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Development of novel small molecules targeting neurotrophic HGF signaling for the treatment of Alzheimer's, Parkinson's, and ALS

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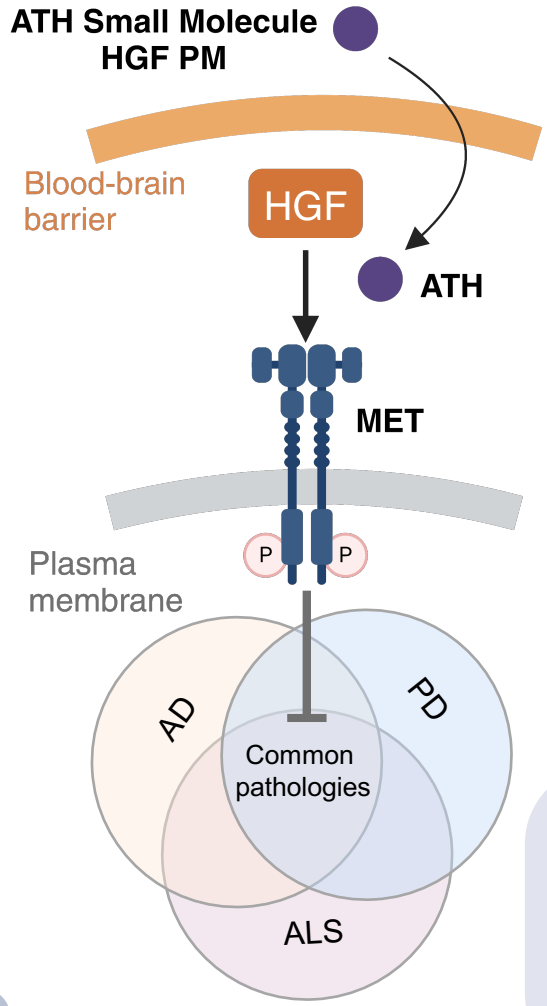
Positive modulation of HGF for the treatment of neurodegenerative disorders

- Neurodegenerative disorders including AD, PD, and ALS:
  - Distinct symptomology
  - Multiple shared pathologies
- Deficits in neurotrophic signaling render neurons vulnerable to neurodegenerative mechanisms
- Activation of the neurotrophic hepatocyte growth factor (HGF) system promotes:
  - Neuronal health and repair
  - Neuroprotection
  - Anti-inflammatory effects



ATH small molecule HGF PMs

Fosgonimeton	ATH-1020	ATH-1105
SC Injectable, CNS	Oral, CNS	Oral, CNS/PNS

- All ATH small molecules positively modulate pleiotropic HGF activity
- Individual molecules have distinct administration and distribution characteristics

Common Pathologies:
- Protein pathology
- Mitochondrial dysfunction
- Excitotoxicity
- Autophagic impairment
- Neuroinflammation
- Neurodegeneration

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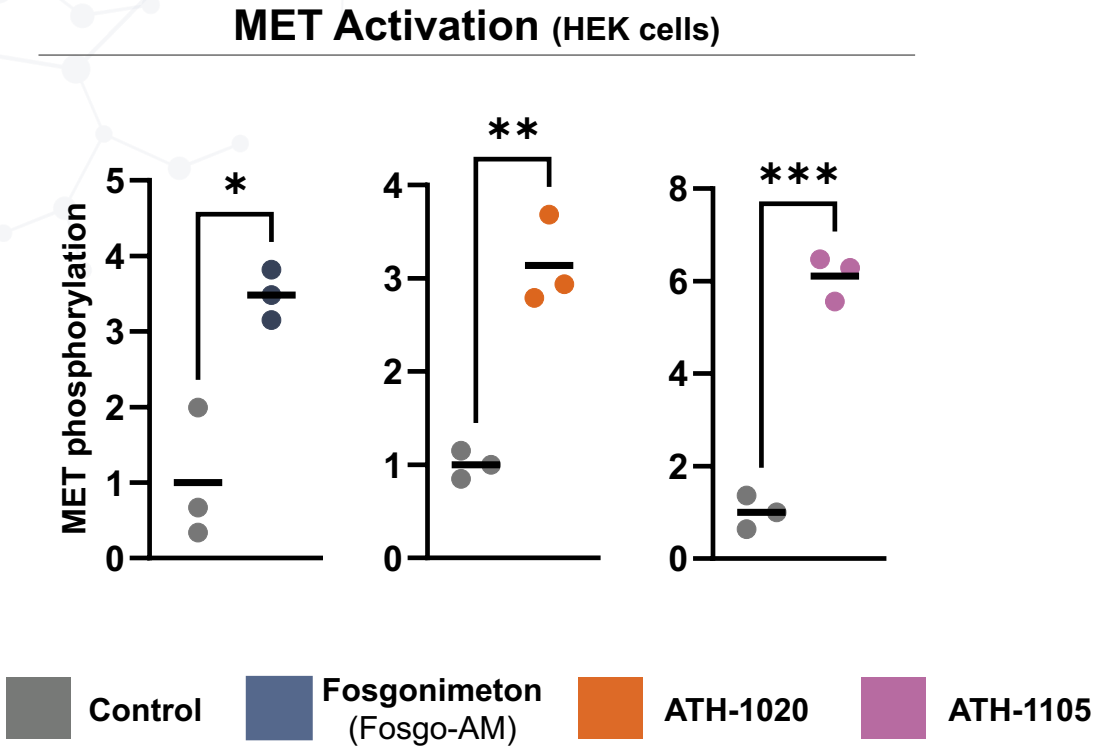
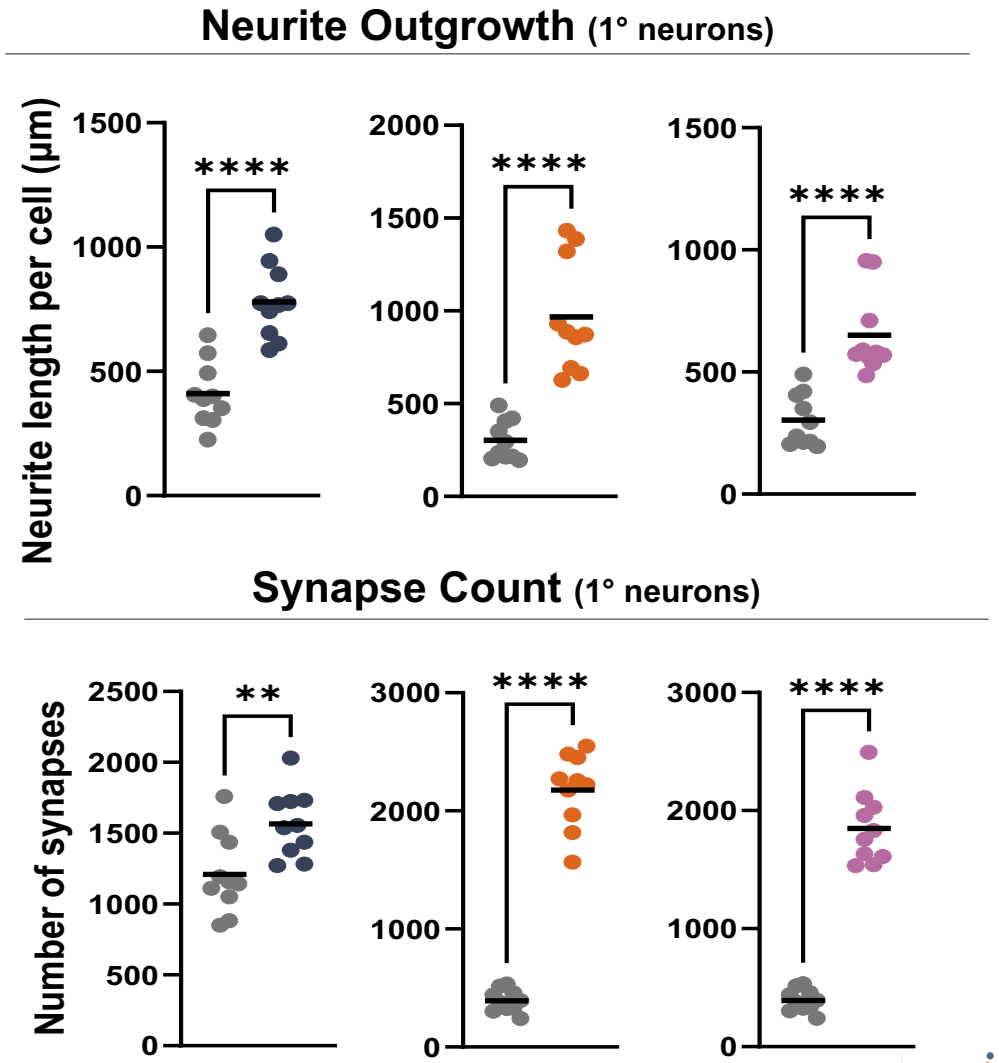
HGF positive modulators have neurotrophic effects in vitro

Increased activation of MET by HGF positive modulators promotes neurite outgrowth and synaptogenesis in primary neurons





HEK293 cells were treated with the indicated ATH molecule in vehicle containing a low dose of HGF (1 ng/ml). MET phosphorylation (Y1234/1235) was quantified via ELISA.
Primary hippocampal neuron cultures were treated with ATH compounds for 3-4 days and evaluated for morphological hallmarks of mature neurons.
Fosgonimeton, ATH-1020, and ATH-1105 produced greater neuron outgrowth and increased synapse counts, indicating that these compounds enhance neurotrophic HGF signaling.
Statistics: Student's t-test, ** = p< 0.01, **** = p < 0.0001

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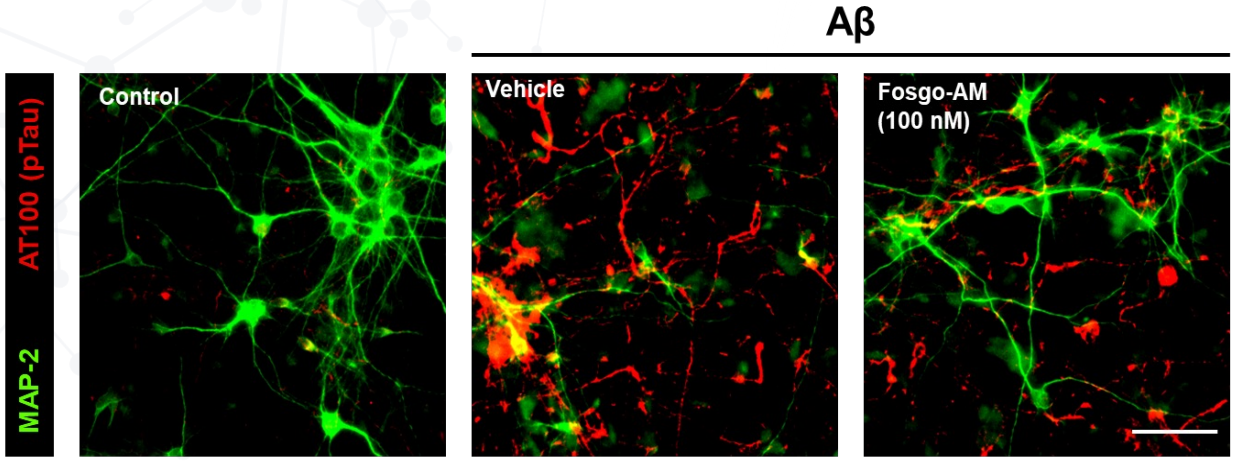
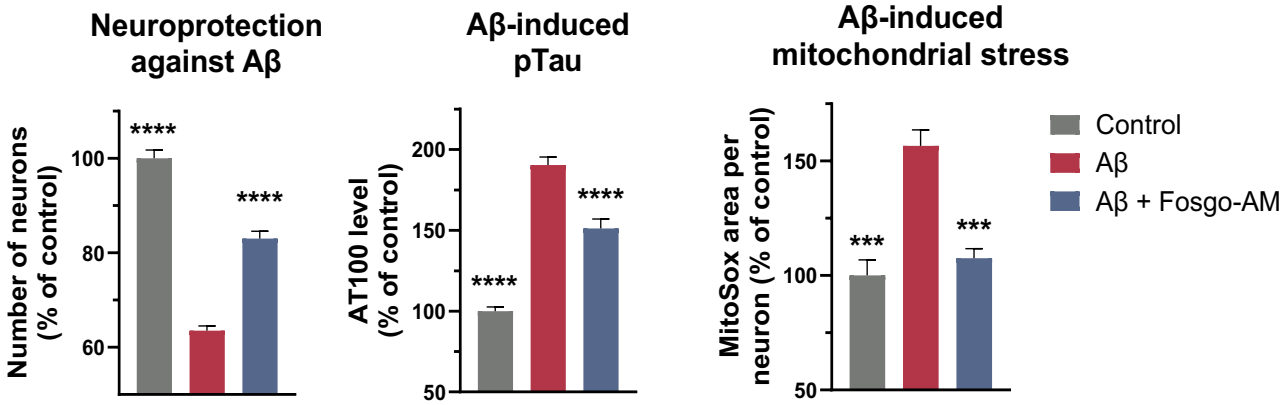
Positive modulation of the HGF system in preclinical models of AD

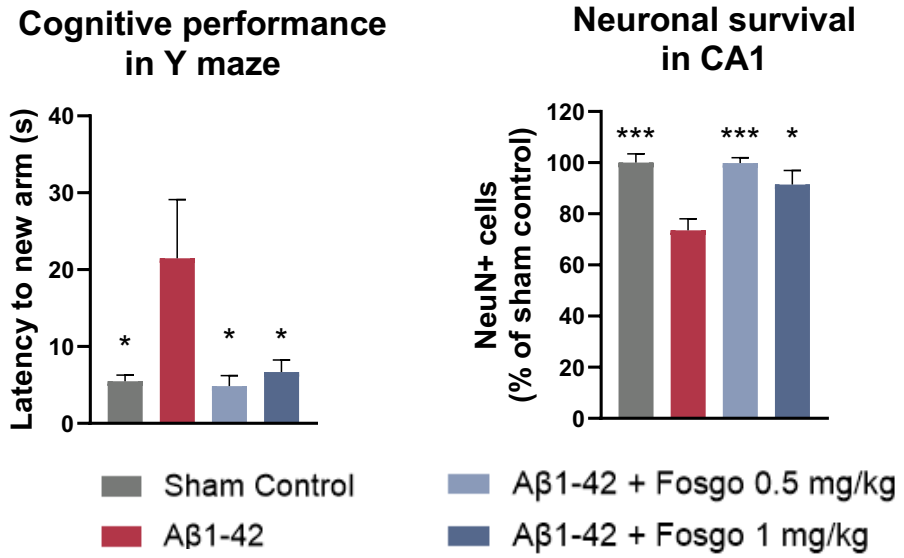
Primary cortical neurons challenged with Aβ





Primary rat cortical neurons in culture were incubated with Aβ oligomers and processed for imaging with the following assessments: Neuron survival by number of MAP2+ cells, pTau accumulation by AT100 staining, and mitochondrial stress by MitoSox.
Statistics: One-way ANOVA with Fisher's LSD, *** p< 0.001, **** p < 0.0001 vs Aβ

Intrahippocampal delivery of $A\beta_{1-42}$ in aged mice



Aβ1-42 oligomers were delivered to the hippocampus of aged (18 month) male mice as a model of AD-related pathology. Spatial memory performance was assessed by latency to enter the new arm of a Y-maze and neuronal survival was assessed by NeuN+ cells in hippocampal CA1 area. Statistics: One-way ANOVA with Dunnett's post test, * p< 0.05, *** p< 0.001 vs Aβ, outliers by Grubb's test removed from Y-maze.

Treatment with fosgonimeton attenuates Aβ-induced pathology in both in vitro and in vivo systems

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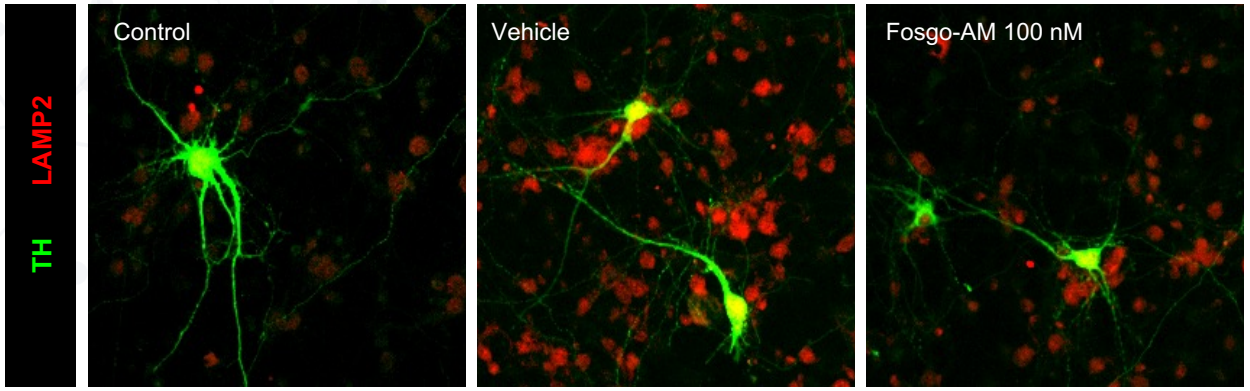
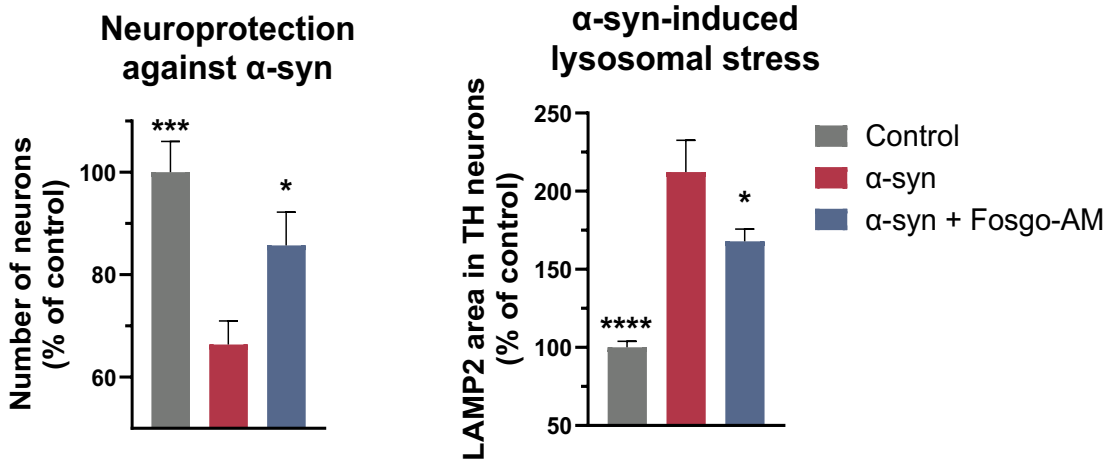
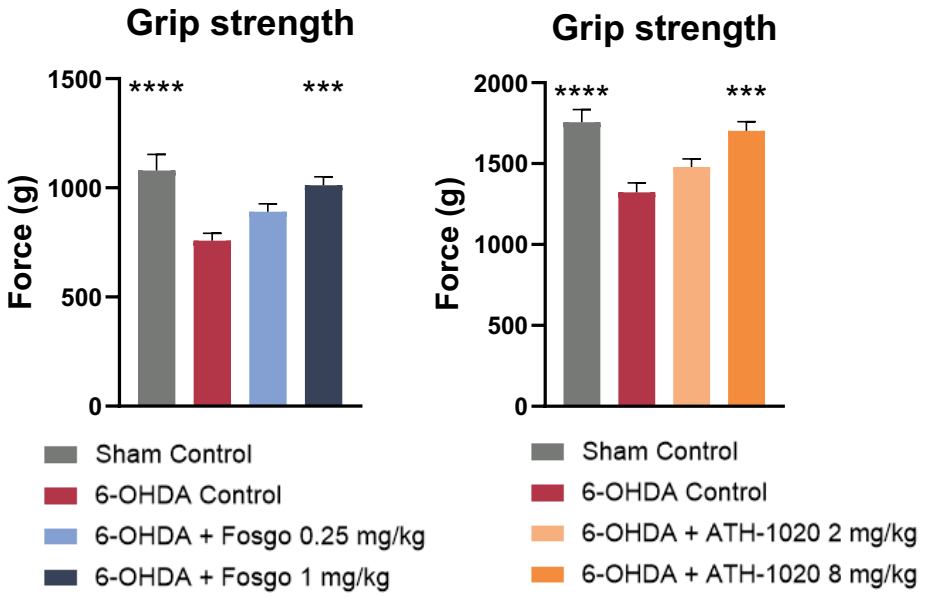
Positive modulation of the HGF system in preclinical models of PD

Primary dopaminergic neurons challenged with α-syn





6-OHDA model of Parkinson's disease in rats



Treatment with fosgonimeton or ATH-1020 attenuate PD-relevant pathologies in both in vitro and in vivo systems

α-synuclein PFF were used to produce PD-related phenotypes in primary dopaminergic neuron culture. Treatment effects of fosgo-AM (100nM) were assessed in imaging experiments using TH+ cell counts and staining for LAMP2. Statistics: One-way ANOVA with Fisher's LSD, * p< 0.05 *** p< 0.001, **** p< 0.0001 vs α-syn
6-OHDA was delivered to the striatum of male rats to produce PD-like pathology. Preclinical efficacy of ATH-1020 via oral gavage was assessed by measurement of grip strength. Statistics: One-way ANOVA with Dunnett's post test, *** p< 0.001, **** p< 0.0001 vs 6-OHDA

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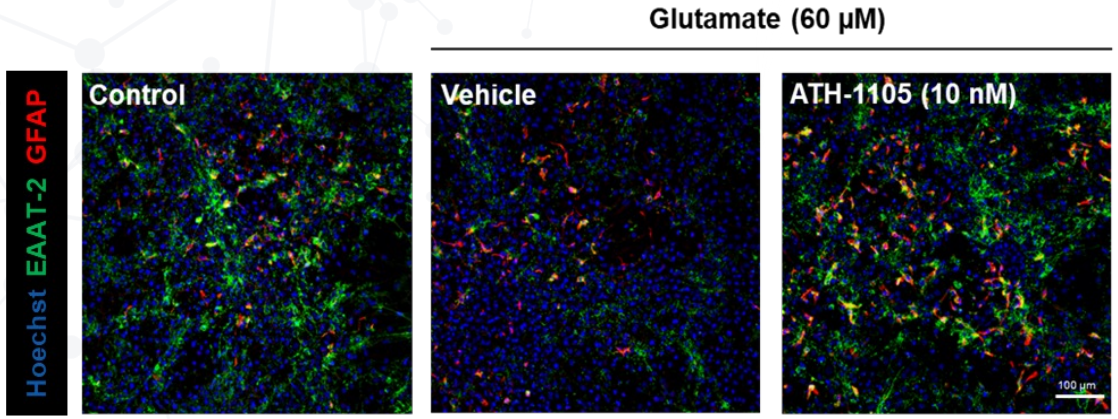
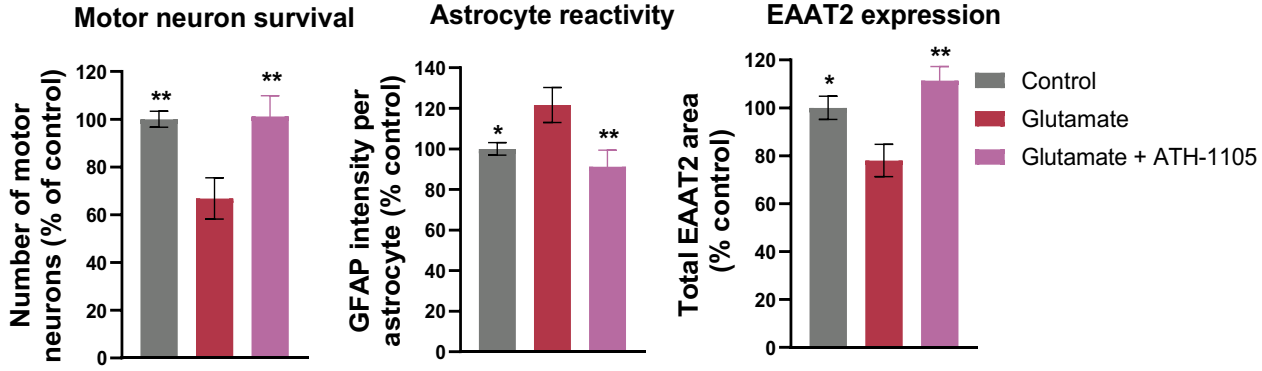
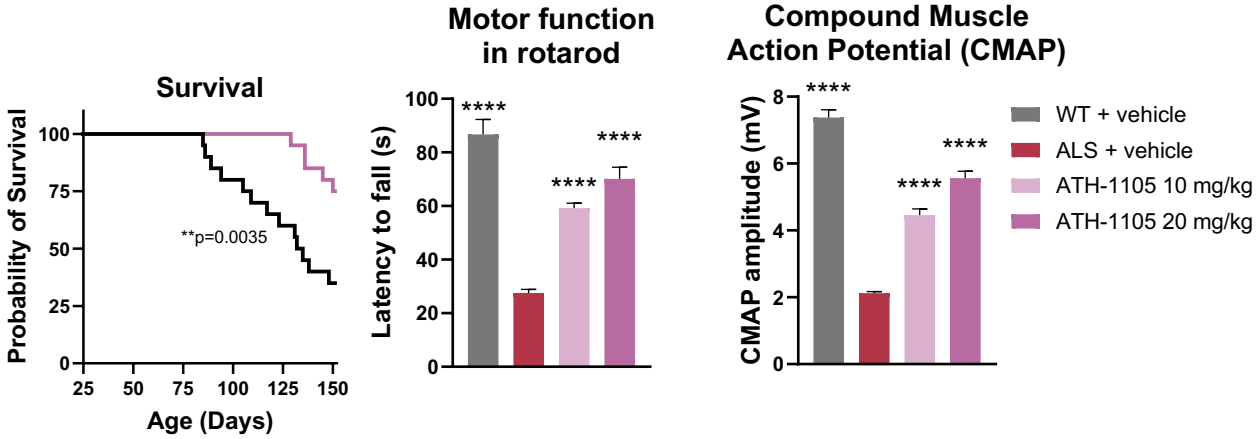
Positive modulation of the HGF system in preclinical models of ALS

Primary motor neurons challenged with glutamate





Prp-TDP-43^{A315T} transgenic mouse model of ALS



Treatment with ATH-1105 attenuates ALS-related pathology, improves motor and nerve function and extends survival in preclinical models of ALS

GFAP, Glial fibrillary acidic protein; EAAT2, Excitatory amino acid transporter-2,
Statistics applied: One-way ANOVA with LSD; *p<0.05, **p<0.01 vs. Glutamate alone. n = 5-6. Scale bar = 100 µm. Rat primary cell cultures treated with glutamate (60 uM) and/or ATH-1105 (1 nM).
Prp-TDP43^{A315T} transgenic mice develop progressive ALS-like phenotypes including deficits in both motor behavior and nerve function. Animals were treated with ATH-1105 via oral gavage at the indicated doses. Motor behavior was assessed by latency to fall in rotarod and nerve function was assessed by measuring the amplitude of compound muscle action potential between the sciatic nerve and the muscles of the foot. Statistics: One-way ANOVA with Dunnett's post test, **** p < 0.0001 vs ALS + vehicle

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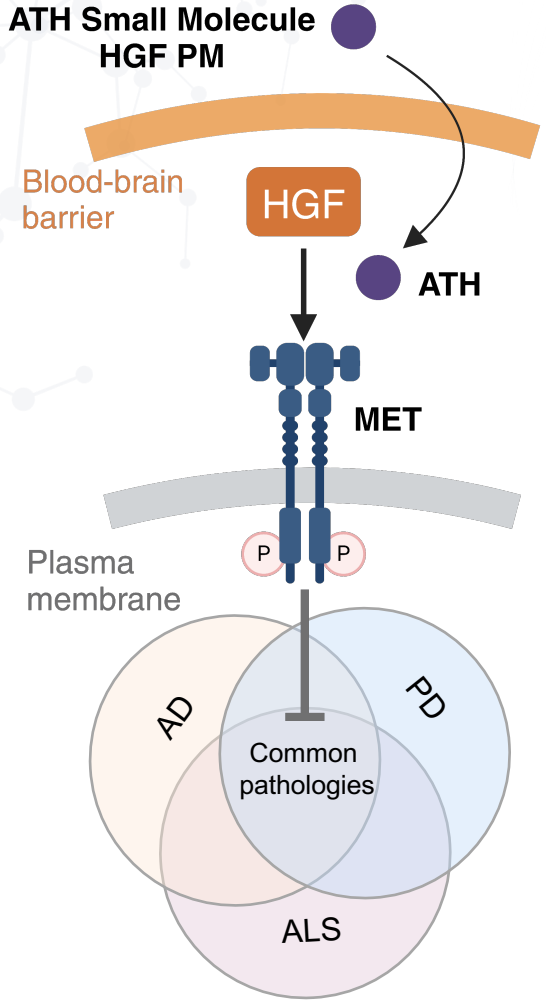
Positive modulators of HGF are in development for the treatment of neurodegenerative diseases



Program	Indication	PRECLINICAL: Early Discovery	PRECLINICAL: IND-Enabling Studies	CLINICAL: Phase 1	CLINICAL: Phase 2	CLINICAL: Phase 3
Fosgonimeton (Prodrug administered via SC injection)	AD (LiftAD)			Phase 2/3 Clinical Trial		Open-Label Extension
	AD (ActAD*)			Phase 2 Clinical Trial		Open-Label Extension
	PD (Shape*)			Exploratory Phase 2 Clinical Trial		
ATH-1020 (oral)	Neurodegenerative Disease			Phase 1 Clinical Trial		
ATH-1105 (oral)	ALS			IND-Enabling studies		IND Filing in 2024

*These trials are complete with topline data reported in June 2022 and December 2023, respectively.

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