



Challenges faced by the investigator: focus on the treatment of ALS as a rare disease

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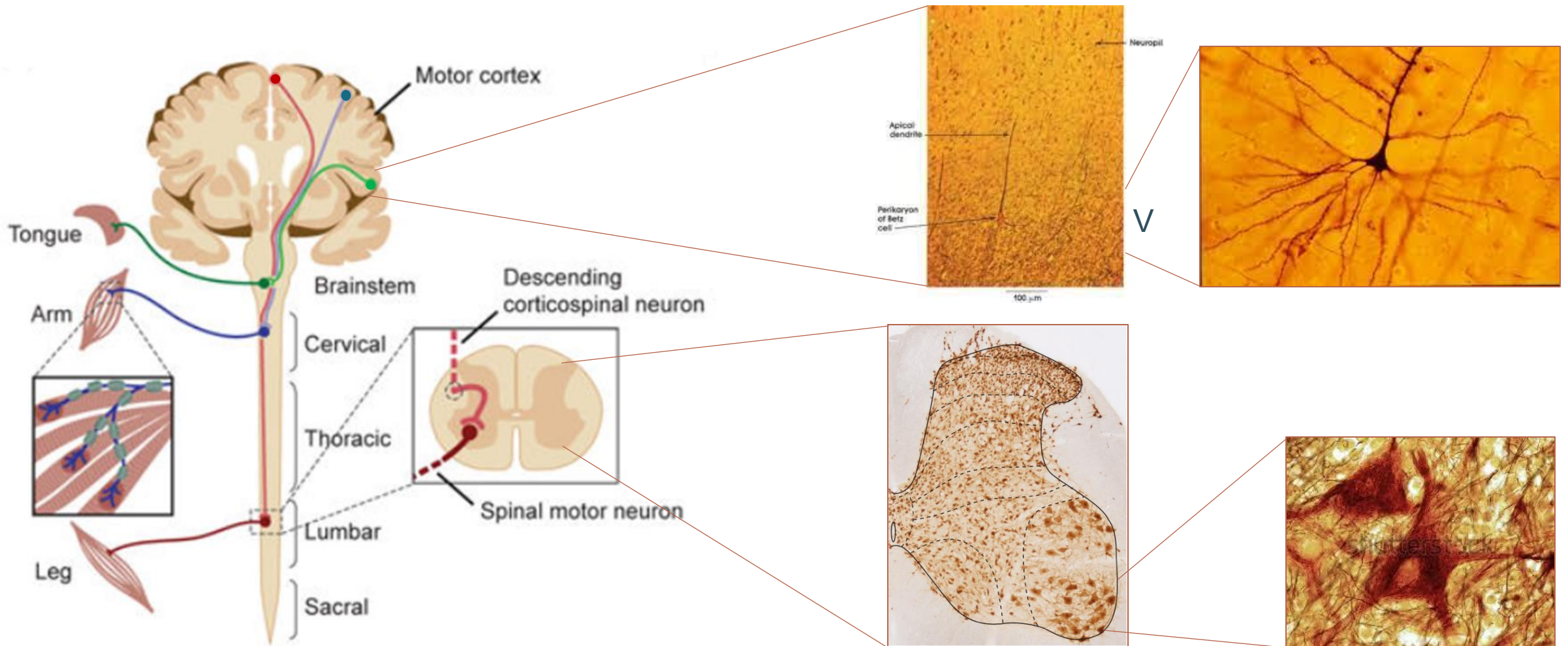
My disclosures

- Honoraria for lectures for Biogen, Amylyx (paid to institution)
- Participation in Advisory Board meetings for Biogen, UCB, argenx, Cytokinetics, Ferrer, Muna Therapeutics, Augustine Therapeutics, Alector, Alexion, QurAlis, VectorY, Sapreme Technologies, Prilenia, Novartis, Trace Neuroscience, NRG Therapeutics (paid to institution)
- Grant from CSL Behring (E. von Behring Chair for Neuromuscular and Neurodegenerative Disorders; paid to institution)
- Chair of the ALS guideline panel of the European Academy of Neurology

Overview

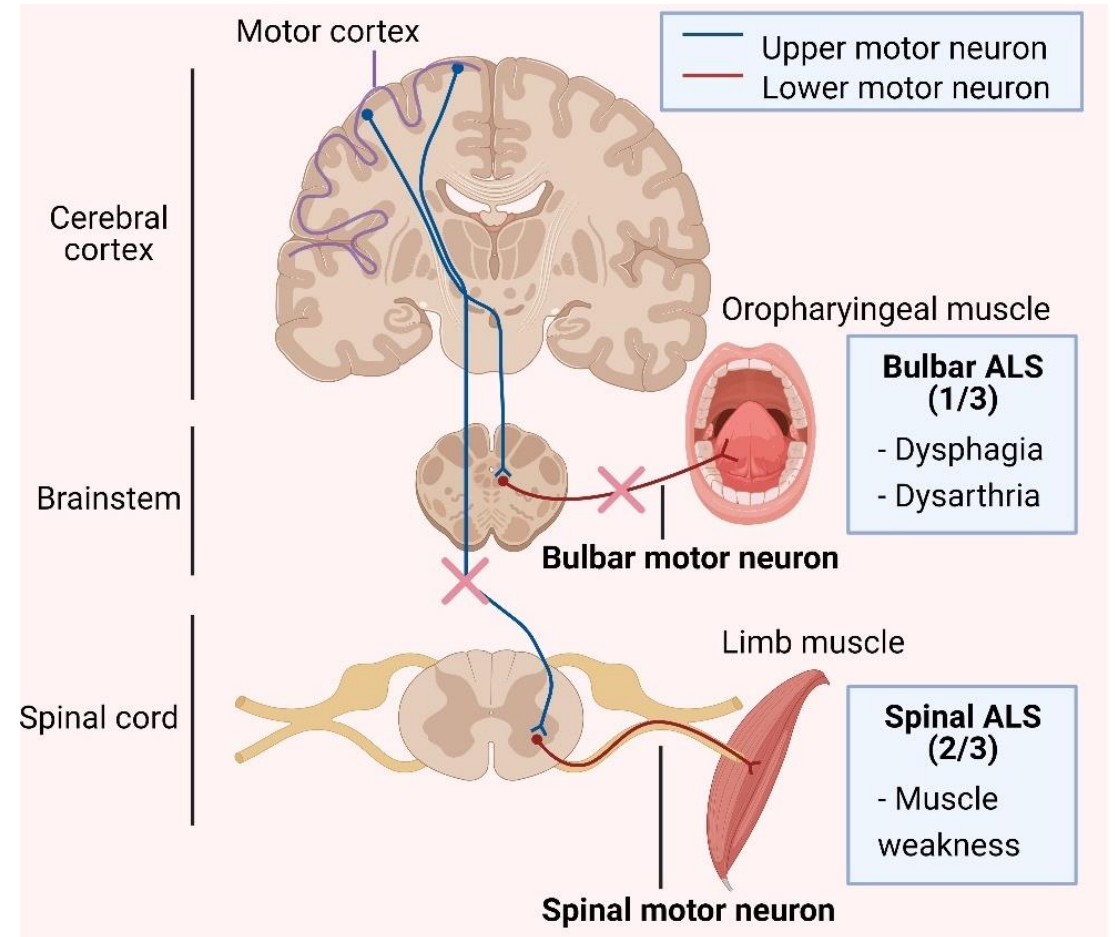
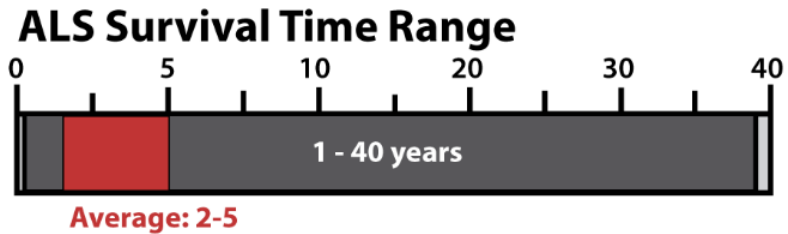
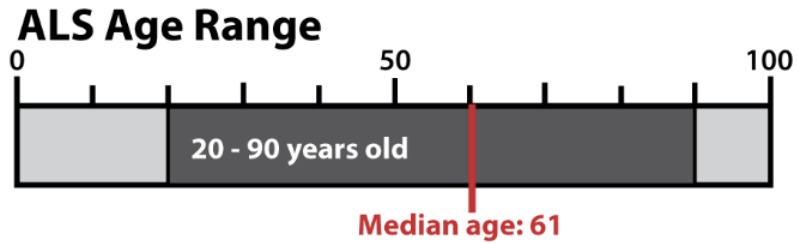
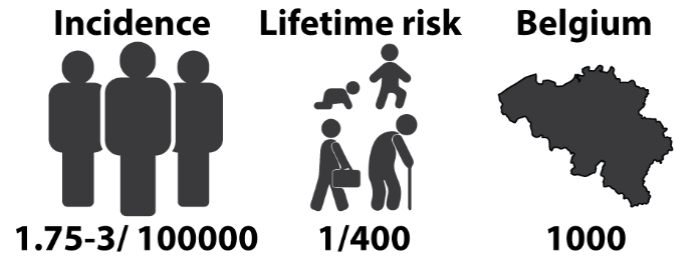
- Brief introduction to ALS
- Recent progress in innovative therapies for ALS
- Challenges for early phase clinical trials faced by the investigator

What is amyotrophic lateral sclerosis?

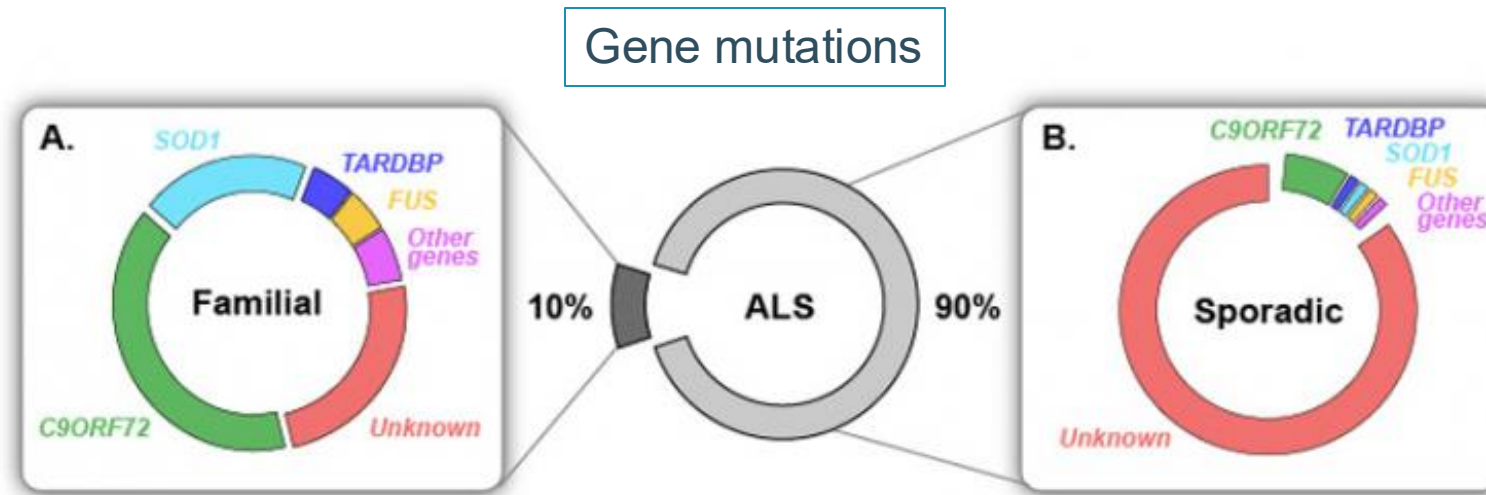




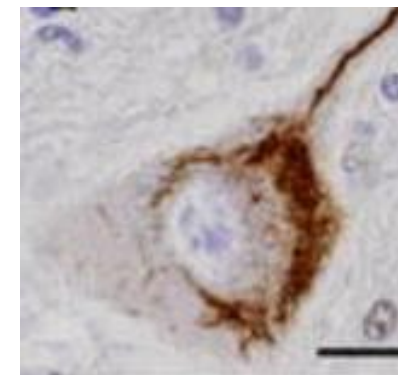
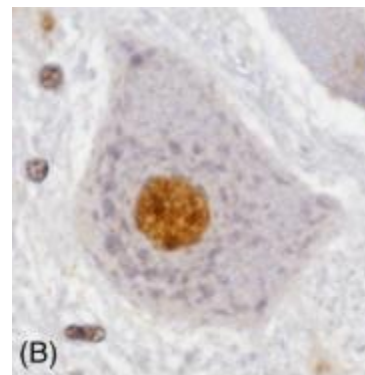
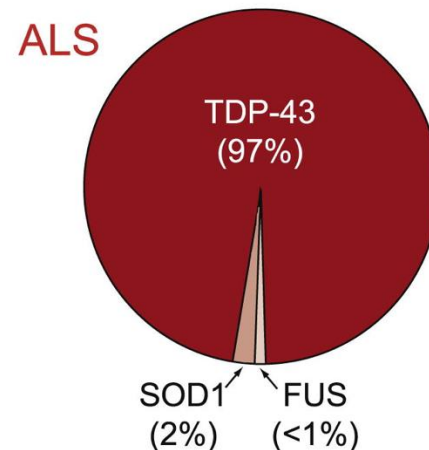
Heterogeneity in disease presentation



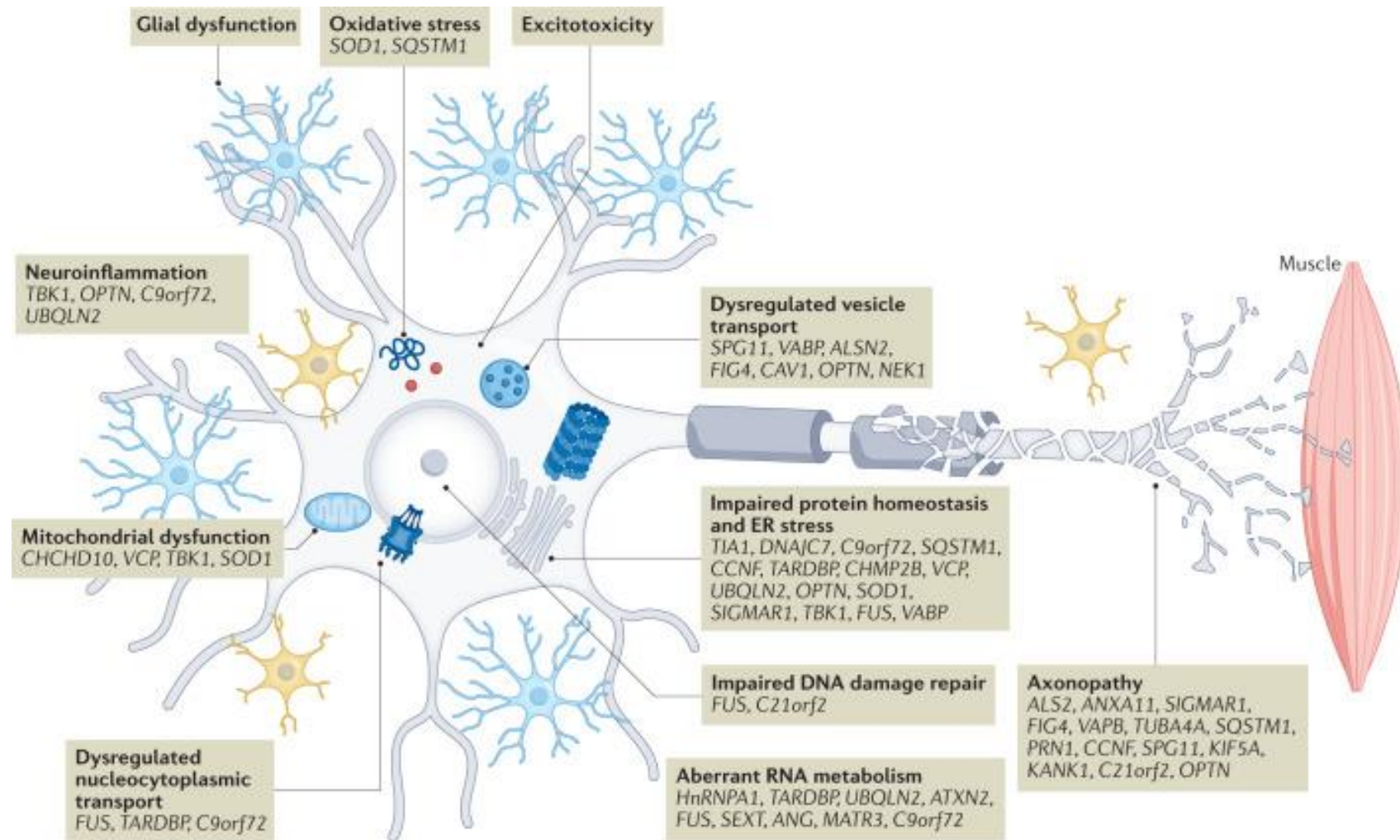
Heterogeneity in causes of ALS



Protein aggregation

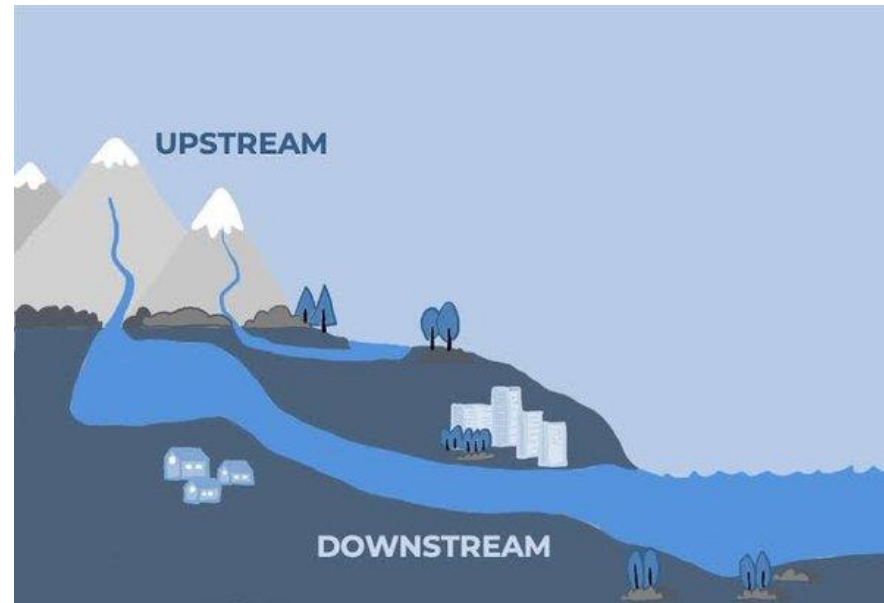


ALS disease mechanisms are heterogeneous



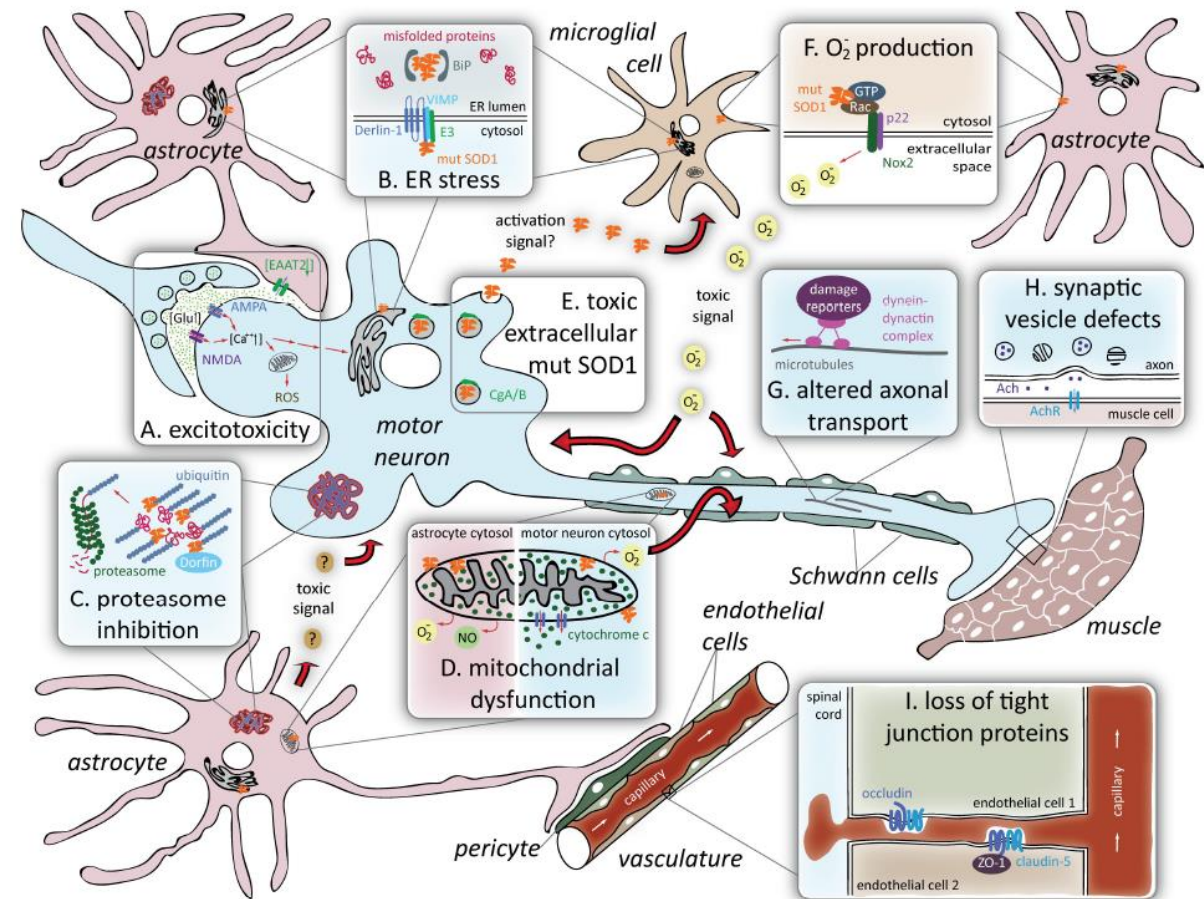
Recent progress in innovative therapies for ALS

- Target upstream disease cause
- Interfere with downstream disease mechanisms (> 50 negative trials)

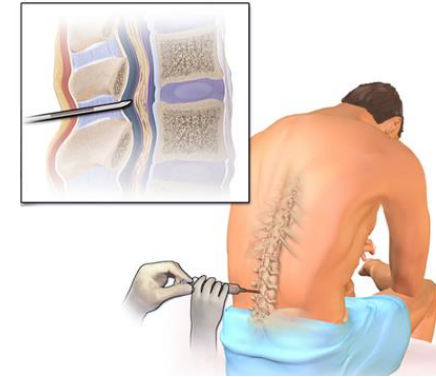
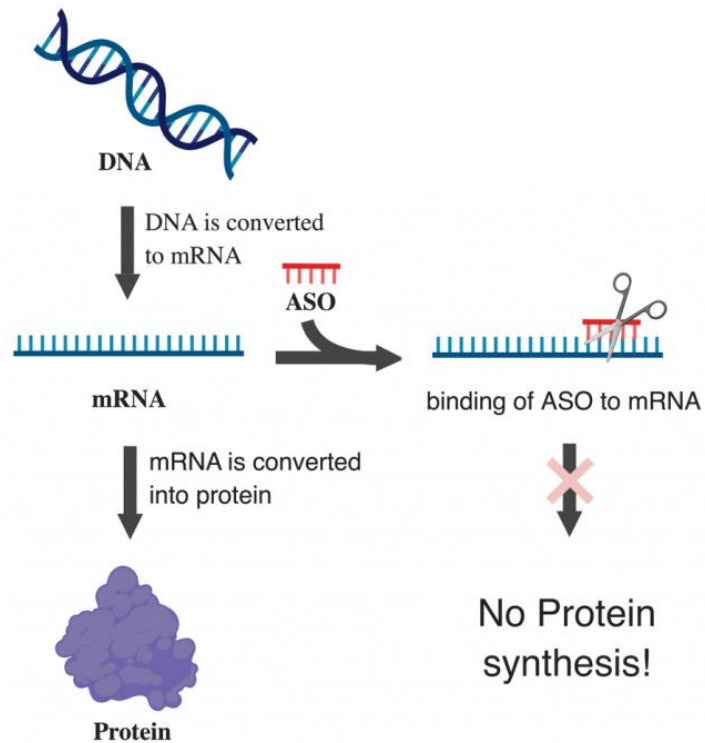


SOD1-ALS

- **Mutations**
 - Autosomal dominant (rarely recessive)
 - Missense mutations
 - fALS 20%, sALS 1-2%
- **Phenotypes**
 - Onset on average 10 years earlier than sALS
 - Onset in lower limbs more common
 - LMN predominant
 - Slow or fast disease progression
- **Mechanisms**
 - Highly abundant in motor neurons
 - Role in detoxification of superoxide radicals
 - Aggregation of mutant SOD1 causes toxicity



ASO-based gene silencing for *SOD1* (tofersen)

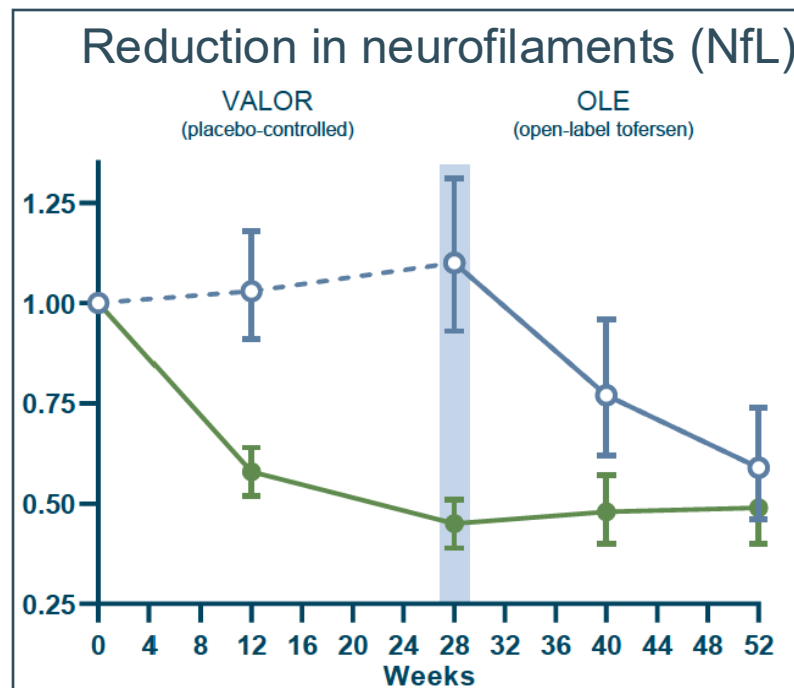
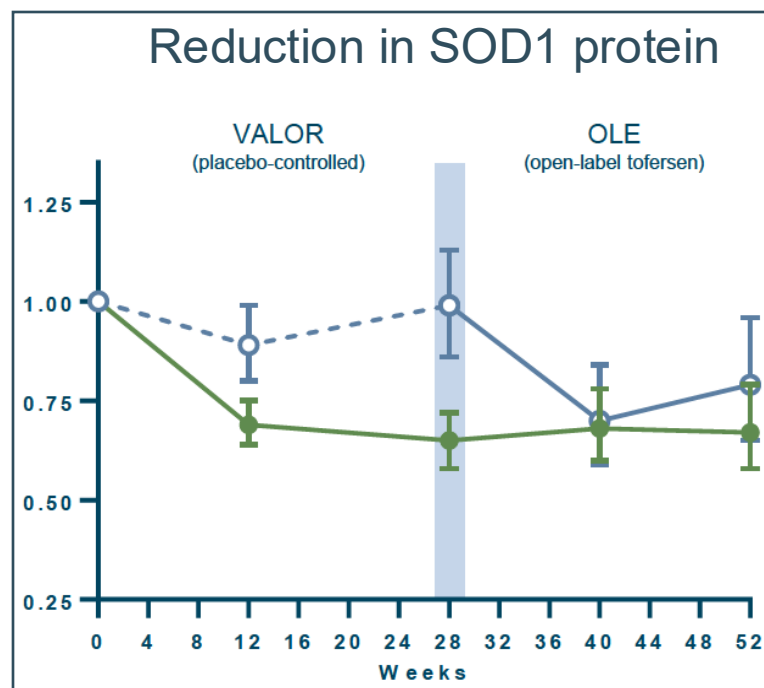
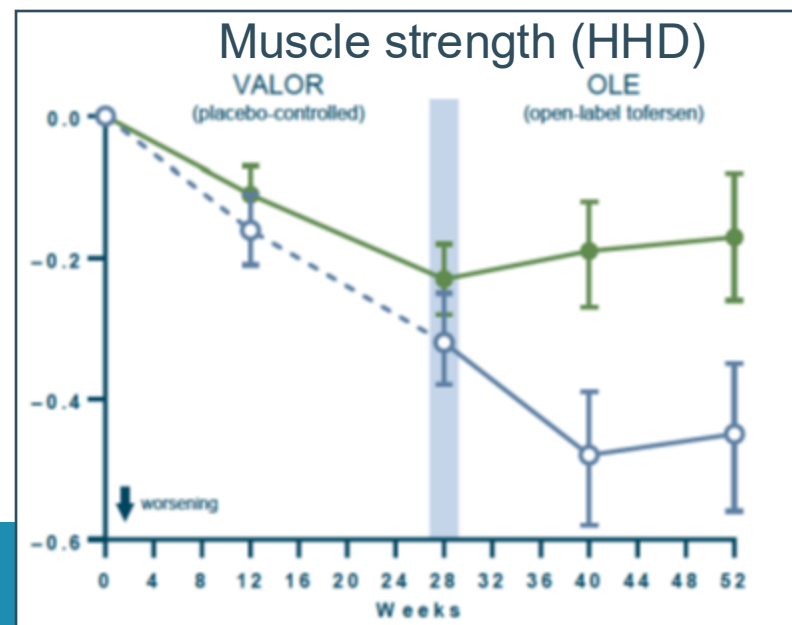
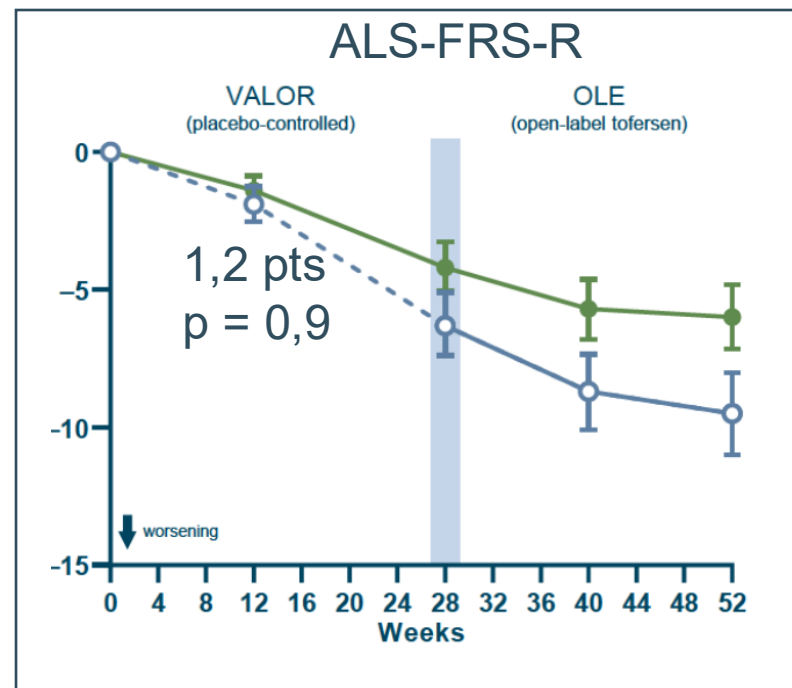


Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T. Miller, M. Cudkowicz, P.J. Shaw, P.M. Andersen, N. Atassi, R.C. Bucelli, A. Genge, J. Glass, S. Ladha, A.L. Ludolph, N.J. Maragakis, C.J. McDermott, A. Pestronk, J. Ravits, F. Salachas, R. Trudell, P. Van Damme, L. Zinman, C.F. Bennett, R. Lane, A. Sandrock, H. Runz, D. Graham, H. Houshyar, A. McCampbell, I. Nestorov, I. Chang, M. McNeill, L. Fanning, S. Fradette, and T.A. Ferguson

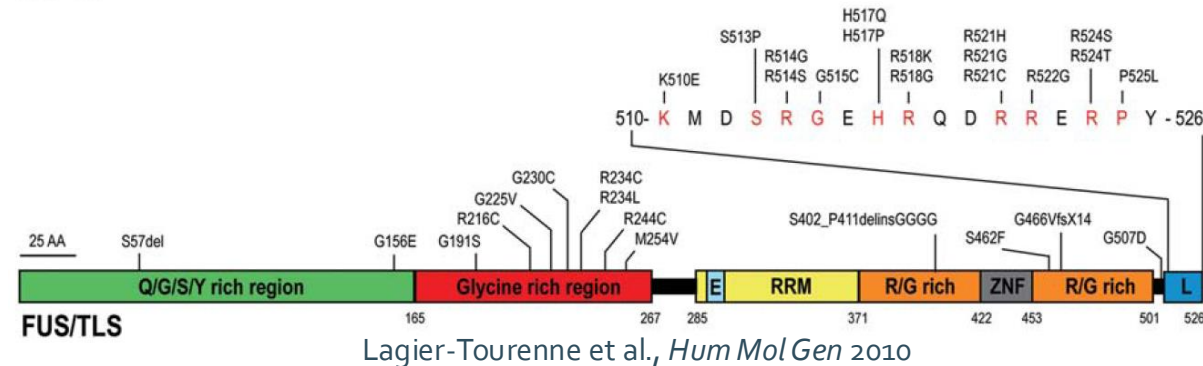
Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T.M. Miller, M.E. Cudkowicz, A. Genge, P.J. Shaw, G. Sobue, R.C. Bucelli, A. Chiò, P. Van Damme, A.C. Ludolph, J.D. Glass, J.A. Andrews, S. Babu, M. Benatar, C.J. McDermott, T. Cochrane, S. Chary, S. Chew, H. Zhu, F. Wu, I. Nestorov, D. Graham, P. Sun, M. McNeill, L. Fanning, T.A. Ferguson, and S. Fradette, for the VALOR and OLE Working Group*

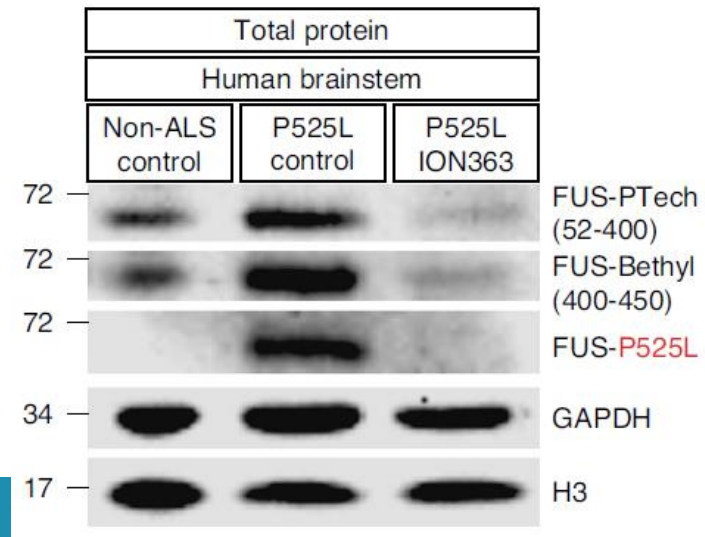
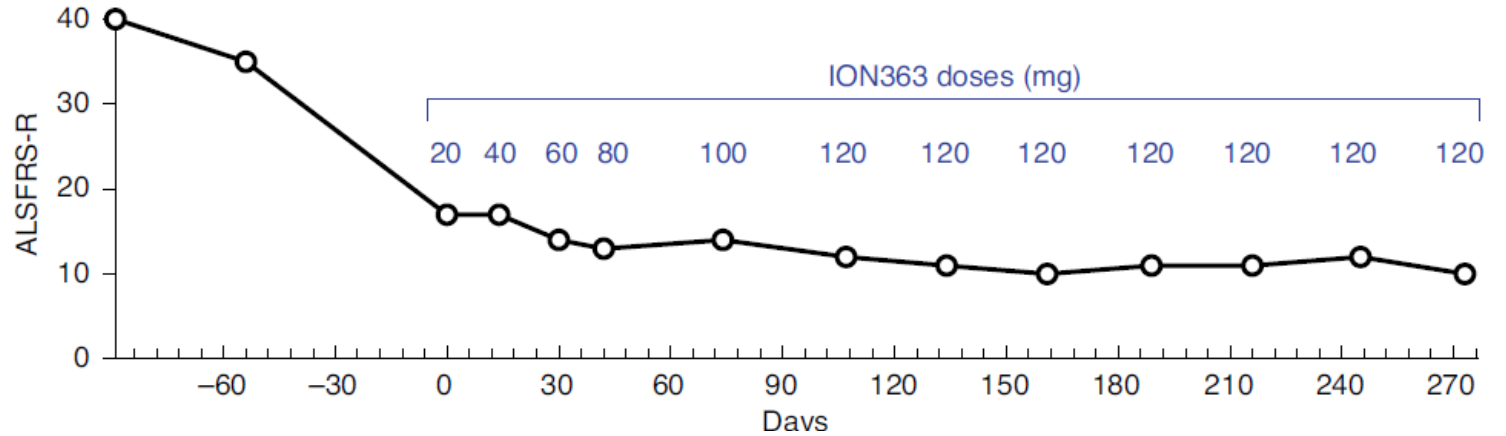
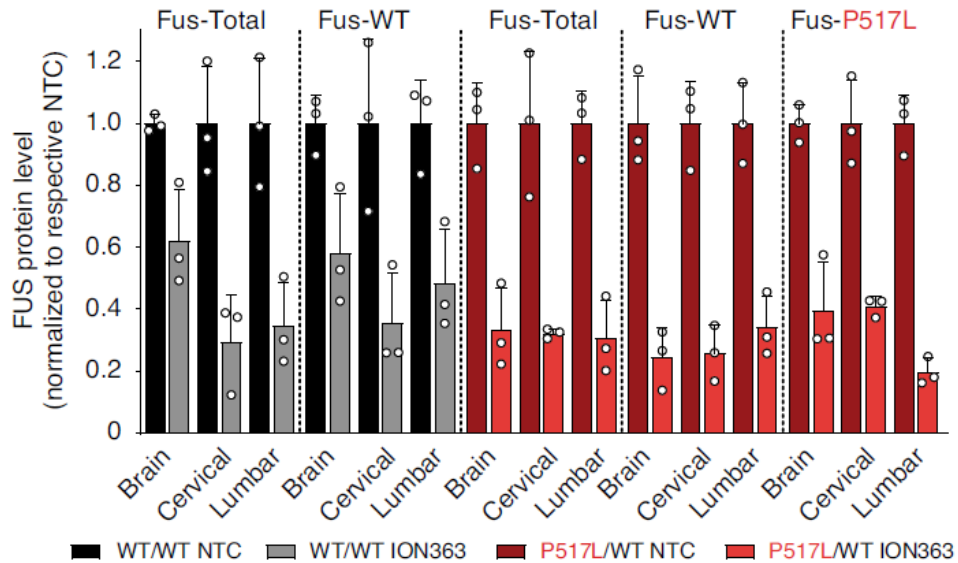


FUS-ALS

- *Mutations*
 - Autosomal dominant (rarely recessive)
 - Missense mutations, deletions, insertions, frameshift, de novo
 - fALS 1-3%, sALS <1%
 - Most frequent cause of juvenile ALS (P525L)
- *Phenotypes*
 - Early onset
 - Fast progression
 - Prominent neck extensor/hip flexor weakness
 - Prominent LMN involvement
- *Mechanisms*
 - DNA/RNA binding protein
 - Mutant FUS mislocalizes to cytoplasm, forms aggregates



ION-363 for *FUS*-ALS



Challenges faced by the investigator

- Trial design
 - Patient selection is difficult
 - No biomarkers of disease mechanisms
 - Unclear what is best outcome measure (survival, function,...)
 - Neurofilaments are good marker to measure treatment effect
- Trial execution
 - Finding participants for first in human trials with innovative therapies
 - Intensive safety monitoring
 - Heavy trial logistics (travel, heavy protocol, multiple assessments, invasive procedures, overnight monitoring,...)
 - Ethical challenges (effective therapies raise questions about placebo arm and duration of double-blind placebo-controlled phase of trial)

Conclusions

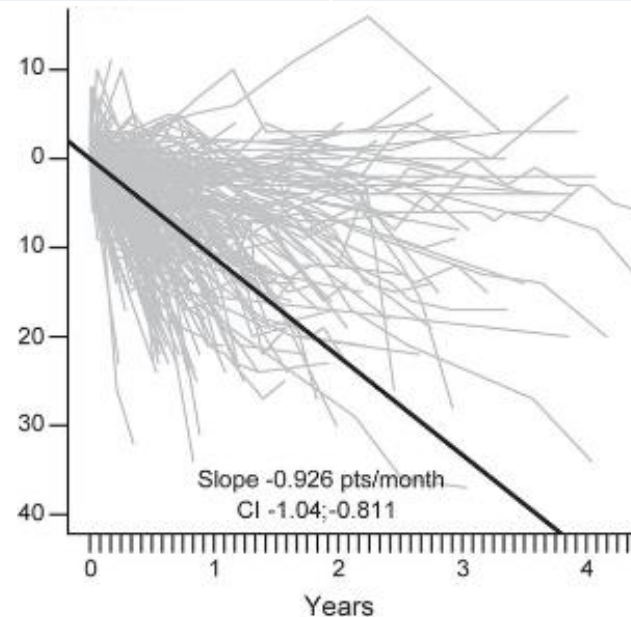
- ALS is a neurodegenerative disorder primarily affecting the motor system
- ALS is a heterogeneous disorder with variable clinical presentation, diverse causes and disease mechanisms
- Clinical trials targeting downstream disease mechanisms have largely failed
- Tofersen is the first molecular therapy for patients with a *SOD1* mutation which significantly improves the disease course
- Many more molecular therapies for targeted ALS populations are underway

Acknowledgements



Disease progression (ALS-FRS-R)

Bulbar	Fine Motor	Gross motor	Breathing
1. Speech	4. Handwriting	7. Turning in bed, adjusting bed clothes	10. Dyspnea
2. Salivation	5. Cutting food	8. Walking	11. Orthopnea
3. Swallowing	6. Dressing/hygiene	9. Climbing stairs	12. Respiratory insufficiency



Acknowledgements



Multidisciplinary care team



Clinical trial team

