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

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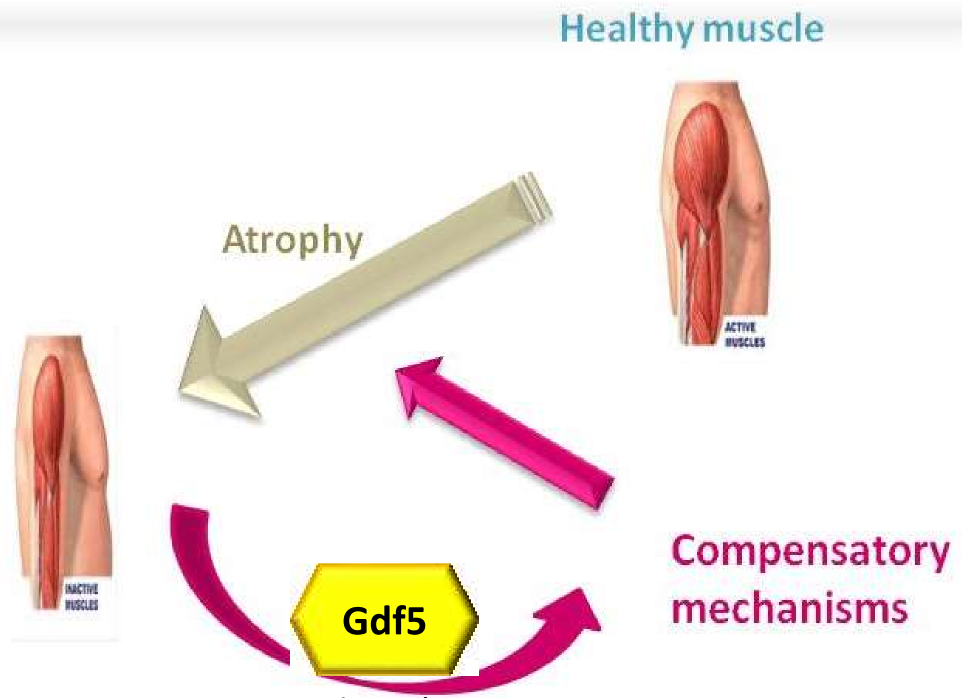
Muscle plasticity and compensatory response



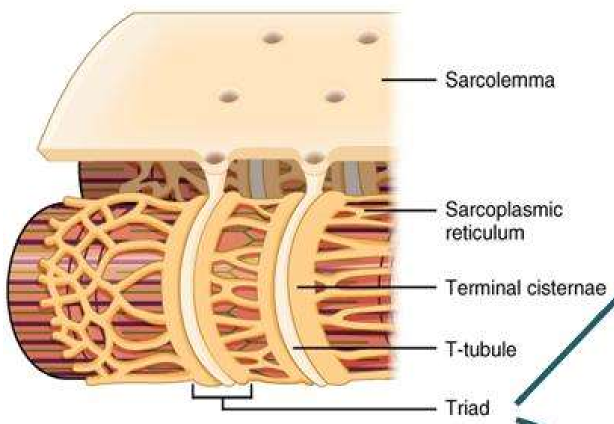
Sartori R. et al. Nat. Gen. 2013

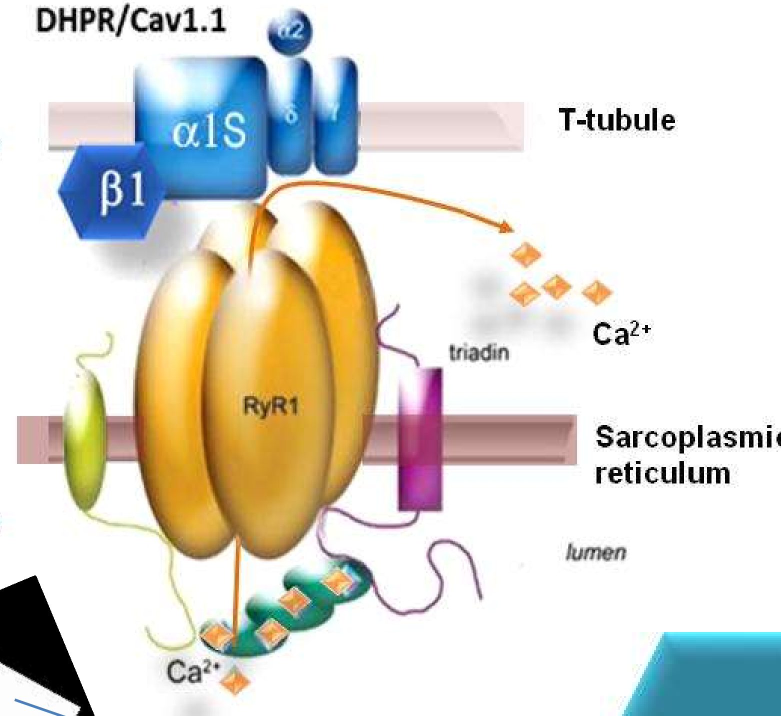
Causes :

- ✓ Myopathies-neuromuscular diseases
- ✓ Nerve damage
- ✓ Disuse-immobilization

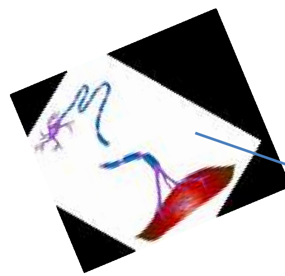
Excitation-Contraction coupling

Abstract Number: P17-168-#155

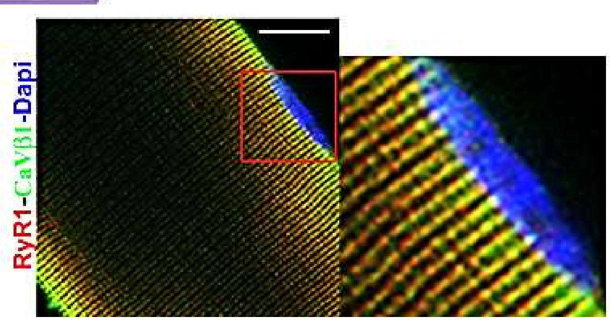


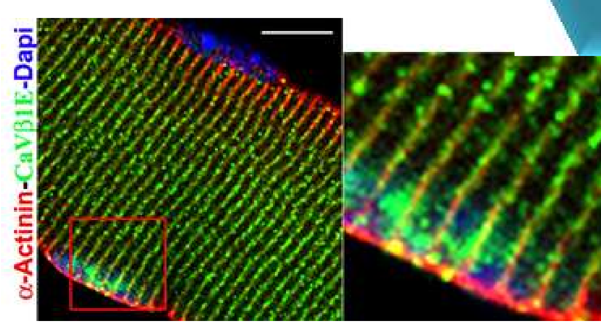


Constitutive



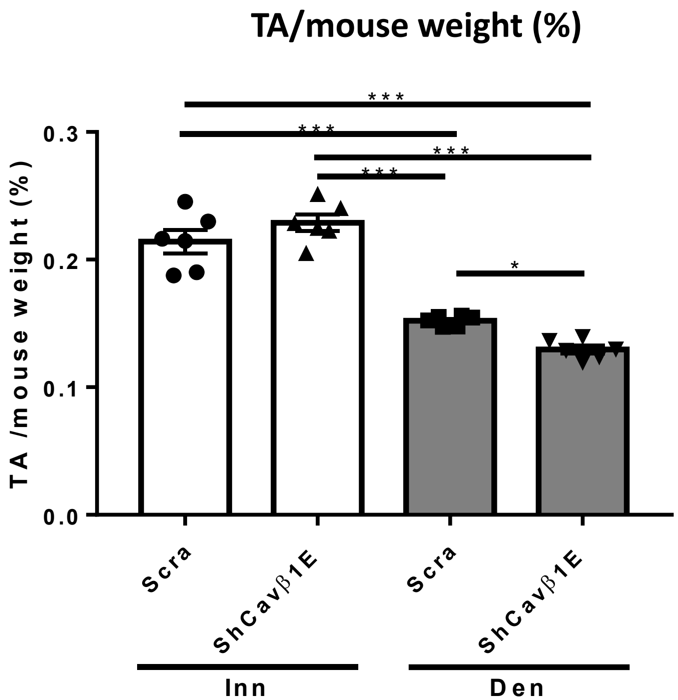
Induced

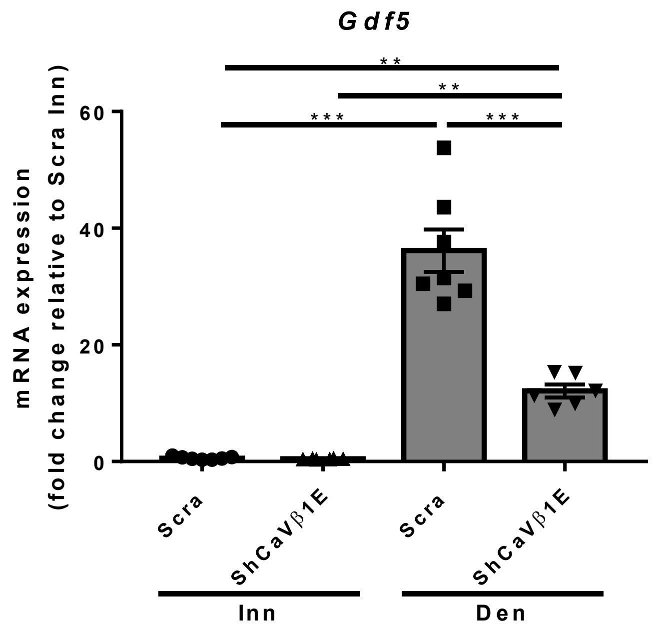




$Ca_v\beta1E \rightarrow$ Gdf5 signaling and muscle mass maintenance (compensatory response)

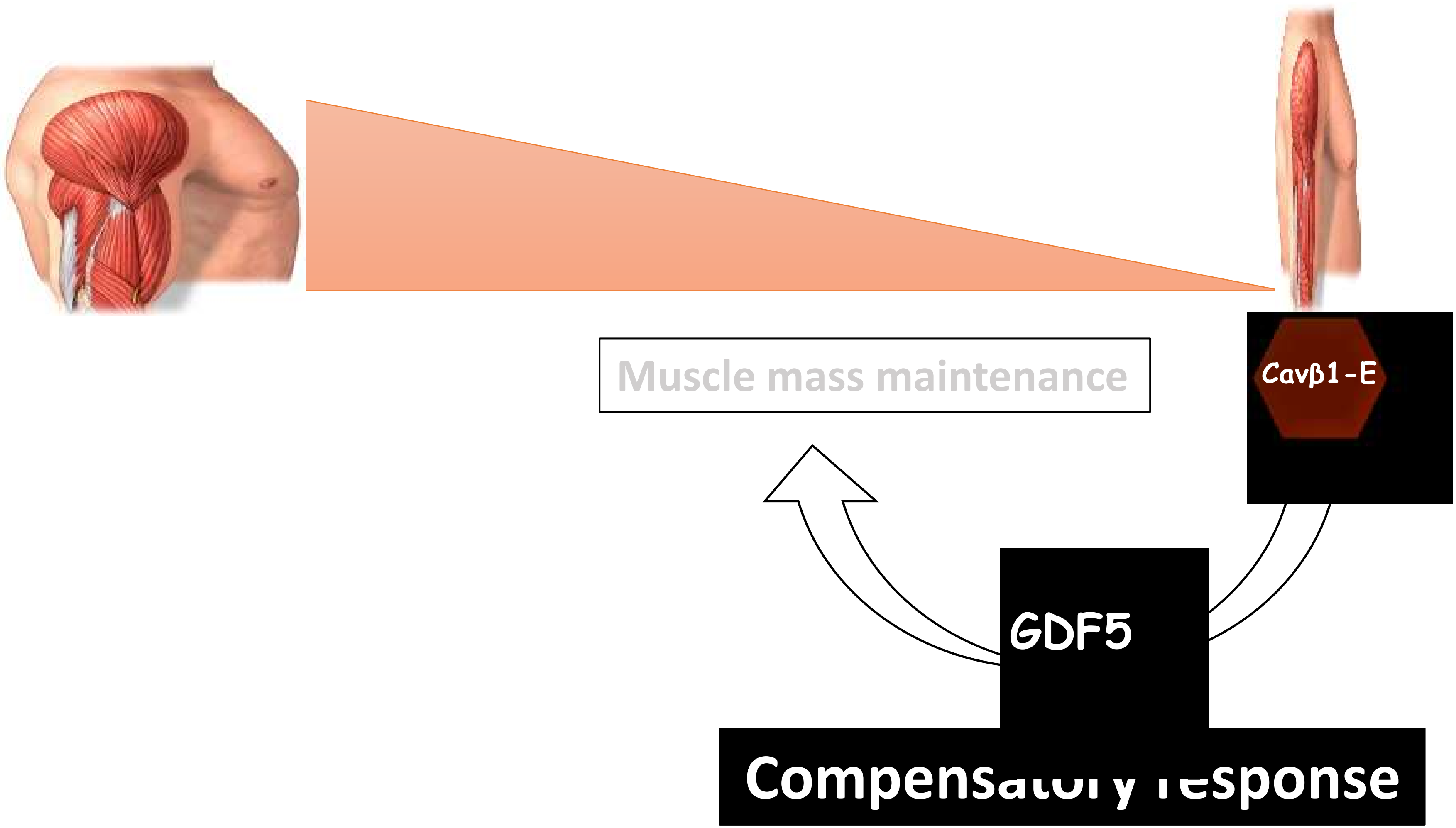
Abstract Number: P17-168-#155





The absence of $Ca_v\beta1E$ exacerbates atrophy by inhibiting Gdf5 pathway

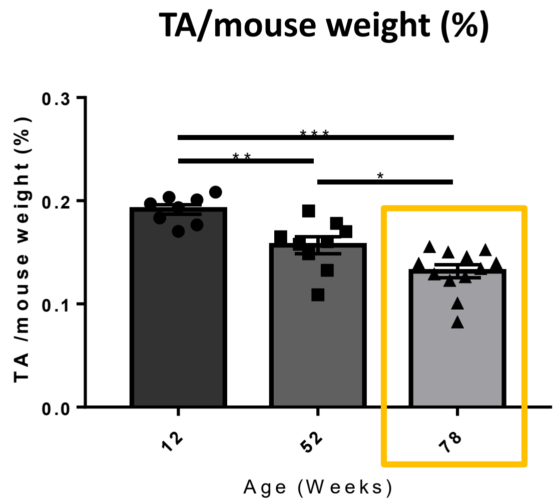
Compensatory response in ageing muscle

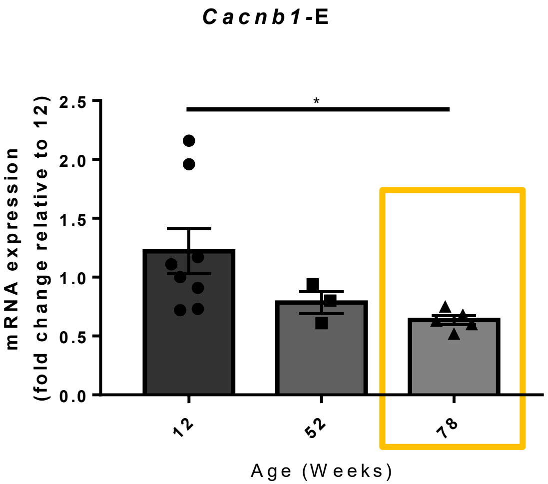


The $Ca_v\beta$1E/ Gdf5 axis is altered in ageing muscle

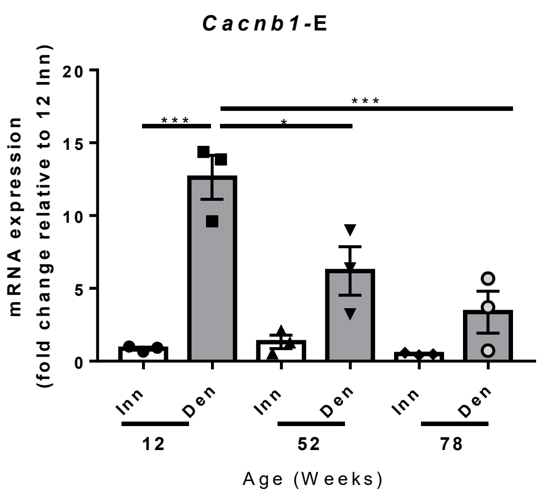
Abstract Number: P17-169-#282

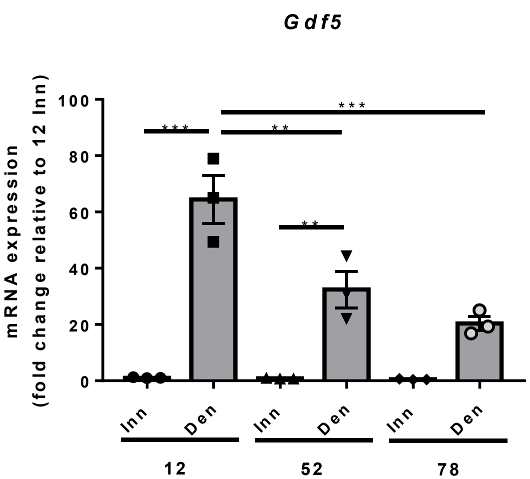
Basal condition





After denervation



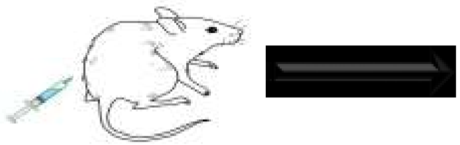


Effect of $Ca_v\beta$1E overexpression in ageing muscle?

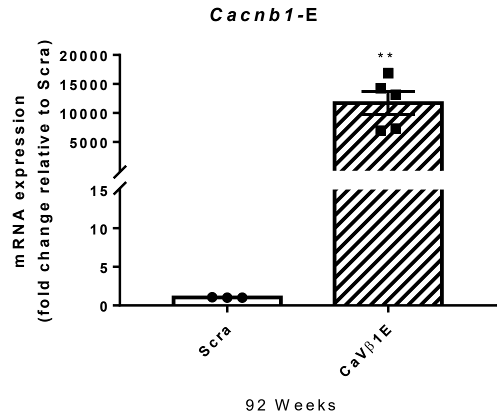
$Ca_v\beta1E$ Over-Expression in ageing muscle

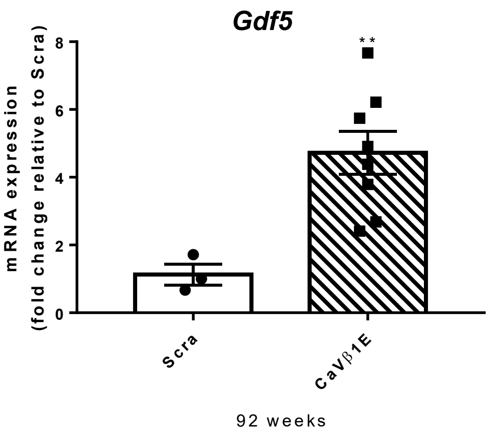
Abstract Number: P17-169-#282

Old (78 Weeks)

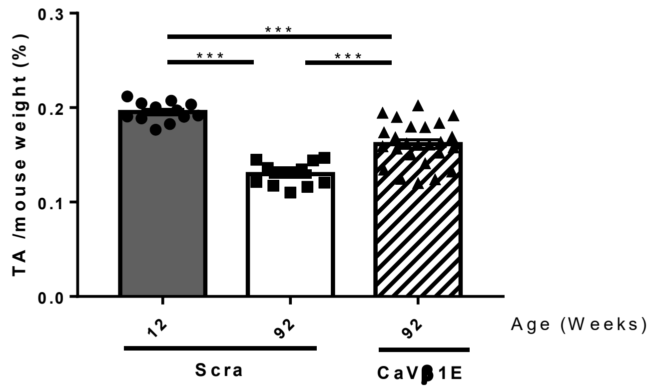


AAV-Cav β1-E

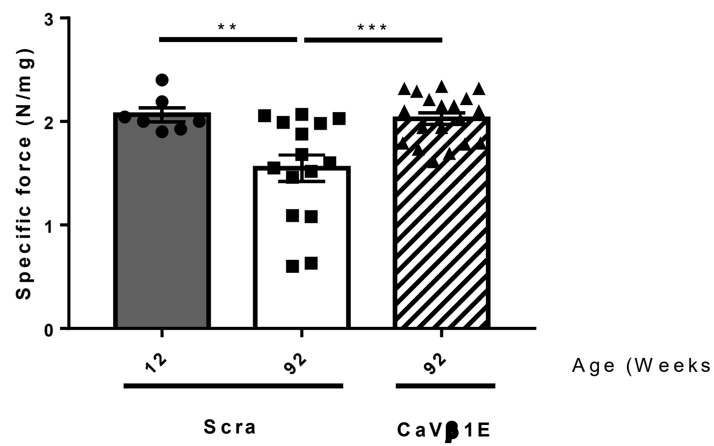




TA/mouse weight (%)



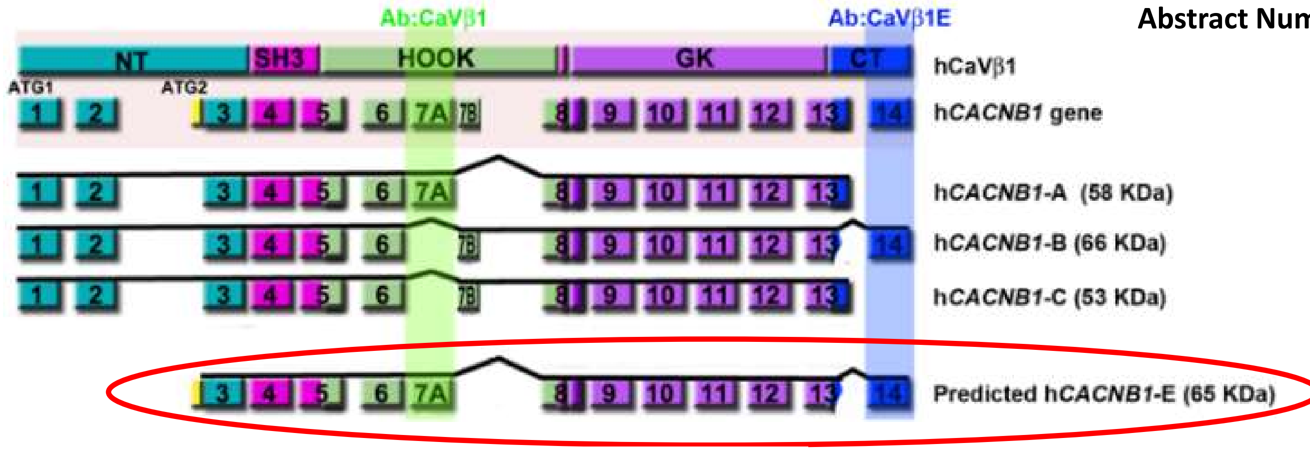
Specific Force



$Ca_v\beta1E$ overexpression increases Gdf5 and improves aged muscle mass and function

Ca$_v$β1E in HUMANS

Abstract Number: P17-169-#282



Young: n=8;

21-42 years

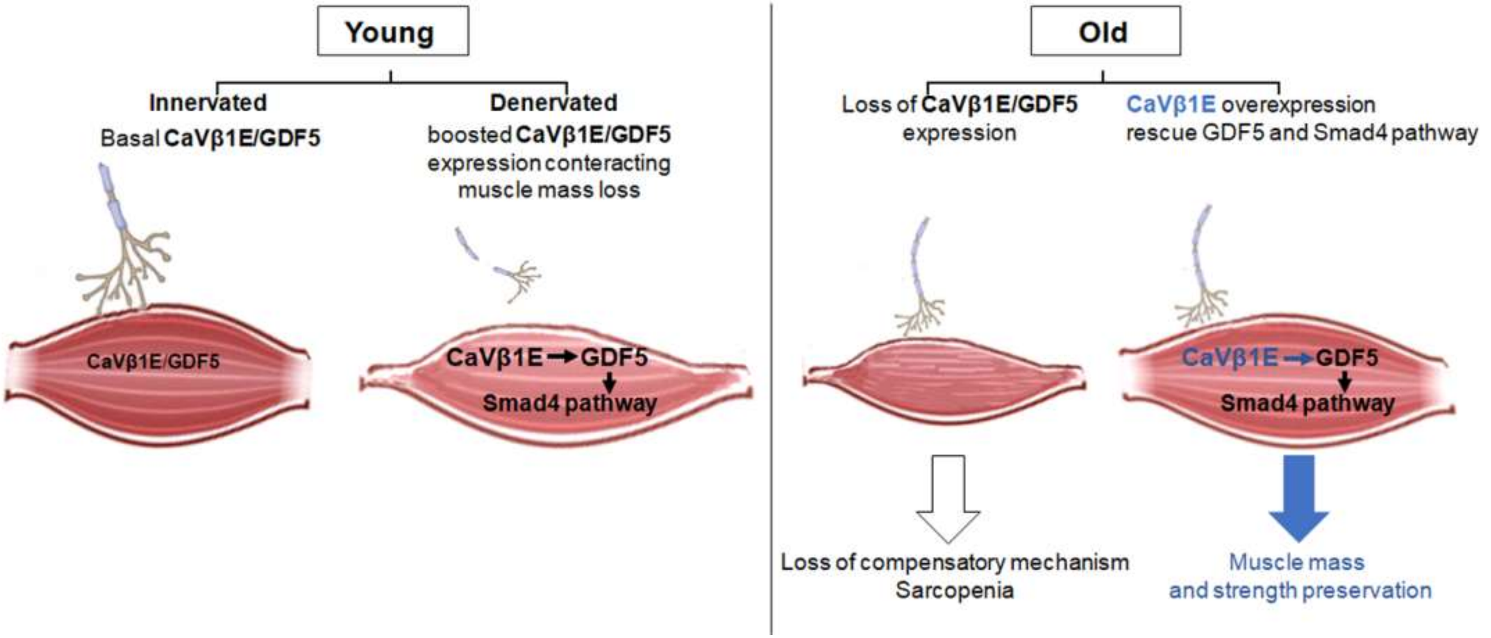
Old: n-17;

71-82 years

Participant	Gender	Age (years)	Height (m)	Weight (kg)	Lean mass (%)	Power (W/Kg)
Y1	M	20.9	1.82	84.4	82.3	54.7
Y2	F	24.5	1.63	56.2	78.4	51.1
Y3	F	26.1	1.53	53.0	70.4	38.4
Y4	M	26.4	1.76	56.7	89.2	48.6
Y5	M	27.1	1.83	73.8	75.9	42.4
Y6	M	37.0	ND	ND	ND	ND
Y7	M	38.0	ND	ND	ND	ND
Y8	M	42.0	ND	ND	ND	ND
O1	F	70.8	1.68	70.2	58.9	22.3
O2	M	70.9	1.58	65.1	70.4	34.5
O3	M	71.4	1.76	90.7	64.5	29.7
O4	M	71.4	1.68	84.4	66.3	27
O5	F	71.5	1.61	53.3	67.6	21.2
O6	M	71.7	1.67	69.4	79.2	35.3
O7	M	72.5	1.67	74.3	70.4	34.7
O8	M	72.9	1.74	91.6	64.2	28.1
O9	M	73.8	1.67	76.0	71.7	36
O10	F	74.2	1.54	58.3	64.0	26.3
O11	M	75.0	1.69	80.0	68.3	29.4
O12	M	76.4	1.58	67.7	74.7	25.6
O13	M	76.7	1.76	85.5	67.4	25.8
O14	F	77.8	1.58	55.5	70.8	22.2
O15	M	78.0	1.75	80.3	68.5	22.6
O16	M	79.6	1.67	67.9	80.9	26.3
O17	F	80.6	1.59	56.3	71.2	29

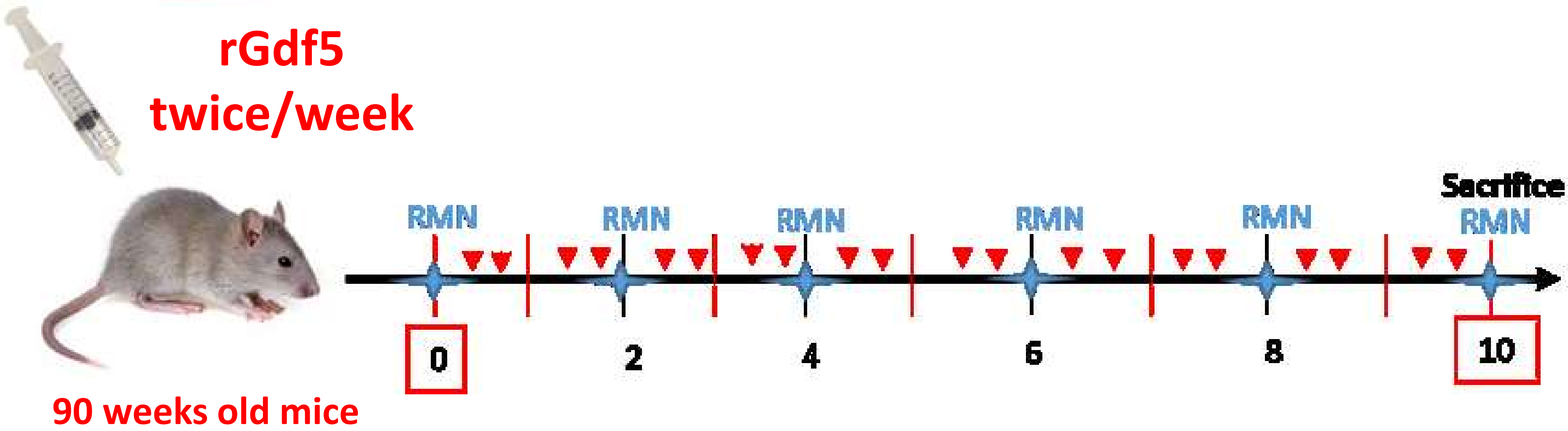
hCa$_v$β1-E expression is negatively associated to aging and muscle decline in HUMANS

Conclusions



Recombinant Gdf5 implementation: a therapeutic tool to reverse age-related muscle waste?

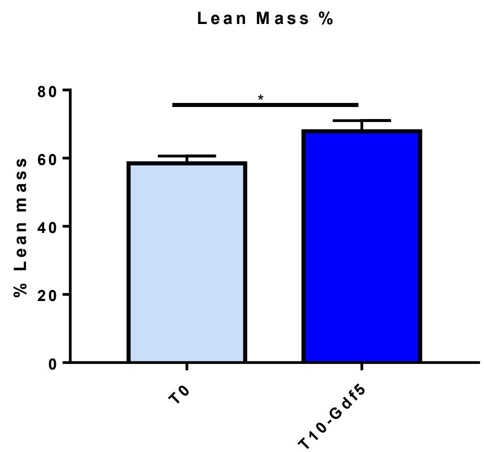
Pilot study: systemic rGdf5 implementation in ageing mice

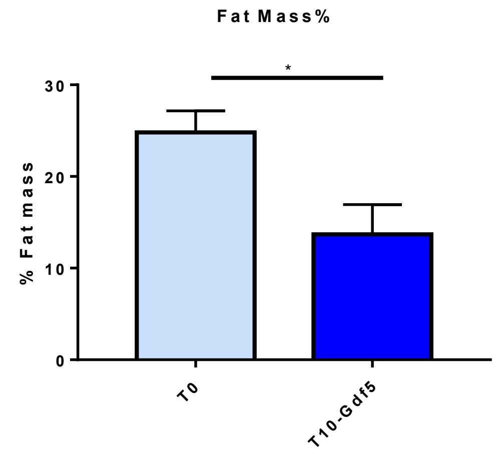


- Lean and fat mass %
- Hind limb muscles weight

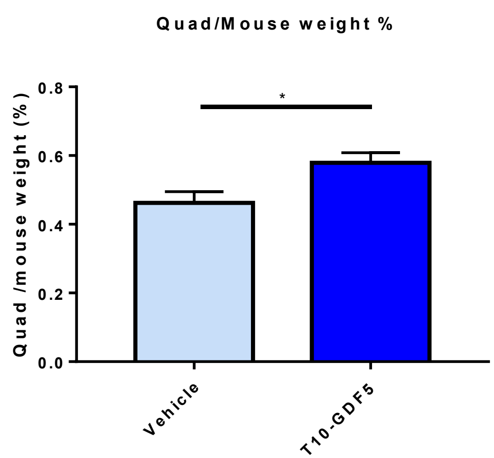
Aged mice two months after rGdf5 treatment

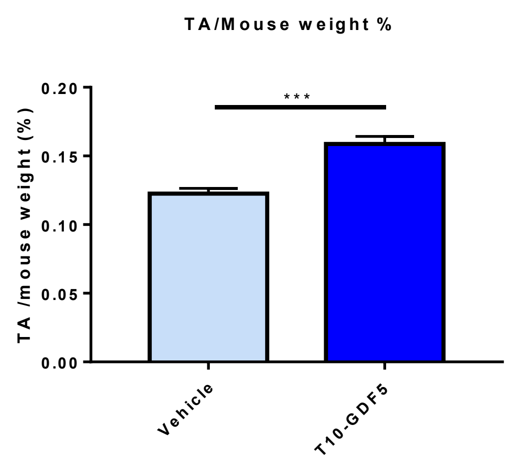
Gain of lean mass and decrease of fat mass





Increase of TA and Quad muscle mass



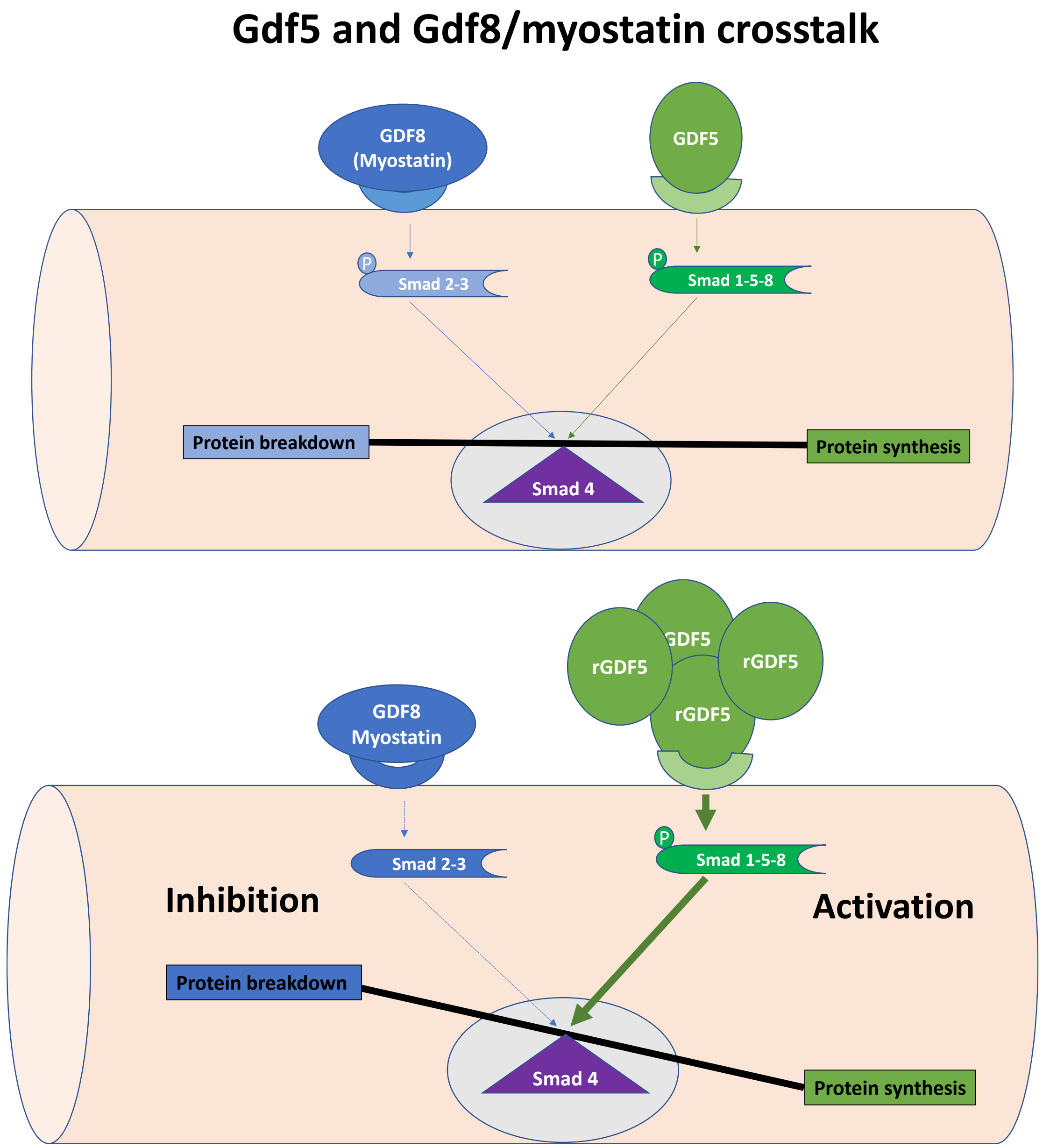


Systemic rGdf5 improves muscle mass in ageing mice

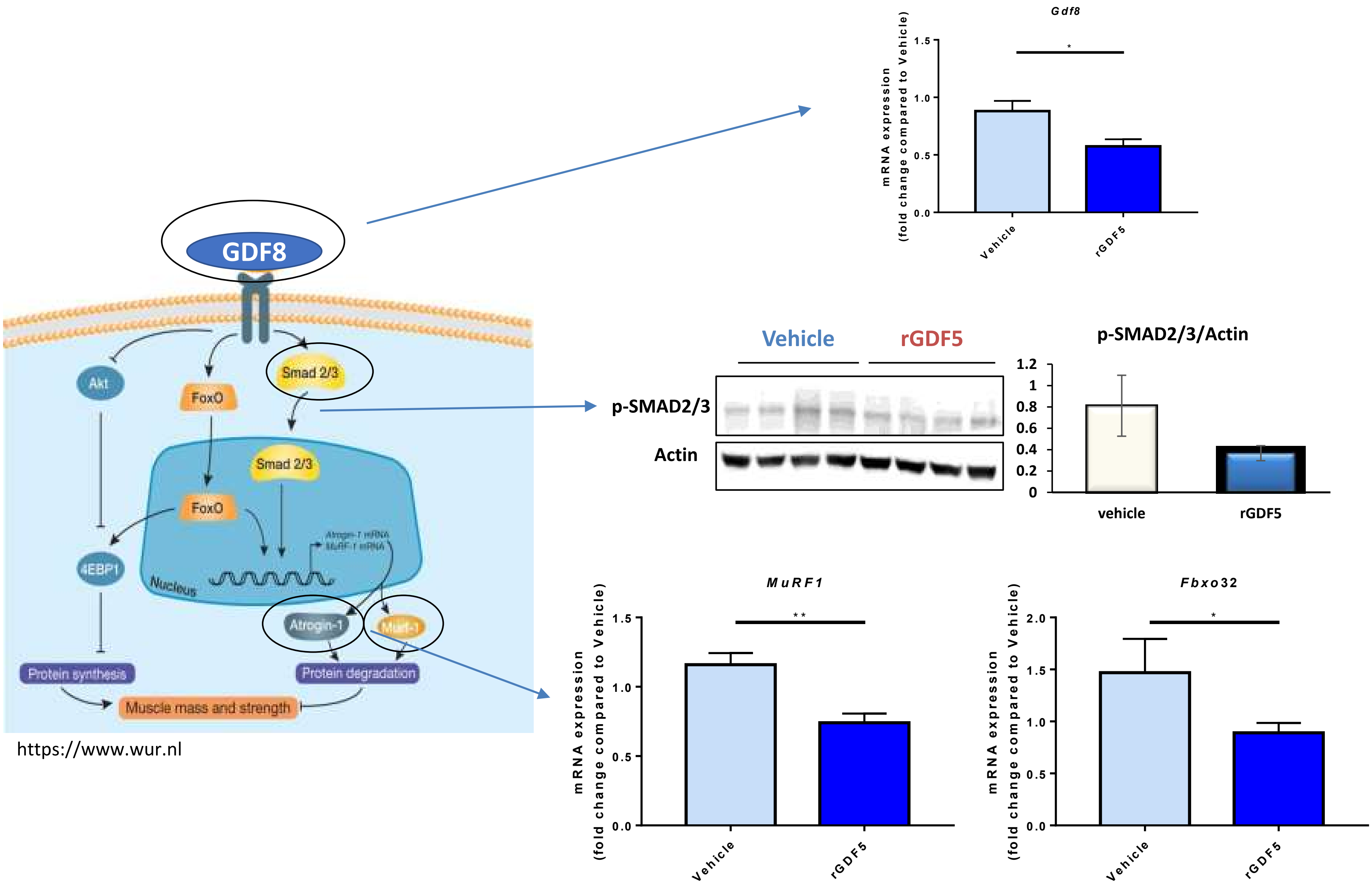
1. Modulation of Gdf8/myostatin pathway?

2. Improvement of innervation?

1. Modulation of Gdf8/myostatin pathway?



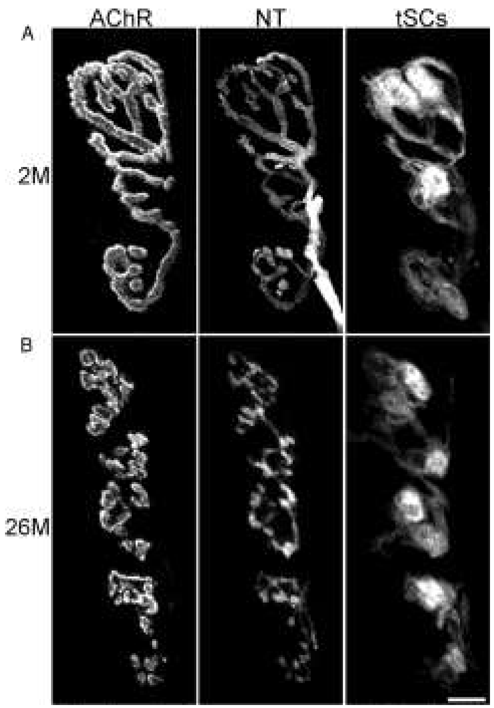
rGdf5 effect on Gdf8/myostatin pathway

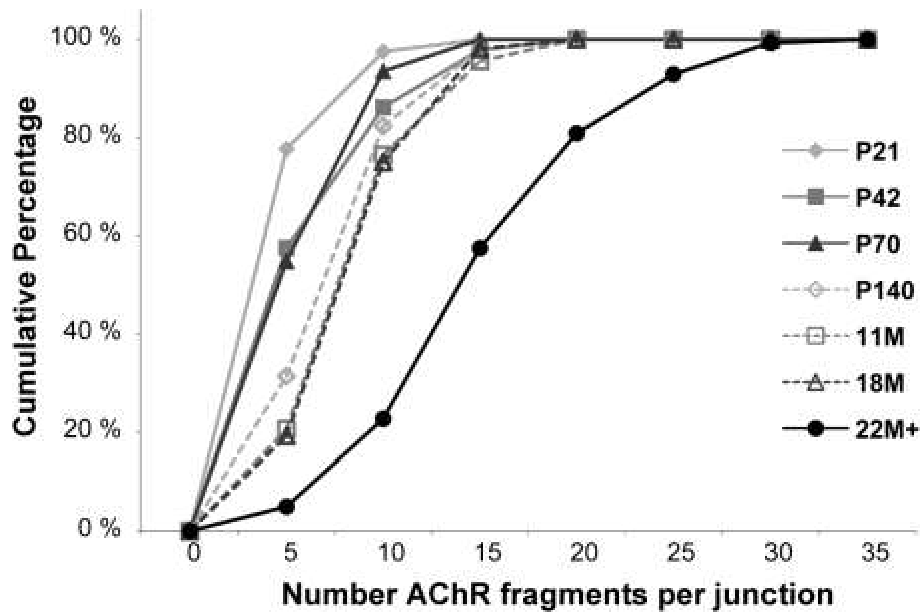


https://www.wur.nl

rGdf5 inhibits Gdf8/myostatin pathway in aged muscles

2. Improvement of innervation?





Yue Li et al. J. Neurosci. 2011

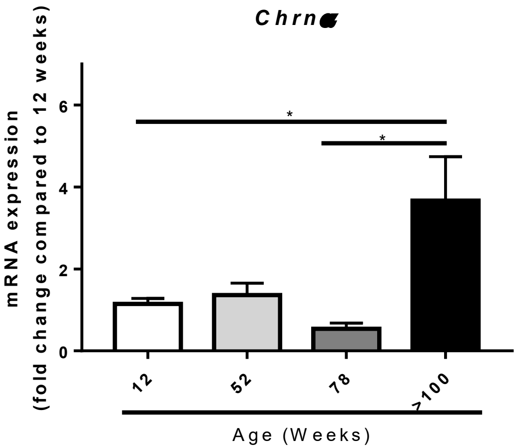
Gdf5 is involved in muscle re-innervation

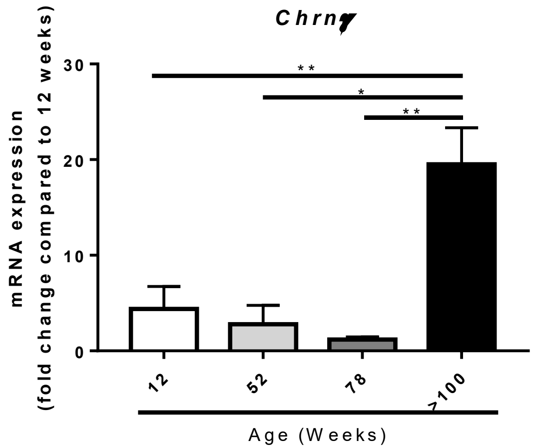
Dach2-Hdac9 signaling regulates reinnervation of muscle endplates

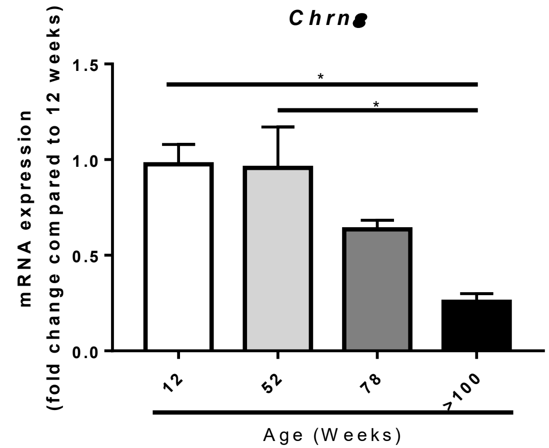
Peter C. D. Macpherson, Pershang Farshi, and Daniel Goldman

2. Improvement of innervation?

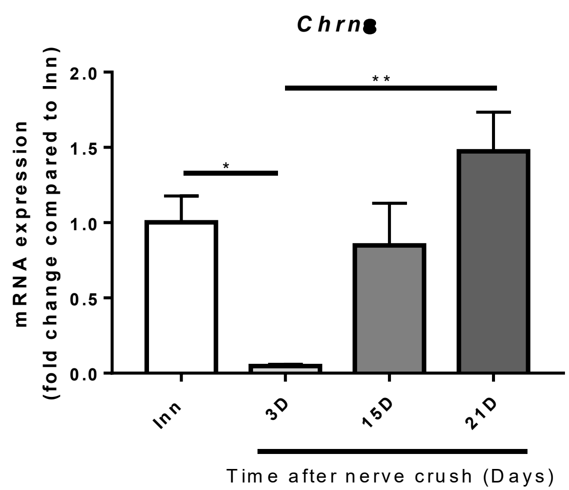
Denervation markers transcription changes in ageing muscles (TA)



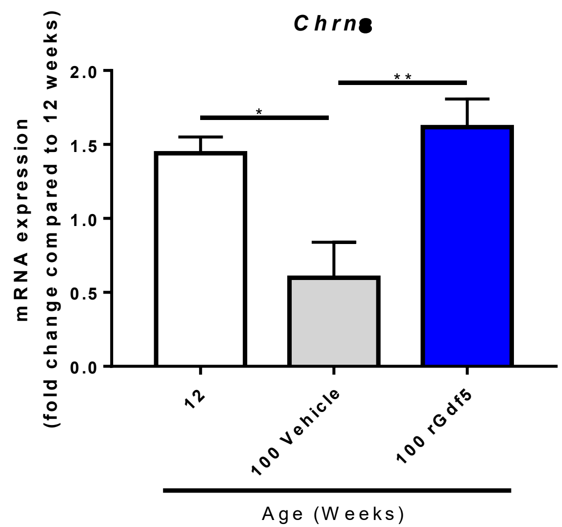




Chrnε expression during re-innervation



Chrnε expression in rGdf5 treated muscles



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

Take home message

Discovery of fondamental role of $Ca_v\beta$1E/Gdf5 axis in muscle mass homeostasis

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

Systemic implementa[redacted] of rGdf5 during aging

- Gain of muscle mass
- Inhibition of myostatin pathway
- Rescue of Chrnε expression, a marker of NMJ integrity

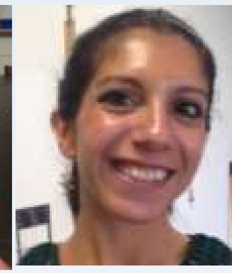
Patent #18184861.5

France Piétri-Rouxel

Christel Gentil

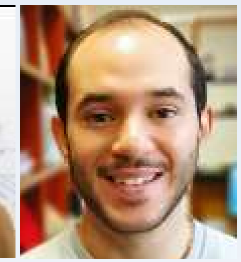
Massiré Traoré

Anne Forand



Chiara Benedetto

Elena Gargaun



Ruben Laskar

Pierre de la Grange
RNAseq data analysis

GenoSplice

Yannick Marie
RNA sequencing

IGENSEQ ICM Institut du Cerveau et de la Moelle épinière

Sofia Benkelifa
Laura Julien
AAV production

Arnaud Ferry
Mégane Lemaitre
Assessment of muscular function

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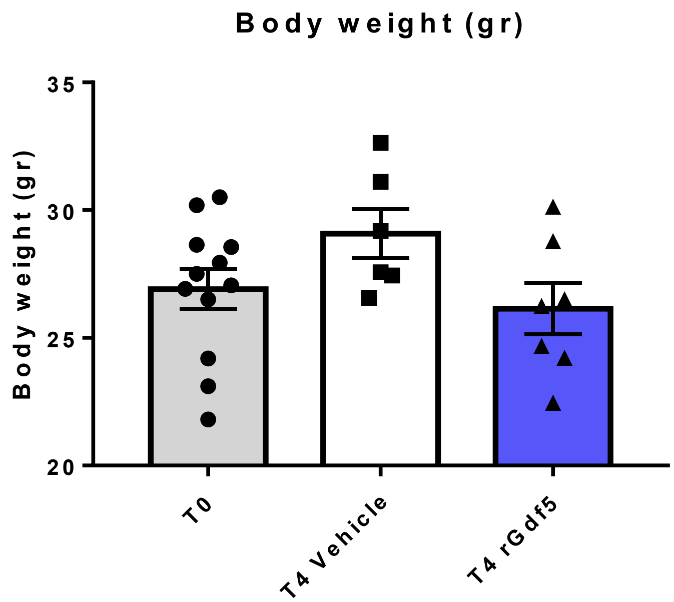
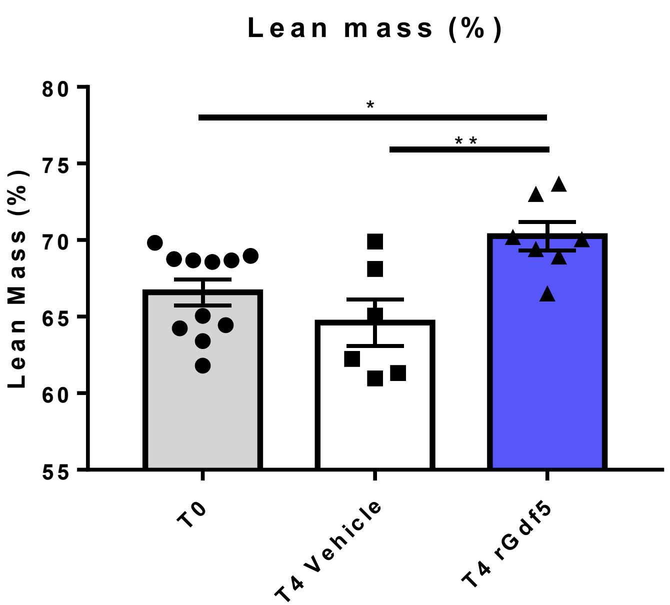
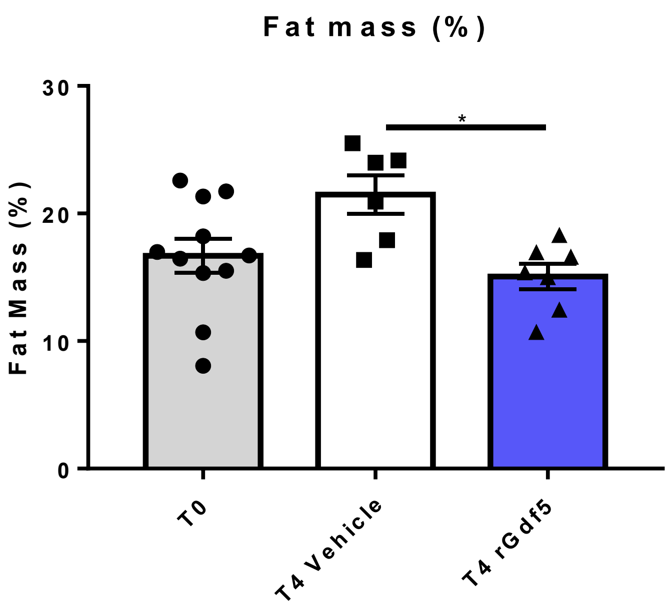

Body weight (gr)
Body weight (gr)
35
30
25
20
T0
T4 Vehicle
T4 rGdf5


Lean mass (%)
Lean Mass (%)
80
75
70
65
60
55
*
**
T0
T4 Vehicle
T4 rGdf5


Fat mass (%)
Fat Mass (%)
30
20
10
0
*
T0
T4 Vehicle
T4 rGdf5