



Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

Sestina Falcone, T. Marais, M. Traoré, C. Gentil, J. Mésseant, B. Cadot, S.
Cottin, M. Zerara, L. Strohlic, P. Smeriglio, et al.

► To cite this version:

Sestina Falcone, T. Marais, M. Traoré, C. Gentil, J. Mésseant, et al.. Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis. 18ème Journée de la Société Française de Myologie, Nov 2021, Saint-Etienne (FR), France. hal-04002180

HAL Id: hal-04002180

<https://hal.sorbonne-universite.fr/hal-04002180>

Submitted on 2 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

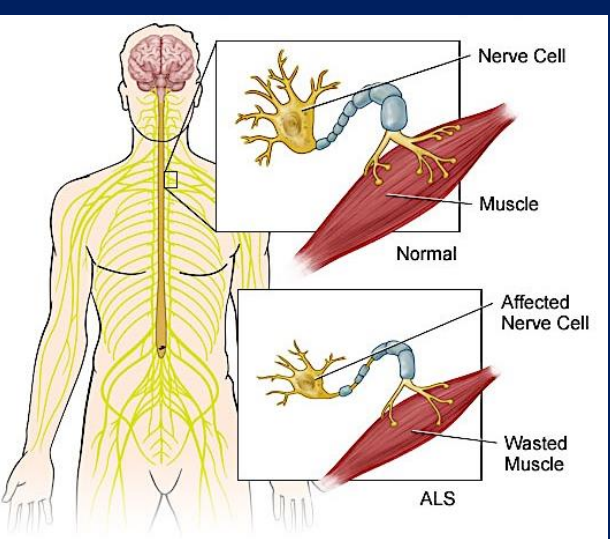
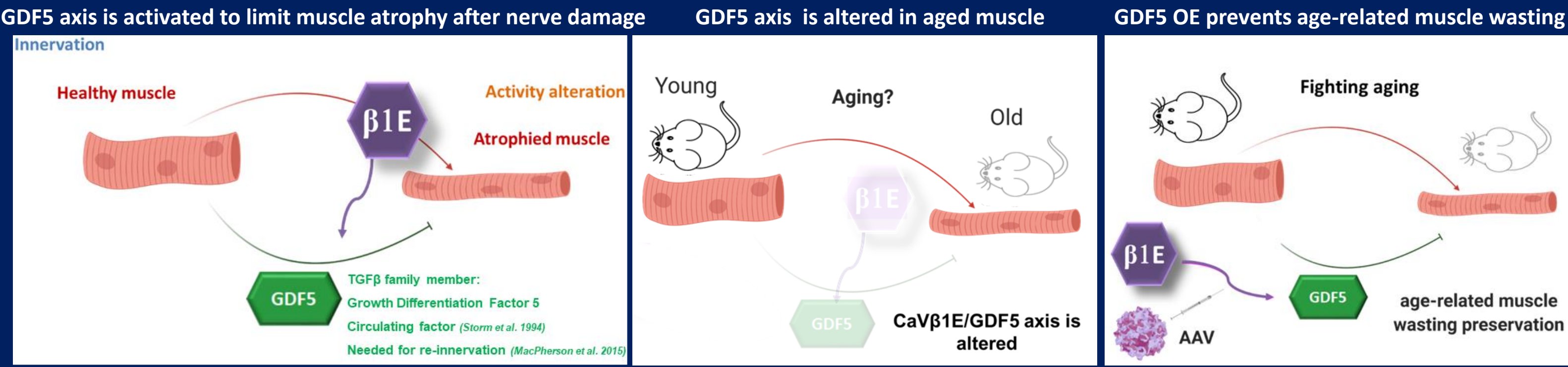
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

S. Falcone¹, T. Marais^{*1}, M. Traoré^{*1}, C. Gentil¹, J. Mésseant¹, B. Cadot¹, S. Cottin¹, M. Zerara¹, L. Stochlic¹, P. Smeriglio¹, M.G. Biferi^{*1} and F. Piétri-Rouxel^{*1}.

¹Sorbonne Université, INSERM, Institut de Myologie, Centre de Recherche en Myologie, F-75013 Paris, France; * Equally contributed

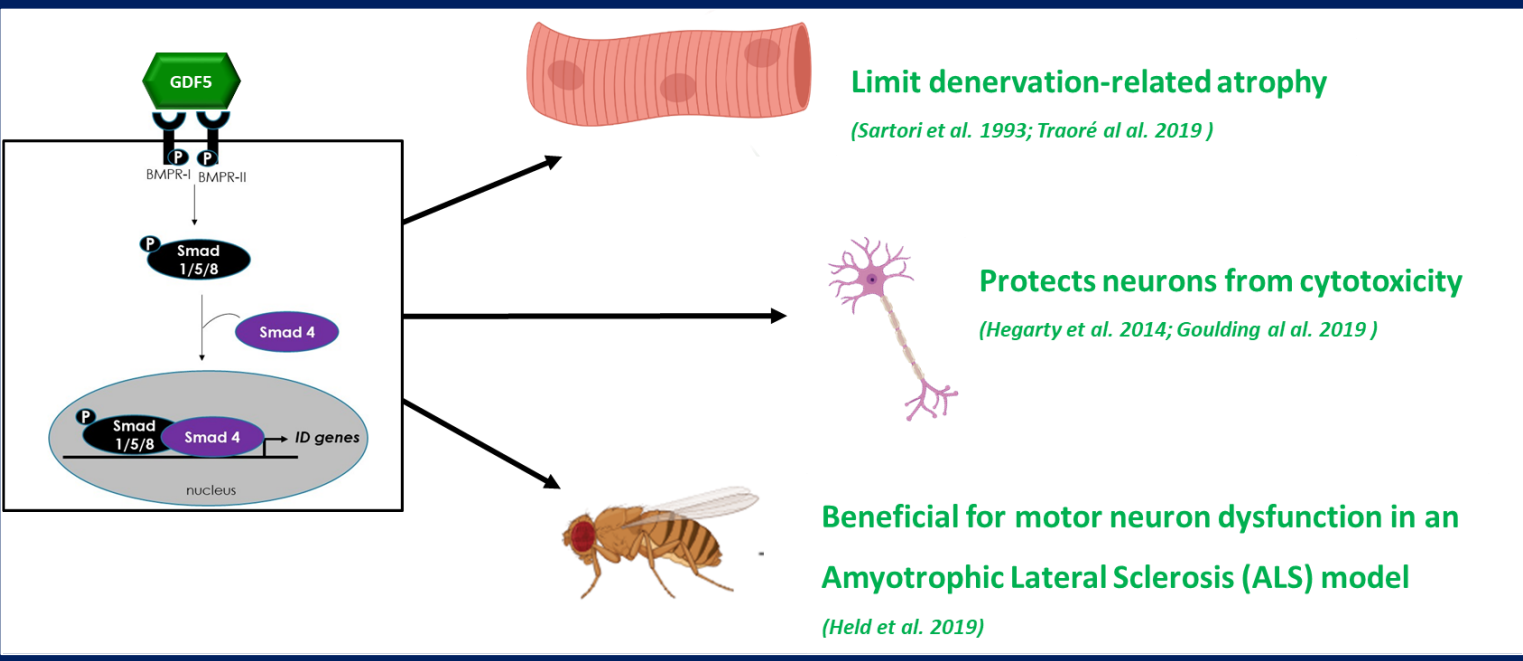
Introduction



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



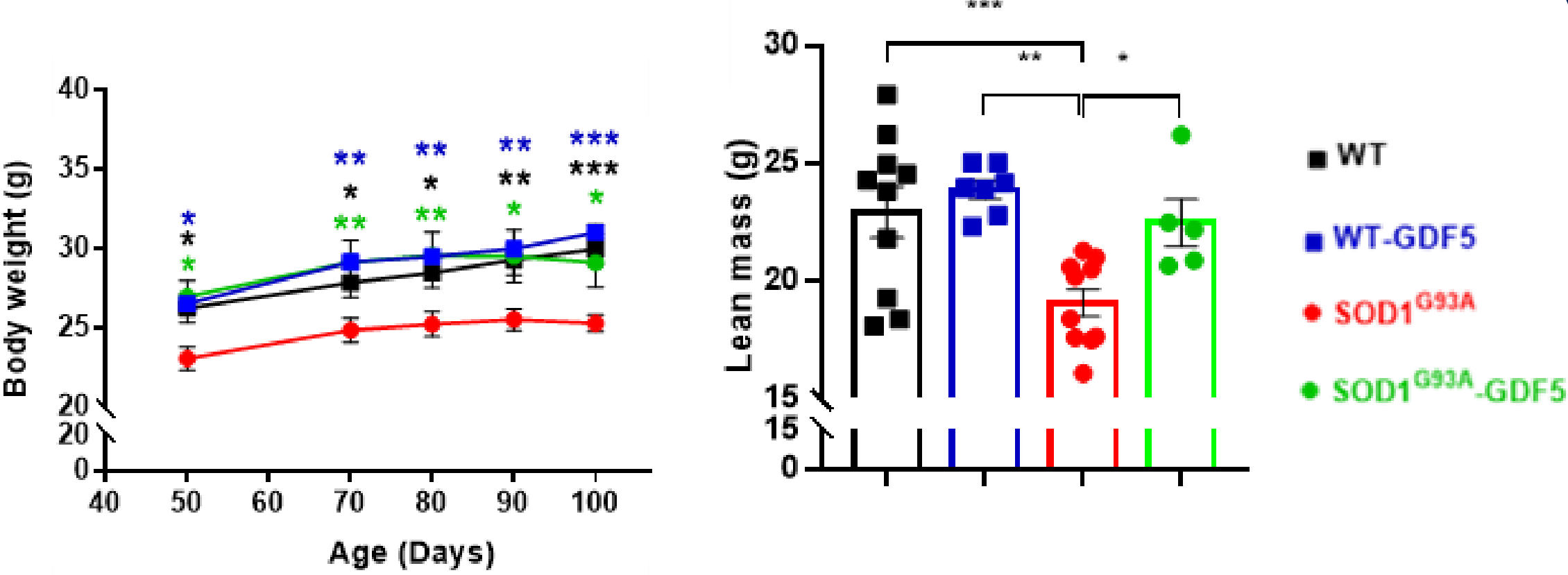
ALS-linked mutations: SOD1

- 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
- ✓ Astroglia
- ✓ Severe muscle weakness

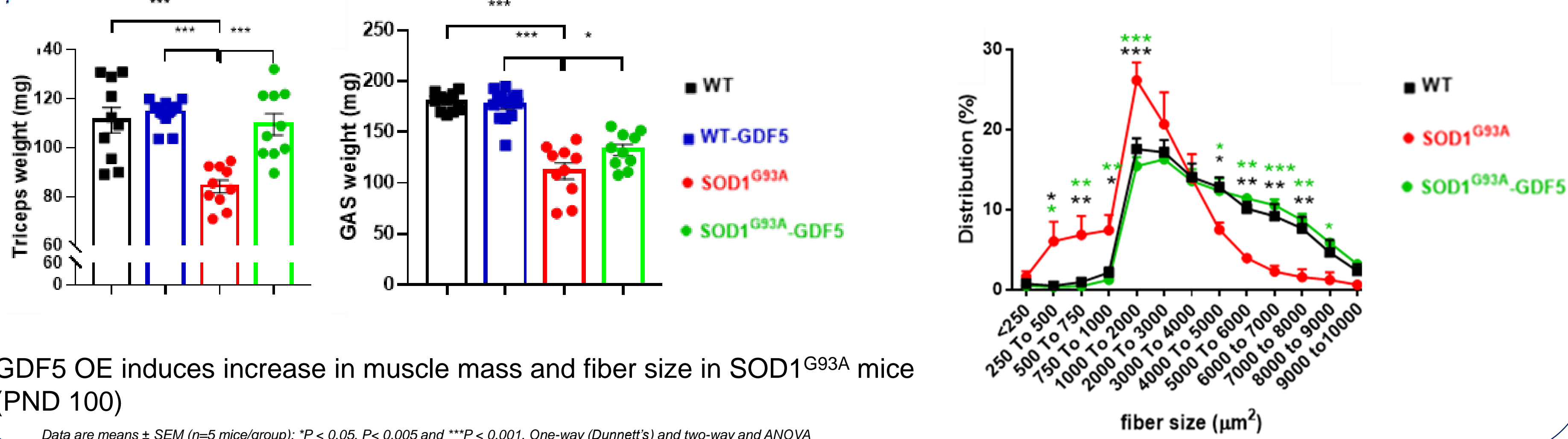
GDF5 overexpression and ALS progression in SOD1^{G93A} mice



GDF5 OE induces increase in BW and lean mass of SOD1^{G93A} 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)

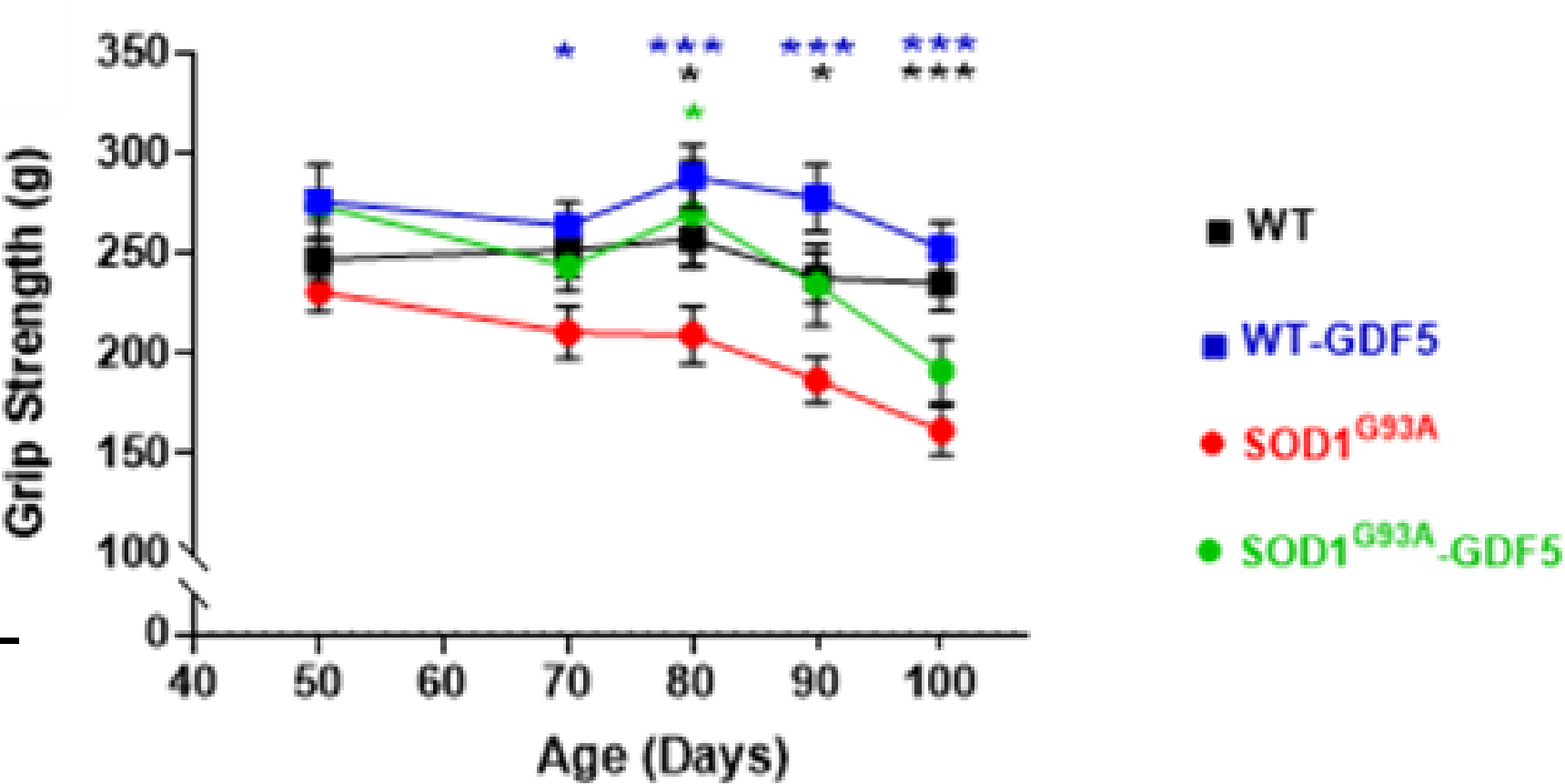
GDF5 overexpression and muscle mass



GDF5 OE induces increase in muscle mass and fiber size in SOD1^{G93A} 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^{G93A} mice

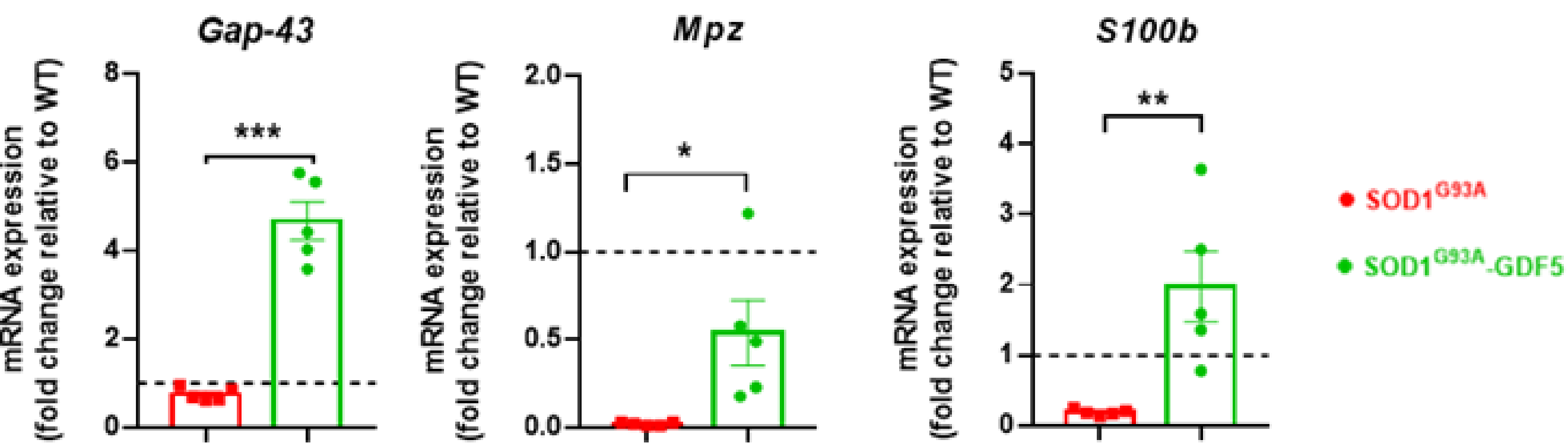


GDF5 OE delays force decline of SOD1^{G93A} mice

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

Nerve regeneration markers

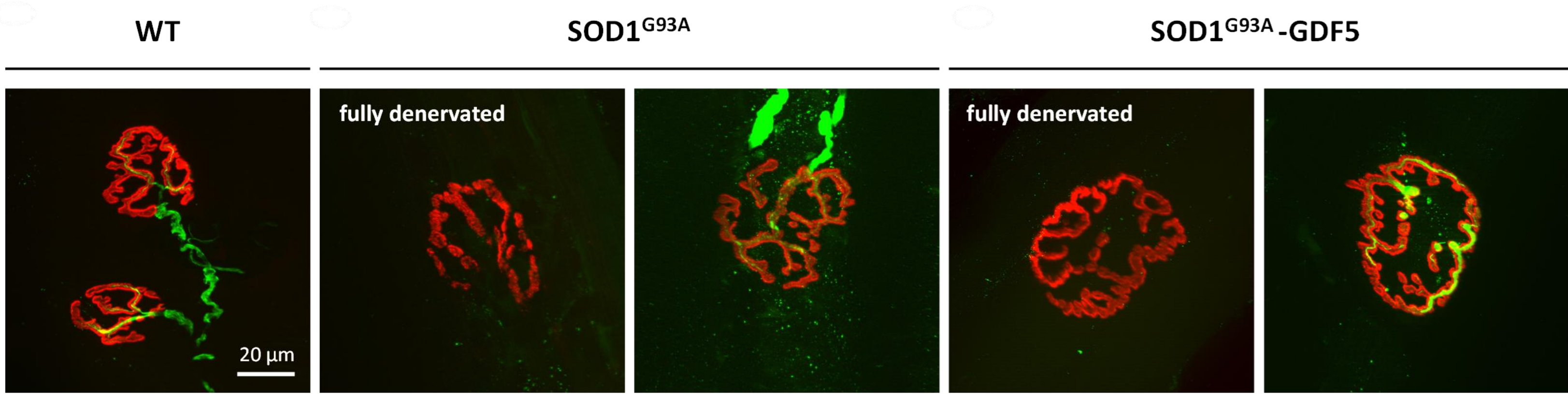
Growth-associated protein 43 (GAP43): associated with regenerating axons and Schwann cells, Myelin Protein Zero (MPZ) and S100b increase during nerve regeneration



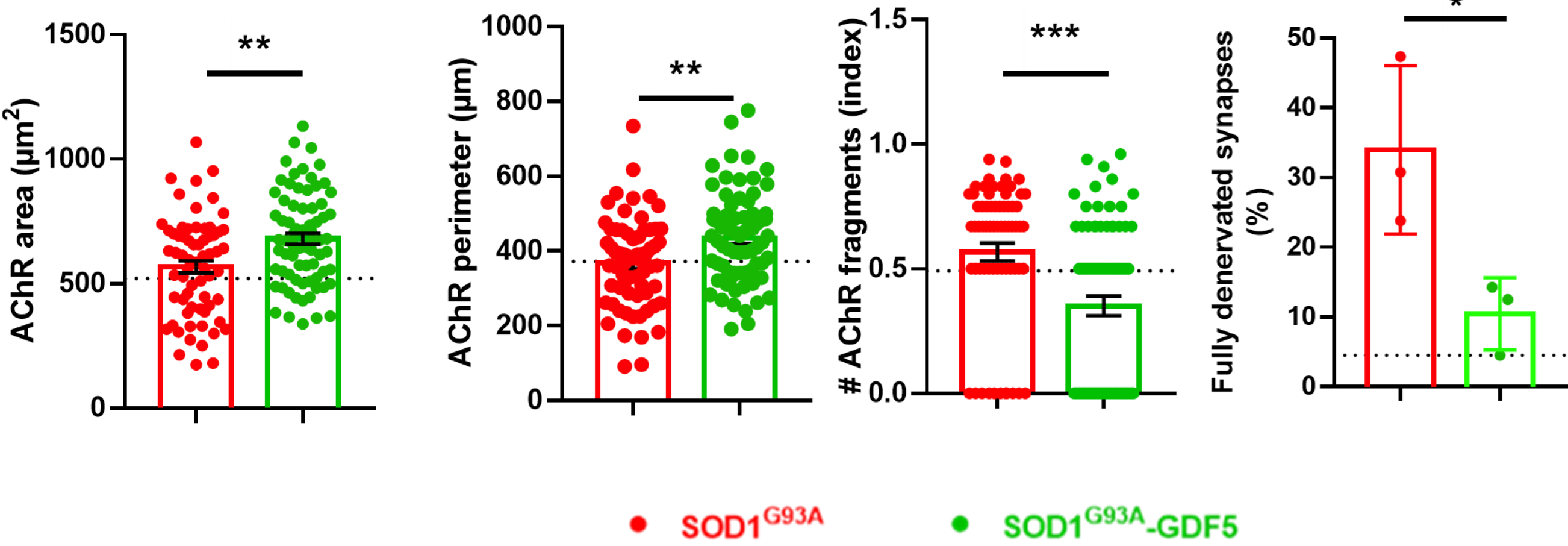
GDF5 OE induces increase of transcripts associated to nerve regeneration suggesting a protective role of this factor against MN degeneration observed in ALS.

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



Acetylcholine Receptor (α-bungarotoxin)
Nerves terminals (Synaptophysin) .



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