

# An embryonic CaV $\beta$ 1 isoform promotes muscle mass maintenance via GDF5 signaling in adult mouse.

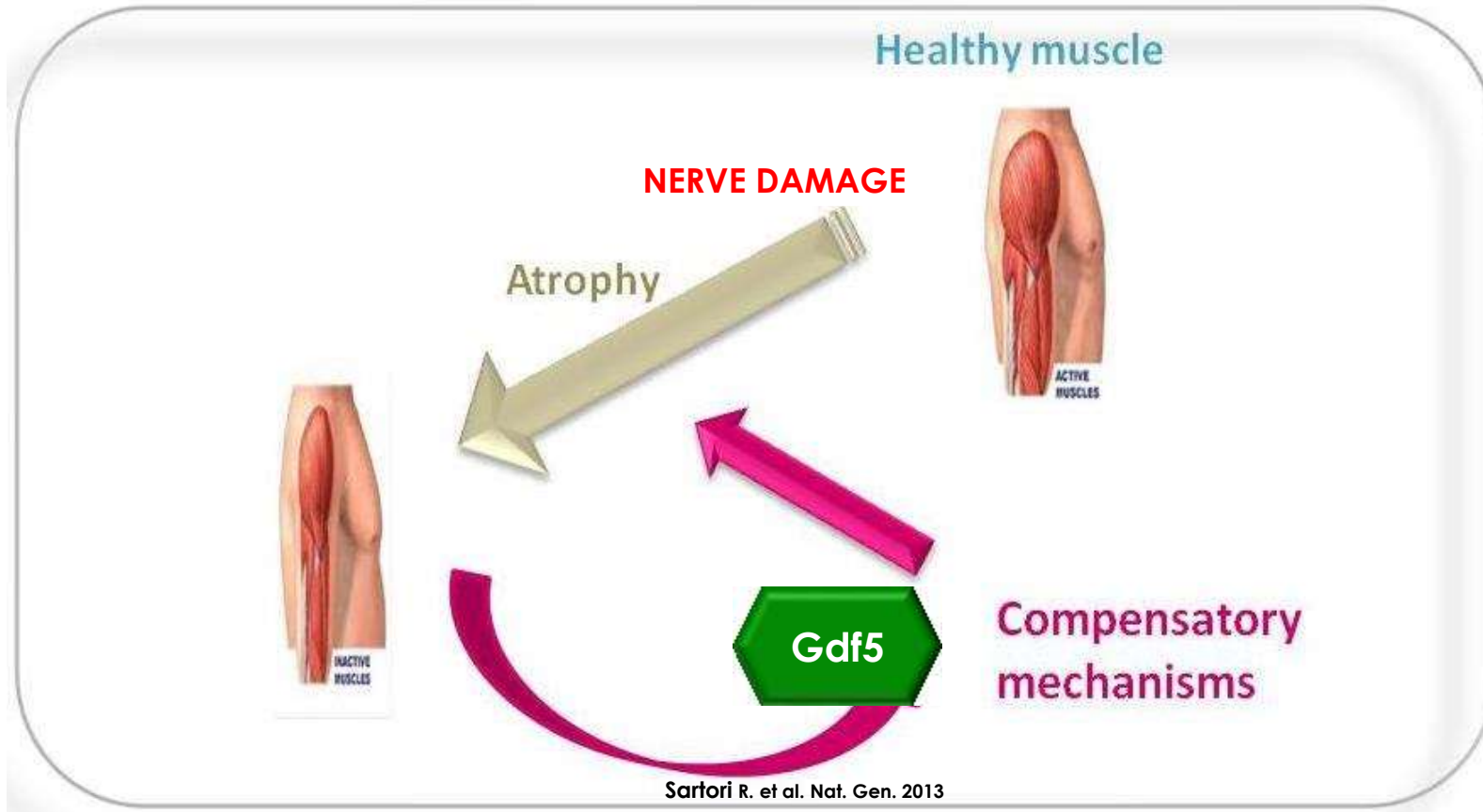
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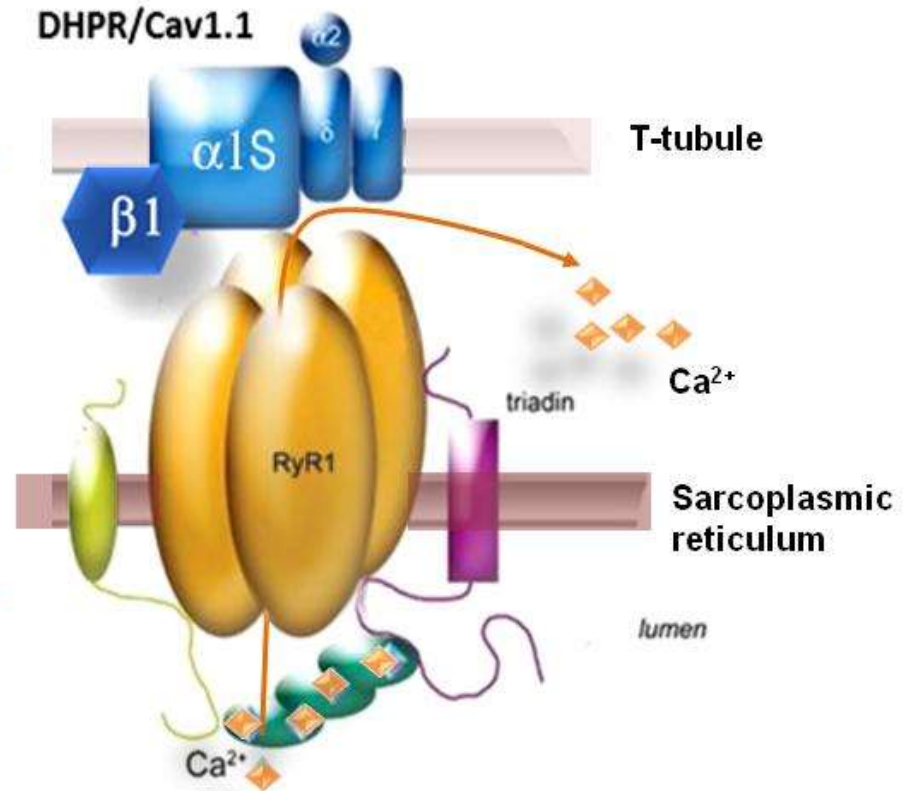
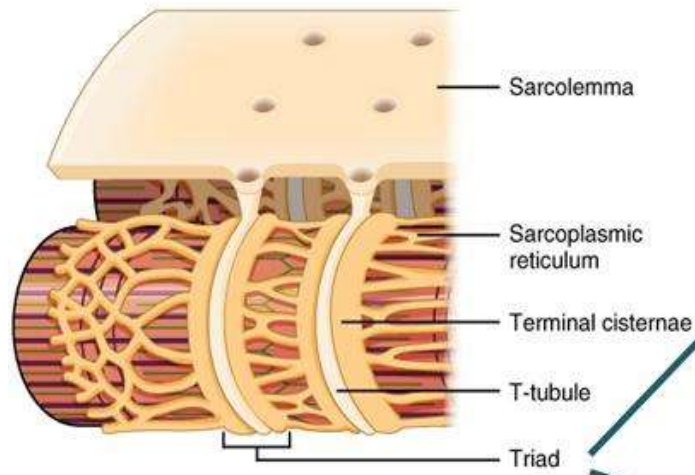
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# Muscle plasticity and compensatory response



## Excitation-Contraction coupling



$\beta 1$

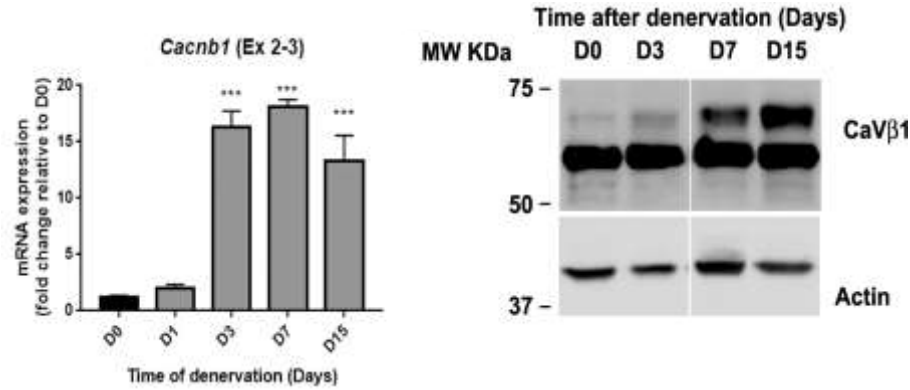
### Adult (healthy) muscle

- Anchors  $CaV\alpha 1S$  at the T-tubule membrane
- Mediates  $CaV\alpha 1S$  -RyR interaction in E-C coupling

### Developing muscle (independent of E-C coupling)

- Transcription factor function in MPCs
- Required for synaptic patterning in embryo (before innervation)

# CaVβ1 expression after nerve damage



Denervation induces a strong increase of mRNA levels of CaVβ1 related to the appearance of an upper extra band: splicing isoform expression?

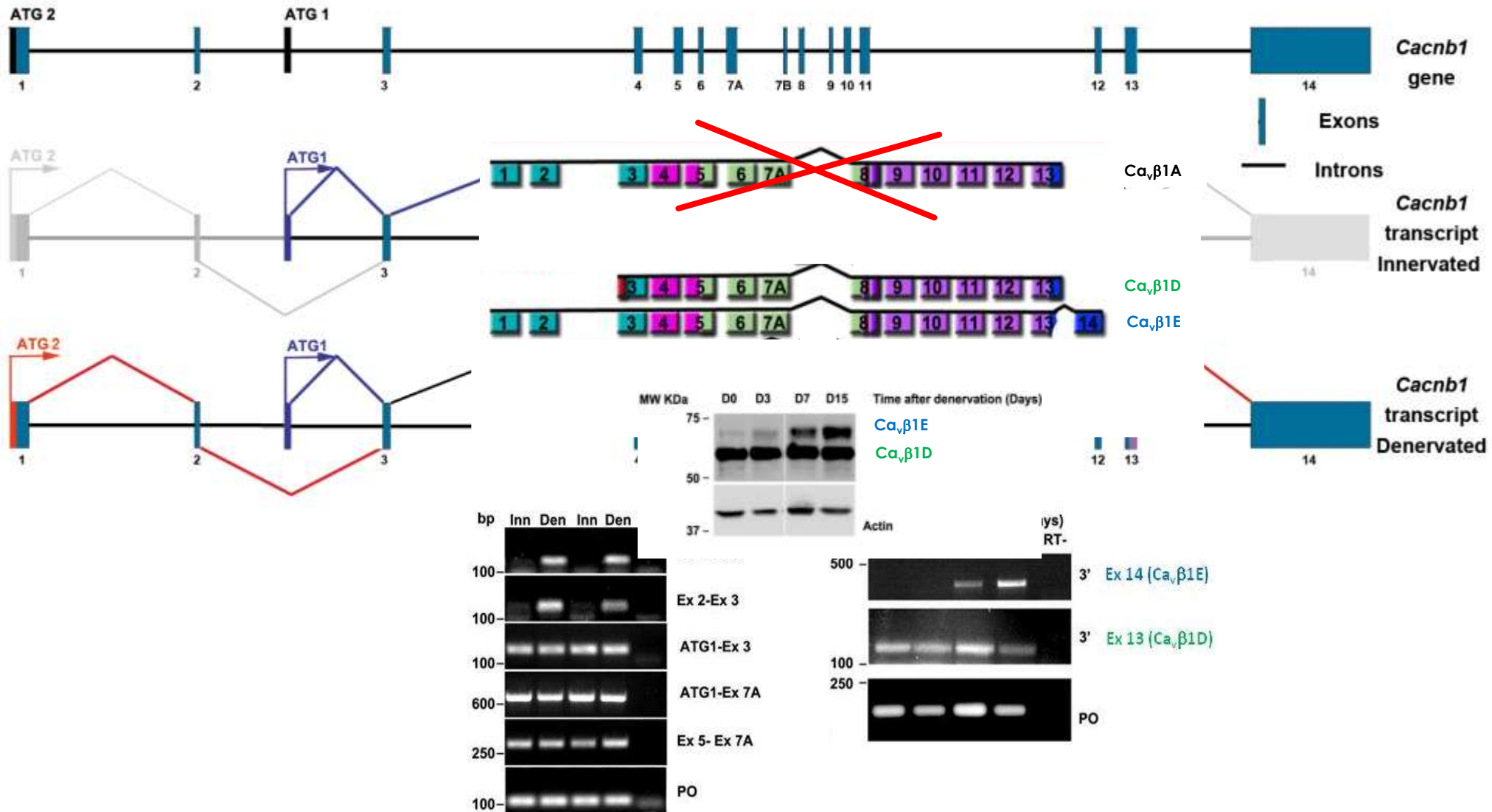


CaVβ1A was considered the isoform “muscle specific”

Upper band size was suggested the expression of CaVβ1E

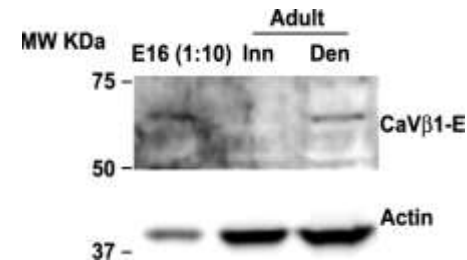
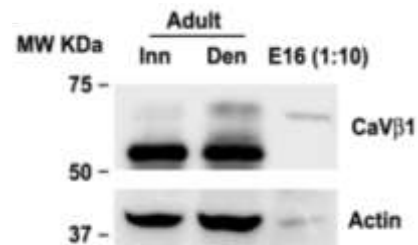
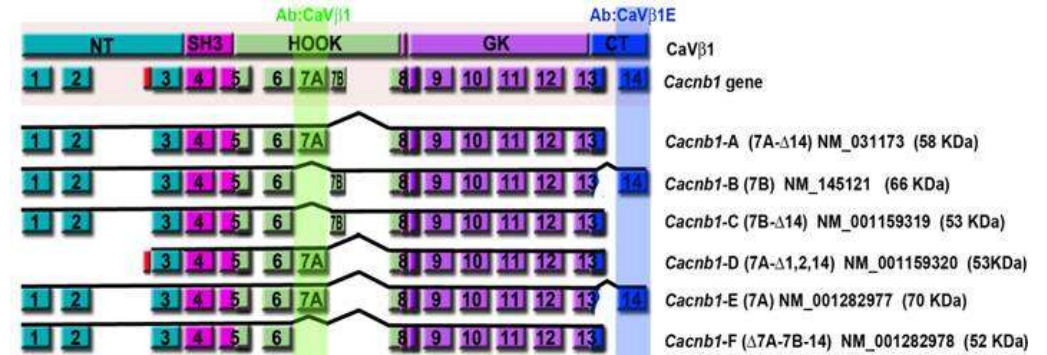
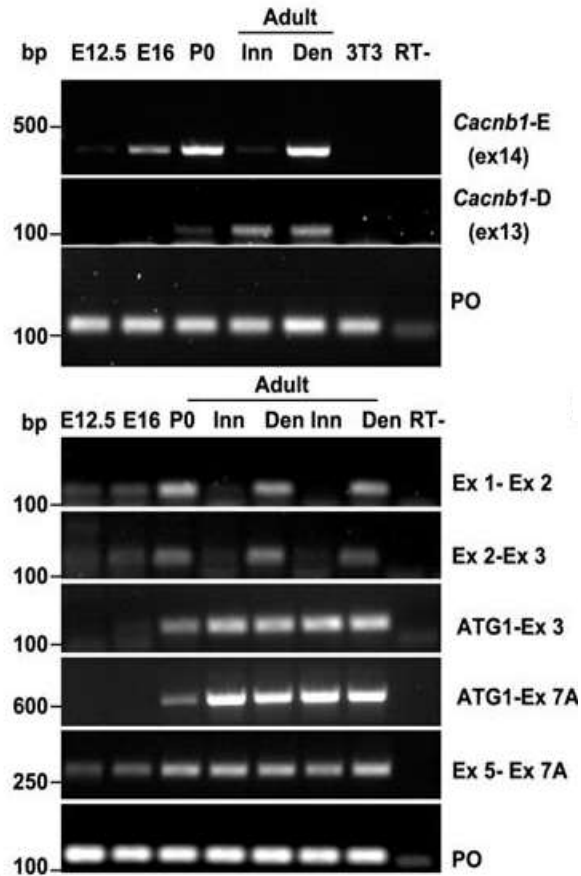


# Alternative first exon splicing of *Cacnb1* in muscle after denervation

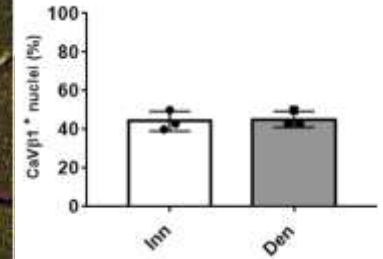
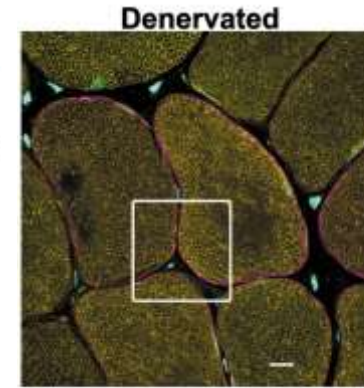
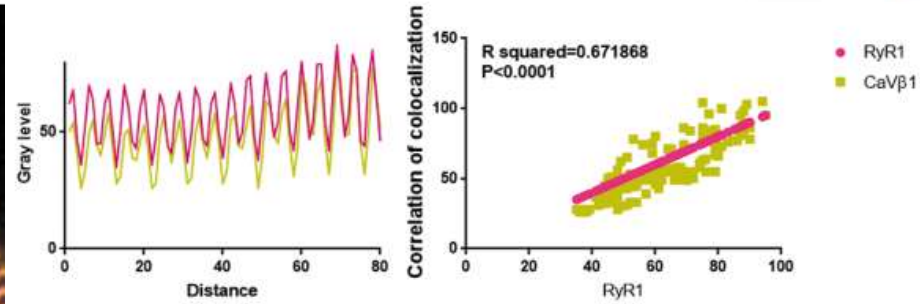
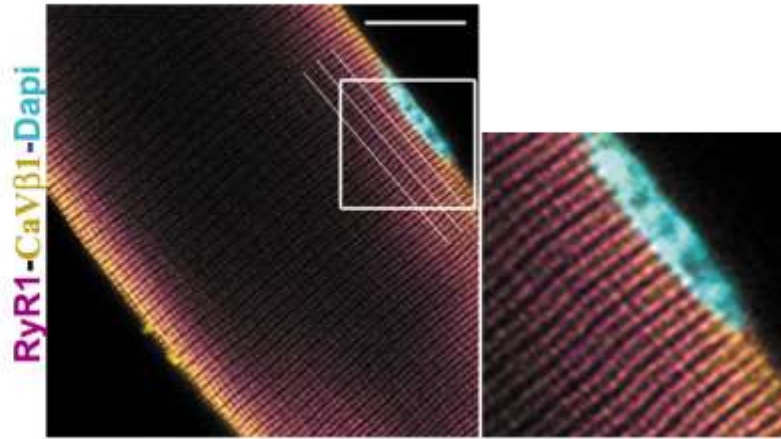


Two different *Cacnb1* transcripts depending on innervation state of muscle

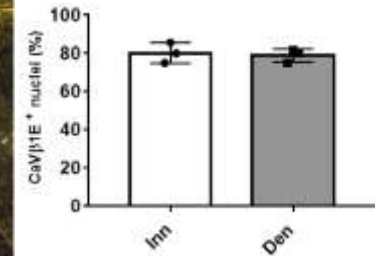
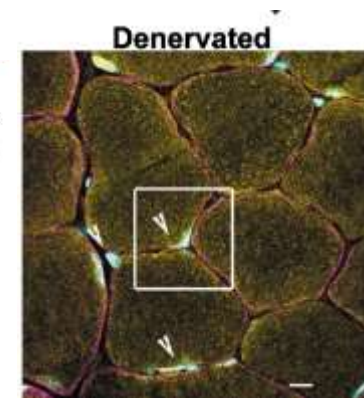
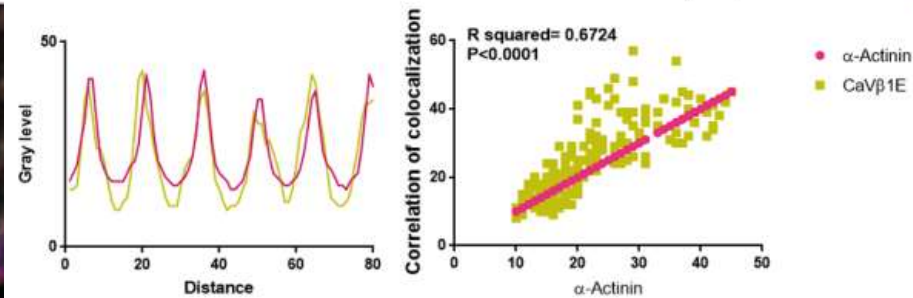
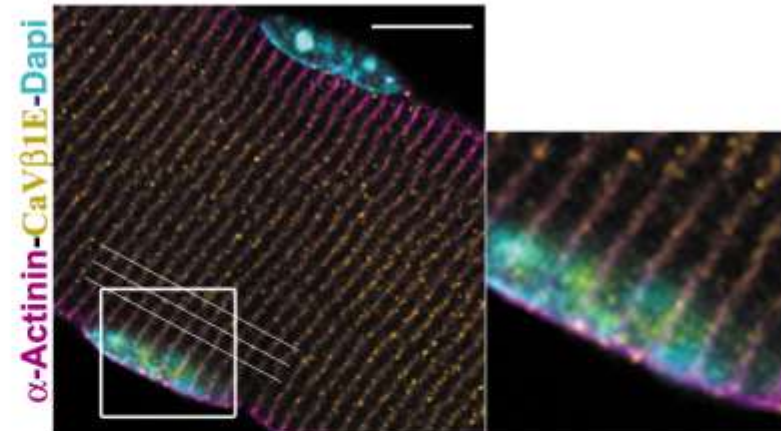
# A new CaV $\beta$ 1 isoform: embryonic?



# Localization of CaV $\beta$ 1 isoforms in adult muscle

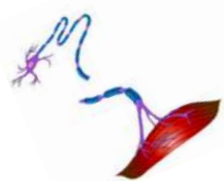


CaV $\beta$ 1D: triadic localization-partially in nuclei



CaV $\beta$ 1E: tethers Z-lines and accumulates into nuclei

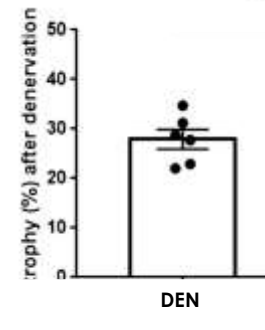
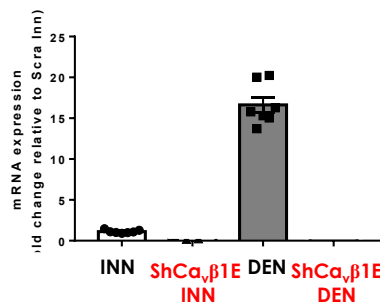
# Role of Cavβ1E in adult muscle



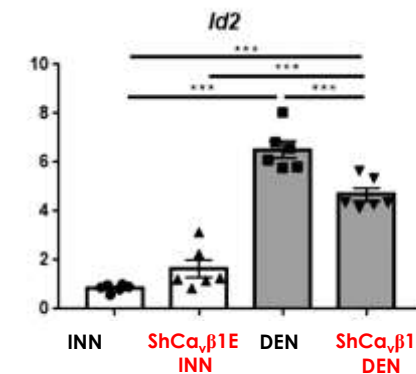
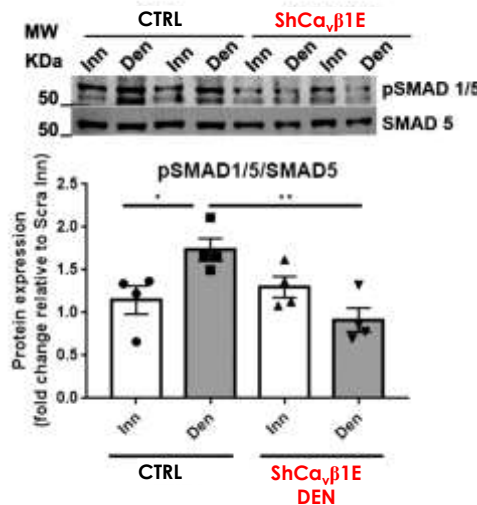
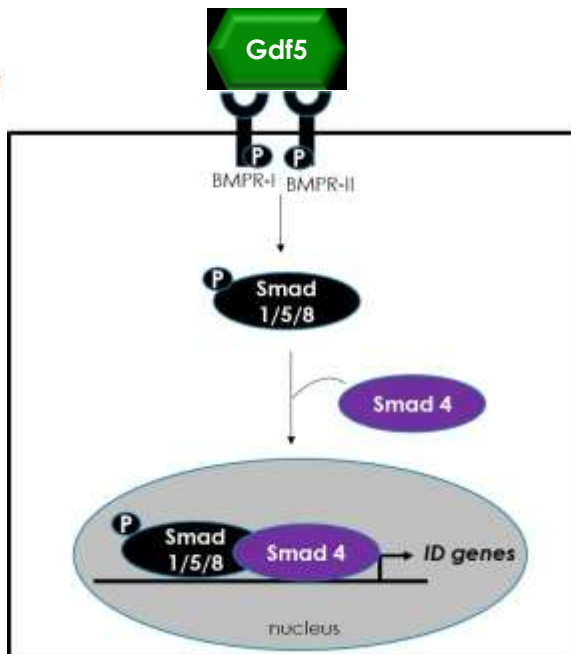
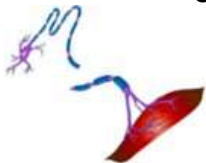
AAV-ShCav β1E

Cavβ1E

Atrophy after denervation (%)



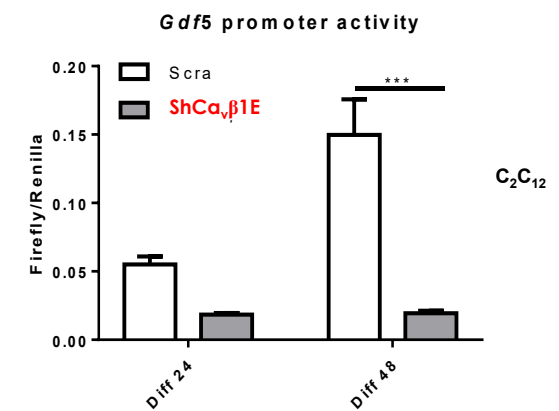
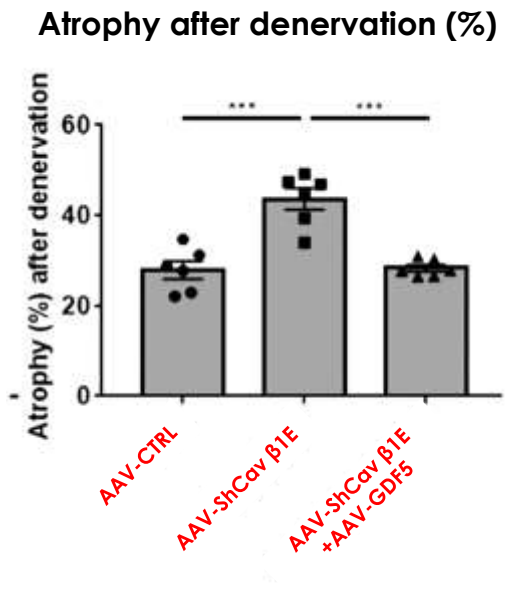
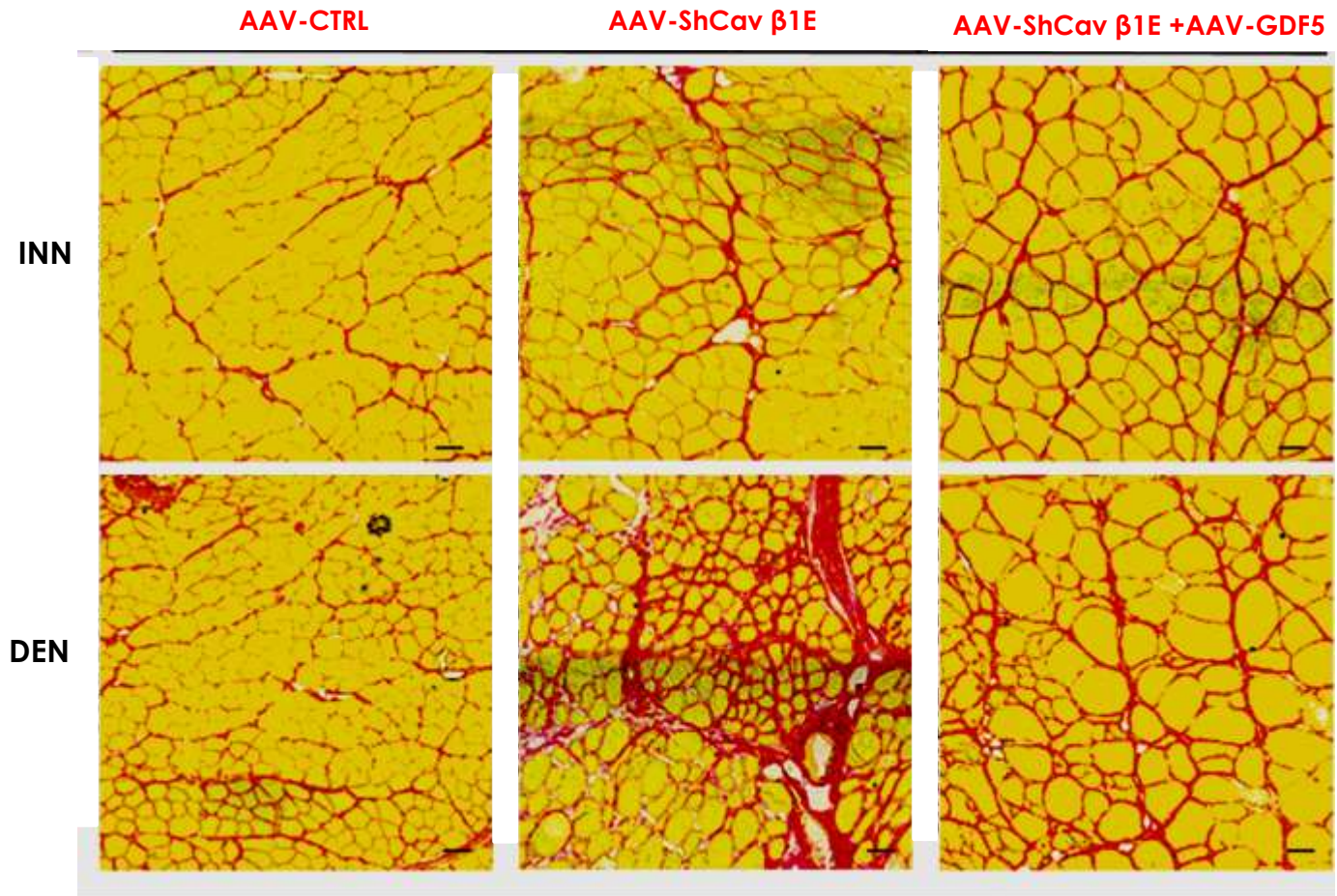
Essential signalling in muscle mass maintenance after nerve damage



Cavβ1E is needed for muscle mass maintenance and regulates Gdf5 signaling

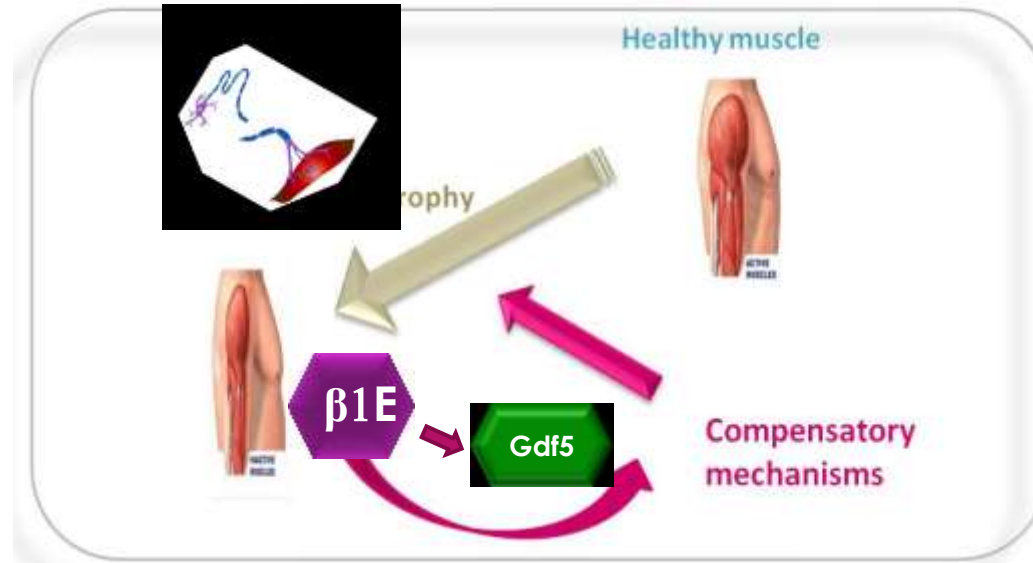


# Gdf5 over-expression rescues the effects of Cav $\beta$ 1E ablation in denervated muscles



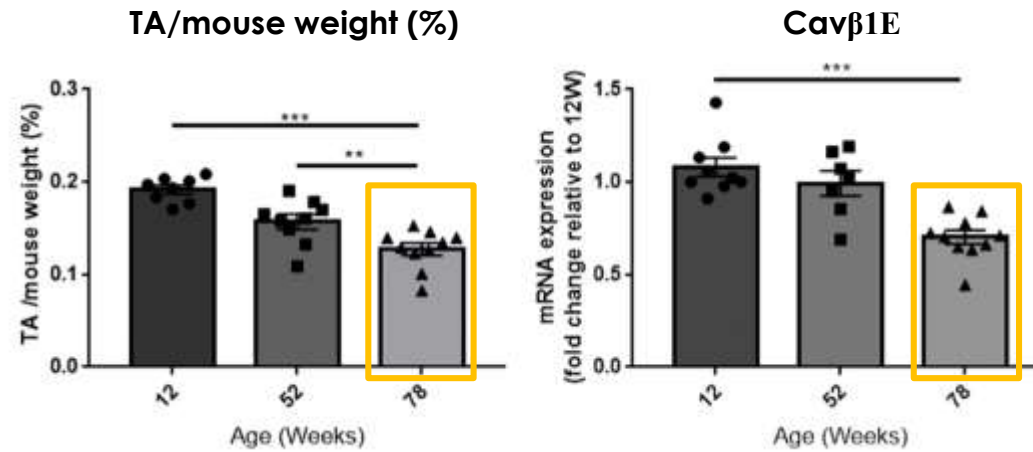
Cav $\beta$ 1E is needed for muscle mass maintenance via Gdf5 activation after nerve damage

## Role of Cav $\beta$ 1E/GDF5 in muscle mass maintenance

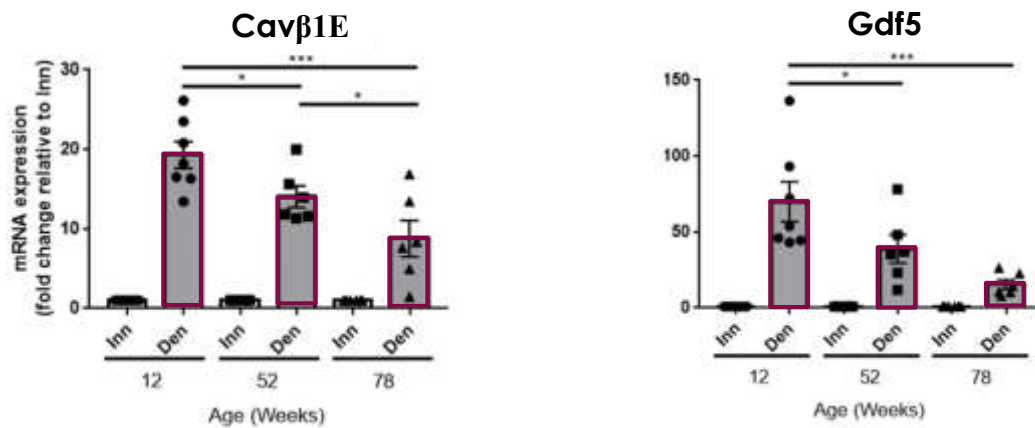


What about Cav $\beta$ 1E/GDF5 axis during age-related progressive muscle mass loss?

## Cav $\beta$ 1E expression decreases in aging muscle

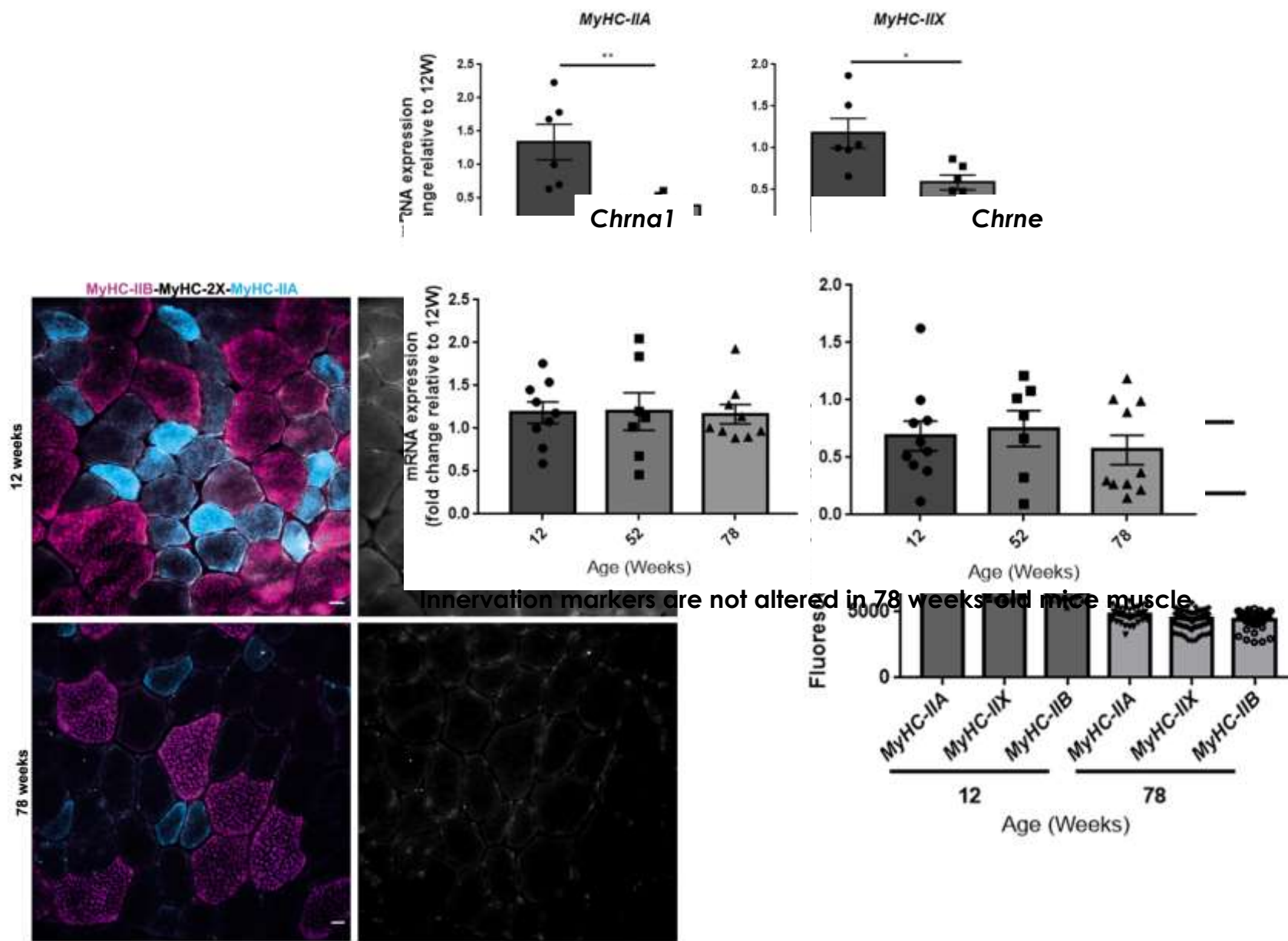


## Cav $\beta$ 1E/Gdf5 axis is impaired....



Effect of Cav $\beta$ 1E expression restoration in aging muscle?

# Innervation, fiber size composition and CaVβ1E in ageing muscle

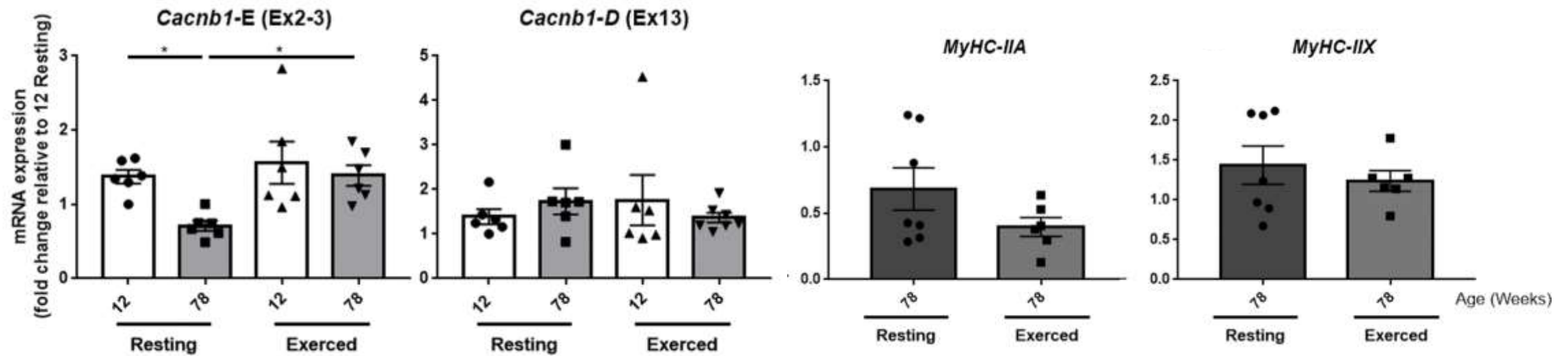


Innervation markers are not altered in 78 weeks-old mice muscle

Cavβ1E expression decreased in all muscle fiber during aging, independently of typing

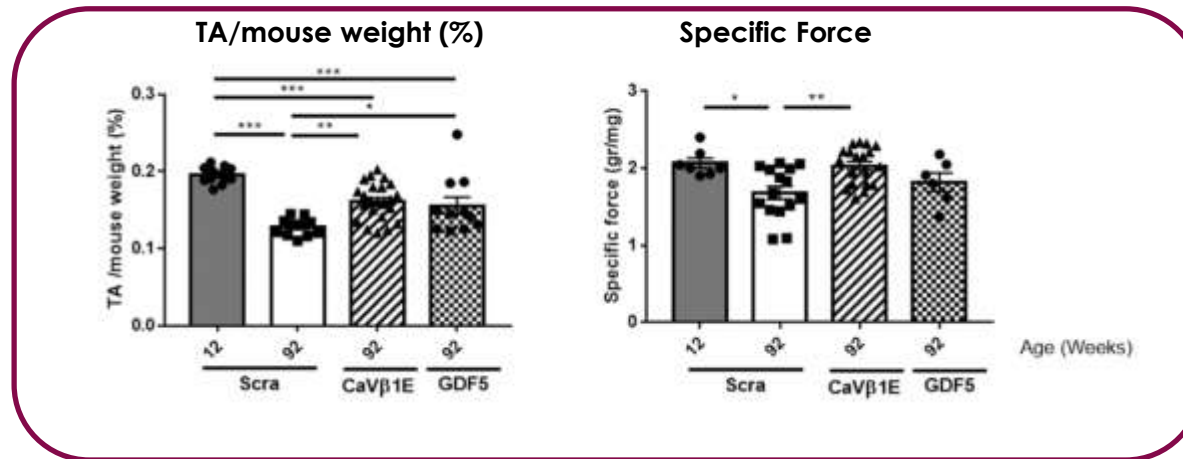
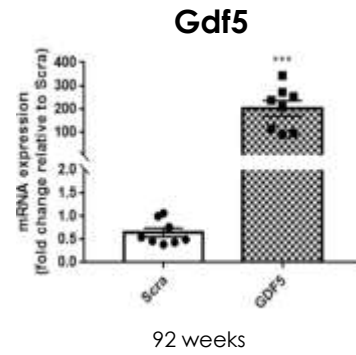
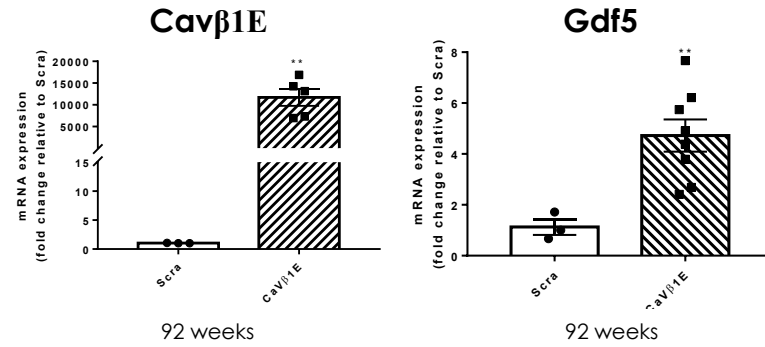
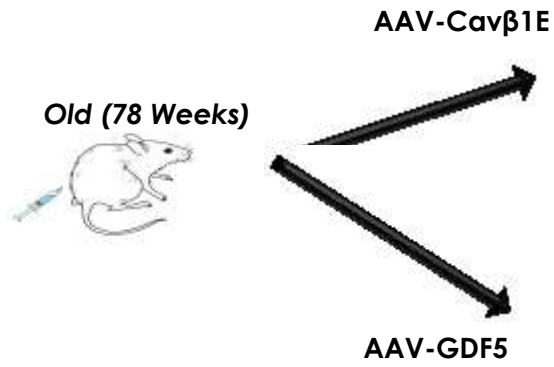


# Exercise and Cav $\beta$ 1E in ageing muscle



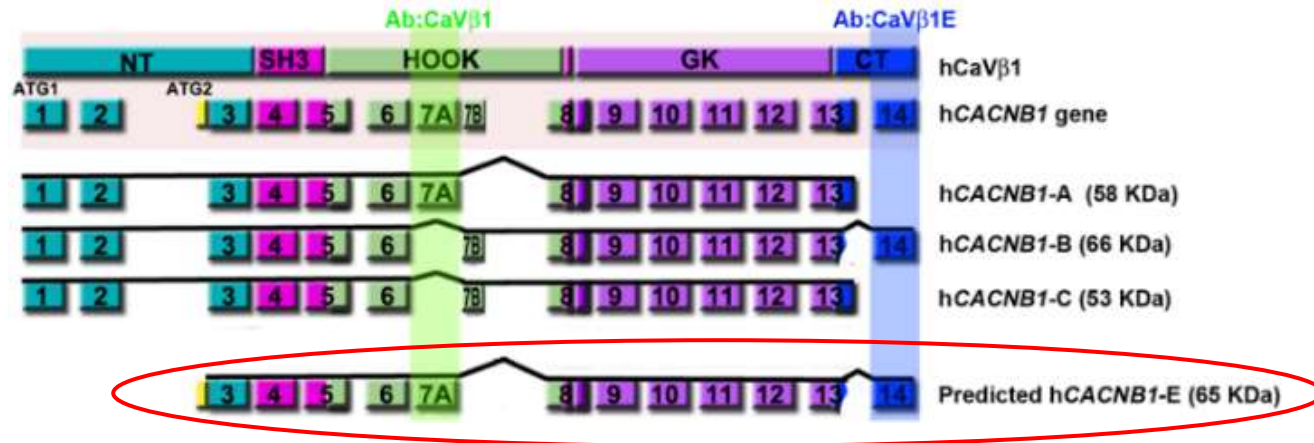
Exercise rapidly restores Cav $\beta$ 1E expression in aged mice, without affecting fiber type composition

# Cav $\beta$ 1E/GDF5 over-expression

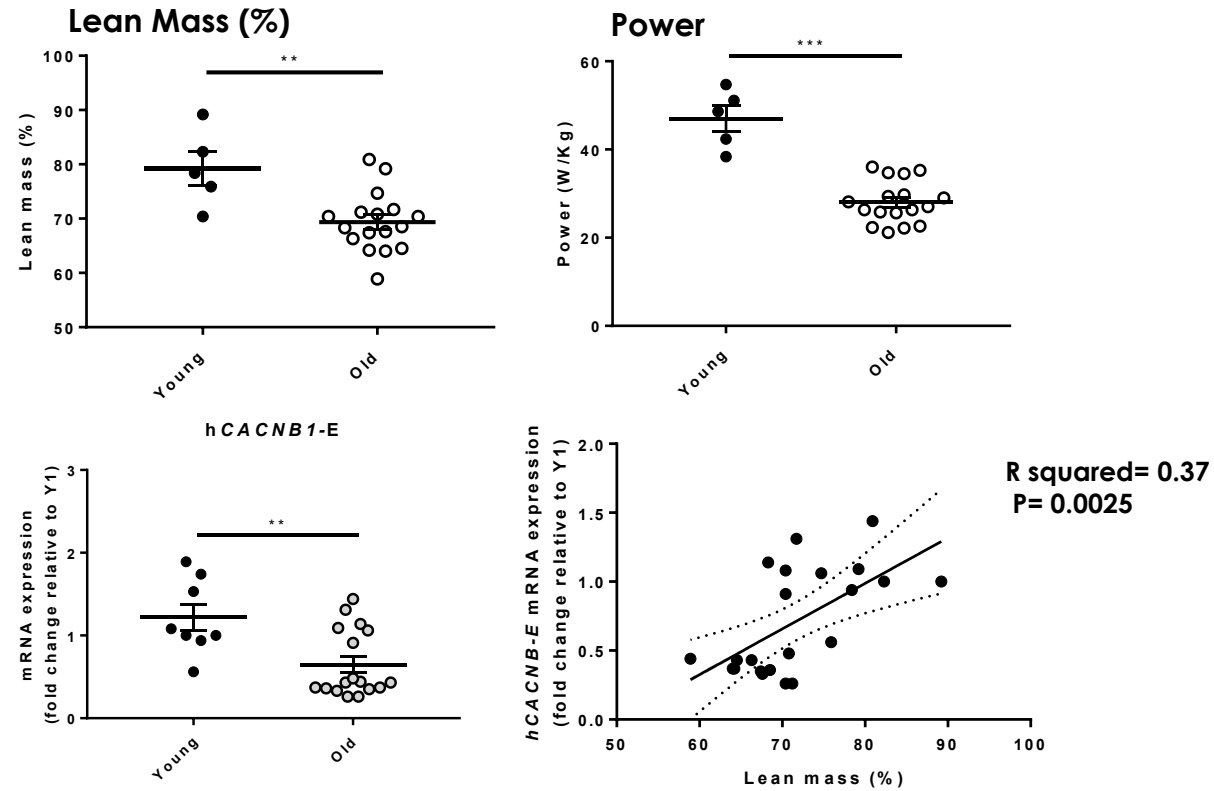


Cav $\beta$ 1E and Gdf5 improve aged muscle mass and function

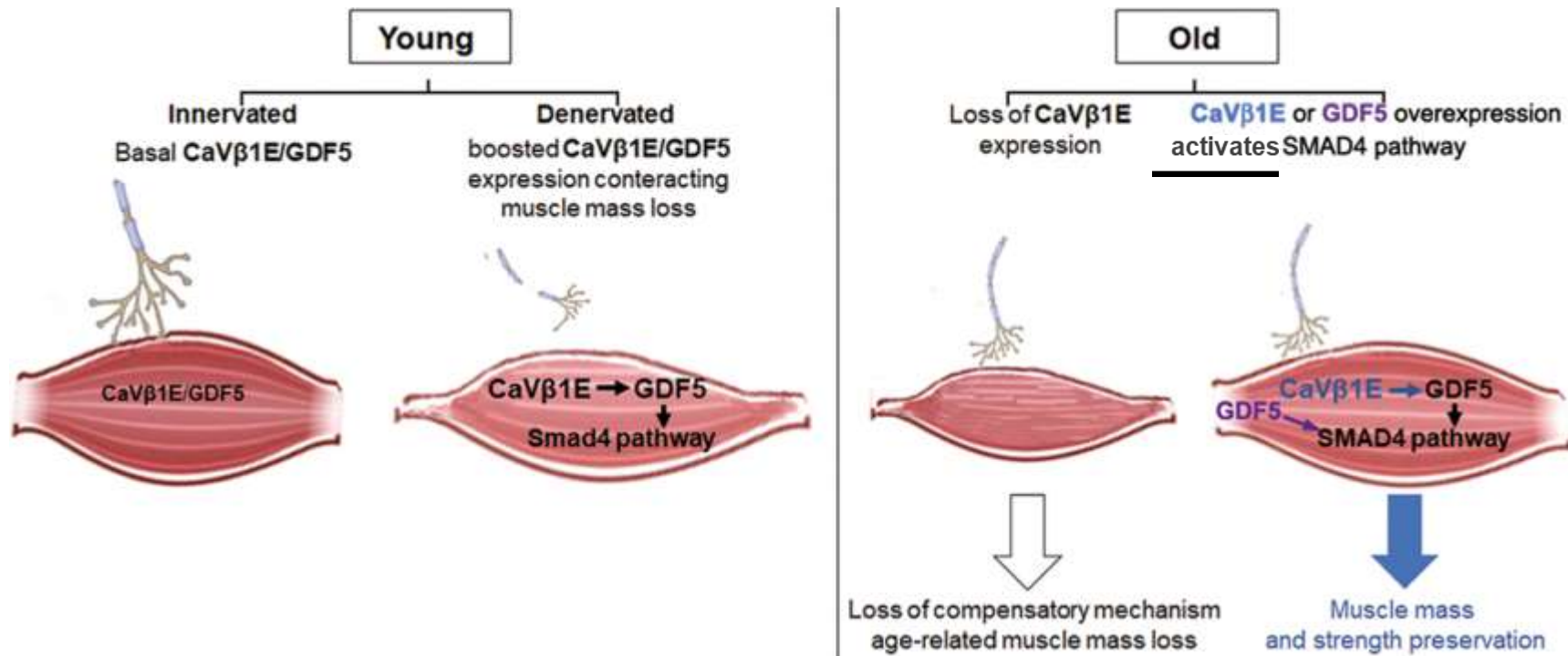
# Ca $\nu$ $\beta$ 1E in HUMANS



Young (20-40 yo n= 8)  
 Old (79-81 yo n=17)



hCa $\nu$  $\beta$ 1E expression is negatively associated to aging and muscle decline in HUMANS





## Take home message

### Discovery of a key role of Cav $\beta$ 1E/Gdf5 axis in muscle mass maintenance

- Inducible embryonic Cav $\beta$ 1E in adult muscle regulates Gdf5 pathway after nerve damage
- Cav $\beta$ 1E/Gdf5 axis is altered in ageing muscle
- Cav $\beta$ 1E overexpression restores aged muscle mass and function by increasing Gdf5 signaling
- Discovery of HUMAN Cav $\beta$ 1E : negatively associated to aging and muscle decline



### Systemic implementation of rGdf5 during aging (Patent #18184861.5)

Improvement of muscle mass and function – mechanism?

## Team Gene therapy for DMD and pathophysiology of skeletal muscle



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