

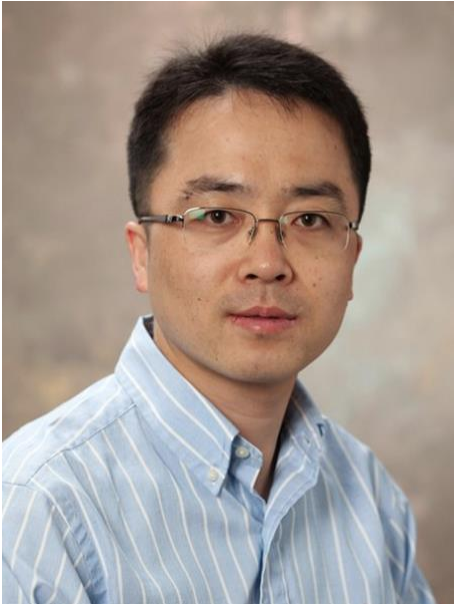


INNOVATING NEURODEGENERATIVE THERAPEUTICS

PIONEERING SMALL MOLECULE
DEVELOPMENT FOR A NOVEL TARGET

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ALS is a Devastating Disease

Amyotrophic lateral sclerosis (**ALS**) or Lou Gehrig's Disease is a **terminal** neurodegenerative disease that impacts motor neurons. ALS patients progressively **lose the ability to move, speak, eat, and breathe.**

Most common
motor neuron
disease

5,000+ patients
diagnosed each
year in US

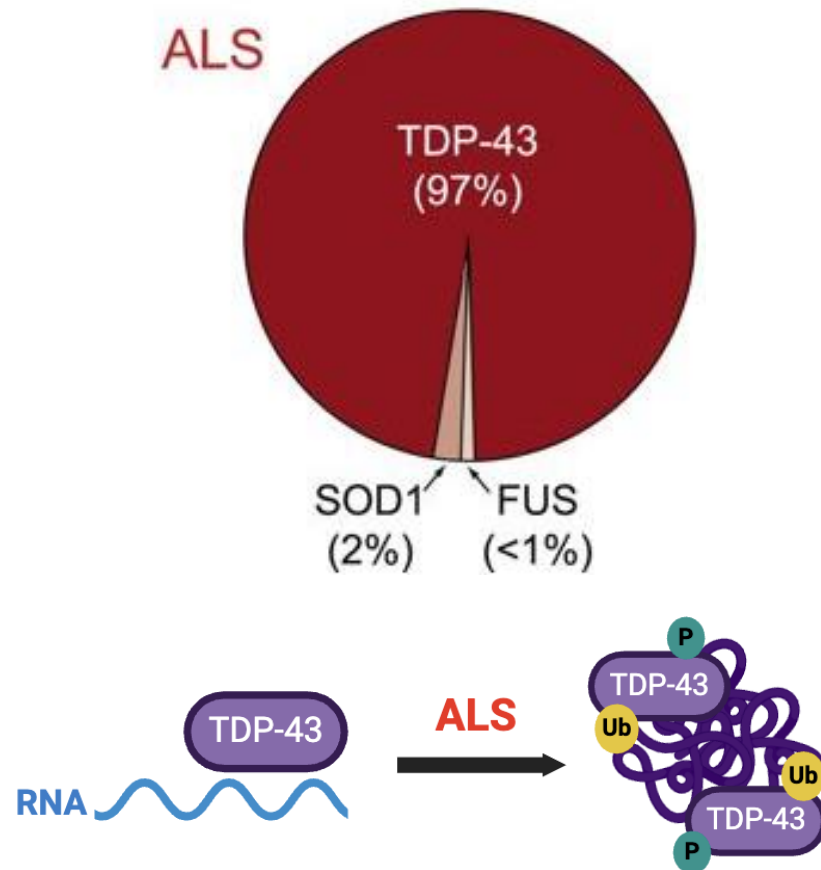
Life expectancy
is **2-5 years**
from diagnosis

There is no cure for ALS patients

Current ALS Treatments have Limited Efficacy

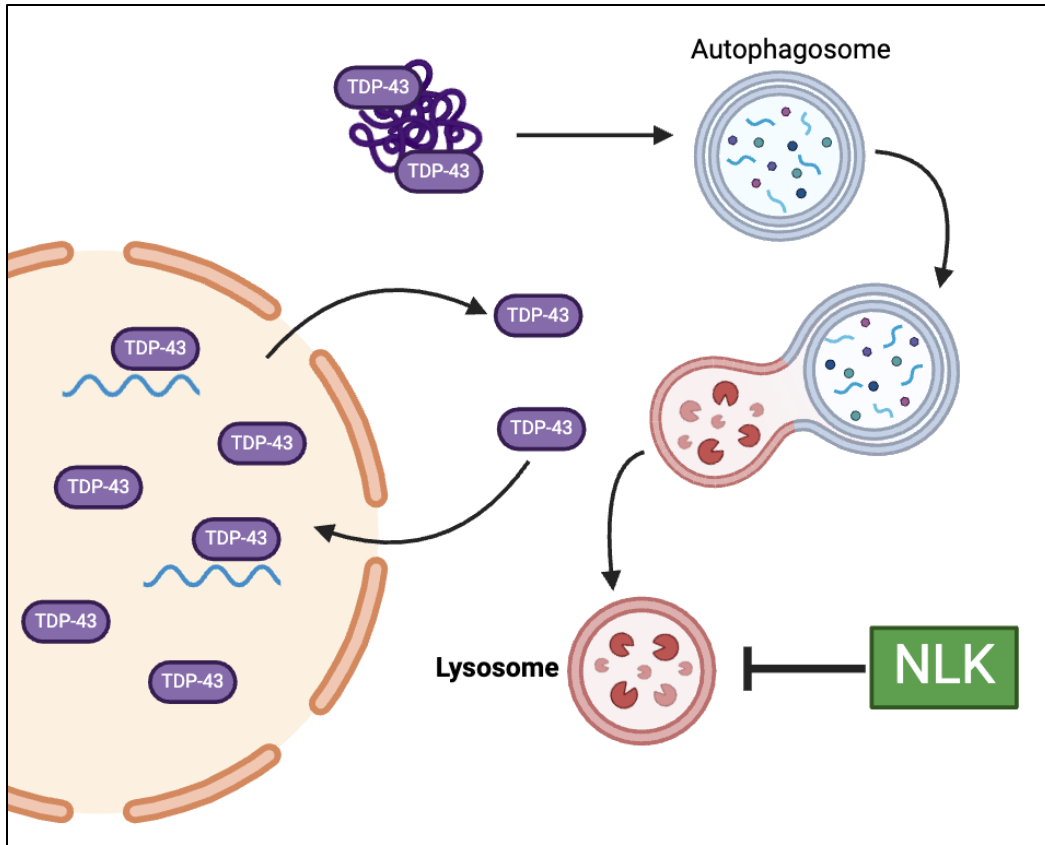
Therapeutic	Life Expectancy Extension	Symptom Improvement	Formulation	FDA Approval	Target Population (%)
<div style="border: 1px solid green; padding: 2px; display: inline-block;">Most Popular Treatment</div> Riluzole	3 months	Marginal	<ul style="list-style-type: none"> • Tablet, • Suspension • Film 	1995	100%
Edaravone	6 months	Marginal	<ul style="list-style-type: none"> • IV • Suspension 	2017	100%
Toferson	TBD	Marginal	<ul style="list-style-type: none"> • Intrathecal injection 	2023	2%
Dextromethorphan and Quinidine	No	Non-motor symptoms	<ul style="list-style-type: none"> • Capsule 	2011	100%

Insoluble TDP-43 is a Neurodegenerative Biomarker of ALS



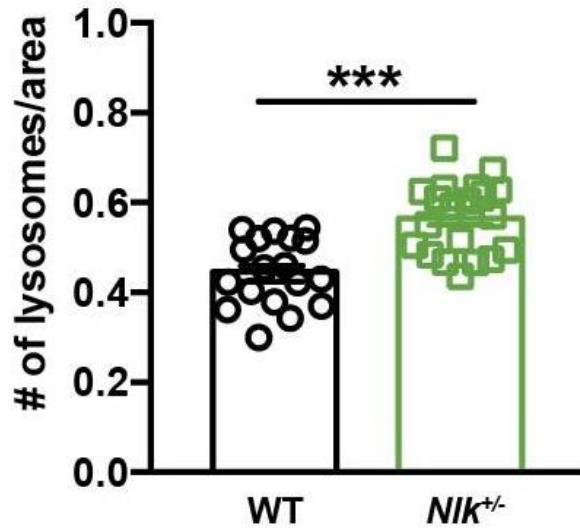
- Found in **97% of ALS cases**
- **Linked** to ALS Pathophysiology
- **Validated** across **Clinical Studies**
- **Correlates** with Disease Progression

NLK Reduction is a Novel Mechanism to Clear Protein Aggregates



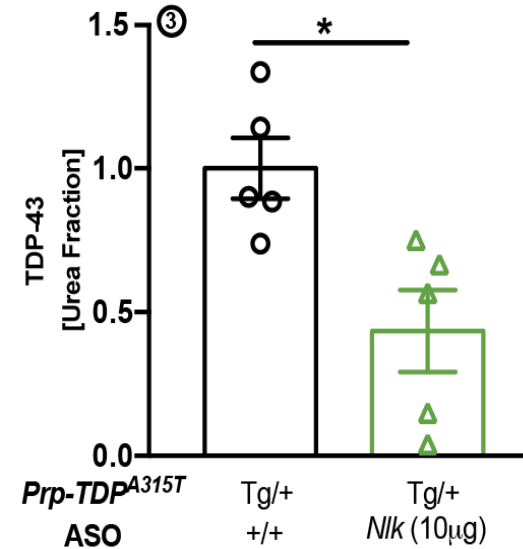
↓ NLK = ↑ Lysosome biogenesis = ↓ Insoluble TDP-43 = ↑ SLOWS ALS Progression (Life Expectancy)

NLK Reduction Increases Lysosome Number and Decreases Pathogenic TDP-43 Levels *in vivo*



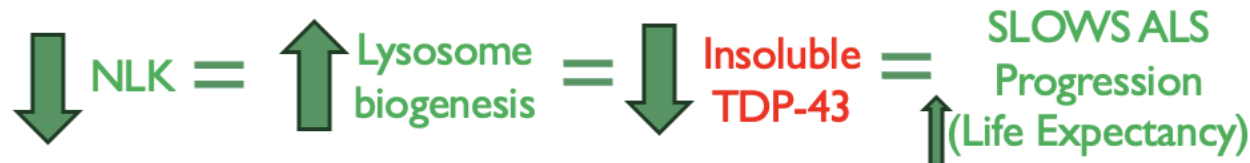
NLK Knockdown

NLK reduction leads to a **30% increase** in lysosome number *in vivo*



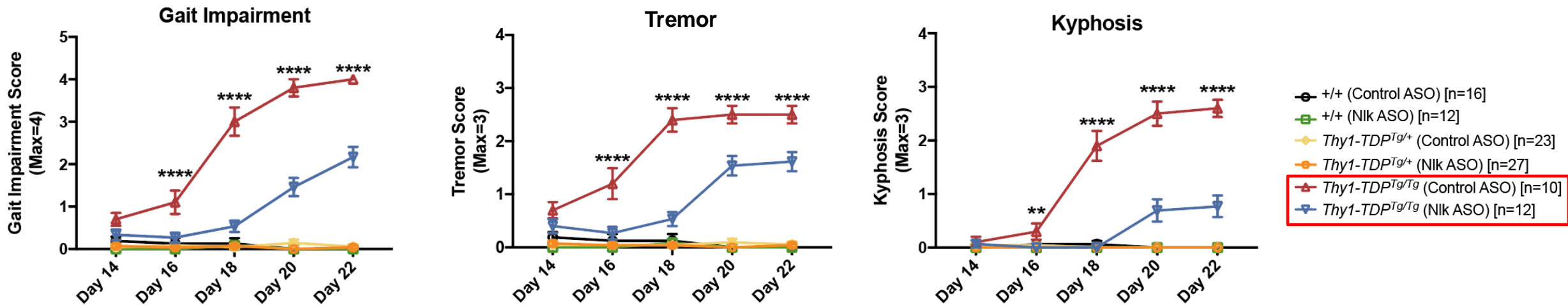
IONIS

NLK ASO (Ionis) administration reduces insoluble TDP-43 by **50%** in *TDP-43*^{A315T} mice



IN VIVO TARGET VALIDATION

NLK ASO (Ionis) Improves Motor Behavior in ALS Mouse Model

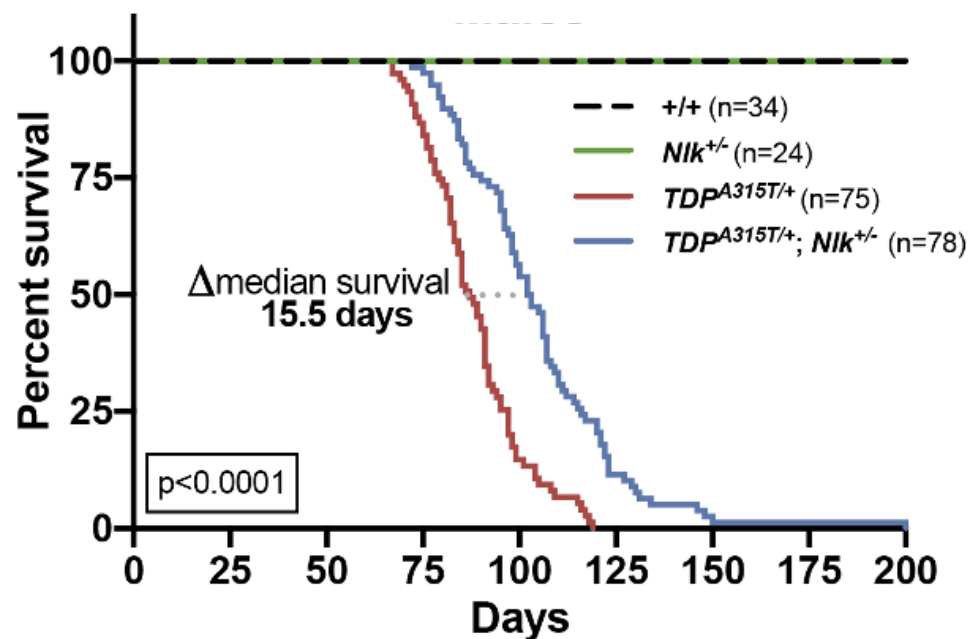


Pharmacological reduction of NLK improves motor phenotypes >50% in Thy1-TDP^{Tg/Tg} mice

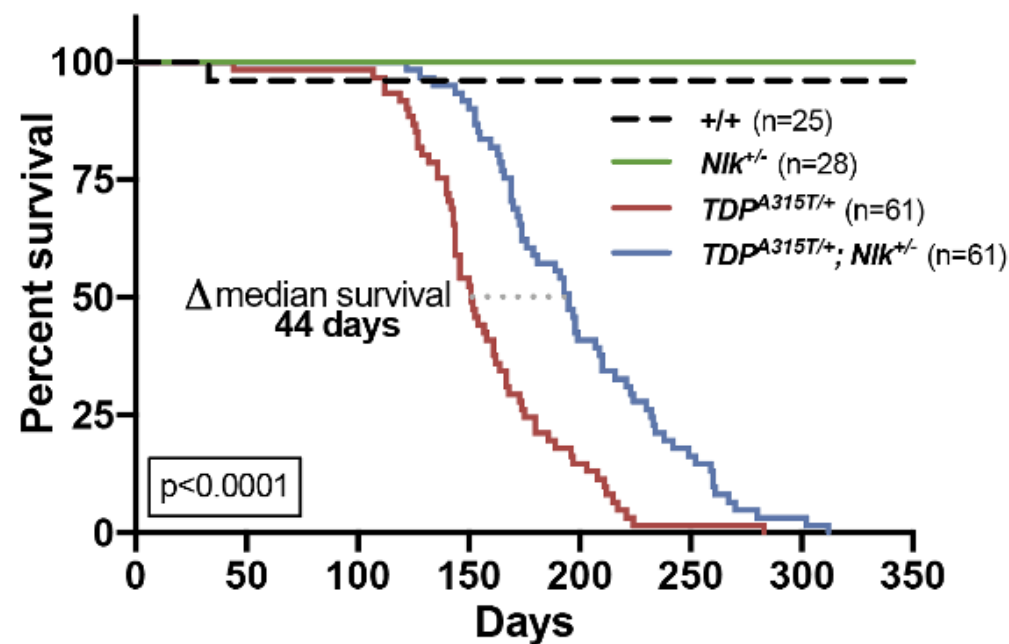
IN VIVO TARGET VALIDATION

NLK Reduction Improves Survival in ALS Mouse Models

Males



Females

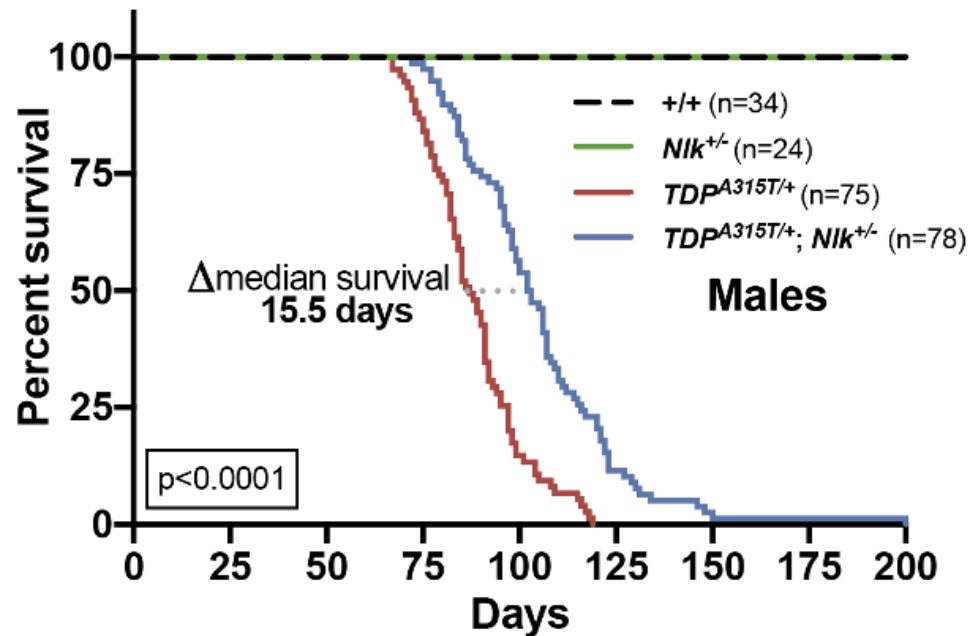


NLK knockdown reduction improves survival by **20%** in *TDP-43*^{A315T}

IN VIVO TARGET VALIDATION

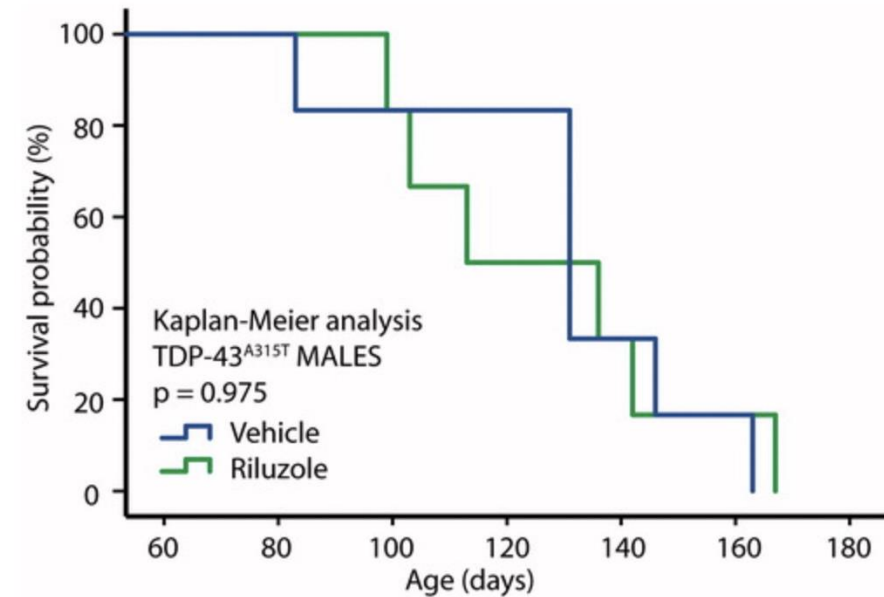
NLK Reduction Outperforms Riluzole Administration

NLK Reduction



Riluzole

Most Popular ALS Treatment in Clinic



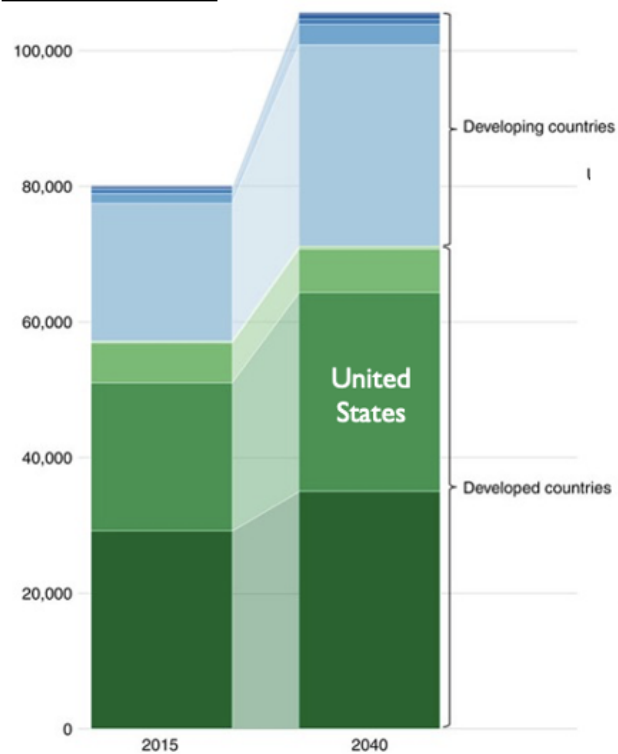
NLK knockdown reduction improves survival by 20% in TDP-43^{A315T} mice.

Riluzole administration does not alter lifespan

IN VIVO TARGET VALIDATION

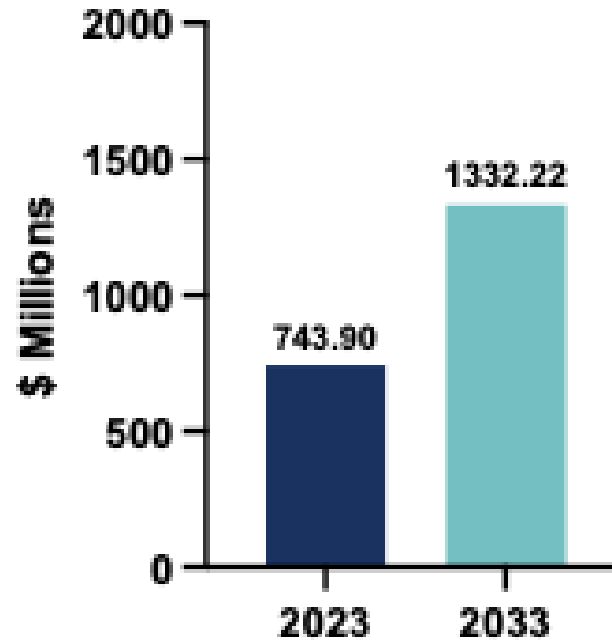
ALS Market Size is Growing

ALS Cases



Arthur et al., 2016

ALS Market



ALS cases are projected to **increase 35%** by 2040 in the US

ALS market is predicted to grow at a **CAGR of 6%**

ALS Competitive Landscape

ALS Interventions



ALS Target Areas

- Neuroinflammation
- Excitotoxicity
- Oxidative stress
- Anti-aggregation
- Cell death

ALS Therapy Types

- Small molecules
- Gene therapies
- Monoclonal antibodies
- Stem cells

Development of Highly Efficacious Oral Small Molecule NLK Inhibitors

