



GDF5 therapeutic potential for DMD

Christel Gentil, Lucile Saillard, Amélie Vergnol, Lorenzo Giordani, Bruno Cadot, Anne Forand, Chiara Noviello, Pierre Meunier, Sestina Falcone, France Piétri-Rouxel

► To cite this version:

Christel Gentil, Lucile Saillard, Amélie Vergnol, Lorenzo Giordani, Bruno Cadot, et al.. GDF5 therapeutic potential for DMD. SFM 2021, Nov 2021, St Etienne, France. hal-03994315

HAL Id: hal-03994315

<https://hal.science/hal-03994315>

Submitted on 24 Feb 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.

Copyright

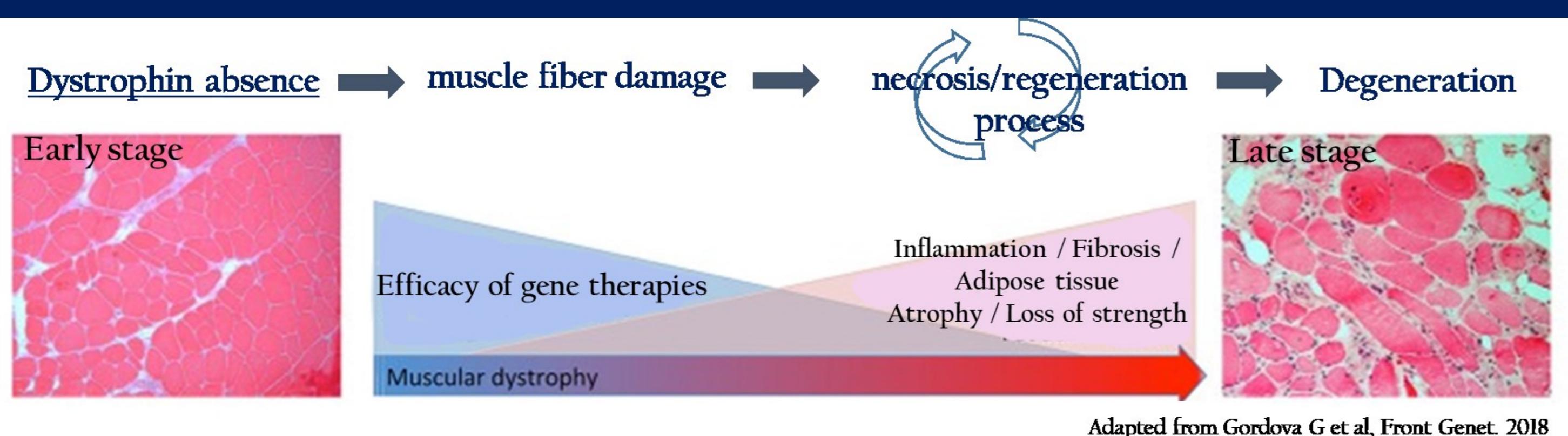
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

GDF5 therapeutic potential for DMD

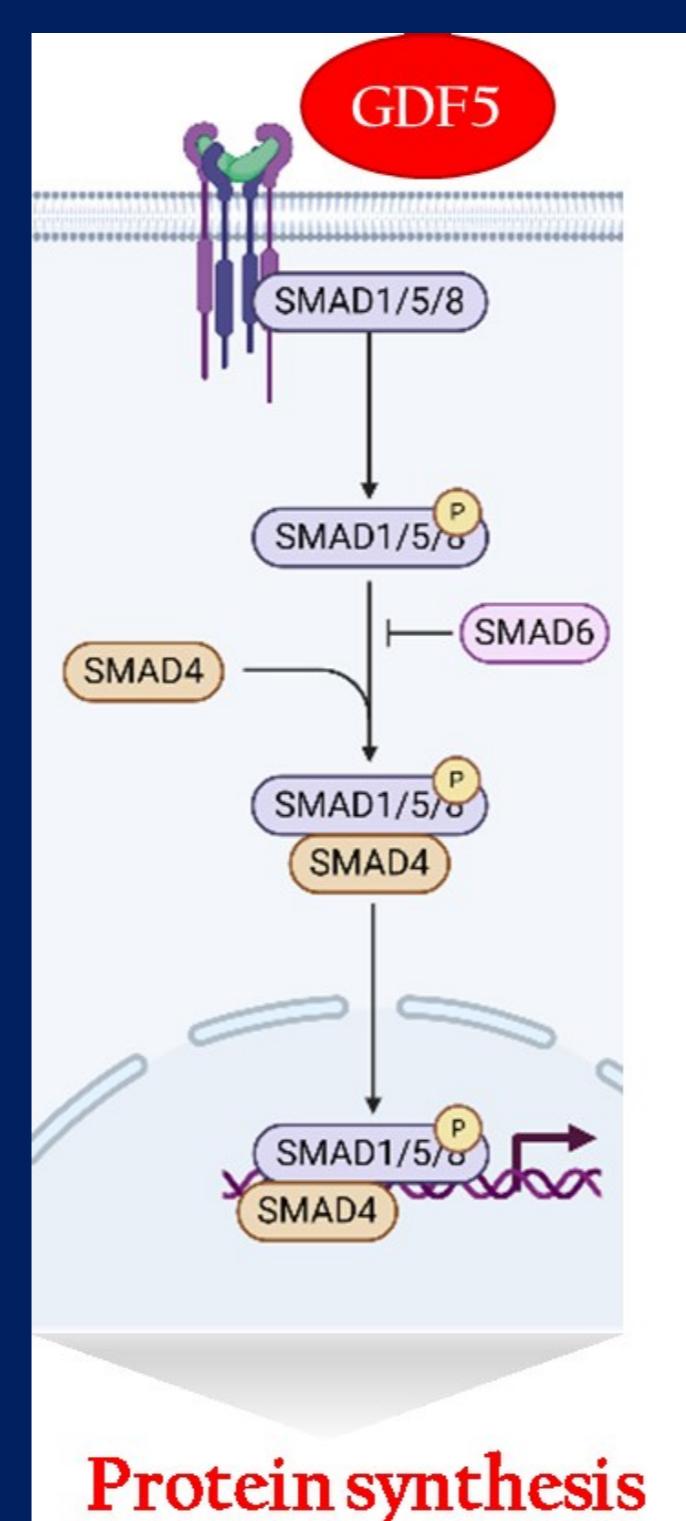
Christel Gentil¹, Lucile Saillard¹, Amélie Vergnol¹, Lorenzo Giordani¹, Bruno Cadot¹, Anne Forand¹, Sophie Moog¹, Chiara Noviello¹, Pierre Meunier¹, Sestina Falcone¹ and France Piétri-Rouxel¹

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

Introduction



Duchenne muscular dystrophy (DMD) is a devastating neuromuscular disease caused by the lack of the dystrophin. Among therapeutic strategies, clinical trials with AAV administration of microDystrophin (AAV-microDys) are underway and the first data indicate the potential of gene therapy as treatment to respond to unmet need for DMD. However, these approaches target the degenerating musculature and a major limitation is the loss of therapeutic benefits during necrosis/regeneration process. 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.



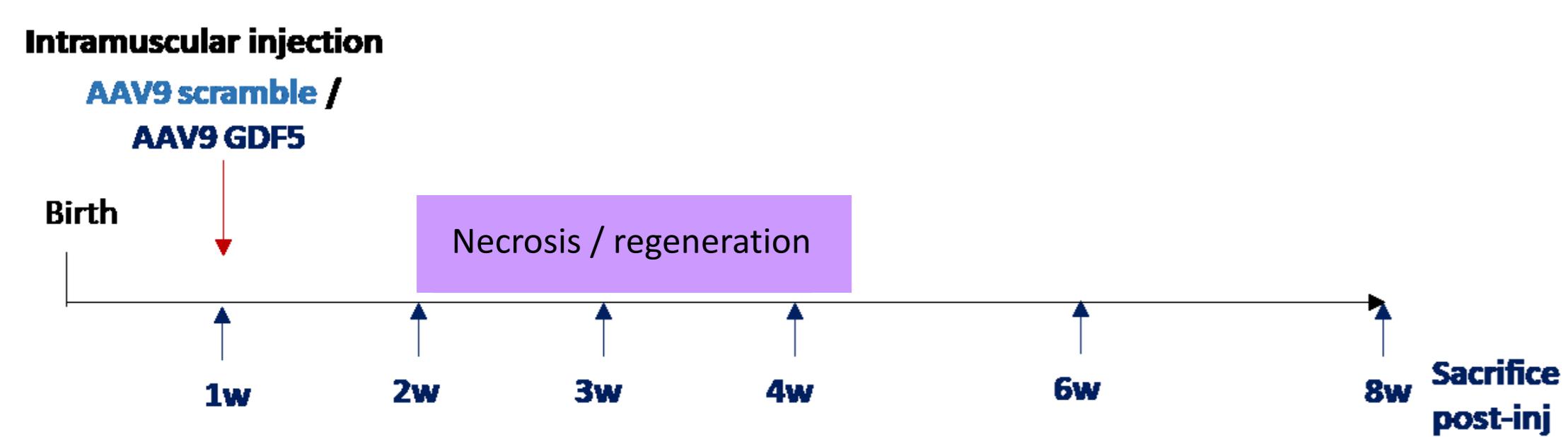
In terms of muscle tissue homeostasis, an emerging relevance is observed for components of Bone Morphogenetic Protein (BMP) family such as BMP14 also called Growth Differentiation Factor 5 (GDF5). GDF5 signaling includes the phosphorylation of intracellular SMAD1/5/8 complex, which translocate to the nuclei and controls gene transcription.

GDF5 has been shown to prevent both muscle mass loss and force decline during ageing (Traoré et al, 2019).

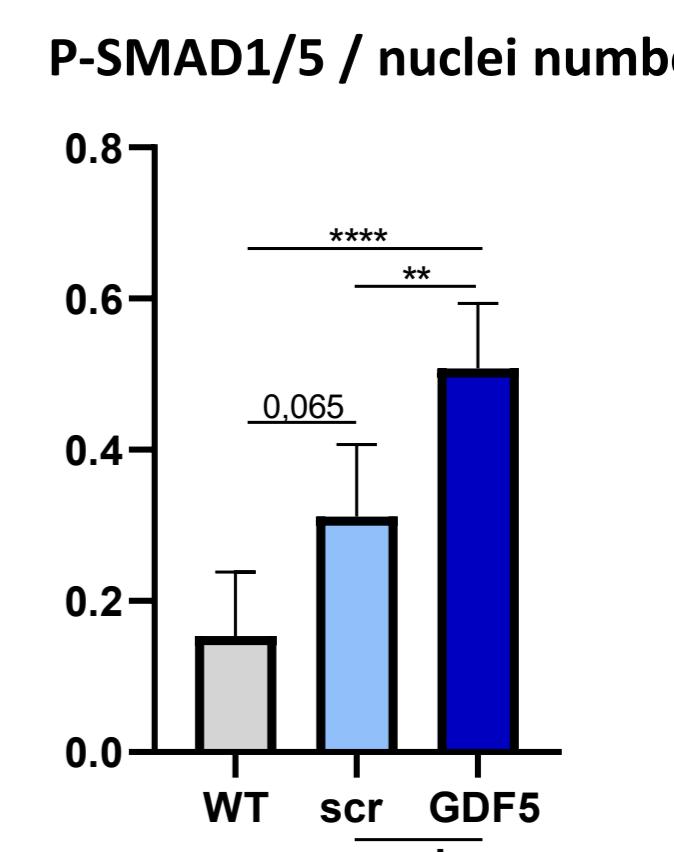
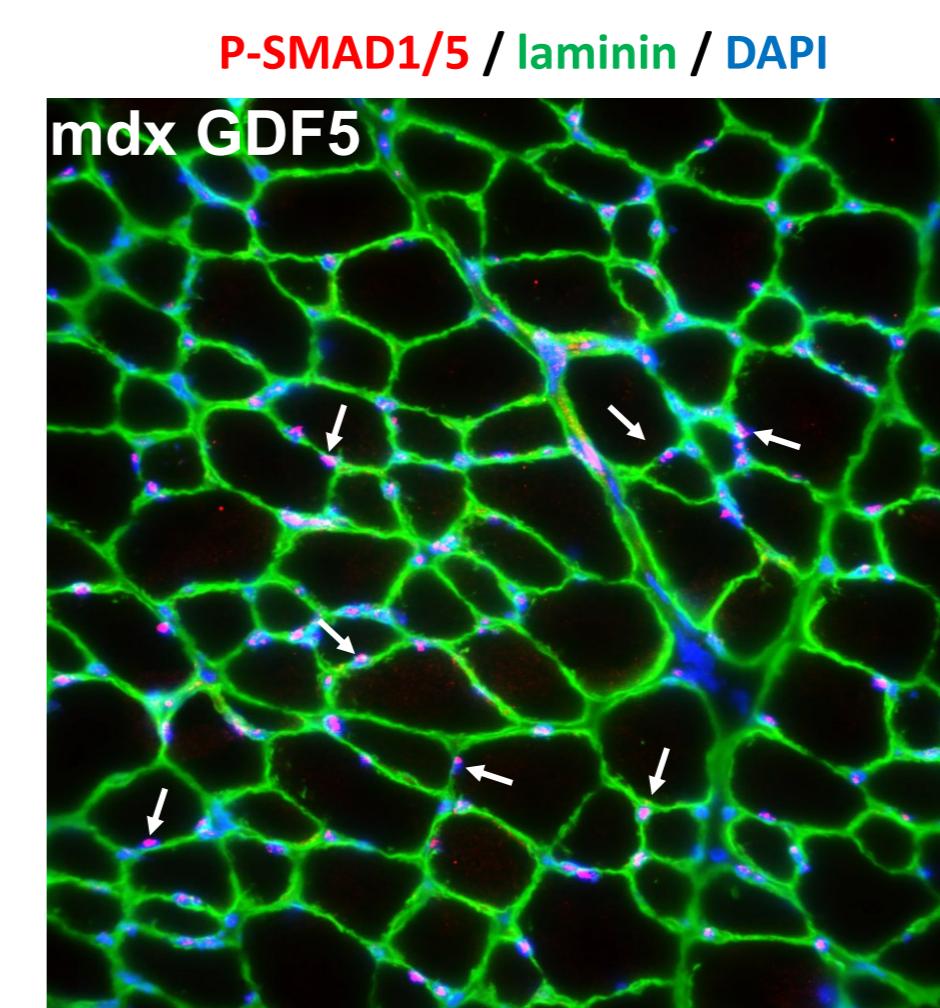
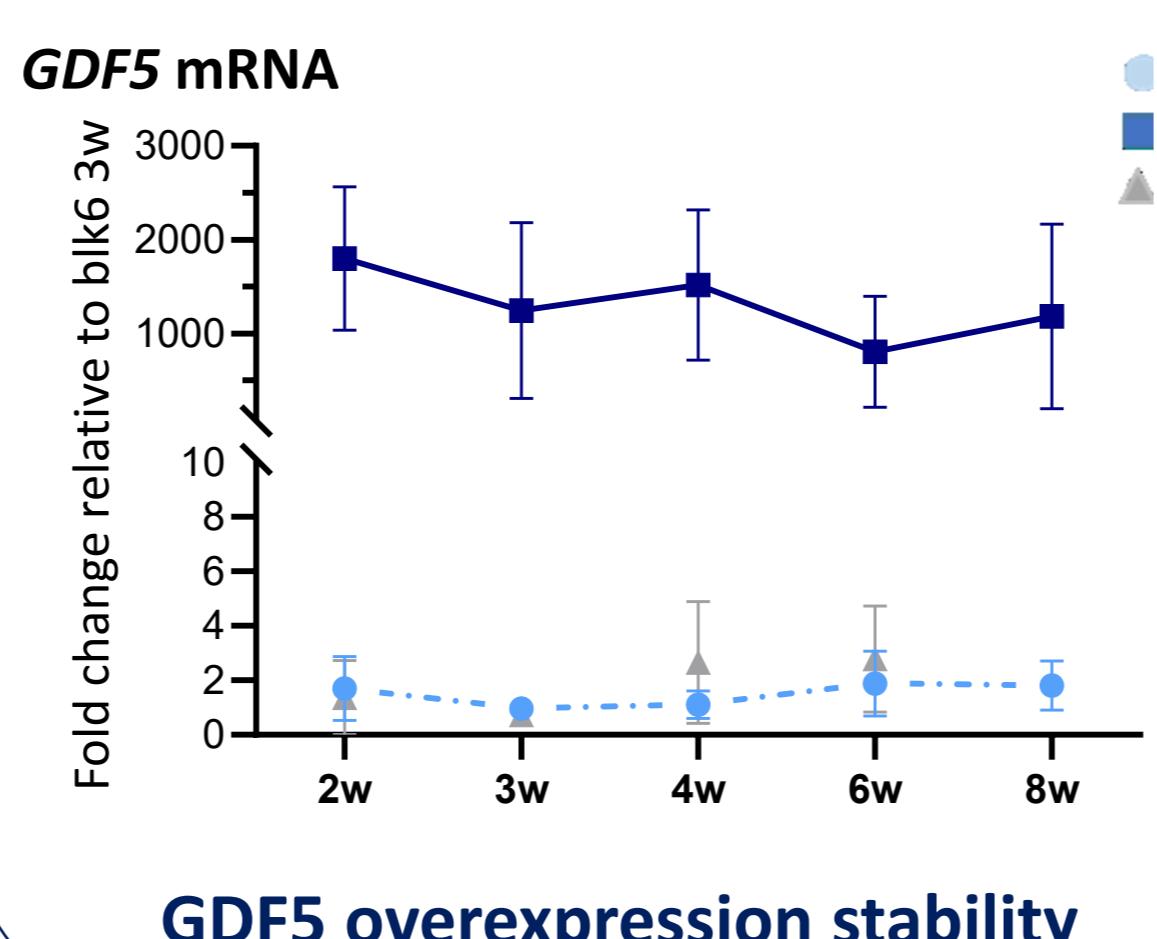
In addition, this factor has been described as a positive modulator of muscle mass homeostasis and a potential regulator of muscle repair (REF).

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

Protocol

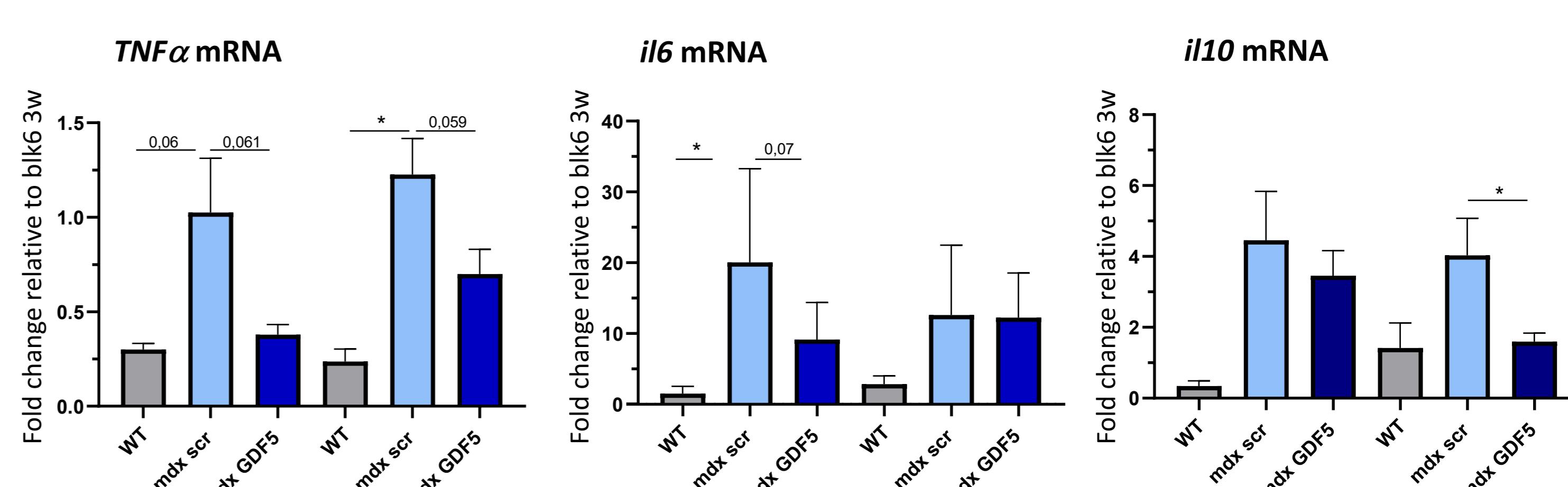
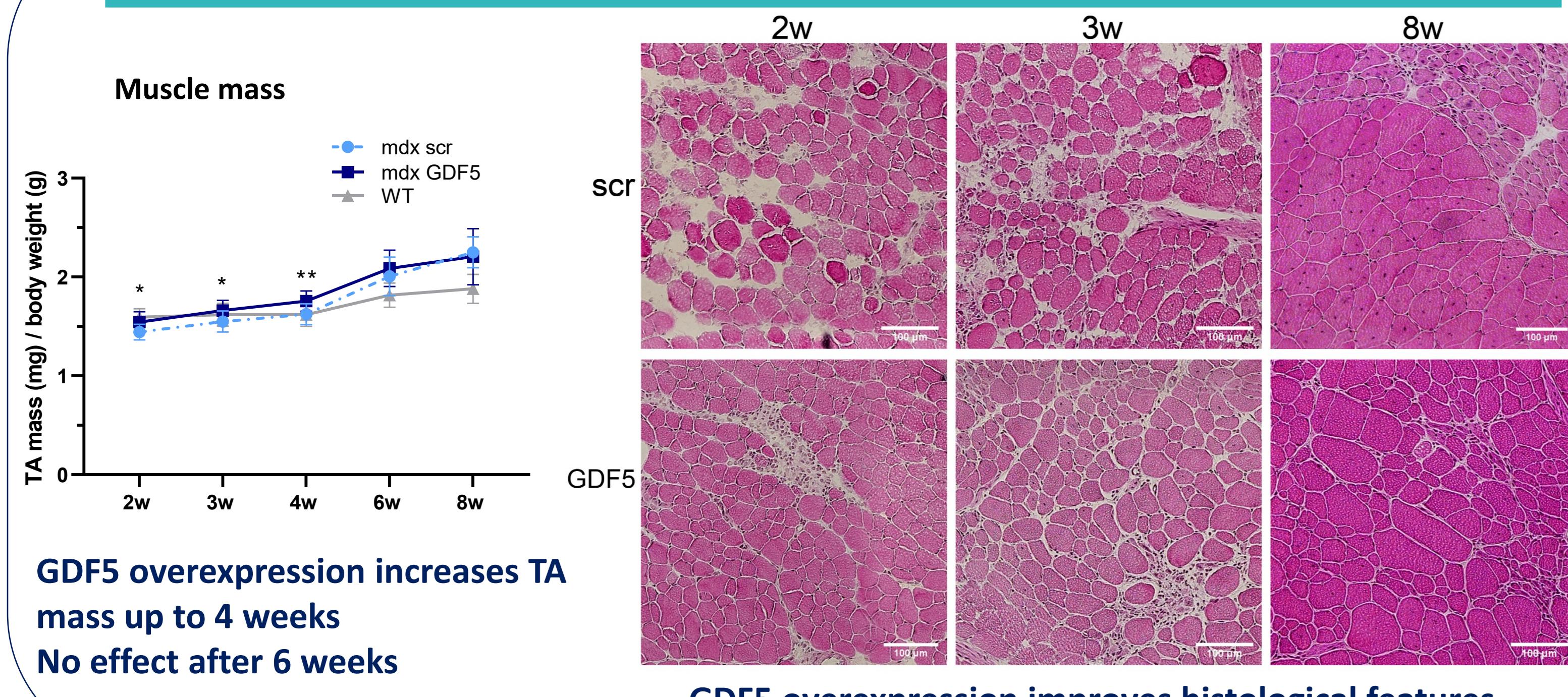


Activation of the GDF5 pathway

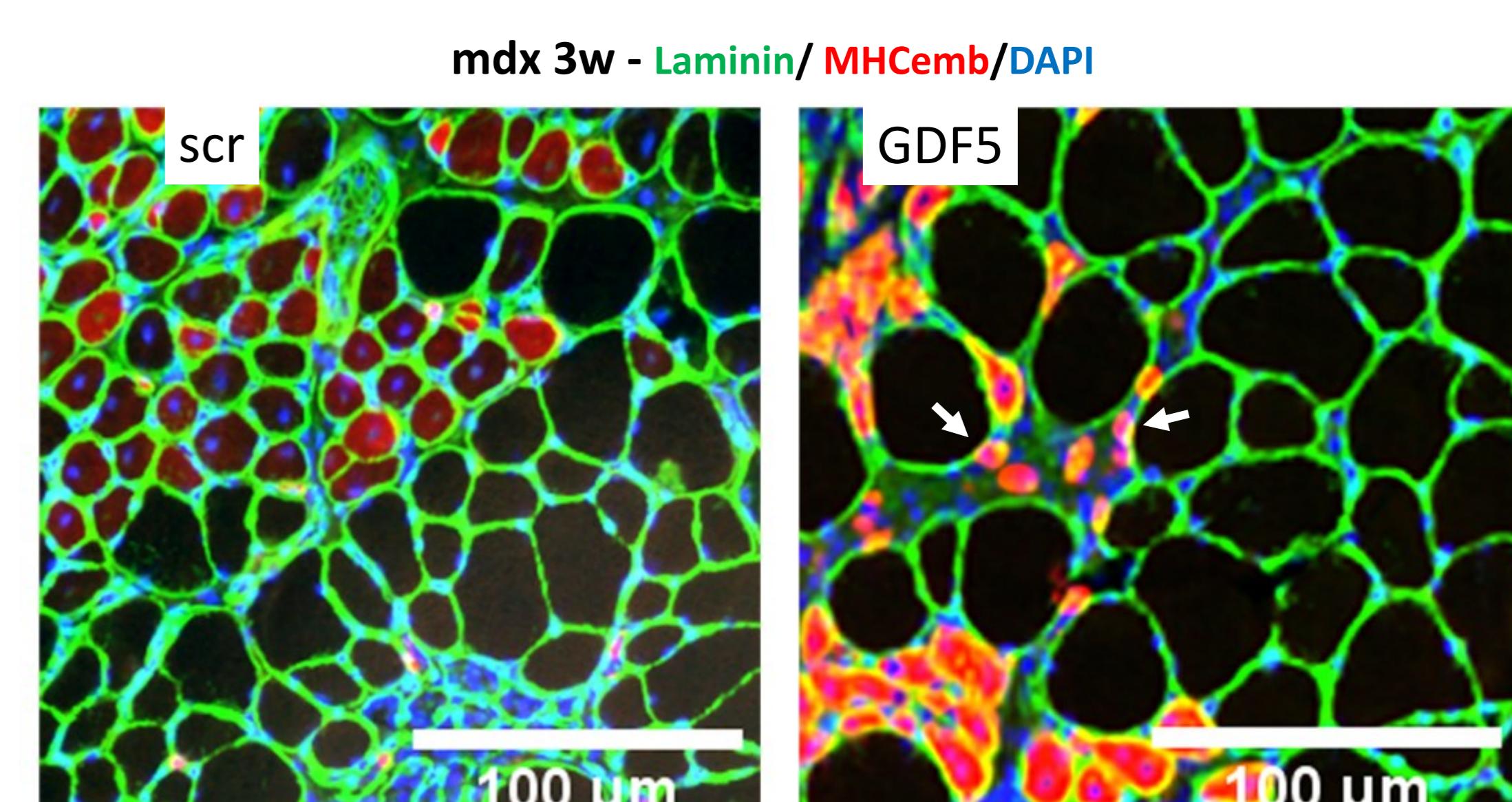
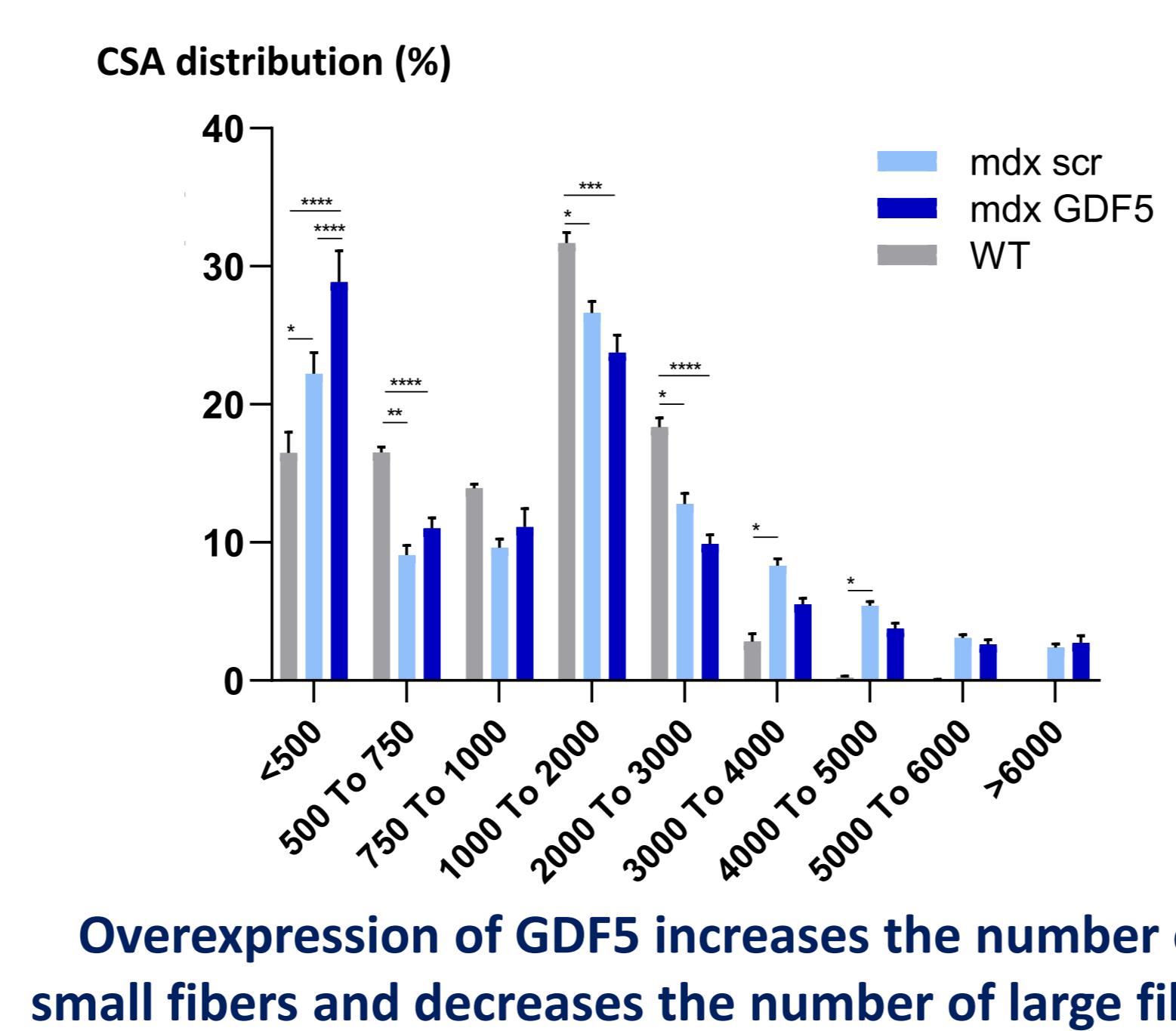
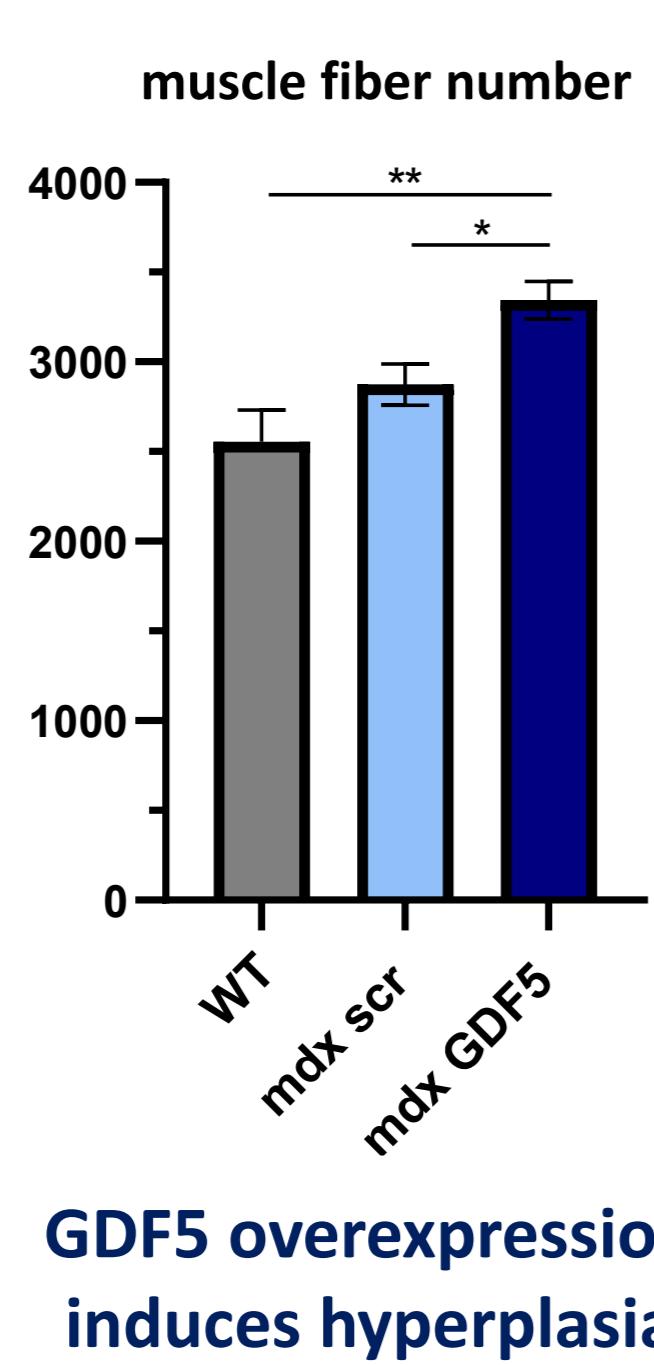
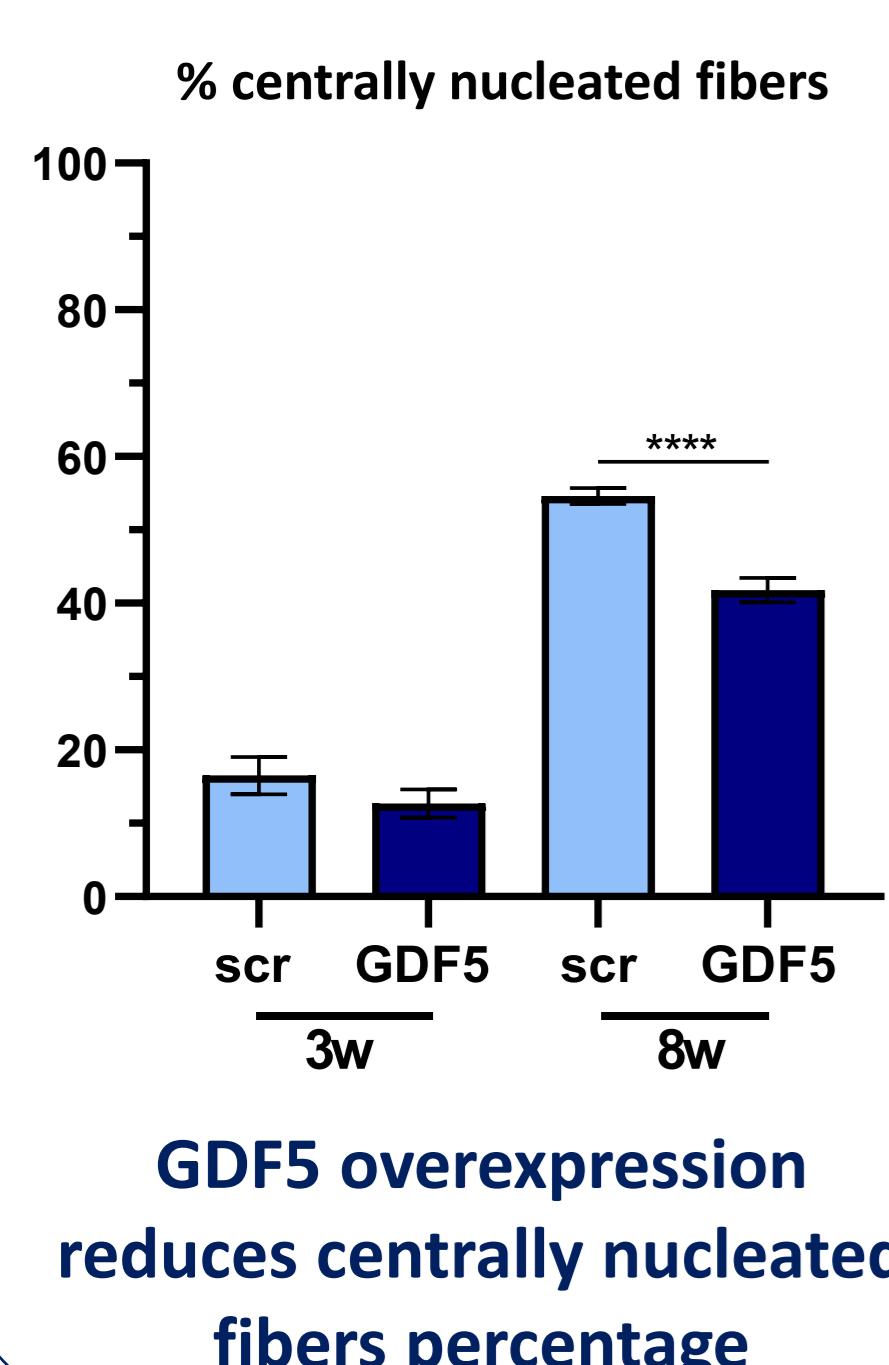


GDF5 overexpression induces SMAD1/5 phosphorylation

GDF5 overexpression effect on the DMD muscle pathophysiology



GDF5 overexpression on the differentiation / regeneration process



Presence of newly fused fibers in interstitial regions of GDF5 treated TAs

Conclusions

GDF5 overexpression seems to slow down the necrosis/regeneration process in mdx muscle

GDF5 overexpression promotes fiber formation in muscle interstitial regions

Perspectives

Identification of different cellular players underpinning the observed hyperplasia.

Does GDF5 activate muscular progenitors differentiation ?

Investigate potential benefits of AAV-GDF5 in DMD gene therapy