GSK-3 INHIBITORS AS NEW LEADS FOR PARKINSON’S DISEASE PHARMACOTHERAPY

C. Susín¹, J.A. Morales-Garcia¹, D.I. Perez², S. Conde², C. Gil², A.M. Perez-Castillo¹, A. Martinez²

¹Instituto de Investigaciones Biomedicas ‘Alberto Sols’-CSIC, ²Instituto de Química Medica-CSIC, Madrid, Spain

Introduction: Parkinson’s disease (PD) is a devastating neurodegenerative disorder characterized by degeneration of the nigrostriatal dopaminergic pathway. As the current therapies only lead to temporarily limited improvement, and have side effects, new approaches to treat Parkinson’s disease need to be developed. Aims. To discover new leads for further pharmaceutical development as new therapeutic strategies for PD treatment.

Methods: In-house chemical library screening on a well established cellular model of PD is used to select the first compounds. In depth in vitro studies to look for the mechanism of action of the selected compounds are pursued.

Results: From the screening of more than 400 chemically diverse molecules, we have selected among others compound SC001, a small heterocyclic molecule. After different enzymatic assays, we found this compound to be a GSK-3 inhibitor with an IC₅₀=3 µM. In vitro studies showed that this compound is able to protect the human dopaminergic cell line SH-SY5Y from 6-OHDA-induced cell death. Moreover, SC001 also presented a significant neuroprotective effect in the hippocampal murine cell line HT22 after an excitotoxic insult. Additionally, this compound attenuates the production of nitrites in primary glial cultures after an inflammatory insult, also suggesting an effect upon the inflammatory reaction that contributes to the dopaminergic cell death observed in PD. Currently we have ongoing studies to analyze the in vivo effects of this compound.

Conclusions: Our findings led us to propose the potential therapeutic value of GSK-3 inhibitors, specifically of SC001 in Parkinson's disease.