MAKING THE PERFECT BABY

Genetic modification with the CRISPR/Cas9 method

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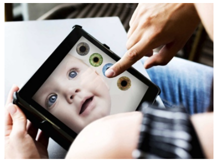


Should your baby have brown or blond hair? Blue or Green eyes? Do you prefer a boy or a girl? Should the baby be muscular, intelligent or even both? While designing your unborn child may seem impossible to you right now, with modern technology it will be doable in only a few years.
We first heard about the practice of modifying human DNA in biology class. All of this might sound like a huge possibility for human evolution, for example making the elimination of diseases a lot easier. However even with a little research this topic raises a lot of moral and ethical questions. Therefor we think the most fascinating part of our topic isn't the technical background but rather the moral question and effects on our society. In the following Paper about modifying the human DNA to produce a "perfect" next generation, we will explain the CRISPR/Cas9 method, discuss the ethical perspective and lastly asses our interviews.

Introduction:

Over the years our society has become obsessed with perfection. In attempts to become their ideal self, people undergo plastic surgeries, get Botox injections or spend a lot of money on eyelash extensions. Only in 2017 1.8 million cosmetic surgery procedures were performed. The most popular surgical intervention was breast augmentation, followed closely by Liposuction, Nose reshaping and Eyelid surgery. In the same year, 15.7 million people underwent minimally invasive cosmetic procedures, like smoothing out wrinkles, lip fillers or laser hair removal.

However, with recent technological advances people cannot only change their own physical characteristics, but couples could genetically modify their unborn child to perfection. In the near future, parents have the possibility to choose their child's gender, hair and eye color, height, body shape, and more. Nowadays modification processes are mostly used to prevent hereditary disorders. However, for only 19'000 Dollars it's possible for couples to determine the gender of their future child.

The first genetically modified babies have been born in November 2018 in China. The two Chinese girls, Lulu and Nana, have been engineered to be immune against HIV. According to the scientist He Jiankui, the newborns are perfectly healthy and acting just like any other baby their age. The modification was carried out with the still young CRISPR/Cas9 procedure. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats and is the most effective, least complicated and cheapest method for genetically engineering embryos. Other procedures are called TALENs (transcription activator-like effector nucleases) and ZFNs (zinc-finger nucleases). Since the discovery of Crispr / Cas9 in 2012, researchers have been debating vigorously whether genetically modifying embryos should be allowed.

In Germany, the USA and many other countries such manipulations of human genetic material are prohibited, because so far, the risks are not predictable. Furthermore, changes like this have significant effects on our future generations.

Engineering techniques:

When modifying the genome of a soon to be human extreme accuracy is necessary to prevent mutations that could otherwise lead to genetic disorders. The newest, most effective and cheap tool used for these procedures is called "Clustered Regularly Interspaced Short Palindromic Repeats" or short "CRISPR/Cas9". The CRISPR/Cas9-method can be viewed as a pair of molecular scissors that cuts out specific sequences of the DNA strand. Since its discovery this system has already been put to use in many fields, including but not limited to the modification of crop plants, the treatment of cancer and other genetic diseases and disorders.

Francisco Mojica of the university of Alicante in Spain was the first to discover CRISPR in *Escherichia coli* bacteria in 1993. In 2005 he found that the genome of *E. coli* had sequences of DNA from bacteriophages between the reoccurring strings of the bacteria's own DNA. He hypothesized that this was a sort of immune system for the bacteria to protect them from infection by bacteriophages. The protein Cas9 was discovered by Alexander Bolotin as he was researching *Streptococcus thermophilus* at the French national institute for agricultural Research (INRA) in 2005. In 2010 Sylvain Moineau proved that Cas9 can be programmed to target specific sequences of their choosing. In 2013 Feng Zhang was the first able to adapt Cas9 to be fit for use in eukaryotic cells.

The following explanation of the function and key terms associated with the CRISPR/Cas9-system refers to the model organism *E. coli* in the case of the cell being infiltrated by bacteriophage DNA. These principles can be transferred to the genome of a eukaryotic cell and sequences where there is a desire to cut said sequence out or replace it with different genetic material. This translation from nature to clinical and industrial use will also be explained later.

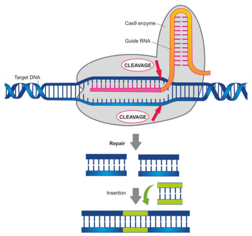
"Short Palindromic Repeats" indicates a reoccurring palindromic consecution of base pairs in a strand of DNA. In the context of the CRISPR/Cas9-system these sequences are called CRISPR-genes.

Palindromic in a linguistic sense means a combination of letters resulting in a meaningful word or combination of words that can be read backwards and still have the same meaning. For example, DNA-land backwards is dnal-AND. This refers to the complementary base pairing on the two strands of the double helix. These CRISPR-genes are interspaced by the so-called spacer DNA, which is what the first three letters of the acronym stands for "Clustered Regularly Interspaced". Spacer-DNA does not repeat, so each sequence of it is unique.

It was found that these spacer-sequences in *E. coli* match up with DNA of bacteriophage viruses. Viruses have the ability to inject their DNA into bacteria cells or other cells for that matter and hereby hijack them to produce more viral DNA, which will end up killing the bacteria cell. But bacteria have evolved to have a special immune system to stop viral infections before they even start. The bacterial DNA also has another part, which is vital for the CRISPR/Cas9-system. It is called the Cas-complex, which is responsible for the synthesis of the Cas proteins. The Cas-complex-proteins are generally helicases and nucleases, so enzymes that unwind DNA and ones that cut DNA.

So, what happens in bacterial cells is that the Cas-complex genome and the different spacer-DNA-sequences are transcribed and translated to form the CRSPR RNA (short crRNA) and to synthesize the Cas-proteins.

The crRNA perfectly fits into the Cas-proteins so that they can bind together to prepare the cell to be able to fight viral infections. Now, when bacteriophagal or any other strange DNA gets into the cell the helicase part of the Cas-crRNA-complex will detect it by unwinding the target DNA and binding the crRNA to it. If the base pairs of the target DNA and the crRNA are complementary it is confirmed that this is viral DNA and the nuclease part of the Cas-protein will make the foreign DNA harmless by cutting it. If the intruding target DNA does not fit any of the crRNA that can be transcribed from the genome another class of Cas-protein will add this new foreign sequence as a new piece of spacer-DNA to the genome of the cell. This enables the cell to recognize this DNA in the future and destroy it effectively.



To introduce this concept to eukaryotic cells and direct the Cas-crRNA-complex to the desired locations some steps have to be taken. Clinical and industrial applications use the Cas9-protein from *Streptococcus pyogenes.*

The procedure that is used to modify a genome with CRISPR/Cas9 goes as follows: The Cas9-protein has a nuclease to cut DNA and fits a strand of crRNA, which will match up with the viral DNA (in the E. coli model) and a tracrRNA that holds the crRNA in place inside the protein. So, what is done to apply this system is that the Cas9-protein from *S. pyogenase* is extracted and a crRNA of choice is added. To simplify the three-part system consisting of the crRNA, tracrRNA and the Cas9-protein, scientists were able to connect the crRNA to the tracrRNA, which together form the tracrRNA-crRNA chimera that is alternatively known as guide-RNA (gRNA). So now there is a two-part system including the Cas9-protein and the gRNA. Now if there is a part of DNA that needs to be changed, a piece of gRNA (universal tracrRNA and specific crRNA) that corresponds to the gene that should be modified or inhibited and the Cas9-protein. The DNA strand will then be fed through the Cas9–protein with the engineered gRNA and be cut at the sequence that the gRNA directs to. To exchange the original DNA, we simply need to add the RNA strand of the DNA we want replace the old sequence with (hostRNA). The cell will then complete the other strand using complementary base pairing.

The result is a strand of DNA that has been cut at the site that matched the crRNA in the gRNA-protein and replaced with a new sequence in order to fix a genetic disorder or just made inactive.

Regarding our Interview, we could not find a laboratory that is preforming these procedure as it is illegal to do so in Switzerland and many other countries in Europe. Therefore, we are not able to include any pictures of laboratories nor could we get an interview with a professor. This is why we decided to focus on the moral aspect of our topic in the interviews we conducted.

Interview Questions:

1. Is it okay to use modification processes to prevent hereditary disorders?
2. Is it okay to use modification processes to determine the sex of your child?
3. Is it okay to use modification processes to change other physical attributes such as hair or eye color?
4. Have you heard about CRISPR?
5. What do you think is already possible today/ How important is this topic today?
6. Should it be allowed to interfere with human DNA at all?
7. What is the difference between this and plastic Surgery?

Discussion:

Question 1

The question was most often answered with “yes”, whether this was hesitantly or clearly. However, despite the positive feedback, many were also worried about its effects on the people who suffer from a disorder which could have been prevented using such measures. Some feared that the knowledge about preventative measures would lead people to question why a child would have to suffer. If it severely affects a person’s life quality, it would be immoral not to prevent it. People with visible disabilities might experience bullying and rejection from their peers. The person might get self-conscious and develop severe mental disorders such as anxiety and depression. One candidate (AB) said that it was even inhumane or unethical not to use genetic modification procedures to prevent people from suffering, given that the risk-reward equilibrium is given. As long as it is done to help the child and has no negative effects on the human being it should be legal.

Question 2

In general, the opposition to this question was greater. Some people thought that choosing the sex of a child goes against nature and should not be interfered with. One candidate (AL) was very confused why someone would even want to do that. Reasons for such a decision might be based on socio-cultural pressure of a country. One candidate (CS) mentioned the former one-child policy in china and its effects on gender-specific selective abortion. As we know, this resulted, in an unequal gender ratio in China. Another person (LM) said that both sexes are equally allowed to live, and parent shouldn't have the possibility to choose.
However, another opinion (KB) is, that while we should not encourage it, we shouldn't forbid it either. If the opportunity of changing the sex reduces gender-specific selective abortions, then maybe this is a good idea after all.

Question 3

This was a very interesting question to ask, because the responses ranged from outrage at the audacity that one would even dare to ask such a question to people feeling that it is not too different from undergoing plastic surgery. The people who responded with outrage were mostly concerned with the increased social status genetically modified people could receive. Someone feared that especially in our region there would again be people who declare the superiority of blonde, blue-eyed people. Others said that the attributes chosen would go into a completely different direction. But all people who oppose to changing physical attributes said they were against the rise of a new norm in such a way and that it would be harmful to society to engineer an army of uniform children. In society, character should be valued more than appearance.
The people who did not react that drastically pointed out, that norms already exist in our society and that allowing parents to modify their children was not that much different from letting people undergo plastic surgery to change their physical attributes. Also, in the long run, the wish to change physical attributes is only going to grow and the possibilities to do so will as well. Therefore, it is inevitable especially as the future of plastic surgery holds even more diversity and accuracy. The stride for perfection is not slowing down!

Question 4

Some people have never heard of it, while others have had a great knowledge on the topic from biology classes or personal interest. CRISPR was generally regarded as an interesting topic by all candidates and they are all interested to see what the future holds, regardless of their conviction of what should or shouldn't be done with it.

Question 5

While there were candidates who thought that too much is possible already, others are convinced there is still a lot of potential for the future and further options should be explored. Especially with regards to non-coding DNA, and the lack of knowledge on it.

Question 6

The majority of people we interviewed agreed that it is okay to analyze DNA. However, changing or maybe even cloning it should not be allowed, except for the prevention of genetic disorders. An aspect to consider is that people fear the future in this specific field of science. This might come from a lack of knowledge and should not prevent scientists from conducting further research. The important thing is that if we allow alteration of the human body, we must ensure that it is possible for everyone. If not, we end up with a split society, the "super-humans" and the "common people".

Question 7

The people we interviewed all agreed that is it morally very questionable to make decisions about cosmetic changes for people who do not even exist yet. Also, there is a large difference between modifying a baby's DNA and plastic surgeries as a person can alter their appearance based on their personal perception of beauty, this freedom gets taken from embryos whose genome is changed.

Overall

Overall the majority of the candidates mentioned the uncertainty of the development in this field in the future. The interviewed mentioned that interfering with human DNA in the first place, even if only to prevent hereditary disorders, might eventually lead to people wanting to change more, as one candidate (RT) put it "wanting to play god".
Other things that were mentioned were the effects on our society with regards to acceptance of not genetically modified individuals and non-conformity in general. The trend of what is considered "perfect" or is the most beautiful, changes greatly over the years.
We also suspect that the differences between the rich and poor population would be even more grave as the rich and wealthy people could buy their future generations a huge advantage in life. Families with less financial possibilities could simply not afford this luxury for their children.

Summary:

The modification of human DNA is a very hot and controversial topic that our society needs to evaluate and for which we need to come to a conclusion. The advantages like being able to cure genetic disorders or if desired to change the appearance of your future child are tempting but the risks involved should make us think twice. This is also the reason why these kinds of procedures are forbidden in many countries.

Moving on to the technical aspect of genetically modifying a human. The method used to change the DNA of any organism is called CRISPR/Cas9. It basically consists of an enzyme discovered in *Streptococcus pyogenes* and engineered pieces of RNA that direct the Cas9-protein to a specific site on the DNA strand.

Our interviews show that people react hesitantly to genetic modifications in humans but did agree with the idea of using this technology to prevent diseases. However, these people rejected using CRISPR/Cas9 for cosmetic reasons as opposed to improving health.

In conclusion, genetic modification of human DNA is still a very questionable topic, especially considering the ethical aspects.

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Interviewed People:
Annika Bogner (19J)
Alessio Lindner (45J)
Caroline Störmer (41J)
Luis Müller (18J)
Kevin Baumgartner (19J)