TITLE: CRISPR: Let us Leave the Germline Alone.

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ABSTRACT

This work showcases some CRISPR applications and how the ethical debates around this technology have yet to result in a feasible roadmap for its use. After revising legislation and guidelines, philosophical and theological views, we are still without a clear path to conduct germline modifications. Moreover, this paper argues against germ-cell editing and showcases CRISPR's intricate maze of ethical predicaments.

Keywords: CRISPR, DNA, Genetically modified organisms, Human Genome, Ethics.

INTRODUCTION

For millennia, those of us that have tried to cure sicknesses have done so from a reactive stance. Even before Hippocrates, healers were concerned about symptoms rather than the cause of illnesses. Modern science has helped us to understand –to some extent, the intricate details behind diseases. Even though we have significantly developed preventive medicine, our reactive approach to diseases is still the status quote. All this passivity is about to change. A revolutionary technique borrowed from the bacterial defense system has opened new horizons for scientists. CRISPR-Cas9 is a highly accurate gene-editing system that has given us the power of rewriting life itself. Up until now, gene-editing techniques have been expensive, time-consuming, and flawed. However, this new method allows scientists and non-scientists to quickly and inexpensively tinker with the threads of life, DNA.

Along with the prospect of eradicating diseases, CRISPR presents us with the possibility of rewriting the genome of any living *thing*. Should we play God? If so, who gets to be God? The engineering of somatic cells to combat specific pathologies is already happening; however, modifying germ cells in humans poses a more significant ethical dilemma. Should we as species

take control of what has been for billions of years Natures' job? This work showcases some CRISPR applications and how the ethical debates around this technology have yet to result in a feasible roadmap for its use. Moreover, this paper argues against germ-cell editing and showcases CRISPR's intricate maze of ethical predicaments.

DISCUSSION

CRISPR-Cast9 or Clustered Regularly Interspaced Short Palindromic Repeats/Cas9 is a gene-editing system that serves as an immunity mechanism in and most archaea (Sontheimer and Barrangou 2015). This fascinating molecular device protects bacteria against viruses by excising viral DNA, later stored on the bacterial DNA. If the same virus attacks again, the organism defends itself by recognizing the viral DNA and deploying the Cast-9 complex. This complex works like molecular scissors that cut and destroy the virus. (Hirsch et al. 2019). In 2012 Jennifer Doudna and Emmanuelle Charpentier harnessed the power of this ancient molecular mechanism to program DNA editing. These remarkable scientists isolated the CRISPR–Cas9 system components, adapted them to function in the test tube and showed that the system could be programmed to cut specific sites in isolated DNA (Jinek et al. 2012). From this landmark discovery, geneticists have been able to generate a guide RNA molecule (gRNA) that acts as a guide sequence; this, in turn, recognizes a specific DNA sequence in the genome. The other part of the mechanics is a CRISPR-associated (Cas) nuclease. The gRNA identifies the desired segment of DNA, and the Cas9 enzyme cuts at the targeted location (Thurtle-Schmidt and Lo 2018). This precise molecular mechanism has opened a world of genetic progress. This technology is currently under scrutiny to determine the extent to which it should be used in humans.

CRISPR-Cas9 Applications

It would be an understatement to say this ancient yet powerful molecular technique has revolutionized the field of biology. If we consider we hold in our hands the power to change the most intricate fabric of life, DNA, quickly, then we could fully comprehend the power of CRISPR. Theoretically, gene editing could solve any biological-related problem. An example of a powerful application of CRISP is the creation of transgenic animals to model genetic diseases. The CRISPR approach to animal-based research can expand biological inquiry beyond traditional, genetically

tractable animal model organisms. (Sander and Joung 2014). Even though new conventional breeding techniques are more efficient, they are not likely to keep up the pace to deal with the environmental challenges. Using this technology, scientists can scrutinize the results of introducing precise and subtle genetic chances on the model organism.

Furthermore, this system has allowed the creation of model organisms with extensive genetic modifications; also, it has been shown effective in a wide variety of animals, from early-branching metazoans to primates (Shrock and Güell 2017). Before CRISPR, genetic screening was an excruciating process relegated to some unlucky graduate students. Today, genetic screening is relatively easy, inexpensive, and fast because of CRISPR.

Genetically edited crops such as corn, tomato, and wheat have shown high levels of resistance and yield. In maize, for example, the application of Site-Directed Nucleases-3 (SDN-3) to the Argos8 gene promoter "conferred constitutive expression of the endogenous gene and resulted in improved maize yield during drought stress." (Gao 2018). Genetically modified organisms (GMO) have been around for a while. GMO crops, in particular, have been the center of debate for decades. Indeed, it takes more resilient, fast-growing crops to feed the world. CRISPR paves the way toward a new horizon for crop improvement and consequently revolutionizes plant breeding (Wang et al. 2019). Although GMOs are a highly controversial topic, CRISPR brings in a new way of creating genetic modification. Instead of the classic hybridization approach for GMO crops, this technique produces genetic changes using the organism's own DNA library (Williams 2016). This method helps us to circumvent some of the previous challenges of crop modification. Yet, it lends itself an opportunity to revise and update the current agricultural biotechnology practices and governances.

Undeniably, the field of gene therapy has experienced a significant boost after the CRISPR revolution. For example, "In the past five years, several teams of researchers have independently shown that genome editing can reliably eliminate the gene that encodes mutant huntingtin, thereby halting the production of the toxic protein and its accumulation into clumps in experimental models." (Eisenstein 2018). This promising therapy could mean completely eradicating Huntington's disease, which affects hundreds of thousands of people. CRISPR is also revolutionizing the energy industry. The ExxonMobil-Synthetic Genomics research team has

successfully modified algae to enhance its oil content from 20% to more than 40% (Ajjawi et al. 2017). With this move, ExxonMobil seeks to generate biofuel from genetically modified organisms.

Another practical use of this technology is on the employment of gene drives. A gene drive is a self-propagating mechanism by which a desired genetic variant can be spread through a population faster than traditional Mendelian inheritance (Akbari et al. 2015). Gene drives represent a potential solution for hurdles such as vectors disease, control of invasive species, and combating pesticide resistance. (Gantz et al. 2015). None of the approaches mentioned above are without challenges; technical difficulties, lack of understanding, error-prone mechanisms, and ethical quandaries are some hurdles to overcome. Even though the possible implication and consequences of using CRISPR are yet to be determined, something is evident; this system grants us seemingly unlimited power.

Somatic and Germ Cells Gene Editing

When it comes to genome editing, the targets can be somatic and or germline cells. Editing the somatic cells consists of changes that do not pass genetic information to the next generation; the germline cells (sperm and eggs) pass genetic information to the organism's offspring. Thus, germline changes potentially further genetic modification into the future and can scape the confines of the modified organism. The transformation of human somatic cells, to some extent, has been well-received. The fact that patients have agency when getting treated, plus the specific benefits of such therapy, makes somatic cell editing less controversial. More importantly, the applications of this genetic technology have been set within the boundaries of well-established, carefully regulated gene therapies (National Academies of Sciences and Medicine 2017). Though somatic cell alterations have been welcomed, some believe the treatment of nonlethal diseases could lead to people losing their uniqueness (Check Hayden 2016). Genetic variability makes not only phenotypic distinctions but also a plethora of idiosyncratic behavior. To some, the alteration of our genetic makeup is a step towards losing our individualities.

In contrast to somatic cells line modifications, germline modification has been historically objectionable (Morrison and de Saille 2019). Concerns about this application come in two

flavors; technical issues related to the novelty of the technology and lack of an appropriate ethical framework to deal with such a powerful tool. When it comes to germline editing, the apparent concern is the perpetuation of certain genetic modifications. This problem intensifies when we think this mechanism still renderers off-target effects that alter the sequences elsewhere in the genome. When transmitted over a generation, the consequences of these off-target mutations are unpredictable (Hartwell et al. 2018). Though CRISPR is by no means ready for germline editing, "its suitability for targeted disruption of individual genes, can provide us with a robust tool to gain fundamental knowledge of early human embryonic development." (Reyes and Lanner 2017). Hundreds of labs around the works are working tirelessly to get CRISPR ready for the new genetic revolution.

The practical difficulties associated with this technology could be evaded with enough research and more accurate protocols. Nevertheless, even though high levels of accuracy can be achieved by experimentation, the ethical dilemma of whether to edit germline stills stands. *Should we, as a society, embark on the Odyssey of changing the course of humanity by altering our genetic makeup?* Even though CRISPR is a new technique, gene manipulation has been around for half a century. Therefore, guidelines for molecular genetics experimentation are already in place. Before continuing with the question at hand, a review of such policies is necessary to determine whether the current precepts provide a reliable framework for using CRISPR on germline modifications.

Analysis of the Framework and Current Ethical Consideration for Germline Editing.

As early as 1975, the scientific community was concerned about adopting proper guidelines to deal with the inevitability of a biotechnology revolution. In the famous 1975 "Asilomar Conference on Recombinant DNA" conference, scientists and legislators wrestled with the idea of an encompassing framework to deal with this matter. The goal of the Asilomar conference was to address the biohazards presented by recombinant DNA technology. In pursuing this goal, participants reached two main consensuses. One, containment should be made an essential consideration in the experimental design. Two, the effectiveness of the containment should match the estimated risk as closely as possible (Berg et al. 1975).

Even though the consensus achieved at the meeting was controversial, vague, and mainly concerned with containment, it was the ruling document until earlies 1990s (Hanna 1991). Considering that today anyone could buy a *DIY* CRISPR kit just as quickly as one can buy a pair of shoes from Amazon (Sneed 2017), it is safe to assume we are looking at the outcome of the Asilomar summit in the rearview mirror.

In 2017, the United States National Academies of Sciences, Engineering (NASEM) and Medicine Committee on Human Gene Editing established a series of guidelines for using new gene-editing technologies. The meeting held as paramount the idea that gene-editing, specially germline editing, goes beyond the "individual-level concerns and toward significantly more complex technical, social, and religious concerns regarding the appropriateness of this degree of intervention" (Brokowski 2018). Clinical trials using germline modification are only allowed if they meet the following criteria: 1) The absence of reasonable alternatives. 2) Restriction to preventing a severe disease or condition. 3) Restriction to editing genes that have been convincingly demonstrated to cause or to predispose to the disease or condition strongly.

4) Limit to converting such genes to versions prevalent in the population and 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 the procedures' risks and potential health benefits. 6) Ongoing, rigorous oversight during clinical trials of the effects of the process on the health 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 health and societal benefits and risks, with broad ongoing participation and input by the public. 10) Reliable oversight mechanisms to prevent extension to uses other than preventing a severe disease or condition (Sciences et al. 2017).

Even though the guidelines for germline editing seem to be well established, scientific curiosity and the basic human need for acknowledgement are hard to evade. Sometimes this curiosity, or perhaps ulterior motives, push scientists beyond ethical boundaries. This is the case of Dr. He Jiankui, a Chinese scientist that became the target of global criticism when he allegedly made the first CRISPR-edited babies, twin girls named Lulu and Nana. Dr. He focused on a gene called

CCR5, the protein product of which HIV uses as an entry door for infiltrating human cells. Although Nana and Lulu's father is HIV-positive, neither of the infants had HIV(Yong 2018). On December 30, 2020, a Chinese court sentenced Dr. He to three years in prison for "illegal medical practice" on top of and a three million yuan fine (Cyranoski 2020). The case of Nana and Lulu is a cautionary tale, a testament to the capabilities of this theology and how wrong it can go if left unchecked.

The question is evident, what is wrong with preventing two babies from a life of suffering? Numerous things are inappropriate with this reckless behavior! First, Dr. He did not address a life or death condition; second, the procedure was not well executed, as only half of the cells of the babies were indeed immune to the disease (Musunuru 2019). Moreover, the consequences of such genetic modification will not be evident until after birth (Lanphier et al. 2015). All the previous transgressions are severe; nevertheless, the more enraging violations were that Dr. He completely skipped animal modeling, and as The Atlantic reports, "It's not clear if the participants in He's trial were aware of what they were signing up for." (Yong 2018). The supposed consent form Dr. He used did not include information about the consequences of deactivating CCR5 and gave He's team rights to use photos of the babies as an advertisement (Yong 2018). Ethically appalling, Dr. He's action can be perceived as a one-off. The international scientific community must be vigilant and ready to reject any CRISPR-related unethical behavior. The prevention of such infringements starts at the educational institutions where future scientists should be trained under humanistic principles. Political, economic, or personal gains should not be the propellor of scientific endeavor, in particular, when it comes to gen editing. Is there any ground in China's current ethical framework for Dr. He's actions? A comprehensive review of the legal status of the human embryo in the three domains of China's legal system (Jiang and Rosemann 2019) described what seems to be conflicting ideas of the legal status of the fetus. A particular line in this meta-analysis appears to capture the possible roots of the current state of germline editing in China:

"*the normalization of pregnancy termination and the existence of a more secular and utilitarian view of in-vitro fertilized embryos and aborted embryos, at least among many scientists,*

clinicians, and informal political discourse, may well have supported the rapid move ahead in human embryo gene editing."

This assessment sheds light on the core socio-political framework that allows for careless scientific praxis and can help us understand how ethical behavior in science is a multidimensional phenomenon. Society's underlying axioms are decisive when embracing or rejecting the adoption of a particular technology.

I share the view of (Lanphier et al. 2015) regarding germline editing. I, too, believe genome editing in human embryos using current technologies could have unpredictable effects on future generations. Moreover, the lack of strict guidelines and the availability of this technology could allow this procedure to be exploited for non-therapeutic modifications. Therefore, though I believe CRISPR is an extraordinary tool capable of improving human life, I reject the notion that germline modification should be used in the pursuit of well-being.

Exploration of Germline Editing from a Deontological Perspective.

This section will analyze germline editing through different ethical lenses, deontological, consequentialist. Most of the guidelines governing scientific efforts are based on deontological/consequentialist frameworks, and to some extent, they have worked. However, CRISPR represents a unique instance as it can redirect the faith or the entire human species. Deontology regards an action as ethical so long it follows a particular set of rules (Alexander and Moore 2007). Therefore, germline editing from a deontological viewpoint would be deemed appropriate insofar guidelines are followed. However, when we apply Kantian philosophy to the issue of germline modifications, we quickly run into two roadblocks. One, who will be in charge of rewriting the rules that took nature billions of years to hone?; and two, what are we to do with the deontological dismissiveness towards consequences? Scientists have, in general, followed whatever set of rules is put in place by society. Such regulations come with the marks of human imperfections. Let us, for a moment, imagine we can produce the *perfect* set of regulations to lead our germline editing efforts, and as good Kantians, we follow the rules. The unpredictable nature of biological systems could lead us to a dead end as off-target genetic alterations can be devastating (Naeem et al. 2020). Are we going then to follow the rules

despite the consequences? It would be impossible to achieve a just and mindful use of germline editing with a deontological framework. Lack of concern for future consequences and the incapability of creating an all-encompassing set of rules to follow makes deontology not useful as a framework in this situation.

One could argue that by managing possible future adverse consequences, we could develop a plan of action so that germline editing would create the greatest good for the greatest number. If this is the case, we could apply utilitarianism as our frame of reference for germline editing. This line of thought asserts that the morally right action is the action that produces the most good (Driver 2009). From the start, we can spot a few of the downfalls of this philosophy. For example, who gets to decide what constitutes a good outcome? Furthermore, what portion of the population benefits from the "good" result? Arguably, the major pitfall of this approach is dealing with the inevitable power imbalance this technique would bring. In that, although engineering superhumans is a sci-fi concept, the first in line to get them, if available, will be the most influential individuals. Lastly, the main concern about a utilitarian approach to germline editing is that this philosophy does not account for justice or individual rights. Not only would the rights of the future generation be forsaken, but also that of the current portion of the population that has little value. A utilitarianism approach to germline is, therefore, not helpful.

Examination of Germline Modification Through the Lens of Religion

So far, secular approaches to creating a practical framework for germline editing have proven not helpful. Let us then examine this phenomenon from a theological point of view. An argument could be made against this practice on the same terrain of abortion or euthanasia. In the book *The Righteous Mind*, Jonathan Haidt introduces the principle of sanctity as one of the pillars of religion. Haidt argued that:

"*Conservatives—particularly religious conservatives—are more likely to view the body as a temple, housing a soul within, rather than as a machine to be optimized, or as a playground to be used for fun*."(Haidt 2012)

The notion of preserving the purity of the human body is a staple of religious conservatism. In that, no harm should be inflicted upon God's given body. Even non-religious people would jump

to the conclusion that germline modification is a forbidden matter within religious groups. The reality has proven to be not as clear.

In a 2009 book titled *Design and Destiny: Jewish and Christian Perspectives on Human Germline Modification*, many religious scholars and leaders decided to set the record straight regarding germline alteration. Even though the views regarding this topic vary between denominations, the consensus was that:

"*Contrary to popular opinion, religious scholars and leaders are not unanimously opposed but are, in fact, generally open to the possibility of a morally acceptable approach to human germline modification. Ever since the idea of genetic surgery was first discussed in the 1960s, some theologians and religious ethicists have recognized that germline modification may be technologically farfetched, but it is not obviously immoral or irreligious*." (Cole-Turner 2008)

Although this book asserts that not all religious leaders and theologians are in favor of germline modification, it has a clear prescription, "any use of germline modifications must be for therapeutic rather than enhancement purposes." (Cole-Turner 2008). Another element noted in this book is that germline editing must be consistent with the religious principles of social and economic justice. I challenge the idea of Cole-Turner that germline modifications are "*not obviously immoral or irreligious.*" (Cole-Tuner 2008) Although I would not embark on an argument against the religiosity of this technique, I believe germline editing is "not obviously immoral" so long it is conducted for therapeutical purposes. Tampering with germline information for other reasons is not only immoral but a danger to our species.

CONCLUSIONS

After revising legislation and guidelines, philosophical and theological views, we are still without a clear path to conduct germline modifications. Throughout the years, we have been just another player in the evolutionary process. Even though genetic engineering has been possible for many years, the use of CRISPR/Cas-9 can catapult us to the driver seat of evolution. I believe the employment of germline modification could represent an evolutionary leap in humanity. Still, the risk and challenges this technique poses are far beyond our current capability of handling them—international guidelines aid in establishing the process of somatic and germline modifications. However, instances of misconduct, as in the case of Dr. He, show

the permeability of such guidelines. The challenges of CRISPR go beyond technicalities. Even if we mitigate the risk of random mutations, we will face ethical issues that transcend individualities.

When it comes to the ethical postulates to hold as a framework for gene editing, none of the standing philosophical principles help us clear the way to achieve a helpful, viable consensus. Moreover, the religious community appears to be on the fence about this issue. Religiosity, even though it has a solid divine foundational principle, has been unable to guide us in the process of deciding whether to use this technology. What should we do? Do we allow ourselves to take control of evolution? Should we put our trust in a system prone to error? Or do we set back and let this be our pandora box? The reality is that this technology is already a prominent biological tool; there is no going back. The mere uncertainty of a future in which germline editing is a reality is enough to outweigh the benefits of its use. We must refrain from using this tool therapeutically until we can control it, and the sociopolitical circumstances are more favorable for those at the bottom. I am afraid this technology will bestow a future in which social divides will ned. How about if we leave germline cells alone? Perhaps there are some things we are not to fix.

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