Preclinical testing of histone deacetylase 6 inhibitors in a FUS mouse model of ALS

Acronym: ALS – HDAC6

Principal Investigator: Ludo Van den Bosch

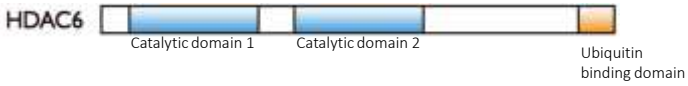
Grant : 120 000€

Duration : two years

Summary of the research project

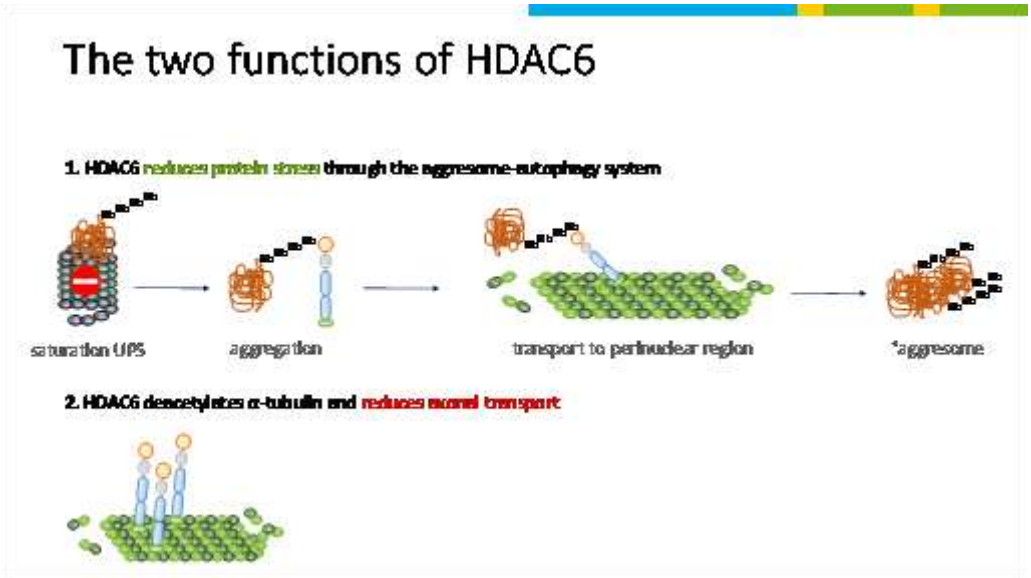
This project focuses on investigating the therapeutic potential of histone deacetylase 6 (HDAC6) inhibitors using a FUS mouse model of ALS.

Histone deacetylase 6 (HDAC6)



- Cytosolic protein
- Main substrates α-tubulin, poly-ubiquitinated proteins and HSP90
- Reduces axonal transport by deacetylating α-tubulin
- Regulates protein degradation and reduces protein stress through the aggresome-autophagy system

HDAC6 is one of the major tubulin deacetylating enzymes and plays an important role in the regulation of axonal transport in neurons. In addition, HDAC6 can mediate transport of ubiquitinated proteins along the microtubule tracks Disturbances of axonal transport and the presence of ubiquitinated aggregates are both hallmarks of ALS.



As a consequence, we hypothesize that HDAC6 might also play a crucial role in the disease process underlying ALS. This hypothesis is supported by the observation that treatment with the non-specific HDAC inhibitor, trichostatin A (TSA), delays disease progression and increases survival in the mutant SOD1 mouse model and that genetic removal of HDAC6 in mutant SOD1G93A mice prolongs survival.

Preclinical testing of histone deacetylase 6 inhibitors in a FUS mouse model of ALS

In this project, we concentrate on the FUS mouse model, recently created by the group of C. Shaw, as these mice show a clear motor phenotype as well as motor neuron loss. We will inhibit pharmacologically HDAC6 and monitor the effect of this treatment on the phenotype of this transgenic mouse model. Our preliminary data indicate that treatment with one of the new HDAC6 inhibitors can increase the survival of FUS mice with more than 50%, while no effect on disease onset was observed.
Additionally, we aim to identify the underlying mechanism responsible for the positive effect on disease duration by investigating the effect of the HDAC6 inhibitors on the (re)innervation of muscles.
Moreover, in vitro assays on cultured motor neurons will be used to find out whether HDAC6 inhibitors have an effect on axonal outgrowth, on axonal transport of mitochondria and on the acetylation level of □-tubulin.

In conclusion, we want to provide further preclinical evidence for a role of HDAC6 in ALS and we hope that HDAC6 inhibition with improved HDAC6 inhibitors can be developed as a new therapeutic strategy for ALS.

Relevant research articles for this project are:

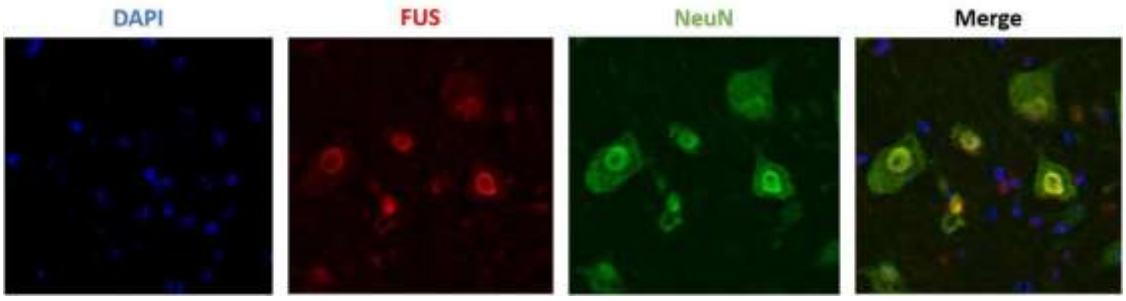
- d'Ydewalle et al. (2011) HDAC6 inhibitors reverse axonal loss in a mouse model recapitulating mutant HSPB1-induced Charcot-Marie-Tooth disease. Nature Medicine, 17, 968-974.

- Mitchell et al. (2013) Overexpression of human wild-type FUS causes progressive motor neuron degeneration in an age- and dose-dependent fashion. Acta Neuropathol, 125, 273–288.

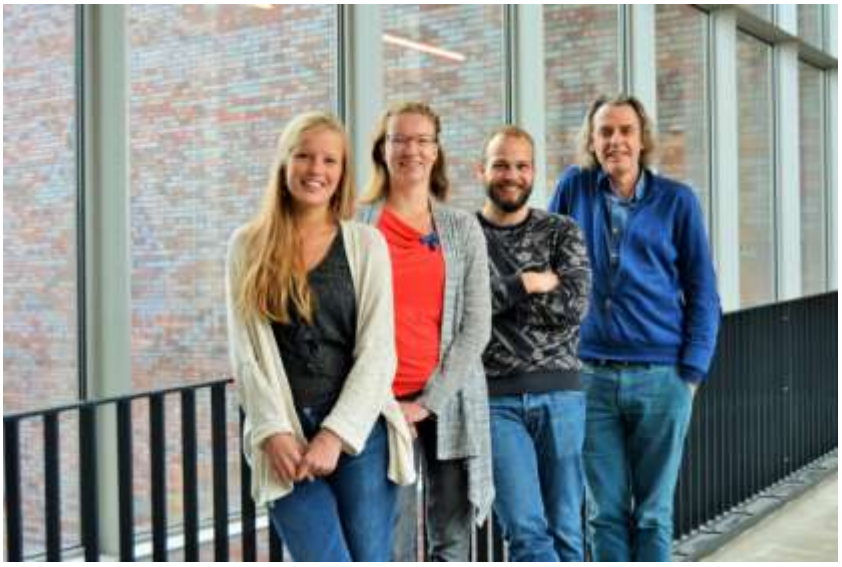
- Pollari et al. (2015) Genetic removal of histone deacetylase 6 (HDAC6) delays the disease progression in a FUS mouse model of ALS. ALS & Frontotemporal degeneration,16 supplement 1, 57.

- Taes et al. (2013). Hdac6 deletion delays disease progression in the SOD1G93A mouse model of ALS. Human Molecular Genetics, 22, 1783-1790.

FUS (red) is expressed intensely in the nucleus of the neuronal cells (green) in the spinal cord of the transgenic FUS mice.



This project is conducted by Pr Ludo Van Den Bosch, group leader, Neurobiology, Experimental Neurology (KU Leuven) and Vesalius Research Center (VIB) in Belgium



Team working on this project:

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