2019 Call for projects

Investigating the therapeutic potential of HDACs in a FUS mouse model of ALS

Acronym: HDACALS

Principal Investigator: Ludo Van Den Bosch

Grant: 180 000€

Duration: three years

Summary of the research project

In this research project, we want to investigate the therapeutic potential of histone deacetylase (HDAC) inhibition in amyotrophic lateral sclerosis (ALS). HDACs are major regulators of protein acetylation, a post-translational modification that controls a variety of cellular processes. We previously discovered that chronic treatment of *FUS*-ALS mice with ACY-738, a potent HDAC inhibitor that can cross the blood-brain barrier, ameliorated the motor phenotype and substantially extended the life span of the *FUS*-ALS mice. Those results have recently been published:

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RESEARCH Open Access

Restoration of histone acetylation ameliorates disease and metabolic abnormalities in a FUS mouse model

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At the molecular level, ACY-738 increased the acetylation of several HDAC-target proteins. It is however not known which HDAC(s) is inhibited by this treatment, mediating the observed therapeutic effect. The exact identification of this target will be critical to achieve maximal therapeutic efficacy in conjunction with limited side effects in ALS patients.

The first aim of this project is to investigate the contribution of the individual HDAC members in the significant survival effect of ACY-738 on FUS-ALS. To this end, we will crossbreed the *FUS* mice with

selected conditional HDAC knock-out mice to recapitulate the beneficial effect and hence find out which member is the key effector and the likely target of ACY-738 treatment. Detailed phenotypic monitoring of motor function and electrophysiological measurements will be used to assess disease progression. Next, we want to determine whether HDACs play a pathogenic role in the *FUS*-ALS mice. This will be achieved by assessing changes in HDAC expression (translation and protein levels) and function (acetylomics) in our mouse model. Finally, we want to unravel the molecular mechanism modulated by the identified HDAC inhibitor (HDACi) in order to identify potential downstream targets. This knowledge is a prerequisite for ameliorating HDACi-based therapies and will provide a stepping stone for more advanced, mechanism-based therapies for ALS.

The study is conducted by **Ludo Van Den Bosch**, Neurobiology, Experimental Neurology (KU Leuven) and Center for Brain & Disease Research (VIB), Belgium.

Ludo Van Den Bosch presenting the final results of the 2016 project at the Foundation's annual scientific meeting in Tours on May 14, 2019.