New gene therapy for C9ORF72-linked ALS

Acronym: GeneTherC9

Principal Investigator: Martine Barkats / Maria Grazia Biferi

Grant: 80 000€

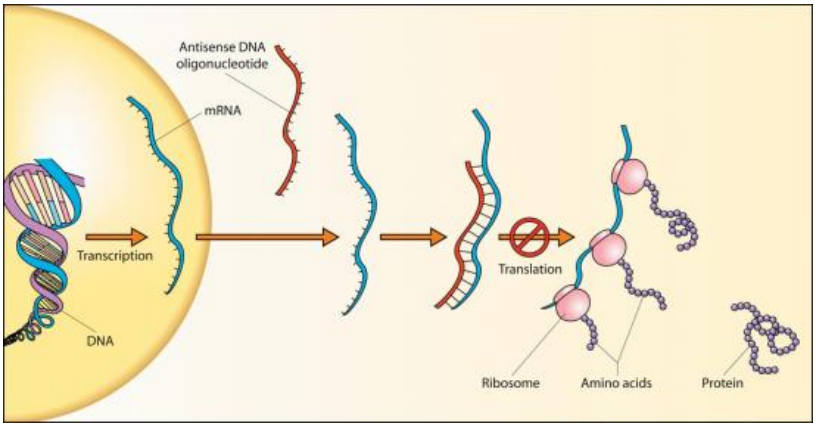
Duration: one year

Summary of the research project

The most common genetic cause for ALS/FTD, an hexanucleotide repeats expansion (HRE) in an uncharacterized gene (C9ORF72), has been recently discovered (Renton et al., 2011; DeJesus-Hernandez et al., 2011). Many studies are currently undergoing to understand the associated pathological mechanism. Mouse models have been generated recapitulating the major molecular features of the disease, such as the accumulation of RNA foci and the production of toxic dipeptide repeats (DPR) in neurons.

One of the most promising approaches to treat this disorder is the use of antisense (AS) oligonucleotides, to block the transcription and translation of the repeats, by counteracting the formation of RNA foci and DPRs (Lagier-Tourenne et al., 2013).

Antisense oligonucleotides are synthetic single stranded strings of nucleic acids that bind to RNA and thereby alter or reduce the protein synthesis:



Martine Barkats research team is devoted to the identification of efficient strategies to target the central nervous system (CNS) and to the development of novel therapies for motor neuron disorders, such as Spinal Muscular Atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS).

Their studies opened new perspectives and applications for the treatment of CNS diseases and other diseases, based on the use of Adeno-Associated Virus (AAV) vectors. Indeed, this team discovered the unique therapeutic potential of self-complementary AAV serotype 9 vectors (AAV9) for gene transfer to the CNS following systemic delivery (Barkats, patent PCT/EP2008/063297, 2007; Duque et al., 2009).

Taking advantage of AAV vectors potential to target CNS, Barkats' group developed an efficient gene therapy for SMA able to extend survival and improve the phenotype of a severe SMA mouse model (Dominguez et al., 2011).

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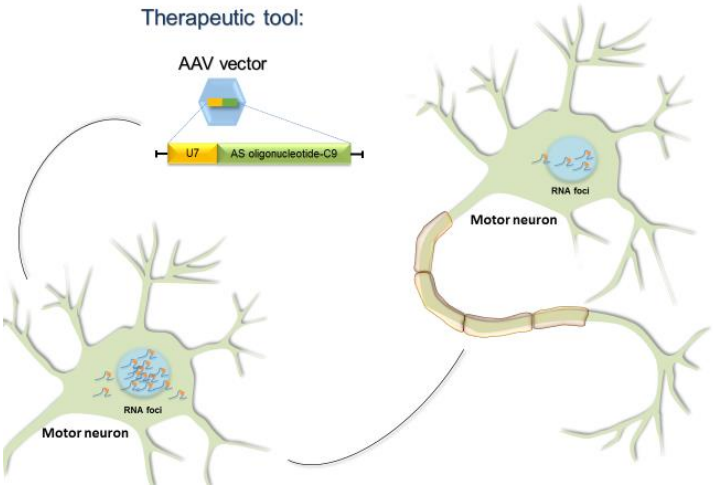
Interestingly, a phase I/II clinical trial, using a similar approach, is currently undergoing in USA for SMA type 1 patients (NCT02122952).

For SOD1-linked ALS, this team has developed a system of removal of toxic SOD1 in a well-characterized SOD1 mouse model. The inhibition of the transcription of the SOD1 was conducted through the use of AS against the mutant SOD1. The AS were delivered by the modified small nuclear RNA U7, then inserted into the vector derived from the adeno-associated virus. AAV vectors were injected in vivo to target neurons and other cells involved in the pathology. This strategy has provided an excellent therapeutic effect to newborn mice with a survival rate augmented to about 100% and important one for adult mice with a survival rate increased by more than 50% (Biferi et al., 2017).

Their new objective is to develop a treatment for C9ORF72-linked ALS. They propose to develop an AAV-U7 mediated gene therapy for the disease by delivering AS sequences. The U7 particle will protect the oligonucleotides sequences and the use of AAV vectors for in vivo delivery will increase the therapeutic effect.



The first step will be to design AAV plasmids carrying the U7 RNA and different AS against the C9 repeats (pAAV-U7-C9). The silencing efficacy of these plasmids will be tested in vitro.

The most effective pAAV-U7-C9 plasmid (in terms of reduction of the number of C9 foci) will be used to produce the AAV10-U7-C9 vectors. Upon the results obtained in vitro, in a second phase of the project (second year) the therapeutic vector, and a control vector, will be tested on C9ORF72 mice in order to determine its therapeutic effect.

The project is conducted within the Research Center in Myology of the Institute of Myology in Paris in the research group led by Martine Barkats.

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From left to right: Top: Mathilde Cohen-Tannoudji, Benoit Giroux and Thibaut Marais
Bottom : Stéphanie Astord, Aurore Besse and **Maria Grazia Biferi**.