Designer babies

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1 Preface:

1.1 Motivations and interests:

What would happen, if I could build myself my child just the way I wanted it? CRISPR is a biomolecular method that is able to selectively cut DNA. Therefore it allows selective interventions into the genome, possibly that of our descendants.
We chose the topic of designer babies, as it is one of the most recent forms of genetic engineering, that interests the both of us a lot. Especially since it concerns us humans directly and is able to give the group of people, that will be able to be the first ones to use it efficiently, a huge advantage. We want to know what exactly we are able to do. We also want to show why so many countries have such strict laws on the use of CRISPR/ Cas9 even though the method is for example used in agriculture. About that: our interview with Professor Markus Affolter of the biocentre Basel.

1.2 Our questions:

- Why is CRISPR/ Cas9 forbidden?
- Is it possible to genetically change babies using CRISPR/Cas9?
- Is the term “designer baby” realistic?
- What experiments or studies are currently being made?
- Lastly, a rather personal question to our interviewed person: Where does he draw the line and does he see need for improvement in the current legal situation regarding CRISPR/Cas9?

2 Introduction:

2.1 Recent events regarding designer babies:

Up until now, CRISPR was mainly used in agriculture. However, there was one kind of obscure story about it’s use on humans. In 2018, the Chinese biologist He Jiankui announced the birth of the first genetically modified babies using CRISPR/ Cas9.
The twin girls’ mother, Grace, started her pregnancy with a regular in-vitro fertilization, but with one major difference, which makes this case so incredibly fascinating.
“when Lulu and Nana were only a singular cell” so Jiankui “we made one genetic modification on the embryos.”. Since the twin girls’ father is infected with the HI-virus, the scientists claim to have closed the “gate through which HIV can infect us”.
Jiankui is currently imprisoned for conducting human experiments.
Little is known about Lulu and Nana, but their immunity against the HI virus has never been tested and they seem to be living a relatively normal life.

As scientists deem CRISPR/ Cas9 to be in it's beginning stages, most believe it not to be. Safe for use on humans. So the case of Lulu and Nana seems to be the only possibly successful case of genome editing on human embryos using CRISPR/ Cas9. (2)

2.2 Current uses of CRISPR/ Cas9:

At the moment, the CRISPR/ Cas9 technique is mainly used in the production of crops. These are called genetically modified organisms, GMO for short. Worldwide, there are over 60 million different GMOs being cultivated. Here in Switzerland however, they are not allowed yet. On the internet, we found the following statement:

> In Switzerland the cultivation of GMO crop is not yet allowed. Nevertheless the topic of coexistence is on the political agenda and research as well as politics are challenged to propose answers to many questions and to deliver a basis for future decisions.
> Products of apiculture are especially exposed to the GMO issue since honey bees will not stop collecting at the border of a GMO field. Pollen and nectar of GMO crop are as much attractive as from conventional origin. One question arising is: are active substances from transgenic plants harmful to the insects especially the honeybees. (3)

2.3 Alternatives to CRISPR/ Cas9:

On the 24th of January 2022, we visited Professor Markus Affolter in the Biocentre in Basel. Professor Affolter conducts experiments on zebrafishes and drosophila flies using CRISPR/ Cas9. Due to our chosen technique being illegal to use in regard of human cells in most countries, it's nearly impossible to find any official experiments or researchers. However the chosen technique of engineering is the same on any eukaryotic cell, professor Affolter is an expert on the subject nonetheless
He was so kind to give us an interview and to explain the CRISPR technique to us.
According to professor Affolter, there are alternatives to CRISPR/ Cas9, that lack the techniques precision such as the treatment of crops using rays or mustard gas.
In case of an embryo that is feared to have a genetic disease, instead of using CRISPR/ Cas9, we can test the given cells and only develop the ones that do not suffer the given mutation. (1)

3. *Description of engineering technique:*

3.1 How does CRISPR/ Cas9 work?

Before our interview with him, we asked professor Affolter to explain the CRISPR technique to us in detail, so we could understand the following answers to our questions as well as possible. He answered as following:

> "Imagine the double stranded DNA in our cells. It breaks quite often due to sunlight and other factors. It's like a thread that needs repairing quite often. For the

reparation, the cell takes the second chromosome and uses it as a template to fix the break. That mechanism is, what our technique uses to it's advantage. We thought if we have an enzyme, that cuts a certain base sequence, we can bring in a template that I can decide upon from the outside. The changes, that I build into the template are included when the DNA is repaired.
The second possibility would be to let the cell fix the strand by itself. Normally, that leads to the strand being reconstructed as it was before, but that does not matter, as the Cas9 simply cuts it again. This cycle of the Cas9 cutting and the cell repairing is repeated until the cell includes, excludes or changes as little as a single base in the sequence; a mutation. That leads to the sequence connected to the Cas9 not recognizing the part of the DNA anymore and thereby not cutting it.
Therefore, the CRISPR method can be used to inactivate certain genes, as well as to add new genetic material into the cell. The use of the specific base sequence makes the CRISPR method more precise than any previous genetic engineering method." (1)

3.2 How CRISPR/ Cas9 could be used on human embryos

So now we know: through CRISPR, we can either replace or cut away- assuming that the cell replaces these sections by itself- selected sections of DNA. But what if that cell was a human zygote?
First of all, scientists would use the in vitro fertilization to get a human zygote. This method is simply the fertilization of an egg cell by a sperm, that takes place in a lab, rather than in the womb. When this is reached, the CRISPR/ Cas9 with the desired mutations is injected into the cell. The previously explained steps take place and when the cell divides, all daughter cells have the same mutations. When there are a few more cells, the scientists take a sample and see, if the engineering process was successful. If it is, the zygote is placed into the mother's uterus where the fetus continues to grow as it normally would.

4. Documentation

4.1 Documentation of the visited institution:

Here our questions to professor Affolter and his answers:

There is currently a debate going on whether or not GMOs should be legalized. Why is it forbidden in the first place?

Us humans have been cultivating plants for a very long time. Very early on, we started to select the best plants, whose seeds we would use to optimize our crops. We tried to reach a desired mutation by simply using, for example, x-rays on crops, plant them and select the "best ones".
To be able to tell the difference between the treated crops and regular ones, we would include a resistance to antibiotics or a certain bacteria into the treated crops. This addition counts as genetic modification, which is forbidden. When we

experimented on crops with CRISPR/ Cas9, we used the same principle, so it fell under GMOs and was forbidden. (1)

Could you go into more detail?

If you want to change, for example, a plant to something, that is bigger or might produce more crops, you have to do that via the genome and change the chromosome in a way, that the desired mutation takes place.
Back in the day, we used methods, such as x-ray, mustard gas or radioactive rays on small plants and waited for coincidences. Then we selected the plants showing the desired mutation not using the genome.
We started adding a resistance to antibiotics to every plant we modified, so that we could recognize the modified ones from the ones, that weren't. This was for the sole purpose of being able to prove a modification. Today we don't have to do that anymore. If we desire, for example, a resistance to mildew, we have to change the chromosome on four different spots. It's not possible to reach that by coincidence or at least very unlikely. This would be possible using CRISPR/ Cas9. (1)

Now, how would it be to use CRISPR on human zygotes. Is that technically possible and what are the moral concerns?

First of all: it's forbidden. The first scientist to conduct such an experiment is Chinese. He supposedly genetically modified babies to be immune to the HI-virus. People with that illness aren't accepted in China's society, as it's sadly still associated with homosexuality, which is frowned upon. This scientist's intention was to help parents protect their children from the discrimination, that comes with HIV. I think most people can understand the desire to protect your children against illness, be that a genetic one, that you pass on to them, or something that they are exposed to during their lifetime.
However, in case of a genetic disease in the parents, there is the legal possibility to go to a clinic, where the zygote is checked for mutations and if there are any present, it isn't reinserted into the uterus. Of course, this method isn't ethically perfect as well. However, these cases are a bit of a dilemma, as if someone has the possibility to spare their child of a chronic illness and doesn't take that chance, what will they tell the child, when it asks, why they let it be born with such an avoidable disadvantage? Regardless, it's forbidden and there is no debate in most countries yet, except for example China, but that is in my opinion just the huge difference in culture and mindset. (1)

But in theory, it is possible?

Yes, as the previously mentioned experiment has shown. (1)

Another question is: If we had such a technique, wouldn't the people who would be able to access it first would be the rich?

Yes, that is always the case. A nice example is the ongoing pandemic. Us wealthy countries have access to the booster, while poor nations often times struggle to get enough vaccines. (1)

Wouldn't that lead to an even bigger inequality between rich and poor?

Well, technically yes however this inequality already exists. A child of Elon Musk or Jeff Bezos will have more chances than us and we will have more chances than a child born to parents in extreme poverty. (1)

Could parents model their children to fit our society's beauty standard?

The altering of one's physical appearance is also something that we are already doing. We go to the gym, we dye our hair, we even undergo surgery to look a certain way. But this kind of modification isn't something, that scientists are wishing for. I think the focus would mainly be on the avoiding of diseases through this technique. So me and many others don't see the use in such alterations. (1)

If such an experiment is conducted, how far would we be able to go?

I must say, not very far. Most traits are controlled by so many genes from which we don't know the way they influence each other. Things like blue eyes are possible, but it's probably easier to wear blue contact lenses.
Currently, there is an experiment being conducted by George Church, who is trying to make what he calls a mammoth. He is trying to recreate mammoths using part elephant and mammoth DNA. (1)

Do you see room for improvement regarding the legal situation surrounding the use of CRISPR/ Cas9?

Regarding humans, I personally don't think we need to change anything. To me, this is a bit of a "holy grail". I also only work on flies and fishes, for which you don't need a special permit. For the same experiments on a bit larger animals, such as mice, you need one, that has to be approved by an ethnics commission. I think these experiments should only be done if they benefit us humans. Where I do see room for improvement is the use on crops. We have to blindly shoot x-rays on plants, all while having a much more precise technique, where we would be certain of what we are doing, but we can't. (1)

5 Discussion:

5.1 Development of CRISPR/ Cas9

The development of the first CRISPR locus into a genome editing tool is the work of many scientists around the world. Here a quick strongly simplified summary by the broad institute on the exact timeline:

- Discovery of CRISPR and it's function:
  In 1993, Spanish researcher Francisco Mojica was the first scientist to report a CRISPR locus. He studied these until 2000, when he recognized, that the loci shared common features, in response to which he coined the term CRISPR in correspondence with Ruud Jansen.
  In 2005, he reported, that the sequences in CRISPR matched parts of the genomes of bacteria. This led him to make the correct hypothesis, that CRISPR is an adaptive immune system. (4)

- Discovery of Cas9:
  In 2005, French researcher Alexander Bolotin discovered an unusual CRISPR locus in the bacteria Streptococcus thermophilus. It lacked some of the previously reported systems and instead had new cas genes, one of them encoding a large protein that was predicted to have nuclease activity. This protein is today known as Cas9. Additionally, a sequence, that is necessary for target recognition, the PAM, was found in the spacers of cas9. (4)

- Experimental demonstration of adaptive immunity:
  In 2007, French scientists wanted to see, how a bacterium used in yogurt and cheese production, reacts to phage attack, which is a common problem in this field. They found Mojica's hypothesis to be true. The bacteria integrates phage DNA into the CRISPR array, which allows them to fight off following phage attacks.
  They also proved, that the only required protein for inactivating the attacking phage, is the Cas9. However, the details surrounding the inactivation were not known yet. (4)

- Discovery of guide RNAs:
  In 2008 in the Netherlands, John van der Oost showed, that in E-coli, the phage DNA is transformed into small RNAs, termed CRISPR RNAs. These CRISPR RNAs guide the Cas proteins to the target DNA. (4)

- Genome editing using Cas9:
  In 2013, researcher Feng Zhang was the first to successfully use CRISPR-Cas9 for genome editing in eukaryotic cells. (4)

5.2 What will the future look like

As already briefly mentioned in the interview, any use of CRISPR/ Cas9 on human zygotes is forbidden. However, some scientists or nations may wish to change that in the future.

If there is gene edited babies, it most likely would be for medical reasons, not to create an aesthetically pleasing child. (1)

5.3 Ethical debate around designer babies

The ethics surrounding the application of CRISPR/ Cas9 on human embryos are quite complicated. On one hand, most deem it morally wrong to design your child, as it is not a doll but a human being. If someone decides to have a child, that decision should not be tied to the looks of said baby. On the other hand, if someone with a chronic illness has the possibility to spare their child of living with that illness, some see it as unethical to not to take that chance.
Another concern, that professor Affolter agrees upon is, that if there really were to be a technology to influence a child's looks, immunity to diseases and so on, the people who would be able to access said technology first would be the ones who have the money, namely the rich. This would make the difference between extreme wealth and extreme poverty even bigger than it already is.

6 Summary:

CRISPR is a very promising new method, that is, among other things, used to genetically modify crops. Up until now, we had to do these things almost blindly through rays et cetera. Today with CRISPR, we have an extremely precise method. CRISPR can modify much more in a perfectly precise manner, that has clearly definable aftereffects on the plant. Now humans aren't crops, so the situation, considered in the long term, is much more complicated.
Due to human experiments with CRISPR/ Cas9 being forbidden, we can't say what the future will look like. However, professor Affolter told us, that it is widely agreed upon, that if we decide to do such a step, it would be medically motivated. The concern, that we would create a split society isn't as big as we previously thought. Not because chances would be evenly distributed, but because the chances, that one has are already determined by what family they are born into, where they live, et cetera. Therefore, the chance to make children immune to certain diseases prematurely wouldn't make such a large difference as we might think.
The term "designer baby" is polemic. Even though scientists agree today, that a child's beauty isn't a medical concern, the decision to do such things would be a political one. We think, that CRISPR's possibility to free children of genetic diseases is a great one, but see it as ethically wrong to change your child's looks to your liking. For one, your decision to have a child shouldn't be tied to said child's looks. Second of all: In our society as it is today a child, that looks a certain way will undeniably have advantages over other children, which is in our opinion unfair.

7 References:

Images:

Figure 1(front page)

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