

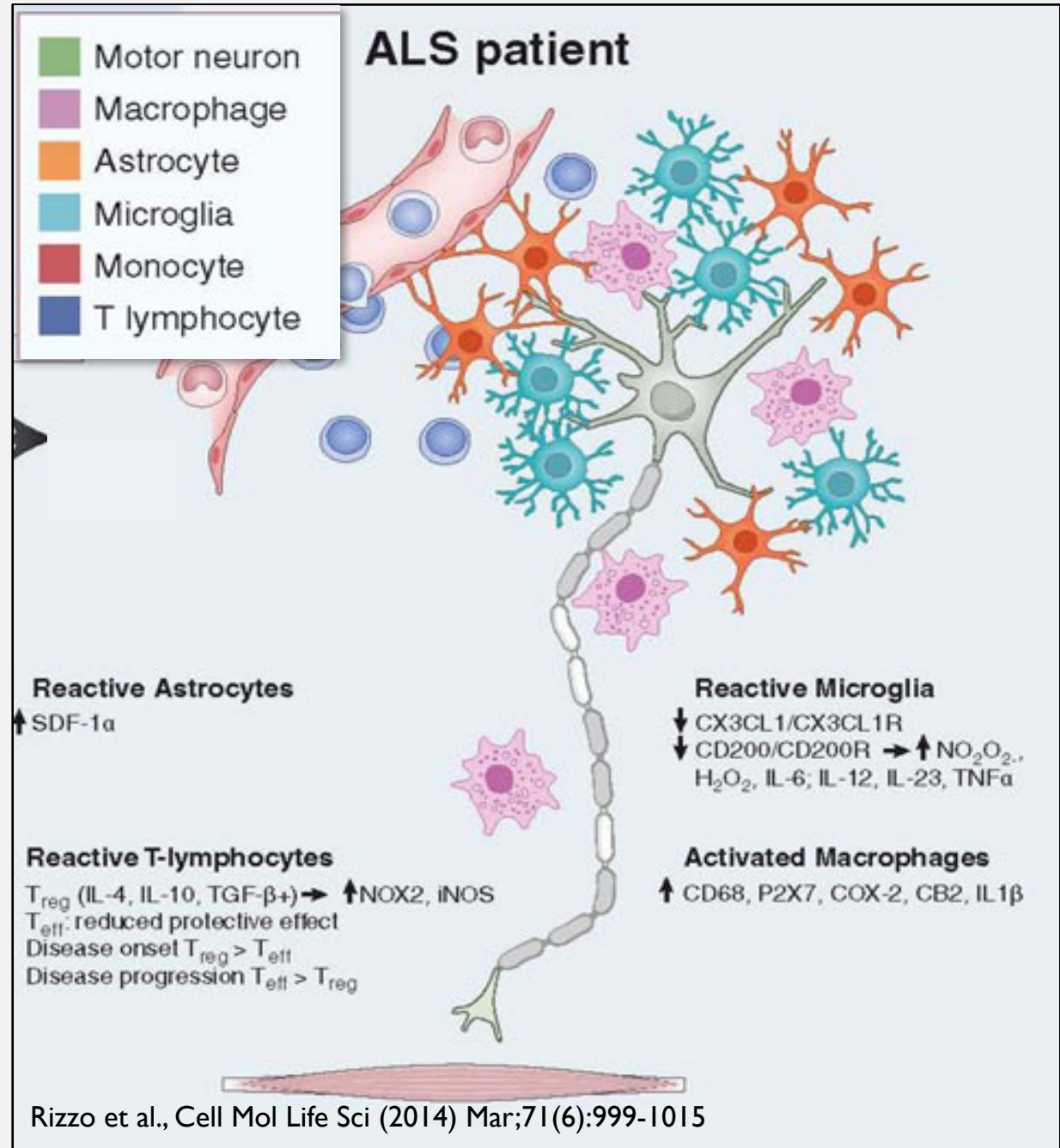
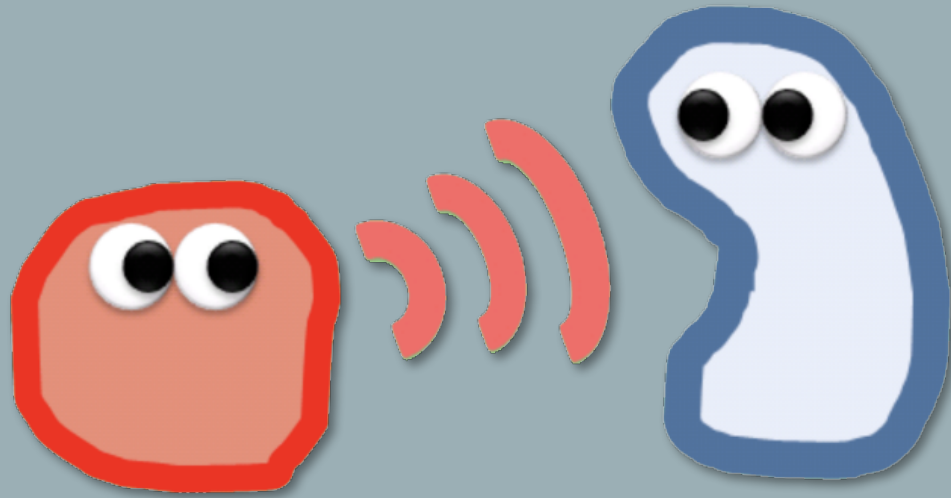
SECRETION OF TOXIC EXOSOMES BY MUSCLE CELLS OF ALS PATIENTS: ROLE IN THE PATHOGENESIS

ViTAL: Vesicles in the transmission of ALS



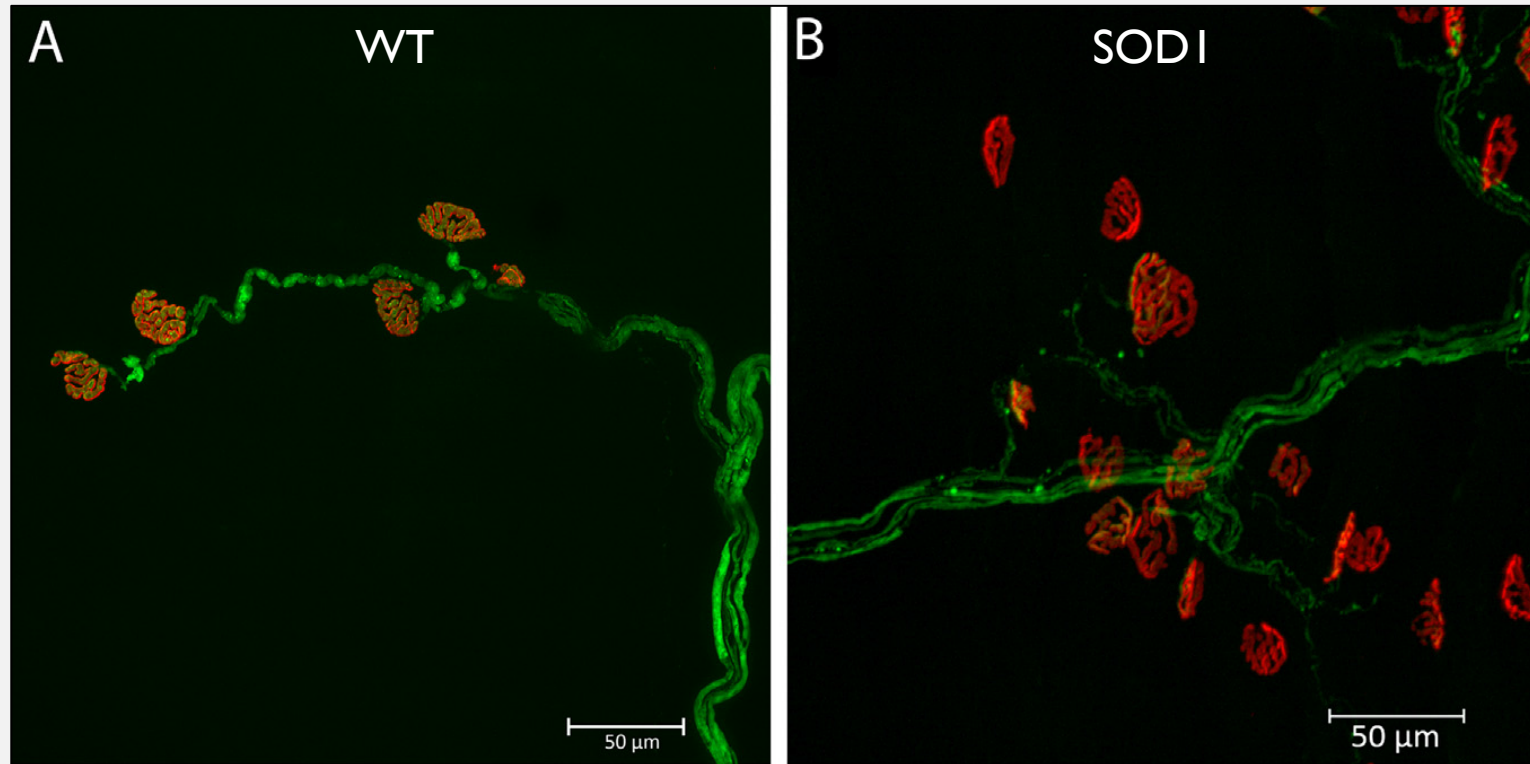
Stephanie Duguez
s.duguez@ulster.ac.uk

AMYOTROPHIC LATERAL SCLEROSIS (ALS)



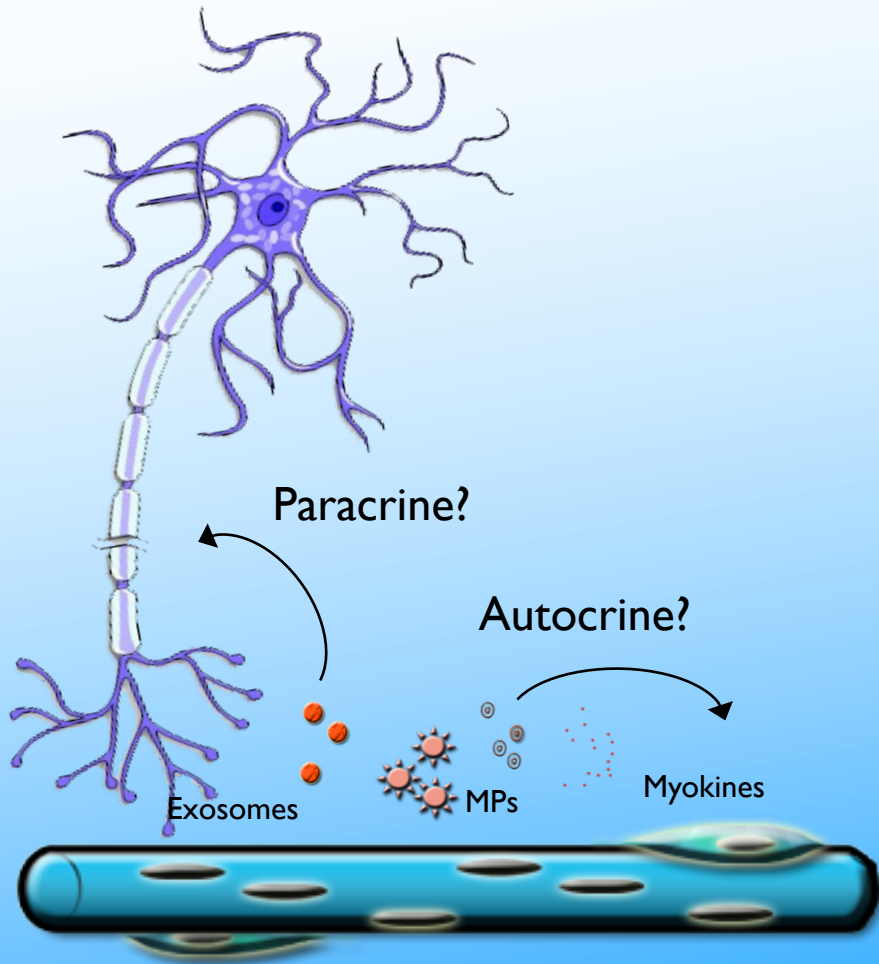
DYING BACK

In SOD1 mice, axonal degeneration start at 60 days, in the caudal region



C Tallon, et al., *Neuroscience* 312 (2016) 179–189;
LR Fischer et al., *Experimental Neurology* 185 (2004) 232– 240

Intercellular communication muscle-nerve altered?

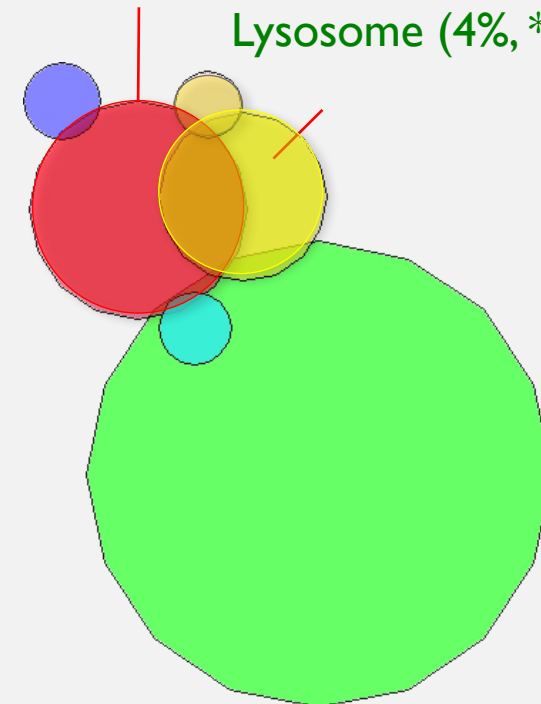


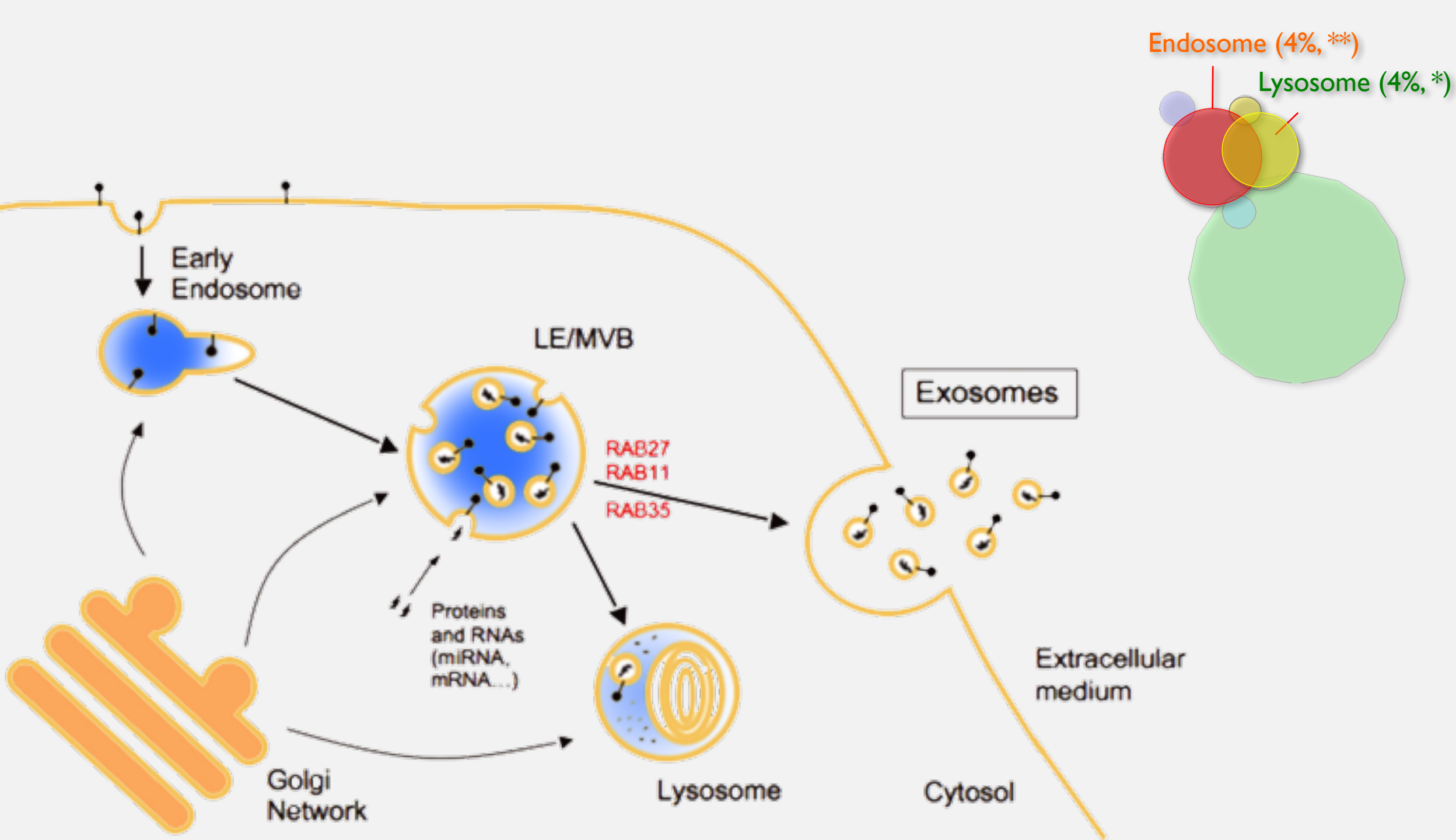
TRANSCRIPTOMIC ANALYSIS OF ALS MUSCLES

Secretome *in silico* performed using
Bakay et al, 2006 & Pradat et al., 2012

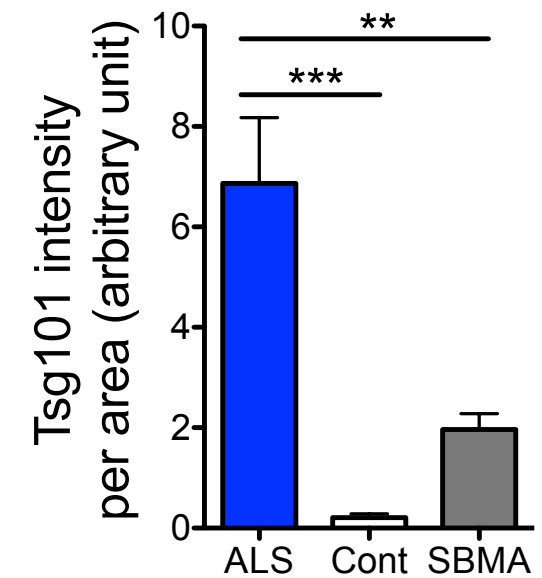
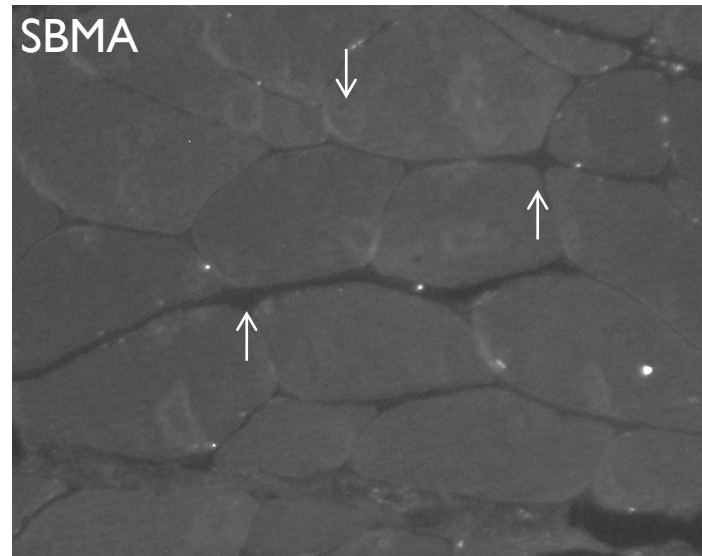
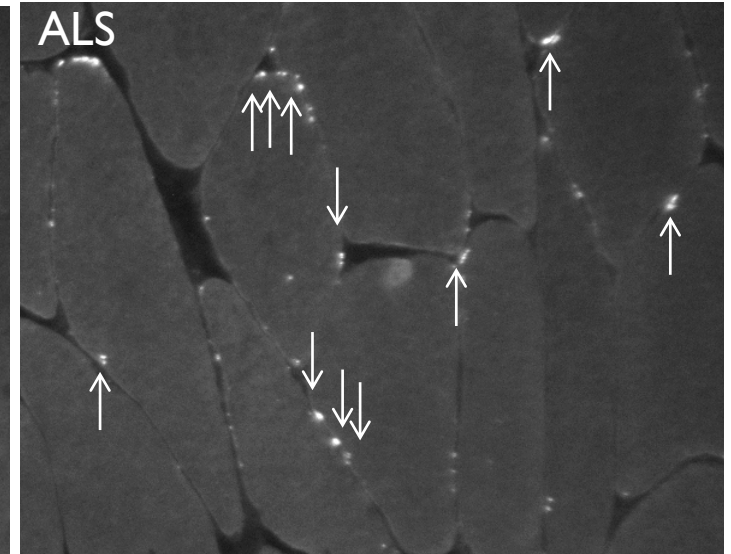
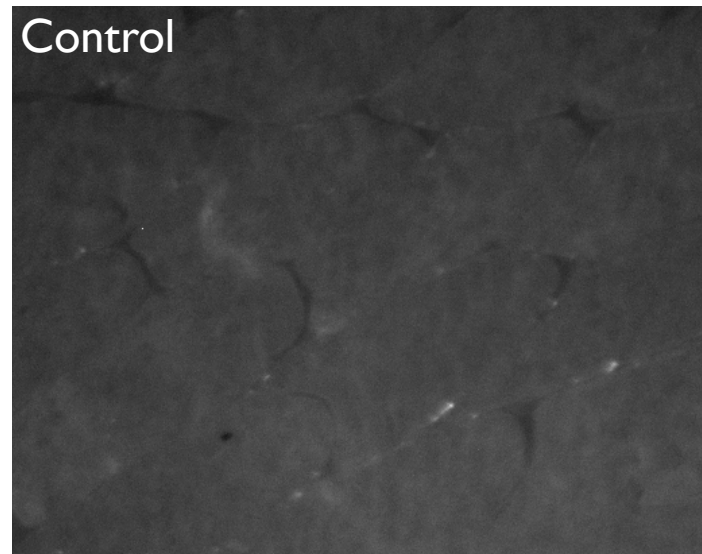
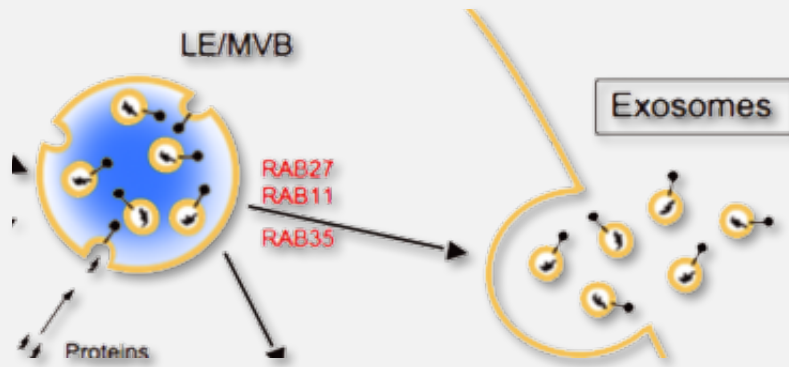
Endosome (4%, **)

Lysosome (4%, *)

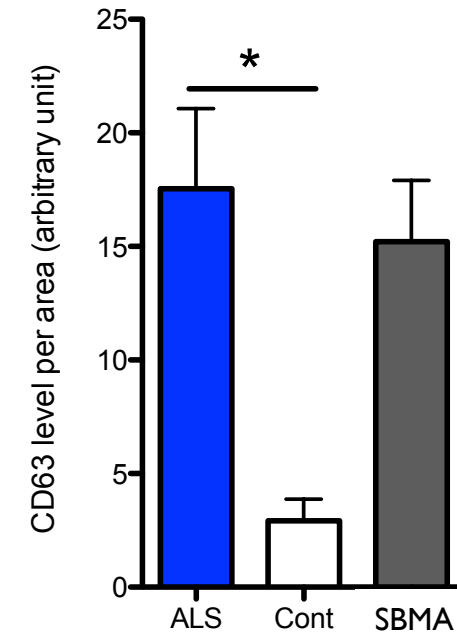
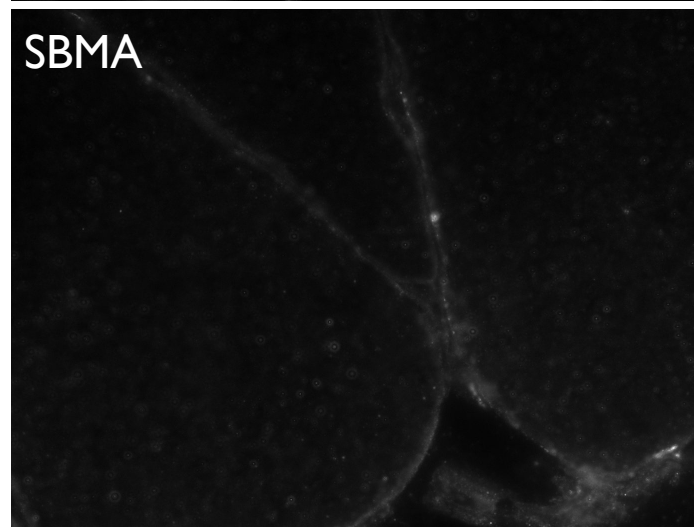
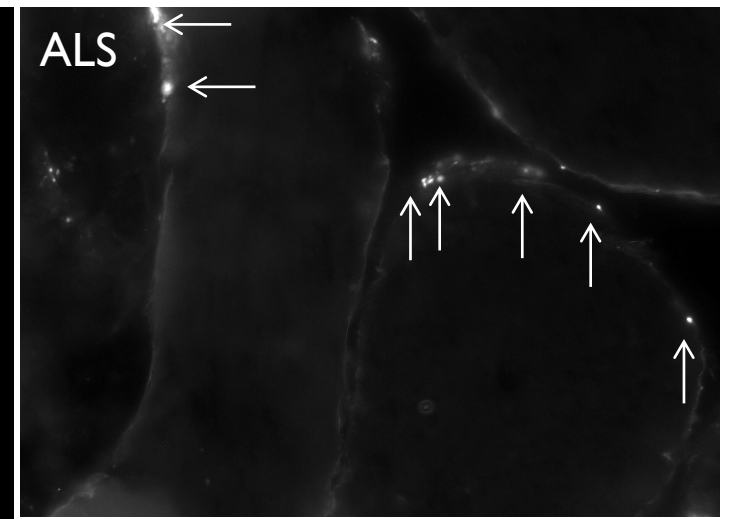
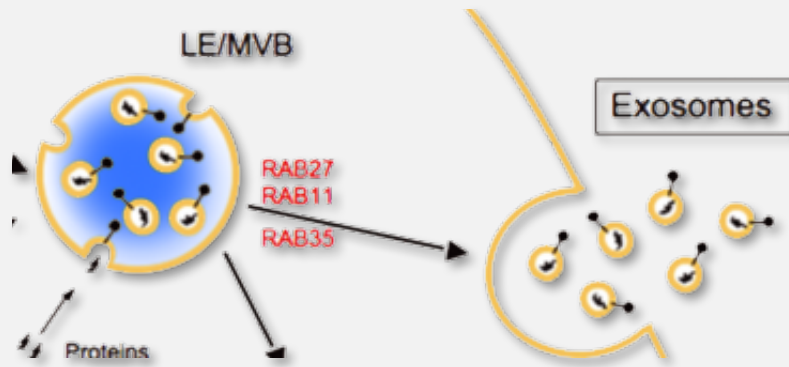




SUB-SARCOLEMNAL ACCUMULATION OF MVBs IN ALS MUSCLES



SUB-SARCOLEMNAL ACCUMULATION OF EXOSOMES IN ALS MUSCLES



ACCUMULATION OF MVBS FULL OF EXOSOME-LIKE VESICLE IN ALS MUSCLE BIOPSIES

4.7x more frequent in ALS than in healthy muscles (n=3 /group)

sarcomere

Extracellular matrix

Multivesicular Bodies

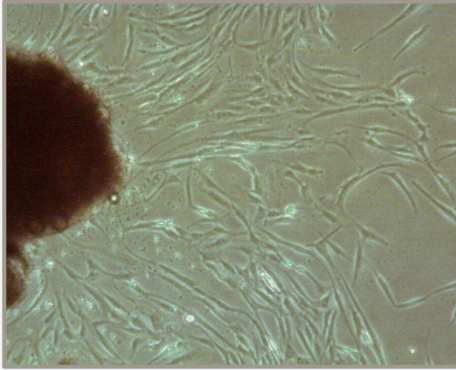
Secreted exosomes

Plasma Membrane:
Sarcolemme

200nm

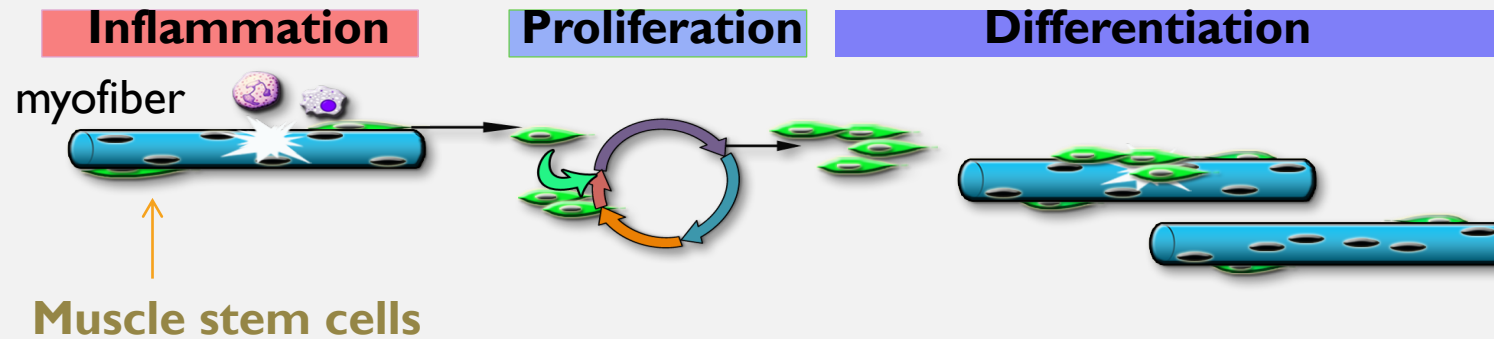
	I MVB / nb of sarcomeres
ALS	I MVB / 69 Sarcomeres
Cont	I MVB / 323 Sarcomeres

ALS SIGNATURE IN MUSCLE STEM CELLS?



- Do muscle stem cells of all ALS patients have a shared signature?

=> if yes: independent to denervation



ALS n=18

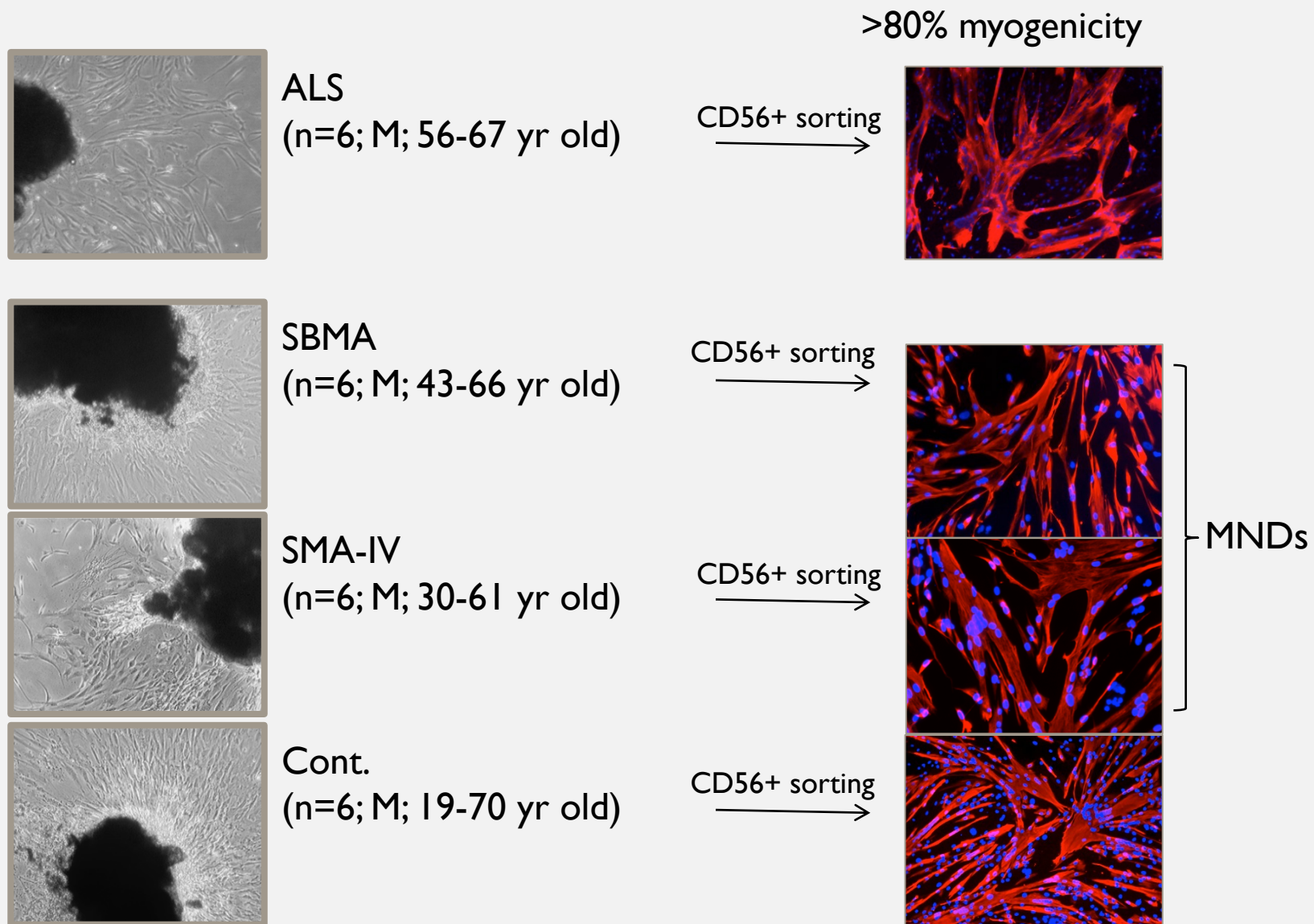
SBMA=12

SMA-III/IV

n=12

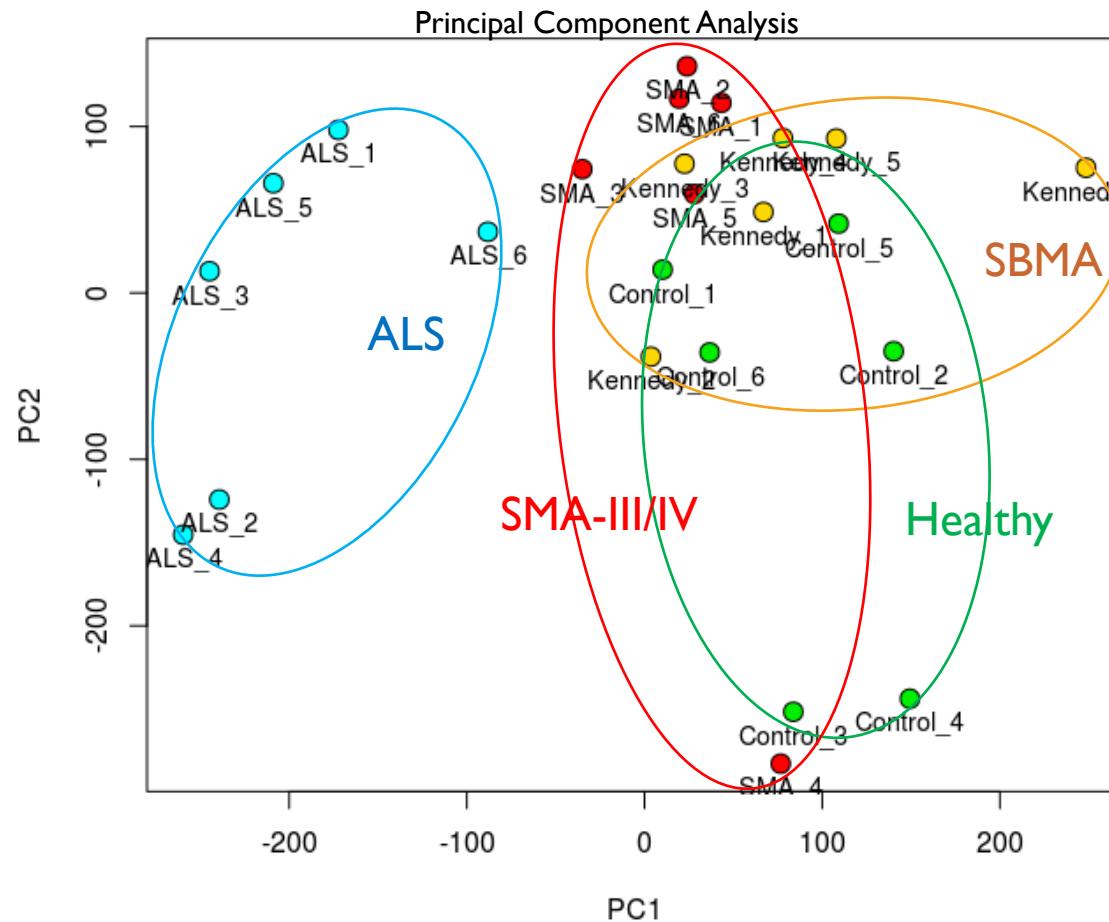
controls n=18

TRANSCRIPTOMIC ANALYSIS



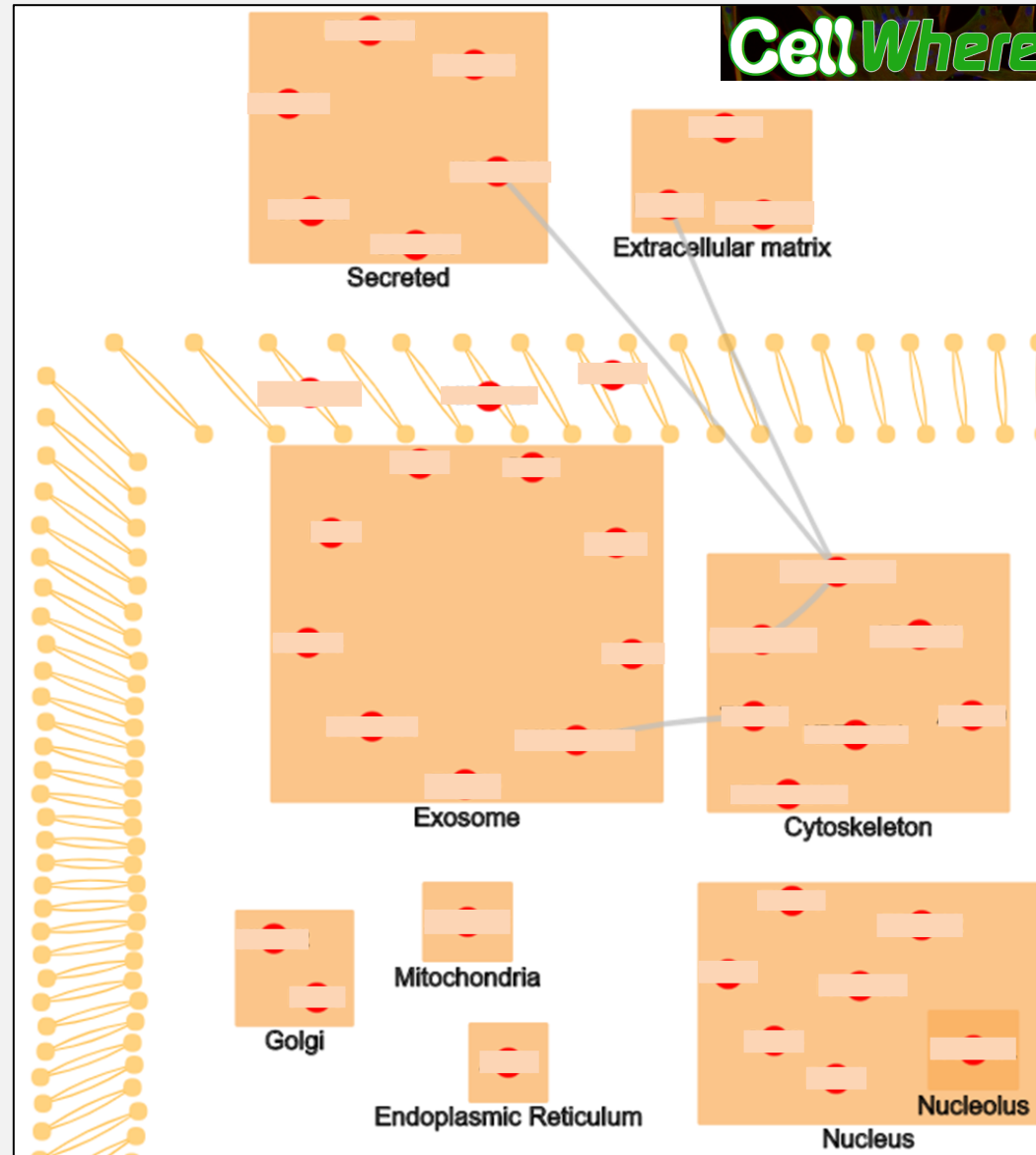
WE HAVE IDENTIFIED AN ALS SIGNATURE IN MUSCLE STEM CELLS

Transcriptome analysis of ALS, SMA, SBMA and Control Cells

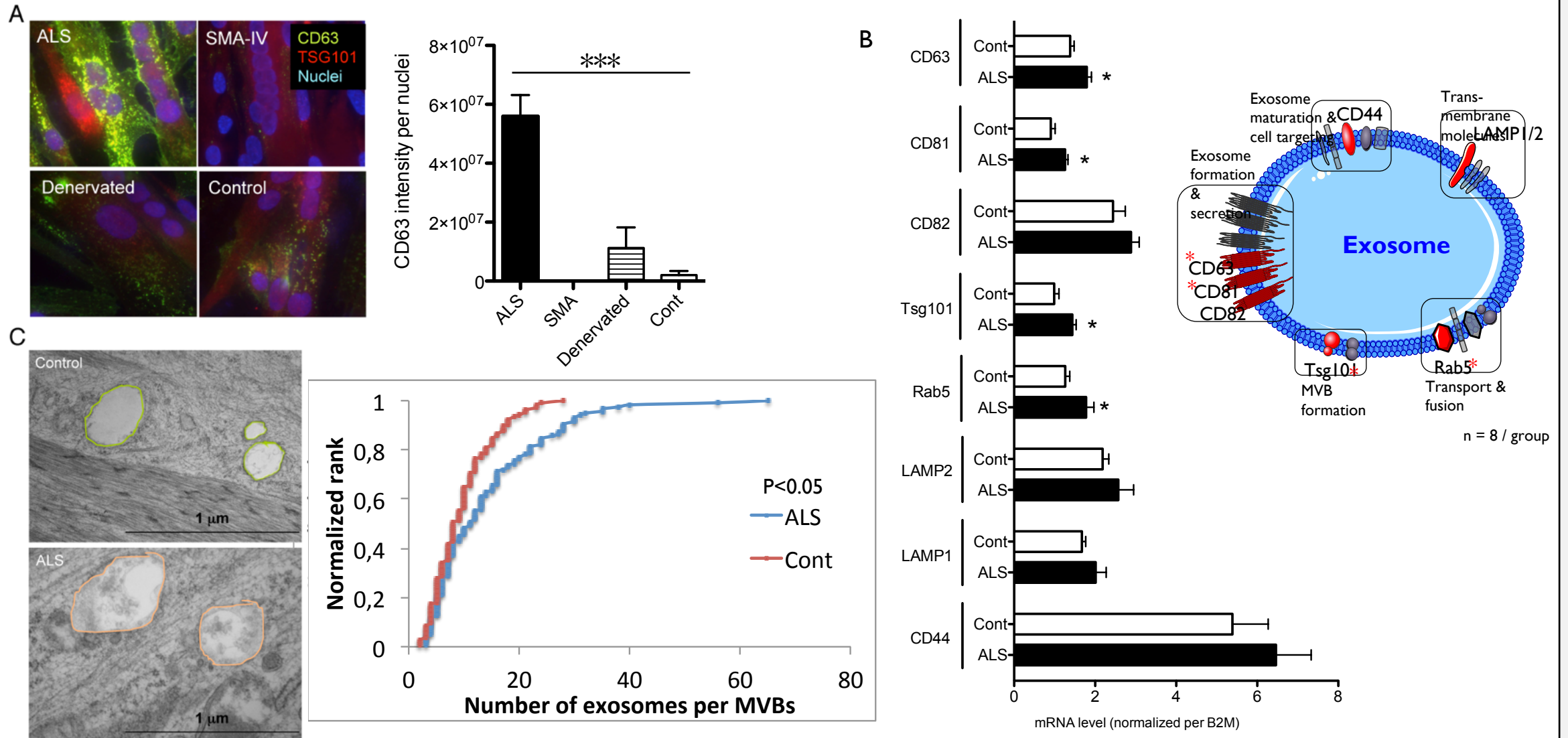


Collaboration:
JP Loeffler,
Jose Gonzalez de Aguilar

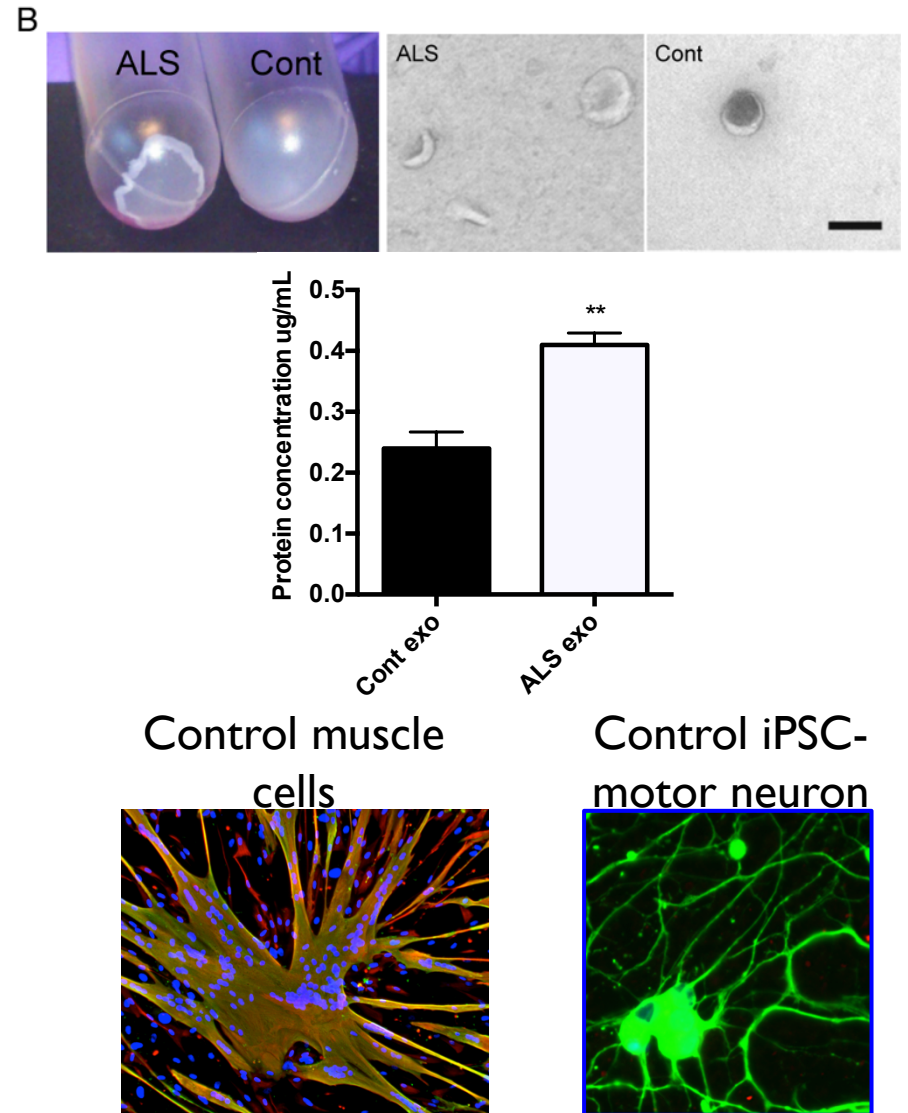
Secretome signature in ALS muscle stem cells



ACCUMULATION OF EXOSOMES IN MYOTUBES

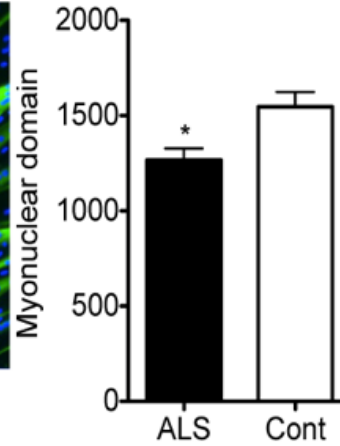
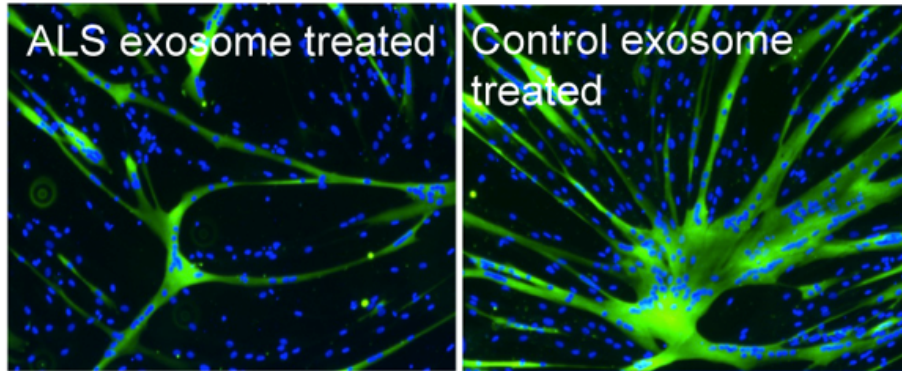


INCREASED EXOSOME SECRETION

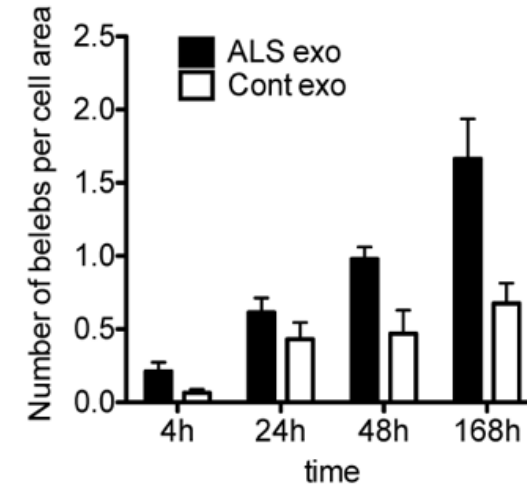


ALS EXOSOMES ARE TOXIC

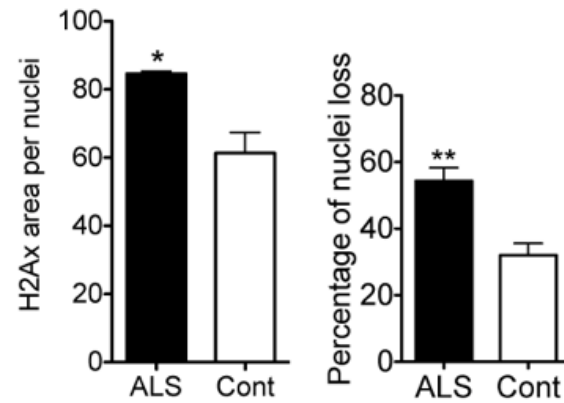
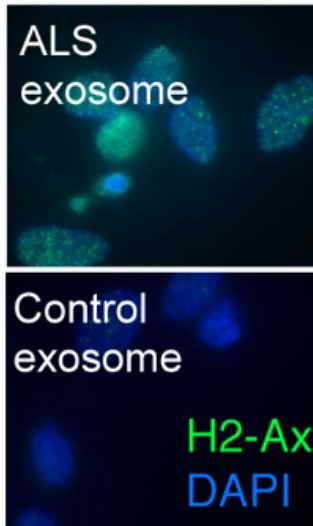
A



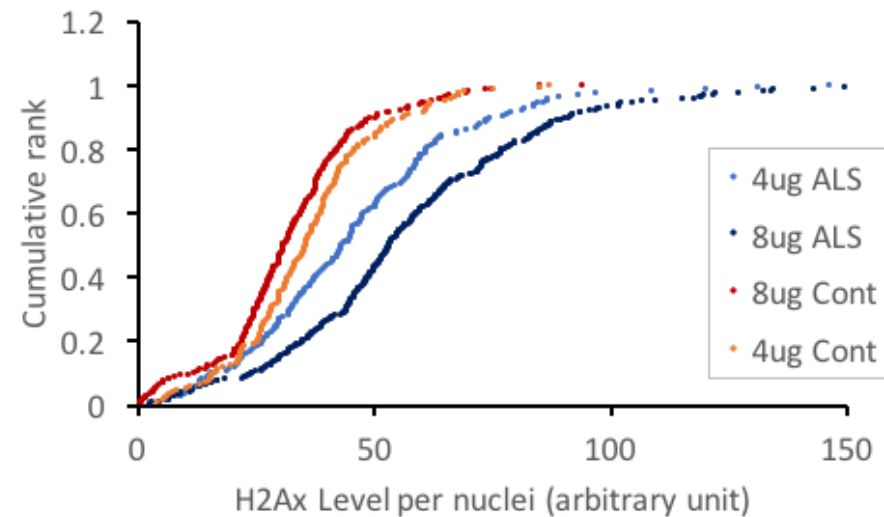
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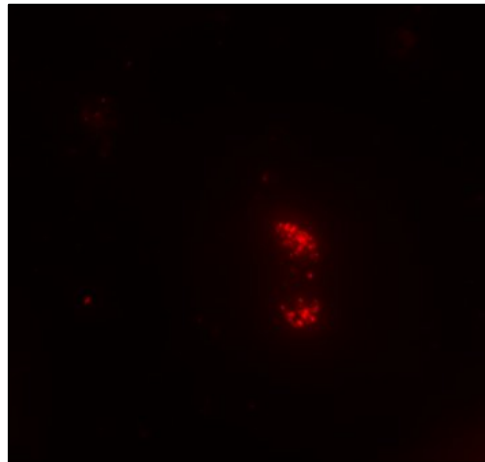
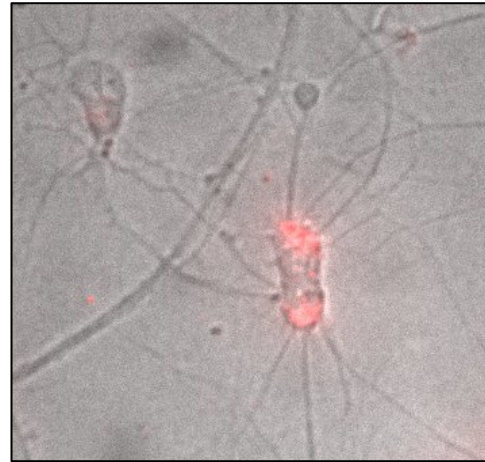
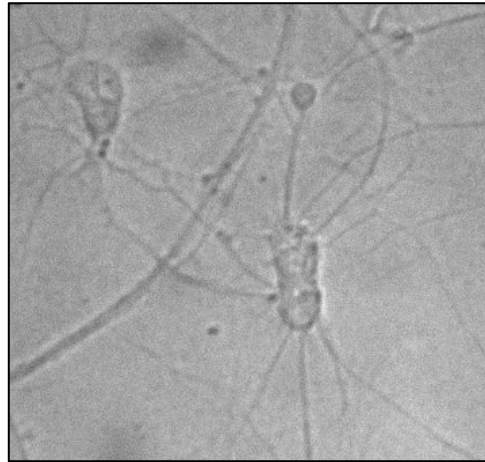
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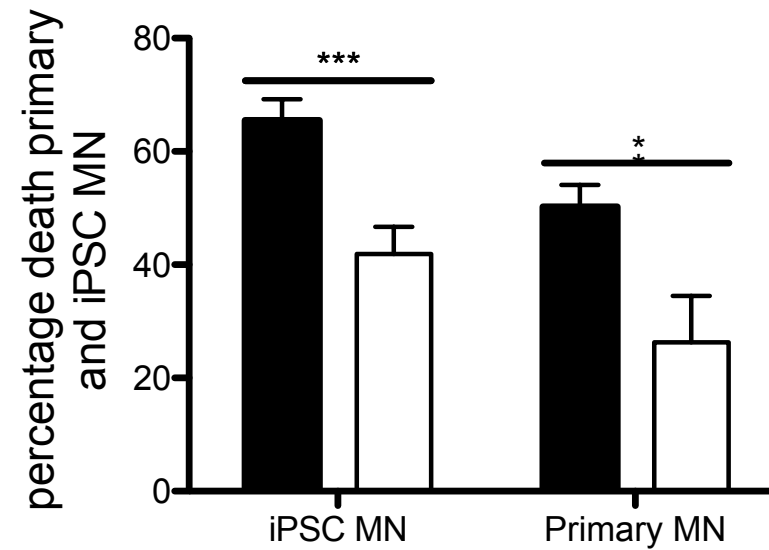
D



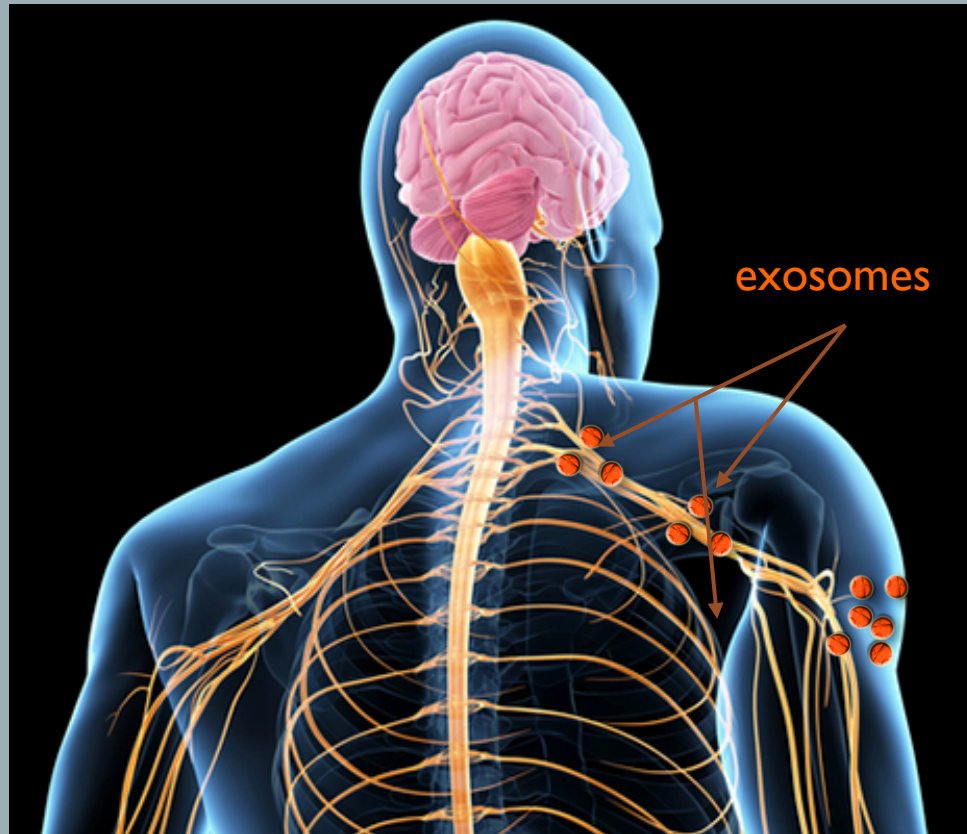
ALS EXOSOMES ARE TOXIC



■ ALS exosomes
□ Cont exosomes



Take home message

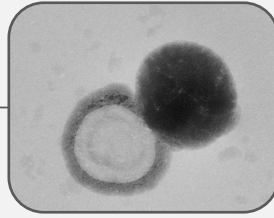


ALS signature in muscle stem cells

Target the ALS exosome for
therapeutic strategy

ALS exosomes can explain how the
disease spreads

ALS exosomes
are toxic



WP1:

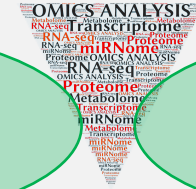
Characterization of the exosome
effect on Motor neurons

WP2:

Exploration of the exosomes content

Identification of
secreted toxic
candidates

Identification of
potential
biomarkers



WP3:

Regulation of toxic
elements secreted

WP4:

Validation of circulating
biomarkers

ViTAL Consortium

UK

Neuromuscular and Musculoskeletal health



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Vanessa Milla
Owen Connolly
William Duddy

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Stratified Medicine

Research | Education | Innovation

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