

Boros Project Update Abstract

The majority of neuron to neuron communication or synapses occur on actin-rich protrusions along neurons called dendritic spines, and cognitive function and activity are inseparably linked to the structure of dendritic spines and the remodeling of their morphology (plasticity). Detrimental alterations in dendritic spine number, shape, or size have been reported in nearly all neurologic disorders, including autism, Alzheimer's disease, Frontotemporal Dementia, Parkinson's disease, and schizophrenia. In tauopathies such as Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), strong evidence suggests that synapse loss is a contributor of movement and cognitive dysfunction. Therefore, dendritic spine numbers and morphology are likely negatively altered. Repairing or regenerating spines could greatly benefit PSP and CBD patients.

In this project, we tested therapeutic targets with clinically-available drugs that both diminish tau protein levels and enhance dendritic spine structural plasticity. Our group discovered that activity of the Rho-associated protein kinases (ROCKs) are elevated in PSP and CBD patient brains. Currently, drug inhibitors of ROCKs are used to treat glaucoma and cerebral vasospasm in humans. I demonstrated that treating cultured hippocampal neurons with drug inhibitors of ROCKs both reduces tau protein level, increases dendritic spine density, and enhances dendritic spine morphology. Furthermore, I revealed that genetic deletion of the ROCKs in a mouse model diminishes tau levels and stimulates dendritic spine structural plasticity. Based on these results we predicted that ROCK inhibitors can be repurposed to combat harmful tau accumulation and reverse pathologic dendritic spine alterations. Our goal is to translate these findings to future studies that will explore the potential benefit of ROCK inhibitors in PSP and CBD patients.

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Greathouse KM, **Boros BD**, Deslauriers JF, Henderson BW, Curtis KA, Gentry EG, Herskowitz JH. Distinct and Complementary Functions of Rho kinase isoforms ROCK1 and ROCK2 in Prefrontal Cortex Structural Plasticity. *Brain Structure and Function*. Submitted.

Boros BD, Greathouse KM, Gearing M, Herskowitz JH. Dendritic spine structure remodeling accompanies Alzheimer's disease pathology in cognitively normal aging. *Neurobiology of Aging*. Submitted.

Boros BD, Greathouse KM, Gentry EG, Curtis KA, Birchall EL, Gearing M, Herskowitz JH. Dendritic spines provide cognitive resilience against Alzheimer's disease. *Annals of Neurology*. 82: 602–614, 2017. PMID: 28921611.