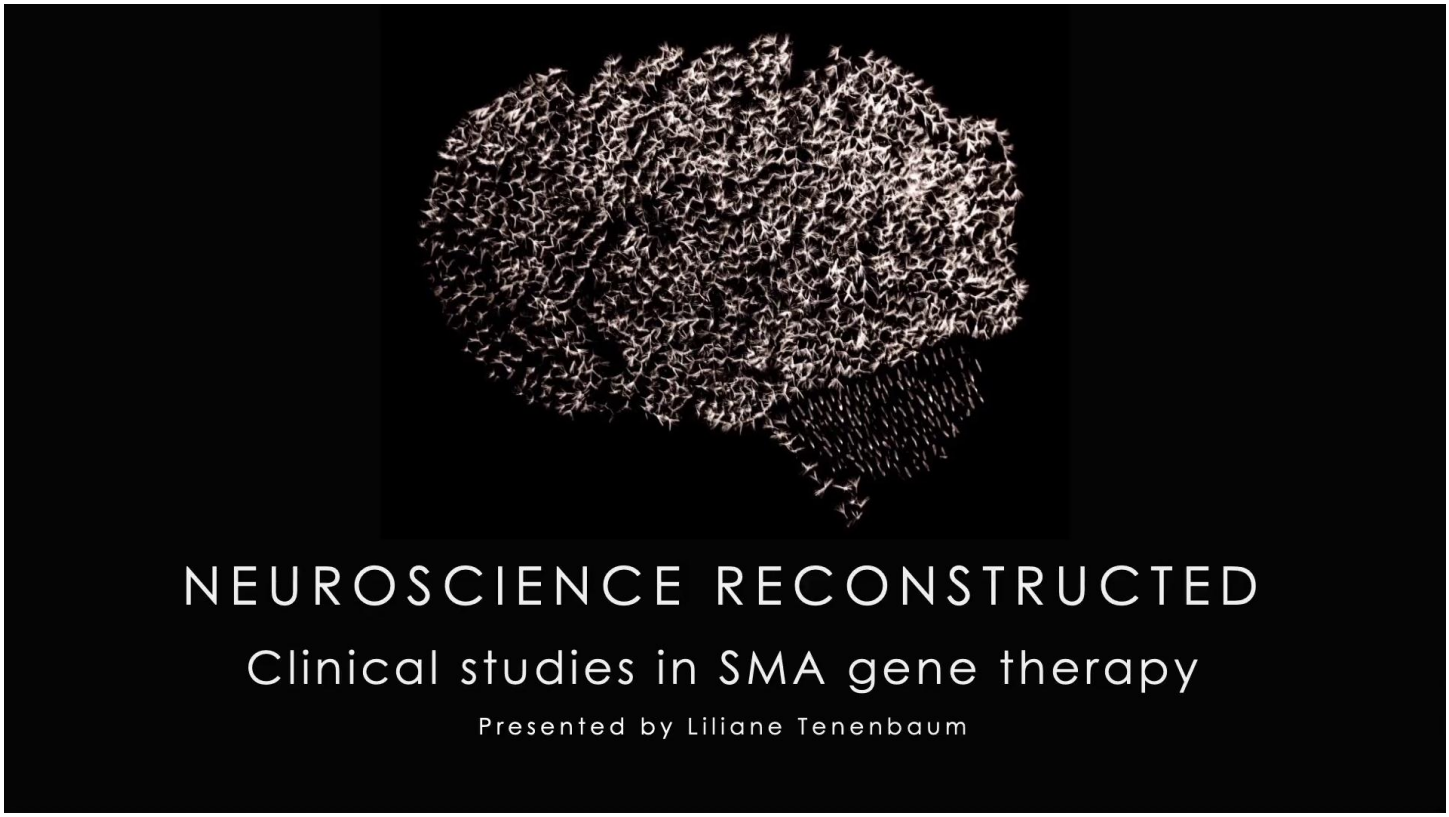


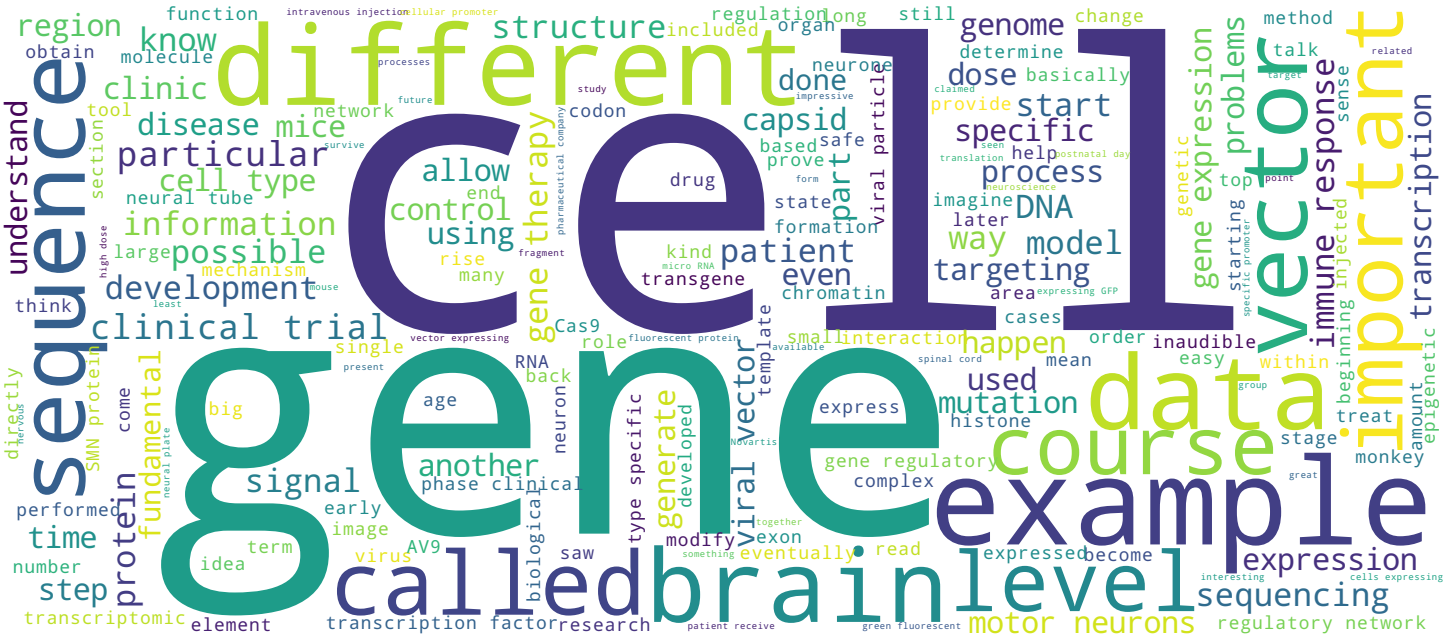


EPFL

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Video

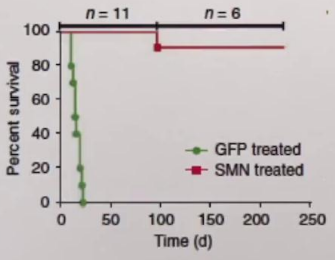
# SMA type 1: preclinical

**Preclinical demonstration of potency in mice**

Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of *SMN*

- Mice SMA type 1 model: SMN1 (-/-), SMN2+/+,
- Vector: AAV2/9-CBA-SMN,
- Intravenous injection

Improved survival:




Age of treatment matters:

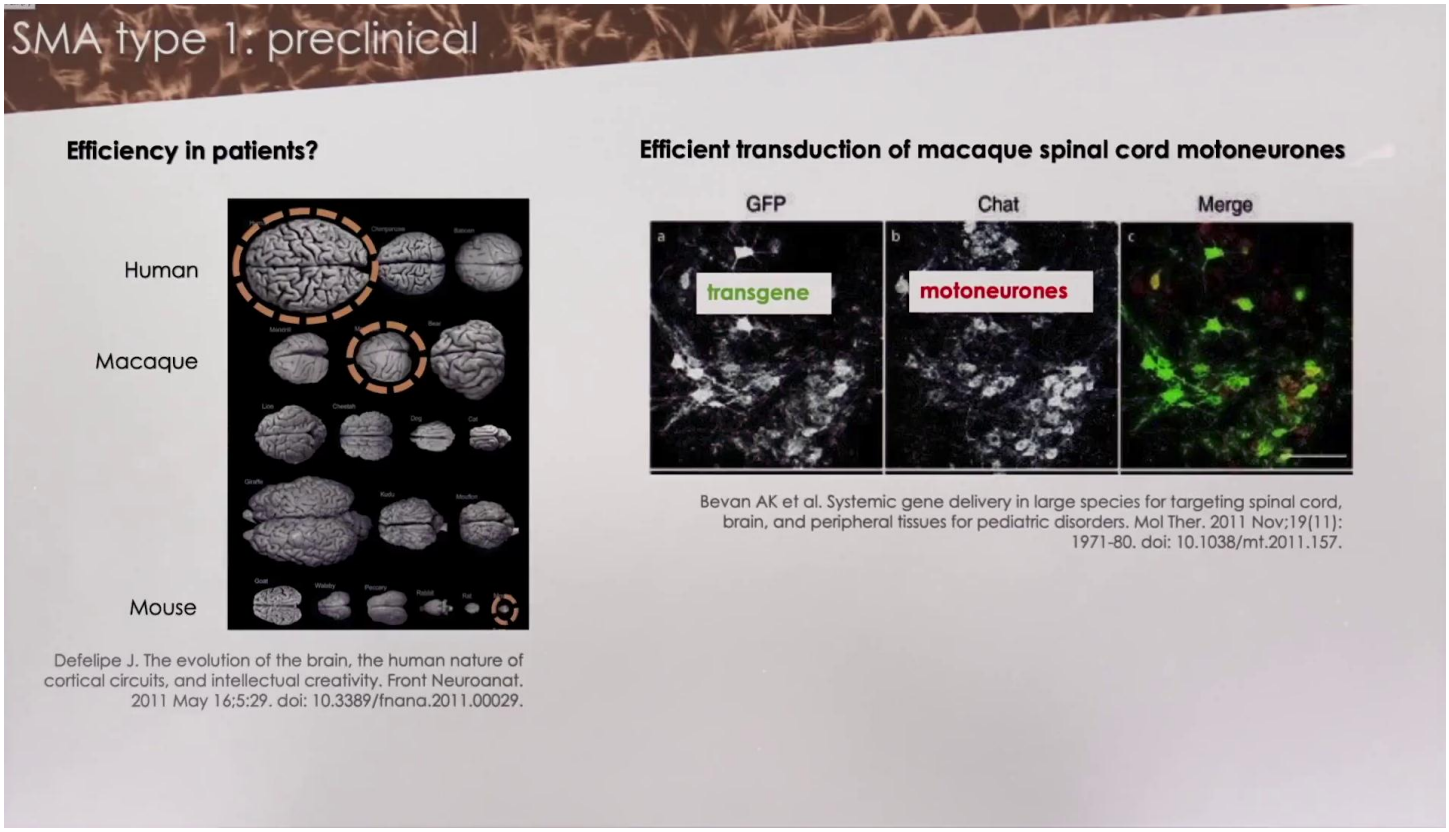

Foust KD et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. Nat Biotechnol. 2010 Mar;28(3):271-4. doi: 10.1038/nbt.1610

First you have to demonstrate that your therapy works and this is performed in rodents. In case of genetic diseases, we have a nice tool with mice. You know that mice can be made transgenic. We have a mice model in which the SMN1 gene is deleted, which has an SMN2 copy. The vector is going to be an AV9 with this ITR from AV2 and a capsid from AV9. The promoter used was a very strong promoter derived from the chicken beta-actin promoter to which a viral enhancer has been added. This is considered as the strongest promoter in gene therapy. The injection was intravenous. The results of this pre-clinical trial was that the vector containing the SMN gene allowed the mice to survive for a very long time. Whereas when they were injected with a vector expressing green fluorescent protein, which is just a marker gene, they die within a few weeks Interestingly, the age of treatment matter. If you treat the mice at postnatal day 2, so very early, they survive very well. If you treat them later, at postnatal day 10, there is no benefit. You can understand that since the SMN mutation has impact on the development of motor neurons, at a certain point, it will be too late to provide the SMN protein to revert phenotype.

Notes

Summary

0m 06s

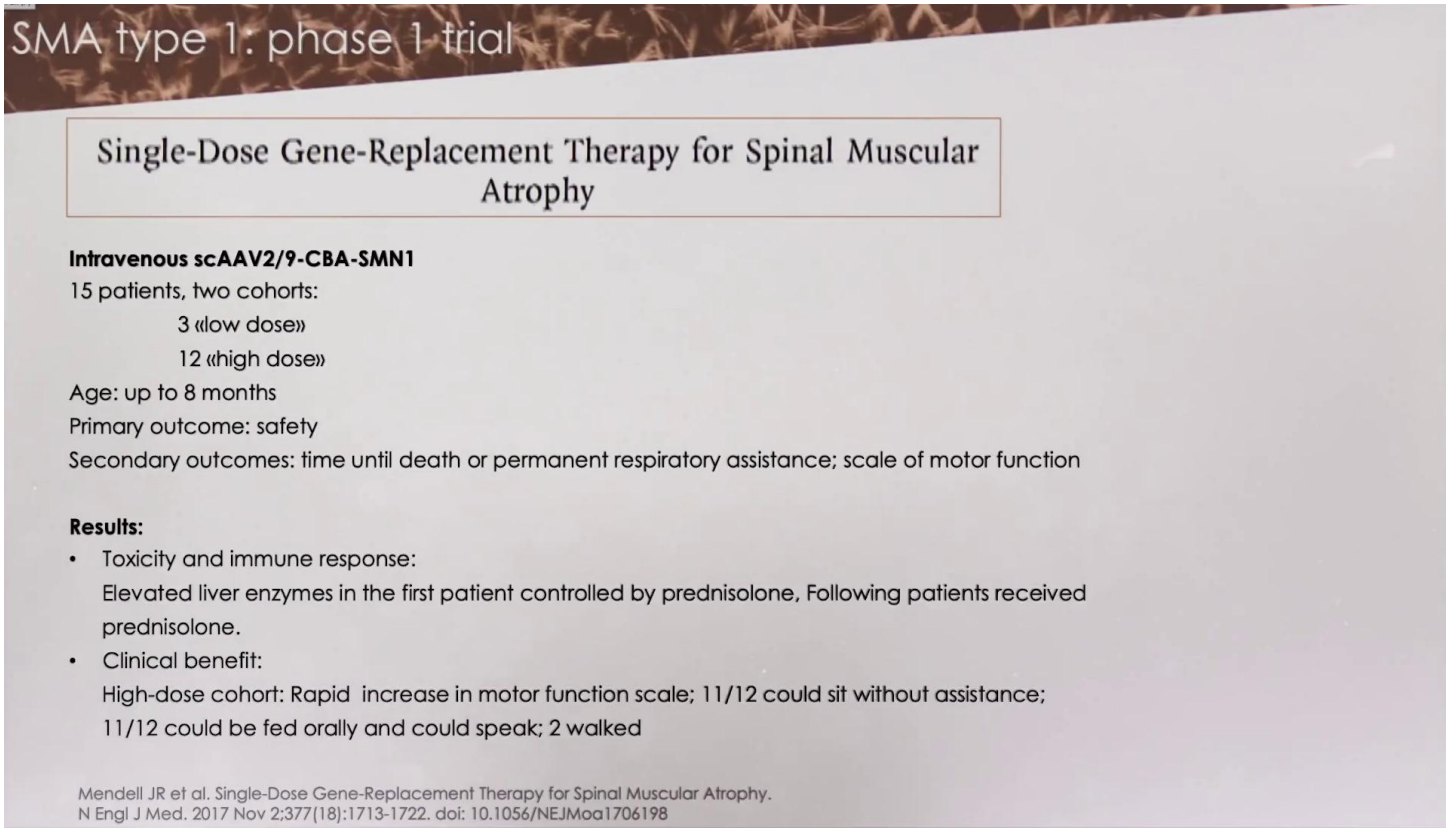



Now, we face a very big problem with the efficiency of the vectors. Most of these preclinical model are first performed in mouse or in rats. As you see, as compared to a human brain, the brain of a mice is really very small. Before going to the clinics, you have to prove that your therapy is working in a large animal. This is usually done in monkey. But unfortunately, we don't have a SMA model in monkey. Nevertheless, what could be done is at least to prove that the vector is efficiently transducing the motor neurons in monkey. This is what they did. They injected the vector expressing GFP intravenously to monkeys. Here you see section of the spinal cord where you can see cells expressing GFP, which is a green fluorescent protein, and cells expressing a marker of a motor neurone, which is this chat. You see that many cells are both green and red, meaning that motor neurons have been transduced efficiently.

Notes

Summary

2m 26s

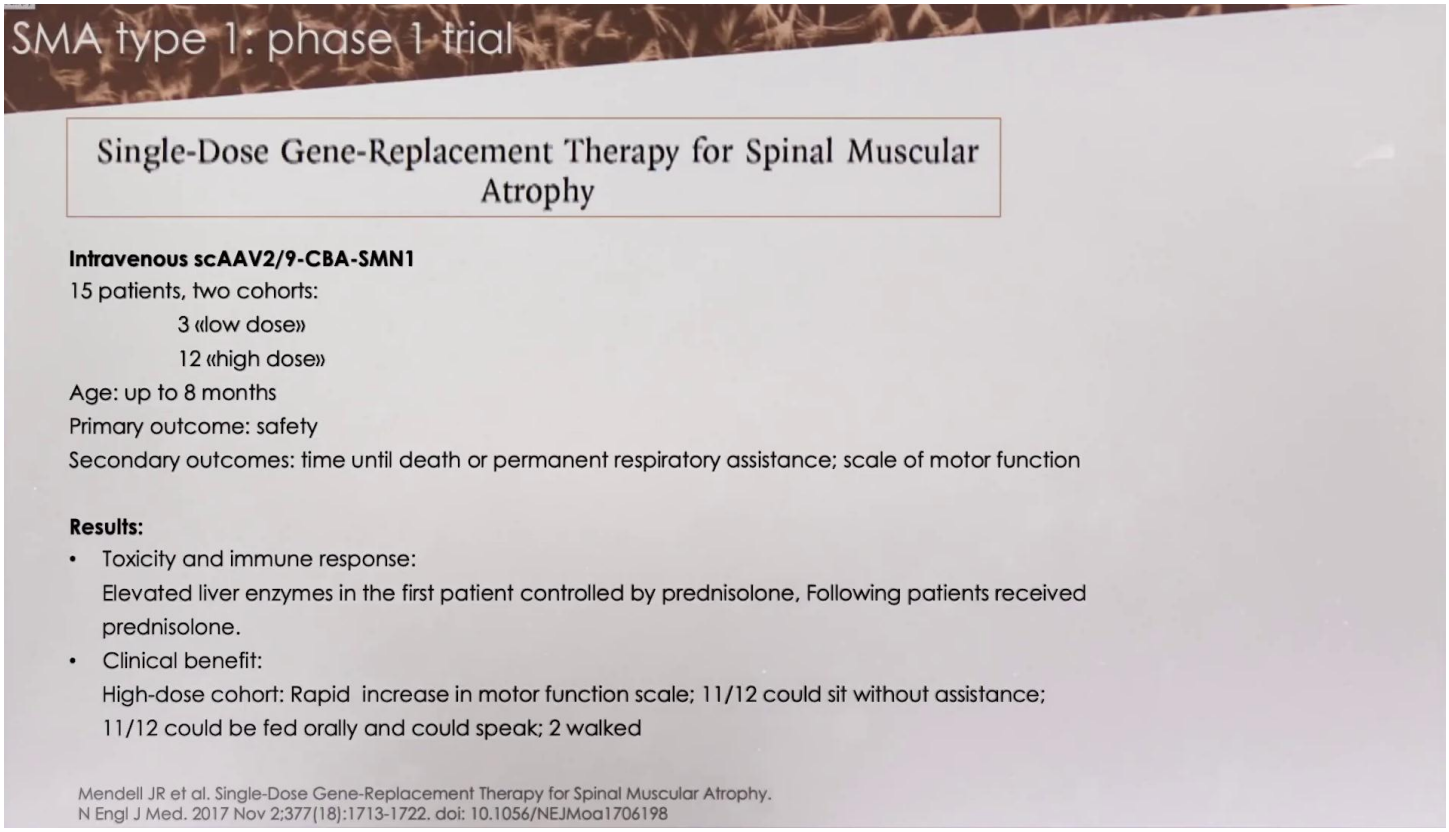



In the first clinical trial, the patient receive one single intravenous injection of the viral vector, but the patient were divided into two groups. The first received a lower dose of vector, and the other group, 12 patients out of 15, received high dose of vector. The patient were included in a very early age before eight months. Of course, since it's a first phase 1 clinical trial, the outcome expected was the safety. But nevertheless, you can imagine that they also looked at the clinical symptoms, the respiratory assistance, and the motor functions. First of all, they evaluated the toxicity and the immune response. In case of immune response, we know from other clinical trials, for example, in hemophiliogen therapy, that it is easy to measure it because the patient have elevated liver enzymes in the blood. This was the case with the first patient and they then gave an immunosuppressant, Prednisolone. Later on, and until now, the patient receive Prednisolone. It was easy to predict it since the vector is injected intravenously, the immune response is efficient much more than if we would inject it directly in the brain. I must say that all the patients that have antibodies against AV9 were not included, but these were really very few.

Notes

Summary

4m 11s




The clinical benefit that cannot be claimed because it's a famous one, but nevertheless was very impressive since 11 children out of the 12... So the 12 that had the high dose could sit without assistance. This has never been seen with untreated patient. Even two of them at the age they should started to walk. This provided a big excitement in gene therapy and was very much published in all kind of media.

Notes

Summary

6m 21s

# SMA type 1: phase 1 trial results

SMA type I babies: cannot sit and need artificial repirators.

AveXis babies: some patients can "breath, swallow, talk, move".

*April 09, 2018:*

**Novartis enters agreement to acquire AveXis Inc. for USD 8.7 bn to transform care in SMA and expand position as a gene therapy and Neuroscience leader**

https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-avexis-inc-usd-87-bn-transform-care-sma-and-expand-position-gene-therapy-and-neuroscience-leader

*To learn more:* https://www.novartis.com/about/innovative-medicines/novartis-pharmaceuticals/novartis-gene-therapies

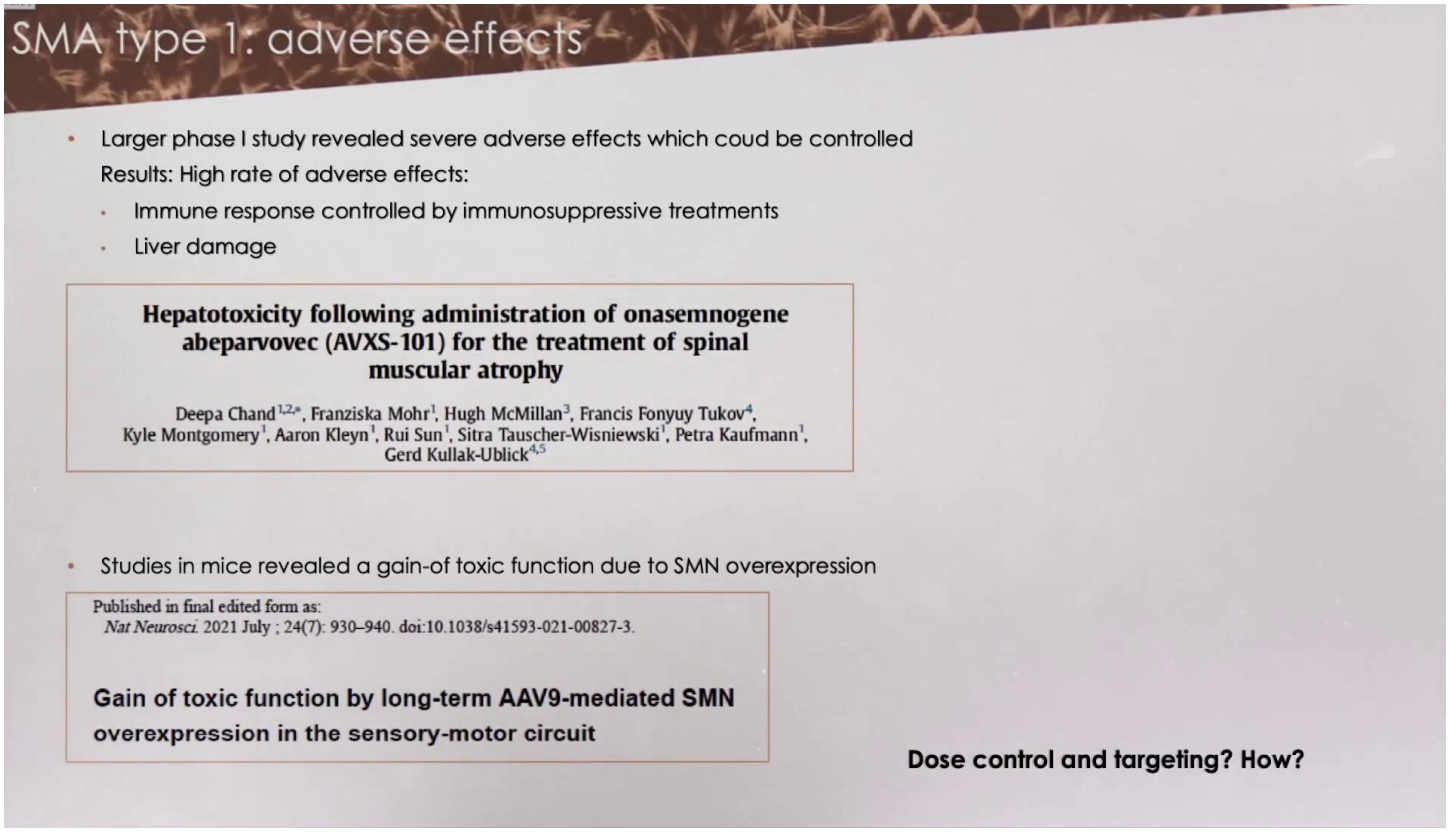
https://www.researchtriangle.org/news/gene-therapy-firm-avexis-to-expand-in-durham-county-adding-200-jobs-and-60-million-in-investment/

These treated babies were named AveXis babies. Why? Because the startup company which developed the vector and did the preclinical test and also the phase 1 clinical trial was AveXis, a small company created by the researcher. Thus, it was so striking to have these very nice results that AveXis was then acquired by a big pharmaceutical company, Novartis. This is very recent in gene therapy that the pharmaceutical company start to be interested in gene therapy. You see the amount of money, 8.7 billion of US dollars is really impressive. But of course, they have the idea to go further than SMA and have a pipeline in neurological disease, thanks to AV gene therapy.

Notes

Summary

7m 03s

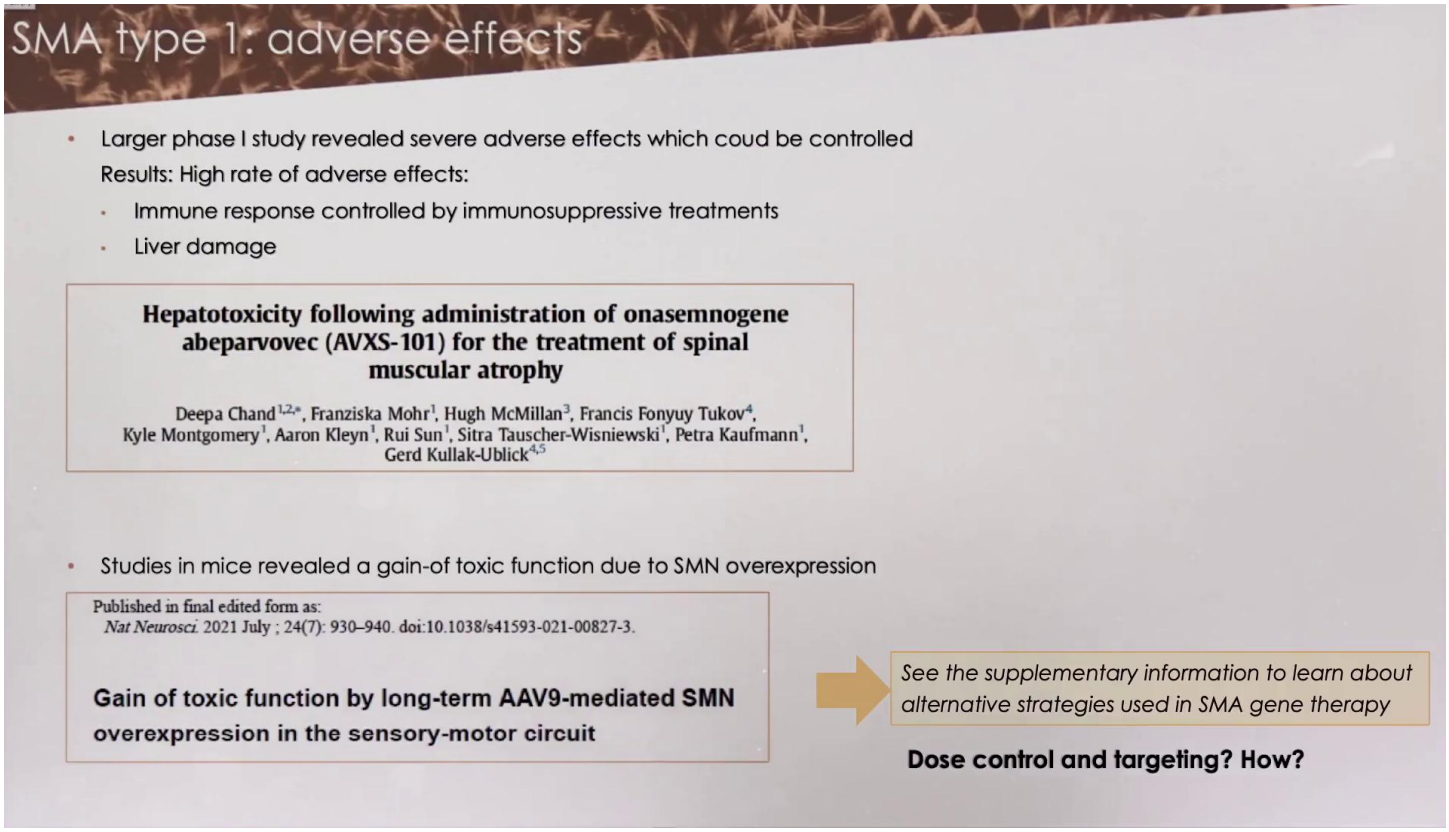



There were several phase 1, 2 clinical trials and finally phase 3, still with intravenous injection and now supported by Novartis. This results start to come out. In some cases, some children nevertheless died since the beginning of this clinical trial, actually one. Now for the first time, we can see in the postmortem tissue, the bio-distribution of the vector. This is claimed by Novartis. I didn't find the image, but this is what they claimed. Concerning the immune response, they control it quite well with immunosuppressant and only 5% of the initially screened patient could not be enrolled because of the immune status. Despite this very promising result, during phase 1 safety trials some problems with this therapy, with these vectors arise. So there is still room for improvement. Indeed, because of the immune response, it can give rise to hepatotoxicity, liver damage. More preclinical studies were done, and some people report toxicity of over-expressed SMN protein, not in motor neurons, but in sensory neurons. For the moment, the dose was as high as possible since we want to reach as much motor neurons as possible. But probably, it has to be taken into account that for some cells, a level of SMN higher than physiological can become toxic.

Notes

Summary

8m 22s

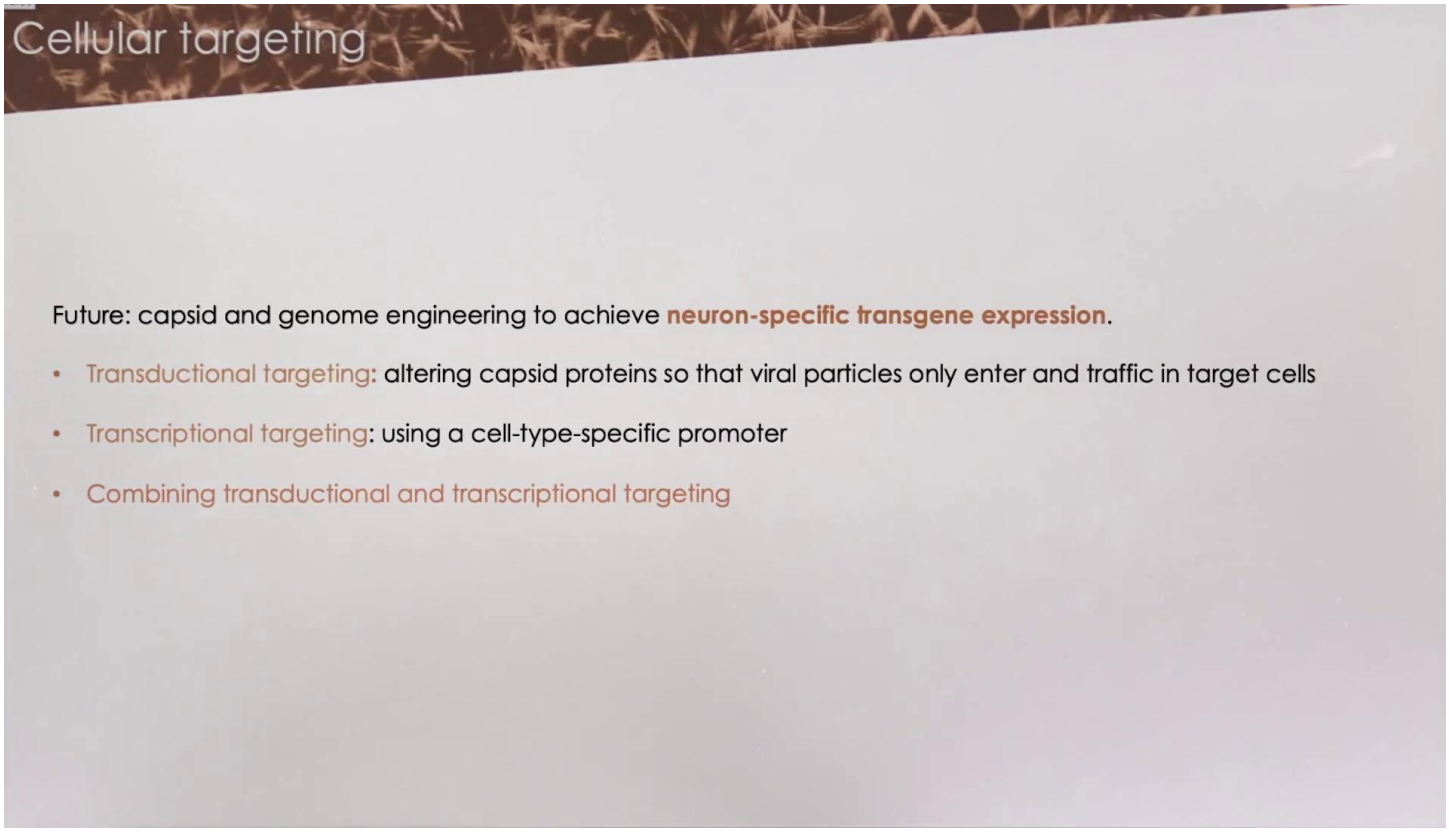



In the future, the dose and also the targeting will have to be more precise. That's why now they are starting to do trials with intrathecal instead of intravenous administration, which already reduces the amount of virus that is going to other organs than the brain.

Notes

Summary

10m 53s

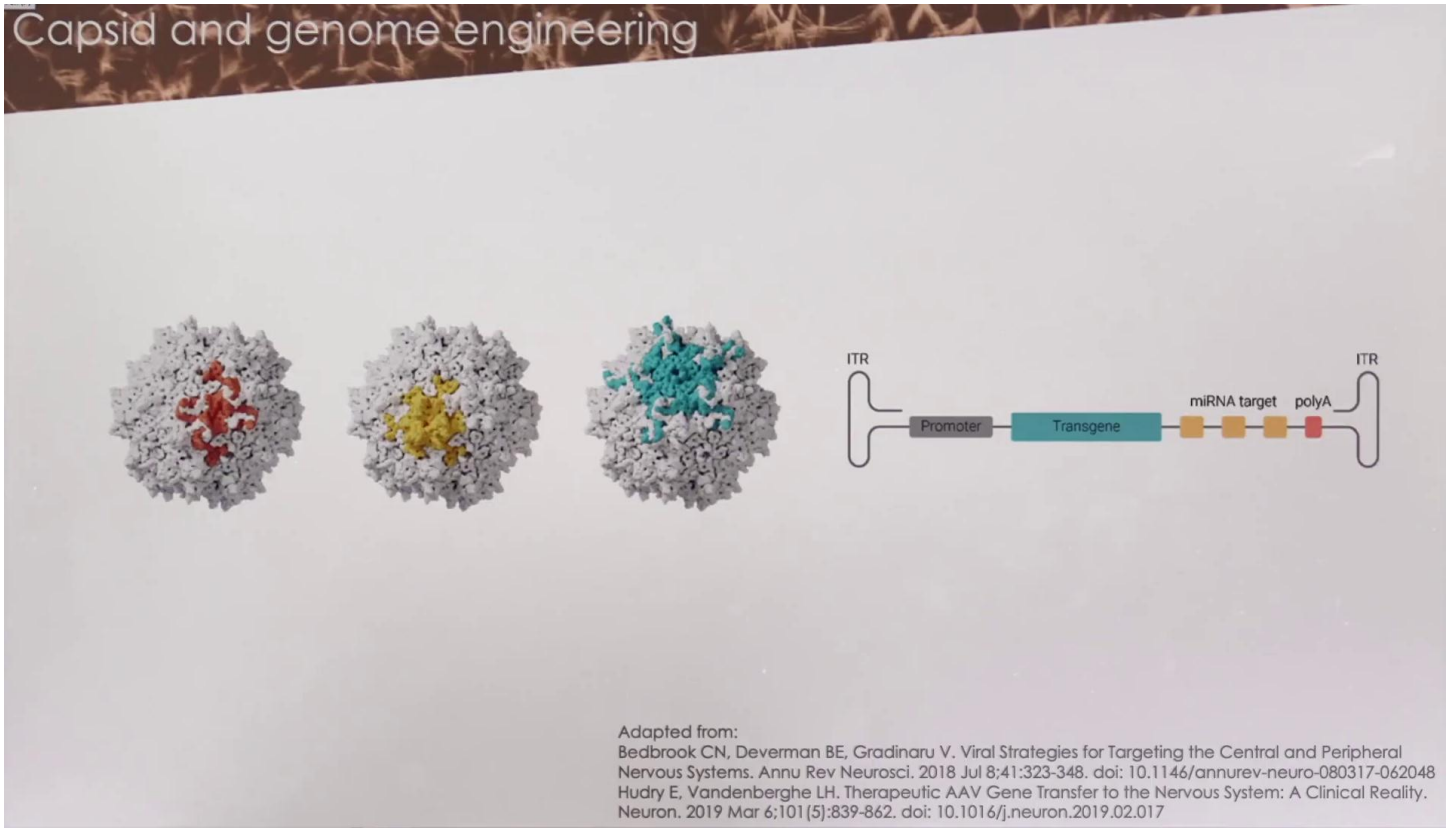



What improvement can still be made? Of course, everybody believes that the dose is important. Like when you give a drug, you have to stay within the curative dose and not higher. Otherwise, you get undesired effect and targeting because not all cells will feel well if you over-express your transgene. Can we better control and target the viral particles? This is a wide field of research. You can control the dose by using an inducible promoter. But then you need a drug to induce the transcription of your transgene, and you have to find drugs that are safe. But you can also modify the capsid of the viral particles, and you can try to find cell type specific promoter. This is also not an easy task because cellular promoter are very large and cannot be introduced into AV or even larger vectors. This, we have to find in the cellular promoter, the elements, the sequences that are necessary and sufficient to obtain a cell-type-specific expression. The future will be to modify the capsid and the regulatory elements and finally obtain a targeting and if possible, also a control of the dose.

Notes

Summary

11m 22s

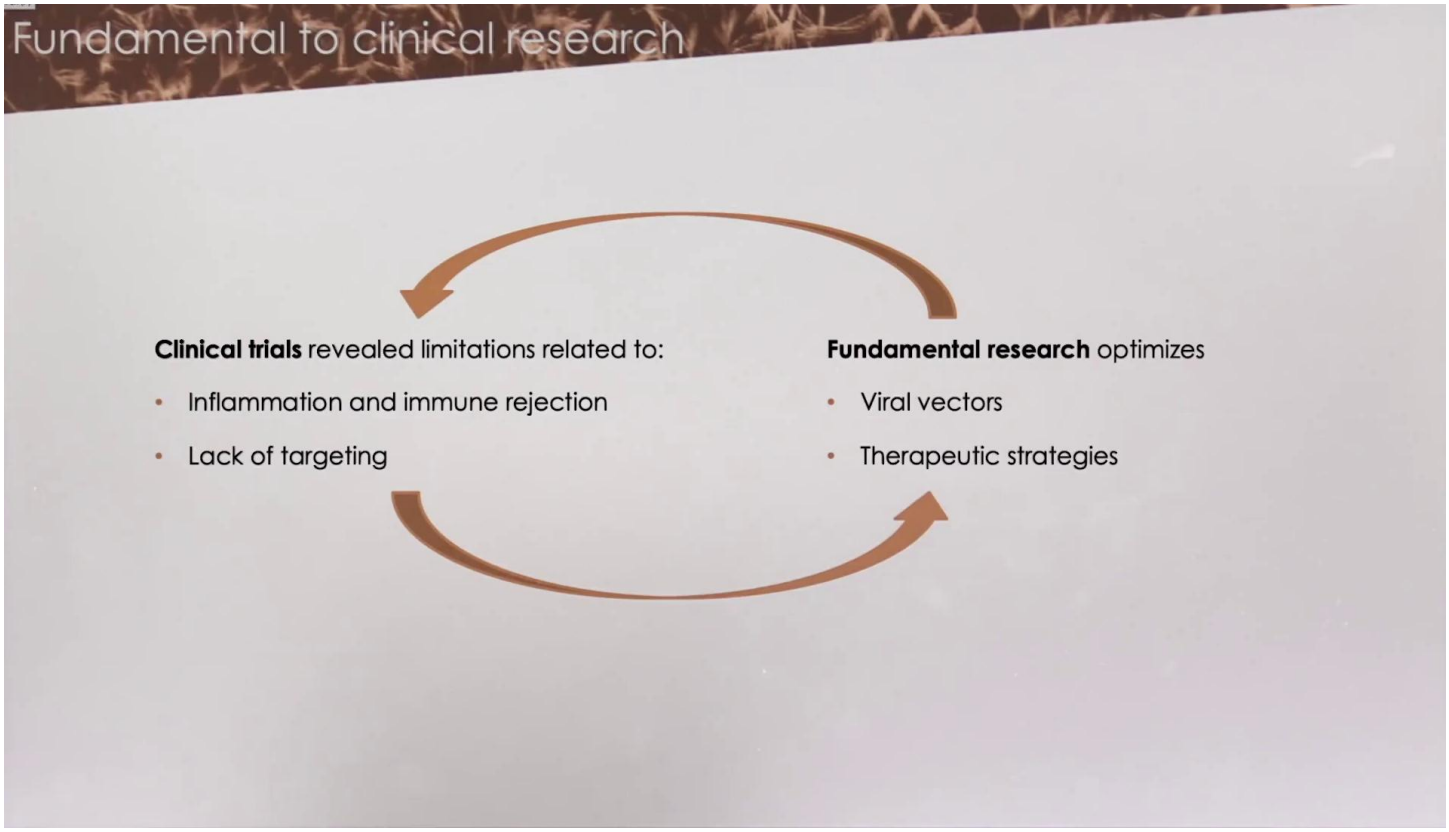



We have now a lot of new tools allowing to do that. The capsids are very well known. They have been characterized using X-ray and cryo electron-microscopy. By introducing mutation and deleting some fragments, we know exactly where are the residues responsible for the attachment to the cell. Similarly, for the regulation of transcription, now with the big amount of transcriptomic and epigenomic data that are available, it's possible to build new cell-type-specific promoter, and even to play with the three prime UTR region which, for example, contains binding site for micro RNAs. Thanks to transcriptomic, we start also to know which micro RNAs are expressed in which cells. There is a big field of research that undoubtedly we'll allow to really refine these tools.

Notes

Summary

13m 27s

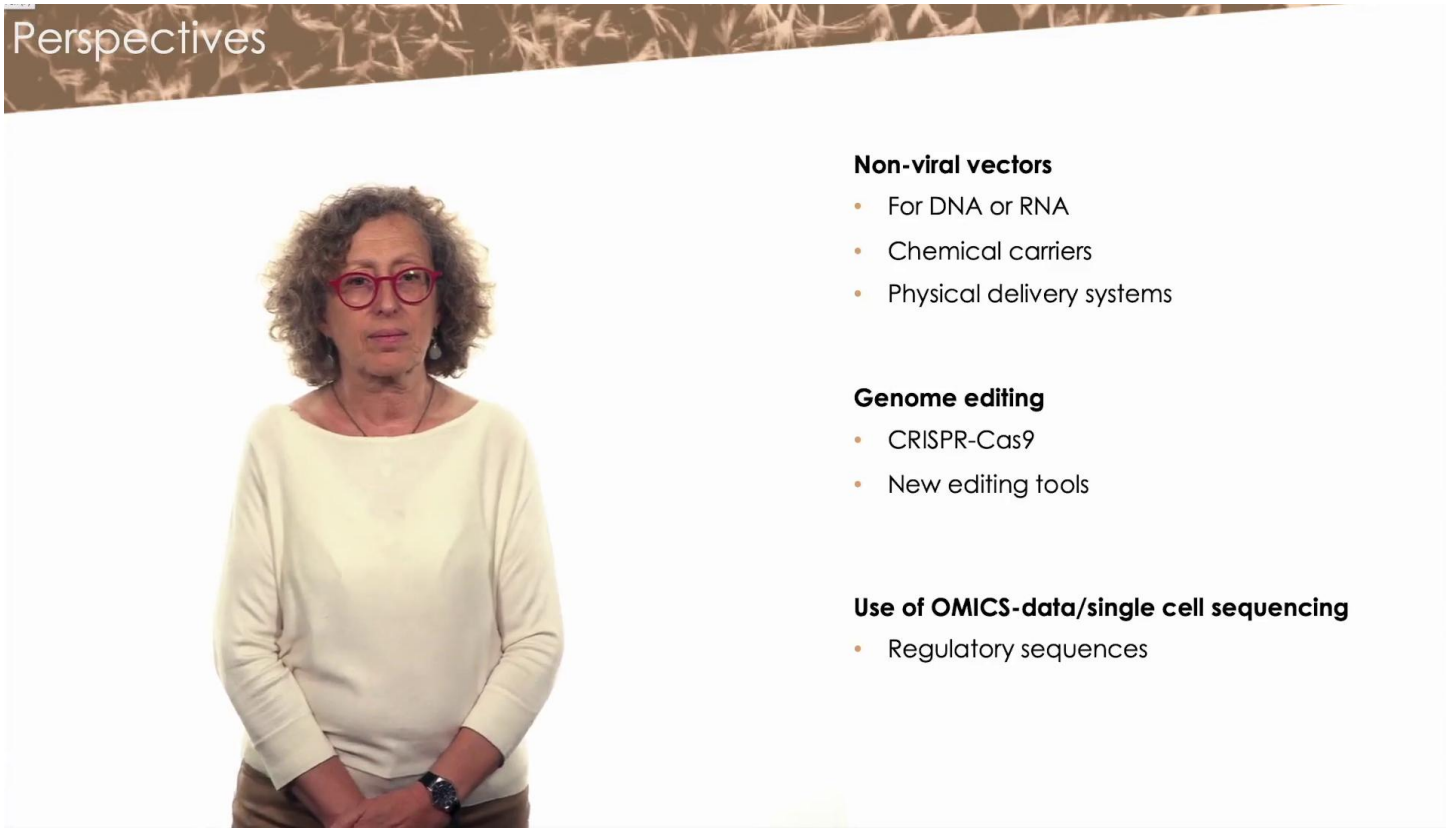



I would like to conclude by emphasizing the dialogue between the clinics and fundamental research is important. Both fields are feeding each other. And you can really see it very well in the gene therapy field where the first vectors when they were tested in the clinics were not optimal, but the problems were often revealed only in clinical trials and not in the animal experiment. Based on this experience, scientists went back to the bench and developed improved viral vector. Few years later, because this development are, as you saw, very long, they can go back to the clinic by reducing the problems that have shown like immune and inflammatory response and the lack of targeting.

Notes

Summary

14m 57s




What are the perspective? Very largely, it would be really great if we could have non-viral vectors, not to have this immune response. It would be great if the genome editing technology could be made efficient and safe. I didn't talk about it, but Cas9 is also a bacterial protein, so there are also problems with the immunogenicity of Cas9. Another problem of Cas9 is that it can do off-target double-strand breaks. This is important to control because it could introduce mutations. Finally, the OMICS data that are constantly being generated will help to define the regulatory sequences that can be used for targeting. We are coming to the end of this course. I would like to thank you very much for your attention.

Notes

Summary

16m 10s