Light-based regulation of autophagy processing to target pathological forms of tau

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Principal Investigators

WEICK, JASON P

Institution

UNIVERSITY OF NEW MEXICO HEALTH SCIS CTR

Contact information of lead PI
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USA

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Light-based regulation of autophagy processing to target pathological forms of tau

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Research Abstract

PROJECT SUMMARY/ABSTRACT The objective of this project is to create an optical strategy with high spatio-temporal specificity to regulate the expression of genes that may provide benefit to neurons prone to degeneration. While we will focus on the clearance of pathological forms of microtubule associated protein tau (MAPT), our study will lay the foundation for a variety of future examinations of regulated biological pathways related to disease. Previously reported in expression systems, our study will seek to be the first to use plant phytochromes

that are bi-directionally regulated by red light (ON) and far red light (OFF), to induce transcription of a master autophagy regulating protein Transcription Factor EB (TFEB) in neurons. We will then test the capacity of this system to: (i) reduce the presence of pathological MAPT in vitro using cell lines expressing mutant MAPT and human pluripotent stem cells from patients with Down syndrome (DS) and sporadic Alzheimer's disease (AD), (ii) validate that TFEB is causative for, and the autophagy-inducing effects are positively correlated with, reductions in MAPT, and (iii) test whether application of light-induced TFEB expression in the hippocampus of a mouse model of AD can reduce cell death and cause improvements in learning and memory. The main hypothesis is that repeated, transient increases in autophagy can be used to inhibit MAPT-mediated degeneration in brains that cause various forms of tauopathy. Previous studies have shown that sustained increases in TFEB-mediated autophagy can clear MAPT aggregates and improve cell survival. However, chronic induction of autophagy can itself be deleterious and may exacerbate other neurological insults highly prevalent in aging individuals, the target population for tauopathy treatments. Thus, we believe the proposed strategy will provide therapeutic benefits (increased autophagy and reduced MAPT pathology) while reducing the likelihood of side effects such as autophagy-mediated cell death in response to additional cell stresses (e.g. ischemia/vascular dementia). Furthermore, once developed, this system may be applied to many neurological disorders for which regulated gene expression may be desirable, including Parkinson's disease, Epilepsy, Amyotrophic Lateral Sclerosis, and multiple forms of poly-glutamine disorders (e.g. Huntington's disease) to name a few.

Further information available at:

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