



Weill Cornell Medicine

Inhibition of the UFMylation Cascade for Treatment of Alzheimer's Disease and 4R Tauopathies

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Background & Unmet Need

- Tauopathies are a heterogeneous group of neurodegenerative diseases characterized by accumulation of tau aggregates in the brain
- Tauopathies include common diseases like Alzheimer's Disease (AD) and Traumatic Brain Injury (TBI) as well as rare conditions like Frontotemporal lobar degeneration with Tau pathology (FTLD-Tau)
- Tau aggregates in the brain can be formed from the 3R or 4R isoforms of tau, or a combination of both
- Tauopathies are classified as 3R tauopathies, 4R tauopathies, or 3R/4R tauopathies depending on which isoforms are present
- The mechanistic underpinnings of tauopathies are poorly understood and there are currently no effective treatments for these diseases
- **Unmet Need:** Improved understanding of the mechanisms underlying tauopathies and new treatments for these diseases

Technology Overview

- **The Technology:** Inhibition of the UFMylation cascade for treatment of 4R tauopathies such as AD of FTLD-Tau
- **The Discovery:** The inventors engineered a novel model for 4R tauopathies using iPSCs expressing 4R-tau carrying the P301S MAPT mutation, an FTLD-tau-related mutation
- A CRISPRi screen of genes associated with Tau pathobiology identified the UFMylation cascade as top modifier of seeding-induced Tau propagation
- **PoC Data:** Inhibition of the UFMylation pathway via shRNA knockdown of UBA5 significantly reduces seeding-induced Tau propagation in vitro and in vivo
- Free UFM, an inverse measure of UFMylation cascade activity, is reduced in tangle-bearing neurons in human AD brains, indicating that the UFMylation pathway promotes Tau pathology in AD

Inventors:

Li Gan
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Zeping Zhao

Patents:

Provisional Filed

Publications:

[Bravo et al. bioRxiv. 2023](#)
(preprint)

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Cornell Reference:

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Technology Applications

- Treatment of primary tauopathies with 4R tau involvement, such as FTLD-Tau, Progressive supranuclear palsy, Corticobasal degeneration, and Argyrophilic grain disease
- Treatment of secondary tauopathies with 4R tau involvement including AD and chronic traumatic encephalopathy (CTE)

Technology Advantages

- New mechanism of action that isn't related to amyloid beta for treatment of AD and other tauopathies
- Multiple potential drug development targets within the UFMylation cascade were identified as hits from a CRISPRi screen

Supporting Data / Figures

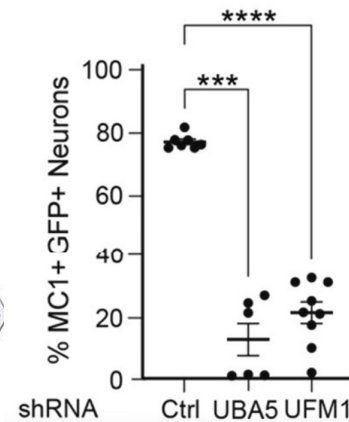
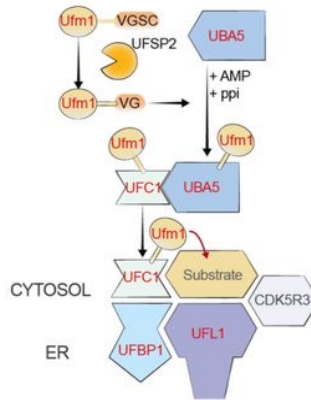


Figure 1: Left: Representation of UFMylation cascade. Right: shRNA inhibition of UBA5 or UFM1 suppresses seeding-induced Tau propagation (measured by significantly fewer MC1+/GFP+ neurons).

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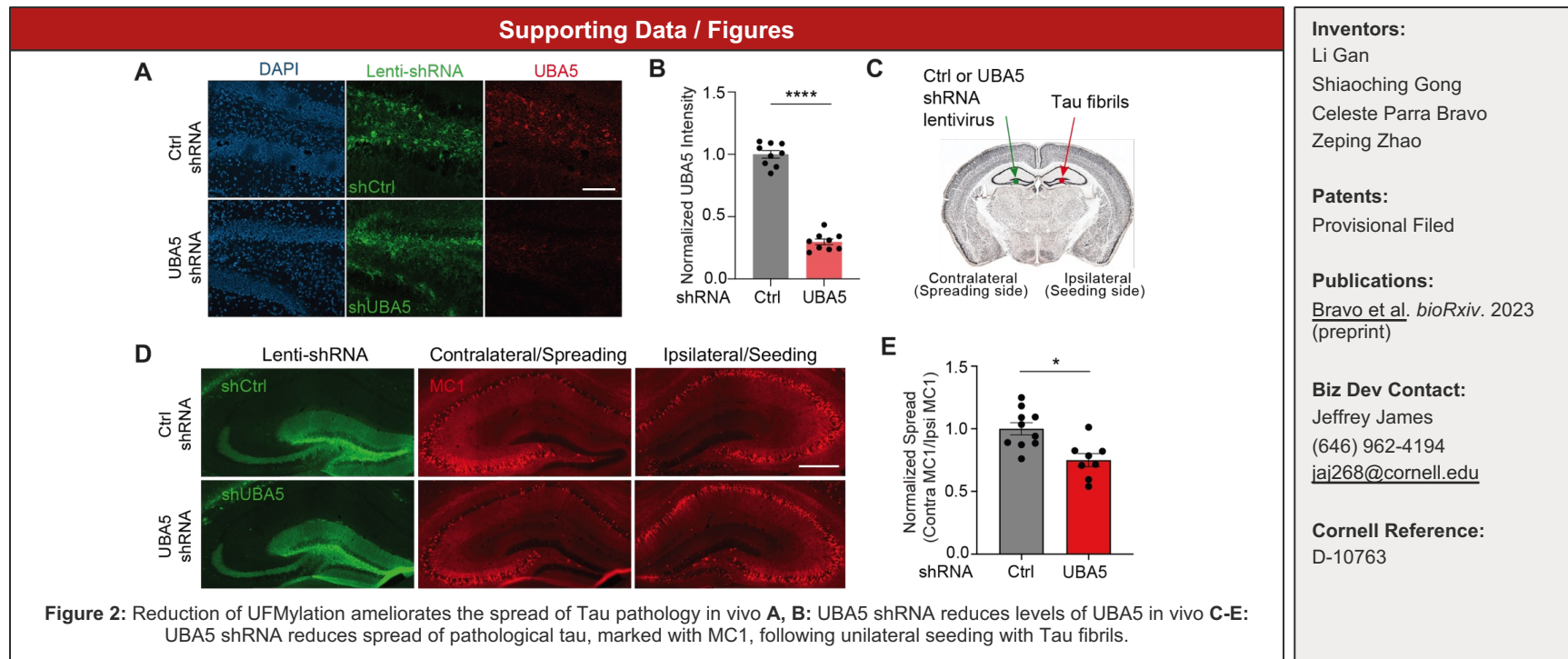
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