MOTOR NEURON DISEASES

Pathophysiology, genetics, proteins, therapies

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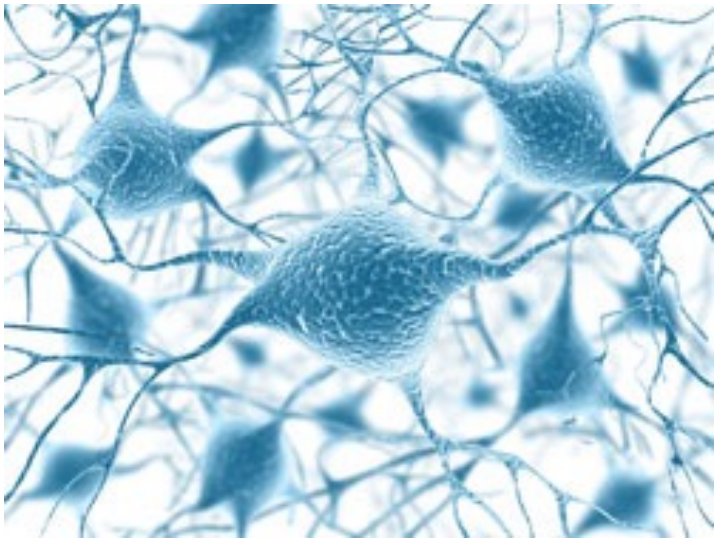


MN diseases - Question 1

For diseases affecting the function of the basal ganglia, which of the following primary symptoms would you expect?
(by order of most to least likely)

A. Paralysis

B. Cognitive deficits

C. Difficulty to initiate movement

D. Memory loss

E. Loss of movement control

Motor neuron diseases: question 2

A neurodegenerative disease is causing the loss of **lower** motoneurons.

What are the possible symptoms ?

A. Sensory defects in the limb
B. Limb paralysis
C. Hyper reflex
D. Weakness
E. Respiratory failure

Motor neuron diseases: question 3

A neurodegenerative disease is causing the loss of **upper** motoneurons.

What are the possible symptoms ?

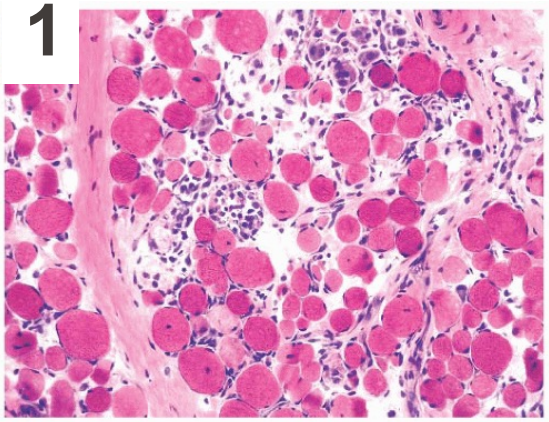
A. Sensory defects in the limb
B. Limb paralysis
C. Hyper reflex
D. Weakness
E. Respiratory failure

EPFL

MN diseases - Question 4

Here are three images characteristics of skeletal muscle in various conditions.
Put these images in the order: normal – myopathy (Duchenne) – neuromuscular disease (SMA) and define the correct answer.

1



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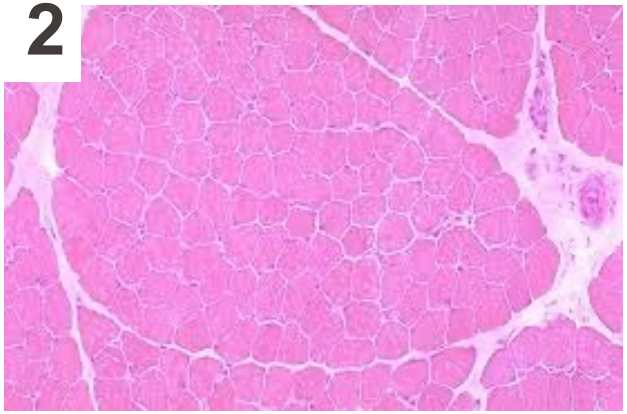

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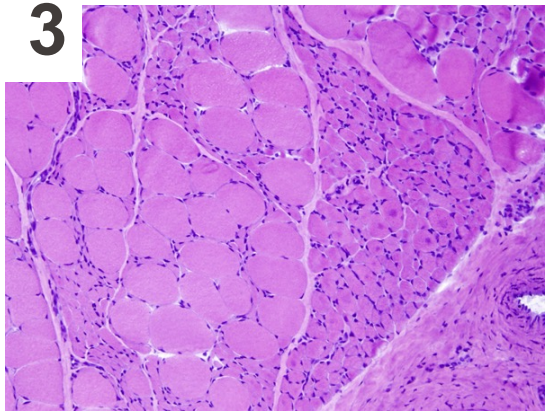


A. 1-2-3

B. 3-2-1

C. 2-1-3

D. 1-3-2

E. 2-3-1

F. 3-1-2

MN diseases - Question 5

You are developing implantable electrodes to stimulate the local motor circuit in the spinal cord.

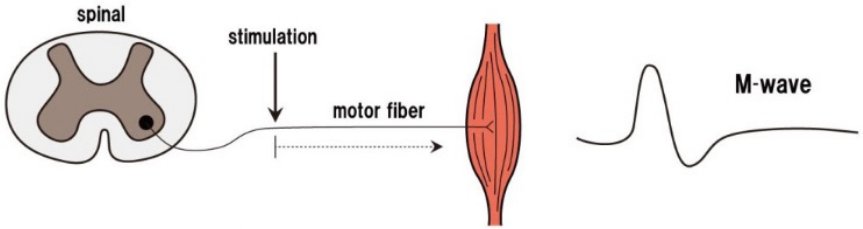
Rank the following applications according to their chance to be addressable by your technology (from most likely to least likely)

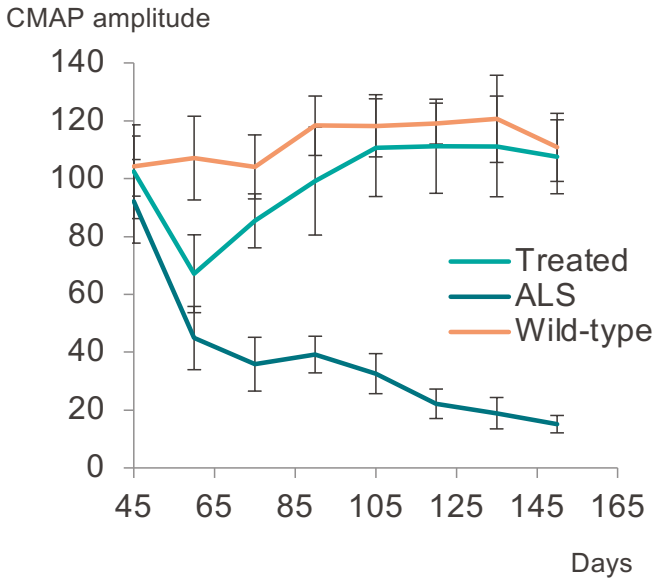
1. **Partial spinal cord injury**
2. **Complete spinal cord transection**
3. **Disease leading to neuronal degeneration of the sensory system**
4. Myopathy
5. Disease leading to motoneuron degeneration

Motor neuron diseases: question 6

The following graph shows the monitoring of the compound muscle action potential (EMG) in a mouse model of amyotrophic lateral sclerosis.

How would you interpret the result in the treated group?





A. The treatment is fully protecting the neuromuscular function

B. There is no loss of motoneurons in the spinal cord, because the EMG is rescued

C. After a first loss of neuromuscular junctions, the remaining motoneurons reinnervate the muscle.

D. The decrease in action potential amplitude reflects a transient atrophy of the muscle

Motor neuron diseases: question 7

Researchers have compared the transcriptional profile of motoneurons that are resistant or vulnerable to disease. What is your opinion on this approach?

A. This is irrelevant as these pools of neurons differ in their integration in the local circuit

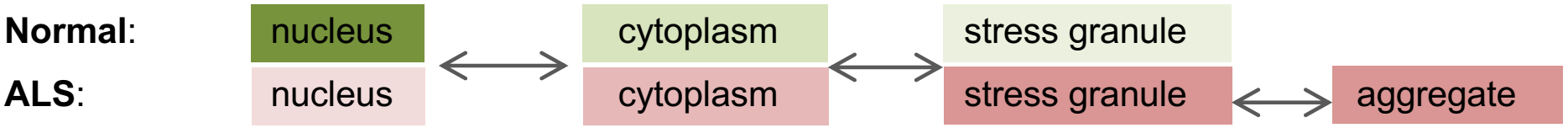
B. This is the most effective approach to identify protective genes

C. This approach may identify mechanisms that are inherent to motoneurons but will fail to identify possible cause of disease in muscle or glial cells.

D. The vulnerability of neurons is unlikely to be the same in humans and in animal models

Motor neuron diseases: question 8

TDP-43 biology in normal and diseased conditions shows that pathology affects the protein distribution across 4 different compartments:



Based on these observations, would you think that neurodegeneration is caused by…

A. the changes in the dynamic transfer across these compartments.
B. the formation of protein aggregates, the main pathological hallmark.
C. the loss of the effects of nuclear TDP-43 on RNA and gene expression.
D. the combination of all of the mechanisms mentioned above.

Motor neuron diseases: question 9

You want to start a research program to explore why motoneurons are particularly vulnerable to perturbations of RNA metabolism in ALS.
What would be your work hypothesis (one possibility)?

A. **These cells are highly specialized and therefore the distribution of RNA in specific cell compartments is very important**
B. **Splicing is important in motoneurons because they need a broader variety of proteins**
C. **Motoneurons have high gene expression levels in general, therefore they are sensitive to changes in RNA metabolism**
D. **Expression of miRNA is more important in this cell type than in other cell types**
E. There is one specific RNA species which is perturbed and causes disease. It needs to be found.

Motor neuron diseases: question 10

In $SOD1^{G93A}$ mice (with 16 to 24 copies of the human SOD1 gene), blocking individual pathways leading to cell death only increases animal survival by 5-10%.

What is your interpretation (responses are ranked)?

1. **Multiple pathways act in parallel to cause neuronal degeneration**
2. **This indicates that it is poorly efficient to act downstream in the pathologic cascade**
3. The level of expression of mutated SOD1 in transgenic mice is too high to reliably test therapeutic approaches
4. The exact cause of the pathology has not been identified yet
5. This animal model is not relevant for testing treatment efficacy

Motor neuron diseases: question 11

From the previous experiments on the role of mutated SOD1 in various cell types, which one(s) are the correct conclusion(s)?

A. It will be impossible to achieve therapeutic efficacy by suppressing SOD1 toxicity only in motoneurons

B. Strategies that prevent astroglial and microglial cell activation are more effective than the ones targeting motoneurons

C. At the time the disease is diagnosed, mainly strategies targeting glial/microglial pathology should be applied

D. Mutated SOD1 leads to a pathogenic crosstalk between neuronal and glial cells