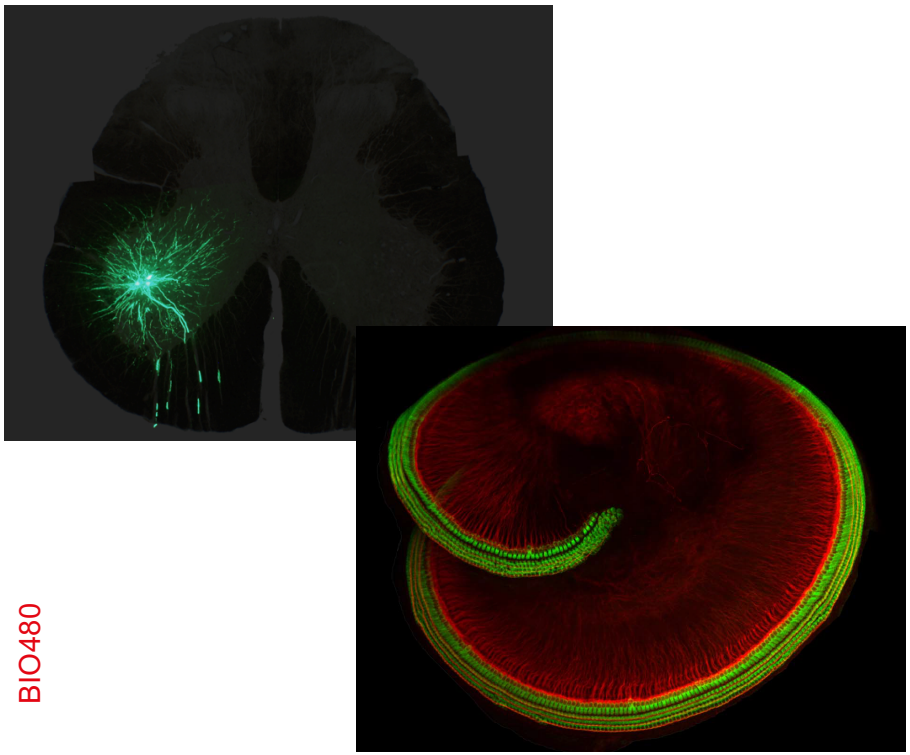
EPFL

Therapeutic applications in neurologic and sensory disorders



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Gene therapy: question 1

Novel capsid variants can provide specific properties to adeno-associated vectors to deliver genes in the central nervous system.

Why is it so ?

A. The vector particles better diffuse in the cerebrospinal fluid.

B. These novel vectors will no more be degraded following entry into the cell.

C. **The modification of the capsid protein structure allows interaction with different cell receptors, conferring novel properties**.

D. Differences in the biophysical properties of the capsid allow to pass the blood-brain barrier.

Gene therapy: question 2

The intravenous injections of Zolgensma is the first effective disease-modifying gene therapy for a neurological disease.

What do you think has been the parameter(s) critical for efficacy?

A. The use of a promoter allowing for SMN expression in key cell types

B. The use of a highly active SMN variant

C. **The dose of vector injected**

D. **The use of an AAV capsid able to enter the central nervous system following peripheral injection**

Gene therapy: question 3

One consider a gene therapy approach against SOD1 as a treatment for SOD1-related familial ALS.

What would you consider as a realistic strategy? (consider gain- or loss-of-function as a cause of SOD1 toxicity as well as the number of mutations)

A. Silence selectively the mutated SOD1 protein by RNA interference

B. **(Gene edit the mutated SOD1 allele)**

C. Overexpress the normal SOD1 protein

D. **Silencing all forms of the SOD1 protein to reduce overall SOD1 level**

Gene therapy: question 4

For gene therapy against mutated SOD1 to be successful, assuming that you have an effective vector for each of them, which cell type would you target?

A. Mainly glial cells (astrocytes and microglia)

B. Mainly motoneurons

C. Mainly the skeletal muscle

D. Approaches targeting two or more key cell types should be preferred

Gene therapy: question 5

From these data, what is your strategy for the most effective approach for RNA interference against mutated SOD1 ?

Indicate all correct answers.

A. Design a vector to target as many astrocytes as possible by increasing the vector dose.

B. **If possible, design a single vector to target multiple cell types, preferably astrocytes and neurons.**

C. Co-inject the astrocyte-targeting vector with a second AAV to target mutated SOD1 in neurons.

D. **Target mutated SOD1 in the entire central nervous system using a vector with non-cell selective expression of RNAi.**

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Gene therapy: question 7

In your view, what are the main challenges of CRISPR/Cas RNA-guided gene editing to rescue CNS genetic disorders *in vivo*?
[rank the following answers from highly likely to unlikely]

1. **Off-target effects of CRISPR/nuclease in the host genome due to non-specific sequence targeting.**
2. **Effective delivery of CRISPR/Cas + gRNA to large cell populations**.
3. **Poorly effective DNA repair mechanisms in post-mitotic cells.**
4. **Chromosomal reorganization caused by imperfect DNA repair mechanisms.**
5. Effective and precise CRISPR/Cas gRNA –guided DNA cleavage.