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Grant Title: Role of glycan chain of ganglioside GM1 in modulating neural signaling

Progress Report:

a) Abstract

It is well over a century that glycosphingolipids are matter of interest in different fields of research. The hydrophilic oligosaccharide and the lipid moiety, the ceramide, both or separately have been considered in different moments as the crucial portion of the molecule, responsible for the role played by the glycosphingolipids associated to the plasma-membranes or to any other subcellular fraction. Glycosphingolipids are a family of compounds characterized by thousands of structures differing in both the oligosaccharide and the ceramide moieties, but among them, the nervous system monosialylated glycosphingolipid GM1, belonging to the group of gangliosides, has gained particular attention by a multitude of Scientists.

In recent years, we performed a series of studies that have been conducted on the functional roles played by the glycan chain of GM1, its oligosaccharide (OligoGM1). These studies allowed to shed new light on the mechanisms underlying the properties of GM1 defining the role of the OligoGM1 in determining precise interactions with membrane proteins instrumental for the neuronal functions.

Within this project we aimed to further investigate on the cascade of events modulated by OligoGM1, as the bioactive portion of GM1, to support neuronal differentiation and trophism together with preclinical studies on its potential to modify the progression of Parkinson's disease (PD). To address that we investigated 3 main specific objectives: i) verify the OligoGM1 ability to modulate neurotrophic pathways, in which GM1 role has been well defined in relation to both physiological and pathological (PD) status; ii) elucidate whether the αS accumulation onset is related to the OligoGM1; and iii) verify whether OligoGM1 could improve the pathological phenotype of PD model considering mitochondrial impairment and αS toxicity rescue. In order to achieve these objectives, we are using: *i) in vitro* procedures to elucidate the αS molecular shaping regulated by GM1 interaction, focusing on putative OligoGM1-αS binding inhibiting the fibril formation; *ii)* cellular models to study the protective/restorative signaling pathways activated by OligoGM1.

We address to validate that the specific role of ganglioside GM1 in neuronal homeostasis is mediated by its oligosaccharide: this bioactive portion, protruding in the extracellular environment, acts at the cell surface by a direct interaction with specific proteins. Importantly, we aim to provide a significant advance in the understanding how the GM1 oligosaccharide deficiency is responsible for the onset of sPD providing at the same time a new promising strategy to counteract the progression of the disease.