Advancing gene therapy for C9-ALS

Acronym: GeneTherC9

Principal Investigator: Maria Grazia BIFERI

Grant: 150 000€

Duration: two years

Summary of the research project

Gene therapy approaches are emerging as promising therapeutic options for the treatment of motor neuron disorders. In particular, viral vectors derived from Adeno Associated Virus (AAV) have been used to mediate gene transfer in patients affected by Spinal Muscular Atrophy (SMA) type 1, with very promising outcomes. Based on the results of the first-in-men study, the Food and Drug Administration (FDA) approved Zolgensma, an AAV-mediated treatment for SMA.

Our group recently developed an AAV-mediated gene therapy for a genetic form of Amyotrophic Lateral Sclerosis (ALS), caused by mutations in the SOD1 gene (representing about 20% of familial ALS cases). Using an exon-skipping approach to silence the expression of the toxic SOD1 protein through the expression of antisense (AS) sequences, we reported a therapeutic effect in a mouse model of the disease. This gene therapy and similar silencing strategies are currently under preclinical development for clinical translation. Our objective is now to test a gene-targeting approach for the most common genetic form of familial ALS, characterized by hexanucleotide repeat expansion (HRE) in the C9ORF72 (C9) gene. The HRE exerts its pathological effects through three non-exclusive mechanisms including, loss of protein function, toxicity of nuclear HRE RNA and accumulation of dipeptide repeats. We recently assessed the effects of viral-mediated expression of AS sequences directed to the HRE of the C9 pre-mRNA in patient-derived cellular models. We observed the reduction of RNA foci, one of the three non-exclusive pathological mechanisms of the disease, in treated C9-ALS cells, compared to untreated controls.

The aim is now to test this approach in a mouse model of the disease. We will inject the AAV-AS-C9 in C9-ALS mice and we will analyse the effect of the approach on mice phenotype. A positive outcome of this gene therapy will open concrete translational perspectives.

The study will be conducted by **Maria Grazia BIFERI**, Center of Research in Myology – Sorbonne Université – INSERM U974 - Institut de Myologie, Paris, France.