



## rGdf5, an unexpected treatment against age-related muscle mass loss

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# rGdf5, an unexpected treatment against age-related muscle mass loss

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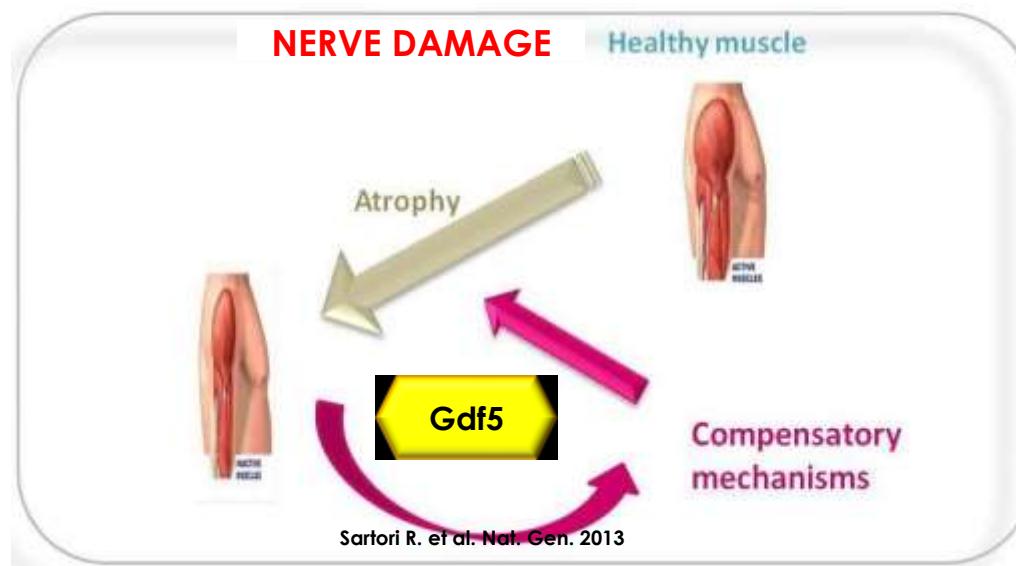


24<sup>th</sup> International Annual Congress  
of the World Muscle Society (WMS)

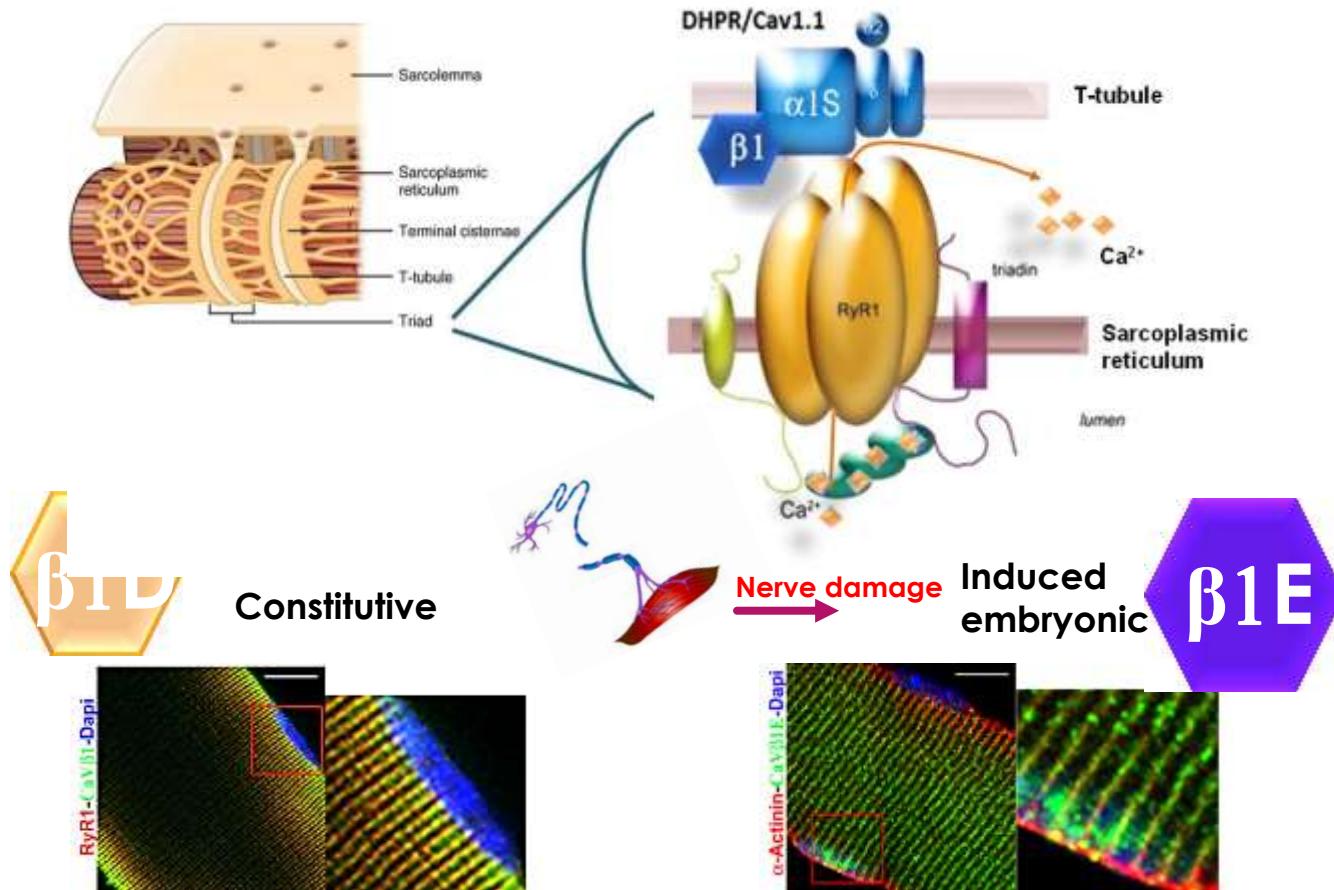
1<sup>st</sup> – 5<sup>th</sup> October 2019  
Copenhagen - Denmark



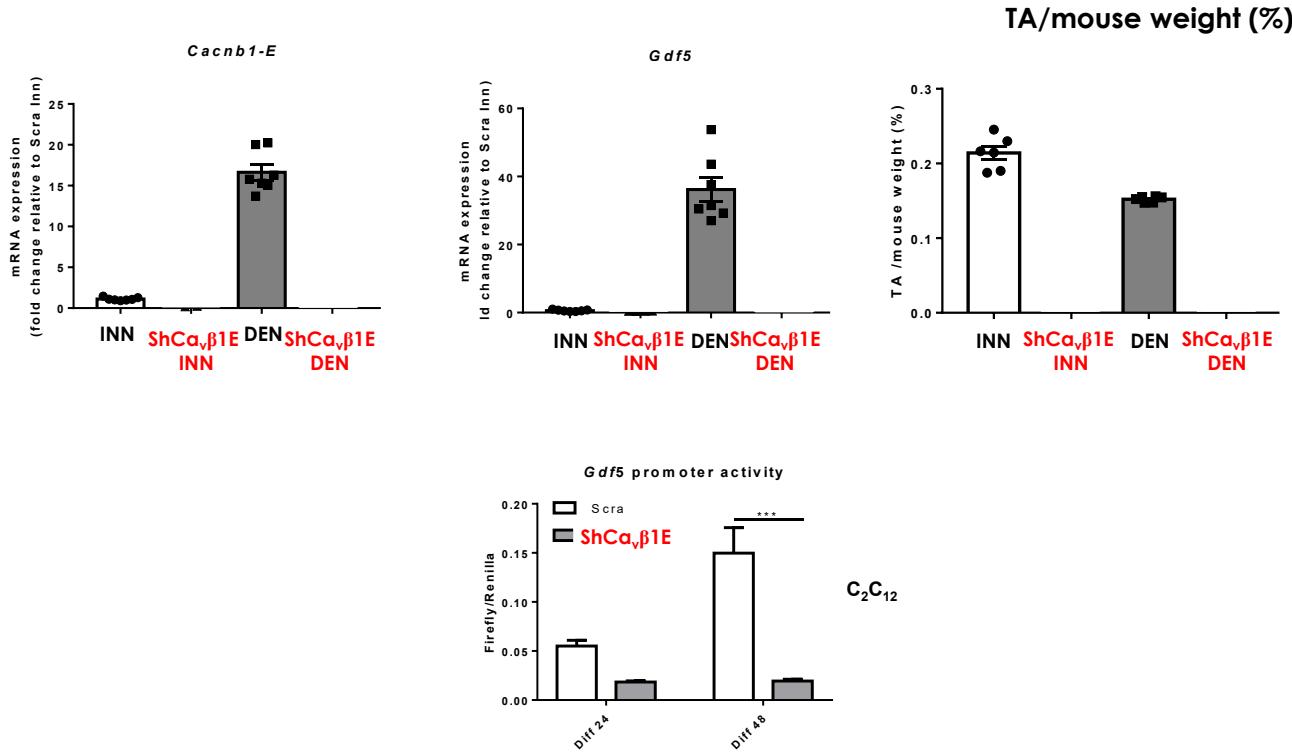
# Muscle plasticity and compensatory mechanism



# Excitation-Contraction coupling

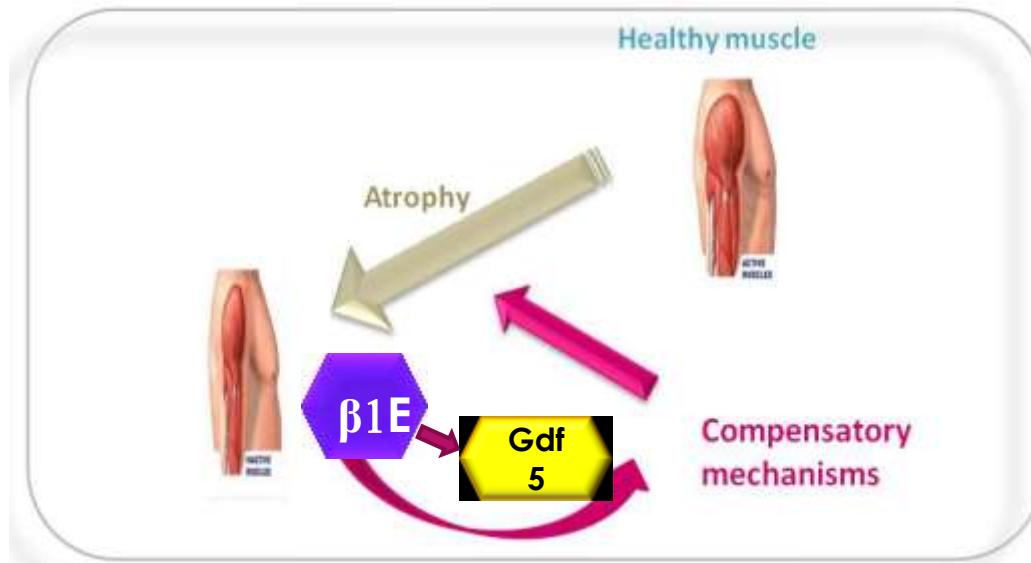


## Role of Cav $\beta$ 1E in adult muscle



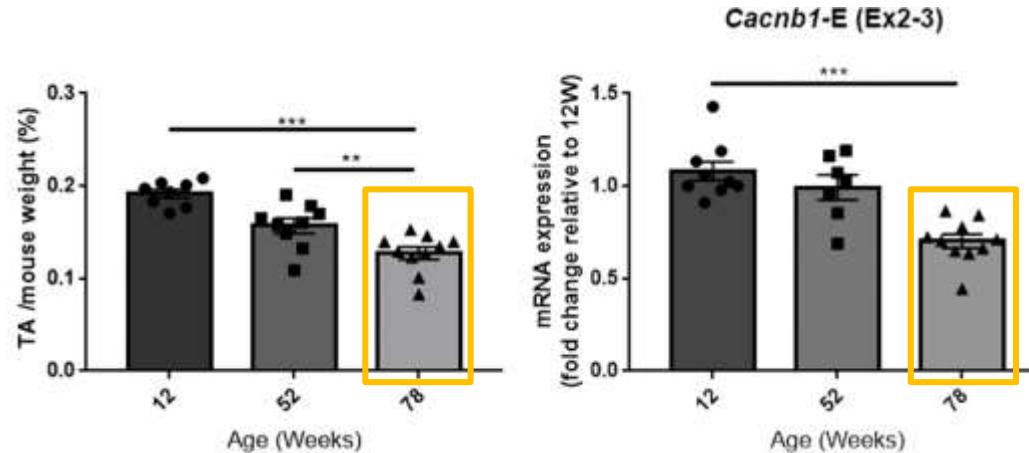
**Cav $\beta$ 1E is needed for muscle mass maintenance via Gdf5 activation  
after nerve damage**

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

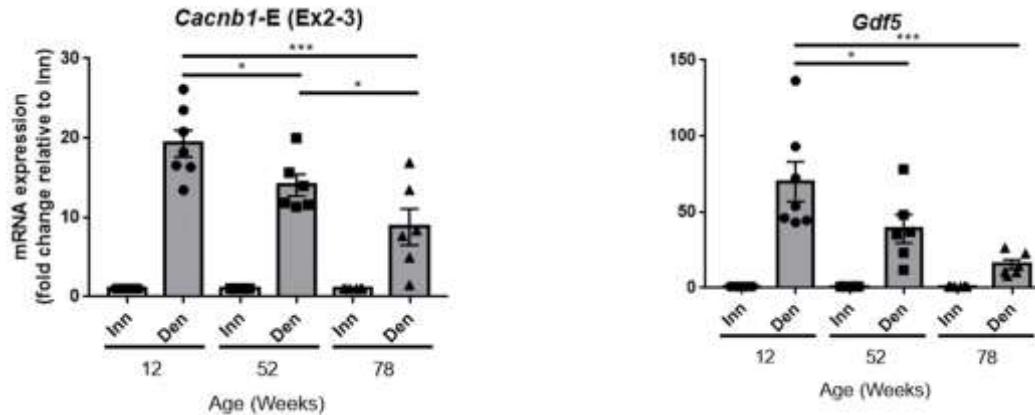


What about Cav $\beta$ 1E/GDF5 axis during age-related progressive muscle mass loss?

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



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

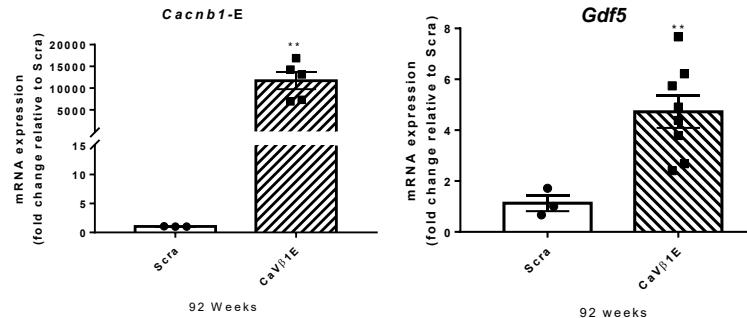


Effect of Cav $\beta$ 1E expression restoration in aging muscle?

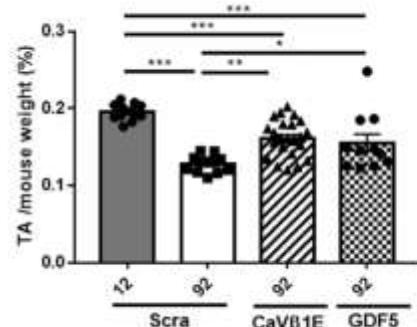
# Cav $\beta$ 1E/GDF5 over-expression



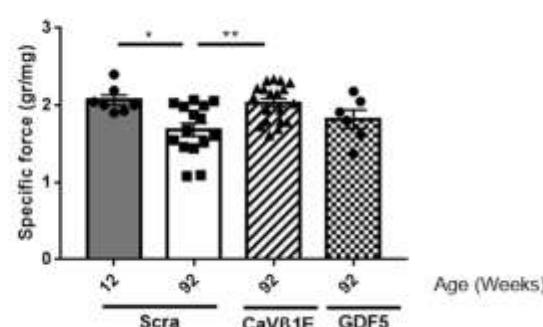
AAV-Cav  $\beta$ 1-E  
AAV-GDF



TA/mouse weight (%)

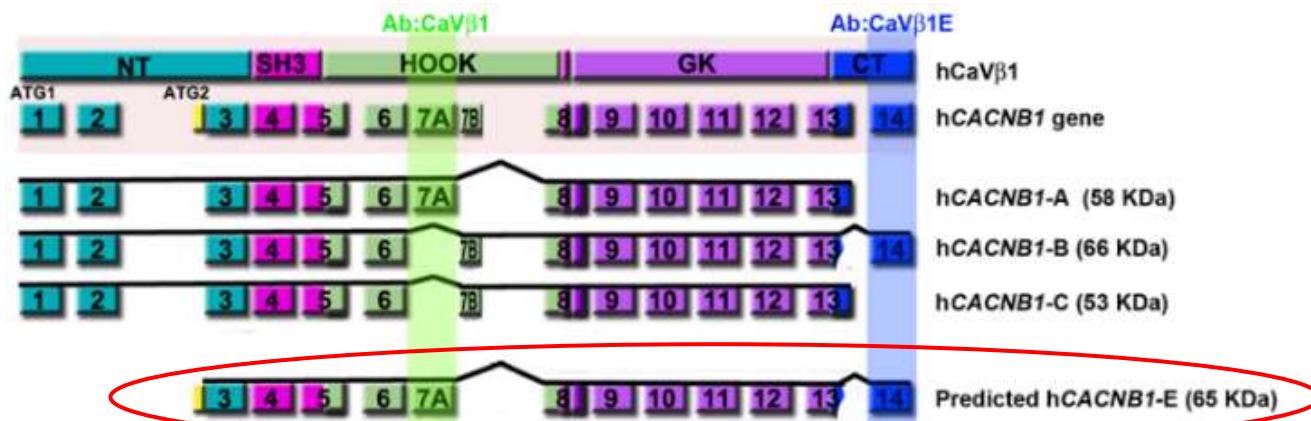


Specific Force

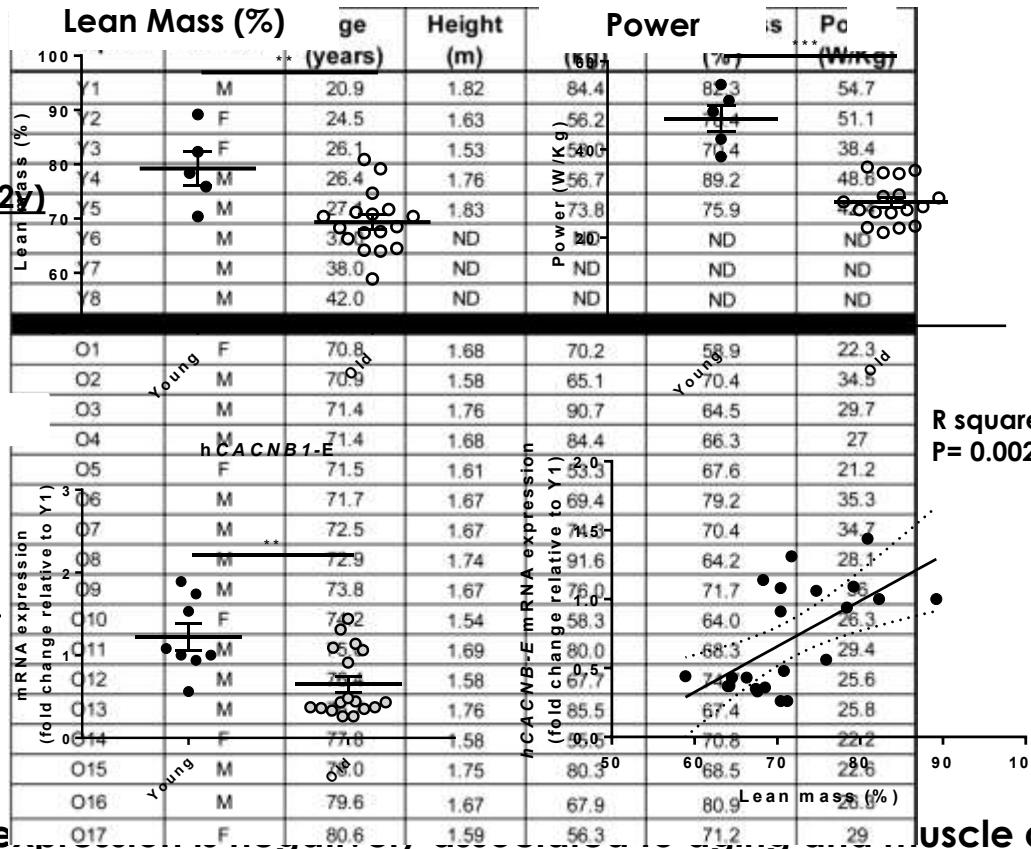


Cav $\beta$ 1E/Gdf5 improve aged muscle mass and function

# Cav $\beta$ 1E in HUMANS



Young: (21-42y)

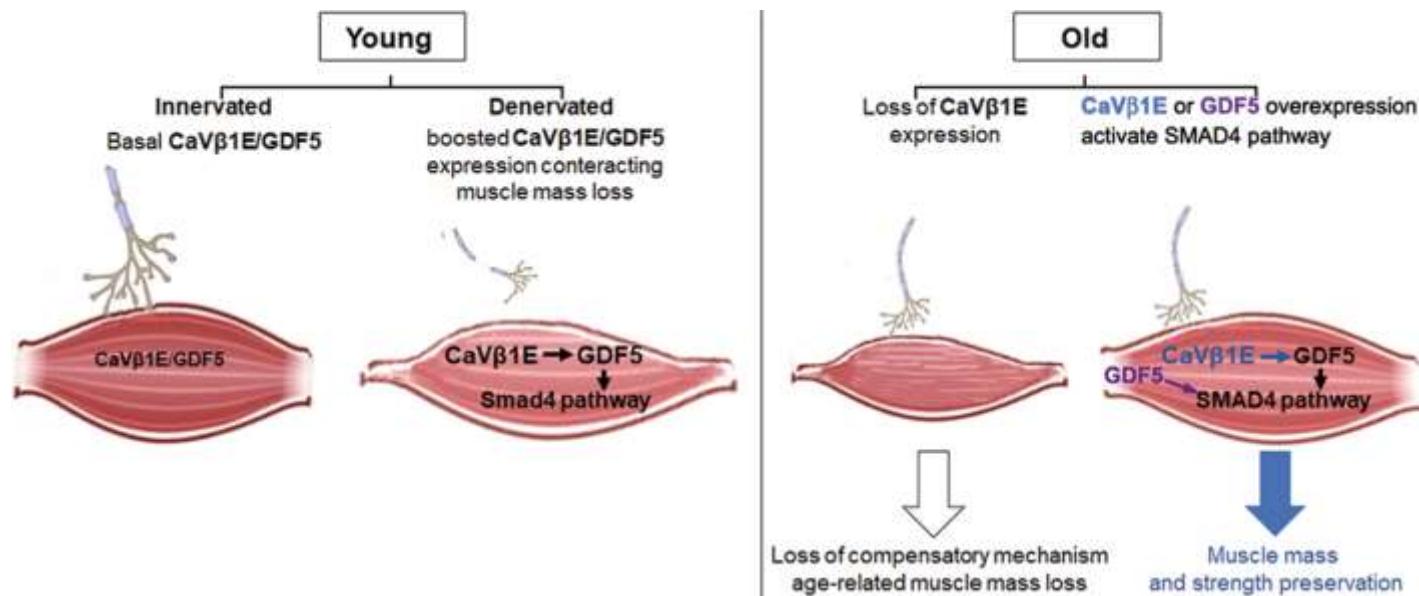


Old: (71-82y)

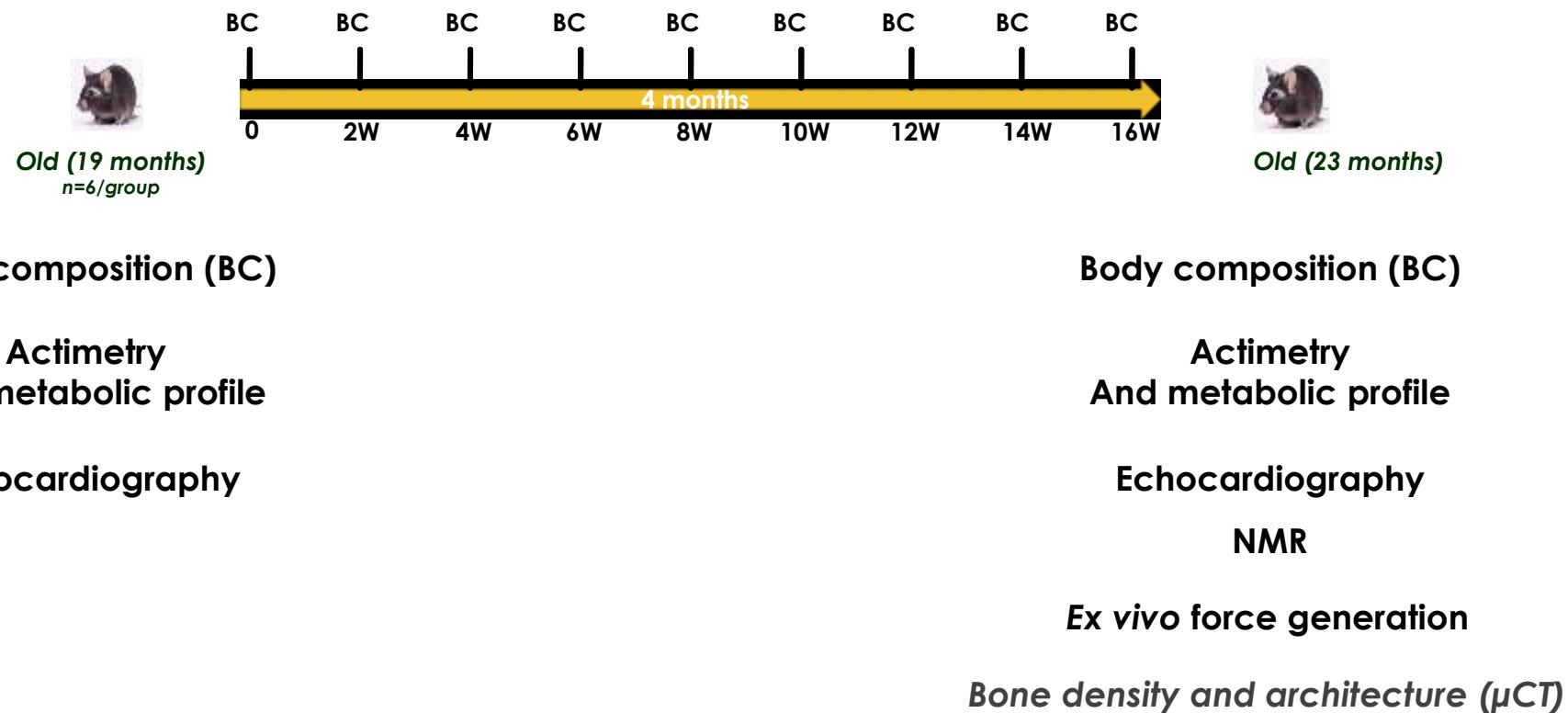
hCav $\beta$ 1-E e

muscle decline in HUMANS

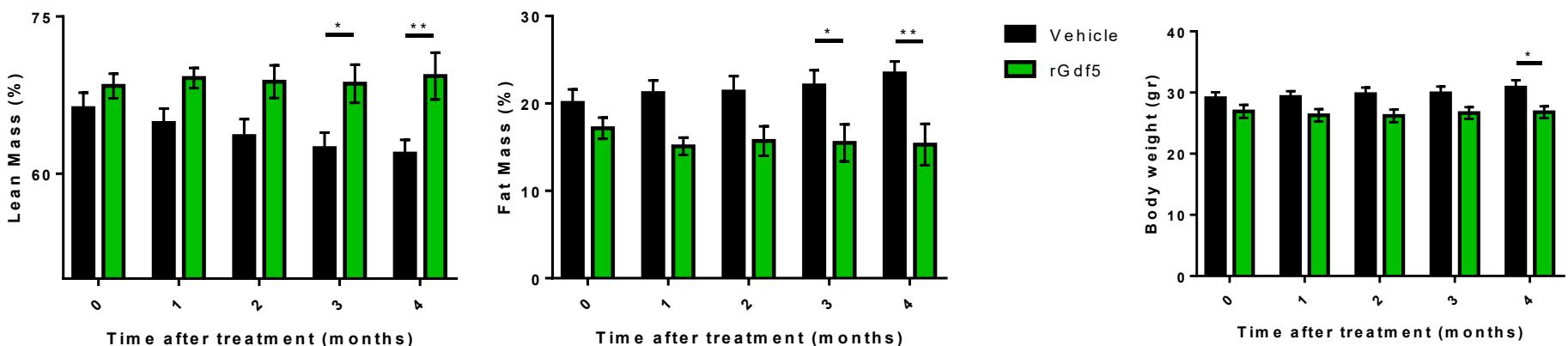
# CONCLUSIONS



## Recombinant Gdf5 implementation: a therapeutic tool to reverse age-related muscle wasting



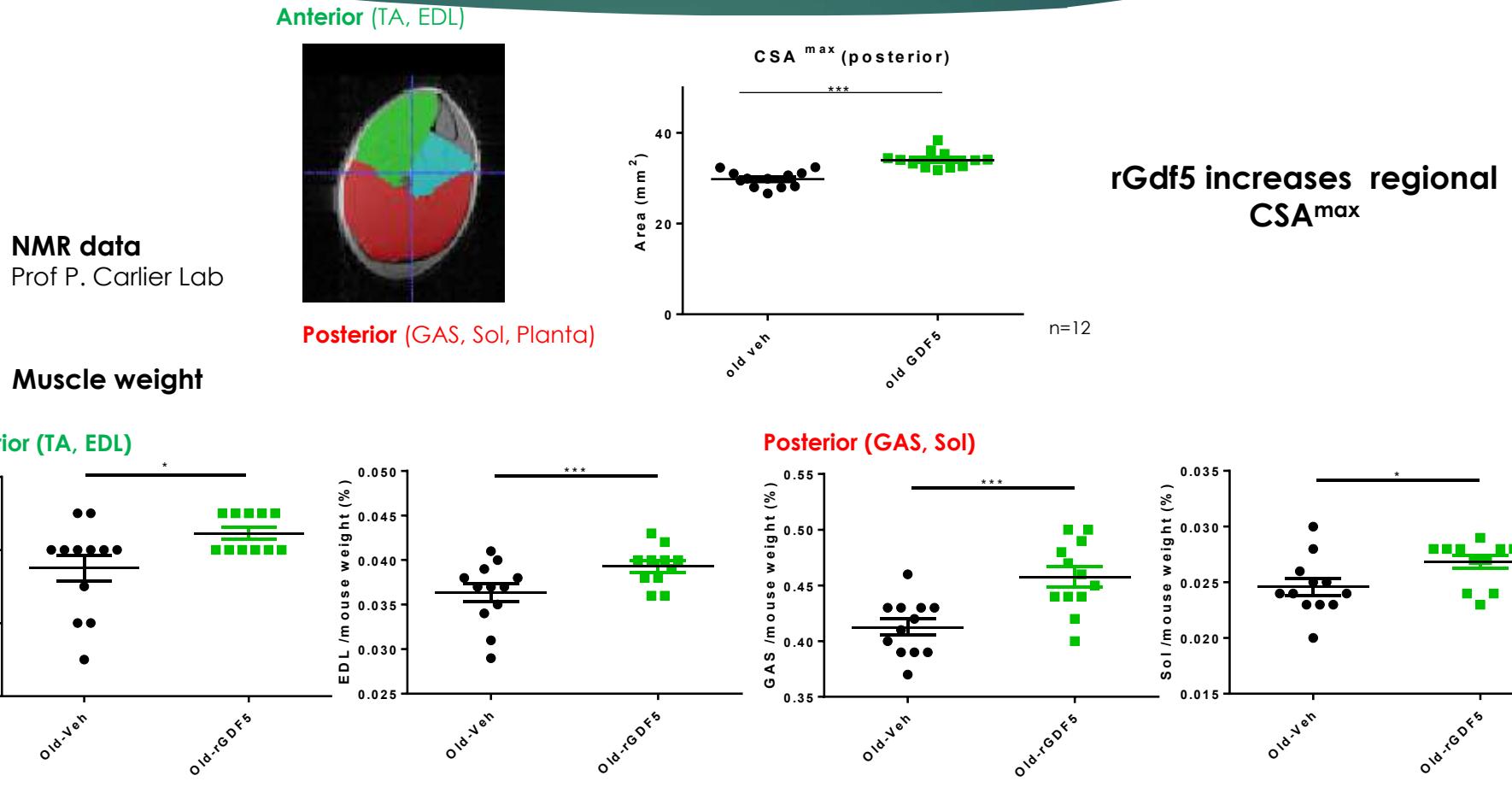
## Body composition (BC) follow-up



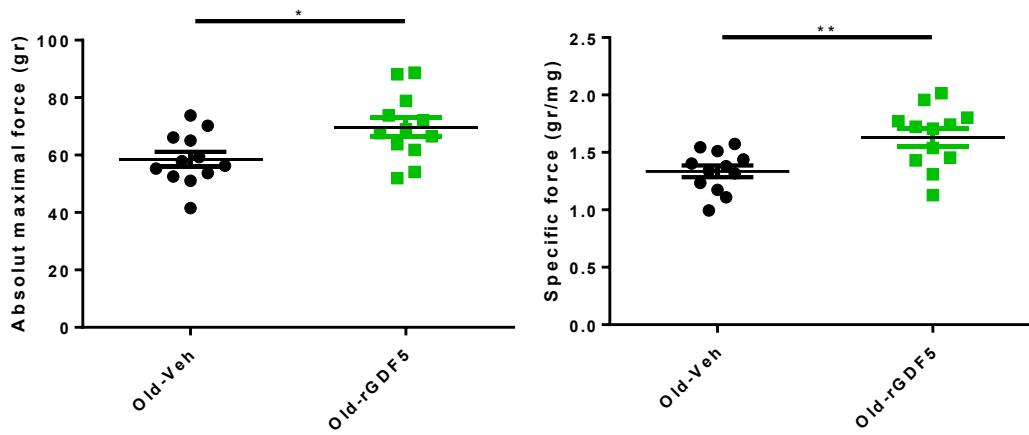
n=6; Two-way Anova

**rGdf5 prevents age-related decrease of lean mass and increase of fat mass**

# Muscle mass measurement

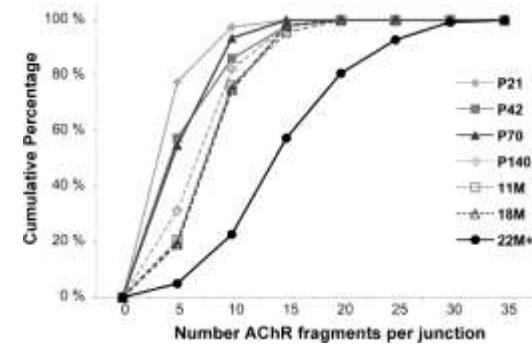
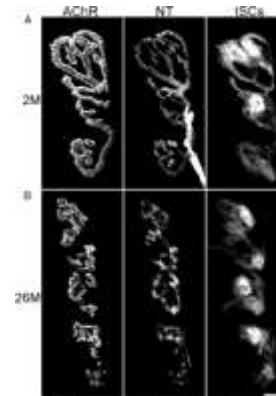


## Muscle function measurement



rGdf5 improves muscle function in old mice

## Improvement of innervation?



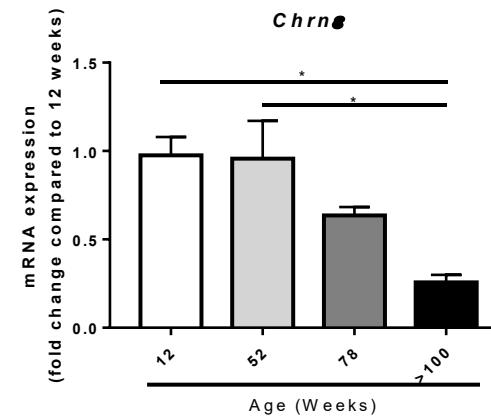
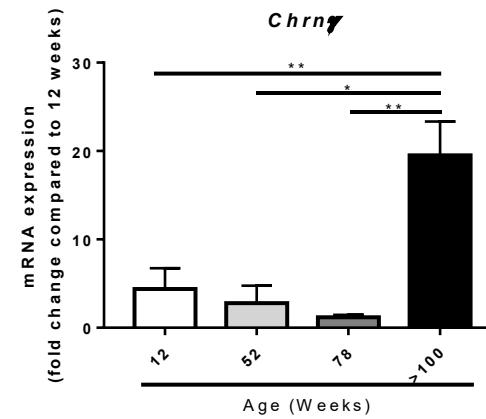
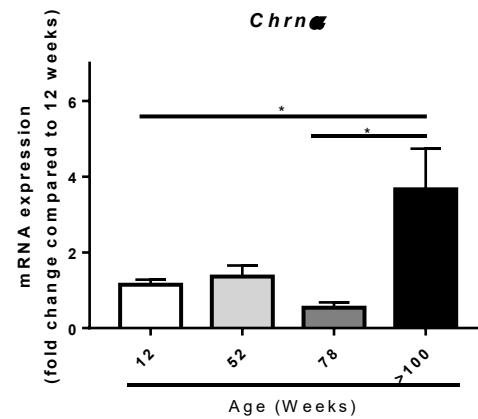
Yue Li et al. J. Neurosci. 2011

**Gdf5 is involved in muscle re-innervation**

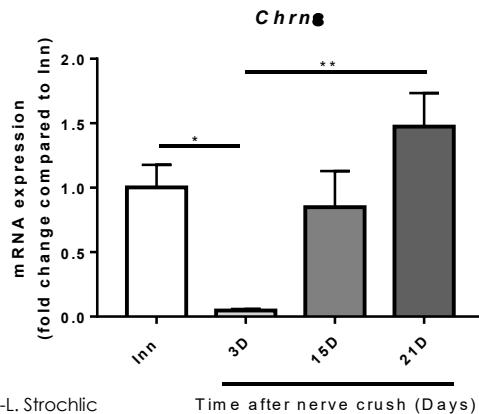
Dach2-Hdac9 signaling regulates reinnervation of muscle endplates

Peter C. D. Macpherson, Pershang Farshi, and Daniel Goldman

# Denervation markers transcription changes in ageing muscles (TA)

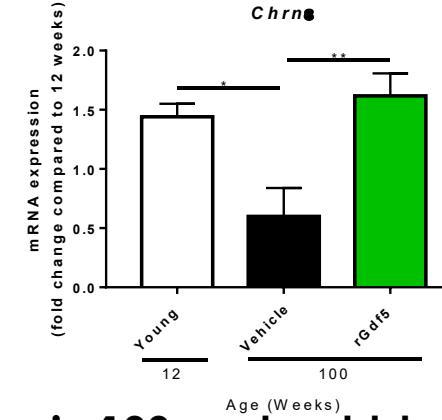


**Chrnε expression during re-innervation**



J. Messéant-L. Strochlic

**Chrnε expression in rGdf5 treated muscles**



**rGdf5 rescues the expression of Chrnε in 100weeks old-treated muscle**

## Take home message

### Discovery of fundamental role of $\text{Ca}_v\beta 1E/Gdf5$ axis in muscle mass homeostasis

- Inducible embryonic  $\text{Ca}_v\beta 1E$  in adult muscle regulates Gdf5 pathway after nerve damage
- $\text{Ca}_v\beta 1E/Gdf5$  axis is altered in ageing muscle
- $\text{Ca}_v\beta 1E$  overexpression restores aged muscle mass and function via increase of Gdf5 signaling
- Discovery of HUMAN  $\text{Ca}_v\beta 1E$ : conserved compensatory mechanism



### Systemic implementation of rGdf5 during aging

- Improvement of muscle mass and function
- Rescue of  $\text{Chrn}\epsilon$  expression, a marker of NMJ integrity

Patent #18184861.5



**malakoff médéric**  
PRÉSENTS POUR VOTRE AVENIR

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AAV  
production  
facility

**Amélie  
Lacombe-ICAN**  
Phénotypage  
du petit animal  
Body  
Composition  
Metabolic  
profile

## Gdf5 is implicated in:

- **Bone and cartilage healing**

- J Craniomaxillofac Surg. 2009 A preliminary report on the effect of dimeric rhGDF-5 and its monomeric form rhGDF-5C465A on bone healing of rat cranial defects. Dupoirieux L et al.
- Ann Rheum Dis. 2011 GDF5 deficiency in mice is associated with instability-driven joint damage, gait and subchondral bone changes. Daans M et al

- **Heart repair after infarction**

- J Am Coll Cardiol. 2010 Jan Growth differentiation factor 5 regulates cardiac repair after myocardial infarction. Zaidi SH et al

- **Fat metabolism**

- Diabetes. 2014 Jan;63Growth differentiation factor-5 promotes brown adipogenesis in systemic energy expenditure. Hinoi E et al

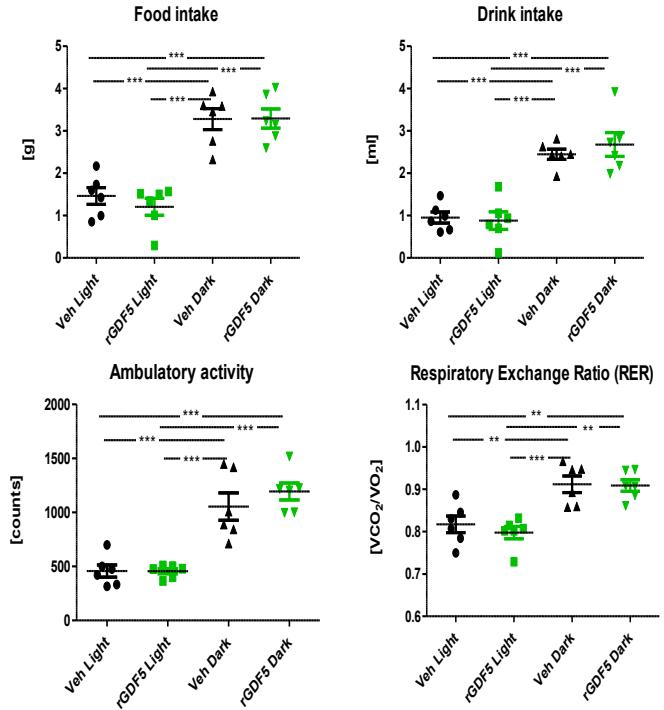
- **Central nervous system physiology**

- Development. 2013 Growth differentiation factor 5 is a key physiological regulator of dendrite growth during development. Osório C et al.
- J Cell Mol Med. 2012 Transplantation of novel human GDF5-expressing CHO cells is neuroprotective in models of Parkinson's disease. Costello DJ et al

## Cardiac echography parameters

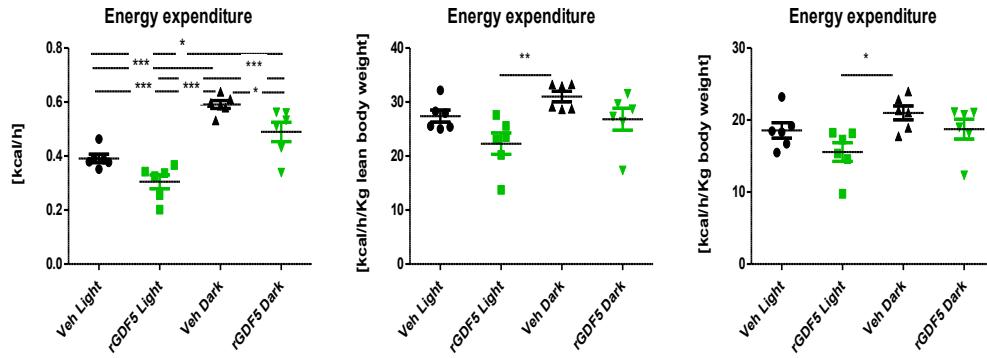
Cardiac Echography parameters	Adult-Veh (n=5)	Adult-rGDF5 (n=4)	pValue Adult veh vs rGDF5	Old-Veh (n=6)	Old-rGDF5 (n=7)	pValue Old veh vs rGDF5
<b>SIVd (cm)</b>	0,066±0,002	0,070±0,000	<0,05	0,070±0,000	0,067±0,001	<0,05
<b>VGd (cm)</b>	0,32±0,015	0,33±0,007	<0,05	0,36±0,010	0,36±0,009	<0,05
<b>PPVGd (cm)</b>	0,058±0,002	0,065±0,003	<0,05	0,068±0,001	0,068±0,002	<0,05
<b>SIVs (cm)</b>	0,102±0,002	0,112±0,005	<0,05	0,116±0,004	0,112±0,003	<0,05
<b>VGs (cm)</b>	0,184±0,012	0,185±0,005	<0,05	0,205±0,006	0,204±0,008	<0,05
<b>PPVGs (cm)</b>	0,102±0,002	0,105±0,003	<0,05	0,113±0,005	0,117±0,004	<0,05
<b>Vol.Teled (ml)</b>	0,09±0,011	0,09±0,007	<0,05	0,125±0,010	0,123±0,009	<0,05
<b>Vol.Teles (ml)</b>	0,018±0,003	0,015±0,003	<0,05	0,025±0,002	0,025±0,003	<0,05
<b>EF (%)</b>	81,36±1,30	83,49±0,26	<0,05	81,08±0,39	80,69±1,05	<0,05
<b>FS (%)</b>	44,01±1,29	46,20±0,27	<0,05	43,73±0,40	43,43±1,04	<0,05
<b>Vol eject (ml)</b>	0,074±0,008	0,082±0,006	<0,05	0,10±0,008	0,10±0,008	<0,05
<b>h/r</b>	0,381±0,015	0,398±0,009	<0,05	0,374±0,008	0,367±0,009	<0,05
<b>Temps (ms)</b>	95,26±1,43	94,62±1,19	<0,05	95,96±0,95	99,28±1,75	<0,05
<b>FC ( BPM)</b>	633±11,4	634±8,24	<0,05	625±6,12	605±10,31	<0,05
<b>Débit card l/min</b>	0,048±0,006	0,052±0,002	<0,05	0,063±0,005	0,057±0,005	<0,05

## Metabolism exploration



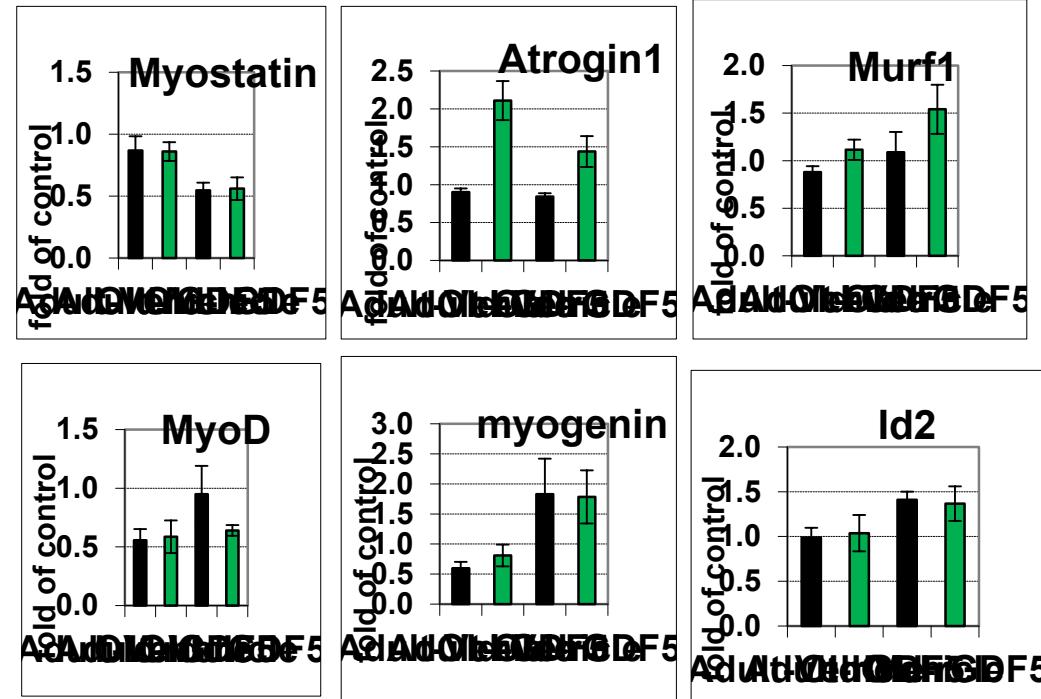
3 consecutives days (Dark 12h, light 12h )

## Metabolism exploration

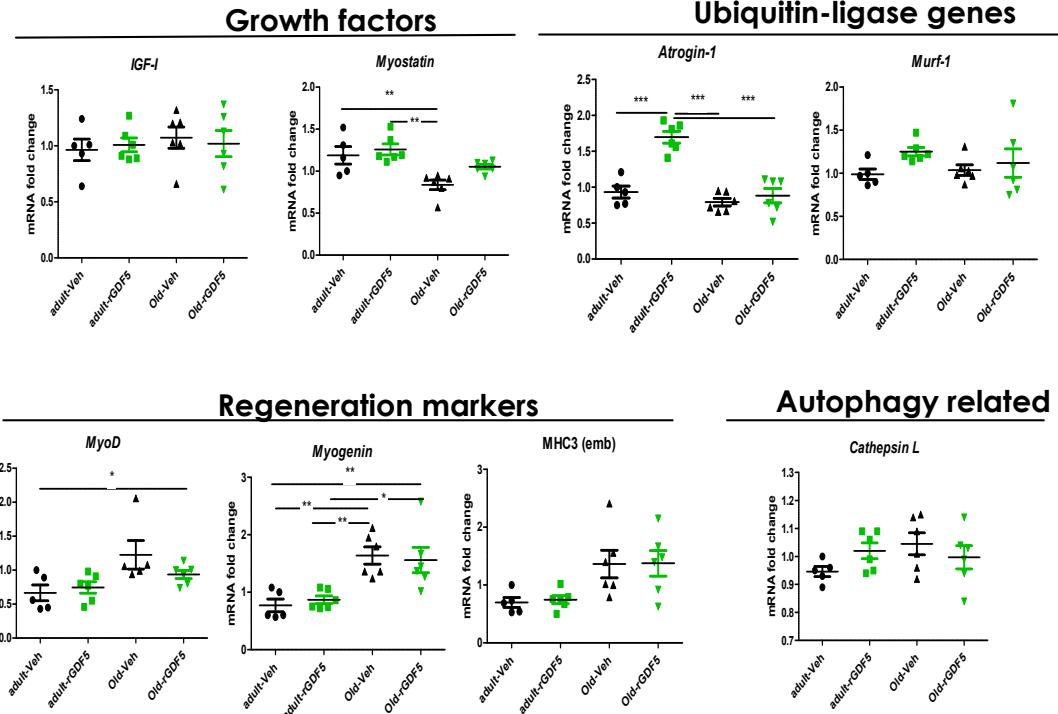


**rGDF5 decreases energy expenditure in old mice**

### Genes expression in TA muscle

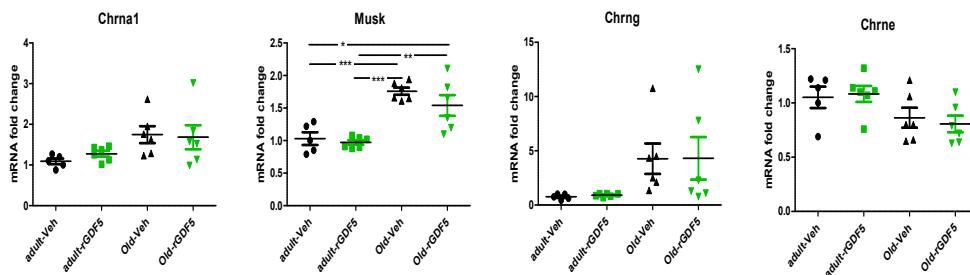


## Genes expression in GAS muscle

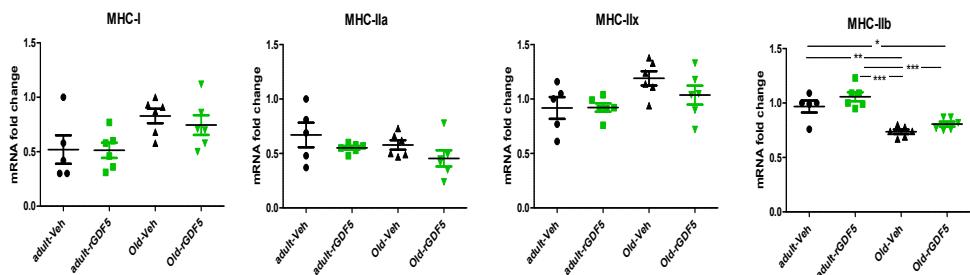


## Genes expression in GAS muscle

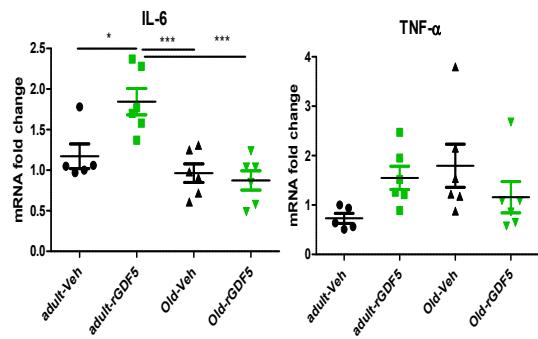
### NMJ markers



### Fiber type



### Pro-inflammatory cytokines



#### Next step :

- Akt/foxo/mTOR pathway
- ROS related genes
- CSA and typage (TA/GAS)
- NMJ morphology EDL (julien)
- Micro CT