A Human Neuromuscular Platform for Amyotrophic Lateral Sclerosis (ALS) Modelling and Drug Testing

Afonso Malheiro[12], David Barata[1], Katharina Henning[1], Inês Martins[1], William Roman[1], Edgar Gomes[1]

1 Gulbenkian Institute for Molecular Medicine, Avenida Professor Egas Moniz, 1649-028, Lisbon, Portugal
2 Colab Accelbio, Biocant Park, 3060-197, Cantanhede, Portugal

The ALS Problem

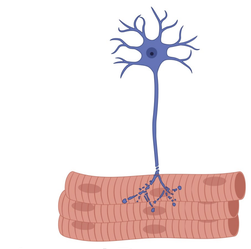
50,000
New Diagnoses Annually

2-5 years
Average Survival Time

90%
Of Cases Are Sporadic (no animal models)

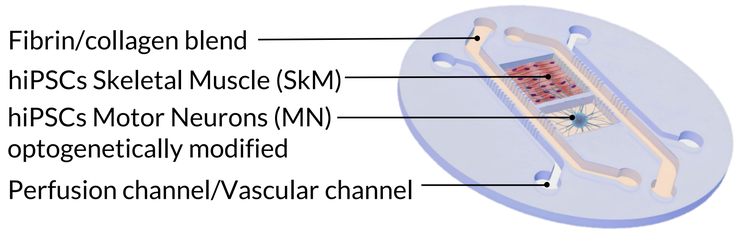
Only 3
Drugs Available

Lack of Relevant Human Models

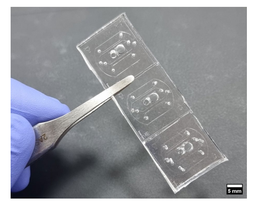


Axonal Degeneration
↓
Muscle Denervation
↓
Muscle Atrophy
↓
Paralysis

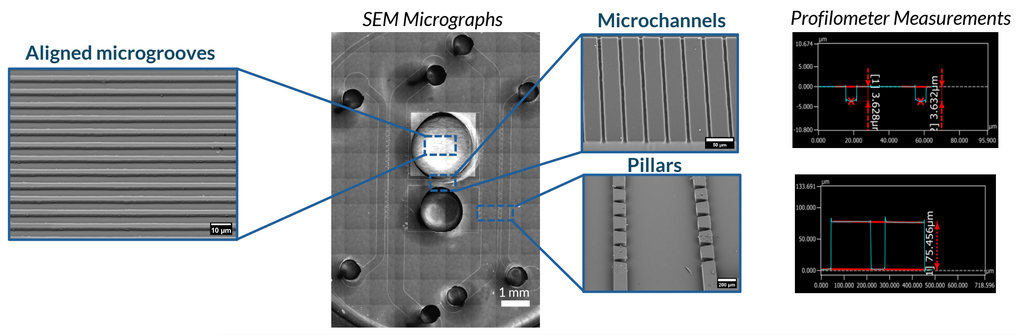
Human Neuromuscular Platform



PDMS Casing (Glass Bottom)

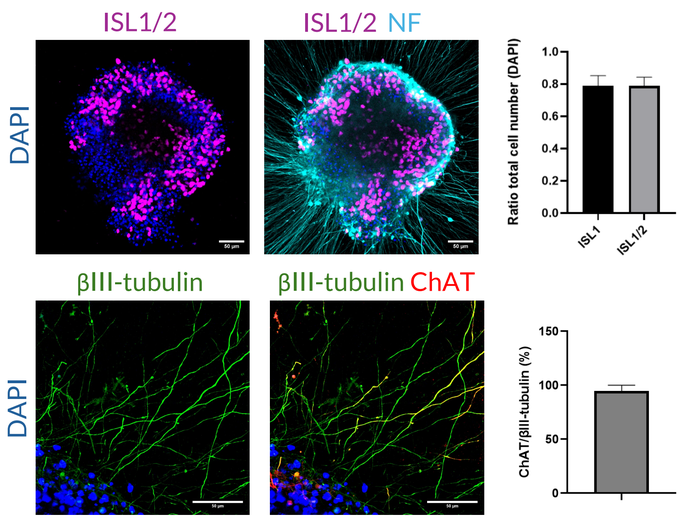


International Patent Application: PCT/IB2025/053988



Healthy MNs

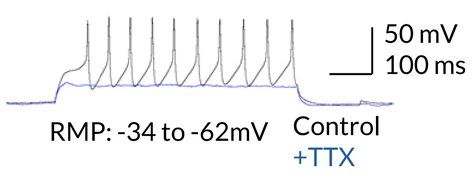
MN Identity



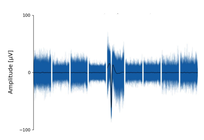
Dif Protocol: Maury et al, Nat Bio, 2014

Electrophysiology

Patch Clamping Measurements (current mode)



High Density Microelectrode Array Measurement

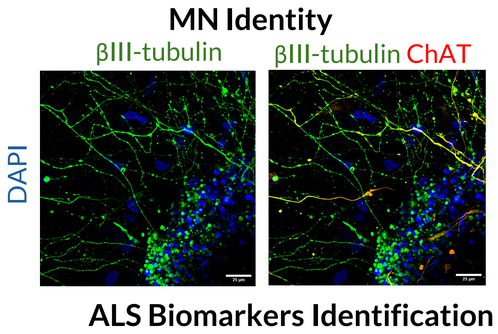


Parameter	Value
Firing Rate (Hz)	0.64 ± 0.55
Spike Amplitude (μV)	39.01 ± 14.17
Interspike Interval (ms)	115.6 ± 32.51

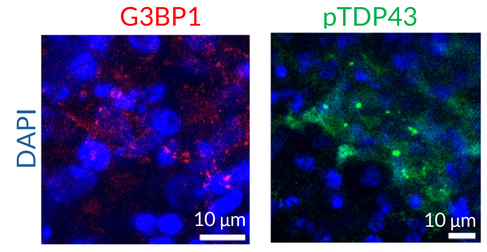
High yield of mature and functional cholinergic neurons

Sporadic ALS (sALS) MNs

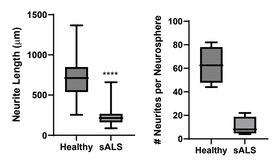
MN Identity



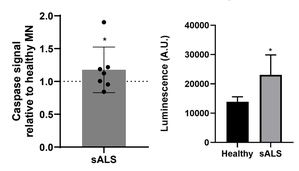
ALS Biomarkers Identification



ALS Phenotype



Cell Viability



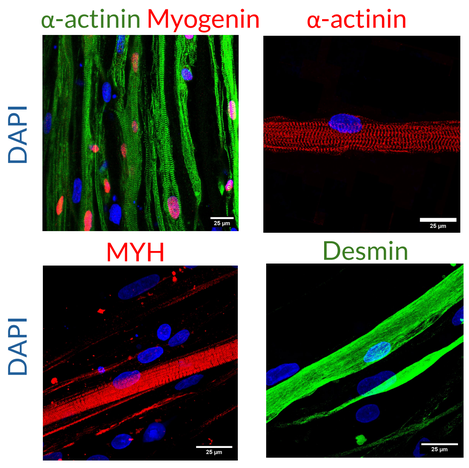
Electrophysiology

Parameter	Value
Firing Rate (Hz)	0.19 ± 0.15
Spike Amplitude (μV)	13.98 ± 2.83
Interspike Interval (ms)	42.4 ± 30.57

Sporadic ALS neurons exhibit mature MN characteristics but also an ALS phenotype

Human Neuromuscular Junction (NMJ) Model

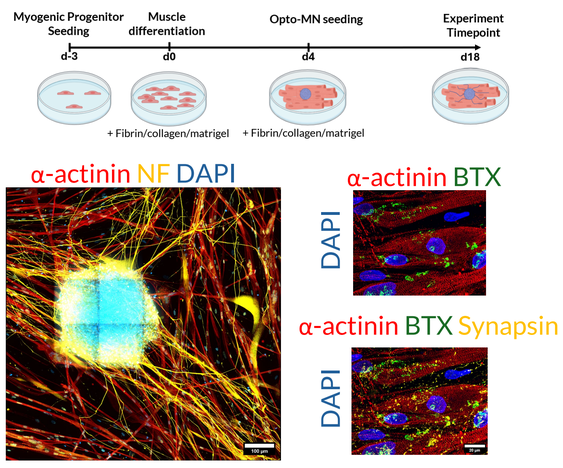
SkM Fiber Formation



Striated SkM Fiber generation

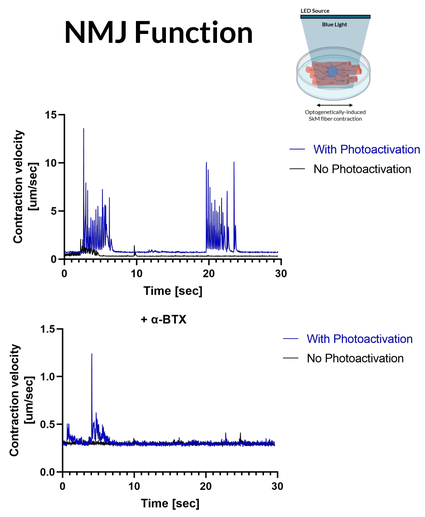
Dif Protocol: Van der Wal et al, Stem Cell Rep, 2018

NMJ Model Assembly



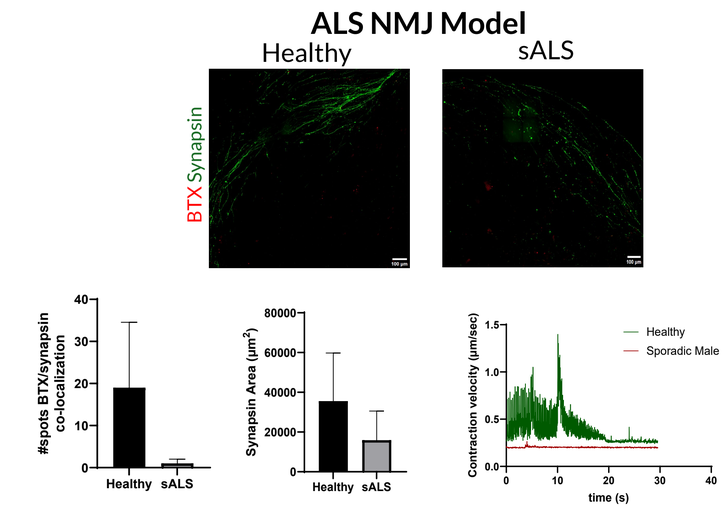
NMJ formation in co-cultures

NMJ Function



NMJ Activation Light-based Control

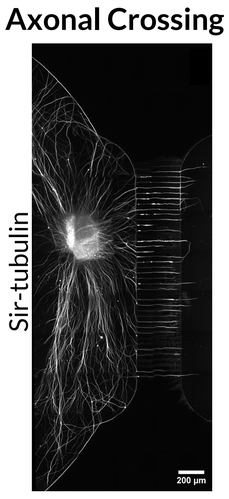
ALS NMJ Model



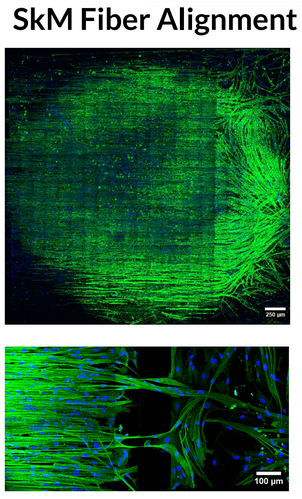
Impaired NMJ Formation and Activity in sALS co-cultures

Human NMJ Platform

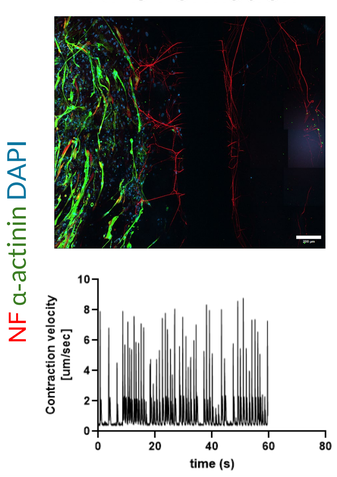
Axonal Crossing



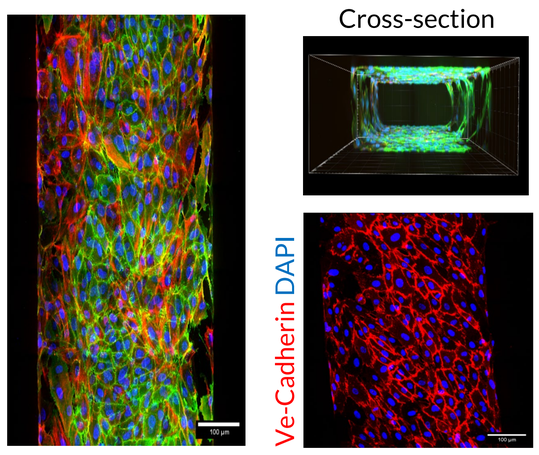
SkM Fiber Alignment



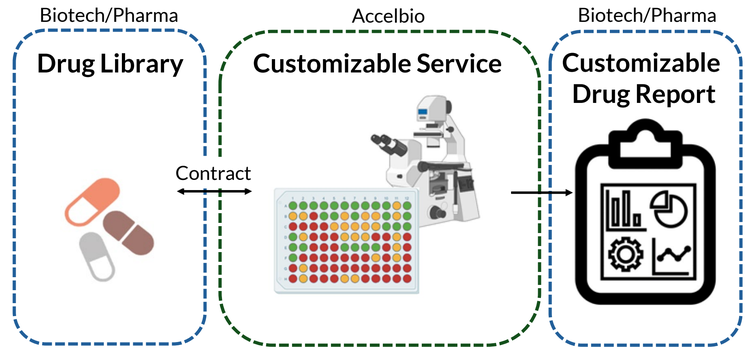
NMJ Formation



Vascularization



Future Direction



Improving Drug Development Efficiency for ALS

Contact: afonsomalheiro@accelbio.pt

SCAN ME

European Innovation Council

This research was supported by the European Innovation Council (ID: 801423) and the Fundació La Caixa (ID: LCF/BQ/PR25/12110007)