axoltis pharma

# A multi-properties peptide (NX210c) for the treatment of ALS

October 7th, 2022

ALS ONE

# The Company in a Nutshell

axoltis pharma a French biopharmaceutical company

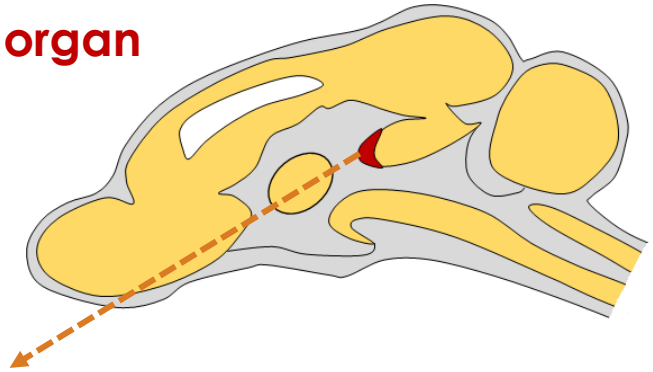
dedicated to develop **drugs for neurological pathologies**

**First-in-class peptide (NX210c)** for indications with **high unmet medical needs**

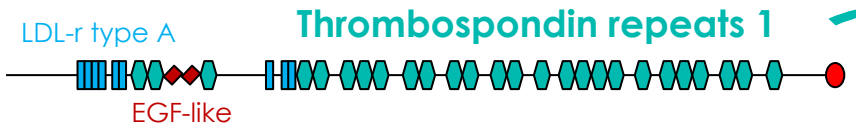
- **Preclinical POC** for: - **motor injuries/diseases** (including SCI & ALS)
  - **cognitive disorders** (including AD)
- First-in-Human **phase I** in 2020 showed a **good safety profile** (Bourdès *et al.*, 2022)
- **Phase Ib** multiple ascending dose in H1 2023

# NX210c Origins

**Subcommissural organ (SCO)**



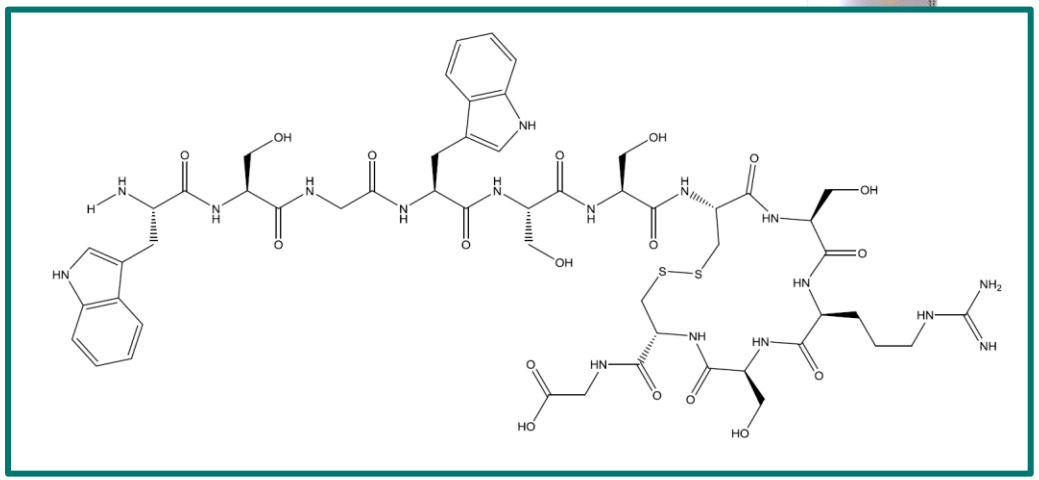
**SCO-spondin: a multifunctional glycoprotein with several conserved domains**




- Regulator of **CSF activity**
- **Neurogenesis** & **Axonal guidance**
  (Sepulveda *et al.*, 2021)

- Synthesis of **oligopeptides** derived from TSR and LDLr domains of the SCO-spondin
- A **12 aa-peptide** derived from TSR1 markedly increased **cell adhesion** and **neurite growth** of **cortical & spinal cord neurons**
  (Monnerie *et al.*, 1998)

## NX210c peptide

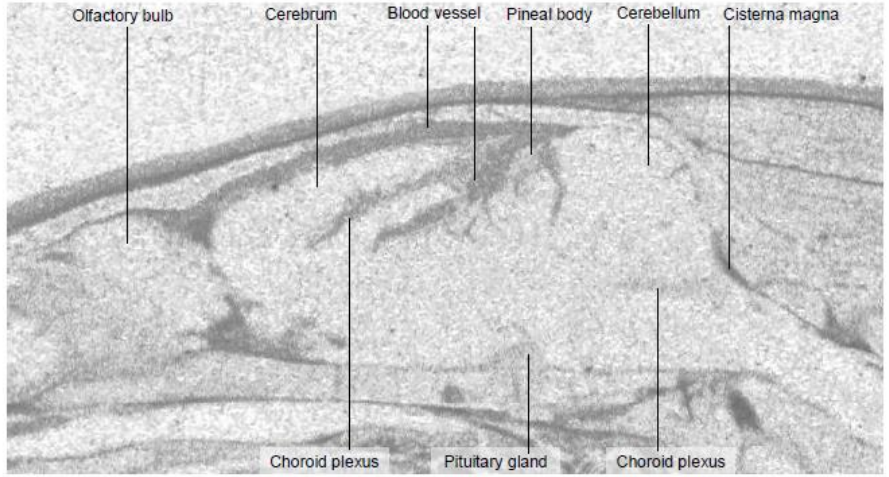



# CNS Biodistribution of NX210c in Rats

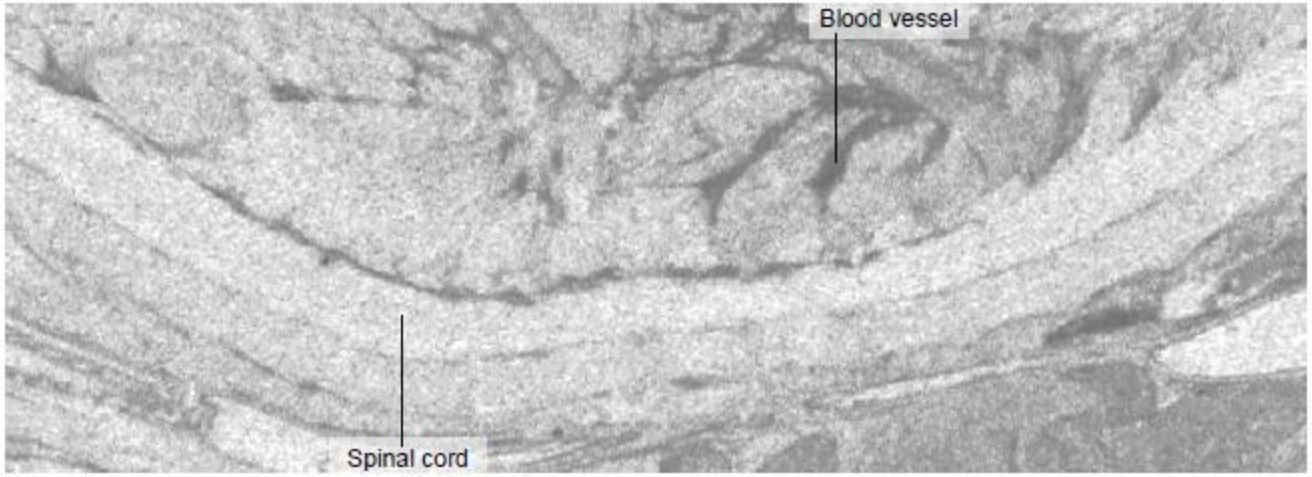
Concentration of radioactivity in the CNS following a single intravenous injection of [$^3$H]NX210c to rats at 10 mg/kg

| | | | Tissue: blood ratio | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Animal no: | 01M | 02M | 03M | 04M | 05M | 06M | 07M | 08M | 09M |
| Tissue type | Tissue | Time-point: | 0.25 h | 0.5 h | 2 h | 5 h | 8 h | 24 h | 48 h | 72 h | 96 h |
| CNS | Brain | | 0.09 | 0.35 | NC | NC | NC | NC | NC | NC | NC |
| | Choroid plexus | | 0.27 | 0.55 | NC | NC | NC | NC | NC | NC | NC |
| | CSF | | 2.47 | 1.65 | NC | NC | NC | NC | NC | NC | NC |
| | Spinal cord | | 0.09 | 0.33 | NC | NC | NC | NC | NC | NC | NC |

## Brain

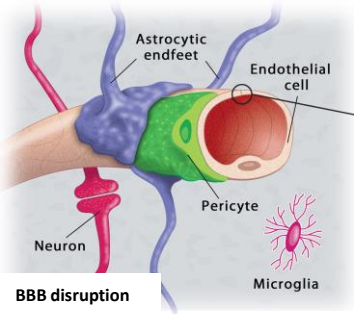



## Spinal cord



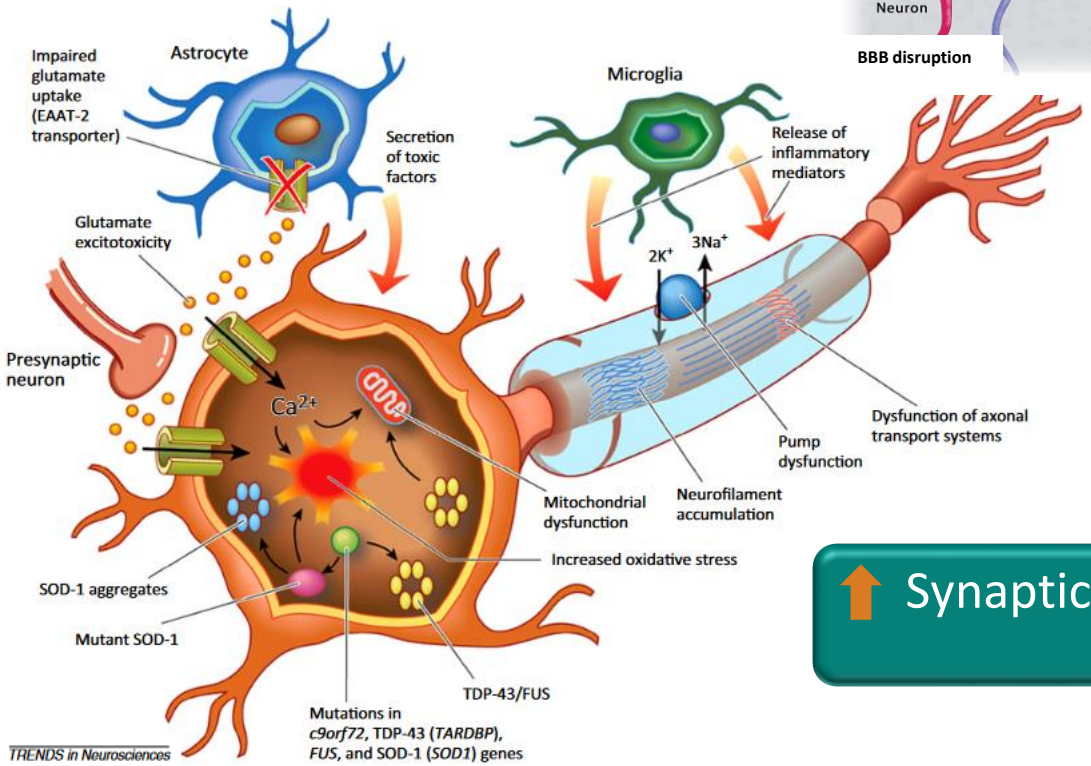
# Rational to Use NX210c for the Treatment of ALS

Blood-CNS barrier integrity
(1)



BBB disruption

Neuroprotection against:
- excitotoxicity (2)
- oxidative stress (3)




Synaptic transmission
(4-5)

**Supported by the following articles/studies:**

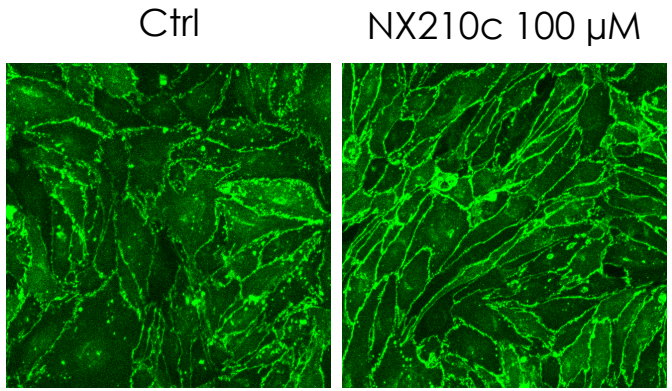
(1) TCD-21-001, BBB_001_2020
(2) Delétage *et al.*, Neuroscience, 2021
(3) Sakka *et al.*, PLoS One, 2014
(4) Lemarchant *et al.*, Int J Mol Sci, 2022
(5) EPS-21-003, EPS-21-004

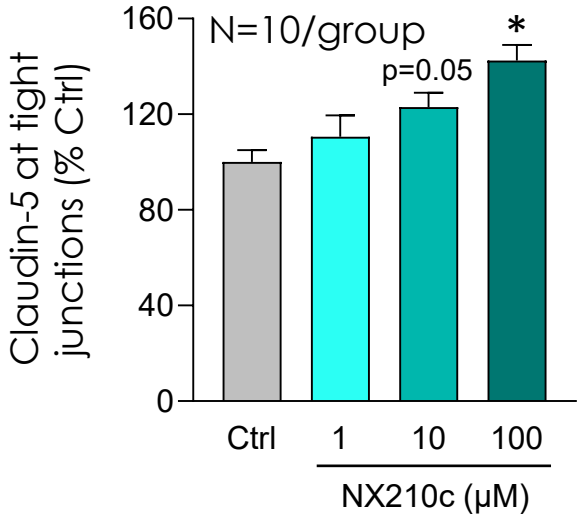
# A Multi-Properties Peptide: Blood-CNS Barriers Integrity

Endothelial cultures

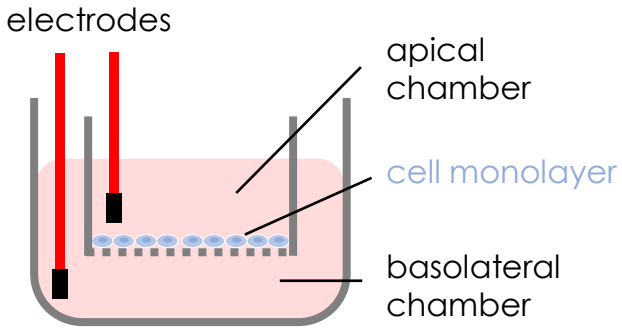
*** p<0.001, * p<0.05 vs Ctrl

## 24-h treatment

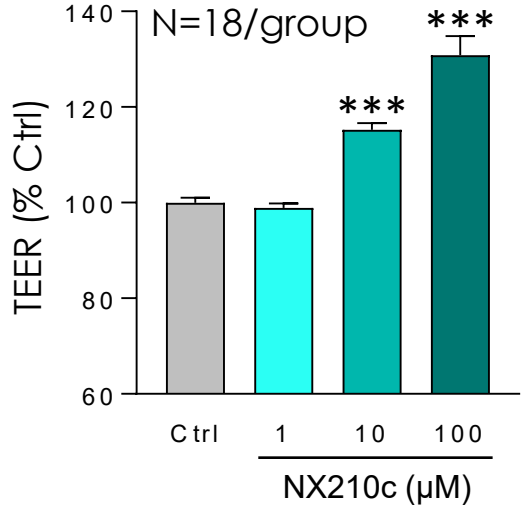


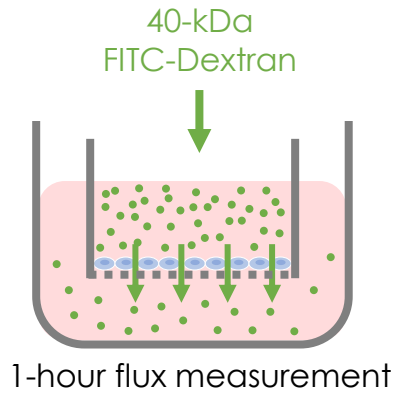

## Transendothelial electrical resistance

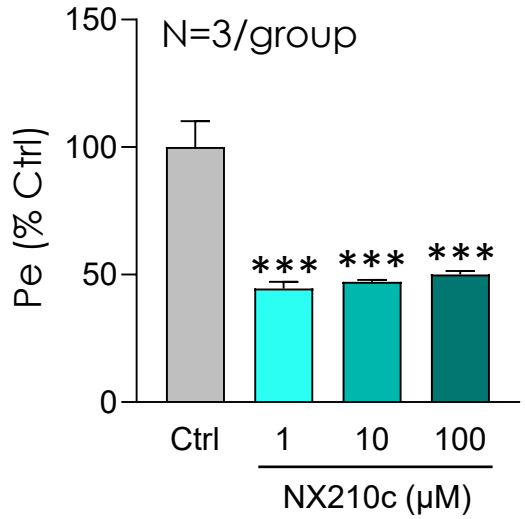



## 72-h treatment




## Permeability



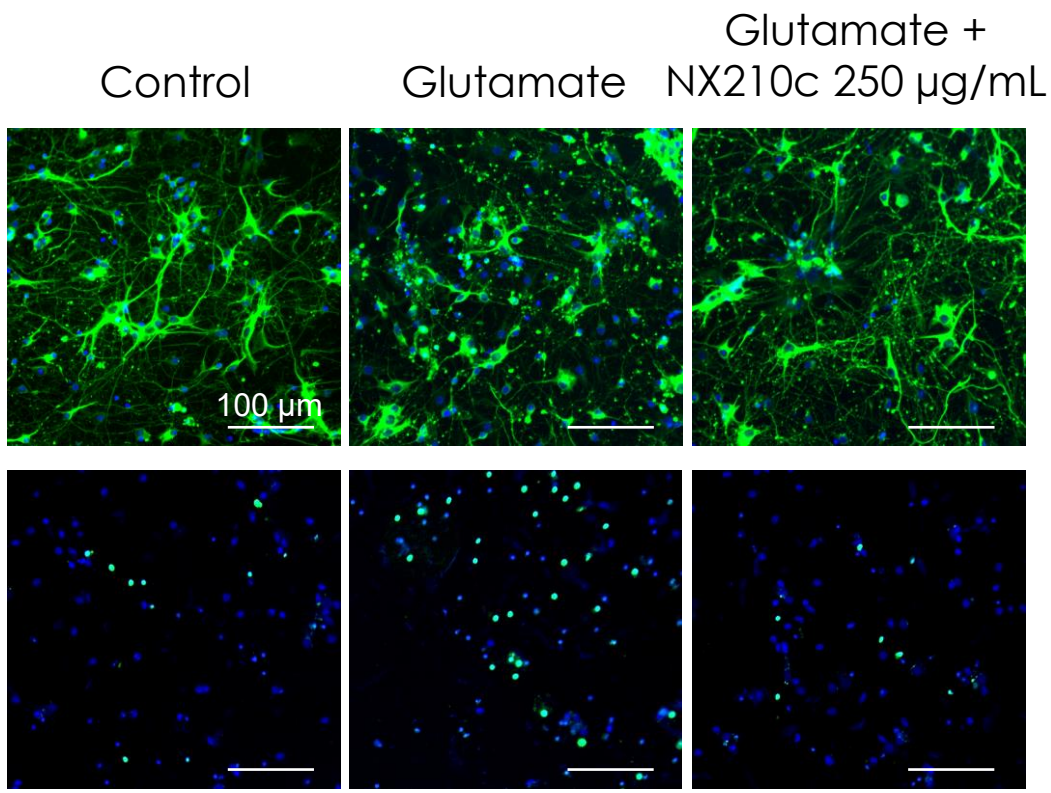




Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

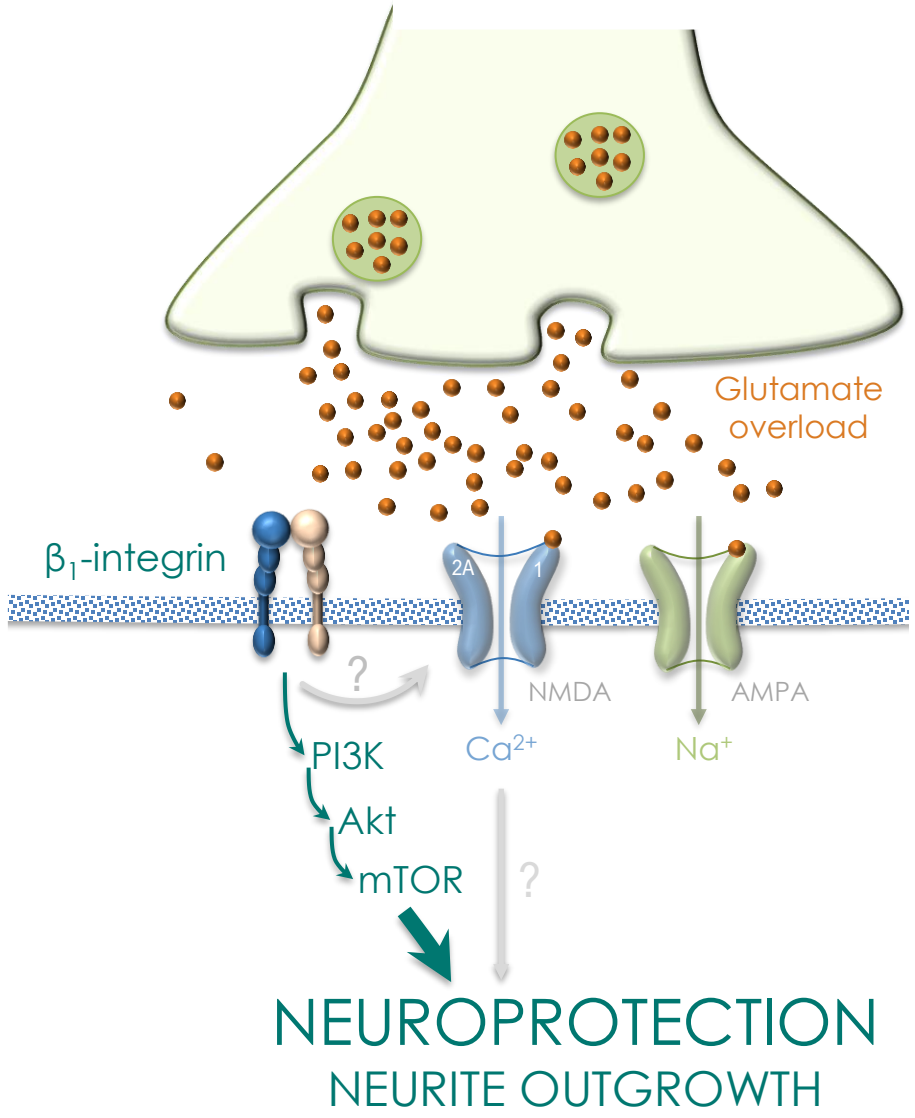
# A Multi-Properties Peptide: Neuroprotection

Neuronal cultures

**Human cortical neurons**



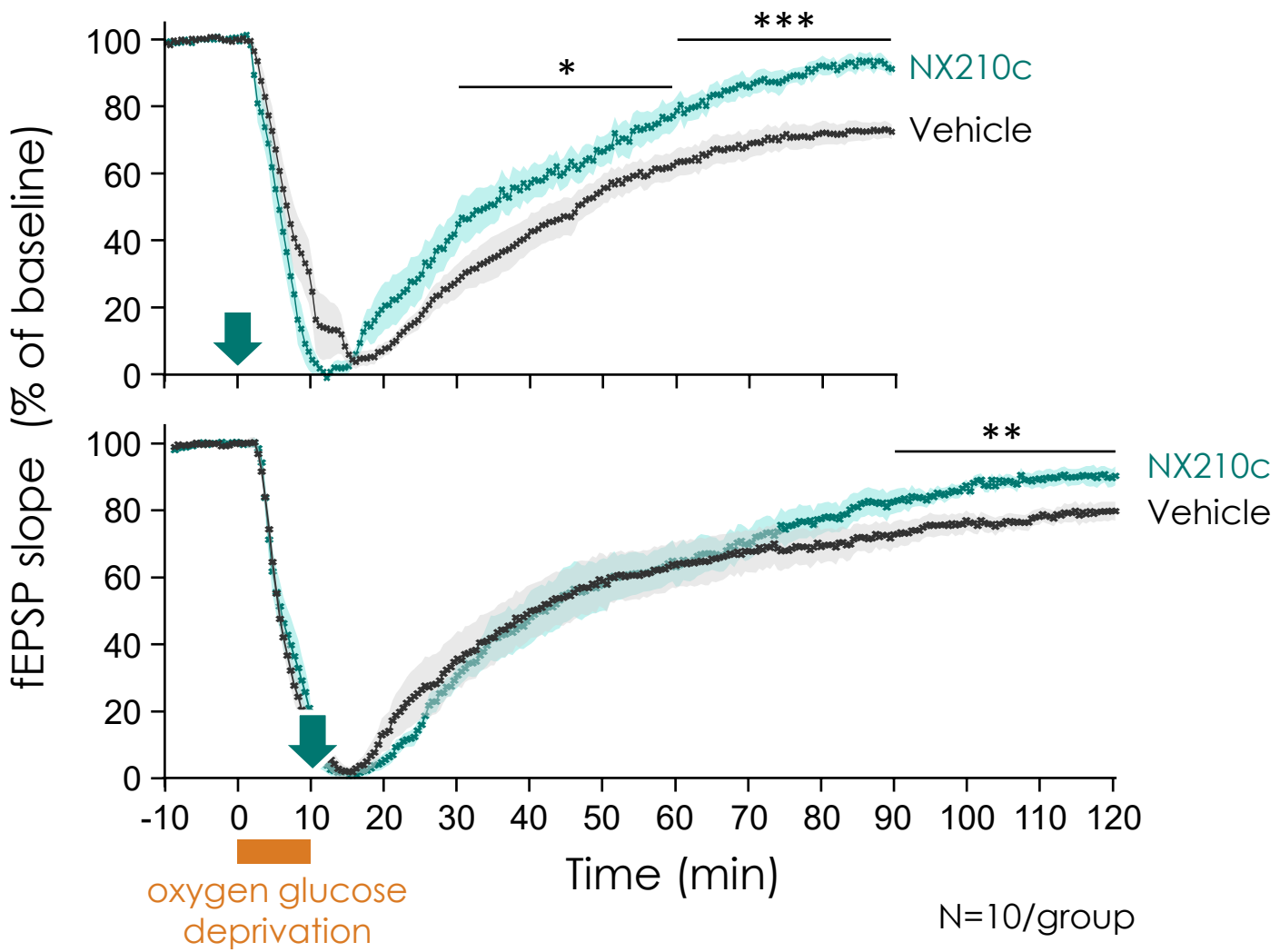

Delétage *et al.*, Neuroscience, 2021



# A Multi-Properties Peptide: Synaptic Transmission

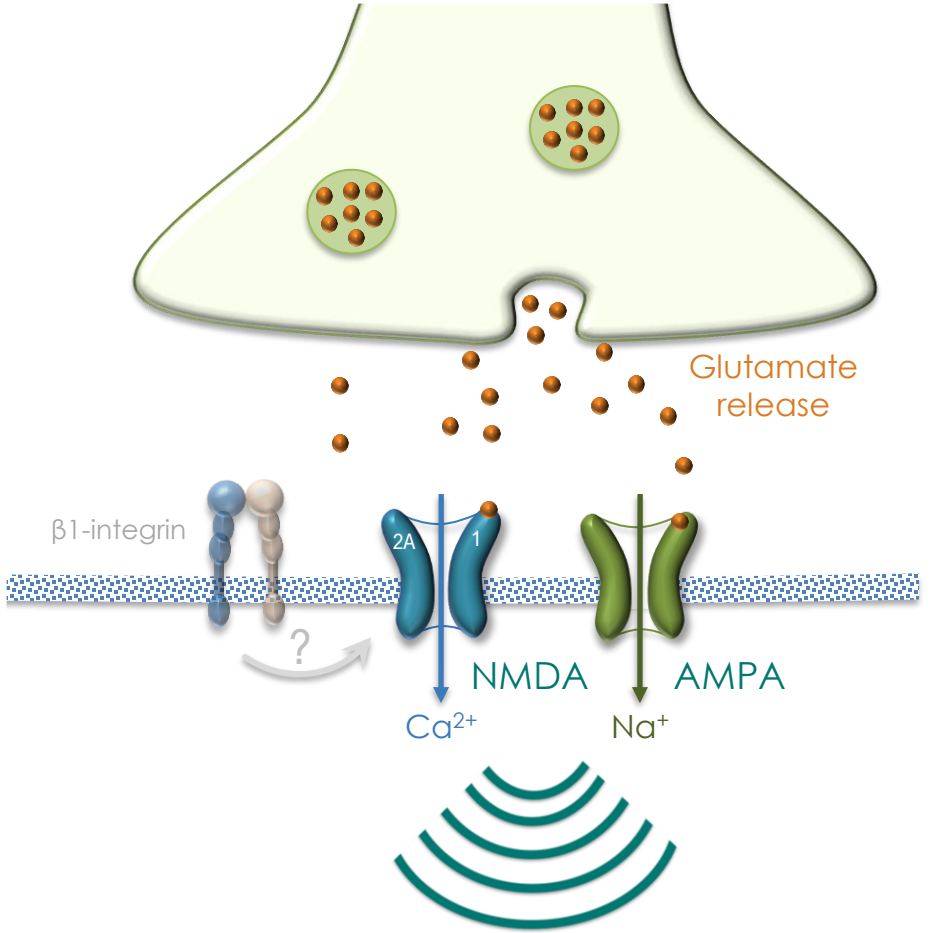
Mouse brain slices

*** p<0.001, ** p<0.01, * p<0.05 vs Vehicle




N=10/group

Lemarchant *et al.*, Int J Mol Sci, 2022

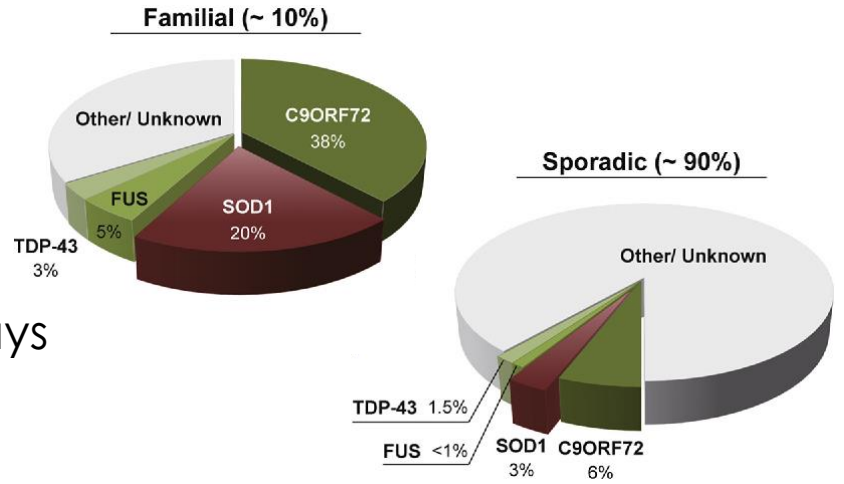


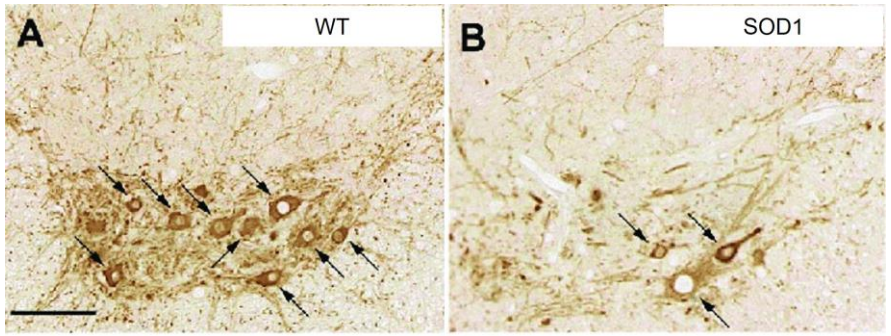

SYNAPTIC TRANSMISSION ENHANCER

# SOD1$^{G93A}$ Mouse Model of ALS

## SOD1$^{G93A}$ mouse model = most widely used ALS model

- SOD mutation accounts for 20% of familial cases
- Familial & sporadic forms of ALS are clinically indistinguishable and share many pathogenic pathways



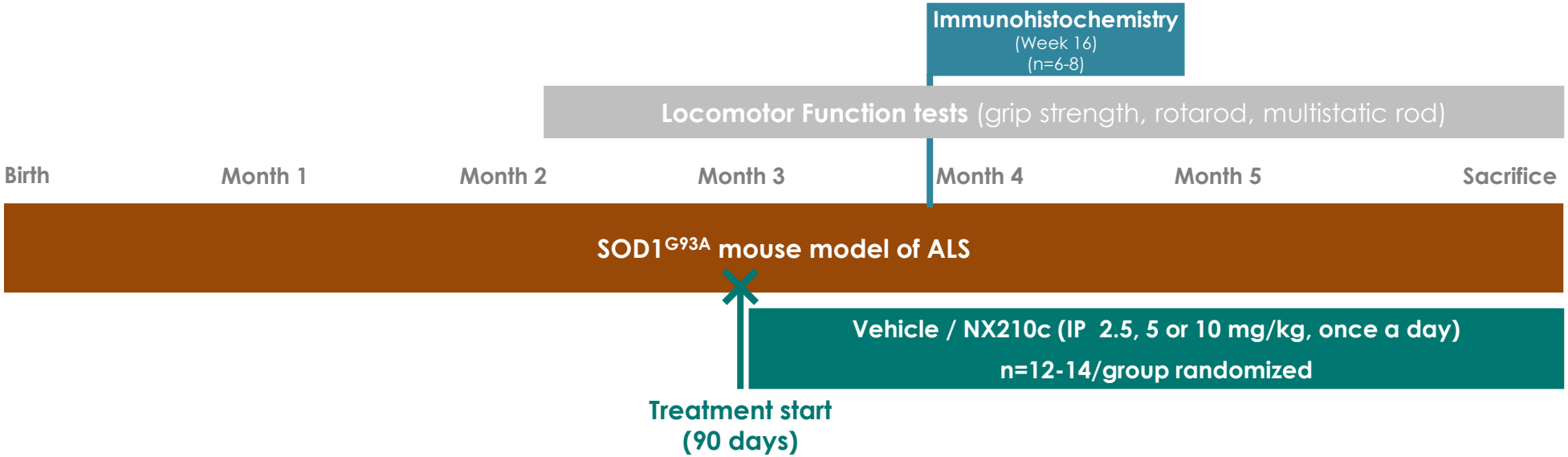





- Rapid **motoneuron degeneration** leading to **muscle paralysis** and **death** within 5 months of life
  - Phenotype similar to that of patients with ALS

- Model used in the development of **FDA-approved ALS therapeutics** (Riluzole and Edavarone)

# ALS Proof of Concept: Experimental design



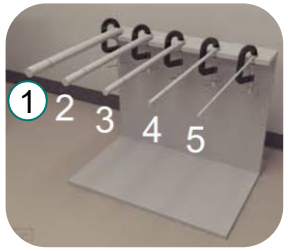

**Readouts:**

- **Clinical score** (two times a week)
- **Body weight** *(two times a week)*
- **Locomotor function assessments:**
  - Rotarod *(weekly)*
  - Multiple static rods *(every other week)*
  - Grip strength *(weekly)*
- **Spinal cord sampling:**
  - Immunohistochemistry *(Week 16)*

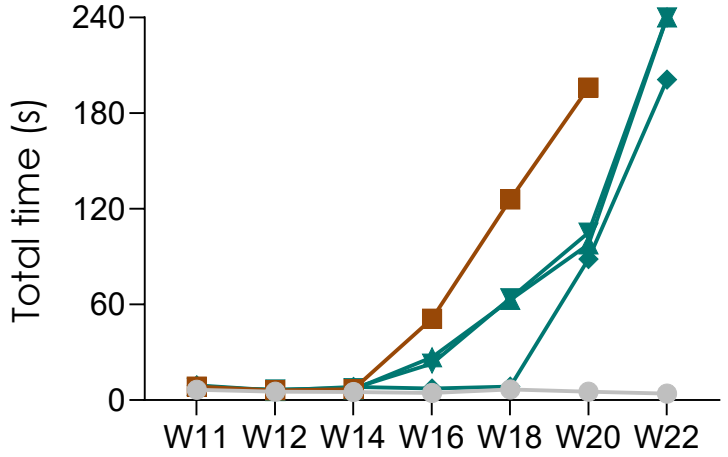
*Operators were blind to the treatment groups*

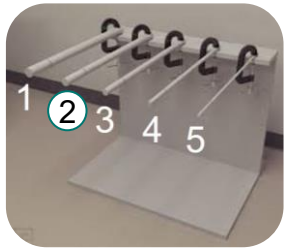
# NX210c Improves Trunk Stability of SOD1$^{G93A}$ Mice

Multistatic rod

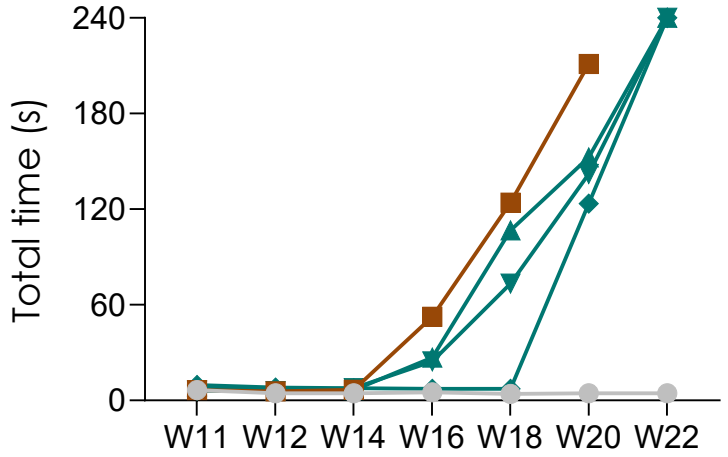



Rod 1 (easiest)



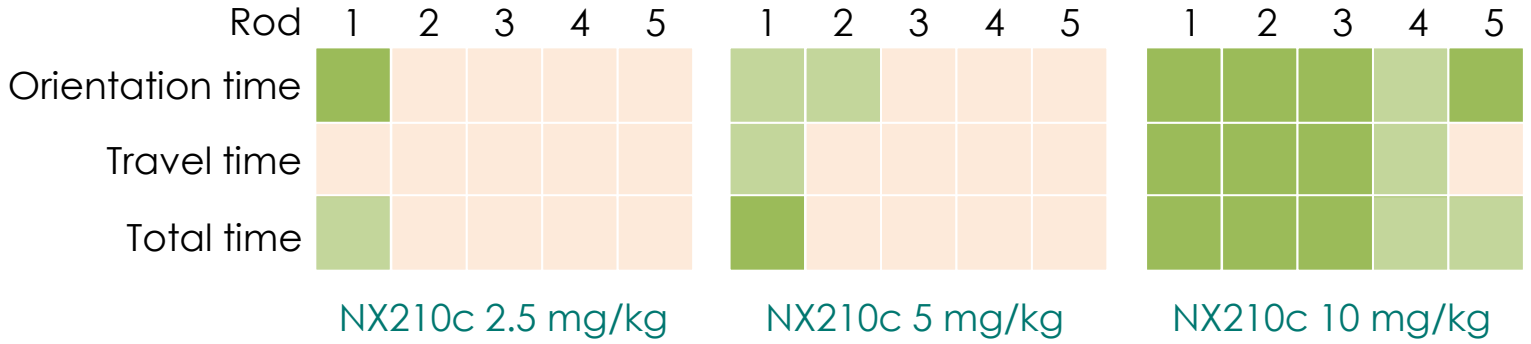




Rod 2




- WT Vehicle (n=23)
- SOD Vehicle (n=22)
- SOD NX210c 2.5 mg/kg (n=21)
- SOD NX210c 5 mg/kg (n=23)
- SOD NX210c 10 mg/kg (n=20)

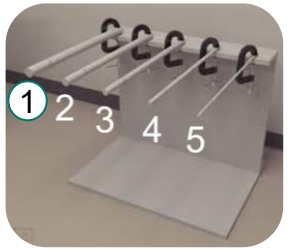
Statistical summary compared with SOD Vehicle:

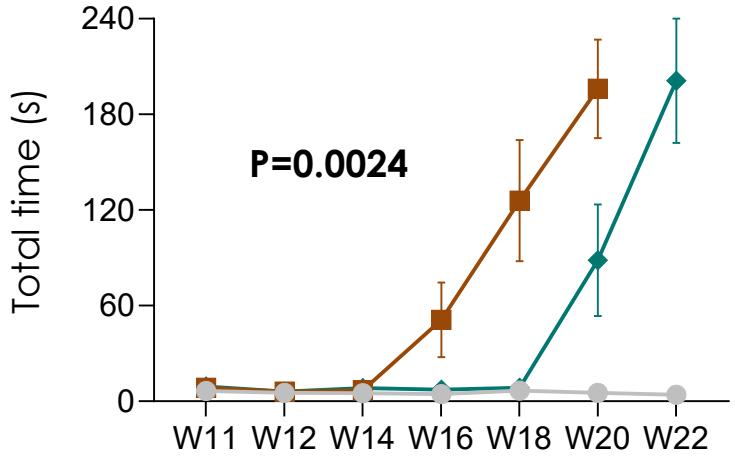


# NX210c Improves Trunk Stability of SOD1$^{G93A}$ Mice

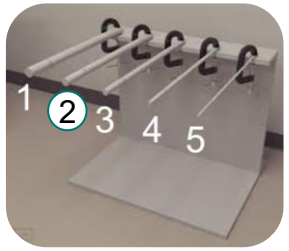
Multistatic rod

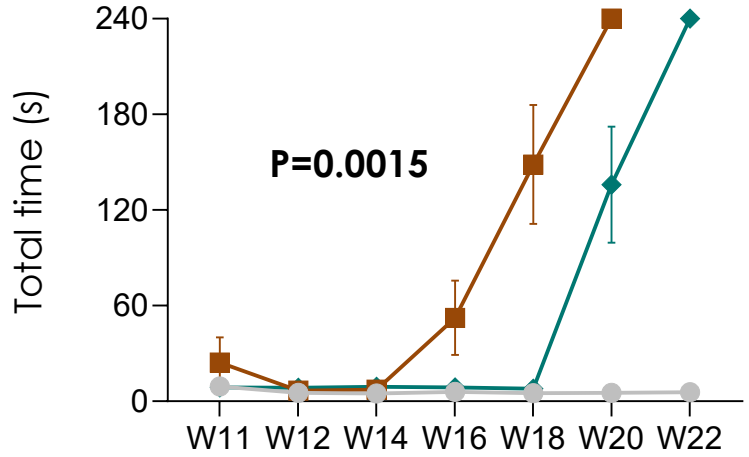
Rod 1 (easiest)




Rod 2



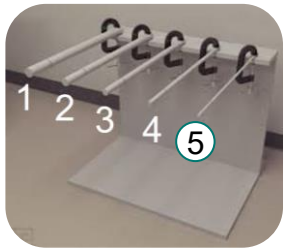



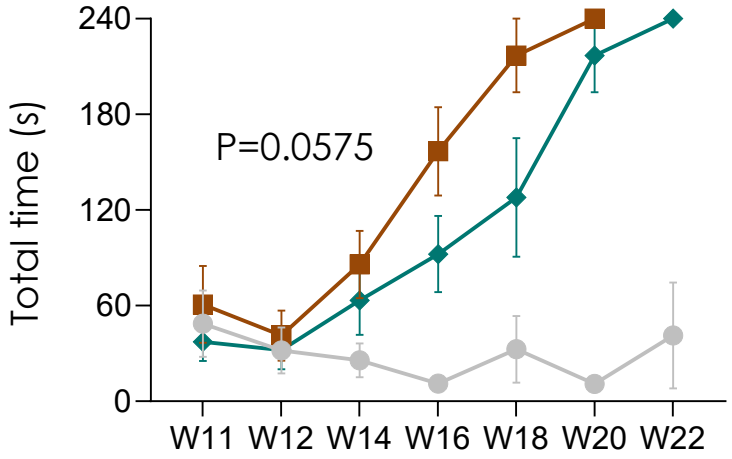

WT Vehicle (n=23)

SOD Vehicle (n=22)

SOD NX210c 10 mg/kg (n=20)

Rod 5 (hardest)

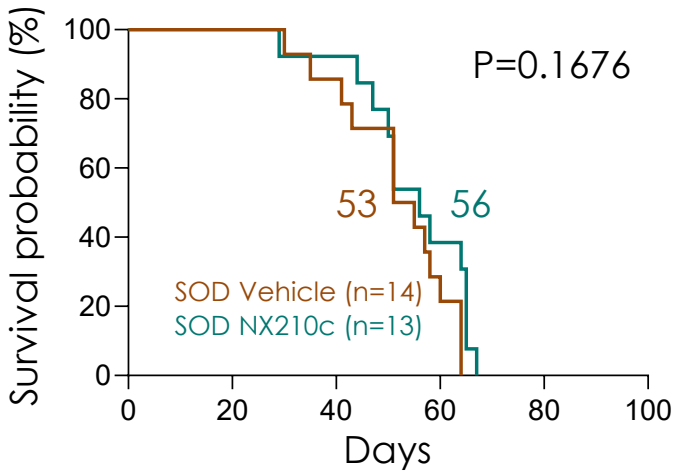


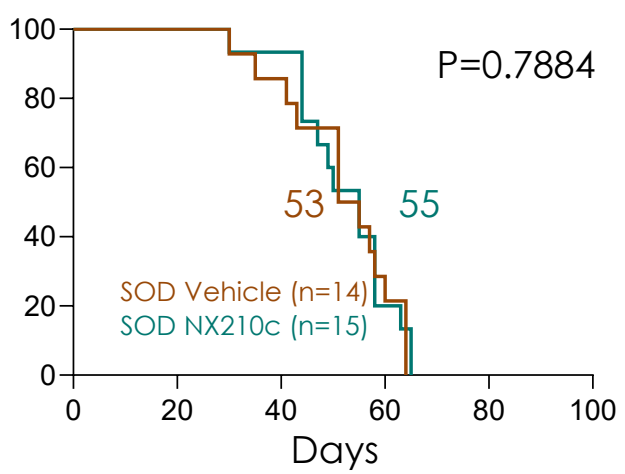
# NX210c Prolongs Survival of SOD1$^{G93A}$ Mice

Mouse survival

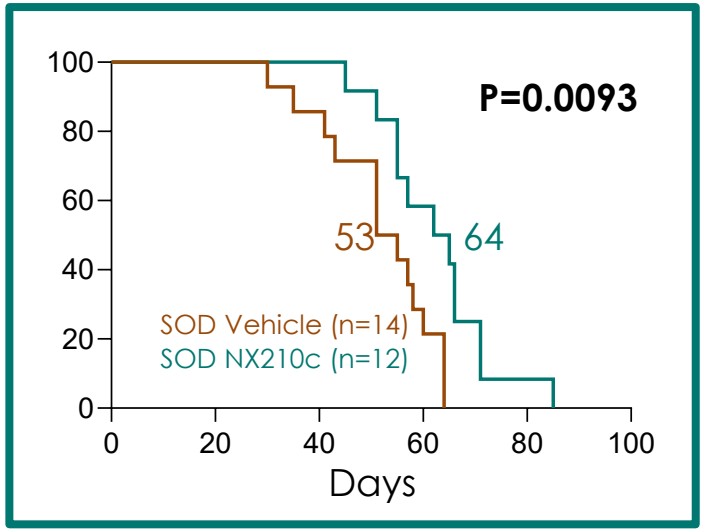
NX210c 2.5 mg/kg




NX210c 5 mg/kg




NX210c 10 mg/kg



# Discussion

- NX210c – **multiple properties** relevant to ALS:
  - blood-brain barrier integrity
  - neuroprotection
  - neurotransmission (cognition)

- NX210c – a promising drug candidate for ALS:
  - prolongs the **survival** (lifespan)
  - improves **trunk stability & motor coordination** (quality of life)

- To support the **clinical trial application** package, we aim to:
  - decipher NX210c mechanism of action on ALS pathology
  - confirm NX210c efficacy at 5 and 10 mg/kg in another model

# Thank You for Your Attention


axoltis pharma

60 Avenue Rockefeller
69008 Lyon
FRANCE

www.axoltis.com


## Our partners

**Merja VOUTILAINEN**, PhD
**Liam BECKETT**, MSc

**Katja KANNINEN**, PhD
**Irina BELAYA**, PhD

## Financing support