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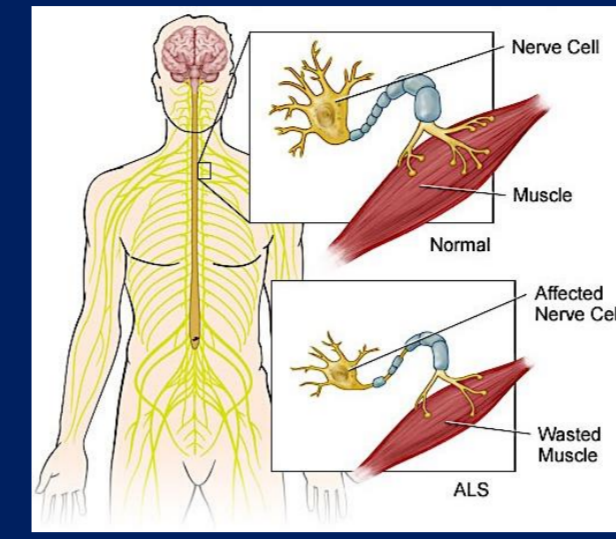
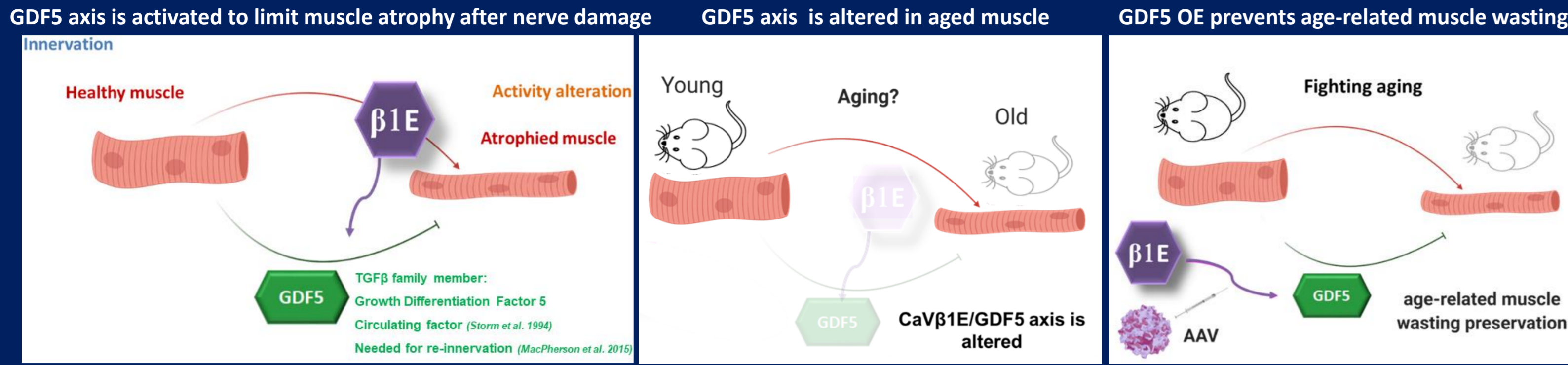
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# Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

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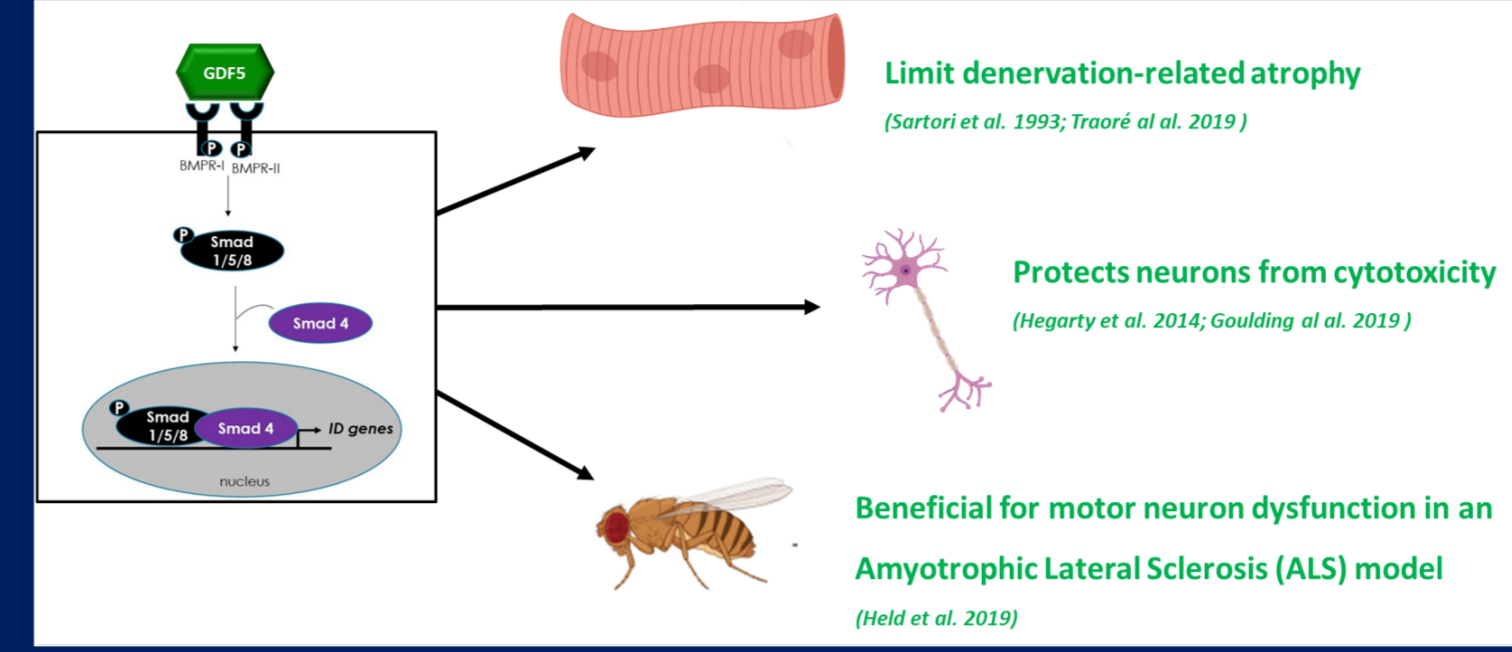
## Introduction



### ALS

- The most common adult-onset motor neuron disorder (1-4 per 100.000 live birth per year)
- 90% sporadic forms, 10% familial forms
- Very rapid progression: death often occurs within 3 - 5 years of diagnosis
- Multifactorial pathophysiological mechanisms
- No cure: More than 50 negative randomized controlled clinical trials in the past 50 years

### Therapeutic potential of GDF5 in ALS



### ALS-linked mutations: SOD1

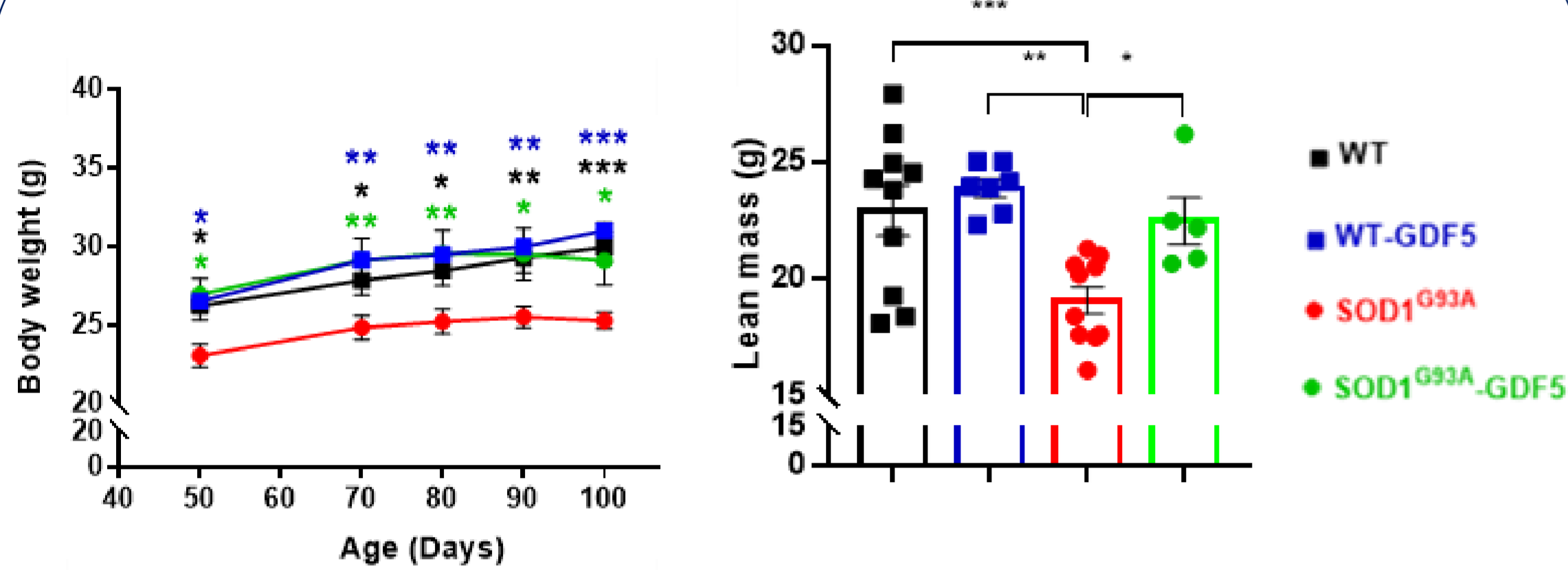
- 20% of the familial cases are caused by toxic gain of function mutations in the Cu/Zn superoxide dismutase-1 gene (SOD1)
- Modeling by mutant hSOD1 overexpression

### SOD1-G93A mouse

- ✓ Abbreviated lifespan (128.9±9.1 days)
- ✓ Paralysis
- ✓ Rapid disease progression
- ✓ Motor neuron degeneration
- ✓ Astrogliosis
- ✓ Severe muscle weakness

Muscle denervation is a common hallmark of several neuromuscular diseases and accounts for skeletal muscle atrophy and dysfunction associated to their pathophysiology. In non-pathologic muscle, the induction of GDF5/SMAD1/5 pathway is essential for avoiding excessive atrophy but also for promoting re-innervation after nerve damage. Recently, we demonstrated that alterations of GDF5 pathway can be implicated in human and mouse age-related muscle wasting and that its overexpression prevents muscle mass loss and force decline during ageing in mice. SMAD1/5 pathway activation has been described as beneficial for motor neuron dysfunction in an Amyotrophic Lateral Sclerosis (ALS) model. We thus hypothesize that GDF5 implementation could have a positive impact on pathophysiology of the disease. We propose a strategy potentially applicable to different ALS forms and/or to optimize gene therapy-based approaches.

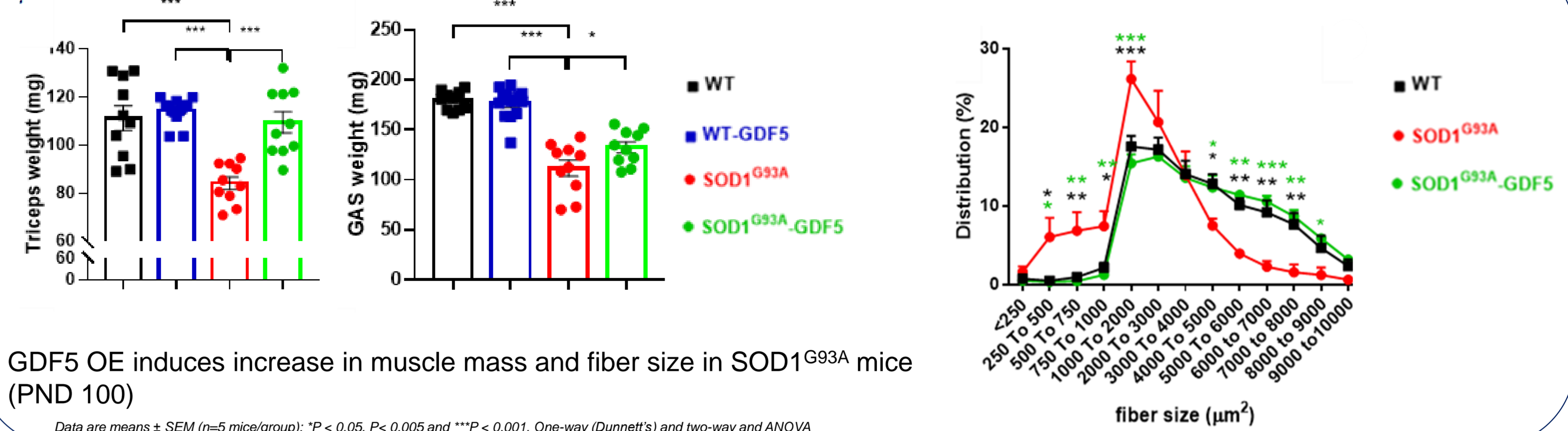
### GDF5 overexpression and ALS progression in SOD1<sup>G93A</sup> mice



GDF5 OE induces increase in BW and lean mass of SOD1<sup>G93A</sup> mice (PND 100)

Data are means ± SEM (n=5 mice/group); \*P < 0.05, \*\*P < 0.005 and \*\*\*P < 0.001. Two-way and one-way ANOVA (Dunnnett's)

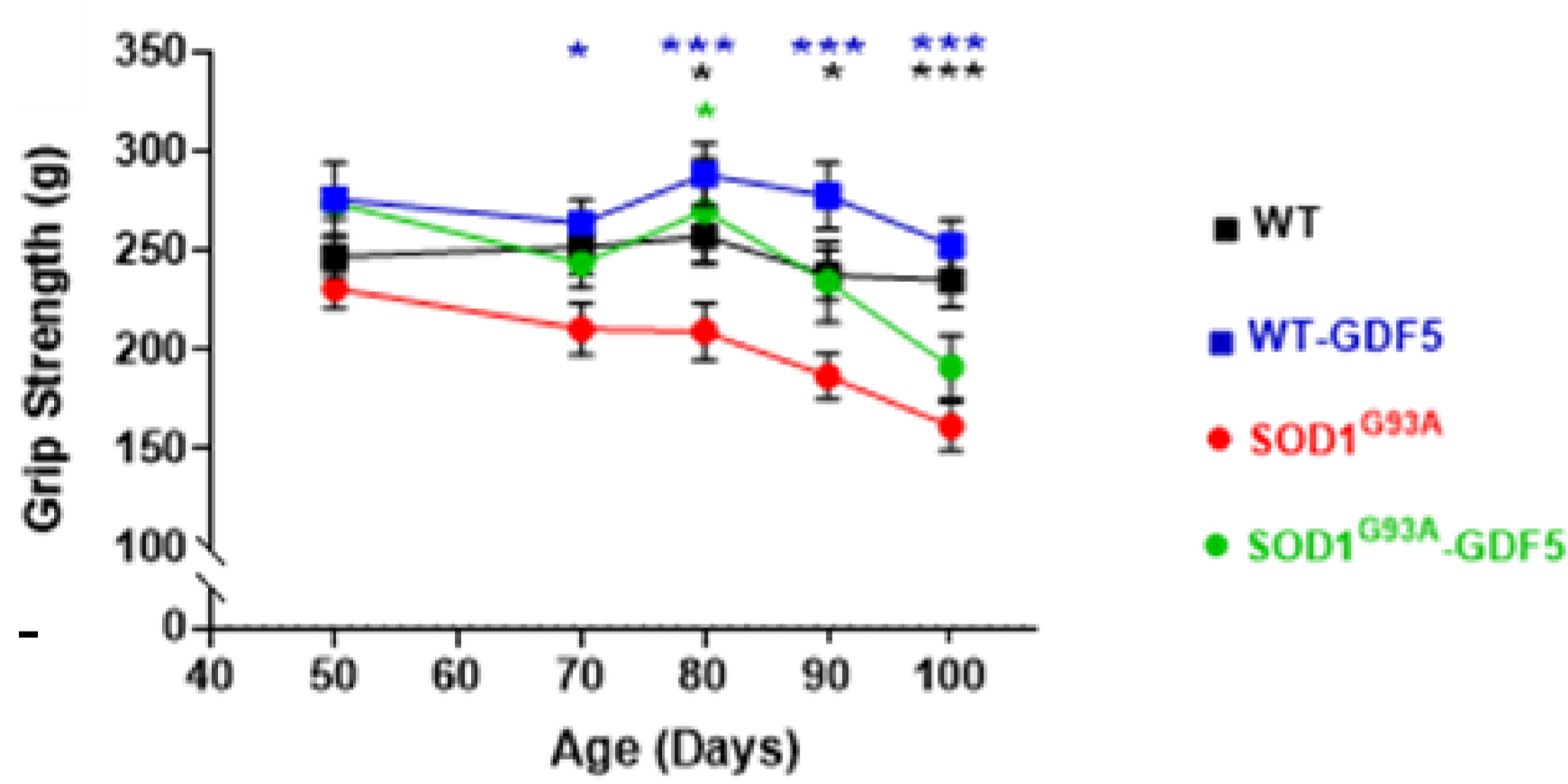
### GDF5 overexpression and muscle mass



GDF5 OE induces increase in muscle mass and fiber size in SOD1<sup>G93A</sup> mice (PND 100)

Data are means ± SEM (n=5 mice/group); \*P < 0.05, \*\*P < 0.005 and \*\*\*P < 0.001. One-way (Dunnnett's) and two-way and ANOVA

### Force generation of GDF5 overexpressing SOD1<sup>G93A</sup> mice

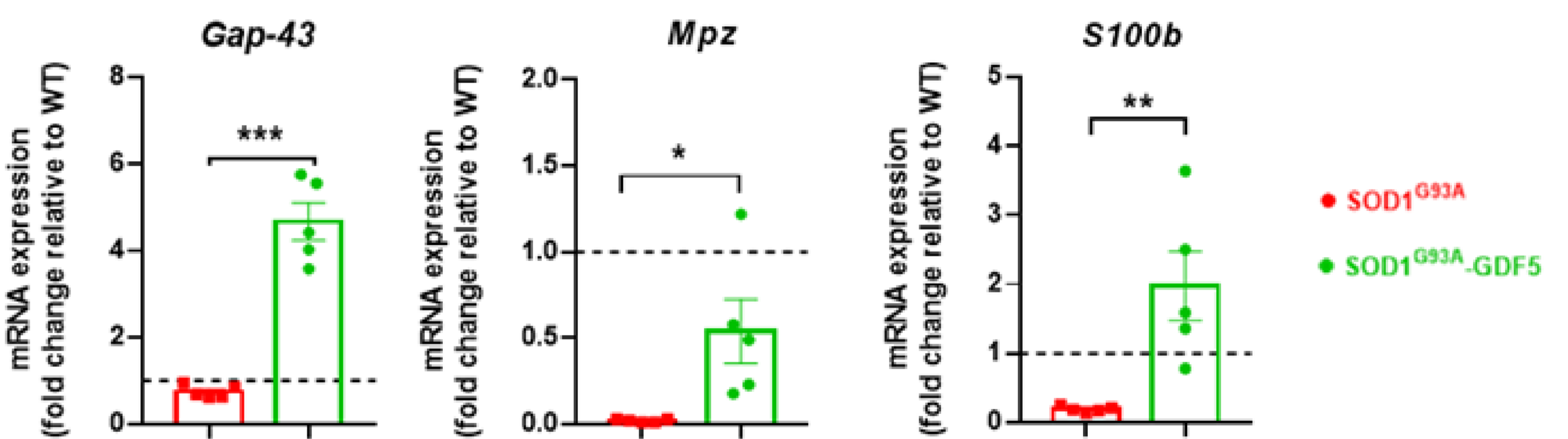


GDF5 OE delays force decline of SOD1<sup>G93A</sup> mice

Data are means ± SEM (n=5 mice/group); \*P < 0.05, and \*\*\*P < 0.001. one-way ANOVA; Dunnnett's test;

### Nerve regeneration markers

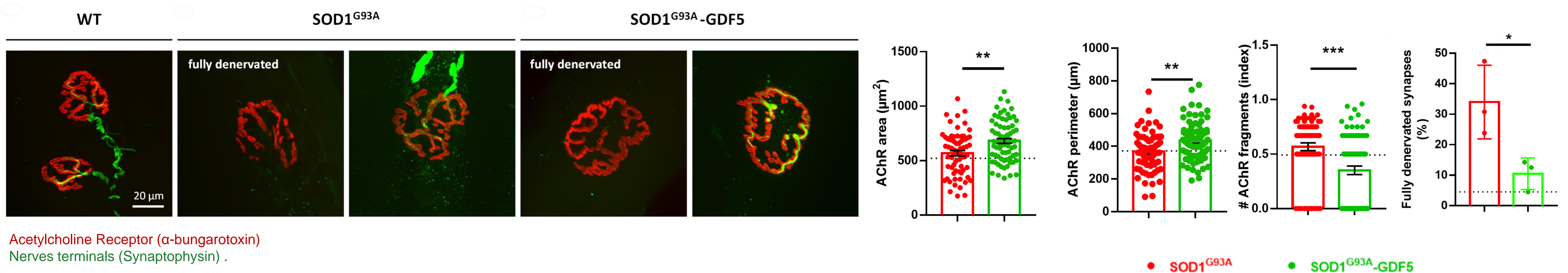
Growth-associated protein 43 (GAP43): associated with regenerating axons and Schwann cells, Myelin Protein Zero (MPZ) and S100b increase during nerve regeneration



GDF5 OE induces increase of transcripts associated to nerve regeneration suggesting a protective role of this factor against MN degeneration observed in ALS.

Data are means ± SEM (n=5 mice/group); \*P < 0.05, \*\*P < 0.005 and \*\*\*P < 0.001. Independent samples t-test (two tailed). Dotted black lines indicate the average of expression in age-matched WT mice.

### Neuromuscular junction morphology and innervation



Synapses are more stable in GDF5 OE muscles, with increased endplates area and perimeters and decreased AChR fragmentation index and percentage of fully denervated synapses

Data are means ± SEM (n= 66/75 counted endplates=3 mice/group); \*P < 0.05, \*\*P < 0.005 and \*\*\*P < 0.001. Independent samples t-test (two tailed). Dotted black lines indicate the average of expression in age-matched WT mice

## Conclusions

### Benefits of GDF5 overexpression in ALS:

- ✓ Maintains muscle mass and fibers size and delays grip strength decline
- ✓ Shows a positive impact on nerve regeneration markers
- ✓ Exerts a protective effect against muscle denervation

## Perspectives

### Establishment of GDF5 therapeutic potential in ALS

- ✓ Effects of GDF5 on neuro-inflammation, motor neuron viability and survival
- ✓ Evaluation of tissue-specific GDF5 expression on ALS pathophysiology
- ✓ Therapeutic test of GDF5 in adult ALS mice and in combination with a gene therapy