Modulating motor neuron vulnerability using the oculomotor restricted genes IGF-2 and SYT13 for ALS therapy

Acronym: IS- ALS

Principal Investigator: Stefania Corti

Grant: 144 000€

Duration: two years

Summary of the research project

The research project is a joint collaboration between the University of Milan in Italy (Stefania Corti) and the Karolinska Institutet in Sweden (Eva Hedlund).

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by the selective and progressive **death of somatic motor neurons** that innervate voluntary muscles in arms, legs, trunk and face, with resulting muscle wasting. However, **not all somatic motor neurons degenerate in ALS**; certain groups of motor neurons, including those in the oculomotor nucleus, which innervate the muscles around the eyes, appear resistant to degeneration and persist throughout the disease progression. Mechanisms responsible for motor neuron subtype-selective resistance and vulnerability in ALS remain largely unknown. Elucidating the molecular basis for the selective resistance of oculomotor neurons may lead to development of new therapies to prevent the relentless MN loss in ALS.

Our teams have already **identified two genes, insulin-like growth factor 2 (*IGF-2*) and synaptotagmin 13 (*SYT13*), that are preferentially active in oculomotor neurons and protect also sensitive spinal motor neurons when introduced to these**. In particular, we have demonstrated that the delivery of each of these genes protects ALS patient spinal motor neurons from degeneration *in vitro* and prolong the life-span of ALS mice by preserving motor neurons. The pathophysiological mechanisms underlying the development of ALS are multifactorial, with emerging evidence of a complex interaction between genetic and molecular pathways. Consequently, it is highly likely that an effective therapy needs to target multiple mechanisms. We therefore believe that a combination of these two genes could be more beneficial than each gene alone.

Within the proposed project, we will evaluate if combined administration of IGF-2 and SYT13 gives a synergistic effect in promoting survival of ALS patient motor neurons *in vitro* and in prolonging survival of transgenic ALS mice. **Overall, this work aims to evaluate IGF-2 and SYT13 combined administration as a possible gene therapy approach for ALS**.

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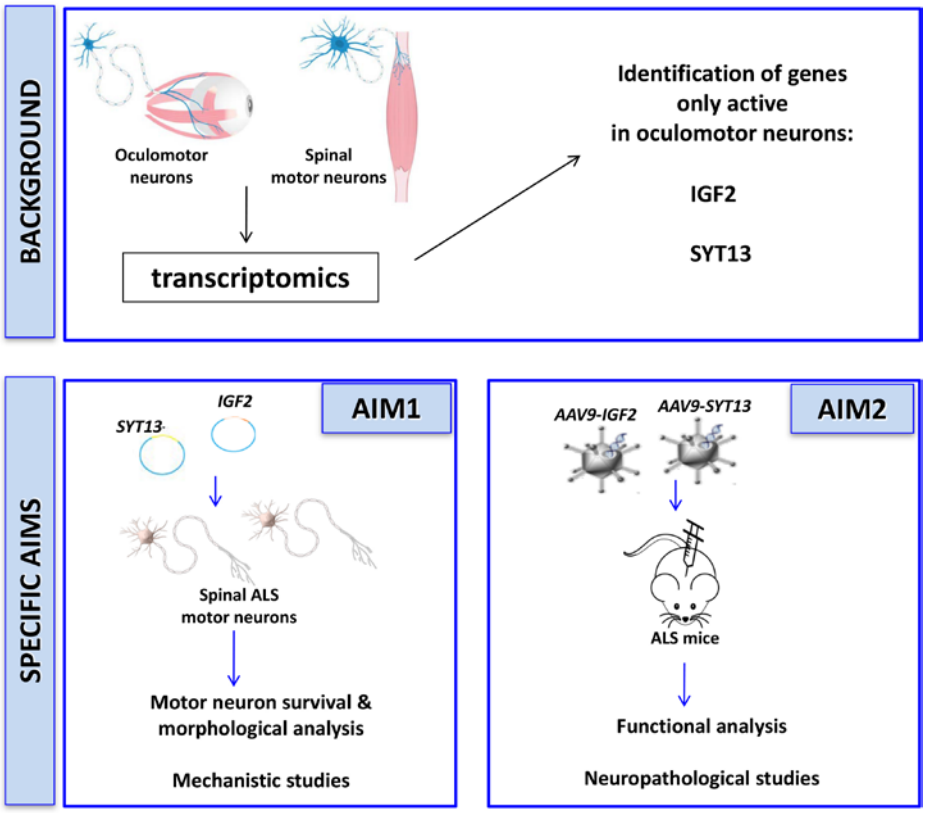
Schematic presentation of the research project:



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