

# Discovery and Early Clinical Development of MK-8719, a Novel Inhibitor of OGA for the Treatment of Progressive Supranuclear Palsy (PSP)

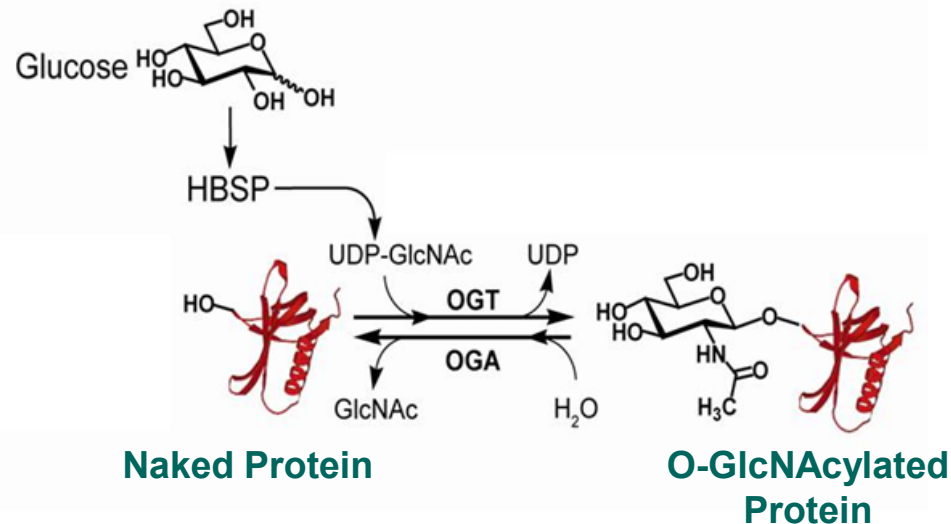
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# O-GlcNAcylation Influences Activity, Stability and Localization of Proteins



## O-GlcNAc transferase (OGT)

- Mediates addition of O-GlcNAc

## O-GlcNAcase (OGA)

- Mediates removal of O-GlcNAc

- O-GlcNAcylation is a common post translational modification of proteins that is nutrient responsive
- In healthy adult brain, tau is O-GlcNAcylated at several sites
- Abnormal O-GlcNAcylation is associated with Tauopathies
  - Protein O-GlcNAcylation is reduced in Alzheimer's Disease
- OGA inhibitors increase tau O-GlcNAcylation and show efficacy in multiple tau transgenic models



# In Vitro and Pharmacokinetic Profile of MK-8719

## In Vitro Profile

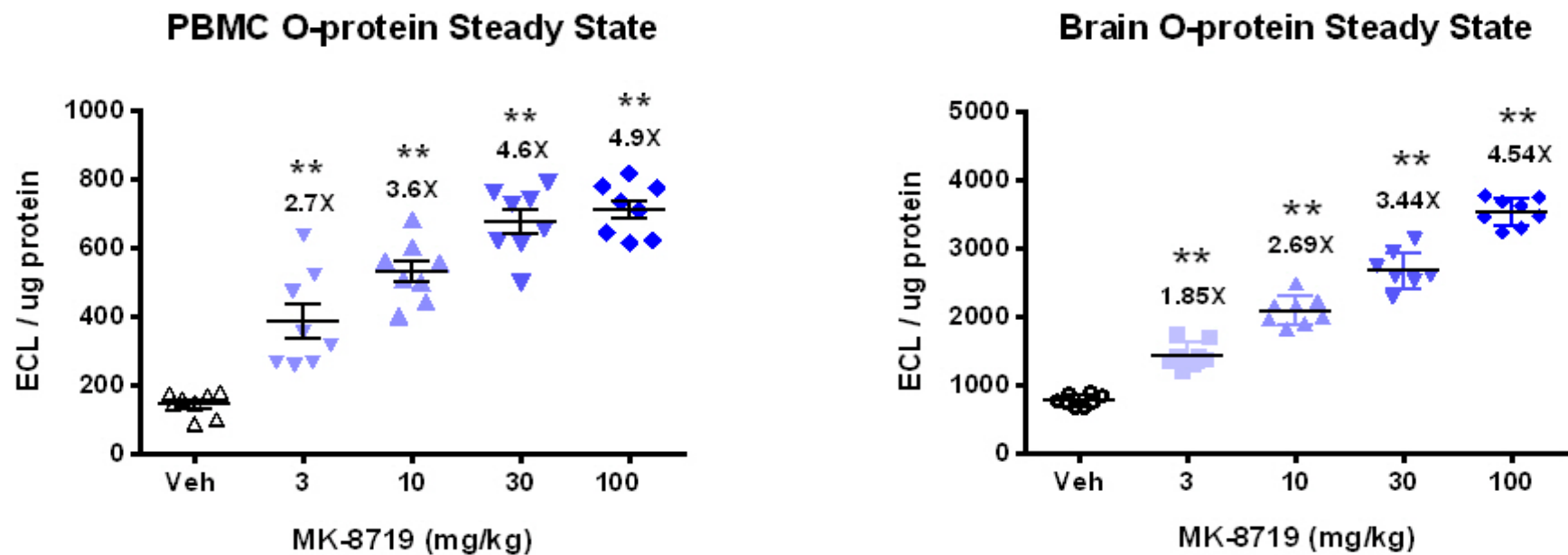
Assay	IC <sub>50</sub> (μM)
hOGA (enz Ki / cell IC <sub>50</sub> )	< 0.010 / < 0.100
Hex A/B; NAGLU	> 1,000
Cav1.2, Nav1.5, hERG	> 30
CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4	> 100
Off target binding	No hits at 10 μM
CNS penetrant, devoid of Pgp transport	✓

## Pharmacokinetics

Parameter	Mice 2 mg/kg IV 10 mg/kg PO	Rats 2 mg/kg IV 10 mg/kg PO	Dogs 1 mg/kg IV 3 mg/kg PO	Monkeys 1 mg/kg IV 3 mg/kg PO
IV				
AUC <sub>0-∞</sub> (μM*hr)	2.9 ± 0.15	3.5 ± 0.7	5.3 (5.6, 5.1)	2.2 ± 0.4
CLp (mL/min/kg)	43.4 ± 2.2	36.7 ± 7.2	11.5 (11, 12)	28.3 ± 4.7
Vd <sub>ss</sub> (L/kg)	2.0 ± 0.1	4.7 ± 2.0	2.3 (2.0, 2.6)	3.4 ± 0.5
t <sub>1/2</sub> terminal (hr)	1.7 ± 0.4	2.9 ± 1.7	5.4 (4.7, 6.0)	1.7 ± 0.5
PO				
C <sub>max</sub> (μM)	10.7 ± 2.2	10.6 ± 5.7	8.3 ± 0.6	0.40 ± 0.13
T <sub>max</sub> (hr)	0.25	0.25	0.25	0.25
AUC <sub>0-∞</sub> (μM*hr)	7.8 ± 1.2	14.0 ± 1.8	14.2 ± 1.2	0.61 ± 0.17
Bioavailability (%)	54 ± 8	80 ± 11	90 ± 3	9.0 ± 1.2



# Effects of MK-8719 on Protein O-GlcNAcylation in Rat



- MK-8719 produced a dose-dependent elevation of O-GlcNAcylated protein in rat brain and peripheral blood mononuclear cells (PBMCs)
- O-protein was measured by ELISA using the RL2 antibody following WGA capture
- **Changes in PBMC O-protein mirror changes in brain O-protein levels**

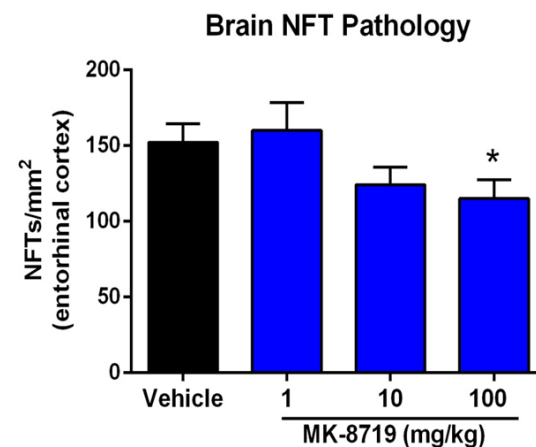
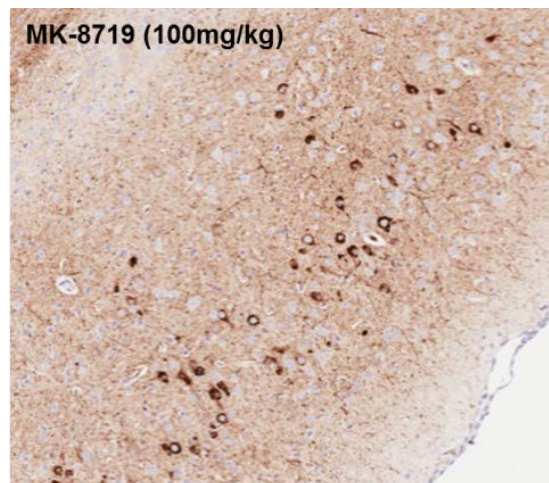
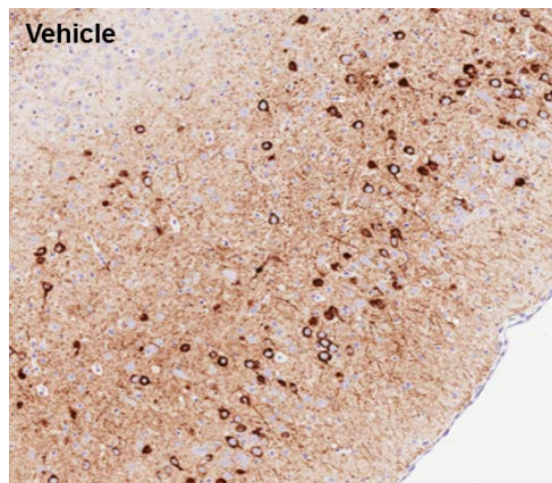


# MK-8719 Reduces Neurofibrillary Tangles (NFTs) in the Entorhinal Cortex of Tg4510 Mice



Tg4510 mice express a repressible form of human tau containing the P301L mutation that has been linked with familial FTD

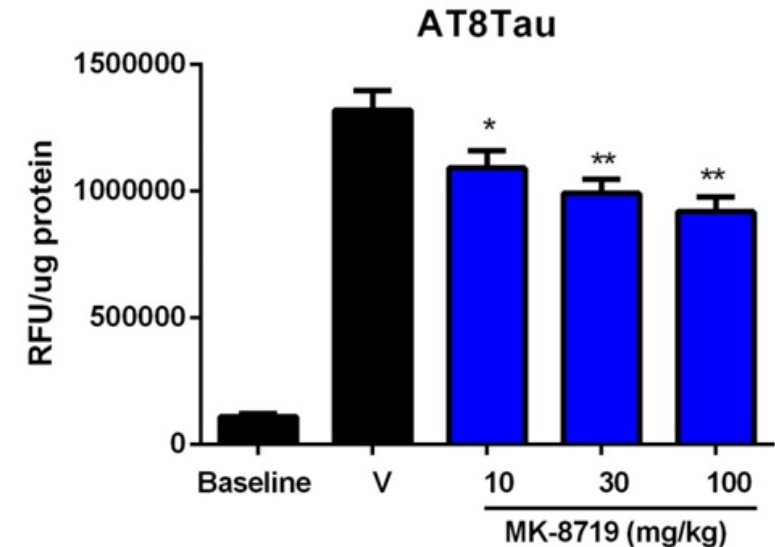
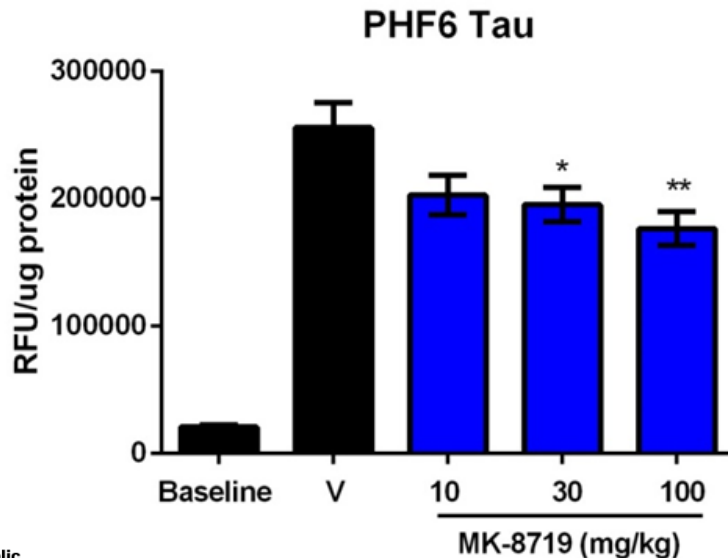
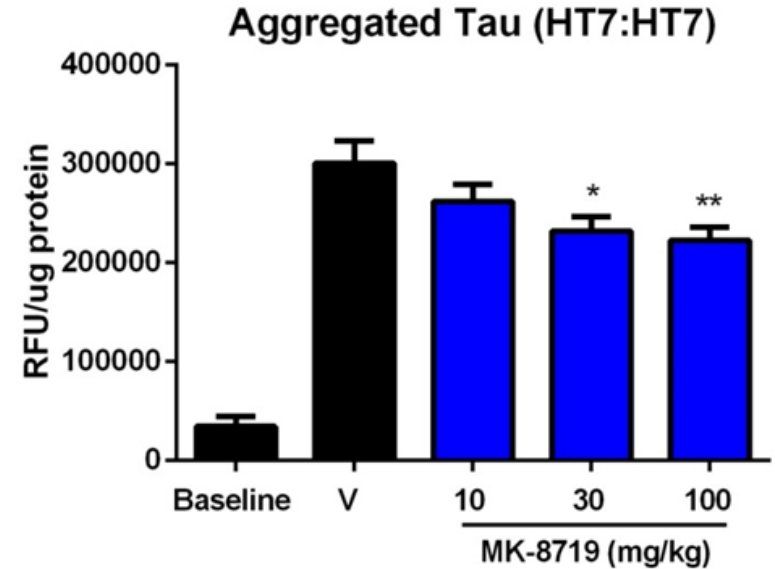
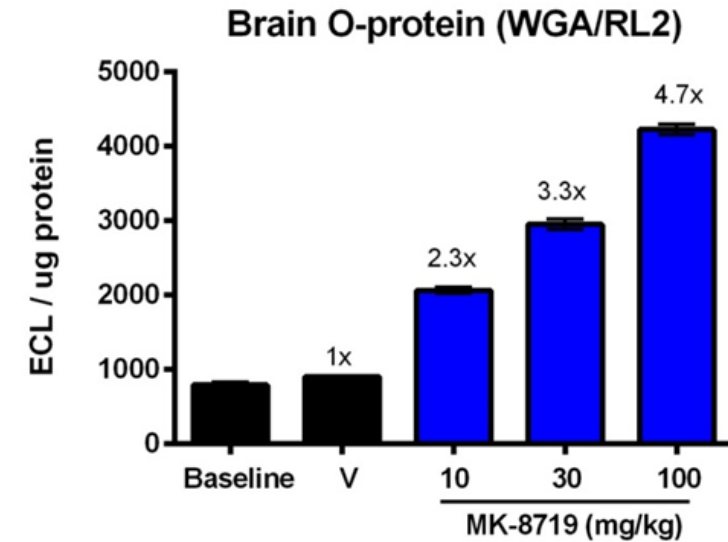
\*  $p < 0.05$



- NFTs were detected using the AT-8 mAb against phosphorylated Tau
- Tg4510 mice were administered MK-8719 (1 – 100 mg/kg) or vehicle from 8 to 16 weeks of age
- Efficacy of MK-8719 was evaluated in 16-week old Tg4510 mice



# MK-8719 Increases Total O-protein and Reduces Pathological Tau in Tg4510 Mice



\* $p < 0.05$   
\*\* $p < 0.01$

n=55







# MK-8719 PN001: A Single Rising Dose Study of MK-8719 in Healthy Subjects

- **Single doses of MK-8719 were generally well tolerated in healthy subjects**

**MK-8719 PN001 Dosing schedule**

Panel	Period 1		Period 2		Period 3		Period 4		Period 5	
<b>A</b>	5 mg		20 mg		80 mg		300 mg		80 mg (fed)	
<b>B</b>		10 mg		40 mg		160 mg		600 mg		1200 mg

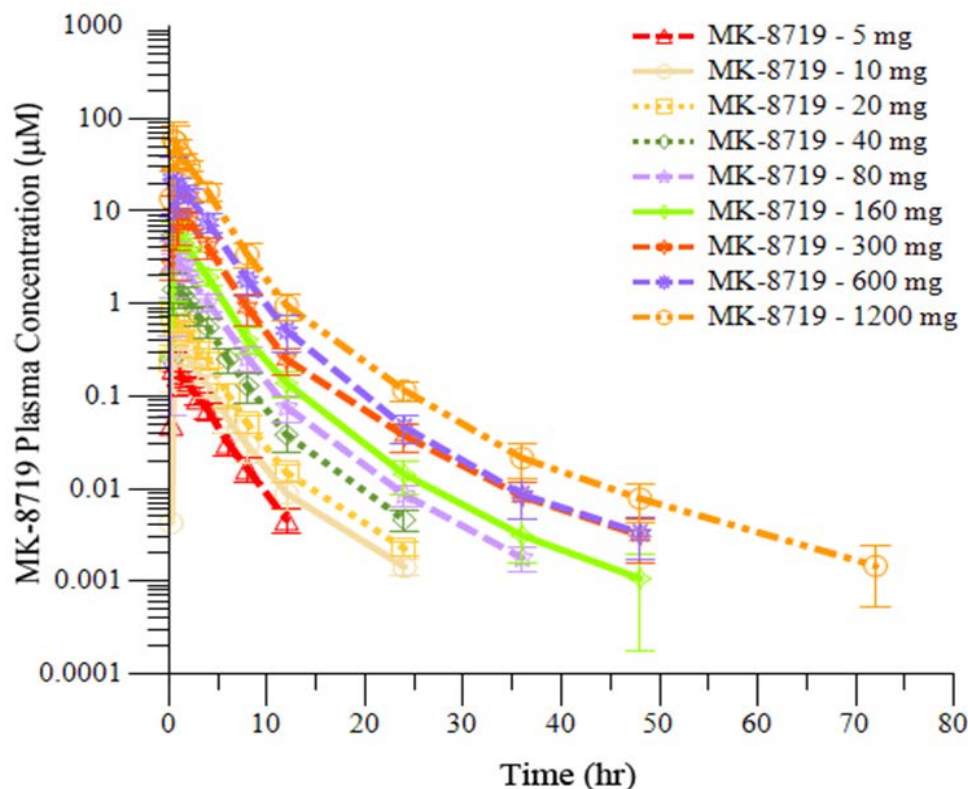
## **Safety and Tolerability:**

- Most frequent AE was “headache”
  - No increase in AE incidence or severity with increase in doses
- No serious adverse experiences
- No laboratory, ECG or vital sign observations
- No effects on blood glucose levels



# Human Pharmacokinetics of MK-8719

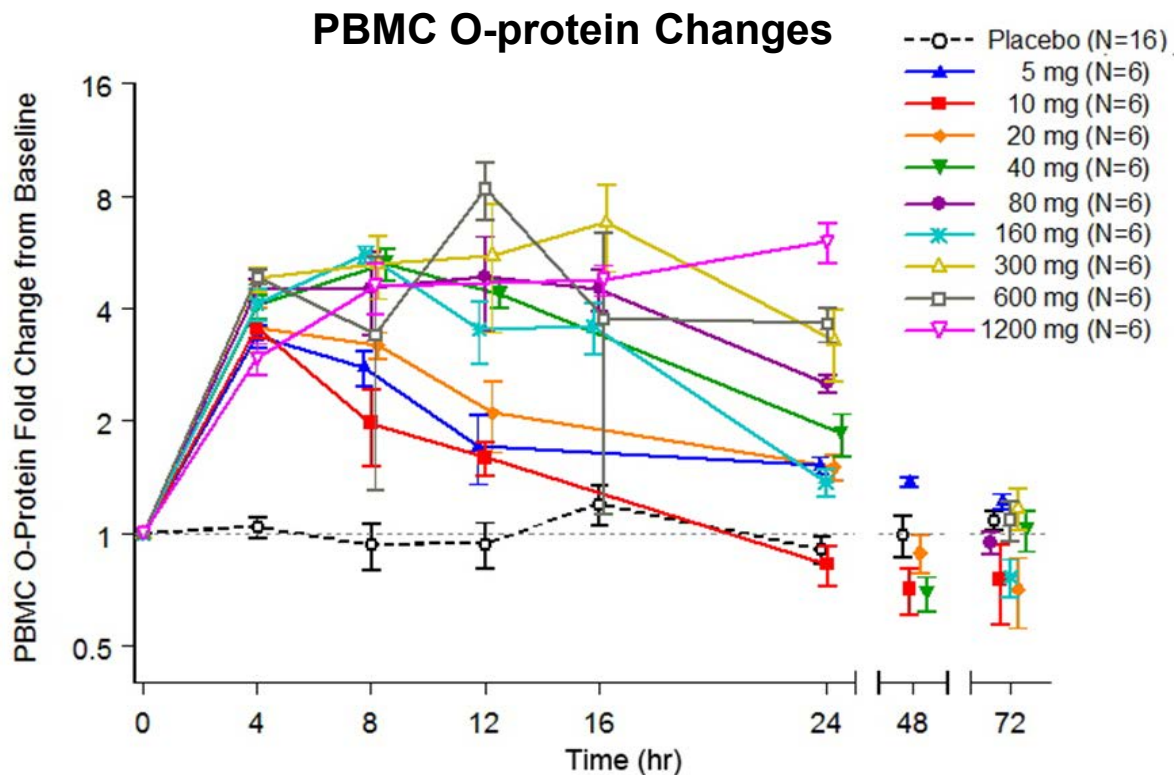
## Plasma Exposure



- Plasma exposure increased in a dose-proportional manner
- Peak plasma levels of MK-8719 were observed at a median  $T_{max}$  of 0.75 hours
- The fractional clearance at the pharmacological dose was 6.9 mL/min/kg and the half-life was ~4.7 hr



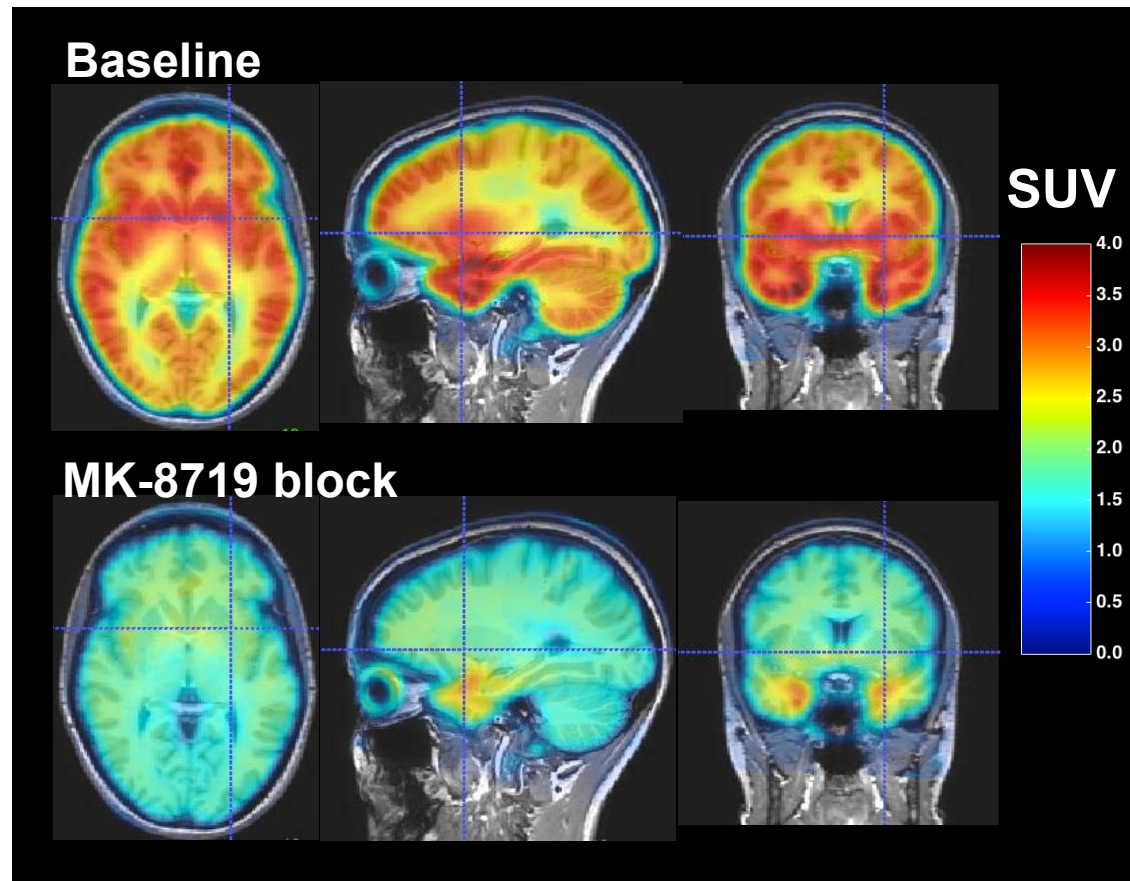
# Pharmacodynamics of MK-8719 in Humans



- MK-8719 dose-dependently increased PBMC O-protein levels after single doses
- The O-protein response persisted up to 24 hr postdose, even after MK-8719 was eliminated from the plasma.



# OGA PET Tracer [ $^{18}\text{F}$ ]MK-8553 was Used to Measure MK-8719 Target Engagement in Humans



- [ $^{18}\text{F}$ ]MK-8553 regional distribution is consistent with preclinical species and the known distribution of the OGA enzyme
- Blocking studies with MK-8719 demonstrate the ability of [ $^{18}\text{F}$ ]MK-8553 to be used as a tool to measure OGA target engagement and guide dose selection



# MK-8719 Program Summary

## Preclinical Validation

- MK-8719 is a selective and potent small molecule inhibitor of the O-GlcNAcase (OGA) enzyme
- Oral administration of MK-8719 produces a sustained elevation in O-Protein levels in brain and peripheral tissues
- OGA inhibition significantly reduces pathological tau and brain atrophy in Tg4510 transgenic mice

## Clinical Results

- MK-8719 was safe and generally well tolerated in a single rising dose study in healthy subjects at doses ranging from 5 to 1200 mg
- Robust increases in PBMC O-protein were detected in response to MK-8719 administration
- The selective OGA PET tracer [ $^{18}$ ]FMK-8553 was used to demonstrate central target engagement of MK-8719 in humans



# Acknowledgments

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