To see what the future holds...

GYMNASIUM KIRSCHGARTEN

BIOLOGY TERM PAPER: Genetic Engineering

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Preface

Blindness is a topic not many of us are confronted with but if we take a minute to think about it, it's something that frightens all of us. Losing one of your senses will affect your life and way of living greatly so it makes sense for us to investigate the topic and find ways we can cure such conditions and help the people affected to make their life as easy as possible. Recent treatments of blindness and conditions associated with it include genetic technology, like the pharmaceutical "Luxturna" which we will be focusing on in the following paper.

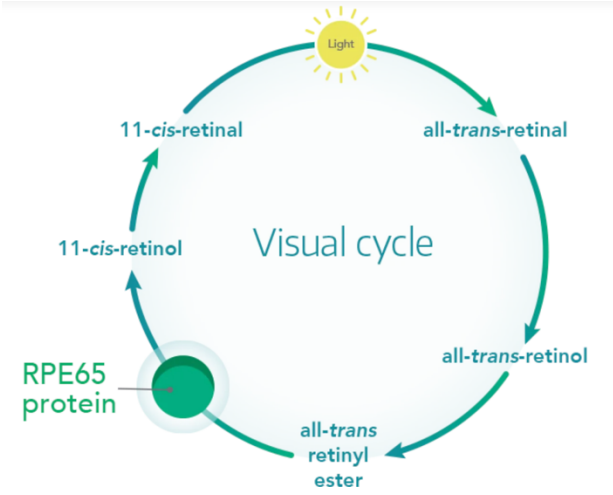
When we first read that there was gene therapy to cure blindness[1], we were shocked and immediately interested because before that, we just assumed that blindness was not curable. We were wondering how it works, how accessible it is and if there are any risks to the treatment. To find answers to these questions, we contacted one of the two surgeons that did the surgery here in Basel a couple of years ago, Prof. Christian Prünte.

We were also surprised how near the surgery was. To know that someone was cured of blindness a couple minutes away from us made us realize how local gene therapy is and how it may be more common and usual in the future.

Introduction

Retinal dystrophy is a monogenetic inherited eye disease, where a gene variation leads to wrongly produced proteins that are needed for our sight[2,3]. This leads to decreased vision over time. The mutation is in the gene RPE65 which is used to turn all-trans retinal to 11-cis retinal in the visual cycle[4,5,6,7]:

The RPE65 gene provides the instructions for producing the protein RPE65 that is needed for vision. The RPE65 protein plays an important role in the visual cycle. This cycle is responsible for converting light that enters the eye into electrical signals, which are then transmitted to the brain. When light hits the photosensitive pigments in the retina, it converts a molecule called 11-cis retinal into all-trans retinal. This conversion triggers a series of chemical reactions that generate electrical signals. RPE65 is a key enzyme in the visual cycle, as it converts all-trans retinal back into 11-cis retinol. After that, other enzymes produce 11-cis retinal from 11-cis retinol, allowing the visual cycle to restart and continue capturing light.



Graph 1 : The role of the RPE65 protein in the visual cycle

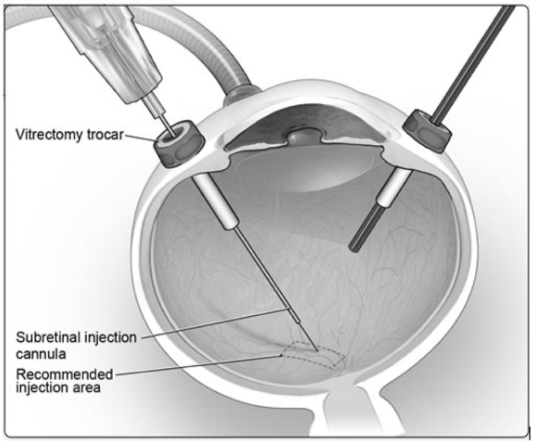
This mutation causes the retinal cells to work incorrectly and break down over time. It's a very rare disease, there are around five to ten people in Switzerland, that are affected by this.

On the 31 of March 2022 the Unispital Basel did a surgery for one form of the retinis pigmentosa with the help of a gene therapeutic pharmaceutical called Luxturna[1]. This is the first approved for clinical use AAV viral vector product by the FDA[8], and therefore a historic landmark. Until this point there aren't any alternative treatments for treating retinal dystrophy and as a first such product, Luxturna can pave the way for new pharmaceuticals to treat other monogenetic diseases.
The doctors Prof. Christian Prünte and Prof. Hendrick P.N. Scholl inserted Luxturna into the retina of a 51-year-old patient that suffered from a retinal dystrophy. It contains the correctly working gene RPE65, which can be taken up by the cells in the retina and used to produce the prior wrongly produced protein. The more time passes, the more photoreceptor cells die, so it's better to do the surgery as soon as possible. This increases the success rate, which is also influenced by other factors such as age and the state of vision of the patient. As mentioned before, we had the pleasure to ask Prof. Christian Prünte himself to tell us about the pharmaceutical, the surgery and everything that comes with it.

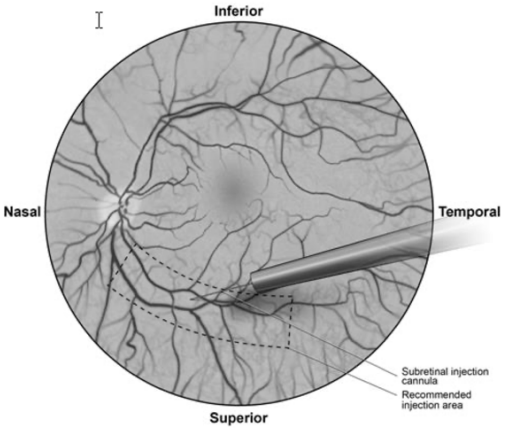
Description of the technique:

The pharmaceutical for the surgery is called Luxturna and is owned by Novartis[9]. Luxturna is a genetherapy that uses a recombinant-Adeno-Associated-Virus-Vector (rAAV2) to insert a healthy RPE65 gene into the cells of the retina[10]. The AAV is a virus that is modified to be used as a vector by removing the virus genes, thereby making it non-pathogenic. Then, scientist insert a healthy form of the RPE65 gene into the vector. The AAV that is used is found in humans and is highly effective while producing a minimal systemic immune response[11].

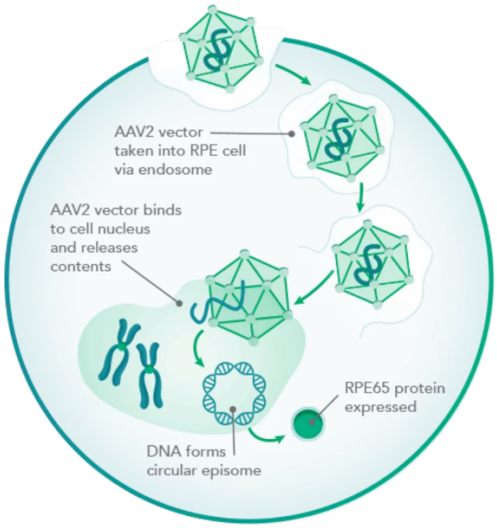
Luxturna is surgically placed directly underneath each of the retina of the patient. The gene is transferred to the photoreceptor cells. In the cell, the gene is not integrated into the genome but remains as an extra chromosomal episome[12]. In the cell it starts to produce the lacking protein.



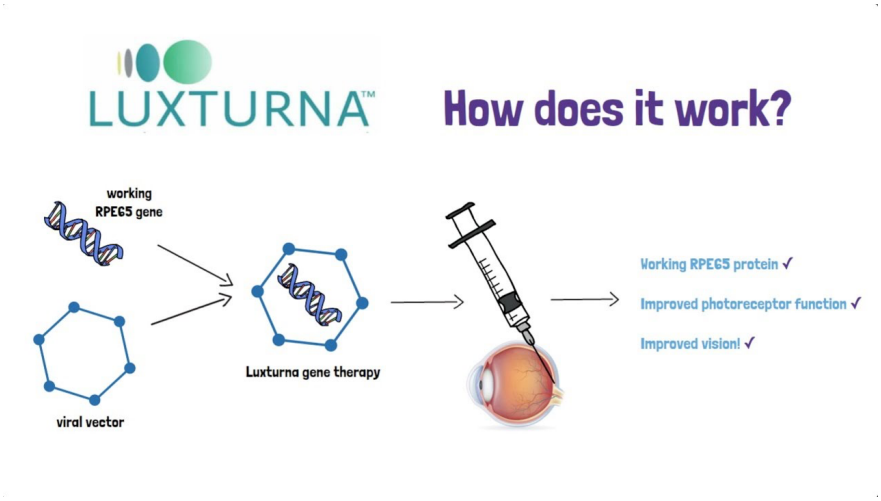
Graph 2 : Insertion of Luxturna into the retina during surgery



Graph 3 : Insertion of Luxturna into the retina during surgery, view of the surgeon



Graph 4 : Transfer of the gene into the photoreceptor cells



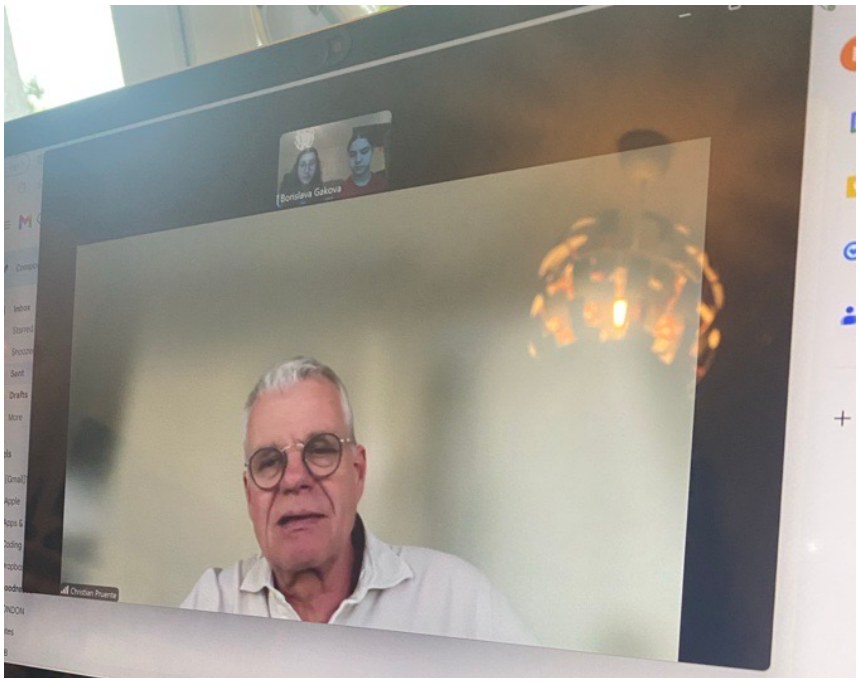
Graph 5 : Short summary of how the production of Luxturna, the surgery and the results

Because the gene isn't integrated into the genome of the patient, the patient may pass the disease on to their children.

Documentation

When we started the project, unfortunately, we couldn't find any interviews. We tried to track down the surgeons who performed the surgery but, on our way, we've been sent back and forth. Seeking another specialist wasn't easy either because most of the specialist didn't know much about the surgery or the pharmaceutical.

But on the 15th of May we got a reply by the surgeon Prof. Christian Prünte and we're able to arrange an interview.



Picture 1 : Interview with Prof. Christian Prünte on May 24, 2024 via Zoom

On the 21th of May, we had an Interview with Prof. Christian Prünte, one of the surgeons who was mentioned in the article that inspired us. In the interview we discussed the disease, the technique of the therapy, his experience with the surgery, the surgery, how the surgery went, whether it may has to be repeated for the patient, whether it will occur more frequently in the future, whether similar diseases can be treated in a similar way, the medication, what Luxturna is, how it is produced, whether it could be improved, the availability of the surgery, at what age this therapy is possible, prices, whether health insurance companies may not want to pay for the surgery, whether there are reasons why some patients are refused the operation, alternatives, if there are any, if yes, how effective they are, cons for the operation, risks, social aspects, how convinced are the people who work in this field, if there is criticism of this therapy, ethical questions and his opinion.

Discussion:

This gene technology is a big step in medical research, because it enables for monogenetic diseases such as retinal dystrophy, which were long considered to be incurable, to be treated successfully. As before mentioned, Luxturna is one of the first genetic medications approved for use in many countries. Many other pharmaceuticals were derived from it for treatment of other monogenetic diseases, especially treatments for the eye, because it is so accessible. Luxturna itself doesn't necessarily require improvements, though the long term effects of this therapy still need to be observed. Despite everything, since it's only being used for a few years, there is still constant development aiming to reduce side effects such as inflammation by creating new virus capsules that are less antigen active.

The surgery itself isn't all that expensive, but what makes the treatment less accessible is the cost for the pharmaceutical itself. The surgery ranges from 3'000 to 8'000 francs but the pharmaceutical costs a couple of hundred-thousand francs. There are many other aspects to be considered, such as the ethical aspects. To find out which type of retinal dystrophy a patient has, genetic testing needs to be done. But the question is: Does a patient really want to know what his genome is? There is a possibility of a more lethal condition to be found, that the patient had no idea of. If by chance it is discovered that the patient has a very bad disease or is prone to some health complications and the health insurance companies find out about this, they would decline that patient. Another ethical question is if the patient is a child, should the parents be able to decide whether to do genetic testing on their child or not and thus deprive the child from getting treatment to improve their vision? Or should the patient get old enough to be able to decide for himself – but in turn time passing will worsen the condition and therefore increase the risk of side effects and decrease the success rate of the surgery. Considering the surgery is more effective the younger the patient and the earlier the state of the condition is, the topic genetic testing is even more controverse. Even next to all the pros of this gene technology, all these variables must be considered too and could be regarded as cons on the topic.

Summary

It's fascinating, how the invention of one pharmaceutical can change blind people's lives to be cured of diseases that they were born with and once seemed incurable. Luxturna paved the way for many other pharmaceuticals to be produced and more diseases to be treated. Gene technology opens a whole new world for medicine and is a major step forward in treating more and more diseases with years to come.

References

Pictures:

Cover picture:

https://www.br.de/kinder/blind-blindenstock-sehbehindert-100~_v-img__16__9__xl_-d31c35f8186ebeb80b0cd843a7c267a0e0c81647.jpg?version=2c4c7

Picture 1: Made by ourselves

Graphs:

Graph 1 & 4:

https://luxturnahcp.com/about-luxturna/mechanism-of-action/

Graph 2 & 3:

https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf#:~:text=URL%3A%20https%3A%2F%2Fwww.ema.europa.eu%2Fen%2Fdocuments%2Fproduct

Graph 5 :

https://i.ytimg.com/vi/dh9c6-GVqOQ/maxresdefault.jpg

1: https://www.unispital-basel.ch/newscenter/kliniknews/augenklinik-news/07-04-2022

2: https://www.chop.edu/treatments/gene-therapy-inherited-retinal-dystrophy-luxturna

3: https://luxturnahcp.com/about-luxturna/mechanism-of-action/

4: Redmond et al.1998 - Rpe65 is necessary for production of 11-cis-vitamin A in the retinal visual cycle

5: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821785/

6: https://medlineplus.gov/genetics/gene/rpe65/

7: Dr. Mathias Herrmann 2020 - Luxturna® – erste Gentherapie in der Augenheilkunde

8: Jonathan J. Darrow 2019 - Luxturna: FDA documents reveal the value of a costly gene therapy-

9: https://www.novartis.com/news/media-releases/novartis-exclusively-licenses-first-ophthalmology-gene-therapy-all-markets-outside-us-milestone-patients-rare-inherited-vision-loss

10: Albert M. Maguire et al. 2021 - Durability of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease -

11: Recombinant Adeno-Associated Virus Gene Therapy in Light of Luxturna (and Zolgensma and Glybera): Where Are We, and How Did We Get Here? Allison M. Keeler and Terence R. Flotte 2019

12: https://go.drugbank.com/drugs/DB13932

13: https://www.asgct.org/publications/news/december-2017/luxturna-fda-approval-spark

Whom it may interest:

This is a video of the surgery.

Warning: Don’t watch the video if you may be sensitive to these kinds of things:

https://youtu.be/WhxUfK_-oLI?si=at2JOf26sJ3wjsX8

Interview with Prof Christian Prünte

K&Z Perfect. So it's about the operation that you did curing retinal dystrophy with the Luxturna. We wanted to ask you some questions - general and more in-depth questions. Yeah. Should we just start? So, how would you define or what exactly is retinal dystrophy?

Dr. Christian Prünte Retinal distrophy is a disease, which is inherited. So it's based on your genes and more or less, you are born with it. And so some something goes wrong because you do have the wrong genes.

K&Z Yes. So it's more like the protein that we need to see is not produced. Is that correct?

Dr. Christian Prünte It can be. It can be many different things. So mostly it's a wrongly produced protein that cannot do what it should do. And, it can be a missing protein. And also bacteria, but usually it's a wrong protein.

K&Z And there are many mutations. Right?

Dr. Christian Prünte Yes, exactly. There are lots of new mutations. And the vast majority we don't know, actually.

K&Z And how do you recognize which type of retinal dystrophy a patient has?

Dr. Christian Prünte So it can be by phenotype. So every dystrophy looks a little bit different. But there are many dystrophies that look more or less the same. And so what we do, we have to do the genetic testing.

K&Z And how would you define the pharmaceutical Luxturna? What is it actually?

Dr. Christian Prünte Actually, it's one of the first gene therapies available. And so maybe we should go back to what, in principle, you can do in gene therapy, because you have to deliver or change genes, which means you have to get inside the cell that you want to treat. So this means, for the moment, many, many diseases, might be genetic. So there are various genes involved at the same time. So for the moment, we can only treat diseases that are monogenic, where we exactly know where the defect is. And it has to be a single defect. And the way to get into a cell, which is well known from infectious disease, is a virus. So, you can take a virus that is infecting the cell, but you don't use the virus genome. You just take the cover off the virus, as a, let's say a transport piece. And, put in what you want and what you want. So it's various things you can do in gene therapy, but, what you want is maybe you want to get in a new gene. So you need to get the gene in for genetic information. And of course, you need a tool that works with genes that you can place it where you want it.

K&Z So this isn't the first try to use Luxturna or a similar gene therapy on a patient. There was, I think, some research and some trial in the Philippines. Do you know about that?

Dr. Christian Prünte Luxturna is one of the first genetic medication that is registered in many countries. So this can be routinely used.

K&Z So in the Philippines, it wasn't the same?

Dr. Christian Prünte If it's with Luxturna, it can be the same. But there are many other gene therapies we do. I do a lot of gene studies. Therapy studies with many more patients than just this Luxturna.

K&Z It's not just blindness or are all gene therapies to cure blindness?

Dr. Christian Prünte Until now these are all, diseases which cause blindness but we start to do other things also. So what you can do with gene therapy, you can, let's say we pair a gene by exchanging the nucleotide. This is possible. This is named gene editing. That can be done. And, what you also can do is place a gene. Cut some pieces out and put another one in. CRISPR is one of these examples. And what you also can do is you can just put an artificial gene in, in any cell, whatever you want. Which means, finally, the cell is producing what you want. So if you have a disease, for example, age related macular degeneration, you can put a gene into the cell that produces the medication you usually have to give every four weeks into the eye. This is well, this is possible too. And with Luxturna it's a principle also the same. There is one protein that doesn't work. But we are not replacing the protein, we are just putting in a new one that produces the protein which is needed.

K&Z And it doesn't use a plasmid, right? It's another type of gene technology?

Dr. Christian Prünte Yeah, you know it's the vector that you put it in, yeah. But in this case, with Luxturna, which is the one where you deposit a new gene into the cell - this is not going into the genome. So which means in theory, this is not inherited after that, because this is an additional gene that does not go to the nucleus. And so it's not in the genome.

K&Z So are there any side effects after putting in this new gene?

Dr. Christian Prünte Not really, of course, it's a virus. And usually, virus does an infection and you get the reaction of the body so you can have inflammation. This is maybe the main side effect. And of course you have to do surgery so you get all the side effects of surgery.

K&Z Now that you mentioned the surgery, how long did it take? And how did the patient feel or during or after the surgery?

Dr. Christian Prünte Okay. The patient was sleeping, so general anesthesia, and it took about half an hour. And, after that, it's like a normal surgery. That's nothing special for the patient. Because it's in the retina, he has to keep a special position. And, so the medication is staying where we need it for as long as possible.

K&Z And so the patient wasn't blind, he was in an earlier stage in the disease. Did he see improvement directly or did it take some time?

Dr. Christian Prünte Oh, it takes some time. It takes about two, three months. You should calculate until it works.

K&Z Was the surgery difficult for you?

Dr. Christian Prünte Not for me. I did it a couple of times for other reasons, actually. But, it's, let's say one of the complex surgeries, yeah.

K&Z How did the patient recover? Is the patient now having complications or did everything go to plan and he's now cured?

Dr. Christian Prünte [00:08:12] Everything went to plan. Yes. And there was not much inflammation. Actually there were not many side effects. And so everything was to plan.

K&Z Will the patient need another visit or another surgery to freshen up?

Dr. Christian Prünte Actually, we don't know. But from the principal what we do, one surgery should be sufficient. I think this is because we treat cells that do not part - they are forever. So you you start life with your retinal cells and you end your life is the same retinal cells. So, if you do something with these cells, it should be forever. It's still so far because we only have experience for a couple of years. But in theory, yes, it should be forever.

K&Z And, how many people are affected by such diseases generally?

Dr. Christian Prünte The one for Luxturna is very rare, the disease. So maybe in Switzerland it will be 5 to 10, not more.

K&Z [And how much did the surgery cost?

Dr. Christian Prünte So the surgery itself is is not too expensive. It's about, I don't know exactly about 3 to 8000 francs. But to be patient is very expensive.

K&Z So the medication is apart from these 8000 that you said, it's additional?

Dr. Christian Prünte Yeah, this is an extra couple of hundred thousands.

K&Z And so would you say it's accessible or rather not?

Dr. Christian Prünte It depends where you are. In Switzerland in principle the insurance company should pay for it, but they always come up with lots of argumentation that this is not the right patient. So then they try not to pay. To be honest, 800,000 francs is a lot of money. Or 300,000, depends on which one you use. But they are all about a couple of hundred thousands. And so they try to argue as much as possible. In other countries it's not covered by insurance. So the patient has to find somebody or has to pay by myself.

K&Z And how long was the pharmaceutical, researched?

Dr. Christian Prünte This usually is many, many years. So you can calculate until you can do something like this it takes 10 to 15 years. Something in between that.

K&Z Are there any other possibilities to cure, such diseases?

Dr. Christian Prünte So far, that's the only way to do it.

K&Z And were there people who were also specialists like you, who are not convinced of the surgery or thought that it may not work?

Dr. Christian Prünte That's all of us in the scientific community. Some believe in something and others do not. And that's the reason we have scientific documentations, we have congresses, we have discussions, and so. And finally, you have to prove what you do. So before the medication comes on the market, it has to be proven that it really works.

K&Z And how do you prove that?

Dr. Christian Prünte This means you have to treat a couple of patients. And you have to do the same procedure without medication on a couple of other patients and compare these two outcomes.

K&Z So the pros of the surgery are very obvious. Do you see any cons about the whole thing?

Dr. Christian Prünte Yeah. It's, let's say there are mainly two sides. One is the possible side effects, you have to calculate, and maybe also the costs. And, who is covering that? And, the second, doing this surgery does not mean that you necessarily have success. So it depends on how many cells are left that you can treat. Or how many are already dying and so you can't do anything anyway. So you have to find the right patients. Patient selection is crucial.

K&Z So you say the earlier you do it, the better?

Dr. Christian Prünte The earlier you do it, the better. And the earlier you do it, the more you will avoid any side effects, because they still have good vision. So you don't want to risk too many side effects. But on the other hand, this is the best way to do it because it's the best success you can have.

K&Z Yeah. Could you say there is something like a success rate or is it more depending on the age and everything?

Dr. Christian Prünte There is a success rate of course depending on age, on how many cells are left and all things like that.

K&Z Yeah. Is there still any research being done in that aspect or in this environment?

Dr. Christian Prünte Oh, yeah. We do a lot of research for other diseases that are monogenetic to get the same effect, and even a better effect, to be honest. And, yeah, there's a lot going on, even for Luxturna. There's a lot going on because we we

need to know the long term outcome. As I said, is it a one time treatment? Or are there any side effects that show up late?

K&Z Do you think there will be any, side effects that show up later?

Dr. Christian Prünte I don't know. It could be. Yes. I have no idea. That's not something necessarily that will show up, but, yes. You never can sort it out.

K&Z Do you think there will be a need to improve Luxturna?

Dr. Christian Prünte Maybe not Luxturna, but from the experience, from Luxturna, other medications for other diseases were derived that, you know, let's say better because we can avoid some of the side effects that we know. One is, for example, inflammation by creating new virus capsules that are less antigen active.

K&Z And are there any future research steps for this exact surgery?

Dr. Christian Prünte Yes. We are applying now as a viruses as a gene. And so yes we are developing this. Once you start you get a lot of experience. You find out what is what is working well and what is working not well. And so you try to avoid everything that's not good and, and try to further develop all things that said, work perfectly. And so there's constant development, of course.

K&Z Do you see any unethical aspects in this kind of surgery?

Dr. Christian Prünte Yeah. If you change the genome, there are lots of ethical considerations. Of course it's already starting with doing the genetic testing. Because you do not only find out this gene in principle, you find out any gene or you can find out any gene. And the problem is: does a patient really want to know what his genome is? Or should anybody else know it? For example, if this is somewhere, let's say on a health care, electronic card and by chance, you find out he has a very bad disease. And if this comes across the insurance company, they may say, oh no, we will not take this patient anymore. So there are lots of ethical considerations. And is it, for example, if it's a child, can the parents decide they want to know the genome of their child? Because this has consequences for the child when it's getting older. So there are lots of possibilities of what you can do. But we are not sure if everything is okay. Now we are sure, definitely everything is not okay.

K&Z Yeah, it's a bit contradicting. Wanting to have the patient as young as possible and also having it be able to decide for itself.

Dr. Christian Prünte Yeah.

K&Z At last, we want to ask you what is your opinion on this surgery and on this gene therapy?

Dr. Christian Prünte Oh, It's fascinating. It's a completely new field of therapy. We can we can cure diseases, treat diseases that has never been possible before. And I'm pretty sure the gene therapy will be one of the major steps forward in medicine for the next decades.

K&Z I think that's all of our questions. Thank you very much, for taking the time to to this with us.

Dr. Christian Prünte Sure, I hope you're successful.

K&Z [00:18:50] Thank you. Would you like maybe to have the paper? In the end? We could send it to you if you wanted to.

Dr. Christian Prünte Great idea. Really good idea.

K&Z Okay, good. Sure. Then we will send you the paper in, like, a week or something. Thank you very much.

Dr. Christian Prünte Thank you, thank you.

K&Z Have a nice day. Bye.