Discovery of 2,6-Dimethoxy-4-(5-Phenyl-4-Thiophen-2-yl-1H-Imidazol-2-yl)-Phenol (DPTIP) a Small Molecule Inhibitor of Neutral Sphingomyelinase 2 (nSMase2) for the Treatment of Neurodegenerative and Oncologic Diseases

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Technology description

Unmet Need

Alzheimer’ s disease (AD) is the most common form of dementia, affecting approximately 5.7 million people in the United States in 2018. Yet, no cure exists for AD, and AD therapeutics presently on the market fail to treat the disease’ s underlying causes. Recent studies in mice reveal that exosomes released from glial cells contribute to the propagation of tau, which are a hallmark of AD. Neutral sphingomyelinase 2 (nSMase2), which is critically involved in exosome synthesis, achieves this in part through its production of ceramide, a lipid that is elevated post-mortem in human AD. Further, pharmacological inhibition or genetic deletion of nSMase2 significantly has been shown to decrease tau propagation and improve cognition. Taken together, these provide a compelling rationale for the development of nSMas2 inhibitors as AD therapeutics. However, current inhibitors to nSMase2 have low potency, poor solubility and limited brain penetration, thereby limiting their therapeutic potential.

Technology Overview

JHU researchers have identified an inhibitor of human nSMase2, MS882, with nanomolar potency.

Advantages

This noncompetitive inhibitor is metabolically stable and exhibits high brain penetrance. When dosed systemically in mice, MS882 blocked IL1-beta-induced glial exosome release, prevented brain cytokine upregulation, and attenuated neutrophil migration into the brain. Additionally, no overt toxicological signs were observed in mice treated with MS882.

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