# Therapeutic Potential of Fosgonimeton, a Small-Molecule Positive Modulator of the Neurotrophic HGF/MET Pathway, in Neurodegenerative Conditions

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**Presented by:** Kevin J. Church

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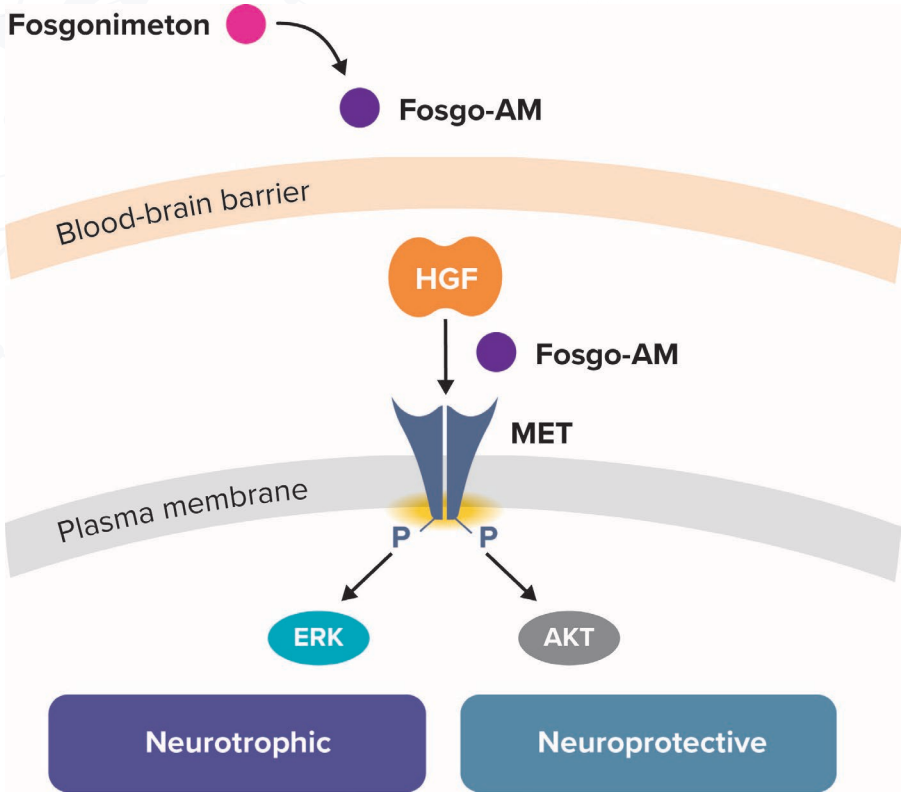
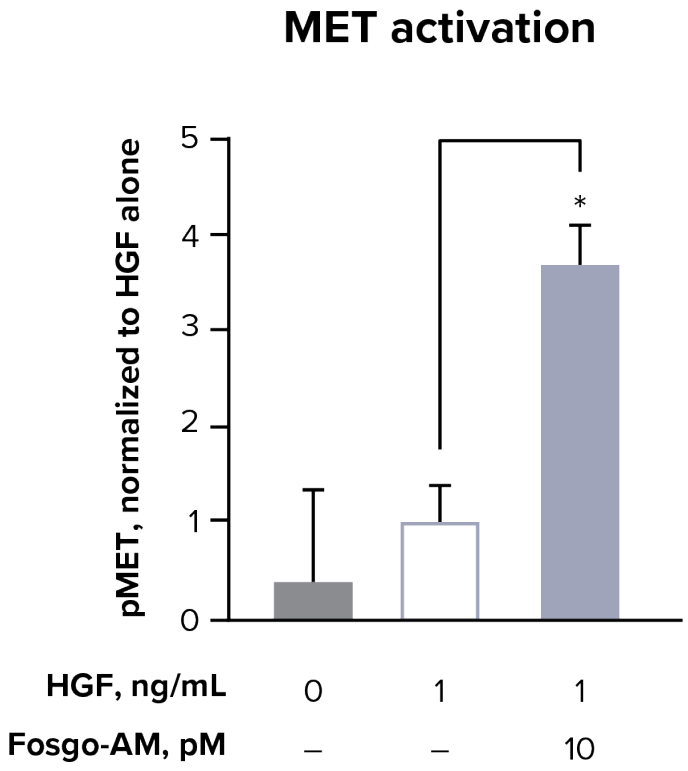
# Disclosures

- Sherif Reda, Robert Taylor, Jewel Johnston, Andrée-Anne Berthiaume, Sharay Setti, and Kevin J. Church are employees and stockholders of Athira Pharma, Inc.

# Positive modulation of the HGF/MET system by fosgonimeton promotes neuroprotective and neurotrophic effects




- Fosgonimeton, a novel small molecule, rapidly converts to its active metabolite (fosgo-AM)
- In the presence of HGF, fosgo-AM significantly enhances activation of the MET receptor[1]

AKT, protein kinase B; ERK, extracellular signal-related kinase; HGF, hepatocyte growth factor; P, phosphorylation; pMET, phosphorylated MET.
Statistics applied – One way ANOVA with Dunnett's posttest; *$p < 0.05$ vs. HGF 1 ng/ml.

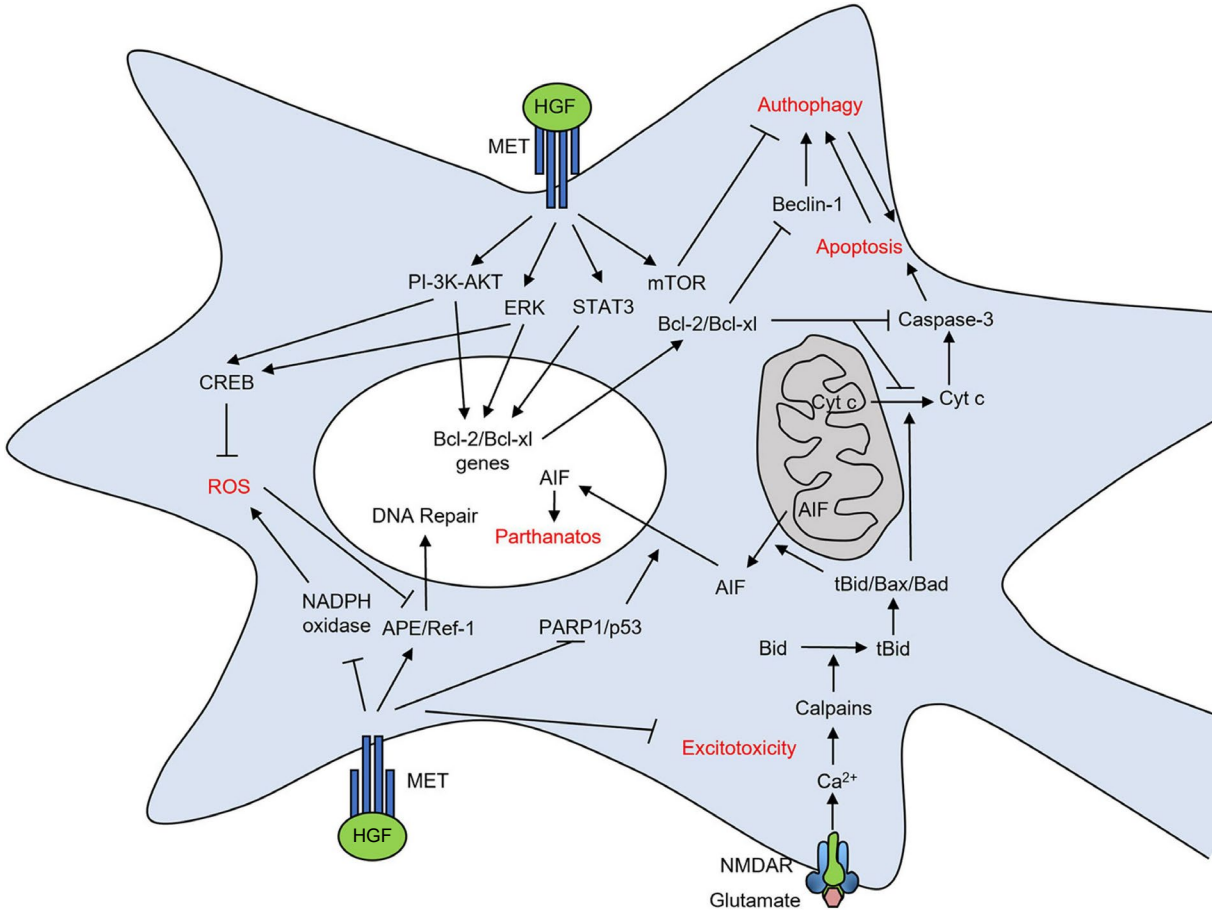
**1.** Johnston JL et al. *Neurotherapeutics*. 2022;19:1413-1431.

# HGF/MET as a therapeutic target

- HGF is a neurotrophic factor and the exclusive ligand for the MET receptor
  - The importance of HGF/MET activity for CNS health and repair is well-established[1-3]
- HGF/MET signaling induces multimodal effects, including
  - Neuroprotection[4-6]
  - Neuro-regeneration[7-9]
  - Anti-inflammation[10,11]

**Targeting the HGF/MET system may address the complex pathology in neurodegenerative diseases, such as AD and PD**

**HGF/MET signaling in neurons**

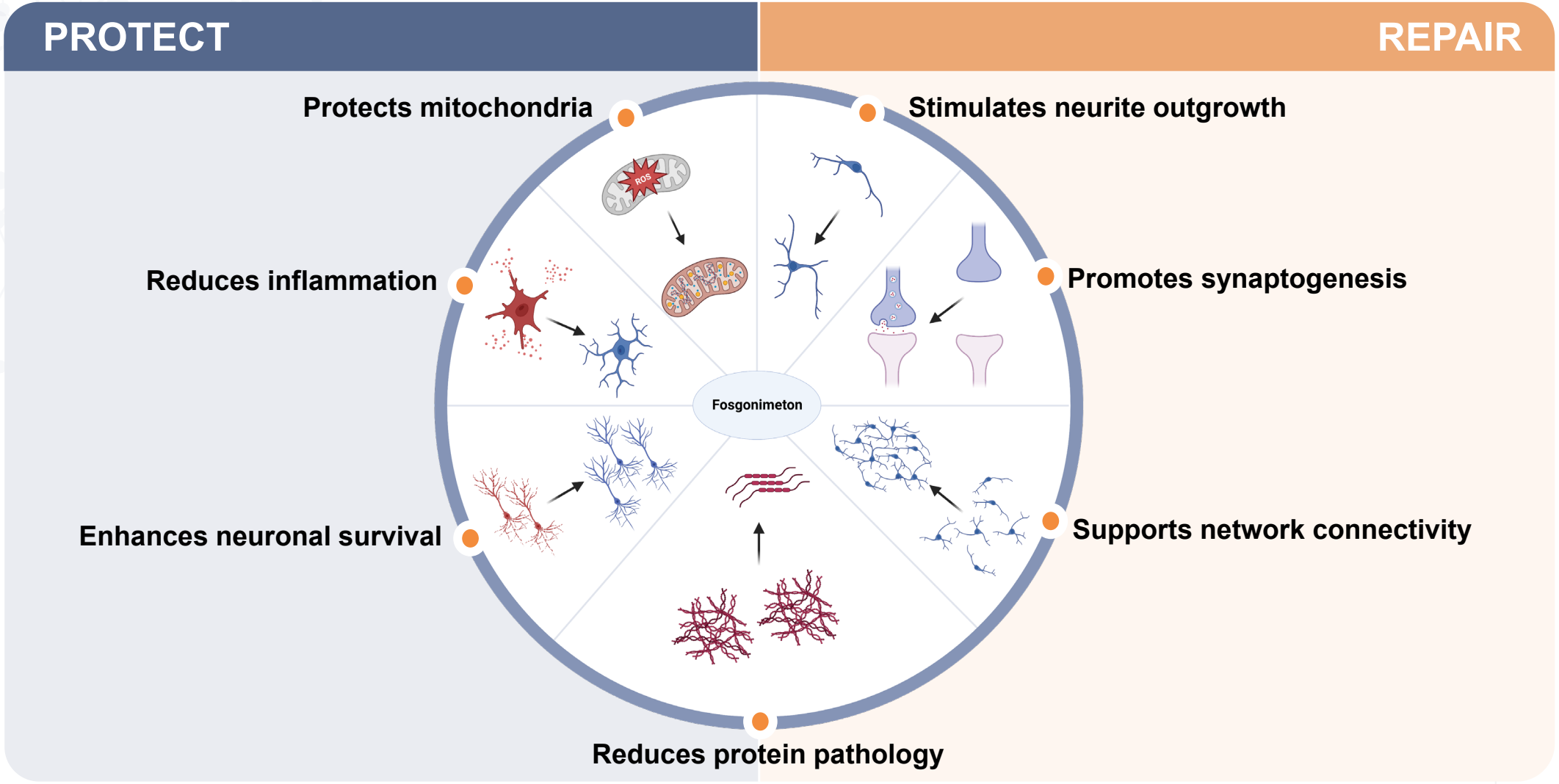



AD, Alzheimer's disease; CNS, central nervous system; HGF, hepatocyte growth factor; PD, Parkinson's disease.

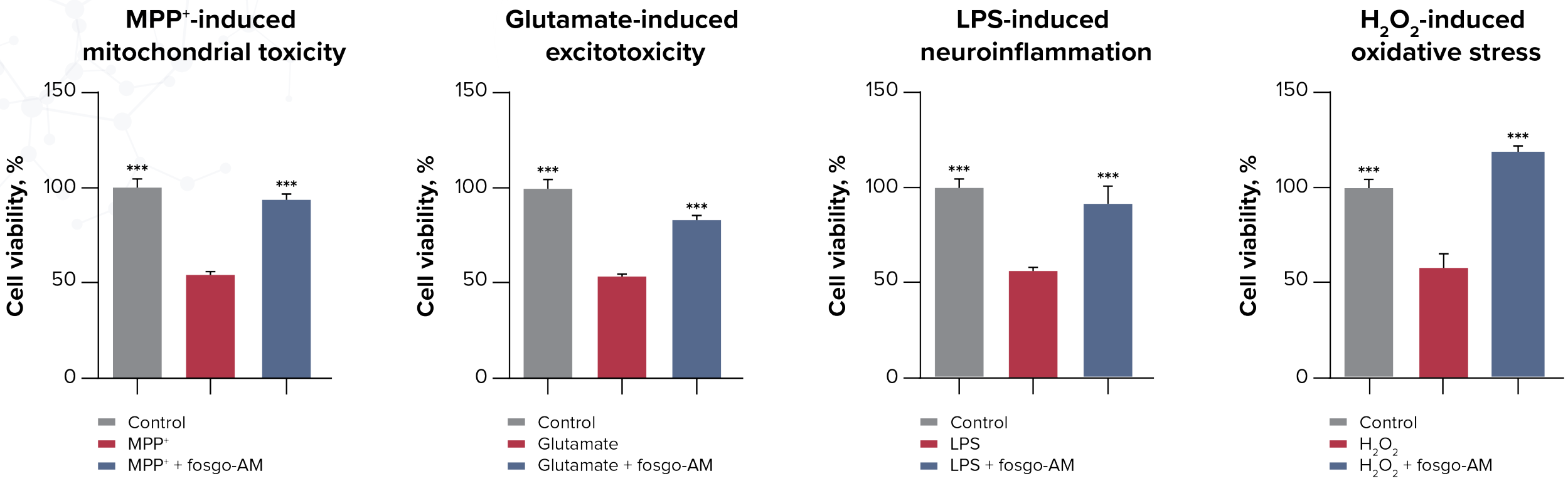
**1.** Desole C et al. *Front Cell Dev Biol*. 2021;9:683609. **2.** Funakoshi H et al. *Curr Signal Transduct Ther.* 2011;6:156-167. **3.** Matsumoto K et al. *Biomedicines.* 2014;2:275-300. **4.** Ishihara N et al. *J Neurochem.* 2005;95:1277-1286. **5.** Akita H et al. *Exp Neurol*. 2008;210:83-94. **6.** Takeuchi D et al. *Gene Ther*. 2008;15:561-571. **7.** Kokuzawa J et al. *Mol Cell Neurosci*. 2003;24:190-197. **8.** Ko KR et al. *Sci Rep.* 2018;8:8316. **9.** Song P et al. *Stem Cell Res Ther.* 2020;11:178. **10.** Coudriet GM et al. *PLoS One.* 2010;5:e15384. **11.** Niskikoba N et al. *Front Immunol.* 2020;11:2135.

Figure adapted from HGF and MET: From Brain Development to Neurological Disorders by Desole C et al. *Front Cell Dev Biol.* 2021;9:683609. This figure is licensed under CC BY. 4.0.

# Fosgonimeton protects and repairs neuronal networks

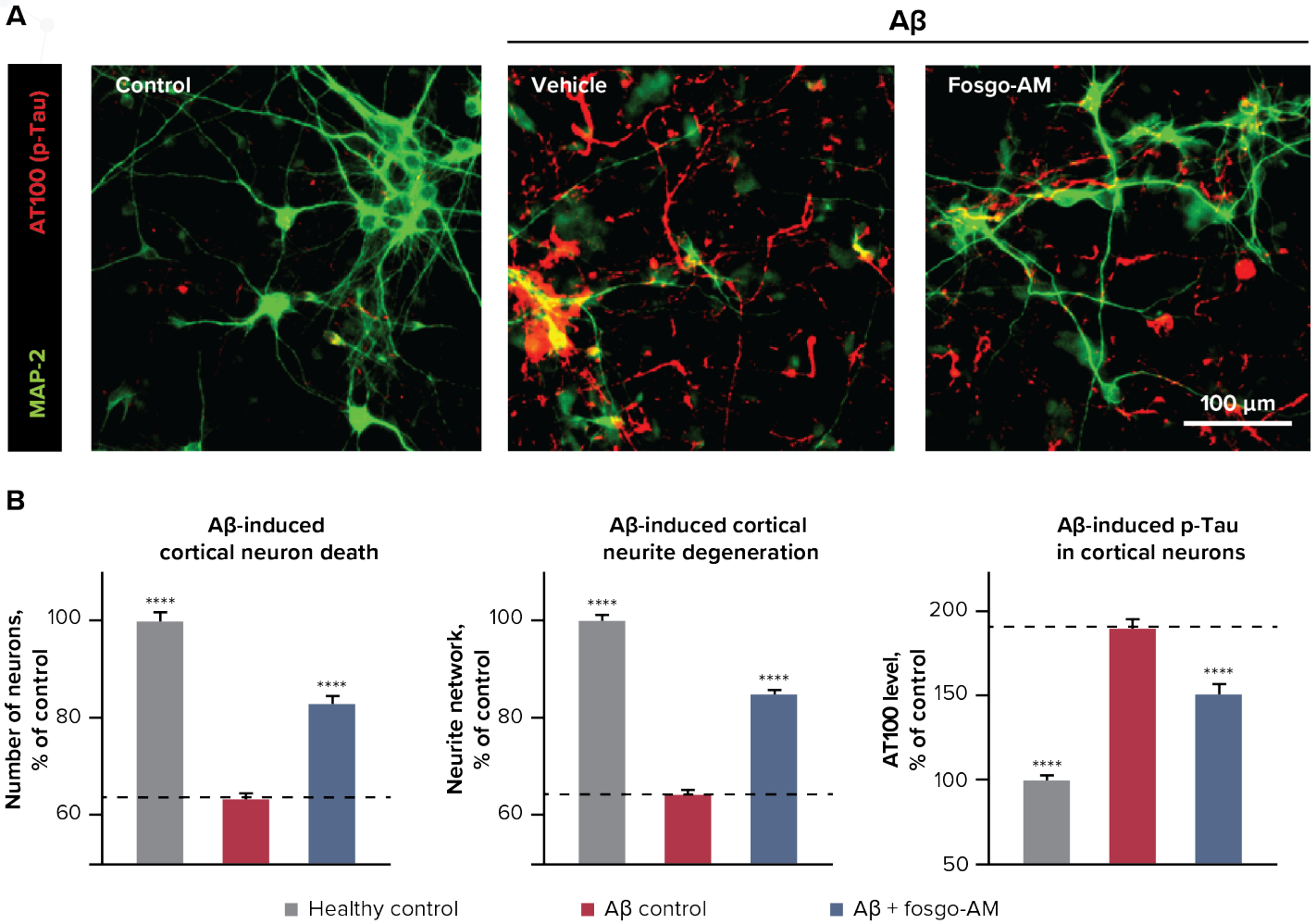


# Fosgo-AM promotes survival of primary neurons subjected to various neurotoxic insults



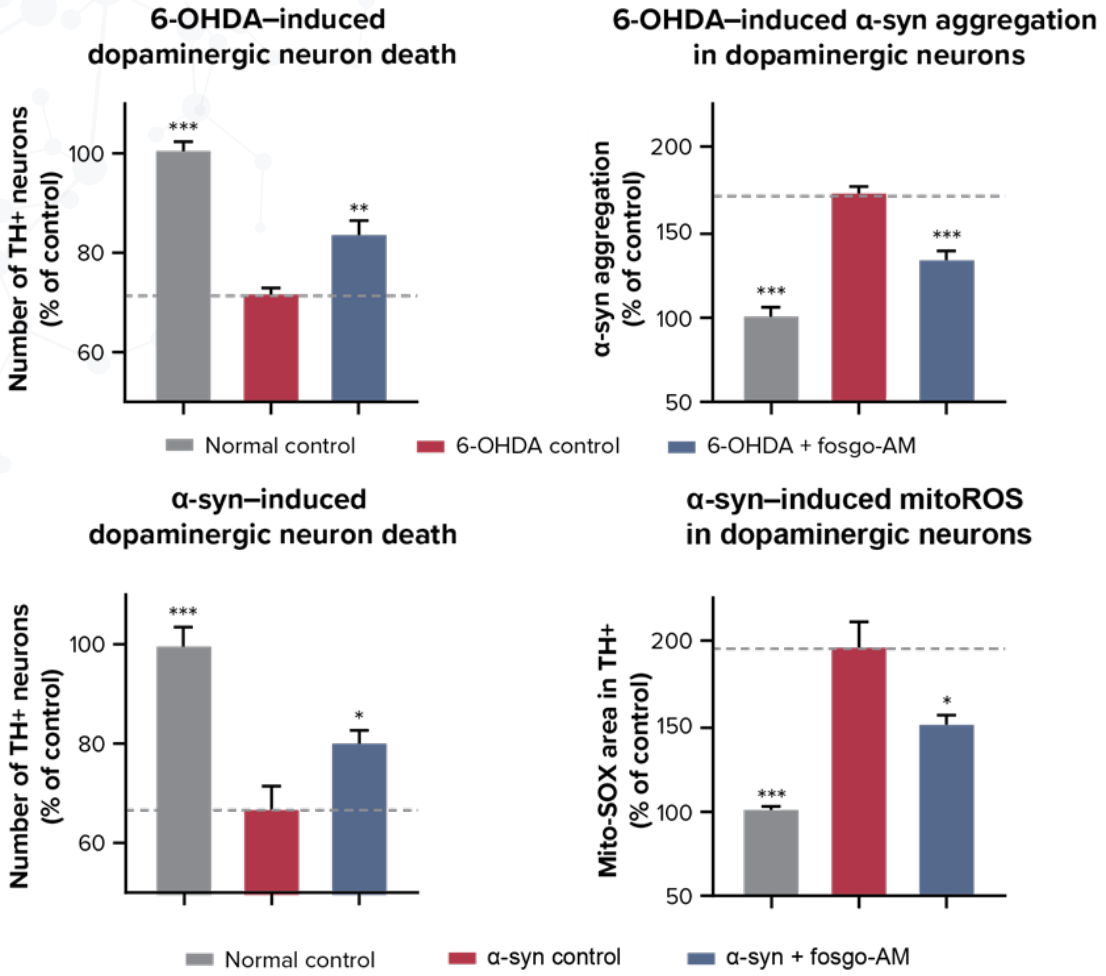

Aβ, amyloid beta; $H_2O_2$, hydrogen peroxide; LPS, lipopolysaccharide; $MPP^+$, 1-methyl-4-phenylpryidinium.
Fosgo-AM, 100 nM; $MPP^+$ 500 µm; Glutamate, 25 µm; LPS, 1 µm; $H_2O_2$, 1 µm. Data presented as mean + SEM. Statistical significance was determined by 1-way ANOVA with Tukey's posttest (n = 4).
Cell viability was determined via CellTiter-Glo (Promega).
***$p < 0.001$ versus insults (red).
Figure adapted from Johnston JL et al. *Neurotherapeutics*. 2022;19:1413-1431. This work is licensed under CC BY. 4.0.

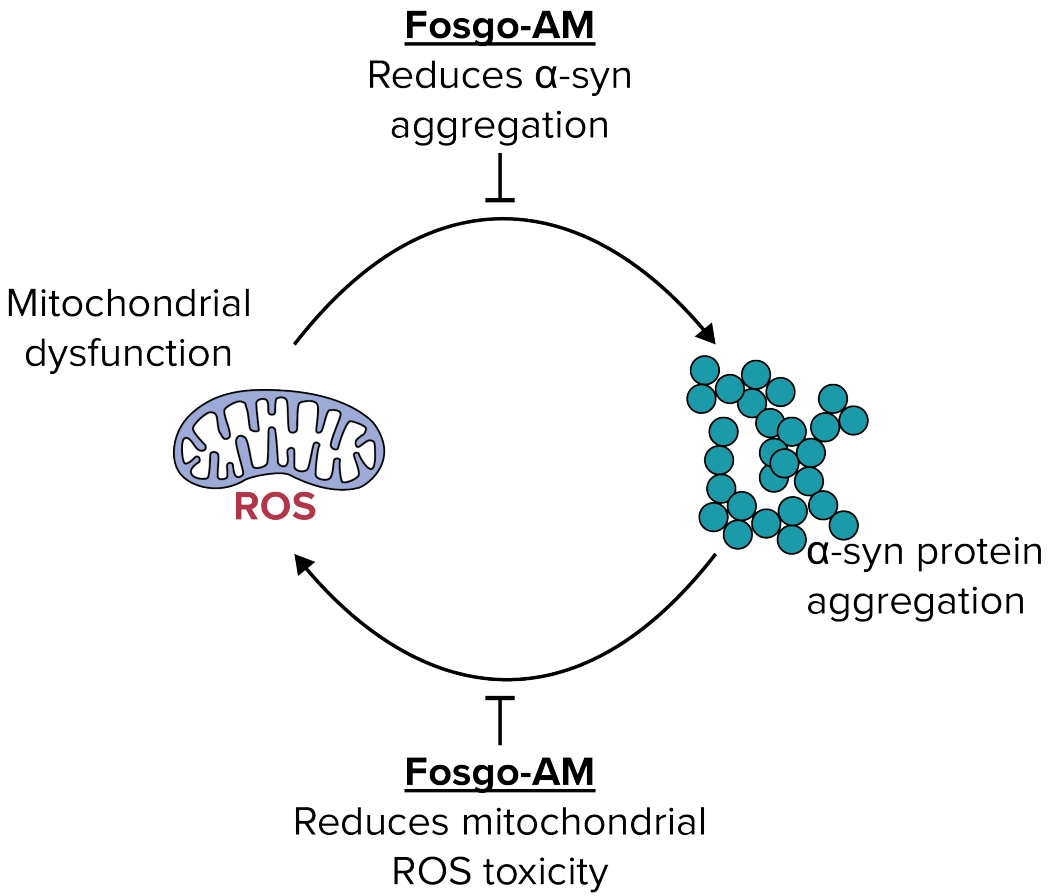
# Fosgo-AM attenuates Aβ-induced toxicity and reduces p-Tau in primary culture of cortical neurons




Aβ, amyloid beta; LSD, least significant difference; MAP-2, microtubule-associated protein 2; p-Tau, phosphorylated tau.
(A) Fosgo-AM, 100 nM. Scale is 100 µm (all panels). Aβ1-42, 15 µM; 2 µM oligomers.
(B) Data presented as mean + SEM. Statistical significance was determined by 1-way ANOVA with Fisher's LSD (n = 5-6).
****$p < 0.0001$ versus Aβ control.

# Fosgo-AM attenuates 6-OHDA– and α-syn–induced toxicity in primary dopaminergic neurons

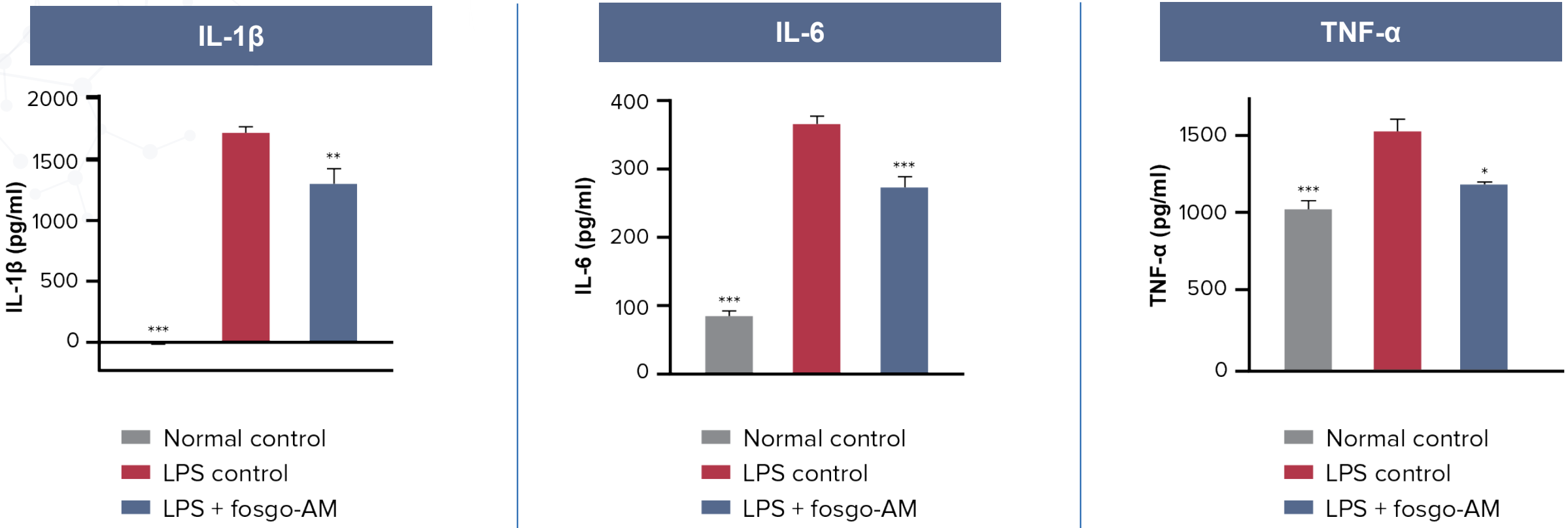



6-OHDA, 6-hydroxydopamine; α-syn, alpha synuclein; mitoSOX, fluorescent mitochondrial superoxide indicator; PFF, preformed fibrils; ROS, reactive oxygen species; TH+, tyrosine hydroxylase-positive.
Rat primary dopaminergic neuron cultures. Fosgo-AM (100 nM) and 6-OHDA (20 μM) for 24 hours OR fosgo-AM (500 nM) and α-syn PFFs (250 nM) for 96 hours.
Data displayed as mean + SEM. One-way ANOVA with Fisher's LSD (n = 5-6).
*$p$ < 0.1, **$p$ < 0.01,***$p$ <0.001 versus 6-OHDA control or α-syn control.

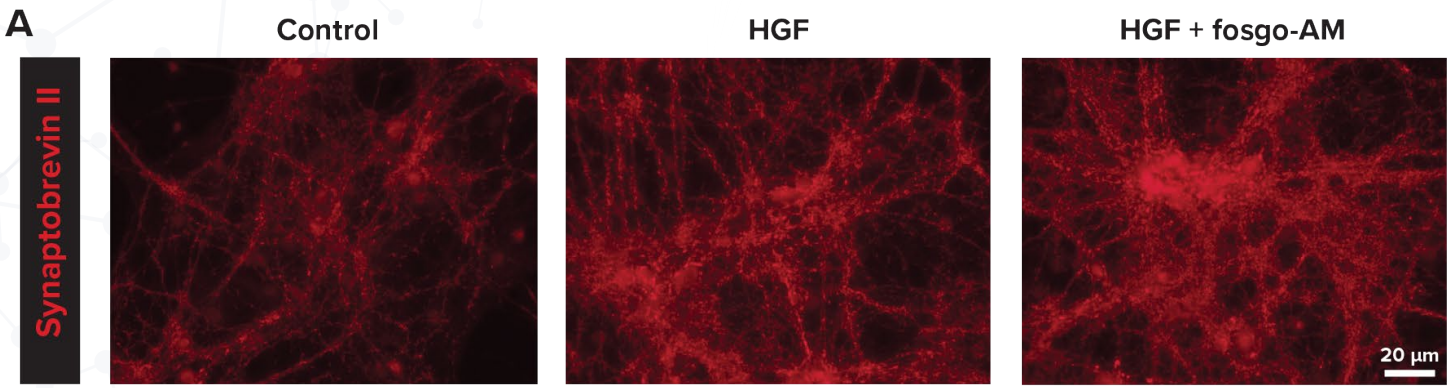
# Fosgo-AM reduces expression of inflammatory cytokines implicated in neurodegeneration

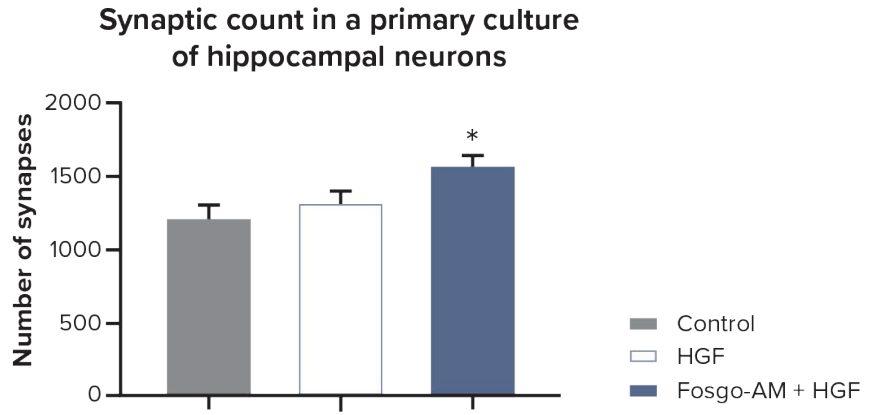
***Model system: LPS stimulation of THP-1 differentiated macrophages***

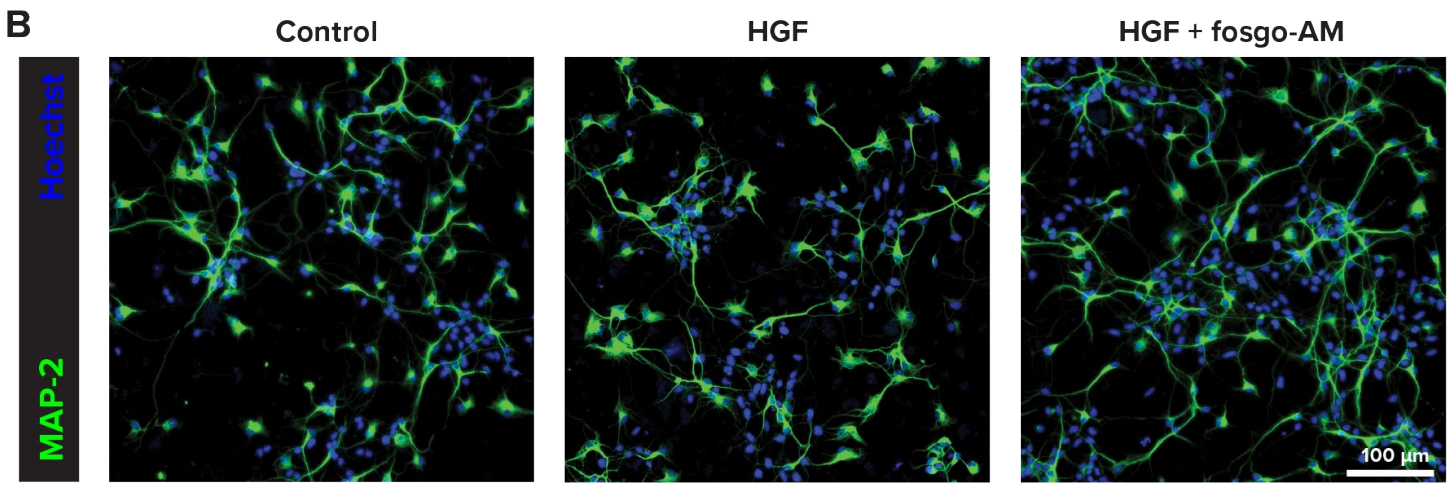


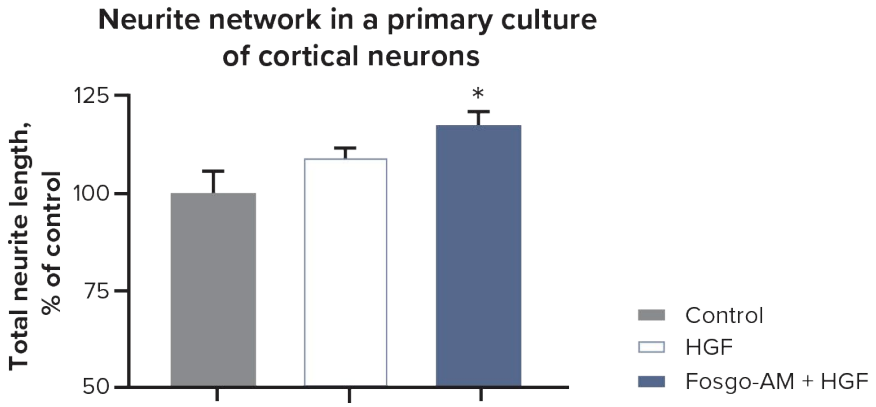

IL-1β, interleukin 1 beta; IL-6, interleukin 6; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor alpha
Data presented as mean + SEM. One-way ANOVA with Dunnett's test.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. LPS Control; n = 3. THP-1 cells.
Figure adapted from Johnston JL et al. *Neurotherapeutics*. 2022;19:1413-1431. This work is licensed under CC BY. 4.0.

# Fosgo-AM enhances synaptogenesis and promotes neurite outgrowth in primary neuron cultures



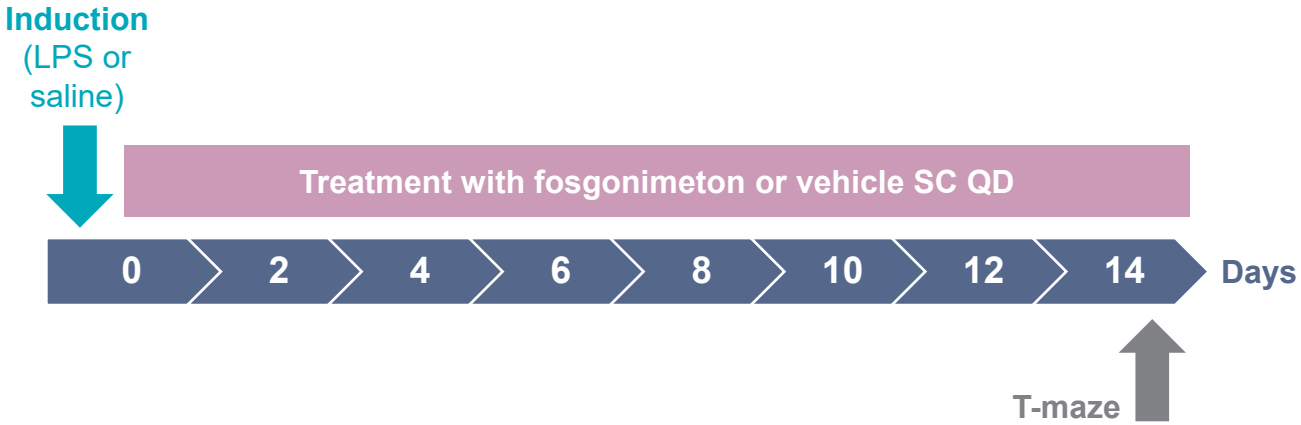



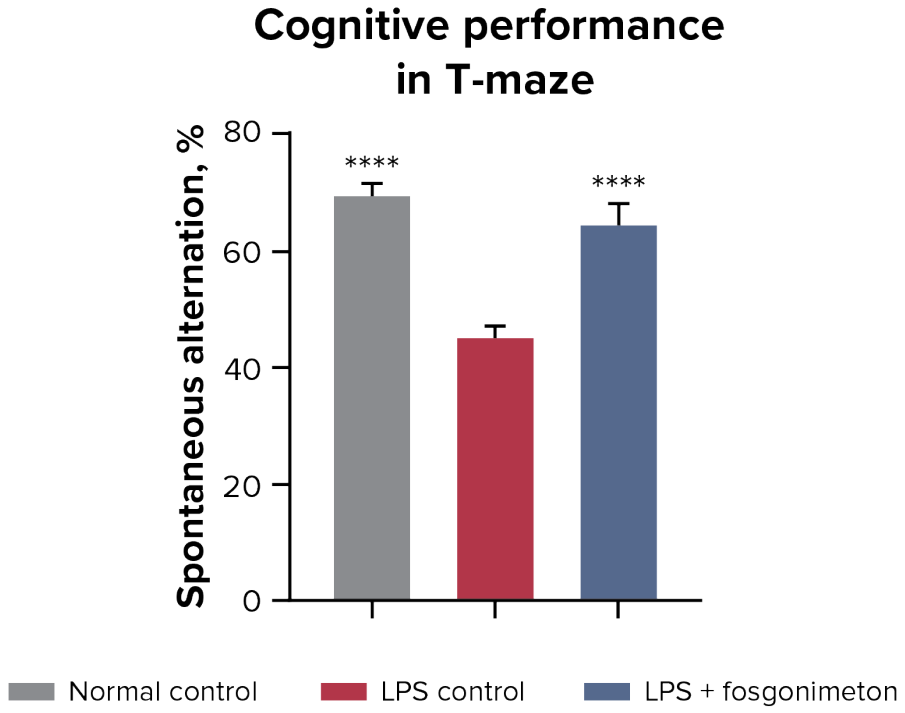




HGF, hepatocyte growth factor; MAP-2, microtubule-associated protein 2.
(A) Fosgo-AM (1 nM). Scale is 20 µm and applies to all panels in A. HGF (5 ng/mL). Data presented as mean + SEM (n = 10; images from 3 wells per treatment). (B) Fosgo-AM (1 nM). Scale is 100 µm and applies to all panels in B. HGF (0.01 ng/mL). Data presented as mean + SEM. Statistical significance was determined by 1-way ANOVA with Dunnett's posttest (n = 5-6). *$p < 0.05$ versus control.

# Fosgonimeton improves cognitive performance in a mouse model of neuroinflammation

- Systemic LPS administration causes an inflammatory response leading to cognitive deficits[1,2]
- Spontaneous alternation in a T-maze is used as an index of cognitive function in rodents[3]
  - Cognitively intact mice have a natural drive to explore, alternating between each arm of a T-maze
  - In contrast, cognitively impaired mice have reduced rates of spontaneous alternation



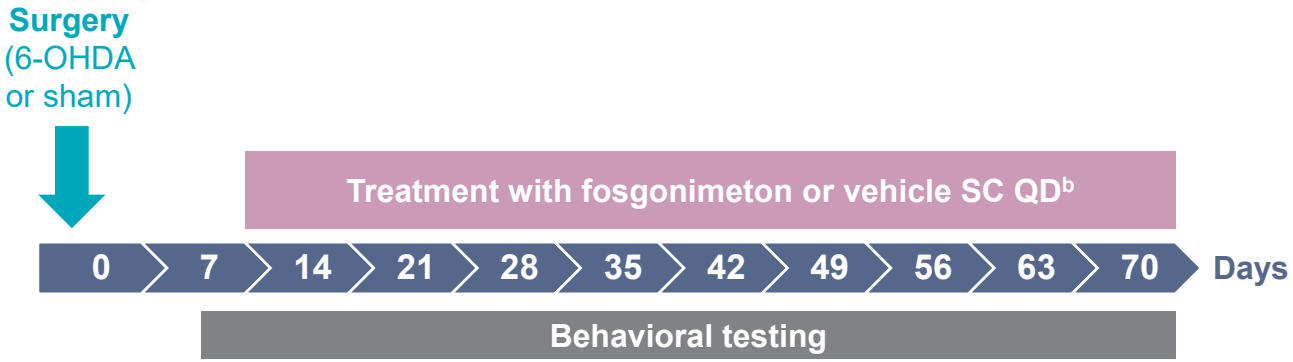



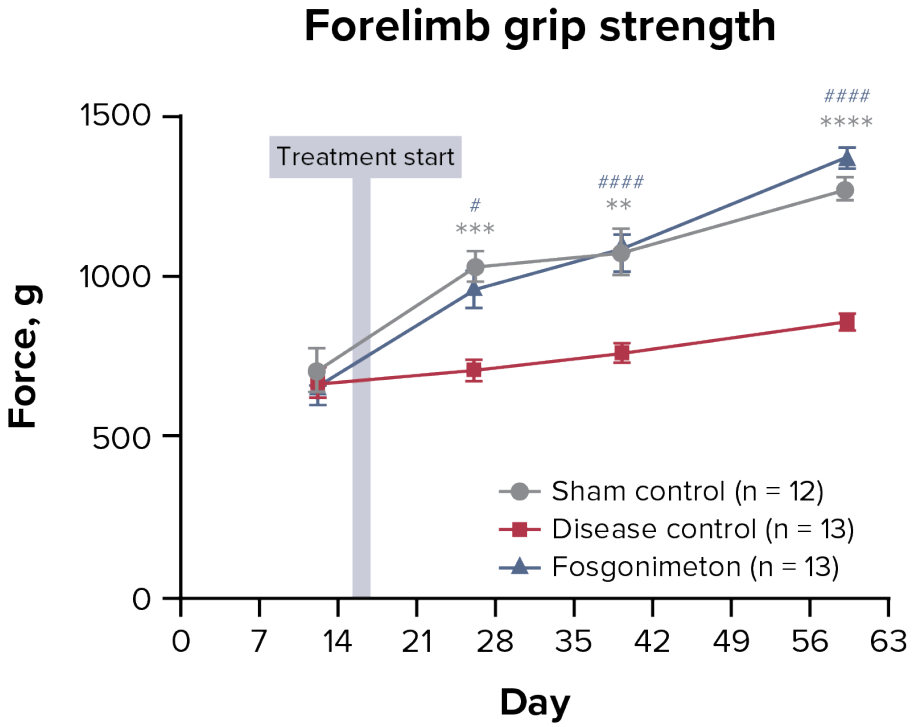

**Fosgonimeton administration attenuated LPS-induced cognitive deficits, suggesting procognitive activity**

LPS, lipopolysaccharide; QD, daily; SC, subcutaneous.
Fosgonimeton, 0.5 mg/kg. Data displayed as mean + SEM. One-way ANOVA with Dunnett's test (n = 10). ****$p < 0.0001$ versus LPS control.
**1**. Zhao J et al. *Sci Rep*. 2019;9:5790. **2**. Johnston JL et al. Neurotherapeutics 2022; 19:1413-1431. **3**. Wu C et al. *J Vis Exp*. 2018;131:56694.
Figure adapted from Johnston JL et al. *Neurotherapeutics*. 2022;19:1413-1431. This work is licensed under CC BY. 4.0.

# Fosgonimeton rescues grip strength in a rat model of PD

- 6-OHDA, which induces dopaminergic neurotoxicity, can be injected into the striatum[a] of rats to model PD[1]
- Unilateral injections cause motor impairment on the contralateral side of the body
- Rats have consistently weaker grip strength following a 6-OHDA injection[1]

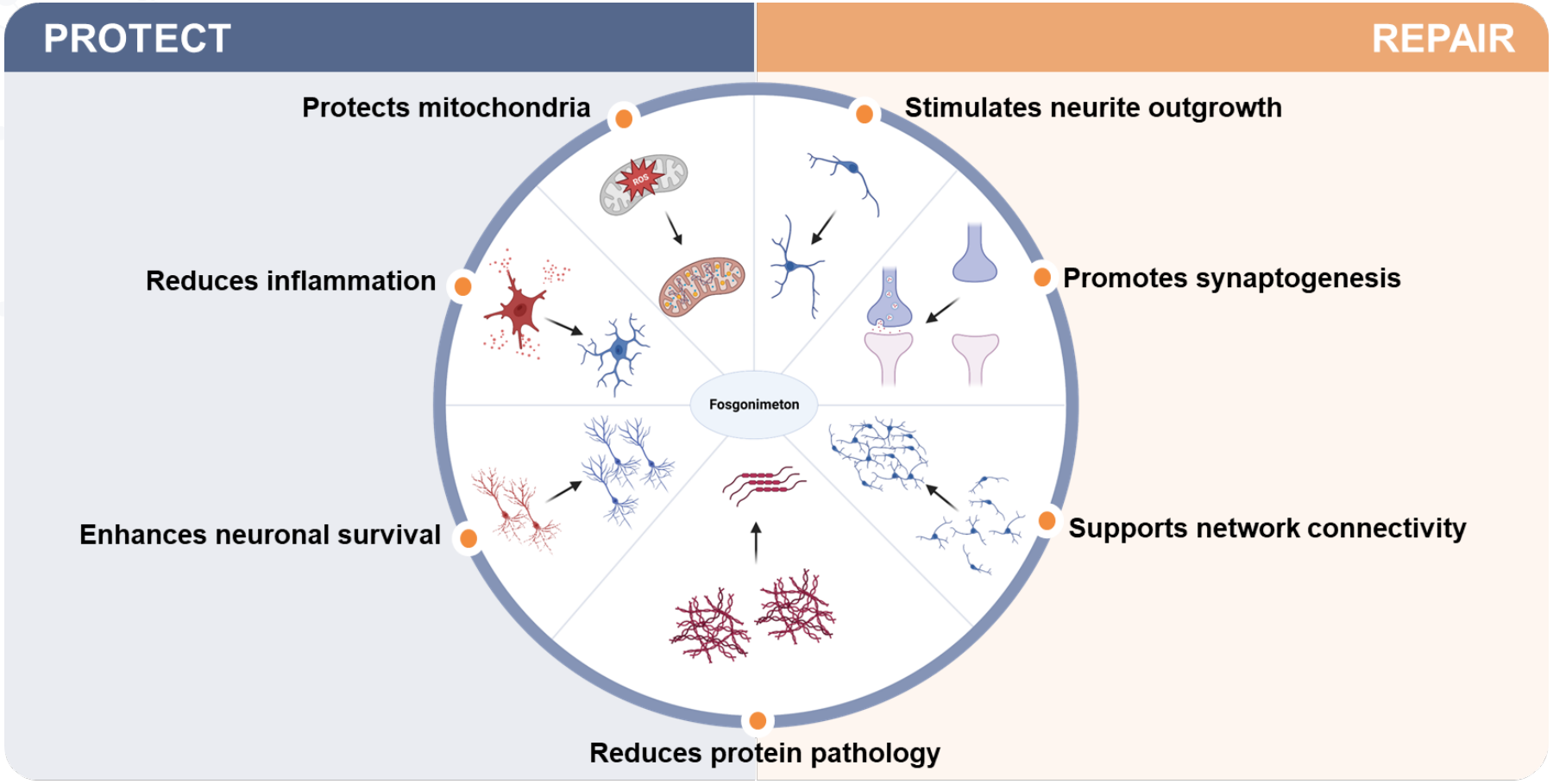



**Lesioned rats treated with fosgonimeton exhibit robust recovery in grip strength over time**

6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; QD, daily; SC, subcutaneous.
[a]Unilateral 6-OHDA or vehicle injections were targeted to the right caudate nucleus at stereotaxic coordinates −0.21 anteroposterior; −3.0 mediolateral; −7.0 dorsoventral.
[b]To accommodate surgery and behavioral testing schedules for all 90 animals, treatment started on day 15 or 16 for each animal. Animals were randomly assigned to type of treatment after an apomorphine-induced rotation test.
Data displayed as mean ± SEM. Two-way ANOVA with Dunnett's test. *Indicates sham control versus disease control; # indicates fosgonimeton versus disease control.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ versus disease control.
**1.**Tiwari P et al. *Ann Neurosci.* 2021;28:137-149.

# Fosgonimeton protects and repairs neuronal networks




Improved function

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