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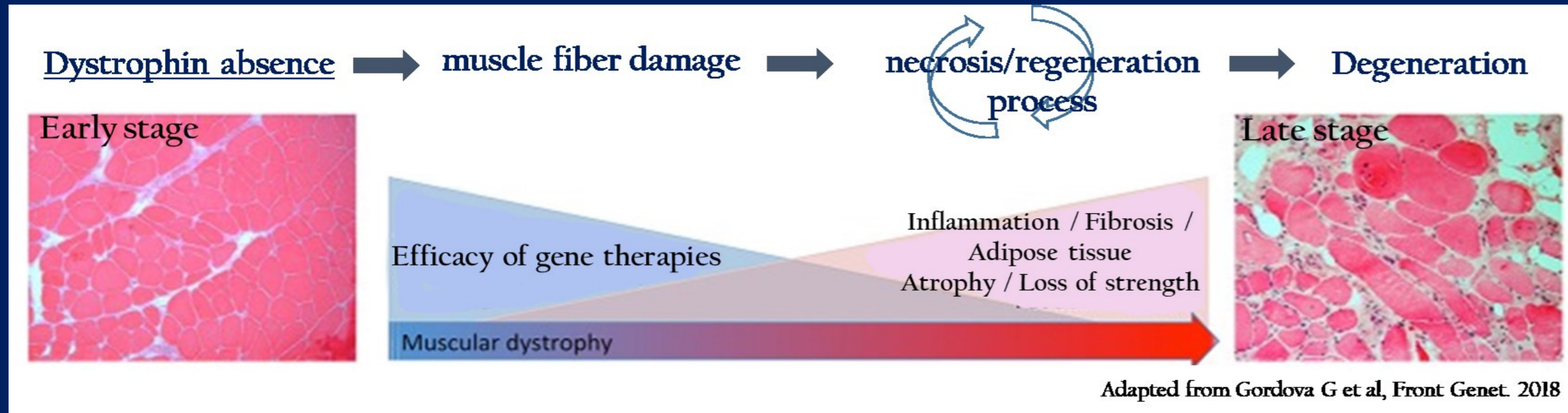
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GDF5 overexpression improves pathophysiology of DMD in mdx muscle

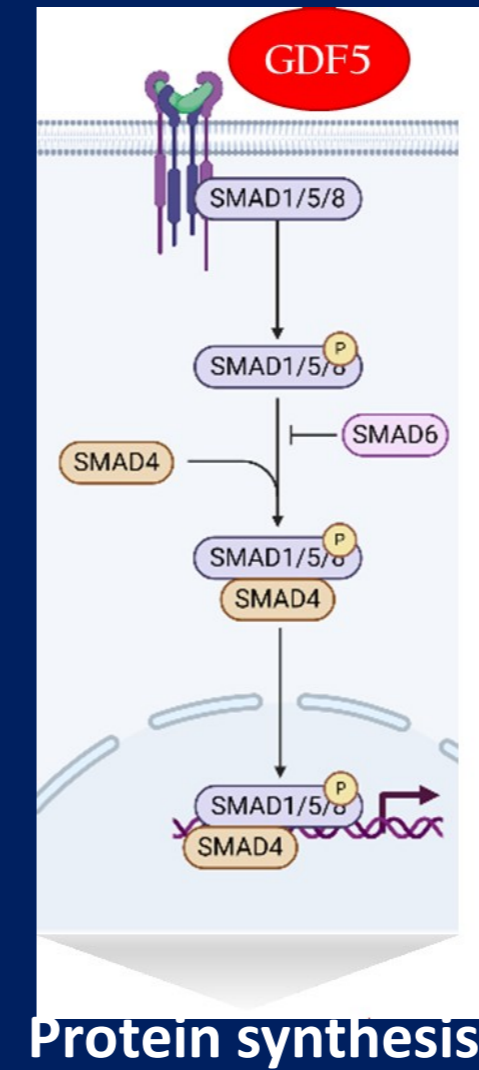
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Introduction



Duchenne muscular dystrophy (DMD) is a myopathy caused by the lack of the dystrophin protein. Clinical trials with AAV administration of microDystrophin are underway and data indicate the potential for this treatment to respond to an unmet need for DMD. However, these approaches target the degenerating musculature and maintaining muscle mass for as long as possible in order to optimize gene therapy is of major interest for the long-term success of these strategies.

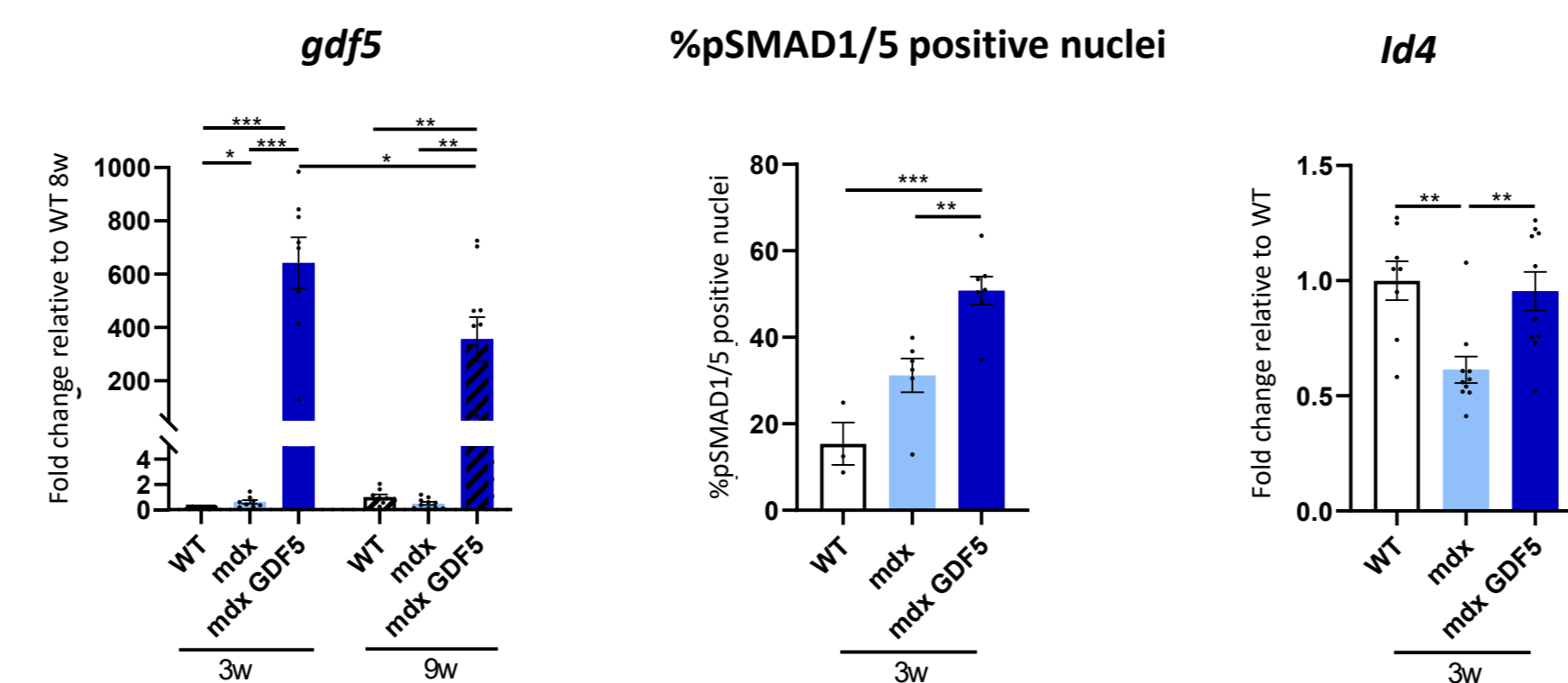
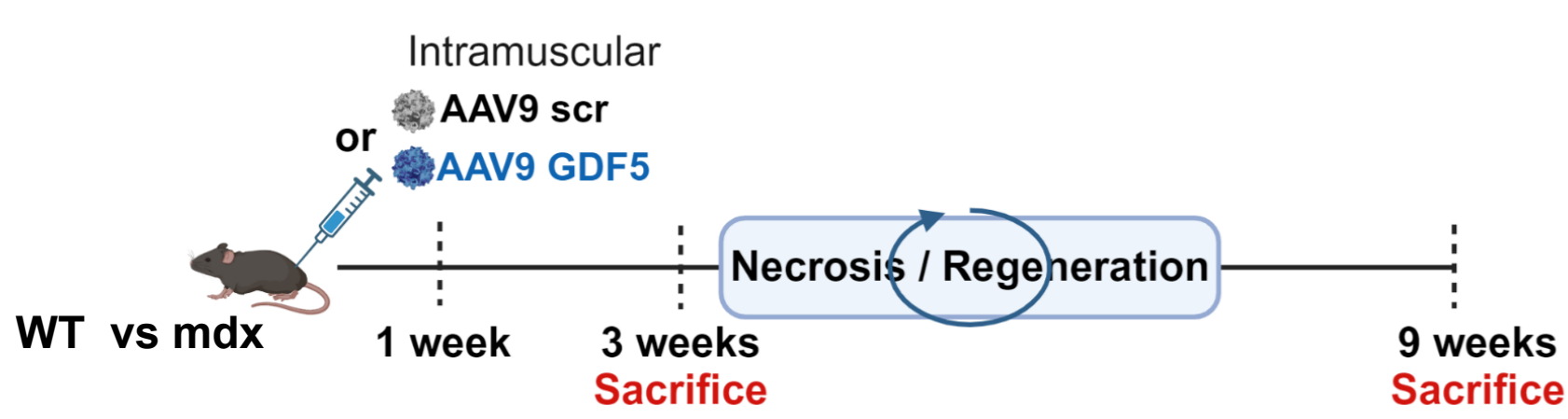


Bone Morphogenetic Protein (BMP) family member BMP14 also called Growth Differentiation Factor 5 (GDF5) is a key actor of compensatory response to limit muscle mass loss after denervation (Sartori et al, Nat Gen 2013) and was recently described to play an essential role in preserving muscle mass and neuromuscular junctions during ageing (Traoré et al, Sci Transl Med 2019, Traoré et al, Brain 2024). GDF5 signaling induces the phosphorylation of intracellular SMAD1/5/8 complex, which translocates to the nuclei and controls targeted gene transcription.

Here, we investigated the impact of GDF5 overexpression (OE) on the progression of DMD pathophysiological features in mdx mice (DMD mouse model).

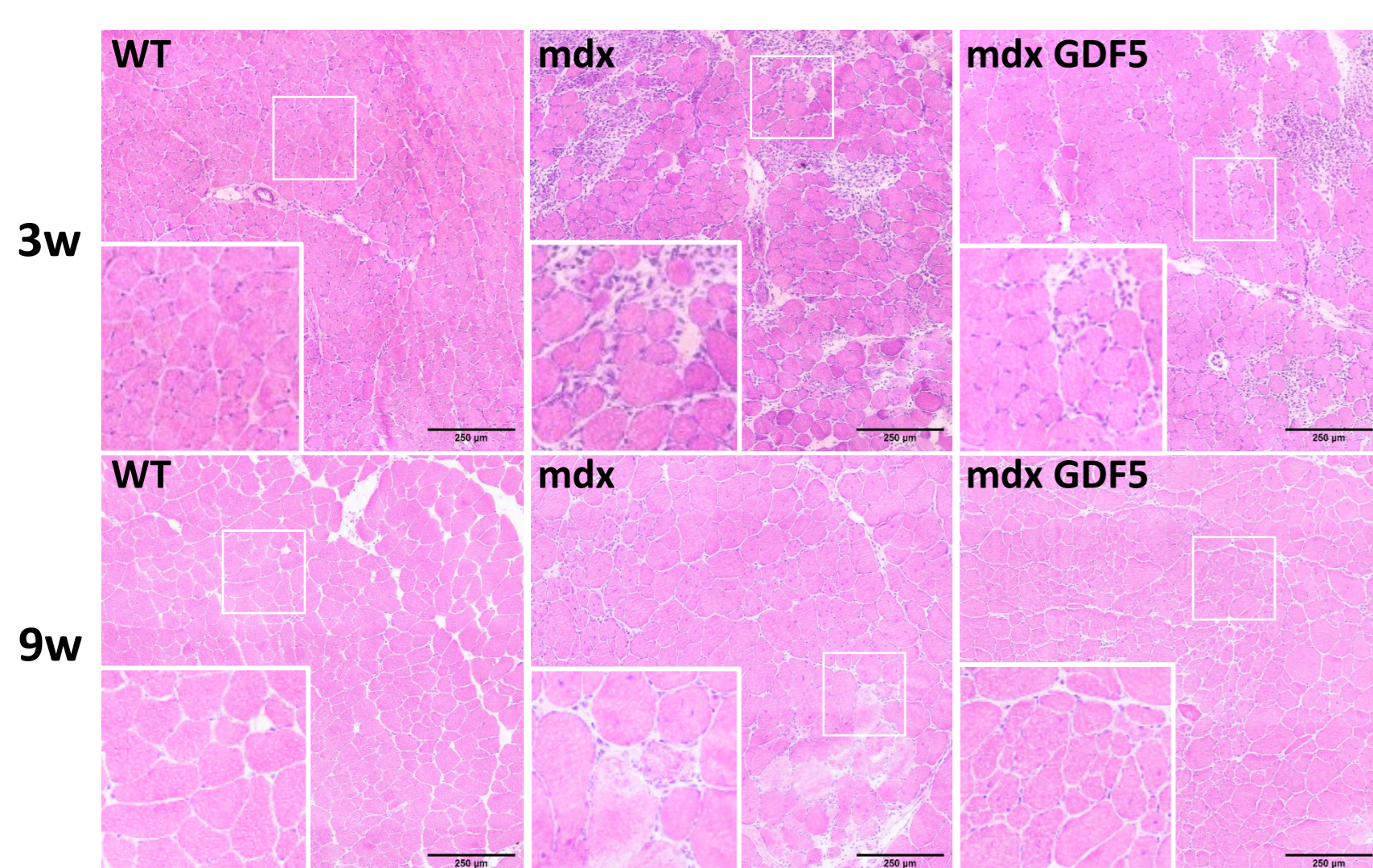


GDF5 OE in DMD mouse model (mdx)

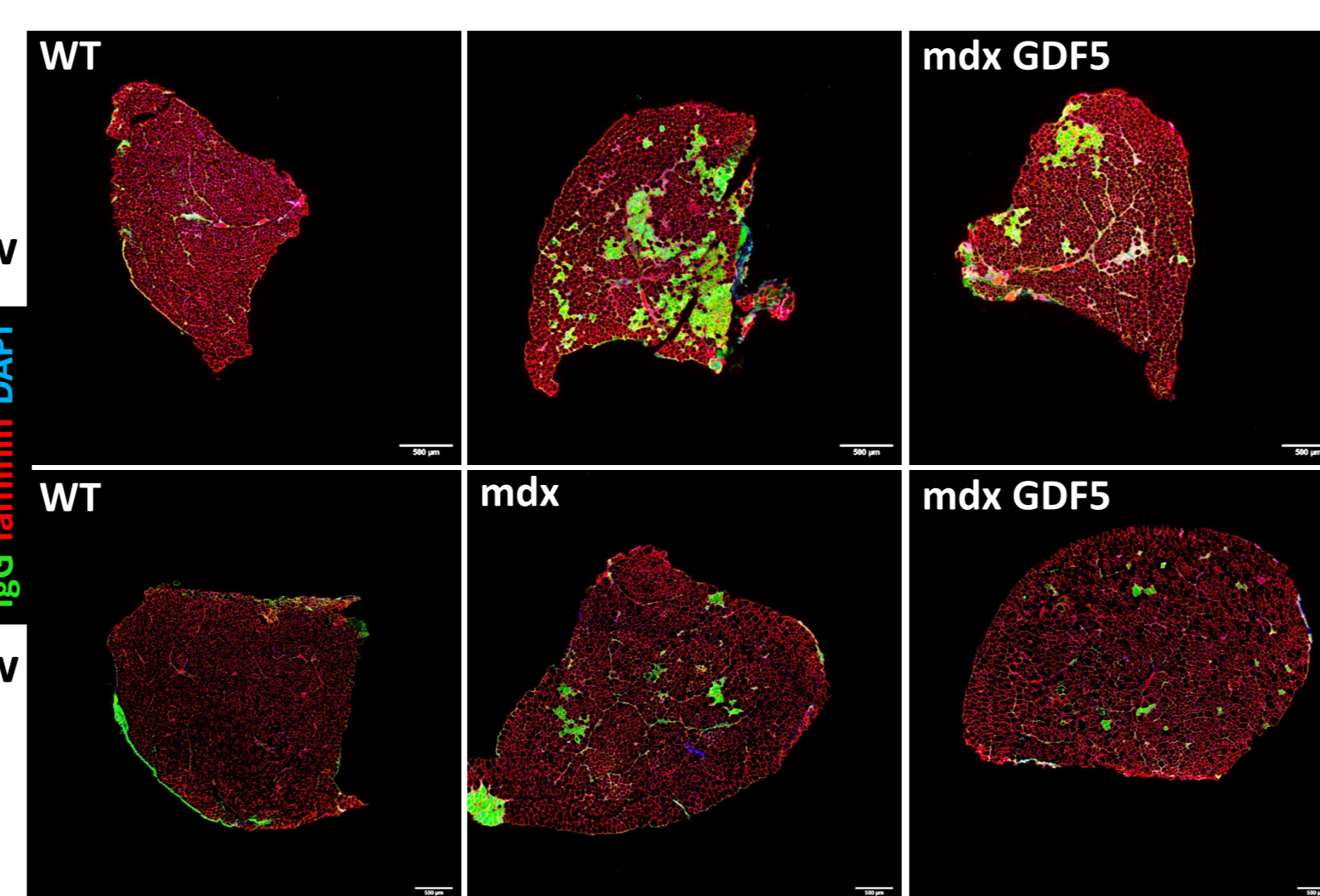


- ✓ GDF5 OE in injected muscle with a reduced expression in 9-week-old mice
- ✓ Activation of GDF5-SMAD1/5 signalling

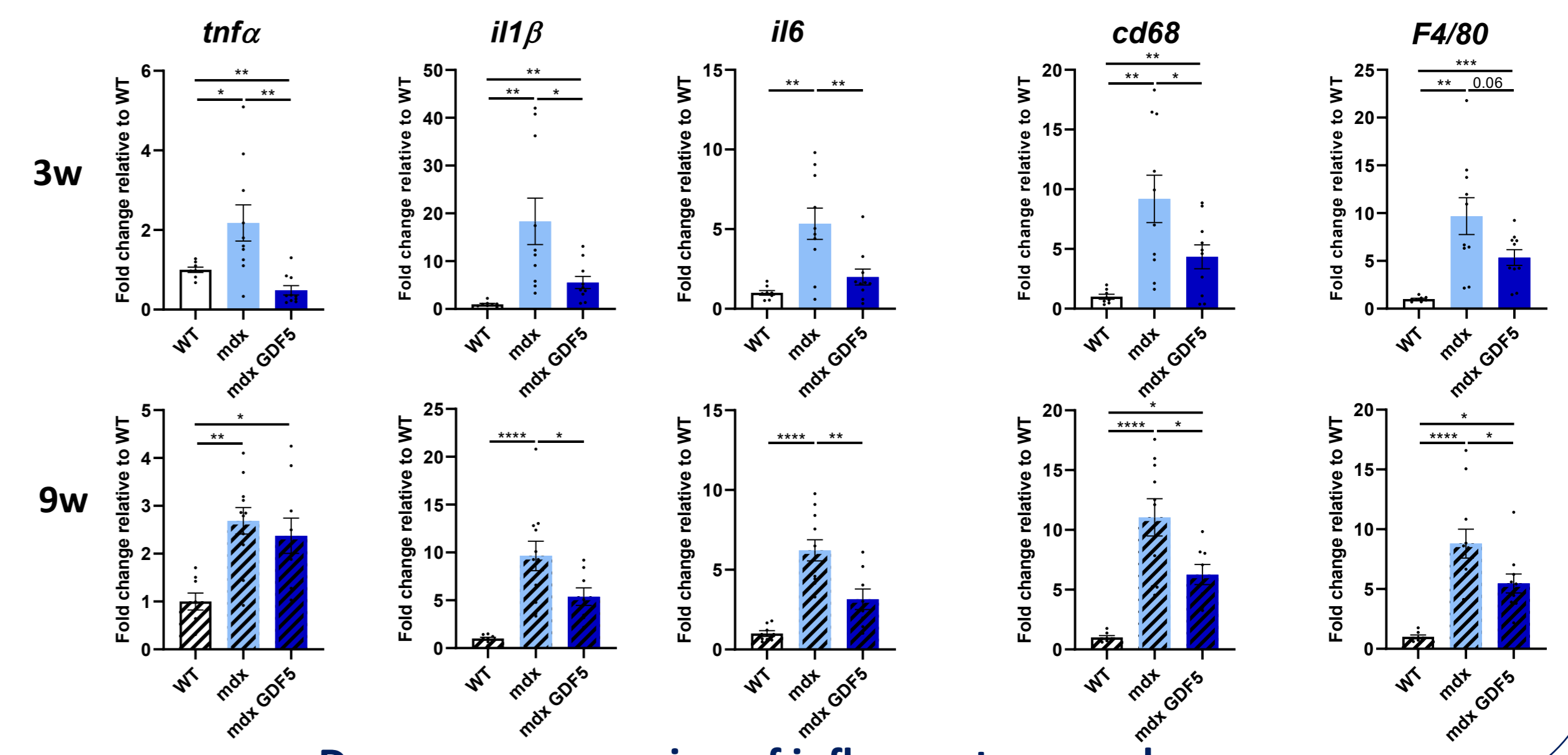
GDF5 OE improves mdx muscle histology, decreases necrosis and inflammation marker expression



Improves histological features

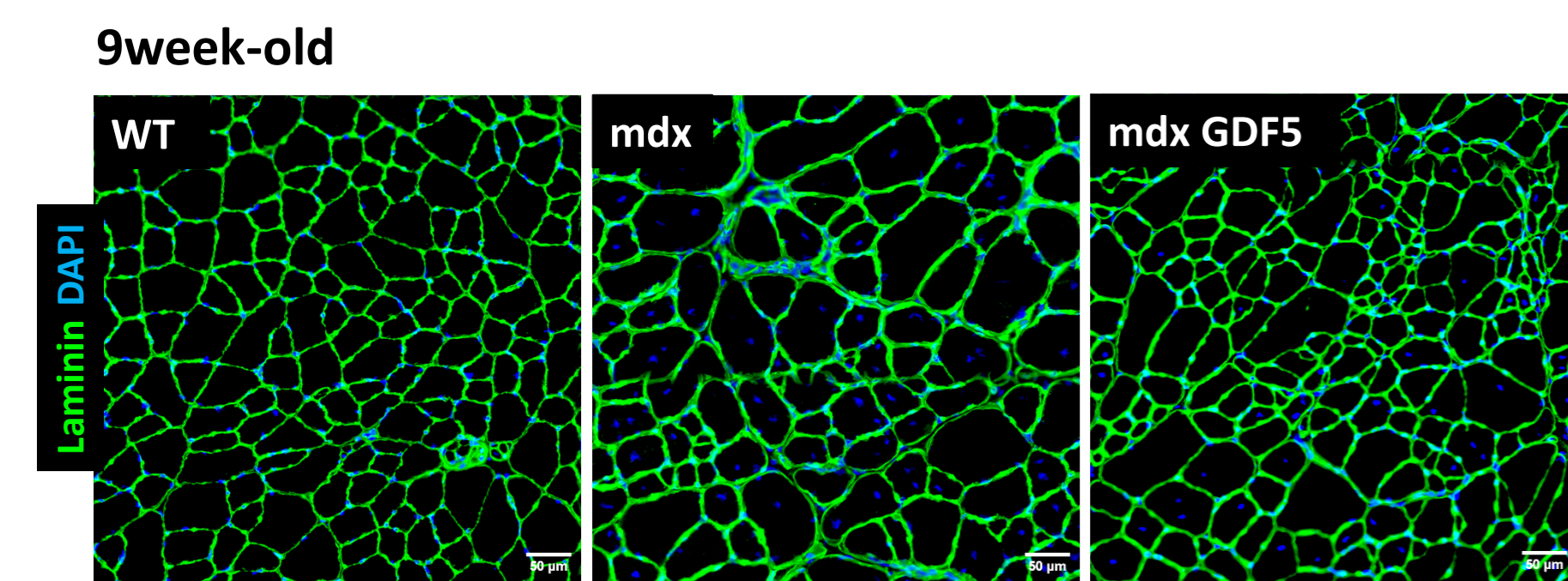


Reduces necrosis process

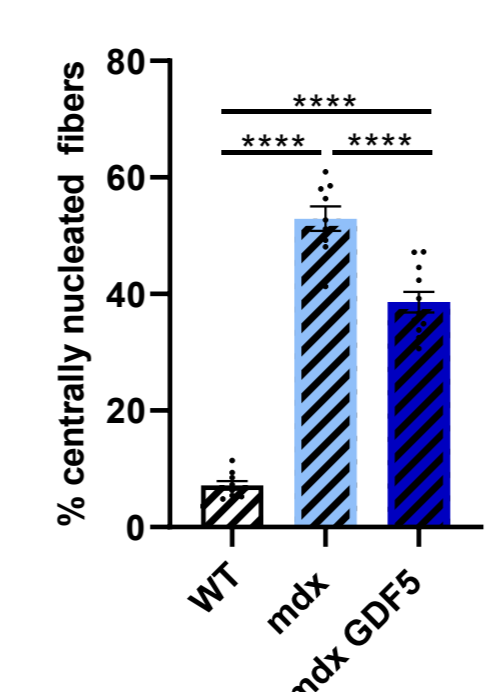


Decreases expression of inflammatory markers

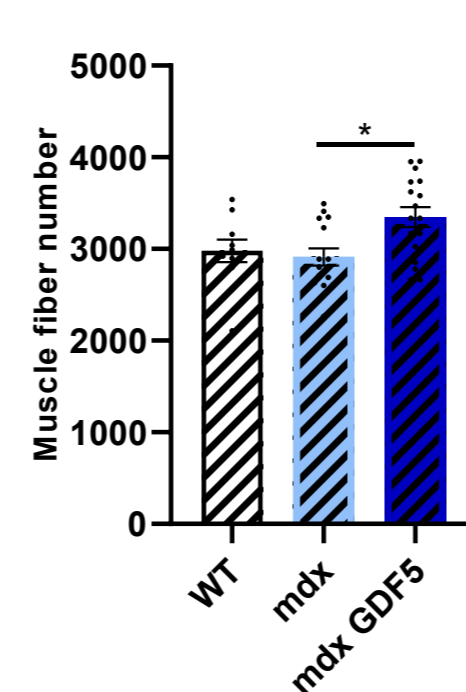
GDF5 OE decreases regeneration and leads to new fiber formation



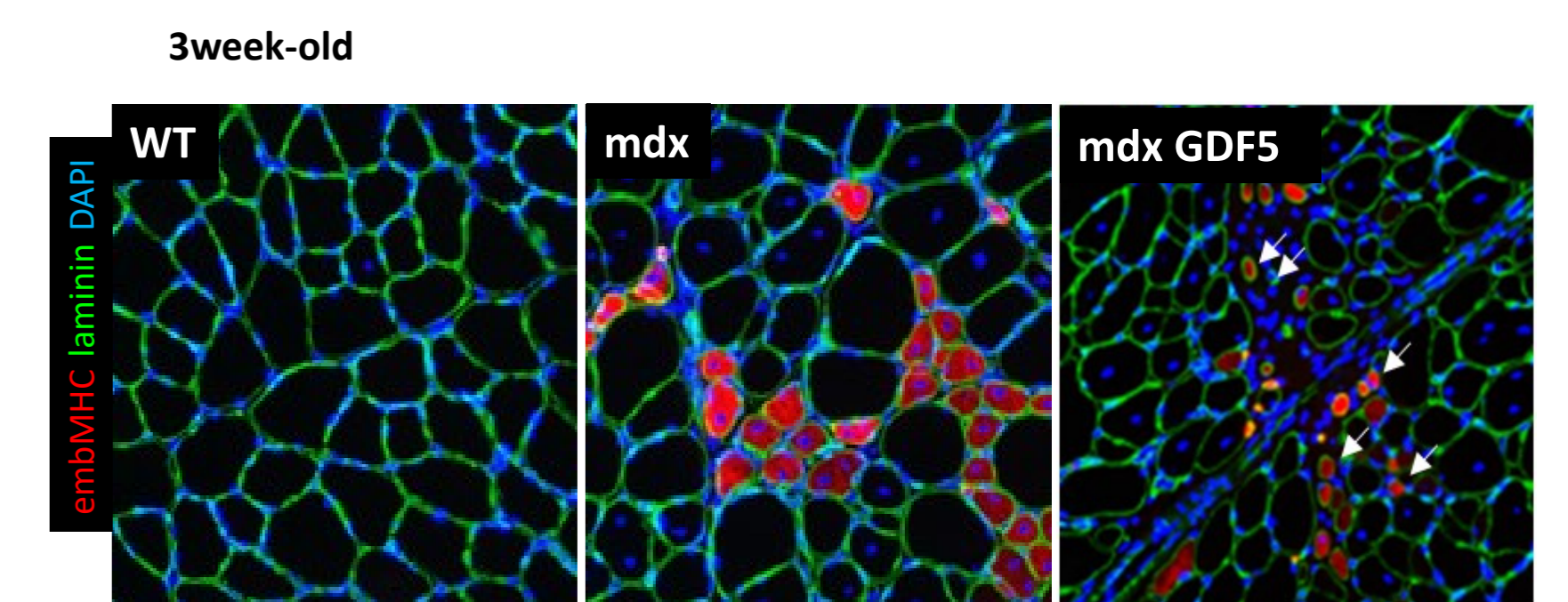
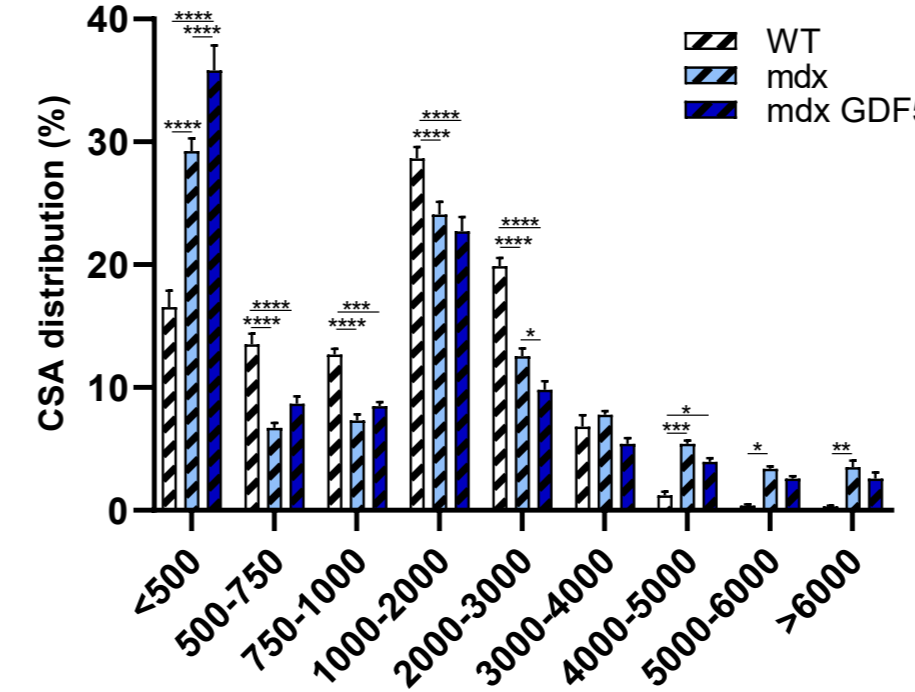
Centrally nucleated fibers (%)



Fiber number



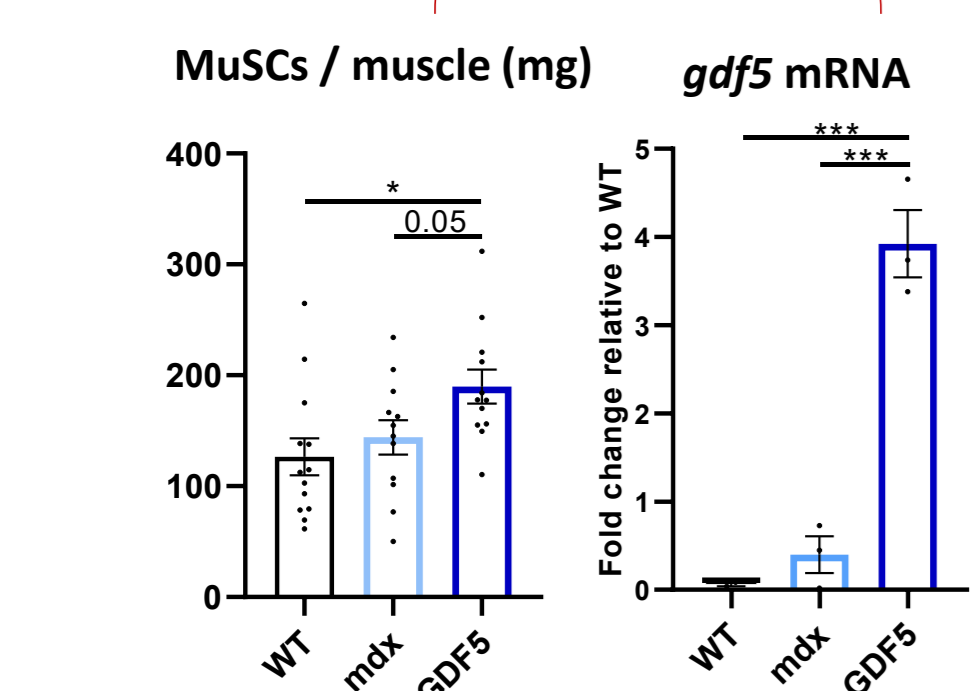
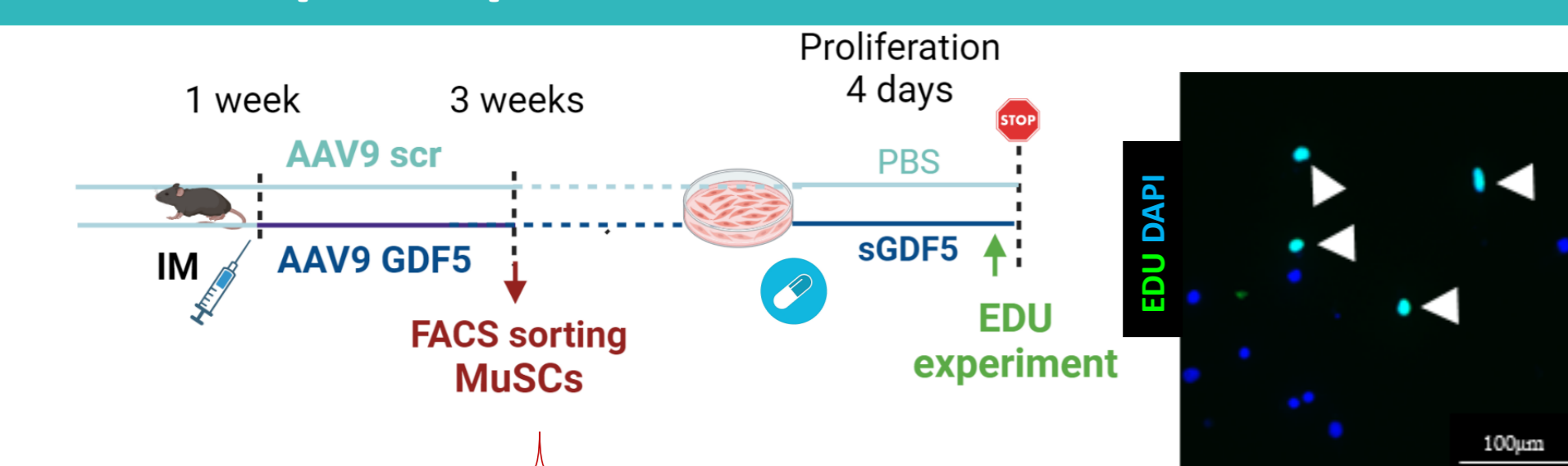
CSA distribution (%)



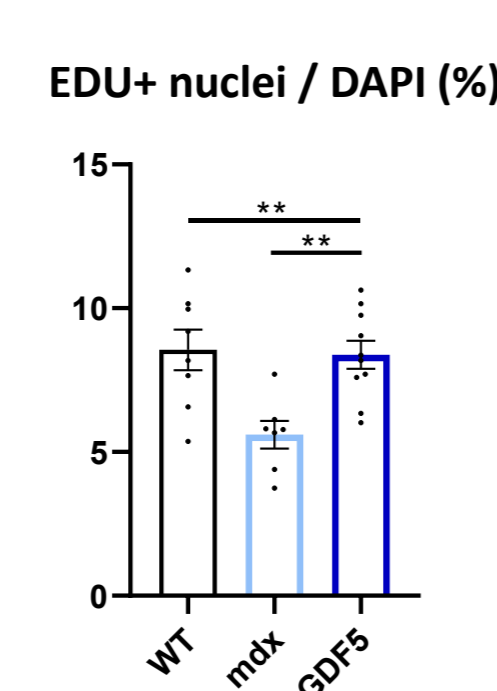
GDF5 OE leads to emergence of small fibers

What could be their origin?

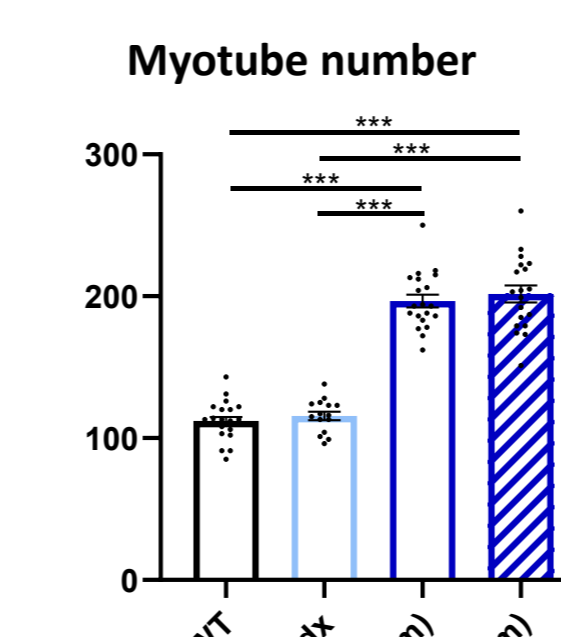
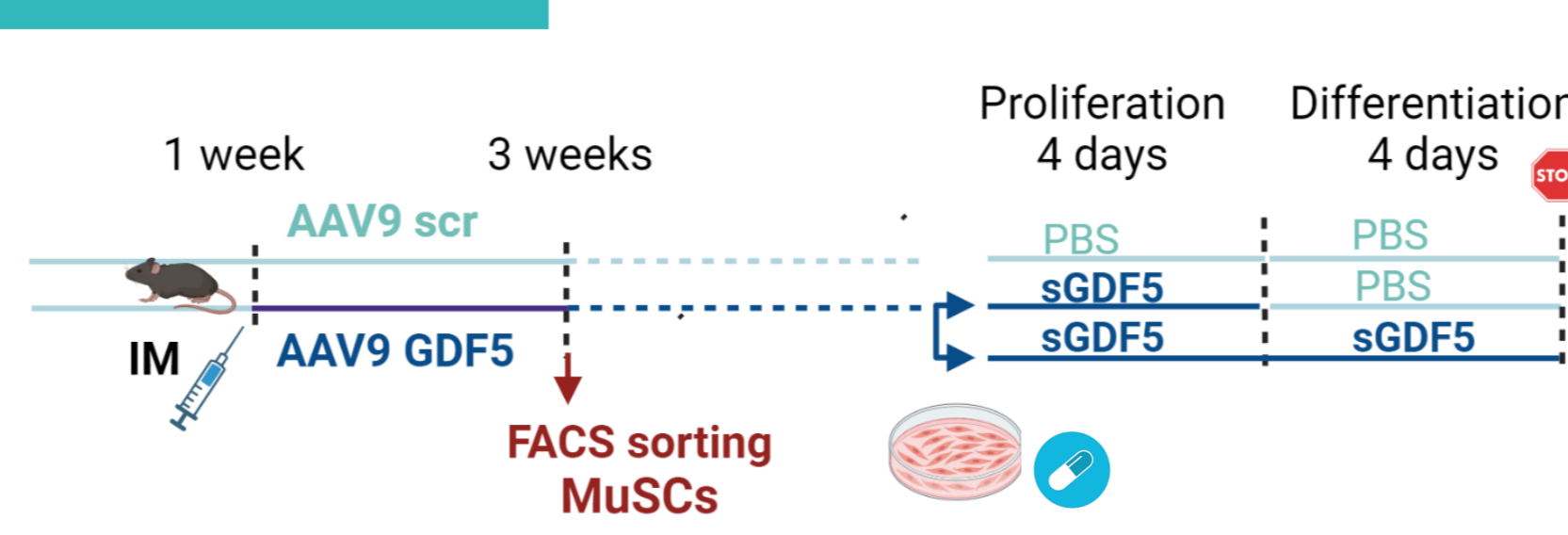
GDF5 impacts proliferation / differentiation balance of MuSCs



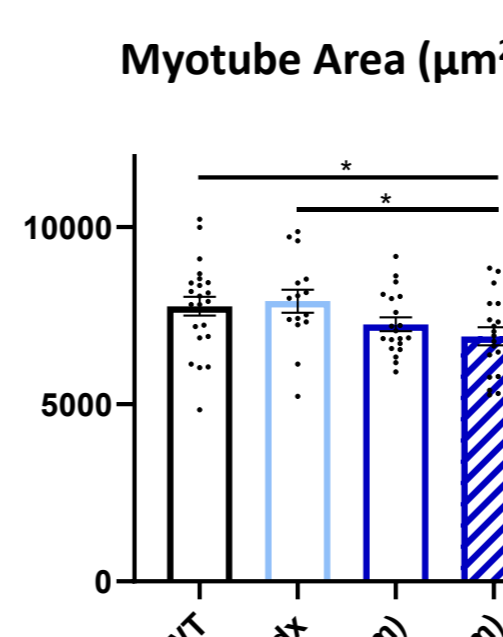
More MuSCs in mdx GDF5 muscles



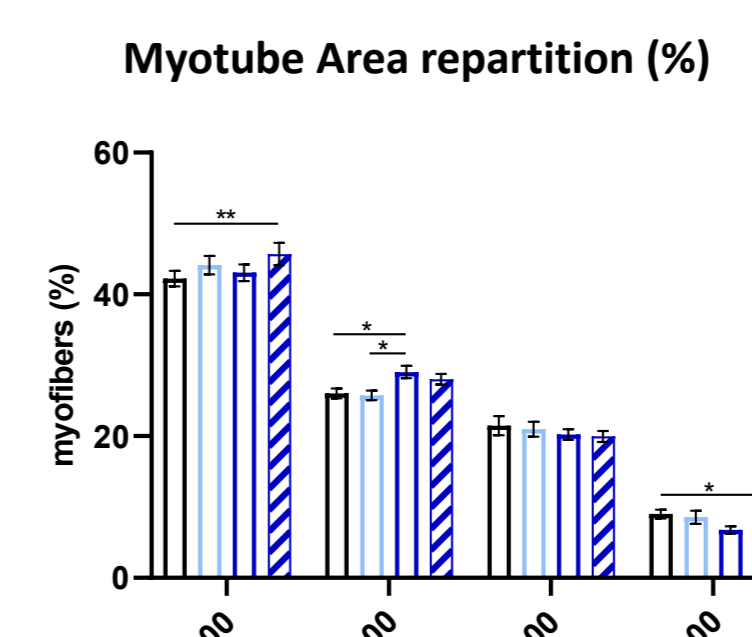
GDF5 OE restores MuSCs proliferation



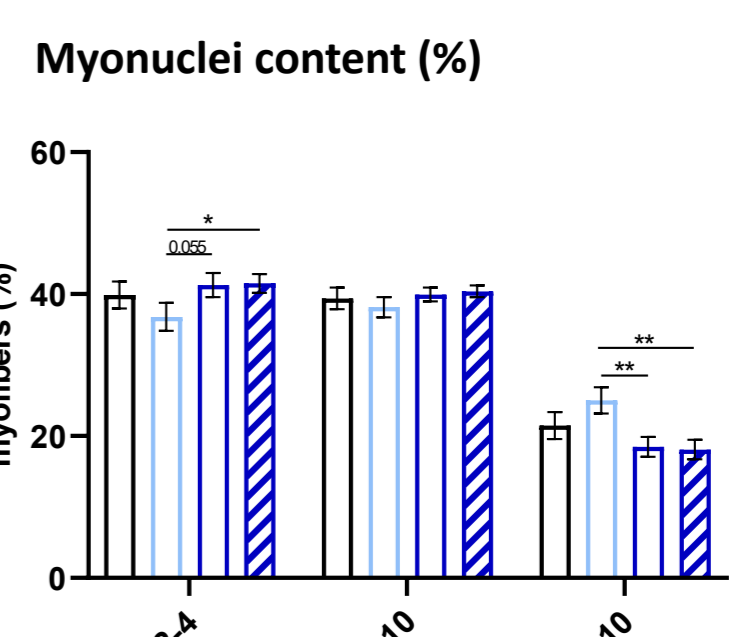
Myotube number



Myotube Area (μm²)



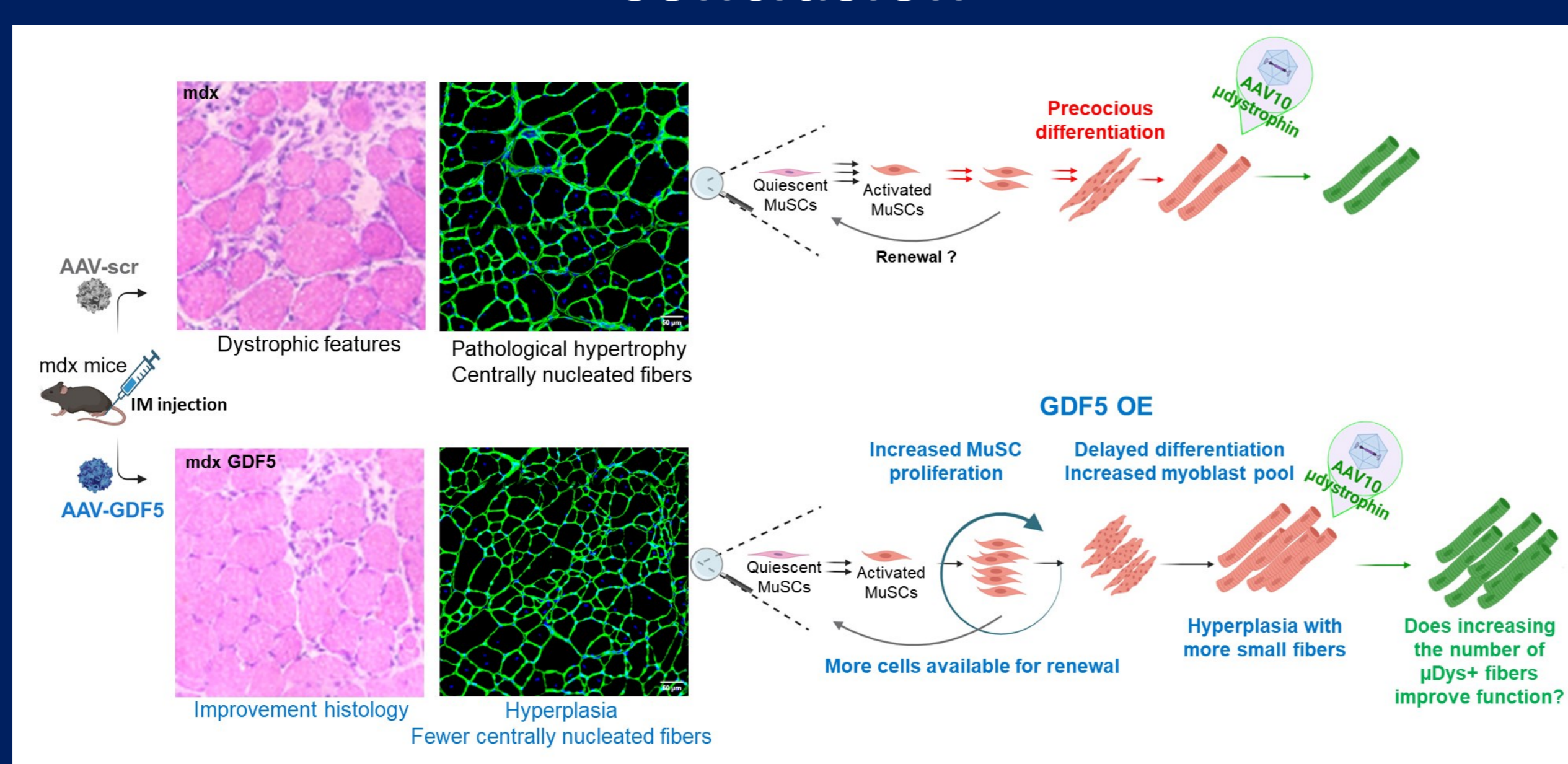
Myotube Area repartition (%)



Myonuclei content (%)

sGDF5 during proliferation increased newly formed myotubes

Conclusion



Perspectives

Better decipher mechanisms involved in balance between proliferation and differentiation

➔ RNA-sequencing from single nuclei ongoing (collaboration L.Giordani)

POC achieved : Synergic effects of combining AAV-GDF5 with AAV-μdystrophin vs AAV-μdystrophin alone (Intramuscular injection of mdx muscle)

➔ Combining sGDF5 with AAV-μdystrophin in DMDdel52 rat model (collaboration F.Relax team)

➤ Dose determination of sGDF5

➤ sGDF5 pre-treatment before systemic AAV-μdystrophin injection