Your Partner for Drug Discovery

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a rare and fatal neurodegenerative disease that results in the progressive loss of motor neurons that control voluntary muscles, leading to death 2–4 years post-diagnosis, usually due to respiratory failure.

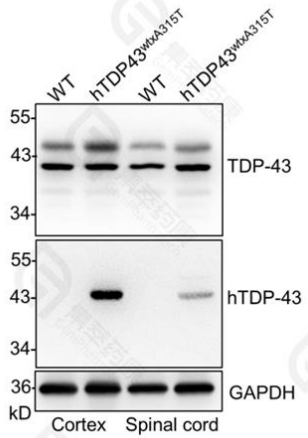
Like in other pathologies (Alzheimer disease, Frontotemporal lobar degeneration…), a key characteristic of neurodegenerative diseases is the identification of abnormal protein aggregates in neurons. These aggregates contain the human nuclear ribonuclear protein TAR DNA-binding protein 43 (TDP-43). The TDP-43 observed in degenerating neurons in ALS tissues is abnormally cytoplasmic and hyperphosphorylated. TDP-43 is primarily a nuclear protein, thus the cytoplasmic mislocalization and aggregation of TDP-43 are considered important pathogenic mechanisms in ALS, and consequently as a major target for treatments.

By reproducing the physiopathological features of ALS, the mutant strain that overexpresses hTDP43 is an interesting experimental model for studying potential therapeutic solutions.

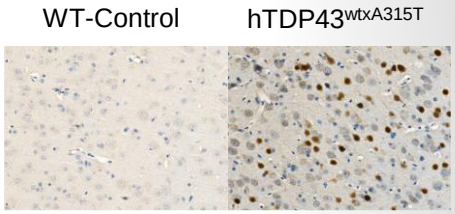
The company GemPharmaTech has created a mutant mouse strain, the B6-hTDP43^{wtxA315T} that overexpresses both wildtype and mutated (A315T mutation) forms of human TDP43 via the CNS promotor Thy1.

GemPharmaTech has characterized at biochemical and histological levels some physiopathological characteristics of the hTDP43wtxA315T transgenic mouse.

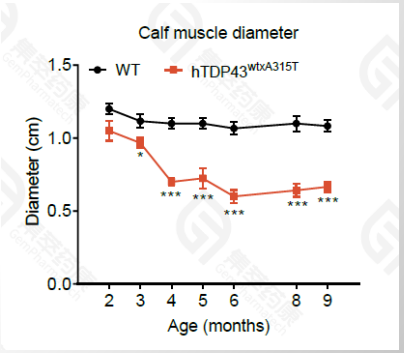
✓ ***TDP43 protein expression in B6-hTDP43wtxA315T mutant***



✓ ***IHC : TDP43 inclusions accumulate in the cortex and spinal cord***



✓ ***hTDP43^{wtxA315T} mice exhibit significant skeletal muscle atrophy***



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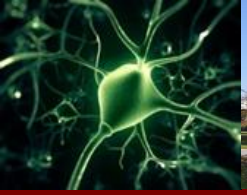




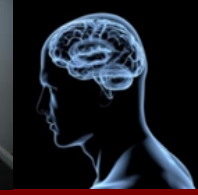

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At Key-Obs we have performed a complete functional phenotyping of the hTDP43^{wtxA315T} transgenic mouse strain. This phenotyping shows functional deficits that are detectable from 2 months of age in various tests: **grip strength, gait impairment, wire maneuver, rotarod test**.

The deficits become very significant around 4 months of age and then gradually worsen.

hTDP43^{wtxA315T} transgenic mice also show a dramatic increase in the plasmatic concentration of Neurofilament light chain (NfL), a proposed biomarker of ALS.

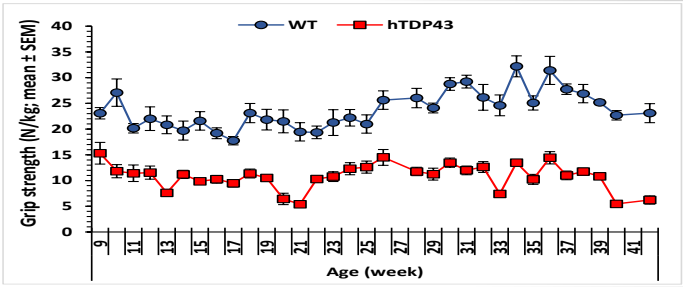
In contrast to other TDP-43 mouse mutants, hTDP43^{wtxA315T} does not display intestinal occlusions, resulting in a regular body weight evolution that does not enforce specific nutritional diet, thus eliminating any bias for treatment studies. Comparing to other ALS mouse models (e.g. SOD1), the lifespan of this strain allows a longitudinal follow-up during chronic treatment studies.

Furthermore, due to an agreement with GemPharmaTech, the hTDP43^{wtxA315T} strain is available for drug testing.

By reproducing the physiopathological and functional features of ALS, the hTDP43wtxA315T transgenic mouse strain is a relevant preclinical model for evaluating efficacy of drug treatments.

Grip strength (Hindpaws)

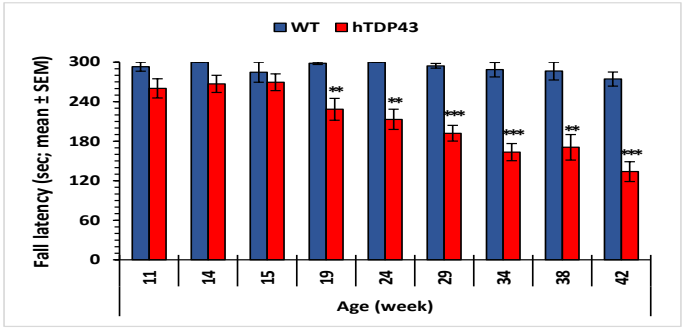
✓ ***Strength deficits***



Difference hTDP43 vs. WT: p ≤ 0.05 at all time points

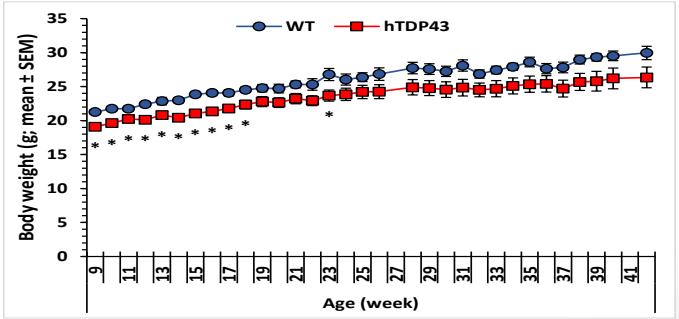
Rotarod

✓ ***Motor deficits***



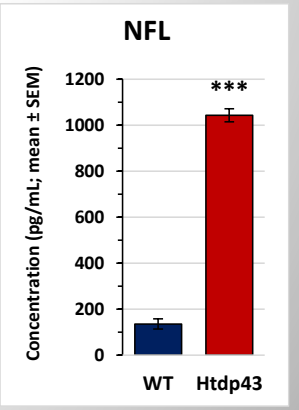
*Difference hTDP43 vs. WT: ** p ≤ 0.01; *** p ≤ 0.001*

✓ ***Body weight***



*Difference hTDP43 vs. WT: * p ≤ 0.05*

✓ ***Plasmatic biomarker***



*Difference hTDP43 vs. WT: *** p ≤ 0.001*

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