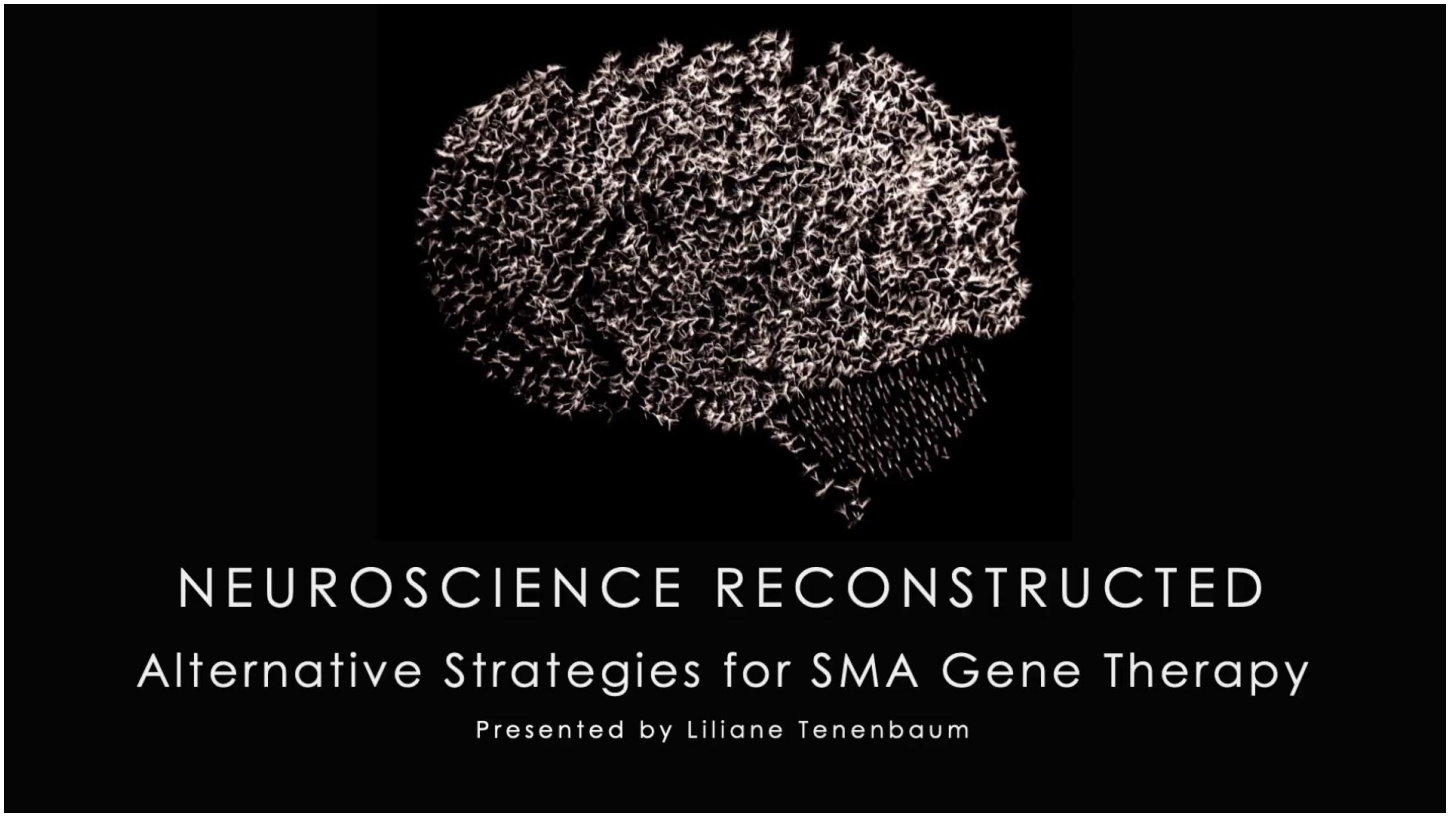
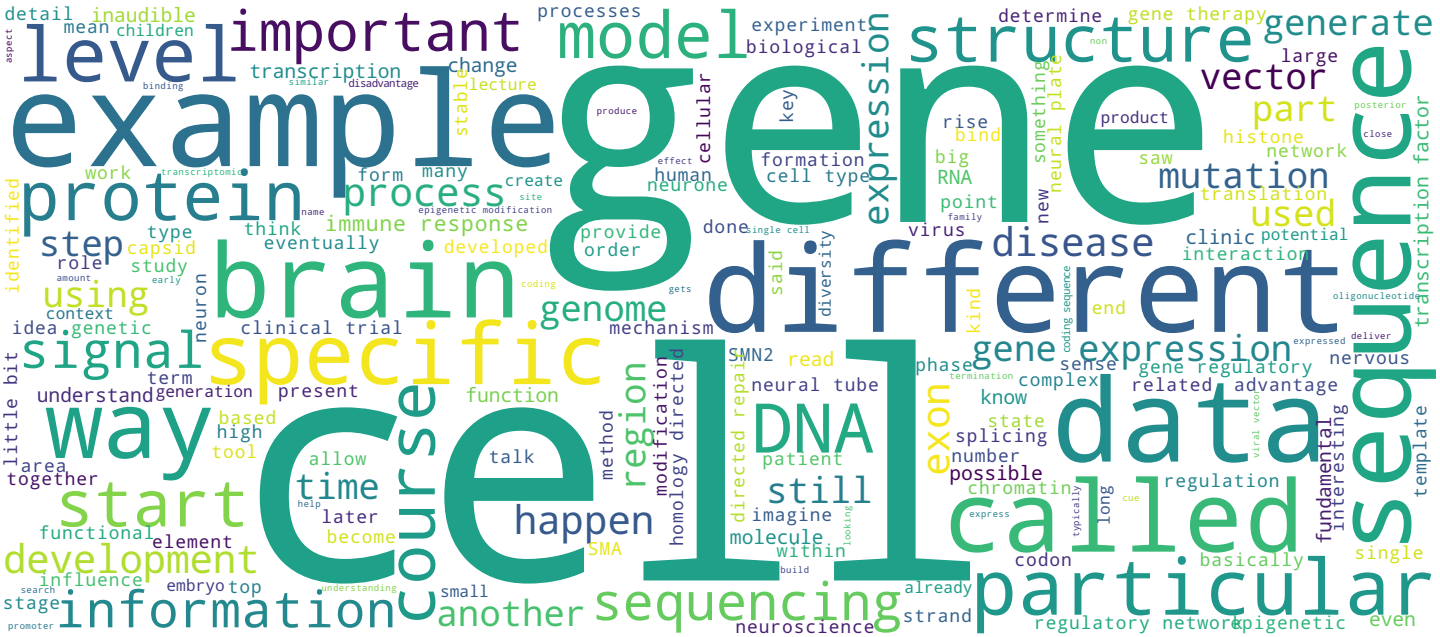




Search MOOC

Video

EPFL

Gene therapy for SMA: strategy 2

Strategy 2a aims to restore normal splicing in SMN2 using antisense oligonucleotides (ASO)

Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy

David R Corey

NATURE NEUROSCIENCE VOLUME 20 | NUMBER 4 | APRIL 2017

Corey DR. Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy. Nat Neurosci. 2017 Apr;20(4):497-499. doi: 10.1038/nn.4508

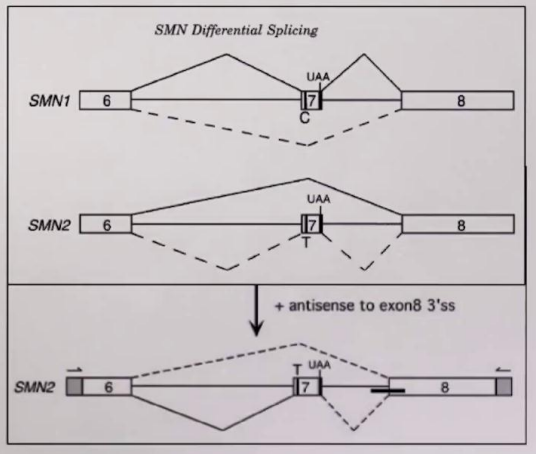
ASOs targeting ISS ("intron splicing silencer") promotes exon 7 inclusion

Advantage:

No viral capsid-related immune response

Disavantage:

Requires repeated intrathecal injections



Lim SR, Hertel KJ. Modulation of survival motor neuron pre-mRNA splicing by inhibition of alternative 3' splice site pairing. J Biol Chem. 2001 Nov 30;276(48):45476-83. doi: 10.1074/jbc.M107632200

Just to mention, other strategies have been developed for gene therapy of SMA one that is in the clinic is using antisense oligonucleotides to actually inhibit the splicing of exon 8. As I said before, SMN2, the exon 7 is excluded is not present in the most of the messenger RNA. That's why the protein is not functional. By using an antisense to... An enhancer of exon 8 inclusion, people managed to have a higher level of inclusion of exon 7. It was 10% originally, improved it. This is tested in the clinics also there are clinical trials. The advantage is that we don't need a virus. So there will be no immune response related to the capsid. But the disadvantage is that it's not stable. You have to inject regularly these oligonucleotides to work a long-term. Since it's intrathecal injections, it's not so nice for the children.

Notes

Summary

0m 05s

Gene therapy for SMA: strategy 2

Strategy 2b aims to restore normal splicing in SMN2 using genome editing

Novel genome-editing-based approaches to treat motor neuron diseases: Promises and challenges

Annarita Miccio,[1] Panagiotis Antoniou,[1] Sorana Ciura,[2] and Edor Kabashi[2]

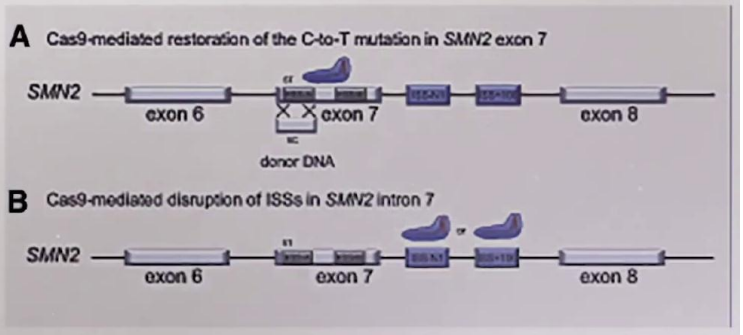
Correct C>T mutation: Homology-directed repair

Deletion of Intron splicing silencer: Non-homologous end joining

Requires a viral vector to deliver Cas9 nuclease and sgRNA

Limitations:

- Exceeds the capacity of single AAV vectors. Alternatives?
  - Use 2 AAVs
  - Use another vector
  - Discover smaller nuclease
- Low efficiency of genome editing
- Immune response to viral capsid and toxicity.



Miccio A et al. Novel genome-editing-based approaches to treat motor neuron diseases: Promises and challenges. Mol Ther. 2022 Jan 5;30(1):47-53. doi: 10.1016/j.ymthe.2021.04.003

Of course, you can imagine to do genome editing, and this has been done in the preclinical experiments. One way is to do a homology-directed repair in the SMN2 gene dose restoring the sequence in the start of the exon 7. So that again, seven will be included. This needs homology-directed repair. Up to now, it's not probably efficient enough to do it in human. The other way is to use non-homologous repair of the [inaudible 00:02:47]. This has also been tried by deleting and an inhibitor [inaudible 00:02:56] for inclusion of SMN2. This is still under development. It's not ready for the clinics, but there is potential. However, there are still limitations to deliver the elements of the CRISPR-Cas9 system. You will still need the vector. The problem of the immune response will still exist. In addition, Cas9 and the single [inaudible 00:03:32]. The coding sequences are too large for one AAV vector, so you need to use two AAVs. Fortunately, no smaller gas nuclease have been identified. This again, let's see what will happen. But still, we will have the problem of the immune response.

Notes

Summary

1m 54s