Poster 11

# FUNCTIONNAL ANALYSIS OF GENETIC VARIANTS IN AMYOTROPHIC LATERAL SCLEROSIS BY STUDYING EARLY MARKERS OF NEURODEGENERATION

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Amyotrophic Lateral Sclerosis (ALS), also known as Charcot disease, is a neurodegenerative disease that causes the death of motor neurons resulting in the death of the patient 3 years after symptoms onset. 20% of cases of ALS are due to pathogenic genetic variants. Over 30 genes have been linked to the development of the disease to date, and the gene *SOD1* coding for the enzyme Superoxide Dismutase 1 is one of them. Over 200 different *SOD1* gene variants have been identified in the disease. Patients with a pathogenic variant in *SOD1* can be treated with Tofersen, an anti-SOD1 antisense strategy.

Several variants identified in ALS patients are considered potentially pathogenic or of unknown significance, these patients cannot receive Tofersen. A part of my project aims to study these particular variants in more detail, by performing *in vitro* studies to identify whether or not they are pathogenic. We are currently studying the function of 20 of these variants.

The different variants are created by site-directed mutagenesis on a plasmid expressing the human wild-type SOD1 protein. The plasmids are used for various *in vitro* functional analyses such as the propensity to form protein aggregates, one of the main hallmark of ALS. Some of the variants of interest will be studied *in vivo*, in collaboration with a team from Montpellier (INM).

The results obtained by theses studies could be exported to the to the clinic. In addition, the *in vitro* and *in vivo* models developed could be used for therapeutic studies under development.