Genome Editing

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Introduction: Why Should We Be Concerned?

Gene editing or gene modification techniques are not entirely new to modern society. Everyone knows we now have the skills and tools to somehow change and "fix" genes so that human bodies could be stronger as well as eliminate some types of disease conditions. This technology is advancing more quickly than expected, especially with the recent introduction of the CRSPR-CAS9 gene editing techniques.

Although there is plenty of research about the application of various gene editing methods, the conditions under which these techniques should be applied to humans remains controversial. However, the momentum is building rapidly. According to a report from QUARTZ, since 2015 a Chinese hospital has conducted gene therapies on 86 cancer patients without any international consent. Although the doctors claim there are some positive consequences, the reality is that there are at least 15 confirmed deaths. In 2016, a team of Chinese researchers edited human embryonic genes in a quest to increase resistance to HIV, but the results again were disappointing. Clearly, there is more development work to be done to perfect the technique, but in the meantime, at what consequence? China has a relatively relaxed regulatory position on this issue-- the Chinese government apparently approves all gene-related clinical trials within the country.

According to an article from the Independent, during a 3-day summit in Washington D.C. in December 2015, a joint committee of scientists from the United States, United Kingdom and China agreed that genetic engineering of human eggs, sperm or embryos should only be allowed for research purposes and not for the creation of genetically-modified babies "unless and until" ethical and safety issues are resolved. Other scientists are calling for a ban on genetic modification. In June 2015, Congress moved to block editing of human embryos, by banning the use of public funds for that purpose. However. It is not per se illegal, and such research may be carried out with private funds.

However, it seems like that all the sudden the rules have changed. In 2018 the National Institutes of Health, (NIH), initiated a special program, Somactic Cell Genome Editing Program, with approximately $190 million funds for the 6 years beginning in 2018 to support accelerate and support gene editing for health issues. Since the discovery of CRISPR-CAS9, the US government has begun to relax the constraints on researching genome editing and even started to help with the adoption of genomic treatment. NIH director Francis S. Collins states that "Genome editing technologies such as CRISPR/Cas9 are revolutionizing biomedical research." It is widely viewed that this technique can be applied to solve many health issues. Although the NIH is signaling a change in attitude to genome editing, the bottom line is that NIH still cannot fund any research that involves editing human embryos.

Regulators aren't the only stakeholders who are beginning to support embryonic gene editing. Scholars also think it is the time to study and develop genome editing. According to *The New York Times*, a group of scientists from the National Academy of Science and

National Academy of Medicine vocalized their support for editing human embryos in February 2017. This proposition was prohibited prior to that, yet it has gained approval. Moreover, in 2017, Shoukhrat Mitalipov, professor of Oregon Health and Science University, and his team successfully edited human embryos for the first time in United States.

Clearly the constraints on human genome editing have become more relaxed since 2015, with that advent of the CRISPR-CAS9 technology, which provides a more accurate and affordable method to achieve gene editing. Additionally, even though U.S. regulators still prohibit human germline editing research, other countries, like China and Russia, have conducted many such experiments. Human germline editing will continue to progress regardless of the U.S. stance. If U.S government does not want to be left behind in the field of genome editing, it has to make the change now. But at what cost?

A Brief History

The origins of gene editing can be tracked back to the 19th century, when humans for the first time discovered that the gene could be passed from generation to generation. Approximately 10 years after the discovery of the characteristics of genes, a Swiss doctor, Friedrich Miescher, discovered that DNA is actually a type of molecule in blood cells. In 1953, scientists from England learned that the structure of DNA is a double-helix structure. This significant discovery became the foundation of genetic engineering.

In 1961, people decoded the secret behind DNA, which is RNA or ribonucleic acid. As we all know, there is genetic information stored in DNA, and this information is used to create one of the most important molecules: protein. The protein creation process contains mainly two stages: transcription and translation, and RNA plays a very important role in transcription. First, DNA transfers its information into RNA, which has a very similar molecule structure. Thereafter these RNA with transferred information will go through the translation stage to produce protein[1]. Therefore, the discovery of RNA in the 20th century decoded the processes of how genes actually make protein.

In 1977, British scientist Fredrick Sanger, discovered DNA sequencing. DNA molecules are made up with four different types of chemical building blocks: adenine, thymine, cytosine and guanine, which are also called "bases." DNA sequencing simply means that humans are able to figure out the exact order of how these four chemical blocks combine to form DNA molecules. This is very useful since by using DNA sequencing scientists can know what information is stored in a specific DNA part, and this information is called sequence data. These sequence data also contain information about which DNA segment carries significant genes that may cause certain diseases or benefits. In other words, in 1977 humans had the ability to understand which part of DNA went wrong and needed to be "fixed" by looking at the sequencing data[2].

[1] U. S. National Library of Medicine (2018, July 17). How do genes direct the production of proteins? - Genetics Home Reference - NIH. Retrieved July 20, 2018, from https://ghr.nlm.nih.gov/primer/howgeneswork/makingprotein

[2] Rifai, R. (2015, November 30). US scientists urge ban on human genetic modification. Retrieved July 20, 2018, from https://www.aljazeera.com/news/2015/11/scientists-urge-ban-human-genetic-modification-151130163522308.html

The research did not just stop, and in 1983 an American biochemist, Kary Mullis, for the first time invented an innovative method to copy massive amounts of DNA molecules from very tiny and limited samples, and the technique is called polymerase chain reaction (PCR). PCR is a fast way to copy and amplify DNA segments, and this technique is not expensive so that its application is widely used. An example is the world's largest collaborative biological project: the Human Genome Project, and DNA fingerprinting. By using the PCR technique, scientists are able to copy millions of DNA from a single hair or a single drop of blood, and these copies can be used to analyze hereditary disease and conduct other genetic experiments. At this stage, the major goal in the study of genomics was to discover the full image of DNA or map DNA sequences, and this was indeed the initial goal of Human Genome Project. In April 2003, the sequence was completed.

After the mapping of human sequence, gene editing was still not quite feasible, due to its price and difficulty. The discovery of epigenetics editing[3] totally changed the game. Epigenetics was first created and studied in the mid-20th century by scientists Conrad H. Waddington and Ernst Hadorn. The world "epigenetic" means "in addition to changes in genetic sequence". In other words, epigeneticists study and analyze any process that changes gene activity without affecting the DNA sequence, and these changes can be transmitted to daughter cells. These cell modifications can also be affected by outside variables, such as age, environment and disease. Since then, the genome structure could be modified by artificially making inactive genes "invisible" and only active genes can be read.

Finally at the beginning of the 21st century, one of the most advanced genome engineering technique was invented: CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), or more specifically CRISPR-Cas9. Cas9 is a type of protein that can cooperate with RNA so that it can find and clean specific DNA segments. The Cas9 protein can be activated by RNA in a CRISPR system and once the protein is "online", it can locate and modify the target sequence inside DNA. As a result CRISPR-Cas9 is able to "take away" only a fraction of an entire DNA sequence, so that it can enable scientists to analyze or fix DNA accurately. CRISPR is a part of certain bacteria's defense organism. When a bacteria encounters a virus, it will copy and absorb the virus' DNA segment into its own gene around CRISPR. Thereafter the bacteria knows what the virus looks like because the virus' copies are obtained, and then when the virus occurs again, the bacteria would know where it is and "command" Cas9 proteins to attack and eliminate it. As a result, scientists could just reprogram CRISPR appropriately and let the Cas9 protein finish the work[4].

This technique of using a bacterial immune system as a gene editing tool enables scientists to make extremely accurate change to humans,' or any animal's DNA.

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[3] Epigenetics: Fundamentals, History, and Examples. (n.d.). Retrieved July 20, 2018, from https://www.whatisepigenetics.com/fundamentals/

[4] Woollaston, V. (2018, June 12). Controversial gene-editing tool CRISPR "could give rise to cancer", worrying studies find. Retrieved July 20, 2018, from http://www.alphr.com/bioscience/1001654/crispr-cas9-gene-editing

Current Issues

Even though there have been many academic research papers on the gene editing methods and their real-world application, applying gene editing to real persons is still prohibited in the majority of countries in the world. However, as the understanding of gene editing techniques grows, there are many ethical issues that cannot be avoided and need to be considered for society.

Is It Fair?

Let us first assume that our gene editing technique is well developed and can be applied to adjust our next generation. Parents can literally choose their babies' physical characteristics: blue eyes, blonde hair, strong muscles, 6-feet tall and so on. Scientists might even make babies smarter than the historically average levels, and that enables humans to decide how they want to evolve. However, does anyone think about giving the babies choices? If there were no reversible therapy for those babies, then they would be forced to live with the genetic characteristics that their parents believe are the best. Maybe some of these 'genetically engineered' babies grow to adulthood wishing their eyes were their natural color instead of the ones their parents chose. This application of gene editing could potentially take away children's choices and freedom. This statement might sound cliché, but just imagine a world in which all kids are identical to each other, and all kids are so-called flawless in their appearance.

It also could be unfair to the parents. It is highly possible that such gene editing technology would be commercialized once it gets fully developed. As a result, because of the expensive equipment and highly educated professionals (doctors), gene-edited babies would possibly become the privilege of the parents who can afford the technology. As a result, discrimination in society would grow quickly and strengthen social class divides, since wealthier families would always opt for smarter kids. The end of the story could be that those humans who cannot afford gene editing would be wiped out by nature, and only the "edited" humans will remain.

Too Many Unknowns in the Equation

A Chinese research team tried to use CRISPR-Cas9 on human embryos to change genes that cause certain disease in cells. These embryos are so called "unviable" meaning they cannot result in babies. However, the results are disappointing. Of the 86 embryos in the sample, and only a few contained the desired results. More importantly, it is possible that the CRISPR-Cas9 could cut the wrong places, and as a result, the cost of repairing such damage could be enormous.

This off target error happens more frequently in humans than in mice. One of the main reasons is that in large genomes, some DNA may contain similar or even identical sequences to the target DNA sequences. Therefore, it is very hard for CRISPR-Cas9 to identify those homogeneous DNA sequences and only cut and replace the target sequences.

Moreover, gene editing humans' germline also contains many unknowns. Since every human's germline is unique, it is impossible to know whether the gene editing technology could be applied to everyone and result in the same outcomes. Due to possibilities of off target, CRISPR-Cas9 can cause many side effects including creating unintended mutations. If such unintended mutations occurred in germline editing, they would be transmitted to the next or even multiple generations, and these changes are permanent.

Furthermore, even though some people are willing to take the risks, how do we make it fair to the kids? Do we still let the risk takers sign a document in hospitals which indicates that the patients are willing to risk their kids' lives for a more desirable look or more IQ points? Even with the advances in CRISPR-Cas9 technology, genome editing is still in this early stage of applying to real people and changing the paths of humans. In 2015, the International Summit on Human Gene Editing, which invited scientists from all over the world, reached a consensus about conducting more basic and clinical research on genome editing under legal guidelines, and agreed that it was irresponsible to perform any gene editing on human embryos.

Gene Editing for Enhancement and Regulation

When the early life scientists dreamt of gene editing, they may only have considered this technology as a tool to improve human health. The same occurs with today's scientific community. However, once gene editing is commercialized, health won't be the only purpose, and other offerings, like body enhancement, will appear in the markets. CRISPR-Cas9 is capable of editing genes to match our lifestyle interests. For example, scientists have lately discovered that CRISPR-Cas9 is able to turn "off" or "on" the signals for genes that could make mice addicted to cocaine. As a result, genome editing could be used to improve human behavior such as fixing addiction or even violence.

Under these circumstances, it is very difficult for regulators to draw boundaries in gene editing. Fixing addiction and removing violence could also be called therapy. But is it possible that in the future all addicts or all violent criminals will be forced to get "repaired?" These questions are all the ones we can imagine today, there are surely many other possible applications for this technology. It is very difficult to see how regulators can react given this infinite set of possible applications and the time it takes to review and set policy for any one of them.

Some Possible Ethical Questions

1. Should genome editing on human embryos be approved?

2. Should academic research on genome editing be slowed down?

3. Should there be an organizational governance structure to oversee the development? How will international policy work? How will it be implemented?

4. What roles do regulators should play?

5. Can genome editing focus on purpose other than health therapy?

6. Should we leave any choices to the next generation?

7. How should the pressures for commercialization be managed and controlled?