June 1, 2021

President Joe Biden
The White House
1600 Pennsylvania Avenue
Washington, DC 20500

Dear President Biden:

Attached is our report “Managing the Ethics of Gene Editing with Global Regulation” as a recommendation to the United States and its international allies.

In this report, we discuss two ethical dilemmas surrounding CRISPR gene editing technology. The first is editing human embryos and the second is using CRISPR to revive extinct species and traits. Our report aims to emphasize that the technology can be used for both benefit and harm depending on the user, and if used well CRISPR has great potential for curing disease and preventing further environmental damage.

The report first covers the basics and current situation surrounding CRISPR in the scientific community before then explaining the two ethical dilemmas, including potential benefits and drawbacks. Then, we cover the current CRISPR regulations in the United States and abroad, highlighting the ambiguity and unclear authority that is present in the legal landscape. We recommend that you take action to place control of CRISPR regulations firmly under the jurisdiction of a joint federal agency regulatory board, and additionally use the United States’ position as a human rights leader and international powerhouse to address the need for strong international regulation.

If any questions or comments arise, please do not hesitate to contact our team via email at dgyotoku@uw.edu.

Sincerely,

Dillon Gyotoku

Jay Lee

Selena Ren

Flora Chen

Managing the Ethics of Gene Editing with Global Regulation

By Dillon Gyotoku, Selena Ren, Jay Lee, and Flora Chen
June 6, 2021

Executive Summary

The CRISPR-Cas9 genome editing technique, first realized by Emmanuelle Charpentier and Jennifer Doudna in 2012, has since become widespread in a variety of fields such as biological research and disease treatment. CRISPR stands for “Clustered Regularly Interspaced Short Palindromic Repeats,” which refers to the DNA sequences used by researchers to precisely locate and cut a specific DNA sequence using the Cas9 protein. Cas9 is the enzyme that can cut, splice, and connect DNA strands using RNA to guide the complex to the correct location, and this has many possible applications.

The potential future uses of CRISPR include treating viruses and even eliminating genetic diseases through germline editing. There is also the exciting possibility of using CRISPR to genetically reconstruct and revive extinct species or preserve endangered ones, as well as restore ecosystems that are currently being damaged by human-caused climate change.

Despite these possibilities, there have been ethical concerns regarding the use of CRISPR, particularly when it comes to studies performed on humans. The most illuminating example of these concerns is the recent controversy surrounding He Jiankui, a Chinese scientist who used CRISPR technology to edit the genome of two human embryos using germline editing. While tantalizing in the possibility that germline editing may be able to eliminate genetic diseases, the main issues with Jiankui’s actions were that he was not qualified to perform the procedure and there is yet to be sufficient research conducted to verify the safety and efficacy of CRISPR germline editing. Further ethical concerns include the potential negative impacts that reconstructed or new species made through CRISPR may have on our current ecosystems, as well as whether we, as humans, have the ethical right to perform these procedures to begin with.

We have concluded that there is an imminent need for the world’s governments to clearly lay out regulations for researchers to follow regarding genome editing using CRISPR, preferably following a model given by the World Health Organization that lays out ethical boundaries regarding biosecurity. Additionally, in the United States, we would recommend that an overarching regulatory board be established in order to properly oversee future research using the expanding technology of CRISPR germline editing.

Table of Contents

Table of Figures

Introduction

Genome editing is attracting more and more attention from people due to the myriad of potential life-changing uses it has. Genome editing using CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is one of the most popular methods because it is cheap, precise, and easy to implement. Some possible applications of CRISPR technology include fixing the heritable mutations that lead to diseases, reviving extinct species, developing healthier foods, and reducing the spread of disease by eliminating mosquitoes. Humanity can potentially gain many benefits by further mastering the CRISPR technology.

However, there is heated debate over the ethics of genome editing. Some voices argue that editing heritable genes in human embryos is not yet confirmed safe nor morally justified. Furthermore, regarding using CRISPR technology to revive extinct species, it was suggested that it is challenging for species revived by CRISPR technology to get used to living in the wild. Others question whether the genetically engineered species can truly be considered the same as the extinct species.

As a result, the future of CRISPR technology is widely argued in the scientific community, raising several important questions: Is it ethical to modify human genes as well as animal genes? What possible consequences can we afford? What further regulations do we need to make CRISPR work the best for humans?

Background

What is CRISPR?

CRISPR gene editing is a technique that can be used to edit the genomes of living creatures. Unlike previous gene editing methods, CRISPR is both precise and cheap, allowing researchers to easily make changes to eukaryotic cells (the cells that form all multicellular life) in order to create new medicines, genetically modify existing organisms and combat genetic disease.

The original CRISPR locus was discovered in 1993, but it was not until 2012 that its potential was fully realized. In 2005, researchers discovered the protein Cas9 and hypothesized that it could be used to cut and edit DNA, a theory that would be validated only a few years later when Sylvain Moineau demonstrated that it was the only protein required to cut DNA in the CRISPR-Cas9 system. Finally, in 2012, Emmanuelle Charpentier and Jennifer Doudna reported that CRISPR RNA (crRNA), which determines the cut location, could be artificially synthesized with any sequence, revealing a simple and effective way to edit DNA genomes [1].

How CRISPR Works

CRISPR proteins were first observed in bacteria with “spacer” DNA sequences in between the repeats that exactly match viral sequences. Fig. 1 shows the method of gene editing by CRISPR. When a cell is invaded by a virus, the CRISPR system creates two long strips of RNA, one of which contains a sequence that matches the invading virus and dictates where the DNA will be cut. The CRISPR RNAs (crRNAs) will fit into a protein called CRISPR Associated Protein 9 (Cas9). Cas9 guides RNA for genome editing and cuts DNA sequences. When the crRNA matches with the DNA sequence that is affected by the virus, Cas9 will cut the target sequence in the DNA to disable the virus. Then, a DNA sequence will be added to connect the broken DNA sequence and it will be fixed on the other side by itself. These processes can happen in any living cell, including human cells [2].

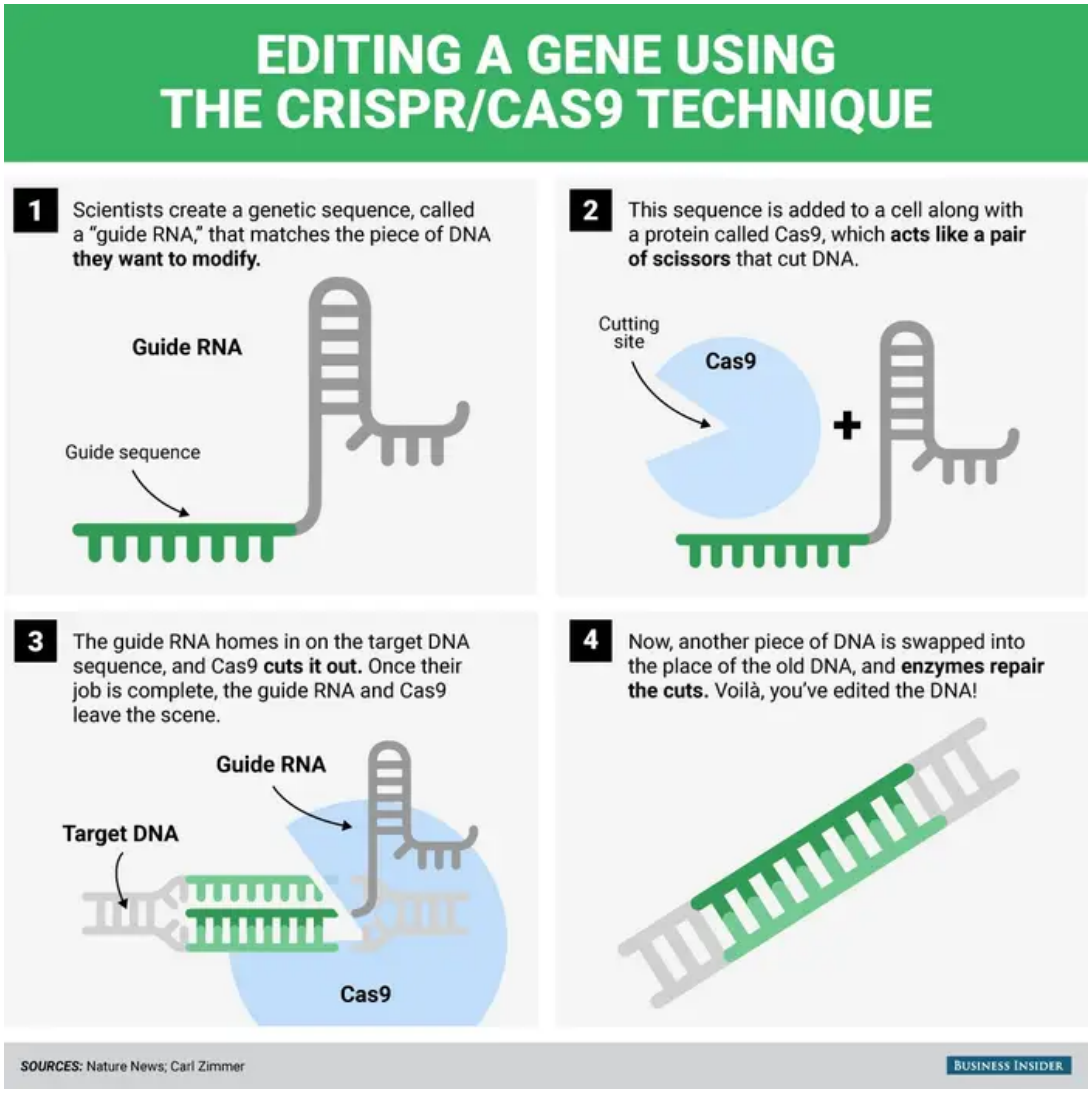

Fig. 1. Gene editing method of CRISPR. Image from [3].

Current Applications of CRISPR

Since its discovery in 2012, CRISPR has become an essential tool for not only genetics, but any biological and medical research. By synthesizing custom crRNA, scientists are able to target practically any DNA sequence of interest due to the base pair compatibility of RNA and DNA. This allows scientists to edit any area of DNA with ease. Additionally, altered Cas9 proteins that do not splice can be used to tag certain areas of genetic material and allow for scientists to track the material with live imaging. Other altered Cas9 proteins can act as repressors or activators for gene transcription, therefore affecting the expression of specific coding regions.

Past Controversy with CRISPR

In 2018, He Jiankui, a scientist from China, announced that he used CRISPR gene editing to help give birth to twin girls with edited genomes. However, when it was revealed that he neglected to do adequate safety testing and failed to follow standard procedures in procuring participants, he was met with public scorn [4]. He disabled a gene called Chemokine Receptor 5, or CCR5. This gene is used by HIV to enter the cell. Ten percent of Europeans have the CCR5 gene disabled, which grants them immunity to HIV. Despite the fact that his work benefited the twins, his work with CRISPR is frowned upon because the long-term consequences of human genetic mutation are unknown. Jiankui's changes could cause these twin girls to be vulnerable to different diseases, or have other yet unknown effects.

Discussion

Stakeholders Surrounding CRISPR

Gene editing in living cells can have wide-reaching consequences in human society and the natural environment, which causes many stakeholders to take interest in CRISPR. These are the stakeholders we are going to talk about in the following sections:

1. *Experimental subject*. This living being can be either a human or animal. There is a risk that CRISPR procedures can go wrong or produce unpredictable results, or cause the individual to have other unprecedented effects on their environment.
2. *The general public*. As CRISPR advances, its experimental achievements can be used to help more and more members of the public.
3. *Animals*. CRISPR can be used to improve animal health and global biodiversity. Genetically engineered animals are often used to produce food, human therapeutic products, industrial products, and models for human disease [5]. CRISPR can also be used to revive extinct species or add traits to existing ones.

Editing Genes with CRISPR

CRISPR's ability to make efficient and precise DNA splices has opened up a wide range of possibilities for research and new discoveries, particularly in the prevention and treatment of genetic diseases. Single-gene diseases such as cystic fibrosis and sickle cell anemia, which are currently incurable, may be able to be completely treated through the use of gene editing [6]. A potential future exists where the mutation in the gene that causes these conditions can be eradicated from not only the patient, but from future generations, effectively eliminating the threat of the disease being passed onto their children. A more distant possibility would be the treatment and prevention of heritable cancer, heart disease, and even mental health disorders [6].

While CRISPR is currently being used, for the most part, as a tool in biological studies, research has begun on editing the genome — the entire genetic makeup of an organism — using animal and bacterial models [6]. Right now, in humans, CRISPR is used only for editing in somatic cells, which are any cells that are not reproductive cells. The ethics of human germline editing, referring to gene editing conducted on cells that can pass onto the next generation, are still heavily debated. The differences between the two are detailed in Fig. 2.

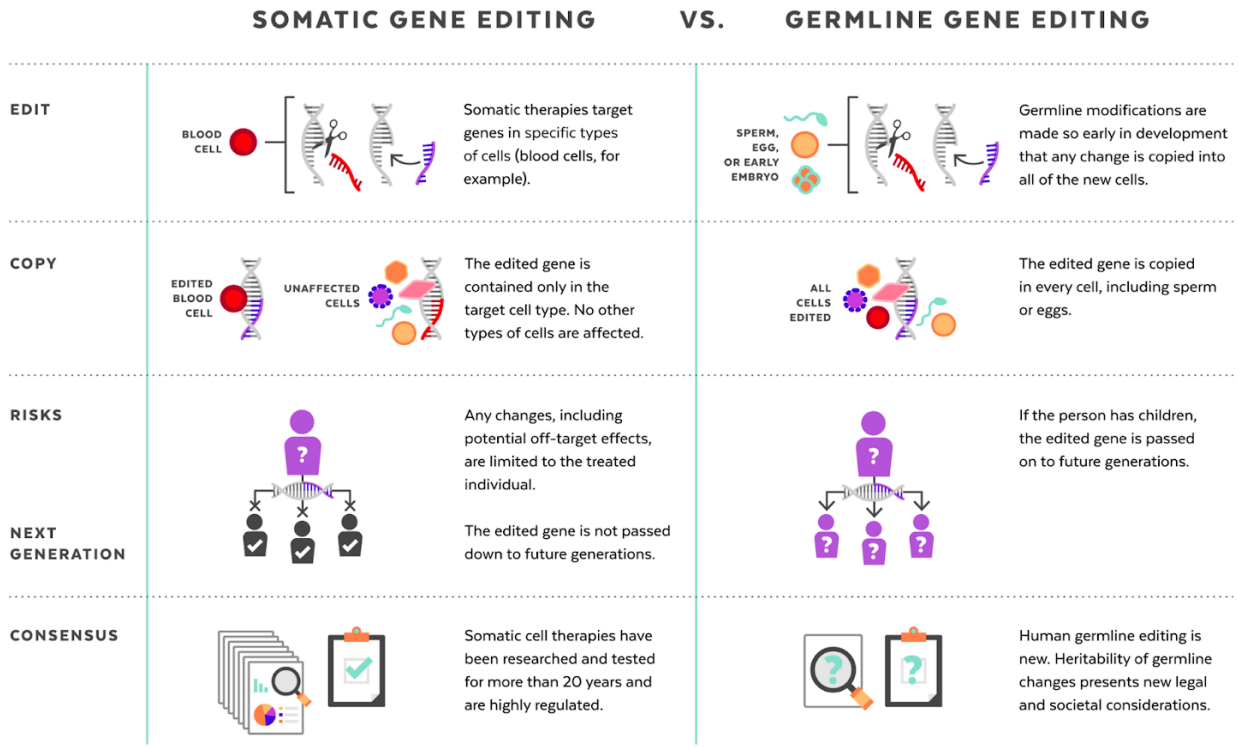

Fig. 2. Comparison of somatic gene editing and germline gene editing. Image from [7].

The Ethics of Genome Editing in Human Embryos

Germline editing in human embryos raises a multitude of possibilities for the future of humanity, and an equal number of ethical concerns. First and foremost, current germline editing procedures using CRISPR gene editing have yet to be proven as safe or even effective, as further research must be conducted [4]. However, as knowledge of genome editing inevitably expands, the policies that surround science and the extent to which scientists may act must also conform to what is possible.

The clear benefits of gene editing of human embryos would be the elimination of future human suffering due to heritable diseases. However, once the elimination of diseases caused by mutations is made reality, there becomes a seemingly superficial difference between gene editing conducted on mutations and gene editing conducted on regular genes. The goal of alleviating human suffering could morph into using CRISPR technology to approach epigenetic “perfection,” where an embryo is designed with “superior” genes that would lead to the resulting human being smarter, stronger, or more beautiful [4].

How the scientific community proceeds with the use of CRISPR in germline editing hinges on whether the benefits outweigh the ethical issues associated with the alteration of the human genome on a case-by-case basis. We must also consider the societal and cultural differences between areas, and how that will influence the jurisdictions of policies in play. Also, regarding policies, it is necessary to decide whose decisions will influence how the policies are written, and make sure to strike a balance between public and scientific expert opinion [4].

Using CRISPR to Revive Extinct Species

CRISPR has also been considered as a means of reviving extinct species. Given that it is impossible to clone species with no living cells, genome editing with CRISPR may be the only way to bring back extinct species and traits. In 2015, scientists succeeded in editing the genome of an elephant to include mammoth DNA sequences that increased the species’ resistance to cold [8]. This process is accomplished by assembling a genome for the extinct species, in this case the mammoth, from preserved remains. Many mammoth skeletons and other archeological remains exist that can provide this material. Thanks to modern DNA isolation and assembly technology, the recovered DNA can be sequenced and then scanned to find differences between the ancient DNA and a close modern ancestor. These differences then become prime targets for CRISPR gene editing [9]. Although this requires a large number of edits to the modern genome (around 1.5 million in the case of the elephant), this number can be reduced by

replacing only phenotypically relevant genes (genes that visibly affect the organism) or replacing large segments at once [10]. This strategy has been analyzed and found to be both efficient and practical for scientific use.

The Benefits and Risks for Humans and Natural Ecosystems

Naturally, given the power of this technology, there is potential to undo ecological damage and restore existing ecosystems in addition to creating new ones. One example is the effort to revive the passenger pigeon, a bird that was key to driving “forest disturbances”- disturbances in the forest canopy that allows sunlight to reach lower layers, stimulating growth of both animal and plant communities as the forest regenerates [11]. Although the project is still in its early stages, CRISPR technology would be key in recreating the Passenger Pigeon genome. Fig. 3 shows how CRISPR would be used to edit primordial germ cells to carry the passenger pigeon genome.

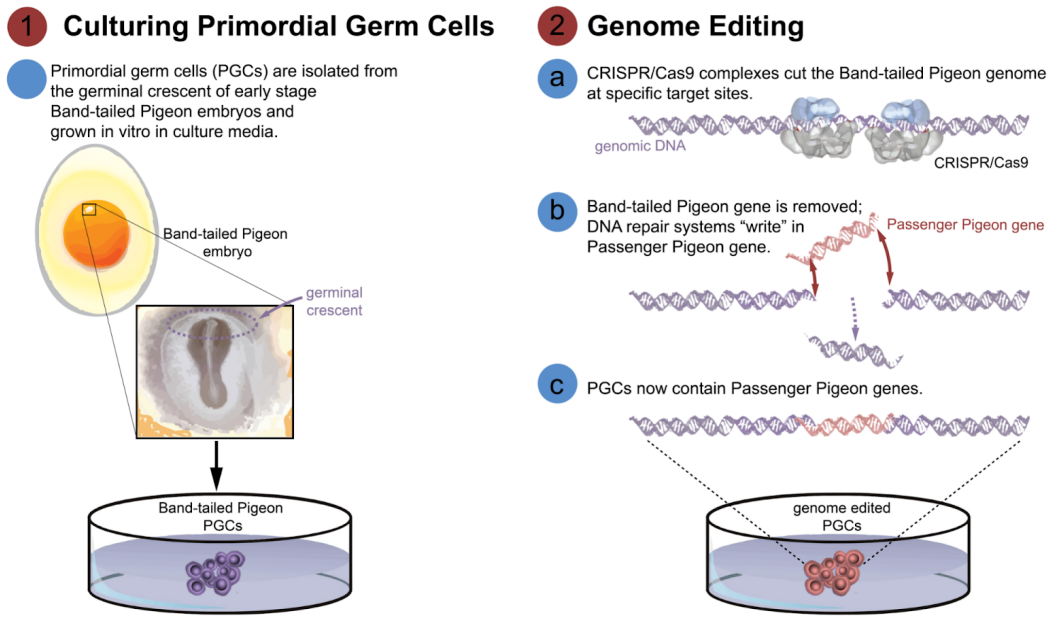

Fig. 3. Primordial germ cells from the Band-tailed Pigeon would be edited using CRISPR to carry Passenger Pigeon genes. Image from [11].

CRISPR de-extinction would also help to preserve species that are affected by the rapid pace of human-driven climate change, enable the reintroduction of lost traits, and allow struggling species to survive by manually adding helpful traits. Allowing animal gene editing would preserve existing biodiversity and potentially even add to it by bringing back extinct species.

However, this process is not without its ethical concerns. Several questions currently exist surrounding the technique: not only is it difficult to find a maternal host to carry the engineered embryo, some species such as birds are incompatible with nuclear transfer, which is the technique used to create the engineered embryos, and other methods will be required [9]. The possibility of genetic failures is another issue that cannot be ignored. Furthermore, the created animals will have to be raised in captivity, which raises further concerns about whether their behavior will truly be identical to the original species, not to mention their chances of survival in the wild. Finally, even if an engineered species does reach the wild, it could cause wide-ranging and unprecedented effects on the gene pool thanks to its added traits, which would require extensive analysis and has potential to cause massive environmental damage [12].

Recommendations

Current CRISPR Policies

The United States prohibits using federal funds to conduct research in which a human embryo is intentionally created or modified to include a heritable genetic modification [13]. Since people attach great importance to genetic research, engineers should be cautious toward any gene editing behavior. There are eight rules which should be followed in any heritable germline editing research, which are suggested by the US National Academies of Sciences and Medicine in their report [5]. According to our current mastery of CRISPR technology, editing genes in human embryos violates the criteria of “conversion only to gene variants that are prevalent in the population and known not to have adverse effects”, and lacks “credible preclinical and clinical data on risks and potential health benefits” [13].

Notably, there is no explicit law for gene editing in animals. As a result, there is no violation of law in studies of reviving extinct species by CRISPR. However, as stated earlier, there can be both benefits and risks which are influential on human and natural ecosystems, and thus further regulation is needed to avoid irreparable losses.

The Need for Further Regulation

There is not an international standard on regulating gene editing with CRISPR [14]. The law on gene editing differs from country to country as seen in Fig. 4. Some countries outright ban gene editing of human embryos, but many countries have no ambiguous rules or no regulation at all. Governments around the world struggle to deal with regulating this emerging field of genetic engineering because of a lack of understanding of the differences in research and applications between classical genetic

engineering and CRISPR. This is further compounded by the difficulty of defining what is considered as a genetically modified organism. For instance, under the regulatory framework of the European Union, a genetically engineered species would not be considered a genetically modified organism if the result of using CRISPR is identical to what could occur in nature, which means that de-extinction efforts using CRISPR would likely be legal despite their effects being largely unknown. Due to this ambiguity, it makes regulation a complicated issue because the regulation is trying to design a framework of rules that regulates only the end result of using CRISPR [15]. This leaves the possibilities of loopholes that scientists could abuse in the other steps of the process.

Fig. 4. A world map that shows the legal restrictions on gene editing of human embryos around the world. Image from [14].

In the United States, there are three agencies that regulate genetically modified organisms: Environmental Protection Agency, Food and Drug Administration, and United States Department of Agriculture. This adds unnecessary complexity and the current guidelines from these agencies only address safety and efficacy. This means that the US government does not have the power to mandate regulations that concern moral, cultural, and socioeconomic issues, and therefore would have a difficult time handling the legal use of CRISPR [16].

Our Proposal

Current regulations are designed based on classical genome engineering, which has led to a lack of regulation on germline editing. This is evident in the United States. They

have three agencies that govern Genetically Modified Organisms (GMOs), but none of the agencies have the power to make decisions about gene modification of a human embryo nor use of ancestor species to revive extinct species, among other possible applications. When considering the potential ramifications of this technology, action is required to regulate research using CRISPR.

Thus, we strongly recommend that countries around the world implement regulations by following a model created by the World Health Organization for preventing biosecurity risk [17]. This model is a great guideline for designing regulation to have preventive measures from researchers stepping over ethical boundaries. Also, the regulation should promote researchers voicing their concerns about the work of other researchers. This system will prevent researchers from pursuing illegal research by themselves.

In the United States, it is not only a problem of regulation, but also conflicting and overlapping powers. Implementing an overarching regulatory board of the three agencies would help simplify unnecessary complication and allow the government to address moral and socioeconomic concerns. We also recommend establishing international standards on genetic engineering based on our recommendation. We say this because although some countries outright bans any form of gene editing, CRISPR is not the issue. The problem is the lack of oversight, safety precautions, and ethical reasoning behind gene editing. With better regulation on both a national and international level, there is a greater chance that CRISPR could serve as an engineering advancement that could safely prevent a multitude of fatal diseases and help safely bring back extinct species that could help our current ecosystems instead of an ecological disaster.

Conclusion

The discovery of CRISPR technology around the world is met with controversy and optimism. With Charpentier and Doudna's research paving the way for practical applications of CRISPR RNA, scientists now have a relatively simple method of editing the genome of any eukaryotic cell. In the future, this technology could help eliminate genetic diseases and revive extinct species. However, this can also provide any scientist with an easy and efficient method to edit human embryos without considering the safety and ethics concerns. This action is problematic because there is not enough research to fully understand the ramifications. Furthermore, there is no international standard in place to prevent scientists from overstepping ethical boundaries with their experiments.

CRISPR is a great solution to prevent genetic diseases because changes made with the gene pool are heritable, but the heritability raises concerns about mutations in the gene pool that would be a problem for future generations. There could be further problems when people view CRISPR as a tool to reach “perfection”, leading to a lack of diversity. Despite these downsides, CRISPR when used correctly could help revive extinct species and help repair ecological damage by recreating species like a passenger pigeon. However, this solution raises ethical concerns on genetically modifying a bird species to recreate a passenger pigeon bird and it could do more harm than good to the gene pool because of its engineered added trait. Further research under new regulation can help address these concerns.

With the current policies, the United States has restrictive rules on the use of CRISPR technology to edit the human gene pool and does not regulate gene editing of animals. These rules make it difficult for scientists in the United States to conduct research or even get funding, and scientists could engineer gene-edited animals that could do irreversible damage to the natural ecosystem with no regulation to stop it. There is a need for further regulation when countries like the United States make it challenging to research, other countries outright ban the topic, and still others have no policies on editing the gene of a human embryo. This could mean a scientist from a country like Korea could go to a country with no restrictions and legally edit a human embryo without any care for safety and efficacy.

We believe that CRISPR is inherently not the problem, and the problem lies within the users who disregard moral and socioeconomic concerns. Thus, we recommend that we design an international regulation standard based on WHO’s guidance on preventing biosecurity risk. The system should encourage scientists to voice any concerns for red flags in other scientist’s work. Then, we could safely use CRISPR technology to create a world where scientists around the world could work together to put a stop to all genetic diseases and strengthen our natural ecosystems.

References

[1] “CRISPR Timeline,” *Broad Institute*, 07-Dec-2018. [Online]. Available: https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-timeline. [Accessed: 01-Jun-2021].

[2] “What is CRISPR?,” *The Jackson Laboratory*. [Online]. Available: https://www.jax.org/personalized-medicine/precision-medicine-and-you/what-is-crispr#. [Accessed: 01-Jun-2021].

[3]

[4] B. A. Townsend, “Human genome editing: how to prevent rogue actors,” *BMC Medical Ethics*, vol. 21, no. 1, Oct. 2020.

[5] “Guidance for Industry-Regulation of Genetically Engineered Animals Containing Heritible Recombinant DNA Constructs.” Food and Drug Administration, Washington, DC, USA, Rep. no. FDA-2008-D-0394-0274, Jan. 15, 2009. [Online]. Available: https://www.regulations.gov/document/FDA-2008-D-0394-0274. [Accessed: 01-Jun-2021].

[6] “What are genome editing and CRISPR-Cas9?,” *MedlinePlus*, 18-Sep-2020. [Online]. Available: https://medlineplus.gov/genetics/understanding/genomicresearch/genomeediting/. [Accessed: 01-Jun-2021].

[7] M. T. Bergman, “Perspectives on gene editing,” *Harvard Gazette*, 28-Oct-2019. [Online]. Available: https://news.harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/. [Accessed: 01-Jun-2021].

[8] B. Yirka, “Researchers take another step in bringing back a wooly mammoth,” *Phys.org*, 23-Mar-2015. [Online]. Available: https://phys.org/news/2015-03-wooly-mammoth.html. [Accessed: 01-Jun-2021].

[9] B. Shapiro, “Mammoth 2.0: will genome engineering resurrect extinct species?,” *Genome Biology*, vol. 16, no. 1, 2015.

[10] V. J. Lynch, O. C. Bedoya-Reina, A. Ratan, M. Sulak, D. I. Drautz-Moses, G. H. Perry, W. Miller, and S. C. Schuster, “Elephantid Genomes Reveal the Molecular Bases

of Woolly Mammoth Adaptations to the Arctic," *Cell Reports*, vol. 12, no. 2, pp. 217–228, Jul. 2015.

[11] "PASSENGER PIGEON PROJECT," *Revive & Restore*. [Online]. Available: https://reviverestore.org/about-the-passenger-pigeon/. [Accessed: 01-Jun-2021].

[12] M. P. Phelps, L. W. Seeb, and J. E. Seeb, "Transforming ecology and conservation biology through genome editing," *Conservation Biology*, vol. 34, no. 1, pp. 54–65, 2019.

[13] R. O. Hynes, B. S. Coller, and M. Porteus, "Toward Responsible Human Genome Editing," *JAMA*, vol. 317, no. 18, p. 1829, May 2017.

[14] S. Gould and K. Loria, "This map shows where researchers might design the first genetically engineered baby," *Business Insider*, 20-Oct-2015. [Online]. Available: https://www.businessinsider.com/what-countries-allow-researchers-to-edit-human-embryos-2015-10. [Accessed: 02-Jun-2021].

[15] K. M. Vogel, "Crispr goes global: A snapshot of rules, policies, and attitudes," *Bulletin of the Atomic Scientists*, 10-Aug-2020. [Online]. Available: https://thebulletin.org/2018/06/crispr-goes-global-a-snapshot-of-rules-policies-and-attitudes/. [Accessed: 01-Jun-2021].

[16] R. Globus and U. Qimron, "A technological and regulatory outlook on CRISPR crop editing," *Journal of Cellular Biochemistry*, vol. 119, no. 2, pp. 1291–1298, Jul. 2017.

[17] M. Skipper, Ed., "Germline gene-editing research needs rules," *Nature News*, 13-Mar-2019. [Online]. Available: https://www.nature.com/articles/d41586-019-00788-5. [Accessed: 03-Jun-2021].