# Gene therapy and gene-modified cell therapy in rare diseases

Brought to you by

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**Dr. ir. Tonke L. de Jong**
Gene therapy and gene modified cell therapies have a great potential for rare diseases to either help patients to cure their disease or improve their lives. Did you know that gene therapy will probably become a major treatment option for many rare diseases in the near future? Keep listening to find out.

Thanks for listening to this Rare Diseases medical conversation podcast from COR2ED, Independent Medical Education. This episode is supported by an independent educational grant from the American Society of Gene and Cell Therapy and Pfizer. Today's topic is all on gene therapy and gene modified cell therapy in rare diseases. I'm honoured to introduce to you today's two experts in the field of gene therapy and hematology, Professor Dr. Cédric Hermans and Professor Dr. Miguel Escobar. Could you please introduce yourself, Professor Hermans, and also explain to our listener why it's important that we know more about gene therapy?

**Prof. Dr Cédric Hermans**
Thank you, Tonke. Thank you for this great invitation and opportunity. So I'm based in Brussels. I'm a Haematologist. And over the last 20 years, I have been involved in the care of many patients with rare disease, including hemophilia. And I've had the opportunity to witness and contribute to many innovations. And the most recent one is probably gene therapy. Gene therapy trials are going on in my centres. I've had the chance to include patients in gene therapy trials, and I'm very happy, very honoured today to share my local experience with you.

**Dr. ir. Tonke L. de Jong**
Thank you so much, Professor Hermans. I'm also happy to welcome Professor Escobar for this podcast. Welcome.

**Prof. Dr Miguel Escobar**
Well, thank you very much for the invitation. And very similar to Cedric, I've been treating patients with bleeding disorders for over 25 years. I'm based in the University of Texas in Houston. We also have a very large hemophilia centre. And we've actually been participating in clinical trials, including gene therapy for the last probably 30 years. And it's very exciting to see how these new therapies really are changing the lives of our patients with hemophilia and other bleeding disorders.

**Dr. ir. Tonke L. de Jong**
Thank you, Professor Escobar. Very useful to already have an improved understanding of why gene therapy is important for our listeners and also for the patients, of course. I hope you have a great discussion. We're excited to listen and understand in greater detail why we need gene therapy for rare diseases, what it actually is, and how it is becoming reality within the context of hemophilia.

**Prof. Dr Cédric Hermans**
Well, clearly, why do we need gene therapy? This is a very common, usual question in 2023. Well, I think no hesitation, we need gene therapy, and we need gene therapy for several reasons, and I'll come back to this. So what do we really mean by gene therapy? Well, I think there are different types of gene therapy, gene therapy itself, but also what we refer to as gene-modified cell therapy. These treatments are in my view, instrumental and increasingly important for the treatment, the care of many rare diseases, and they have a great potential. So, you could ask yourself, well, what would be the benefit of gene therapy for this disease? Well, there are many diseases, and for many of these diseases, there is currently no treatment available. Major advances have been achieved in the field of genetics. So, we have identified many rare diseases. We know exactly the mutation. We know that for many of these diseases, a specific protein or any other compound is lacking. But for many of these diseases, in spite of the development of biotechnology, we haven't been able to replace or compensate what the body of this patient is not able to do. So it's clear that for many of these patients, gene therapy could really help. And to what extent could it help? First of all, and we'll come back to this later on, there are many rare diseases which could be fatal in the absence of treatment. So clearly, if you do not provide these patients with a treatment that's efficient, it's very likely that these patients will die sometimes very soon in life. So clearly one of the objective of many of these gene therapy or gene modified cell therapy is to avoid early death of these patients of a fatal disease.

Also, for many of these diseases, clearly the ambition is to cure the disease when it's possible. It's not always possible to fully cure the disease, but at least the ambition is to improve the patient's life, the patient's quality of life when the treatments currently available are burdensome or are associated with multiple limitations, and I'm sure that we will discuss this later on. So clearly, in my view, there is a clear need for gene therapy and gene modified cell therapy for many, many diseases. Considering that 80% of the rare disease have a known monogenic code. So we know exactly where the gene defect is located, so we know more or less what sort of correction would be needed to treat, cure or improve this disease. And what we will try to do during the next 20 minutes is give you an overview of what gene therapy can provide in 2023 and maybe, Miguel, one of the first

steps would be to provide some overview of the different rare diseases for which gene therapy is currently used or in current development.

**Prof. Dr Miguel Escobar**
Yes, absolutely. As you mentioned, these are monogenic diseases. We know a specific, where the mutation is, so it makes a lot of sense certainly to be able to develop techniques like gene transfer or gene therapy. Right now, we know there are probably more than 7,000 hereditary rare diseases that affects millions of people worldwide. And I think a therapy like this certainly could be very beneficial to many of the diseases. And to some examples, we have, for example, neuromuscular diseases like the spinal muscular atrophy. This is a devastating neurodegenerative disorder that results from progressive loss of motor neurons. Children usually die very early, and gene therapy got approved in 2019 specifically for this using adeno-associated vector. We have shown a very good safety profile as well as being quite efficacious in the translation. We also have other diseases like ocular diseases. A typical example is the Leber congenital amaurosis. Again, it's a disease that impairs vision at birth or very soon after. And by using this type of technology again, it delivers a normal copy of the gene that is directly introduced into the retinal cells, and it can make a big difference for these individuals. Then from the hematology point of view, we got another disease called beta- thalassemia. This is an inherited blood disorder that in these patients it reduces the production of hemoglobin. Patients develop severe anaemia and many other complications from this. The treatment has been always just red cell transfusion and also iron chelation therapies. They get a lot of complications from the iron overload. The FDA also approved therapy for beta-thalassemia. Specifically, what it does, it adds a functional copy of the modified beta-globin gene into the patient's own hematopoietic stem cells, and it really decreases the amount of transfusion. Many patients actually are free of transfusions from this. And another one that is also being seen is the adrenoleukodystrophy is another degenerative condition that also attacks the neurons on the brain. It is quite progressive, but it's also it's been done a lot of investigation using gene therapy as well. So here we can see that it's got a broad application in the different diseases when we use something like gene therapy. So here is when different technologies could be used, like I think Cédric already mentioned it could be the gene transfer or other type of technology or even vectors that could be used to certainly modify the disease.

**Prof. Dr Cédric Hermans**
And certainly, Miguel, because while considering the gene therapy of this disease, while it looks quite ambitious, we know it's not that difficult to treat hypertension. It's a little bit more complicated to replace missing protein that has to be produced by biotechnology and then introduced into the body. But here, we are really talking about how to correct or supplement in some way a genetic defect. So this is quite ambitious. And this is, in fact, no longer science fiction. And I think there are different technologies here that could be used to do that. And classically, we make a clear distinction between gene therapy and gene-modified cell therapy and I think it's very important to understand this. Gene therapy really refers to some sort of direct manipulation of a patient's genes to treat or prevent a disease. And the technology here is based on the elegant introduction of a functional gene into the patient. So really what you want to do, the cells are not able to produce something because there is a genetic defect. And what you would like to do is to introduce in that cell the right functional genetic information so that the faulty or the missing gene would be completely

compensated. And so that this cell would have again or restored this ability to express a protein. So this is one of the first approaches. So this is an *in vivo* approach. But clearly, if you want to achieve this, you should be able to introduce in the cells, in the body of this patient, the genetic material that is missing or faulty. And what we do today is using vectors and mainly viral vectors. We'll come back to that.

Another approach would be what we refer to as gene-modified cell therapy. So here it involves some sort of modification of patient cells, but that will take place outside the body. So how does that work? Ideally, for instance, if you work on bone marrow stem cells, you need to be able to collect the stem cells and *ex vivo* in the lab, you will modify genetically the cells and after engineering these cells will be reintroduced in the patient and you expect that the cells will be able to produce the missing protein. So this is another strategy. It's a little bit more invasive since you have to collect cells, modify them *ex vivo* and then reintroduce them. So this is really the strategy that we use. And the most common one I think, Miguel, you would agree with me, is the one that would introduce in the body a good copy of the gene that will enter the cell, remain in the cell, ideally, episomal, so it will not be introduced in the whole genetic material of the patient. And so the patient will have an extra copy that will help him to produce a missing protein. It's clear that to do that, we need vectors. We need viral vectors. But maybe, Miguel, one of the best examples recently has been hemophilia, if I'm correct. Both in factor VIII deficiency, and factor IX deficiency, well, many colleagues have been quite successful in making this technology a reality.

**Prof. Dr Miguel Escobar**
Yes, that is absolutely correct. And just to clarify, I guess based on the data that we have available right now, certainly gene therapy or gene transfer is what we've been using lately in the clinical trials in hemophilia, as Cédric mentioned, and a typical example is for hemophilia A. We do have right now a therapy that has been approved based on the clinical trials that we've been doing for many, many years. And in this specific trial for hemophilia A, what was used is a B-domain deleted factor VIII that was transferred using an AVV virus vector, and it was transferred into the hepatocytes, as Cédric mentioned, in persons with hemophilia A. This trial was about 134 men that were included here, received a single dose of the vector. And we have data now, at least from the phase three up to two years, from the phase one and two is probably a little bit longer, but it's very interesting that the data that came out from those two years in this group of individuals, what we saw that there was a mean, analysed, treated bleed rate decreased by 85%. When you compare to those individuals that came from prophylaxis, received a single dose of gene therapy, and the reduction in the bleeding was by 85%. Also, the reduction in the amount of factor that they utilized through the year was also quite substantial. It was close to the 98% reduction on the amount of factor. Now, it's interesting to see that the amount of factor VIII that they were producing or the activity, increasing a mean of about 22 to 35, depending on the type of assay that we use at two years. Now it's interesting to see that in this trial, there were really no evidence of any thrombosis and there were no development of any inhibitors. The main thing that we've seen was an elevation of the liver enzymes that we see most of the time with this type of therapy, but those individuals usually received treatment to decrease some

of this inflammatory response that is seen in the liver. But like I said, so far the results look very, very promising.

**Prof. Dr Cédric Hermans**
Well, I think it's also true for hemophilia B. So for those of you who are less familiar with this entity, hemophilia B is factor IX deficiency. It has many similarities with factor VIII. So this patient, if their liver is totally unable to produce factor IX, well, their classical treatment has been replacement therapy by regular intravenous infusions of factor IX and major advances have been made, but not everyone is able to do that. The good news for hemophilia B, which is much less common, is that factor IX gene is much smaller. Also, this protein is typically produced by hepatocytes. So that makes gene therapy of hemophilia B quite attractive. It was easier, probably compared to hemophilia A, to package the hemophilia B gene in the viral vector, which was also an AAV, and to target the cells that physiologically do produce factor IX. So there has been a good trial, very nice and large trial recently conducted in more than 50 patients. Yourself, Miguel, myself, we had a few patients in that fascinating trial that showed that nearly all patients had a very good response, considering that their factor IX, which in the absence of treatment was zero, well, was now around 20-30% in most of the patients with a major impact on their bleeding phenotype, the number of bleeds. And also for most of these patients, factor IX injections were no longer required.

Also, we know that, that's nice, how you can use recent development in genetics. It was found a few years ago in Italy, in the city of Padua. There was a family who had very high factor IX levels and these people have thrombosis. And a point mutation was identified. We call it factor IX Padua. And we are now valuing this sort of thrombophilia and gene therapy. So we are now using this mutation to increase the potency of this factor IX. So this is really nice. And also the tolerance of the treatment was good. I need to emphasise that well, since both of these factor IX and factor VII gene therapies, we use AAV vectors. Well, it's a little bit challenging because if antibodies, pre-existing antibodies to these viruses that are quite common in our environment, so they cannot always be treated. And that was certainly true for hemophilia A. For hemophilia B, by contrast, it was possible to treat patients who had pre-existing antibodies against AAV, clearly showing that this is a complex technology and that we need to consider each disease separately. But maybe Miguel, since both of us, we have been quite active in this trial, it could be nice to share with our colleagues here what was our real-life experience with gene therapy in the few patients who could be enrolled in our centres?

**Prof. Dr Miguel Escobar**
Yes, this is a very important point because as you mentioned, we do have other therapies as well, and we do participate or have patients that participate in other clinical trials. But specifically for gene therapy, I think it's been a very interesting journey because it has really changed the life of these patients. It's just interesting to see that with a single infusion, these individuals are able to stop prophylaxis and pretty much stop worrying about what their levels really are: if they're high, if they're low, and they can go on with their life. It's important to, when we started this trial, it's really to have a lot of discussions with the patient or with the family, with the caregivers about really what this meant, because it is certainly a single infusion and when it's given there is really no reverse in this type of therapy. But as was explained here in the clinical trials, all these patients have done

extremely well in regard to decreasing the amount of bleeding and definitely decreasing the amount of product that they're using for the management of their hemophilia. I think it's important to definitely involve our patients. This is a shared decision making when it comes to use a therapy like this, like gene therapy. It's very important to do that. And I'm sure you have the same experience with your population.

**Prof. Dr Cédric Hermans**
Well, certainly, and I would like to emphasise that although this is a treatment which is given as a single infusion, it's a major process because you need to inform the patients, the patient has to be well educated, understand what it is about, give an informed consent. And then, depending on the type of hemophilia and the study protocol, some patients will not have access to the treatment in spite of a great enthusiasm because their neutralising antibodies. And then let's be honest and fully transparent. Although this treatment works, there is a lot of variability in terms of response. So you do not know what level of correction the patients will achieve in the short term, in the long term. There are still some uncertainties regarding the duration. So I think this is a very interesting process, but there are still a lot of unknowns, uncertainties, and we need to make sure that our patients and the entire community is fully aware of this. And this is certainly clear for hemophilia, but this is also clear for other therapeutic areas, but it's clearly a fascinating treatment. And I'll never forget one of my patients who in fact told me, Dr I now have two dates of birth, the real one and the second one, when I came to your hospital on a day in November four years ago, and when I received that infusion of billions of vectors containing the factor IX gene, that changed my life. So that guy has had a new start in his life. And honestly, this is so stimulating for him, for the whole multidisciplinary team, my centre, and the entire community. Have you had similar positive experience, Miguel?

**Prof. Dr Miguel Escobar**
Absolutely. I mean, I remember I have a patient that actually participated in a previous trial, and he's now eight years out from his only single infusion of a factor IX as well. And he hasn't infused in eight years. And every time I see him, he is the most thankful person that I've seen because, again, it really changed his life. This is a patient that was infusing twice a week of factor IX for prophylaxis. And again, he hasn't infused in eight years and still making very good amount of factor IX and has not required a single infusion. So it could definitely change the life of our patients.

**Prof. Dr Cédric Hermans**
Yes. I need to emphasise one of the limitations that currently gene therapy has not been validated in children, and the reason for that is that we have alternative treatment in children. It's clear that trials will be conducted in much younger patients in the future. But let's be well aware that for many other rare diseases, the priority will be children, because clearly for many genetic diseases where there is no treatment, well, clearly gene therapy would be lifesaving. So in other therapeutic areas, the priority will be given to children. Make sure that we provide these children with early correction of their genetic disease so that they can at least survive and then have a normal life. But again, this is a new therapeutic area, but I'm sure that many of our colleagues listening to us are waiting for this new gene therapy options.

So while I think it's nearly time to conclude and maybe come with some important messages that we would like to share with us. Well, most of the time I compare gene therapy in 2023 with travelling to the moon. So the beauty of the science, recent science has shown us that it's possible to perform gene therapy. If we take the example of hemophilia, but also other rare diseases, it's possible to achieve it. So we are able to overcome many of the challenges of gene therapy, and this is a major success. This is nice, but let's be honest. I think that in the field of hemophilia, there have been approximately 400 patients who have access to gene therapy. So it's just the beginning. It's unlikely that all of us will spend our next holiday on the moon. Maybe in the future, but for the time being, it's a little premature, but we know that we can do it. And I think this is the most important message. So we need to continue our efforts in as many as possible therapeutic areas. Would you share my view, Miguel?

**Prof. Dr Miguel Escobar**
Yes absolutely. I think that right now technology is moving very fast, and we are going to have many more clinical trials. We're starting to open other trials with maybe similar technology, but I think this is the future of the treatment of all these inherited diseases.

**Prof. Dr Cédric Hermans**
Yes and it's very likely that, well, techniques will evolve. There are plenty of ways to modify the gene. I think it's just the beginning of the success. And both of us, we have a major interest for people who live in low-income countries where limited access to treatment and care. And both of us, we also have the ambition that gene therapy could provide as many as possible patients with rare diseases, genetic diseases globally with a change of treatment and cure. Don't you agree with me?

**Prof. Dr Miguel Escobar**
Absolutely. That will be the ideal to be able to provide something like gene therapy or similar technology worldwide where we don't have to be worrying about anymore the utilisation of factor or the cost of factor with a single infusion that could last for years. Or I guess potentially even a cure, we don't know that yet, could certainly make a big difference for all these populations.

**Prof. Dr Cédric Hermans**
I think we both share the same enthusiasm for the future.

**Dr. ir. Tonke L. de Jong**
Thank you both for sharing your views on the principles of gene therapy for rare diseases. We've learned a lot about gene therapy in general from this discussion, and it was very insightful to hear about your experiences with the implementation of gene therapy for hemophilia. I'm wondering, what would be your main clinical takeaway for our listeners, Professor Escobar?

**Prof. Dr Miguel Escobar**
I can say that gene therapy and gene-modified cell therapies offer the potential to help patients with rare diseases to cure or improve the quality of their lives. Also, implementation

of gene therapy is expected to become a multidisciplinary approach with the patient being central.

**Dr. ir. Tonke L. de Jong**
Yes I understand. Would you have anything to add to these messages, Professor Hermans?

**Prof. Dr Cédric Hermans**
Well, as we shared with you, gene therapy will probably become a major treatment approach for many rare diseases in the near and late future. So clearly, all of you, physicians, but all your teams, well you should learn about it, you should invite colleagues to listen to us, learn more about gene therapy, because you need to get ready for the journey of gene therapy.

**Dr. ir. Tonke L. de Jong**
Thanks. That's a very clear message. We need to get ready! Thank you again. We're excited to find out what the future of gene therapy for rare diseases will bring.

**Prof. Dr Cédric Hermans**
Thank you.

**Prof. Dr Miguel Escobar**
Thank you. It was really a pleasure recording this episode. And just to remind our listeners, we have developed a flashcard with suggested further readings for your interest.

**Dr. ir. Tonke L. de Jong**
As Professor Escobar just said, if you like this episode and want to find out more about gene therapy and gene modified cell therapies for rare diseases, then please download the flashcard that comes with this podcast episode. You can find this flashcard by visiting COR2ED.com and selecting rare diseases and podcast. Also, don't forget to rate this episode on your preferred podcast platform, subscribe to the channel or inform your colleagues about it. Thank you for listening and see you next time. This podcast is an initiative of COR2ED and developed by the experts. The views expressed are the personal opinions of the experts. They do not necessarily represent the views of the experts' organisations. For expert disclosures on any conflict of interest, please visit the COR2ED website.