Genetic Editing: Technology Ahead of Its Time

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Introduction

Imagine a society where customizing children was as easy as ordering a personalized mug on Etsy. In 2012, technology capable of editing the human genome shifted from being a plot device in a dystopian novel to reality. The publication of CRISPR/Cas9 changed the boundaries of science and health care. Not only does this technology offer treatment for chronic congenital conditions, but it prevents them from existing in the first place – amazing…right? On the surface it may seem like a clear solution, but a closer look reveals complex ethical implications associated with the application of such powerful technology. Widespread use of genetic editing could be detrimental scientifically and socially for current and future generations. It is imperative that an interdisciplinary conversation be had to determine and define the appropriate clinical use of genetically modifying the human genome before it becomes commonplace.

Background

Before one can participate in a discussion about the ethics of genetic editing, one should have a basic understanding of the science and technology that makes it possible. DNA makes up the human genome and is the blueprint for life (Martini et al., 2018). Before DNA can be read, it must be written. Instead of an instruction manual, picture DNA as a multicolored staircase where two-toned steps alternate between red/blue and orange/green pairs. Let the colored steps represent the A/T, C/G base pairs respectively. If one side of a step is red the other side must be blue; if one side is green the other side must be orange. Broaden the picture to be a collection of 46 staircases, 1 for each chromosome. Given the size of the staircase it is easy for the builders (enzymes) to make a mistake. They might put a step in the wrong place, add an extra, or skip one completely. Mutations are the result of these construction errors. Sickle cell anemia is a point mutation or the result of one wrong step shifting the rest of the sequence (Mattison, 2018). The

idea behind gene editing is to send in a new construction crew with updated instructions to replace the targeted segment with the new one. They do this repair with a system known as CRISPR/ Cas9.

Clustered regulatory interspaced short palindromic repeats (CRISPR) and CRISPR associated proteins (Cas9) are primary components in bacterial immune systems (Melillo, 2017). The CRISPR/Cas9 system is a naturally occurring process used by certain types of bacteria in response to a viral infection. Viruses are non-living pathogens that infect living cells by hijacking cells' DNA production systems (Bozeman Science, 2016). The nucleus of a cell is like a car factory with conveyor belts and assembly lines but instead of vehicles it produces DNA. If an animatronic bypassed factory security and altered the machines' programming to produce animatronics rather than cars, the factory would shut down because it had no cars to sell. In viral pathogenesis, cells are hijacked to produce more viruses which get released when the cells eventually die. The cycle is then repeated by the released viruses infecting more cells. Bacterial cells use a CRISPR/Cas9 immune response to prevent the virus from hijacking production.

The process the bacterial cells use has two parts: CRISPR and CRISPR associated proteins (Cas9). CRISPR is a short sequence of DNA, about 20-40 base pairs (or steps). The base pairs of this sequence are repeated palindromes meaning that they are read the same forwards and backwards. These repeated segments are interspaced with unique sequences of DNA creating an alternating pattern (Bozeman Science, 2016). The unique sequences of DNA code for specific viruses, like viral fingerprints in a criminal database. This allows the cell to identify the intruder and destroy it before the virus infects the cell. The CRISPR associated protein (Cas9) binds to the viral DNA and severs it, effectively deactivating the virus (Lim & Kim, 2022). When a new virus enters and needs to be added to a cell's database a protein copies the code,

creating CRISPR RNA (crRNA). RNA is single stranded DNA that acts as a paper copy that is later transcribed into DNA and added to the database (Bozeman Science, 2016). Scientist were able to manipulate this process and use it for genetic editing.

In gene editing, CRISPR acts as a guide to identify the location of the mutation and guide Cas9 to the mutation site. Using the staircase analogy, CRISPR directs the handyman, Cas9, to the broken stairs (Bozeman Science, 2016). Cas9 cuts the DNA, turning off the gene expression, like severing powerlines. Scientists equip Cas9 with a guide RNA (gRNA) strand containing the correct coding (Lim & Kim, 2022). Like IKEA furniture, some assembly is required. Once the gRNA is inserted, replacing the mutation, the matching base pairs get filled in by the cell. This technology allows scientists to alter DNA with the precision of "a word processor, capable of effortlessly editing a gene down to the level of a single letter" (Melillo, 2017). While the technology capable of editing the genome exists in theory, clinical trials are revealing some short comings.

Clinical Trials

Most people tend to associate gene editing with embryo manipulation, however most clinical trials are being conducted today are on adults. There are two main methods of introducing CRISPR to cells of living organisms: in vivo and ex vivo (Lim & Kim, 2022). The primary difference between the two methods is the setting in which CRISPR is introduced to the cells. In ex vivo, the targeted cells are cultured from the patient and injected with CRISPR in a lab. Once tests are run confirming the success of CRISPR, the cells are injected back into the patient (Lim & Kim, 2022). For in vivo delivery, CRISPR/Cas9 is injected into the patient and programmed to locate the target cells and alter the DNA within the patient’s body. The idea for both methods is for the cells with the corrected DNA to multiply and shed their new DNA to

neighboring cells (Zhan et al., 2019). Each method comes with its own set of challenges, risks, and benefits.

To understand the safety checks and problems associated with the processes, further explanation is needed. Injecting CRISPR into cells requires more than a syringe and a needle for in vivo and ex vivo. Cells have semi-permeable membranes acting as bouncers that decide what is allowed in and out of the cell. As described previously, viruses can bypass the cell membrane and inject DNA into the cell. Scientists were able to copy the viral mechanism and use it for CRISPR delivery. The most popular form of this is called adeno-associated virus (AAV) (Lim & Kim, 2022). Predictably, one of the issues associated with viral delivery is the host's immune response.

The body is not able to differentiate between natural pathogenic viruses and synthetic CRISPR ones. A benefit of ex vivo is being able to bypass a majority of the host's immune system. Inversely, this creates one of the biggest challenges seen with in vivo as CRISPR may never reach its target (Redman et al., 2016). Another benefit of ex vivo over in vivo is having more control over CRISPR reaching the desired target. Introducing CRISPR to host cells outside the body ensures that the correct cells are being altered. It is possible for CRISPR to get lost with in vivo application (Lim & Kim, 2022). Different cells make up different organs and allow the organs to function correctly. There is no *undo* button if CRISPR was programmed to target the kidneys and ended up in the lungs. Currently, there is no fool proof way to prevent CRISPR from getting lost in in vivo (Lim & Kim, 2022). The downfall with ex vivo editing is the limited number of defects it can treat. Many target cells associated with genetic defects are difficult to culture from a host severely limiting the use of ex vivo despite the numerous benefits (Lim & Kim, 2022). Some animal trials have been conducted to test the clinical application of CRISPR.

Studies tested various delivery methods of CRISPR on mice to target corneal dystrophies. The cornea is a membrane that makes up the outer most layer of the eye. The primary purposes of the cornea are protecting the eye and refracting light as it enters the eye (Martini et al., 2018). Some congenital diseases exist that can result in progressive vision loss. The cornea has a few key traits that made it a popular candidate for CRISPR studies (Nesbit & Moore, 2022). Its location and size allow for direct introduction of CRISPR using in vivo. The cornea is not heavily connected to the circulatory system because it is avascular. This means that there is a lower chance of CRISPR traveling outside of the target area to the rest of the body. The cornea also has a low immune response (Nesbit & Moore, 2022). The findings of the study did not support the use of topical delivery for CRISPR application. Temporary improvement was seen in the mice using injections. The results however did not appear to be replicable to the size of the human eye (Nesbit & Moore, 2022). One of the issues discovered was a lack of cell division in the cornea to spread the converted cells "however, various AAV serotypes have been shown to successfully transduce all layers of the cornea both ex vivo in human and in vivo in mouse" (Nesbit & Moore, 2022). Overall, significant progress was not made in using gene therapy for corneal dystrophy treatment. Many roadblocks relating to the use of CRISPR were identified which is useful for further development of the technology.

A study was conducted on the use of CRISPR/Cas9 for hemoglobinopathies or blood disorders such as sickle cell anemia and beta-thalassemia. Instead of directly targeting the mutated genes that caused the issue, the trial targeted genes further down that were impacted by the original mutation (Lim & Kim, 2022). Two patients, one diagnoses with sickle cell, and one diagnoses with beta-thalassemia were given CRISPR/Cas9 with fetal hemoglobin enhancing coding. Both disorders have impaired hemoglobin production, and the hypothesis was that

increasing hemoglobin production via CRISPR would reduce the number of complications related to the patients' diagnoses (Lim & Kim, 2022). While both patients suffered from severe side effects following treatment, including sepsis and cholecystitis, neither required transfusions related to their blood disorders for over a year. According to the article, ongoing trials are showing similar results (Lim & Kim, 2022). These findings may be promising for patients if some of the adverse effects can be reduced. While it does not appear to be a cure, it may improve quality of life and reduce some of the limitations associated with congenital blood disorders.

CRISPR and Cancer

Uses of CRISPR for cancer treatment are also being explored as cancer is the result of mutated cells. However, this also gives CRISPR the power to cause cancer. Like people, cells have a life cycle that is broken up into different stages. Cells grow from immature stem cells to differentiated cells that have specialized functions, like adolescents graduating college and starting a career. As the circle of life goes, the cycles eventually end with death. Unlike people, the life cycle of a cell is determined by its DNA and can be paused at different points along the cycle (VanMeter & Hubert, 2018). Differentiated cells have different functions to make up different organs in the body. Intestinal cells facilitate the absorption of nutrients; kidney cells allow for filtration of blood. Another part of the cell cycle is mitosis, or cell division, where one cell splits and becomes two identical cells. Mitosis is a process that allows cells to multiply and is regulated by genes signaling the cells when to divide and when to stop (VanMeter & Hubert, 2018). During mitosis, DNA is copied which allows for typos or mutations to occur. To prevent the mutations from spreading the cells have safety checks.

An example of a safety check is the p53 pathway. It is a genetic check point that assesses the progress of the cell and determines if the cell is developing as it is expected to (Enache et al.,

2020). If a cell fails the p53 check point, the cycle can be paused or terminated early by apoptosis, programmed cell death. This check points catches mutated cells, so they do not become cancerous (Enache et al., 2020). Cancerous cells are mutated cells that passed the check points and continued to multiply making tumors. Tumors are clusters of cells, often immature cells that severe no purpose or fulfil an unneeded purpose. This overproduction of unwanted cells steals the nutrients of the needed surrounding cells and inhibits them from accomplishing their tasks (VanMeter & Hubert, 2018). The cancer cells are non-responsive to normal body signals attempting to trigger apoptosis or halting mitosis.

One study conducted showed CRISPR caused mutations of the p53 pathway. This shuts off the safety check and can result in the development of cancer (Enache et al., 2020). When considering the risks verses benefits of a treatment, possible cancer development – especially when treating a non-cancerous disease – is a major risk. Other uses of CRISPR as cancer treatment have not yielded promising success rates. Twelve cancer patients participated in a CRISPR clinical trial. Only two patients showed any positive response to the treatment and eleven of them eventually died from their cancers (Lim & Kim, 2022). Based on the trials that have been conducted and are currently being conducted CRISPR technology is still in its early stages.

Is Science Ready?

Not only is the technology in the early stages but the scientific knowledge of the subject matter being manipulated is still inadequate for responsible application of the technology. The subject matter in question being the human genome. In 1990 the Human Genome Project was initiated and in 2003 it was completed (The Human Genome Project 2020). The goal of the Human Genome Project (HGP) was to map out the human genome in its entirety. Prior to the

completion of the project, it was estimated that the human genome consisted of 50,000 to 140,000 base pairs (The Human Genome Project 2020). Any guess as to what the actual number is? At the completion of the HGP the total number of base pairs added up to over 3 billion (The Human Genome Project 2020). There is an infinite number of ways to mess up and rearrange a sequence 3 billion pairs long. To put it in perspective, picture a deck of 52 playing cards. The number of possible combinations in a deck of cards is fifty-two factorial (52!), which equals $8x10^{67}$ in scientific notation. The number in standard notation would be 8 followed by 67 zeros. That is such a large number that it is statistically likely that each time a deck of cards is shuffled it is the first time that order has ever occurred. That is an insane number, and it is just a deck of 52 cards. It is inconceivable what the possible number of combinations would be for 3 billion and that leaves a lot of room for error.

Very few of the 3 billion genes have been discovered and researched to know what they code for. Everything that makes people people and makes them unique from other people is contained in DNA. Personality traits, physical characteristics, athleticism, creativity etc., is all written down somewhere in the 3 billion pairs (Anomaly et al., 2020). Too little is known about the human genome to be confident about the changes that occur with CRISPR. Humans are an impatient species, always skipping the tutorials and stumbling through life without reading the instructions. This is not one of those times where impatience can be celebrated as curiosity and determination. There is no correcting mistakes made while editing the genome. No one knows what happens when you turn off X until the loss of Y and Z are observed once it is too late. This makes the application of CRISPR irresponsible health care practice.

Patients must sign informed consent before receiving treatment or participating in clinical trials. Informed consent is a patient right and must be obtained prior to treatment. When a patient

signs an informed consent form it means that they have been educated about the process, the possible risks and benefits, alternative treatment methods and they consent to receiving the treatment (Potter et al., 2021). It is a legal document that must be obtained before patients undergo any type of treatment, procedure, or clinical trial. The amount of possible unknown risks and complications from the use of CRISPR/Cas9 makes the use of it on humans unethical. A comprehensive explanation of possible risks cannot be provided to patients volunteering in clinical trials because the possible risks are not yet known. Biotech entrepreneur, Dr. Greg Licholai in an interview with *Yale Insights* stated, "this field is moving so quickly, and some researchers want to get into human clinical trials right away, even before the CRISPR technology paradigm has been fully validated" (Mattison, 2018). The technology and clinical results are based on too many assumptions to be confident about the actual outcomes. There is a high possibility of changes occurring to the genome that could go undetected for generations.

Biological benefits are intertwined with diseases which means eradicating diseases can have apocalyptic outcomes. Multiple studies have found a connection between cystic fibrosis (CF) and cholera resistance related to increased production of a protein present in CF patients (Withrock et al., 2015). Abolishing congenital diseases could leave humanity defenseless to transmittable diseases in the future. Natural selection did not stop applying to humans after Darwin discovered it. It plays a role in the continuation of mankind today and will continue to do so tomorrow. People have tried to play God and manipulate nature for centuries. Examples of it going wrong can be seen in the media with *Frankenstein* and *Jurassic Park,* as stated in the later "nature finds a way." Despite being fictional, the warnings of these stories should be heeded by the science community. Because of the irreversible repercussions CRISPR could have if used

prematurely, it is important to establish the parameters of use to prevent problems rather than chase them.

Current Regulations

Governments look to the past to determine how to move forward. They attempt to learn from previous mistakes to prevent history from repeating itself. One of the biggest issues genetic editing poses, intentional or unintentional, is eugenics. This was the driving concept behind Hitler's goal in World War II. Eugenics is the idea or action of promoting the reproduction of desirable traits in humans with the goal of improving mankind (Melillo, 2017). Without proper regulation, genetic modification will unintentionally become eugenic practice. Genetic modification walks a fine line between therapeutic treatment and eugenic action (Melillo, 2017). When used on one patient it's treatment, when used on a population it become eugenic. It is important to regulate the use of this technology so that it does not have eugenic effects.

Minimal regulations currently exist regarding the direct use of CRISPR technology. The United States and Europe have "self-imposed moratorium" regarding germline manipulation (Mattison, 2018). Meaning, that experiments using CRISPR in the U.S. and U.K. cannot target reproductive coding. Any changes made to test subjects cannot be passed on to offspring (Mattison, 2018). Despite the U.S. not having laws directed at gene editing practices, there are laws that limit research. In 1996, the Dickey-Wicker Amendment was passed to prevent government funding from being used to create or harm human embryos for research purposes (Kearl, 2010). It does not however, regulate the use of embryos in privately funded research. More research needs to occur, and more regulations need to be implemented before CRISPR reaches health care.

China did not follow this example and has begun to see the consequences. Chinese biophysicist, He Jiankui, was the first person to implant genetically modified human embryos into a woman to be carried to term (Cryanoski, 2020). The woman gave birth to twin girls in 2018. He's goal was to manipulate their genes to be more resistant to HIV. The gene was present in one of the twins. He did not have permission to complete this experiment and as a result received 3 years in prison. Some of his other colleagues involved in the experiment had to pay fines (Cryanoski, 2020). China taking legal action in response to this experiment sets a president that these experiments are happening prematurely. Nations must learn from this and implement guidelines before it occurs again.

Is Society Ready?

Surveys conducted with the general public inquiring about their opinions of genetic editing technology yielded many valid concerns. A survey conducted by the Pew Research Center showed that 50% of Americans would use gene editing to reduce their babies' risk of disease and 50% of them would not (Funk et al., 2020). The more religious participants were, the less likely they were to support the use of gene editing. The survey results also show that people expect to have more negative than positive outcomes as a result of this technology (Funk et al., 2020). Another article facilitated discussions with a focus group where participants voiced apprehension regarding negative impacts on society. They were concerned about the loss of social diversity and the possible negative effects for the disabled community (Riggan et al., 2019).

Social diversity is extremely important but not always celebrated or encouraged. Differences promote change and progress, and it is important to remember this when considering the diagnoses that warrant intervention. Everyone has something unique that they bring to the

table, “people with disabilities have always played pivotal roles in society. People with dwarfism were hired as engineers to work in the engines of 747 jets. Deaf scientists Henrietta Swan Leavitt and Annie Jump Cannon created the field of astrophysics” (Cokley, 2017). Different is not the equivalent of bad, though people often view it with a negative connotation. Albert Einstein is famously quoted for saying “Everybody is a genius. But if you judge a fish by its ability to climb a tree, it will live its whole life believing it is stupid.” The disabled community has made significant progress in the last few years and coining the term “differently abled” as an alternative to disabled. This shift towards positive labels fits with Einstein’s analogy. It forces the monkeys of the world to focus on how well fish can swim, rather than their lack of climbing skills. Certain applications of CRISPR threaten the social progress that has been made in celebrating diversity.

Former executive director of the National Council on Disability, Rebecca Cokley, spoke on behalf of the disabled community which she is a member of herself. She explained that the announcement of gene editing progress was met with fear from the disabled community (Cokley, 2017). Disabilities come with a sense of identity and culture. People of the disabled community have been fighting for a voice and a seat at the table for centuries. They are finally starting to be recognized and feel seen. The excitement abled people expressed in reaction to gene editing “says to disabled people: "We don't want you here. We're actively working to make sure that people like you don't exist” (Cokley, 2017). It is important to make sure the technology is treating the correct problem. For certain diseases CRISPR could be the answer to long term treatment or possibly a cure. For other genetic disorders however, it may not be an appropriate solution.

Conclusion

In health care, it is important that the treatment is not worse than the ailment being treated. You are not going to amputate a finger over a paper cut. For people diagnosed with dwarfism their biggest hinderance may not be their altered bone development but rather being born into a society where assistive equipment is not as easily accessible as it should be (Stamell, 2017). Just because the technology exists does not mean we need to use it (Healey, 2018). Why do abled people believe it their right to determine who needs to be fixed when no one complained about being broken (Cokley, 2017)?

There are many social and legal questions that need to be answered before CRISPR becomes a widespread treatment option. For example, who decides and how do they decide which disorders and diseases are appropriate for CRISPR to treat? Is it purely physiological defects, such as cystic fibrosis and sickle cell, or is a diagnosis of autism eligible for gene editing therapy? How does the use of this technology impact society and preexisting health care disparities? How will society veiw parents of a disabled child who were not able to afford or chose not to undergo treatment? How will they look at the kids? These are important questions that need answers and difficult conversations that need to be had by a diverse group of people. Scientists, health care professionals, legislators, people of the public, and possibly most importantly, representatives of the disabled community must be present for this discussion.

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