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

Sestina Falcone, Massiré Traoré, Christel Gentil, Chiara Benedetto, Jean-Yves Hogrel, Arnaud Ferry, Mégane Lemaitre, France. Pietri-Rouxel

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

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<sup>4</sup>Sorbonne Université, INSERM, UMS28, F-75013, Paris, France

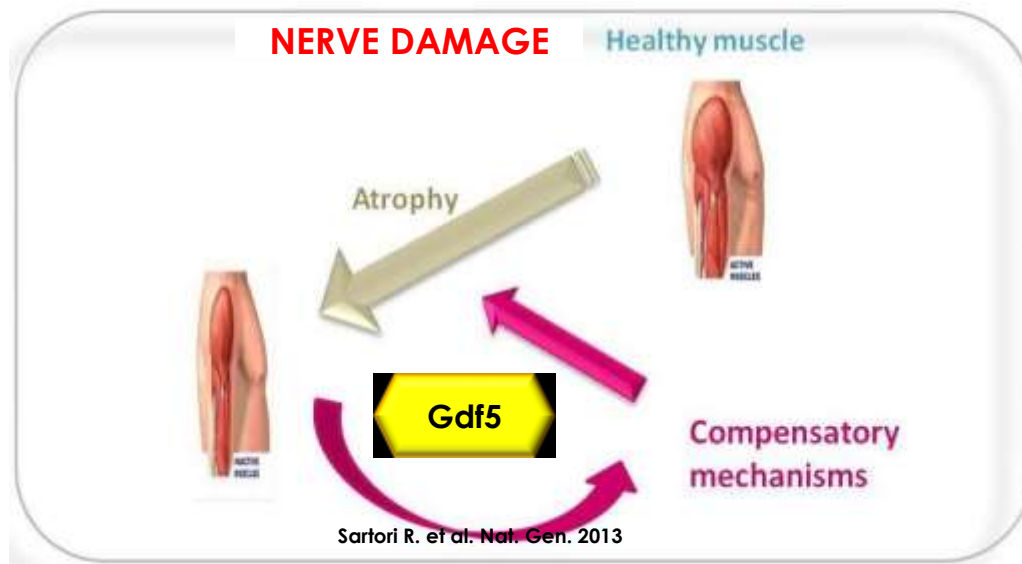


24<sup>th</sup> International Annual Congress  
of the World Muscle Society (WMS)

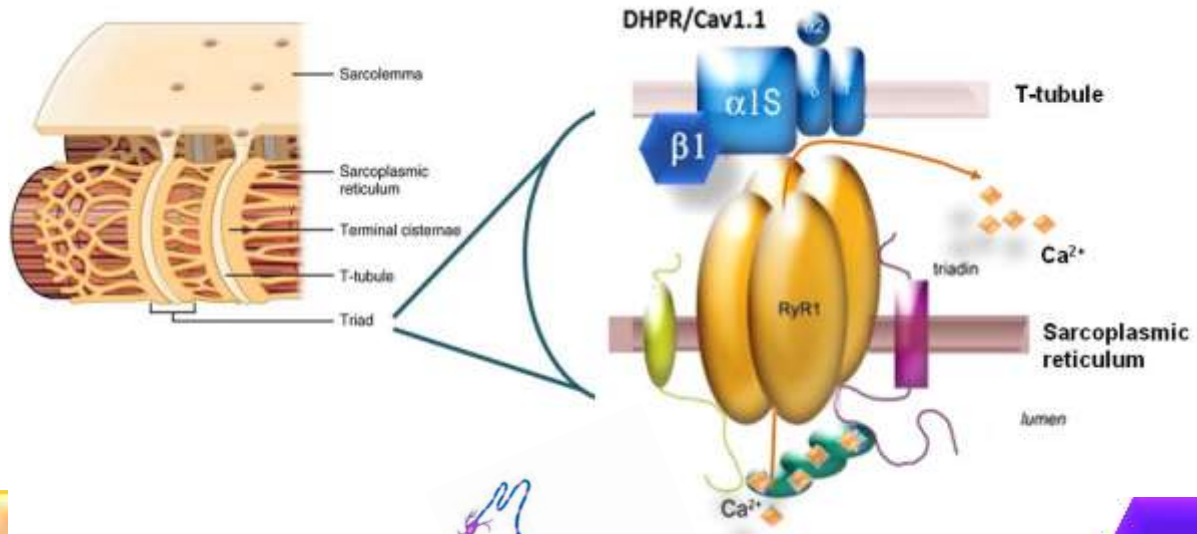
1<sup>st</sup> - 5<sup>th</sup> October 2019  
Copenhagen · Denmark



# Muscle plasticity and compensatory mechanism

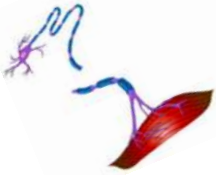
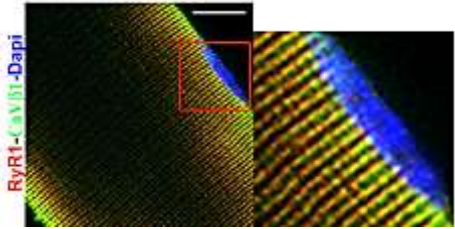


# Excitation-Contraction coupling



**β1D**

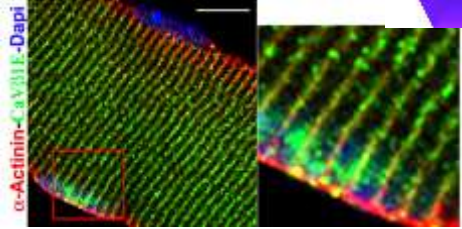
Constitutive



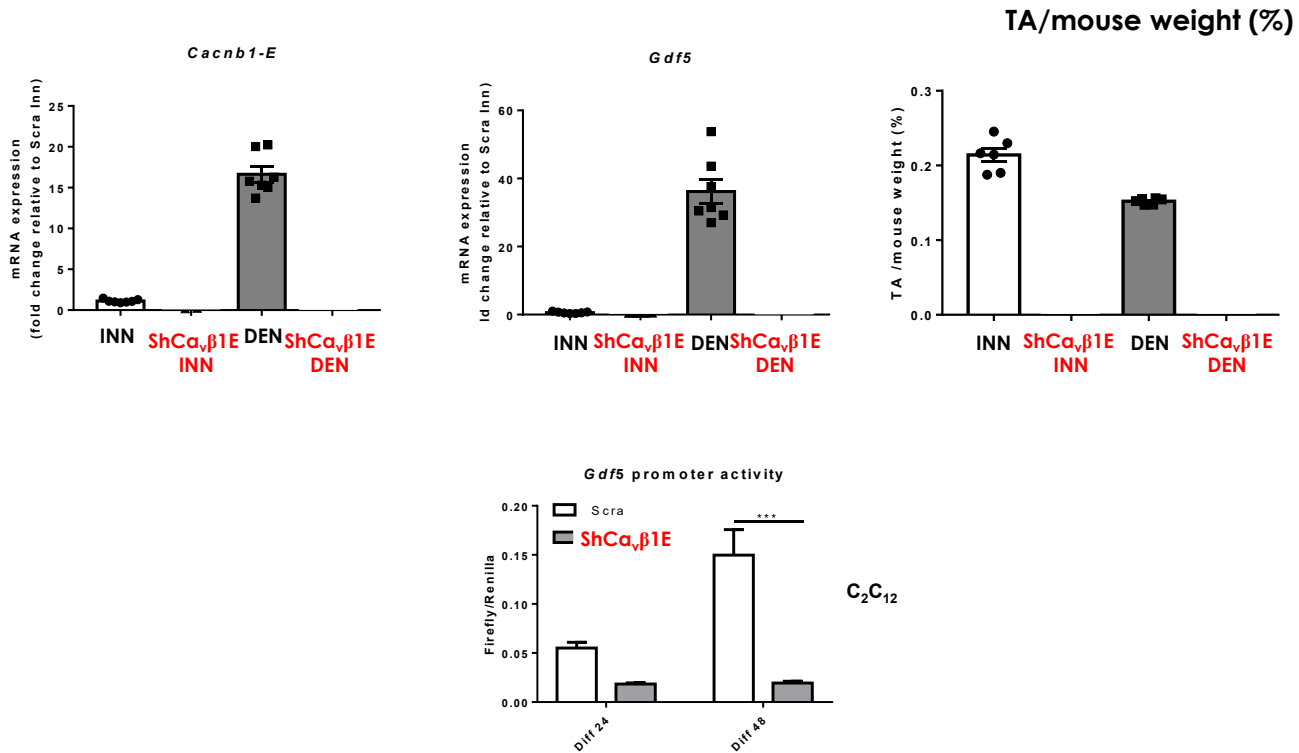
Nerve damage

Induced embryonic

**β1E**

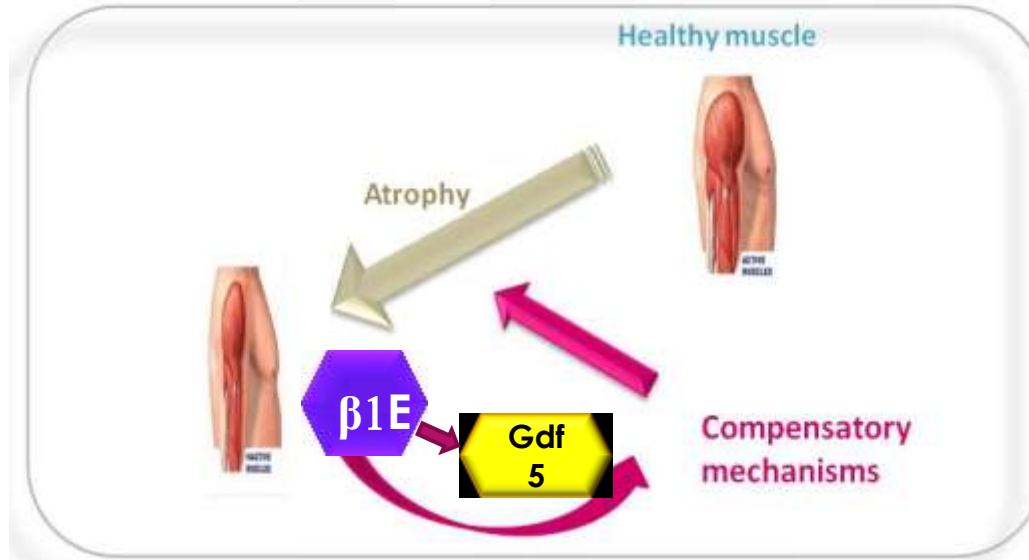


# Role of Cav $\beta$ 1E in adult muscle



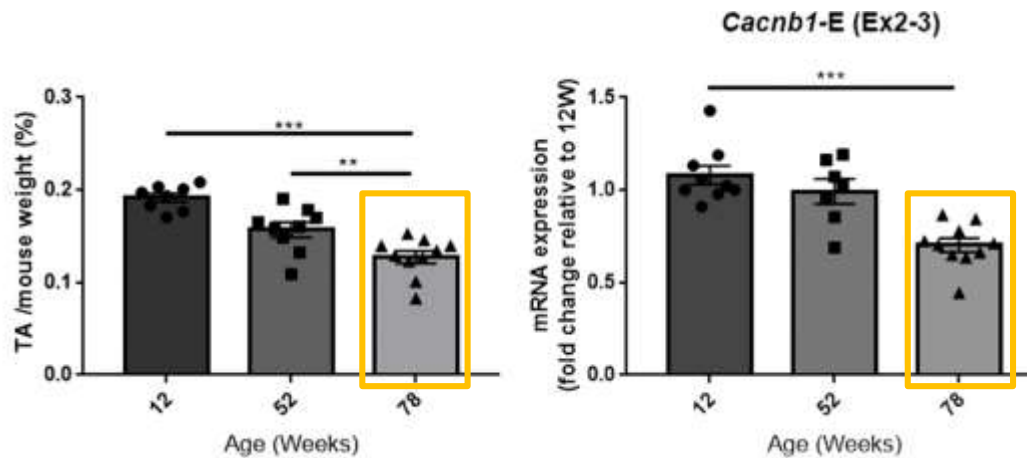
Ca $\nu$  $\beta$ 1E is needed for muscle mass maintenance via Gdf5 activation after nerve damage

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

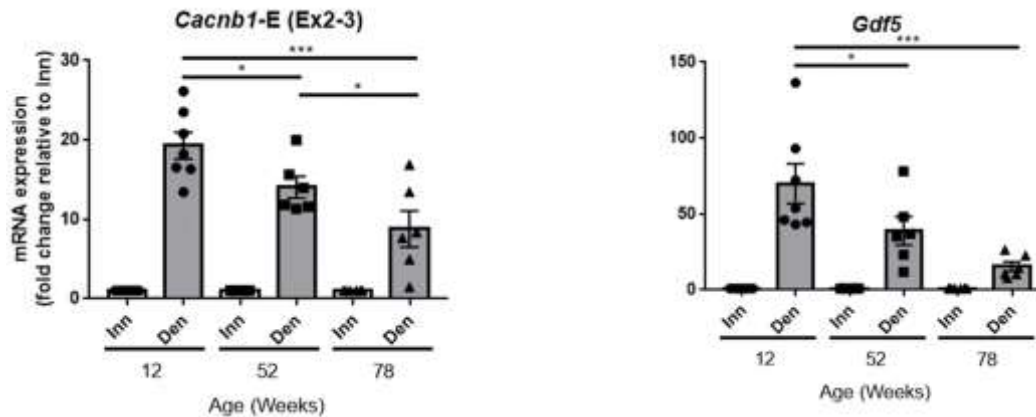


What about Cav $\beta$ 1E/GDF5 axis during age-related progressive muscle mass loss?

## Cavβ1E expression decreases in aging muscle

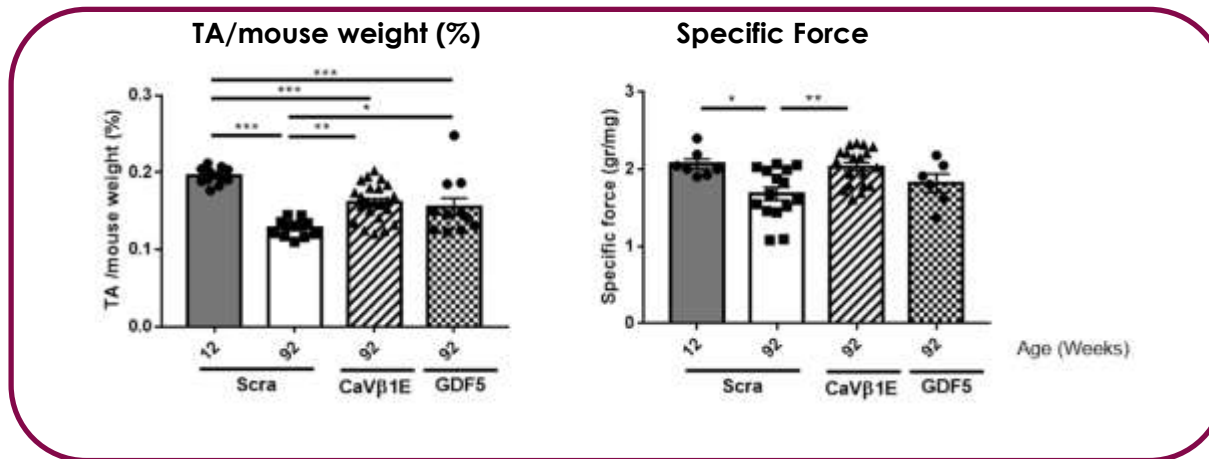
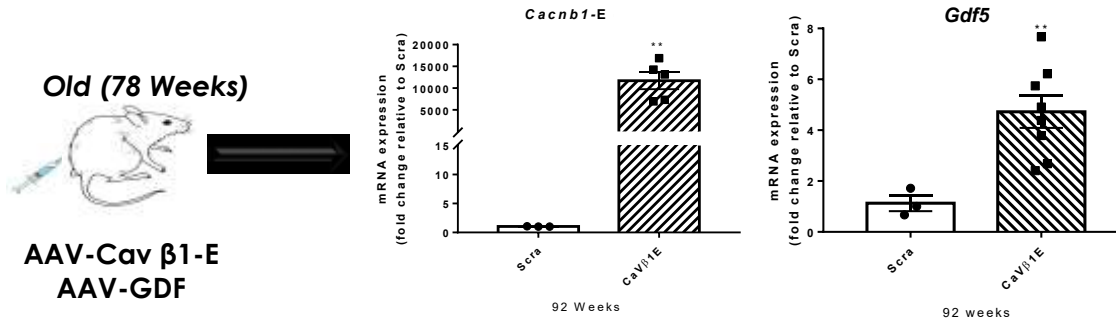


## Cavβ1E/Gdf5 axis in impaired....



Effect of Cavβ1E expression restoration in aging muscle?

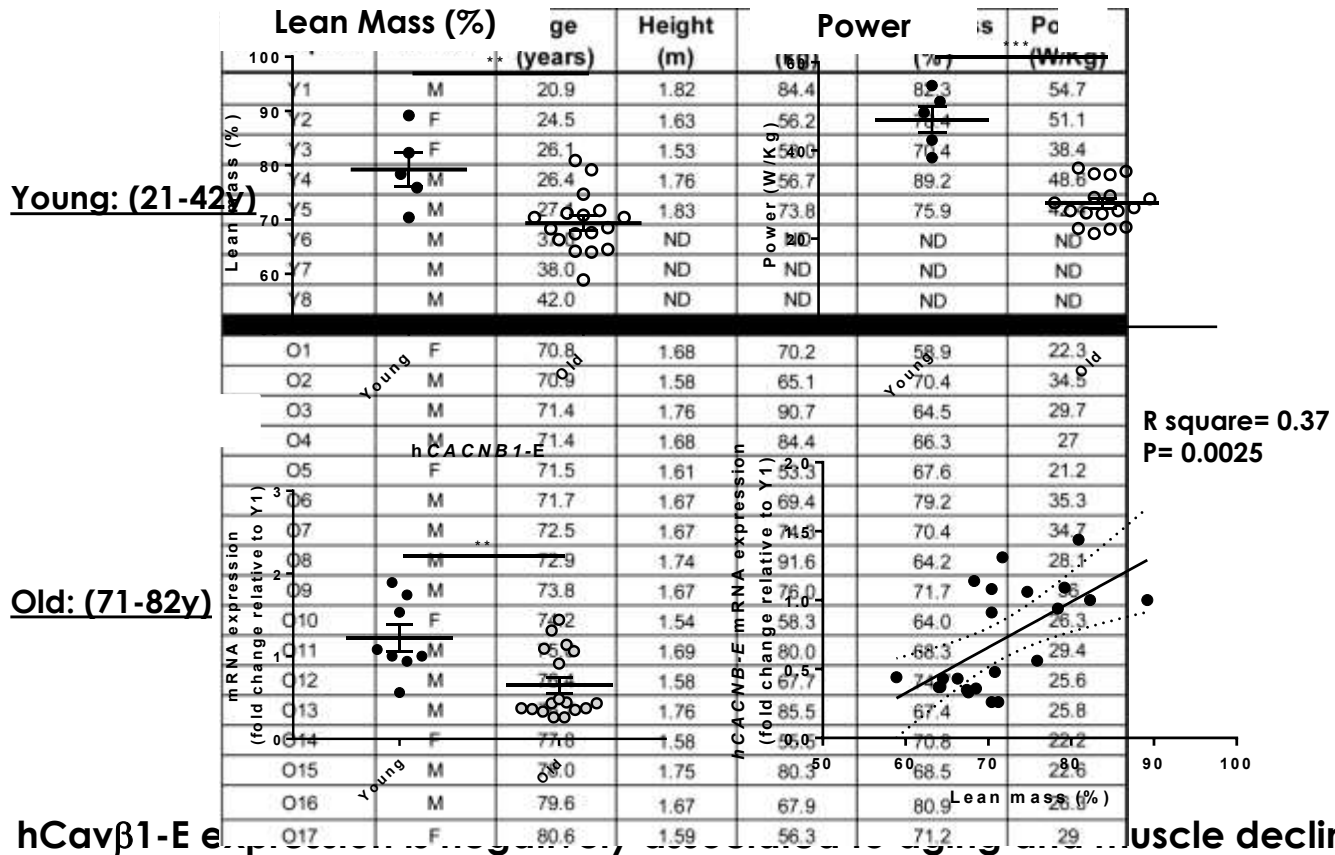
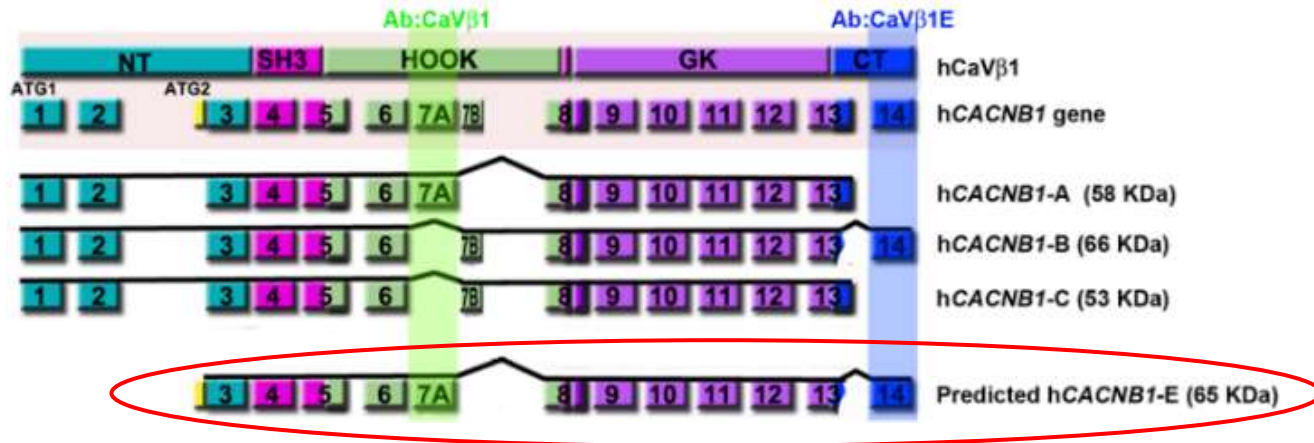
# Cav $\beta$ 1E/GDF5 over-expression



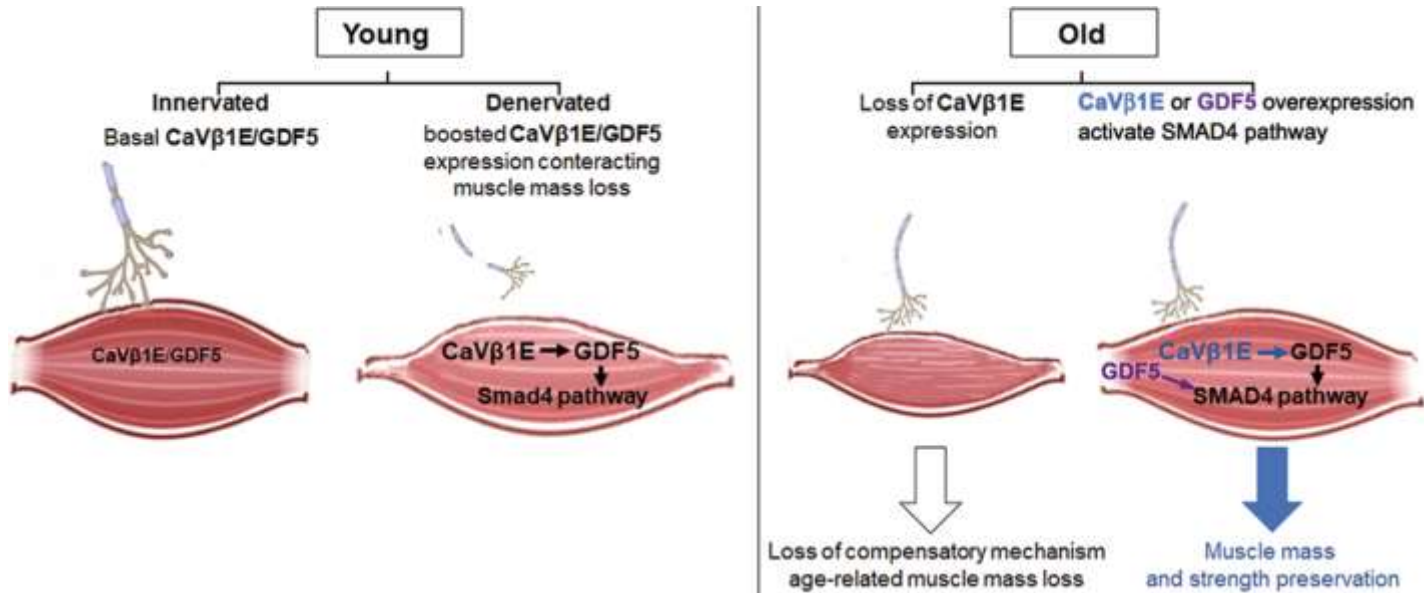
**Ca $\beta$ 1E/Gdf5 improve aged muscle mass and function**



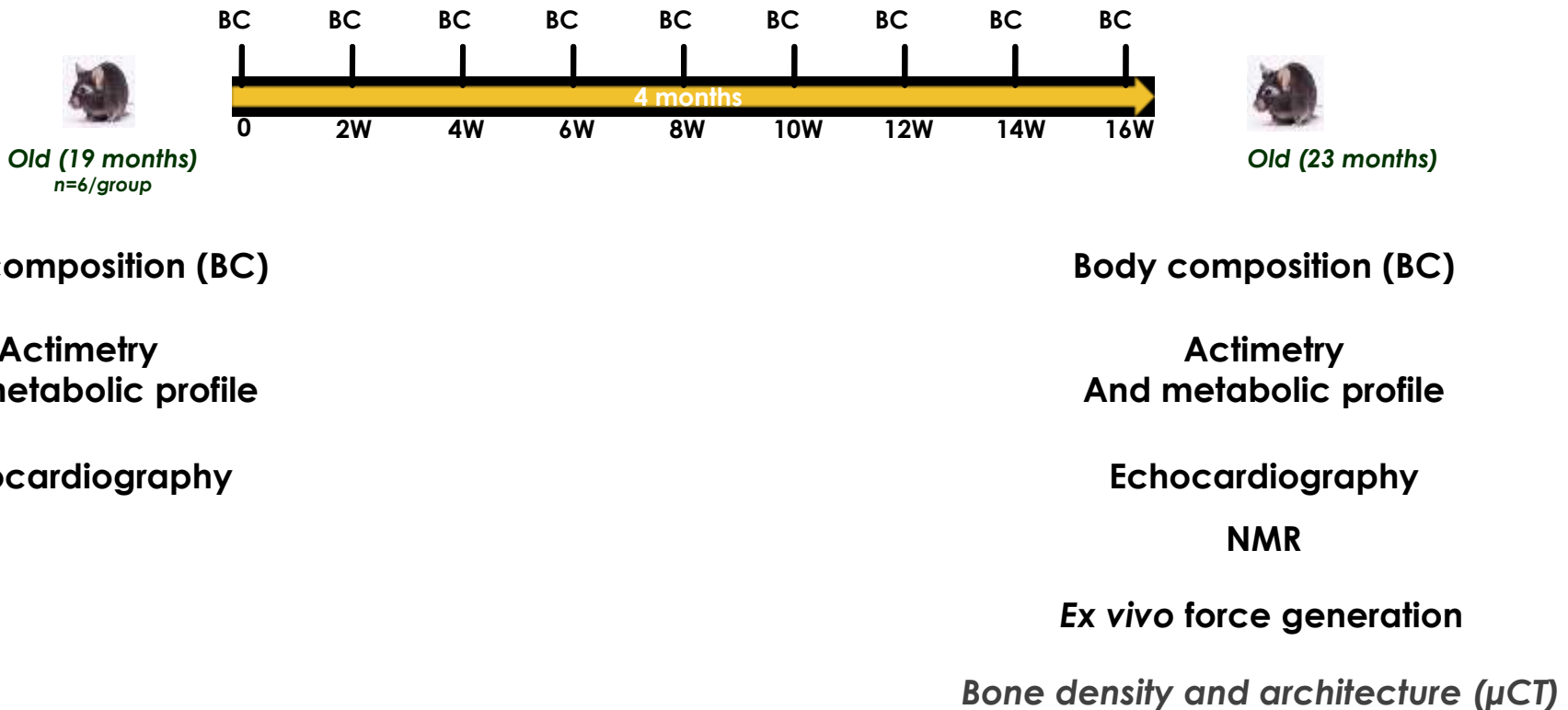
# Cavβ1E in HUMANS



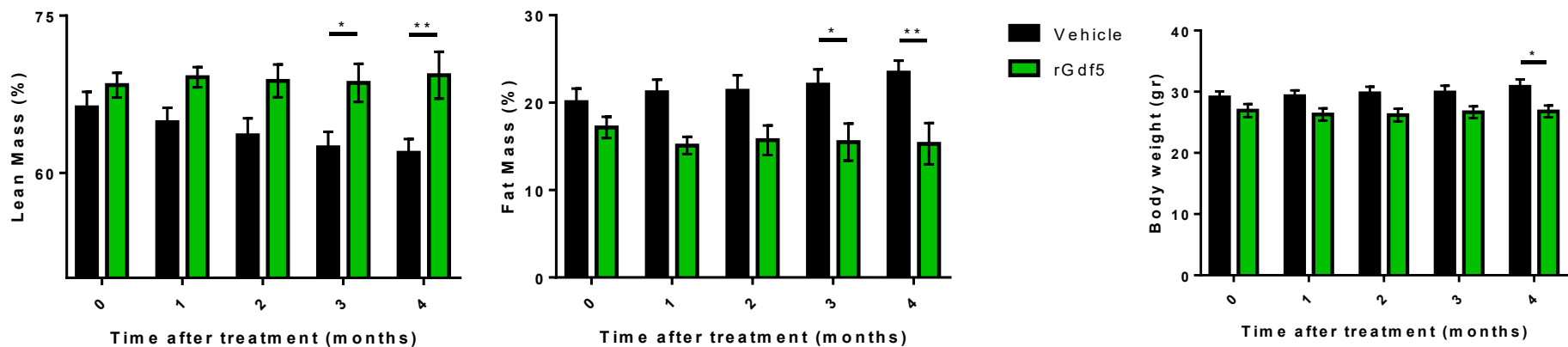
# CONCLUSIONS



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



## Body composition (BC) follow-up

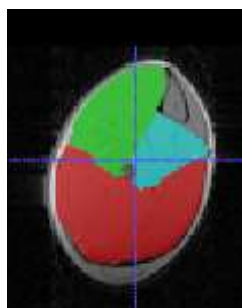


n=6; Two-way Anova

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

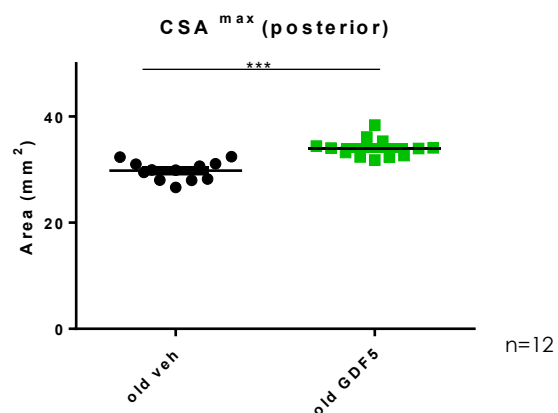
# Muscle mass measurement

Anterior (TA, EDL)



Posterior (GAS, Sol, Planta)

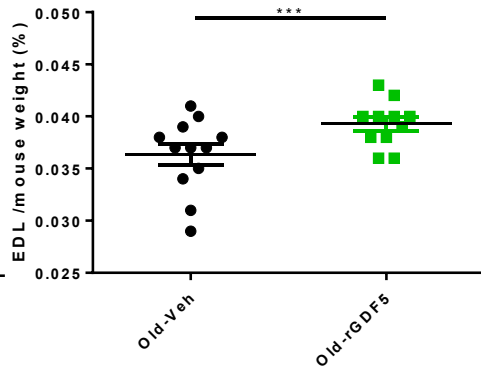
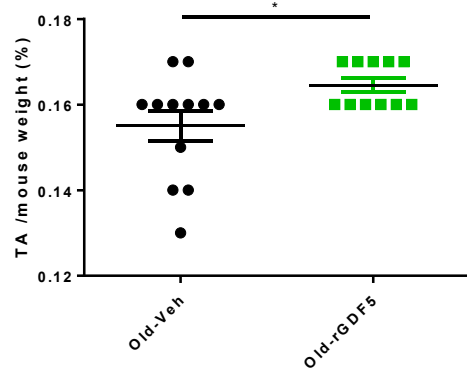
NMR data  
Prof P. Carlier Lab



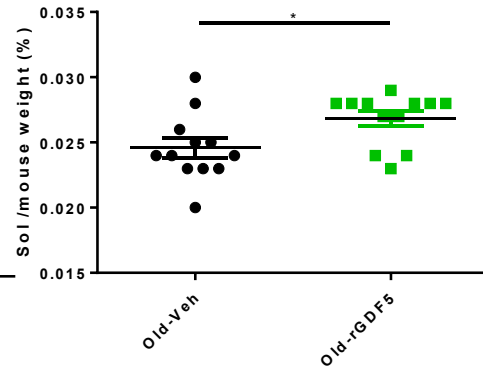
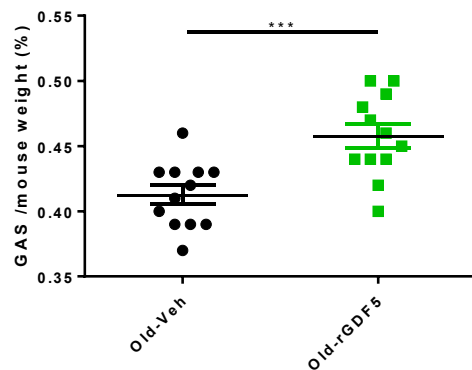
rGdf5 increases regional CSA<sup>max</sup>

## Muscle weight

Anterior (TA, EDL)

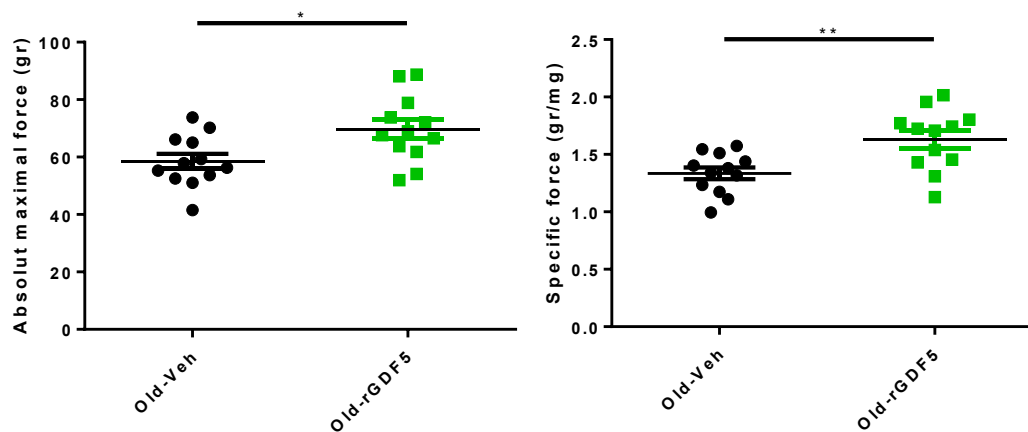


Posterior (GAS, Sol)



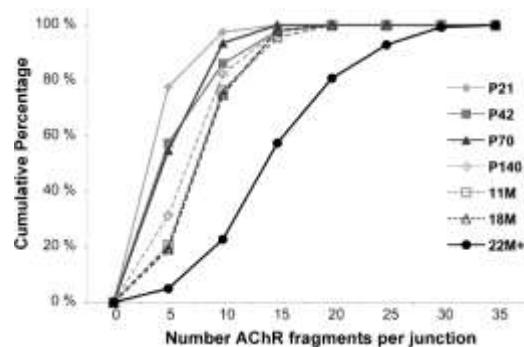
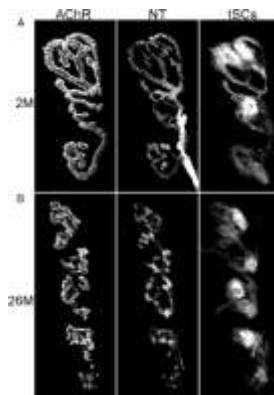
rGdf5 improves muscle mass in old mice

# Muscle function measurement



**rGdf5 improves muscle function in old mice**

## Improvement of innervation?



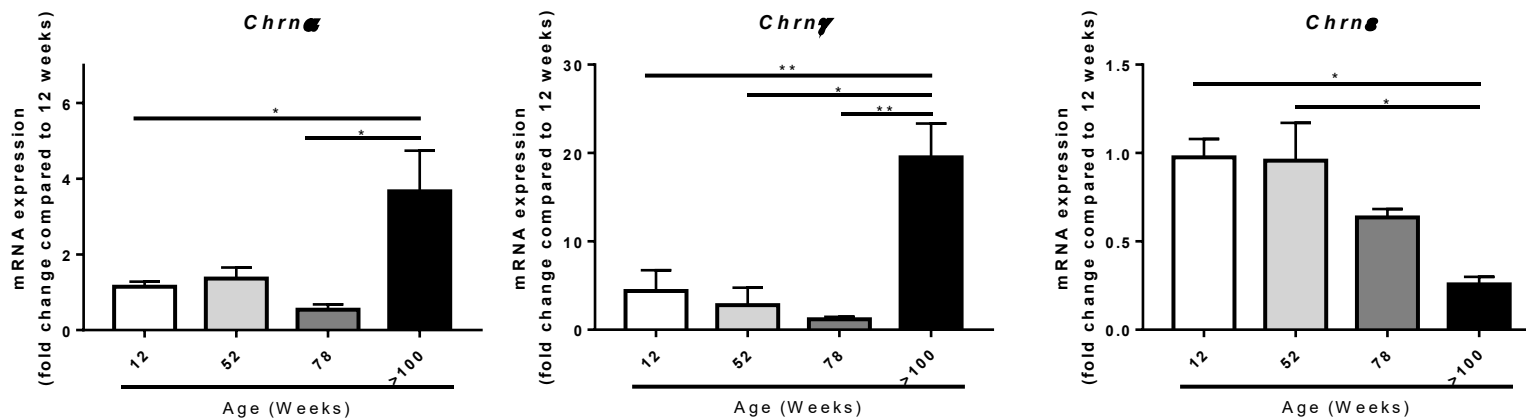
Yue Li et al. J. Neurosci. 2011

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

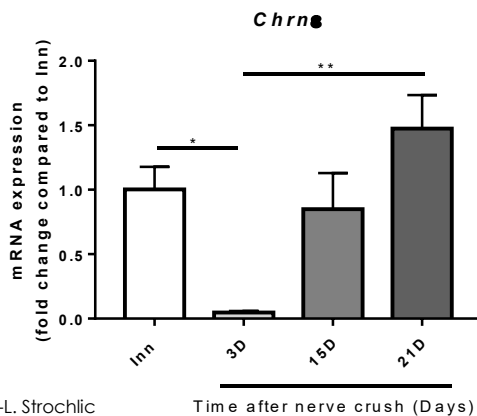
Dach2-Hdac9 signaling regulates reinnervation of muscle endplates

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

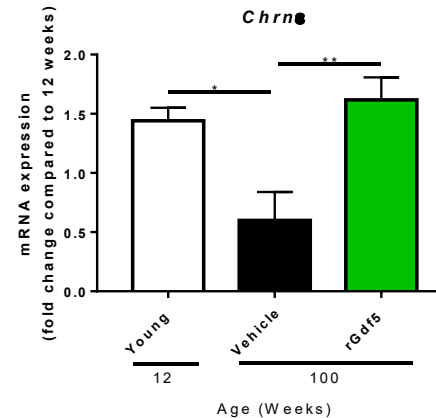
# Denervation markers transcription changes in ageing muscles (TA)



## *Chrna* expression during re-innervation



## *Chrna* expression in rGdf5 treated muscles



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



## Take home message

### Discovery of fundamental role of $Ca_v\beta1E$ /Gdf5 axis in muscle mass homeostasis

- Inducible embryonic  $Ca_v\beta1E$  in adult muscle regulates Gdf5 pathway after nerve damage
- $Ca_v\beta1E$ /Gdf5 axis is altered in ageing muscle
- $Ca_v\beta1E$  overexpression restores aged muscle mass and function via increase of Gdf5 signaling
- Discovery of HUMAN  $Ca_v\beta1E$ : conserved compensatory mechanism



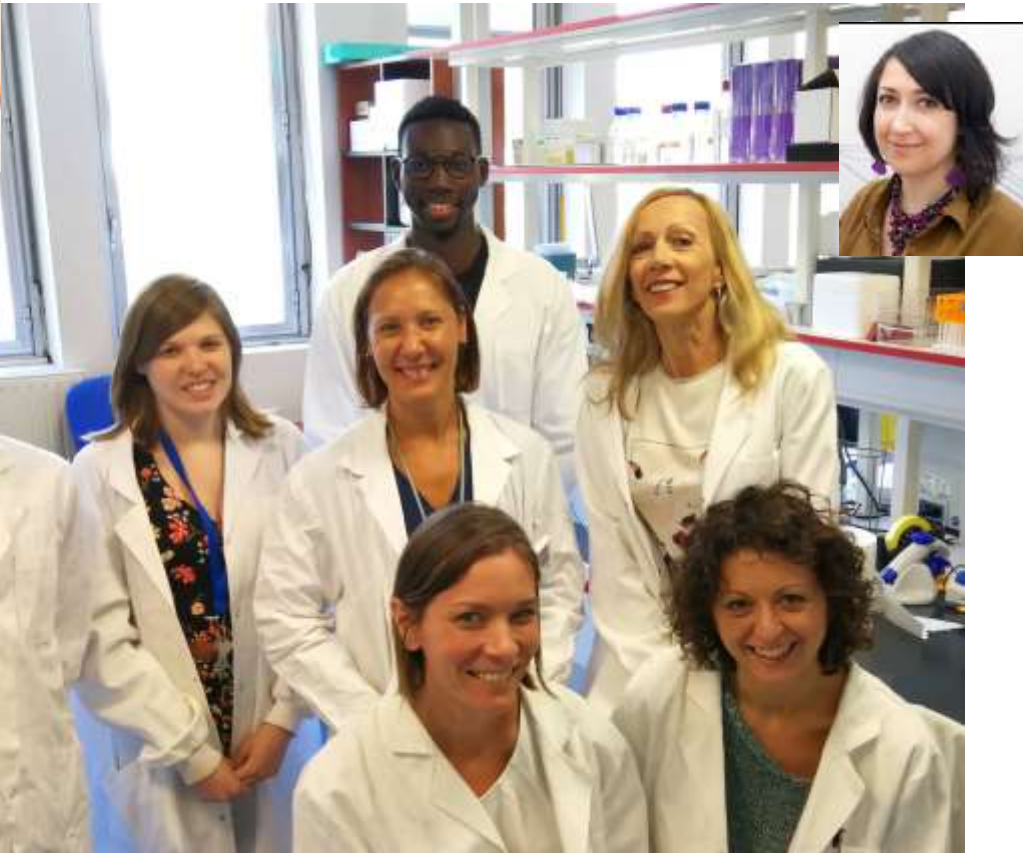
### Systemic implementation of rGdf5 during aging

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

Patent #18184861.5



**malakoff médéric**  
PRÉSENTS POUR VOTRE AVENIR



**Pierre de la  
Grange**

RNAseq  
data  
analy



**Yanni  
Marie**

RNA  
sequencing



CENTRE DE  
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Assessment  
of muscular  
function

AAV  
production  
facility

**Pierre Carlier  
Ericky Caldas**  
NMR

**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;63**Growth 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.

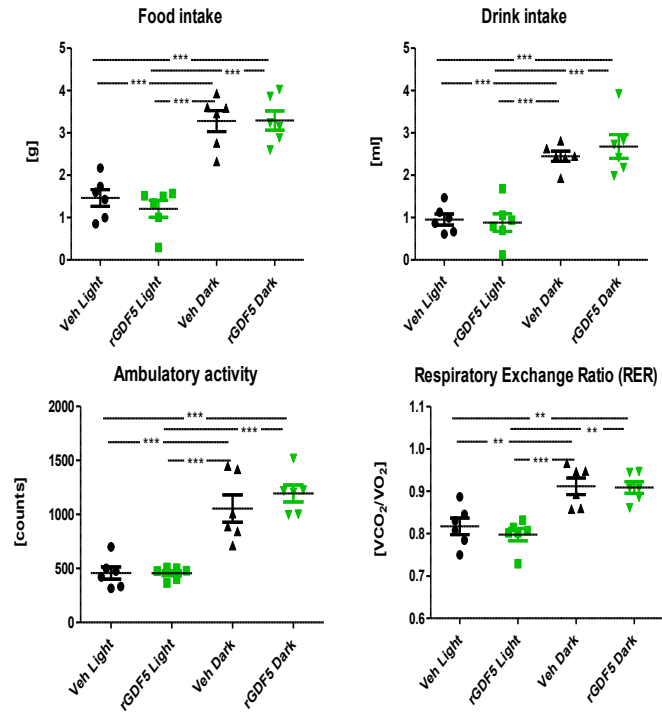
J Cell Mol Med. 2012 **Transplantation of novel human GDF5-expressing CHO cells is neuroprotective in models of Parkinson's disease.**

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

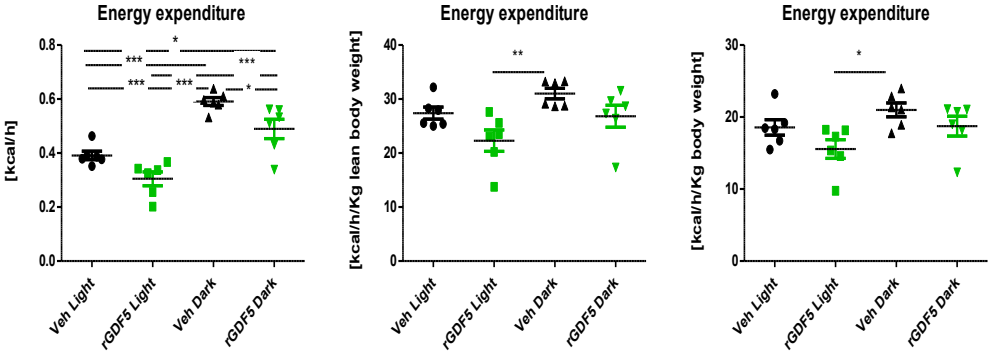
## Metabolism exploration



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



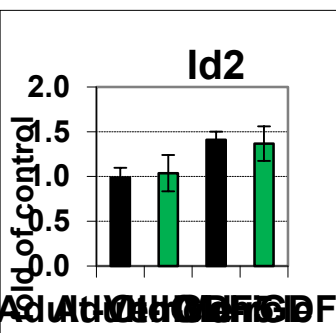
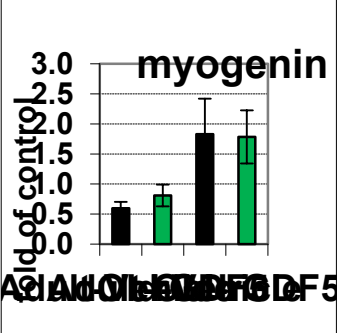
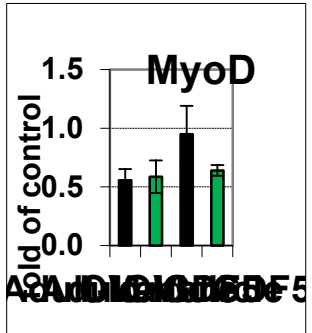
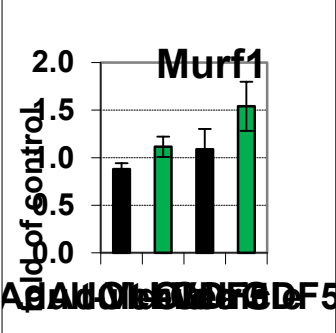
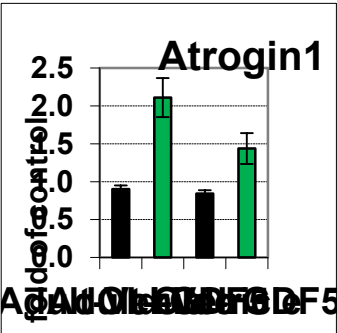
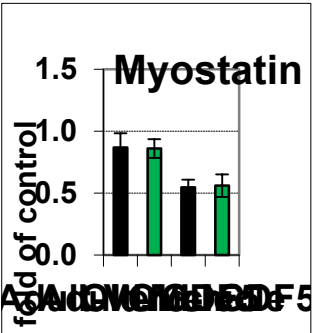
# Metabolism exploration



rGDF5 decreases energy expenditure in old mice

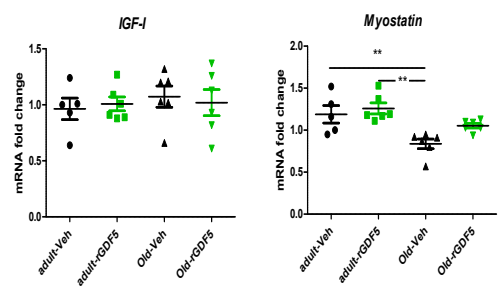


### Genes expression in TA muscle

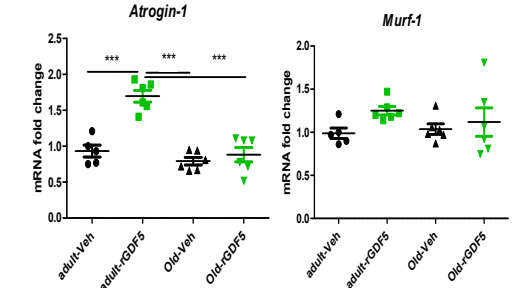


# Genes expression in GAS muscle

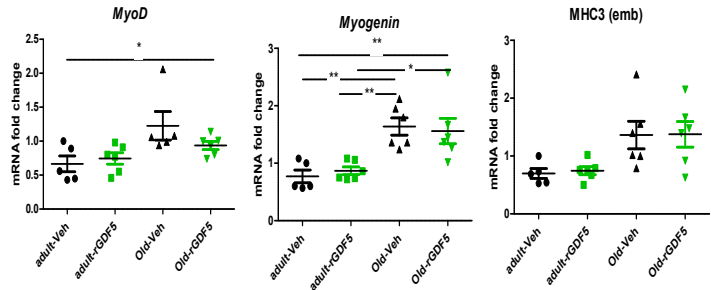
## Growth factors



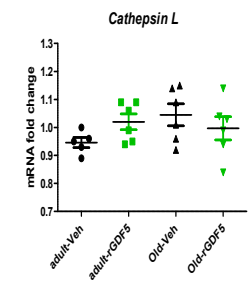
## Ubiquitin-ligase genes



## Regeneration markers



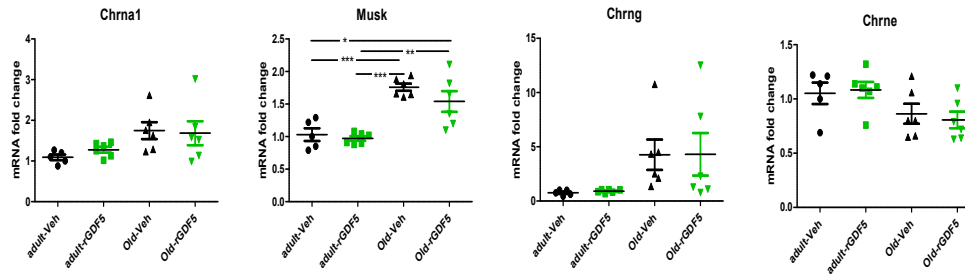
## Autophagy related genes



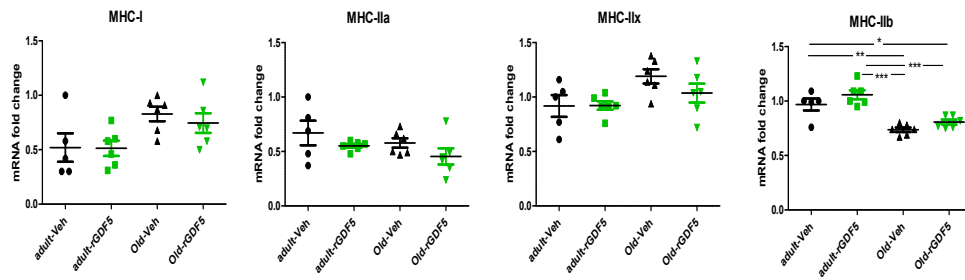


# Genes expression in GAS muscle

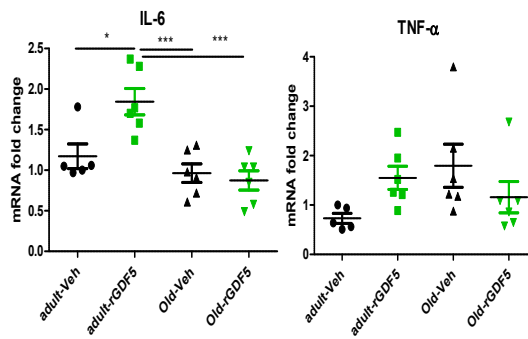
## NMJ markers



## 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