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Discovery and development of novel functionally-selective S1R ligands as potential Alzheimer's disease-modifying therapeutics

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Unless disease-modifying treatments for Alzheimer's disease (AD) are discovered, the prevalence and the associated financial and caregiver burden of AD is projected to increase dramatically. To address this urgent unmet medical and societal need, our research is focused on discovering drug treatments capable of preventing or slowing the progression of AD. Brain inflammation triggered by chronic oxidative-nitrosative stress is a proven component in the pathogenic cascade leading to mild cognitive impairment (MCI) and AD. When surplus inflammatory nitric oxide and superoxide molecules combine they form the brain-impairing reactive species peroxynitrite. This perpetuates inflammation thereby leading to the progressive neurodegeneration seen in AD. Accordingly, our innovative strategy includes simultaneously interrupting the cycle of peroxynitrite generation by blocking unsafe elevations in nitric oxide, and enhancing resilience to inflammatory brain insults by facilitating the secretion of brain-derived neurotrophic factor (BDNF). Because the Sigma-1 receptor (S1R) protein is capable of regulating nitric oxide levels and mediating BDNF secretion when brain cells experience high levels of inflammatory stress, we are developing drugs that selectively target the S1R. By exploiting functionally selective signaling pathways measured with a unique *in vitro* high throughput platform, we have engineered small molecules that both reduce nitric oxide levels in response to an AD-type stressor and increase secretion of BDNF in neuronal and glial cells. Our drug discovery efforts have led to the identification of a novel class of orally-active compounds, exemplified by EPGN296, which are being optimized for CNS drug-like properties.

Biography

John A Schetz holds a Baccalaureate in Chemistry, a doctorate in Neuroscience and he completed post-doctoral training in molecular neuropharmacology at the NIH and in pharmacokinetics and metabolism, and business and management development. He is currently a tenured Associate Professor of Pharmacology and Neuroscience with cross-appointments in Psychiatry and Health Management and Policy. He serves on national and international grant review panels and his research has been published in reputed journals and featured in print, radio and televised media reports. His current interest is on innovative and mechanistically unique approaches for preventing or slowing the progress of Alzheimer's disease.

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