

Glycosaminoglycan-Interacting Small Molecule (GISMO) as Parkinsons Therapeutic

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USA

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Glycosaminoglycan-Interacting Small Molecule (GISMO) as Parkinsons Therapeutic

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Research Abstract

Glycosaminoglycan-Interacting Small Molecule (GISMO) As Parkinson's Therapeutics
ABSTRACT Current approved drugs for Parkinson's Disease (PD) treat the symptoms of the disease but do not stop disease progression. This project is focused on developing a new disease-modifying PD therapeutic with a novel mode of action that is expected to block disease progression. Recent data indicate that heparan sulfate glycosaminoglycans (HS-GAGs) are the

receptors responsible for internalization and spreading of alpha-synuclein proteopathic seeds across the CNS. We propose that the inhibition of the HS-GAG-mediated internalization can be achieved by interfering with the interaction between alpha-synuclein and HS-GAGs, and that targeting this interaction will lead to the identification of new treatments for PD and other synucleinopathies. We have previously shown that Glycosaminoglycan-Interacting Small Molecule (GISMO) are a new, structurally-diverse class of compounds that are biologically active in vitro and in vivo and we aim to target the HS-GAG – mediated internalization and aggregation of alpha-synuclein proteopathic seeds with GISMOs. In preliminary work for this project, we screened a library of GISMO-like compounds using a new alpha-synuclein – HS-GAG interaction assay on 96-well plates and identified 15 hit compounds (with inhibitory activity >30%), that have been selected for further development. In the proposed project, we will first screen the 15 hit compounds for inhibition of alpha-synuclein internalization in neuronal cells, and cytotoxic effects. GISMO compounds are expected to inhibit HS-GAG-mediated alpha-synuclein uptake. Lead series of compounds with acceptable efficacy, selectivity and safety in vitro will be then subjected to chemical optimization via medicinal chemistry. The selected 4-5 lead compounds will be evaluated by pharmacokinetics, for oral bioavailability and brain-penetrant properties. Three chosen lead compounds will be subsequently tested in an animal model of Parkinson's Disease, in collaboration with team of Dr. Patrik Brundin (Van Andel Research Institute, Grand Rapids, MI). The successful completion of these studies will enable identifying a Preclinical Candidate for IND-enabling studies. The development of a disease-modifying therapeutic would be the most significant advancement in Parkinson's disease therapeutics since the development of levodopa in the 1960s.

Further information available at:

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