Weill Cornell Medicine

Prohibitin Gene Therapy for the Treatment of Alzheimer's Disease

Lead Inventor:

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Background & Unmet Need

- Alzheimer's Disease (AD) affects over 5 million Americans annually and is the most common form of age-related cognitive impairment
- AD is linked to the formation of plaques in the brain by the synaptic protein amyloid-beta precursor protein (APP) through poorly understood mechanisms
- AD onset is also associated with mitochondrial dysfunction that may contribute to cognitive impairment
- Prohibitin (PHB1) is involved in mitochondrial lipid maturation and stabilized respiratory chain supercomplexes to promote respiratory functions in neural cells
- PHB1 gene silencing increases vulnerability of neurons to injury
- **Unmet Need:** Novel therapeutic strategies for AD

Technology Overview

- **The Technology:** Method to treat AD through upregulation of PHB1
- **Discovery:** Baseline PHB1 expression in reduced in Tg2576 mice, a mouse model of AD
- PHB1 knockout mice exhibit significant behavioral abnormalities, and display features consistent with neurodegeneration (e.g., protein aggregation, Tau hyperphosphorylation)
- The inventors also identified a novel regulatory mechanism for PHB1, based on nitric oxide (NO) mediated protein S-nitrosylation on residue Cys^{69}
- PHB1 Cys^{69} S-nitrosylation is significantly reduced in the brains of APP mice and AD patients
- **PoC Data:** Administration of an AAV-based gene therapy to increase PHB1 expression induced functional improvements in AD symptoms and increased synaptic long-term potentiation (LTP)

Inventors:
Ping Zhou
Constantino Iadecola

Patents:
US Patent 10,087,224

Publications:
Anderson et al. *Cell Death Differ.* 2020.
Qu et al. *J. Neurosci.* 2020.
Kurinami et al. *Stroke.* 2014.
Zhou et al. *J. Neurosci.* 2012.

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Technology Applications

- Targeted gene therapy to reverse cognitive impairments in AD
- Method for up-regulating prohibitin expression in neurodegenerative diseases associated with mitochondrial dysfunction

Technology Advantages

- Applicable to multiple neurodegenerative diseases linked to mitochondrial function (e.g., AD, Creutzfeldt-Jakob disease)
- Selectively targets gene expression in a single brain region
- MOA operates by increasing expression of an endogenous protein

Supporting Data / Figures

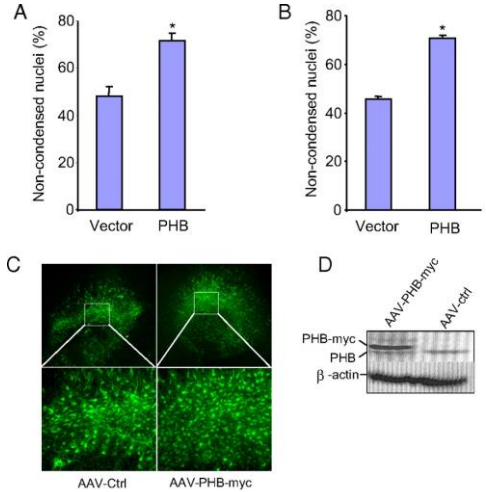

Figure 1: A: PHB1 expression improves viability of neurons exposed to STS. **B:** PHB1 expression improves viability of neurons exposed to X/XO. **C:** AAV mediated PHB1-myc-GFP expression in hippocampal slices. **D:** Myc-tagged PHB1 is expressed in high level in the slices infected with AAV-PHB1-myc but not control vector (AAV-ctrl).

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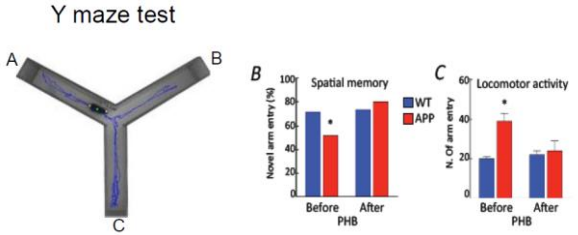

Figure 2: AAV-mediated PHB1 gene transfer restores spatial memory loss in old APP-Tg mice.

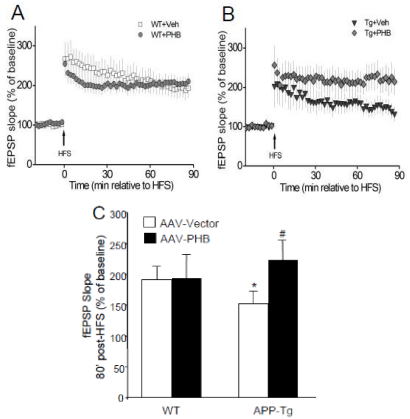

Figure 3: AAV-mediated PHB1 gene transfer rescues the long-term potentiation (LTP) impairment in hippocampal slices of APP-Tg mice. mice. AAV vector or AAV PHB1 were injected into either 12-month-old APP Tg mice **(A)** or WT control **(B)**. **(A)** Hippocampal LTP was impaired in APP Tg mice, and the impairment was rescued by AAV PHB1 gene transfer. **(B)** Hippocampal LTP was maintained in slices from WT mice. PHB1 did not alternate the LTP in WT slice. **(C)** Cumulative data showing mean fEPSP slopes 80 minutes post HFS based on the LTP experiments in panel A and B.

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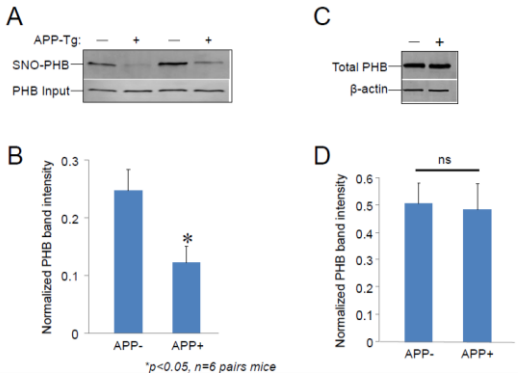

Figure 4: PHB1 S-nitrosylation is reduced in the brains of APP mice.

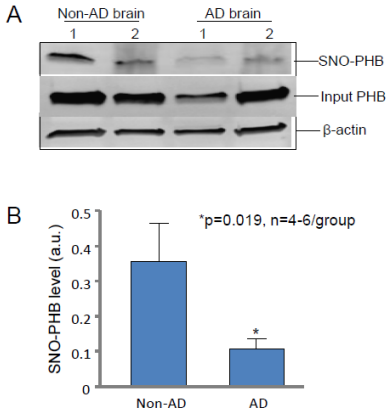

Figure 5: PHB1 S-nitrosylation is significantly reduced in the brains of AD patients. AD and non-AD brains were obtained from donors 79 – 86 years old, both males and females.

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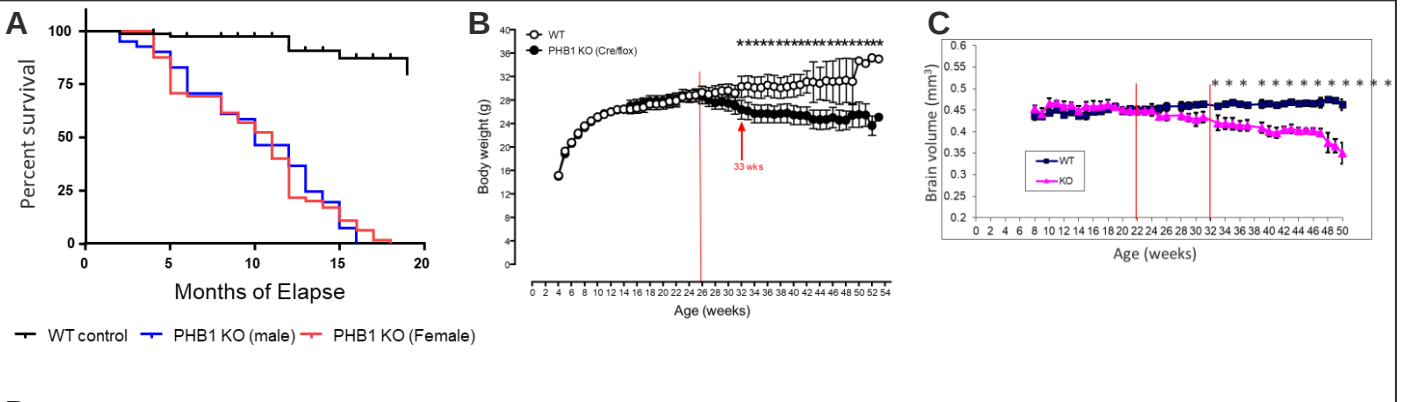

Figure 6: A: Neuron-specific PHB1 KO mouse model. Neuron-specific PHB1 KO mice have significantly reduced survival compared to WT control, with a mean survival of ~11 months. **B-C:** PHB1 KO mice begin to lose body weight starting at 6 months, accompanied by brain atrophy as measured by MRI. **D:** Western blot showing Tau protein hyperphosphorylation in brains of PHB1 neuronal KO mice detected by AT8 antibody. Tau phosphorylation increased starting from 6 month of age, concurrent with loss of brain volume.

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