PsychoGenics

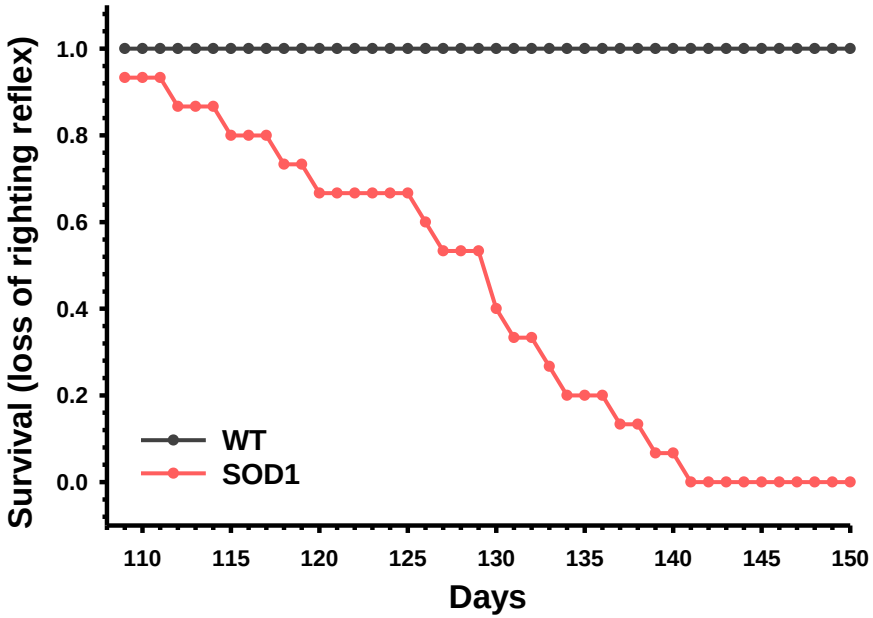
Redefining Drug Discovery Through Innovation

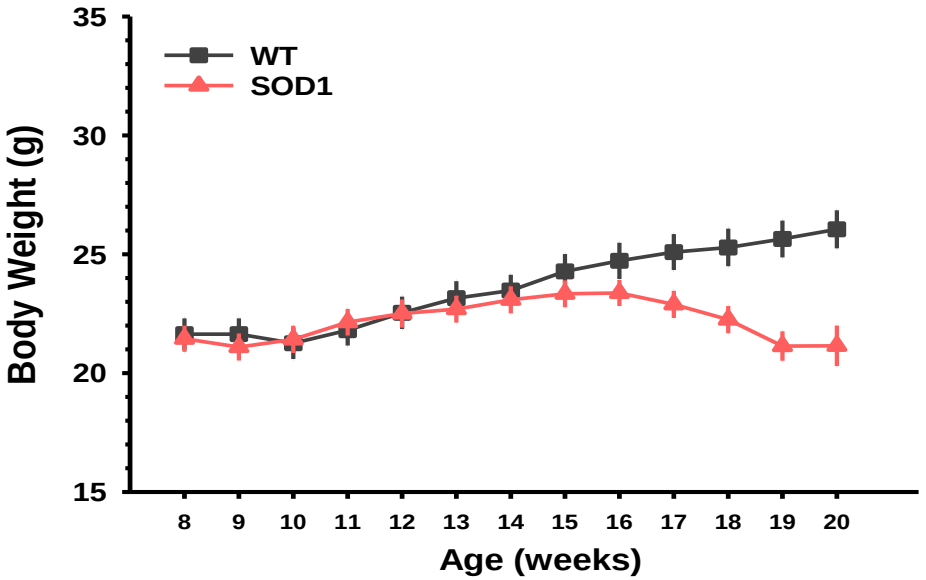
Amyotrophic Lateral Sclerosis Models
SOD1G93A

SOD-1 (G93A) Mouse Model

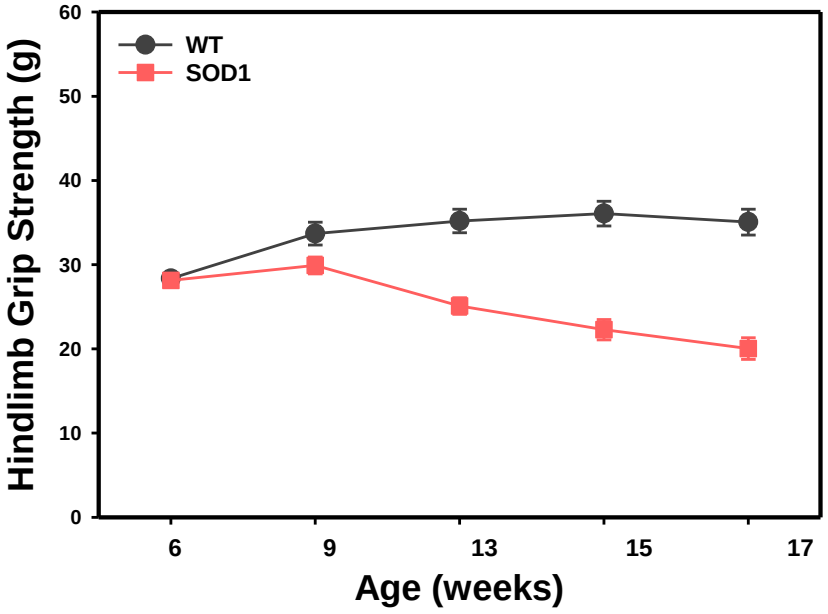
- Amyotrophic Lateral Sclerosis (ALS) is a progressive paralytic disorder marked by the degeneration of motor neurons in the brain and spinal cord.
- ALS patients are classified into two main categories, sporadic (SALS) and familial (FALS). Mutations in the superoxide dismutase 1 gene (SOD1) contribute to some cases of FALS.
- SOD1 (G93A) mice overexpress the human SOD1 gene containing a substitution of glycine to alanine at position 93 (SOD1G93A) under the control of the human SOD1 promoter.
- Phenotype includes: changes in body weight, declines in grip strength and general motor activity

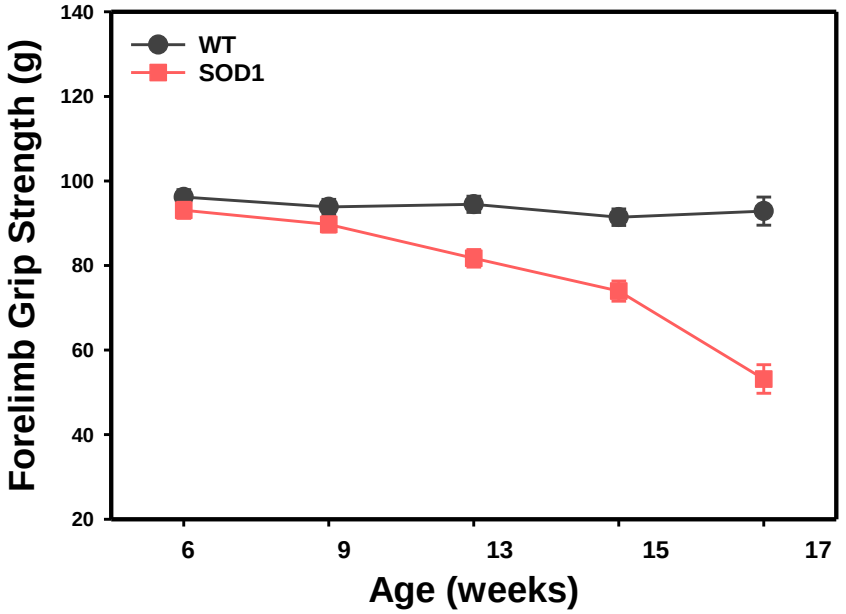
Decline in Survival and Body Weight with Disease Progression in SOD1 Mice



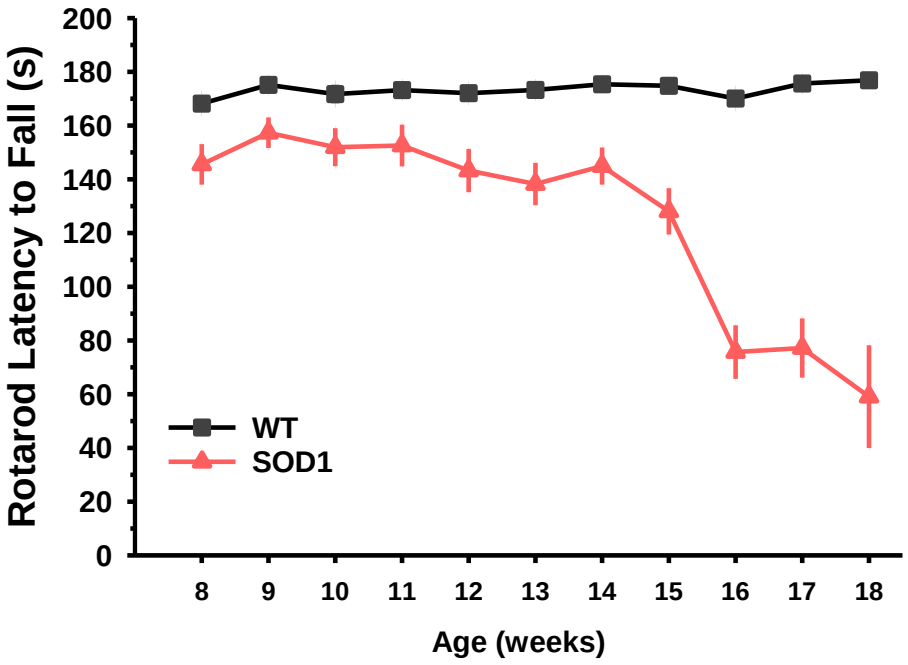


SOD-1 Mice Exhibit a Steady Decline in Grip Strength with Disease Progression



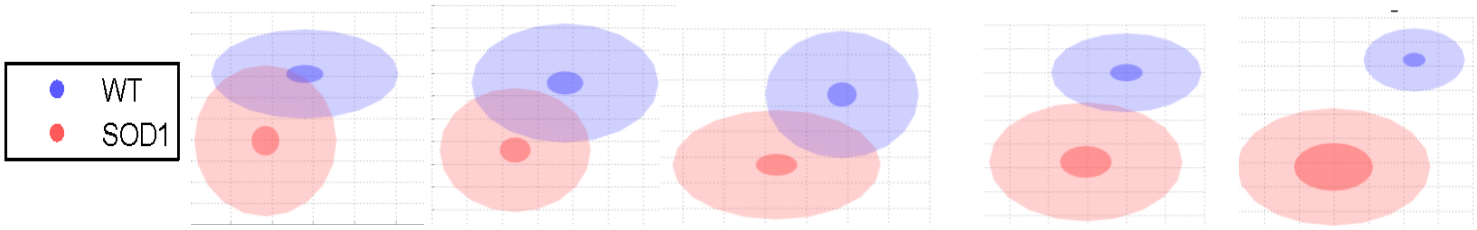


Decline in Motor Coordination with Disease Progression in SOD1 Mice

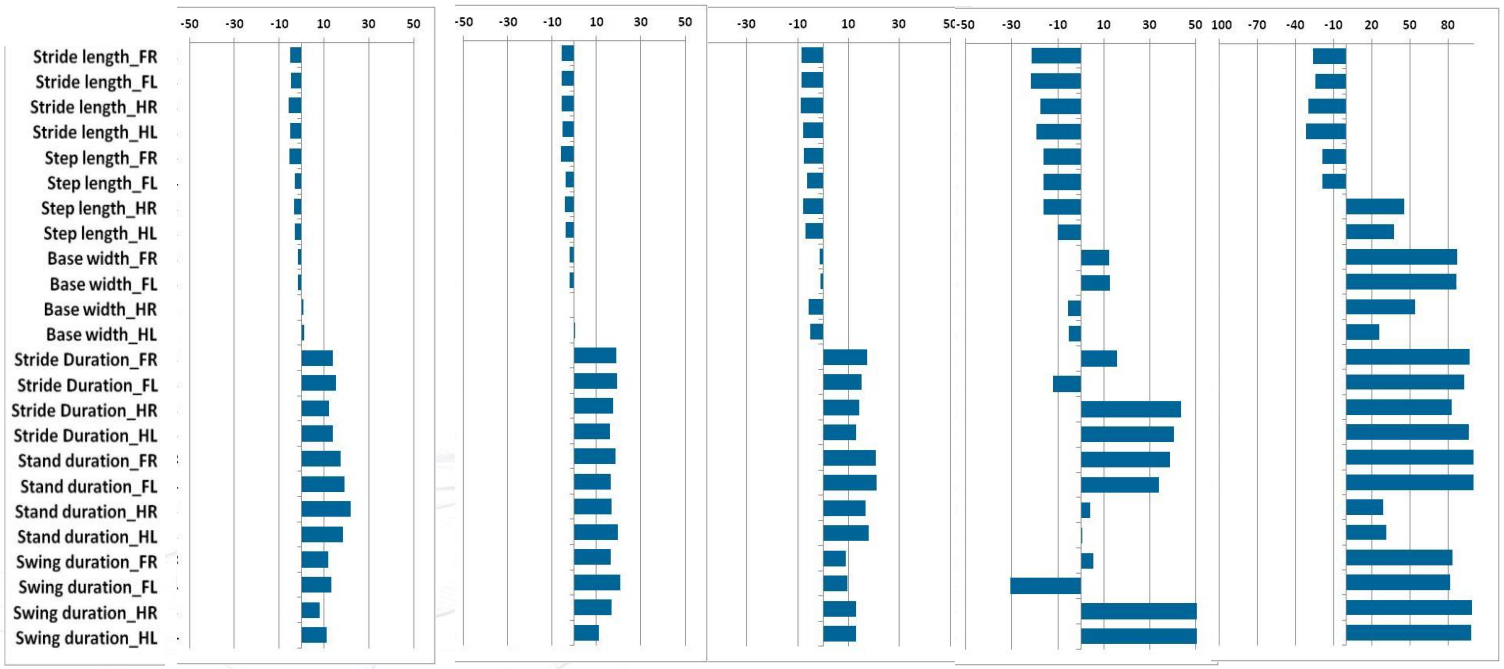


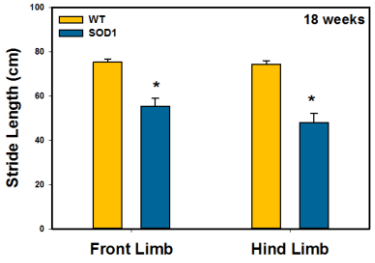
Disease Progression of Gait Features Using NeuroCube ® System in SOD1 Compared to Wild-type Mice

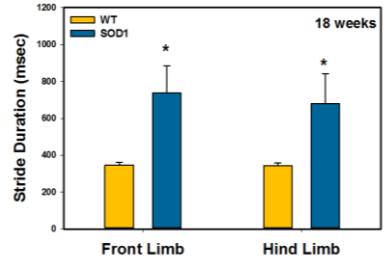
Age:	8 weeks	11 weeks	14 weeks	16 weeks	18 weeks
Disc Probability:	59%	62%	68%	80%	86%



Gait Deficits at 18 weeks





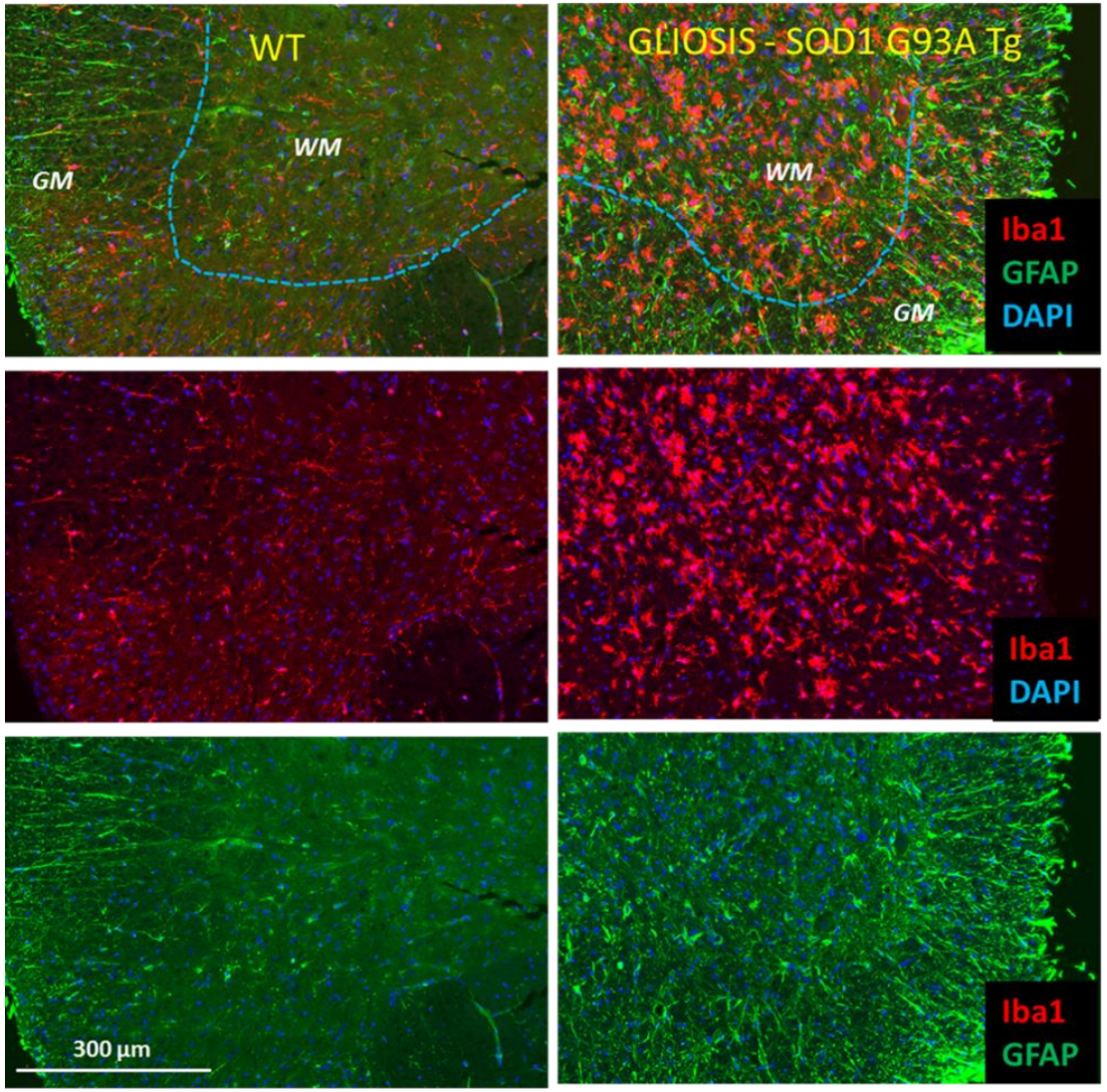


Gliosis in Lumbar Ventral Horn of Diseased SOD1 compared to WT mice.

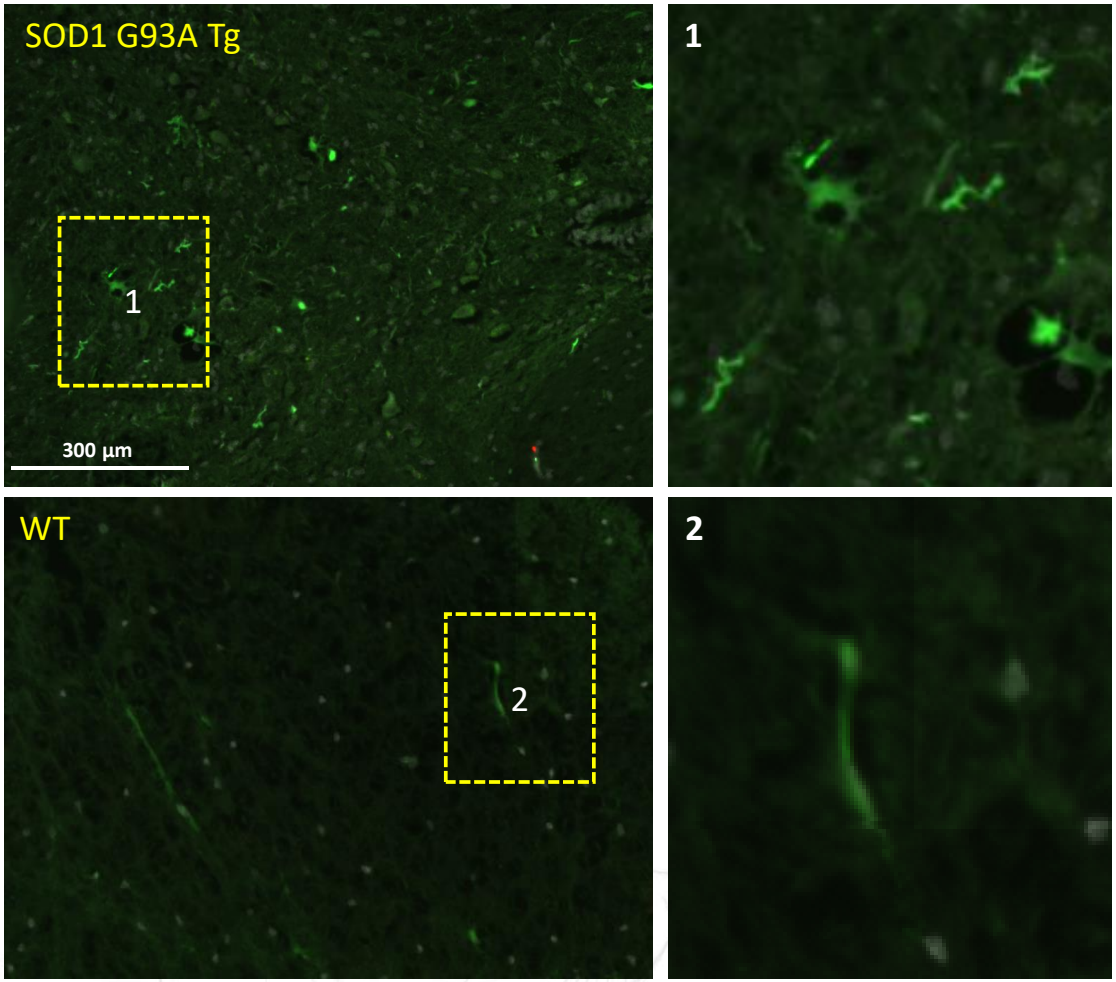
Drastic activation of microglia (**red**) being largely hypertrophic and the increased density of astroglial processes especially in the grey matter (GM).

However, also in the white matter (WM) all variables of measured gliosis were significantly above those found in wildtype littermate controls.

Upper images show the full composite images, lower either Iba1 (microglia; red) or GFAP (astroglia; green) labeling alone combined with DAPI (blue).



SOD1 aggregates visualized by NSC500 (oligothiophene)

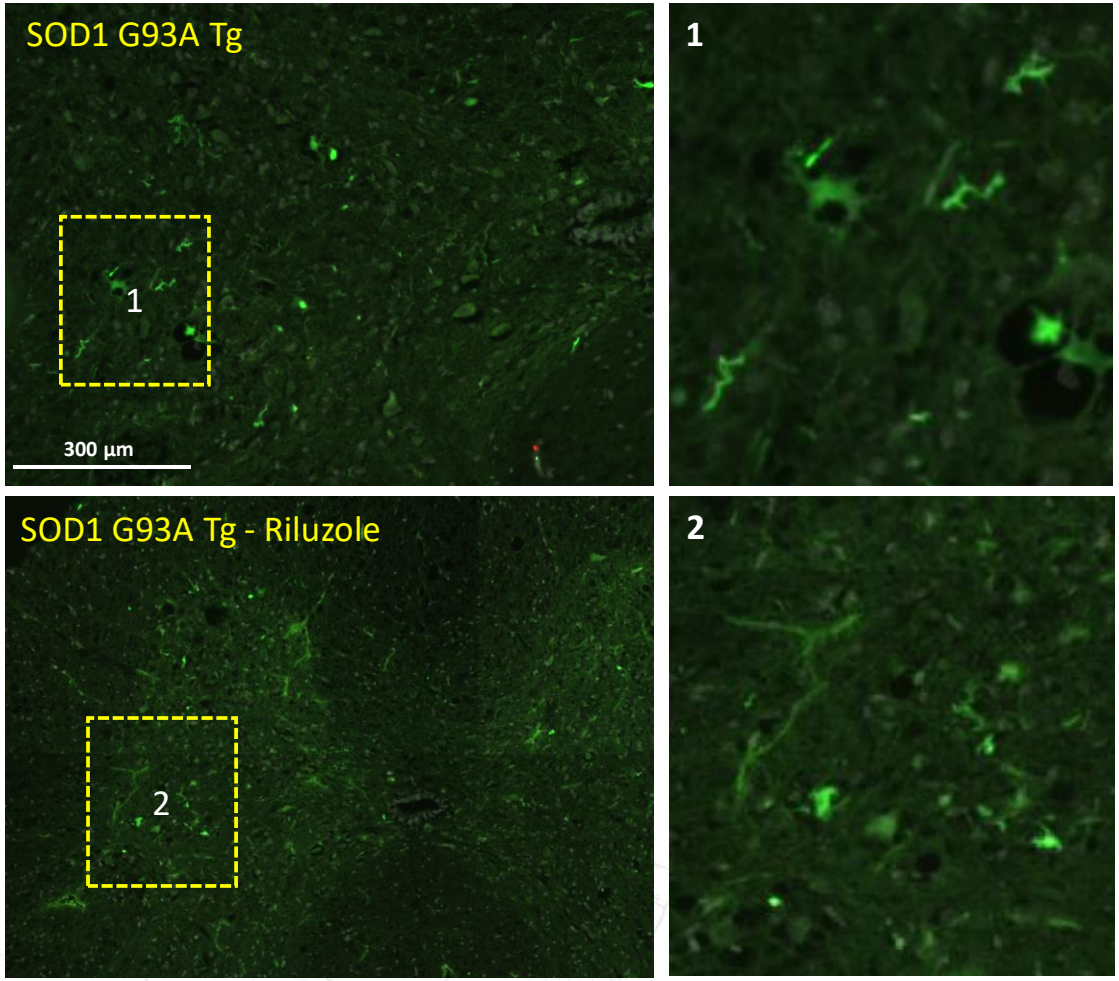


Comparison of NSC500 oligothiophene staining to SOD1 aggregates in SOD1G93A transgenic (upper) and WT littermate (lower).

NSC500 selectively binds to maturated aggregates, which can be found within neuronal processes, but also in astro- and microglia in these mice.

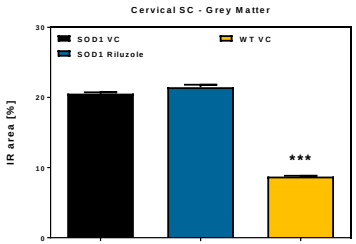
WT animals do not have SOD1 aggregates, the only visible signal derives from some autofluorescence in vasculature.

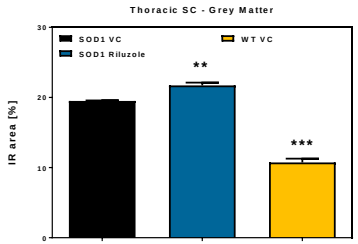
SOD1 aggregates visualized by NSC500 (oligothiophene)

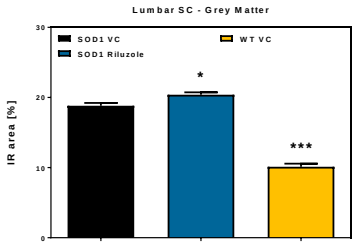


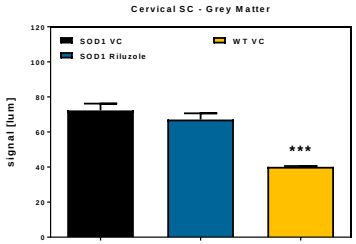
Comparison of NSC500 oligothiophene staining to SOD1 aggregates in a SOD1G93A transgenic vehicle control (upper) and a Riluzole treated mouse (lower).
NSC500 selectively binds to maturated aggregates, which can be found within neuronal processes, but also in astro- and microglia in these mice. On a qualitative level, Riluzole treatment rather indicates an increased SOD1 aggregate deposition when visualizing with this marker.

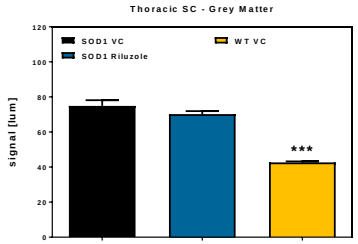
Grey matter – Astrogliosis (total GFAP IR)

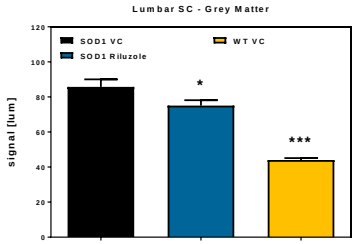


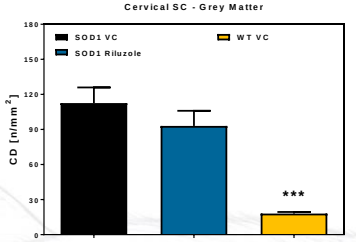


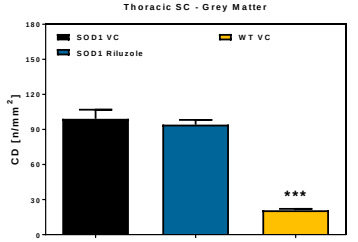


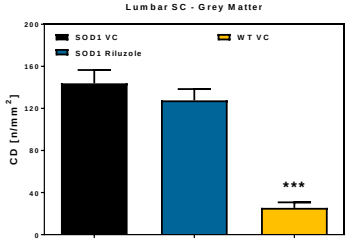






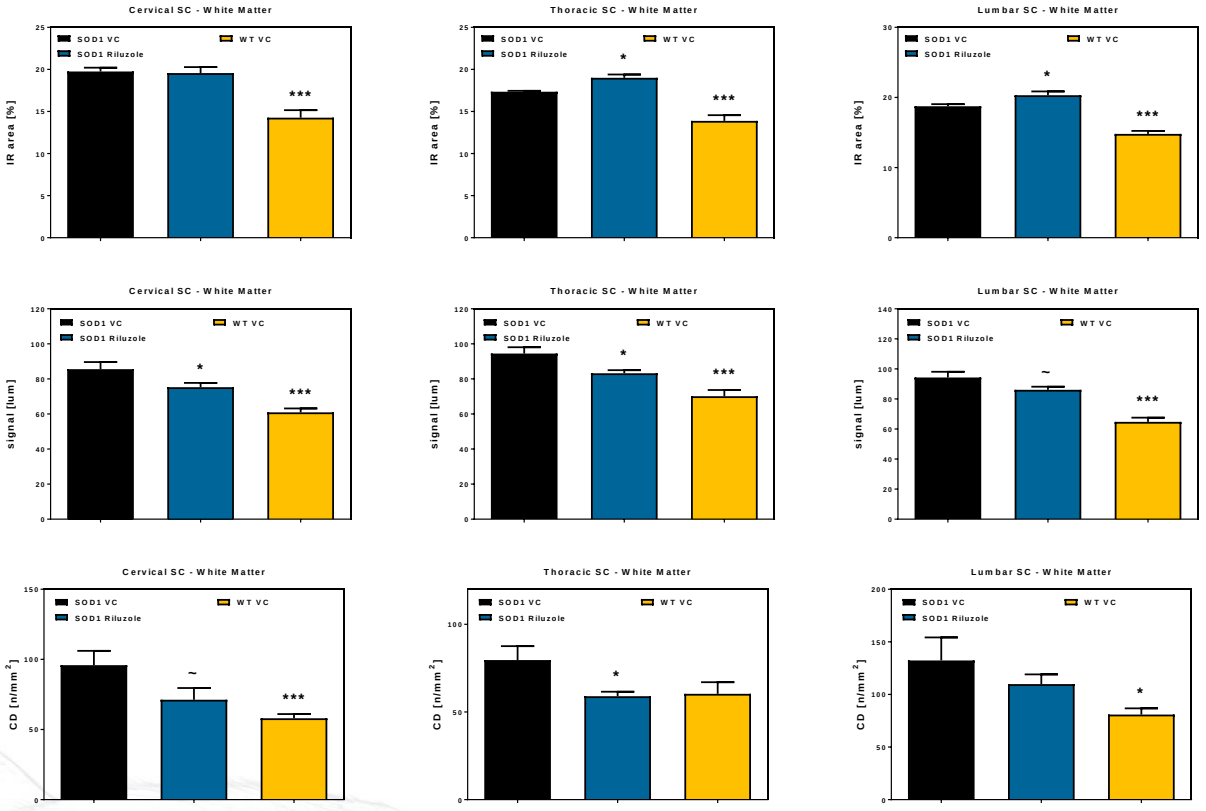






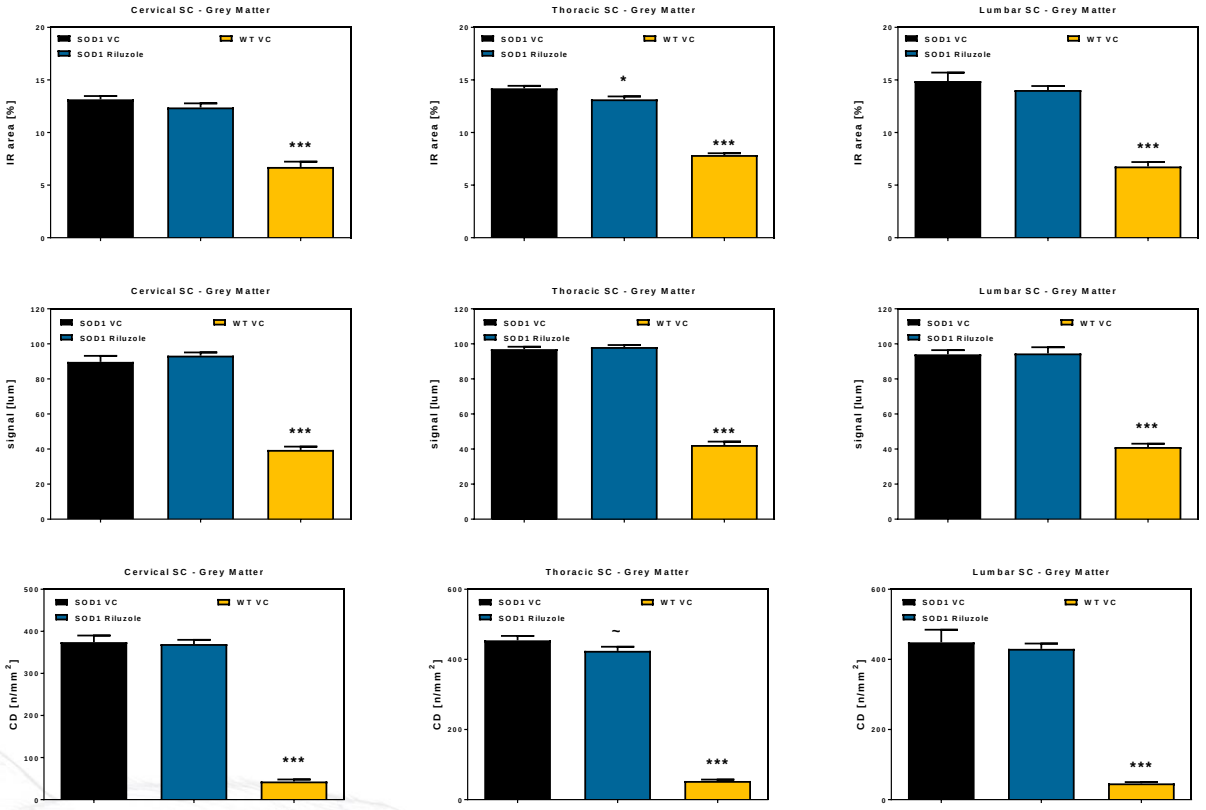
CERVICAL THORACIC LUMBAR

White matter – Astrogliosis (total GFAP IR)



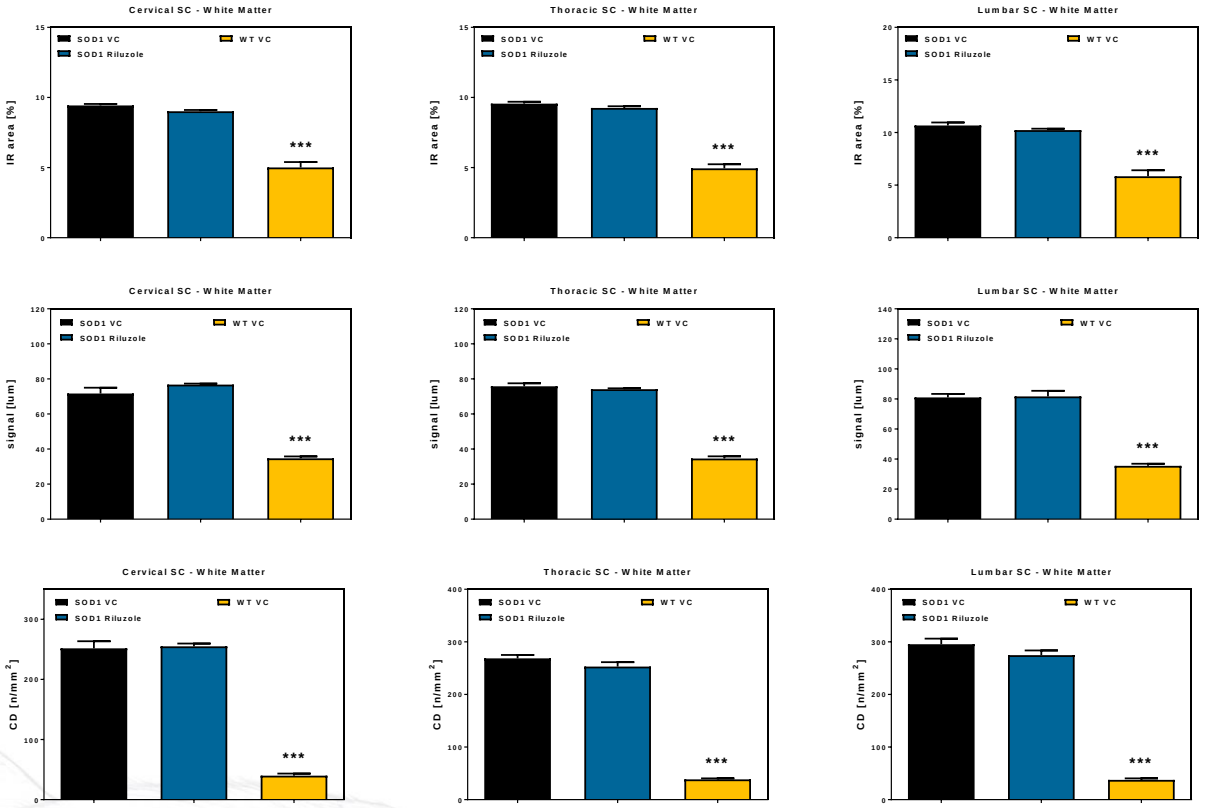
CERVICAL THORACIC LUMBAR

Grey matter – Microgliosis (total Iba1 IR)



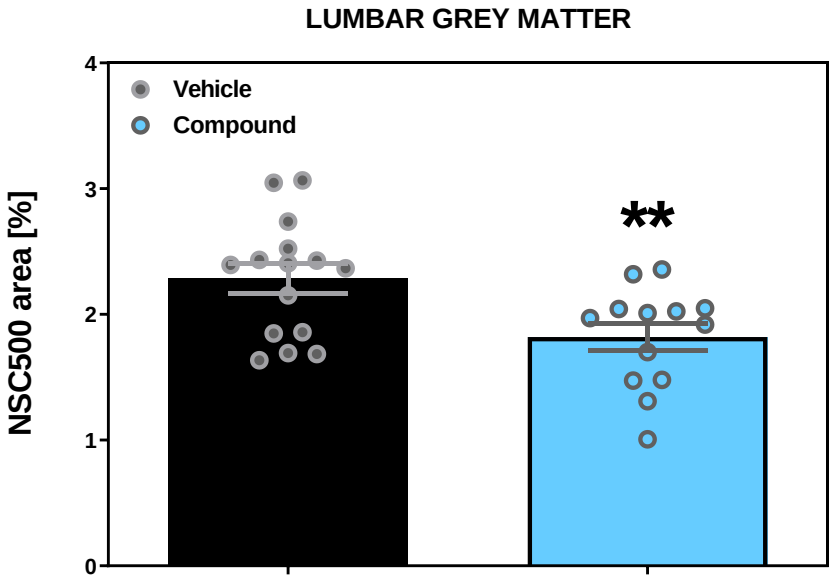
CERVICAL THORACIC LUMBAR

White matter – Microgliosis (total Iba1 IR)



CERVICAL THORACIC LUMBAR

SOD1 Aggregates



N=15/group

Summary of histology

- SOD1G93A mice show a very high degree of spinal cord inflammation. The same is true for brain stem and midbrain regions ending in subthalamic regions (not shown)
- Microglia is vastly hypertrophic and also clustering and it is not only based on morphological growth but also on a severe cytosis (more microglial cells in general). It is present and strong in both grey and white matter of spinal cords and at any transversal level.
- Astrogliosis is as well significant in all parts of the spinal cord and in white and grey matter, whereas the window in white matter is smaller due to natural structural astrocytes in these regions. Also astrogliosis is as well based on a severe cytosis, especially in grey matter.
- A high degree of SOD1 aggregate accumulation can be shown by oligothiophene binding
- Riluzole treatment led to little effect on gliosis in general. In the thoracic white matter, astrocytosis was lower than in controls, however, at the same time IR area was growing which hints at greater reactivity. Thus the only measured probably beneficial effect was leveled by more reactivity.
- A similar trend of lower microglial cytosis with Riluzole treatment in the thoracic grey matter was measured in total Iba1, however, also with little absolute benefit.
- On a qualitative level, SOD1 aggregate load seems not to be positively altered by Riluzole treatment.