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Glycopeptide drugs

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Parkinson's disease (PD) is the 2nd most common neurodegenerative disorder, affecting over 1 million people in the US. Parkinson's disease causes difficulties with movements such as walking, writing and speaking that occur because of deficiencies of the chemical dopamine in the brain. Current therapies for PD only treat the symptoms and do not reverse underlying disease processes that cause dopamine-producing brain cells to die. This situation has led to widespread interest in new strategies of neuroprotection or neurorestoration. The mostpromising approaches to modifying the disease process in the laboratory have relied on natural brain chemicals known as "growth factors". Several growth factors have demonstrated the ability to reverse the disease process in animal models of PD. A few of these growth factors have shown sufficient promise that they have been tested in clinical trials in humans with PD. One promising approach is offered by the peptide "secretins" vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) which plays important roles in neuronal survival, neuroprotection, inflammation and immunomodulation. PACAP seems to be protective against the loss of dopamine-producing brain cells in rodent model of Parkinson's, but only after being injected directly into the brain. The proposed glycopeptides are surfactants, chemically speaking, and have extended half-lives *in vivo* and unlike their peptide counterparts, these molecules can efficiently cross the blood-brain barrier (BBB). We have developed a new technology platform to develop glycopeptide analogues that show increased stability. We will synthesize a series of novel glycopeptides based on PACAP and VIP to screen their efficacy at PAC1, VPAC1 and VPAC2 receptors expressed in CHO reporter cells and test the most promising compounds in animal models of Parkinson's disease. We will be assisted greatly in this endeavor by micro-dialysis data that will allow us to quantify brain levels of the drug over time, and direct measurements of drug stability *in vivo*. This is accomplished by multiple collision-induced fragmentation mass spectroscopy (MSn). In this way we hope to produce one or more drug candidates for further study, ultimately leading to clinical application.

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