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CRISPR and the Future of Genome Engineering: A Bold New World

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Abstract

The field of genome engineering has grown rapidly in the past decades, culminating in the discovery of the CRISPR/Cas9 system in 2012. The method has proven to be revolutionary, displaying immense potential for research and medicine. It exhibits incredible precision for reading and editing the genome and has lowered the price of gene editing technologies drastically. Possible applications of the system generally lie in either gene *therapy*, the treatment of diseases, or gene *enhancements*, the selection/augmentation of embryotic genes in so-called "designer babies." Currently, many reason against the adoption of the CRISPR system, citing the myriad ethical issues associated with the ability to manipulate genes. In this paper, I argue that CRISPR, and more generally genome engineering, are necessary technologies for the future. I aim to show that, with the necessary precautions, the system can, and should, be safely embraced for the betterment of society.

Introduction: Huxley's Frightening Prophecy

> 'Reducing the number of revolutions per minute,' Mr. Foster explained. 'The surrogate goes round slower; therefore passes through the lung at longer intervals; therefore gives the embryo less oxygen. Nothing like oxygen-shortage for keeping an embryo below par.' Again he rubbed his hands. 'But why do you want to keep the embryo below par?' asked an ingenuous student. 'Ass!' said the Director, breaking a long silence. 'Hasn't it occurred to you that an Epsilon embryo must have an Epsilon environment as well as an Epsilon heredity?' (Huxley, 2006, p. 14)

In 1931, in the midst of the Great Depression, Aldous Huxley published *Brave New World,* a gripping critique on similar utopian novels and a biting commentary on civilization at the time. Huxley paints a grim picture of what he envisioned a possible future for human society to be, one stripped of individualism and consumed by hedonism. Human embryos are mass produced in factories, precisely engineered to fulfill specific roles in a five-caste system. In this society dominated by a World State, lower caste citizens are not only built weaker and less intelligent, but are actually conditioned to be perfectly content with their inferiority. The aforementioned "Epsilons" unfortunately occupy the lowest tier in this system.

Huxley's novel came twenty years before the structure of DNA had been established and several decades before the first attempts at editing the genome. While other critiques predicted by *Brave New World* began to take shape in the real world soon after the novel's publishing—such as the shift to a consumer-based society where distractions are ubiquitous—it was not immediately obvious that biotechnology would advance to its present levels. Huxley's depiction of "embryo engineering" came from the eugenics movement, which was quite popular at the time. In fact, one of his brothers, Julian, was a biologist involved in the movement. Although the popularity of the eugenics movement quickly died after World War II, during which the Nazis adopted its principles, many of the fears associated with eugenics have returned due to present developments in biotechnology.

But, are these fears justified in regard to recent advancements, which could be of an entirely different nature than the eugenics movement? Is Huxley's nearly century old prediction still relevant today? Arguably, no. Genome engineering—specifically the CRISPR/Cas9 system—is a necessary technology for the future of human society and should be embraced, albeit with reasonable discretion.

The Genetic Revolution

Nowadays we find ourselves in the midst of a new age of human evolution—the genetic revolution is upon us. In 1990, the Human Genome Project was launched, seeking to sequence and map every gene in human DNA. A truly ambitious goal, and yet it was completed in 2003 (Collins et al., 2003). But what is even more significant than the ability to read the genome is the ability to *edit* the genome. In 2012, an extremely powerful

and versatile new method of genome engineering, called the CRISPR/Cas9 system, was established. The system was first discovered in 1993 by a Spanish graduate student, Francisco Mojica, who found "multiple copies of a near-perfect, roughly palindromic, repeated sequence of 30 bases" in a microbe called *Haloferax mediterranei*. Mojica devoted his work to the study of this mysterious discovery and would later go on to coin the term "Clustered Regularly Interspaced Short Palindromic Repeats," or CRISPR, to describe the sequences. In 2003, Mojica was able to conclude that the purpose of CRISPR was that of adaptive immunity, protecting bacteria from infections by phages (Lander, 2016).

After years of extensive research, biologists began to see the extent of CRISPR's power beyond its biological purpose of adaptive immunity, especially in the case of precise gene editing. This eventually culminated in the breakthrough in 2012, when Jennifer Doudna's group at the University of California, Berkeley established this property of programmability of CRISPR along with the "CRISPR-associated" protein, Cas9 (Jinek et al., 2012). In 2013, Feng Zhang, an investigator from the Broad Institute at MIT, optimized this system and demonstrated several uses for genome editing in mammals, including "precise cleavage at endogenous genomic loci" and "simultaneous editing of several sites" (Cong et al., 2013). CRISPR cut the cost per target gene from $2500-$7000 for Zinc Finger Nucleases and TALENs—the precursors to CRISPR for gene editing—down to $50-$100 for the Cas9 system. Moreover, it cut the "Target Validation Time"—measuring the time taken to confirm proper gene targeting—down from 8 weeks to just 2-4 weeks (Hyun & Clarke, 2015). CRISPR combined low cost, easy programmability, wide applicability, and high specificity, paving the way for a true genetic revolution. Clearly, CRISPR is making an impact in *labs* across the world, but what does this entail for *society*? How does this change the life of the average person?

Possibilities for Therapeutics

CRISPR has already been shown to have powerful therapeutic applications. In 2015, at the Comprehensive NeuroAIDS Center at Temple University, Kamel Khalili and his team utilized the system to "precisely remove the entire HIV-1 genome…from latently infected human CD4+ T-cells." The group then showed, by sequencing the edited cells, that the genome of the cells had not been compromised and that there was no effect on cell health (Kaminski et al., 2016). Note, however, that this study was conducted *ex vivo*—the cells were in a lab environment, outside the body. Still, having been conducted a mere three years after the establishment of CRISPR's genome engineering abilities, this study is a testament to the significant potential the technique has for the future. In fact, within a year, Khalili and his team went on to conduct an *in vivo* study in the bodies of rats and mice. The rodents were engineered "to incorporate specific HIV genes into nearly every cell in their body." Then,

Khalili demonstrated that two injections into the rodents' tails were enough to remove the virus in a majority of the infected cells (Park, 2016). Other groups have been equally successful at showing success in treating *human* somatic cells—non-reproductive cells. One study published in the journal *Cell* demonstrated the ability to remove a receptor called CCR5 from human T-cells. CCR5 is what HIV binds to during infection, and cells with the receptor removed can be returned to the bloodstream where they display infective resistance to HIV (Mandal et al., 2017).

In addition to the potential for curing HIV, CRISPR could in the very near future be used to fight another of mankind's deadliest enemies: cancer. Researchers at the University of Pennsylvania, led by Edward Stadtmauer, are looking into improving current cancer therapies, which have already shown much promise but have not yet overcome the issue of disease relapses. Stadtmauer's group is performing a trial wherein T-cells from patients with various forms of cancer will be removed and have three CRISPR edits performed on them. Each edit will play a specific role in fighting cancer: the first "will insert a gene for a protein engineered to detect cancer cells and instruct the T-cells to target them," the second "removes a natural T-cell protein that could interfere with this process," and the third "will remove the gene for a protein that identifies the T-cells as immune cells and prevent the cancer cells from disabling them" (Reardon, 2016). What is also incredibly valuable about the gene editing technique in cancer research is its ability to model the disease more precisely. Other cancer researchers such as Lukas Dow, a cancer geneticist at Weill Cornell Medical College in New York City, and Wen Xue from the University of Massachusetts Medical School in Worcester have found the use of CRISPR significantly critical in improving accuracy and speed in their studies. Dow's team engineered their own specific CRISPR-Cas9 system in order to model mutations in human colorectal cancers. Similarly, Xue's team is "systematically sifting through data from tumour genomes, using CRISPR-Cas9 to model the mutations in cells grown in culture and in animals" (Ledford, 2016).

As mentioned earlier, the treatment of both of these diseases thus far have involved somatic cell therapies—editing the non-reproductive cells in the body. The same techniques could be used to cure a variety of other diseases of the same nature. For example, establishing a cure for HIV could give key insight into the treatment of other viruses that display latency—the ability to remain dormant inside a cell—including the Herpes simplex virus. But, what of therapy for *genetic* diseases? In this realm, CRISPR is of paramount importance, yet therapy of this type involves manipulation of the germline itself. It is at this point that the ethics of genome engineering begin to see controversy. However, before we discuss the moral ramifications of CRISPR gene therapy, let us first establish the tremendous positive potential that it holds.

Editing the Human Germline

Genetic diseases could be all but eradicated in the not so distant future. Take for instance, cystic fibrosis, a heritable disease caused by mutations in the cystic fibrosis transmembrane conductance regulator, or CFTR, protein. The "most common lethal genetic disease in white populations," cystic fibrosis affects nearly 1 in 3000 births (O'Sullivan & Freedman, 2009). Yet, in 2013, just one year after the CRISPR/Cas9 genome editing system was established, researchers used the technology to repair genes encoding the CFTR protein "in cultured intestinal stem cells of CF patients" (Schwank et al., 2013).

Another group of genetic diseases being studied is muscular dystrophy, which leads to the steady weakening of skeletal muscles of those afflicted over time. The most common form is known as Duchenne muscular dystrophy, resulting from mutations of the gene encoding a muscle fiber protein called dystrophin. Symptoms include "progressive muscle degeneration and weakness" and begin in very early childhood ("Duchenne," 2016). Again, researchers have employed the CRISPR/Cas9 system in the germline of mice to successfully correct dystrophin gene mutations. They were able to produce "genetically mosaic animals containing 2 to 100% correction of the *Dmd* gene" with "the degree of muscle phenotypic rescue in mosaic mice [exceeding] the efficiency of gene correction" (Long et al., 2014).

Finally, autism research is likewise improving due to developments in genome engineering. In one such case, it is again the aspect of disease modeling that is advancing. For years, scientists have had difficulty engineering transgenic monkeys that could serve as better models than mice for human genetic diseases. Yet again, CRISPR can now be tested on "fertilized monkey eggs…to disrupt a gene called SHANK3, which has been implicated in some human cases of autism" (Shen, 2013).

There are *many* more implementations of CRISPR to gene therapy being explored currently—as is expected from a technique with such wide scale applicability—and it would be nearly impossible to thoroughly discuss each and every project being conducted currently in the world. Nevertheless, the point has been made that CRISPR is in many aspects already benefitting the world greatly. Moreover, it is important to remember that the technique has only existed for half a decade, and subsequent research will only further refine it, advancing even more possibilities for therapies. Soon, thousands of genetic diseases, ranging from the rather tame, such as color blindness, to the horribly fatal, such as Huntington's disease, could be all but eradicated. The question now is, why the hesitation towards its embracement? Why do people fear the future of the genetic revolution?

The Cases Against

Some scientists are worried that CRISPR in its current state is too unpredictable. Bo Huang, a biophysicist at the University of California,

San Francisco voiced the concern that, due to the extremely rapid development of the method, "People just don't have the time to characterize some of the very basic parameters of the systems…There is a mentality that as long as it works, we don't have to understand how or why it works" (Ledford, 2015). It is true that CRISPR has its limitations, as noted by Jin-Soo Kim, from Seoul National University and the Institute for Basic Science. During an International Summit on Human Gene Editing, a point was brought up that "[CRISPR] can alter DNA at locations other than the target, which could inactivate essential genes, activate cancer-causing genes, or cause chromosomal rearrangements. It can change the DNA in some cells but not all, resulting in a mosaic of altered and unaltered cells. It can generate immune responses if introduced into the body." Yet, as is the case with almost every emergent biotechnology, there is a long way to go from the stages of initial research to the final product. The conference members themselves noted that "the CRISPR-Cas9 system is still undergoing development to reach the level of safety where it could be used in clinical applications" (Olson, 2015). Of course, the "embracement" of CRISPR does not imply immediacy, as would be practically impossible given the myriad regulations in medical research. It is only after the necessary safety checks are passed that the genome engineering should be embraced. However, there still remain many issues that must be mentioned before a conclusion can be made.

The biggest ethical dilemmas in the discussion of genome engineering are those related to germline editing, in which human embryos are directly altered. The immediate objection towards such a power is the idea that in doing so, humans would be going against nature's way. As Princeton theologian Paul Ramsey put it, "Man as a manipulator is too much of a God" (Kozubek, 2016). We would begin to take control of our own destiny; our initial fate would no longer be completely deterministic and external to the will of the people. But, in subverting nature's way, we would begin a new era of human evolution. In our present state, natural selection has all but stagnated. Diseases that once put selective pressure against certain populations can now be mitigated long enough for these populations to reproduce. Thus, we find that genetic diseases persist through the generations, unable to be "removed" by nature. But, with the power of CRISPR and genome engineering, we can replace this selective pressure *against* certain groups and replace it with a negative selective pressure that bridges the gap between the genetically disadvantaged and the healthy.

To those who still claim that humans are not meant to have this type of power and that nature should not be renounced, one could argue that, given the knowledge that an embryo possesses a certain genetic defect, it would be morally reprehensible to condemn the child to a lifetime of suffering. In fact, techniques of this nature are already in practice today. Parents "can use prenatal genetic screening to check for conditions…and choose whether or not to carry a fetus to term. Preimplantation genetic

diagnosis allows couples undergoing in vitro fertilization to select embryos that do not have certain disease-causing mutations" (Lanphier et al., 2015). Given that this is already deemed acceptable, CRISPR gene editing would give parents an even better option: instead of not carrying a certain embryo to term, one could instead simply remove the diseases from the genome itself.

Observe, for instance, the case of John Sabine, "once described as one of the brightest legal minds…in England. Now, he is in the advanced stages of Huntington's disease." His brother, Charles Sabine, is also a carrier for the disease and thus is aware that, "he is destined to undergo the same deterioration of brain and body." Furthermore, between the two brothers, they have five children, who are all susceptible to inheriting the disease. Therefore, "To Charles…there is no legitimate ethical argument about whether gene editing should be used, either to treat people living with the condition now or to spare their children from it." To others like John, who suffer from diseases that could very soon be preventable, the ethics of this debate would seem almost ludicrous, and a waste of precious time in which therapies for their diseases could be developed. Even to those who would reject such an opportunity, it would remain just that: an opportunity. It would be left as a choice to the patient whether or not to accept the therapy. Indeed, there are cases in which a certain genetic predisposition's classification as a "defect" could be seen as subjective, as is evident with autism, which some argue is merely a "part of the spectrum of human variation" (Hayden, 2016).

Up to this point, only the use of genome engineering in regard to *therapy* has been discussed, but it is the question of whether or not we should consider genetic *enhancement* that has caused much debate over ethical implications. With CRISPR, it is possible that, in addition to ridding an embryo of genetic diseases, we could begin to artificially enhance certain traits. In creating these "designer babies" we would have the power to augment the child's physical abilities, improve its intelligence, and select for specific phenotypes that are deemed desirable. One argument against enhancement is the idea that a child loses autonomy, or the "right to an open future." Children would lose a sense of freedom of choice if their parents were to predetermine certain talents and skills for them. However, even now, children do not necessarily have autonomy. "The alternative to a…genetically enhanced child is not one whose future is unbound by particular talents but one at the mercy of the genetic lottery" (Sandel, 2004). Moreover, there is a degree of *nurture,* as opposed to *nature,* in a child's development. It is certainly not the case nowadays that children have complete control over their values, opinions, or even hobbies. Much of that is susceptible to the social and political environments in which the children are raised.

Another pressing concern raised is the idea that genome engineering could further exacerbate existing socioeconomic divides. At the International Summit on Human Gene Editing, Benjamin and Françoise

Baylis pointed out that "The use of gene editing techniques is seeded with values of interests, economic as well as social, that without careful examination could easily reproduce existing hierarchies" (Olson, 2015). It is here where we begin to see the need for discretion. If genetic enhancement technologies were to be released to the market unregulated, this very well could be a potential consequence. Thus, it is absolutely necessary that the government implement policies that prevent unequal distribution of enhancements. For example, in the case of height enhancements, lack of accessibility for the poor could lead to a height divide between populations. Yet, this could be remedied "by publicly subsidizing height enhancements. As for the relative height deprivation suffered by innocent bystanders, we could compensate them by taxing those who buy their way to greater height" (Sandel, 2004). Of course, the intricacies of socioeconomic hierarchies can be more complex than a simple case of height inequality. But the general idea can be seen: provide aid to those who lack access to enhancements and enact preventative measures against those who abuse them. In any case, governmental regulation over the eventual commercialization of enhancements is paramount to the prevention of large-scale changes in social and economic structure, yet this regulation must also be limited to restriction and subsidization. Having a government that mandates genetic enhancements is a slippery slope that could eventually lead to a pseudo-*Brave New World*.

In fact, this returns us to the initial discussion of a similarity to the concept of eugenics. In essence, eugenics is "a set of beliefs and practices that aims at improving the genetic quality of the human population" ("Eugenics," 2017). There has always been a strong stigma associated with eugenics. However, it still has enjoyed quite a number of proponents in the past, as evidenced by the existence of the eugenics movement in the US. Although the Nazi adoption of its principles made eugenics largely taboo after World War II, the unrestricted embracement of enhancements yet again brings us dangerously close to this idea. Some modern political philosophers believe that there is a distinction to be made: "'While old-fashioned authoritarian eugenicists sought to produce citizens out of a single centrally designed mould,' writes Nicholas Agar, 'the distinguishing mark of the new liberal eugenics is state neutrality.' Government may not tell parents what sort of children to design" (Sandel, 2004). Yet there is still a fundamental issue with this so-called "liberal eugenics." By transferring *all* power of eugenic decisions from the government to the public, these decisions become "governed by profit orientation and preferential demands" and are at the will of the "anarchic whims of consumers and clients" (Habermas, 2003). As established previously, giving complete freedom of enhancements to society would inevitably aggravate socioeconomic inequalities and could create an avenue for discrimination against certain "conditions" which cannot objectively be considered imperfections. To truly avoid these problems

associated with eugenics, we must establish a middle ground by allowing the government to regulate access to, and the nature of, enhancements, while prohibiting full authority over their implementation.

Conclusion: A Bold New World

Huxley's pessimistic depiction of the future of human society was motivated by the eugenics movement of his time. Several decades later, we find that the world could really be headed in the direction of his imagined dystopia. Yet as long as the necessary precautions are taken, this can be avoided, allowing for the implementation of a powerful new biotechnology with immense potential for the future. A genetic revolution, ushered in by the discovery of the CRISPR/Cas9 system and its genome engineering capabilities, has paved the way for a new era of biological advancement. Diseases that have plagued mankind for centuries could be eradicated in the near future with gene *therapy*. One potential form of therapy is the treatment of *somatic*, or non-reproductive, cells. In this realm, scientists have already demonstrated significant advancements in HIV and cancer research. With the ability to directly manipulate the human germline there are also therapeutic possibilities for *reproductive* cells. Due to CRISPR's wide applicability, thousands of genetic diseases could be cured with this technique. In this way, the divide between the genetically disadvantaged and the healthy can be closed. Also, as an alternative to preimplantation genetic diagnosis, gene therapy allows parents to save an embryo that would otherwise be thrown away. In addition to therapy, we now have the power to advance the process of evolution artificially with genetic *enhancements*. Traits like athleticism, physical features, intelligence, artistic ability, etc. could be altered and augmented in an embryo's genome. But, as a society, we must embrace the idea of enhancement with caution. It is prudent in this regard to both heed Huxley's warning by restraining governmental power and avoid a new form of "liberal eugenics" by still allowing for the regulation and restriction of enhancements. With all of this kept in mind, we can confidently proceed into the genome engineering future, where a bold, new world awaits us.

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