CRISPR: A Revolutionary Technique… For Humans?

Chrissa Barroma

Abstract

CRISPR/Cas9 is a revolutionary technique that carries the possibility of altering the genomic sequence of an organism. Discovered in a bacterial immune system, CRISPR/Cas9 has been a popular topic of discussion since its first publication in 2012. In this essay, the opposing arguments on the use of CRISPR/Cas9 are discussed based on the practical uses in human genetic engineering. First, the technique is described along with a comparison of other successful gene editing techniques. Secondly, the ethical and clinical implications are also discussed, as well as the effects of CRISPR use on human germline and somatic cells. This essay aims to answer whether CRISPR/Cas9 should be used to edit the genome of humans.

Tomatoes, bananas, corn, cotton, vaccinations, Persian cats, and the Welsh Corgi all have one thing in common: they are all in some way genetically modified. Selective breeding, transgenics, RNA interference, and mutagenesis are all forms of organism modification that humans have used for many decades. Despite all of these techniques used to modify other organisms, there have not been successful genetic modifications of humans. The possibility of genetically engineering humans has been widely dreamt of throughout society. From science fiction movies to the aim of highly renowned biologists, the idea of changing the genomic sequence of a human was once thought to be impossible. This was true until the introduction of the CRISPR/Cas9 system.

Initially found in the bacterial immune system of *Escherichia coli* by Japanese researchers in 1987, CRISPR/Cas9 became a revolutionary technique that was believed to have evolved as a tool for DNA repair. Experimenters continued to delve into the possibilities of CRISPR/Cas9 and eventually the first application of CRISPR was used to provide immunity against phages in dairy cultures (Doudna and Charperntier 2014). But first, what exactly is the CRISP/Cas9 system?

CRISPR/Cas9 is an RNA guided system, utilized in the immune system of a variety of bacteria and archaea. CRISPR stands for “clustered regularly interspaced palindromic repeats,” and works with a protein called Cas9. In bacteria, the CRISPR/Cas9 system directs specific double stranded breaks in the DNA of viruses that enter bacteria. This immune system “cuts” out segments of the viral DNA and can integrate them into its own genome, which comprises the “repeat” segments of CRISPR. By pairing this Cas9 protein with a 20-nucleotide strand of single guide RNA, or sgRNA, that matches a sequence of DNA through complementary base pairing, Cas9 can directly cut a specific target sequence. If a virus re-enters the bacteria, it can take the segment of DNA incorporated as a “repeat” and translate a strand of sgRNA that is used to cleave the invading viral DNA with Cas9 (Port et al. 2014).

This system was harnessed and used as a method of producing breaks in any desired DNA strands which are more specific than previous DNA altering techniques (Hwang et al.

2013). The target specificity of the Cas9 endonuclease is what makes this system so desirable because it is easier to control the imprecise mutations that are caused by other genetic engineering techniques (Doudna and Charperntier 2014). If a strand of template strand with the correct sequence of DNA is inserted into cells along with the CRISPR/Cas 9 system, there is also the possibility of repairing genes. Therefore, inserting a strand of template DNA with a gene not originally found in the organism allows CRISPR to insert new genes into the organism's genome (Ran et al. 2013).

It is believed that, with genetic engineering, the applications are endless. Mutant genes could be removed and replaced with normally functioning genes so that diseases could be eliminated from the human population. Cosmetic changes can also be made, such as changing the colour of your child's eyes to anything you want. While these applications seem incredible, we must ask: should genetic engineering in humans even be attempted? What would people do with the ability to change characteristics of others? Where do we draw the line?

CRISPR use in humans is still debated, but CRISPR has worked in other organisms. For instance, CRISPR/Cas9 was compared to other gene engineering techniques (TALENs and ZFNs, which both create double stranded breaks in DNA) used in *Danio rerio,* more commonly known as zebrafish (Hwang et al. 2013). The researchers found that the efficiency of CRISPR is closely matched to TALENs and ZFNs, but the overall technique is simpler to carry out. Even before the discovery of CRISPR, other genetic engineering tools were commonly used. For example, genetically modified foods were designed from transgenic techniques. These include food products that are enriched with nutrients that are otherwise hard to obtain, such as vitamins and minerals. An example is Golden Rice, which is used as a method of improving the nutrition intake in impoverished countries (Paine et al. 2005). Golden Rice was created as a crop with an increase of vitamin A. This rice was created by transforming the DNA of rice strains and inserting a gene from daffodils, tomatoes, maize and peppers that increased the vitamin levels in rice. Researchers used the same gene (the *psy* gene) from each organism and transformed the rice to determine which caused the most Vitamin A production. Basically, the DNA sequence, and consequently, the genetic components of the rice, was altered.

CRISPR and gene insertions are not the only forms of genetic engineering that are known to science. Genetic engineering can also be conducted through the use of micro-RNAs. In one particular case, micro-RNAs were used as a way to supress the expression of cancer cells. In fact, this is a reason why CRISPR is sought after in human genetic engineering research. If there is a way to stop the development of cancer, why shouldn't we explore it? Micro-RNAs, known as miRNA, are gene suppressors; they target genes whose products are no longer needed in an organism and block the translation of the consequent products. In a family of a particular miRNA, it is shown that this miRNA could potentially supress the rate of cell overgrowth, also known as cancer. In vitro cellular experiments were conducted with this miRNA gene family, where the delivery of this gene family was given to patients and was shown to be a potential tumor suppressor (Esquela-Kerscher and Slack 2006).

In these cases, genetic engineering has been proven to be successful in helping organisms around the world. Genetic engineering is a very beneficial technique that has improved the lifestyle of many people. But the use of CRISPR in zebrafish has opened the door to many more possibilities of what this technique could do. Particularly, CRISPR has been proven to reduce the number of mistakes and off-target effects that other gene editing

techniques are often prone to. While these possibilities seem endless and hopeful, there are many ways to exploit this technique. CRISPR could cure cancer, but what else could it do?

In November of 2018, Chinese biologist He Jiankui announced that he had edited the genes of two twin baby girls who had just been born (Cyranoski, 2018). In the genome of these two twin girls, he claimed that he disabled the gene involved in HIV infection, CCR5, and therefore prevented any possibility of the twins contracting HIV. While this may seem like a complete breakthrough for the scientific community, Jiankui had failed to do what is expected of all scientists; he failed to follow standard ethical procedures. Because of his neglection of safety protocols, Jiankui is now expected to face criminal charges. Jiankui had done one thing with CRISPR that many people have criticized- he edited the germline cells of these children.

Germline cells, otherwise known as gametes, have been debated endlessly by those involved or interested in genetic engineering. Is it ethical to alter the cells that will be passed on to future offspring? Genetic engineering carries the risk of unintentionally changing DNA sequences which were not the targets. This is a likely side effect as many sequences can differ slightly, and therefore can be mistakenly recognized as a target by CRISPR. If this occurred in germline cells of an individual, their children could inherit an accidental DNA change that could be drastic. Because of this, most scientists involved in genetic engineering agreed that in order to face the possibility of gamete alterations, we must first perfect the alteration of body cells. This is something that Jiankui ignored and is now facing serious scrutiny.

The argument between germline and somatic cell engineering has been widely debated for a long time. Many people question whether or not scientists should be able to modify the DNA of patient's germline cells. Questions arise such as whether or not it is ethical because future generations are not able to provide consent for DNA modification. There are concerns about whether or not these genetic modifications would result in irreversible and detrimental consequences that are not able to be seen until these children are older.

In fact, because of these concerns, many countries have prohibited gene editing in germline cells completely (Polcz and Lewis, 2016). Furthermore, the world of science is always under the close eye of critics and the public: for example, the negative implications of genetically modified foods. As stated above, Golden Rice has been proven to improve the life of many people. However, there have been negative side effects of other genetically modified organisms. One example is the Starlink maize (Zhang et al. 2016). This strain of maize had been genetically modified by gene insertion of a protein that provides insect resistance. However, this gene insertion had been taken from a Brazilian nut and caused allergic reactions in many people with nut allergies. It is also possible that the integration of foreign genetic material into the genome of organisms may cause the production of a protein that could negatively impact important pathways or structures.

It is also possible that people will take advantage of a technique that is new and fascinating. In fact, athletes are often the first people to take risks and attempt therapies to improve their overall performance (Polcz and Lewis 2016). Who is to say that CRISPR/Cas 9 is not one of those techniques? Thus, it is important to consider whether humans should be utilizing CRISPR to better themselves athletically, which may result in an unfair advantage.

We are also subject to scientists taking advantage of this readily available tool and injecting themselves with CRISPR. Josiah Zayner, a biohacker, stood in front of a crowd of people and injected his arm with CRISPR (Zhang, 2018). He told the crowd that this would

increase the size of his muscles and that he desired a world where people could use CRISPR on themselves. Despite his claims that his decision to inject himself with a genetic engineering tool was reckless and should not have been done, the repercussions of his actions are still dangerous. In fact, Zayner currently owns a company where he sells kits allowing consumers to inject themselves with CRISPR.

Despite all of the successful uses of genetic engineering, there are drawbacks and negative consequences that can arise. Unexpected side effects and people who will take advantage of this revolutionary technique are all things that we must be wary of. The question then arises of whether these consequences should deter the scientific world away from CRISPR. Are the stakes too high for scientists and the world to continue to develop CRISPR technology? Is it worth risking so much for something that *might* work?

CRISPR/Cas9 is a ground-breaking and impressive technique that has great potential to change the lives of many people. The ability to target specific DNA sequences to alter the function of or fix a “broken” gene is astonishing. By comparing successful stories of other examples of genetic engineering and even some trials of CRISPR/Cas9 in other organisms, it is not a stretch to claim that CRISPR/Cas9 can change the world. However, CRISPR is not yet a perfected technique. In fact, no form of genetic engineering is perfected and CRISPR is an example of this. Many people also fear that a tool this powerful could be taken advantage of. If CRISPR is abused, the consequences could be detrimental. As well, a tool that could be used to improve the medical world in such a large way could be adapted to changing the lives of people who are otherwise healthy. Would this prevent sick people, who need medical tools like this, from actually getting help? Finally, the ability to change the genetic sequence of unborn children is something that frightens most people. Would our generation be considered selfish for attempting to change the DNA of a child who has no ability to give consent? Is it ethical to make such decisions for them? All of these questions are what one must consider when debating the role that CRISPR/Cas9 plays in society.

After taking into consideration all of the possibilities that come with CRISPR/Cas9, I can confidently say that I support the use of CRISPR in human genomes. The possibilities of changing lives and curing numerous diseases are too great for us to ignore. While I agree that the implications of such a powerful tool are far too dangerous now, I argue that, like many things, CRISPR is not yet perfected, but we are in an age where science is the most advanced it has ever been. With time, CRISPR can be developed and put through many experimental trials with model organisms before any approved experiments are conducted on humans. Just as the trials of genetically modified organisms had not been successful in its first few applications, CRISPR will not be perfected immediately. Genetically modified foods were seen as taboo but are now seen in grocery stores all around the world, benefitting many people. We always run the risk of having tools such as CRISPR abused by people. However, I believe that the potential benefits will outweigh these risks. CRISPR can be used to continue the search for targeted cancer treatments, the prevention of HIV, and the ability to cure conditions that are otherwise considered incurable. I strongly believe that if we, as a scientific community, were to prevent the future use of CRISPR as a human genetic therapy tool, we would be doing our world a disfavour.

References

Cyranoski, D. (2018). CRISPR-baby scientist fails to satisfy his critics. *Nature, 564*(7734), 13-14.

Doudna, J.A. and E. Charpentier (2014). The new frontier of genome engineering with CRISPR-Cas9. *Science, 346*(6213), 1077-1087.

Esquela-Kerscher A. and F.J. Slack (2006). Oncomirs-microRNAs with a role in cancer. *Nature Reviews Cancer, 6*(4), 259-269.

Hwang, W.Y., Y.F. Fu, D. Reyon, M.L. Maeder, S.Q. Tsai, J.D. Sander, R.T. Peterson, J.R.J. Yeh, and J.K. Joung (2013). Efficient genome editing in zebrafish using a CRISPR-Cas system. *Nature Biotechnology, 31*(3), 227-229.

Paine, J.A., C.A. Shipton, S. Chaggar, R.M. Howells, M.J. Kennedy, G. Vernon, S.Y. Wright, E. Hinchliffe, J.L. Adams, A.L. Silverstone, and R. Drake (2005). Improving the nutritional value of Golden Rice through increased pro-vitamin A content. *Nature Biotechnology, 23*(4), 482-487.

Polcz, S., and A. Lewis (2016). CRISPR-Cas9 and the non-germline non-controversy. *Journal of Law and the Biosciences, 3*(2), 413-425.

Port, F., H.M. Chen, T. Lee, and S.L. Bullock (2014). Optimized CRISPR/Cas tools for efficient germline and somatic genome engineering in Drosophila. *Proceedings of the National Academy of Sciences of the United States of America, 111*(29), E2967-E2976.

Ran, F.A., P.D. Hsu, C.Y. Lin, J.S. Gootenberg, S. Konermann, A.E. Trevino, D.A. Scott, A. Inoue, S. Matoba, Y. Zhang, and F. Zhang. (2013) Double Nicking by RNA-Guided CRISPR Cas9 for Enhanced Genome Editing Specificity. *Cell, 154*(6), 1380-1389.

Zhang, C, R. Wohlhueter and H. Zhang (2016). Genetically modified foods: A critical review of their promise and problems. *Food Science and Human Wellness, 5*(3),116-123.

Zhang, S. (2018). A Biohacker Regrets Publicly Injecting Himself with CRISPR. *The Atlantic*. Accessed October 29, 2019. www.theatlantic.com/science/archive/2018/02/biohacking-stunts-crispr/553511/