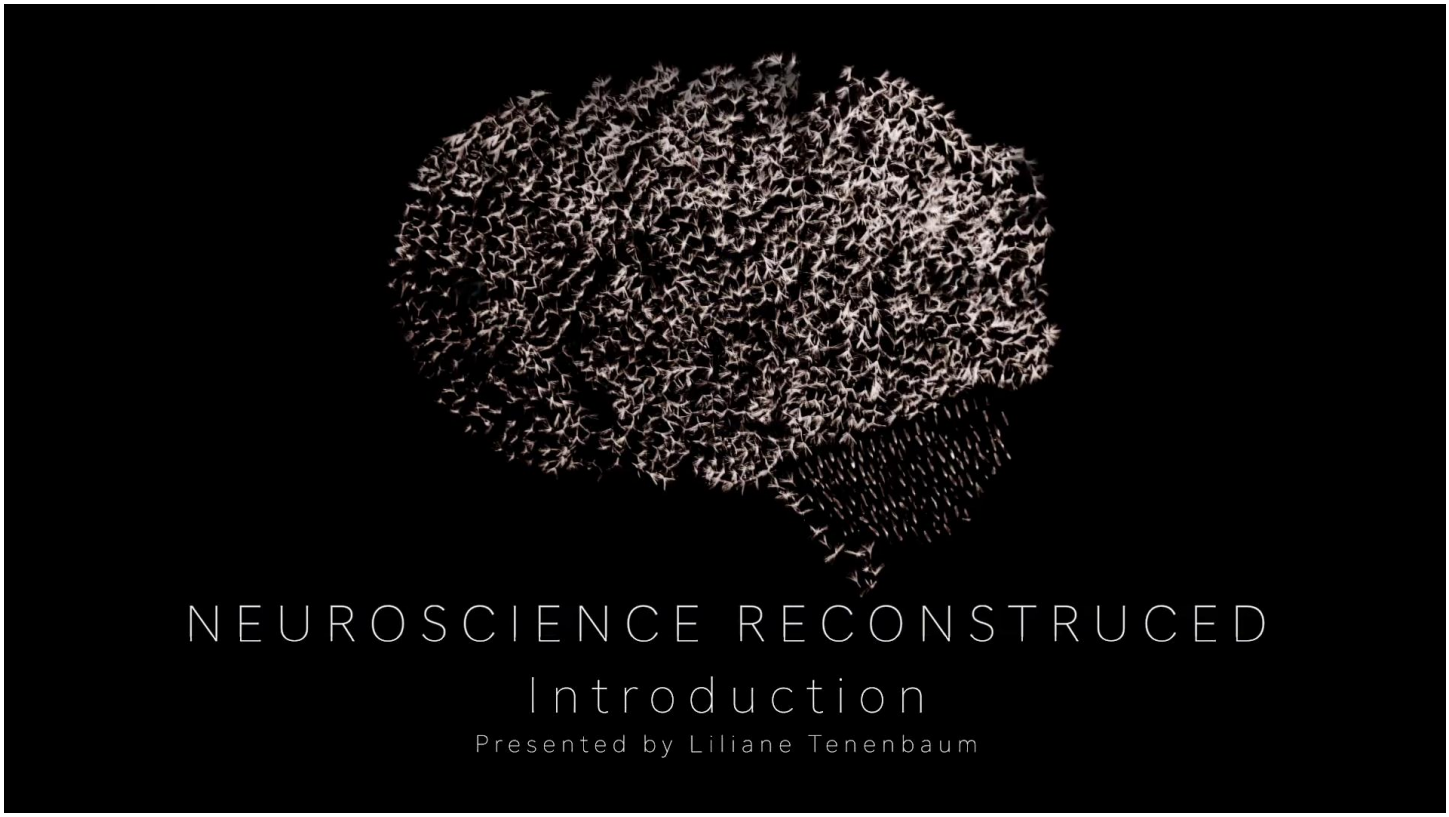
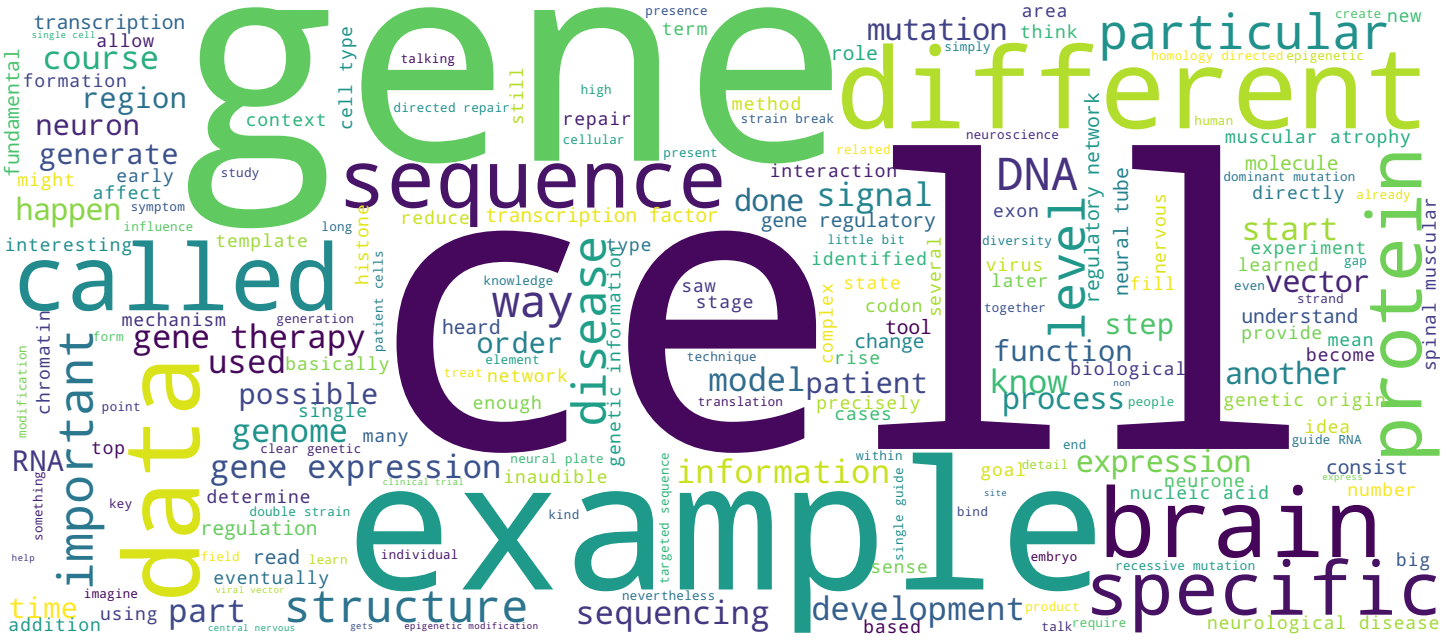




EPFL

Search MOOC

Video

Coming up

Last lectures

- Gene expression and regulation
- Genetic variation, epigenetics
- Methods in neurogenetics
- The birth of the nervous system

Today

- Gene therapy
- Genetic material delivery
- Illustration in the context of spinal muscular atrophy (SMA)

Welcome to this online course on gene therapy in the central nervous system. In the last lectures, you learned a lot about gene expression and regulation. You also learned about genetic variation. You know that not all individuals have different genomes, that they have variants in their genes. You know that epigenetic is also playing an important role in the modulation of gene expression. You have heard about the methodology, the techniques that have been recently developed, which helped a lot to study neurogenetics. Finally you have heard about the development of the nervous system, and this will be also important for this course. Today, we will discuss how all this knowledge has allowed to develop gene therapies. You will learn about the tools that can be used to deliver additional genetic material into patient cells. To make it more concrete, we will illustrate gene therapy and all the necessary developments in the context of genetically inherited disease, which is a spinal muscular atrophy. This is a rare but very severe disease affecting children very early in life.

Notes

Summary

0m 10s

Etiology of neurological diseases

Monogenic diseases; recessive: missing or inactive protein

- Canavan disease
- Mucopolysaccharidosis
- **Spinal Muscular Atrophy**
- ...

Monogenic diseases; dominant: gain of toxic function

- Huntington's disease
- Spinocerebellar ataxia type I
- ...

Multifactorial: genetic and environmental (epigenetic?) components

- Alzheimer's disease
- Parkinson disease
- Amyotrophic lateral sclerosis
- ...

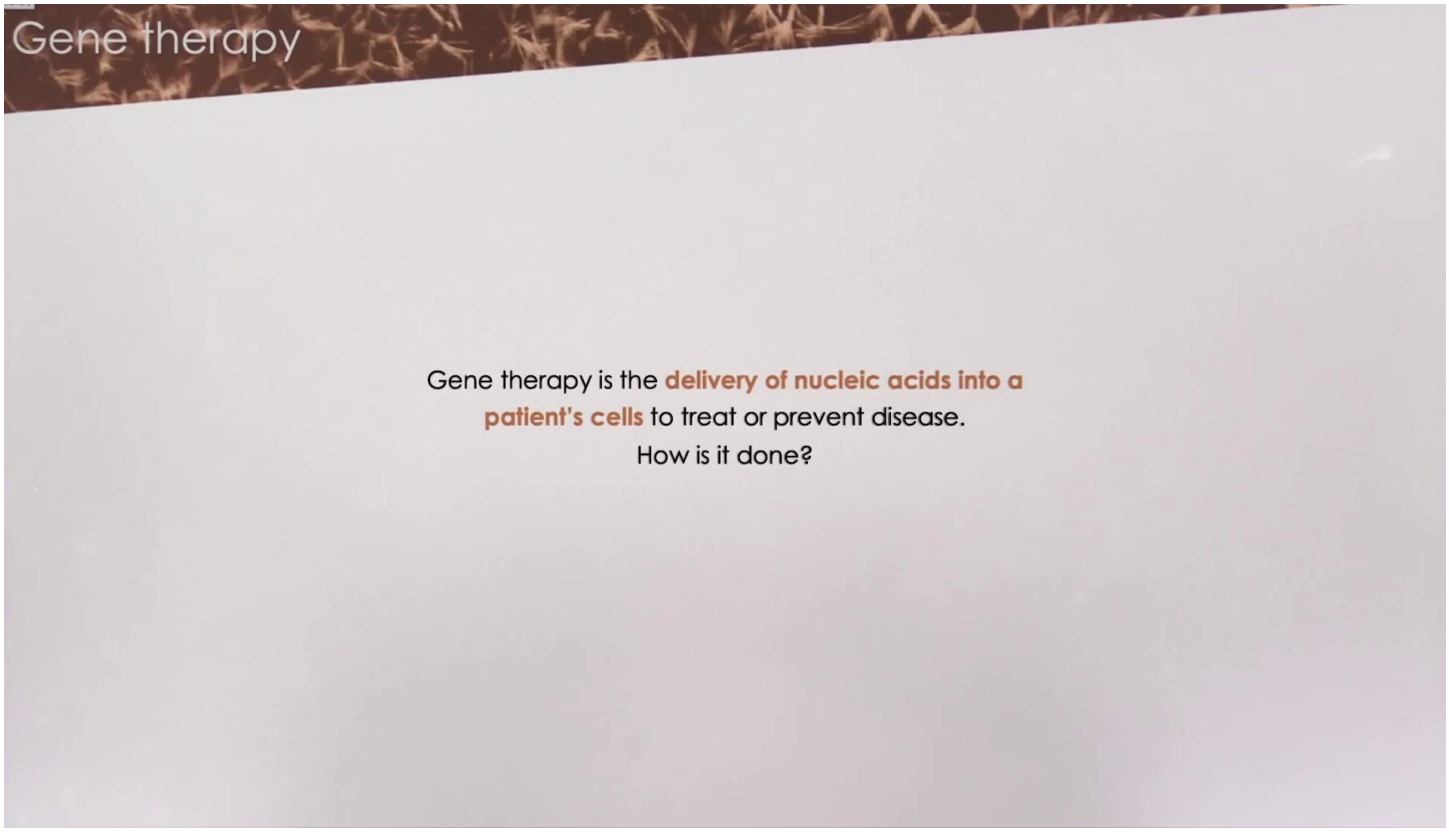
See the supplementary information for more on multifactorial neurological diseases

Neurological diseases comprise both genetic deficiencies that have been identified and diseases for which there is no clear genetic origin. Among the genetic origin, we have monogenic diseases with recessive mutations. These are mutation that inactivate a protein, or also simply the protein could be missing. This is the case of spinal muscular atrophy. But there are several other such diseases like canavan disease, mucopolysaccharides dosis. Among the monogenetic diseases, a part of them are due to a dominant mutation. What is a dominant mutation? It's a gain of a toxic function. The mutated protein is toxic. This is the case of huntington disease and few other diseases, so called Triplet repeat diseases. Actually the main neurological diseases, about which you hear a lot because they are very frequent and affect a lot of people, they are multifactorial disease for which a clear genetic origin has not been identified. Actually, it is believed that these diseases are multifactorial, that might have a genetic factor playing a role, but there are also environmental factor, ageing, and maybe even epigenetic factors. This is the case for Alzheimer's disease and Parkinson's disease, and also for ALS, amyotrophic lateral sclerosis. These diseases are much more complex and they will require more complex approach.

Notes

Summary

2m 00s

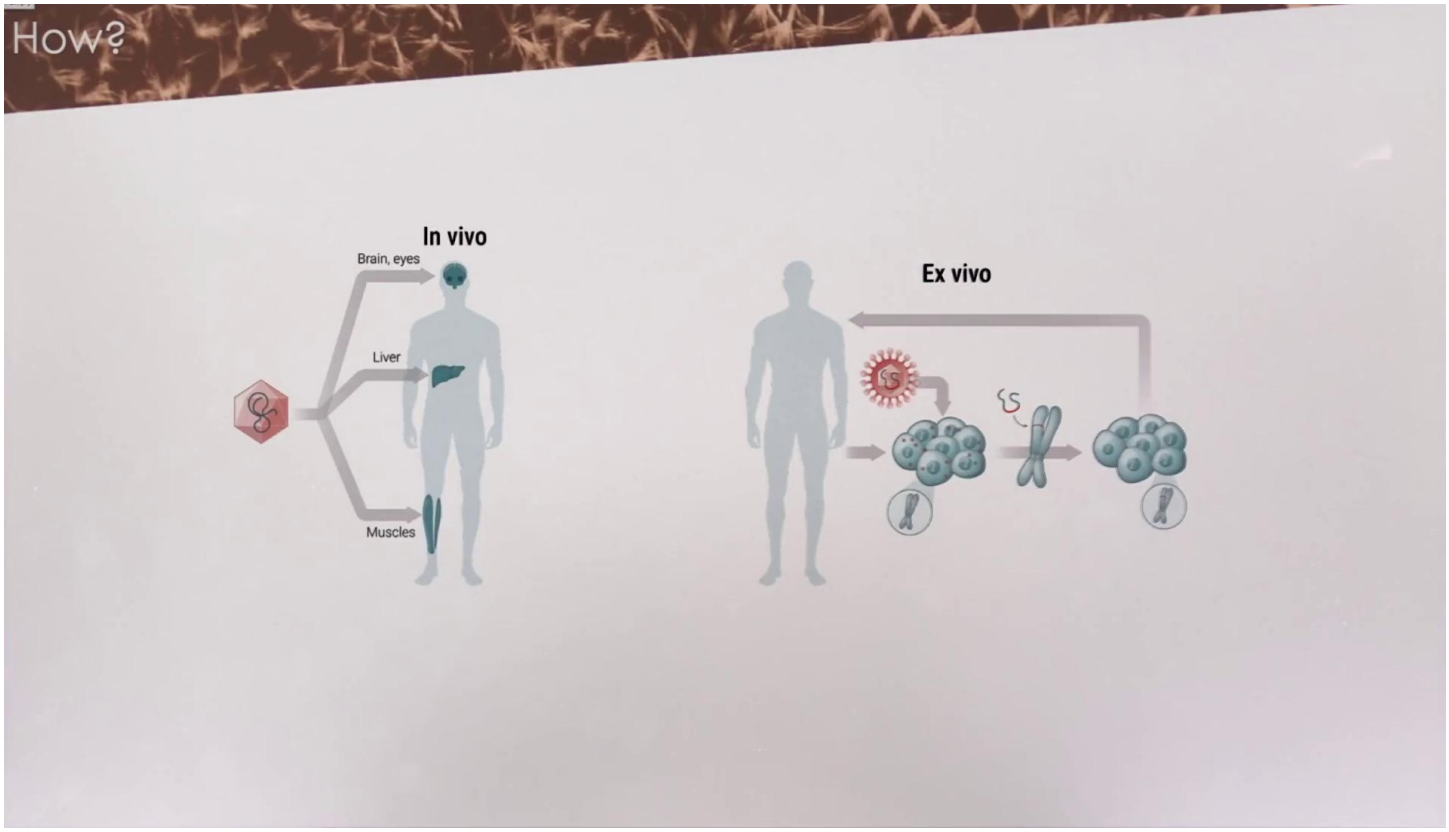


What is gene therapy? We can define it as the delivery of nucleic acid. It can be the DNA or RNA into patient cells with the goal to treat or prevent disease. How can we do that?

Notes

Summary

4m 36s

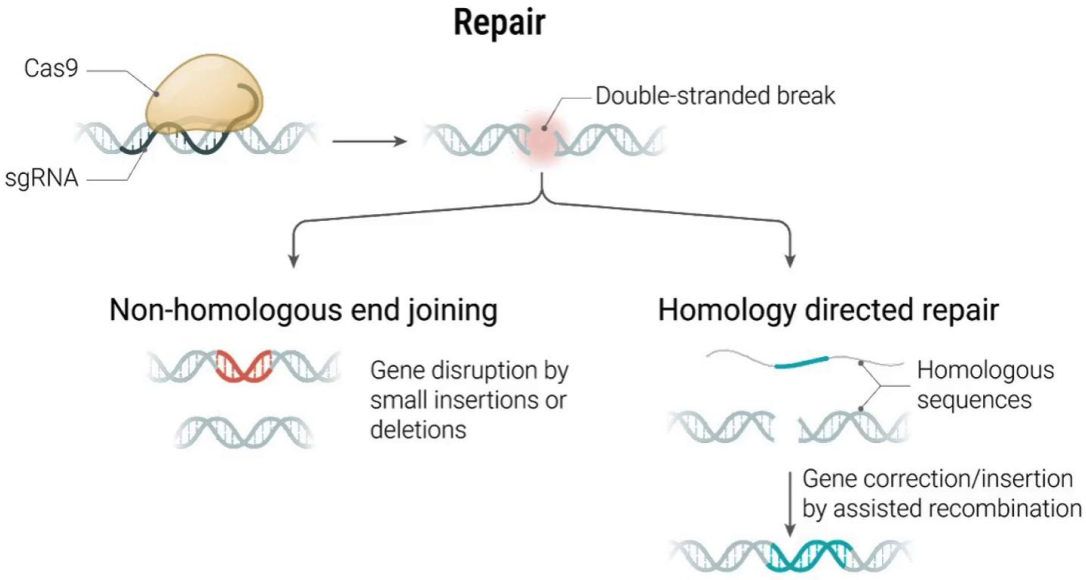


There are globally two way of performing gene therapy. The first one is directly In vivo. We will use a vector, meaning transporter of the genetic information and injecting deliver it directly in the target organ, so in our case, the brain. But we can also do it in what is called an Ex vivo way. This consists of isolating, harvesting cells from the patient, then modify them with a vector. This is done in cell culture in a lab. Then when the cells are genetically modified to have the new desired function, they are re transplanted into the patient.

Notes

Summary

4m 55s

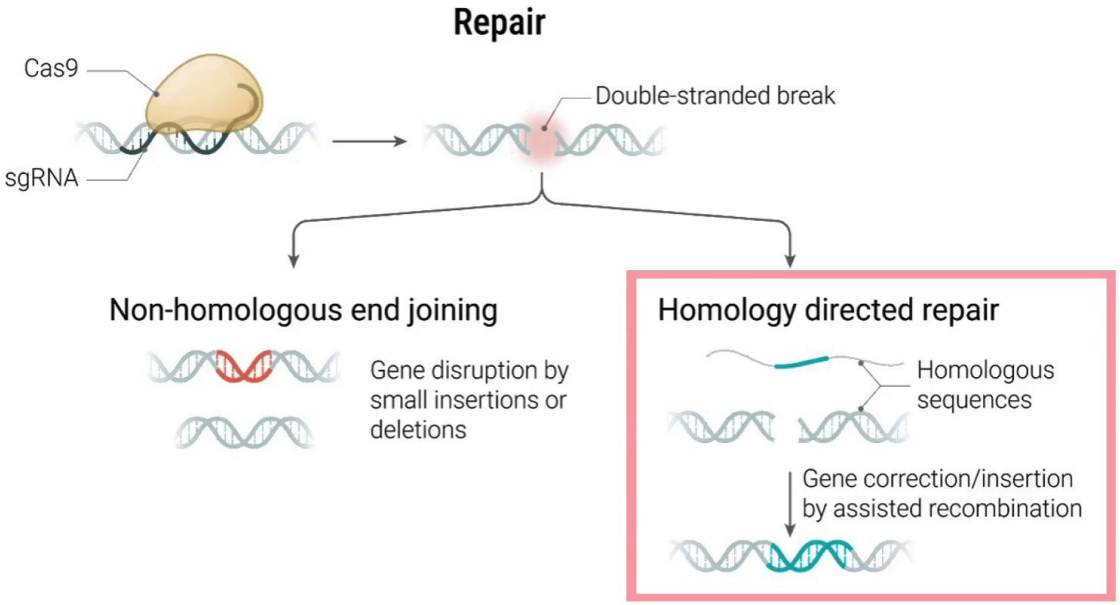


Now, what genetic information are we going to introduce into the cells in order to cure or reduce the symptoms of a disease. We have also several possible strategy. It's possible to replace the gene. This consists in adding a functional copy of a deficient gene. This can be done in case of a recessive mutation that can be complemented by a functional gene. But sometimes it's performed even when there is no mutation in order to obtain a functional impairment. For example, with ageing, some genes are less expressed, and it could be very interesting and important to reinforce some functions like Neuro protection, since we are talking about neurological disease, to reduce the degeneration of neurons. Then the goal of all gene therapist would be to really precisely correct the genome. This is really very attractive, but you will see that it's not that easy. You might all have heard about the CRISPR cas9 bacterial system. You know that a Nobel prize has been given to a French and an American woman for this discovery. It's indeed a breakthrough in the field because now we can dream of repairing mutations directly. This, again, can be done in different ways depending on the goal and on the disease.

Notes

Summary

6m 06s



The system consists of the Cas9 nuclease and of single guide RNA. In the presence of this single guide RNA, which has homology region with the targeted sequence, the Cas9 will make a double strain break into the genome. Then we can do two different things. The easiest way is to let the cell use its own DNA repair system to join this gap to fill the double strain break. The cell will do that efficiently, but not precisely. In this corrected sequence, we will have either small insertion or small deletion, but we will need to sequence the genomes to know what the cells have done. We cannot direct the repair. But nevertheless, you will see in some cases it is enough and it can be used for gene therapy. Now, it's also possible to repair more precisely the mutation using homology directed repair. What is homology directed repair? In addition, in this case, there is a third actor, which is another DNA sequence, also, which homologous parts to the targeted sequence, but containing the corrected mutation. Again, it's the cell which is going to make the job to fill the gap, but in this case, by introducing the perfectly repaired sequence.

Notes

Summary

8m 08s