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► **To cite this version:**

France Piétri-rouxel, Aly BOURGUIBA VILLENEUVE, Sestina Falcone, Sonia Pezet, Massiré Traoré, et al.. Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis. *Myology* 2024, Apr 2024, Paris, France. hal-04782464

HAL Id: hal-04782464

<https://hal.science/hal-04782464v1>

Submitted on 14 Nov 2024

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Unraveling the role of GDF5 therapeutic potential in Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis : 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 after diagnosis
- Multifactorial pathophysiological mechanisms
- No cure: More than 50 negative randomized controlled clinical trials in the past 50 years

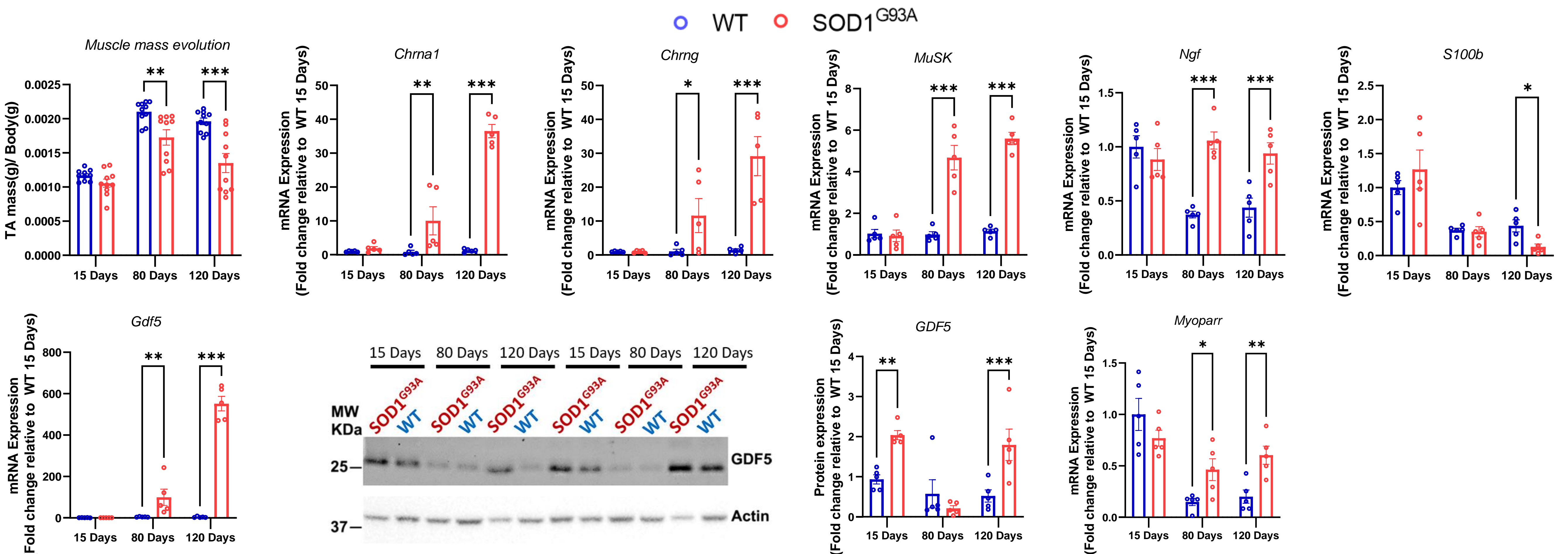
Therapeutic potential of GDF5 in ALS

- Limit denervation-related atrophy (Sartori et al. 2013, Traoré et al. 2019)
- Protects neurons from cytotoxicity (Hegarty et al. 2013, Goulding et al. 2019)
- Beneficial for motor neuron failure in an Amyotrophic Lateral Sclerosis (ALS) model (Heid et al. 2019)

ALS-linked mutation: 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 mouse model of mutant *hSOD1*^{G93A}

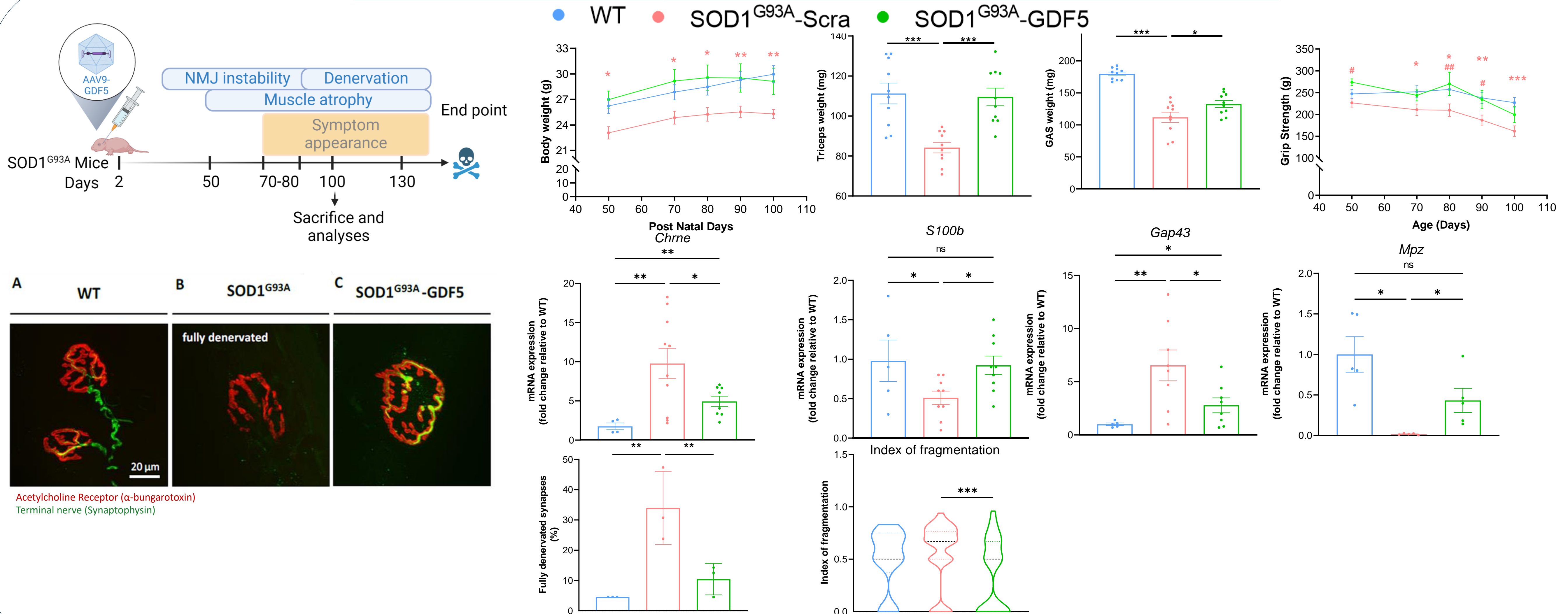
Disease progression and neuromuscular degeneration markers in ALS



- NMJ remodelling markers are altered in SOD1^{G93A} mice
- GDF5 protein expression increases early in non-symptomatic 15 days-old SOD1^{G93A} mice and decreases at 80 days
- *Myoparr* lncRNA, shown as inhibiting GDF5 expression, is increased in SOD1^{G93A} mice

Data are means ± SEM (n=5 mice/group); *P < 0.05, **P < 0.01 and ***P < 0.001. Two-way ANOVA (Fisher's).

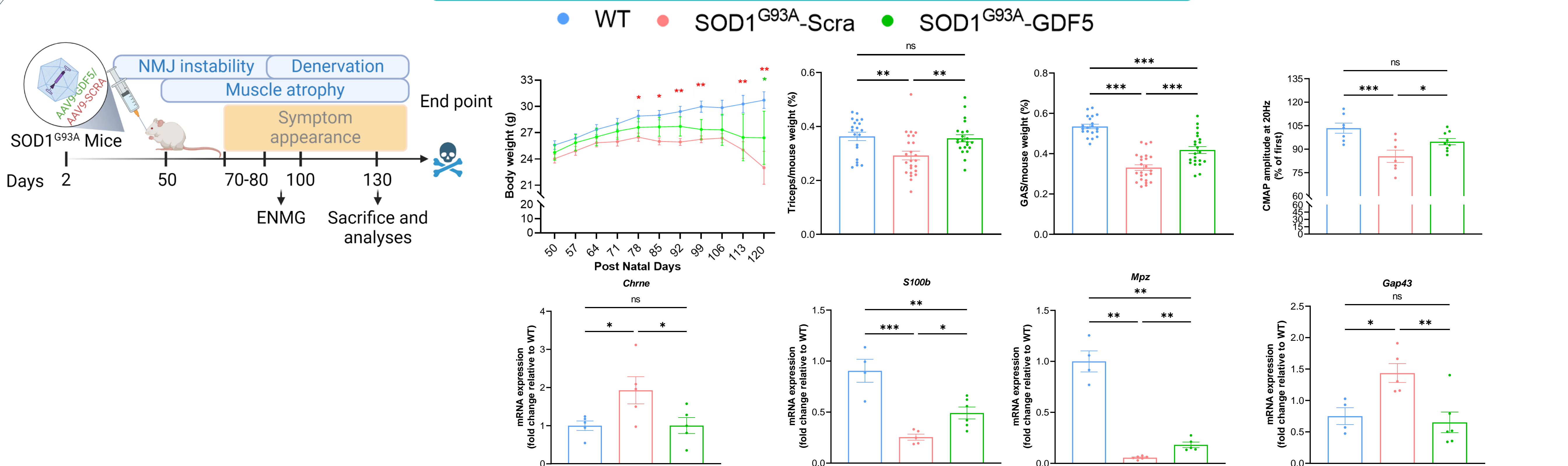
GDF5 overexpression in neonatal SOD1^{G93A} mice



GDF5 OE maintains muscle mass, partially rescues the expression of NMJ remodelling markers and improves endplate's morphology

Data are means ± SEM (n=5-9 mice/group); *P < 0.05, **P < 0.01 and ***P < 0.001. One-way ANOVA (Fisher's).

GDF5 overexpression in adult SOD1^{G93A} mice



GDF5 OE improves muscle mass, neuromuscular connectivity and NMJ remodelling markers

Data are means ± SEM (n=4-8 mice/group); *P < 0.05, **P < 0.01 and ***P < 0.001. One-way ANOVA (Fisher's).

Conclusion

- Systemic GDF5 OE in neonatal mice preserves muscle mass and NMJ integrity
- Systemic GDF5 OE in adult mice maintains neuromuscular connectivity

Perspectives

- Evaluation of increased GDF5 protein as potential « early biomarker »
- Effects of GDF5 on motor neuron viability and survival