Fosgonimeton, a Small-Molecule Positive Modulator of the HGF/MET System, Attenuates Amyloid-β–Mediated Toxicity in Preclinical Models of Alzheimer's Disease

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https://bit.ly/3PVQaA2

CONCLUSIONS

1. Fosgo-AM counteracted mechanisms of Aβ-induced toxicity, reduced tau pathology, and promoted neuronal survival in vitro
2. Fosgonimeton treatment led to improved cognition in an Aβ-driven rat model of AD, suggesting that the cellular effects of fosgo-AM against Aβ toxicity translate to functional benefits

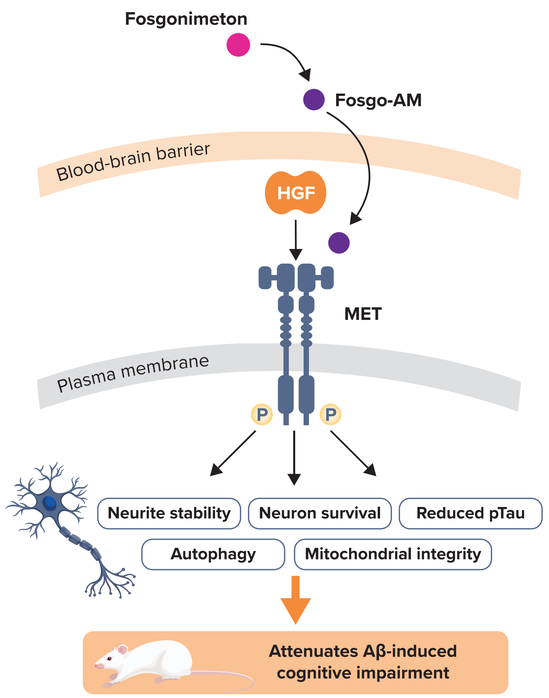
KEY TAKEAWAY

The neuroprotective and procognitive effects of fosgonimeton highlight its potential to address key aspects of AD pathology, including Aβ-mediated toxicity

INTRODUCTION

- AD is a progressive neurodegenerative disease characterized by the presence of oxidative stress, neurotoxicity, neuroinflammation, and the abnormal accumulation of proteins such as Aβ and pTau in the brain[1,2]
- Aβ and pTau are core diagnostic biomarkers in AD clinical trials because of their association with underlying AD pathology[3]
- The neurotrophic HGF system (**Figure 1**) exhibits multimodal neuroprotective and anti-inflammatory effects, which makes it a promising therapeutic target with which to address the complex pathophysiology of AD[4-6]
- Fosgonimeton, a small-molecule positive modulator of the HGF system, has demonstrated neuroprotective, neurotrophic, and anti-inflammatory effects in preclinical models of dementia[7]
- Fosgonimeton is under clinical investigation for safety and efficacy in the treatment of mild to moderate AD (NCT04488419)

Figure 1. Positive modulation of the HGF system promotes multiple neurotrophic and neuroprotective cellular effects which result in cognitive performance improvement in vivo



Fosgonimeton is converted in the blood to the active metabolite fosgo-AM, which crosses the blood-brain barrier and promotes HGF/MET-mediated neurotrophic and neuroprotective signaling cascades in the brain.

OBJECTIVES

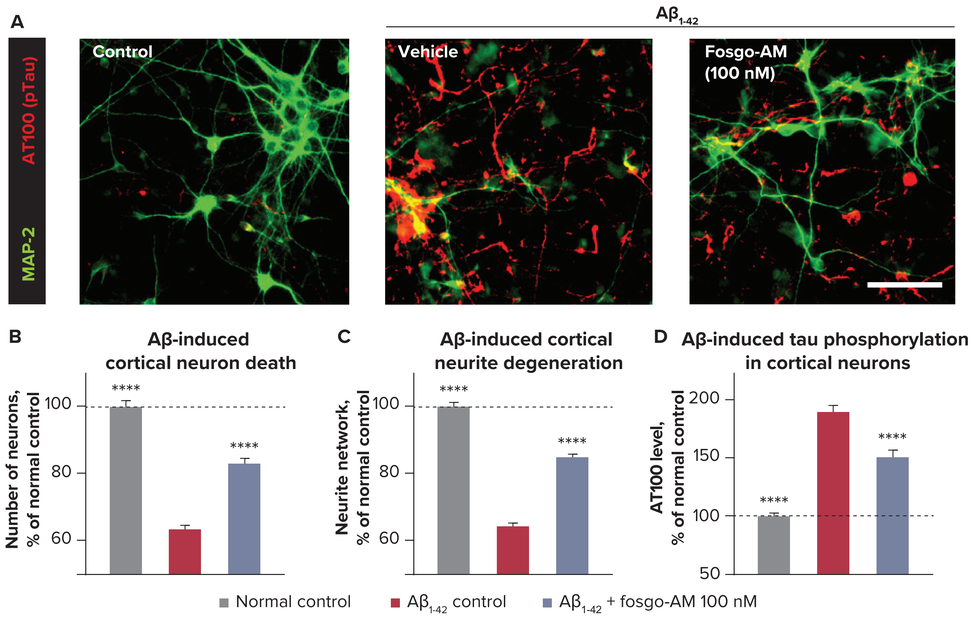
To investigate the mechanism by which fosgonimeton and its active metabolite, fosgo-AM, induce neuroprotective and procognitive effects in preclinical Aβ models of AD

METHODS

- In vitro assays to analyze the effects of fosgo-AM on Aβ neurotoxicity, cellular signaling, and levels of key proteins involved in the induction of autophagy are described in the Supplemental Information (**QR code**)
- Methods for in vivo evaluation of the effects of fosgonimeton on cognitive performance in an ICV-$Aβ_{25-35}$-induced rat model of AD are also described in the Supplemental Information (**QR code**)

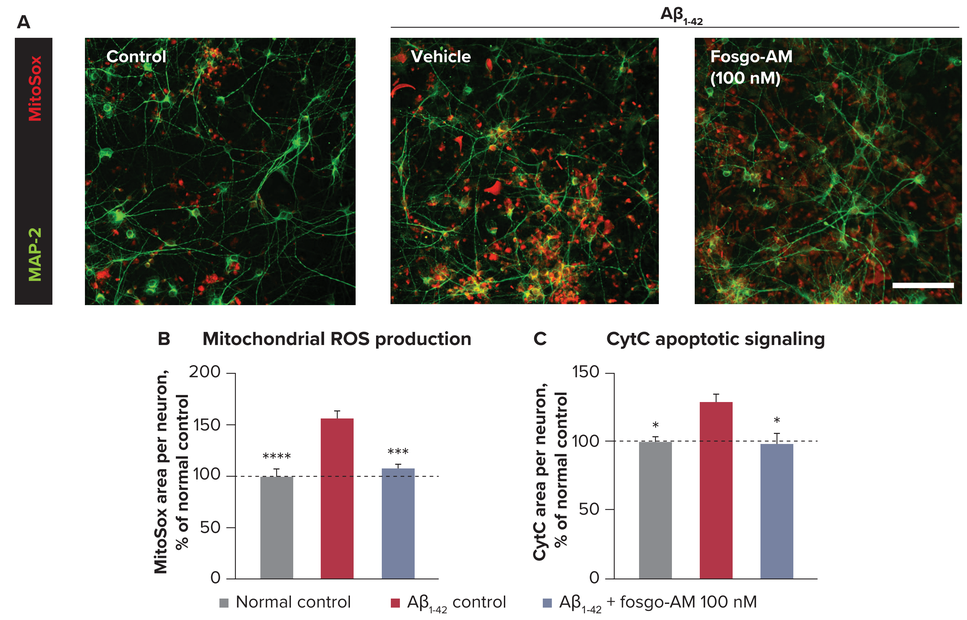
RESULTS

Figure 2. Fosgo-AM attenuates $Aβ_{1-42}$-induced neuronal death, neurite degeneration, and tau hyperphosphorylation in vitro



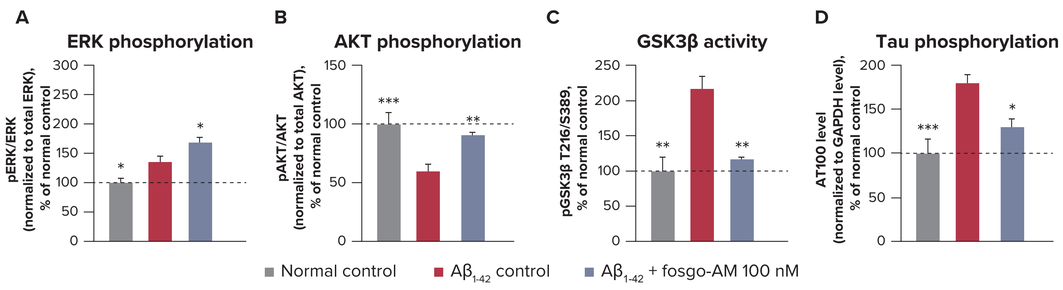
(A) Representative images highlighting the effect of $Aβ_{1-42}$ on rat primary cortical neurons in the presence or absence of fosgo-AM; neurons labeled with MAP-2 and pTau labeled with AT100 (scale bar = 100 µm). Quantification of (B) neuronal survival (number of MAP-2+ neurons), (C) neurite network (total length of MAP-2+ neurites, in µm), and (D) pTau (overlapping area of AT100 and MAP-2+, in $µm^2$) expressed as percentage of normal controls (100%).
Data presented as mean + SEM; n = 5 or 6 technical replicates. Statistical differences were determined by one-way ANOVA followed by Fisher's LSD test.
****$p < 0.0001$ versus $Aβ_{1-42}$ control.

Figure 3. Fosgo-AM attenuates $Aβ_{1-42}$-induced mitochondrial oxidative stress and CytC release in vitro



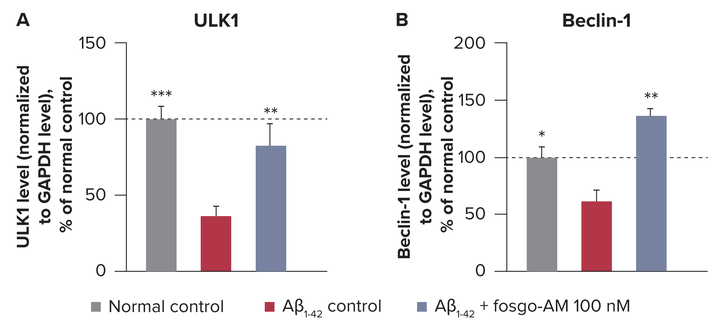
(A) Representative images of rat primary cortical neurons highlighting the effect of $Aβ_{1-42}$ on mitochondrial ROS generation in the presence or absence of fosgo-AM; neurons labeled with MAP-2 and MitoSox (scale bar = 100 µm). (B) Quantification of mitochondrial ROS (MitoSox area per neuron, in $µm^2$) expressed as percentage of healthy controls (100%). (C) Quantification of CytC release (overlap of CytC and MAP-2, in micrometers squared) expressed as percentage of normal controls (100%).
Data presented as mean + SEM; n = 4 or 6 technical replicates. Statistical differences were determined by one-way ANOVA followed by Fisher's LSD test.
*$p < 0.05$, ***$p < 0.001$, ****$p < 0.0001$ versus $Aβ_{1-42}$ control.

Figure 4. Fosgo-AM increases ERK and AKT phosphorylation and reduces GSK3β activity and tau phosphorylation in response to $Aβ_{1-42}$ injury in vitro



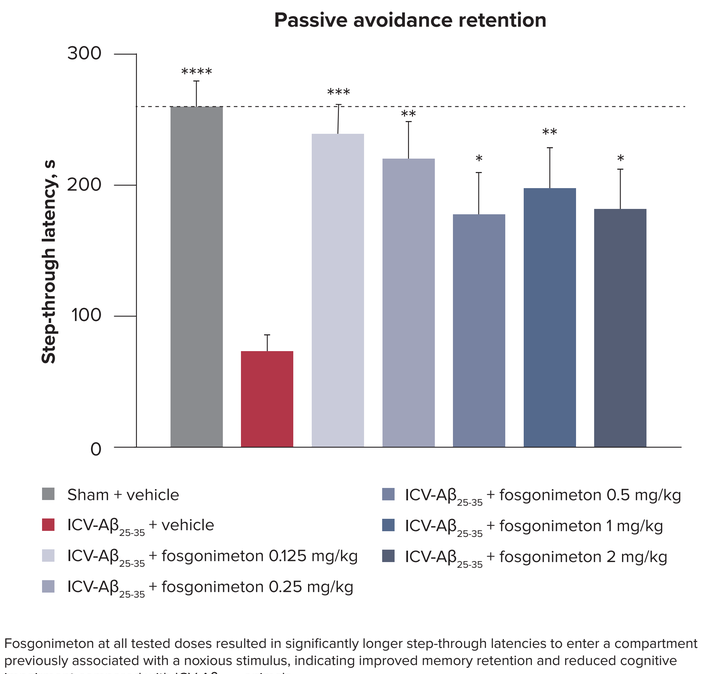
Quantification of (A) ERK phosphorylation (pERK/ERK), (B) AKT phosphorylation (pAKT/AKT), (C) active GSK3β [pTyr216] and (D) levels of tau phosphorylation after $Aβ_{1-42}$-induced injury and treatment with fosgo-AM.
Data presented as mean + SEM; n = 4 biological replicates. Statistical differences were determined by one-way ANOVA followed by Fisher's LSD test.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus $Aβ_{1-42}$ control.

Figure 5. Fosgo-AM increases levels of the autophagy inducers ULK1 and Beclin-1 following AB_{1-42} injury in vitro



Quantification showing expression levels of (A) ULK1 and (B) Beclin-1 normalized to GAPDH after $Aβ_{1-42}$-induced injury and treatment with fosgo-AM.
Data presented as mean + SEM; n = 4 replicates. Statistical differences were determined by one-way ANOVA followed by Fisher's LSD test.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus $Aβ_{1-42}$ control.

Figure 6. Fosgonimeton improves cognitive performance in an ICV-$Aβ_{25-35}$-induced model of AD



Fosgonimeton at all tested doses resulted in significantly longer step-through latencies to enter a compartment previously associated with a noxious stimulus, indicating improved memory retention and reduced cognitive impairment compared with ICV-$Aβ_{25-35}$ animals.
Data presented as mean + SEM; n = 12 rats. Statistical differences were determined by one-way ANOVA followed by Dunnett's multiple comparisons test.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ versus ICV-Aβ + vehicle.

Abbreviations: **Aβ**, amyloid-β; **AD**, Alzheimer's disease; **AKT**, protein kinase B; **ANOVA**, analysis of variance; **CytC**, cytochrome c; **ERK**, extracellular signal–regulated kinase; **fosgo-AM**, active metabolite of fosgonimeton; **GAPDH**, glyceraldehyde 3-phosphate dehydrogenase; **GSK3β**, glycogen synthase kinase-3 beta; **HGF**, hepatocyte growth factor; **ICV**, intracerebroventricular; **LSD**, least significant difference; **MAP-2**, microtubule-associated protein 2; **P**, phosphorylation; **pAKT**, phosphorylated AKT; **pERK**, phosphorylated ERK; **pGSK3β**, phosphorylated glycogen synthase kinase-3 beta; **pTau**, phosphorylated tau; **ROS**, reactive oxygen species; **SEM**, standard error of the mean; **ULK1**, Unc-51–like kinase-1.

References: **1.** Alzheimer's Association. *Alzheimers Dement.* 2023;19(4):1598-1695. **2.** Dar KB et al. *Cell Mol Neurobiol.* 2020;40(3):313-345. **3.** Hampel H et al. *Nat Rev Neurol.* 2018;14(11):639-652. **4.** Funakoshi H, Nakamura T. *Curr Signal Transduct Ther.* 2011;6(2):156-167. **5.** Tyndall SJ, Walikonis RS. *Cell Cycle.* 2006;5(14):1560-1568. **6.** Molnarfi N et al. *Autoimmun Rev.* 2015;14(4):293-303. **7.** Johnston JL et al. *Neurotherapeutics.* 2023;20(2):431-451.

Acknowledgments

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Disclosures

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

Disclaimer

Fosgonimeton is an investigational therapy that has not received FDA approval and has not been demonstrated to be safe or effective for any use.

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