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Shining City on a Hill at the Edge of Tomorrow: CRISPR-Cas9, Dickey-Wicker, and the Inner Space Race

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SHINING CITY ON A HILL AT THE EDGE OF TOMORROW: CRISPR-CAS9, DICKEY-WICKER, AND THE INNER SPACE RACE

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PREFACE

"As to the Soviet satellite, we congratulate Soviet scientists upon putting a satellite into orbit."
-Dwight D. Eisenhower, Oct. 9, 1957[1]

On October 4, 1957, the Union of Soviet Socialist Republics became the first world power to successfully put a human-made satellite into Earth's orbit.[2] The Sputnik I satellite was modest by today's standards: it was less than two feet in diameter, weighed less than 200 pounds,[3] and was only capable of emitting pulsed radio signals.[4] By many accounts, it was little more than a large beach ball floating around and around the Earth.[5] Nevertheless, the propaganda value of the Soviet achievement in the burgeoning Cold War was significant and unmistakable.[6] The Space Race had begun, and the Soviets had won the first leg of it. The American response was swift. On January 31, 1958—119 days after the Sputnik I launch—Explorer-I successfully

1. Dwight D. Eisenhower, President of the United States, Statement by the President Summarizing Facts in the Development of an Earth Satellite by the United States (Oct. 9, 1957), *available at* https://www.eisenhower.archives.gov/research/online_documents/sputnik/10_9_57.pdf.

2. *Sputnik 1*, NASA, https://www.nasa.gov/multimedia/imagegallery/image_feature_924.html (last visited Feb. 5, 2018).

3. *Sputnik and The Dawn of the Space Age*, NASA, https://history.nasa.gov/sputnik/ (last visited Feb. 5, 2018).

4. Paul Dickson, *Sputnick's Impact on America*, PBS (Nov. 11, 2017), http://www.pbs.org/wgbh/nova/space/sputnik-impact-on-america.html, ("Listen now, for the sound that forevermore separates the old from the new," reported the NBC radio network announcer. *Id.*).

5. *Id.*

6. *Id.* ("No event since Pearl Harbor set off such repercussions in public life," WALTER A. MCDOUGALL, THE HEAVENS AND THE EARTH: A POLITICAL HISTORY OF THE SPACE AGE (Johns Hopkins University Press 1997)).

launched and entered Earth's orbit.[7] It was the result of a multi-disciplinary collaboration between civilian and military scientists, consisting of Dr. William H. Pickering and the Jet Propulsion Laboratory at the California Institute of Technology, Dr. James Van Allen[8] of the University of Iowa, and Dr. Wernher von Braun's United States Army Redstone Arsenal team.[9] The United States Congress also acted swiftly: on July 29, 1958, President Eisenhower signed into law the National Aeronautics and Space Act,[10] establishing, among other things, the National Aeronautics and Space Council,[11] and the civilian National Aeronautics and Space Administration ("NASA").[12] Its 1958 budget was $89 million, 0.1 percent of the Federal Budget. But by the height of the Space Race in 1966, NASA's budget totaled nearly $6 billion, or 4.41 percent of the Federal Budget.[13] The Race to master Outer Space had begun and, although the United States was behind, it was running to win.

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7. *Explorer-I and Jupiter-C, The First United States Satellite and Space Launch Vehicle*, NASA, https://history.nasa.gov/sputnik/expinfo.html (last visited Feb. 5, 2018).

8. The same Van Allen for which the subsequently-discovered eponymous radiation belts are named; *See James A. Van Allen*, *in* ENCYCLOPÆDIA BRITANNICA (2018).

9. *Sputnik and The Dawn of the Space Age*, *supra* note 3.

10. National Aeronautics and Space Act of 1958, Pub. L. No. 85-568, 72 Stat., 426 (unamended).

11. *Id.* at § 201(a)(1)-(6) (comprising of the President, Secretary of State, Secretary of Defense, NASA Administrator, the Chairman of the Atomic Energy Commission, and not more than one additional government appointee).

12. National Aeronautics and Space Act of 1958 at § 204(a) (showing that the 1958 Act also provides for a Civilian-Military Liaison Committee comprising a Presidentially-appointed Chairman, one or more representatives from the Departments of Defense, Army, Navy, and Air Force, as assigned by the Secretary of Defense, and NASA-assigned representatives, equal in number to the military members).*See also* Gerhard Peters & John T. Wooley, *Dwight D. Eisenhower: Statement by the President Upon Signing the National Aeronautics and Space Act of 1958*, THE AMERICAN PRESIDENCY PROJECT, http://www.presidency.ucsb.edu/ws/?pid=11146 (noting that the "nucleus" for NASA was rooted in the 1915-established National Advisory Committee for Aeronautics).

13. *NASA Budgets: US Spending on Space Travel Since 1958 UPDATED*, THE GUARDIAN, https://www.theguardian.com/news/datablog/2010/feb/01/nasa-budgets-us-spending-space-travel (last visited Jan. 2, 2018). Adjusted for inflation in January 2017: $89 million in Jan. 1958 = $755.69 million; $5.933 billion in Jan. 1966 = $45.307 billion. *See* CPI Inflation Calculator, *available at* https://data.bls.gov/cgi-bin/cpicalc.pl?cost1=5933&year1=196601&year2=201701)).

INTRODUCTION

"One test result is worth one thousand expert opinions."
-Wernher von Braun[14]

One of the many fascinating and potentially revolutionary developments in the field of biomedical research in recent years has been the development of molecular tools that enable scientists to engage in Targeted Genomic Editing ("TGE"). TGE empowers scientists to efficiently and precisely modify or delete a gene of interest or to add new genetic sequences to a target of interest.[15] Recently, through the combined efforts of many United States and international researchers, a system known as CRISPR-Cas9 has emerged as both a relatively inexpensive and more precise method of TGE than any previously recognized in the field.[16] With the discovery of CRISPR-Cas9, the potential for TGE-mediated gene therapies has never been greater. It is likely that, with time and effort, TGE may revolutionize medicine as we know it, giving new hope to both current patients and carriers of heritable genetic disorders. TGE could also result in "human enhancement."[17] The very idea that we could "exert control over human heredity with this technique"[18] raises questions as to whether tinkering

14. *International Space Hall of Fame, Wernher Von Braun,* NEW MEXICO MUSEUM OF SPACE HISTORY, http://www.nmspacemuseum.org/halloffame/detail.php?id=29 (last visited Feb. 5, 2018) (von Braun is thought to have said this in 1972; *see* Duncan Haughey, *10 More Quotes That Make You a Better Project Manager*, PROJECT SMART (Feb. 23, 2013), https://www.projectsmart.co.uk/10-more-quotes-that-make-you-a-better-project-manager.php.

15. *See* Jennifer Walker-Daniels, *Genomic Engineering*, 3 MATERIALS & METHODS (last updated Aug. 2, 2016), *available at* https://www.labome.com/method/Genomic-Engineering.html#ref29.

16. *See* Le Cong, et al., *Multiplex Genome Engineering Using CRISPR/Cas System*, 339 SCIENCE 819, 819 (2013). *See also* Prashant Mali, et al., *RNA-Guided Human Genome Engineering via Cas9*, 339 SCIENCE 823, 823 (2013).

17. *See* David Masci, *Human Enhancement: The Scientific and Ethical Dimenstions of Striving for Perfection*, PEW RES. CTR. INTERNET & TECH. (July 26, 2016), http://www.pewinternet.org/essay/human-enhancement-the-scientific-and-ethical-dimensions-of-striving-for-perfection/; *see also Human Enhancement*, INST. ETHICS & EMERGING TECH., https://ieet.org/index.php/tpwiki/human_enhancement (last visited Mar. 27, 2018) (defining human enhance-ment as referring to "any attempt to temporarily or permanently overcome the current limitations of the human body through natural or artificial means").

18. *See* Nathaniel Comfort, *Can We Cure Genetic Diseases Without Slipping Into Eugenics?* THE NATION (July 16, 2015), https://www.thenation.com/article/can-we-cure-genetic-diseases-without-slipping-into

with the blueprint of life is even a good idea to begin with. But only those who have mastered the technology will know the full breadth of its scope. Are we capable of mastering the "Inner Space" of our cells? If we can, should we do so? If this nation is not the first to know *if* we can, will we be able to decide *whether* we should?

The race to explore and, eventually, master this "Inner Space" has already begun. On October 28, 2016, a team of researchers in China initiated the first clinical trial to administer cells containing genes edited with the "revolutionary CRISPR-Cas9 technique."[19] In response to this, Dr. Carl June of the University of Pennsylvania remarked that this would "trigger a biomedical 'Sputnik 2.0'… between China and the United States."[20] Clinical researchers in the United States expect to begin CRISPR-Cas9 human trials within the next year,[21] three years behind their Chinese counterparts.[22] This lag is owed, in part, to the "few[er] regulatory hurdles [in China] to testing it on humans."[23] After the tragic death in 1999 of Jesse Gelsinger,[24] a profound "chilling effect

eugenics/ (quoting American biologist and 1975 Nobel laureate in Physiology or Medicine David Baltimore).

19. David Cyranoski, *CRISPR Gene-Editing Tested in a Person for the First Time*, NATURE NEWS (Nov. 15, 2016), http://www.nature.com/news/crispr-gene-editing-tested-in-a-person-for-the-first-time-1.20988; *see also China Is Surging Ahead In The Race To Beat Cancer With CRISPR,* WALL STREET PIT (2017), https://www.wsj.com/articles/china-pushes-ahead-with-human-gene-trials-1493380057 (reporting Jia Wei at Nanjing Clinical Cancer Institute initiated the second such trial on Apr. 28, 2017).

20. *See* Cyranoski, *supra* note 19.

21. Preetika Ranaet et al., *China Unhampered by Rules, Races Ahead in Gene-Editing Trials*, THE WALL STREET JOURNAL (Jan. 21, 2018), https://www.wsj.com/articles/china-unhampered-by-rules-races-ahead-in-gene-editing-trials-1516562360; *see also* Emily Mullin, *CRISPR in 2018: Coming to a Human Near You*, MIT TECH. REV. (Dec. 18, 2017).

22. *Id.*

23. *Id.*

24. Jesse was an 18-year old afflicted with ornithine transcarbamylase deficiency ("OTCD"), and was participating in an experimental gene therapy trial at the Institute for Human Gene Therapy ("IHGT") at the University of Pennsylvania. *See Institute for Human Gene Therapy Responds to FDA*, ALMANAC BETWEEN ISSUES (Feb. 14, 2000), *https://almanac.upenn.edu/archive/between/FDAresponse.html.* He "died from complications of vector administration," resulting in "substantial reform[]" in regulatory oversight of human subjects research. *See* James M. Wilson, *Lessons Learned from the Gene Therapy Trial for Ornithine Transcarbamylase Deficiency*, 96 MOLECULAR GENETICS & METABOLISM 151, 151, 153 (2009).

on the field"[25] of gene therapy occurred,[26] but clinical researchers have been gradually returning to the prospect of modifying genes in humans to ameliorate disease. For example, on November 13, 2017, California clinicians treated Brian Madeux with an infusion of "billions of copies of a corrective gene and a genetic tool to cut his DNA in a precise spot."[27] Brian suffers from Hunter syndrome, an inherited condition resulting from a mutation in a gene[28] for an enzyme[29] that cells need to break down large sugar molecules.[30] Because of Hunter syndrome, Brian has had to undergo twenty-six operations—approximately one surgery for each 1.6 years of life.[31] This trial, using a more tried TGE tool in Zinc Finger Nucleases ("ZFNs")[32], has given Brian and others renewed hope that their disease state may not be one of permanence.[33]

25. JAMES KOZUBEK, MODERN PROMETHEUS: EDITING THE HUMAN GENOME WITH CRISPR-CAS9 157 (2016) (quoting Richard C. Mulligan, Ph.D., Harvard Stem Cell Institute).

26. Indeed, there has even been a chilling effect in the language used to refer to such studies, as some scientists and bioethicists prefer the term "gene transfer" as more accurate than of "gene therapy," as "therapy" implies effective/efficacious treatment that is out of the experimental stages. *See, e.g.*, Ranaet et al., *supra* note 21.

27. Marilynn Marchione, *AP Exclusive: US Scientists Try 1st Gene Editing in the Body*, ASSOCIATED PRESS (Nov. 15, 2017), https://www.apnews.com/4ae98919b52e43d8a8960e0e260feb0a/AP-Exclusive:-US-scientists-try-1st-gene-editing-in-the-body; *see also* Jocelyn Kaiser, *A Human has been Injected with Gene-Editing Tools to Cure His Disabling Disease. Here's What You Need to Know*, SCIENCE (2017), http://www.sciencemag.org/news/2017/11/human-has-been-injected-gene-editing-tools-cure-his-disabling-disease-here-s-what-you.

28. *See* Genetics Home Reference, *Mucopolysaccharidosis Type II*, U.S. NAT'L LIBR. MED., NIH, https://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-ii#genes (last visited Feb. 5, 2018).

29. *See id.*

30. *Id.*

31. Marchione, *supra* note 27.

32. *See* Walker-Daniels, *supra* note 15.

33. *Id.* Said Madeux after the procedure: "I'm nervous and excited, I've been waiting for this my whole life, something that can potentially cure me."

TGE, as a molecular tool, may be employed in a variety of organisms, including humans. Two routes of directing therapies exist for TGE: one, in gene transfers aimed to treat patients living with myriad genetic disorders, or two, to modify the human germline: that is, the sex cells (sperm and egg) which form an embryo during the process of fertilization.[34] In bridging the gap between the laboratory bench and the patient's bedside, researchers must be empowered to study closely the utility of TGE in a human context, including on human embryos. Unfortunately, current federal law and regulation of federal funding of scientific research precludes TGE utilizing human embryos, an effective barrier to innovation.[35] The Dickey-Wicker Amendment, incorporated into annual Congressional appropriations bills since 1996, prohibits appropriated funding from being used to conduct research in which human embryos are destroyed.[36] The National Institutes of Health ("NIH") distributes federal funding of biomedical research with more than 80 percent of its $32.3 billion annual budget going to research universities and institutions.[37] NIH Guidelines presently comply with established law, noting that the agency " . . . will not at present entertain proposals for germ line alteration."[38] By contrast, at least three international governments—

34. *See generally* R.C. Wykes & G. Lignani, *Gene Therapy and Editing: Novel Potential Treatments for Neuronal Channelopathies*, 132 NEUROPHARMACOLOGY 108 (2018).

35. This is not to say there exist *no* options for scientists to secure funding for these kinds of projects. Private funds may be available, as well as in several states, where State Initiatives have been authorized over the years to fund stem cell and other embryonic research. *See generally* CONG. RES. SERV., DOMESTIC SOC. POL'Y DIVISION, *Stem Cell Research: State Initiatives* (May 19, 2006). The California Stem Cell Initiative, under the California Institute for Regenerative Medicine ("CIRM") is one such example of a State Initiative (*see, e.g.,* Joel W. Adelson & Joanna K. Weinberg, *The California Stem Cell Initiative: Persuasion, Politics, and Public Science*, 100 AM. J. PUB. HEALTH 446, 446 (2010)).

36. Embryos, Pub. L. No. 104-99, § 128, 110 Stat. 34 (1996).

37. Or, put differently, more than $25.84 billion *per annum*. *See What We Do: Budget*, NIH, (2017), https://www.nih.gov/about-nih/what-we-do/budget (last visited Jan. 30, 2018).

38. Francis S. Collins, Director, NIH, *Statement on NIH Funding of Research Using Gene-Editing Technologies in Human Embryos*, NAT'L INST. OF HEALTH (Apr. 28, 2015), https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos [hereinafter *Collins Statement*].

the People's Republic of China,[39] the United Kingdom,[40] and Sweden[41]—have tentatively embraced the idea by funding research projects that include CRISPR-Cas9 experimentation on human embryos, and at the same time pushing the United States even further behind in this 'Inner Space Race.'

If we consider ourselves to be—and if we are intent on remaining—the preeminent intellectual superpower of the world, we must embrace a national policy that, at least, opens the door to contemplating federally-funded embryonic research with respect to TGE, and accelerates research and development in this area. It is in both the national interest—and the public interest—to allocate the requisite resources to develop this technology and its likely successors. If we fail to do so, we risk: (1) falling behind more ambitious nations who seek to know, as an unambiguous matter of government policy, the metes and bounds of TGE; (2) being dictated to by those nations about what should and should not be done once the technology has been mastered; and (3) prospectively forfeiting subsequent intellectual property rights, including the right to exclude, likely to result from the fruits of the scientific exercise.[42] Our national interest demands that such reasonable action be taken as to both enable and empower our scientific community to more effectively chart this potential "final frontier" of Inner Space.

This Note advocates for the federal government funding of TGE experimentation on human embryos, and recommends additional funding to accelerate scientific development and inquiry. It also reconsiders the question of prohibiting the federal funding of embryonic experimentation in a controlled research environment, while suggesting ways of overcoming the short- and medium-term ethical questions certain to arise. **Part I** will provide a brief scientific and historical

39. *See* David Cyranoski & Sara Reardon, *Embryo Editing Sparks Epic Debate*, NATURE NEWS (Apr. 29, 2015), http://www.nature.com/news/embryo-editing-sparks-epic-debate-1.17421#/b1.

40. *See* Ewen Callaway, *UK Scientists Gain Licence to Edit Genes in Human Embryos*, NATURE NEWS (Feb. 1, 2016), https://www.nature.com/news/uk-scientists-gain-licence-to-edit-genes-in-human-embryos-1.19270.

41. *See Interview with Fredrik Lanner Who is CRISPR'ing Healthy Human Embryos*, THE NICHE: KNOEPFLER LAB STEM CELL BLOG, (Sep. 26, 2016), *available at* https://ipscell.com/2016/09/interview-with-fredrik-lanner-who-is-crispring-healthy-human-embryos/ [hereinafter *Lanner Interview*].

42. Of the total 589,410 total US Utility Patent filings in 2015, 301,075 or more than 51% were filed by inventors outside of the United States. *Number of Utility Patent Applications Filed in the United States, By Country of Origin, Calendar Years 1965 to Present*, U. S. PATENT & TRADEMARK OFFICE, (2018), https://www.uspto.gov/web/offices/ac/ido/oeip/taf/appl_yr.htm.

background of TGE, emphasizing CRISPR-Cas9. **Part II** will discuss recent and ongoing developments at home and abroad and demonstrate the risk of an emerging knowledge gap in this field. **Part III** will discuss where the debate stands in this country, and examine the barriers to research in this field. Finally, **Part IV** will outline a number of recommendations in view of Part III, and how we might overcome legitimate concerns about what kinds of research are in the public and national interest.

I. ON TARGETED GENOME EDITING: TOWARDS MASTERING (AND POSSIBLY REDESIGNING) THE BLUEPRINT OF LIFE; A "BRIEF" HISTORY OF CRISPR-CAS9 DEVELOPMENT

"I have learned to use the word 'impossible' with the greatest caution."
-Wernher von Braun[43]

TGE, also referred to as genome engineering, was first recognized by *Nature Methods* as "Method of the Year" in 2011.[44] The genome refers to an organism's entire deoxyribonucleic acid ("DNA") sequence, which is arranged by a double helical base that pairs between two of four nucleotide bases: adenine (A), thymine (T), cytosine (C), and guanine (G). Approximately three billion base pairs make up the human genome and are arranged into twenty-three pairs of chromosomes contained within the nucleus of all human cells. Within these chromosomes, DNA sequences form functional units known as genes that provide the blueprints for proteins to carry out cellular functions.[45]

43. Quoted by Michael Yarus, in *Life From an RNA World: The Ancestor Within* (2010).

44. Nature Publishing Group, *Method of the Year 2011*, 9 NATURE METHODS 1, 1 (2012), *available at* http://www.nature.com/nmeth/journal/v9/n1/full/nmeth.1852.html [hereinafter *Method 2011*]. *Nature Methods* is noted by the NIH as a "high-impact journal," a highly influential journal in the field of medical and biological research. The *Nature* family of journals includes 11 of the top 20 high-impact journals according to the NIH. *See High Impact Journals*, NAT'L INST. ENVTL. HEALTH SCI., https://tools.niehs.nih.gov/srp/publications/highimpactjournals.cfm (last visited Mar. 5, 2018).

45. "Francis Crick's 'central dogma' of molecular biology, put simply, is [. . .] 'DNA makes RNA, RNA makes proteins, proteins make us.'" *See* Sarah A. Leavitt, *Deciphering the Genetic Code: Marshall Nirenberg*, OFFICE OF NIH HISTORY (2010), https://history.nih.gov/exhibits/nirenberg/glossary.htm. *See also* Francis Crick, *On Protein Synthesis*, *in* SYMPOSIA OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY, NUMBER XII: THE BIOLOGICAL REPLICATION OF MACROMOLECULES, 138-63 (1958). Although the actual science of molecular biology has been found to be far

The genome is simultaneously the blueprint for and the manufactory of life. Like any good factory, the genome has undergone renovations throughout evolutionary time. TGE has the potential to technologically accelerate such renovations.

Essentially, TGE enables scientists to "introduce targeted, tailored changes into the genomes of several species."[46] Considered a "reverse genetics" approach, TGE effectively enables scientists to synthetically engineer particular gene sequences of interest.[47] The researcher may then analyze the subsequent phenotypic[48] consequences of that engineering. Reverse genetics is contrasted with the classical, "forward genetics" approach, where scientists begin by observing a mutant phenol-type in an organism, and then identifying the relevant mutation.[49] Reverse genetics afford greater flexibility and precision to researchers, because with reverse genetics, she can create the cause[50] and analyze the effect, rather than observe an effect and study the cause.[51]

Until recently, the three major methods for TGE were DNA binding protein-based transcription activator-like effector nucleases ("TALENs"),[52] ZFNs,[53] and meganucleases ("MGNs").[54] The CRISPR/ Cas-9 system is the "new kid on the block" in the realm of TGE, though it has been

more complex than the central dogma articulated by Crick in 1958, the essential principle remains substantially true.

46. *Method 2011*, *supra* note 44.

47. *Reverse Genetics*, *in* AN INTRODUCTION TO GENETIC ANALYSIS (7th ed. 2000), *available at* https://www.ncbi.nlm.nih.gov/books/NBK21843/.

48. "Phenotypic" means of or relating to phenotypes, or the observable features of or differences between organisms. Often contrasted with genotypic. *Phenotypic*, OXFORD ENGLISH DICTIONARY (3rd Ed., 2005), http://www.oed.com/view/Entry/262706?redirectedFrom=phenotypic#eid.

49. *Reverse Genetics, supra* note 47.

50. By introducing a mutation in a gene or DNA sequence of interest. *See id.*

51. *Id.*

52. *See* Jean-Paul Iyombe-Engembe & Jacques P. Tremblay, *The Advances and Challenges of Gene Therapy for Duchenne Muscular Dystrophy*, 1 J. GENETICS MED. GENE THERAPY 19, 20 (2017).

53. *Id.*

54. *Id.*

studied around the world and as far back as 1993.[55] Francisco Mojica[56] and colleagues studied the Clustered Regularly Interspaced Short Palindromic Repeats ("CRISPR") for a number of years.[57] They predicted that CRISPR sequences function as a sort of prokaryotic[58] immune system[59], utilized to fend off infection by foreign organisms. In 2005, Alexander Bolotin and colleagues found that an interesting

55. In 1993, Francisco Mojica and colleagues at the University of Alicante, Spain, came upon a previously unobserved DNA fragment while studying the halophilic (meaning grows in or tolerates saline conditions; halophilous. *See Halophilic*, OXFORD ENGLISH DICTIONARY (1976), *available at* http://www.oed.com/view/Entry/83636?redirectedFrom=halophilic#eid.Archaeal microbe *Haloferax mediterranei*. *See* Francisco Mojica, *Transcription at Different Salinities of Haloferax mediterranei Sequences Adjacent to Partially Modified PstI* Sites, MOLECULAR MICROBIOLOGY 613 (1993) [hereinafter Mojica 1993]. This fragment comprised "multiple copies of a near-perfect, roughly palindromic, repeated sequence of 30 bases, separated by spacers of roughly 36 bases—that did not resemble any family of repeats known in microbes." *See* Eric S. Lander, *The Heroes of CRISPR.* 164 CELL 18, 21-22 (2016). *See also CRISPR Timeline,* THE BROAD INST., https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-timeline (last visited Jan 23, 2017) [hereinafter *CRISPR Timeline*] (The above history is not exhaustive: the Broad Institute's CRISPR Timeline provides additional highlights regarding the discovery of CRISPR not covered in this Note, including work by Koonin et al. at the NIH, Hovarth et al. at Danisco France SAS, van der Oost at the University of Wageningen, Netherlands, and the work of Marraffini & Sontheimer at Northwestern University, Chicago, IL).

56. Mojica 1993, *supra* note 55.

57. *See* Francisco Mojica, *Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements.* J. OF MOLECULAR EVOLUTION 174, 174 (2005). In 2005, Mojica reported that CRISPR in *Haloferax mediterranei* shared identity with sequences from the bacteriophage (a virus that infects and replicates inside of a bacterium) genome. *See also* C. Pourcel et al., *CRISPR Elements in Yersinia Pestis Acquire New Repeats by Preferential Uptake of Bacteriophage DNA, and Provide Additional Tools for Evolutionary Studies*, 151 MICROBIOLOGY 653 (2005).

58. "Prokaryote" means a single-cell prokaryotic organism, contrasted with eukaryote. Prokaryotes are often classified by phylogenetic kingdom, as either Archaea or Bacteria. *Prokaryote*, OXFORD ENGLISH DICTIONARY (3rd Ed., 2007), *available at* http://www.oed.com/view/Entry/152285?redirectedFrom=prokaryote#eid.

59. In 2007, Rodolphe Barrangou and colleagues affirmatively demonstrated that the CRISPR locus comprised a bacterial adaptive immune system, where the bacteria can resist infection by bacteriophages. *See* Rodolphe Barrangou, *CRISPR Provides Acquired Resistance Against Viruses in Prokaryotes,* 315 SCIENCE 1709, 1709 (2007) (the bacterium can resist infection because it incorporates a part of the invading virus genome into its CRISPR locus).

CRISPR locus[60] in the bacterium *Streptococcus thermophilus* contained what they termed CRISPR-associated ("Cas") genes.[61] One of them, Cas9, was predicted to have nuclease[62] activity,[63] or the ability to 'cut' a DNA sequence. In 2007, Randolphe Barrangou and his team at Danisco[64] in Madison, Wisconsin, showed that bacteria containing both CRISPR and Cas9 can inactivate and defeat infection by bacteriophage.[65] In 2010, Sylvain Moineau and colleagues at the University of Leval, Quebec, reported that the combination of CRISPR and Cas9 (and *only*

60. "Locus" means the place in which something is situated or occurs. In later use also: the effective or perceived location of something abstract. *Locus*, OXFORD ENGLISH DICTIONARY (3rd Ed., 2015), *available at* http://www.oed.com/view/Entry/109673?rskey=HjtkEH&result=1#eid (here, locus refers to the location in the *S. thermophilus* genome where CRISPR was found).

61. Bolotin also demonstrated the need for spacers, called protospacer adjacent motifs (PAMs) were necessary for target recognition. Alexander Bolotin, *Clustered Regularly Interspaced Short Palindrome Repeats (CRISPRs) Have Spacers of Extrachromosomal Origin*, 151 MICROBIOLOGY 2551 (2005).

62. "Nuclease" means an enzyme that catalyzes the hydrolysis of a phosphodiester bond of a nucleic acid, cleaving the nucleic acid into smaller units. *Nuclease*, OXFORD ENGLISH DICTIONARY (3rd Ed., 2003), *available at* http://www.oed.com/view/Entry/128933?redirectedFrom=nuclease#eid.

63. CRISPR Timeline*, supra* note 55. *See also* Bolotin, *supra* note 61.

64. Danisco is a subsidiary of DuPont. *See Dupont Major Subsidisaries*, DU PONT, http://www.dupont.com/subsidiaries.html (last visited Apr. 5, 2018). Du Pont itself a subsidiary of DowDuPont, Inc. as of September 1, 2017. *See* Press Release, Dow Du Pont, DowDuPont™ Merger Successfully Completed (Sept. 1, 2017), http://www.dow-dupont.com/news-and-media/press-release-details/2017/DowDuPont-Merger-Successfully-Completed/default.aspx.

65. *See* Barrangou, *supra* note 59, at 1711. By 2009, several groups had reported the discovery of crRNAs, an abbreviated term for CRISPR-RNAs. *See* Stan J. J. Brouns, et al. *Small CRISPR RNAs Guide Antiviral Defense in Prokaryotes* 321 SCIENCE 960, 960-61 (2008). *See also* Luciano A. Marraffini & Erik J. Sontheimer, *CRISPR Interference Limits Horizontal Gene Transfer in Staphylococci by Targeting DNA*, 322 SCIENCE 1843, 1843 (2008); Caryn R. Hale, et al., *RNA-guided RNA Cleavage by a CRISPR RNA-Cas protein complex.* 139 CELL 945 (2009); Caryn Hale, et al. *Prokaryotic Silencing (psi)RNAs in Pyrococcus Furiosus.* RNA 2572 (2008); Reidun K. Lillestol RK, et al. *CRISPR Families of the Crenarchaeal Genus Sulfolobus: Bidirectional Transcription and Dynamic Properties*, MOLECULAR MICROBIOLOGY 259 (2009). crRNAs are short sequences of RNA generated by the CRISPR locus and were found to target the invading bacteriophage DNA, and form a molecular complex with Cas9. The invading DNA sequence is subsequently cleaved (cut) and thus inactivated. *See* Barrangou, *supra* note 59, at 1711.

Cas9) could effectively promote precise DNA breaks.[66] Cas9 may thus be thought of a molecular 'scissors,' able to cut a target DNA precisely and accurately.[67]

A few more pieces were needed to complete the molecular puzzle of the CRISPR-Cas9 system. In 2011, Emmanuelle Charpentier's group at the University of Umeå, Sweden, discovered that tracrRNA[68] could direct Cas9 to a particular locus.[69] Cas9's molecular mechanism was further elucidated in 2012, when Virginijus Siksnys et al. at Vilnius University in Lithuania "showed that they could *reprogram* Cas9 to target a site of their choosing by changing the sequence of the crRNA.[70] These findings were confirmed and extended by Charpentier in international collaboration with Jennifer Doudna's lab at UC-Berkeley that same year.[71] The potential use for an otherwise intriguing bacterial immune system demonstrated the " . . . potential to exploit the system for RNA-programmable genomic editing."[72] This means CRISPR-Cas9 may represent an *affordable* and *precise* system by which scientists—

66. CRISPR Timeline, *supra* note 55. *See also* J Garneau, *The CRISPR/Cas Bacterial Immune System Cleaves Bacteriophage and Plasmid DNA*, 468 NATURE 67 (2010).

67. Elizabeth Pennisi, *Popular Gene-Editing Technique Gets Sharper Molecular Scissors*, SCIENCE NEWS (Sep. 25, 2015), http://www.sciencemag.org/news/2015/09/popular-gene-editing-technique-gets-sharper-molecular-scissors.

68. "TracrRNA" means "trans-activating crRNA with 24 nucleotide complementarity to the repeat regions of crRNA precursor transcripts." "crRNA" is a short RNA that "silence[s] foreign nucleic acids in a sequence-specific manner . . . the maturation of [which] represents a key event in CRISPR activation." Elitza Deltcheva et al., *CRISPR RNA Maturation by Trans-Encoded Small RNA and Host Factor RNase III*, 431 NATURE 602, 602 (2011).

69. *Id.* at 604.

70. CRISPR Timeline, *supra* note 55 [emphasis added]. The Charpentier-Doudna collaboration showed that crRNAs base-paired with tracrRNA, combining to form a structure that could direct Cas9 to cleave a target DNA. They further showed that a molecularly-engineered chimera tracrRNA:crRNA (also called single guide RNA, or sgRNA) has comparative function to the naturally-observed two-RNA structure. *See* Giedrius Gasiunas et al., *Cas9-crRNA Ribonucleoprotein Complex Mediates Specific DNA Cleavage for Adaptive Immunity in Bacteria*, 109 PROC. NAT'L ACAD. SCI. E2579, E2579 (2012).

71. *See* Martin Jinek et al., *A Programmable Dual-RNA-guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816, 816-21 (2012).

72. *Id.* at 816.

and eventually clinicians—might actually have the capability of engineering the genome itself, curing disease through somatic[73] gene therapy or even enhancing human characteristics through sequence additions or deletions.

The role for the CRISPR-Cas9 system as a tool for TGE was finally revealed in 2013, when Feng Zhang's (Broad Institute of MIT and Harvard) and George Church's (Harvard Medical School, Department of Genetics) groups, published back-to-back articles in *Science* reporting successful editing of cell genomes using CRISPR-Cas9 in eukaryotic[74] cells.[75] Since then, CRISPR-Cas9 has burst on to the publication scene, with scientists all over the world using CRISPR to perform TGE in myriad eukaryotic organisms, from *Drosophila melanogaster* (fruit fly)[76] to *Danio rerio* (zebrafish).[77] In 2015, *Science* declared CRISPR/Cas9 the "Breakthrough of the Year."[78] As 2006

73. "Somatic" means of or relating to the (or a) body; bodily corporeal, physical [. . .] [r]elating to the soma in contrast to the germ. *Somatic*, OXFORD ENGLISH DICTIONARY, *available at* http://www.oed.com/view/Entry/184422?redirectedFrom=somatic#eid (last visited Mar. 8, 2018).

74. Specifically, human and mouse cells. *See* Lander, *supra* note 55, at 25.

75. *See* Cong et al., *supra* note 16, at 822. *See also* Mali et al., *supra* note 16, at 823.

76. See, e.g., Andrew R. Bassett and Ji-Long Hu, *CRISPR/Cas9 Genome Editing in Drosophila,* 41 J. GENETICS & GENOMICS 7 (2014) (One of 162 articles published since 2013 using the following Boolean search in PubMed: "CRISPR AND Cas9 AND Drosophila") (last queried Apr. 8, 2018).

77. *See, e.g.*, Thomas O. Auer & Filippo Del Bene, *CRISPR/Cas9 and TALEN-Mediated Knock-in Approaches in Zebrafish,* 69 METHODS (2013), 142-50. (One of 260 articles published since 2013 using the following Boolean search in PubMed: "CRISPR AND Cas9 AND zebrafish) (last queried Apr. 8, 2018).

78. Science News Staff, *And Science's 2015 Breakthrough of the Year is . . .* , SCIENCE (Dec. 17, 2015), http://www.sciencemag.org/news/2015/12/and-science-s-breakthrough-year.

Nobel Prize winner[79] for Physiology or Medicine Craig Mello[80] noted in 2014, "[CRISPR/Cas9] is really powerful, [. . .] because now you can essentially change a genome at will to almost anything you want. The sky's the limit."[81]

Why is the CRISPR-Cas 9 system such a useful molecular tool? First, it is a system that is relatively simple and inexpensive compared to other known methods as it is comprised of only a few molecular components.[82] Particularly, its components include the CRISPR locus and associated crRNA, the Cas9 protein, and a tracrRNA. Due to the RNA-based nature of CRISPR-Cas9 system, the RNA molecules that direct the system to the gene of interest are much easier and less expensive to synthesize than the other existing technologies mentioned above.[83] Second, CRISPR-Cas9 is more accurate, and thus more effective at generating a desired mutation[84] than other protocols.[85]

79. *The Nobel Prize in Physiology or Medicine 2006*, NOBELPRIZE.ORG, https://www.nobelprize.org/nobel_prizes/medicine/laureates/2006/ (last visited Feb. 5, 2018).

80. Along with Andrew Fire, Mello was one of the discoverers of the RNA interference (or RNAi) system.

81. Joe Palca, *A CRISPR Way to Fix Faulty Genes*, NPR, ALL THINGS CONSIDERED (June 26, 2014), http://www.npr.org/sections/health-shots/2014/06/26/325213397/a-crispr-way-to-fix-faulty-genes.

82. Robert Sanders, *Simple Technology Makes CRISPR Gene Editing Cheaper*, BERKELEY NEWS (July 23, 2015), http://news.berkeley.edu/2015/07/23/simple-technology-makes-crispr-gene-editing-cheaper/.

83. *See* Walker-Daniels *supra* note 15; F. Ann Ran, et al., *Genome Engineering Using the CRISPR-Cas9 System*, 8 NATURE PROTOCOLS 2281, 2281(2013).

84. *See* Woong Y. Hwang, et al., *Heritable and Precise Zebrafish Genome Editing Using a CRISPR-Cas System,* 8 PLOS ONE (2013), e68708, 1-9. *See also* Zhengyan Feng et al., *Efficient Genome Editing in Plants Using a CRISPR/Cas System*, 23 CELL RES. 1229, 1229 (2013).

85. *See* Jeffrey C. Miller, et al., *A TALE Nuclease Architecture for Efficient Genome Editing*, 29 NATUREBIOTECHNOLOGY 143, 143(2011). *See also* Claudio Mussolino, et al., *A Novel TALE Nuclease Scaffold Enables High Genome Editing Activity in Combination with Low Toxicity*, 39 NUCLEIC ACIDS RES. 9283, 9281 (2011). *See also* Morgan L. Maeder, et al., *Rapid "Open-Source" Engineering of Customized Zinc-Finger Nucleases for Highly Efficient Gene Modification*, 31 MOLECULAR CELL 294, 296 (2008).

Finally, the cleavage activity of the CRISPR-Cas9 system is remarkably precise;[86] a key element of a robust TGE system.[87]

Perhaps most importantly, researchers have quickly recognized the potential therapeutic use for this technology in treating both inherited and *de novo* (arising spontaneously) human disease caused by genetic mutation.[88] These works represent "[t]he pinnacle of four decades of research" as CRISPR will potentially take biomedical research to new, unprecedented levels and more effectively study genetic mechanisms of pathology with a "hitherto unimaginable level of model fidelity."[89] A well-deserved "Breakthrough of the Year," to be sure! Researchers could use TGE as a therapy by modifying the genome of a human embryo to add, remove, or replace gene sequences to abrogate genetic mutations. Presuming such a modified embryo could be successfully brought to term[90] and implanted successfully in humans, TGE might lead to the

86. *See* Cong, et al., *supra* note 16, at 819 (Zhang's group "engineered two different type II CRISPR/Cas systems and demonstrate that Cas9 nucleases can be directed by short RNAs to induce precise cleavage at endogenous genomic loci in human and mouse cells.").

However, there are at least two concerns raised in recent studies to bring CRISPR-Ca9 into a clinical setting. The first a concern over CRISPR-Cas9 utilization causing "off-target mutations," a problem that scientists are working towards resolving. *See, e.g.*, Yanfang Fu, et al., *High Frequency Off-Target Mutagenesis Induced by CRISPR-Cas Nucleases in Human Cells*, 31 NATURE BIOTECHNOLOGY 822 (2013). *See also* Adrian Veres, et al., *Low Incidence of Off-Target Mutations in Individual CRISPR-Cas9 and TALEN Targeted Human Stem Cell Clones Detected by Whole-Genome Sequencing*, 15 CELL STEM CELL 27 (2014); Daesik Kim, et al., *Digenome-seq: Genome-Wide Profiling of CRISPR-Cas9 Off-Target Effects in Human Cells*, 12 NATURE METHODS (2015), 237, 237-43.

The second, and more recent, issue was raised by Matthew Porteus' group at Stanford, demonstrating an adaptive immune response to Cas9 in humans. *See* Carsten T. Charlesworth et al., *Identification of Pre-Existing Adaptive Immunity to Cas9 Proteins in Humans*, BIORXIV (Jan. 5, 2018), https://www.biorxiv.org/content/early/2018/01/05/243345.full.pdf+html; Andrew Joseph, *CRISPR Hits a Snag: Our Immune Systems May Attack the Treatment*, STAT (Jan. 8, 2018), https://www.statnews.com/2018/01/08/immunity-crispr-cas9/.

87. *See* Alex Reis, *CRISPR/Cas9 and Targeted Genome Editing: A New Era in Molecular Biology.* NEB® EXPRESSIONS, NEW ENG. BIOLABS 3 (2014).

88. Mark A. DeWitt, et al., *Selection-Free Genome Editing of the Sickle Mutation in Human Adult Hematopoietic Stem/Progenitor* Cells, 360 SCI. TRANSLATIONAL MED. 1, 1 (2016).

89. Simon N. Waddington, et al., *A Broad Overview and Review of CRISPR-Cas Technology and Stem Cells*, 2 CURRENT STEM CELL REP. 9, 9 (2016).

90. This is a separate issue outside of the scope of this Note, but highlights the eventual path that this line of research would likely take.

eradication of certain diseases.[91] Others note that TGE might facilitate the enhancement or alteration of human traits.[92] And while there are no guarantees that the CRISPR-Cas9 system will be the "silver bullet" that revolutionizes medicine or makes genetic disorders a thing of the past, CRISPR-Cas9 represents an unmistakably significant step forward in the field by increasing molecular precision while substantially decreasing cost.[93]

II. THE CRISPR-CAS9 GOLD RUSH: DEVELOPMENTS AT HOME AND ABROAD

"With innovation, there isn't a last nugget. Every new thing creates two new questions and two new opportunities."
-Jeff Bezos[94]

Researchers in the United States and around the world have seized upon CRISPR-Cas9 to facilitate scientific inquiry. In 2016, for example, a collaborative group of researchers from UC-Berkeley and the University of Utah's School of Medicine published their work on transplanting CRISPR-Cas9-engineered human hematopoietic stem/progenitor cells correcting the Beta-globulin ("*HBB*") gene into immunocompromised mice modeling Sickle cell disease (SCD).[95] Notably, this work demonstrated that gene edits to *HBB* were maintained throughout the course of the experiment, likely implying a clinical benefit that could translate into humans. And professional

91. The "low-hanging fruit" of such a therapy would likely begin with single-gene disorders, such as Huntington disease or Fragile X Syndrome. *See, e.g.*, *Diseases Treated by Gene Therapy*, GENETHERAPYNET.COM, http://www.genetherapynet.com/JoomlaTest2/index.php?option=com_content&view=article&id=164:diseases-treated-with-gene-therapy-&catid=97:patient-information&Itemid=14 (last visited Feb. 5, 2018).

92. *See, e.g.*, Comfort, *supra* note 18.

93. Indeed, the lower cost has made rudimentary access to CRISPR systems feasible even for do-it-yourselfers. For example, former NASA researcher Josiah Zayner, CEO of The ODIN, sells "DIY Bacterial Gene Engineering CRISPR Kit[s]" and "Bacterial CRISPR and fluorescent Home Lab Kit[s]" for $159 and $209, respectively. *See* THE ODIN, http://www.the-odin.com/(last visited Apr. 5, 2018); *see also* Harry Pettit, *Former NASA Scientist Wants to Create a New Breed of SUPERHUMANS by 'Helping People Genetically Modify Themselves' Using DNA Injections (And He's Even Tried Them on Himself)*, DAILY MAIL (Dec. 29, 2017), *http://www.dailymail.co.uk/sciencetech/article-5217545/Bohacker-says-wants-help-humans-modify-genes.html.*

94. Jeff Bezos is the founder of Amazon.com. *See The Electricity Metaphor for the Web's Future*, TED at 15:17 (Feb. 2003), https://www.ted.com/talks/jeff_bezos_on_the_next_web_innovation/transcript.

95. DeWitt et al., *supra* note 88.

societies, such as the American Society of Human Genetics ("ASHG") have begun to cautiously embrace *in vitro* germline editing of embryos and gametes, though it stops short of approving experiments that would "culminate[] in human pregnancy."[96]

Several international groups[97] have also experimented with the CRISPR/Cas9 editing system in both nonviable[98] and viable human embryos.[99] Time and efforts will tell, but the implications that precise TGE could have on human disease are potentially limitless: by removing mutations or inserting functional sequences into the genome, genetic-related diseases could be mitigated, or human qualities enhanced. However, the United States does not currently provide federal funding for TGE research on human embryos.[100] Why does this matter? While animal models are incredibly useful research tools, when it comes to direct human benefit, they might not demonstrate an equivalent response in human—there is no substitute for the real thing.[101] Researchers have already begun to incorporate CRISPR/Cas9 into viral vectors for

96. *See* Kelly Ormond et al., *Human Germline Genome Editing,* 101 AM. J. OF HUM. GENETICS 167, 171 (2017).

97. *See* Cyranoski & Reardon, *supra* note 39; *see also* Callaway, *supra* note 40; *see also* Ewen Callaway, *Second Chinese Team Reports Gene Editing in Human Embryos*, NATURE NEWS (Apr. 8, 2016), http://www.nature.com/news/second-chinese-team-reports-gene-editing-in-human-embryos-1.19718#/b1 (last visited Mar. 17, 2017) [hereinafter Callaway*, Second Chinese Team*]; Lanner Interview, *supra* note 41.

98. "Nonviable" means incapable of surviving; specifically (of a fetus) not capable of independent existence. OXFORD ENGLISH DICTIONARY (3rd Ed. 2003), http://www.oed.com/view/Entry/128160?redirectedFrom=nonviable#eid (last visited: Mar. 17, 2017).

99. Viable embryos are capable of implanting in the uterine wall and developing into full-grown humans. *See, e.g.*, Cyranoski & Reardon, *supra* note 39.

100. Steven Latham, *Proceed with Caution*, U.S. NEWS & WORLD REP. (Feb. 8, 2016), http://www.usnews.com/opinion/blogs/policy-dose/articles/2016-02-08/nih-wont-fund-human-embryo-gene-editing-but-others-will (last visited Mar. 17, 2017).

101. The National Academies of Science, Engineering and Medicine's 2017 Consensus Report, *Human Genome Editing: Science, Ethics, and Governance* lays out a number of valid justifications for research on human embryos generally, including "[(1)] Studies of fertilization in vitro[; (2) i]mproved culture of early human embryos[(3) d]evelopment of extraembryonic tissues (yolk sac and placenta)[; (4) i]solation an in vitro differentiation of pluripotent stem cells[; and (5) i]nvestigations of sperm and oocyte development[.]" *Human Genome Editing: Science, Ethics and Governance*, 78 COMM. ON HUM. GENE EDITING: SCI., MED., & ETHICAL CONSIDERATIONS, THE NAT'L ACAD. OF SCI., ENGINEERING, & MED., at 78 (The Nat'l Acad. Press 2017) [hereinafter *2017 Consensus Report*]; *see also* Niall Shanks, et al., *Are Animal Models Predictive for Humans?*, 4 PHIL. ETHICS & HUMAN. MED. 1, 1(2009).

use in conventional somatic gene therapy.[102] These successes should give patients with genetic diseases hope for the future, but what of the generations to come? Genes are passed on from one generation to the next through the germline. Genetic disease can either be inherited from a mutation in one or both parents, or may arise through random mutation.[103] At least three nations: (A) the People's Republic of China; (B) the United Kingdom; and (C) the Kingdom of Sweden have implemented various national policies embracing governmentally-sanctioned (and funded) TGE—including CRISPR-Cas9—in the context of human embryos.

A. The People's Republic of China

China has published several papers reporting successful TGE on human embryos. The first was published April 18, 2015.[104] For the first time, "scientists reported editing the genomes of human embryos."[105] Junjiu Huang and colleagues "used tripronuclear (3PN) zygotes to further investigate CRISPR/Cas9-mediated gene editing in human cells . . . [and] found that CRISPR/Cas9 could effectively cleave the endogenous -globin gene (HBB)."[106] The embryos used by Huang were nonviable and were obtained from local fertility clinics[107] with donor consent.[108] Due to their being nonviable, tripronuclear zygotes would be discarded as part of an IVF treatment. Such embryos[109] thus make for a useful alternative to viable embryos with respect to TGE research.[110]

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102. *See, e.g.* Ignazio Maggio, et al., *Adenoviral Vector Delivery of RNA-Guided CRISPR/Cas9 Nuclease Complexes Induces Targeted Mutagenesis in a Diverse Array of Human Cells*, 4 SCI. REP. 1, 5 (2014); *see also* Elena Senís, et al., *CRISPR/Cas9-Mediated Genome Engin-eering: An Adeno-Associated Viral (AAV) Vector Toolbox*, 9 BIOTECHNOLOGY J. 1402, 1403 (2014). *See generally* Ignazio Maggio, et al., *The Emerging Role of Viral Vectors as Vehicles for DMD Gene Editing*, 8 GENOME MED. 1, 3 (2016).

103. Joris A. Veltman & Han G. Brunner, *De novo Mutations in Human Genetic Disease*, 13 NATURE REV. GENETICS (2012), 565-75 (Aug. 2012) (Box 3).

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

105. *See* Cyranoski & Reardon, *supra* note 39.

106. Liang et al., s*upra* note 104, at 363.

107. *Id.*, at 364; *see also* Cyranoski & Reardon, *supra* note 39.

108. *Id.*, at 370.

109. Or any other kind of embryo that is deemed "nonviable." *See* Cyranoski & Reardon, *supra* note 39, at 593.

110. Liang et al., *supra* note 104, at 364, *relying on* Balakier H., *Tripronuclear Human Zygotes: The First Cell Cycle and Subsequent Development.* 8 HUM. REPROD. 1892, 1892-97(1993).

The second paper was published on April 6, 2016.[111] Yong Fan and colleagues, again working with 3PN zygotes, successfully introduced an HIV-resistance mutation using CRISPR/Cas9 as a proof-of-principle experiment.[112] The egg donors provided informed consent and a local ethics committee approved the project.[113] The latest study, currently ongoing by Lu You's group at Sichuan University, is another world-first: the group is conducting a clinical trial by injecting a lung cancer patient is with cells subjected to TGE by CRISPR/Cas9 to attempt to mitigate the cancer.[114] A group at Peking University intends to begin clinical trials on three other cancers this year.[115]

B. The United Kingdom

On February 1, 2016, the United Kingdom's Human Fertilisation and Embryology Authority (HFEA) approved a research project that developmental biologist Kathy Niakan proposed. Her work, aimed to understand why pregnancies terminate by manipulating the *POU5F1* gene using CRISPR/Cas9.[116] Dr. Niakan's goal was to "understand the genes . . . needed for an embryo to develop into a healthy baby."[117] In June 2016, the Cambridge Central Research Ethics Committee, the local research ethics board, approved the project.[118] The Cambridge Central Research Ethics Committee may be thought of as the UK's equivalent of an Institutional Review Board ("IRB") in the United States. An IRB is an oversight mechanism that reviews research relating to human subjects.[119]

111. *See* Xiangjin Kang, et al., *Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-mediated Genome Editing*, 33 J. ASSISTED REPROD. &GENETICS (2016), 581, 581-88.

112. *See* Callaway, *Second Chinese Team*, *supra* note 97; *See also* Kang, *supra* note 111, at 587.

113. *See* Callaway, *Second Chinese Team*, *supra* note 97; *see also* Kang, *supra* note 111.

114. *See* Cyranoski, *supra* note 19.

115. *Id.*

116. *See* Norah M.E. Fogarty et al., *Genome Editing Reveals a Role for OCT4 in Human Embryogenesis,* 550 NATURE 67, 74 (2017).

117. *Ethics Committee Greenlights UK Gene Editing*, CHRISTIAN CONCERN (Jun. 2, 2016), http://www.christianconcern.com/our-concerns/abortion/ethics-committee-greenlights-uk-gene-editing.

118. Lydia Willgress, *British Scientist Can Genetically Modify Human Embryos, Ethics Committee Says*, THE DAILY TELEGRAPH (2016), http://www.telegraph.co.uk/news/2016/05/27/british-scientist-can-genetically-modify-human-embryos-ethics-co/.

119. To what does this policy apply? *See* 45 C.F.R. §46.101(a)(2) (2009).

The Niakan group published their findings in *Nature* on September 20, 2017, showing among other things that transcription factor OCT4[120] plays a role in the formation of the inner cell mass of blastocysts, and that downstream genes involved in preimplantation are downregulated upon *POU5F1* mutation.[121] Interestingly, a parallel experiment involving mouse embryos yielded significantly different results, suggesting "OCT4 may be required earlier in human development than in mice[.]"[122] The group experimented on healthy fertilized embryos donated by couples who had undergone IVF and provided informed consent, as well as a specific "consent form authorizing the use of genome editing techniques including CRISPR-Cas9 on donated embryos."[123] Significantly, the informed consent included Niakan's disclosure that investigators would cease the subject embryos' development before 14 days post-fertilization.[124] This conforms with the "14-day rule," a policy "line in the sand" limitation on *in vitro* embryo research.[125] At or around 14 days of development the 'primitive streak'[126] forms in the embryonic blastula. After this point, "the being in question *can no longer be anything but a single being* [. . . it] can[not] replicate or divide to form another identical being."[127] Embryonic manipulation after this 14-day mark is thus considered more ethically dubious than manipulation conducted before the mark.[128]

120. OCT4 is the protein encoded by the *POU5F1* gene. *See* Fogarty et al., *supra* note 116.

121. *Id.*

122. *Id.* at 72.

123. *Id.* at S1.

124. *Id.*

125. *See* Insoo Hyun, et al., *Revisit the 14-Day Rule*, 533 NATURE 169, 170 (2016); *See also HEW Support of Research Involving Human In Vitro Fertilization and Embryo Transfer*, ETHICS ADVISORY BOARD, DEP'T OF HEALTH, EDUC., & WELFARE (US Government Printing Office, 1979); *See also* UK DEP'T OF HEALTH & SOCIAL SECURITY, REP. OF THE COMMITTEE OF INQUIRY INTO HUM. FERTILISATION AND EMBRYOLOGY 66 (Her Majesty's Stationary Off. Jun. 26 1984) [hereinafter *UK Report*].

126. *See* Hyun et al., *supra* note 125, at 170.

127. HUM. CLONING & HUM. DIGNITY: AN ETHICAL INQUIRY, THE PRESIDENT'S COUNCIL ON BIOETHICS 10 (2002), *available at* https://bioethicsarchive.georgetown.edu/pcbe/reports/cloningreport/research.html.

128. *Id.* at 13.

C. Sweden

In Sweden, Fredrik Lanner's group at The Karolinska Institute ("KI") has conducted TGE research using healthy human embryos.[129] Dr. Lanner noted in an interview that:

> We applied for and got ethical permits from the Swedish regional ethics board (EPN.SE) last spring, 2015. We have also lifted these experiments in KI's internal ethics board, to inform the KI leadership of our plans and to make sure we had their support.
>
> The Swedish law is clear that genome editing is only allowed within the first 14 days as long as the embryo is not transferred back for a continued pregnancy. This means that heritable genome editing for clinical purposes would not be allowed in Sweden. The clear legislation has been key in us moving ahead with these plans.[130]

Dr. Lanner also noted his funding sources for this work:

> Towards the functional gene studies I have internal funding from KI and external funding from the Knut and Alice Wallenberg foundation and through Lau fellowship. For our embryo research I also have funding from the *Swedish Research Council*, Ragnar Söderberg fellowship and the Swedish Strategic Research Foundation.[131]

Significantly, the Swedish Research Council is a government agency. Thus, it follows that the Swedish government is amenable to funding TGE research on human embryos.

It is not entirely clear what dividends will be seen from these research projects. In response to the second Chinese effort to use TGE on human embryos, Hokkaido University bioethicist Tetsuya Ishii noted that "[i]ntroducing CCR5Δ32 and trying repair, even in nonviable embryos, is just playing with human embryos."[132] As to the question of using viable embryos, Harvard Medical School biologist and Howard Hughes Medical Institute Investigator George Daley cautioned: "the study is a landmark, as well as a cautionary tale . . . [t]heir study should be a stern warning to any practitioner who thinks the technology is ready for testing to eradicate disease genes."[133]

129. Lanner Interview, *supra* note 41.

130. *Id.*

131. *Id.*(emphasis added).

132. *See* Callaway, *Second Chinese Team*, *supra* note 97.

133. *See* Cyranoski & Reardon, *supra* note 39.

While it may be true that even though experimentation on nonviable embryos may be, as Professor Ishii noted, "just playing with human embryos," the proof-of-concept studies are nonetheless groundbreaking.[134] While proof-of-concept research can be met with diminishing returns, the lack of federal funding means that fewer U.S. researchers will be able to break new ground. Practically speaking, the hands that doing the work would become more proficient and with the nuances of applying this technology to the human germline. By not federally funding TGE directed to embryos, the only American hands becoming proficient with the CRISPR/Cas9 system in a human context will be supported with private funding. And while utilization in animal models, such as mice, zebrafish, and fruit flies, produces immensely valuable data and insights, the day may come where the United States must take a hard look at the current legal provisions, most notably the Dickey-Wicker Amendment, and decide whether the times and circumstances dictate a change.

III. THE STATE OF THE DEBATE IN THE UNITED STATES: FUNDING, STATUTES, AND REGULATIONS

Currently, a number of barriers exist within the United States' existing federal statutory and regulatory scheme, effectively preventing federal funding to be allocated toward any TGE usage on human embryos. In referring to TGE in human embryos, we are talking about manipulation of the germline. Even when new techniques emerge to modify the germline using TGE by CRISPR-Cas9, the Federal Food and Drug Administration ("FDA") is prohibited (and has been since 2015) from entertaining applications of a "drug or biological product" resulting from work involving the modification of an embryo.[135] When taking a hard look at existing policy and, one could readily envision two or three competing interests: on one hand, an unquenchable thirst for progress and the desire to unlock the secrets of life itself as it exists; TGE—embodied most recently by CRISPR-Cas9—represents a significant step forward in the quest for that progress. On the other

134. *See* Callaway, *Second Chinese Team*, *supra* note 97.

135. Public Law 114-113, 114th Cong. (2015), Title VII, § 749("None of the funds made available by this Act may be used to notify a sponsor or otherwise acknowledge receipt of a submission for an exemption for investigational use of a drug or biological product under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) or section 351(a)(3) of the Public Health Service Act (42 U.S.C. 262(a)(3)) in research in which a human embryo is intentionally created or modified to include a heritable genetic modification. Any such submission shall be deemed to have not been received by the Secretary, and the exemption may not go into effect.). *See also* I. Glenn Cohen & Eli Y. Adashi, *The FDA is Prohibited from Going Germline*, 353 SCIENCE 545 (2016).

hand, are interests in preserving the sanctity of life, policing the borders of what it is to be human, and the old adage of "playing God." These were the same interests at play in the debate over how we regulate embryonic stem cells and related research. Does TGE, when utilized with human embryos, cross the proverbial Rubicon? It is a close question, and perhaps better left to theologians and philosophers. But it is important to consider a third interest: TGE may quickly become an issue of national security. If we, as a nation, fail to be the first to discover and patent[136] these technologies, in an intellectual property sense, we risk allowing the financial and technological fruits of scientific labor to slip through our fingers. By not being the first to invent, we may well risk losing the right to lead the inevitably larger, global discussion of how to implement these technologies safely, effectively, and ethically.

The first skirmishes on the intellectual property frontier have already begun—and with large monetary values at stake. On February 15, 2017, the Patent Trial and Appeal Board ("PTAB") held that The Broad Institute (of MIT and Harvard), which had filed competing patents for CRISPR-Cas9 against the University of California, Berkeley, held that The Broad Institute's patent applications did not interfere with UC-Berkeley's less detailed patent applications; a win for Broad.[137] Recently, *Forbes* magazine discussed the consequences of the decision (which remains ongoing as of the publication of this Note), and estimated the value of an exclusive license for CRISPR-Cas9 at around $265 million.[138] The licensing of CRISPR-Cas9 itself is being driven in to three pipelines: nonexclusive (a) academic or "noncommercial" research, or (b) "tools" or "kits" to perform CRISPR-Cas9 editing; or exclusive (c) "therapeutics and treatments."[139] Given that scientists are

136. A patent conveys upon a patentee a property right to their invention (35 U.S.C. § 261), including a right to exclude others from using it (35 U.S.C. § 154(a)(1)), though a patentee may authorize its use through contractual license. The lawful use of a U.S. patent would seem more difficult were the patentee of foreign origin. The U.S. Government is not directly precluded from infringing on a patent right, as the only relief available to a patentee under U.S. law is "reasonable and entire compensation" (28 U.S.C. § 1498(a)) for infringement.

137. Sharon Begley, *Disputed CRISPR Patents Stay with Broad Institute, U.S. Panel Says*, SCI. AM. (Feb. 15, 2017), https://www.scientificamerican.com/article/disputed-crispr-patents-stay-with-broad-institute-u-s-panel-rules/.

138. Jacob S. Sherkow, *How Much Is a CRISPR Patent License Worth?*, FORBES (Feb. 21, 2017), https://www.forbes.com/sites/jacobsherkow/2017/02/21/how-much-is-a-crispr-patent-license-worth/#51f139026b77.

139. Jorge L. Conteras & Jacob S. Sherkow, *CRISPR, Surrogate Licensing, and Scientific Discovery*, 355 SCIENCE 698 (2017).

still elucidating the potential of CRISPR-Cas9, and TGE generally, this $265 million figure may just be the tip of a very large monetary iceberg. It behooves us then, as a nation, to maximize our share of the intellectual property that is certain to spring from current and future developments. A key first step is to untie our scientists' hands by opening the door to federally funded TGE research on human embryos. We, as a nation, still may not be the first to discover the next "game changer," but maximizing our odds is a simple thing to accomplish (enabling the funding), if complex to justify. While efforts in the United States are proceeding in animal models as articulated above, American researchers are only just beginning to conduct human trials.[140] China and others are now leading the way, and the United States may quickly fall behind unless we revisit the kinds of projects which are and are not eligible for funding.

While the promise of TGE includes treating disease and understanding basic scientific questions, the specter of eugenics and the rise of superhuman "Übermenschen"[141] flits about in the background. In a critical 2017 Consensus Report from The National Academies of Science, Engineering, and Medicine, TGE in clinical research was endorsed for therapeutic purposes in both somatic and germline contexts—albeit with "caution," "broad public input," and "for compelling reasons and under strict oversight."[142] As for enhancement, the Consensus

140. *See, e.g.*, Press Release, Sangamo Therapeutics, Sangamo Announces Treatment of First Patient in Landmark Phase 1/2 Clinical Trial Evaluating In Vivo Genome Editing for MPS II (Nov. 15, 2017), https://investor.sangamo.com/press-releases/detail/381/sangamo-announces-treatment-of-first-patient-in-landmark ("'For the first time, a patient has received a therapy intended to precisely edit the DNA of cells directly inside the body. We are at the start of a new frontier of genomic medicine,' said Dr. Sandy Macrae, CEO of Sangamo therapeutics.").

141. "Übermenschen" is the plural form of Übermensch, meaning "The ideal superior man of the future who could rise above conventional Christian morality to create and impose his own values, originally described by Nietzsche in "Thus Spake Zarathustra" (1883–5). Literally, a 'super-human person.' *Übermenschen*, ENGLISH OXFORD LIVING DICTIONARIES, https://en.oxforddictionaries.com/definition/ubermensch (last visited Mar. 16, 2017).

142. *2017 Consensus Report*, *supra* note 101, at 7-8 (Significantly, the *Consensus Report* recommends permitting clinical trials introducing heritable changes to the germline only if such a project were to meet a number of criteria: "(1) absence of reasonable alternatives; (2) restriction to preventing a serious disease or condition; (3) restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition; (4) restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects; (5) availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures; (6) ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health

Report recommends against any such research "at this time."[143] Our nation has led the way in many fields of science, and the failure to vigorously pursue all avenues of TGE as a matter of government policy may cause the United States to lose its edge as a preeminent scientific power. If indeed we are on the verge of a new "space race," the most fateful action we can take is no action at all. The rest of the world may not be willing to wait for us to parse out the difficult ethical questions surrounding this technology. As noted above, the governments of China, the UK, and Sweden in particular are taking the lead. As a result, the United States risks falling behind in what might well be a critical technological revolution of the 21st century. In order to poise this nation to win the "Inner Space Race," we must critically re-examine the current legal and regulatory provisions which hamper our progress in this area.

A. The Major Hurdle to Funding TGE Experimentation on Human Embryos: The Dickey-Wicker Amendment & NIH Interpretative Guidance

On May 5, 2017, House Resolution 244—the Consolidated Appropriations Act, 2017—was codified as Public Law No: 115-31.[144] The 2017 Act, like every appropriations Act since 1996, includes a provision that prohibits using any appropriated funding to create a human embryo or modify a human embryo "to include a heritable genetic modification."[145] Such legislation thus prohibits the use of federal funds to support research using CRISPR/Cas9 or another TGE technology to modify human germ cells or human embryos. In effect, this statutory block digs spurs into a horse which has already left the barn. The research will be completed by laboratories eventually, and

and safety of the research participants; (7) comprehensive plans for long-term, multigenerational follow-up that still respect personal autonomy; (8) maximum transparency consistent with patient privacy; (9) continued reassessment of both health and societal benefits and risks, with broad ongoing participation and input by the public; and (10) reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition.").

143. *Id.* at 9.

144. Consolidated Appropriations Act, 2017, Public Law 115-31, §736, 131 Stat. 135, 173 (in relevant part: "(a) None of the funds made available in this Act may be used for— (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b))." §736 incorporates the FDA rider as discussed at *supra* note 135. Public Law 115-31, 115th Cong. (2017), Title VII, §736.

145. *Id.*

while it is understandable that members of the public may be recalcitrant to know their tax dollars might support scientific work involving manipulation embryos, for the federal government to remain "dug-in" to the horse will only slow it down and engenders the risk of losing our edge as the preeminent scientific superpower. During the 2016 election, then-candidate Donald J. Trump called for a vast expansion of military strength and spending;[146] as President, he has proposed a more than "10% increase over current spending levels" in our defense budget.[147] It is clear that the current administration seeks to promote the United States in a "position of primacy," to use the words of Defense Secretary James N. Mattis.[148] Scientific preeminence is a key arrow in our quiver, but the federal prohibition is akin to pulling some of the fletching off of that arrow, dulling the arrowhead, or limiting the archer's draw length.[149]

The statutory basis for this prohibition lies in the Dickey-Wicker Amendment, a bill rider to H.R. 2880, The Balanced Budget Downpayment Act of 1995 signed by President Bill Clinton.[150] Named for its original sponsors—Representatives Jay Dickey (R-AR) and now-Senator Roger Wicker (R-MS)—the Dickey-Wicker Amendment, found at Section 128 of the Act, reads in relevant part:

146. *See, e.g.*, Ashley Parker & Matthew Rosenberg, *Donald Trump Vows to Bolster Nation's Military Capacities*, N.Y. TIMES (Sept. 7, 2016) ("We want to deter, avoid and prevent conflict through our unquestioned military strength.").

147. *See, e.g.,* David S. Cloud, *Trump Proposes Huge Increase in Military* Spending, THE L. A. TIMES (Feb. 12, 2018), https://www.latimes .com/nation/la-na-trump-defense-20180212-story.html. Indeed, President Trump proposed a defense budget of $716 billion for FY 2019, a greater than $74 billion increase. Compare this spending *increase* with the NIH's *proposed* FY 2017 budget of $33.1 billion (*see infra* note 169).

148. *Id.*

149. Yet another concern is the risk of creating a TGE-directed "medical tourism" in the future, wherein individuals, including Americans, seek treatments in nations with lax legal and regulatory standards. *See generally 2017 Consensus Report, supra* note 101, at 135-36; *see also* Kenneth W. Abbott et al., *Transnational Regulation: Reality or Romanticism?*, *in* INTERNATIONAL HANDBOOK ON REGULATING NANOTECHNOLOGIES (Graeme A. Hodge et al., eds., 2010); *see also* R. Alta Charo, *On the Road (to a Cure?) – Stem-Cell Tourism and Lessons for Gene Editing*, 374 NEW ENG. J. MED. 901 (2016); I. GLENN COHEN, PATIENTS WITH PASSPORTS: MEDICAL TOURISM, LAW, AND ETHICS (Oxford Univ. Press, 2015); *see also* Jeff Lyon, *Sanctioned UK Trial of Mitochondrial Transfer Nears*, 317 J. OF THE AM. MED. ASS'N 462 (2017); Leigh Turner & Paul Knoepfler, *Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry*, 19 CELL STEM CELL 154 (2016).

150. *See* H.R. 2880, 104th Cong. § 128 (1996).

> None of the funds made available by Public Law 104–91 may be used for—
>
> (1) the creation of a human embryo or embryos for research purposes; or
>
> (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and 42 U.S.C. 289g(b).
>
> For purposes of this section, the phrase "human embryo or embryos" shall include any organism, not protected as a human subject under 45 CFR 46 as of the date of enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes.[151]

Subsequent Appropriations Bills have incorporated the Dickey-Wicker Amendment every year since 1995.[152] Thus, the Department of Health and Human Services ("HHS"), the supervisory Department over the NIH, was, most pertinently, prohibited from disbursing funds for the purposes of experimenting directly on human embryos.[153]

For example, the Dickey-Wicker Amendment was a focal point of the Human Embryonic Stem Cell ("hESC") debate. In 2009, President Obama issued Executive Order 13505—Removing Barriers to Responsible Scientific Research Involving Human Stem cells—to overturn the George W. Bush-era policy regarding this kind of research.[154] Section 2 of the Executive Order provided that the HHS Secretary (through the Director of NIH) may choose to "support and conduct responsible, scientifically worthy human stem cell research,"—including hESC research,[155] and revoked Bush-era limitations that had been in place.[156]

On July 11, 2009, the NIH issued revised guidelines which enabled federal funding for research projects using hESCs.[157] These guidelines permitted the funding of research using embryonic stem cells previously derived from donor embryos, the embryos provided by individuals

151. *Id.*

152. *See, e.g.*, H.R. 1105, 111th Cong. § 509 (2009).

153. *See id.*

154. *See* Exec. Ord. No. 13,505, 74 Fed. Reg. 46 (Mar. 11, 2009).

155. *Id.*

156. *Id.* at §5.

157. *Guidelines on Human Stem Cell Research,* NAT'L INST. OF HEALTH, (2009), https://stemcells.nih.gov/policy/2009-guidelines.htm. .

(usually IVF patients) who had donated their embryos freely and with their informed consent.[158]

That same year, a legal challenge to the policy was raised in what became known as *Sherley v. Sebelius*.[159] On April 29, 2011, the United States Court of Appeals for the D.C. Circuit held that the NIH's interpretation of the Dickey-Wicker Amendment, as applied to funding research involving human embryonic stem cells, was entitled to *Chevron* deference, in view of the federal government's change in policy.[160] In *Sherley I*, scientists James L. Sherley and Theresa Deisher sued to enjoin the NIH from funding research using human embryonic stem cells. The district court granted a preliminary injunction and the government appealed to the D.C. Circuit. The appellate court vacated the injunction, finding Dickey-Wicker to be ambiguous, and that the NIH's conclusion was reasonable, because "although Dickey–Wicker bars funding for the destructive act of deriving an ESC [line] from an embryo, it does not prohibit funding a research project *in which an ESC* [*line*] *will be used*."[161]

In applying the first step of the *Chevron* doctrine to *Sherley I*, the court held that the text was ambiguous as applied to the term "research," and that, in applying the second step, it was reasonable for the NIH to interpret Dickey–Wicker as "permitting funding for research using cell lines derived without federal funding, even as it bars funding for the derivation of additional lines."[162] *Sherley I* was overturned on remand to the D.C. District Court,[163] the D.C. Circuit Court overturned that decision in *Sherley II*. Plaintiffs then appealed to the United States Supreme Court: on January 7, 2013, the Supreme Court denied certiorari, effectively settling the question.[164] Thus, after *Sherley* was decided, the ES cell lines themselves, although generated using human

158. Exec. Ord. No. 13,505 at §I.

159. Sherley & Deisher v. Sebelius, 644 F.3d. 388, 388-90 (D.C. Cir. 2011) (hereinafter *Sherley I*); *see also* Sherley & Deisher v. Sebelius, 689 F.3d. 776 (D.C. Cir 2012) (hereinafter *Sherley II*).

160. *Id.* Justice John Paul Stevens, writing for the Court in *Chevron U.S.A. v. Natural Resources Defense Council, Inc.*, articulated a two-part test for judicial review of administrative construction of statutory language: a reviewing court must consider (1) "whether Congress has directly spoken to the precise question at issue[,]" and, if Congress had not done so, consider (2) "whether the agency's answer is based on a permissible construction of the statute." If so, the reviewing court would afford the agency "*Chevron* deference." 467 U.S. 837, 842-44 (1984).

161. *Sherley v. Sebelius*, 644 F.3d. 388 at 390 [emphasis added].

162. *Id.*, at 394, 396.

163. Sherley, v. Sebelius, 704 F.Supp.2d 63 (D.D.C. 2010).

164. *Id.*, *cert. denied*, 133 S.Ct. 847 (2013).

embryos *without* federal funding, could be used in research projects supported by federal funding.

However, this holding is insufficiently broad to apply and thus permit federal funding of using TGE on human embryos, in which the research project involves manipulation of a human embryo. Executive Order 13505 was limited in scope to "human embryonic stem cell research."[165] The key difference is that Executive Order 13505 was limited to funding research on hESCs *derived* from human embryos, not research or experimentation on the embryos themselves.[166] Therefore, Dickey-Wicker still controls with respect to TGE on human embryos, and such projects may not be federally funded.[167]

B. Federal Funding of Scientific Research: Why it Matters and How it is Done

"It is false to suggest that medical breakthroughs come only through government research."
-Sen. Roger Wicker[168]

The NIH is America's most significant public source of funding for biomedical research in the field of life sciences.[169] In 2012, public funding for biomedical research and development accounted for about 41 percent of total funds, while private organizations and industry accounted for the remaining 59 percent.[170] The United States is fortunate to have a robust scientific community of passionate investigators with diverse research interests. In recent decades, the Human Genome Project ("HGP")[171] stands out as a success story: when government is willing to get the ball rolling and financially support

165. Exec. Ord. No. 13,505 at §2.

166. "These guidelines therefore recognize the distinction, accepted by Congress, between the derivation of stem cells from an embryo that results in the embryo's destruction, for which federal funding is prohibited, and research involving hESCs that does not involve an embryo nor result in an embryo's destruction, for which federal funding is permitted." NAT'L INST. OF HEALTH, GUIDELINES FOR HUMAN STEM CELL RESEARCH (2009).

167. H.R. 2880, 104th Cong. § 128 (1996).

168. 152 CONG. REC. 95, 5437 (2006).

169. *See* Justin Chakma et al., *Asia's Ascent—Global Trends in Biomedical R&D Expenditures*, 370 NEW ENG. J. MED. 3, 3 (2014); *see also Universities Report Continuing Decline in Federal R&D Funding in FY 2014* NATIONAL SCIENCE FOUNDATION (2015), https://www.nsf.gov/statistics/2016/nsf16302/.

170. *Id.* at 4.

171. *See generally* NAT'L INST. OF HEALTH, GENOME RESEARCH INSTITUTE, *All About The Human Genome Project (HGP)*, *available at* https://www.genome.gov/10001772/all-about-the--human-genome-project-hgp/.

research, the scientific community proves more than capable or rising to the challenge. During the years of, and immediately following, the HGP, the NIH's overall funding increased steadily, from about $7.6 billion in 1990 to $31.2 billion in 2010.[172] In 2016, NIH's estimated total budget was about $32.3 billion[173], with NIH requesting about $33.1 billion in Congressional appropriations for FY 2017.[174] Part of the NIH's stated mission for FY 2017 is to:

> [S]eek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. In pursuit of this mission, NIH conducts or supports research designed to understand the basic biology of human health and disease; apply this understanding towards designing new approaches for preventing, diagnosing, and treating disease and disability; and ensure that these new approaches are available to all.[175]

By its own numbers, "[m]ore than 80% of [NIH] funding" is awarded in "almost 50,000 competitive grants to more than 300,000 researchers at more than 2,500 universities, medical schools, and other research institutions in every state and around the world."[176] The HGP's extraordinary success answered many questions but, as is often the case with empirical science, raises far more. To paraphrase the Roman philosopher Cicero: 'the sinews of war are infinite money.'[177] The same argument should be made for the sinews of science.

1. The HGP Corollary: Big Science Works Best when Supported with Big Dollars (In this Case, Government Dollars)

The HGP was inaugurated in 1990. It was an ambitious international collaboration of scientists tasked with mapping all genes

172. *History of Congressional Appropriations, Fiscal Years 2000-2016*, NAT'L INST. OF HEALTH (2016), *available at* https://officeofbudget.od.nih.gov/pdfs/FY16/Approp%20History%20by%20IC%20FY%202000%20-%20FY%202016.pdf.

173. Francis S. Collins, Director, *Congressional Justification for F.Y. 2017*, NAT'L INST. OF HEALTH 1, 3(2016), https://officeofbudget.od.nih.gov/pdfs/FY17/31-Overview.pdf..

174. *Id.*

175. *Id.* at 2.

176. *What We Do: Budget*, *supra* note 37.

177. MARCUS TULLIUS CICERO, THE FIFTH ORATION OF M.T. CICERO AGAINST MARCUS ANTONIUS, OTHERWISE CALLED THE FIFTH PHILIPPIC. (44-43 BC) ("[. . .] first of all, with the sinews of war, money in abundance [. . .]"; in the Latin: 'Nervos belli, pecuniam infinitam'), *available at* http://www.perseus.tufts.edu/hopper/text?doc=Perseus%3Atext%3A1999.02.0021%3Aspeech%3D5.

that comprise the genome of the *Homo sapiens* species.[178] The United States Congress approved a funding scheme for the HGP totaling $3 billion with an estimated completion date of 2005—or sixteen years—to facilitate this mapping of the blueprint of life and to affirm the nation's preeminence as an intellectual superpower.[179] This was perhaps the most significant single federal investment in the field of life sciences, and the results were no less significant. Astoundingly, the HGP completed two years early (2003) and under budget (about $2.7 billion).[180] It produced an intellectual explosion of novel techniques, methods, and especially data.[181]

Today, the National Human Genome Research Institute ("NHGRI"), operating under the NIH, estimates that "the cost to generate a high-quality 'draft' whole human genome sequence in mid-2015 was just above $4,000; by late 2015, that figure [fell] below $1,500."[182] Within the next few years, the cost is expected to dip further, eventually reaching the idealized "$1000 genome" after which it is anticipated that personalized genomic sequencing may become a part of standard medical practice.[183] The HGP demonstrates that when the United States needs scientific progress, government support empowers the scientific community to meet and exceed the most ambitious expectations.

When considering the very notion of using taxpayer money to support TGE research on embryos, it would be in the public's best interest to support the work which those most in need: namely, TGE directed to mitigate or abrogate genetic diseases. This would require an examination and prioritization of which projects should receive funding, those projects directed to therapeutic intervention for genetic-associated disease could receive priority, thus distributing the funds in that such

178. *See An Overview of the Human Genome Project*, NAT'L HUM. GENOME RES. INST., https://www.genome.gov/12011238/an-overview-of-the-human-%20genome-project/ (last updated May 11, 2017).

179. *The Human Genome Project Completion: Frequently Asked Questions*, NAT'L HUM. GENOME RES. INST., (2010), *available at* https://www.genome.gov/11006943/human-genome-project-completion-frequently-asked-questions/..

180. *Id.*

181. Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome.* 409 NATURE 860, 914 (2001).

182. *The Cost of Sequencing a Human Genome*, NAT'L HUM. GENOME RES. INST., (2016), https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/ (using the $4000 figure, the cost to sequence a genome today is about 0.00015% of the initial cost of the HGP, or about 0.000056% using the $1500 figure).

183. *See generally* KEVIN DAVIES, THE $1,000 GENOME: THE REVOLUTION IN DNA SEQUENCING AND THE NEW ERA OF PERSONALIZED MEDICINE (2010).

a way that is both compassionate and goal-oriented. To achieve that, it is necessary to examine the standards of review, and why they should be further refined in view of the TGE revolution. We examine these issues in the next section.

2. The Present Regulatory Framework is Insufficient to Accommodate TGE Research on Human Embryos

a. From Grant Application to Bench: Initial and Ongoing Review and Oversight

A typical grant application to the NIH must pass two separate levels of peer review before being recommended for funding. First, a Scientific Review Group (SRG), made up of non-federal scientists with expertise in scientific research, reviews the grant application.[184] Next, the research must be approved by the National Advisory Council of the Institute and Center (IC). Scientific and non-scientific citizens who have demonstrated prowess in health and disease-related issues make up this second step of peer review.[185] A grant application must be approved by steps one and two before receiving a recommendation for funding, which would then be approved by IC Directors.[186] Thus, a researcher who wants to conduct biological research using NIH funding must first pass the two NIH levels of peer review. Once NIH Funding is Obtained for a Human Study, a Research Laboratory is Subject to Ongoing Oversight by an Institutional Review Board (IRB).[187] With respect to ongoing research involving human subjects, a Congressionally-authorized National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont Report in 1979.[188] The Belmont Report provided a number of recommendations guiding the ethical conduct of research involving human subjects.[189] Regulations grew out of these recommendations and

184. *Peer Review*, NAT'L INST. OF HEALTH, OFF. OF EXTRAMURAL RES., https://grants.nih.gov/grants/peer-review.htm (last visited Mar. 17, 2017).

185. *Id.*

186. *Id.*

187. *See* Basic HHS Policy for Protection of Human Research Subjects 45 C.F.R. §46, Subpart A (2009).

188. *The Belmont Report*, THE NAT'L COMMISSION FOR THE PROTECTION OF HUM. SUBJECTS OF BIOMEDICAL & BEHAVIORAL RES., (Apr. 18, 1979), *available at* https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf.

189. *Id.*

numerous federal agencies adopted them,[190] including HHS.[191] Today, the ensuing body of regulations is better known as the "Common Rule."[192] The Common Rule establishes the IRB, a committee comprising at least five members of varying and diverse backgrounds.[193] The function of an IRB is:

> [T]o promote complete and adequate review of research activities commonly conducted by the institution . . . to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects . . . to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice . . . . [i]f an IRB regularly reviews research that involves a vulnerable category of subjects, such as children . . . consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.[194]

The IRB thus serves as an intra-institutional check on research programs involving human subjects.[195] It relies on both scientific expertise and regulatory compliance to foster, in the words of the Belmont Report, "the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects."[196]

The 2009 NIH Guidelines on Human Stem Cell Research,[197] with respect to the Common Rule, recite that "IRB review may be required" in certain circumstances, for "certain research involving [human Embryonic Stem Cells] hESCs."[198] The rationale is that "[t]he HHS

190. *See* MAXWELL J. MEHLMAN, TRANSHUMANIST DREAMS AND DYSTOPIAN NIGHTMARES: THE PROMISE AND PERIL OF GENETIC ENGINEERING 174-76 (2012).

191. U.S. DEP'T OF HEALTH AND HUM. SERV., OFF. FOR HUM. RES. PROTECTIONS, FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS ('COMMON RULE'), https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/ (last visited Mar. 17, 2017).

192. *Id.*; *The Belmont Report*, *supra* note 188. *See also* Basic HHS Policy for Protection of Human Research Subjects 45 C.F.R. §46, Subpart A (2009).

193. *See* Basic HHS Policy for Protection of Human Research Subjects, 45 C.F.R. § 46, Subpart A

194. *Id.*

195. *Id.*

196. *The Belmont Report*, *supra* note 188; *see also* Basic HHS Policy for Protection of Human Research Subjects 45 C.F.R. §46, Subpart A (2009).

197. Collins Statement, *supra* note 38.

198. *Id.* at Section 9, Subsection I., Paragraph 3.

Office for Human Research Protections ("OHRP") considers biological material, such as cells derived from human embryos to be individually identifiable . . . "[199] A similar rationale might support the case of TGE and human embryos: an intra-institutional check through the IRB is important to protect the privacy rights of embryo donors, including obtaining donors' informed consent.[200] This ethical check could continue to serve as an appropriate concurrent oversight mechanism for projects featuring TGE directed to embryos, once funded. Since the donors supply the fertilized, cryopreserved eggs—the "extras" of an IVF procedure—OHRP regulations require obtaining and documenting informed consent from prospective donors.[201]

b. Additional Oversight through the FDA and DAC.

Additional layers of regulatory oversight exist in addition to the grant application review process. The FDA, in interpreting its statutory authority under the Federal Food, Drug, and Cosmetic Act ("Act"), determined in 1993 that the Act's definitions of "biological product" and "drug" was sufficiently broad to encompass products that would eventually emerge from the research into "somatic cell and gene therapies."[202] Similarly, the NIH maintains a federal Recombinant DNA Advisory Committee ("RAC") to advise the NIH Director about "recombinant or synthetic nucleic acid molecules."[203] The scope of

199. *Id.*

200. *See Human Embryo Research*, COMM. ON PEDIATRIC RES. AND COMM. ON BIOETHICS, AM. ACAD. OF PEDIATRICS (Sep. 2001), *available at* http://pediatrics.aappublications.org/content/108/3/813.

201. 45 C.F.R. § 46.111 (4-5) (2009).

202. U.S. Food and Drug Administration, Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53248 (1993).

203. The establishment of the RAC by the NIH director is authorized under The Public Health Service Act of 1944 § 402(b)(16), 42 U.S.C. § 282(b)(16): "[. . .]the Secretary [of HHS], acting through the Director of NIH [. . .] may, [. . .] establish such technical and scientific peer review groups and scientific program advisory committees as are needed to carry out the requirements of this subchapter and appoint and pay the members of such groups [. . .]." *See* DEP'T OF HEALTH AND HUM. SERV., NAT'L INST. OF HEALTH, CHARTER: RECOMBINANT DNA ADVISORY COMMITTEE (Jun. 30, 2017)("*Objectives and Scope of Activities:* The Committee will provide advice to the Director, National Institutes of Health (NIH), on matters related to (1) the conduct and oversight of research involving recombinant DNA, including the content and implementation of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), as amended, and (2) other NIH activities pertinent to recombinant or synthetic nucleic acid technology. There will be a continuing need for the Committee to serve

review would also encompass TGE as applied to human embryos. As of April 2016, RAC reviews gene transfer[204] protocols that institutional oversight bodies, such as IRBs or Institutional Biosafety Committees ("IBCs") refer to it.[205] Additionally, at least one of the following must be satisfied to trigger RAC review:

> a. The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk;
>
> b. The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or
>
> c. The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously.[206]

It is important to note here that, currently, the IRB or IBC must refer the study to RAC for review. However, were the *NIH Guidelines* appropriately revised, we could "bring back the RAC"[207] as the primary oversight body for NIH-funded gene transfer experiments generally, or perhaps specifically for TGE directed to human embryos. An expansion

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these functions so long as the NIH supports activities involving recombinant or synthetic nucleic acids.").

204. "Gene transfer" means "the deliberate transfer into human research participants of either recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or synthetic nucleic acid molecules." *Biomedical Technology Assessment: Oversight of Human Gene Transfer Research* NAT'L INST. OF HEALTH, OFF. OF SCI. POL'Y, http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt (last visited Mar. 17, 2017). *See also* UCI Office of Research, *Human Gene Transfer Research,* https://research.uci.edu/cascade/compliance/human-research-protections/researchers/human-gene-transfer-research.html (last visited Apr. 9, 2018).

205. *Charter Recombinant DNA Advisory Committee*, DEP'T. OF HEALTH & HUM. SERV. (May 22, 2017), *available at* https://osp.od.nih.gov/wp-content/uploads/RAC_Charter_2017_508.pdf.

206. *FAQ: Registration and Review Process for Human Gene Transfer Protocols*, NIH, http://www.osp.od.nih.gov/sites/default/files/FAQs%20on%20the%20NIH%20Review%20Process%20for%20Human%20Gene%20Transfer%20Trials%20%28October%202016%29.pdf (last visited Jan. 22, 2017).

207. *E.g*, Helen Thompson, *After 40 Years, Fate of Recombinant DNA Committee Under Review*, 19 NATURE MED. 1074 (2013) ("But the RAC now faces a potential reduction or modification of its powers [. . .]").

of the RAC might serve well to examine the ethical implications of TGE research on embryos.

As illustrated above, there are considerable ethical implications to such research. But as the United States risks lagging behind other countries that embracing government-funded TGE research on embryos, the impetus to progress in this field warrants a measure of urgent expediency, and it should be enshrined as government policy. It is therefore imperative that, despite the ethical oversight that exists within the NIH vetting process for grant applications, the federal government should provide the means for an adequate hearing of opposing views.

The next section proposes changes to Dickey-Wicker—either through NIH promulgating new interpretive guidance of the amendment or amending the statute itself—in addition to a novel plan for an additional, two-tiered system of ethical oversight and review of potential projects that would be considered for federal funding under a permissive policy of TGE research on embryos.

INTERLUDE: THE SOVIET UNION WINS ROUND TWO OF THE SPACE RACE

On April 12, 1961, aboard his 5-ton Vostock I spacecraft, Cosmonaut Yuri Gagarin became the first human being to orbit the Earth.[208] Although American astronaut Alan Shepard achieved the same feat aboard Freedom 7 less than a month later,[209] the United States remained profoundly behind their great rival in the Space Race; the Soviet Union had won round two. Newsweek, in an aptly titled article "Why We're Behind—Will We Catch Up?"[210] pondered whether the first man on the moon would "carry the hammer and sickle."[211] Undeterred, President Kennedy, in a speech before a joint session of Congress, made it a national priority "before this decade is out, of landing a man on the moon and returning him safely to the Earth."[212] NASA's budget increased by 89 percent that year, and increased

208. *A History of Human Spaceflight*, NASA, https://www.nasa.gov/topics/history/features/gagarin/gagarin.html (last visited Mar. 28, 2018).

209. May 5, 1961 to be exact. *See* David Hitt, *Who Was Alan Shepard?*, NASA (May 11, 2011), https://www.nasa.gov/audience/forstudents/k-4/stories/nasa-knows/who-was-alan-shepard-k4.html.

210. *Why We're Behind—Will Catch Up?*, NEWSWEEK: THE VOYAGE—SPECIAL SECTION (Apr. 24, 1961), *available at* http://www.newsweek.com/april-24-1961-us-response-yuri-gagarin-1860.

211. *Id.*

212. John F. Kennedy, *Special Message to the Congress on Urgent National Needs*, AM. PRESIDENCY PROJECT (May 25, 1961), http://www.presidency.ucsb.edu/ws/?pid=8151.

another 101 percent the next.[213] In his now-famous address at Rice Stadium in Houston, Texas that next year, Kennedy said in part:

> We choose to go to the moon. We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win, and the others, too.[214]

It is precisely because the questions surrounding the current subject of TGE are hard, that we should choose to pursue them, to accept the challenges and confront them, head on. For if we do not, we leave the door open for others to answer them for us.

IV. RECOMMENDATIONS

This Section provides putative recommendations for the federal government to begin to open the door to embryonic research, specifically as applied to TGE. These recommendations recognize the primacy of TGE for therapeutic ends, in accordance with The National Academies Consensus Report discussed in Section II.[215] I propose reinterpreting or amending the Dickey-Wicker text to expand permissible funding to some or all human embryos obtained from donors with informed consent, while simultaneously advocating for interdepartmental and interdisciplinary *ad hoc* committees to specifically and unambiguously lay out the reasonable ethical boundaries of frontier research and, significantly, prioritize and favor funding those conditions most detrimental to public health, or possibly single gene disorders.[216] We explore these options below.

213. John M. Logsdon, *John F. Kennedy and NASA*, NASA (Aug. 7, 2017), https://www.nasa.gov/feature/john-f-kennedy-and-nasa.

214. John F. Kennedy, President of the United States, speech at Rice Stadium (Sep. 12, 1962), *available at* https://er.jsc.nasa.gov/seh/ricetalk.htm.

215. *See 2017 Consensus Report*, *supra* note 101.

216. The National Academies' *Consensus Report* lists several potential therapeutic applications for somatic cell TGE, including sickle-cell disease, -thalassemia, X-linked severe combined immunodeficiency, hemophilia B, cystic fibrosis, HIV, Deuhenne's muscular dystrophy, Huntington's disease, etc., which could also form the basis for embryonic research priorities. *Id.* at 92-93; *see also Diseases Treated by Gene Therapy*, *supra* note 91.

A. Reinterpreting or Reevaluating Dickey-Wicker

As mentioned in Part IV.B., federal funding is the largest source of research funding for life sciences in the United States and currently, there is a prohibition on funding as applied to TGE on human embryos.[217] In order to meliorate this, the federal government could either permit federal funds to support TGE research on nonviable embryos,[218] or permit federal funds to support research on both viable *and* nonviable embryos.[219] The first option might be the more promising option in the short term, because the Dickey-Wicker Amendment's statutory text could simply be amended with the addition of a single word, so as to permit such funding. The textual change may be simple, but it is profound and, again, the political hurdles are complex and challenging. Although some have suggested an outright repeal of Dickey-Wicker,[220] such a drastic shift from established congressional policy is unlikely to gain much political traction in the near future.

A more politically feasible option might be for Congress to amend Dickey-Wicker and carve out exceptions, as was done during the stem cell debate.[221] Such exceptions, as the one proposed by George Annas,[222] would keep the *creation* of embryos for the purposes of research within the scope of prohibition, while enabling funding to support the actual research itself. The creation of the embryo remains the decision of the couple undergoing IVF, and preserves their decision-making autonomy: namely, the couple giving their informed consent to scientists who want to use for research those embryos not used specifically for implantation. This could allay public concern regarding the notion that scientists would be "creating" embryos—or life—solely for the purposes of research. Briefly, IVF is an assisted reproductive technology ("ART") that achieves fertilization artificially and outside of the body (*in*

217. H.R. 2029, 114th Cong. §§ 508, 749 (2015); *see also* H.R. 2880, 104th Cong. § 128 (1996).

218. *See* Liang, *supra* note 104.

219. This option would likely manifest as an outright repeal of Dickey-Wicker.

220. *See, e.g.,* Don C. Reed, *Repeal Dickey-Wicker: Time to Stop Renewing the Anti-Research Law*, THE HUFFINGTON POST (Nov. 9, 2010), https://www.huffingtonpost.com/don-c-reed/remove-dickeywicker-time-_b_780071.html.

221. *See, e.g.,* George J. Annas, *Resurrection of a Stem-Cell Funding Barrier—Dickey-Wicker in Court*, 363 NEW ENG. J. MED. (2010), 1687, 1689. (Here, Annas proposes amending Dickey-Wicker by adding a provision reading: "[n]othing in part (2) prohibits the NIH from funding research using embryos created for procreation, including the derivation of stem cells, *when the couple no longer wants to use them* for procreation *and has provided their informed authorization* for them to be used in NIH-funded research [emphasis added].")

222. *Id.*

vitro).[223] Fertilized eggs, called zygotes, divide and become embryos.[224] The embryo may then be transferred into the woman's womb or frozen for later implantation or donation.[225] Alternatively, the text of Dickey-Wicker could be amended so that subsection (a)(2) of the amendment adds the word "viable" to the term "human embryo." Doing so would unambiguously carve out an exception for research on nonviable human embryos, which would at least enable some projects. Each of these alternatives is explored below. The text of Dickey-Wicker could also further be amended to at last explicitly incorporate something akin to the 14-day-rule into the text as an exception to the funding prohibition, in order to impose a developmental time-limitation on subsequent research projects.[226] The 14-day rule, first proposed in the United States in 1979, specifies that "[. . .]no embryos will be sustained *in vitro* beyond the stage normally associated with the completion of implantation (14 days after fertilization) [. . .]" [227]. Furthermore, the United Kingdom's Warnock Committee endorsed the 14-day rule five years later,[228] and as of 2016 is codified into law in 12 countries.[229] While there have been proposals to extend the 14-day rule (to 21-days, for

223. *In Vitro Fertilization (IVF*), U.S. NAT'L LIBR. OF MED.: MEDLINE PLUS, https://medlineplus.gov/ency/article/007279.htm (last visited Apr. 8, 2018) [hereinafter *IVF*].

224. *FAQ: How Does a Fertilized Egg Develop?*, NATURE, http://www.nature.com/stemcells/2007/0706/070614/full/stemcells.2007.13.html (last visited Jan. 30, 2018).

225. *IVF*, *supra* note 223.

226. Hyun, et al, *supra* note 125.

227. ETHICS ADVISORY BOARD, DEP'T OF HEALTH, EDUC., AND WELFARE, REP. AND CONCLUSIONS: HEW SUPPORT OF RES. INVOLVING HUM. *IN VITRO* FERTILIZATION AND EMBRYO TRANSFER 107 (U.S. Gov't Printing Off. May 4, 1979); *see also* Hyun et al., *supra* note 125, at 170.

228. "We accordingly recommend that no live human embryo derived from in vitro fertilisation, whether frozen or unfrozen, may be kept alive, if not transferred to a woman, beyond fourteen days after fertilisation, nor may it be used as a research subject beyond fourteen days after fertilisation. This fourteen day period does not include any time during which the embryo may have been frozen." *UK Report*, *supra* note 125, at 66.

229. Hyun et al., *supra* note 125, at 170-71. The nations which have codified into law some variant of the 14-day rule include Australia, Canada, Denmark, Iceland, the Netherlands, New Zealand, Slovenia, South Korea, Spain, Switzerland, Switzerland (7 days), and the United Kingdom. But it is worth noting that "[t]he 14-day rule was never intended to be a bright ling denoting the onset of moral status in human embryos. Rather, it is a public-policy tool designed to carve out a space for scientific inquiry and simultaneously show respect for the diverse views on human-embryo research." *Id.* at 170.

example),[230] the notion of a strict developmental time restriction on embryonic research represents a reasonable balance between enabling embryonic research and acknowledging public concerns; it has been employed in other countries, and is certainly worth considering.[231]

B. NIH Guidance Should Interpret Dickey-Wicker to Permit TGE That Uses Nonviable Human Embryos

Yet another suggestion—as a possible first step—would be for the NIH to reinterpret the statutory language to exempt *nonviable* embryos from the funding prohibition, and revise its Guidelines to reflect that reinterpretation. In so doing, it would thus be useful to analyze Dickey-Wicker in its entirety under the *Chevron* framework, using the reasoning of the to what the D.C. Circuit in *Sherley I* as a template, to determine whether, first, if Congress had spoken to the precise question at issue relating to TGE in nonviable human embryos and second, if it had not done so, whether an interpretation of the text to permit some or all of the experiments contemplated above would constitute a reasonable or permissive interpretation of the statute.[232] In *Sherley I*, the majority adopted a narrow reading of the word "research," as there was "no basis for th[e] inference" to read it more broadly as urged by the plaintiffs.[233] Because of this narrow interpretation, the majority ultimately found the text of Dickey-Wicker to be ambiguous, and thus proceeded to step two of the *Chevron* analysis.[234] Subsection (a)(1) prohibits federal funds from supporting research that contemplates the "creation of a human embryo or embryos for research purposes."[235] The United States' current practice regarding derivation of embryonic stem cell lines permits acquisition of embryos from donors who underwent IVF treatment with their informed consent.[236] The act of *in vitro*

230. *See, e.g.*, John Harris, *It's Time to Extend the 14-Day Limit for Embryo Research*, THE GUARDIAN (May 6, 2016).

231. For example, we could amend the text of subsection (a)(2) of Dickey-Wicker to read: "(a) None of the funds made available in this Act may be used for—[. . .] (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)) (Title 42, Section 289g(b), United States Code) *after 14 days post-fertilization* (emphasis added)."

232. *See Chevron,* 467 U.S. at842-44..

233. *Sherley v. Sebelius*, 644 F.3d. 388 at 394.

234. *Id.*

235. H.R. 2880, 104th Cong. § 128 (1996).

236. Exec. Ord. No. 13,505 at §I ("The Guidelines allow for funding of research using hESCs derived from embryos created using in vitro fertilization (IVF) for reproductive purposes and no longer needed for these purposes,

fertilization is the "creation of a human embryo[.]"[237] This explains, in part, why government health insurance programs like Medicaid do not cover IVF treatments,[238] and why many people seeking IVF will have to pay out-of-pocket for the procedure.[239] IVF-generated embryos from donors form the bulk of the embryos utilized to generate stem cell lines and the like. Scientists could perform similar TGE studies with donor embryos. Therefore, a TGE project hypothetically funded by federal sources need not require that the researcher create their own embryos: researchers can obtain them from IVF donors with informed consent, as is done for stem cell line derivation.[240] This piece—that is, Dickey-Wicker subsection (a)(1)—is no different from the currently-funded research on stem cells, except that the stem cell lines have technically been derived from embryos *separately* from the downstream, federally funded, research. But with TGE on embryos, the research is being performed on the embryos themselves.

The challenge is in Subsection (a)(2).[241] It follows that after a TGE experiment in which the experimental embryos are not implanted into a uterus, the experimental embryos would be destroyed. The UK and Sweden pioneer studies both operate under a legal framework that require this.[242] However, if Dickey-Wicker intended to promote a culture of life, then perhaps *nonviable* embryos—those which are incapable of developing into a human—would not fit into this category. The Huang group (China), in their seminal publication, employed tripronuclear zygotes in their study demonstrating CRISPR/Cas9 editing of human embryos.[243] The tripronuclear zygotes consist of "one oocyte nucleus

assuming the research has scientific merit and the embryos were donated after proper informed consent was obtained from the donor(s).").

237. *See* H.R. 2880, 104th Cong. § 128 (1996).

238. *Medicaid Coverage & Fertility Treatment*, UNIV. OF COLORADO, https://arm.coloradowomenshealth.com/resources/medicaid-fertility-treatments/ (last visited Mar. 16, 2017).

239. Couples and individuals seeking fertility treatment might pay anywhere from $10,000 to more than $60,000 out of pocket. *See, e.g.*, Nina Bahadur, *The Cost of Infertility: This is How Real People Pay for IVF*, SELF (Jan. 8, 2018), https://www.self.com/story/the-cost-of-infertility.

240. *See, e.g., Stem Cell Research: Embryo Donation*, UNIV. OF MICH., http://www.stemcellresearch.umich.edu/donation/donors.html (last visited Mar. 16, 2017).

241. Prohibiting federal funds for "(2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research under [applicable Federal regulations] . . . " H.R. 2880, 104th Cong. § 128 (1996).

242. Fogarty, *supra* note 116, at S1; *see also* Lanner Interview, *supra* note 41.

243. *See* Liang et al., *supra* note 104. *See also* David Cyranoski & Reardon, *supra* note 39.

and two sperm nuclei"[244] and would not likely result in a live birth, even if later implanted in a uterus. Thus, IVF procedures screen against embryos having aneuploidy (including triploidy).[245] Contrast the scenario of modifying a nonviable embryo with modifying a viable one (that is, capable of developing into a full-grown human). If the nonviable embryo were implanted in a uterus, then, it would not develop into a fetus; in other words, there is no potential for life from the get-go.[246] Indeed, if researchers used only nonviable, tripronuclear embryos for their experiments, one could even argue that the "creation" of tripronuclear zygotes, inherently incapable of life, may be permissible with respect to provision (1) of Dickey-Wicker. These issues a very narrow line on defining "life," or "an organismic state characterized by capacity for metabolism, growth, reaction to stimuli, and reproduction."[247] Such properties are not ascribed to a nonviable embryo.[248] Thus, in applying *Chevron*'s second step, a court could reasonably conclude that a "permissible interpretation" of the decidedly ambiguous wording of the statute[249] could encompass nonviable embryos. If the NIH chose to do so, it might well revise their Guidelines to render nonviable embryos permissible for federally-funded TGE research. This reasoning would appear to be in tandem with the D.C. Circuit's holding in *Sherley I*, in which it agreed with the government's position and reliance on the 2009 NIH Guidelines which "expressly distinguished" between the derivation of ESCs and "research involving [ESCs] that does not involve an embryo nor result in an embryo's destruction" [. . .] mak[ing] clear the agency's understanding that 'research involving [ESCs]' does not

244. *Id.*, at 364.

245. *See, e.g.*, *Preimplantation Genetic Screening*, ADVANCED FERTILITY CTR. CHI., https://www.advancedfertility.com/pgs-ivf-genetic-testing.htm (last visited Mar. 28, 2018).

246. Except, perhaps, from TGE methods or experiments which could *restore* or *impute* viability to an otherwise nonviable embryo. In such a case, the resultant, TGE-modified embryo would go from being inherently nonviable to becoming viable. *See, e.g.,* Cyranoski & Reardon, *supra* note 39.

247. *Definition of* Life, MERRIAM-WEBSTER DICTIONARY, *available at* http://www.merriam-webster.com/dictionary/life (last updated Jan. 25, 2018).

248. *See* Wolfe v. Isbell, 208 So.2d 758, 759 (Ala. 1973) ("By nonviable we mean not capable of living, growing, or developing and functioning successfully, the antithesis of viable, which is defined as having attained such form and development of organs as to be normally capable of living outside the uterus."). *See* Mack v. Carmack, 79 So.3d 597, 602, 606 (Ala. 2011) (recognizing the abrogation).

249. *E.g.*, *Sherley v. Sebelius*, 644 F.3d. 388.

necessarily include the antecedent process of deriving cells."[250] This reasoning is consistent with Clinton HHS General Counsel Harriet Rabb's determination that "federally funded research that utilizes hPSCs [human pluripotent stem cells] would not be prohibited by the HHS appropriations law prohibiting human embryo research, *because such cells are not human embryos* (emphasis added)."[251] But herein is the critical question: are nonviable embryos, particularly tripronuclear embryos, still considered "human embryos?"

It would appear so. Subsection (b) of Dickey-Wicker provides the answer: "the term 'human embryo or embryos' includes any organism, not protected as a human subject[. . .]that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."[252] Tripronuclear embryos—and all aneuploid embryos for that matter—are still the result of fertilization: sperm and egg, and would thus qualify as a human embryo under the defined term. Although tripronuclear embryos are not entirely rare,[253] the prognosis is almost universally grim, nearly always resulting in miscarriage.[254] This is why abnormally fertilized oocytes are not transferred in IVF procedures.[255] But since there is a potential for live birth, tripronuclear embryos would not, strictly speaking, be thought of as inherently nonviable. While the Supreme Court of the United States has yet to issue a ruling on the personhood of a nonviable embryo, some states have distinguished nonviable embryos from viable embryos: for example, Louisiana defines a nonviable embryo as an

250. *Sherley v. Sebelius*, 644 F.3d. 388 at 396 (quoting NIH 2009 Guidelines, 74 Fed.Reg. 32, 172/2).

251. National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells, 64 Fed. Reg. 51795, 51976 (Aug. 25, 2000).

252. Consolidated Appropriations Act, 2017, Pub. L. No. 115-31, § 508(b), 131 Stat. 135, 563 (2017); *see also* O. Carter Snead, *Science, Public Bioethics, and the Problem of Integration*, 43 U.C. DAVIS L. REV. 1529, 1547 note 76 ("Accordingly, there is strong support for the proposition that a blastocyst is clearly an individuated organism, that is, a whole, individual member of the human species.").

253. Triploidy is thought to occur in 2-3% of pregnancies, often resulting in spontaneous abortion, but "occasionally results in the fetal or newborn period with the birth of an abnormal fetus or infant." D.E. McFadden & W.P. Robinson, *Phenotype of Triploid Embryos*, 43 J. MED. GENETICS 609, 609 (2006).

254. *Abnormally Fertilised Embryos in IVF Biology Essay*, UKESSAYS (March 23, 2015), https://www.ukessays.com/essays/biology/abnormally-fertilised-embryos-in-ivf-biology-essay.php.

255. *Id.*; *see also* Katie Feenan & Mary Herbert, *Can 'Abnormally' Fertilized Zygotes Give Rise to Viable Embryos?*, 9 HUM. FERTILITY 157, 164 (2006).

embryo that is not "considered a juridical person."[256] While not federally authoritative, such distinctions might help establish a fundamental distinction between viable and nonviable embryos. But assuming, arguendo, that the tripronuclear embryos from IVF would still fit the definition of "human embryo," the Dickey-Wicker text, as written, would not inherently exempt these embryos from the funding prohibition. What is left? The only remaining category of embryos that, strictly speaking, are nonviable are those "deemed to have 'arrested irreversibility[,]'" [257] which have been shown as a potential source for ESC derivation.[258] These embryos would have to be empirically examined after fertilization to determine whether they are, in fact, nonviable. In such a case, the potential for life in these 'dead' embryos is zero.

C. Congress Should Amend Dickey-Wicker to Limit the Prohibition of Federal Funds to 'Viable' or 'Diploid' Human Embryos

An alternative option to the one discussed in the preceding subsection would be for Congress to amend Dickey-Wicker by introducing a minor but profound change to the language of the statute that would qualify the viability of embryos so currently prohibited.[259]

256. LA. STAT. ANN. § 9:129 Destruction ("A viable in vitro fertilized human ovum is a juridical person which shall not be intentionally destroyed by any natural or other juridical person or through the actions of any other such person. An in vitro fertilized human ovum that fails to develop further over a thirty-sixhour period except when the embryo is in a state of cryopreservation, is considered nonviable and is not considered a juridical person."). *See also* Jeter v. Mayo Clinic Arizona, 121 P.3d 1256, 1261 (App. App. Div. 1 2005). *But see, e.g.,* People v. Kurr 654 N.W.2d 651, 654 (Mich. App. 2002).

257. Asma Shaikh, *Dead Embryos Give Life,* ISSUES BERKELEY MED. J. AT UC BERKELEY (2007), https://www.ocf.berkeley.edu/~issues/articles/14.2_Shaikh_A_Dead_Embryos_1.html ("meaning the blastomeres had not undergone any cleavage division for at least 24 to 48 hours after conception[. . .] so-called dead embryos[. . .]").

258. *See, e.g.*, Xin Zhang, et al., *Derivation of Human Embryonic Stem Cells from Developing and Arrested Embryos*, 24 STEM CELLS 2669, 2671, 2672 (2006).

259. Thus, the text of Dickey-Wicker might read: "(a) None of the funds made available in this Act may be used for: (1) the creation of a *viable* human embryo or embryos for research purposes; or (2) research in which a *viable* human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research under 45 CFR 36.204(b) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For the purposes of this section, the term "human embryo or embryos" includes any *diploid* organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any

Amending the statutory language to only encompass those embryos with propensity to develop into a fully-grown human (subsection (a)(1), (2)) may be more politically suitable and expedient, as permitting nonviable embryo modification only could be more palatable to pro-life politicians. This would unambiguously carve out an exception for researchers to use federal support in using TGE on 'dead' embryos. The second modification adds the qualifying word 'diploid' to the definition of "human embryo or embryos," which would carve out an exception for tripronuclear embryos, and other embryos having an abnormal gamete copy number.[260] The addition of this qualifier opens the door, if only a crack, to TGE research on embryos. This crack may be just enough, however, to empower American scientists to begin to close the knowledge gap that is emerging, as other nations entertain and embrace these controversial research proposals.

Because an outright repeal of Dickey-Wicker is unlikely, certain research proposals would be rejected out-of-hand. Take Dr. Niakan's study (discussed below in Section III.B), for example: her work focuses on genes involved in organismal development and why pregnancies terminate.[261] This project would clearly be prohibited from being federally funded under the present-day Dickey-Wicker[262] language, since the embryos are destroyed at the end of the experiment.[263] Under a hypothetical revision (further qualifying "human embryo" by adding the word "viable"), work like Dr. Niakan's would probably still be prohibited from receiving federal funds, since her work is being done with viable embryos. Some may argue that modifying an existing embryo meets the definition of "the creation of a [new] human embryo."[264] But the argument could also be made that introducing synthetic changes (or, alternatively, animal copies of the gene/mutation of interest) result in the creation of something novel, and not quite a *human* embryo.[265] This argument, however, is fraught with peril: if

other means from one or more human gametes or human diploid cells (emphasis added)."

260. This may include monopronuclear (1PN) or polypronuclear (4PN) zygotes. *See, e.g.*, Yoshiteru Kai, et al., *Diagnosis of Abnormal Human Fertilization Status Based on Pronuclear Origin and/or Centrosome Number*, 32 J. ASSISTED REPROD. GENETICS 1589, 1589 (2015).

261. Callaway, *supra* note 40.

262. H.R. 2880, 104th Cong. § 128 (1996).

263. *Id.*

264. H.R. 2880, 104th Cong. § 128 (1996).

265. Our legal system recognizes that a substantially altered biologic is regarded as something substantively different from the source material. *See, e.g.,* Diamond v. Chakrabarty, 447 U.S. 303, 317-18 (1980). The United States Patent and Trademark Office ("USPTO") affords patent protection to modified biologics, including cell lines. *See, e.g.*, U.S. Patent

today we justify enabling research that modifies an embryo by claiming that the end product is no longer a human embryo, we prospectively set ourselves up for a legal morass if the day ever came that these so-modified embryos were to be brought to term. Would a newborn, perceptively human but borne of embryonic modification, be considered something *other* than human? Would that newborn be afforded the same rights and protections as any other baby? Instinctively, we would say 'yes,' but preemptively categorizing its embryonic state as something other than a human embryo would clearly carry with it its own set of legal risks.

D. Proposed ad hoc *Committee Solution*

If embryonic research using TGE were putatively allowed, by either legislative or administrative action, it would be necessary to set clear and unambiguous ethical standards. One possibility of providing first-blush ethical oversight would be to expand the regulatory power to two *ad hoc* committees: a governmental Inter-Departmental Advisory Committee, as well as a Citizens' Advisory Committee. Both Inter-Department Advisory Committees[266] and Citizens' Advisory

No. 4,438,032 (filed Jan. 6, 1983). More relevantly, the United States Supreme Court in *Ass'n. for Molecular Pathology v. Myriad Genetics* distinguished between naturally occurring DNA sequences, which are ineligible for patent protection, and synthetic creations ("complimentary-DNA or cDNA"), which are patent-eligible. Ass'n for Molecular Pathology v. Myriad Genetics, 133 S.Ct. 2107, 2119 (2013). Importantly, the Court held that the "creation of a cDNA sequence from mRNA results in an exons-only molecule that is *not naturally occurring* [emphasis added]." *Id.* at 2119. That the Court would recognize the patentability of a biologic that is not "naturally occurring" (*Id.* at 2111) and is "unquestionably [. . .] something new" (*Id.* at 2119) at the very least signals a distinction between organic matter found in nature and synthetically modified or altered matter. The CRISPR/Cas9 technology has been found by the U.S. Patent Trial and Appeal Board ("PTAB") to be patentable subject matter. The Broad Institute, Inc. v. The Regents of the Univ. of Cal., No. 106,048 (P.T.A.B. Feb. 15, 2017), 1-51, at 49 (holding for The Broad Institute over Univ. of California's claim of patent interference; Univ. of California has appealed this decision to the U.S. Court of Appeals for the Federal Circuit. *See also* Jon Cohen, *Ding, Ding, Ding! CRISPR Patent Fight Enters Next Round*, SCIENCE NEWS (Jul. 26, 2017, 9:00 AM)). Inevitably, inventive products including TGE-modified human embryos will be claimed by inventors in applications to U.S. Patent and Trademark Office ("USPTO") for patent protection. Under the *Myriad* framework, such constructs may be patent-eligible, as TGE-modified embryos are not "naturally occurring" and are "something new." *Myriad Genetics*, 133 S.Ct at 2111, 2119. Does this intellectual property definition distinguish TGE-modified human embryos as something different than naturally-occurring "human embryos" under Dickey-Wicker?265. It remains a close question.

266. *See, e.g.*, *Federal Interagency Committee on Indoor Air Quality (IAQ)*, U.S. ENVTL. PROTECTION COMMISSION, https://www.epa.gov/indoor-air-

Committees[267] have been developed for other purposes, when the issues presented are amenable to varied opinions and forethought. The NIH Director would have the authority (through the HHS Secretary and, ultimately, the President) to establish the two Advisory Committees, under 42 U.S.C. § 282(b)(16)[268] and the Federal Advisory Committee Act of 1972.[269] The purpose of these Advisory Committees would be to address the questions: "[w]hat embryonic TGE research deserves priority?" and "What are the ethical limits to such research?" These committees could weigh various factors such as *which* genetic disorders warrant priority over others[270] or whether and how much animal model data would be required for a TGE-directed gene transfer. More than likely, HHS would spearhead the development of these committees through the Administrative Procedures Act's rule-making process.[271] The committees might adopt a bicameral approach, such that each committee convene individually to draft its recommendations, then reconcile the two before issuing a final report.

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quality-iaq/federal-interagency-committee-indoor-air-quality (last visited Jan. 2, 2018). Established by Congress in 1983, IAQ is co-chaired by the EPA, the Consumer Product Safety Commission, the Department of Energy, the National Institute for Occupational Safety and Health, and the Occupational Safety and Health Administration.

267. *See, e.g.*, Gerhard Peters & John T. Wooley, *Richard M. Nixon: Statement Announcing the Creation of the Environmental Quality Council and the Citizens' Advisory Committee on Environmental Quality*, THE AMERICAN PRESIDENCY PROJECT, http://www.presidency.ucsb.edu/ws/?pid=2077 (last visited Apr. 9, 2018) (established a 15-member committee to "examine the full range of variables which affect environmental quality."); *see also* 42 U.S.C. §4345 (1970).

268. This is the same authority by which the NIH Director could establish the RAC. *See supra* note 203.

269. Federal Advisory Committee Act of 1972, 5 U.S.C. App. §§1-16. Specifically, at § 7(a) established "[. . .] a Committee Management Secretariat, which shall be responsible for all matters relating to advisory committees. [. . .]" and § 9(a) "No advisory committee shall be established unless such establishment is – [. . .] (2) determined as a matter of formal record, by the *head of the agency involved* after consultation with the Administrator [of General Services], with timely notice published in the Federal Register, to be *in the public interest* in connection with the performance of duties imposed on that agency by law" (emphasis added).

270. For example, single gene and more commonly prevalent disorders (e.g., monogenic, or single-gene, disorders which are most common, like cystic fibrosis, may warrant higher priority and, thus, greater fund accessibility). *See e.g.*, *Genes and Human Disease*, WORLD HEALTH ORG., http://www.who.int/genomics/public/geneticdiseases/en/index2.html (last visited Mar. 1, 2018).

271. *See* 5 U.S.C. § 553 (1966).

The first tier, an inter-Department Advisory Committee might include representatives from relevant Independent Agencies and Executive Agencies including NIH, FDA, the National Science Foundation ("NSF"), the Department of Defense, and the Department of Agriculture ("USDA").[272] The Departments and Agencies might designate an appropriate employee of the Department or Agency versed in the scientific terminology to facilitate obtaining a swift, but deliberate decision on a particular grant proposal. Hypothetically, each Department/Agency listed above would be included, making for at least a 5-member committee. The 'Citizens' Advisory Committee,' could be styled much like an IRB. Significantly, IRB membership requires that members have "varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution . . . " including "at least one member whose primary concerns are in nonscientific areas . . . [and] at least one member who is not otherwise affiliated with the institution . . . "[273] A prototypical Committee might consist of:

> (1) at least one Member or Elected Fellow of the American Association for the Advancement of the Sciences (AAAS), preferably with expertise in the life sciences;
>
> (2) at least one Member of the American Medical Association (a licensed medical doctor, for example);
>
> (3) at least one Member of The National Academy of Sciences;
>
> (4) at least one Member of The National Academy of Medicine; and
>
> (5) at least one member whose primary concerns are in nonscientific areas (much like the IRB).

One would argue that a spiritual, religious, or otherwise "pro-life" voice should be a part of the process. Such a voice would fit into group (3) in the hypothetical example above. This additional layer of scrutiny, while cumbersome at first blush, nevertheless imparts a deserved degree of gravity to the ultimate decision of whether or not to finance a given research proposal with taxpayer dollars. Whatever the system might look like in the end, it is absolutely critical that dissenting opinions against such projects receive a fair hearing.

272. Possibly, if plant or animal genetic material were to be used in conjunction with the research on embryos.

273. IRB Membership Rule, 45 C.F.R. § 46.107 (2010).

CONCLUSION

Targeted Genomic Editing is and will remain a controversial subject, especially as applied to humans and human embryos. The ethical questions are hard but, as President Kennedy said, that is precisely why we should choose to accept such a challenge.[274] In the same spirit as how in the industrial revolution we harvested coal to fuel factories, which mass produced the modern conveniences that enhanced the lives of so many, the genomic revolution has arrived. Directed biological evolution is no longer mere science fiction. If TGE—through CRISPR-Cas9 or its possible future successor technologies—provides humanity with a safe and effective means of command over the genetic sequence, ethical and moral questions abound; this is undeniable. Is it right to manipulate human embryos, considering that we have been legally manipulating embryos for decades (emergency contraception, abortion, IVF). Should we be playing God or have we already crossed the Rubicon? Consider also that the entire genome is up for grabs now, and the drive to achieve human enhancement will be as insatiable as for healing the sick. Private donors are free to fund whichever laboratory or project they wish. The public benefit has already deemed scientific research worthy of taxpayer support—through it we have a robust, diverse, largely collaborative (at home and abroad) manufactory of knowledge that can save lives and make them better. If TGE lives up to its realistic potential, genetic disease as we know it could cease to be. Prospective mothers may never again be forced to face the impossible situation of choosing to abort a pregnancy for fetal health reasons—a win for the pro-life movement.

EPILOGUE

We knew that we had created a new means of warfare, and the question as to what nation, to what victorious nation we were willing to entrust this brainchild of ours was a moral decision more than anything else. We wanted to see the world spared another conflict such as Germany had just been through, and we felt that only by surrendering such a weapon to people who are guided by the Bible could such an assurance to the world be best secured.

-Wernher von Braun[275]

274. Kennedy, *supra* note 214.

275. *Von Braun's Surrender*, A WELL-DESIGNED FAITH (Dec. 8, 2014), http://welldesignedfaith.net/2014/12/08/von-brauns-surrender/; Arts & Entertainment, Biography (1959–1961 series). Mike Wallace, television biography of Wernher von Braun, video clip of the press statement (May 1945).

History has shown us that, where the national interest is sufficiently compelling, it is worse to do nothing than act in a manner which, in hindsight, could be seen as morally questionable. In the quest for technological supremacy, the ends tend to justify the means. On July 20, 1969, American astronauts Neil Armstrong and Buzz Aldrin became the first humans to walk the surface of the moon.[276] The Apollo 11 mission was a success and, for all intents and purposes, the United States had won the Space Race. The United States and NASA had fulfilled the goal articulated by President Kennedy more than seven years prior, and more than four months ahead of the December 31, 1969 deadline. The Saturn V rocket, which enabled the Apollo 11, was a joint project between NASA and the Douglas Aircraft Company, and was developed at the Marshall Space Flight Center in Huntsville, Alabama.[277] The first director of the Marshall Center was Wernher von Braun.[278] Dr. von Braun was one of the preeminent aerospace engineers and physicists of the 20th century.[279] He was also a member of the Nazi Party,[280] and was recruited to the Schutzstaffel (SS) in 1940.[281] His work proved instrumental in the development of the German V-2 rocket in 1942 and revolutionized modern warfare.[282] In 1944, he and about 125 other prominent German scientists were recruited to the United States under Project Paperclip.[283] He spent the next twenty-eight years serving the United States, and was instrumental in the nation's development of rocketry and the Space Program. Viewed through the lens of history, it would be easy to judge the actions of our forbearers harshly. Colluding with Nazis?[284] Unacceptable! But the national interest

276. Sarah Loff, *Apollo 11 Mission Overview*, NASA (Dec. 21, 2017), https://www.nasa.gov/mission_pages/apollo/missions/apollo11.html.

277. Wernher von Braun, *Saturn the Giant* , NASA, https://history.msfc.nasa.gov/saturn_apollo/giant.html (last visited March 28, 2018).

278. *Id.*

279. Jennifer Harbaugh, *Biography of Wernher Von Braun*, NASA (Aug. 3, 2017), https://www.nasa.gov/centers/marshall/history/vonbraun/bio.html.

280. *See* MICHAEL J. NEUFELD, VON BRAUN: DREAMER OF SPACE, ENGINEER OF WAR 96 (2007) (Nazi Party number 5,738,692).

281. *See* BOB WARD, DR. SPACE: THE LIFE OF WERNHER VON BRAUN (2009).

282. Harbaugh, *supra* note 279.

283. ANNIE JACOBSEN, OPERATION PAPERCLIP: THE SECRET INTELLIGENCE PROGRAM TO BRING NAZI SCIENTISTS TO AMERICA ix.(2014); *see also Joint Intelligence Objectives Agency*, U.S. NAT'L ARCHIVES & REC. ADMIN. https://www.archives.gov/iwg/declassified-records/rg-330-defense-secretary (retrieved Oct. 9, 2008); *see also* CLARENCE G. LASBY ET. AL., PROJECT PAPERCLIP: GERMAN SCIENTISTS AND THE COLD WAR, 79 (1971); *see also* Harbaugh, *supra* note 279.

284. Albeit reluctantly.

demanded it. Rocketry was a game changer, both militarily and with respect to space exploration, to "slip[] the surly bonds of Earth and dance[] the skies on laughter-silvered wings . . . "[285] To let the intellectual capital, epitomized by von Braun and others, be extinguished was an unacceptable loss to the United States. Instead, Project Paperclip snatched up this intellectual capital and put it to use, and the results speak for themselves. To have done nothing? *That* would have been unacceptable. It was true then, and remains true today.

285. John Gillespie Magee, Jr., *High Flight*, *available at* http://www.davidpbrown.co.uk/poetry/john-magee.html.