Quralis™

Stathmin-2, a New Target for ALS, and Development of QRL-201

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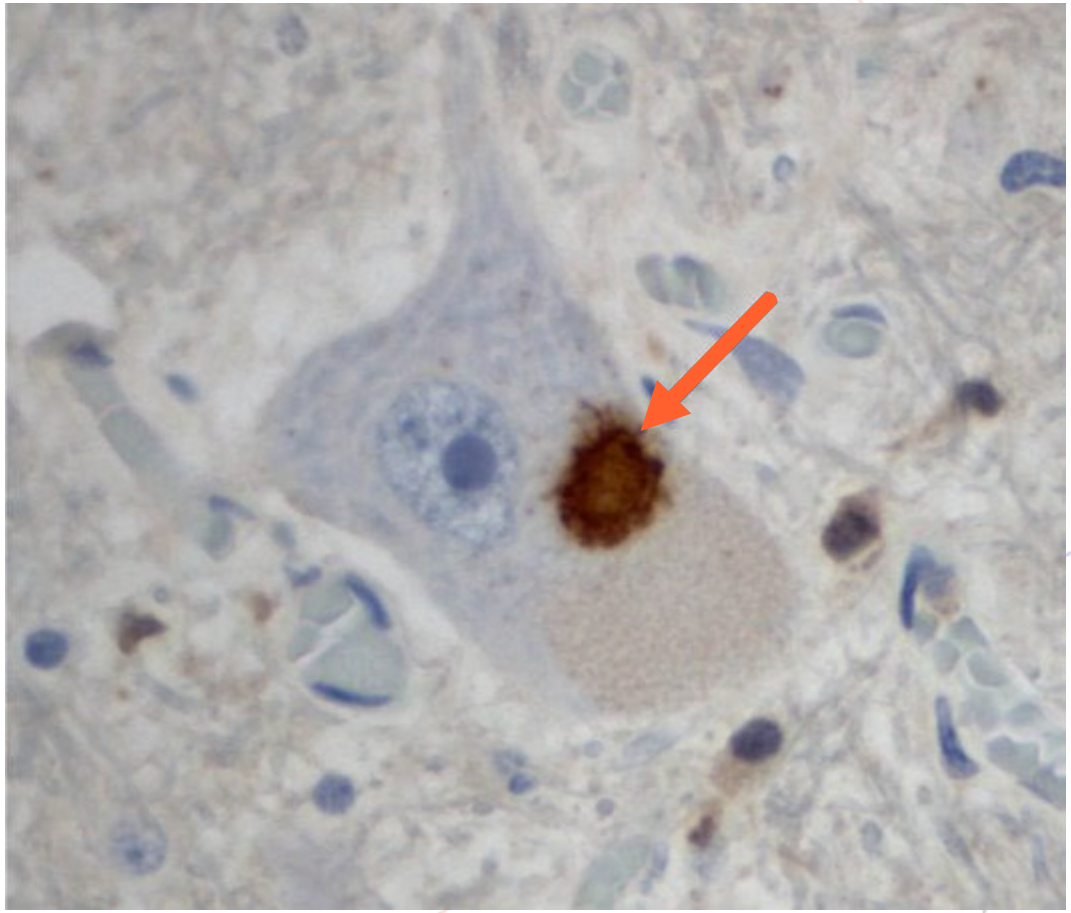
This presentation contains forward-looking statements based on current expectations that involve a number of risks and uncertainties. All opinions, forecasts, projections, future plans, or other statements, other than statements of historical fact, are forward-looking statements and include words or phrases such as "believes," "will," "expects," "anticipates," "intends," "estimates," "our view," "we see," "would" and words and phrases of similar import. The forward looking statements in this presentation are also forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and involve substantial risks and uncertainties. We can give no assurance that such expectations will prove to have been correct. Actual results could differ materially as a result of a variety of risks and uncertainties, many of which are outside of the control of management.

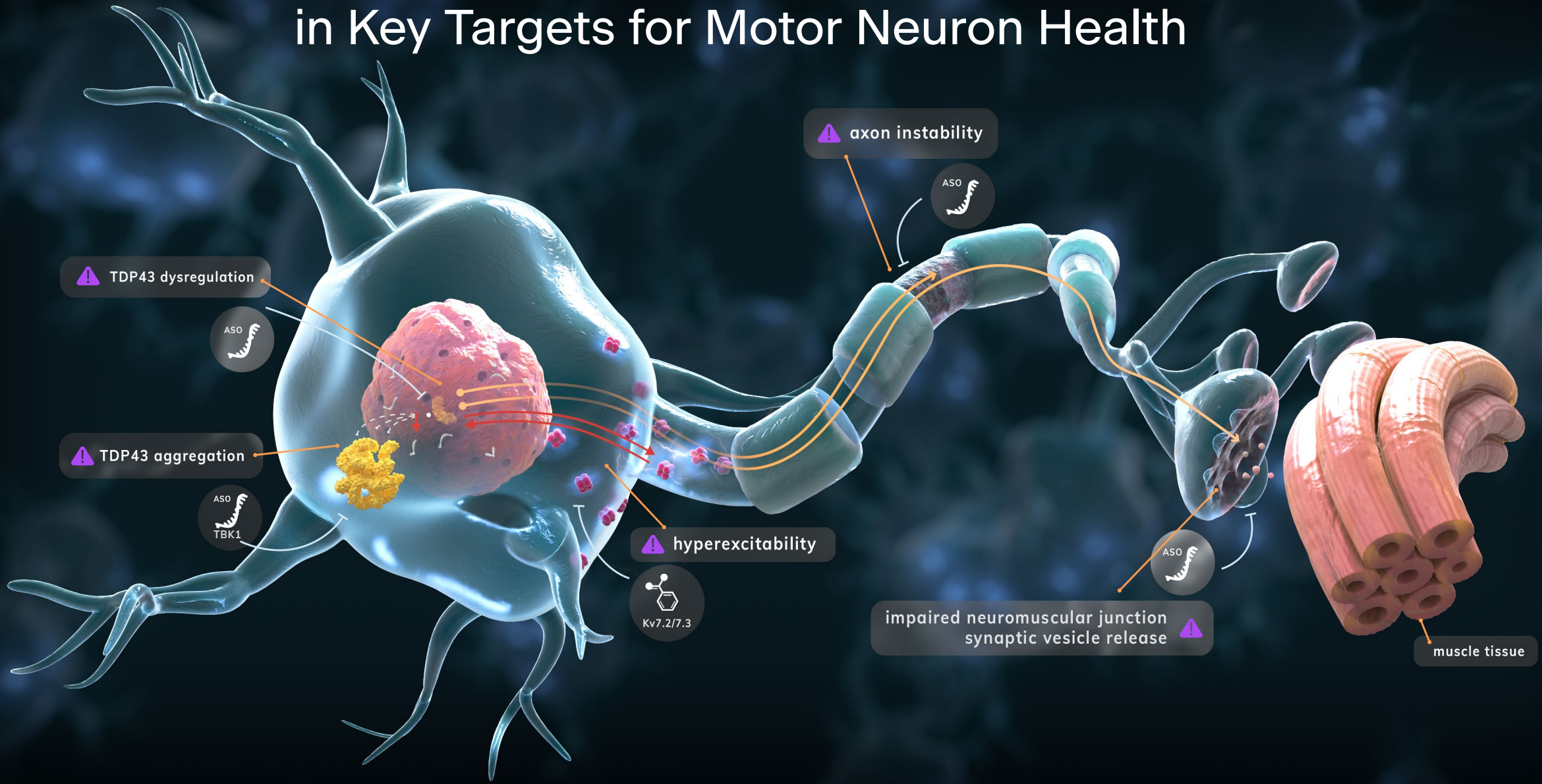
Hallmark of ALS: TDP-43 Mis-localization and Aggregation

- Post-mortem tissue from ALS patients shows TDP-43 cytoplasmic aggregation
- Seen in >90% of ALS patients (all except SOD1 and FUS)
- Aggregation indicates end stage of TDP-43 disease



Neumann et al. *Science.* **2006**, *314*, 130-133.

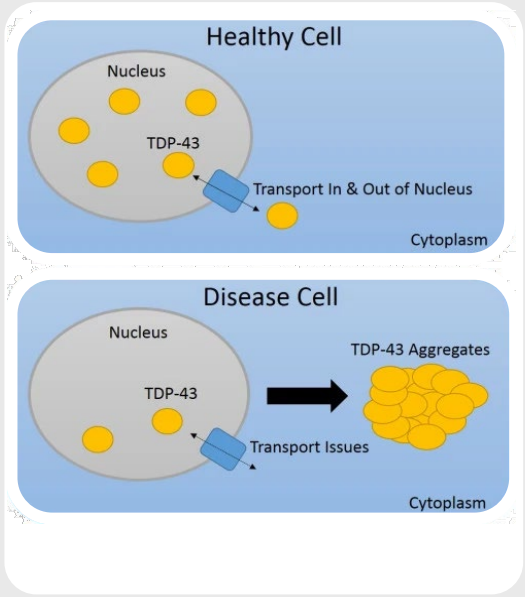
TDP-43 Loss in ALS Leads to Dysfunction in Key Targets for Motor Neuron Health



STATHMIN-2 (STMN2): A Genetic Target For The Sporadic ALS Population

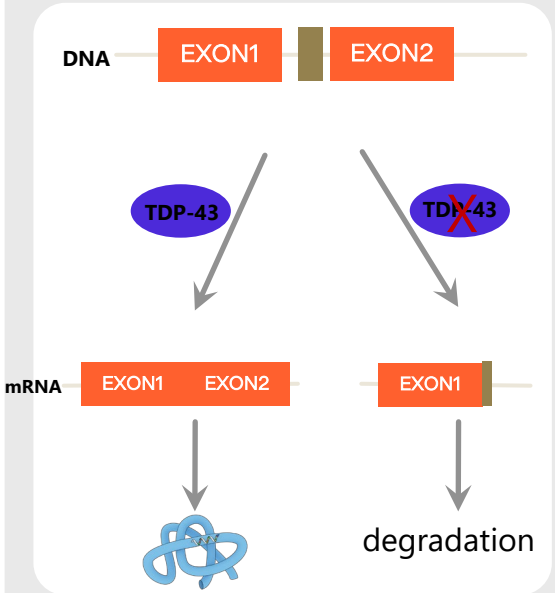
QurAlis' Therapeutic Strategy

In ALS motor neurons TDP-43 leaves the nucleus



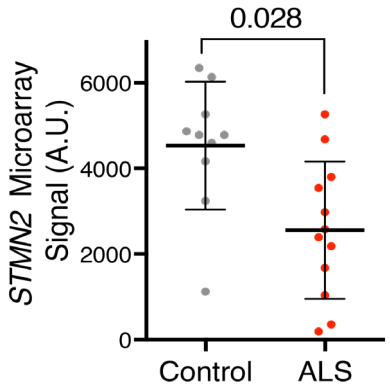
QurAlis niche

Loss of TDP-43 controlled cryptic exon splicing



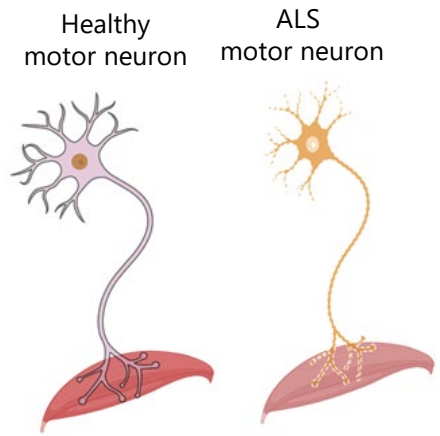
TDP-43 regulation of STMN2

Loss of full length STMN2



Cryptic splicing-ASO approach to restore STMN2

Axonal degeneration and impaired repair

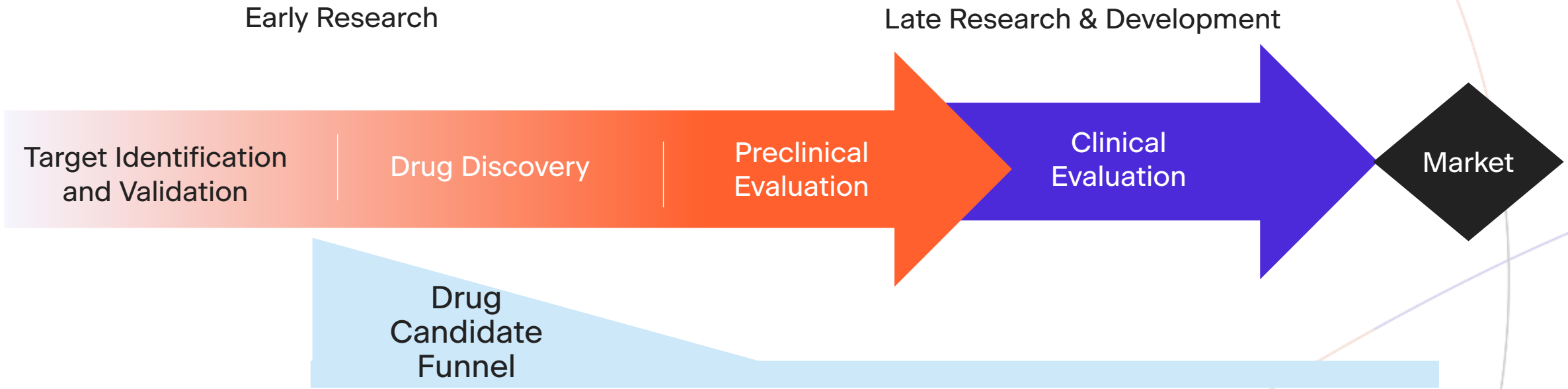


Rescue of axonal stability and repair

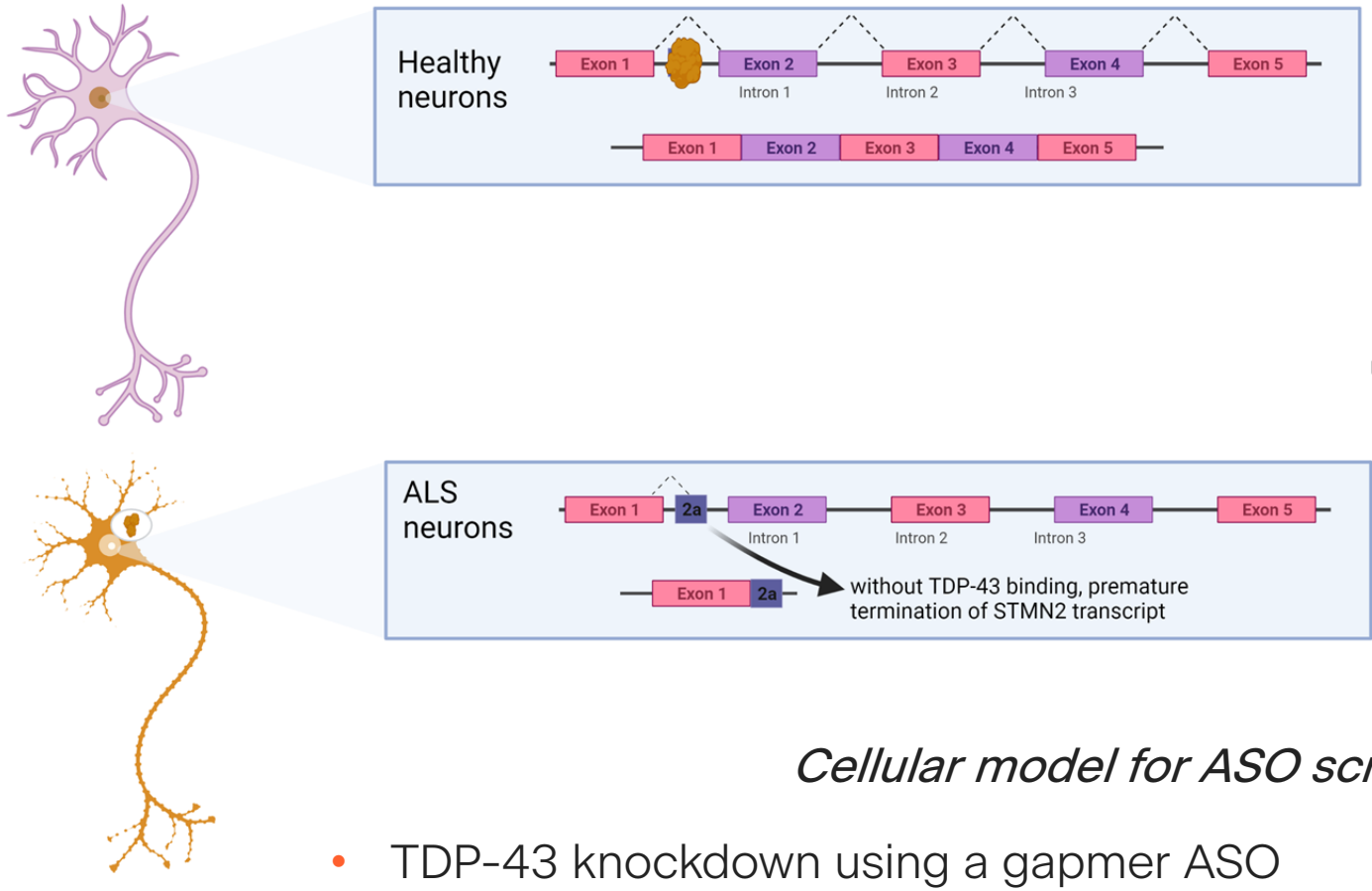
Nat. Neurosci. Feb 2019, Eggan ALS One 2020, Li et al., 2009, Morii et al., 2006, Shin et al., 2012, Shin et al., 2014, Xu et al., 2010

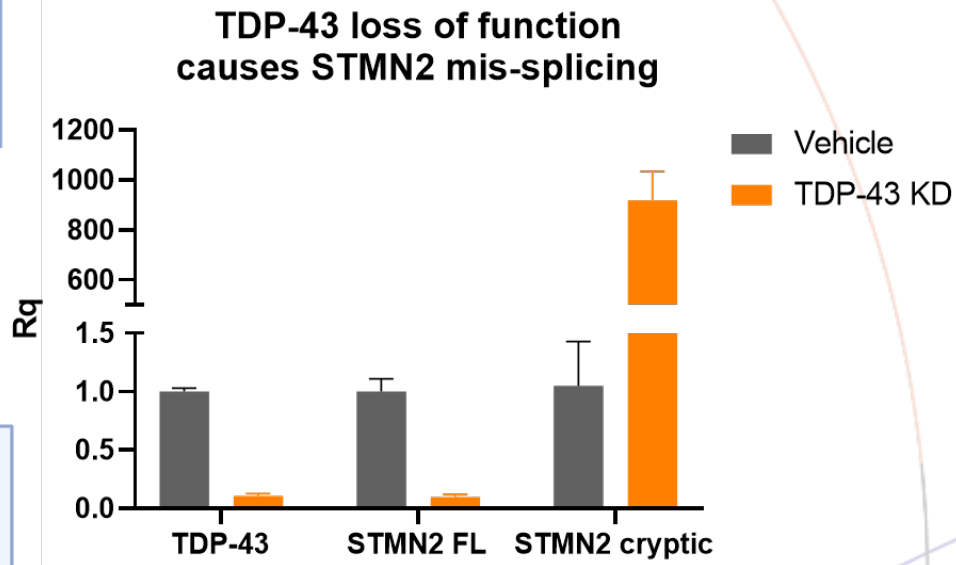
Discovery and Development for QRL-201

Target based Drug Discovery



TDP-43 Loss of Function Human Cellular Model to Study STMN2

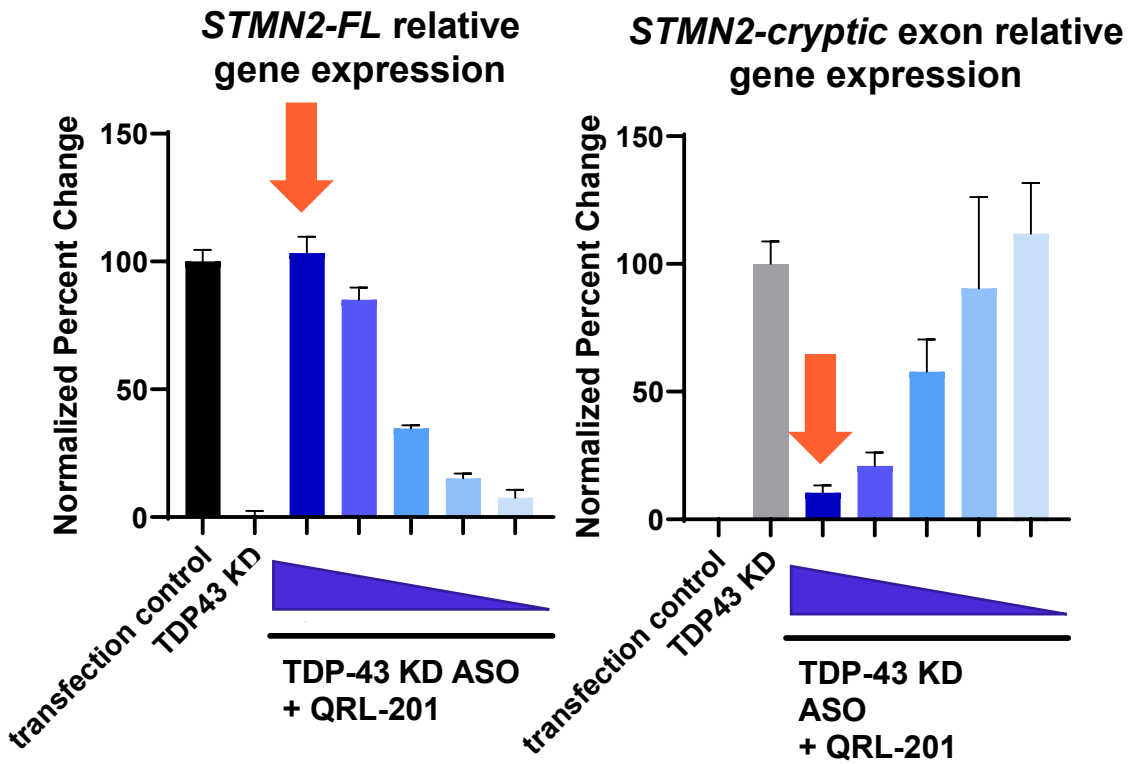




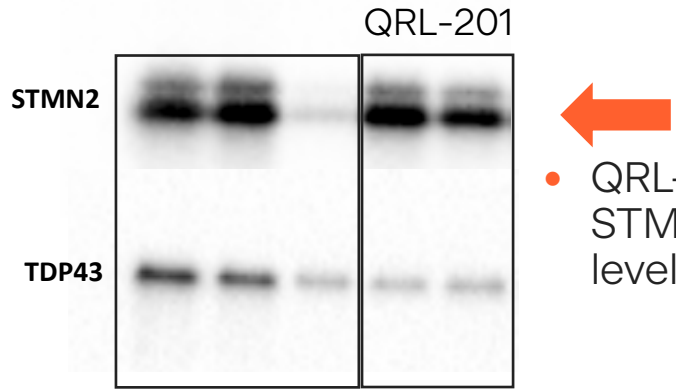
Cellular model for ASO screening

- TDP-43 knockdown using a gapmer ASO
- Loss of full length Stathmin-2 (STMN2; RNA and protein can be quantified)
- Induction of cryptic exon expression (RNA can be quantified)
- QRL-201 increases FL STMN2 & reduces cryptic transcript expression

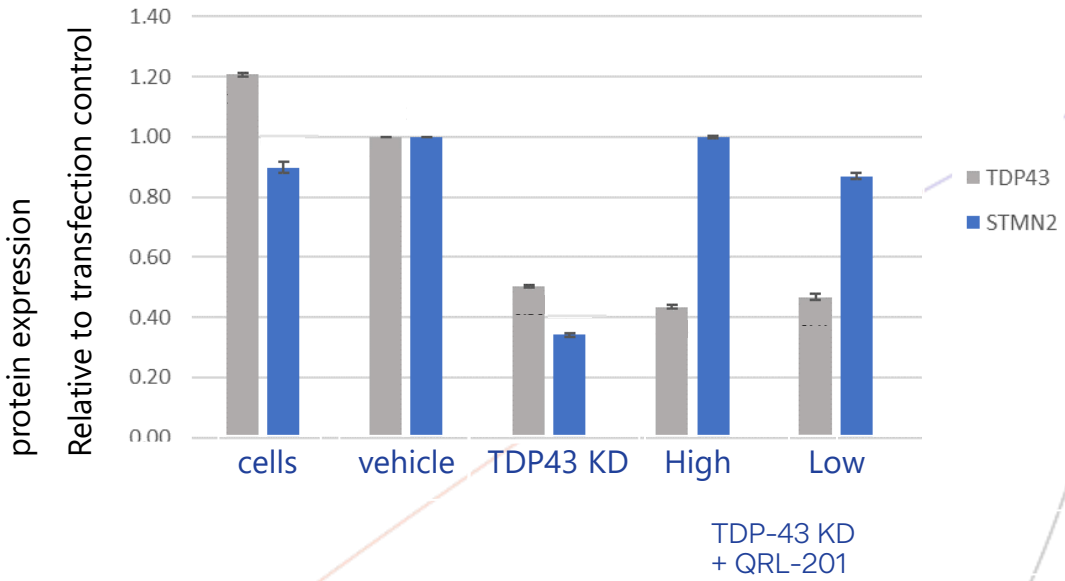
Loss of TDP-43 Results in a Loss of STMN2 mRNA and Protein: QRL-201 Restores STMN2 in a Dose-Dependent Manner



Stathmin-2 relative protein expression



- QRL-201 restores STMN2 protein levels to normal



QRL-201 Clinical Program Overview

- Phase 1 ANQUR clinical trial – first-in-human global, multi-center, randomized, double-blind, placebo-controlled multiple-ascending dose (MAD) study of QRL-201 vs. placebo in participants living with ALS (NCT05633459)
  - **First-ever clinical trial to evaluate a potential therapy to rescue STMN2 expression in people living with ALS**
  - Study primary objective: determine safety and tolerability of multiple doses of QRL-201 in people living with ALS
- Study has received regulatory authorization in Canada, the United Kingdom, and the European Union
- Cohort 2 is ongoing

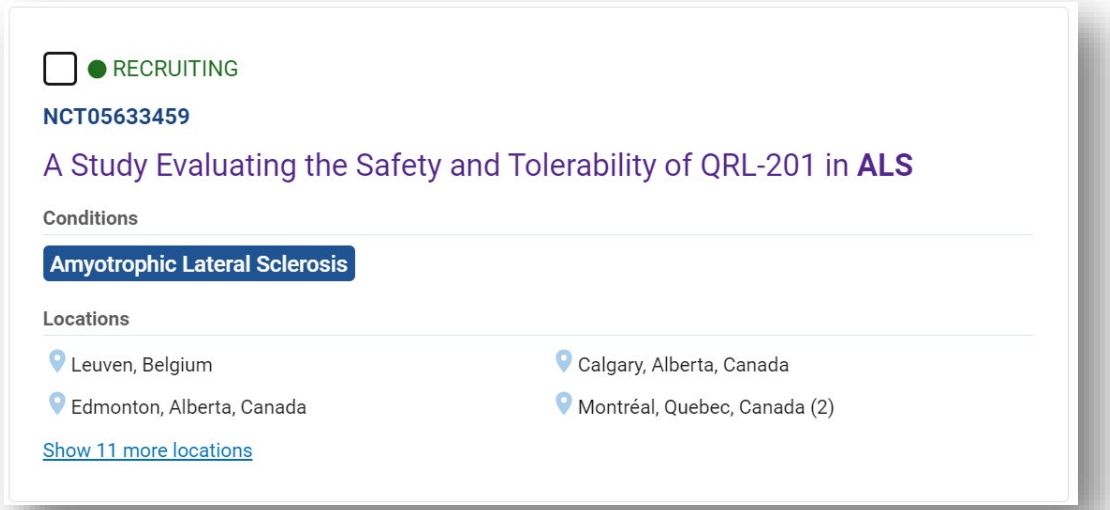
Phase 1 Clinical Trial for ALS

Phase I
Checking Safety

Phase II
How Well it Works

Phase III
Confirm Results & Compare

Phase IV
Continue to Track



QRL-201 Clinical Program Overview

QRL-201	•Splice-switching ASO against STMN2 pathology
Function/MoA	•Aims to correct STMN2 mis-splicing & restoration of STMN2 protein
Route of Administration	•Intrathecal injection
Dosing Regimen	•3 loading doses •Monthly dosing thereafter
Placebo	•Supplied; artificial CSF •Same route of administration and regimen as QRL-201

QRL-201-01 Study Design

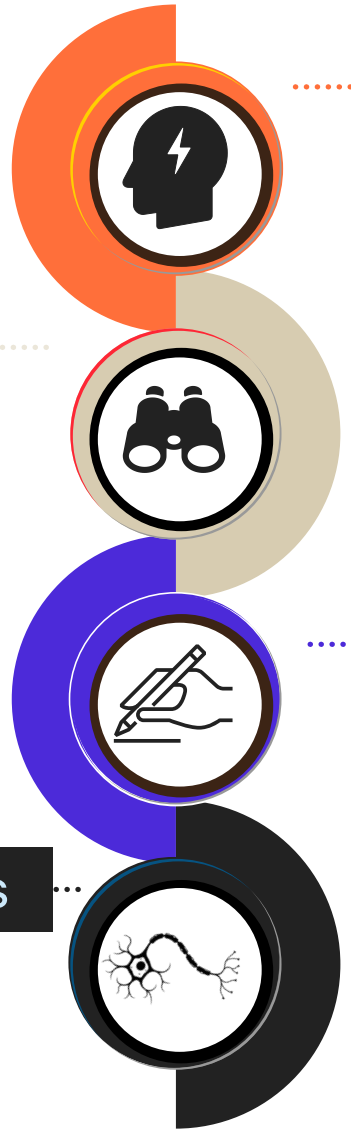
OBJECTIVES	ENDPOINTS
PRIMARY: To determine the safety and tolerability of multiple doses of QRL-201	Incidence of AEs and SAEs associated with QRL-201
SECONDARY: To determine the plasma PK profile of QRL-201 after multiple doses	Multiple dose PK

KEY INCLUSION CRITERIA*	KEY EXCLUSION CRITERIA*
• Male or female participants aged 18 to 80 years diagnosed with ALS • ALS symptom onset within 24 months • Slow vital capacity >50% • Clinical evidence of lower motor neuron involvement • Not pregnant and not nursing • Willing and able to practice effective contraception • Able to tolerate lumbar puncture • If on approved therapies for the treatment of ALS during the course of the study, must be on a stable dose (at the Sponsor's discretion)	• Pathogenic variant, likely pathogenic variant, or variant of uncertain significance in the superoxide dismutase 1 (SOD1) and/or fused in sarcoma (FUS) genes • Currently enrolled in any other clinical study involving either an investigational product (IP) or off-label use of a drug or device • Prior exposure to stem cell or gene therapy products • Any contraindication to intrathecal drug administration • Abnormal laboratory values deemed clinically significant by the Investigator • Significant infection, or known inflammatory process

*Additional I/E criteria may apply

Comprehensive Biomarkers and Phenotypic Assessments to Measure Activity

AnQur



Electrophysiology

- Established NMJ innervation measurements (STMN2 MOA/efficacy)
- Motor excitability recordings (CMAP, RNS)

Target Engagement

- STMN2 levels

Clinical Measurements

- ALSFRS-R
- ROADS
- SVC
- HHD
- Ventilation assistance-free survival
- Time to event measures

Biomarkers of Neuronal Loss

- NfL and other exploratory biomarkers

Summary

- QurAlis' mission is to bring breakthrough precision medicine technology to people living with ALS. QRL-201-01 is designed to evaluate the safety and tolerability of multiple doses of QRL-201 in people living with ALS and explore the hypothesis that restoration of STMN2 is a suitable disease modifying approach in ALS.

- QRL-201 is an investigational ASO for the recovery of STMN2 expression and function in ALS patients, even in the continued presence of TDP-43 pathology.

- To investigate QRL-201, QurAlis has designed a first-in-human study evaluating the safety and tolerability of multiple doses of QRL-201 in people living with ALS.

- This study is expected to enroll 64 study participants, at up to 16 sites, in Canada, the UK and Europe. Enrollment began in 2023. Refer to www.clinicaltrials.gov for further details and updates: **NCT05633459**


NIH
National Institute of Neurological Disorders and Stroke
ALS ASSOCIATION
AFTD
The Association for Frontotemporal Degeneration
FIND HELP·SHARE HOPE
TARGET ALS
DEPARTMENT OF DEFENSE
UNITED STATES OF AMERICA
mnda
motor neurone disease association
QurAlis™
Thank You!
Questions?