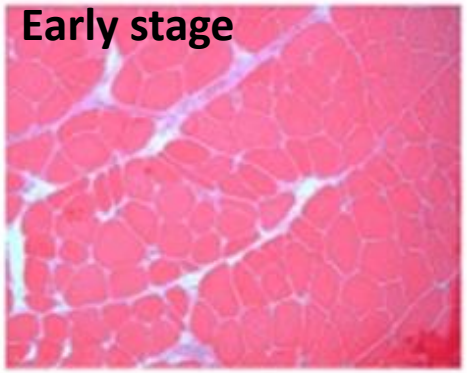
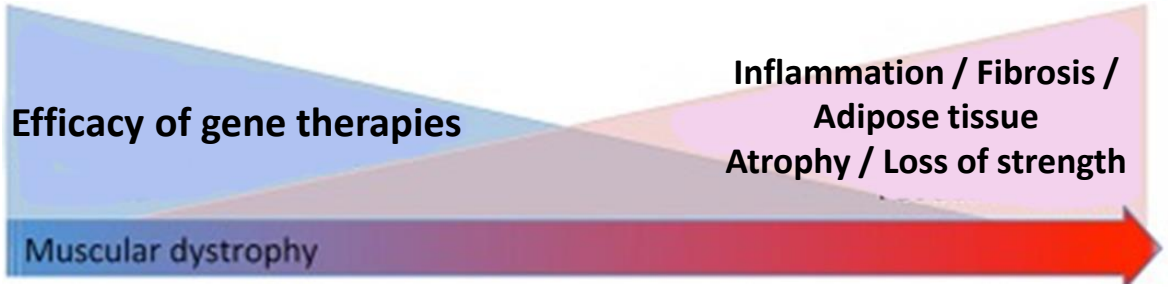
GDF5 therapeutic potential for Duchenne Muscular Dystrophy gene therapy optimization

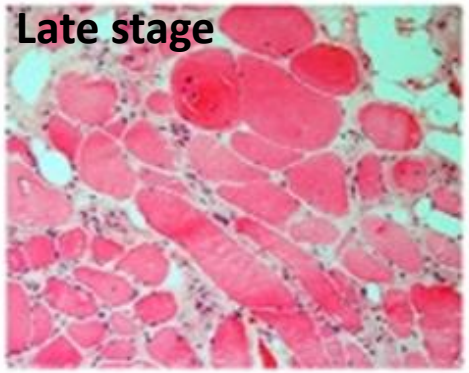
France Piétri-Rouxel

Duchenne Muscular Dystrophy - DMD

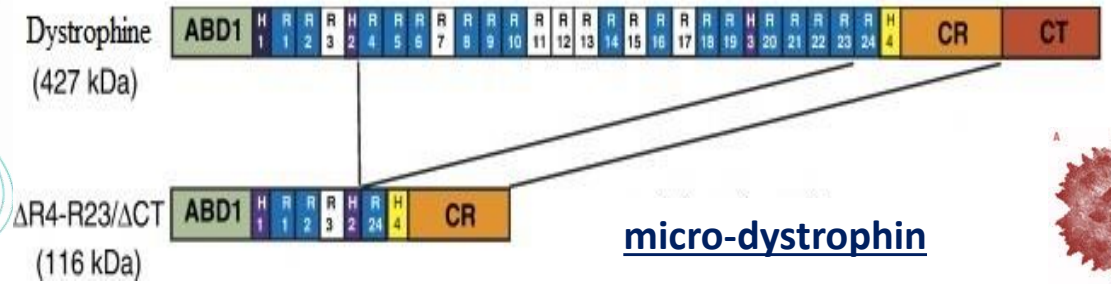
Lack of Dystrophin → **muscle fiber damage** → **necrosis/regeneration process** → **Degeneration**



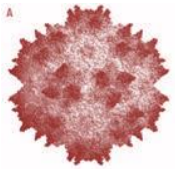




Adapted from Gordova G et al, Front Genet. 2018



micro-dystrophin



Limitation for AAV gene therapy : loss of viral genome

Need for a combined treatment to optimize dystrophin restoration

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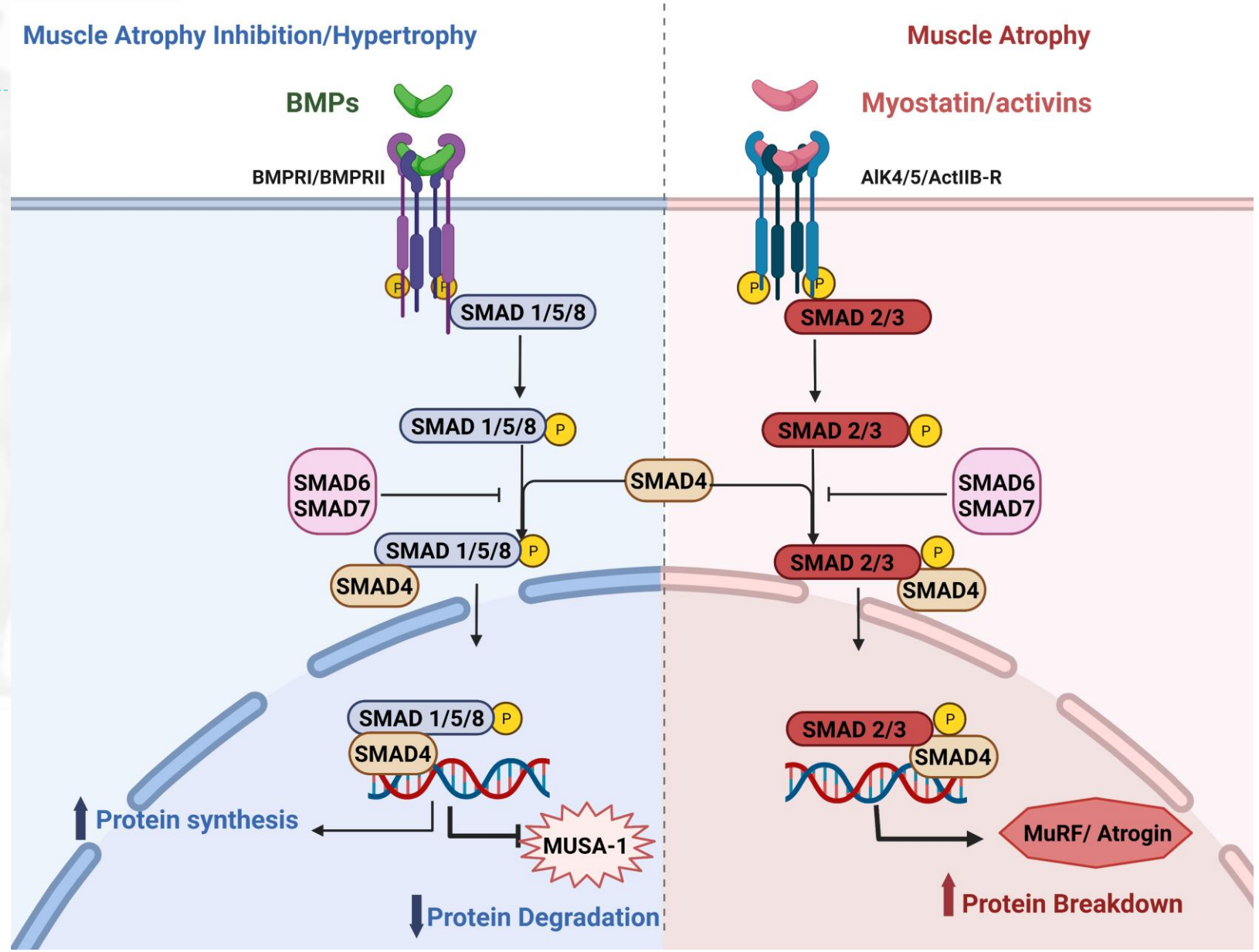
Muscle mass homeostasis



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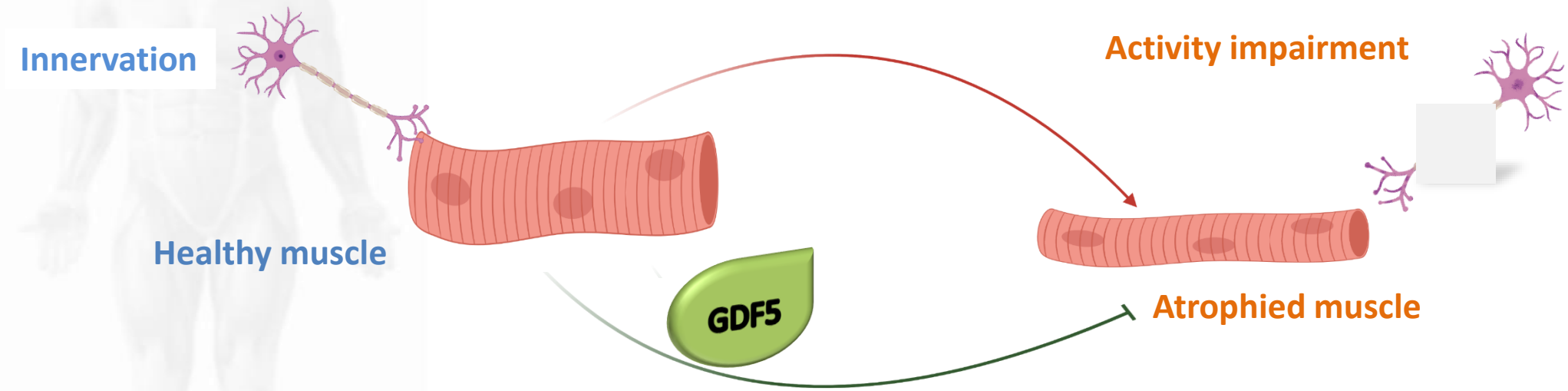
BMP14/GDF5 conteracts muscle atrophy after electrical activity impairment



TGFβ family member: Growth Differentiation Factor 5

Circulating factor *(Storm et al. 1994)*

Compensatory response to limit muscle mass loss
Sartori et al, Nat Gen 2013

Needed for re-innervation *(MacPherson et al. 2015)*

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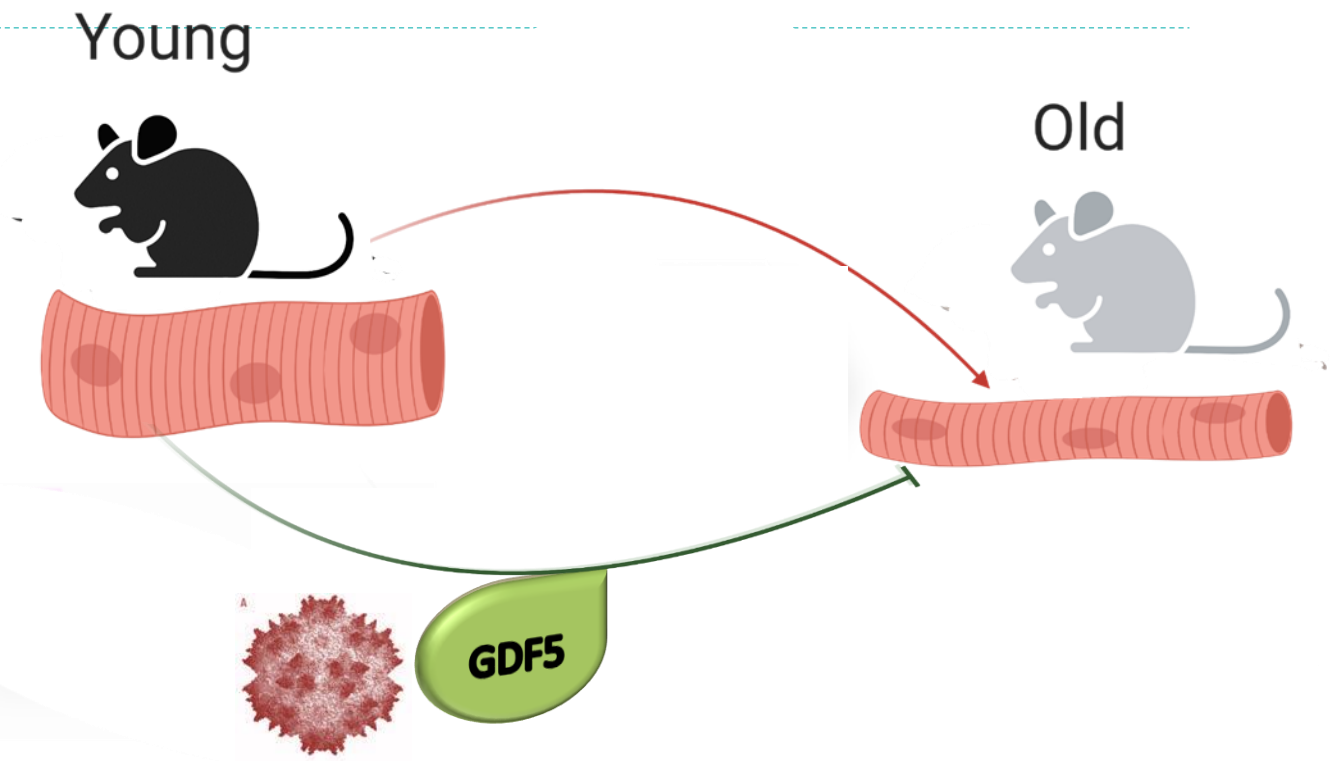
Counterbalancing age-related muscle atrophy through novel identified molecular pathways



Preservation of age-related muscle mass and function wasting

Traoré et al. Science Translational Medicine, 2019

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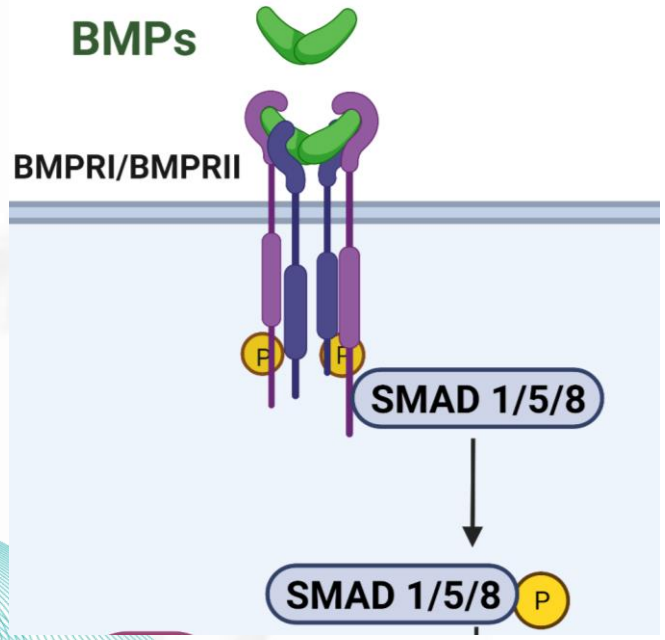
BMP signaling and skeletal muscle regeneration



Balances proliferation and differentiation of satellite cell descendants (Friedrichs et al., 2011).

Regulates myogenic differentiation in muscle satellite cells (Ono et al., 2011).

Has a key role in adult muscle regeneration (Clever et al., 2010).

Inhibits intramuscular adipogenesis (Huang et al., 2014).

Effects of GDF5 in DMD?

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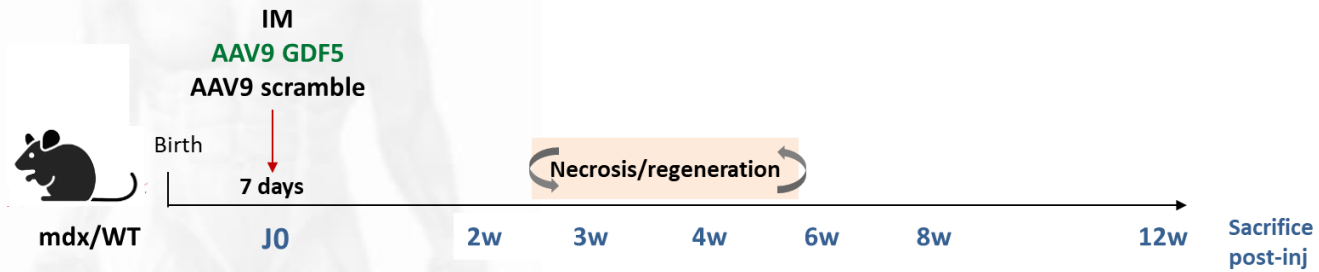
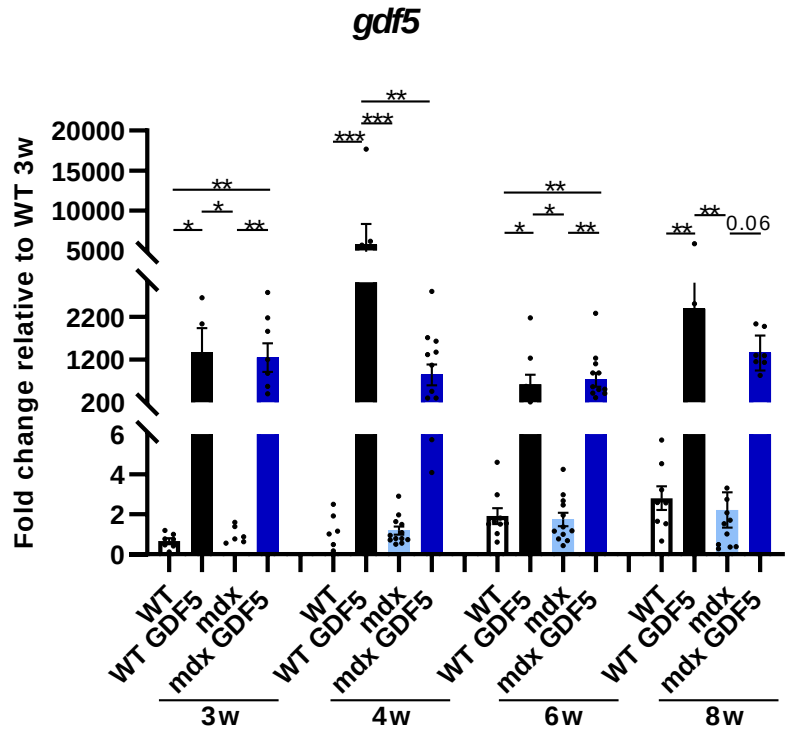
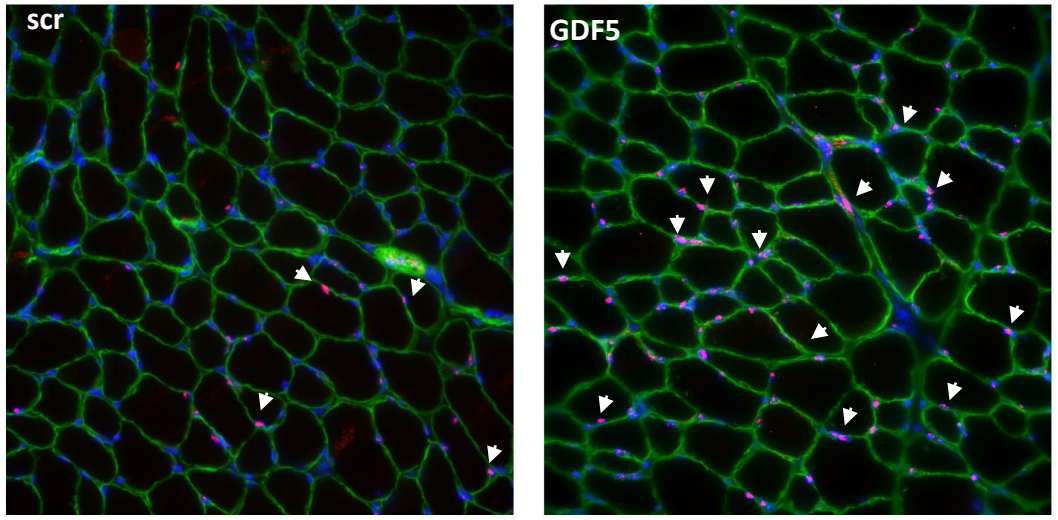
GDF5 overexpression in DMD mouse model (mdx)



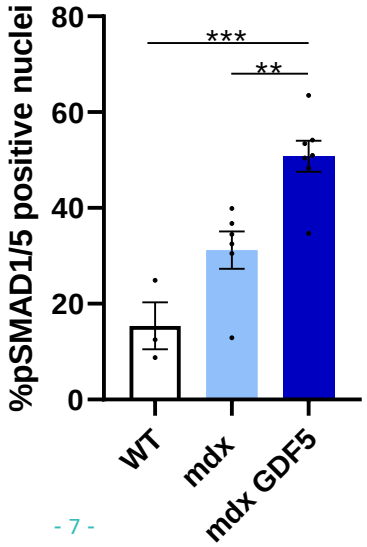


Overexpression of GDF5

mdx P-SMAD1/5 / laminin / DAPI



2w post-inj



Activation of GDF5 pathway

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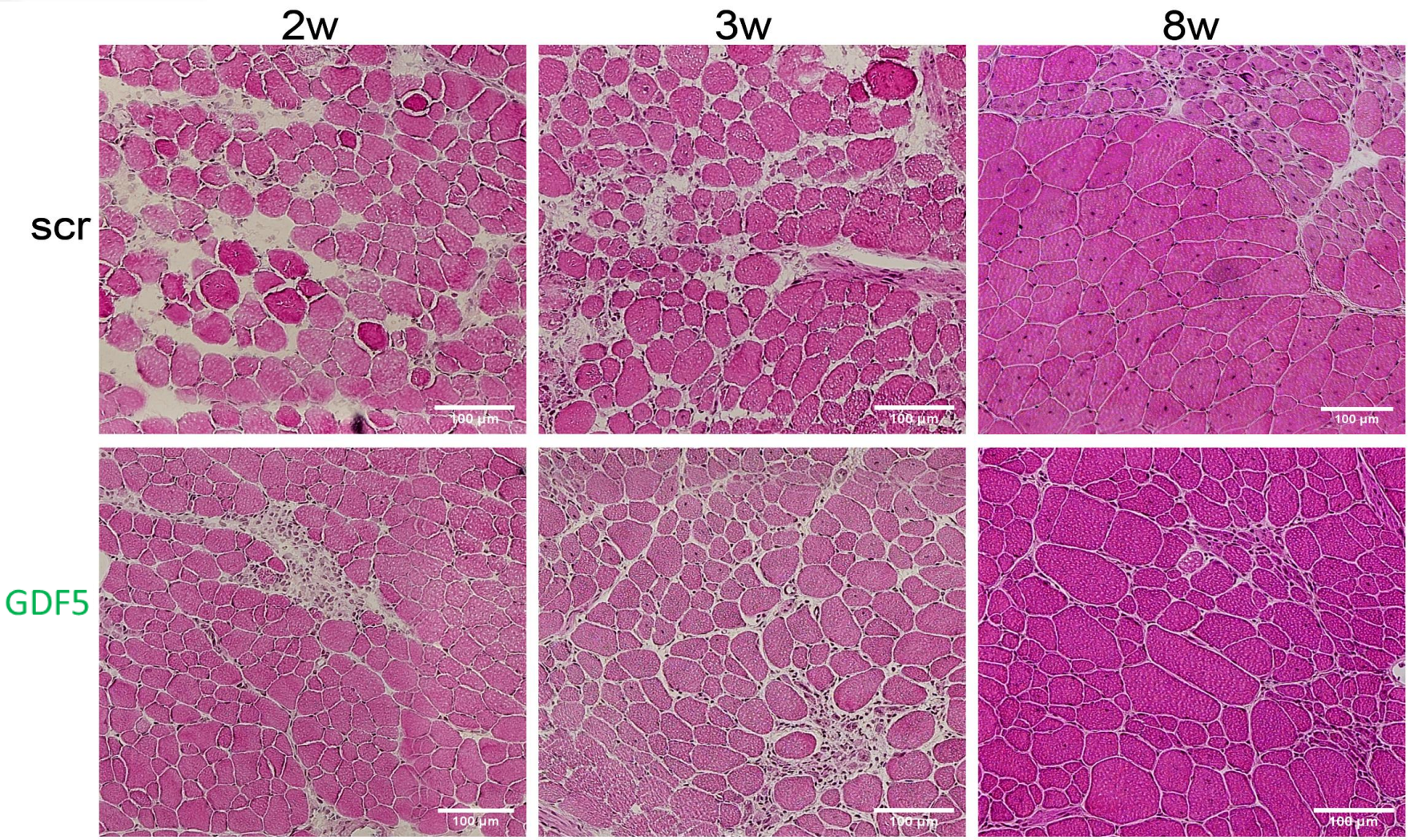
Effect of GDF5 overexpression on DMD muscle



Improvement of DMD muscle histology

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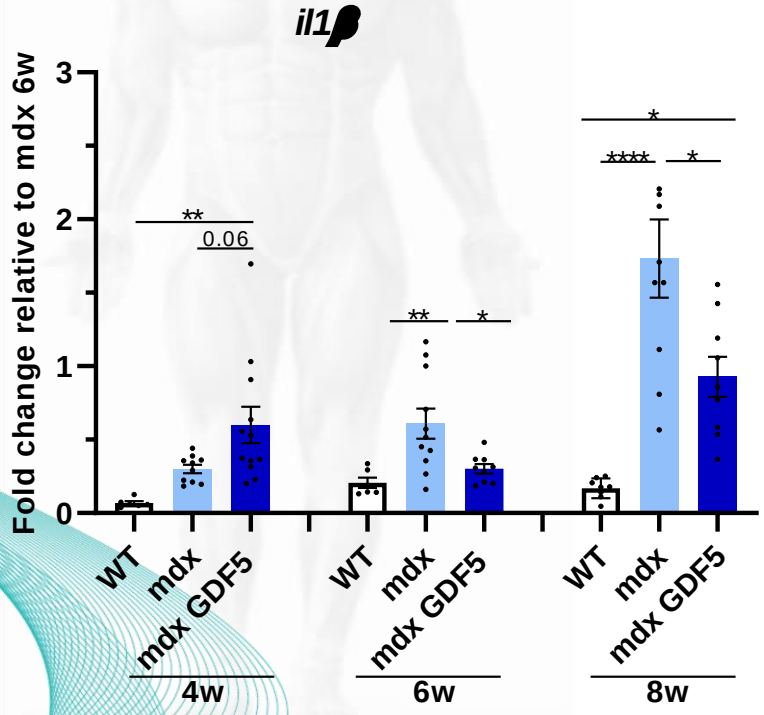
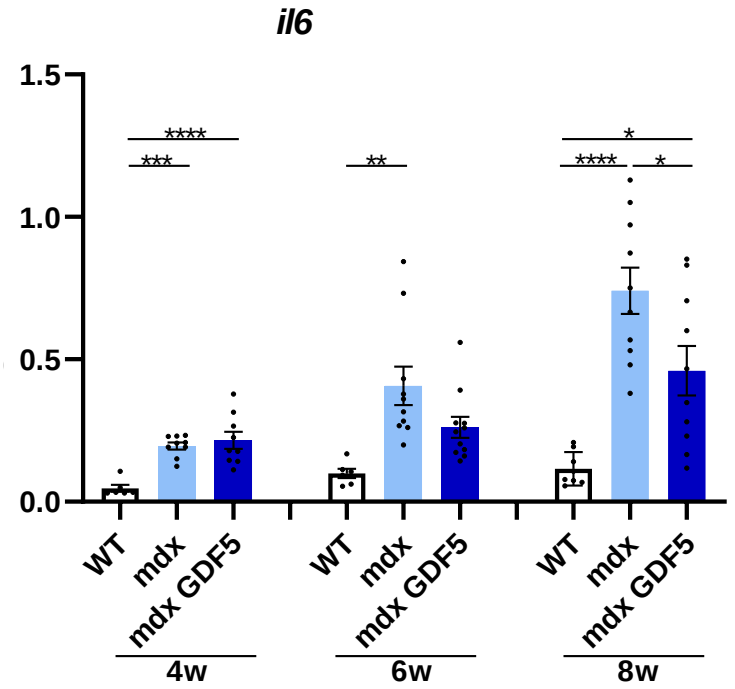
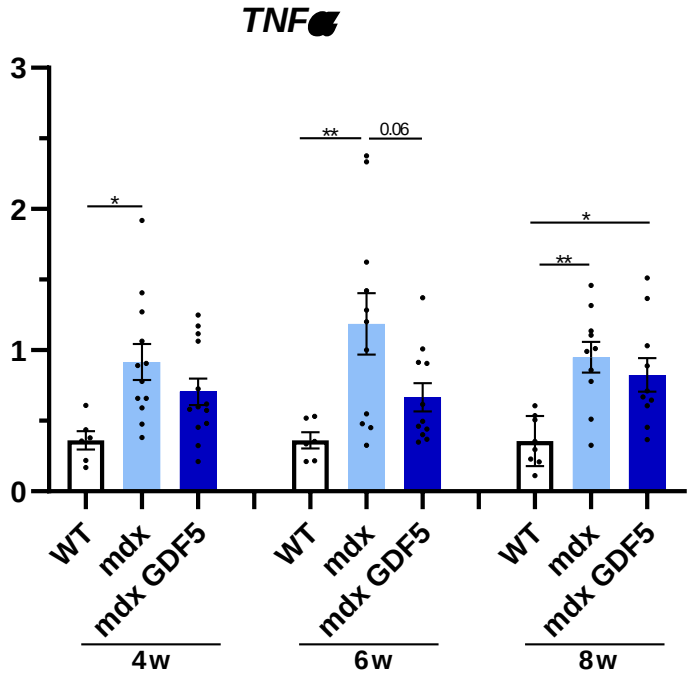
GDF5 overexpression and inflammatory marker expression



Pro-inflammatory



pro-inflammatory cytokine
and anti-inflammatory myokine



Pro-inflammatory

Decrease of pro-inflammatory markers at 6and 8 weeks post- treatment

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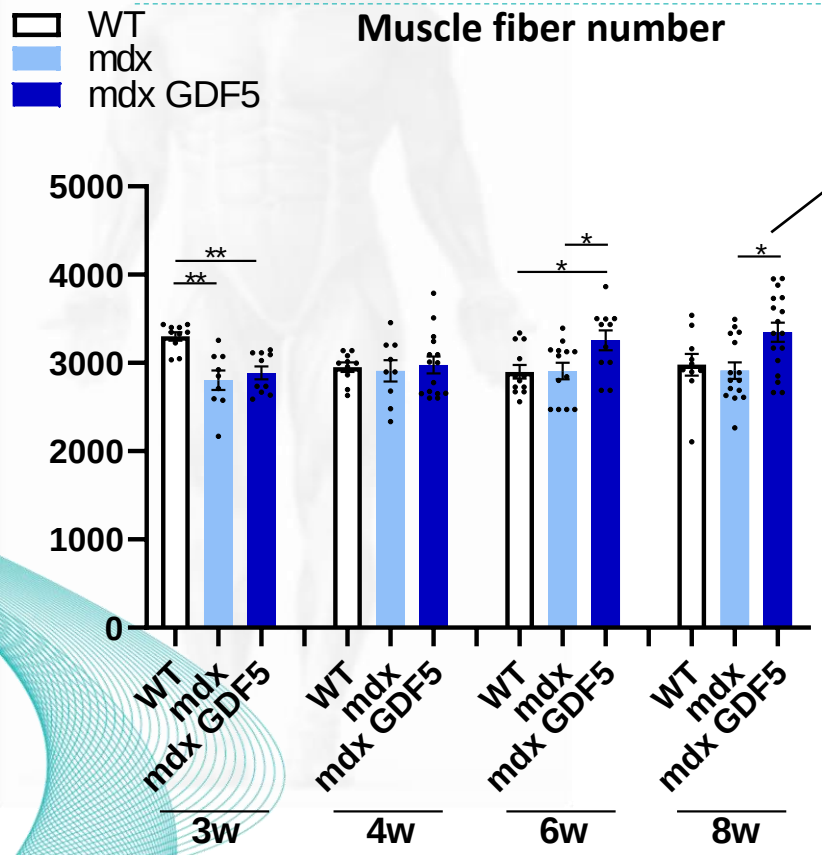
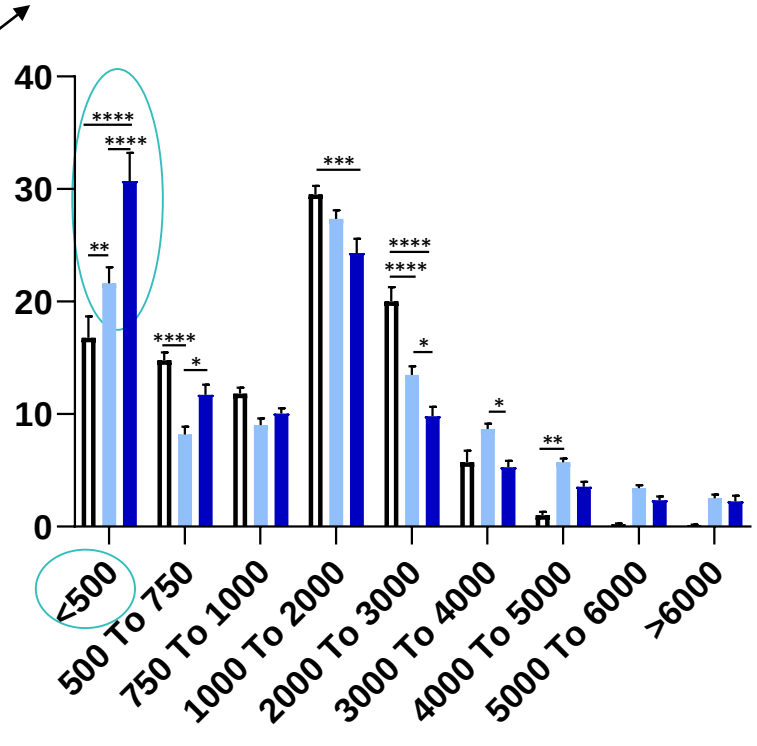
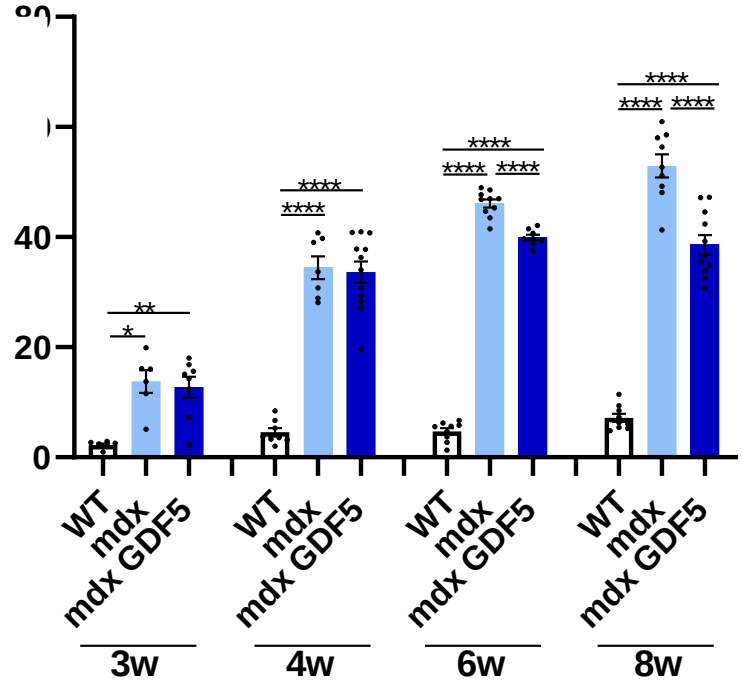
GDF5 overexpression and differentiation / regeneration process







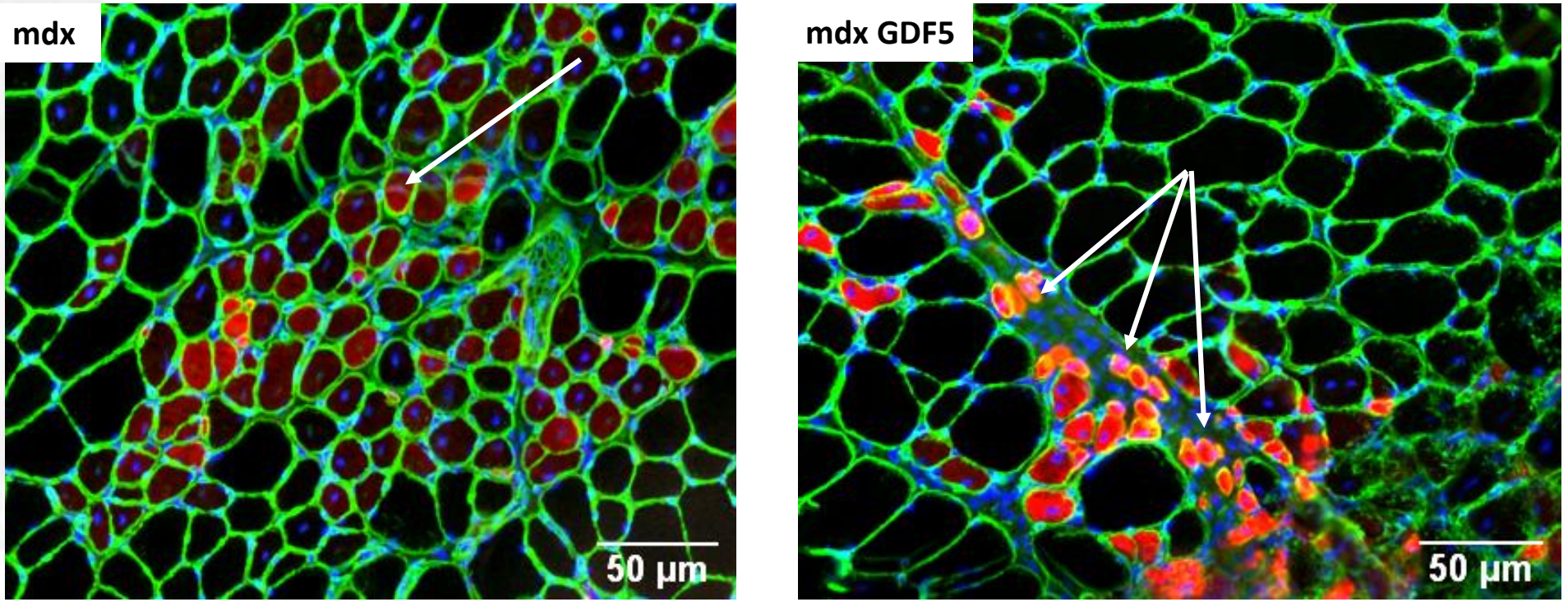
Hyperplasia with
Increase of small fiber number

Decrease of centrally nucleated fibers
->modulation of regeneration

GDF5 and hyperplasia

eMHC/laminin / DAPI

3w post-inj



Presence of new fibers in interstitial space

GDF5 could regulate myogenic commitment of resident muscle cells

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GDF5 overexpression effects in mdx muscle

- ✓ Improvement of DMD muscle histology
- ✓ Modulation of inflammatory markers and regeneration
- ✓ Increased of small fiber number
  - ->hyperplasia
  - ->appearance of new small fibers

Could GDF5 optimize AAV-microDystrophin gene therapy?

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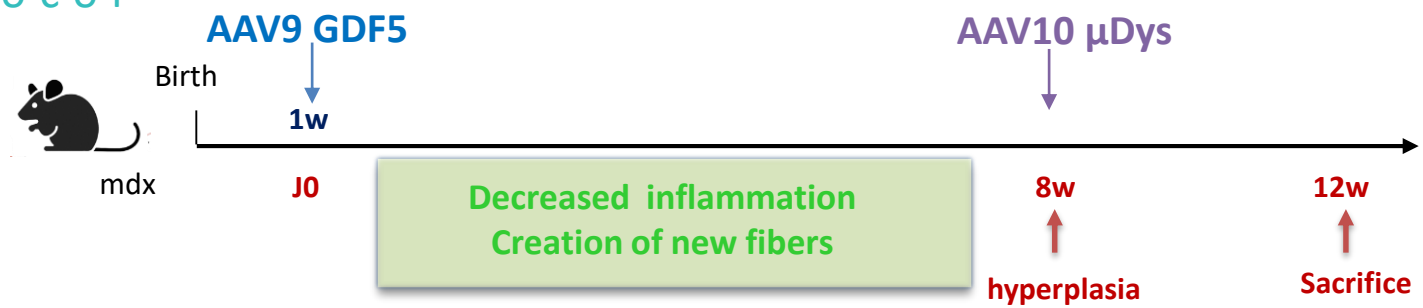
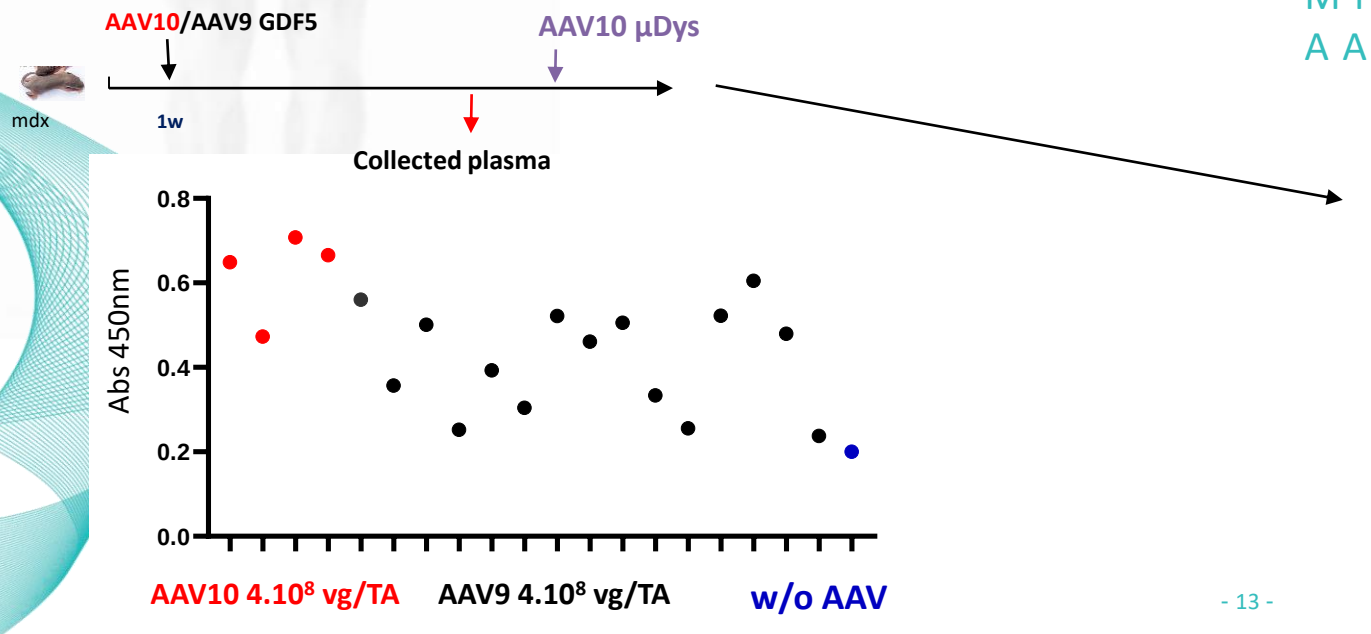
A combined treatment to optimize DMD gene therapy
AAV-GDF5 and AAV-microDystrophin

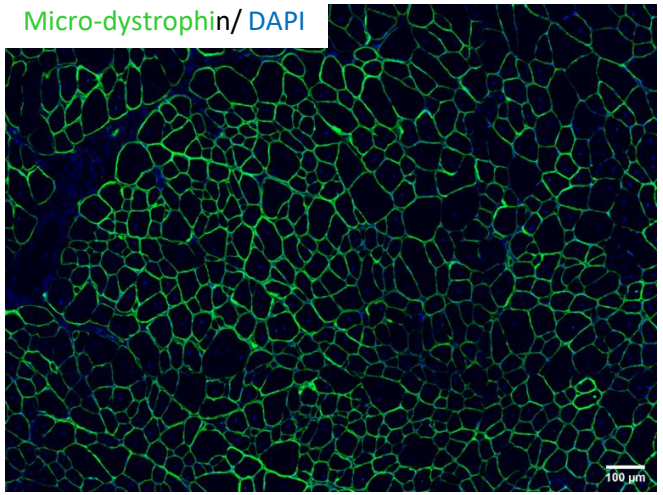
An innovative protocol



AAV10-Ab serology



MicroDystrophin expression
AAV9-GDF5 then AAV10-microDystrophin



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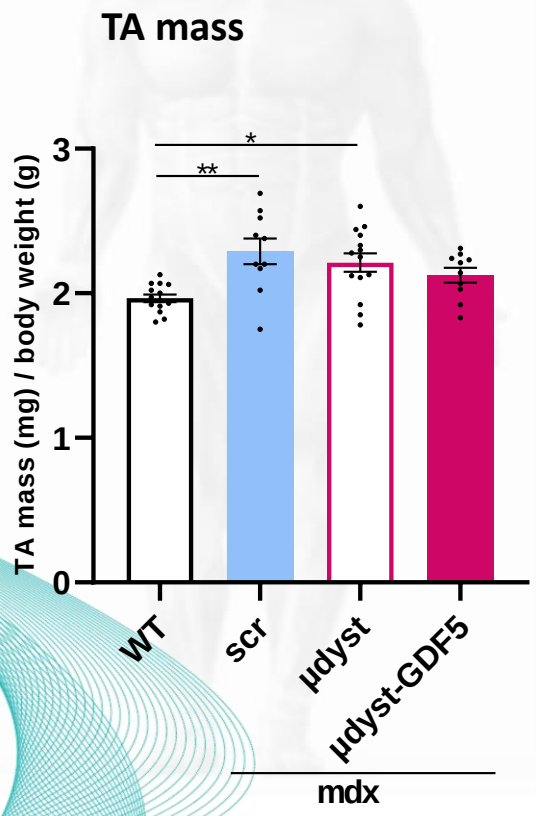
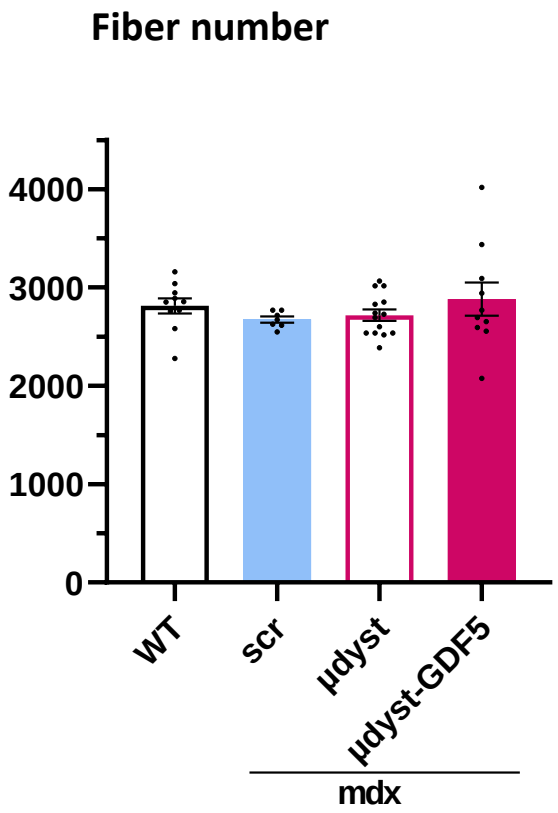
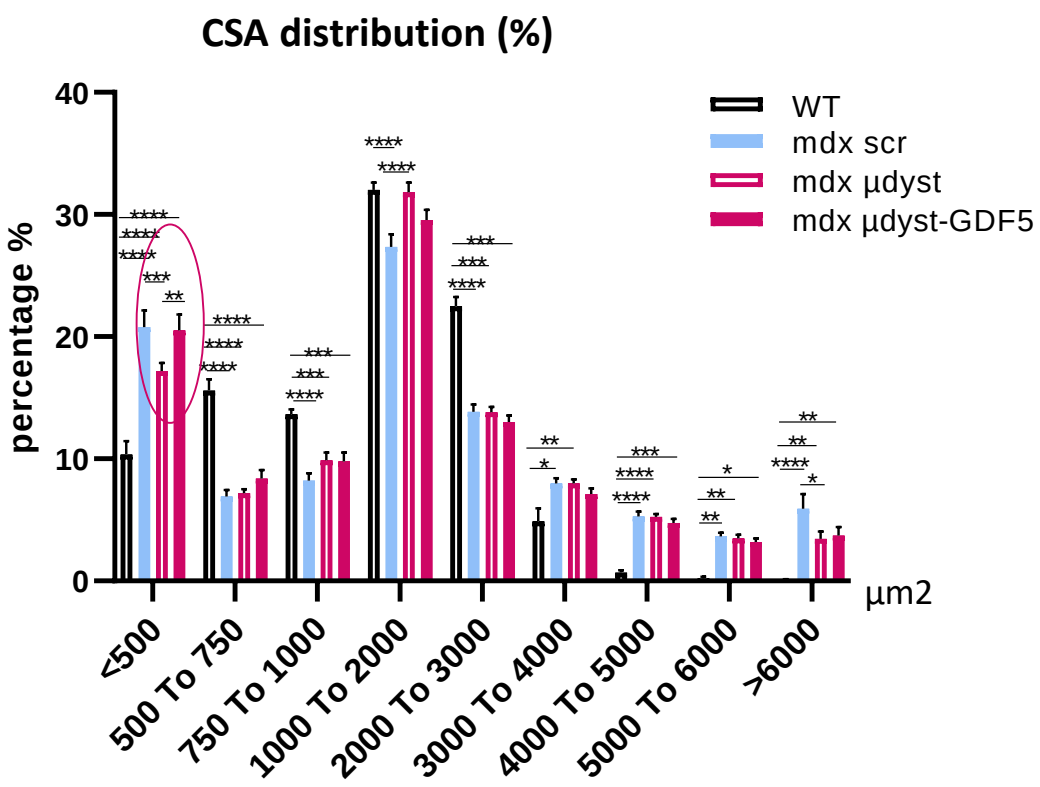
AAV-GDF5 + AAV-µDystrophin treatment on muscle mass homeostasis







Increase of small fibers in GDF5+µDyst *vs* µDyst

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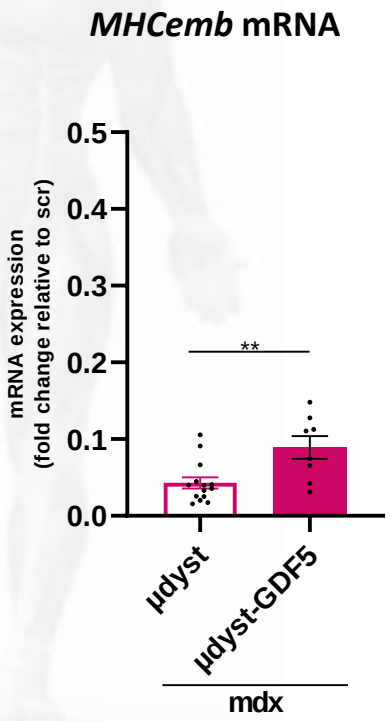
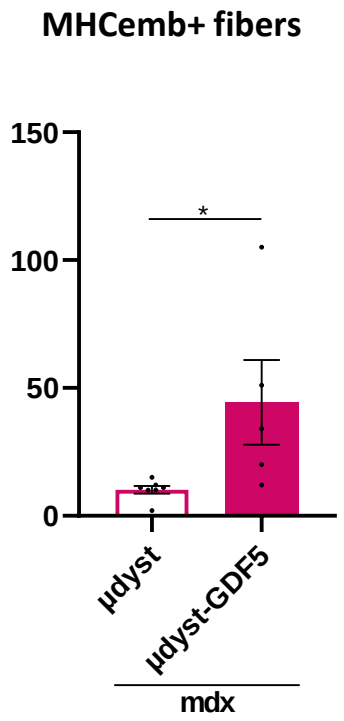
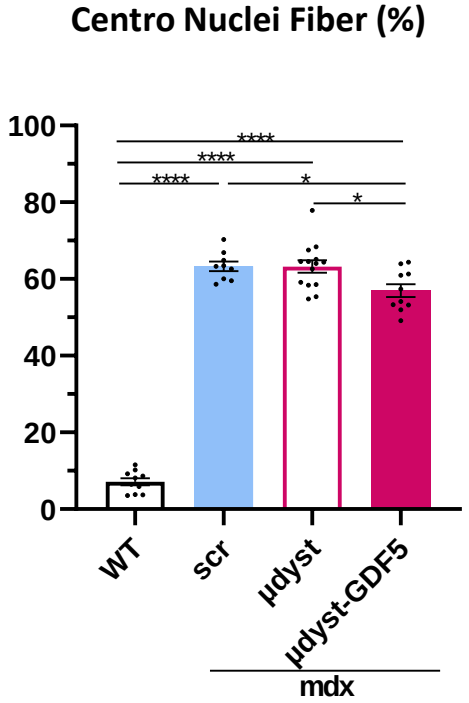
AAV-GDF5 + AAV-µDystrophin treatment on muscle regeneration process







Increase of MHCemb expression in GDF5+µDyst *vs* µDyst

Decrease of centro nuclei fiber % in GDF5+µDyst *vs* µDyst

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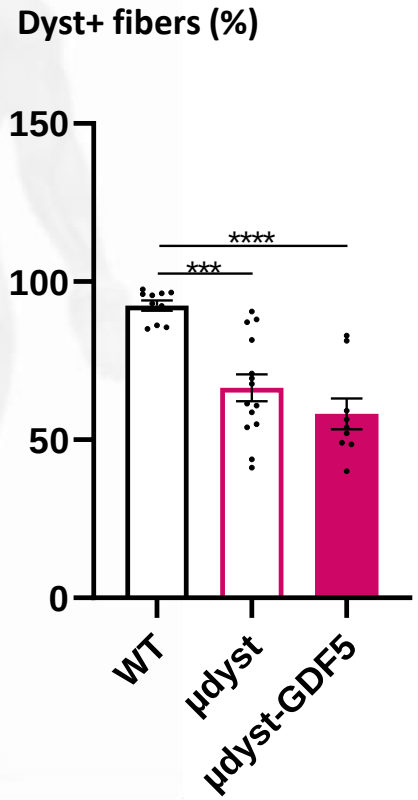
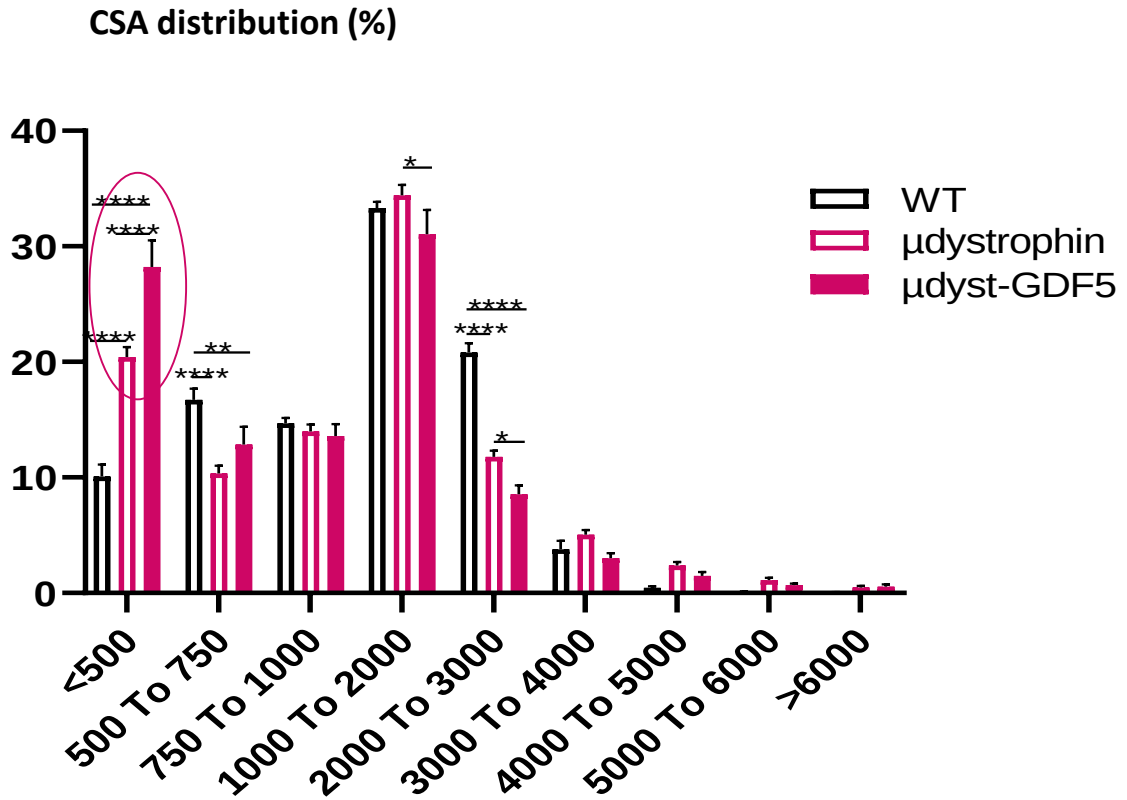
A synergic effect of AAV-GDF5 + AAV-µDystrophin treatment





Increased number of small µdystrophin positive fiber in GDF5+µDyst *vs* µDyst alone

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AAV-GDF5 + AAV-µDys combo *vs* AAV-µDys alone

- ✓ Increases of small fiber number
- ✓ Increases of MHCemb expression
- ✓ Modulates of regeneration
- ✓ **Increases the number of small µdys positive fibers**

Synergic effects to optimize AAV-µDys therapy

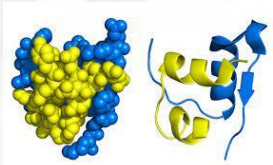
1/COMPOSITIONS FOR TREATMENT OF SARCOPENIA OR DISUSE ATROPHY / A1/EP3823662
2/COMBINED THERAPY FOR MUSCULAR DISEASES/A1/WO2021089736

Muscle Tibialis Anterior (TA)

AAV9-GDF5 + AAV10-µDys (intramuscular)

1

Proof of concept → **DONE**



sGDF5

RAT-DMD

sGDF5 (systemic)

sGDF5 + AAV10-µDys (systemic)

2

Therapeutic approach

Valentina Taglietti, et al. **Duchenne muscular dystrophy trajectory in R-DMDdel52 preclinical rat model identifies COMP as biomarker of fibrosis**. *Acta Neuropathologica Communications* 2022 10:60 https://doi.org/10.1186/s40478-022-01355-2

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AAV-microDystrophin and AAV-GDF5:
A combined treatment to optimize DMD gene therapy

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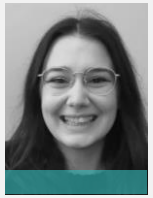

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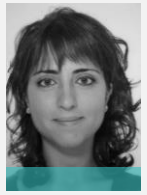

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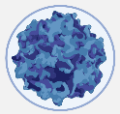
AAV production



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