SYNTHETIC BIOLOGY

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INTRODUCTION

This Technology Explainer will explore the growing field of synthetic biology. Although other fields of science may fall under the umbrella of synthetic biology, the scope of this piece will be limited to the generally accepted view that synthetic biology is a branch of bioengineering dedicated to the creation of artificial, unnatural, or synthetic forms of life via gene-editing techniques.[1] The discussion begins with an analysis of the underlying principles of synthetic biology. It then describes the innovative examples, standardization efforts, and common criticisms of this controversial science.

I. BACKGROUND

Life is a simulation. Or so the synthetic biologists believe.[2] To them, all living things are generated by lines of code found in DNA. These lines of code are known as **nucleotides**, and only four are necessary for life on Earth: adenine (A), cytosine (C), guanine (G),

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[1] *Synthetic Biology*, NAT'L HUM. GENOME RSCH. INST. (Aug. 14, 2019), https://www.genome.gov/about-genomics/policy-issues/Synthetic-Biology [https://perma.cc/WD9F-HS6B].

[2] John Sullins, *Synthetic Biology: The Technoscience of Artificial Life*, 39 THE PAIDEIA ARCHIVE: TWENTIETH WORLD CONG. OF PHIL. 46-53 (1998).

and thymine (T).[3] Although nucleotides operate differently than the binary code that instructs computers, synthetic biologists consider nucleotides analogous to computer code because the sequence of an organism's nucleotides programs its cells to display certain features.

To better understand this programming analogy, the following biological information is instructive. Bacteria, fungi, plants, and animals are made of cells that contain DNA in its iconic double helix shape. DNA is comprised of a long sequence of nucleotides linked together in base pairs. The order of an organism's base pairs instructs its cells to generate particular proteins, which are essential for supporting life.[4] Thus, nucleotides are responsible for life as we know it: the differentiating factor among species is the order and length of the base pairs. For humans, the sequence of three billion base pairs spread across our DNA makes up the human **genome**.[5] The genome contains every identifiable aspect of a person, from eye color to height.[6] But the genome contains more sinister details as well, like the risk of cancer,[7] Alzheimer's disease,[8] and heart disease.[9]

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[3] A fifth nucleotide, uracil (U), is used in RNA and viral genetic material, but synthetic biologists focus on the DNA-specific nucleotides when "programming" synthetic organisms. Laurence Brody, *Nucleotide*, NAT'L HUM. GENOME RSCH. INST. (Oct. 27, 2023), https://www.genome.gov/genetics-glossary/Nucleotide#:~:text=A%20nucleotide%20is%20the%20basic,)%20and%20thymine%20(T) [https://perma.cc/63V7-XTH4].

[4] *Id.*

[5] Alice Park, *The Human Genome Is Finally Fully Sequenced*, TIME (Mar. 31, 2022), https://time.com/6163452/human-genome-fully-sequenced/

[6] Neil Lamb, *Biotech Basics: Genetics of Eye Color*, HUDSONALPHA INST. FOR BIOTECHNOLOGY (2009), https://www.hudsonalpha.org/the-genetics-of-eye-color/ [https://perma.cc/DM5Y-XHVT].

[7] *The Genetics of Cancer*, NAT'L CANCER INST., https://www.cancer.gov/about-cancer/causes-prevention/genetics [https://perma.cc/R575-TTMY].

[8] *Alzheimer's Disease Genetics Fact Sheet*, NAT'L INST. ON AGING, https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet [https://perma.cc/7KNM-CF3C].

[9] Rachel Hajar, *Genetics in Cardiovascular Disease*, 21 HEART VIEWS 55 (2020).

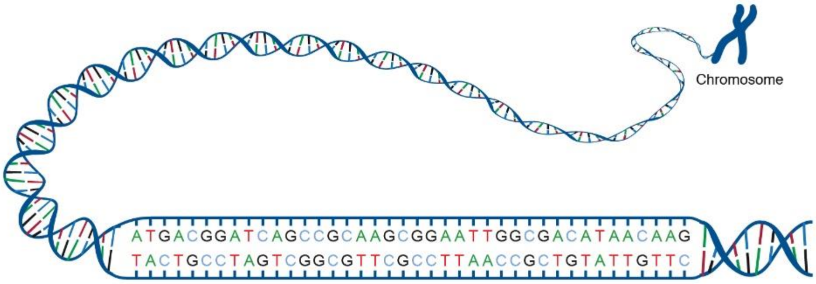

Figure 1: Simple diagram of a genome. Note that there are only four nucleotides: A, C, G, and T. Each sequence of 3 base pairs instructs the cell to produce a specific amino acid. Using gene-editing techniques like CRSPR, these base pairs can be edited to produce different effects on the cell. (Source: National Genome Research Institute[10])

Synthetic biologists view an organism's genome as its software, and its biological material as its "wetware," which is an analogue to "hardware" in classical computing.[11] In the same way that computer programmers assign functions to specific strings of code, synthetic biologists assign functions to genomic sequences. The bacteria *E. coli* is generally used as the base for genetic programming because its genome was one of the first to be fully sequenced.[12] The *E. coli* genome is made up of 4,639,221 base pairs of nucleotides.[13] Of these 4.6 million base pairs, approximately 1,762,903 do nothing at all,[14] but the other 2,876,317 base pairs are *functional*.[15] The functional base pairs code for proteins that strengthen the cell membrane, transport materials around the cell, regulate PH in response to

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[10] *ACGT*, NAT'L HUM. GENOME RSCH INST., genome.gov/genetics-glossary/acgt.

[11] OPENWETWARE, https://openwetware.org/wiki/Main_Page [https://perma.cc/GZ7B-4PAJ].

[12] Natividad Ruiz & Thomas Silhavy, *How Escherichia coli Became the Flagship Bacterium of Molecular Biology*, 204 J. BACTERIOLOGY (2022),.

[13] Frederick R. Blatner, Guy Plunkett III, Craig A. Bloch, Nicole T. Perna, Valerie Burland, Monica Riley, Julio Collado-Vides, Jeremy D. Glasner, Christopher K. Rode, George F. Mayhew, Jason Gregor, Nelson Wayne Davis, Heather A. Kirkpatrick, Michael A. Goeden, Debra J. Rose, Bob Mau & Ying Shao, *The Complete Genome Sequence of Escherichia Coli K-12*, 277 SCI. 1453 (1997).

[14] *Id.*

[15] *Id.*

changing environments, and satisfy many other single-celled needs.[16]

While classical molecular biologists focus on the effects *produced* by genomic sequences, synthetic biologists *edit* genomic sequences to generate desired outcomes. Genetic traits are added and subtracted with gene-editing techniques that program specific nucleotide sequences into the genome. The most common gene-editing technique is CRISPR-Cas9, which is a biotechnology that tricks an organism's immune system into injecting its DNA with desired nucleotide sequences.[17] Think of CRISPR-Cas9 as a toolkit of molecular "scissors and glue" that synthetic biologists use to cut the genome and paste new sequences with surgical precision.[18] .

Using gene-splicing techniques, synthetic biologists have reprogrammed *E. coli* to output desired results on its wetware. Such results include producing human insulin,[19] converting glucose into commercial-grade fuel,[20] and detecting specific chemicals in the environment by glowing green.[21] But *E. coli* is not the only organism that has been edited. Although the size of the genome increases with the complexity of the organism, synthetic biologists can and have

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16 *Id.*

17 Patrick D. Hsu, Eric S. Lander & Feng Zhang, *Development and Applications of CRISPR-Cas9 for Genome Engineering*, 157 CELL 1262 (2015).

18 *The Genesis of CRISPR's Molecular Scissors*, COLUM. UNIV. IRVING MEDICAL CTR, https://www.cuimc.columbia.edu/news/genesis-crisprs-molecular-scissors#:~:text=CRISPR%2DCas9%20comes%20from%20jumping,slice%20apart%20the%20viral%20genome [https://perma.cc/25JB-TR6E].

19 Nabih A. Baeshen, Mohammed N. Baeshen, Abdullah Sheikh, Roop S. Bora, Mohamed Morsi M. Ahmed, Hassan A. I. Ramadan, Kulvinder Singh Saini & Elrashdy M. Redwan, *Cell Factories for Insulin Production*, 13 MICROBIAL CELL FACTORIES (2014).

20 Rebecca Summers, *Bacteria Churn Out First Ever Petrol-Like Biofuel*, NEWSCIENTIST (Apr. 24, 2013), https://www.newscientist.com/article/dn23431-bacteria-churn-out-first-ever-petrol-like-biofuel/ [https://perma.cc/M9CK-2H33].

21 Bradley J. Feilmeier, Ginger Iseminger, Diane Schroeder, Hannali Webber & Gregory J. Phillips, *Green Fluorescent Protein Functions as a Report for Protein Localization in Escherichia Coli*, 182 J. BACTERIOLOGY 4068 (2000).

edited the genomes of yeast,[22] sheep,[23] and even humans.[24] As opposed to "mutant" organisms, whose genomes change via random and naturally occurring phenomena, the resultant organism from these cited experiments are *synthetic*. They are not and cannot be the result of natural processes.

II. EXAMPLES

There are numerous examples of synthetic biology in practice. One of the most successful applications of synthetic biology arose when the start-up Genentech genetically edited *E. coli* to produce human insulin. This met a long felt need because the most widely available insulin was previously taken from pigs and caused allergic reactions in many patients.[25] The resulting FDA approval of the drug Humulin was the first time that a human therapeutic produced via synthetic biology was introduced to the market.[26] Today, the majority of insulin is produced from genetically edited organisms.[27]

Other applications of synthetic biology include editing rice to produce vitamin A to reduce blindness in malnourished children,[28] modifying microorganisms to "eat" hydrocarbons after an oil spill,[29] and engineering yeast to produce rose oils as an eco-friendly

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[22] Daniel Schindler, *Genetic Engineering and Synthetic Genomics in Yeast to Understand Life and Boost Biotechnology*, 7 BIOENGINEERING (BASEL) (2020).

[23] Peter Kalds, Shiwei Zhou, Bei Cai, Jiao Liu, Ying Wang, Bjoern Petersen, Tad Sonstegard, Xiaolong Wang & Yulin Chen, *Sheep and Goat Genome Engineering: From Random Transgenesis to the CRISPR Era*, 10 FRONTIERS IN GENETICS (2019).

[24] Jing-ru Li, Simon Walker, Jing-bao Nie & Xin-qing Zhang, *Experiments That Led to the First Gene-Edited Babies: The Ethical Failings and the Urgent Need for Better Governance*, 20 J. ZHEJIANG UNIV. SCI. B 32 (2019).

[25] Laura Fraser, *Cloning Insulin*, GENENTECH (Apr. 7, 2016), https://www.gene.com/stories/cloning-insulin [https://perma.cc/52SY-QN6V].

[26] John Cumbers, *Can Synthetic Biology Make Insulin Faster, Better and Cheaper?*, FORBES (Sept. 21, 2019), https://www.forbes.com/sites/johncumbers/2019/09/21/can-synthetic-biology-make-insulin-faster-better-and-cheaper/?sh=3a51dd6c5192.

[27] Baeshen et al., *supra* note 19.

[28] Guangwen Tang, *Golden Rice is An Effective Source of Vitamin A* , 89 AM. J. CLINICAL NUTRITION 1776 (2009).

[29] Adam Wolski, *Bioremediation The Pollution Solution*, MICROBEPOST (Oct. 30, 2023), https://microbepost.org/bioremediation-the-pollution-solution/ [https://perma.cc/DHD2-XU24].

alternative for the perfume industry.[30] Whether creating "biosensing" cells that detect stimuli or programming biological computers that store memory, the possibilities arising from synthetic biology are only limited by the imagination of the scientist.[31]

III. STANDARDIZATION

Synthetic biologists have used screws, transistors, traditional biochemical pathways, and other schematic systems as the nomenclature, or language, of synthetic biology.[32] In contrast to fields like engineering and chemistry, where symbols have been set in stone for over a hundred years, synthetic biology's lack of uniform nomenclature obstructs advancements in the field because research is not as easily communicated across the scientific community. In the early 2000s, Synthetic Biology Open Language (SBOL) emerged as a prominent, though not universal, nomenclature of synthetic biology.[33] SBOL allows for the computerized exchange of synthetic biology designs with a set of uniform symbols that represent genetic components without extremely long nucleotide sequences. Moreover, it is entirely free and open source.

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[30] Aviva Rutkin, *Would You Wear Yeast Perfume? Microbes Used to Brew Scent*, NEWSCIENTIST (Mar. 4, 2015), https://www.newscientist.com/article/mg22530113-600-would-you-wear-yeast-perfume-microbes-used-to-brew-scent/ [https://perma.cc/5S3W-Z5CK].

[31] Ahmad Khalil & James Collins, *Synthetic Biology: Applications Come of Age*, 11 NATURE REVS. GENETICS 367 (2010).

[32] Kristian M. Muller & Katja M. Arndt, *Standardization in Synthetic Biology*, *in* SYNTHETIC GENE NETWORKS: METHODS AND PROTOCOLS 22-43 (2011).

[33] SYNTHETIC BIOLOGY OPEN LANGUAGE, https://sbolstandard.org/datamodel-about/ [https://perma.cc/N36Q-38PT].

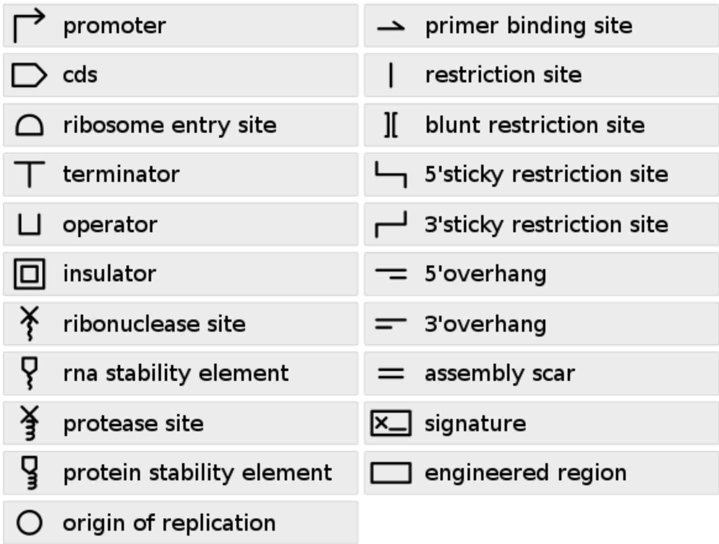

Figure 2: Chart of SBOL symbols. Researchers use these symbols to depict their designs of synthetic organisms. In the lab, BioBrick parts are often used to supply the specific nucleotide sequences of the symbols.[34]

While SBOL is used to depict the design, BioBrick parts are used to supply the nucleotide sequences of the design's genetic components. BioBrick parts are interchangeable biological building blocks housed in the online Registry of Standard Biological Parts.[35] After pledging not to assert intellectual property rights against other designs, researchers can access over 20,000 BioBrick parts to design synthetic organisms.[36] In an analogy to a LEGO kit, think of SBOL as the instruction manual, and BioBrick parts as the pieces used to build the structure.

Synthetic biology's movement towards a standardized nomenclature is complemented by a parallel drive for consistency in experimental practices.[37] Standardized laboratory practices are important to increasing reproducibility by other researchers, a key

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[34] *SBOL Visual Glyphs*, SBOL, https://sbolstandard.org/visual-glyphs/ [https://perma.cc/H2BB-RQ6X].

[35] *Registry of Standard Biological Parts*, IGEM, https://parts.igem.org/Main_Page [https://perma.cc/Y34U-MYAP].

[36] BIOBRICKS FOUNDATION, https://biobricks.org/bpa/developers/; BioBricks are used every year at the International Genetically Engineered Machine (iGEM) competition, where undergraduates from across the globe compete to develop new and innovative cells through gene-editing. IGEM, https://competition.igem.org/ [https://perma.cc/9FQM-C9AQ].

[37] *BioRoboost in a Nutshell*, BIOROBOOST, https://standardsinsynbio.eu/bioroboost/ [https://perma.cc/8TNK-E6Y3].

factor in determining the reliability of results and advancing the body of knowledge.[38] The BioRoboost project aims to create universal experimental standards by collaborating with researchers to establish the best characteristics, specifications, and requirements for synthetic biology research.[39] With growing standards for symbology, nomenclature, and experimentation, synthetic biology is poised to flourish as a premier scientific field.

IV. CRITICISMS AND CONCERNS

Synthetic biology has been criticized for applying an engineering approach to biology. In a scathing rebuke of the standardization effort, biologist Jamie A. Davies argues that the "unique features of biological systems" make the "classical engineering approach of less value."[40] Dr. Davies asserts that the rigid nature of engineering should not be allowed to constrain the efforts of synthetic biology.[41] This argument is premised on the notion that predictive modeling cannot be used to accurately predict cellular behavior due to the complexity and dynamic nature of cellular mechanics.[42] Cellular behavior is notoriously hard to simulate with computer models because the exact operations of intracellular mechanics, environmental influences, and gene sequences are poorly understood, unlike the traditional engineering analogues of transistors, gears, and chassis.[43] Thus, the analogy of synthetic biology to computer engineering may not be the smooth simplification that synthetic biologists purport it to be.[44] Despite Davies' rebuke, advancements in computing power and artificial intelligence may provide the calculations necessary to accurately predict biological behavior in the future.[45]

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[38] William Harris, *How the Scientific Method Works*, howstuffworks (Aug. 19, 2021), https://science.howstuffworks.com/innovation/scientific-experiments/scientific-method9.htm [https://perma.cc/TQ74-DUD7].

[39] BIOROBOOST, *supra* note 44.

[40] Jamie Davies, *Real-World Synthetic Biology: Is It Founded on an Engineering Approach, and Should It Be*?, 9 LIFE (BASEL) (2016).

[41] *Id.*

[42] *Id.*

[43] *Id.*

[44] *Id.*

[45] Marcin Frackiewicz, *The Potential of AI Quantum Effect Prediction in Biological Exploration*, TS2 SPACE (Oct. 16, 2023), https://ts2.space/en/ai-quantum-effect-prediction-a-revolutionary-tool-for-biological-exploration/#:~:text=In%20conclusion%2C%20AI%20Quantum%20Effec

Bioethicists have raised concerns regarding the synthetic alteration of the human genome. The most controversial experiment to date occurred in 2018 when biophysicist He Jiankui illegally edited the CCR5 gene of twin embryos to create HIV-resistant babies.[46] The birth of the twins marked the first time in history that humans have been genetically engineered, an undeniable scientific landmark, but the experiment was met with universal condemnation by the scientific community for its blatant disregard of bioethical norms and unknown long-term health effects.[47] Bioethicists Thomas Douglas and Julian Savulescu liken the rise of synthetic biology to the advent of the atomic bomb because of the potential for genetically engineered weapons and failed experiments to cause catastrophic harm.[48] In a challenge to the traditional scientific notion that all research is intrinsically valuable because it progresses the community's body of knowledge, Douglas and Savulescu advocate for narrowing the pursuit and dissemination of synthetic biology research to only applications that benefit humanity.[49] In practice, this narrowing may take the form of a global ban on bioweaponry research or an approval process for research on synthetic organisms that requires a justification beyond the mere pursuit of knowledge.

There are also a number of ways that synthetic biology intersects with the legal system. First, this rising field results in the filing of many patent applications with the United States Patent and Trademark Office, which houses a special department for receiving deposits of biotechnological inventions.[50] Navigating the doctrine of patentable subject matter is important for inventors seeking to patent synthetic organisms and genes. The Patent Act contains an implicit exception that prevents inventors from receiving patents on "natural phenomena," which includes organisms and genes found in nature.[51] However, in *Diamond v. Chakrabarty*, the Court held that synthetic organisms that are "markedly different" from their naturally

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t,complex%20dynamics%20of%20biological%20systems [https://perma.cc/GVW8-VZF3].

[46] Yuanwu Ma, Lianfeng Zhang & Chuan Qin, *The First Genetically Gene-Edited Babies: It's "Irresponsible and Too Early,"* 2 ANIMAL MODEL EXP. MED. 1–4 (2019).

[47] *Id.*

[48] Thomas Douglas & Julian Savulescu, *Synthetic Biology and the Ethics of Knowledge*, 36 J. MED. ETHICS 687 (2010).

[49] *Id.*

[50] Biological Deposits, 37 C.F.R. § 1.801–09.

[51] Mayo Collaborative Servs. v. Prometheus Labs., 566 U.S. 66, 70 (2012).

occurring counterparts are eligible for patent.[52] There, the Court applied this rule to an *E. coli* strain that was genetically modified to consume oil and determined that the synthetic bacterium was different enough from naturally occurring *E. coli* to be patent eligible.[53] The Court later clarified this rule with respect to human genes in the landmark case *Association for Molecular Pathology v. Myriad Genetics*.[54] There, the Court investigated the patentability of a synthetic gene that contained only the coding portions of the BRCA1 breast cancer gene.[55] Although the naturally occurring BRCA1 gene was not patentable, the Court held that the synthetic gene was patentable because it was synthesized in a laboratory, not found in nature, and contained a different nucleotide sequence than BRCA1.[56] Thus, under the doctrine of *Diamond* and *Myriad*, synthetic biologists may patent synthetic organisms and genes as long as those inventions are sufficiently distinct from their naturally occurring counterparts.[57]

Second, there are regulatory issues in dealing with the reality that synthetic organisms can both help and hurt the environment. A 2016 study identified major risks posed by synthetic biology to human health and the environment.[58] The study concluded that introducing genetically engineered organisms to the environment threatens human health by increasing the amount of potential allergens, carcinogens, pathogens, and antibiotic-resistant strains of bacteria.[59] Those organisms also change or deplete the environment by competing with native species and spreading their genes via "horizontal gene transfer," which is the movement of genes or genetic material among organisms.[60] To alleviate these risks, the study urged for mandatory risk assessments to accompany synthetic biology practices.[61]

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52 Diamond v. Chakrabarty, 447 U.S. 303, 310 (1980).

53 *Id.*

54 Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569–96 U.S. 576 (2013).

55 *Id.*

56 *Id.*

57 *Id.*

58 Joel P. Hewett, Amy K. Wolfe, Rachael A. Bergmann, Savannah C. Stelling & Kimberly L Davis., *Human Health and Environmental Risks Posed by Synthetic Biology R&D for Energy Applications: A Literature Analysis*, 21 APPLIED BIOSAFETY 177 (2016).

59 *Id.*

60 *Id.*

61 *Id.*

Third, the threat of bioterrorism generates major security concerns. The Combatting Terrorism Center at West Point concluded that advancements in synthetic biology have lowered the "education, training, cost, time, and equipment threshold required to modify and employ pathogenic organisms as biological weapons" to the point that an individual with only undergraduate training could deploy such weapons.[62] It also cautioned that the threat posed by bioterrorism is rivaled only by nuclear war.[63] The danger lies in the potential for bioterrorists and governments to increase the lethality of pathogens through gene editing.[64] Imagine an antibiotic-resistant bacteria with the symptoms of smallpox and the transmissibility of Covid-19. To prepare for such attacks, the Center urged for anticipation and planning at "all levels of government."[65]

CONCLUSION

The dueling dragons of synthetic biology are its simultaneous capacity for innovation and destruction. Humanity is rapidly advancing towards an age of utilizing synthetic biology to spawn fully-functioning organs *in-vitro*,[66] cure genetic diseases at the genomic level,[67] and reverse the cellular aging process.[68] Yet, there are unanswered environmental, existential, and ethical questions regarding the introduction of synthetic organisms into the natural world. It is up to innovators, lawyers, and legislators to use the tools at their disposal to maximize the benefits and minimize the harms in the brave new world of synthetic biology.

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[62] J. Kenneth Wickiser, Kevin J. O'Donovan, Michael Washington, Stephen Hummel, & F. John Burpo, *Engineered Pathogens and Unnatural Biological Weapons: The Future Threat of Synthetic Biology*, 13 CTC SENTINEL 1 (2020).

[63] *Id.*

[64] *Id.*

[65] *Id.*

[66] Sean Stevens, *Synthetic Biology in Cell and Organ Transplantation*, 9 COLD SPRINGS HARBOR PERSP. IN BIOLOGY 1 (2017).

[67] Aoife Brennan, *Development of Synthetic Biotics as Treatment for Human Diseases*, 7 SYNTHETIC BIOLOGY (OXFORD) (2022).

[68] Kwang-Hyun Cho, Sugyun An & Junsoo Kang, *Systems Biology for Reverse Aging*, 13 IMPACT J.: AGING 14549 (2021).