Targets, Development Progress, & Licensing Deals in Amytrophic Lateral Sclerosis (ALS)

From Pullan's Pieces #215

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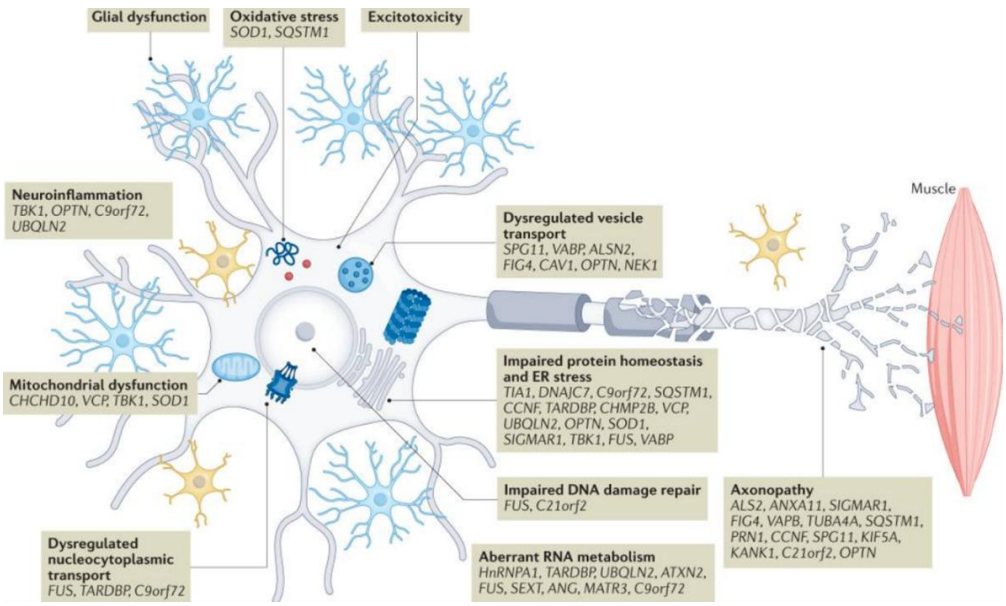
ALS Drug Development – *Why has clinical success been so limited?*

- ALS is a neurodegenerative disease characterized by the loss of cortical and spinal motor neurons.
- ALS is a progressive disease with highly complex biology which has contributed to daunting challenges in drug development progress.
- ~ 10% of ALS cases are familial while ~ 90% are sporadic.
- Advances in large scale genomic analysis have led to the identification of numerous ALS-associated genes, both in familial and sporadic cases, with the superoxide dismutase 1 (*SOD1*), fused in sarcoma (*FUS*), TAR DNA binding protein (*TARDBP*) and chromosome 9 open reading frame 72 (C9orf72), among the most frequent.



ALS-associated genes are implicated in protein homeostasis, altered RNA-binding proteins and cytoskeletal proteins.

Translational science has been handicapped by an over-reliance on the SOD1-mediated transgenic mouse model, which replicates motor neurodegeneration, muscle weakness and atrophy quite well but does not reflect TDP-43 proteinopathy which is now known to be involved in **~97% of ALS cases.**

A high degree of disease heterogeneity has undermined clinical trial success; future ALS trial protocols are likely to stratify patients by underlying pathogenic mechanism, genetic profile and disease progression rate.

Combination therapies and drug candidates that target multiple mechanisms are viewed as highly promising approaches.

Limitations of the ALSFRS-R scoring system have contributed to drug trial disappointments

The ALSFRS-R is an evaluator-administered instrument that assesses patient functional independence**,** with an array of activities that reflect bulbar, fine motor, gross motor and respiratory muscle function.

ALSFRS-R is a measure of how patients are functioning, and a slower rate of decline, or a higher score, correlates with longer survival.

While routinely used as primary endpoint in ALS clinical trials, investigators have come to identify several key limitations of this scale, including:

- Its vulnerability to bias given that it is a subjective measure of how patients are functioning
- Lack of linear weighting across different domains, with some domains having more substantial influence and weight on the total score
- Clinical ceiling and floor effects
- Lack of domains assessing cognition, mood and pain which are now recognized as important features of the disease.

On top of the intrinsic limitations of the ALSFRS-R scoring system, heterogeneity in the rate of disease progression across patients, manifesting as large variation in the rate of change of the ALSFRS-R scores, typically renders Phase II trials under-powered (if they are relying on clinical endpoints rather than biomarkers).

ALS targets and mechanisms with high therapeutic potential have been shown to exhibit:

- Genetic and histopathological validation
- Potential to hit multiple key mechanisms underlying motor neuron degeneration
- Potential to impact axonal degeneration
- Effect on key biomarkers such as Neurofilament light (NfL)
- Mechanistic validation in ALS models
- Positive early clinical phase data

Promising Targets in ALS:

TDP-43

(TAR DNA Binding Protein 43) is a highly prevalent proteinopathy, affecting ~ 97% of ALS patients

TDP-43 cytosolic gain-of-function or nuclear loss-of-function or combination of both may be responsible for ALS pathology

Mechanism: proteostasis

Companies working on **TDP-43** (all are preclinical or earlier):

- Dewpoint Tx has a small molecule program with NfL biomarker assessment; partnered with Mitsubishi Tanabe
- Celosia Tx has pioneered a genetic proteolysis targeting chimera (genProTAC) which is a degrader targeting TDP-43
- Promis Neuroscience and AC Immune are developing mAbs

- VectorY Therapeutics is progressing a vectorized antibody

SPTLC1

(Serine palmitoyltransferase, long chain base subunit 1)

SPTLC1 acts upstream to TDP-43 and is a component of the SPT enzyme complex; essential for the first step in the de novo synthesis of sphingolipids

Mechanism: Lipid Metabolism

A novel target, recently identified as an ALS genetic driver

Leal Therapeutics plans to initiate a Phase I/II trial of its ASO candidate in H2, 2025 with PoM data by end of ’25 and clinical trial readout in 2026. NfL and other biomarkers are incorporated into Leal’s clinical development plan.

UNC13A

is a synaptic gene directly regulated by TDP-43

If UNC13A translation is dysfunctional, it leads to UNC13A misplacing, with consequent loss of function; UNC13A genetic variants have been associated with reduced survival in people with ALS

Mechanism: Neurotransmission; Neuromuscular junction

Trace Neuroscience, AcuraStem and QurAlis (partnered with Lilly) are all developing ASO assets targeting UNC13A

Sigma-1 receptor (S1R)

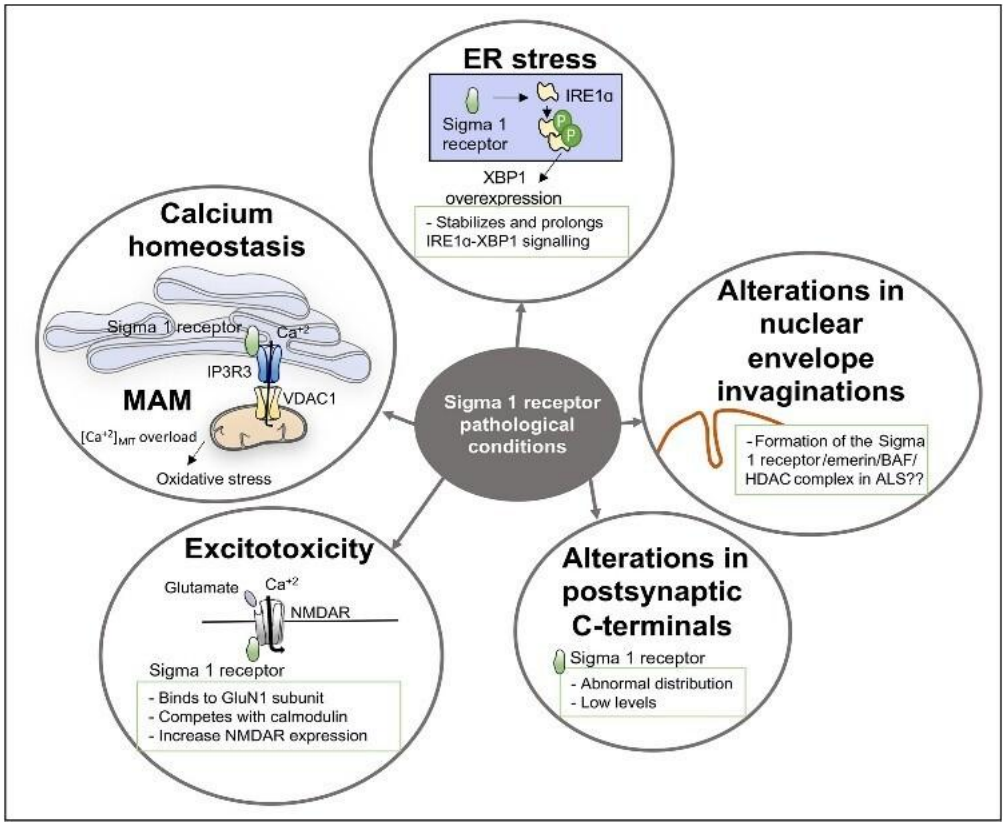
is a protein ubiquitously expressed in the CNS and particularly enriched in motor neurons

S1R is involved in ion channel modulation, synaptic function, protein and lipid transport, ER stress response and mitochondrial function.

S1R loss of function variants cause a severe juvenile form of ALS and missense variants are associated with an adult form, showing a correlation between S1R function and age of ALS onset

Mechanism: Neuroprotection

Prilenia is developing an oral therapy, Pridopidine, now in a Phase III trial; positive impact on NfL and other biomarker levels shown in Phase II



Companies in registrational trials or with pending regulatory decisions:

MEDICINOVA

NEUVIVO

TRANSPOSON

BRAINSTORM THERAPEUTICS

AB SCIENCE

RAPA THERAPEUTICS

NeuroSense Therapeutics

CLene NANOMEDICINE

Renewed Enthusiasm for Neuro-Therapeutics in ALS Is Reflected in Big Pharma's Recent Investments

Company	ALCHEMAB THERAPEUTICS	QurAlis	insitro	DEWPOINT THERAPEUTICS	VERGE genomics	prilenia
Partner	Lilly	Lilly	Bristol Myers Squibb		Lilly	ferrer for good
Deal Type	Partnership & License	License	Milestone Payment	Partnership	Partnership	Collaboration & License
Deal Value	**$415M**	**$577M**	**$25M**	**$480M**	**$700M**	**$500M**
Indications	ALS	ALS	ALS	ALS	ALS	ALS
Modality	mAb	ASO	AI / Platform	Small Molecule	Not Disclosed	Oral
Targets	UNC5C	UNC13A	Not Disclosed	TDP-43	Not Disclosed	S1R