SCREENING FOR INHIBITORS OF ALPHA-SYNUCLEIN AGGREGATION AND TOXICITY AS A POTENTIAL NOVEL DRUG FOR PARKINSON’S DISEASE

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Introduction: Convergent biochemical and genetic evidence suggests that the formation of alpha-synuclein deposits is an important step in the development of Parkinson's disease (PD). Therefore, small molecules able to inhibit alpha-synuclein aggregation could be a promising therapeutic application for PD and related diseases.

Aim: In this study we screened the effect of eighteen small compounds on alpha-synuclein aggregation and toxicity.

Methods: We tested the inhibition effect of small compounds on alpha-synuclein fibrillation using Thioflavin-S assay, and their effect on alpha-synuclein oligomerization (early aggregates) were also tested using novel immunoassay developed in our laboratory. Electron microscopy was also used to study the effect of our compounds on the amyloid fibrils formation.

Results: In our study thirteen of the small compounds have shown complete inhibition of amyloid fibrils formation by alpha-synuclein, and five compounds were partially able to inhibit alpha-synuclein fibrils formation. However, we found two compounds that can inhibit both early aggregates (oligomers) and late aggregates (amyloid fibrils) of alpha-synuclein. The inhibition pattern for these compounds was concentration dependent. These results were also confirmed by western blotting and electron microscopy. The effect of these compounds against the extracellular toxicity induced by alpha-synuclein aggregates is now under investigation.

Conclusion: In this study we have identified compounds that can inhibit both early and late aggregate formation of alpha-synuclein. These compounds could represent the starting point for designing new molecules, which may be used as new drugs for the treatment of Parkinson's disease in the future.