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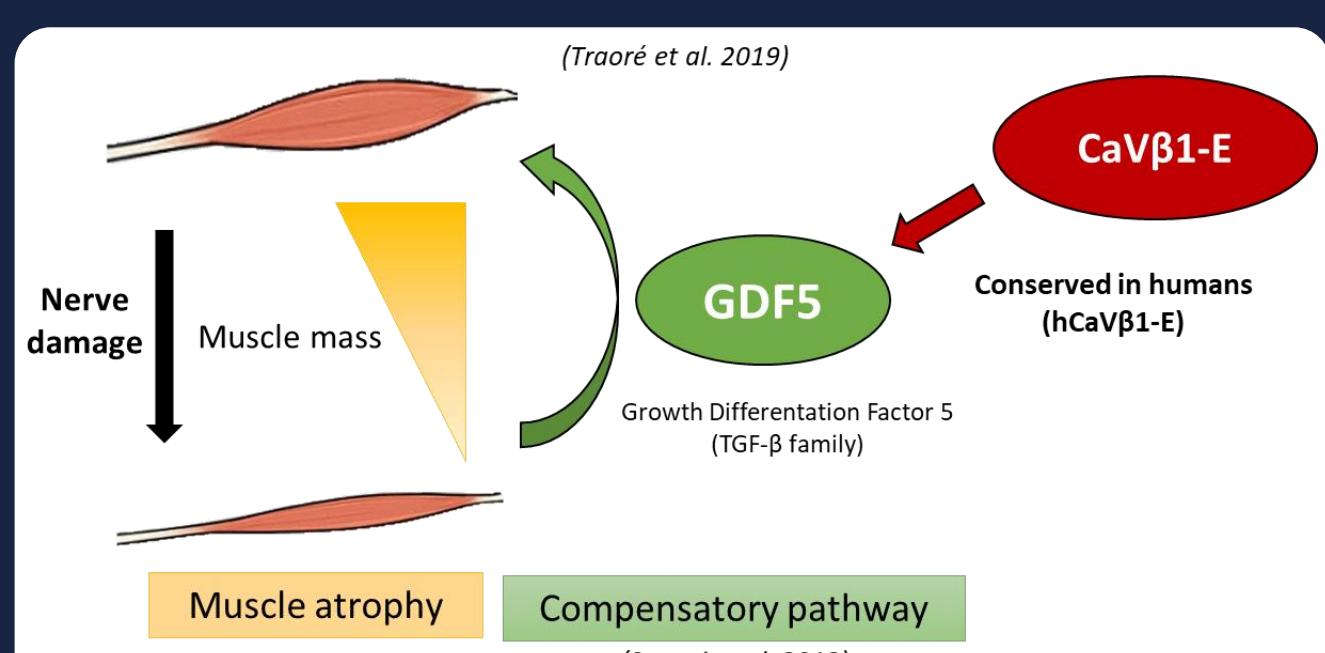
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# Role of MuscleBlind-Like proteins in the regulation of expression of CaV $\beta$ 1 isoforms in adult skeletal muscle

A. Vergnol<sup>1</sup>, A. Sureau<sup>1</sup>, M. Traoré<sup>1</sup>, X. Lornage<sup>1</sup>, G. Gourdon<sup>1</sup>, D. Furling<sup>1</sup>, F. Pietri-Rouxel<sup>1\*</sup> and S. Falcone<sup>1\*</sup>

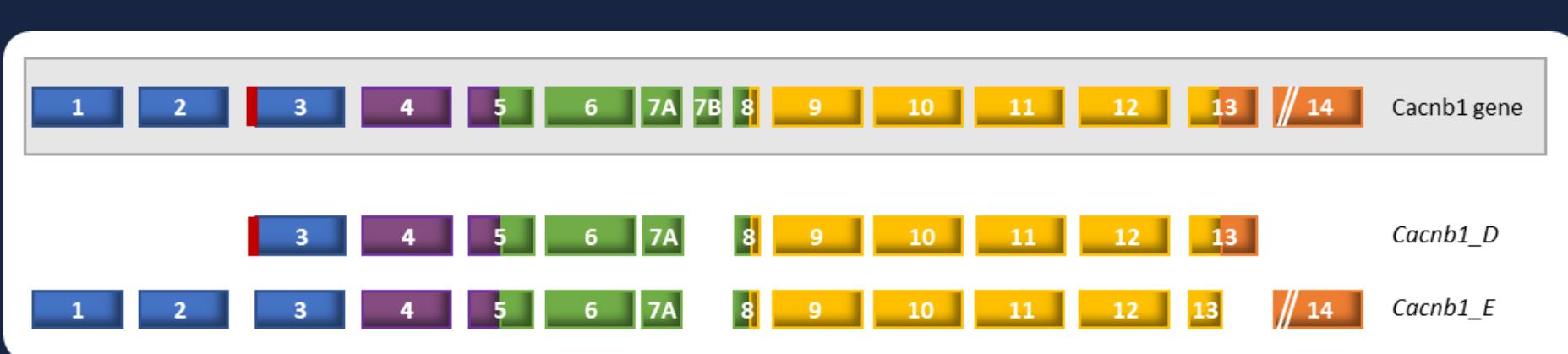
<sup>1</sup> Sorbonne Université, Inserm, Institut De Myologie, Centre De Recherche En Myologie F-75013 – Paris (France), \* Equally contributed to this work

## CaV $\beta$ 1-E/GDF5 axis in muscle mass homeostasis

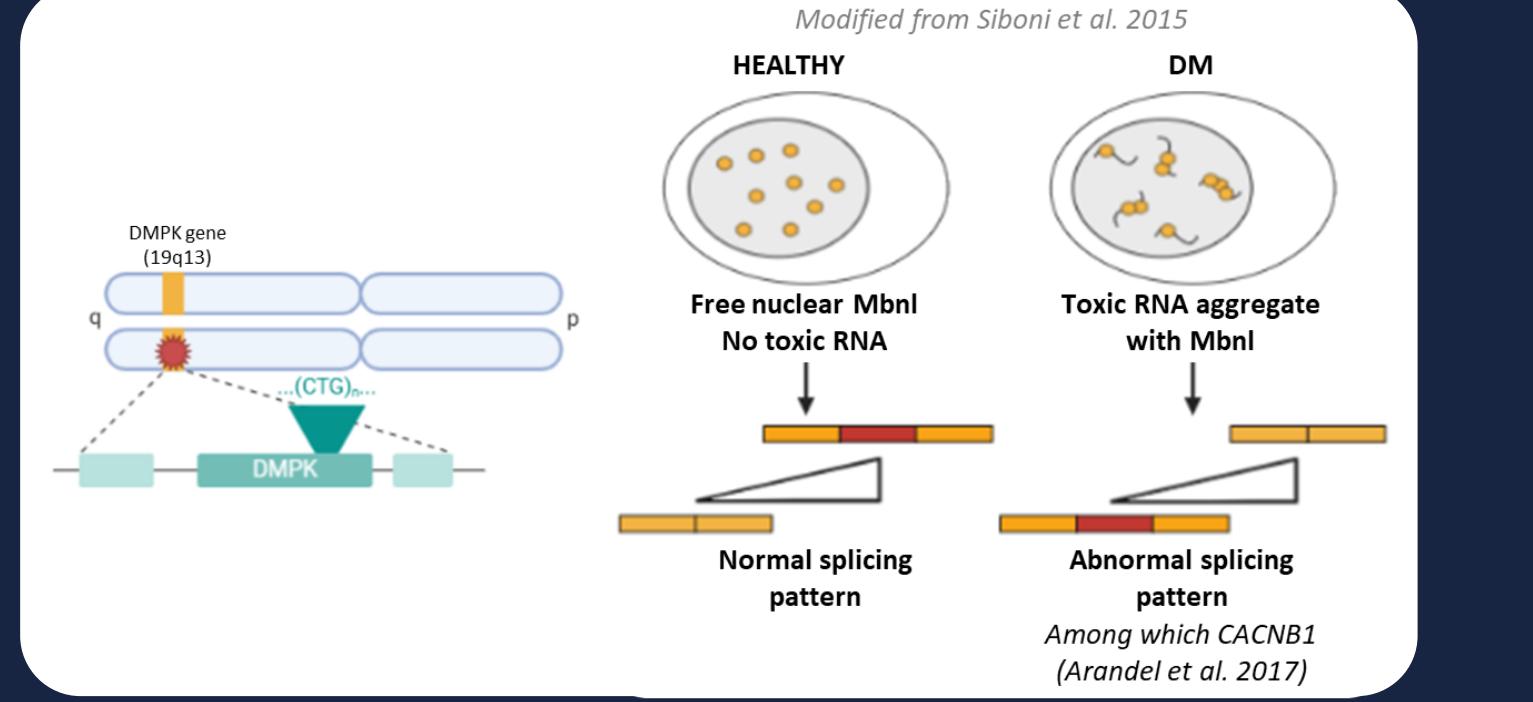


## INTRODUCTION

### Cacnb1 isoforms in skeletal muscle

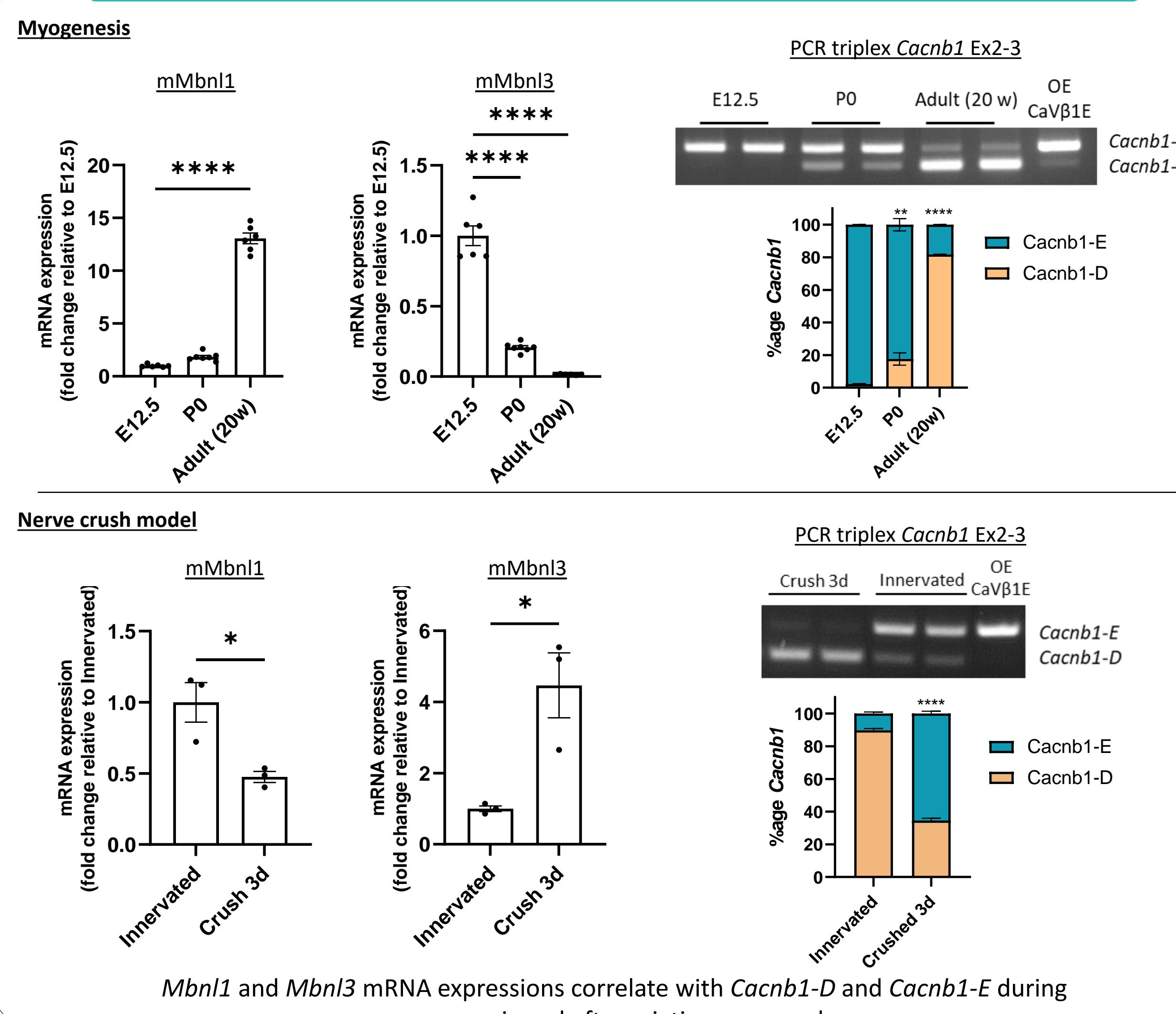


## Implication of MBNLs in DM1 pathophysiology

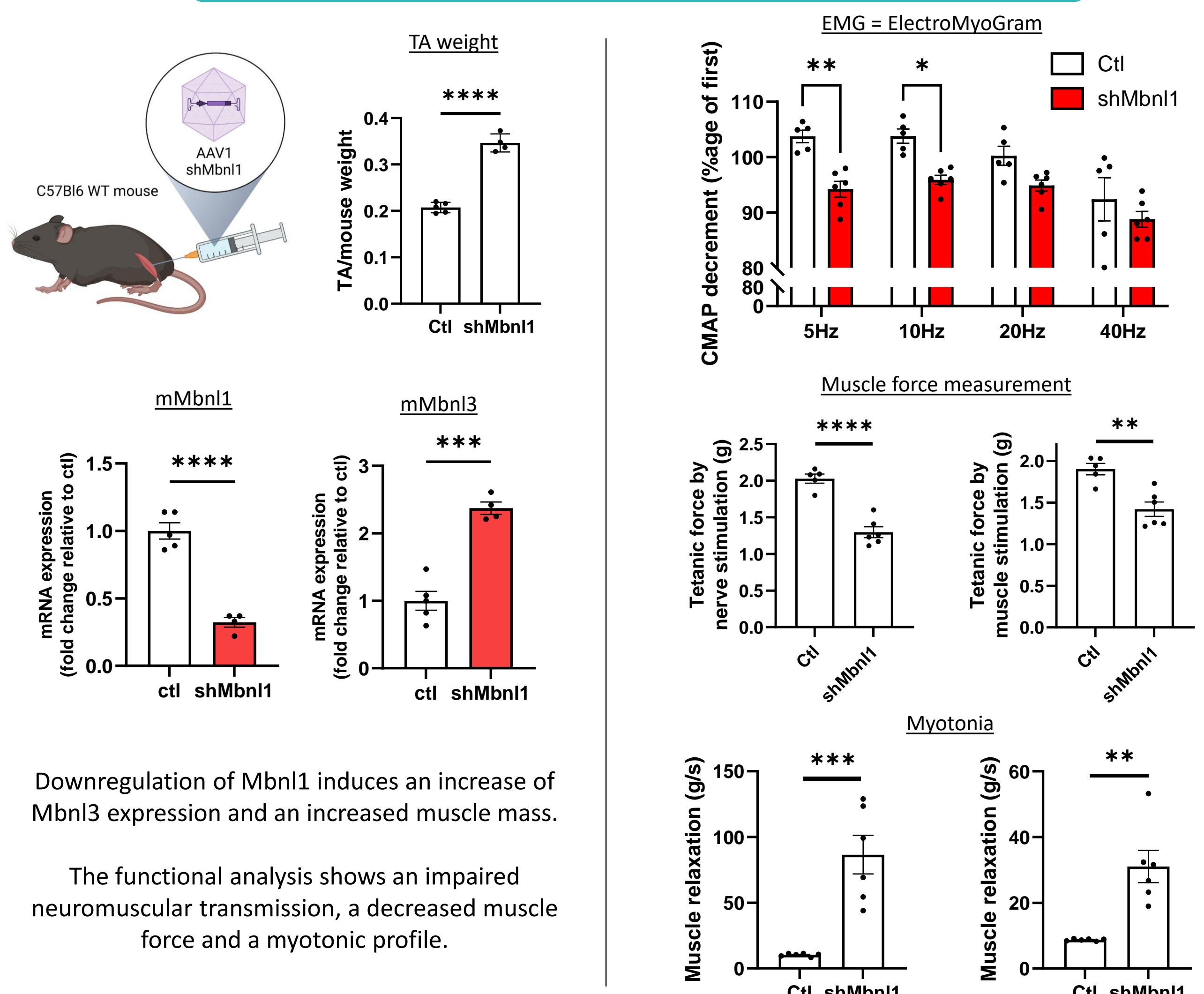


Voltage-gated calcium channels (CaVs or VGCCs) are major regulators of calcium-related cellular functions. In skeletal muscle, though the essential component of the pore channel is the CaV $\alpha$ 1 subunit, the CaV $\beta$ 1 subunit is an essential subunit guaranteeing CaV fine-tuning activity. CaV $\beta$ 1-E and CaV $\beta$ 1-D are two different isoforms of CaV $\beta$ 1 protein in skeletal muscle, expressed during embryogenesis and in healthy innervated adult muscle, respectively. Importantly, our recent study demonstrated that the embryonic CaV $\beta$ 1-E expression increases after a nerve damage in adult skeletal muscle and enables the expression of GDF5 (Growth Differentiation Factor 5) to counteract excessive muscle wasting (Traoré et al. 2019). However, the mechanisms leading to the increase in CaV $\beta$ 1-E expression are unknown to date. Our RNAseq data analysis in innervated versus denervated muscles revealed MuscleBlind-Like (MBNL) proteins as potential candidates regulating CaV $\beta$ 1 expression in skeletal muscle. Interestingly, in a human model of Dystrophy Myotonic 1 (DM1), the sequestration of MBNLs in toxic nuclear aggregates is related to an impaired splicing of CaV $\beta$ 1 transcript (CACNB1) (Arandell et al. 2017). Here, we evaluate the effect of a modulation of MBNLs protein levels on the expression of CaV $\beta$ 1 isoforms in both *in vitro* and *in vivo* systems as well as in pathological mouse models of DM1.

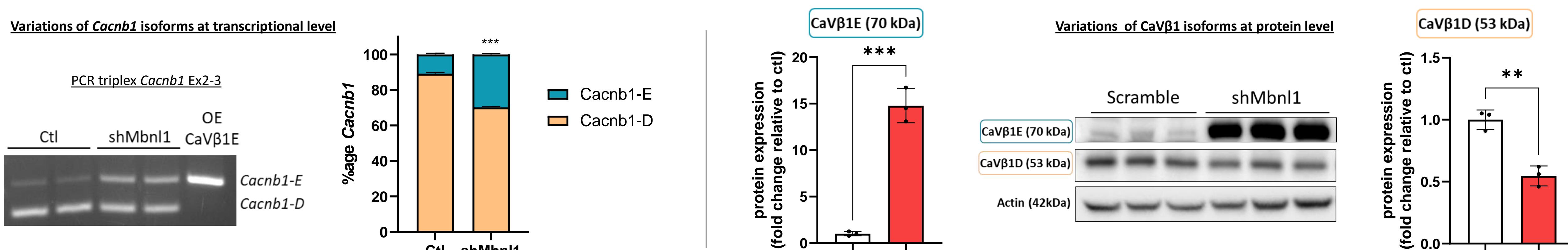
## Correlation between MBNLs and Cacnb1 expressions



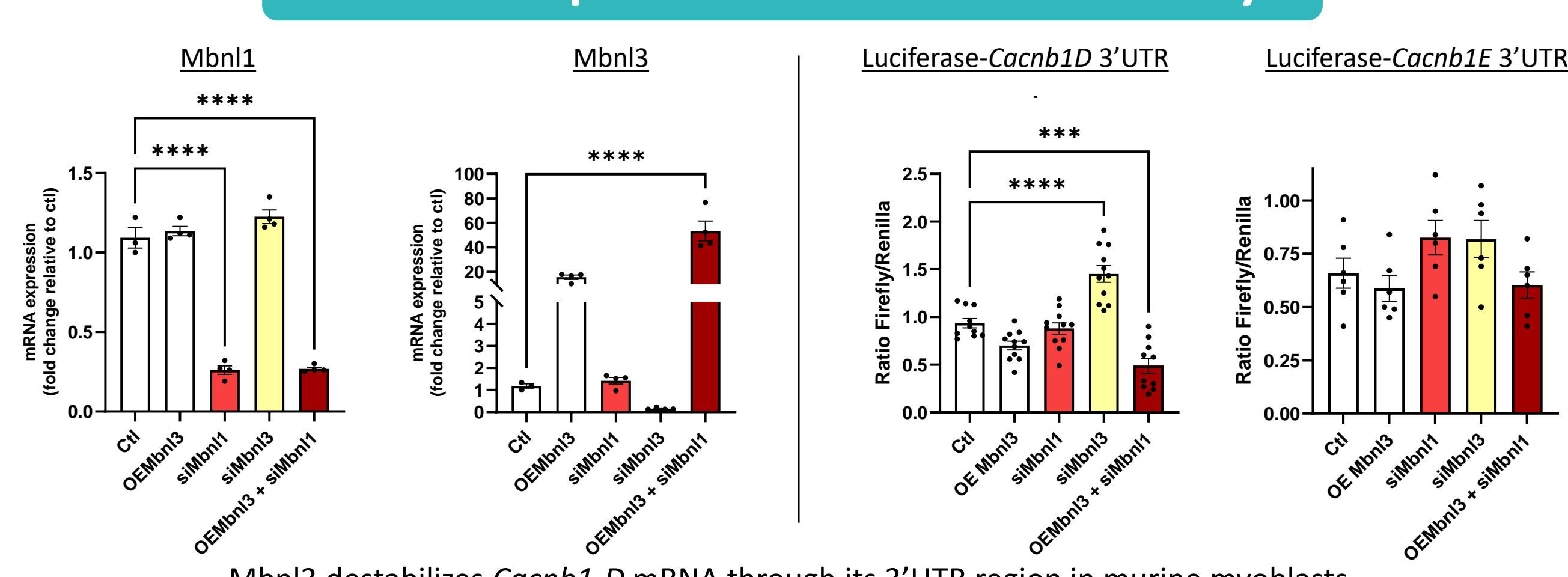
## Mouse model of Mbml1 downregulation



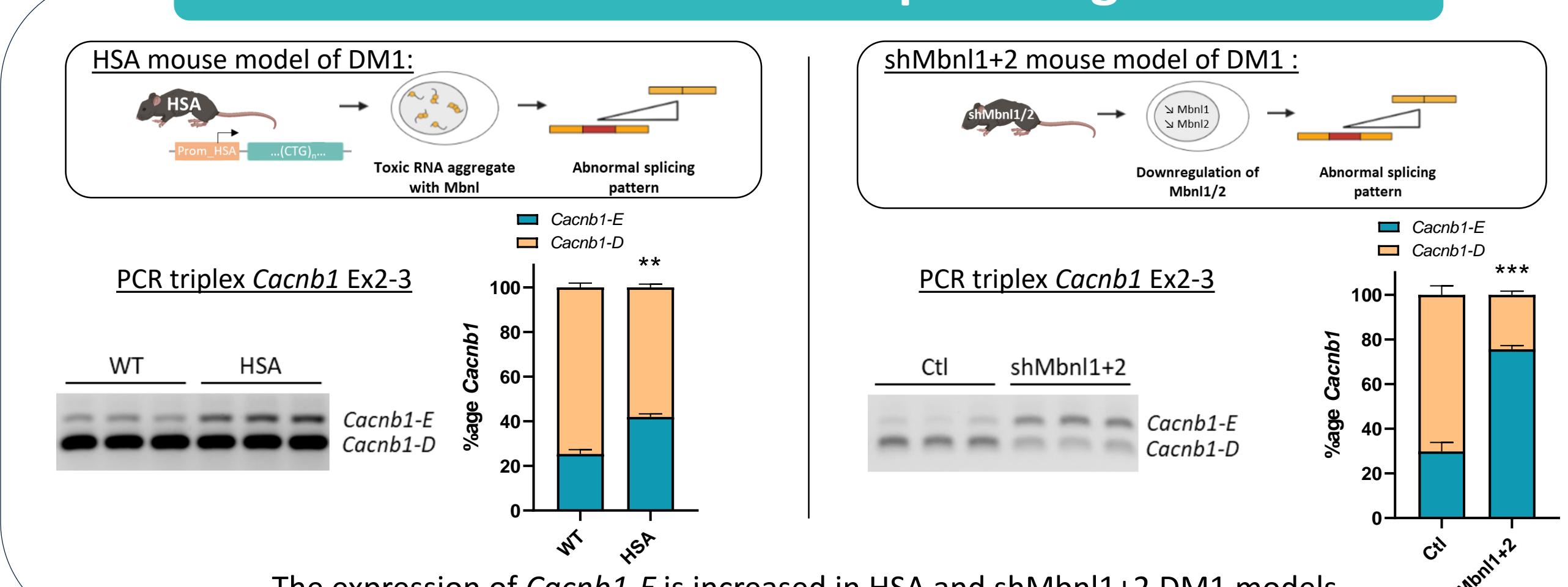
## MBNLs modulates the expression of CaV $\beta$ 1 isoforms *in vivo*



## MBNLs impacts Cacnb1 mRNA stability



## Cacnb1-E increases in DM1 pathological models



- Mbml1 negatively regulates Mbml3
- Downregulation of Mbml1 *in vivo* is associated with impaired muscle and neuromuscular functions
- A downregulation of Mbml1, associated with an increase of Mbml3, leads to increased CaV $\beta$ 1-E and decreased CaV $\beta$ 1-D expression levels *in vivo*
- Cacnb1 transcripts stability is modulated by MBNLs *in vitro* through their 3'UTR
- Mouse models of DM1 are associated with an increased Cacnb1-E expression

## CONCLUSIONS & PERSPECTIVES

- Characterization of the splicing events occurring at Cacnb1 Ex2-3 and Ex13-14
- Studying a potential cross-regulation of CaV $\beta$ 1-D on CaV $\beta$ 1-E expression
- Deciphering the role of CaV $\beta$ 1-E in DM1 pathophysiology