261 Nuak1 Inhibitor

Asset Overview

Product Type	Small molecule
Indication	Alzheimer disease (AD) and Progressive supranuclear palsy (PSP)
Current Stage	Hit
Target(MoA)	Nuak1 Inhibition
Brief Description	• The researchers identified Nuak1, an AMPK-related kinase, as directly regulating tau at serine 356. Decreasing Nuak1 reduced tau levels and suppressed phenotypes and neurodegeneration in tau expressing Drosophila and a tauopathy mouse model • A Nuak1 inhibitor could be a first in class drug for neurodegenerative disorder treatment
Organization	The Alborada Drug Discovery Institute

Differentiation

□ **Tau protein**

- Tau is well established as a microtubule-associated protein in neurons. Aberrant assembly of tau into insoluble aggregates is accompanied by synaptic dysfunction and neural cell death in a range of neurodegenerative disorders
- Partial reduction of tau increases resistance to chemically induced seizures, and markedly diminishes Ab-driven neuronal and cognitive impairment in vivo. Decreasing tau levels is a feasible therapeutic approach for tauopathies

□ **Importance of downregulation of Nuak1**

- Nuak1 is associated with tau pathology in AD and PSP patients
- Nuak1 directly phosphorylates tau at serine 356
- Reduction of Nuak1 rescues the phenotypes in tauopathy models

□ **The main benefits of the Nuak1 Inhibitior**

- The reduction of Nuak1 by 50% was sufficient to decrease total tau levels and reverse the deficits
- Research team has a number of molecules with good Br:Bl and their main series seems to generally have good brain penetration

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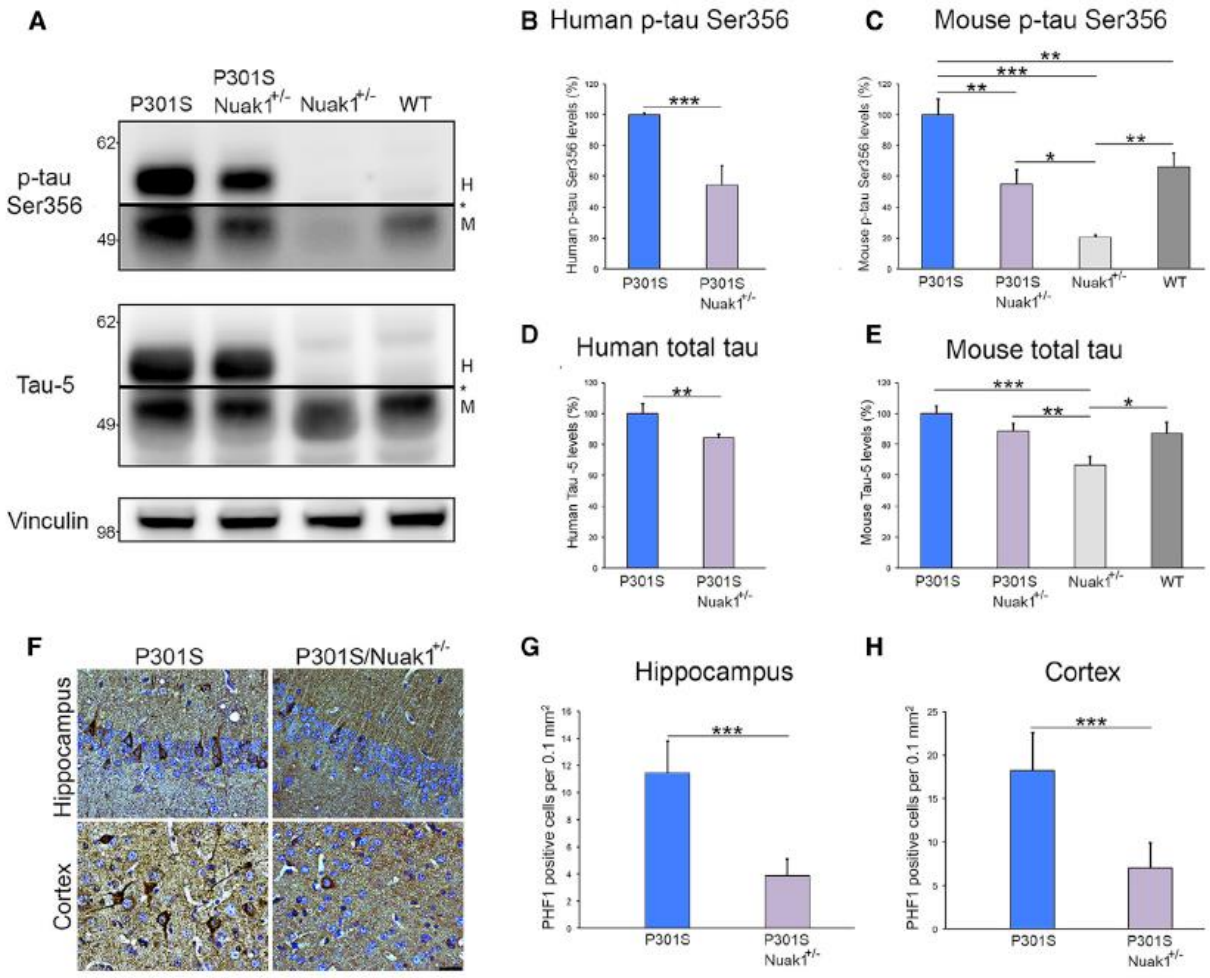
Key Data

Nuak1 Downregulation Prevents Tau Accumulation and NFT Formation



P301S/Nuak1+/- mice presented lower levels of human phosphorylated tau at Ser356 than P301S mice (A and B). The P301S/Nuak1+/- mice also showed lower levels of endogenous murine phospho-Ser356 tau than the P301S mice (A and C).Remarkably, this phospho form of tau was almost absent in the Nuak1+/- mice (A and C). When they measured total levels of tau using the tau-5 antibody, P301S/Nuak1+/- mice presented lower levels of total human tau than P301S mice (A and D). When they analyzed the levels of total endogenous mouse tau, they observed that only the Nuak1+/- mice showed a decrease in total mouse tau levels in comparison with the other three groups (A and E).

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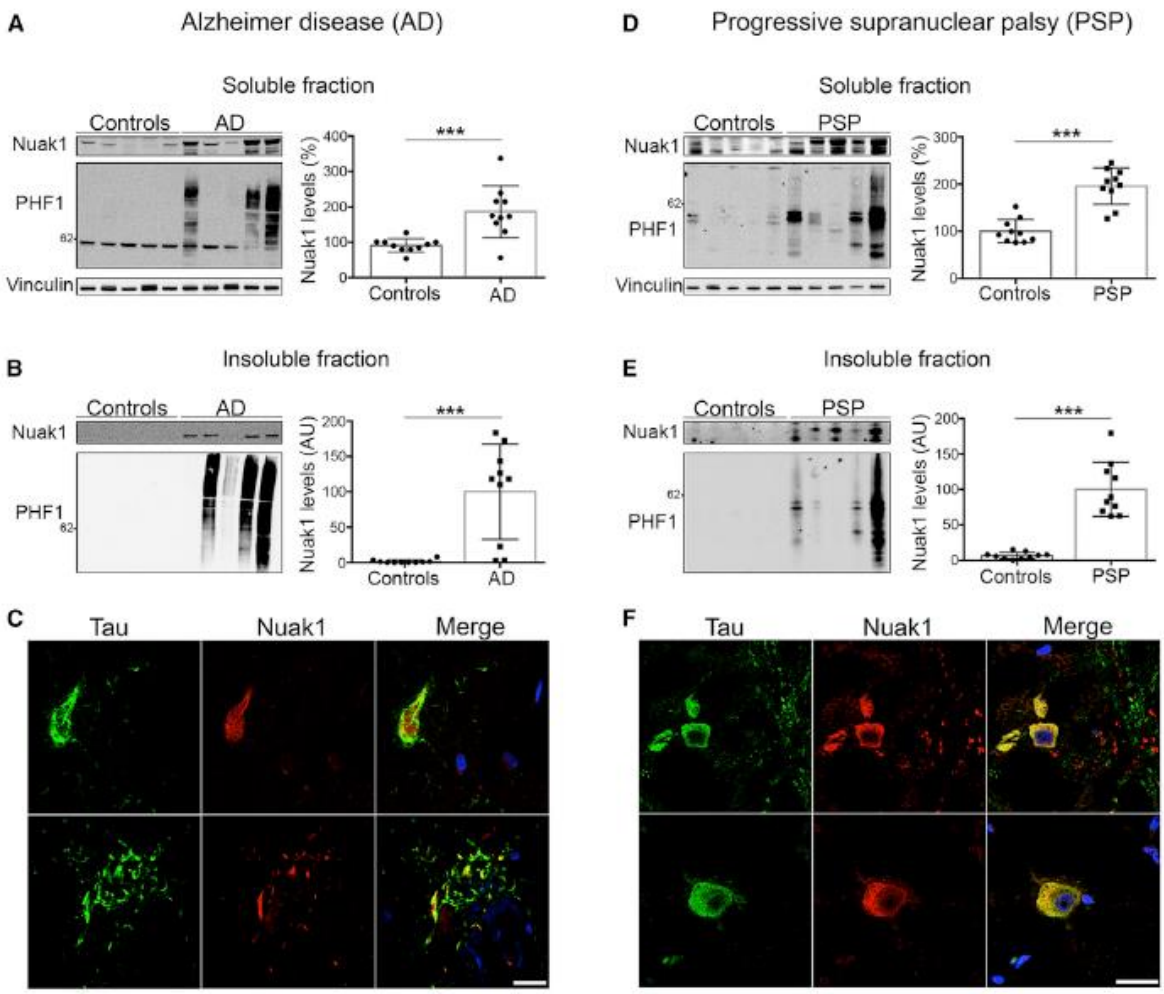
Nuak1 Levels Are Increased and Associated with Tau Pathology



Nuak1 Levels Are Increased and Associated with Tau Pathology in Human AD and PSP (A) Nuak1 levels are elevated in soluble fractions of AD cases in comparison with age-matched controls. (B) Nuak1 is also elevated in AD insoluble fractions in relation with age-matched controls. (C) Double staining in AD brain sections showed co-localization of tau (green) and Nuak1 (red) in NFTs (top) and Neuropil threads. (D) Nuak1 levels are elevated in soluble fractions of PSP cases in comparison with age-matched controls. (E) Nuak1 is also elevated in PSP insoluble fractions in comparison with age-matched controls. (F) Double staining in PSP brain sections showed co-localization of tau (green) and Nuak1 (red) in globose NFTs. Scale bar, 20 mm. For all quantifications, n = 10,

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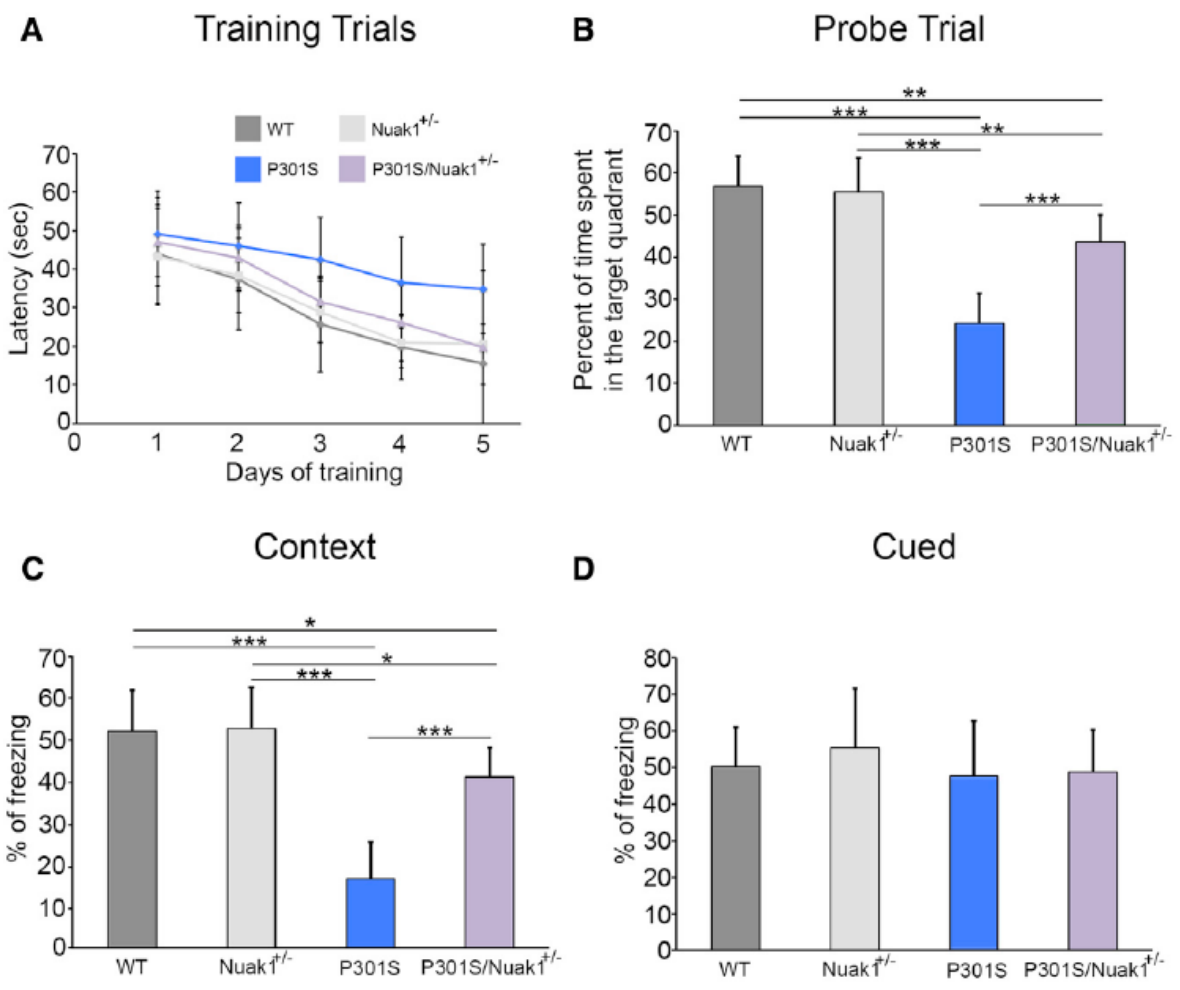
Reduction of Nuak1 by 50% Reverses Memory Deficits



Reduction of Nuak1 by 50% Reverses Memory Deficits in Tau P301 Transgenic Mice (A) Morris water maze analysis of invisible platform training sessions expressed as the latency to find the platform. (B) Probe trial for Morris water maze. P301S mice showed less time in the target quadrant. (C) Contextual fear conditioning results. Freezing was statistically reduced in the P301S in context testing. (D) Cued fear conditioning. No statistical difference was observed between groups. For all experiments, n = 20, mean ± SD; *p < 0.05, **p < 0.01, and ***p < 0.001.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

Contact Information

Contact Person	Dr. John Skidmore (Chief Scientific Officer)
Email	js930@cam.ac.uk
URL	https://cambridge-ddi.alzheimersresearchuk.org/