Amyotrophic lateral sclerosis

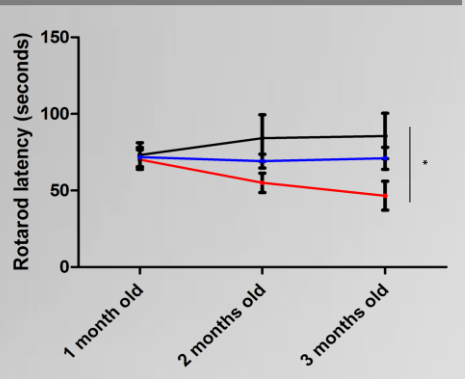
Amyotrophic Lateral Sclerosis (ALS) is a fatal progressive neurodegenerative disease, which results in the destruction of the motor neurons in the brain and spinal cord, and affecting people between 40 and 60 years old.

The first mouse model of the disease was developed by Gurney and collaborators following the identification of mutations in the copper/zinc superoxide dismutase 1 (SOD1) gene linked to 20% of familial ALS cases. Unfortunately, no effective therapy for ALS patients has been identified to date in the SOD1 mouse. The failure to translate positive preclinical results from the SOD1 mouse model into clinical efficacy has raised questions about the translational suitability of this model.

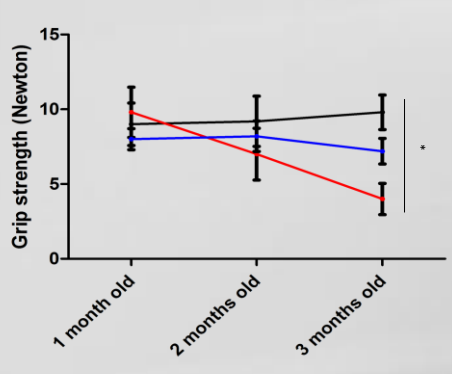
Some years later, the protein TDP-43 was identified as one of the main hallmarks of sporadic and familial ALS, showing accumulations in the cytoplasm of cortical and spinal motor neurons. Mutations in this protein have been associated with cases of ALS but also with tau protein-independent cases of frontotemporal dementia. Today, it is recognized that TDP-43 proteinopathy, characterized by hyperphosphorylation, truncation, ubiquitination, and/or nuclear depletion in neurons, is the prominent and common pathological feature of sporadic and familiar ALS. For this reason, a second transgenic mouse model was developed by overexpressing the mutant human TDP-43 gene, harboring the alanine to threonine mutation at amino acid 315, under the control of the mouse prion promoter. The Prp-TDP43^{A315T} mice reportedly developed a progressive and fatal neurodegenerative disease with pathology reminiscent of ALS. This strain recapitulated many of the pathological features of ALS in humans and it promised to become an important in vivo screening tool for ALS therapies.

Behavioral test

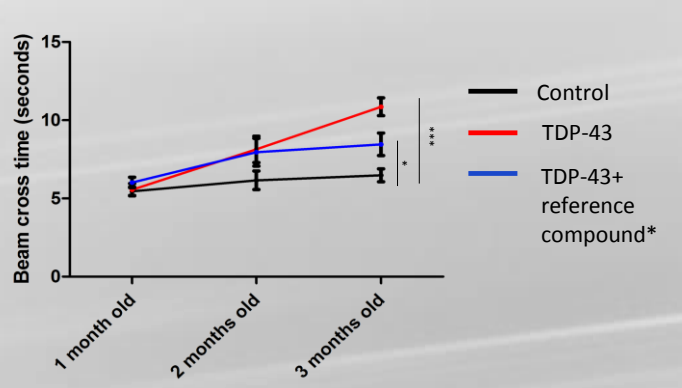
Rotarod (balance and coordination)



Grip test (neuromuscular strength)

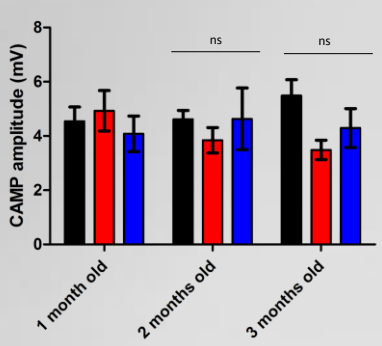


Balance beam (walking performance)

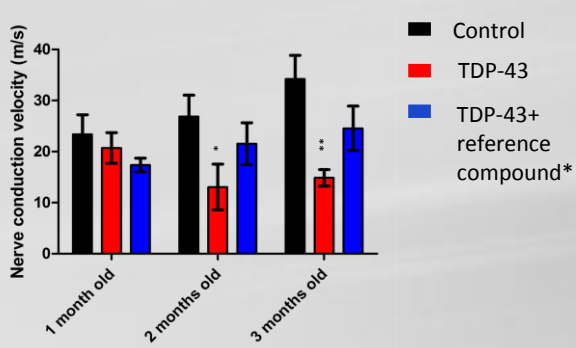


Electrophysiology

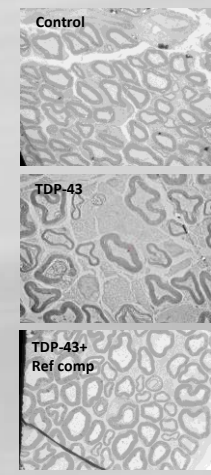
Amplitude

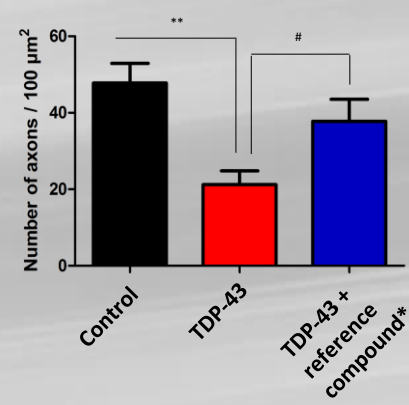


Nerve conduction velocity



Neuromotor histology





Neuromotor disorders, peripheral nervous system electrophysiological impairment and histological anomalies were observed in the preclinical ALS mouse model TDP-43 at 3 months old. Moreover, intrathecal injection of the 'reference compound' allows to attenuate the peripheral degenerative phenotype in this ALS model. Taken together, these results confirm that TDP-43 mouse strain is a robust and reproducible preclinical model to analyze the efficacy of new treatment targeting ALS neuropathy.

**** reference compound = CDA***