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Abstract

CRISPR/Cas9 is a novel technology that allows scientists to edit genomes for purposes related to research, livestock improvement, and eradication of disease. The use of CRISPR/Cas9 is highly debated in the scientific community due to its significant advantages and disadvantages when evaluating its use from a bioethical standpoint. Biomedical ethics in scientific research evolved due to historical events that violated human rights in the name of science, and currently studies must respect *The Georgetown Mantra of Bioethics* in which the values of beneficence, non-maleficence, autonomy, and justice are required to be upheld when conducting biomedical research. This review assesses two studies that utilize CRISPR/Cas9 technology in line with the identified values of bioethics. The results show that there both an instance that violated *The Georgetown Mantra* and an instance that adhered to the accepted values, suggesting that CRISPR/Cas9 has the potential to be studied and applied in a way that is highly beneficial to society but can be easily used for unethical purposes if left unregulated.

History of Research Ethics

Dating back to the 1600s, many tragic events in scientific history have occurred which, in the name of research, have violated human rights. In response to these violations, and to prevent this from happening again,

scientists and ethicists have worked together to establish laws and codes that regulate biomedical research which require the scientific community to ensure the well-being of human research subjects and the general safety of humanity.

During World War II, unethical and non-consensual research was carried out on groups of marginalized individuals who were placed in internment camps. These experiments included subjecting the prisoners to inhumane conditions – freezing temperatures, exposure to radiation, purposeful infections – to better understand how the human body would react in such situations. Some of the individuals died as a direct result from the experimentation, and many others were permanently disabled. Consequently, *The Nuremberg Code*, a document detailing ethical research principles but not enacted as a law, was implemented in 1948 stating that the voluntary participation and obtained consent from human participants for scientific experimentation was “absolutely essential.” This Code acts as the first instance in which regulation of research using humans was attempted, even though it was not yet legally enforced.

Eighteen years later, the World Medical Association developed *The Declaration of Helsinki* as “a statement of ethical principles for medical research involving human subjects.” *The Declaration of Helsinki* set forth several principles, recommendations, and guidelines that should be followed when conducting human research – testing on animals first, protocol review by committee, obtaining informed consent, research be conducted only by

qualified professionals, and the principle that risks of the experiment should not exceed the benefits. Although *The Declaration of Helsinki* was not legally binding, it is considered one of the foundational documents for modern human experimentation laws that followed.

The notorious *Tuskegee Syphilis Study* took place from 1932-1972 in which four hundred African-American men were intentionally infected with syphilis for the sole purpose of studying the consequences of not treating the disease. Treatment was withheld from these individuals, although penicillin became widely available to the public, as a way for the researchers to observe the detriments of the disease over time. The public outrage over this study motivated the formation of the *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* ("The Commission"). The Commission created *The Belmont Report* (1979) in response to the *Tuskegee Syphilis Study*, stating that human research ethics require respect of the participant's autonomy, non-maleficence, beneficence, and justice. These four principles are also commonly referred to as *The Georgetown Mantra of Bioethics*, or *principalism*, and are used widely today as guidelines for ethics of human research.

The Federal Policy for the Protection of Human Subjects ("The Common Rule", 1991), heavily influenced by *The Belmont Report*, was approved in almost all federal government agencies (excluding only the EPA) and has now established regulations that include ensuring compliance by researchers, obtaining and documenting informed consent of participants,

review and documentation requirements, as well as further protection for vulnerable groups like children, prisoners, and pregnant women. As in the United States, many other countries around the world have established modern guidelines for human research that must be adhered to (Mandal, et al., 2011) (Resnik, 2020).

Bioethics Relevant to CRISPR/Cas9

CRISPR/Cas9 is a ground-breaking gene editing tool whose use brings into consideration significant ethical concerns. When used in the right hands, this technology may be able to eradicate diseases that currently have no cure and can make agriculture more efficient and nutritious. When used in the wrong hands, however, this technology may disrupt ecosystems and evolutionary processes.

CRISPR/Cas 9 is a cost-effective and straightforward way to edit genomes when compared to zinc finger nucleases and other genome editing technologies. Scientific and clinical benefits are seen in food and animals as well as in humans. Genetically modified organisms (GMOs) are created in a variety of foods, from grains to fruits and vegetables to dairy products. GMOs in food are beneficial not only to the producers and suppliers, but also to the consumer. These foods are made to be more nutritious by introducing genes in the organisms that promote the transcription and production of healthy molecules. GMOs also ensure a higher output of crops and promote a longer shelf-life, helpful qualities for both the supplier and consumer. These crops can be made to be disease- and drought-resistant, ensuring that the supplier

will have a productive harvest rather than leaving their income for the year up to the uncertainties of the environment to determine (Caplan, et al., 2015). CRISPR/Cas9 can also genetically modify animals for the purpose of making animals with desired traits for experiments, especially when applied to making primate genes more-human like for human research that does not require human participation. Agricultural animals may also be genetically modified for an increase in livestock productivity, produce disease- and drought-resistant animals, similar to results obtained in plants, and can reduce the necessity for antibiotic use, the adverse effects of which are most notably seen in bovine milk and meats. Furthermore, editing the genes of insects may make them unable to infect their hosts, as in the case of editing mosquito genes that carry and transmit malaria to human hosts, or simply by eradicating the insect population entirely (de Graeff, et al., 2019).

Additionally, there are human-related benefits to CRISPR/Cas9 use that have the intent of improving the overall condition of human health. As in plants and animals, humans can also be made disease resistant due to alterations in the genome. Editing genes may also create new treatments or cures for diseases that currently have none, effectively immunizing the population against various viruses, like HIV, and other pathogens, thereby eradicating genetic diseases. Editing primate genes to be more human-like may allow for non-human animal models to stand in place of humans for experimentation and research. This gene editing technology may also be used to create “designer babies” in which the parents can choose

phenotypes that appeal to them and scientists can alter the respective genes to produce a desired result. There are further beneficial implications of CRISPR/Cas9 use in creating biologically synthesized medicines, developing cancer immunotherapies, and creating stem cell disease models that can all act to enhance the ways in which doctors understand and treat disease.

Although use of this technology may seem extremely therapeutic, there are substantial disadvantages to CRISPR/Cas9 genome editing that inform the debate regarding its use in the scientific community. Because it is such a modern technology, there has not been enough time to study the long-term consequences of its use. Editing genomes may attempt to actually re-direct evolution and disrupt the processes that have acted on species since the beginning of time. Due to the novelty of this technology, the effects of human consumption of genetically modified animals are unknown, and the FDA has put off their approval of genetically modified animals for human consumption. Genetically modified organisms may crossbreed, distributing the modified genes to unintended species and populations, affecting the organisms and their ecosystems in unknown, possibly harmful, ways. Editing genes of animals, plants, and insects as well as eradicating entire populations may disrupt ecosystems and such effects certainly have the potential to alter relationships between species or even accidentally eradicate species as a result. The effects of human genome editing remain unknown, and there are many arguments that these unknowns may prove to be dangerous. The CRISPR/Cas9 technology may also be used in selfish ways

- researchers may edit genes to study the consequences without regard to what may happen to the subject as a result. More cynically, CRISPR/Cas9 may be used in biological warfare to make pathogens more virulent in their host, providing a more efficient way to incapacitate many people at once (Caplan, et al., 2015) (de Graeff, et al., 2019).

Georgetown Mantra Evaluation of CRISPR/Cas9 Research

The He Experiment was an infamous CRISPR/Cas9 experiment that was conducted in 2018, and although little is known about the experiment, it has been the cause of much debate in the CRISPR/Cas9 community.

Dr. He Jiankui, a Chinese geneticist, used CRISPR/Cas9 genome editing system to edit embryonic genes, with the intent of making these babies immune to HIV through the editing of the CCR5 gene. Dr. He Jiankui allegedly edited thirteen embryos, in two of which the mothers pregnancy was brought to term, and in one the mother birthed fraternal twin girls. Dr. He Jiankui stated that the CCR5 gene was the only one altered in the embryos, and as a result he had given lifetime HIV immunity to the twins. However, due to little documentation or publishing, the truth of this statement cannot be verified. The limited data that has been gathered on the He experiment is based on very few, unreliable sources, all directly or indirectly associated to Dr. Jiankui himself. There is no formal publication of the research in its participants, methods, or conclusions, and some believe that these twins do not actually exist (Greely, 2019).

The Georgetown Mantra utilizes the criteria of autonomy, in which proper documentation of informed consent is mandated; non-maleficence, in which no intentional harm is to be done to the participants; beneficence, in which the benefits of the study should outweigh the risks; and justice, in which there should be no populations or participants taken advantage of for the sake of the study. Applying these principles to Dr. He Jiankui's gene-editing experiment, it appears to have violated the principle of autonomy because the informed consent documents required for all experimental research on humans were removed from the internet, and those who had read the documents stated they were inadequate. Because no true publication of the experiment or data was made, researchers are unsure that Dr. He Jiankui truly edited the HIV CCR5 gene and did not use the genome editing technology for more selfish purposes, i.e., to edit other genes for the sole purpose of studying the consequences. Non-maleficence was also violated due to the inadequate sharing of data, indicating that this experiment could have been performed to intentionally harm the participants. Beneficence was not violated, however, as the intent of the experiment was to create embryos that were expected to be HIV-resistant, and therefore protected from this viral infection. If true, this would help slow the spread of HIV and could be used to develop a cure for patients diagnosed with the disease. Justice is violated in that there was no proper publication of the experiment and no provision for caring for the twins should any future

problems arise, therefore neither the women who participated in the study, nor the twin girls themselves, were not done justice for their participation.

Melika Lotfi and Nima Rezaeib are currently studying the use of CRISPR/Cas technology with Cas13 as a possible COVID-19 treatment in wake of the current pandemic. Their study, *CRISPR/Cas13: A Potential Therapeutic Option for COVID-19*, focuses on how to use the CRISPR/Cas13 genome editing system to edit the virus's genome in the human body, degrading its genome and mRNA to inactivate the virus and halt replication in the host. CRISPR/Cas13 recognizes highly conserved sequences in the COVID-19 virus and works in infected patients to destroy the viral genome. Their innovative research has used the huMAN cell line as a cell model in place of animal models for pre-clinical trials, and although the research as of right now shows limitations, like route of delivery, it has many implications not only in our understanding not only of the CRISPR/Cas13 technology, but also in our understanding of the COVID-19 virus itself (Lotfi, et al., 2020). If the experimental use of CRISPR/Cas13 proceeds through the proper pathways, this could present an option for COVID-19 treatment that does not violate any of the principles in *The Georgetown Mantra*. As long as it is ensured that the future research participants and subsequent patients who are treated with this technology are fully informed - they understand how the CRISPR/Cas13 edits the genome, which gene is being edited, intended results, and unintended side effects of its use, then autonomy would not be violated. Non-maleficence is not violated because the intent of this study is

to offer a more specific treatment for patients infected with COVID-19 and therefore harm is not being purposefully inflicted. Beneficence is not violated because there are very few treatment options for COVID-19, and none of them target the viral genome itself. The overall goal while seeking solutions to treat those infected during this pandemic is to promote the health of the patient, although some side effects may occur. Justice is not violated so long as the participants in clinical trials are not from vulnerable populations or taken advantage of during the research and the resulting treatment option is made available to the public, is not privatized, or made available only to select populations.

Conclusion

In conclusion, the CRISPR/Cas9 gene editing technology may have a long way to go before its application is widely accepted and utilized. There is substantial weight to the arguments both advocating for and against its use which are seen not only in the implications, but also in the past instances where this technology has been studied. Strict rules and regulations regarding the use of the gene editing tool may help gain more public acceptance of CRISPR/Cas9; however, the long-term effects will remain unknown for the near future, limiting the ways in which this tool may be used for the time being.

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