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► **To cite this version:**

Christel Gentil, Lucile Saillard, Amélie Vergnol, Lorenzo Giordani, Bruno Cadot, et al.. GDF5 therapeutic potential for DMD. *Myology* 2022, Sep 2022, Nice, France. hal-03994325

HAL Id: hal-03994325

<https://hal.science/hal-03994325v1>

Submitted on 24 Feb 2023

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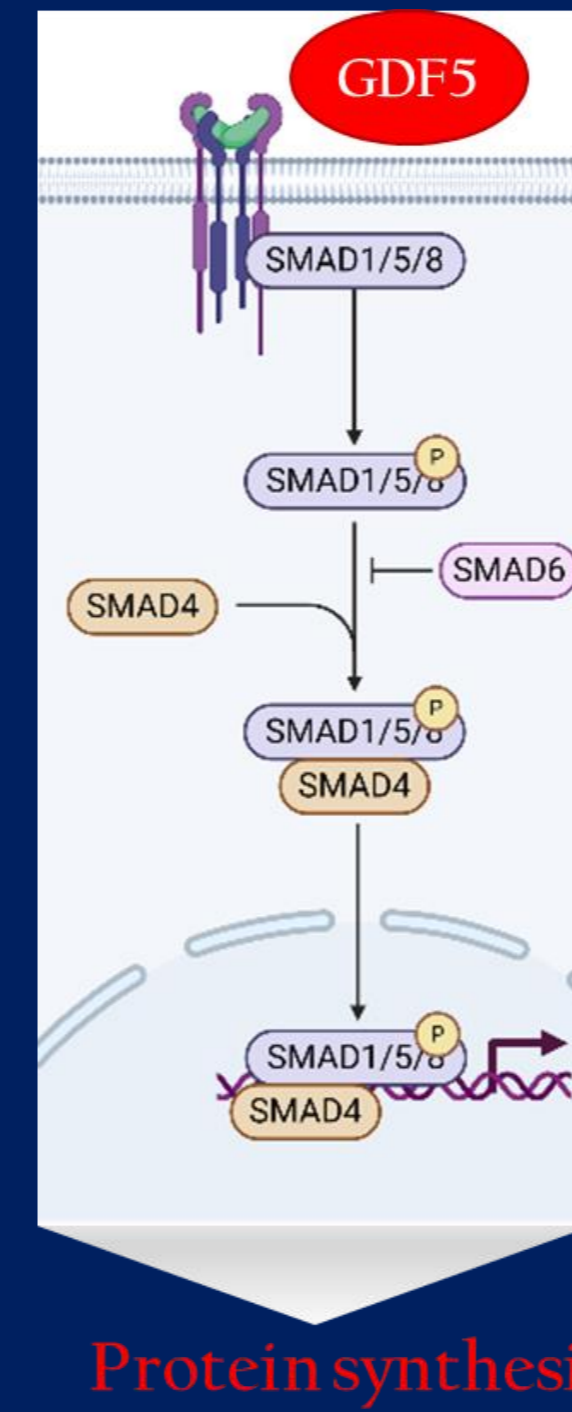
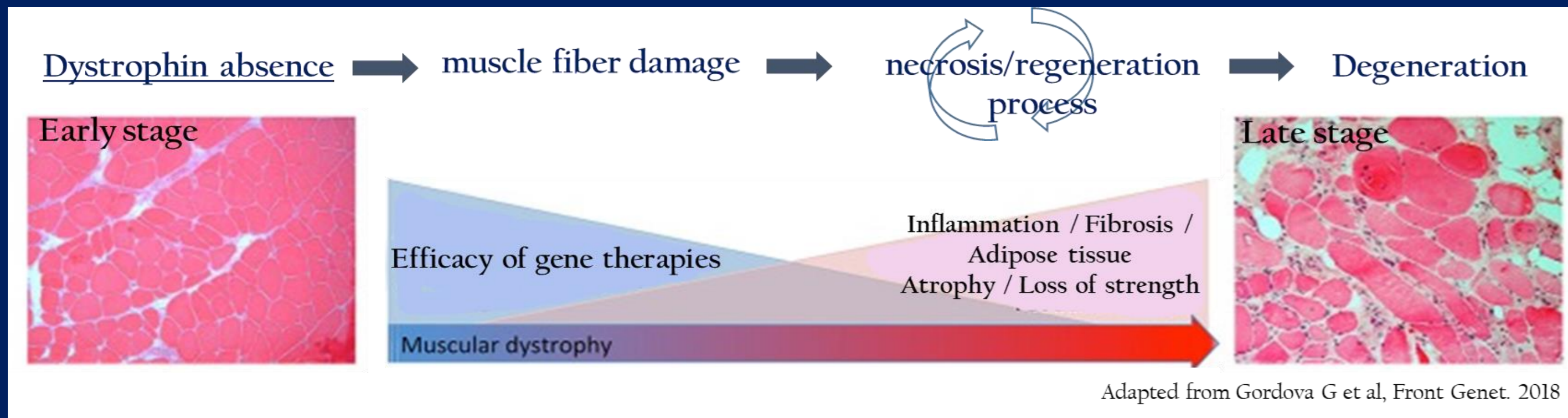
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GDF5 therapeutic potential for DMD

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Introduction

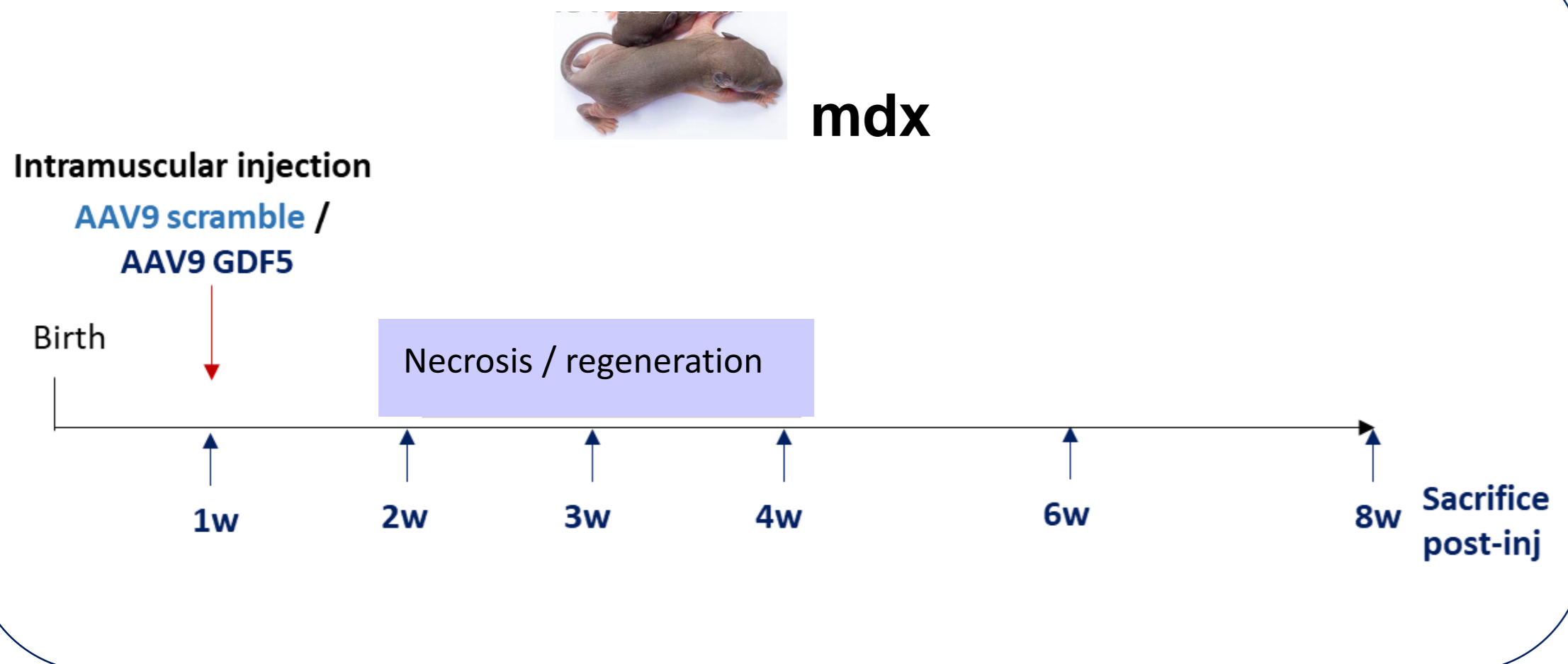


In terms of muscle mass homeostasis, an emerging relevance is observed for components of Bone Morphogenetic Protein (BMP) family such as BMP14 also called Growth Differentiation Factor 5 (GDF5). GDF5 signaling includes the phosphorylation of intracellular SMAD1/5/8 complex, which translocates to the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

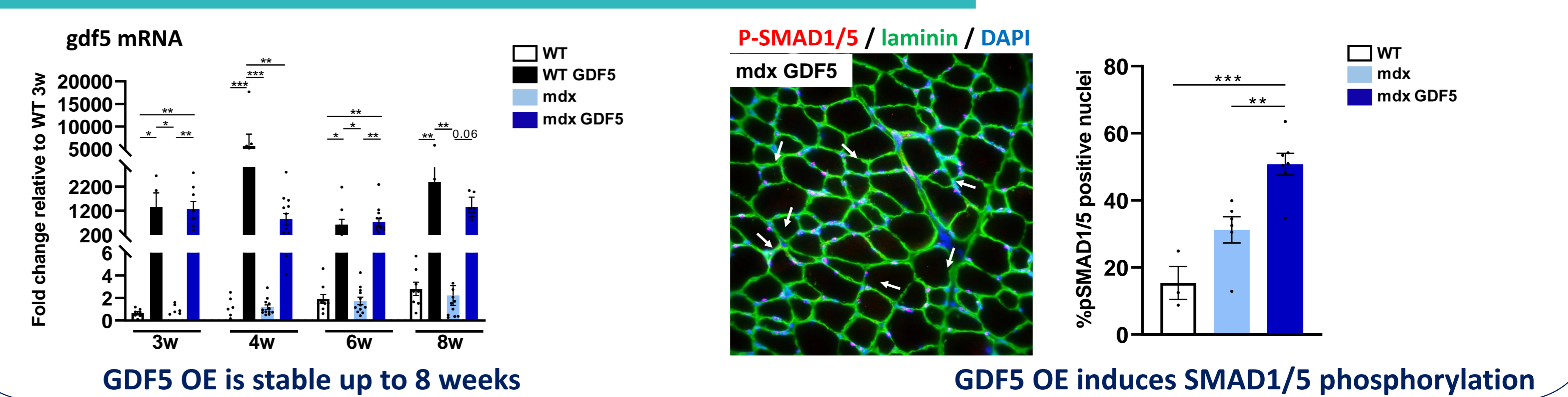
Our previous work showed that GDF5 prevents both muscle mass loss and force decline during ageing (Traoré et al, 2019). In addition, its signaling has been described as a positive modulator of muscle mass homeostasis (Winbanks et al, 2013) and a potential regulator of muscle repair (Borok et al, 2020).

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

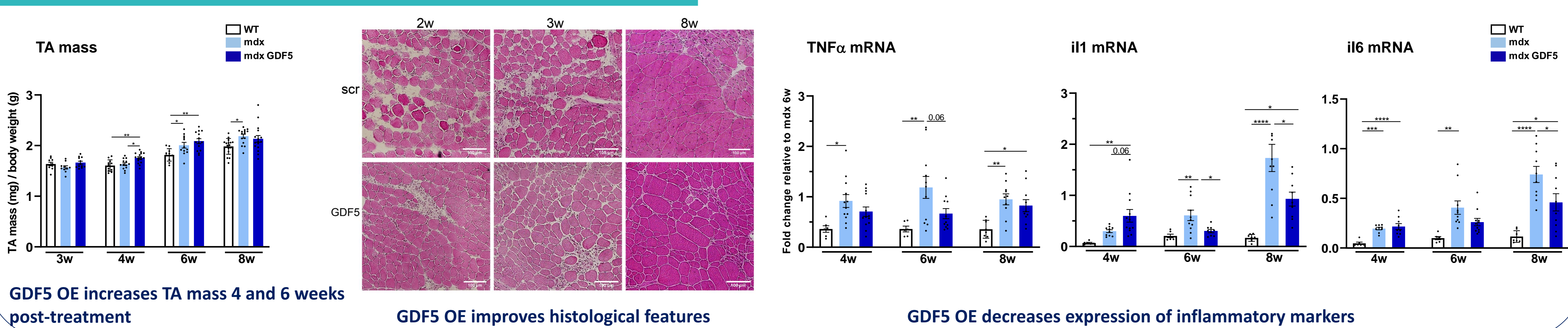
Protocol



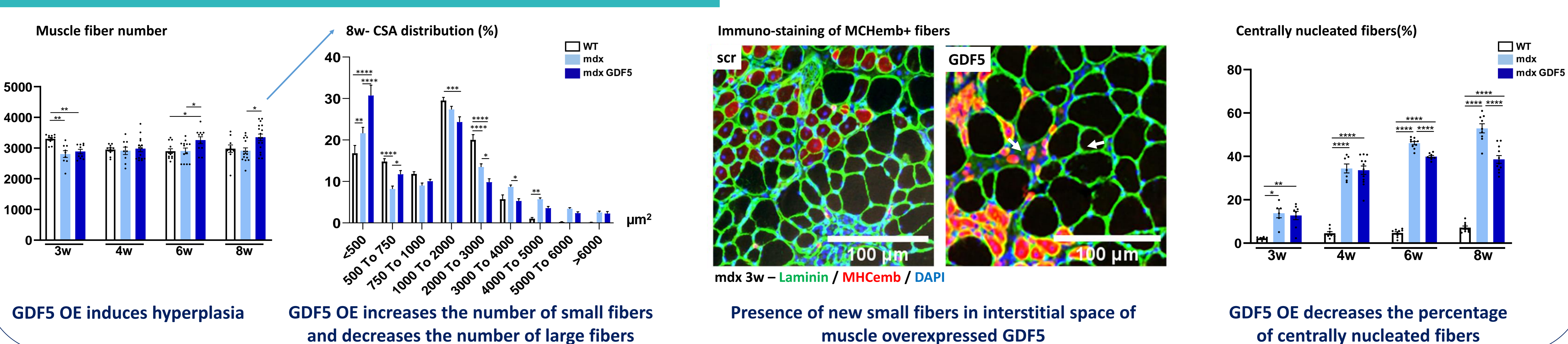
GDF5 overexpression and SMAD1/5 pathway activation



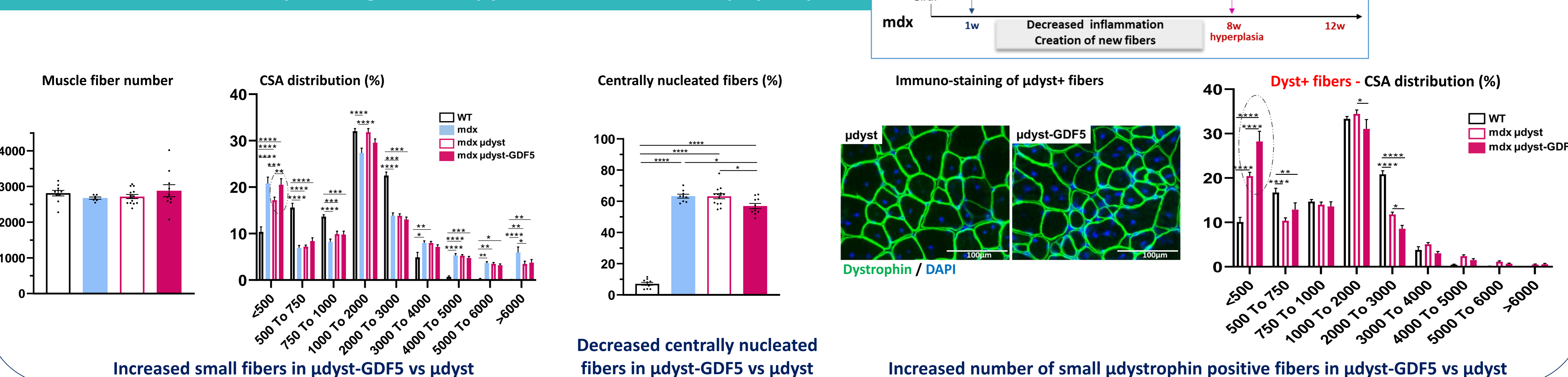
Effects of GDF5 overexpression on DMD muscle pathophysiology



GDF5 overexpression and the differentiation / regeneration process



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



Conclusions

- GDF5 overexpression in muscle of DMD mice model (mdx)
- Improves histological features and slows down the necrosis/regeneration process
- Induces hyperplasia with new small fibers in muscle interstitial space
- Increases number of small μdystrophin positive fibers in μdyst+GDF5 vs μdyst treatment alone

Perspectives

- Identify of GDF5 target cells underpinning the observed hyperplasia
- Investigate benefits of a combined treatment with sGDF5 protein and AAV-μDyst