologies.

Part IV examines current applications of genome editing in a number of fields ranging from stem cell research and agriculture to

40. Although this term has not been used in the context proposed in this Article, it has appeared in legal scholarship, at least as early as 1937. See *The Availability of a Principal’s Defense to His Uncompensated Surety*, 46 YALE L.J. 833, 839 (1937); see also, e.g., Brief for Respondent, *Tan v. Phelan*, 333 U.S. 6 (1948) (No. 370), 1947 WL 44413, at *12; Georg Schwarzenberger, *The Inductive Approach to International Law*, 60 HARV. L. REV. 539, 569 (1947); Frederick M. Rowe, Note, *Price Discrimination, Competition, and Confusion: Another Look at Robinson-Patman*, 60 YALE L.J. 929, 961 n.210 (1951); Note, *State Law and Uniformity in Federal Taxation*, 55 HARV. L. REV. 255, 255 (1941).

41. Enríquez, *supra* note 24, at 1269, 1336. CRISPR-based technologies are poised to raise ethical and social problems with global implications. See, e.g., *UN Panel Warns Against ‘Designer Babies’ and Eugenics in ‘Editing’ of Human DNA*, U.N. NEWS CTR. (Oct. 5, 2015), <http://www.un.org/apps/news/story.asp?NewsID=52172> [<https://perma.cc/7YHS-9KQ4>].

42. Einstein, *supra* note 29, at 349.

43. See also *infra* notes 53–55 and accompanying text.

44. The search for meaning in ambiguous statutory text lacking robust definitions has, in recent years, lead to increased use of dictionaries in judicial opinions. See, e.g., James J. Brudney & Lawrence Baum, *Oasis or Mirage: The Supreme Court’s Thirst for Dictionaries in the Rehnquist and Roberts Eras*, 55 WM. & MARY L. REV. 483 (2013) (pointing out that as many as one-third of statutory decisions in modern Supreme Court jurisprudence consult dictionaries in often highly subjective modes).

biofuels production and human pathophysiology. It meticulously acquaints the reader with prospective genome editing uses in each field, relying exclusively on primary scientific sources. Importantly, the Article deliberately contemplates genome editing from diverse viewpoints and recognizes that every technology endowed with awe-inspiring powers should be handled responsibly and with respect.⁴⁵ This Part argues that, taken together, genome editing biotechnologies are not mere tools for basic research, but rather epitomize prolific mines for future significant medical and scientific breakthroughs. The goal is to engage the legal community in discussions about the technology's potential for good and bad, including what should or should not be done to legally promote or hinder it.⁴⁶

Finally, Part V concentrates on deceptive simplicity and implements the normative framework articulated in this preamble to delineate adequate contours for a discussion that avoids the squabbles frequently set forth by manufactured fears; the kerfuffle concerning “designer babies”⁴⁷ is one example relevant to genome editing. To that end, it reconsiders *Buck v. Bell*⁴⁸ and the indelible scar it left on

45. Consider the advent of the atomic bomb. Some argue that the technology changed the world for the better as it brought an end to the bloodiest conflict the world has ever witnessed. MICHAEL KORT, *THE COLUMBIA GUIDE TO HIROSHIMA AND THE BOMB* 8, 46–49 (2007); Winston Churchill, *Leader of the Opposition, Where Do We Stand?*, (Aug. 16, 1945), in 11 *VITAL SPEECHES DAY* 738 (1945), <http://www.ibiblio.org/pha/policy/1945/1945-08-16c.html> [<https://perma.cc/7RS7-C76R>]. Others decry the bomb as an instrument that led to utter destruction in two cities, nearly a half-million deaths, and political instability for decades after War World II. GOSLING, *supra* note 5, at 51, 54, (stating that the bombs dropped on Japan eventually killed an estimated 340,000); KORT, *supra*, at 76–78, 81 (describing political instability); Martin J. Sherwin, *The Atomic Bomb and the Origins of the Cold War: U.S. Atomic-Energy Policy and Diplomacy, 1941-45*, 78 AM. HIST. REV. 945, 945 (1973). Computers and the Internet have changed—in both positive and negative ways—how humans communicate, access information, shop, and even perceive reality. See generally, e.g., Kaveri Subrahmanyam et al., *The Impact of Home Computer Use on Children's Activities and Development*, 10 CHILD. & COMPUTER TECH. 123 (2000). Genome editing is no different in this sense. Although this Article highlights many potential benefits, it by no means argues that the biotechnology should be viewed as a panacea for all world problems.

46. To some extent, the scientific community has begun engaging in this debate. See, e.g., *Scientists Debate Ethics of Human Gene Editing at International Summit*, GUARDIAN (Dec. 1, 2015), <https://www.theguardian.com/science/2015/dec/01/human-gene-editing-international-summit> [<https://perma.cc/FY62-EJCL>]. However, the legal community has not assumed a leadership role to direct a pervasive discussion of legal issues framed by genome editing technologies.

47. See, e.g., Joan Mahoney, *Genome Mapping and Designer Babies*, 79 UMKC L. REV. 309, 313 (2010) (citing not a single primary scientific source for the proposition that new technology may presumably allow parents to decide eye color and sexual orientation of designed babies); discussion *infra* Section V.A.

48. *Buck v. Bell*, 274 U.S. 200 (1927).

American jurisprudence from a novel perspective—namely, to illustrate the dangers of unchecked deceptive simplicity.

Much has been written about *Buck* in legal scholarship and this Article will not belabor what has already been said about the case. The conventional view is that *Buck*'s holding is illegitimate because it rests on false, or pseudo, science⁴⁹ and incorrect moral and ethical principles.⁵⁰ This Article rejects that view and applies a jurisprudence of scientific empiricism to instead contend that *Buck* is a direct product, not of false science, but of rampant *deceptive simplicity* that permeated every aspect of elite circles at the time it was decided.⁵¹

The distinction between false science and deceptive simplicity is crucial. Whereas false, or pseudo, science refers to a system of theories and rules configured to give the appearance of being grounded in scientific methodology, deceptive simplicity strips logic beyond a bare minimum using vague intuition born out of second-hand, reductive explanations that diminish a scientific concept to a deceptively simple catchphrase. To support this proposition, the Article studies *Buck*'s substantively porous decision, which cited not a single scientific source for the Court's lending of credence to the notion that "heredity plays an important part in the transmission of insanity, imbecility, etc."⁵²

Lastly, this Part sets the stage for a series of upcoming articles that aim to analyze the prospective benefits and risks associated with the use of genome editing biotechnologies from statutory, regulatory, constitutional, international, ethical, egalitarian, scientific, and policy standpoints. In so doing, it encourages scholarly debate and highlights the pivotal synergistic roles that law, science, and public policy will play on the development of this truly exceptional and transformative emerging biotechnology.

49. Pseudoscience is defined as "a system of theories, assumptions, and methods erroneously regarded as scientific." *Pseudoscience*, MERRIAM-WEBSTER ONLINE DICTIONARY, <http://www.merriam-webster.com/dictionary/pseudoscience> [<https://perma.cc/8FKP-4GVS>] (last visited Feb. 23, 2017); see also discussion *infra* Section V.C.

50. See, e.g., Stephen Jay Gould, *Carrie Buck's Daughter*, 2 CONST. COMMENT. 331, 339 (1985); Victoria Nourse, *Buck v. Bell: A Constitutional Tragedy from a Lost World*, 39 PEPP. L. REV. 101, 107 (2013) (arguing *Buck* is not part of constitutional law curricula partly because it is seen as a case about a false science).

51. See discussion *infra* notes 558–70 and accompanying text.

52. *Buck*, 274 U.S. at 206.

II. GENOME EDITING—A SYNOPSIS

Genome editing,⁵³ as referred to in this Article, encompasses scientific technological advances that enable rational genetic engineering⁵⁴—at a local (gene) or global (genome) level—to facilitate precise insertion, removal, or substitution of fragments of Deoxyribonucleic acid (DNA) molecules, comprising one or more nucleotides—Adenine (A), Thymine (T), Cytosine (C), Guanine (G), and possibly others which may be synthetically derived⁵⁵—into the cell(s) of an organism's genome. This process of manipulation of

53. Different colloquial permutations of the term 'genome editing' exist including, but not limited to, 'gene editing,' 'genetic editing,' 'genetic engineering,' 'gene engineering,' 'gene targeting,' 'gene splicing,' and 'genome surgery.' Although the line between these terms is often blurred beyond discernible recognition, this Article proposes that genome engineering may be best interpreted as the rational *design* of genomes, while genome editing may describe the *process of bringing the design* to fruition. However, for purposes of this discussion, they are all used interchangeably to denote genome editing as an umbrella term with the definition provided. Notwithstanding, other definitions abound. For instance, *Merriam-Webster Dictionary* defines *genetic engineering* as "the group of applied techniques of genetics and biotechnology used to cut up and join together genetic material and especially DNA from one or more species of organism and to introduce the result into an organism in order to change one or more of its characteristics." *Genetic Engineering*, MERRIAM-WEBSTER ONLINE DICTIONARY, <http://www.merriam-webster.com/dictionary/genetic%20engineering> [<https://perma.cc/E3VG-KDMU>] (last visited Feb. 23, 2017). Genome editing involves the precise modification of the nucleotide sequence of the genome. See, e.g., Matthew H. Porteus, *Towards a New Era in Medicine: Therapeutic Genome Editing*, 16 *GENOME BIOLOGY* 1 (2015); accord Ignazio Maggio & Manuel A.F.V. Gonçalves, *Genome Editing at the Crossroads of Delivery, Specificity, and Fidelity*, 33 *TRENDS BIOTECHNOLOGY* 280, 280 (2015); Nature Am., Inc., *Method of the Year 2011*, 9 *NATURE METHODS* 1, 1 (2012). The propounded definition in this Article is presented as a more robust and inclusive definition than that found in the current scientific literature.

54. The term genetic engineering was coined in the 1940s as the "purposive manipulation of genetic material." BRIAN STABLEFORD, *SCIENCE FACT AND SCIENCE FICTION: AN ENCYCLOPEDIA* 207 (Routledge 2006). At the time, the term was meant to describe the molecular surgical cutting and stitching of chromosomes to remove or rearrange sets of genes. *Id.* Genetic engineering, eugenics, and selective breeding were main themes in Robert A. Heinlein's novel *Beyond This Horizon*, which originally appeared as a two-part serial in the spring of 1942. *Beyond This Horizon*, WIKIPEDIA, https://en.wikipedia.org/wiki/Beyond_This_Horizon [<https://perma.cc/N9B8-GCF9>] (last updated Dec. 18, 2016). The term was also independently imported into science fiction by Jack Williamson in *Dragon's Island* (1951). STABLEFORD, *supra*, at 207.

55. Synthetic, non-natural nucleotides to expand the natural four-letter (A, C, T, G) genetic alphabet or "code" have been reported in the scientific literature. See, e.g., Millie M. Georgiadis et al., *Structural Basis for a Six Nucleotide Genetic Alphabet*, 137 *J. AM. CHEMICAL SOC'Y* 6947 (2015); Denis A. Malyshev et al., *A Semi-Synthetic Organism with an Expanded Genetic Alphabet*, 509 *NATURE* 385 (2014); Itaru Okamoto et al., *High Fidelity, Efficiency and Functionalization of Ds-Px Unnatural Base Pairs in PCR Amplification for a Genetic Alphabet Expansion System*, 5 *ACS SYNTHETIC BIOLOGY* 1220 (2016); Joseph A. Piccirilli et al., *Enzymatic Incorporation of a New Base Pair into DNA and RNA Extends the Genetic Alphabet*, 33 *NATURE* 33 (1990); Liqin Zhang et al., *Evolution of Functional Six-Nucleotide DNA*, 137 *J. AM. CHEMICAL SOC'Y* 6734 (2015).

endogenous nucleotide sequences constitutes the bedrock of modern biotechnology and molecular biology. It can be accomplished through a variety of methods using DNA-cutting nucleases (proteins that act as molecular scalpels), viral-based systems, chemistry-based DNA scission systems, and, most recently, Ribonucleic acid (RNA)-guided DNA nucleases.⁵⁶

Despite the recent fervor surrounding genome editing in the last three years,⁵⁷ the concept itself is not new. Following the discovery of genes by Gregor Mendel in 1866,⁵⁸ DNA in 1869 by Friedrich Miescher,⁵⁹ and the subsequent work of Nobel Laureate Thomas Morgan, who demonstrated that genes are carried on chromosomes and constitute the molecular basis of heredity,⁶⁰ the notion of manipulating genetic material took root in the popular culture.⁶¹ A peculiar finding concerning reduced efficiency of viral infection in bacterial hosts—i.e., bacterial defensive mechanisms to viral infection—in the 1950s⁶² led to the hypothesis of the existence of “restriction and modification” systems, which functioned as effective

56. For a detailed discussion of these methods, see *infra* Sections III.A–D.

57. See, e.g., Meeri Kim, *Scientists Are Growing Anxious About Genome-Editing Tools*, WASH. POST (May 18, 2015), https://www.washingtonpost.com/national/health-science/scientists-are-growing-anxious-about-genome-editing-tools/2015/05/18/0a4db63c-ef4e-11e4-8abc-d6aa3bad79dd_story.html [<https://perma.cc/LKH8-6EB9>]; Vivek Wadhwa, *Why There's an Urgent Need for a Moratorium on Gene Editing*, WASH. POST (Sept. 8, 2015), <https://www.washingtonpost.com/news/innovations/wp/2015/09/08/why-theres-an-urgent-need-for-a-moratorium-on-gene-editing/> [<https://perma.cc/L83M-4FM9>].

58. Peter Little, *The Book of Genes*, 402 NATURE 467, 467–68 (1999). Although Mendel did not coin the term “gene,” he described the presence of discrete inherited units that give rise to observable physical characteristics—now called genes. See generally Gregor Mendel, *Versuche über Pflanzenghybriden* [*Experiments in Plant Hybridization*] (1866), <http://www.esp.org/foundations/genetics/classical/gm-65.pdf> [<https://perma.cc/ZX84-RT2K>]. Mendel’s seminal 1866 paper was largely overlooked for over thirty-five years, long after his death in 1884, until three scientists rediscovered his work and independently verified some of his original findings. Thomas H. Morgan, *The Relation of Genetics to Physiology and Medicine*, in NOBEL LECTURES, PHYSIOLOGY OR MEDICINE 1922-1941, at 313–15 (Elsevier Publishing Co. 1965), http://www.nobelprize.org/nobel_prizes/medicine/laureates/1933/morgan-lecture.pdf [<https://perma.cc/5TNV-YRU6>] (original lecture by Thomas H. Morgan delivered in 1934).

59. See generally Ralph Dahm, *Discovering DNA: Friedrich Miescher and the Early Years of Nucleic Acid Research*, 122 HUM. GENETICS 565 (2008).

60. Edward B. Lewis, *Thomas Hunt Morgan and His Legacy*, NOBELPRIZE.ORG, http://www.nobelprize.org/nobel_prizes/medicine/laureates/1933/morgan-article.html [<https://perma.cc/L8AZ-RSNU>].

61. Numerous works in scientific romance and science fiction began to incorporate themes of biological engineering and genetic manipulation in creative ways during the 1910s, 1920s, and every decade thereafter. For a detailed list of such popular works in the 20th Century, see STABLEFORD, *supra* note 54, at 207–09.

62. S.E. Luria, *Host-Induced Modifications of Viruses*, 18 COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY 237, 237 (1953).

barriers to DNA uptake.⁶³ And in 1970, the first “restriction enzyme”⁶⁴ was characterized,⁶⁵ thus offering proof-of-concept that a protein can trigger sequence-specific enzymatic cleavage of DNA molecules.

The restriction enzyme quantum leap underscored the requirement of DNA double-stranded breaks⁶⁶ (DSBs) as the critical first step in genome editing. However, as time passed, it became apparent that these breaks in DNA were highly deleterious⁶⁷ because they promoted genome instability,⁶⁸ interfered with the pivotal processes of replication and transcription,⁶⁹ led to chromosomal rearrangements—inversions and translocations—associated with cancers and other diseases,⁷⁰ and often induced apoptosis (cell death).⁷¹ Due to the hazardous nature of DSBs to DNA stability,

63. Werner Arber, *Host-Controlled Modification of Bacteriophage*, 19 ANN. REV. MICROBIOLOGY 365, 370–72 (1965).

64. Restriction enzymes, also known as restriction endonucleases, are proteins capable of cutting DNA at or near specific nucleotide sequences. See Richard J. Roberts & Kenneth Murray, *Restriction Endonucleases*, 4 CRITICAL REV. BIOCHEMISTRY 123, 123 (1976).

65. Thomas J. Kelly & Hamilton O. Smith, *A Restriction Enzyme from Hemophilus Influenzae: II. Base Sequence of the Recognition Site*, 51 J. MOLECULAR BIOLOGY 393, 393 (1970). To date, more than 3,800 restriction enzymes have been biochemically or genetically characterized. Richard J. Roberts, Tamas Vincze, Janos Posfai & Dana Macelis, *REBASE—Enzymes and Genes for DNA Restriction and Modification*, 35 NUCLEIC ACIDS RES. D269, D269 (2007).

66. Structurally, DNA comprises two single-stranded molecules that come together via hydrogen bonds to form the famous DNA double helix. See James D. Watson & Francis H.C. Crick, *A Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737, 737 (1953). Accordingly, introducing a double-stranded, rather than a single-stranded, break is necessary to complete full scission of DNA.

67. E.g., Thomas Bonura et al., *Enzymatic Induction of DNA Double-Strand Breaks in Gamma-Irradiated Escherichia Coli K-12*, 72 PROC. NAT'L ACAD. SCI. U.S. 4265 (1975); David O. Ferguson & Frederick W. Alt, *DNA Double Strand Break Repair and Chromosomal Translocation: Lessons from Animal Models*, 20 ONCOGENE 5572 (2001); Paul Howard-Flanders & Lee Theriot, *Mutants of Escherichia coli K-12 Defective in DNA Repair and in Genetic Recombination*, 53 GENETICS 1137 (1966).

68. Cynthia J. Sakofsky et al., *Break-Induced Replication and Genome Stability*, 2 BIOMOLECULES 483, 483 (2012).

69. Andriy Khobta & Bernd Epe, *Interactions Between DNA Damage, Repair, and Transcription*, 736 MUTATION RES. 5, 5 (2012).

70. E.g., Giovanni Bosco & James E. Haber, *Chromosome Break-Induced DNA Replication Leads to Nonreciprocal Translocations and Telomere Capture*, 150 GENETICS 1037 (1998); Janet D. Rowley, *A New Consistent Chromosomal Abnormality in Chronic Myelogenous Leukaemia Identified by Quinacrine Fluorescence and Giemsa Staining*, 243 NATURE 290 (1973); L. Zech et al., *Characteristic Chromosomal Abnormalities in Biopsies and Lymphoid-Cell Lines from Patients with Burkitt and Non-Burkitt Lymphomas*, 17 INT'L J. CANCER 47 (1976); Chengming Zhu et al., *Unrepaired DNA Breaks in p53-Deficient Cells Lead to Oncogenic Gene Amplification Subsequent to Translocations*, 109 CELL 811 (2002).

71. Anthony J. Davis & David J. Chen, *DNA Double Strand Break Repair Via Non-Homologous End-Joining*, 2 TRANSLATIONAL CANCER RES. 130, 130 (2013).

complex mechanisms associated with deployment of specialized macromolecules that trigger repair of an injured DNA site have evolved within cells.

To date, at least three DSB repair pathways have been characterized⁷²:

(1) Nonhomologous End Joining (NHEJ),⁷³ (2) Microhomology-Mediated End Joining (MMEJ),⁷⁴ and (3) Homology-Directed Repair (HDR).⁷⁵ NHEJ is an error-prone DSB repair mechanism that can efficiently introduce small, random nucleotide mutations—insertions and deletions—capable of disrupting gene expression.⁷⁶ MMEJ is also an error-prone pathway, but uses microhomologous sequences—short homology sequences of a few nucleotides flanking the initial DSB site—to anneal and ligate broken DNA ends.⁷⁷ MMEJ DSB repair often leads to deletion mutations that play a role in cancers involving chromosomal translocation and telomere fusions.⁷⁸ Unlike NHEJ and MMEJ, HDR is significantly more precise, but requires the presence of an undamaged, homologous, donor template for repair.⁷⁹ This is the case in Homologous Recombination (HR), the most common form of HDR, where the requirement of longer sequence homology between the donor and acceptor DNA ensures highly accurate rates of DSB

72. Other DNA repair mechanisms—Direct Reversal, Base Excision Repair, Nucleotide Excision Repair, and Mismatch Repair—have been identified and act exclusively on single-stranded DNA breaks (SSB), rather than DSB. See generally GEOFFREY M. COOPER, *THE CELL: A MOLECULAR APPROACH* (2d ed. 2000), <http://www.ncbi.nlm.nih.gov/books/NBK9900/> [<https://perma.cc/JJJ2-M9RE>]. In addition, a recent report describes what appears to be a novel chromatin structure-specific mechanism of DNA repair involving nucleosomal DNA SSB. See Nikolay A. Pestov et al., *Structure of Transcribed Chromatin Is a Sensor of DNA Damage*, 1 SCI. ADVANCES e1500021 (2015). Although three pathways for DSB repair are known to date, there may be others awaiting characterization.

73. J. Kent Moore & James E. Harber, *Cell Cycle and Genetic Requirements of Two Pathways of Nonhomologous End-Joining Repair of Double-Strand Breaks in Saccharomyces Cerevisiae*, 16 MOLECULAR & CELLULAR BIOLOGY 2164, 2164 (1996); Thomas E. Wilson et al., *Yeast DNA Ligase IV Mediates Non-Homologous DNA End Joining*, 388 NATURE 495, 495 (1997).

74. Mitch McVey & Sang Eun Lee, *MMEJ Repair of Double-Strand Breaks (Director's Cut): Deleted Sequences and Alternative Endings*, 24 TRENDS GENETICS 529, 529–30 (2008). MMEJ is also known as “Alternative End Joining” or “Alternative NHEJ.” S. Sharma et al., *Homology and Enzymatic Requirements of Microhomology-Dependent Alternative End Joining*, 6 CELL DEATH & DISEASE e1697, e1697 (2015).

75. HARVEY LODISH ET AL., *MOLECULAR CELL BIOLOGY* § 12.5 (4th ed. 2000).

76. For an overview of the mechanism of NHEJ repair, see Davis & Chen, *supra* note 71, at 131–37.

77. McVey & Lee, *supra* note 74, at 529.

78. *Id.* at 535–36, 552 tbl.3; Catherine T. Yan et al., *IgH Class Switching and Translocations Use a Robust Non-Classical End-Joining Pathway*, 449 NATURE 478, 481 (2007).

79. Xuan Li & Wolf-Dietrich Heyer, *Homologous Recombination in DNA Repair and DNA Damage Tolerance*, 18 CELL RES. 99, 99 (2008).

repair. Together, these mechanisms of DNA repair constitute the second critical element required to facilitate genome editing.

A. The Rise of Recombinant DNA

The discovery of restriction enzymes capable of inducing DNA double-stranded breaks prone for repair marked the genesis of modern molecular medicine and biotechnology and gave rise to the era of recombinant DNA technology. As the list of restriction enzymes grew, the rational manipulation of genes and DNA sequences to study function yielded important research with pharmaceutical applications such as the large-scale production of insulin,⁸⁰ other hormones,⁸¹ and vaccines.⁸² The fundamental knowledge derived from the research fueled innovation in genetic engineering,⁸³ gave rise to new intellectual property,⁸⁴ and spawned a multi-billion-dollar biotechnology industry. At the same time, scientific fears of the repercussions of gene editing technologies began to percolate through popular discourse.⁸⁵

The concept of genome editing is well rooted in history. Scientists have long recognized the value of developing methods to

80. Lydia Villa-Komaroff et al., *A Bacterial Clone Synthesizing Proinsulin*, 75 PROC. NAT'L ACAD. SCI. U.S. 3727, 3727 (1978).

81. E.g., David V. Goeddel et al., *Direct Expression in Escherichia coli of a DNA Sequence Coding for Human Growth Hormone*, 281 NATURE 544 (1979); Keiichi Itakura et al., *Expression in Escherichia coli of a Chemically Synthesized Gene for the Hormone Somatostatin*, 198 SCIENCE 1056 (1977).

82. E.g., Cladd E. Stevens et al., *Hepatitis B Vaccine: Immune Responses in Haemodialysis Patients*, 316 LANCET 1211 (1980).

83. See, e.g., Stanley N. Cohen et al., *Construction of Biologically Functional Bacterial Plasmids in Vitro*, 70 PROC. NAT'L ACAD. SCI. U.S. 3240 (1973); David A. Jackson, Robert H. Symons & Paul Berg, *Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia Coli*, 69 PROC. NAT'L ACAD. SCI. U.S. 2904 (1972); Peter E. Lobban & Armin D. Kaiser, *Enzymatic End-to-End Joining of DNA Molecules*, 78 J. MOLECULAR BIOLOGY 453 (1973); Janet E. Mertz & Ronald W. Davis, *Cleavage of DNA by R1 Restriction Endonuclease Generates Cohesive Ends*, 69 PROC. NAT'L ACAD. SCI. U.S. 3370 (1972); Daniel Nathans & Hamilton O. Smith, *Restriction Endonucleases in the Analysis and Restructuring of DNA Molecules*, 44 ANN. REV. BIOCHEMISTRY 273 (1975).

84. E.g., Process for Producing Biologically Functional Molecular Chimeras, U.S. Patent No. 4,237,224 (filed Jan. 4, 1979).

85. The famous Asilomar Conference on Recombinant DNA took place in 1975 to discuss the potential safety hazards of emerging recombinant DNA biotechnologies. See generally Paul Berg, *Meetings That Changed the World: Asilomar 1975: DNA Modification Secured*, 455 NATURE 290 (2008), <http://www.nature.com/nature/journal/v455/n7211/full/455290a.html> [<https://perma.cc/G9XD-E8C2>].

induce DNA breaks and modify nucleotide sequences.⁸⁶ However, recent additions to the technological toolbox of genome editing have overruled long-held views of what is technologically feasible. Remarkable, cost-effective, easy-to-use, programmable tools developed in the last few years finally allow researchers to precisely engineer genomes in ways originally envisioned decades ago, yet methodologically beyond reach to prior generations of scientists.⁸⁷

The next Section surveys the transformative technologies of modern day genome editing that have revolutionized, and are revolutionizing, molecular biotechnology and biomedicine. Together, these biotechnologies offer potential promising applications for agriculture, synthetic biology, gene therapy, and eradication of diseases.

III. THE GENOME EDITING TOOLBOX

Armed with the bipartite insights of restriction enzyme-mediated DSBs and DNA repair, scientists began to explore genome engineering apace. As of this writing, the genome editing toolbox consists of systems that fit four categories: chemistry-based synthetic DNA scission, viral-based editing, nucleases that rely on protein-DNA interactions for targeting, and a revolutionary RNA-guided DNA nuclease system.

A. Chemistry-Based Synthetic DNA Scission

Early methods of chemical-mediated DNA scission involved the use of oligonucleotides⁸⁸—short DNA or RNA molecules—coupled to chemical reagents.⁸⁹ These complexes successfully induced site-specific cleavage of DNA⁹⁰ and activated DNA repair⁹¹ in yeast and

86. Stewart Scherer & Ronald W. Davis, *Replacement of Chromosome Segments with Altered DNA Sequences Constructed in Vitro*, 76 PROC. NAT'L ACAD. SCI. U.S. 4951 (1979); see also *supra* notes 65, 80–84 and accompanying text.

87. See discussion *infra* Part III.

88. See *Oligonucleotide*, MERRIAM-WEBSTER ONLINE DICTIONARY, <http://www.merriam-webster.com/dictionary/oligonucleotide> [<https://perma.cc/DP46-8MXP>] (last visited Feb. 25, 2017) (defining oligonucleotide as “a short nucleic-acid chain usually consisting of up to approximately 20 nucleotides.”).

89. Barbara C.F. Chu & Leslie E. Orgel, *Nonenzymatic Sequence-Specific Cleavage of Single-Stranded DNA*, 82 PROC. NAT'L ACAD. SCI. U.S. 963, 963 (1985).

90. Scott A. Strobel & Peter B. Dervan, *Site-Specific Cleavage of a Yeast Chromosome by Oligonucleotide-Directed Triple-Helix Formation*, 249 SCIENCE 73, 73 (1990); Scott A. Strobel et al., *Site-Specific Cleavage of Human Chromosome 4 Mediated by Triple-Helix Formation*, 254 SCIENCE 1639, 1639 (1991).

mammalian cells without the use of nucleases. Alternative DSB approaches also emerged involving Peptide Nucleic Acids (PNA)⁹² that associate with nucleases⁹³ and synthetic polyamides that bind DNA's minor groove.⁹⁴ Reports that the element Cerium⁹⁵ Ce(IV) species is highly stable and capable of cutting DNA via hydrolysis⁹⁶ paved the way for more sophisticated artificial DNA-cutting methods involving complexation of Ce(IV) with the chelating reagent Ethylenediaminetetraacetic acid (EDTA).⁹⁷ In recent years, a research team conceived a novel chemistry-based artificial restriction DNA cutter strategy featuring pseudo-complementary PNA and the metal complex Ce(IV)EDTA for targeting and cleavage.⁹⁸ Although these synthetic scission platforms—with or without the use of nucleases—have not been widely adopted, they demonstrate the value of chemistry-based cutting tools for genome editing.

B. Viral-Based Editing

A nuclease-free, viral-based system consisting of vectors using adeno-associated viruses⁹⁹ (AAV) has proven able to introduce specific

91. A. Fawad Faruqi et al., *Recombination Induced by Triple-Helix-Targeted DNA Damage in Mammalian Cells*, 16 MOLECULAR CELL BIOLOGY 6820, 6820 (1996).

92. PNA is an artificial molecule that resembles DNA or RNA, but has a protein-like, rather than a sugar phosphate, backbone. Peter E. Nielsen et al., *Sequence-Selective Recognition of DNA by Strand Displacement with a Thymine-Substituted Polyamide*, 254 SCIENCE 1497, 1498 fig.1 (1991).

93. Vadim Demidov et al., *Sequence Selective Double Strand DNA Cleavage by Peptide Nucleic Acid (PNA) Targeting Using Nuclease S1*, 21 NUCLEIC ACIDS RES. 2103, 2103 (1993).

94. Joel M. Gottesfeld et al., *Regulation of Gene Expression by Small Molecules*, 387 NATURE 202, 202 (1997).

95. Cerium is the fifty-eighth element on the Periodic Table. It is an iron-gray, malleable, lustrous metal that is susceptible to rapid oxidation at room temperature. C.R. HAMMOND, THE ELEMENTS 4–7 (n.d.), http://www.d0.fnal.gov/hardware/cal/lvps_info/engineering/elements.pdf [<https://perma.cc/986X-Z2L4>].

96. Makoto Komiyama et al., *Catalytically Active Species for CeCl₃-Induced DNA Hydrolysis*, 115 J. BIOCHEMISTRY 809, 809 (1994).

97. Wen Chen & Makoto Komiyama, *Site-Selective DNA Hydrolysis by CeIV–EDTA with the Use of One Oligonucleotide Additive Bearing Two Monophosphates*, 6 CHEMBIOCHEM 1825, 1825 (2005); Jia-Ming Yan et al., *(Ethylenediaminetetraacetic Acid)cerium(IV) [CeIV(EDTA)] Complexes with Dual Hydrophobic Binding Sites as Highly Efficient Catalysts for the Hydrolysis of Phosphodiesteres*, 85 HELVETICA CHIMICA ACTA 1496, 1496 (2002).

98. Makoto Komiyama et al., *Artificial Restriction DNA Cutter for Site-Selective Scission of Double-Stranded DNA with Tunable Scission Site and Specificity*, 3 NATURE PROTOCOLS 655, 655 (2008).

99. AAV is a nonpathogenic, nonenveloped virus featuring a 4.7 kilobase long linear single-stranded DNA genome. David V. Schaffer et al., *Molecular Engineering of Viral Gene Delivery Vehicles*, 10 ANN. REV. BIOMEDICAL ENGINEERING 169, 171 (2008).

genetic modifications at high frequencies.¹⁰⁰ With this approach, engineered recombinant AAV vectors can replace some or all of the viral genes with packaged foreign DNA sequences of interest for efficient cellular delivery.¹⁰¹ Subsequent cargo release into the nucleus mediates HR at selected loci, which demonstrates promising therapeutic gene targeting applications.¹⁰² Because they have proven to be safe and effective, commercialization of AAV vectors¹⁰³ and testing in clinical trials are underway.¹⁰⁴ Despite a modest commercial performance, likely due to the platform's labor-intensive manufacturing and costs, preliminary results from clinical testing show significant improvement of patients with an incurable, inherited retinal disease.¹⁰⁵

C. Nuclease Genome Editing Based on Protein-DNA Interactions

1. Meganucleases

Meganucleases, also known as Homing Endonucleases,¹⁰⁶ are naturally occurring DSB nucleases that target relatively long DNA

100. David W. Russell & Roli K. Hirata, *Human Gene Targeting by Viral Vectors*, 18 NATURE GENETICS 325, 325 (1998). The term "high frequencies" used by the authors is ambiguous without an explanation. A closer look at the study reveals that high frequencies relate to gene-targeting events in cell populations and stem directly from a comparative analysis of gene-targeting frequencies between AAV-transduction (10^{-3}) and other methods (10^{-5} to 10^{-8}). *Id.* at 328.

101. Manuel A.F.V. Gonçalves, *Adeno-Associated Virus: From Defective Virus to Effective Vector*, 2 VIROLOGY J. 43, 49–50 (2005), <http://virologyj.biomedcentral.com/articles/10.1186/1743-422X-2-43> [<https://perma.cc/3J83-P674>].

102. Russell & Hirata, *supra* note 100, at 328–29.

103. For instance, Horizon Discovery Group plc, a biotechnology company based in Cambridge, UK, markets a proprietary version of nuclease-free, recombinant AAV genome editing. See rAAV, HORIZON, <https://www.horizondiscovery.com/about-us/our-science/raav> [<https://perma.cc/Y3TZ-3APR>] (last visited Feb. 25, 2017).

104. See, e.g., SPARK THERAPEUTICS, A PHASE 1 SAFETY STUDY IN SUBJECTS WITH LEBER CONGENITAL AMAUROSIS (LCA) USING ADENO-ASSOCIATED VIRAL VECTOR TO DELIVER THE GENE FOR HUMAN RPE65 INTO THE RETINAL PIGMENT EPITHELIUM (RPE) [AAV2-HRPE65V2-101] (2007), <https://clinicaltrials.gov/ct2/show/study/NCT00516477> [<https://perma.cc/C8KS-W6TN>].

105. See, e.g., Artur V. Cideciyan et al., *Human RPE65 Gene Therapy for Leber Congenital Amaurosis: Persistence of Early Visual Improvements and Safety at 1 Year*, 20 HUM. GENE THERAPY 999 (2009); Albert M. Maguire et al., *Age-Dependent Effects of RPE65 Gene Therapy for Leber's Congenital Amaurosis: A Phase 1 Dose-Escalation Trial*, 374 LANCET 1597 (2009); Albert M. Maguire et al., *Safety and Efficacy of Gene Transfer for Leber Congenital Amaurosis*, 358 NEW ENG. J. MED. 2240 (2008).

106. The term "homing" refers to a gene conversion process, whereby a mobile sequence is copied and inserted into a new cognate site lacking the sequence. Maria J. Marcaida et al., *Homing Endonucleases: From Basics to Therapeutic Applications*, 67 CELLULAR & MOLECULAR LIFE SCI. 727, 727 (2010).

sequences ranging from twelve to forty base pairs.¹⁰⁷ Meganucleases have been instrumental in the study of DSB repair.¹⁰⁸ They were initially identified as potential site-specific DNA nucleases for genome editing from the use of self-splicing¹⁰⁹ introns¹¹⁰ and became the first type of nucleases with demonstrable ability to modify the mammalian genome with precision.¹¹¹ Long recognition sequences intrinsic to meganucleases confer high target specificity, but often render them futile because lengthy target sequences in particular arrangements occur rarely in a whole genome.¹¹² The problem, therefore, is that a researcher might have a very specific nuclease at her disposal for a DNA sequence she has no interest in targeting. Complex protein engineering strategies to alter DNA preference of the meganuclease can ameliorate this predicament.¹¹³ However, due to inherent intricacies of protein engineering, and the fact that meganuclease DNA binding and cleavage functions are interlaced in a single domain,¹¹⁴ this platform for genome editing has found it challenging to progress into translational medicine.

107. *Id.*

108. Tamas Lukacsovich et al., *Repair of a Specific Double-Strand Break Generated Within a Mammalian Chromosome by Yeast Endonuclease I-SceI*, 22 NUCLEIC ACIDS RES. 5649, 5650 (1994).

109. Steven Zimmerly et al., *A Group II Intron RNA Is a Catalytic Component of a DNA Endonuclease Involved in Intron Mobility*, 83 CELL 529, 529 (1995). See generally Bruce A. Sullenger & Thomas R. Cech, *Ribozyme-Mediated Repair of Defective mRNA by Targeted Trans-Splicing*, 371 NATURE 619 (1994).

110. An intron is a noncoding piece of RNA transcript, or the DNA encoding it, that is removed before translation into a protein. See *Intron*, SCITABLE, <http://www.nature.com/scitable/definition/intron-introns-67> [<https://perma.cc/RZH2-DBNA>] (last visited Feb. 25, 2017).

111. See, e.g., Philippe Rouet et al., *Expression of a Site-Specific Endonuclease Stimulates Homologous Recombination in Mammalian Cells*, 91 PROC. NAT'L ACAD. SCI. U.S. 6064 (1994); R. Geoffrey Sargent et al., *Repair of Site-Specific Double-Strand Breaks in a Mammalian Chromosome by Homologous and Illegitimate Recombination*, 17 MOLECULAR & CELLULAR BIOLOGY 267 (1997); Jian Yang et al., *Efficient Integration of an Intron RNA into Double-Stranded DNA by Reverse Splicing*, 381 NATURE 332 (1996).

112. Marcaida et al., *supra* note 106, at 727.

113. See Jordan Jarjour et al., *High-Resolution Profiling of Homing Endonuclease Binding and Catalytic Specificity Using Yeast Surface Display*, 37 NUCLEIC ACIDS RES. 6871, 6878 (2009) (investigating DNA binding and catalysis for protein engineering); Pilar Redondo et al., *Molecular Basis of Xeroderma Pigmentosum Group C DNA Recognition by Engineered Meganucleases*, 456 NATURE 107, 107 (2008) (engineering a meganuclease derivative to target a particular gene).

114. Julianne Smith et al., *A Combinatorial Approach to Create Artificial Homing Endonucleases Cleaving Chosen Sequences*, 32 NUCLEIC ACIDS RES. e149, 2, 6–7 (2006).

2. Zinc Finger Nucleases

A study of transcription in the African clawed frog first revealed that zinc-binding domains, potentially looped into finger-like arrangements, were required for transcription factor-mediated gene regulation.¹¹⁵ These modules rely on interactions between Cysteine and Histidine residues with a zinc ion ligand,¹¹⁶ which together form three-dimensional structures where one zinc finger recognizes three contiguous nucleotides of DNA.¹¹⁷ Scientists quickly realized that the modular DNA recognition of each zinc finger motif could be exploited by coupling it to the nuclease domain of FokI—a restriction endonuclease known at the time—to engineer artificial fusion proteins¹¹⁸ called Zinc Finger Nucleases (ZFNs).¹¹⁹

Combining a non-specific nuclease like FokI to zinc fingers capable of recognizing specific sequences of DNA provided a solution to the barriers posed by meganucleases.¹²⁰ Thus, ZFNs became the first method to demonstrate the practicability of genome editing in human cells¹²¹ and animals *in vivo*.¹²² A decade later, ZFNs entered clinical trials amid high expectations.¹²³ However, as critical as ZFNs have been to promote the progress of genome editing technologies, their widespread use has been limited by the high technical expertise needed to engineer them—due primarily to context-dependent

115. J. Miller et al., *Repetitive Zinc-Binding Domains in the Protein Transcription Factor IIIA from Xenopus Oocytes*, 4 EMBO J. 1609, 1612 (1985).

116. *Id.*

117. Nikola P. Pavletich & Carl O. Pabo, *Zinc Finger-DNA Recognition: Crystal Structure of a Zif268-DNA Complex at 2.1 Å*, 252 SCIENCE 809, 813 (1991).

118. Yang-Gyun Kim et al., *Hybrid Restriction Enzymes: Zinc Finger Fusions to Fok I Cleavage Domain*, 93 PROC. NAT'L ACAD. SCI. U.S. 1156, 1156 (1996).

119. Although the name 'zinc finger nuclease' has become standard in biotechnology, in the past, the terms 'chimeric restriction enzyme' and 'chimeric nuclease' have also been used. See Jeff Smith et al., *Requirements for Double-Strand Cleavage by Chimeric Restriction Enzymes with Zinc Finger DNA-Recognition Domains*, 28 NUCLEIC ACIDS RES. 3361, 3361 (2000).

120. See *supra* Section III.C.1.

121. See, e.g., Matthew H. Porteus & David Baltimore, *Chimeric Nucleases Stimulate Gene Targeting in Human Cells*, 300 SCIENCE 763 (2003); Matthew H. Porteus, *Mammalian Gene Targeting with Designed Zinc Finger Nucleases*, 13 MOLECULAR THERAPY 438 (2006); Fyodor D. Urnov et al., *Highly Efficient Endogenous Human Gene Correction Using Designed Zinc-Finger Nucleases*, 435 NATURE 646 (2005).

122. See, e.g., Marina Bibikova et al., *Enhancing Gene Targeting with Designed Zinc Finger Nucleases*, 300 SCIENCE 764 (2003); Marina Bibikova et al., *Targeted Chromosomal Cleavage and Mutagenesis in Drosophila Using Zinc-Finger Nucleases*, 161 GENETICS 1169 (2002).

123. See generally *Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases SB-728 for HIV (Zinc-Finger)*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/study/NCT00842634> [<https://perma.cc/RB7E-VGE3>] (last visited Feb. 13, 2017).

specificity—and extensive screening processes to validate them.¹²⁴ Adoption has lagged even despite frequent reporting of strategies designed to simplify and update engineering challenges associated with ZFNs.¹²⁵

3. TALENs

For a number of years, ZFNs and meganucleases dominated the genome editing landscape despite their technical shortcomings. Then, in 2007, two research teams independently discovered that a particular bacterial strain, pathogenic to certain crop plants, secretes effector (transcription activator-like effector—TALE) proteins capable of specific DNA binding by mimicking transcription factors.¹²⁶ The mechanism and code responsible for DNA recognition was promptly deciphered.¹²⁷ And borrowing from its ZFN predecessor, versions of TALE proteins fused to the FokI nuclease domain led to the creation of TALE nucleases (TALENs).¹²⁸

TALENs and ZFNs share similar architectural features, most prominently the fusion of the FokI nuclease domain to the DNA recognition domain.¹²⁹ However, TALENs exhibit greater simplicity of design because a single TALE recognizes one nucleotide, in contrast to

124. Scot A. Wolfe et al., *DNA Recognition by Cys2His2 Zinc Finger Proteins*, 29 ANN. REV. BIOPHYSICS & BIOMOLECULAR STRUCTURE 183, 199–201, 203–05 (2000); see also *infra* note 126 (reporting various ways to address challenges inherently associated with ZFNs.).

125. See, e.g., Ankit Gupta et al., *An Optimized Two-Finger Archive for ZFN-Mediated Gene Targeting*, 9 NATURE METHODS 588 (2012); Seokjoong Kim et al., *Preassembled Zinc-Finger Arrays for Rapid Construction of ZFNs*, 8 NATURE METHODS 7 (2011); Morgan L. Maeder et al., *Rapid “Open-Source” Engineering of Customized Zinc-Finger Nucleases for Highly Efficient Gene Modification*, 31 MOLECULAR CELL 294 (2008); David A. Wright et al., *Standardized Reagents and Protocols for Engineering Zinc Finger Nucleases by Modular Assembly*, 1 NATURE PROTOCOLS 1637 (2006).

126. Sabine Kay et al., *A Bacterial Effector Acts as a Plant Transcription Factor and Induces a Cell Size Regulator*, 318 SCIENCE 648, 650 (2007); Patrick Römer et al., *Plant Pathogen Recognition Mediated by Promoter Activation of the Pepper Bs3 Resistance Gene*, 318 SCIENCE 645, 646 (2007).

127. Jens Boch et al., *Breaking the Code of DNA Binding Specificity of TAL-Type III Effectors*, 326 SCIENCE 1509, 1509 (2009); Matthew J. Moscou & Adam J. Bogdanove, *A Simple Cipher Governs DNA Recognition by TAL Effectors*, 326 SCIENCE 1501, 1501 (2009).

128. See, e.g., Michelle Christian et al., *Targeting DNA Double-Strand Breaks with TAL Effector Nucleases*, 186 GENETICS 757 (2010); Ting Li et al., *TAL Nucleases (TALNs): Hybrid Proteins Composed of TAL Effectors and FokI DNA-Cleavage Domain*, 39 NUCLEIC ACIDS RES. 359 (2011); Magdy M. Mahfouz et al., *De Novo-Engineered Transcription Activator-Like Effector (TALE) Hybrid Nuclease with Novel DNA Binding Specificity Creates Double-Strand Breaks*, 108 PROC. NAT'L ACAD. SCI. U.S. 2623 (2011); Jeffrey C. Miller et al., *A TALE Nuclease Architecture for Efficient Genome Editing*, 29 NATURE BIOTECHNOLOGY 143 (2011).

129. *Id.*

zinc fingers, which recognize three nucleotides.¹³⁰ Engineering of TALE arrays is therefore less onerous than zinc finger arrays, and TALENs lead to decreased toxicity thanks to higher specificity for cognate DNA targets.¹³¹ Simplicity has contributed to a relatively healthy expansion of TALENs in recent years, surpassing even ZFNs.¹³² Indeed, TALENs have successfully been used to modify cells,¹³³ as well as plant¹³⁴ and animal¹³⁵ genomes. Nonetheless, TALENs are not without limitations. The size and highly repetitive nature of TALEN-coding sequences pose great challenges for delivery using standard viral vectors.¹³⁶ Construction of TALENs is also costly and can require up to four times the materials needed for comparable ZFN constructs.¹³⁷

D. Programmable, RNA-guided, DNA Nuclease Genome Editing

The latest and most remarkable additions to the genome editing toolbox are programmable, RNA-guided, DNA nucleases. Of these, the best-known and characterized system is the Clustered, Regularly Interspaced, Short Palindromic Repeat (CRISPR) and CRISPR-associated (Cas) proteins.¹³⁸ Unlike the nuclease genome editing methods based on protein-DNA interactions discussed above, RNA-guided, DNA nucleases circumvent the intricate and often cumbersome requirement of protein engineering to target DNA

130. Boch et al., *supra* note 127, at 1509–10.

131. Marine Beurdeley et al., *Compact Designer TALENs for Efficient Genome Engineering*, 4 NATURE COMM. art. no. 1762, at 6 (2013), <http://www.nature.com/ncomms/journal/v4/n4/pdf/ncomms2782.pdf> [https://perma.cc/2QYH-YML5].

132. *Id.*

133. See, e.g., Dirk Hockemeyer et al., *Genetic Engineering of Human Pluripotent Cells Using TALE Nucleases*, 29 NATURE BIOTECHNOLOGY 731 (2011); Deepak Reyon et al., *FLASH Assembly of TALENs for High-Throughput Genome Editing*, 30 NATURE BIOTECHNOLOGY 460 (2012).

134. See, e.g., Ting Li et al., *High-Efficiency TALEN-Based Gene Editing Produces Disease-Resistant Rice*, 30 NATURE BIOTECHNOLOGY 390 (2012).

135. See, e.g., Victoria M. Bedell et al., *In Vivo Genome Editing Using a High-Efficiency TALEN System*, 491 NATURE 114 (2012); Daniel F. Carlson et al., *Efficient TALEN-Mediated Gene Knockout in Livestock*, 109 PROC. NAT'L ACAD. SCI. U.S. 17382 (2012); Laurent Tesson et al., *Knockout Rats Generated by Embryo Microinjection of TALENs*, 29 NATURE BIOTECHNOLOGY 695 (2011).

136. Jia Liu et al., *Cell-Penetrating Peptide-Mediated Delivery of TALEN Proteins via Bioconjugation for Genome Engineering*, 9 PLOS ONE e85755, e85755–56 (2014).

137. Beurdeley et al., *supra* note 131, at 6.

138. Ruud Jansen et al., *Identification of Genes That Are Associated with DNA Repeats in Prokaryotes*, 43 MOLECULAR MICROBIOLOGY 1565, 1565 (2002).

sequences.¹³⁹ Instead, RNA-guided, DNA nucleases harness nature's principles of Watson-Crick base-pairing of nucleic acids to mediate DNA recognition.¹⁴⁰

The origins of CRISPR can be traced back nearly three decades when a team of Japanese researchers published findings of a mysterious repeat cluster of unknown function in the bacterium *Escherichia coli* (*E. coli*).¹⁴¹ The accumulation of sequenced bacterial genomes in public databases by the turn of the millennium revealed that such particular clusters are pervasive in numerous bacterial and archaeal strains.¹⁴²

Soon after, scientists coined the term CRISPR and identified a group of *Cas*¹⁴³ genes encoding proteins involved in catalyzing biochemical reactions using nucleic acids as substrates.¹⁴⁴ These findings sparked a great deal of interest in the scientific community for CRISPR systems. Then in 2007, two decades after their discovery, key experiments performed at Danisco presented the first empirical evidence that CRISPR was, in fact, an adaptive immunity system used by bacteria and archaea,¹⁴⁵ a mnemonic—so to speak—designed to provide immunological memory against viral infection.

As research into CRISPR systems has accelerated, so too has our knowledge of the mechanistic details of this adaptive immunity phenomenon. To date, five CRISPR types and sixteen subtypes have been classified on the basis of phylogenetic analyses, with more likely awaiting characterization.¹⁴⁶ Among CRISPR systems, CRISPR-Cas9 has emerged as the foremost genome editing platform, partly due to being the first RNA-guided, DNA nuclease discovered. However, other

139. See discussion *supra* Section III.C.

140. Watson-Crick base pairing refers to the principle through which DNA bases—Adenine-Thymine and Guanine-Cytosine—pair up with each other via hydrogen bonds to allow DNA to maintain its double-helical structure. See Watson & Crick, *supra* note 66, at 738.

141. Yoshizumi Ishino et al., *Nucleotide Sequence of the Iap Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia coli, and Identification of the Gene Product*, 169 J. BACTERIOLOGY 5429, 5432 (1987).

142. Francisco J.M. Mojica et al., *Biological Significance of a Family of Regularly Spaced Repeats in the Genomes of Archaea, Bacteria and Mitochondria*, 36 MOLECULAR MICROBIOLOGY 244, 244 (2000).

143. In standard genetic scientific nomenclature, gene names are generally italicized. In contrast, gene products such as proteins are designated using the same gene name, but in non-italicized font.

144. Jansen et al., *supra* note 138, at 1568–69. Helicase—unwinding of double-helical nucleic acids—and nuclease activities are two such biochemical reactions.

145. Rodolphe Barrangou et al., *CRISPR Provides Acquired Resistance Against Viruses in Prokaryotes*, 315 SCIENCE 1709, 1711 (2007).

146. Kira S. Makarova et al., *An Updated Evolutionary Classification of CRISPR-Cas Systems*, 13 NATURE REVIEWS MICROBIOLOGY 722, 724 (2015).

CRISPR systems,¹⁴⁷ such as CRISPR-Cpf1,¹⁴⁸ have very recently been identified and are likely to offer valuable alternatives for DNA targeting.

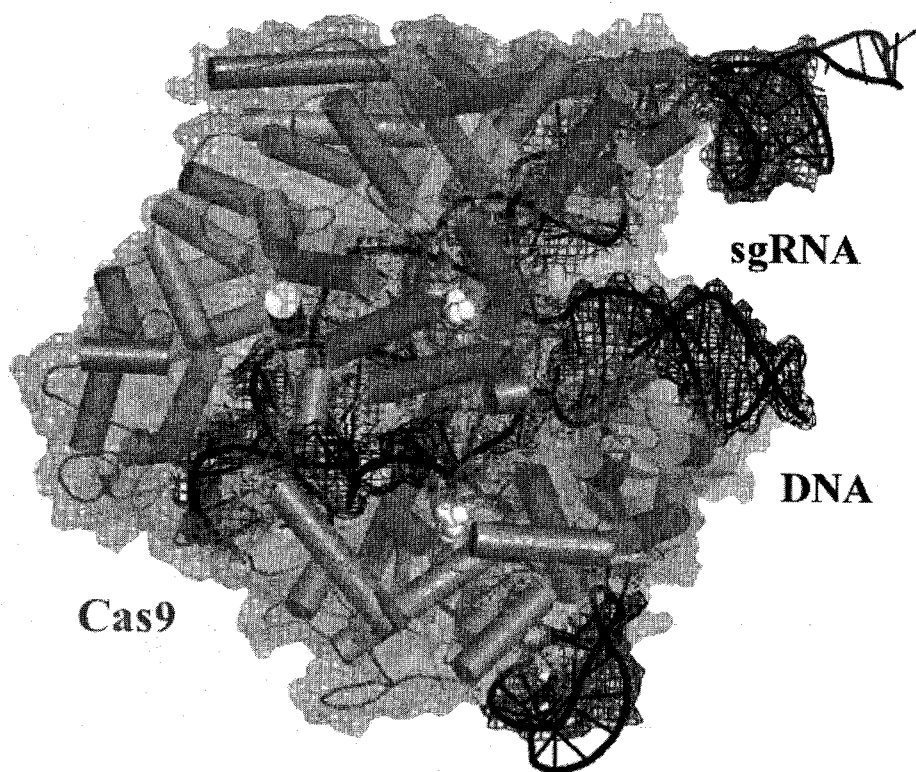


FIGURE 1¹⁴⁹

X-Ray, three-dimensional structure of the CRISPR-Cas9 endonuclease (gray) from *Streptococcus pyogenes* in complex with a sgRNA (blue) and double-stranded DNA (red) primed for target DNA cleavage. Yellow spheres represent the two active site residues indispensable for enzyme catalysis (Aspartate 10, bottom; Histidine 840, top). The figure appears in color in the online version of this Article.¹⁵⁰

147. See Sergey Shmakov et al., *Discovery and Functional Characterization of Diverse Class 2 CRISPR-Cas Systems*, 60 MOLECULAR CELL 385, 386 (2015).

148. Bernd Zetsche et al., *Cpf1 Is a Single RNA-Guided Endonuclease of a Class 2 CRISPR-Cas System*, 163 CELL 759, 760 (2015).

149. The model was built using the atomic coordinates deposited in the Protein Data Bank, accession code 5F9R (2016), <http://www.rcsb.org/pdb/explore/explore.do?structureId=5F9R> [<https://perma.cc/F5TB-7T9P>].

150. The online version can be accessed at the Journal's website, JETLaw.org, by clicking on the "Journal Archives" tab, Volume 19, Issue 3. [<https://perma.cc/6BKD-D5DQ>].

From a genome editing standpoint, CRISPR-Cas9 has garnered worldwide attention largely because the Cas9 enzyme is part of the CRISPR type II system, which requires only a single protein (Cas9) for RNA-guided, DNA cleavage.¹⁵¹ DNA targeting and formation of DSBs by the CRISPR-Cas9 complex require three essential components: (1) a short CRISPR RNA (crRNA) that recognizes the target DNA; (2) a short trans-activating crRNA (tracrRNA) that hybridizes with crRNA and helps recruit the nuclease;¹⁵² and (3) Cas9, the enzyme that cuts DNA.¹⁵³ When assembled into a complex, this machinery seeks, detects, and cuts the target DNA a few nucleotides away from a proto-spacer adjacent motif (PAM) site.¹⁵⁴

A defining moment for the future of genome editing came in 2012 when an article published in *Science* revealed that Cas9 is an RNA-guided, DNA endonuclease and the two small RNAs it associates with can be fused together into a synthetic, single-guide RNA (sgRNA) that could be engineered to direct Cas9 to any target DNA sequence of interest.¹⁵⁵ This finding earned two scientists—a biochemist and a microbiologist—\$3 million each and the *Breakthrough Prize*.¹⁵⁶

Thus, the landscape of genome editing changed. Scientists are no longer confined to the tedious process of protein design inherent in other nuclease-based tools. Today, any researcher armed with an active Cas9¹⁵⁷ needs merely to design and order an inexpensive

151. Josiane E. Garneau et al., *The CRISPR/Cas Bacterial Immune System Cleaves Bacteriophage and Plasmid DNA*, 468 NATURE 67, 70 (2010) (discussing *cas9*'s involvement in DNA cleavage while it was still labeled as *cas5*); Rimantas Sapranasauskas et al., *The Streptococcus Thermophilus CRISPR/Cas System Provides Immunity in Escherichia Coli*, 39 NUCLEIC ACIDS RES. 9275, 9279 (2011).

152. Notably, unlike CRISPR-Cas9, the CRISPR-Cpf1 system does not require a tracrRNA. Zetsche et al., *supra* note 148, at 760.

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

154. The PAM site is a very short nucleotide sequence in the target DNA critical for initial DNA binding of the CRISPR-Cas9 complex, before Cas9 cuts the DNA. Samuel H. Sternberg et al., *DNA Interrogation by the CRISPR RNA-Guided Endonuclease Cas9*, 507 NATURE 62, 63–64 (2014).

155. See generally Jinek, *supra* note 153.

156. Jennifer Doudna, a biochemist, and Emmanuelle Charpentier, a microbiologist, received the *Breakthrough Prize* for “harnessing an ancient mechanism of bacterial immunity into a powerful and general technology for editing genomes, with wide-ranging implications across biology and medicine.” See *Recipients of the 2015 Breakthrough Prizes*, BREAKTHROUGH PRIZE, <https://breakthroughprize.org/News/21> [<https://perma.cc/U7RY-79BK>] (last visited Feb. 25, 2017). Their discovery may one day also earn them a *Nobel Prize*.

157. A multitude of Cas9 plasmids for a researcher's experiment of choice are widely available from commercial sources for as little as \$65.00. See, e.g., *eSpCas9(1.1)*, ADDGENE, <https://www.addgene.org/71814/> [<https://perma.cc/8AT6-TK38>] (last visited Feb. 25, 2017).

sgRNA,¹⁵⁸ wait for it to be delivered to the lab, and—voilà!—edit her favorite genome for less than one hundred dollars. Even more striking, to edit additional sites, the researcher may use the same Cas9 with another made-to-order sgRNA. The inexpensive, accurate, and easy-to-use essence of CRISPR-Cas9 has changed the rules of the genome editing game; to such an extent, it has been hailed as a tool for the democratization of genome editing.¹⁵⁹

Widespread use of a biotechnology may not occur for years after it is first introduced to the scientific community. However, unlike its predecessor technologies, CRISPR-Cas9 has been adopted by laboratories around the world with unprecedented speed.¹⁶⁰ Within months of the *Science* publication, reports of genome editing in human cancer cells¹⁶¹ and pluripotent stem cells¹⁶² surfaced. And soon after, a flurry of publications followed detailing genome editing studies on various organisms including mice,¹⁶³ nematodes,¹⁶⁴ fruit flies,¹⁶⁵ zebrafish,¹⁶⁶ frogs,¹⁶⁷ rabbits,¹⁶⁸ pigs,¹⁶⁹ goats,¹⁷⁰ cattle,¹⁷¹ rice,¹⁷² wheat,¹⁷³ tobacco,¹⁷⁴ thale cress,¹⁷⁵ sorghum,¹⁷⁶ and others. In just

158. At a cost of as little as \$10. See Wadhwa, *supra* note 57.

159. *Id.*

160. Jacob Corn, *The Explosion of CRISPR/Cas9*, INNOVATIVE GENOMICS (July 18, 2015), <https://innovativegenomics.org/blog/crispr-cas9-explosion/> [<https://perma.cc/ZS4P-5C8B>].

161. See Prashant Mali et al., *RNA-Guided Human Genome Engineering via Cas9*, 339 SCIENCE 823 (2013).

162. *E.g., id.*; Martin Jinek et al., *RNA-Programmed Genome Editing in Human Cells*, 2 ELIFE e00471 (2013).

163. See generally Bin Shen et al., *Generation of Gene-Modified Mice via Cas9/RNA-Mediated Gene Targeting*, 23 CELL RES. 720 (2013).

164. See generally Ari E. Friedland, *Heritable Genome Editing in C. elegans via a CRISPR-Cas9 System*, 10 NATURE METHODS 741 (2013).

165. See generally Zhongsheng Yu et al., *Highly Efficient Genome Modifications Mediated by CRISPR/Cas9 in Drosophila*, 195 GENETICS 289 (2013).

166. See generally Li-En Jao et al., *Efficient Multiplex Biallelic Zebrafish Genome Editing Using a CRISPR Nuclease System*, 110 PROC. NAT'L ACAD. SCI. U.S. 13904 (2013).

167. See generally Takuya Nakayama et al., *Simple and Efficient CRISPR/Cas9-Mediated Targeted Mutagenesis in Xenopus tropicalis*, 51 GENESIS 835 (2013).

168. See generally Dongshan Yang et al., *Effective Gene Targeting in Rabbits Using RNA-Guided Cas9 Nucleases*, 6 J. MOLECULAR CELL BIOLOGY 97 (2014).

169. See generally Wenfang Tan et al., *Efficient Nonmeiotic Allele Introgression in Livestock Using Custom Endonucleases*, 110 PROC. NAT'L ACAD. SCI. U.S. 16526 (2013).

170. *Id.*

171. *Id.*

172. See generally Wenzhi Jiang et al., *Demonstration of CRISPR/Cas9/sgRNA-Mediated Targeted Gene Modification in Arabidopsis, Tobacco, Sorghum and Rice*, 41 NUCLEIC ACIDS RES. e188 (2013).

173. See generally *id.*; Qiwei Shan et al., *Targeted Genome Modification of Crop Plants Using a CRISPR-Cas System*, 31 NATURE BIOTECHNOLOGY 686 (2013).

174. See generally Jiang et al., *supra* note 172.

over three years, more than 2,500 papers¹⁷⁷ referring to this nascent biotechnology have been published. CRISPR systems have had a major impact on genome editing and will likely soon be applied for translational applications in agriculture, synthetic biology, biomedicine, and human therapeutics.

This Article next presents a comprehensive survey of the current applications of genome editing technologies in general, but with particular emphasis on CRISPR-derived advances. It further propounds positive claims for prospective applications of genome editing that are firmly grounded in empirical evidence.

IV. CURRENT AND PROSPECTIVE APPLICATIONS OF GENOME EDITING

A. Editing to Target Somatic Cells and Stem Cells

Genome editing technologies have already shown great promise in the treatment of human diseases. Editing of somatic cells¹⁷⁸—that is, differentiated cells, not including germline or undifferentiated stem cells—for example, is revolutionizing therapeutic approaches to HIV and AIDS.

A rationale for genome editing-based HIV treatment first appeared after an article in *Cell* reported that some individuals' resistance to HIV-1, the most commonly transmitted strain of HIV, had a genetic basis.¹⁷⁹ To enter its host cells, the HIV virus requires a CD4 receptor and a chemokine coreceptor, predominantly the cell-surface protein called C-C Chemokine Receptor Type 5 (CCR5).¹⁸⁰ Approximately 1% of Caucasians carry a 32-nucleotide deletion in the *CCR5* gene that renders the coreceptor unable to detect the HIV virus.¹⁸¹ The effect of this mutation is that individuals who are

175. *Id.*

176. *Id.*

177. A search on the PubMed scientific database using the "CRISPR" acronym filtered by title and abstract returned 2,565 hits. PubMed.gov Search Results for CRISPR, PUBMED.GOV, [http://www.ncbi.nlm.nih.gov/pubmed/?term=CRISPR\[Title%2FAbstract\]](http://www.ncbi.nlm.nih.gov/pubmed/?term=CRISPR[Title%2FAbstract]) [<https://perma.cc/7PC2-BNN8>] (last visited Feb. 10, 2016) (search for CRISPR filtered by title and abstract by using the language "CRISPR[Title/Abstract]"). Note that the search does not include papers that refer to CRISPR in the body of the paper, which may return more hits.

178. Somatic cells are all of the body's cells except the reproductive cells. *Somatic Cells*, BIOLOGY ONLINE, http://www.biology-online.org/dictionary/Somatic_cells [<https://perma.cc/A8ZT-MRZ6>] (last visited Feb. 13, 2017).

179. Rong Liu et al., *Homozygous Defect in HIV-1 Coreceptor Accounts for Resistance of Some Multiply-Exposed Individuals to HIV-1 Infection*, 86 CELL 367, 370 (1996).

180. Gero Hütter et al., *Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation*, 360 NEW ENG. J. MED. 692, 695 (2009).

181. *Id.*

homozygous—those who inherit the deletion from both parents—are virtually immune to HIV.¹⁸²

The potential for interrogating CCR5 was later clinically validated when Timothy Brown,¹⁸³ an HIV-infected patient, received a bone marrow transplant from a donor who had the CCR5 deletion.¹⁸⁴ The procedure led to restoration of normal CD4⁺ T-cell counts and undetectable levels of HIV in Brown's body, even two years post-transplantation.¹⁸⁵ This remarkable study, and its long-lasting effects, confirmed that conversion of a patient's genome—although not through genome editing—could potentially lead to a cure for HIV and AIDS.

Inspired by the critical role of CCR5 in HIV infection, scientists at Sangamo, the California-based biopharmaceutical company, in collaboration with academic researchers, tested whether genome editing could be used to trim out a piece of the *CCR5* gene in human T-cells and a mouse model of HIV infection.¹⁸⁶ Using ZFNs, they demonstrated the feasibility of this approach as a strategy to confer robust protection against HIV.¹⁸⁷

A recent phase I clinical trial featuring this principle sought to remove CD4⁺ T-cells from HIV patients, edit them with ZFNs targeting the *CCR5* locus, and transplant the edited cells back into the patients.¹⁸⁸ Remarkably, results show that infusion of autologously modified CD4⁺ T-cells in which the CCR5 receptor had been rendered dysfunctional by ZFN targeting is safe,¹⁸⁹ thereby paving the path for a phase II trial¹⁹⁰ and potential cure in the near future. Furthermore, scientists have now used the CRISPR platform not only to target T-cells, but also to successfully disrupt expression of latently integrated

182. *Id.*

183. Timothy Brown remains HIV free to this day. *Timothy Ray Brown*, FRED HUTCH, <https://www.fredhutch.org/en/news/timothy-ray-brown.html> [<https://perma.cc/G42T-UKM7>] (last visited Feb. 25, 2017).

184. Hütter et al., *supra* note 180, at 692.

185. *Id.*

186. Elena E. Perez et al., *Establishment of HIV-1 Resistance in CD4⁺ T Cells by Genome Editing Using Zinc-Finger Nucleases*, 26 NATURE BIOTECHNOLOGY 808, 808 (2008).

187. *Id.*

188. *Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases SB-728 for HIV (Zinc-Finger)*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/study/NCT00842634> [<https://perma.cc/RB7E-VGE3>] (last visited Feb. 13, 2017).

189. Pablo Tebas et al., *Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV*, 370 NEW ENG. J. MED. 901, 908 (2014).

190. Sangamo BioSciences Presents Phase 2 Clinical Data from Two SB-728-T HIV Studies, PR NEWswire (Dec. 11, 2015), <http://www.prnewswire.com/news-releases/sangamo-biosciences-presents-phase-2-clinical-data-from-two-sb-728-t-hiv-studies-300191693.html> [<https://perma.cc/G2X6-5AUF>].

HIV-1 provirus and excise it from the host genome altogether in T-cells,¹⁹¹ microglial cells,¹⁹² promonocytic cells,¹⁹³ and human-induced pluripotent stem cells.¹⁹⁴ These studies are a vivid testament to the power of genome editing technologies to provide long-term, adaptive immunity against viral infections by introducing a disease-resistant allele—in the case of *CCR5*—or to completely deracinate a virus from its host genome. The implications of this research go far beyond HIV and could apply to other acquired diseases.

Progress has not been confined to one disease. Genome editing has successfully corrected a mutation associated with hereditary tyrosinemia type I (HTI), a fatal genetic disorder, in the liver cells of a mouse model of the disease.¹⁹⁵ Cystic Fibrosis (CF), a debilitating disease in which viscous mucus accumulates in the pulmonary and gastrointestinal tracts of patients—leading to a life expectancy of approximately forty years¹⁹⁶—appears to be vulnerable to genome editing as well. CRISPR-Cas9 editing of the Cystic Fibrosis Transmembrane Conductor Receptor (CFTCR or CFTR) protein in cultured intestinal stem cells isolated from CF patients corrected a one-amino-acid deletion mutation associated with the most common form of the disease.¹⁹⁷

Furthermore, a mutation in the Leucine-Rich Repeat Kinase 2 (*LRRK2*) gene associated with a hereditary form of Parkinson's Disease was rectified in induced pluripotent stem cells derived from patients afflicted with the disease, resulting in functional phenotypic rescue of differentiated neurons.¹⁹⁸ Correction of an *IL2RG*¹⁹⁹ gene mutation in hematopoietic stem cells (HSCs) derived from patients suffering from X-linked Severe Combined Immunodeficiency

191. E.g., Hirotaka Ebina et al., *Harnessing the CRISPR/Cas9 System to Disrupt Latent HIV-1 Provirus*, 3 SCI. REP. 2510 (2013).

192. E.g., Wenhui Hu et al., *RNA-Directed Gene Editing Specifically Eradicates Latent and Prevents New HIV-1 Infection*, 111 PROC. NAT'L ACAD. SCI. U.S. 11461, 11462 (2014).

193. *Id.*

194. E.g., Hsin-Kai Liao et al., *Use of the CRISPR/Cas9 System as an Intracellular Defense Against HIV-1 Infection in Human Cells*, 6 NATURE COMM. 6413 (2015).

195. Hao Yin et al., *Genome Editing with Cas9 in Adult Mice Corrects a Disease Mutation and Phenotype*, 32 NATURE BIOTECHNOLOGY 551, 551 (2014).

196. Gerald Schwank et al., *Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients*, 13 CELL STEM CELL 653, 655 (2013).

197. *Id.* at 653.

198. Peter Reinhardt et al., *Genetic Correction of a LRRK2 Mutation in Human iPSCs Links Parkinsonian Neurodegeneration to ERK-Dependent Changes in Gene Expression*, 12 CELL STEM CELL 354, 354 (2013).

199. Interleukin 2 Receptor Subunit Gamma, also known as Cytokine Receptor Common Subunit Gamma.

Syndrome (SCID-X1) gave rise to functional lymphoid cells.²⁰⁰ Editing of HSCs is of particular significance given that they differentiate into all hematopoietic cell types and can be autologously transplanted.²⁰¹ Thus, genome editing using HSCs could open treatment avenues for many genetic blood disorders.

Efforts are underway to develop treatments for other types of monogenic diseases. For instance, an allele-specific editing strategy to combat Meesmann's Epithelial Corneal Dystrophy (MECD) demonstrates that a faulty allele can be ablated without affecting the healthy allele in a heterozygous disease.²⁰² Promising applications of genome editing could soon change therapeutic approaches in a multitude of hereditary diseases including Huntington's disease, where a single mutation repeat causes a devastating neurodegenerative disorder;²⁰³ Achondroplasia, where one of two mutations leads to dwarfism;²⁰⁴ Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, in which point mutations trigger death of neurons;²⁰⁵ Nicolaides-Baraitser syndrome (NBS), where mutations in a chromatin-remodeling gene lead to severe intellectual disability;²⁰⁶ or Tay-Sachs disease, where deleterious mutations prompt deterioration of nerve cells that render a child dead by age four.²⁰⁷

Finally, it bears noting that although monogenic diseases are likely to be the focus of early genome editing therapies,²⁰⁸ in the long-run, genome editing biotechnologies will likely tackle more complex,

200. Pietro Genovese et al., *Targeted Genome Editing in Human Repopulating Haematopoietic Stem Cells*, 510 NATURE 235, 235 (2014).

201. See generally R. Aggarwal et al., *Hematopoietic Stem Cells: Transcriptional Regulation, ex Vivo Expansion and Clinical Application*, 12 CURRENT MOLECULAR MED. 34 (2012).

202. D.G. Courtney et al., *CRISPR/Cas9 DNA Cleavage at SNP-Derived PAM Enables Both in Vitro and in Vivo KRT12 Mutation-Specific Targeting*, 23 GENE THERAPY 108, 108 (2016).

203. Mahru C. An et al., *Genetic Correction of Huntington's Disease Phenotypes in Induced Pluripotent Stem Cells*, 11 CELL STEM CELL 253, 253 (2012).

204. Douglas J. Wilkin et al., *Mutations in Fibroblast Growth-Factor Receptor 3 in Sporadic Cases of Achondroplasia Occur Exclusively on the Paternally Derived Chromosome*, 63 AM. J. HUM. GENETICS 711, 715 (1998).

205. Thomas Gaj, *Therapeutic Genome Editing for Amyotrophic Lateral Sclerosis*, GRANTOME, <http://grantome.com/grant/NIH/F32-GM113446-01A1> [<https://perma.cc/JS5M-9ZC6>] (last visited Feb. 25, 2017).

206. Jeroen K.J. Van Houdt et al., *Heterozygous Missense Mutations in SMARCA2 Cause Nicolaides-Baraitser Syndrome*, 44 NATURE GENETICS 445, 448 (2012).

207. Rachel Myerowitz, *Tay-Sachs Disease-Causing Mutations and Neutral Polymorphisms in the Hex A Gene*, 9 HUM. MUTATION 195, 196 (1997).

208. The probable focus on monogenic diseases is likely due to the perception that targeting a single gene is inherently simpler than targeting multiple genes.

non-monogenic diseases as well—think cancer²⁰⁹ and even aging. Indeed, recent evidence in HSCs shows CRISPR-Cas9 can target noncoding regions—sections of chromosomal DNA without genes—of the genome to interrogate the *BCL11A*²¹⁰ erythroid enhancer²¹¹ involved in regulation of hemoglobin disorders.²¹² This proof-of-concept suggests viable, alternative therapeutic strategies to treat sickle-cell disease and thalassemias. Likewise, genome editing offers an opportunity to tackle other complex pathologies like Alzheimer's Disease,²¹³ HIV,²¹⁴ cardiovascular disease,²¹⁵ and Acute Lymphoblastic Leukemia²¹⁶ by conferring protective mutations as treatment for affected patients or as prophylactic measures for those unaffected. These and other examples demonstrate both the feasibility and inevitability of applying genome editing technologies to rid society of congenital disorders—whether recessive or dominantly inherited—and acquired diseases.

209. See, e.g., B. Berdien et al., *TALEN-Mediated Editing of Endogenous T-Cell Receptors Facilitates Efficient Reprogramming of T Lymphocytes by Lentiviral Gene Transfer*, 21 GENE THERAPY 539 (2014); Elena Provasi et al., *Editing T Cell Specificity Towards Leukemia by Zinc Finger Nucleases and Lentiviral Gene Transfer*, 18 NATURE MED. 807 (2012).

210. B-cell Lymphoma/Leukemia 11A is a gene that encodes a C₂H₂ zinc finger protein involved in normal lymphoid development. Yang-Jun Gao et al., *Expression of the B-Cell Lymphoma/Leukemia 11A Gene in Malignant Hematological Cell Lines Through Quantitative Reverse Transcription Polymerase Chain Reaction*, 8 CLINICAL ONCOLOGY & CANCER RES. 242, 242 (2011); Pentao Liu et al., *Bcl11a Is Essential for Normal Lymphoid Development*, 4 NATURE IMMUNOLOGY 525, 525 (2003).

211. Enhancers generally refer to distal genetic elements involved in the regulation of gene expression in an orientation-independent manner. Matthew C. Canver et al., *BCL11A Enhancer Dissection by Cas9-Mediated in Situ Saturating Mutagenesis*, 527 NATURE 192, 192 (2015) (citing Julian Banerji et al., *Expression of a β -globin Gene Is Enhanced by Remote SV40 DNA Sequences*, 27 CELL 299 (1981)).

212. *Id.* at 196.

213. Thorlakur Jonsson et al., *A Mutation in APP Protects Against Alzheimer's Disease and Age-Related Cognitive Decline*, 488 NATURE 96, 96 (2012).

214. See discussion *supra* notes 179–94 and accompanying text.

215. Jonathan Cohen et al., *Low LDL Cholesterol in Individuals of African Descent Resulting from Frequent Nonsense Mutations in PCSK9*, 37 NATURE GENETICS 161, 162 (2005) (identifying two *PCSK9* mutations having a protective effect against hypercholesterolemia); The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, *Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease*, 371 NEW ENG. J. MED. 22, 23 (2014) (identifying rare *APOC3* mutations associated with a lower risk of heart disease).

216. Shannon L. Maude et al., *Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia*, 371 NEW ENG. J. MED. 1507, 1512 (2014).

B. Gene Drives

In what might seem like a concept straight out of a sci-fi script, reshaping entire populations of wild organisms with relatively short lifespans is now within technological reach thanks to a method coupling genome editing technology with old-fashioned sexual reproduction. This method, called a gene drive, encompasses the alteration of traits in wild populations²¹⁷ via self-propagating, synthetic, genetic constructs that can artificially disseminate—i.e., drive—a gene modification through an organism's progeny with unprecedented speed.

The notion of gene drives dates back to the late 1960s, when a theoretical comment published in *Nature* proposed the hypothetical utility of chromosomal translocations as a way to control insect pest populations.²¹⁸ At the time, that possibility was merely hypothetical because the technology to test the hypothesis—namely, the tools and knowledge required for triggering translocations via enzyme manipulation—simply did not exist.²¹⁹ However, by the turn of the century, interest in gene drives resurfaced following insights that meganucleases²²⁰ could be used as drivers.²²¹ The premise of targeting the fertility genes of vermin species provided a roadmap to carry out population-wide genetic engineering.²²² And by 2011, the first validation of a meganuclease-based gene drive—aimed at controlling the human malaria vector—established proof-of-principle for the genetic manipulation of an entire population starting from only a few laboratory individuals.²²³

It was not long before others realized that the same concept could be used to engineer drives by integrating genes encoding the more efficient Cas9 enzyme alongside specific sgRNAs. Less than two years ago, US scientists used the CRISPR-Cas9 system to develop the Mutagenic Chain Reaction (MCR).²²⁴ In contrast to classic laws of

217. James E. DiCarlo et al., *Safeguarding CRISPR-Cas9 Gene Drives in Yeast*, 33 NATURE BIOTECHNOLOGY 1250, 1250 (2015).

218. Christopher F. Curtis, *Possible Use of Translocations to Fix Desirable Genes in Insect Pest Populations*, 218 NATURE 368, 368 (1968).

219. The requisite tools and knowledge to test these synthetic gene drives are now available to the scientific community. See discussion *supra* Part III.

220. See *supra* notes 108–111.

221. Austin Burt, *Site-Specific Selfish Genes as Tools for the Control and Genetic Engineering of Natural Populations*, 270 PROC. ROYAL SOC'Y B: BIOLOGICAL SCI. 921, 921 (2003).

222. *Id.*

223. Nikolai Windbichler et al., *A Synthetic Homing Endonuclease-Based Gene Drive System in the Human Malaria Mosquito*, 473 NATURE 212, 212 (2011).

224. Valentino M. Gantz & Ethan Bier, *The Mutagenic Chain Reaction: A Method for Converting Heterozygous to Homozygous Mutations*, 348 SCIENCE 442, 442 (2015).

genetic inheritance, in which there is a 50% chance that a given offspring will inherit a modified allele, MCR-mediated gene drive introduced biased inheritance patterns to swiftly spread a select gene through an entire population of laboratory fruit flies.²²⁵ With an average 97% success rate—as opposed to 50%—gene drives can convert heterozygous mutations into homozygous mutations in as little as two generations.²²⁶

In the last few months, researchers have used CRISPR-Cas9-based gene drives to introduce genes that confer resistance to the malaria parasite, *Plasmodium falciparum*, into a South Asian mosquito species.²²⁷ An alternate approach to suppress a different species of mosquito vector for human malaria succeeded by targeting female mosquitoes that overwhelmingly—and helplessly—relinquished fertility by gene drive.²²⁸ The former strategy seeks to spare mosquitoes by making them malaria-resistant and incapable of spreading the disease, whereas the latter aims to drastically reduce—or even wipe out—mosquito populations from an ecosystem. Ultimately, both share the goal of suppressing a disease that places half the total world population at risk, particularly in low-income countries.²²⁹

Yeast,²³⁰ fruit flies,²³¹ and mosquito species²³²—including the potent vector for the chikungunya, yellow fever, and dengue

225. *Id.* at 443.

226. *Id.*

227. Valentino M. Gantz et al., *Highly Efficient Cas9-Mediated Gene Drive for Population Modification of the Malaria Vector Mosquito Anopheles stephensi*, 112 PROC. NAT'L ACAD. SCI. U.S. E6736, E6736 (2015).

228. Andrew Hammond et al., *A CRISPR-Cas9 Gene Drive System Targeting Female Reproduction in the Malaria Mosquito Vector Anopheles gambiae*, 34 NATURE BIOTECHNOLOGY 78, 78 (2016).

229. The World Health Organization estimates that as of 2013, ninety-seven countries had ongoing malaria transmission and approximately 3.4 billion people were at risk of contracting malaria, 1.2 billion of whom were at a high risk. *Factsheet on the World Malaria Report 2013*, WORLD HEALTH ORG. (Dec. 2013), http://www.who.int/malaria/media/world_malaria_report_2013/en/ [<https://perma.cc/Z2XH-JLPN>].

230. See DiCarlo et al., *supra* note 217, at 1250 (reporting gene drive systems in wild and laboratory strains of the yeast *Saccharomyces cerevisiae*).

231. See Gantz et al., *supra* note 227, at E6737 (testing a gene drive in *Drosophila melanogaster*).

232. See, e.g., *id.* at E6736 (experimenting with *Anopheles Stephensi*); Hammond et al., *supra* note 228, at 78 (targeting *Anopheles gambiae*); see also Andrea L. Smidler et al., *Targeted Mutagenesis in the Malaria Mosquito Using TALE Nucleases*, 8 PLOS ONE e74511, e74511 (2013) (using transgenic expression of TALENs for genetic manipulation of mosquitoes instead of CRISPR-Cas9).

viruses²³³—have thus far been the subjects of CRISPR-mediated gene drive, or related, research. Though the technology remains enclosed within laboratory walls for now, some researchers have begun to study and model how releasing mosquitoes in the wild would spread certain engineered traits.²³⁴ Others have used mathematical and quantitative modeling to estimate the rate of fixation of a mutant allele and caution the release of gene drives in the wild.²³⁵

Already, Oxitec, a British firm, has developed transgenic *Aedes aegypti* mosquitoes—through older technologies—and released them in field trials in Brazil, Malaysia, the Cayman Islands, and Panama with results showing up to a 90% reduction of insect populations.²³⁶ Trial successes led to Brazilian approval of the first genetically modified insect for commercial use.²³⁷ However, in the United States, Oxitec has faced intense criticism for releasing genetically modified moths in small outdoor trials in New York,²³⁸ and Florida rejected a proposal to permit Oxitec to release mosquitoes in the wild without federal approval.²³⁹

Diametric public views concerning the apt use of genetically modified insects highlight the pivotal role that public opinion will play in the development of gene drive biotechnologies. Consider the recent threat to global human health posed by the Zika virus in the past year. Zika outbreaks have already been reported in more than fifty

233. Kathryn E. Kistler et al., *Genome Engineering with CRISPR-Cas9 in the Mosquito Aedes aegypti*, 11 CELL REP. 51, 51 (2015).

234. See Hammond et al., *supra* note 228, at 80 (demonstrating that alleles inserted at female-fertility loci can spread rapidly in mixed caged populations—of 600 mosquitoes per cage—with high gene drive activity).

235. Robert L. Unckless et al., *Modeling the Manipulation of Natural Populations by the Mutagenic Chain Reaction*, 201 GENETICS 425, 427–28 (2015).

236. See *United States*, OXITEC, <http://www.oxitec.com/programmes/united-states/> [<https://perma.cc/D2LH-7RF4>] (last visited Feb. 9, 2017); see also Kerry Grens, *Mutant Mosquitoes Deployed to Stop Zika, Dengue*, SCIENTIST (Jan. 19, 2016), <http://www.the-scientist.com/?articles.view/articleNo/45128/title/Mutant-Mosquitoes-Deployed-to-Stop-Zika-Dengue/> [<https://perma.cc/94DJ-AV9X>].

237. Press Release, Oxitec, Oxitec's Solution for Controlling the Dengue Mosquito Is Approved by CTNBio (Apr. 10, 2014), <http://www.oxitec.com/press-release-high-tech-solution-for-controlling-the-dengue-mosquito-is-approved-by-ctnbio/> [<https://perma.cc/5MXV-XHQX>].

238. Christina Sarich, *Genetically Modified Moths Released in New York*, NAT. SOC'Y (June 19, 2015), <http://naturalsociety.com/outrage-oxitecs-gm-moths-are-released-in-new-york/> [<https://perma.cc/C4HB-SCA4>].

239. William Axford, *Keys Bug Board Says No to Contract for Genetically Modified Mosquitoes Unless Feds Approve*, MIAMI HERALD (Apr. 22, 2015), <http://www.miamiherald.com/news/local/community/florida-keys/article19207230.html> [<https://perma.cc/TJJ7-KGGH>].

countries.²⁴⁰ The World Health Organization declared a public health emergency of international concern as more than 4,000 microcephaly cases and neurological disorders have been documented in areas affected by the Zika virus.²⁴¹ The first case of Zika-related microcephaly in a new born baby in the United States surfaced in January 2016,²⁴² which prompted the Centers for Disease Control and Prevention to issue warnings for pregnant women to avoid traveling to countries with Zika outbreaks.²⁴³ Fears were further augmented when studies revealed that, although mosquito bites are the main source of transmission, the virus can be spread through sexual intercourse and blood transfusions.²⁴⁴

Throughout 2015 and 2016, Zika brought panic to many areas of the world. Babies born with microcephaly and intracranial calcification became a fixture in the news.²⁴⁵ Public support for the release of genetically modified insects as a method of population control in areas affected by Zika may be low at this point in time, particularly in the United States.²⁴⁶ However, the prospect of an epidemic at home coupled with laggard progress in research toward development of a vaccine could awaken the public's appetite for drastic measures to prevent the spread of the virus. Groups that vehemently oppose genetic engineering under any circumstances might soon find themselves fighting a losing battle in the court of

240. Sandee LaMotte, *Zika Around the World: Where Do We Stand?*, CNN, <http://www.cnn.com/2016/08/30/health/zika-around-the-world/> [https://perma.cc/2AGH-CVXJ] (last updated Aug. 30, 2016, 7:54 AM).

241. *Public Health Emergency of International Concern (PHEIC) Declared for Zika and Clusters of Microcephaly and Neurological Disorders*, EUROPEAN CTR. DISEASE PREVENTION & CONTROL (Feb. 3, 2016), http://ecdc.europa.eu/en/activities/sciadvicelayouts/forms/Review_DisForm.aspx?List=a3216f4c-f040-4f51-9f77-a96046dbfd72&ID=790 [https://perma.cc/2KAD-HBXL] cf. Dom Phillips & Lena H. Sun, *Brazil May Have Fewer Zika-Related Microcephaly Cases than Previously Reported*, WASH. POST (Jan. 29, 2016), https://www.washingtonpost.com/news/worldviews/wp/2016/01/29/brazil-may-have-fewer-zika-related-microcephaly-cases-than-previously-reported/?utm_term=.130b760628a2 [https://perma.cc/22HZ-3GXG] (reporting that many of the documented microcephaly cases in Brazil may not actually be microcephaly, nor related to the Zika virus).

242. Donald G. McNeil, Jr., *Hawaii Baby with Brain Damage Is First U.S. Case Tied to Zika Virus*, N.Y. TIMES (Jan. 16, 2016), <https://www.nytimes.com/2016/01/17/health/hawaii-reports-baby-born-with-brain-damage-linked-to-zika-virus.html> [https://perma.cc/2MD6-FXS3].

243. See, e.g., Donald G. McNeil, Jr., *To Protect Against Zika Virus, Pregnant Women Are Warned About Latin American Trips*, N.Y. TIMES (Jan. 15, 2016), <https://www.nytimes.com/2016/01/16/health/zika-virus-cdc-pregnant-women-travel-warning.html> [https://perma.cc/K8DF-F63T].

244. See, e.g., Adrija Hajra et al., *Zika Virus: A Global Threat to Humanity: A Comprehensive Review and Current Developments*, 8 N. AM. J. MED. SCI. 123 (2016).

245. See, e.g., McNeil, *supra* note 242.

246. See, e.g., Axford, *supra* note 239; Sarich, *supra* note 238.

public opinion. Such an outlook is not hypothetical; other countries confronting mosquito-related health crises have weighed the social and economic costs and benefits of releasing bioengineered insects into the environment and opted to avail themselves of biotechnology to allay the spread of disease.²⁴⁷

It is only a matter of time—and a brief one, at that—before the technological knack required for large-scale testing of a CRISPR gene drive is refined. Indeed, field trials could likely be ready to launch anytime now if a general consensus to support them formed and gave the green light to proceed.²⁴⁸

The stark imminence of these developments has prompted a debate about biosecurity and the benefits and harms of using gene drives for biological control of certain species, including how to safeguard gene drive testing in laboratory settings.²⁴⁹ In fact, scientists wary of the potential consequences of unintended release of species carrying gene drives into the environment have already designed and tested *split-drives*—to separate the pieces of a gene drive—and *reversal-drives*—to overwrite changes of the original gene drive—as molecular confinement insurance strategies to guard against inadvertent escape of mutant organisms.²⁵⁰

The wondrous capacity to circumvent Mendelian genetics constraints to guarantee that a gene can fix itself in a population is unprecedented. Regardless of the future regulatory decisions made to promote, control, or curtail gene drives altogether, no one can deny the power of the technology. For better or worse, the ability to hack genomes in pests finally bestows upon the world a weapon with the potential to help eradicate a long list of vector-borne

247. See, e.g., *supra* notes 236–37 and accompanying text.

248. Carl Zimmer, *A Call to Fight Malaria One Mosquito at a Time by Altering DNA*, N.Y. TIMES (July 17, 2014), http://www.nytimes.com/2014/07/17/science/a-call-to-fight-malaria-one-mosquito-at-a-time-by-altering-dna.html?_r=0 [<https://perma.cc/D27C-K2MS>] (quoting George Church, senior author of one of the papers targeting malaria mosquito vectors, as stating: “In a year or two, we could be doing field trials if there was a general consensus this was a good idea.”).

249. See, e.g., Omar S. Akbari et al., *Safeguarding Gene Drive Experiments in the Laboratory*, 349 SCIENCE 927 (2015); Keith G. Kozminski, *Biosecurity in the Age of Big Data: A Conversation with the FBI*, 26 MOLECULAR BIOLOGY CELL 3894 (2015); Bruce L. Webber et al., *Opinion: Is CRISPR-Based Gene Drive a Biocontrol Silver Bullet or Global Conservation Threat?*, 112 PROC. NAT’L ACAD. SCI. U.S. 10565 (2015); Katie Langin, *Genetic Engineering to the Rescue Against Invasive Species?*, NAT’L GEOGRAPHIC (July 18, 2014), <http://news.nationalgeographic.com/news/2014/07/140717-gene-drives-invasive-species-insects-disease-science-environment/> [<https://perma.cc/K9WH-EBH6>]; *Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct*, NAT’L ACAD. SCI., ENG’G, & MED., <https://www8.nationalacademies.org/cp/projectview.aspx?key=49717> [<https://perma.cc/VAT3-WVPM>] (last visited Feb. 26, 2017).

250. See DiCarlo et al., *supra* note 217, at 1252–53.

diseases—malaria, dengue, yellow fever, Zika, epidemic typhus, Lyme disease, Rocky Mountain spotted fever, etc.—as well as neglected tropical diseases²⁵¹ (NTDs) caused by parasitic organisms—e.g., schistosomiasis, caused by helminth parasites of the genus *Schistosoma*, which has brought suffering to hundreds of millions of people worldwide.²⁵² Science has produced a method that offers a meaningful opportunity to strike back at the mosquito, the deadliest animal in the world.²⁵³

By the same token, science has produced a tool to reshape entire ecosystems. On one hand, given the reported success of gene drives to endow a species with anti-parasite resistance,²⁵⁴ one can imagine possible scenarios where an endangered species could be generously armed with a gene drive to help it cope with changes in its habitat, or become immunized against parasites and opportunistic organisms driving it into extinction. On the other hand, CRISPR-based gene drives could be used to deliver a coup de grâce to invasive and noxious species like the Asian carp in the Great Lakes,²⁵⁵

251. NTDs are a group of parasitic and bacterial diseases affecting more than one billion people worldwide, predominantly in low-income countries. *Neglected Tropical Diseases*, CTRS. DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/globalhealth/ntd/> [<https://perma.cc/TK9L-9LZ3>] (last updated June 7, 2016). NTDs cause substantial illness and death, impair physical and cognitive development, and limit productivity in the workplace. *Id.* They are considered neglected because they are largely nonexistent in developed nations, but persist only in the poorest, most marginalized areas of low-income countries. *Id.* The list of common NTDs includes Buruli ulcers, Chagas disease, Cysticercosis, Dengue fever, Echinococcosis, Fascioliasis, Leprosy, Onchocerciasis, Rabies, Schistosomiasis, and others. See *Diseases*, CTRS. DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/globalhealth/ntd/diseases/index.html> [<https://perma.cc/BE7T-4HPN>] (last updated Feb. 17, 2017), for a list and information about NTDs.

252. See *Chapter 3: Infectious Diseases Related to Travel*, CTRS. DISEASE CONTROL & PREVENTION, <https://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/schistosomiasis> [<https://perma.cc/2MM8-5C73>] (last updated July 10, 2015). In terms of impact, schistosomiasis is second only to malaria as the most devastating parasitic disease. *The Burden of Schistosomiasis (Schisto, Bilharzia, Snail Fever)*, CTRS. DISEASE CONTROL & PREVENTION, http://www.cdc.gov/globalhealth/ntd/diseases/schisto_burden.html [<https://perma.cc/9MP3-LR7K>] (last updated June 6, 2011). In more than seventy-five countries spanning tropical and sub-tropical areas, 800 million people are at risk of contracting schistosomiasis, and more than 200 million people are infected with schistosomes. Sutas Suttiprapa et al., *Genetic Manipulation of Schistosomes – Progress with Integration Competent Vectors*, 139 *PARASITOLOGY* 641, 641 (2012).

253. Bill Gates, *The Deadliest Animal in the World*, GATES NOTES (Apr. 25, 2014), <https://www.gatesnotes.com/Health/Most-Lethal-Animal-Mosquito-Week> [<https://perma.cc/7T6Z-L8F3>].

254. See Gantz et al., *supra* note 227 (using a gene drive to make the mosquito *Anopheles Stephensi* resistant to the malaria parasite).

255. See *Asian Carp Threat to the Great Lakes*, NAT'L WILDLIFE FED'N, <https://www.nwf.org/Wildlife/Threats-to-Wildlife/Invasive-Species/Asian-Carp.aspx> [<https://perma.cc/6YHH-AE2D>] (last visited Feb. 26, 2017); see also *Asian Carp Breed in Great Lakes, Threaten Fishing*, USA TODAY (Oct. 28, 2013), <http://www.usatoday.com/story/news/nation/2013/10/28/asian-carp-great-lakes/3289387/> [<https://perma.cc/R3MB-GPQJ>].

Argentine cactus moth in the Southern United States and Mexico,²⁵⁶ cane toads in Australia,²⁵⁷ tropical fire ants in the Galápagos Islands,²⁵⁸ Giant African snails,²⁵⁹ zebra mussels,²⁶⁰ kudzu,²⁶¹ soybean cyst nematode—affecting soybean crops worldwide²⁶²—and a miscellany of other aquatic²⁶³ and terrestrial²⁶⁴ invasive plant and animal species.

C. Transgenic Animals for Translational and Basic Research

Animals have long played an integral role in scientific inquiry. From Aristotle's experiments on living animals²⁶⁵ to Pasteur's groundbreaking studies on rabbits and dogs,²⁶⁶ scientists have always sought animal models to explore biomedical research. Well over 100 million animals have been used for scientific research in Europe and the United States alone since governmental agencies began tracking

256. *Argentine Cactus Moth* (*Cactoblastis cactorum*), DESERT MUSEUM, http://www.desertmuseum.org/invasors/invasors_cactusmoth.php [<https://perma.cc/KXA5-9RPZ>] (last visited Feb. 26, 2017).

257. *Australian Government Policy on Cane Toads*, AUSTRALIAN GOV'T: DEP'T ENV'T & ENERGY, <https://www.environment.gov.au/biodiversity/invasive-species/publications/cane-toad-policy#why> [<https://perma.cc/X8MQ-EKWN>] (last visited Feb. 26, 2017).

258. *Managing Invasive Ants*, GALÁPAGOS CONSERVANCY, <http://www.galapagos.org/conservation/conservation/project-areas/ecosystem-restoration/managing-invasive-ants/> [<https://perma.cc/GM2Z-2ABN>] (last visited Feb. 26, 2017).

259. Darryl Fears, *This Invasive Giant Snail Is Spreading in Florida—and Bringing Nasty Parasites with It*, WASH. POST (July 10, 2015), <https://www.washingtonpost.com/news/energy-environment/wp/2015/07/10/giant-land-snails-are-on-the-move-and-a-nasty-parasite-is-riding-them-like-a-bus/> [<https://perma.cc/U286-35H2>].

260. *The Lionfish Invasion!: Can We Stop the Invasion?*, NAT'L OCEANIC & ATMOSPHERIC ADMIN., http://oceanservice.noaa.gov/education/stories/lionfish/lion05_stop.html [<https://perma.cc/P5HB-VCJN>] (last visited Feb. 26, 2017).

261. *Kudzu, Control*, MO. DEP'T CONSERVATION, <https://mdc.mo.gov/trees-plants/problem-plant-control/invasive-plants/kudzu-control> [<https://perma.cc/RGL2-NXEJ>] (last visited Feb. 26, 2017).

262. Qing Yu, *Soybean Cyst Nematode* (*Heterodera glycines Ichinohe*), in SOYBEAN PHYSIOLOGY AND BIOCHEMISTRY 461, 461 (Hany El-Shemy ed., 2011), <http://cdn.intechopen.com/pdfs-wm/22782.pdf> [<https://perma.cc/8Q8G-JSES>].

263. *Aquatic Species*, U.S. DEP'T OF AGRIC., NAT'L INVASIVE SPECIES INFO. CTR., <http://www.invasivespeciesinfo.gov/aquatics/main.shtml#aqan> [<https://perma.cc/P6SB-Y3EQ>] (last visited Feb. 26, 2017).

264. *Animals*, U.S. DEP'T AGRIC., NAT'L INVASIVE SPECIES INFO. CTR., <http://www.invasivespeciesinfo.gov/animals/main.shtml> [<https://perma.cc/54VY-A22R>] (last visited Feb. 26, 2017).

265. Rachel Hajar, *Animal Testing and Medicine*, 12 HEART VIEWS 42, 42 (2011).

266. Kendall A. Smith, *Louis Pasteur, the Father of Immunology?*, 3 FRONTIERS IMMUNOLOGY, art. 68, 8 (2012).

animal studies.²⁶⁷ A long list of model organisms²⁶⁸ has helped to elucidate fundamental questions in science over many decades. Without question, animal experimentation has provided insights into anatomy, physiology, and medicine that have dramatically transformed our ability to cope with and ameliorate human suffering.²⁶⁹ It would be nearly impossible to establish safety measures and criteria prior to launching new treatments without the use of animal models of human disease.²⁷⁰

1. Mouse Pre-Clinical Models of Disease

In recent years, genome editing has routinely been utilized to edit a multitude of animal genomes.²⁷¹ Of these, the mouse has become the foremost mammalian model organism for genetic and biomedical pre-clinical research, thanks in part to physiological similarities between mice and humans.²⁷² Indeed, genome editing studies in mice are instrumental for translational purposes and demonstrate great promise in forging a path toward human clinical applications. For instance, last month, three independent US teams published proof-of-concept studies showing how CRISPR-based gene editing can be used to improve skeletal muscle function in adult and neonatal mice models of Duchenne muscular dystrophy (DMD), a fatal genetic disease that causes muscle degeneration, loss of mobility, and premature death.²⁷³ One of the three teams had previously

267. Daniel Butzke et al., *The Advent of the Golden Era of Animal Alternatives*, in ANIMAL MODELS FOR THE STUDY OF HUMAN DISEASE 49–50 (P. Michael Conn ed., 2013). In 2014, 834,453 animals—excluding rats, mice, birds and other species not covered by the Animal Welfare Act—were used in research and teaching in the United States. *Animals Used in Research*, NAT'L ANTI-VIVISECTION SOC'Y, <http://www.navs.org/the-issues/animals-in-research/#.WJ5t05KgQxU> [<https://perma.cc/9BSA-YVBJ>] (last visited Feb. 25, 2017).

268. See *List of Model Organisms*, WIKIPEDIA, https://en.wikipedia.org/wiki/List_of_model_organisms [<https://perma.cc/8T3Y-AXTA>] (last updated Dec. 29, 2016).

269. For a works-in-collection featuring a thorough examination of the use of animal models for human disease in a wide array of fields ranging from ophthalmology and cardiology to genetics, behavior, cancer, and development, see ANIMAL MODELS FOR THE STUDY OF HUMAN DISEASE (P. Michael Conn ed., 2013).

270. See, e.g., Lars Dalgaard, *Comparison of Minipig, Dog, Monkey and Human Drug Metabolism and Disposition*, 74 J. PHARMACOLOGICAL & TOXICOLOGICAL METHODS 80 (2015).

271. See, e.g., *supra* notes 163–71; *supra* Sections IV.A & IV.B.

272. S.K. Chung et al., *Mouse Models for Human Diseases*, 3 H.K. MED. J. 201, 201 (1997); *Background on Mouse as a Model Organism*, NAT'L HUM. GENOME RES. INST. (Dec. 2002), <http://www.genome.gov/10005834> [<https://perma.cc/EJ85-MCV8>] (last reviewed May 31, 2012).

273. Chengzu Long et al., *Postnatal Genome Editing Partially Restores Dystrophin Expression in a Mouse Model of Muscular Dystrophy*, 351 SCIENCE 400, 400 (2016); Christopher E. Nelson et al., *In Vivo Genome Editing Improves Muscle Function in a Mouse Model of Duchenne Muscular Dystrophy*, 351 SCIENCE 403, 403 (2016); Mohammadsharif Tabebordbar et

demonstrated the feasibility of preventing the disease by editing the germline—an organism's sex cells (e.g., eggs and sperm) that pass on genes from one generation to the next during sexual reproduction²⁷⁴—of mice models of DMD.²⁷⁵

Researchers have also corrected a mutation in the *Crygc* gene responsible for cataracts by editing the germline of mice, leading to the birth of fertile pups that went on to pass the corrected allele to their progeny.²⁷⁶ A mouse model of mitochondrial disease demonstrated that germline genome editing can prevent transmission of faulty mitochondria—organelles that supply energy to cells²⁷⁷—to mice offspring.²⁷⁸ CRISPR-mediated genome editing in postmitotic neurons of adult mice brain has been achieved *in vivo*.²⁷⁹ And a separate team showed that Cas9-mediated germline multiplexing—the simultaneous disruption of multiple genes by gene editing—can be accomplished by targeting genes into zygotes, thereby producing animals with desired mutations in various genes.²⁸⁰

Despite the widespread use of mouse models of human disease, there are stark limitations associated with pre-clinical trials in rodents. First, the very characteristics that make mice useful models—relatively short life cycle compared to other mammals, physical size, short gestation periods, abundant progeny, etc.—may render them inadequate for validating the relevance of clinical findings.²⁸¹ Second, metabolic and physiological differences between mice and humans lead to differences in species-specific susceptibility to disease and pharmacological responses.²⁸² Third, mice models of

al., *In Vivo Gene Editing in Dystrophic Mouse Muscle and Muscle Stem Cells*, 351 SCIENCE 407, 407 (2016).

274. *What Are the Ethical Issues Surrounding Gene Therapy?*, U.S. NAT'L LIBR. MED. (Feb. 7, 2017), <https://ghr.nlm.nih.gov/primer/therapy/ethics> [<https://perma.cc/B5HY-R83D>].

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

276. Yuxuan Wu et al., *Correction of a Genetic Disease in Mouse via Use of CRISPR-Cas9*, 13 CELL STEM CELL 659, 659, 662 (2013).

277. *Mitochondrial DNA*, GENETICS HOME REFERENCE (Feb. 7, 2017), <http://ghr.nlm.nih.gov/mitochondrial-dna> [<https://perma.cc/A3DW-4TL4>].

278. Pradeep Reddy et al., *Selective Elimination of Mitochondrial Mutations in the Germline by Genome Editing*, 161 CELL 459, 459 (2015).

279. Lukasz Swiech et al., *In Vivo Interrogation of Gene Function in the Mammalian Brain Using CRISPR-Cas9*, 33 NATURE BIOTECHNOLOGY 102, 102 (2015).

280. Haoyi Wang et al., *One-Step Generation of Mice Carrying Mutations in Multiple Genes by CRISPR/Cas-Mediated Genome Engineering*, 153 CELL 910, 910 (2013). See generally Wataru Fujii et al., *Efficient Generation of Large-Scale Genome-Modified Mice Using gRNA and CAS9 Endonuclease*, 41 NUCLEIC ACIDS RES. e187 (2013).

281. Chung et al., *supra* note 272, at 201.

282. *Id.*; see also Dalgaard, *supra* note 270 (discussing comparative pharmacology and toxicology in humans and other large mammals).

disease often cannot recapitulate features associated with many human pathologies. A quintessential illustration of this phenomenon is the inability of mice to replicate the full panoply of neuropathologies—most notably, overt neurodegeneration in the human brain—that constitute the hallmark of many neurodegenerative diseases such as Parkinson's Disease,²⁸³ Huntington's Disease,²⁸⁴ and Alzheimer's Disease.²⁸⁵ The same holds true for Cystic Fibrosis,²⁸⁶ Lesch-Nyhan syndrome,²⁸⁷ and many other conditions. The lack of accurate pathological reproducibility is problematic and may be linked to the meager impact these mouse models have had in clinical outcomes.²⁸⁸

2. Large Animal Pre-Clinical Models on the Rise

As a result of the natural constraints imposed by mice models of human disease, large animal models have become an increasingly attractive alternative for clinical investigation.²⁸⁹ Indeed, as controversial as the research might be,²⁹⁰ dogs,²⁹¹ cats,²⁹² pigs,²⁹³

283. J.A. Potashkin et al., *Limitations of Animal Models of Parkinson's Disease*, 2011 PARKINSON'S DISEASE art. ID 658083, at 5 (2011).

284. Xiao-Jiang Li & Shihua Li, *Large Animal Models of Huntington's Disease*, in BEHAVIORAL NEUROBIOLOGY OF HUNTINGTON'S DISEASE & PARKINSON'S DISEASE 149 (2013).

285. Karen Duff & Faraha Suleman, *Transgenic Mouse Models of Alzheimer's Disease: How Useful Have They Been for Therapeutic Development?*, 3 BRIEFINGS FUNCTIONAL GENOMICS & PROTEOMICS 47, 49–50 (2004).

286. Isabel Carvalho-Oliveira, *What Have We Learned from Mouse Models for Cystic Fibrosis?*, 7 EXPERT REV. MOLECULAR DIAGNOSTICS 407 (2007).

287. Chao-Liang Wu & David W. Melton, *Production of a Model for Lesch-Nyhan Syndrome in Hypoxanthine Phosphoribosyltransferase-Deficient Mice*, 3 NATURE GENETICS 235 (1993).

288. D.R. Howlett, *APP Transgenic Mice and their Application to Drug Discovery*, 26 HISTOLOGY & HISTOPATHOLOGY 1611 (2011).

289. See e.g., Ashish R. Pinnapureddy et al., *Large Animal Models of Rare Genetic Disorders: Sheep as Phenotypically Relevant Models of Human Genetic Disease*, 10 ORPHANET J. RARE DISEASES 107 (2015).

290. Compare Allyson J. Bennett, *Animal Research: The Bigger Picture and Why We Need Psychologists to Speak out*, AM. PSYCHOL. ASS'N, (Apr. 2012), <http://www.apa.org/science/about/psa/2012/04/animal-research.aspx>, with *Animal Testing Is Bad Science: Point/Counterpoint*, PETA, <http://www.peta.org/issues/animals-used-for-experimentation/animal-testing-bad-science/> [https://perma.cc/2JLH-SAH3] (last visited Feb. 12, 2017).

291. Meg M. Sleeper et al., *Gene Therapy in Large Animal Models of Human Cardiovascular Genetic Disease*, 50 INST. FOR LABORATORY ANIMAL RES. J. 199, 200–01 (2009).

292. *Id.*

293. Nana Fan & Liangxue Lai, *Genetically Modified Pig Models for Human Diseases*, 40 J. GENETICS & GENOMICS 67 (2013).

sheep,²⁹⁴ rabbits,²⁹⁵ goats,²⁹⁶ horses,²⁹⁷ non-human primates,²⁹⁸ and other large animals have contributed greatly to our understanding of human pathologies. Advocates of research on large animals argue that using higher mammalian species offers a more rigorous and reliable system to validate the efficacy of pre-clinical trials in small rodents.²⁹⁹ Accordingly, a tide of experiments on large animals is surfing apace thanks to novel genome editing technologies that have turned the unimaginable into a reality.³⁰⁰

In almost parallel studies, CRISPR systems have been effectively used to create muscular versions of pigs³⁰¹ and beagle dogs,³⁰² the canine breed most widely used in biomedical research, via engineering *MSTN*³⁰³ mutations. At least nine genes, some of which are associated with lipid metabolism and cardiovascular conditions, have been targeted and mutated in rabbits.³⁰⁴ Editing the *vWF* gene, responsible for von Willebrand Disease (vWD)—a bleeding disorder that prevents normal blood clotting³⁰⁵—led to a striking phenotype in mutant pigs; the animals exhibited prolonged bleeding that lasted nearly fifteen times longer than that of non-mutant pigs.³⁰⁶ Because mice models cannot fully recapitulate the severe bleeding phenotype of

294. Pinnapureddy et al., *supra* note 289.

295. V. Duranthon et al., *On the Emerging Role of Rabbit as Human Disease Model and the Instrumental Role of Novel Transgenic Tools*, 21 *TRANSGENIC RES.* 699 (2012).

296. E.J. Olivier ten Hallers et al., *The Saanen Goat as an Animal Model for Post-Laryngectomy Research: Practical Implications*, 41 *LABORATORY ANIMALS* 270 (2007).

297. C.W. McIlwraith et al., *The Horse as a Model of Naturally Occurring Osteoarthritis*, 1 *BONE & JOINT RES.* 297 (2012).

298. David T. Evans & Guido Silvestri, *Non-Human Primate Models in AIDS Research*, 8 *CURRENT OPINIONS HIV & AIDS* 255 (2013).

299. Li & Li, *supra* note 284, at 157.

300. Amy Harmon, *Open Season Is Seen in Gene Editing of Animals*, *N.Y. TIMES*, Nov. 27, 2015, at A1.

301. Kankan Wang et al., *Efficient Generation of Myostatin Mutations in Pigs Using the CRISPR/Cas9 System*, 5 *SCI. REP.* 16623 (2015).

302. Qingjian Zou et al., *Generation of Gene-Target Dogs Using CRISPR/Cas9 System*, 7 *J. MOLECULAR CELL BIOLOGY* 580 (2015).

303. Myostatin, also known as growth differentiation factor-8 (*GDF-8*), is a gene involved in regulation of skeletal muscle growth that has been linked to muscle hypertrophy. See Alexandra C. McPherron et al., *Regulation of Skeletal Muscle Mass in Mice by a New TGF-beta Superfamily Member*, 387 *NATURE* 83 (1997).

304. Yang et al., *supra* note 168.

305. *What Is Von Willebrand Disease?*, *NAT'L HEART, BLOOD, & LUNG INST.*, <http://www.nhlbi.nih.gov/health/health-topics/topics/vwd> [<https://perma.cc/4R7N-WC6G>] (last updated June 1, 2011).

306. Tang Hai et al., *One-Step Generation of Knockout Pigs by Zygote Injection of CRISPR/Cas System*, 24 *CELL RES.* 372, 374 (2014).

vWD,³⁰⁷ the ability of CRISPR-edited pigs to mimic human vWD is a major step toward developing a bona fide model to study the disease.

Similar phenotypic replication of pathologies that could not be realized in mouse models has been accomplished in sheep,³⁰⁸ pigs,³⁰⁹ and other large animals,³¹⁰ lending credence to the hypothesis that large animal models constitute a more precise platform to study some human diseases. Now that CRISPR technologies and their use are starting to become routine, we should fully expect numerous reports in the coming months and years establishing new large animal models for clinical research.

On this point, perhaps the most salient examples of the potential of genome editing for translational applications are the recent publications vis-à-vis CRISPR-edited non-human primates. In a world first, Chinese scientists have recently used genome editing technologies to modify the embryos of cynomolgus³¹¹ and rhesus³¹² monkeys and implant them into surrogate mothers, who delivered transgenic infant monkeys after full-term pregnancies. Proof that non-human primates' genomes can, in fact, be modified at the embryonic stage to produce progeny with desired modifications turns the prospect of human germline modification from a forlorn aspiration into a feasible goal. Indeed, the race to produce monkeys with

307. *Id.* at 372.

308. *See, e.g.,* Eric W.F.W. Alton et al., *The Safety Profile of a Cationic Lipid-Mediated Cystic Fibrosis Gene Transfer Agent Following Repeated Monthly Aerosol Administration to Sheep*, 34 *BIOMATERIALS* 10267, 10276 (2013).

309. *Compare, e.g.,* Bernhardt G. Zeiher et al., *A Mouse Model for the $\Delta F508$ Allele of Cystic Fibrosis*, 96 *J. CLINICAL INVESTIGATION* 2051, 2062 (1996) (introducing the most common CF-associated mutation of *CFTR* into transgenic mice without accurately replicating the CF pathology), *with* Lynda S. Ostedgaard et al., *The $\Delta F508$ Mutation Causes *CFTR* Misprocessing and Cystic Fibrosis-Like Disease in Pigs*, 3 *SCI. TRANSLATIONAL MED.* 74ra24 (2011) (engineering pigs carrying the same mutation— $\Delta F508$ —as was done in the mouse, but observing a range of human CF pathology), *and* Christopher S. Rogers et al., *Disruption of the *CFTR* Gene Produces a Model of Cystic Fibrosis in Newborn Pigs*, 321 *SCIENCE* 1837 (2008) (disrupting the *CFTR* gene in pigs led to development of human CF clinical manifestations). *See also* Huaqiang Yang et al., *Species-Dependent Neuropathology in Transgenic *SOD1* Pigs*, 24 *CELL RES.* 464 (2014) (engineering transgenic pigs that showed nuclear accumulation and ubiquitinated nuclear aggregates in the brain, as seen in some human Amyotrophic lateral sclerosis (ALS) patient brains, but not in ALS mouse models).

310. *See, e.g.,* Xingshen Sun et al., *Disease Phenotype of a Ferret *CFTR*-Knockout Model of Cystic Fibrosis*, 120 *J. CLINICAL INVESTIGATION* 3149 (2010).

311. Yuyu Niu et al., *Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA-Mediated Gene Targeting in One-Cell Embryos*, 156 *CELL* 836 (2014).

312. Hailiang Liu et al., *TALEN-Mediated Gene Mutagenesis in Rhesus and Cynomolgus Monkeys*, 14 *CELL STEM CELL* 323 (2014).

targeted genome modifications for more accurately modeling human diseases is now on.³¹³

In the last year, the birth of monkeys with markedly depleted dystrophin and muscle degeneration seen in early human DMD has been reported.³¹⁴ A one-step method demonstrated successful embryonic editing and delivery of live monkeys carrying homozygous mutations in the tumor suppressor *p53* gene.³¹⁵ Furthermore, scientists recently published an article describing the creation of transgenic monkeys that exhibit autism-like behaviors and, remarkably, showed successful germline transmission of the modified gene by bringing their progeny into this world.³¹⁶ These findings demonstrate that, unlike mouse models lacking higher perceptual and cognitive function seen in primates,³¹⁷ studies using non-human primate genome editing are better equipped to provide models to further our understanding—and ultimately lead to treatments—of the cognitive, behavioral, anatomical, and emotional symptoms associated with a long list of neurological—autism spectrum disorder; behavioral—Attention Deficit Hyperactivity Disorder (ADHD), drug abuse, and alcohol abuse; psychiatric—schizophrenia, obsessive compulsive disorder, and depression; and neurodegenerative disorders—Alzheimer's and Parkinson's Disease—that contribute to human suffering worldwide.

3. Xenotransplantation—A Case Study

Genome editing technologies can now be used to create useful animal models to interrogate the mechanisms of human diseases, which may lead to future diagnoses and treatments, as discussed above. However, other translational applications of animal genome editing are even closer on the horizon, and a prime example is the field of xenotransplantation.³¹⁸

313. See, e.g., *infra* notes 314–16 and accompanying text.

314. Yongchang Chen et al., *Functional Disruption of the Dystrophin Gene in Rhesus Monkey Using CRISPR/Cas9*, 24 HUM. MOLECULAR GENETICS 3764 (2015); Yongchang Chen et al., *Germline Acquisition of Cas9/RNA-Mediated Gene Modifications in Monkeys*, 25 CELL RES. 262 (2015).

315. Haifeng Wan et al., *One-Step Generation of p53 Gene Biallelic Mutant Cynomolgus Monkey via the CRISPR/Cas System*, 25 CELL RES. 258 (2015).

316. Zhen Liu et al., *Autism-Like Behaviours and Germline Transmission in Transgenic Monkeys Overexpressing MeCP2*, 530 NATURE 98 (2016).

317. Jon H. Kaas, *The Evolution of Brains from Early Mammals to Humans*, 4 WILEY INTERDISC. REVS. 33 (2013).

318. Xenotransplantation refers to the process of transplanting living cells, tissues, or organs from one species to another. See *Xenotransplantation*, WORLD HEALTH ORG. (May 2, 2005), <http://www.who.int/transplantation/xeno/en/> [<https://perma.cc/V65A-FZW5>].

Organ donation and transplantation is the best, and often sole, form of treatment for end-stage organ failure worldwide.³¹⁹ In the United States alone, a shortage of organs for transplantation claims approximately twenty-two lives every day—over 8,000 annually.³²⁰ Similarly, massive shortages of organ donors in China and India lead to tens-of-thousands³²¹ and hundreds-of-thousands of deaths,³²² respectively, with worldwide death tolls likely reaching the millions.³²³

319. C. Rudge et al., *International Practices of Organ Donation*, 108 BRITISH J. ANAESTHESIA i48 (2012).

320. *Donation and Transplantation*, U.S. DEP'T HEALTH & HUM. SERVS., <http://www.organdonor.gov/about/data.html> [<https://perma.cc/R77B-YBP6>] (updated Mar. 31, 2015).

321. Wang Yan, *Still Waiting*, NEWS CHINA, (July 2011), <http://old.newschinamag.com/magazine/still-waiting> [<https://perma.cc/XM33-2PT8>].

322. Approximately 500,000 people die annually in India due to a shortage of organs for transplantation. Shruti Saxena, *Organ Donation: Does India Lack Will?*, INDILENS, (Aug. 7, 2014), <http://indilens.com/57441-world-organ-donation-day-does-india-lack-will/> [<https://perma.cc/LJM5-JPHV>]. India has a rate of less than 0.2 donors per one million population. *Id.*

323. It is difficult to determine exactly how many people on organ waiting lists die every year globally due to the lack of reporting mechanisms in most of the developing world. According to the International Registry in Organ Donation and Transplantation (IRODaT), only seventy-one countries currently report national data of donation and transplantation activity for database compilation on IRODaT. *Final Numbers 2013*, INT'L REGISTRY ORGAN DONATION & TRANSPLANTATION 2 (Dec. 2014), <http://www.irodat.org/img/database/pdf/IRODaT%20Newsletter%202013%20.pdf> [<https://perma.cc/7Q2Y-C7A7>]. The World Health Organization (WHO) reported 117,700 solid organ transplants in 2013. *Map: Global Observatory on Donation and Transplantation, Global Transplantation Activities of Solid Organs, 2013*, WORLD HEALTH ORG., (2015), <http://www.transplant-observatory.org/report-2013/> [<https://perma.cc/4MTP-BGCU>]. In contrast, 29,532 individuals received organ transplants in 2014 in the United States, where over 123,000 people are currently on waiting lists for lifesaving organ transplants. U.S. DEP'T HEALTH & HUM. SERVS., *supra* note 320; *Facts and Myths*, AM. TRANSPLANT FOUND., <http://www.americantransplantfoundation.org/about-transplant/facts-and-myths/> [<https://perma.cc/4WS7-TP22>] (last visited Feb. 12, 2017). It is important to point out that organ transplant statistics do not include corneas, veins, heart valves, tendons, bones, skin, and other tissues. *Facts and Myths, supra*. For example, 40,000 corneal transplants—the most routinely transplanted tissue—are performed every year in the United States. *Id.*

An overwhelmingly conservative, low-end estimate of worldwide deaths attributable to organ shortages could, at the very least, be purportedly derived by looking at US statistics. If roughly 6.5% of people on waiting lists die every year (8,000 deaths per annum from a select population of 123,000), and approximately 24% of wait-listed individuals receive transplants (29,532 recipients of a 123,000 applicant pool), we can use the number of reported worldwide transplants (117,700) and US-derived statistical rates to arrive at a baseline putative worldwide organ transplant waitlist population—limited to less than half (seventy-one) of total countries—of nearly a half-million individuals (~491,000), of which ~32,000—or 6.5%—would die annually. Yet, even this figure likely grossly underestimates the actual number given that there are nearly 200 countries in the world, and most of the non-reporting countries house low-income, poverty-stricken populations with limited access to healthcare and education. Undoubtedly, in this context, current statistics on organ transplantation-related data excludes individuals in low-income regions of the world who are in dire need of access to lifesaving organ transplantation.

To mitigate the shortage of organs, scientists began to experiment, decades ago, with xenotransplantation to determine whether animals could provide a supply of organs to humans.³²⁴ Animal kidney, heart, and liver organs were first in line, with catastrophic results for patients as a result of severe infection, immune reactions, and rejection of the organs.³²⁵ However, after decades of research on xenotransplantation and the advent of genome editing technology, researchers may now be on the verge of breaking through the non-human organ donor glass ceiling.

Recent articles published encouraging results from xenotransplantation of hearts³²⁶ and a life-supporting kidney graft³²⁷

Furthermore, many people in both reporting and non-reporting countries may harbor long-held cultural apprehensions regarding transplantation, including distrust of the medical system and religious or ethnic myths and misbeliefs about diseased organ donation and transplantation. See e.g., L.P. Wong, *Factors Limiting Deceased Organ Donation: Focus Groups' Perspective from Culturally Diverse Community*, 42 TRANSPLANTATION PROC. 1439 (2010). Such ethnic, religious, and cultural limitations could even be responsible for under-reporting figures in developed countries with tightly clustered and self-isolating immigrant populations.

One might arrive at a closer estimate using the above, or a similar, mathematical formulation with rates derived from developing countries like China and India where death rates are believed to be in the tens-of-thousands in China and as high as 500,000 in India. See Saxena, *supra* note 322; see also Yan, *supra* note 321. Combining figures stemming from much-needed independent statistical and mathematical modeling among developed and developing countries may shed more light on the actual state of organ transplantation worldwide. Moreover, it bears noting that individuals in need of organ transplantations in some parts of the world may not have the resources or capabilities to get on a waitlist, even if one were available in their country of origin, due to hurdles imposed by corrupt governments and international cartels engaged in organ trafficking. See Bruce Watson, *How Corrupt Governments Make a Killing on Human Organs*, DAILY FIN. (Jan. 7, 2011), <http://www.dailyfinance.com/2011/01/07/human-organ-trafficking-is-big-business-in-kosovo-china/> [<https://perma.cc/ZS64-R9LC>].

Lastly, a statistical caveat involves potentially incomplete figures found on current waitlists across developed and developing nations. For instance, when the United States began tracking organ transplantation data in 1991, there were roughly 16,000 transplants performed and a little over 23,000 people on waitlists. *The Gap Continues to Widen*, U.S. DEPT HEALTH & HUM. SERVS., <https://www.organdonor.gov/statistics-stories/statistics/data.html> [<https://perma.cc/22B7-XCYJ>] (last visited Feb. 12, 2017). Since then, the number of transplants has less than doubled. *Id.* Yet, remarkably, the number of patients waiting for transplants has increased by more than 530% over the past two-and-a-half decades. *Id.* Although it is possible—though not plausible—one can hardly imagine that such a disparate number of people today require transplants compared to yesteryears. A more likely explanation for such soaring numbers includes, *inter alia*, patients with more access to healthcare and well-trained physicians able to characterize a patient as a candidate for organ transplantation.

324. David K.C. Cooper, *A Brief History of Cross-Species Organ Transplantation*, 25 BAYLOR U. MED. CTR. PROC. 49, 51–52 (2012).

325. *Id.*

326. Muhammad M. Mohiuddin et al., *Genetically Engineered Pigs and Target-Specific Immunomodulation Provide Significant Graft Survival and Hope for Clinical Cardiac Xenotransplantation*, 148 J. THORACIC & CARDIOVASCULAR SURGERY 1106 (2014).

from genetically modified pigs to baboons. Last fall, a group of researchers used CRISPR-Cas9 to simultaneously eradicate all sixty-two copies of a porcine endogenous retrovirus (PERV)—a type of pig virus that could be transmitted to humans—in a pig kidney cell line and prevented *in vitro* viral infection and transmission to human cells.³²⁸ The same group also reported a forthcoming publication involving the editing of more than twenty genes in pig embryos, including some known to trigger human immune responses or blood clotting.³²⁹

These and other findings have spurred entrepreneurial interest in using synthetic biology and genome editing methods to generate ready-for-transplant, human-compatible pig organs.³³⁰ Backed by an infusion of venture capital, biotech companies aim to get pig lungs in human clinical trials by 2020,³³¹ and academic researchers funded by the National Institutes of Health are working to carry out parallel studies that may bring clinical trials of pig kidney, heart, and liver transplantation in humans within the realm of possibility.³³² A

327. Hayato Iwase et al., *Pig Kidney Graft Survival in a Baboon for 136 Days: Longest Life-Supporting Organ Graft Survival to Date*, 22 XENOTRANSPLANTATION 302 (2015).

328. Luhan Yang et al., *Genome-Wide Inactivation of Porcine Endogenous Retroviruses (PERVs)*, 350 SCIENCE 1101 (2015).

329. Sara Reardon, *Gene-Editing Record Smashed in Pigs*, NATURE (Oct. 6, 2015), <http://www.nature.com/news/gene-editing-record-smashed-in-pigs-1.18525> [<https://perma.cc/B379-BDKX>].

330. See, e.g., Press Release, United Therapeutics, Synthetic Genomics Inc. Signs Collaborative Research and Development Agreement with Lung Biotechnology Inc., a Subsidiary of United Therapeutics Corporation, to Develop Humanized Pig Organs to Revolutionize Transplantation Field (May 4, 2014), <http://ir.unither.com/releasedetail.cfm?releaseid=845454> [<https://perma.cc/C2G8-6G23>] (announcing a \$50 million equity investment to develop humanized pig organs); Douglas W. House, *United Therapeutics Subsidiary Expands R&D Agreement to Develop Transplant-Ready Pig Organs*, SEEKING ALPHA NEWS (Sept. 22, 2015), <http://seekingalpha.com/news/2792636-united-therapeutics-subsidiary-expands-r-and-d-agreement-to-develop-transplant-ready-pig-organs> [<https://perma.cc/682T-UZGX>] (expanding the multi-year agreement with an additional \$50 million investment); *About Us*, EGENESIS, <http://www.egenesisbio.com/about-us.html> [<https://perma.cc/KRR5-4XE5>] (last visited Feb. 26, 2017).

331. See, e.g., Shelly Banjo, *The Highest-Paid Woman in America Is Working on Robot Clones and Pigs with Human DNA*, QUARTZ (Mar. 16, 2015), <http://qz.com/362933> [<https://perma.cc/GJ95-CZX4>] (reporting on America's highest-paid female and transgender executive and her goal to produce transgenic pig organs to meet the demands for human organ transplantation); Jason Koehler, *Martine Rothblatt Wants to Grow Human Organs in Pigs at This Farm*, MOTHERBOARD (June 14, 2015), <http://motherboard.vice.com/read/martine-rothblatt-wants-to-grow-human-organs-in-pigs-at-this-farm> [<https://perma.cc/HG8M-6TTY>] (describing United Therapeutics CEO's goal of building a farm where production of 100,000 lungs, hearts, and other transplantable organs can grow inside transgenic pigs by 2020).

332. David K.C. & Richard N. Pierson, *Genetically-Engineered Pig Organ Transplantation into Non-Human Primates*, GRANTOME, <http://grantome.com/grant/NIH/U19-AI090959-06> [<https://perma.cc/HR63-RWAN>] (last visited Feb. 13, 2017).

hopeful preview came last year when the Chinese Food and Drug Administration approved the sale of the world's first bioengineered cornea derived from pig's eyes.³³³ Within months, the first transplant was performed in an older patient suffering from a serious corneal ulcer with successful results.³³⁴ As genome editing technologies mature, we should expect further developments in xenotransplantation and other important fields of clinical relevance.

D. Agriculture

1. Crops and Biofuels

The United Nations projects the world population will rise from today's 7.2 billion to 9.6 billion by the year 2050.³³⁵ This gargantuan increase will pose significant challenges to the world's ability to foster food security and meet nutritional needs using limited arable land and water available for irrigation.³³⁶ As a result, sustainability and the contributions of rising agriculture-related pollution to climate change will become global problems.³³⁷ Analyses for global crop demand forecast an increase between 100% and 110% from current levels by 2050.³³⁸ Investment in biotechnologies aimed at increasing food yields and producing pest-resistant genetically modified (GM) crops have been proposed as a solution to the global food crisis.³³⁹

Fervid, and at times intemperate, controversy exists over the use of GM crops—colloquially known as GMOs³⁴⁰—with supporters

333. Jing Yang, *Seeing the World Through Pig's Eyes: Chinese Firm to Launch Artificial Cornea*, S. CHINA MORNING POST (July 29, 2015, 7:12 PM), <http://www.scmp.com/business/china-business/article/1844830/seeing-world-through-pigs-eyes-chinese-firm-launch> [<https://perma.cc/3LFB-G54J>].

334. *Doctors Conduct 'Animal-Human' Cornea Transplant*, CHINA.ORG.CN (Dec. 22, 2015), http://www.china.org.cn/china/2015-12/22/content_37370047.htm [<https://perma.cc/VH6R-VC53>].

335. *Population Projected to Reach 9.6 Billion by 2050*, U.N. DEP'T ECON. & SOC. AFF., (June 13, 2013), <https://www.un.org/development/desa/en/news/population/un-report-world-population-projected-to-reach-9-6-billion-by-2050.html> [<https://perma.cc/3C4E-32H6>].

336. Elliot M. Berry et al., *Food Security and Sustainability: Can One Exist Without the Other?*, 18 PUB. HEALTH NUTRITION 2293, 2300 (2015).

337. *Id.*

338. David Tilman et al., *Global Food Demand and the Sustainable Intensification of Agriculture*, 108 PROC. NAT'L ACAD. SCI. U.S. 20260 (2011).

339. See, e.g., Anurag Chaurasia, *India Needs Home-Grown GM Food to Stop Starvation*, 529 NATURE 439 (2016).

340. The controversy surrounding GMOs—and GM food in particular—is the focus of a forthcoming publication. See Enríquez, *supra* note 31. In that article, I examine the underlying basis for GMO controversies, synthesize the scientific literature concerning the perceived GMO-related human health and environmental risks, analyze the GMO regulatory framework

and critics constantly sparring about the perceived risks and benefits of GM crops to human health, the environment, and food security.³⁴¹ However, although a minor potential for adverse events exists, to date, no overt or deleterious consequences have yet been documented in the scientific, peer-reviewed literature for the more than two decades that bioengineered foods have been available to consumers,³⁴² with the

under current law, and prescribe policy recommendations for the future of genome editing in the GMO realm.

341. See, e.g., *Found. on Econ. Trends v. Heckler*, 756 F.2d 143, 146 (D.C. Cir. 1985) (enjoining the University of California from conducting a “deliberate release experiment” to delay field testing of genetically altered bacteria on select crops); *All. for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 181 (D.D.C. 2000) (rejecting a challenge, brought by a coalition group of scientists and religious leaders, to the Food and Drug Administration’s policy on genetically engineered foods). Compare Ming Zhang et al., *Long-Term Toxicity Study on Transgenic Rice with Cry1Ac and Sck Genes*, 63 FOOD & CHEMICAL TOXICOLOGY 76, 82 (2014) (concluding that insect-resistant GM rice consumption in rodents has no long-term, adverse health effects), with Gilles-Eric Seralini et al., *Republished Study: Long-Term Toxicity of a Roundup Herbicide and a Roundup-Tolerant Genetically Modified Maize*, 26 ENVTL. SCI. EUR. 14 (2014) (documenting a series of long-term deleterious effects, including severe hormone-dependent mammary, hepatic, and kidney disturbances, arising from consumption of GM maize treated with Roundup—the most widely used herbicide worldwide—in rodents). See also, e.g., E.C., A DECADE OF EU-FUNDED GMO RESEARCH 2001-2010, at 15–17 (2010) (compiling results from research studies on the safety of GM organisms funded by the European Union); Allison Kopicki, *Strong Support for Labeling Modified Foods*, N.Y. TIMES (July 27, 2013), http://www.nytimes.com/2013/07/28/science/strong-support-for-labeling-modified-foods.html?_r=1 [<https://perma.cc/JE9Z-NGJL>] (citing a New York Times poll that shows 93 percent of American respondents support labeling GM foods and 75 percent harbor concerns about eating GM foodstuff); *Millions March Against GM Crops*, GUARDIAN (May 25, 2013, 8:26 PM), <http://www.theguardian.com/environment/2013/may/26/millions-march-against-monsanto> [<https://perma.cc/V9XR-HCAU>] (reporting on protest rallies organized in the United States and globally against Monsanto); Lee R. Morisy, *Report on the Council for Public Health: Biomedical Engineering*, AM. MED. ASS’N (2012), <https://web.archive.org/web/20120907023039/http://www.ama-assn.org/resources/doc/csaph/a12-csaph2-bioengineeredfoods.pdf> [<https://perma.cc/DM6U-BS2A>] (recommending that mandatory labeling of GM foods is not consistent with the FDA’s science-based labeling policies despite strong consumer interest in labeling); Lynne Peeples, *GMO Debate Heats up: Critics Say Biotech Industry Manipulating Genes, and Science*, HUFFINGTON POST (Sept. 21, 2012, 8:30 PM), http://www.huffingtonpost.com/2012/09/21/gmo-proposition-37-study-funding-research_n_1904535.html [<https://perma.cc/6UZJ-ZY8P>] (commenting on California’s 2012 Proposition 37, which sought to require labeling of GM foods).

342. Although an exposition of the benefits and risks of GMOs, as well as their legal status and policy recommendations are outside the scope of this Article, a discussion of genome editing for agricultural purposes at least warrants the inclusion of some background on the controversy surrounding public perceptions and scientific evidence for or against GMOs. See *supra* note 341 and accompanying text.

For an exemplification of the scientific debate surrounding GMOs, see Zhang et al., *supra* note 341 (finding no evidence of harmful health effects from GM rice consumption by rodents), and Morisy, *supra* note 341, at 2–5 (filing a report with the American Medical Association House of Delegates that cites literature presenting no evidence of health consequences to humans from two decades of GM crop consumption). Cf. Gilles-Eric Seralini et al., *RETRACTED: Long Term Toxicity of a Roundup Herbicide and a Roundup-Tolerant Genetically Modified Maize*, 50 FOOD &

exception of one highly contentious study.³⁴³ This is not to say that the lack of current scientific evidence—even decades after introduction of GM crops—is *prima facie* evidence of a complete absence of risk. Conversely, at least some evidence suggests that adoption of GM crops reduces food insecurity, improves calorie consumption and dietary quality, and can be a key factor in a broader global food security strategy.³⁴⁴

Reports of the first GM plants—petunia, tobacco, sunflower, and carrot—appeared in the literature thirty-three years ago.³⁴⁵ Within a decade, Calgene, a California-based firm, introduced FLAVR SAVR tomato, the first GM crop product to be approved by the US

CHEMICAL TOXICOLOGY 4221 (2012) (retracting a study that concluded consumption of herbicide-tolerant, GM maize is harmful to rodents). *But cf.* Gilles-Eric Séralini et al., *supra* note 341 (republishing the retracted study, along with all its conclusions, in another journal and refuting an earlier ninety-day feeding study on rodents by Monsanto scientists that showed organ toxicity in the animals was not “biologically meaningful”).

The Séralini article published in *Food and Chemical Toxicology* evaluated lifelong toxic and pathogenic effects of consumption of an herbicide-resistant, GM maize on rodents and concluded that significant biochemical disturbances and physiological failures, including tumors, were the direct result of consumption of popular maize strains sold by Monsanto with or without the use of herbicide. *Id.* However, following publication, a flurry of letters to the Journal’s editor-in-chief calling for the article’s retraction expressed concerns about the validity of the findings due to potential improper use of animals and allegations of fraud. *See Retraction Notice to “Long Term Toxicity of a Roundup Herbicide and a Roundup-Tolerant Genetically Modified Maize”* [*Food Chem. Toxicol.* 50 (2012) 4221–4231], 63 *FOOD & CHEMICAL TOXICOLOGY* 244 (2014).

Ultimately, after an investigation conducted by the journal, the article was retracted due to the “inconclusiveness” of its results, although no evidence was found to support allegations of fraud or intentional misrepresentation of data. *Id.* In particular, the Journal cited the low number of animals used in the experiments and a known high incidence of tumors in the rat strain—Sprague-Dawley—chosen for the study. *Id.* Séralini and colleagues responded to the accusations and the subsequent retraction by, *inter alia*, pointing to unscientific double standards in the Journal’s peer-review process; the fact that the decision to retract the article came after the appointment of a former Monsanto employee as the Journal’s “editor for biotechnology,” a position the authors claim was created specifically for him; a misconception, over-generalization, and failure to understand that the study was about chronic toxicity rather than carcinogenicity; and the result of economic interests. Gilles-Eric Séralini et al., *Conclusiveness of Toxicity Data and Double Standards*, 93 *FOOD & CHEMICAL TOXICOLOGY* 357 (2014). As a result of the article’s retraction, Séralini and colleagues resubmitted the manuscript to *Environmental Sciences Europe* and republished—without peer review—its contents with minor modifications, but standing by its results and conclusions. *See Séralini et al., supra* note 341. Reaction to the republished study, which is substantially the same as the prior article, proved to be just as controversial as the original and faced harsh scrutiny from scientists. *Scientists React to Republished Séralini GMO Maize Rat Study*, GENETIC LITERACY PROJECT (June 24, 2014), <https://www.geneticliteracyproject.org/2014/06/24/scientists-react-to-republished-seralini-maize-rat-study/> [<https://perma.cc/TD6L-PAAT>].

343. *See Séralini et al., supra* note 342 and accompanying text.

344. Matin Qaim & Shahzad Kouser, *Genetically Modified Crops and Food Security*, 8 *PLOS ONE* e64879 (2013).

345. Robert T. Fraley et al., *Expression of Bacterial Genes in Plant Cells*, 80 *PROC. NAT’L ACAD. SCI. U.S.* 4803 (1983).

Food and Drug Administration (FDA) for human consumption and commercialization.³⁴⁶ Today, 190 GM crops ranging from fruits to grains and vegetables have been approved for human consumption in the United States and many more countries worldwide.³⁴⁷ In 2014, a total of 18 million farmers planted GM crops across 448 million acres of farmland in twenty-eight countries.³⁴⁸ GM crop arable land has swollen 10,000% since commercialization of GM crops commenced two decades ago.³⁴⁹

Scientists state that the exponential increase in farmlands devoted to GM crop agriculture is contributing to the global food crisis.³⁵⁰ GM crop supporters point to these statistics to argue that GM crops and further development of biotechnologies are necessary to address population growth, climate change, and global demands for food and feed.³⁵¹ In contrast, opponents argue that the impact of GM crops on human health and the environment is not well established and warrants more research.³⁵² They perceive approval by regulatory agencies as a precocious exercise that sets dangerous precedents to the detriment of humankind.³⁵³

Regulatory controversies notwithstanding, scientists have reported proof-of-concept experiments involving genome editing in many plants, including crops, since CRISPR systems became widely available to the scientific community a mere three years ago. Among the CRISPR-Cas9 modified plants are wheat,³⁵⁴ rice,³⁵⁵ thale cress,³⁵⁶

346. G. Bruening and J.M. Lyons, *The Case of the FLAVR SAVR Tomato*, 54 CAL. AGRIC. 6 (2000).

347. *GM Crop Events Approved in United States of America*, ISAAA, <http://www.isaaa.org/gmapprovaldatabase/approvedeventsin/default.asp?CountryID=US&Country=United%20States%20of%20America> [<https://perma.cc/RD7C-6WG3>] (last visited Feb. 13, 2017).

348. ISAAA, 50 BIOTECH BITES 60 (International Service for the Acquisition of Agri-Biotech Applications ed., 2015), https://www.isaaa.org/resources/publications/50biotechbites/download/50_Biotech_Bites.pdf [<https://perma.cc/4AF7-64FL>].

349. *Id.*

350. Tilman et al., *supra* note 338.

351. *See, e.g.*, discussion *supra* notes 336–44 and accompanying text.

352. *See, e.g.*, discussion *supra* notes 341–43 and accompanying text.

353. *Id.*

354. Qiwei Shan et al., *Targeted Genome Modification of Crop Plants Using a CRISPR-Cas System*, 31 NATURE BIOTECHNOLOGY 686 (2013).

355. *Id.*; Zhengyan Feng et al., *Efficient Genome Editing in Plants Using a CRISPR/Cas System*, 23 CELL RES. 1229 (2013); Jin Miao et al., *Targeted Mutagenesis in Rice Using CRISPR-Cas System*, 23 CELL RES. 1233 (2013); Rong-Fang Xu et al., *Generation of Inheritable and "Transgene Clean" Targeted Genome-Modified Rice in Later Generations Using the CRISPR/Cas9 System*, 5 SCI. REP. 11491 (2015).

356. Friedrich Fauser et al., *Both CRISPR/Cas-Based Nucleases and Nickases Can Be Used Efficiently for Genome Engineering in Arabidopsis thaliana*, 79 PLANT J. 348 (2014); Feng

tobacco,³⁵⁷ sweet orange,³⁵⁸ sorghum,³⁵⁹ maize,³⁶⁰ barley,³⁶¹ wild cabbage,³⁶² tomato,³⁶³ soybean,³⁶⁴ liverwort,³⁶⁵ potato,³⁶⁶ and others.

Two particular studies illustrate well the prototypical uses of genome editing in crop cultivars. The first involves CRISPR-mediated endogenous disruption of the tomato *RIN* gene, which encodes a transcription factor that regulates fruit ripening.³⁶⁷ *RIN*-defective mutations result in peculiar phenotypes in tomatoes including not turning to red color, maintaining flesh firmness for several months, and inhibiting other changes associated with fruit ripening.³⁶⁸ *RIN*-defective tomato cultivars are routinely bred with other tomato plant varieties to create tomatoes with an extended shelf life.³⁶⁹ These mutations occur naturally and, thus, mutant tomatoes are not considered to be transgenic or GMOs.

In the study, the authors used CRISPR-Cas9 to introduce single or few nucleotide changes in select regions of the *RIN* locus, which led to a truncated, nonfunctional *RIN* protein that mirrored the

et al., *supra* note 355, at 2; Jian-Feng Li et al., *Multiplex and Homologous Recombination-Mediated Genome Editing in Arabidopsis and Nicotiana benthamiana Using Guide RNA and Cas9*, 31 NATURE BIOTECHNOLOGY 688 (2013).

357. Li et al., *supra* note 356, at 688–89; Vladimir Nekrasov et al., *Targeted Mutagenesis in the Model Plant Nicotiana benthamiana Using Cas9 RNA-Guided Endonuclease*, 31 NATURE BIOTECHNOLOGY 691 (2013).

358. Hongge Jia & Nian Wang, *Targeted Genome Editing of Sweet Orange Using Cas9/sgRNA*, 9 PLOS ONE e93806 (2014).

359. Wenzhi Jiang et al., *Demonstration of CRISPR/Cas9/sgRNA-Mediated Targeted Gene Modification in Arabidopsis, Tobacco, Sorghum and Rice*, 41 NUCLEIC ACIDS RES. e188 (2013).

360. Sergei Svitashv et al., *Targeted Mutagenesis, Precise Gene Editing, and Site-Specific Gene Insertion in Maize Using Cas9 and Guide RNA*, 169 PLANT PHYSIOLOGY 931 (2015); Hui-Li Xing et al., *A CRISPR/Cas9 Toolkit for Multiplex Genome Editing in Plants*, 14 BMC PLANT BIOLOGY 327 (2014).

361. Tom Lawrenson et al., *Induction of Targeted, Heritable Mutations in Barley and Brassica oleracea Using RNA-Guided Cas9 Nuclease*, 16 GENOME BIOLOGY 258 (2015).

362. *Id.*

363. Christopher Brooks et al., *Efficient Gene Editing in Tomato in the First Generation Using the CRISPR/Cas9 System*, 166 PLANT PHYSIOLOGY 1292 (2014).

364. Xianjun Sun et al., *Targeted Mutagenesis in Soybean Using the CRISPR-Cas9 System*, 5 SCI. REP. 10342 (2015).

365. Shigeo S. Sugano et al., *CRISPR/Cas9-Mediated Targeted Mutagenesis in the Liverwort Marchantia polymorpha L.*, 55 PLANT & CELL PHYSIOLOGY 475 (2014).

366. Shaohui Wang et al., *Efficient Targeted Mutagenesis in Potato by the CRISPR/Cas9 System*, 34 PLANT CELL REP. 1473 (2015).

367. Yasuhiro Ito et al., *CRISPR/Cas9-Mediated Mutagenesis of the RIN Locus That Regulates Tomato Fruit Ripening*, 467 BIOCHEMICAL & BIOPHYSICAL RES. COMM. 76 (2015).

368. *Id.* at 77.

369. *Id.*

RIN-defective tomatoes.³⁷⁰ They also showed that the mutations could be passed on to the next generation of plants.³⁷¹ Hence, this study shows the feasibility of extending the shelf-life of a tomato fruit via genome editing without the use of transgenic constructs or selectable markers. In other words, the mutant tomato lines created in the experiments are, for all practical purposes, the equivalent of naturally occurring cultivars.

The second study concerns wheat resistance to the fungus *Blumeria graminis* f. sp. *tritici*, one of the world's most devastating plant pathogens and the culprit of powdery mildew disease.³⁷² The authors showed that small, single or few nucleotide, CRISPR- and TALEN-induced mutations targeting all six alleles of the *MLO*³⁷³ gene in the hexaploid wheat genome are sufficient to knock out the function of the MLO protein.³⁷⁴ The mutations led to strong resistance to the powdery mildew fungal disease in wheat plants.³⁷⁵ The mutations conferring broad-spectrum resistance to the disease were also shown to be heritable, given that the genetic trait was stable in subsequent generations.³⁷⁶

This remarkable study—the first of its kind—demonstrates the potential of genome editing technologies to address global problems in agriculture via biotechnologies. From a genetics standpoint, the *MLO* knock-out plants are indistinguishable from mutant plants derived via conventional mutation breeding. Moreover, the fact that plants could now acquire disease resistance without the need to introduce DNA from other species or selectable markers highlight the superseding of traditional transgenesis methods with precision genomic targeting.

Fruit ripening and disease resistance are merely the tip of the iceberg. Academic-industry partnerships will ensure a steady supply of scientific breakthroughs with commercial applications.³⁷⁷ As more research unfolds, it may be possible to cultivate crops without the use of pesticides and herbicides altogether by making plants emit

370. *Id.* at 79–80.

371. *Id.* at 80.

372. Yanpeng Wang et al., *Simultaneous Editing of Three Homoeoalleles in Hexaploid Bread Wheat Confers Heritable Resistance to Powdery Mildew*, 32 NATURE BIOTECHNOLOGY 947 (2014).

373. Mildew-resistance locus.

374. Wang et al., *supra* note 372, at 948.

375. *Id.* at 950.

376. *Id.* at 948–49.

377. See, e.g., Press Release, Caribou Biosciences, Caribou Biosciences and DuPont Announce Strategic Alliance (Oct. 8, 2015), <http://cariboubio.com/in-the-news/press-releases/caribou-biosciences-and-dupont-announce-strategic-alliance> [<https://perma.cc/H9CW-F5TF>].

endogenous, natural compounds that aren't toxic to humans, to protect themselves against pathogenic organisms.³⁷⁸

Grain seeds needed to feed the world could be engineered to increase storage tolerance and avoid deterioration and premature spoiling,³⁷⁹ which may help to ameliorate the ever-increasing need for arable lands. Production of allergen-free peanuts and other foodstuffs may now be possible by targeting and disrupting genes that encode allergens and other toxic cyanogens, which threaten the lives of millions of people with food sensitivities worldwide.³⁸⁰ Salt-resistant crop plants could be introduced to permit seawater irrigation.³⁸¹ Drought-resistant crops could help to allay turmoil in water-poor regions of the world.³⁸²

Emergency biotechnological intervention could also be established to pioneer crop diversification efforts where needed, and could even save staple crops from extinction when deadly diseases threaten their existence. For instance, such intervention could be used to mitigate the threat to the Cavendish banana, which is currently in danger of extinction in some parts of the world due to the Tropical Race 4 fungus.³⁸³

Even biofuel production is on the horizon. Oilseeds from the plant *Camelina sativa*, and others, have in recent years been identified as promising sources of renewable biofuels, capable of reducing CO₂ emissions by 78.5% compared to petroleum diesel.³⁸⁴ In

378. Cf. Abdul Rashid War et al., *Mechanisms of Plant Defense Against Insect Herbivores*, 7 PLANT SIGNALING & BEHAV. 1306 (2012).

379. See, e.g., Lei Ma et al., *TALEN-Based Mutagenesis of Lipoyxygenase LOX3 Enhances the Storage Tolerance of Rice (*Oryza sativa*) Seeds*, 10 PLOS ONE e0143877 (2015).

380. Cf. Maria Gallo & Richard Sayre, *Removing Allergens and Reducing Toxins from Food Crops*, 20 CURRENT OPINION BIOTECHNOLOGY 191 (2009) (suggesting use of earlier biotechnologies to remove or reduce allergens and toxic cyanogens from food crops); Lena Y.C. Soo et al., *Using Genome-Enabled Technologies to Address Allergens in Seeds of Crop Plants: Legumes as a Case Study*, in SEED DEVELOPMENT: OMICS TECHNOLOGIES TOWARD IMPROVEMENT OF SEED QUALITY AND CROP YIELD 503 (2012).

381. See, e.g., Edward P. Glenn et al., *Salicornia igelovii* Torr.: An Oilseed Halophyte for Seawater Irrigation, 251 SCIENCE 1065 (1991); Stuart J. Roy et al., *Salt Resistant Crop Plants*, 26 CURRENT OPINION BIOTECHNOLOGY 115 (2014).

382. See, e.g., Honghong Hu & Lizhong Xiong, *Genetic Engineering and Breeding of Drought-Resistant Crops*, 65 ANN. REV. PLANT BIOLOGY 715 (2014).

383. See DAN KOEPPPEL, BANANA: THE FATE OF THE FRUIT THAT CHANGED THE WORLD xiv (2008) (chronicling the alarming destruction of banana plantations around the globe and current efforts to save the world's most beloved fruit); see also Dan Charles, *Our Favorite Banana May Be Doomed; Can New Varieties Replace It?*, NPR (Jan. 11, 2016), <http://www.npr.org/sections/thesalt/2016/01/11/462375558/our-favorite-banana-may-be-doomed-can-new-varieties-replace-it> [https://perma.cc/H2KE-CRTK].

384. See, e.g., John Sheehan et al., *Overview of Biodiesel and Petroleum Diesel Life Cycles* 18 (1998), <http://www.nrel.gov/docs/legosti/fy98/24772.pdf> [https://perma.cc/8MEG-L2KU]; A.

fact, the US Navy, US Air Force, and many private entities have successfully tested *Camelina*-based fuel and announced plans to increase the use of biofuels to meet their energy requirements.³⁸⁵ Renewable biofuels could not only benefit the domestic economy,³⁸⁶ but also help reduce US dependence of foreign petroleum, greenhouse gas emissions, and air pollution.³⁸⁶ Genome editing technologies may finally help to lower current barriers for production of renewable biofuels including yield requirements and commercial viability.

Unlike transgenic crops created from earlier techniques, all these new crop varieties derived via modern genome editing biotechnologies do not require the introduction of any foreign DNA, are genetically indistinguishable from crops developed by mutation breeding protocols over the past three millennia, and bear no genetic manipulation footprints in their progeny. Thus, genome editing represents a powerful tool to protect and enhance important and desirable agronomic traits with vast repercussions for crop agriculture.

2. Animals

To satisfy the predicted food demand by 2050, global food production must increase by at least 70 percent from current levels, which translates into an additional—and quite staggering—400 billion pounds of meat worldwide.³⁸⁷ In the United States alone, red meat³⁸⁸ production totaled 47.4 billion pounds in 2014.³⁸⁹ More than 140 million livestock were slaughtered, including cattle, hogs, sheep, and lambs.³⁹⁰ A total of 8.54 billion broiler chickens and nearly 100 billion

Fröhlich & B. Rice, *Evaluation of Camelina sativa Oil as a Feedstock for Biodiesel Production*, 21 INDUS. CROPS & PRODUCTS 25 (2005).

385. Bryan R. Moser, *Camelina (Camelina sativa L.) Oil as a Biofuels Feedstock: Golden Opportunity or False Hope?*, 22 LIPID TECH. 270, 273 (2010); Mark Matsunaga, *Navy Looks to Biofuels to Sail the Great Green Fleet in 2016*, U.S. DEP'T NAVY (July 3, 2014), http://www.navy.mil/submit/display.asp?story_id=82044 [<https://perma.cc/LM3R-YAZA>]; Terry Maxon, *Southwest Airlines to Use Biofuels Made from 'Forest Residues' Beginning in 2016*, DALLAS MORNING NEWS (Sept. 24, 2014), <http://aviationblog.dallasnews.com/2014/09/southwest-airlines-to-use-biofuels-made-from-forest-residues-beginning-in-2016.html/> [<https://perma.cc/K3SS-A5ZR>].

386. Sheehan et al., *supra* note 384, at iii–iv.

387. *How to Feed the World in 2050*, FOOD & AGRIC. ORG. U.N. 8, http://www.fao.org/fileadmin/templates/wsfs/docs/expert_paper/How_to_Feed_the_World_in_2050.pdf [<https://perma.cc/2P82-6FNK>] (last visited Feb. 25, 2017).

388. According to the USDA, red meat includes beef, veal, pork, lamb, and mutton. USDA REP. 0499-0544, *National Agricultural Statistics Service, Livestock Slaughter 2014 Summary* 6 (2015).

389. *Id.*

390. *Id.* at 8.

eggs were produced in the United States in 2014.³⁹¹ Global agricultural activity, and livestock production in particular, is exerting a colossal impact on the environment and accounts for 22 percent of total greenhouse gas emissions—a greater percentage than the total contribution from the transportation sector (e.g., cars, trucks, airplanes).³⁹²

Aside from translational and basic research purposes,³⁹³ farm animals constitute an important source of commodities such as food nutrients,³⁹⁴ natural fiber,³⁹⁵ and labor.³⁹⁶ A strategy to mitigate the current unsustainable rate of meat consumption involves genome editing in farm animals. One illustration concerns the objective of increasing the muscle mass of livestock for lean meat production by interfering with the *MSTN* gene responsible for muscle growth inhibition.³⁹⁷

Cases of naturally occurring mutations in the *MSTN* locus have been widely reported in animals that exhibit doubling of skeletal muscle mass.³⁹⁸ Proof-of-concept *MSTN*-edited studies aiming to increase mass yield in farm animals have been successfully established, *inter alia*, in pigs,³⁹⁹ cattle,⁴⁰⁰ goats,⁴⁰¹ and sheep.⁴⁰² More importantly, these methods of editing *MSTN* in livestock occur at native sites of the genome and abrogate the need to insert any foreign nucleotides that are not already found naturally inside the animals'

391. USDA REP. NO. 1949-1573, *National Agricultural Statistics Service, Poultry—Production and Value 2014 Summary* 5 (2015).

392. Anthony J. McMichael et al., *Food, Livestock Production, Energy, Climate Change, and Health*, 370 LANCET 1253 (2007).

393. See discussion *supra* Section IV.C.

394. T.F. Randolph et al., *Role of Livestock in Human Nutrition and Health for Poverty Reduction in Developing Countries*, 85 J. ANIMAL SCI. 2788 (2007).

395. Linda L. Lowry, *Niche Markets for Natural Fibers: Strategies for Connecting Farmers Who Raise Fiber Animals with Textile Artists—A New England Perspective*, 52 J. EXTENSION 6FEA6 (2014).

396. See, e.g., LEWIS FALLEY ALLEN, *AMERICAN CATTLE: THEIR HISTORY, BREEDING AND MANAGEMENT* 56–58 (1868).

397. See, e.g., Junjie Luo et al., *Efficient Generation of Myostatin (MSTN) Biallelic Mutations in Cattle Using Zinc Finger Nucleases*, 9 PLOS ONE e95225 (2014).

398. Ravi Kambadur et al., *Mutations in Myostatin (GDF8) in Double-Musled Belgian Blue and Piedmontese Cattle*, 7 GENOME RES. 910, 910 (1997); Alexandra C. McPherron & Se-Jin Lee, *Double Muscling in Cattle Due to Mutations in the Myostatin Gene*, 94 PROC. NAT'L ACAD. SCI. U.S. 12457 (1997).

399. Wang et al., *supra* note 301, at 1.

400. Luo et al., *supra* note 397, at 1.

401. Wei Ni et al., *Efficient Gene Knockout in Goats Using CRISPR/Cas9 System*, 9 PLOS ONE e106718 (2014).

402. M. Crispo et al., *Efficient Generation of Myostatin Knock-Out Sheep Using CRISPR/Cas9 Technology and Microinjection into Zygotes*, 10 PLOS ONE e0136690 (2015).

genomes. This type of genome editing without the use of transgenes stands in contrast to the recent approval of transgenic salmon—genetically modified to grow at accelerated rates—by the FDA,⁴⁰³ which, despite being labeled as safe for human consumption, has engendered controversy from anti-GMO groups.⁴⁰⁴

Another priority in animal agriculture is the development of methods to improve disease resistance to pathogens that threaten animal and human health. Substantial progress toward this goal has been documented by two recent studies. One demonstrated that minimal changes to the *CD163*⁴⁰⁵ gene confer immunity in pigs against Porcine Reproductive and Respiratory Syndrome Virus, the most economically significant swine disease in North America, Europe, and Asia.⁴⁰⁶ The other targeted the *RELA* gene, which has been associated with the African Swine Fever Virus that triggers a deadly immune reaction in pigs.⁴⁰⁷ Although the latter team has not yet exposed edited pigs to the virus, the study showed modern genome editing biotechnologies can adequately deliver live pigs without the use of older, often cumbersome, cloning technologies like Somatic Cell Nuclear Transfer.⁴⁰⁸

These scientific advances open the door for new strategies to combat other pathogenic organisms that affect important animals in agriculture. For example, the *SAL1* gene in chickens has been linked to resistance against certain *Salmonella* strains responsible for food-borne gastroenteritis in humans.⁴⁰⁹ Genome editing now provides an opportunity to exploit this naturally occurring resistance to immunize chickens and avert serious economic losses stemming from human transmission events.⁴¹⁰

403. Bernadette M. Dunham, *AquAdvantage Salmon Approval Letter and Appendix*, FDA (Nov. 19, 2015), <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm466214.htm> [https://perma.cc/Q5ZS-QTGV].

404. See Andrew Pollack, *Genetically Engineered Salmon Approved for Consumption*, N.Y. TIMES, Nov. 20, 2015, at A1.

405. Cluster of differentiation 163.

406. Kristin M. Whitworth et al., *Gene Edited Pigs Are Protected from Porcine Reproductive and Respiratory Syndrome Virus*, 34 NATURE BIOTECHNOLOGY 20 (2016).

407. Simon G. Lillico et al., *Live Pigs Produced from Genome Edited Zygotes*, 3 SCI. REP. 2847 (2013).

408. *Id.*

409. Paul Wigley et al., *In Vivo and in Vitro Studies of Genetic Resistance to Systemic Salmonellosis in the Chicken Encoded by the SAL1 Locus*, 4 MICROBES & INFECTION 1111 (2002).

410. C.f., e.g., Elizabeth Weise, *Salmonella Outbreaks Lead to Food-Safety Changes*, USA TODAY (Apr. 2, 2009), http://usatoday30.usatoday.com/news/health/2009-04-01-nuts-salmonella-food-safety_N.htm [https://perma.cc/WQ75-N32G] (reporting on food-related salmonella outbreaks that caused millions of dollars in economic losses).

Lastly, other potential uses of genome editing for animal agriculture range from the production of textiles—e.g., by triggering modifications in the Shannbei cashmere goat *FGF5*⁴¹¹ gene that controls hair length⁴¹²—to the development of safer dairy products—e.g., by generating animals that secrete milk with natural antibacterial properties⁴¹³—and animal welfare—e.g., by creating hornless cattle breeds with naturally occurring mutations in the *POLLED* gene to avoid painful, costly, and inhumane dehorning of animals.⁴¹⁴ Like every other field mentioned above, genome editing technologies are poised to revolutionize the optimization of livestock production to meet future demands for food and animal products that could affect human health, the environment, intellectual property,⁴¹⁵ the economy, and animal welfare.

E. Human Germline Editing

In 2015, a group of researchers launched humanity into uncharted territory. For the first time in the history of planet Earth and civilization, the human germline—gamete cells (sperm or eggs), zygotes, and embryos—underwent endogenous genetic manipulation by the macromolecular CRISPR-Cas9 system.⁴¹⁶ Genome editing in human germ cells was largely predictable in light of the successes of germline editing in a plethora of animal and plant species over the last four years.⁴¹⁷ Yet, predictability did not allay the global shockwaves created by the research.

In principle, manipulation of the human germline is not much different than germline manipulation in other species. Although

411. Fibroblast growth factor 5.

412. Xiaolong Wang et al., *Generation of Gene-Modified Goats Targeting MSTN and FGF5 via Zygote Injection of CRISPR/Cas9 System*, 5 SCI. REP. 13878 (2015).

413. See, e.g., Xu Liu et al., *Generation of Mastitis Resistance in Cows by Targeting Human Lysozyme Gene to β -Casein Locus Using Zinc-Finger Nucleases*, 81 PROC. ROYAL SOC. B 20133368 (2014); Xu Liu et al., *Zinc-Finger Nickase-Mediated Insertion of the Lysostaphin Gene into the Beta-Casein Locus in Cloned Cows*, 4 NATURE COMM. 2565 (2013) (generating gene-edited cows—though via a transgene—with the ability to secrete milk that kills *Staphylococcus aureus* bacteria).

414. Wenfang Tan et al., *Efficient Nonmeiotic Allele Introgression in Livestock Using Custom Endonucleases*, 110 PROC. NAT'L ACAD. SCI. U.S. 16526 (2013).

415. A parade of patent applications has followed many of the scientific findings discussed throughout this paper. See, e.g., Hornless Livestock, U.S. Patent Application No. 14/154,906 (filed Jan. 14, 2014); Control of Sexual Maturation in Animals, U.S. Patent Application No. 13/067,502 (filed Oct. 30, 2013); Genetically Edited Animal, U.S. Patent Application No. 14/427,776 (filed Mar. 1, 2013).

416. Puping Liang et al., *CRISPR/Cas9-Mediated Gene Editing in Human Trippronuclear Zygotes*, 6 PROTEIN & CELL 363 (2015).

417. See *supra* discussion Section IV.A–D.

humans are biologically more complex than other organisms, the process of CRISPR-mediated genome editing is virtually the same: concoct a lab recipe that combines specific types of all three major bioorganic polymers—a target DNA, a sgRNA designed to hybridize with the DNA, and the Cas9 protein to trigger cuts in the DNA; allow the mix to form a complex inside the germ cells; and let science run its course. A group of Chinese researchers followed that precise formula and used the CRISPR system to interrogate the feasibility and efficiency of genome editing coupled to DNA repair mechanisms in the human germline.⁴¹⁸

To establish proof-of-concept for human germline manipulation, the group chose to target the human β -globin (*HBB*) gene, the mutated form of which is linked to β -thalassemia, a debilitating and sometimes fatal blood disorder.⁴¹⁹ A total of eighty-six non-viable human zygotes—the first cell formed upon a fertilization event—were injected with the CRISPR-Cas9 complex.⁴²⁰ Seventy-one of those zygotes survived the microinjection process and fifty-four were tested to confirm correct editing.⁴²¹

Results revealed that only twenty-eight zygotes had their genome cleaved by the Cas9 enzyme, and a meager four zygotes (14%) had been successfully edited at the *HBB* locus using the template supplied by the scientists.⁴²² From the outset, the team preemptively clarified that the zygotes used were tripronuclear, that is, zygotes that carry an extra set of chromosomes due to fertilization of a single egg by two sperm.⁴²³ This property renders subsequent embryos non-viable, as the zygotes progress through the first stages of cell divisions *in vitro*, but become arrested in development and cannot result in a live birth.⁴²⁴

Three significant findings were identified in the experiment: (1) the editing and repair efficiency was dismally low (only 14% of embryos were successfully edited); (2) off-target mutations formed by cut-and-repair events in unintended DNA sites were detected, which resembled off-target events that typically occur in human cancer cells; and (3) the edited embryos were mosaic—i.e., some of the embryo cells

418. Liang et al., *supra* note 416, at 363.

419. *Id.* at 364.

420. *Id.* at 366–67.

421. *Id.*

422. *Id.*

423. The process of *In Vitro* Fertilization (IVF) typically leads to formation of approximately 5% tripronuclear zygotes from the total zygote pool. *Id.* at 364. Because they cannot become viable embryos, the zygotes are usually discarded in IVF clinics, although they could be used to study human development where it is lawful. *Id.*

424. *Id.*

had the desired mutations while others did not.⁴²⁵ The landmark study showed that CRISPR-Cas9 can mediate DSB and DNA repair via HR in human embryos, but is replete with failures in terms of efficiency, specificity, and fidelity of the CRISPR-Cas9 system.⁴²⁶ More importantly, the data presented automatically preclude clinical use of CRISPR-Cas9 in the reported form⁴²⁷ and demonstrate that human germline editing is not yet ready for primetime.

To be clear, the paper represents a somewhat outdated snapshot of the state of the art at the time of its publication. Other published research around the time had already shown some improvements on efficiency and specificity, and the Chinese team's results were consistent with already months-to-years-old CRISPR technology.⁴²⁸ Scientists at the forefront of genome editing technology were unimpressed with the results of the *Protein & Cell* paper—primarily because the research did not use the latest version of CRISPR-Cas9 technology—and called the attempt to edit human germ cells premature.⁴²⁹ Furthermore, it appears that some of the lackluster results could be attributable to inexperience with using CRISPR protocols.⁴³⁰ Palpably, the first try at human germline editing has gotten off to a rocky start. But tweaks and improvements in the field are occurring at an astounding speed.⁴³¹

From a scientific standpoint, the report did not contribute any novel understanding of the CRISPR system. Indeed, the authors pointed out that similar efficiencies had been reported in other organisms, including mice.⁴³² In effect, the paper was merely a clone

425. *Id.* at 368.

426. *See id.* at 364.

427. *Id.* at 368.

428. *Compare, e.g.,* Benjamin P. Kleinstiver et al., *Engineered CRISPR-Cas9 Nucleases with Altered PAM Specificities*, 523 NATURE 481 (2015) (improving DNA target specificity by a variant Cas9 that reduces off-target effects), *with* Yanfang Fu et al., *High-Frequency Off-Target Mutagenesis Induced by CRISPR-Cas Nucleases in Human Cells*, 31 NATURE BIOTECHNOLOGY 822 (2013) (reporting high frequency of off-target mutations using an older version of the CRISPR system).

429. Jocelyn Kaiser & Dennis Normile, *Embryo Engineering Study Splits Scientific Community*, 348 SCIENCE 486, 487 (2015).

430. *Id.* Not a single study coming out of Junjiu Huang's laboratory in Sun Yat-sen University, Guangzhou, China describes the use of CRISPR-Cas9 predating the tripronuclear zygote study published in *Protein & Cell*, suggesting the investigation marked the first time the laboratory had worked with CRISPR-Cas9. *See Junjiu Huang*, PUBMED.GOV, [http://www.ncbi.nlm.nih.gov/pubmed/?term=junjiu+huang\[author\]](http://www.ncbi.nlm.nih.gov/pubmed/?term=junjiu+huang[author]) [<https://perma.cc/5HNF-3MFE>] (last visited Feb. 13, 2017).

431. *See, e.g.,* Jean-Baptiste Renaud et al., *Improved Genome Editing Efficiency and Flexibility Using Modified Oligonucleotides with TALEN and CRISPR-Cas9 Nucleases*, 14 CELL REP. 1 (2016).

432. Liang et al., *supra* note 416, at 364–66.

of the same studies performed on other organisms. However, this time, the experiments were notable because they were conducted in human germ cells. The paper had first been submitted to *Nature* and *Science*, but was rejected by both journals in part because of ethical concerns.⁴³³ Notwithstanding the article's scientific shortcomings, the true nuances of this momentous report lie in the ethical implications of the research and the subsequent consternation it spawned.

Rumors that Chinese scientists had performed experiments to edit the human germline, purportedly circulated by reviewers or parties privy to the manuscript's content at one or both of the journals to which it was initially submitted, reverberated with a loud echo among scientific circles.⁴³⁴ Alarmed scientists rushed to publish commentaries in response to the leak in both *Nature*⁴³⁵ and *Science*⁴³⁶ to criticize the experiments and preemptively call for either a ban or an outright moratorium on facets of human germline editing research.

The situation was reminiscent of some bygone controversies. Not since the days of *In Vitro* Fertilization (IVF)⁴³⁷ and the birth of Dolly the sheep, the first animal cloned from an adult cell,⁴³⁸ had clamor been so thunderous concerning an emerging technology.⁴³⁹ A stentorian tone began to permeate news and media outlets within days of the published commentaries with several groups, including the Center for Genetics and Society in Berkeley, California,⁴⁴⁰ the Society for Developmental Biology in Bethesda, Maryland,⁴⁴¹ and the International Society for Stem Cell Research⁴⁴² echoing calls to halt

433. Kaiser & Normile, *supra* note 429, at 486. Neither *Nature* nor *Science* confirmed the review or rejection of the manuscript. *Id.* at 487.

434. *See id.*

435. Lanphier et al., *supra* note 28.

436. David Baltimore et al., *A Prudent Path Forward for Genomic Engineering and Germline Gene Modification*, 348 SCIENCE 36 (2015).

437. *See generally* RUTH DEECH & ANNA SMAJDOR, FROM IVF TO IMMORTALITY: CONTROVERSY IN THE ERA OF REPRODUCTIVE TECHNOLOGY (2007).

438. K.H.S. Campbell et al., *Sheep Cloned by Nuclear Transfer from a Cultured Cell Line*, 380 NATURE 64 (1996).

439. *See, e.g.*, Sophie Hutchinson, *Controversy and the Cloning Race*, BBC NEWS (Jan. 17, 2004), http://news.bbc.co.uk/2/hi/uk_news/3406027.stm [<https://perma.cc/2X93-WHF9>]; Michael Cook, *A Decade of Debate over Dolly*, MERCATORNET (Feb. 27, 2007), http://www.mercatornet.com/articles/view/a_decade_of_debate_over_dolly/1479 [<https://perma.cc/7628-ZDLR>].

440. *Public Interest Group Calls for Strengthening Global Policies Against Human Germline Modification*, CTR. GENETICS & SOC'Y (Apr. 22, 2015), <http://www.geneticsandsociety.org/article.php?id=8528> [<https://perma.cc/QM3N-DD54>].

441. Kaiser & Normile, *supra* note 429, at 486.

442. Nicholas Wade, *Scientists Seek Ban on Method of Editing the Human Genome*, N.Y. TIMES, Mar. 20, 2015, at A1.

human germline editing research.⁴⁴³ Declarations of an urgent need to organize meetings about the appropriateness of using CRISPR-like biotechnologies for human germline research have led to meetings such as the International Summit on Human Gene Editing, which took place in December 2015 in Washington, D.C.⁴⁴⁴

Just months earlier in September 2015, British scientists had promptly applied to the UK Human Fertilization and Embryology Authority (HFEA) for a license to edit genes in human embryos.⁴⁴⁵ The license was granted in February 2016. It allows biologists at the Francis Crick Institute in London to commence research on *healthy* human embryos younger than seven days, pending approval by a local research ethics board.⁴⁴⁶

The HFEA approval marks the first time a national regulatory agency condones investigations based on research involving human germline editing.⁴⁴⁷ It is also an important step toward elucidating more knowledge regarding CRISPR systems and their roles in genome editing within a more rigorous and developed framework than that of the research performed by the Chinese scientists, which involved non-viable human embryos and outdated versions of the CRISPR system. Findings derived from this forthcoming and unprecedented UK research will not only have an immediate impact on current reproductive technologies and human development, but may provide clues that will be useful for future clinical applications of genome editing.⁴⁴⁸

Genome editing technologies involving the human germline have far greater prospects for human health and welfare than somatic or stem cell gene editing therapies. In addition to tackling acquired diseases, as well as monogenic and polygenic—dominant or recessive—congenital disorders in a particular individual,⁴⁴⁹ correcting gene errors or conferring prophylactic protection to diseases in the germline means the changes can be inherited in a firm and self-perpetuating configuration to subsequent generations. In essence, human germline editing is truly the holy grail of modern-day medicine.

443. *Id.*

444. Nicholas Wade, *Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited*, N.Y. TIMES, Dec. 3, 2015, at A1.

445. Ewen Callaway, *Embryo Editing Gets Green Light*, 530 NATURE 18 (2016).

446. *Id.*

447. *Id.*

448. *Id.*

449. See discussion *supra* Sections IV.A and IV.C.

The potential benefits are infinite. Further maturation and tweaking of genome editing biotechnologies in combination with other foundational biotechnologies like genome sequencing and induced pluripotent stem cell (iPSC) biology may, sooner rather than later, enable us to ablate, mitigate, counteract, or safeguard against an extensive array of complex human ailments discussed earlier, including neurodegenerative disorders, congenital diseases, cognitive and behavioral anomalies, HIV and other viruses, obesity, cardiovascular disease, cancers, and more.

Contemplate, for a moment, the well-publicized dilemma of actress and director Angelina Jolie. In back-to-back op-eds in *The New York Times*, she shared with the world her decision to endure a preventive double mastectomy to remove her breasts⁴⁵⁰ and a laparoscopic bilateral salpingo-oophorectomy to remove her ovaries and fallopian tubes.⁴⁵¹ Her decisions to undergo the procedures came following genetic testing via a blood test, which revealed she carried common mutations in the *BRCA1* gene that placed her at an 87% risk of developing breast cancer and a 50% risk of ovarian cancer.⁴⁵² Jolie lost her grandmother, aunt, and mother to cancer,⁴⁵³ making her family history a cautionary tale that could likely have foreshadowed her own destiny. In the span of two years, she took a surgical plunge any woman would dread. Her journey rendered her a menopausal woman well before her natural time. However, she also stands strong by her life-altering decision because she feels her children will no longer have to face losing their mother prematurely, as she did.⁴⁵⁴

Jolie's remarkable story mirrors those of millions of women worldwide facing the deadly threat of cancer.⁴⁵⁵ The same can be said of men choosing to part ways with their prostates⁴⁵⁶ or testes,⁴⁵⁷ and millions of men and women all over the world facing tough decisions

450. See Angelina Jolie, *My Medical Choice*, N.Y. TIMES, May 14, 2013, at A25.

451. See Angelina Jolie Pitt, *Diary of a Surgery*, N.Y. TIMES, Mar. 24, 2015, at A23.

452. *Id.*

453. *Id.*

454. See Jolie, *supra* note 450, at A25.

455. *Id.* The World Health Organization estimates that breast cancer alone kills nearly 458,000 people each year, mainly in low- and middle-income countries. *Id.*

456. Prostate cancer was the third most common type of cancer in the United States in 2016, causing an estimated 26,120 deaths last year. *SEER Stat Fact Sheets: Prostate Cancer*, NAT'L CANCER INST., <http://seer.cancer.gov/statfacts/html/prost.html> [<https://perma.cc/LN6M-QNLB>] (last visited Feb. 14, 2017).

457. An estimated 8,720 new cases of testicular cancer were reported in 2016. *SEER Stat Fact Sheets: Testis Cancer*, NAT'L CANCER INST., <http://seer.cancer.gov/statfacts/html/testis.html> [<https://perma.cc/NKW2-VZEJ>] (last visited Feb. 14, 2017).

because of various forms of pervasive cancer diseases.⁴⁵⁸ But what if such drastic choices could be avoided? In Jolie's case, the cancer risk was accentuated based on a familial history of cancer and mutations in the *BRCA1* gene. Had genome editing been safe and readily available to her, her decision to extirpate her breasts and ovaries would not even have been considered.

In the future, humans may be able to identify quantitative-trait loci linked to a genetic basis or predisposition to disease and proactively correct deleterious mutations that could pose grave threats to human life. Genome editing finally brings into the realm of reality clinical applications that had been unreachable for decades. It is quite likely that the next generation of children and grandchildren may grow up in a CRISPR world, where they will no longer have to make Jolie-type choices due to cancers and numerous other human diseases. Even more remarkable is the notion that by correcting those mistakes in the germline DNA, new generations of would-be disease-prone mutation carriers may never have to witness the death of mothers, aunts, and grandmothers at the hands of the same killer.

Despite the vast potential for good by the use of genome editing biotechnologies, to some the notion of human germline modification—no matter what the purpose—conjures up the insidious spirit of eugenics and other potential societal harms.⁴⁵⁹ Frivolous enhancement of human traits, rising inequality, and a multitude of “designer babies” are commonly cited as major threats stemming from the use of genome editing biotechnologies.⁴⁶⁰ Others have chosen to either favorably cherry-pick or denounce certain applications of genome editing, as they worry that widespread opposition to the technology may curtail uses from which they stand to profit.⁴⁶¹ This

458. Cancers are among the leading causes of morbidity and mortality worldwide. *Cancer: Fact Sheet No. 297*, WORLD HEALTH ORG. (Feb. 2015), <http://www.who.int/mediacentre/factsheets/fs297/en/> [<https://perma.cc/A6J3-KLQD>]. In 2012, approximately 14 million new cases of cancer and 8.2 million cancer-related deaths were reported worldwide. *Id.* New cancer cases are expected to increase by 70% in the next twenty years. *Id.*

459. See, e.g., Cook, *supra* note 439 (commenting on the media's perception that cloning research might give rise to “armies of Adolf Hitlers”); Robert Pollack, *Eugenics Lurk in the Shadow of CRISPR*, 348 SCIENCE 871 (2015) (analogizing the introduction of germline modification with a return to an agenda of eugenics that aims to select “good” traits and weed out “bad” ones).

460. See, e.g., Antonio Regalado, *Engineering the Perfect Baby*, MIT TECH. REV. (Mar. 5, 2015), <https://www.technologyreview.com/s/535661/engineering-the-perfect-baby/> [<https://perma.cc/G46W-BQ3N>].

461. See, e.g., Lanphier et al, *supra* note 28, at 410 (providing a pulpit to Sangamo BioSciences executives from which to argue that germline, but not somatic, genome editing should be banned). Sangamo BioSciences holds key patents in ZFN technology directed at somatic cell editing. Newer CRISPR-based technologies could negatively impact Sangamo's business strategies. *Id.*

Article sets the stage to explore some of these themes arising from human germline editing in forthcoming genome editing-related scholarship.

* * *

The applications of genome editing biotechnologies described above constitute the first comprehensive—yet non-exhaustive—representation of the potential uses of this budding biotechnology to appear in legal literature. It is important to note that other uses of genome editing and CRISPR-based biotechnologies currently exist, including development of new antibiotics and antimicrobials,⁴⁶² drug target discovery,⁴⁶³ systematic identification of gene and drug combinations,⁴⁶⁴ targeted epigenome editing,⁴⁶⁵ live imaging to study conformational and cellular dynamics,⁴⁶⁶ cell lineage tracing,⁴⁶⁷ whole genome screening and labeling,⁴⁶⁸ and others.⁴⁶⁹ However, it would be

462. See, e.g., David Bikard et al., *Exploiting CRISPR-Cas Nucleases to Produce Sequence-Specific Antimicrobials*, 32 NATURE BIOTECHNOLOGY 1146 (2014); Robert J. Citorik et al., *Sequence-Specific Antimicrobials Using Efficiently Delivered RNA-Guided Nucleases*, 32 NATURE BIOTECHNOLOGY 1141 (2014); Ido Yosef et al., *Temperate and Lytic Bacteriophages Programmed to Sensitize and Kill Antibiotic-Resistant Bacteria*, 112 PROC. NAT'L ACAD. SCI. U.S. 7267 (2015). Some concerns of biosecurity and bioterrorism have been associated with applications of CRISPR-based biotechnologies such as gene drives. See, e.g., Kozminski, *supra* note 249, at 3896–97; Rhodi Lee, *Government Experts Concerned About Possible Bioterrorism Using GM Organisms*, TECH TIMES (Aug. 5, 2015), <http://www.techtimes.com/articles/74121/20150805/government-experts-concerned-about-possible-bioterrorism-using-gm-organisms.htm> [<https://perma.cc/PY3Y-WN3B>]; Webber et al., *supra* note 249, at 10565–67. Similar concerns may be raised in the future regarding the ability to manipulate deadly bacteria and viruses. See Catherine Jefferson et al., *Synthetic Biology and Biosecurity: How Scared Should We Be?*, KING'S COLLEGE LONDON 1, 9 (2014), <http://www.kcl.ac.uk/newsevents/news/newsrecords/docs/jefferson-et-al-2014-Synthetic-Biology-and-Biosecurity.pdf> [<https://perma.cc/5WHA-YTXX>] (recounting how anthrax was used as a bioweapon during the attacks of September 11, 2001).

463. See, e.g., Junwei Shi et al., *Discovery of Cancer Drug Targets by CRISPR-Cas9 Screening of Protein Domains*, 33 NATURE BIOTECHNOLOGY 661 (2015).

464. See, e.g., Alan S.L. Wong et al., *Multiplexed Barcoded CRISPR-Cas9 Screening Enabled by CombiGEM*, 113 PROC. NAT'L ACAD. SCI. U.S. 2544 (2016).

465. Paul Enríquez, *CRISPR-Mediated Epigenome Editing*, 89 YALE J. BIOLOGY & MED. 471 (2016).

466. See, e.g., Baohui Chen et al., *Dynamic Imaging of Genomic Loci in Living Human Cells by an Optimized CRISPR/Cas System*, 155 CELL 1479 (2013).

467. Aaron McKenna et al., *Whole Organism Lineage Tracing by Combinatorial and Cumulative Genome Editing*, 353 SCIENCE aaf7907 (2016).

468. Andrew B. Lane et al., *Enzymatically Generated CRISPR Libraries for Genome Labeling and Screening*, 34 DEVELOPMENTAL CELL 373 (2015).

469. See, e.g., Lukas E. Dow et al., *Inducible in Vivo Genome Editing with CRISPR-Cas9*, 33 NATURE BIOTECHNOLOGY 390 (2015) (describing a tool for inducible genome editing); Luke A. Gilbert et al., *CRISPR-Mediated Modular RNA-Guided Regulation of Transcription in*

impractical to list them all within the context of a law journal article, particularly given the astounding rate at which new applications continue to emerge.

Next, this Article weaves the genome editing scientific empiricism articulated above with jurisprudence to advocate for a normative approach that will lay a foundation for future examinations of the synergistic roles that law, science, and public policy will play in the development of this truly exceptional and transformative incipient biotechnology.

V. SCIENTIFIC EMPIRICISM AS A BEDROCK FOR GENOME EDITING JURISPRUDENCE

The pervasive reach of genome editing harbingers that the technology will continue to be a source of controversy in legal and policy arenas. Already, signs of impending controversy are coming into focus.⁴⁷⁰ However, the current legal landscape lacks a structural framework to systematically address questions of science in law. This Article proposes a normative framework to consolidate scientific empiricism and jurisprudence and argues that *Myriad* marks a turning point that facilitates the path to link these disciplines. The interdisciplinary approach set forth in this Article can be avidly applied to combat seeds of deceptive simplicity—namely, preposterous, impractical, or sensationalist claims that so often take root in dialogues concerning issues raised by technological advances.

This Article identifies the specter of “designer babies” as one of many quintessential examples of deceptive simplicity that law and policy makers should beware of as they deliberate on the future of genome editing. The doctrinal approach advocated here demonstrates

Eukaryotes, 154 CELL 442 (2013) (introducing a platform to regulate transcriptional activation or repression in cells); Andrew A. Horwitz et al., *Efficient Multiplexed Integration of Synergistic Alleles and Metabolic Pathways in Yeasts via CRISPR-Cas*, 1 CELL SYS. 88 (2015) (explaining a technique to promote identification of biosynthetic pathways); Silvana Konermann et al., *Optical Control of Mammalian Endogenous Transcription and Epigenetic States*, 500 NATURE 472 (2013) (establishing a method for the optogenetic control of epigenetic chromatin modifications); Morgan L. Maeder et al., *Targeted DNA Demethylation and Activation of Endogenous Genes Using Programmable TALE-TET1 Fusion Proteins*, 31 NATURE BIOTECHNOLOGY 1137 (2013) (exploring targeted demethylation and its functional significance in cells); Lei S. Qi et al., *Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression*, 152 CELL 1173 (2013) (introducing a platform to regulate transcriptional activation or repression in cells); Owen W. Ryan et al., *Selection of Chromosomal DNA Libraries Using a Multiplex CRISPR System*, 3 ELIFE 03703 (2014) (developing a CRISPR-based approach to facilitate directed evolution of biomolecules); Yuxin Zhou et al., *High-Throughput Screening of a CRISPR/Cas9 Library for Functional Genomics in Human Cells*, 509 NATURE 487 (2014) (unveiling a large-scale genetic library screen for functional genomics).

470. See, e.g., discussion *supra* notes 435–44 and accompanying text.

the efficacy of adopting a jurisprudence of scientific empiricism as a proverbial herbicide against rapidly spreading deceptive simplicity weeds. In addition, the Article reconsiders the illegitimacy of *Buck v. Bell* to argue that, contrary to the current prevailing wisdom, *Buck* relied not on false science, but on rampant deceptive simplicity instead.

A. The Exorcism of Designer Baby's Specter

Nearly a quarter-century ago, advances in assisted reproductive technology pioneered the emergence of an unusual set of human pregnancies.⁴⁷¹ Scientists had figured out an innovative approach to couple IVF and a novel way of screening fertilized embryos derived from couples at risk of transmitting genetic diseases to their offspring.⁴⁷² The revolutionary method, called pre-implantation genetic diagnosis (PGD), involved screening for the presence of the Y chromosome in cells biopsied from fertilized embryos.⁴⁷³ Embryos carrying the Y chromosome are male⁴⁷⁴ and, thus, susceptible to inheriting recessive X-linked diseases such as X-linked mental retardation, Lesch-Nyhan syndrome, and DMD.⁴⁷⁵ PGD proved scientists could successfully screen embryos from these X-linked disease-carrier parents on the basis of gender and, consequently, it was presented as an alternative to abortion for couples whose only path to becoming parents to a healthy child had been to get pregnant, wait to find out the sex of the fetus—or do prenatal testing—and then decide to terminate the pregnancy if the fetus turned out to be genetically “defective” or male.⁴⁷⁶

It was not long before a debate on the social and ethical implications of PGD commenced. Some immediate concerns regarding PGD technologies initially focused on eliminating certain genetic

471. The first human pregnancies derived from this approach were reported in 1990. See A.H. Handyside et al., *Pregnancies from Biopsied Human Preimplantation Embryos Sexed by Y-Specific DNA Amplification*, 344 NATURE 768, 768 (1990).

472. See *id.*

473. *Id.* at 769.

474. *Id.*; Whitney Akchurin & Ryan Kartzke, *The Ethics of Gender Selection, in THE ETHICAL IMPERATIVE IN THE CONTEXT OF EVOLVING TECHNOLOGIES* 33 (Dan McIntosh et al. eds., 1996), <http://www.ethicapublishing.com/3CH2.htm> [<https://perma.cc/Z4U3-6NNM>] (wildtype human embryos are diploid and inherit one sex-determining chromosome from each parent; embryos carrying X and Y chromosomes are male, while those carrying two sets of X chromosomes are female).

475. Handyside et al., *supra* note 471, at 768.

476. *Id.*

diseases, family balancing,⁴⁷⁷ and the prospect of gender discrimination arising from embryonic sex selection,⁴⁷⁸ all of which were *actual* considerations raised by the technology at the time. However, other more dubious concerns—such as commercialization of children, dehumanization of childbirth, and “playing god”—piggybacked on the discussion.⁴⁷⁹

Unfounded claims predicted the inevitable use of PGD to essentially make people “smarter” or increase brain capacity, “eventually lead[ing] to the entire human race becoming increasingly intelligent.”⁴⁸⁰ Allegations that PGD was the first step in the creation of a “designer baby” as a way to “use money and technology to fulfill superficial desires” began to circulate.⁴⁸¹ Alluring declarations that parents could choose to endow their children with beautiful features and athletic prowess became normalized.⁴⁸² Soon thereafter, PGD became associated with a radical expansion of the old eugenics movement in which parents would be able to select offspring based on non-pathological characteristics in a free-market form of eugenics.⁴⁸³

These sensational perceptions of technological uses to create designer babies who are genetically enhanced to be, *inter alia*, “more intelligent, athletic, musically talented, and the like”⁴⁸⁴ has become an emblem of misinformation in areas of reproductive technology, and now genome editing.⁴⁸⁵ Regardless of why some perpetuate the

477. Family balancing is a term for the use of PGD in families with one or more children of one gender seeking to “balance” the offspring gender ratio by ensuring the next child is of the opposite gender. See Akchurin & Kartzke, *supra* note 474, at 33.

478. See, e.g., Blake Rodgers & Brandon Peterson, *The Ethics of Stem Cell Research and Prenatal Genetic Alteration*, in THE ETHICAL IMPERATIVE IN THE CONTEXT OF EVOLVING TECHNOLOGIES 47 (Dan McIntosh et al. eds., 1996), <http://www.ethicapublishing.com/3CH3.htm> [<https://perma.cc/D5ZU-XBJF>]; Akchurin & Kartzke, *supra* note 474, at 32–33.

479. See, e.g., Rodgers & Peterson, *supra* note 478, at 46–48.

480. *Id.* at 48.

481. See, e.g., Akchurin & Kartzke, *supra* note 474, at 35.

482. Rodgers & Peterson, *supra* note 478, at 47.

483. See, e.g., David S. King, *Preimplantation Genetic Diagnosis and the ‘New’ Eugenics*, 25 J. MED. ETHICS 176, 176–80 (1999).

484. Marcy Darnovsky, *Genetically Modified Babies*, N.Y. TIMES, Feb. 25, 2014, at A25.

485. See, e.g., Michael D. Lemonick, *Designer Babies*, TIME MAG., Jan. 11, 1999, at 64 (arguing—back in 1999—that “[w]ithin a decade or two, it may be possible to screen kids . . . for an enormous range of attributes, such as” height, body type, hair and eye color, intelligence, personality type, etc.). Accord James Gallagher, *Is It Time to Make Designer Babies?*, BBC NEWS (Sept. 10, 2015), <http://www.bbc.com/news/health-34207470> [<https://perma.cc/R8GC-Y96V>]; Antonio Michele Grygotis, *Higher Level of Embryo Testing Raises Questions About Possibility of Creating “Designer Babies”*, TRANSPLANT NEWS, June 30, 2001, at 12; Rubanath Karuthedath, *Biotech Nightmare: Science Fiction Dystopian Visions of Human Genetic Engineering and Cloning with Special Reference to the Boys from Brazil and Beggars in Spain*, 2 RES. J. ENG. LANGUAGE & LITERATURE 1 (2014), <http://www.rjelal.com/2.4.14/RUBANATH>

designer baby canard—whether due to misinformation, intent to deceive, or a desire to sensationalize—the inherent inaccuracies they are promulgating have taken root in the culture and severely interfere with the ability to have a reasoned debate on true issues.

Consider a STAT-Harvard poll on public opinion of genetic editing, testing, and therapy published in early 2016.⁴⁸⁶ Results revealed that 83% of Americans believe modifying “unborn babies” to improve their “intelligence or physical characteristics” should be illegal.⁴⁸⁷ Likewise, 65% believe genetic modifications should be illegal even to reduce the risk of developing serious diseases.⁴⁸⁸

Polling, of course, is not quite a science and certainly is not an exact one. In fact, it is highly vulnerable to the use of specific terminology and ambiguity in framing the questions asked. For instance, there is likelihood of bias in the STAT-Harvard poll’s reference to “changing genes of *unborn babies*”⁴⁸⁹ as opposed to the more technically accurate terms “embryo,” “zygote,” or “germ cells (sperm and eggs),” particularly given the respondents’ probable lack of knowledge that genome editing in a fetus or near full-term baby is not likely to be a viable option. Other polls over the years reflect similar views regarding genetic enhancement to boost intelligence or athletic ability of “designer babies,”⁴⁹⁰ but conflict with the STAT-Harvard poll

%20KARUTHEATH%201-6.pdf [https://perma.cc/5SSU-YQ2Y]; Gautam Naik, *A Genetic Code for Genius?*, WALL ST. J. (Feb. 15, 2013), <https://www.wsj.com/articles/SB10001424127887324162304578303992108696034> [https://perma.cc/FA4L-KRUV]; Regalado, *supra* note 460; Antonio Regalado, *Scientists Call for a Summit on Gene-Edited Babies*, MIT TECH. REV. (Mar. 19, 2015), <https://www.technologyreview.com/s/536021/scientists-call-for-a-summit-on-gene-edited-babies/> [https://perma.cc/4D53-3AX9]; “*Designer Babies*” on the Way? In China, *Scientists Attempt to Unravel Human Intelligence*, CBS NEWS (Mar. 5, 2014), <http://www.cbsnews.com/news/designer-babies-on-the-way-in-china-scientists-attempt-to-unravel-human-intelligence/> [https://perma.cc/W3GE-3Z6B].

486. *The Public and Genetic Editing, Testing, and Therapy*, STAT & HARV. T.H. CHAN SCH. PUB. HEALTH 1 (Jan. 2016), <https://cdn1.sph.harvard.edu/wp-content/uploads/sites/94/2016/01/STAT-Harvard-Poll-Jan-2016-Genetic-Technology.pdf> [https://perma.cc/GK6F-MVGN].

487. *Id.* at 13.

488. *Id.*

489. *Id.* (emphasis added).

490. See, e.g., *United Kingdom: Reproductive and Research Cloning, Genetic Modification and Selection, Sex Selection*, YOUGOV 6 (Aug. 19, 2005) [hereinafter U.K. Poll], http://iis.yougov.co.uk/extranets/ygarchives/content/pdf/TEL050101042_1.pdf [https://perma.cc/ZBD6-2ARY] (reporting that only 4% of total respondents approve of using genetic modification to improve a child’s academic or sporting abilities); VCU *Life Sciences Survey: Public Values Science but Concerned About Biotechnology*, VCU CTR. PUB. POL’Y 4, 10 (2003), <http://lifesciences.vcu.edu/media/life-sciences/docs/survey2003.pdf> [https://perma.cc/MB2A-LJJ2] (94% of respondents opined that “changing a baby’s characteristics for cosmetic purposes such as eye or hair color . . . is taking medical advances too far”).

in regard to the legality of using genetic modifications to prevent or reduce the risk of serious diseases in offspring or embryos.⁴⁹¹

Yet, nothing in these observations detracts from the surprising revelation that, according to this poll, a majority of Americans apparently believe that genome modifications can actually be used for altering inherently polygenic—determined by more than one gene—traits such as intelligence, eye color, athletic ability, and beauty—many of which are intrinsically subjective.

Indeed, even discounting the bias in the premise of the poll questions, namely, that the potential for improving intelligence, athletic ability, or appearance is true, the data suggest that the public is largely unaware of what is technologically feasible or not. More importantly, the poll results suggest that the general population cannot recognize, and is highly susceptible to, technological deceptive simplicity.

Contemplate the claim that genetic modifications can be used to create a superhuman race of geniuses. This claim was precisely the subject matter of an article with a cheeky headline⁴⁹² featured in a popular magazine⁴⁹³ pseudo-reporting on BGI,⁴⁹⁴ a Chinese

491. Biotechnology Australia, *Increasing Public Support for Stem Cell Research* 1–2 (July 7, 2003), http://www.geneticsandsociety.org/downloads/20030707_Biotechnology_Australia.pdf [<https://perma.cc/HZ65-96UX>] (reporting 61% support for genetic testing of unborn children and 79% support for gene therapy to correct any genetic disorders that may be diagnosed); Antonio Regalado, *Patients Favor Changing the Genes of the Next Generation with CRISPR*, MIT TECH. REV. (Dec. 2, 2015), <https://www.technologyreview.com/s/544141/patients-favor-changing-the-genes-of-the-next-generation-with-crispr/> [<https://perma.cc/U7LB-FQ3Y>]; U.K. Poll, *supra* note 490, at 6 (noting that 57% and 43% of respondents approve using genetic modifications to “prevent children from suffering serious genetic diseases” or to reduce the risk of developing diseases such as cancer, Alzheimer’s disease, and heart disease, respectively); *see also id.* (reporting that 51% of respondents believe that it should be legal for parents and doctors to “carry out genetic tests on embryos created during IVF treatment in order to select those with the lowest chances of developing [serious] diseases . . . later in life,” while only 30% believe that such testing should be illegal).

492. The article appears in *Vice Magazine*. It features a picture of school-age Chinese children lined up in a formation that stretches as far as the camera lens can capture and gives the appearance that China is trying to build an army of homogeneous, little human robots. Aleks Eror, *China Is Engineering Genius Babies*, VICE MAG. (Mar. 15, 2013), <http://www.vice.com/read/chinas-taking-over-the-world-with-a-massive-genetic-engineering-program> [<https://perma.cc/4BSB-5Z7S>].

493. *Vice* is a print magazine and website focused on popular culture, news, and entertainment. *See Vice (Magazine)*, WIKIPEDIA, [https://en.wikipedia.org/wiki/Vice_\(magazine\)](https://en.wikipedia.org/wiki/Vice_(magazine)) [<https://perma.cc/HGH5-GF6C>] (last visited Feb. 25, 2017). The magazine expanded into Vice Media LLC, a company that now operates the magazine and a multimedia network including several digital channels, *Vice News*, a record label, a film production studio, and book publishing division. *Vice Media*, WIKIPEDIA, https://en.wikipedia.org/wiki/Vice_Media [<https://perma.cc/S36E-JF3U>] (last visited Feb. 25, 2017). *Vice* is the media company that funded Dennis Rodman’s—the former NBA player—2013 trip to meet North Korea’s dictator. Lindsay Silberman, *Rodman’s Revelations*, DUJOUR, <http://dujour.com/culture/dennis-rodman-north->

biotechnology firm partly funded by the Chinese government, and its Cognitive Genomics Research (CGR) project.⁴⁹⁵ According to BGI, the goal of the CGR branch is to study human cognition and use next-generation DNA sequencing technologies to interrogate the relationships between genes, the environment, and cognitive ability in the human brain.⁴⁹⁶

Although BGI's Gene-Trait Association Study of Intelligence may arguably suffer from cohort methodological flaws related to recruitment of "cognitively gifted" volunteer subjects⁴⁹⁷ who meet peculiar—to say the least—qualifying criteria,⁴⁹⁸ BGI's approach to human cognition research appears to have nothing in common with the bombastic claims made against it. Furthermore, over the past fifteen years, some BGI-sponsored research has been featured in many of the most prominent scientific journals.⁴⁹⁹ There is simply no evidence to suggest that the Chinese government is trying, or even would be able, to create an army of geniuses born out of basic research into human cognition. But that has not prevented the dissemination of misinformation, which is eagerly picked up by diverse media and spreads like wildfire in a dry deciduous forest.⁵⁰⁰

korea-kim-jong-un-interview/ [https://perma.cc/35XY-Q6EV] (last visited Feb. 25, 2017). In recent years, Vice Media has been valued at more than \$2.5 billion following investments from Technology Crossover Ventures (\$250 million), A&E Networks (\$250 million), and Rupert Murdoch's Twenty-First Century Fox (\$70 million). Emily Steel, *Vice Gets 2nd Investment, to Aid Expansion*, N.Y. TIMES, Sept. 4, 2014, at B1.

494. For more information on BGI, see BGI, <http://bgi-international.com/us/about-us/introduction/> [https://perma.cc/8KE5-U5EA] (last visited Feb. 25, 2017).

495. For more information on BGI's Cognitive Genomics Research group, see BGI, <https://www.cog-genomics.org/> [https://perma.cc/2N2V-DVBL] (last visited Feb. 13, 2017).

496. Christopher C. Change et al., *BGI Cognitive Genomics Lab: Proposal for Gene-Trait Association Study of g*, BGI 2, https://www.cog-genomics.org/static/pdf/bgi_g_proposal.pdf [https://perma.cc/VZJ2-BU5H] (last visited Feb. 25, 2017).

497. *Id.*

498. Automatic qualifying criteria include obtaining high scores in select standardized tests (SAT/ACT/GRE), having "performed well" in academic competitions (e.g., the Math, Physics, or Informatics Olympiads, the William Lowell Putnam Mathematical Competition, and TopCoder), and earning a Ph.D. from a "top" US program in physics, math, electrical engineering, or theoretical computer science. *See id.* A volunteer may also qualify by making a case for herself via specification of "exceptional academic credentials or technical accomplishments." *See How to Qualify*, BGI, <https://www.cog-genomics.org/volunteer> [https://perma.cc/787Y-L8HK] (last visited Feb. 13, 2017).

499. *See Our Publications*, BGI, <http://bgi-international.com/us/about-us/our-publications/> [https://perma.cc/7MTV-8G39] (last visited Feb. 25, 2017) (providing a list of scientific articles published in various high-quality, peer-reviewed journals).

500. *See, e.g.,* Eror, *supra* note 492; *republished in Chinese Company Attempts to Engineer Genius Babies*, GENETIC LITERACY PROJECT (Mar. 22, 2013), <https://www.geneticliteracyproject.org/2013/03/22/chinese-company-attempts-to-engineer-genius-babies/> [https://perma.cc/5ZZW-TSLF]; *also republished in How China Is Trying to Engineer*

Even more disheartening is the fact that this kind of deceptive simplicity surrounding designer babies has permeated scholarly fields,⁵⁰¹ including legal scholarship.⁵⁰² Much ink has been spilled entertaining hypotheticals of “made-to-order boutique babies”⁵⁰³ to genetically modify traits such as eye, hair, and skin color,⁵⁰⁴ or even more subjective ones like sexual orientation,⁵⁰⁵ beauty, charm, and intelligence.⁵⁰⁶ Such world of “designer genes” would purportedly give parents a menu of choices “from any genes imaginable, *human or not*.”⁵⁰⁷ It is time to adhere to higher standards in this regard.

Genius Babies, REAL CLEAR POLITICS (Mar. 17, 2003), http://www.realclearpolitics.com/2013/03/17/how_china_is_trying_to_engineer_genius_babies_304097.html [https://perma.cc/GZ9A-MPLW]; referred to in, e.g., George Dvorsky, *Is China Selectively Breeding a New Generation of Genius Babies?*, IO9 (Mar. 18, 2013), <http://io9.gizmodo.com/is-china-selectively-breeding-a-new-generation-of-geniu-455634018> [https://perma.cc/72WA-A5RK]; Roy Klabin, *Chinese Labs Are Engineering Genius Babies, Should the U.S. Follow Suit?*, POLICY.MIC (Mar. 18, 2013), <http://mic.com/articles/30111/chinese-labs-are-engineering-genius-babies-should-the-u-s-follow-suit#.Q5X5YENgb> [https://perma.cc/XM3W-3E4R]; *China to Begin Producing 'Designer Babies' in Horrific Scheme*, CATHOLIC ONLINE (Jan. 16, 2014), <http://www.catholic.org/news/technology/story.php?id=53890> [https://perma.cc/B9A9-K7K5].

501. See, e.g., *supra* notes 479–83 and accompanying text.

502. See discussion *infra* notes 503–07.

503. Peter H. Huang, *Herd Behavior in Designer Genes*, 34 WAKE FOREST L. REV. 639, 659 (1999).

504. See, e.g., *id.* at 642 (arguing that in the near future, genetic selection of hair color, skin color, intellectual ability, or behavior pre-dispositions may be feasible); Mahoney, *supra* note 47, at 313 (proposing that new technology may presumably allow parents to decide eye color and sexual orientation of designed babies).

505. Mahoney, *supra* note 47, at 313.

506. See, e.g., Jason T. Corsover, *The Logical Next Step? An International Perspective on the Issues of Human Cloning and Genetic Technology*, 4 ILSA J. INT'L & COMP. L. 697, 744 (1998) (“One can imagine menus offering a price list of particularly desirable traits. . . . For the right price, one may have the option to purchase the DNA of a world class athlete, award winning actor, or a beautiful supermodel.”); Sarah M. Markwood, Comment, *Creating a Perfect Human Is Not So Perfect: The Case for Restricting Genetic Enhancement Research*, 110 PENN. ST. L. REV. 473, 473–74 (2005) (proposing a scenario where genetic enhancement will lead to producing “athletically gifted,” “physically attractive” children, or “a theatrical prodigy, a strong wrestling champion, or a mathematical genius”); Maxwell J. Mehlman, *The Law of Above Averages: Leveling the New Genetic Enhancement Playing Field*, 85 IOWA L. REV. 517, 528–29 (2000) (entertaining the possibility that new technologies may allow genetic manipulation of traits such as beauty, strength, stamina, charm, cheerfulness, confidence, memory, intelligence, and creativity); Daniel L. Tobey, *What's Really Wrong with Genetic Enhancement: A Second Look at Our Posthuman Future*, 6 YALE J.L. & TECH. 54, 56 n.1 (2003) (asserting that “[g]enetic enhancement will, in the short run, be more concerned with improving present traits such as intelligence, personality, and strength”); Lindsey A. Vacco, Comment, *Preimplantation Genetic Diagnosis: From Preventing Genetic Disease to Customizing Children. Can the Technology Be Regulated Based on the Parents' Intent?*, 49 ST. LOUIS U. L.J. 1181, 1183 (2005) (stating a scenario where PGD will be used “to select for traits such as intelligence, athletic ability, or musical inclination”).

507. Huang, *supra* note 503, at 658 (emphasis added).

B. Dispelling the Myth of IQ Heritability—A Case Study

The source of human intelligence and cognition has been the subject of study for well over a century.⁵⁰⁸ Francis Galton first proposed in the 1860s that genius and mental ability are as heritable as physical traits.⁵⁰⁹ Evidence to support his thesis consisted of “showing how large is the number of instances in which men who are more or less illustrious have eminent kinsfolk.”⁵¹⁰ The “laws” of heredity with respect to genius were thus initially laid out by surveying men of high reputation—judges of England, statesmen, literary men, men of science, poets, musicians, etc.—within hierarchies.⁵¹¹

From the start, this field was destined for controversy and prone to racial animus masquerading as science. The founding father of the field sponsored racial hierarchies, affirmed the superiority of the ancient Greek race, and professed “the average intellectual standard of the negro race is some two grades below [his] own.”⁵¹² Galton’s vitriol had few limits. He even expressed that he often felt ashamed of being human when flagrantly pondering about the “idiocy among the negroes.”⁵¹³ Galton’s ideology cemented racial contempt into the foundation of the pseudoscience surrounding heritable human intelligence and mental cognitive ability.

General cognitive ability (GCA), also known as general intelligence, or *g*, was first formally introduced in 1904.⁵¹⁴ Research on familial⁵¹⁵ and twin⁵¹⁶ studies in the early twentieth century

508. See generally FRANCIS GALTON, *HEREDITARY GENIUS: AN INQUIRY INTO ITS LAWS AND CONSEQUENCES* (1st ed. 1869) [hereinafter GALTON 1st ed.], http://galton.org/books/hereditary-genius/galton-1869-Hereditary_Genius.pdf [<https://perma.cc/82YP-SRMF>]. For the second edition published in 1892, see FRANCIS GALTON, *HEREDITARY GENIUS: AN INQUIRY INTO ITS LAWS AND CONSEQUENCES* (2d ed. 1892), <http://galton.org/books/hereditary-genius/text/pdf/galton-1869-genius-v3.pdf> [<https://perma.cc/LM6D-WNMU>].

509. GALTON 1st ed., *supra* note 508, at 1.

510. *Id.* at 6.

511. See *id.* at 2.

512. *Id.* at 338, 340.

513. *Id.* at 339.

[T]he number among the negroes of those whom we should call half-witted men, is very large. . . . The mistakes the negroes made in their own matters, were so childish, stupid, and simpleton-like, as frequently to make me ashamed of my own species. . . . I have no information as to actual idiocy among the negroes—I mean, of course, of that class of idiocy which is not due to disease.

Id.

514. See C. Spearman, “General Intelligence”, *Objectively Determined and Measured*, 15 AM. J. PSYCHOL. 201, 268–72 (1904).

515. See, e.g., HENRY HERBERT GODDARD, *FEEBLE-MINDEDNESS: ITS CAUSES AND CONSEQUENCES* vii (1914); HENRY HERBERT GODDARD, *THE KALLIKAK FAMILY: A STUDY IN THE*

cemented the notion of the heritability of intelligence. Adoption studies contributed a layer of complexity by concluding that the environment has some considerable effect on a child's intelligence quotient (IQ).⁵¹⁷ Current estimates of *g* heritability attributed to genetic factors ranges from 0.5 to 0.7,⁵¹⁸ and to as high as 0.8.⁵¹⁹ Studies over decades have consistently shown that *g* is a highly heritable trait.⁵²⁰ Although the extent of the range of *g* heritability estimates has been contested,⁵²¹ the bulk of literature demonstrates that *g* is at least reasonably heritable.⁵²²

Empirical evidence for *g* heritability provided by quantitative genetics highlights the issue of whether there are specific genes and Single Nucleotide Polymorphisms (SNPs)—variations in single nucleotides at specific positions in the genome—responsible for intelligence and GCA. Thanks to the advent of DNA sequencing technology in the twenty-first century, attempts to identify the “intelligence” gene(s) at the molecular level are underway.⁵²³ The search, however, has proved the gene(s) to be incredibly elusive.

To date, several Genome-Wide Association Studies (GWAS) have interrogated potential connections between various SNPs and *g*. For instance, a GWAS of intelligence in middle to older adulthood probing nearly 600,000 SNPs in approximately 3,500 individuals found no specific genetic variants robustly associated with human

HEREDITY OF FEEBLE-MINDEDNESS viii (1912); Daniel Starch, *The Similarity of Brothers and Sisters in Mental Traits*, 24 PSYCHOL. REV. 235, 237 (1917) (concluding that mental traits resemblance among siblings is as great as that of physical traits).

516. See, e.g., Curtis Merriman, *The Intellectual Resemblance of Twins*, 33 PSYCHOL. MONOGRAPHS 1, 16–18 (1924) (studying the intellectual level of a population of twin children ages 5–14).

517. See, e.g., Frank N. Freeman et al., *The Influence of Environment on the Intelligence, School Achievement, and Conduct of Foster Children*, in THE TWENTY-SEVENTH YEARBOOK OF THE NATIONAL SOCIETY FOR THE STUDY OF EDUCATION 103, 106 (Guy Montrose Whipple ed., 1928) (using foster children as a cohort to test whether residence in a foster home environment can influence intellectual capacity).

518. Thomas J. Bouchard & Matthew McGue, *Familial Studies of Intelligence: A Review*, 212 SCIENCE 1055, 1056 (1981).

519. Thomas J. Bouchard, Jr., *Genetic Influence on Human Intelligence (Spearman's *g*): How Much?*, 36 ANNALS HUM. BIOLOGY 527, 533 (2009).

520. See, e.g., Beben Benyamin et al., *Large, Consistent Estimates of the Heritability of Cognitive Ability in Two Entire Populations of 11-Year-Old Twins from Scottish Mental Surveys of 1932 and 1947*, 35 BEHAV. GENETICS 525 (2005).

521. See, e.g., B. Devlin et al., *The Heritability of IQ*, 388 NATURE 468, 470 (1997) (arguing that, in addition to genes and environments, the heritability of IQ also depends on maternal effects).

522. Contra Mae-Wan Ho, *No Genes for Intelligence in the Fluid Genome*, 45 ADVANCES CHILD DEV. & BEHAV. 67, 70 (2013) (pointing out that some scientists and popular media tend to mistakenly assume that highly heritable traits are predominantly genetically determined).

523. See *supra* and *infra* notes 518–58 and accompanying text.

intelligence.⁵²⁴ Although a prior published gene-based test for association had found one genome-wide significant association with the gene *FBNP1L*,⁵²⁵ which is highly expressed in neurons in developing brains, the GWAS failed to replicate that result using an independent sample.⁵²⁶

Members of the same team followed up with another GWAS, this time focusing on childhood intelligence from nearly 18,000 individuals (ages six to eighteen) in six discovery and three replication samples.⁵²⁷ Again, the study failed to identify individual SNPs associated with childhood intelligence.⁵²⁸ Gene-based analysis revealed that SNP rs236330, located in *FBNP1L*, was strongly associated with childhood intelligence.⁵²⁹ Yet, not even this SNP could explain more than 0.24% of the total phenotypic variation,⁵³⁰ suggesting that the largest effects of such SNPs are so minuscule that other smaller-effect SNPs are virtually undetectable. Both studies concluded that intelligence is highly heritable and polygenic, yet GWAS results are consistent with a model of intelligence under which many genetic variants have very small additive effects.⁵³¹

A little over one year ago, an independent group attempted to replicate the findings related to general cognitive ability and *FBNP1L* via a more robust method (GWAS Plus) using nearly 2.6 million SNPs.⁵³² Results could not corroborate the aforementioned findings and no gene reached statistical genome-wide significance using the same methodology of the prior report.⁵³³ Polygenic scores from all SNPs considered could not even account for 1% of the total variance (0.7%).⁵³⁴

524. G. Davies et al., *Genome-Wide Association Studies Establish That Human Intelligence Is Highly Heritable and Polygenic*, 16 MOLECULAR PSYCHIATRY 996, 1001 (2011).

525. *Id.* at 999 (citing Jimmy Z. Liu et al., *A Versatile Gene-Based Test for Genome-Wide Association Studies*, 87 AM. J. HUM. GENETICS 139 (2010)).

526. *Id.*

527. B. Benyamin et al., *Childhood Intelligence Is Heritable, Highly Polygenic and Associated with FBNP1L*, 19 MOLECULAR PSYCHIATRY 253 (2014).

528. *Id.* at 257.

529. *See id.* at supp. fig. 6, https://genepi.qimr.edu.au/contents/p/staff/BENYAMIN_FBNPIL_MOLPSYCH_OSI.pdf [<https://perma.cc/QF6H-DYPZ>].

530. *Id.* at 255.

531. *Id.*

532. Robert M. Kirkpatrick et al., *Results of a "GWAS Plus": General Cognitive Ability Is Substantially Heritable and Massively Polygenic*, 9 PLOS ONE 4 (Nov. 10, 2014), <http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0112390&type=printable> [<https://perma.cc/TP2S-KKY6>].

533. *Id.* at 10.

534. *Id.*

A recent GWAS meta-analysis of more than 125,000 individuals identified ten SNPs associated with increased educational attainment, three of which had genome-wide significant associations.⁵³⁵ However, the contribution of each genetic locus was incredibly small and the largest estimated effect was 0.02% of the variance.⁵³⁶ The findings hint that the genetic basis of complex behavioral phenotypes—e.g., intelligence—is far more diffuse than that of complex physical traits.⁵³⁷ Three additional SNPs spanning genomic regions across the *KNCMA1*, *NRXN1*, *POU2F3*, and *SCRT* genes—all predicted to be involved in the glutamate neurotransmission pathway and synaptic plasticity—were identified in a subsequent publication using an alternate method.⁵³⁸ These SNPs were statistically associated with cognitive performance in the cohort, but like other preceding reports, the estimated effect for each SNP was negligible (0.02%).⁵³⁹

The heritability of fluid general cognitive function in middle and older age was studied in a large meta-analysis GWAS of nearly 2.5 million SNPs in approximately 54,000 individuals.⁵⁴⁰ Genome-wide significant SNP associations were identified in three genomic regions comprising thirteen SNP variants, associated with, *inter alia*, *MIR2113*, *AKAP6*, *NPAS3*, *TOMM40*, and *APOE*.⁵⁴¹ Gene-based tests of association yielded one genome-wide significant result for *HMGNI*, a gene that has been linked to some neurodevelopmental disorders.⁵⁴² Together, all SNPs identified barely accounted for 1% of the total variance, corroborating the conclusion that general cognitive function is heritable and highly polygenic as others have shown before.⁵⁴³

Conflicting research and the manifest failure to reproduce GWAS results connecting specific genes with human cognition have prompted some scientists to call into question the validity of nearly a decade's worth of research. For instance, a study published in 2012

535. Cornelius A. Rietveld et al., *GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment*, 340 SCIENCE 1467, 1468 (2013).

536. *Id.* at 1469.

537. *Id.*

538. Cornelius A. Rietveld et al., *Common Genetic Variants Associated with Cognitive Performance Identified Using the Proxy-Phenotype Method*, 111 PROC. NAT'L ACAD. SCI. U.S. 13790, 13793 (2014).

539. *Id.* at 13792.

540. G. Davies et al., *Genetic Contributions to Variation in General Cognitive Function: A Meta-Analysis of Genome-Wide Association Studies in the CHARGE Consortium (N=53 949)*, 20 MOLECULAR PSYCHIATRY 183, 185 (2015).

541. *Id.* at 186–87.

542. *Id.* at 189.

543. *Id.* at 187.

sought to replicate findings related to a dozen other genes reported to be associated with *g*.⁵⁴⁴ Using data sets from three large, independent, and well-characterized longitudinal studies, the group found only one SNP associated with *g* that was nominally significant, despite expectations of finding ten to fifteen significant associations.⁵⁴⁵ The failure to identify unequivocal correlations prompted the group to conclude that most reported genetic associations with GCA are likely false positives.⁵⁴⁶

Given the existing body of literature in quantitative and molecular genetics concerning *g*, it is not surprising that, to date, “[n]o single SNP has yet been replicably associated with human intelligence at genome-wide significance levels.”⁵⁴⁷ Although there is consensus regarding the heritability of *g*, the hunt for the “intelligence gene(s)” has largely proved to be an exercise in futility.

The molecular underpinnings of intelligence may ultimately be a question that science will wrestle with for some time. The genetics-based view that mere SNPs account for highly complex and polygenic traits such as intelligence may very well be a gross underestimation of the unknown truth. The missing heritability of intelligence may be due to uncommon polymorphisms our current technologies cannot detect or Copy Number Variations (CNVs)—deletions or duplications of large sections of DNA.⁵⁴⁸ In other words, entire sections of DNA, as opposed to SNPs, could be responsible for a large proportion of human genetic variation.⁵⁴⁹ On this point, several CNV regions have been shown to carry genes related to development and cognitive ability.⁵⁵⁰

Alternatively, the basis for intelligence may rest in epigenetic mechanisms. In contrast to genetics, which focus on the four nucleotides (A, C, G, T) of the DNA alphabet, epigenetics is far more complex in nature.⁵⁵¹ Epigenetic mechanisms are capable of altering gene expression without ever changing DNA sequences and comprise post-translational modifications of histones and other proteins,⁵⁵²

544. Christopher F. Chabris et al., *Most Reported Genetic Associations with General Intelligence Are Probably False Positives*, 23 PSYCHOL. SCI. 1314 (2012).

545. *Id.* at 1319.

546. *Id.* at 1314.

547. Kirkpatrick et al., *supra* note 532, at 10.

548. *Id.* at 11.

549. See Andrew T.M. Bagshaw et al., *No Effect of Genome-Wide Copy Number Variation on Measures of Intelligence in a New Zealand Birth Cohort*, 8 PLoS ONE e55208 (2013).

550. *Id.* (citations omitted).

551. See Enríquez, *supra* note 465, at 471, 483.

552. See, e.g., Andre Fischer et al., *Recovery of Learning and Memory Is Associated with Chromatin Remodelling*, 447 NATURE 178 (2007) (studying the role of histone acetylation and chromatin remodeling on learning and memory access).

DNA modifications—e.g., methylation⁵⁵³—and regulatory RNA molecules.⁵⁵⁴ Collectively, these epigenetic processes add an incredible degree of complexity to gene regulation that takes into consideration dietary, nutritional, social, cultural, pharmacological, and environmental exposures.⁵⁵⁵

Yet another basis for *g* heritability could rest on principles of pleiotropy—one gene affects many traits—and epistasis—one gene affects expression of one or more genes. An article published recently performed a systems-level analysis of genome-wide expression data to reveal the existence of conserved gene-regulatory networks enriched with genetic variants linked to human cognitive abilities.⁵⁵⁶ One such network comprises up to 150 genes with tight coexpression relationships.⁵⁵⁷ It may be the case that hundreds or thousands of genes clustered into networks contribute to genetic associations and heritability of *g*. It has been proposed that human intelligence is not unitary, but rather rises from multiple cognitive components organized into functionally specialized brain networks.⁵⁵⁸

As detailed in this Section, the potential complexity for highly polygenic traits such as intelligence is remarkable. The take-home message is that deceptively simplistic notions of “gene X is responsible for trait Y” breed mass misperceptions about the role genetic associations play in trait formation and development. In the case of genome editing, one common “concern” advanced by some is that genome editing technologies are inherently insidious because they will eventually lead to creation of “designer babies” with a panoply of artificial traits; high intelligence is purportedly one of them.⁵⁵⁹ However, as documented in this Section, anyone who claims that technology is at the verge of enabling the creation of genius designer babies has simply fallen prey to, or wishes to distract others with, deceptive simplicity.

This Section used intelligence as a model for confronting deceptive simplicity. However, the same principles apply to other

553. See, e.g., Swati Gupta et al., *Histone Methylation Regulates Memory Formation*, 30 J. NEUROSCIENCE 3589 (2010) (investigating the role of the H3K4me3 epigenetic mark in memory formation).

554. See Enríquez, *supra* note 465, at 471.

555. See *id.*

556. Michael R. Johnson et al., *Systems Genetics Identifies a Convergent Gene Network for Cognition and Neurodevelopmental Disease*, 19 NATURE NEUROSCIENCE 223 (2016).

557. *Id.*

558. Adam Hampshire et al., *Fractionating Human Intelligence*, 76 NEURON 1225, 1233 (2012).

559. See, e.g., discussion *supra* note 506 and accompanying text.

designer baby polygenic traits, such as height.⁵⁶⁰ Simply put, human knowledge is vastly incomplete concerning the genetics of these complex polygenic traits. And the lack of knowledge does not justify entertaining far-fetched hypotheticals in legal scholarship. It is imperative that future scholars inform themselves about the scientific matters on which they choose to comment. Scholarly standards ought to be higher. Deceptive simplicity may appear benign at first glance, but, as the next Section demonstrates, misinterpreting science and spreading misinformation can lead to catastrophic societal consequences.

C. Buck v. Bell—The Prototypical Fruit of Deceptive Simplicity

*Buck v. Bell*⁵⁶¹ is among the most horrid illustrations of deceptive simplicity in the exercise of American jurisprudence. In a surreal series of events, government-sanctioned sterilization arrived at the most powerful court in the world: the US Supreme Court. It made its case before learned judges and came out victorious without a single word in opposition. A near unanimous Court upheld—eight to one⁵⁶²—the constitutionality of a Virginia statute that legalized the involuntary sterilization of individuals deemed “mental defectives” in state institutions, provided it was in “the best interest of the patients and of society.”⁵⁶³

Writing for the Court, Oliver Wendell Holmes, Jr. infamously memorialized what is arguably among the most incendiary and ignorant language ever published in the United States Reports. “It is better for all the world, if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. . . . *Three generations of imbeciles are enough.*”⁵⁶⁴

The question presented in *Buck* was whether a statute authorizing compulsory sterilization of the “feeble-minded” violated the Due Process and Equal Protection clauses of the Fourteenth

560. At least 180 genetic variants have been reported to influence height in humans. Hana Lango Allen et al., *Hundreds of Variants Clustered in Genomic Loci and Biological Pathways Affect Human Height*, 467 NATURE 832 (2010). Thus, it is preposterous to claim that, at this time or any time in the near future, genome editing technologies will allow humans to engineer a world-class basketball player in a petri dish. See, e.g., Corsover, *supra* note 506, at 744.

561. *Buck v. Bell*, 274 U.S. 200 (1927).

562. Justice Pierce Butler dissented from the Court’s decision, but filed no opinion of his own. *Id.* at 200, 208.

563. *Id.* at 205–06.

564. *Id.* at 207 (emphasis added) (internal citation omitted).

Amendment.⁵⁶⁵ The Court belabored—in one-third of its nearly three-page decision—the argument that Carrie Buck had sufficient procedural Due Process at law.⁵⁶⁶ Yet, the Court virtually ignored the Equal Protection challenge, ridiculing it as a desperate “last resort” argument for defending individual rights.⁵⁶⁷

The entirety of the opinion cited no constitutional authorities, save for *Jacobson v. Massachusetts*,⁵⁶⁸ an inapposite case that sanctioned the exercise of State police powers to authorize compulsory vaccination statutes. At the same time, the Court ignored a series of State cases dealing squarely with the Equal Protection question.⁵⁶⁹ Applying a primitive form of modern rational basis review, the Court determined the State had a legitimate legal and policy justification to sterilize Buck and promote the welfare of society by severing her fallopian tubes.⁵⁷⁰ Notably, the decision did not examine any scientific evidence to support its assertion that mental deficiencies are congenital.

Appellant Carrie Elizabeth Buck, a *teenager* who had been raped⁵⁷¹ and institutionalized was characterized by the Court as “a feeble-minded white woman . . . daughter of a feeble-minded mother . . . , and the mother of an illegitimate feeble-minded child.”⁵⁷² Reporters and scholars who met Buck before her death in 1983 all agreed that she was not “feeble-minded” as the Court had stated, but appeared to be a woman of normal intelligence.⁵⁷³ Furthermore, research revealed that Vivian, Buck’s daughter who lived until the age of eight, had been an average student in school and was not mentally disabled.⁵⁷⁴ Some have argued that the case itself was fraudulently pursued.⁵⁷⁵ In any event, one can hardly disagree with the view that what was done to Carrie Buck was gravely unjust and remains a stark blemish on American law.

565. *Id.* at 205.

566. *Id.* at 206–07.

567. *Id.* at 208.

568. *Id.* at 207 (citing *Jacobson v. Massachusetts*, 197 U.S. 11 (1905)).

569. *See id.* at 200; *see also* *Haynes v. Lapeer*, 166 N.W. 938, 939, 941 (Mich. 1918) (declaring Michigan’s sterilization law unconstitutional); *Smith v. Bd. of Exam’rs of Feeble-Minded*, 88 A. 963, 964, 967 (N.J. 1913) (striking, on Equal Protection grounds, New Jersey’s sterilization law); *Davis v. Berry*, 216 F. 414, 418 (S.D. Ia. 1914) (prohibiting the enforcement of vasectomies for criminals twice convicted of a felony in Iowa).

570. *Buck*, 274 U.S. at 205.

571. PAUL A. LOMBARDO, THREE GENERATIONS, NO IMBECILES: EUGENICS, THE SUPREME COURT, AND *BUCK V. BELL* 140 (2008).

572. *Buck*, 274 U.S. at 207.

573. *See* Gould, *supra* note 50, at 331, 336.

574. *Id.* at 337–38.

575. LOMBARDO, *supra* note 571, at 154–55.

Many have chronicled the history and legal implications of *Buck* in books⁵⁷⁶ and legal scholarship.⁵⁷⁷ Consequently, this Article will not belabor and rehash what has already been said about the case.⁵⁷⁸ The conventional view is that *Buck*'s holding is illegitimate because it rests on false science⁵⁷⁹ and incorrect moral and ethical principles.⁵⁸⁰ This Article rejects that conventional view and instead contends that *Buck* is not the result of false science, but instead of *deceptive simplicity*. In fact, as this Article argues below, *Buck*'s ruling is grounded more on deceptive simplicity than on the "science" of the time, which was greatly void of empiricism, reproducibility, adequate statistical methodology, and did not even come close to establishing the heredity and genetic contributions of intelligence.

To support this proposition, consider first and foremost the substantively porous decision published by the Court. Holmes cited not a single scientific source for the Court's lending of credence to the precarious notion that "heredity plays an important part in the transmission of insanity, imbecility, etc."⁵⁸¹ In fact, the Court was blatantly clear that its decision relied on "general declarations of the Legislature"⁵⁸² and "experience"⁵⁸³ showing the heritability of traits related to cognitive deficiencies. The "experience" Holmes referred to was quite probably the direct derivation of Galton's showing numerous instances in which illustrious men engender illustrious kindred.⁵⁸⁴ In other words, the Court did not even bother to consider the existing

576. For a good, detailed historical account of the events leading up to the Supreme Court litigation and the decision's aftermath, see *id.* at 149–55.

577. See, e.g., Robert J. Cynkar, *Buck v. Bell: 'Felt Necessities' v. Fundamental Values?*, 81 COLUM. L. REV. 1418 (1981); James C. Dugan, Note, *Conflict Between 'Disabling' and 'Enabling' Paradigms in Law: Sterilization, the Developmentally Disabled, and the Americans with Disabilities Act of 1990*, 78 CORNELL L. REV. 507 (1993); Paul A. Lombardo, *Disability, Eugenics, and the Culture Wars*, 2 ST. LOUIS J. HEALTH L. & POL'Y 57 (2008).

578. For example, some scholars have discussed *Buck*'s dismissal of the Equal Protection Clause as the "last resort of constitutional arguments," *Buck v. Bell*, 274 U.S. 200, 208 (1927). See, e.g., Nourse, *supra* note 50, at 115. Others contend that Equal Protection in state and lower federal courts preceding *Buck* actually afforded strong constitutional claims against involuntary sterilization. See Stephen A. Siegel, *Justice Holmes, Buck v. Bell, and the History of Equal Protection*, 90 MINN. L. REV. 106, 108 (2005).

579. See, e.g., Lombardo, *supra* note 577, at 69 n.84, 69 n.85, 70–71 n.90 (citing Res. 247, 149th Gen. Assem., Reg. Sess. (Ga. 2007), which referred to the "so-called science of eugenics" as a "pseudo-scientific movement"); Nourse, *supra* note 50, at 107 (arguing *Buck* is not part of constitutional law curricula partly because it "is seen as a case about a false science").

580. See, e.g., Gould, *supra* note 50, at 336, 338–39.

581. *Buck*, 274 U.S. at 206.

582. *Id.* at 207.

583. *Id.* at 206.

584. See GALTON 1st ed., *supra* note 508, at 6.

science. Instead, it wholly deferred to the Legislature and treated the heredity of insanity and imbecility as a foregone conclusion.

Consequently, the notion that *Buck's* holding was based on false science rests on an analytically precarious foundation. Simply put, *Buck* relied on *no* science at all.

The case epitomizes an instance where the Supreme Court allowed a State's erroneous scientific assertions to go unchallenged and ruled on the basis of those faulty assertions. Although the Court is not required to cross-examine every statement made by a legislative branch before properly ruling on a given issue, it ought to consider, at the very least, whether "general declarations" and "anecdotal experience" constitute unequivocal evidence that withstands constitutional scrutiny. Such analysis is imperative, more so in cases where fundamental rights may be curtailed. In light of its blank endorsement of compulsory sexual sterilization for mentally defective and undesirable individuals—all justified by public welfare pretenses—the *Buck* Court might as well have been acting as a lifeless extension of a State's legislative branch.

Had the Court bothered to critically examine and analyze the state of the science, it would have discovered that, contrary to popular belief at the time, heredity's role in cognition and other traits was highly inconclusive, contentious, and likely supported by flawed methods. On this point, perhaps one of the most prominent examples was the discovery of inheritance-independent genetic mutations by Thomas H. Morgan, the late Nobel Laureate, in 1910.⁵⁸⁵ Morgan observed that one white-eyed fruit fly had inexplicably appeared from a contained stock of wildtype⁵⁸⁶ red-eyed flies in his laboratory.⁵⁸⁷ The implications of this realization were that certain traits are not merely inherited, but rather appear spontaneously as a result of mechanisms—e.g., mutations—other than Mendelian genetics.

Morgan's observation and subsequent experiments using the white-eyed mutant fly provided the foundations for the establishment of the modern theory of the gene, which expanded and challenged the simple model of Mendelian inheritance⁵⁸⁸ established at the turn of the twentieth century.⁵⁸⁹

585. T.H. Morgan, *Sex Limited Inheritance in Drosophila*, 32 SCIENCE 120 (1910).

586 "Wildtype" refers to the most common phenotype for an organism in a natural breeding population. *Wildtype*, BIOLOGY ONLINE <http://www.biology-online.org/dictionary/Wildtype> [<https://perma.cc/2QPV-S5VU>] (last modified June 10, 2009).

587. Morgan, *supra* note 585, at 120.

588. Mendel's theory of inheritance was derived from his experiments of pea plants that displayed only one physical trait—e.g., seed color (green or yellow), plant height (tall or short), etc. Mendel challenged the existing view that all offspring were a combination of parental traits

Morgan, who initially supported but later renounced the eugenics movement⁵⁹⁰ after uncovering empirical scientific truth through his research, eloquently presented the problem of the modern interpretation of Mendelian inheritance when he stated:

[F]acts are being transformed into factors at a rapid rate. . . . The superior jugglery sometimes necessary to account for the result, may blind us, if taken too naïvely, to the common-place that the results are often so excellently “explained” because the explanation was invented to explain them. We work backwards from the facts to the factors, and then, presto! explain the facts by the very factors that we invented to account for them . . . yet I cannot but fear that we are rapidly developing a sort of Mendelian ritual by which to explain the extraordinary facts of alternative inheritance. . . . [I]t is only fair to state that those who are doing the actual work of progress along Mendelian lines are aware of the hypothetical nature of the factor-assumption. *But those who know the results at second hand and hear the explanations given, almost invariably in terms of factors, are likely to exaggerate the importance of the interpretations and to minimize the importance of the facts.*⁵⁹¹

In time, others too began to publicly oppose eugenics,⁵⁹² along with its racist and classist undertones,⁵⁹³ as a pseudoscience.⁵⁹⁴ However, despite the shouts of a few dissenting voices, eugenics became deeply rooted in American culture, garnering support from elites, scholars, and several institutions, including the Supreme Court.⁵⁹⁵ Between 1907, when the first sterilization statute passed in Indiana, and 1930, a total of twenty-three states had enacted

blended together. Among his scientific contributions are the laws of allele segregation and independent assortment. *See generally* Mendel, *supra* note 58, at 1–2, 4.

589. *See generally* THOMAS H. MORGAN ET AL., *THE MECHANISM OF MENDELIAN HEREDITY* 1–2 (1915).

590. *See* Garland E. Allen, *The Eugenics Record Office at Cold Spring Harbor, 1910–1940: An Essay in Institutional History*, 2 *OSIRIS* 225, 250 (1986).

591. T.H. Morgan, *What Are ‘Factors’ in Mendelian Explanations?*, 5 *J. HEREDITY* 365, 365 (1909).

592. Francis Galton was Charles Darwin’s half-cousin and is considered to be the father of eugenics. *See* LOMBARDO, *supra* note 571, at 7. He defined eugenics as “the science of improving stock . . . which, especially in the case of man, takes cognisance of all influences that tend . . . to give to the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable.” FRANCIS GALTON, *INQUIRY INTO HUMAN FACULTY AND ITS DEVELOPMENT* 17 n.1 (1883) (internal citation omitted).

593. *See* PAUL POPENOE, *APPLIED EUGENICS* 15–16 (1918) (“The distinguished father is likely to have a distinguished son, while the son of two ‘nobodies’ has a very small chance of becoming distinguished. . . . [T]he son of a distinguished judge ha[s] about one chance in four of becoming himself distinguished, while the son of a man picked out at random from the population ha[s] about one chance in 4,000.”).

594. *See, e.g.*, LOMBARDO, *supra* note 571, at 155–56 (describing views from a Harvey Wickham book, critical of outdated Mendelian inheritance, that was published just before the announcement of the *Buck* decision).

595. Paul A. Lombardo, *Taking Eugenics Seriously: Three Generations of ??? Are Enough?*, 30 *FLA. ST. U. L. REV.* 191, 203–07 (2003).

eugenical sterilization laws.⁵⁹⁶ By 1933, four years after *Buck*, twenty-two states introduced new sterilization laws.⁵⁹⁷ During the span of seven decades (1907–1979), a total of more than 65,000 sterilizations in thirty-two states took place in the United States.⁵⁹⁸

Morgan's conceptualization of second-hand explanations that lead to exaggeration, oversimplification, and a poor understanding of scientific progress is precisely the deleterious essence of deceptive simplicity, which is broader and more damaging than mere pseudoscience.

The distinction is crucial. Whereas false, or pseudo, science refers to a system of theories and rules configured to give the appearance of being grounded in scientific methodology,⁵⁹⁹ deceptive simplicity dangles from vague intuition derived from reductive explanations that strip logic beyond a bare minimum.

Accordingly, Galton's elaborate, hyperbolic, cognitive hereditability theses and explanations, which worked backwards "from the facts to the factors," were so "excellently explained"⁶⁰⁰ because he created a counterfeit theoretical basis to support his unscrupulous racist ideology. It was false science. In contrast, Holmes' opinion in *Buck* did not even attempt to embellish its reasoning with false science. *Buck* institutionalized compulsory sterilization using vague intuition born out of second-, third-, and fourth-hand reductive explanations that diminished heredity to a deceptively simple catchphrase *popularized by* false science: imbecility is a heritable disease. Consequently, *Buck* embodies a conclusory ruling bereft of legal or scientific reasoning. It was deceptive simplicity, bred to be more dangerous than false science. Indeed, the Nazi party relied on *Buck* and its deceptive simplicity to legitimize its eugenic agenda.⁶⁰¹

Pseudo-intellectual hogwash became the deceptive simplicity that propelled, maintained, and expanded the eugenics agenda. The

596. HARRY H. LAUGHLIN, THE LEGAL STATUS OF EUGENICAL STERILIZATION 7, 57 (1930).

597. Nourse, *supra* note 50, at 103 n.18 (quoting VICTORIA F. NOURSE, IN RECKLESS HANDS: SKINNER V. OKLAHOMA AND THE NEAR TRIUMPH OF AMERICAN EUGENICS 24 (2008)).

598. LOMBARDO, *supra* note 571, at xiii, 294 app. C.

599. Pseudoscience is defined as "a system of theories, assumptions, and methods erroneously regarded as scientific." *Pseudoscience*, MERRIAM-WEBSTER ONLINE DICTIONARY, <http://www.merriam-webster.com/dictionary/pseudoscience> [<https://perma.cc/RAT7-SH36>] (last visited Feb. 15, 2017).

600. Morgan, *supra* note 591, at 365.

601. See, e.g., TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS VOL. IV 1158–59 (1950) (publishing an extract from a document entered on behalf of Otto Hofmann, a high ranking SS officer and key contributor to Nazi Germany's eugenics laws, citing *Buck v. Bell*, 274 U.S. 200 (1927) to establish that Nazi eugenic practices during World War II were derived from race protection laws in other European countries and the United States).

historical account is crystal clear: *Buck* did not rely on false science; it was the product of pervasive deceptive simplicity concerning a rationale for the heritability of human cognitive abilities and mental deficiencies. No legitimate scientific debate existed regarding the simplistic pre-twentieth century view of Mendelian inheritance adopted by the Court in 1927.

At the time *Buck* made its way into the Supreme Court, eugenics was not a real scientific movement,⁶⁰² but rather a reductive political and social fad that fed off of outdated scientific theories, misinformation, and gossip. The propaganda had been de facto codified into popular culture by deceptive merchants with ulterior motives and dangerous agendas. And Justices of the US Supreme Court, despite all their education and intellect, proved to be highly susceptible to it.

Given the fact that *Buck* lacked any constitutional⁶⁰³ or scientific support for its holding and came thickly veiled with deceptive simplicity, the decision amounts to no more than institutionalized legal quackery built upon social and scientific quackery.

D. Forging a Path Forward

This Article's genome editing primer coupled with the proposed normative legal framework makes the case that a jurisprudence of scientific empiricism is the best available weapon against the deleterious harms of deceptive simplicity. Judicial review is in dire need of structure when addressing questions of science in law.

One promising sign that the Supreme Court is open to adopting a jurisprudence of scientific empiricism is the 2013 decision in *Myriad*.⁶⁰⁴ The case contemplated whether isolated DNA⁶⁰⁵ segments

602. For instance, during the 1920s, only approximately 10 percent of members of the Advisory Council of the American Eugenics Society were trained geneticists. Cynkar, *supra* note 577, at 1426.

603. See discussion *supra* notes 565–70 and accompanying text.

604. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2110 (2013).

605. In *Myriad*, the Supreme Court considered the patentability of two types of DNA molecules: DNA fragments isolated from naturally occurring genomic DNA and complementary DNA (cDNA). The Court held that genic sequences isolated from genomic DNA were not patent eligible under section 101 because they are products of nature. *Id.* at 2120. In contrast, the Court held that cDNA was patent eligible under section 101 because it is “not naturally occurring.” *Id.* at 2119. The decision to distinguish between these types of DNA molecules raises some uncertainty about the patent eligibility of other types of DNA molecules under section 101, many of which are used in biotechnological research. See *id.* at 2120 (withholding judgment on the applicability of section 101 to DNA in which the order of the naturally occurring nucleotides has been altered because it “presents a different inquiry”).

from naturally occurring genes are patent eligible under 35 U.S.C. § 101.⁶⁰⁶ Justice Thomas prefaced the Court's unanimous opinion with a foundation of genetic concepts relevant to the question presented.⁶⁰⁷ Despite some inaccuracies related to protein synthesis,⁶⁰⁸ RNA processing,⁶⁰⁹ and DNA non-coding regions,⁶¹⁰ the Court more or less accurately described the science—certainly enough to competently rule on the merits. The Court's efforts to ground its decision in scientific facts should be commended.⁶¹¹ However, other recent

Similarly, although the Court determined cDNA was patent eligible under section 101, it expressed no opinion regarding cDNA's ability to withstand the test of other statutory requirements under patent law. *See id.* at 2119 n.9. While cDNA has cleared section 101 hurdles, potential future sections 102, 103, and 112 challenges could ultimately render it unpatentable.

Lastly, it bears noting that *Myriad* is important in ways we do not yet fully understand. Future application of *Myriad*'s holding is likely to have significant implications not only for section 101 litigation, but other areas of patent law.

606. *Id.* at 2111.

607. *Id.* at 2111–12.

608. "Sequences of DNA nucleotides contain the information necessary to create strings of amino acids, which in turn are used in the body to build proteins." *Id.* at 2111. This statement is incorrect because amino acid "strings" are *not* used in the body to build proteins. Amino acid "strings" are the proteins themselves in an unfolded state. As ribosomes synthesize polypeptide chains ("strings"), a series of intermolecular forces—ionic interactions, hydrophobic effect, hydrogen bonding, and others—begin the process of protein folding. Thus, the strings of amino acids *fold* into proteins. Proteins can come together to *form* ("build") complexes. *Protein Structure Jmols: Primary Structure*, CTR. BIOMOLECULAR MODELING, <http://cbm.msoe.edu/includes/modules/jmolProteinStructure/primarystructure.html> [https://perma.cc/B6U5-K62V] (last visited Feb. 15, 2017). Alternatively, the Court could have been referring to messenger RNA (mRNA) molecules, which are used by the ribosomes as *templates* to create ("build") the strings of amino acids. CHRIS R. CALLADINE ET AL., UNDERSTANDING DNA: THE MOLECULE AND HOW IT WORKS 14 (3rd ed. 2004).

609. "Transcription results in a single strand RNA molecule, known as pre-RNA." *Myriad*, 133 S. Ct. at 2111. This statement refers to the transcription of DNA into *primary transcripts*—a single stranded RNA molecule that has not been processed. Suzanne Clancy, *DNA Transcription*, 1 NATURE EDUC. 41 (2008). A primary transcript is later processed to yield various forms of RNA molecules—e.g., mRNAs, piRNAs, miRNAs, tRNAs, lncRNAs, rRNAs, etc. Anita Quintal Gomes et al., *Non-Coding RNAs: Multi-Tasking Molecules in the Cell*, 14 INT'L J. MOLECULAR SCI. 16010 (2013). The Court may have been referring to mRNA processing, in which a *pre-mRNA* (not pre-RNA) molecule undergoes processing to become a mature mRNA. *Introducing mRNA Processing*, VIRTUAL CELL ANIMATION COLLECTION, <http://vcell.ndsu.edu/animations/mrnaprocessing/index.htm> [https://perma.cc/7FGX-T9GW] (last visited Feb. 15, 2017).

610. "Nucleotides that do not code for amino acids . . . are known as 'introns.'" *Myriad*, 133 S. Ct. at 2111. This statement is factually inaccurate because many non-coding nucleotides exist in promoter, enhancer, silencer, and other regulatory regions of the genome that are not introns. The Court may have been referring to non-coding nucleotides within a gene's open reading frame (ORF) that are spliced out during processing. Lucy W. Barrett et al., *Regulation of Eukaryotic Gene Expression by the Untranslated Gene Regions and Other Non-Coding Elements*, 69 CELLULAR & MOLECULAR LIFE SCI. 3613 (2012).

611. So should US District Judge Sweet, who published a substantive section on the relevant scientific concepts in his lower court ruling. *See Ass'n for Molecular Pathology v.*

decisions⁶¹² suggest that *Myriad* may have been an outlier case as it dealt with patent law, which is fundamentally scientific and highly technical.

Both the legal and scientific communities should strive to eradicate the influence of deceptive simplicity. Such a task is not monistic and will require interdisciplinary cooperation. For example, the *Buck*-era eugenics movement was successful partly because scientists with the most relevant knowledge were largely confined to a life of research and failed to effectively communicate with the public to correct scientific misperceptions. At the same time, the legal community's disengagement from science was partly responsible for the failure to overcome scientific deceptive simplicity in the judiciary. Building a system structured in a manner that encourages lawyers to weld scientific empiricism and jurisprudence would greatly benefit society.

Many questions will be raised and answered regarding numerous aspects of genome editing biotechnologies in the near future. Lawyers and scientists must be careful to properly frame those questions rationally and fairly. An example of a legitimate issue regarding genome editing is whether the technology will be safe for clinical use in the near future.⁶¹³ However, constructing arguments based on impracticalities when supporting or opposing technological advances should have no place in jurisprudential calculus. Seeking to ban a genome editing technology because of a perceived threat of the possibility of introducing designer babies, when no evidence exists to suggest that the technology is capable of delivering such outcomes, makes as much sense as seeking to ban space travel because we might encounter an extraterrestrial race that will want to annihilate

USPTO, 702 F. Supp. 2d 181, 192–99 (S.D.N.Y. 2010), *aff'd in part, rev'd in part in Myriad*, 133 S. Ct. 2107.

612. See, e.g., *Burwell v. Hobby Lobby Stores, Inc.*, 134 S. Ct. 2751, 2759 (2014) (holding closely held corporations may be exempt from the contraceptive mandate in the Patient Protection and Affordable Care Act of 2010 based on the sincerely held religious beliefs of owners). In *Hobby Lobby*, Justice Alito, writing for the Court, erroneously stated that all four methods at issue in *Hobby Lobby* may operate after an egg's fertilization, which contradicts the scientific empirical evidence available both at the time the case was decided and today. *Id.* at 2777; see also, U.S. Food & Drug Admin., *Birth Control: Medicines to Help You*, FDA, <https://www.fda.gov/forconsumers/byaudience/forwomen/freepublications/ucm313215.htm> [<https://perma.cc/X8RT-ZGPW>] (last updated Sept. 8, 2016) (providing some information on FDA-approved and cleared methods for birth control).

613. Jesse Gelsinger, an eighteen-year-old man suffering from an X-linked genetic disease characterized by an inability to metabolize ammonia in the liver, died on September 17, 1999, after receiving a dose of gene therapy under a clinical trial run by the University of Pennsylvania. See Rick Weiss & Deborah Nelson, *Teen Dies Undergoing Experimental Gene Therapy*, WASH. POST, Sept. 29, 1999, at A01. He was the first person reported to have died from an experimental gene therapy treatment. *Id.*

humankind. At this moment in time, designer babies are as hypothetical as extraterrestrial monsters.

Rather than advocating haphazard bans on genome editing technologies as some have proposed,⁶¹⁴ this Article advocates for a system that lays a doctrinal foundation to proliferate rejection of deceptive simplicity.⁶¹⁵ This concept is more sensible because, unlike outright banning technologies that the public is unfamiliar with, it promotes broad debate of the issues and does not dictate unilaterally what should or should not be permissible in society.

In sum, the normative framework advocated here seeks to cultivate and expand *Myriad's* roots of scientific empiricism. This approach is broadly applicable to other fields of law in which scientific inquiry may play important or dispositive roles.

VI. CONCLUSION

CRISPR systems and their future progeny hold the power to change the world. This nascent biotechnology has incredible potential, but its future is filled with uncertainty regarding how the law will treat it going forward. The scientific community has made efforts to begin a dialogue about genome editing technologies and their implications for the future of humankind. However, the legal community has yet to fully address the significant challenges that genome editing will pose for law and policy making. The void in legal scholarship is quickly growing to the detriment of society. This Article marks a first step toward closing the gap between science and law regarding this momentous scientific breakthrough.

Cooperation between lawyers and scientists will be pivotal as genome editing technologies continue to develop and mature in an increasingly globalized and interconnected world.⁶¹⁶ Thus, a uniform doctrinal structure is sorely needed to address future questions that will be raised by the ensuing applications of CRISPR-based technologies. To that end, this Article presents a robust and comprehensive primer on genome editing as a resource and proposes a jurisprudence of scientific empiricism as a normative legal framework to broadly address questions of science in law. This paradigm seeks to promote a system in which lawyers are able to fuse scientific

614. See Lanphier et al., *supra* note 28 and accompanying text.

615. If there is anything this Article would support banning, it would be the use of the term “designer babies”—alongside its derivations—in future discussions concerning genome editing technologies. See discussion *supra* Part V.A. This Article’s position is that it makes no sense to pollute debate of scientific advances with the use of such misleading terminology.

616. See Enriquez, *supra* note 24, at 1289–91, 1336.

empiricism and jurisprudence to combat scientific illiteracy, as well as the oversimplification and misinterpretation of scientific advances, which are all common substantive impediments to constructive debate. It is time to adhere to higher standards in this regard.

Taken together, a compilation of the genome editing research performed globally over the last three years begins to paint a very specific portrait: genome editing biotechnologies, and CRISPR systems in particular, represent not only tools for basic research, but gateways to significant medical and scientific breakthroughs to come. This Article provides a foundation for a series of forthcoming articles⁶¹⁷ that will analyze many of the prospective benefits and risks associated with the use of genome editing biotechnologies from statutory, constitutional, international, ethical, regulatory, egalitarian, and policy standpoints. The goal is to jumpstart a scholarly dialogue, highlight the crucial roles that law, science, and public policy will play in the development of this emerging technology, and encourage debate grounded in reason rather than baseless conjecture.

We owe it to ourselves and future generations to treat this remarkable new technology with the gravitas it deserves.

617. See, e.g., Enríquez, *supra* note 31. Collectively, these works seek to build a foundation for what may be considered "genome editing law" in general, and "CRISPR law" in particular.

