SynOD

alpha-Synuclein OMICS to identify Drug-targets

Background: Aggregation of the protein alpha-synuclein in neurons and oligodendrocytes in the brain causes a group of neurodegenerative diseases collectively referred to as synucleinopathies, including, among others, Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). In absence of disease – modifying treatment options, it is essential to increase the knowledge about the molecular causes and consequences of alpha-synuclein pathology to identify novel therapeutic targets and to develop more powerful therapeutic interventions. In preparatory pro-jects, members of the group of applicants have already generated large datasets in patients-derived materials (genome-wide association study, epigenome-wide DNA methylation study, miRNA sequencing in MSA and PD) and corresponding cell models (DNA-methylome, miRnome, transcriptome, proteome). In an alpha-synuclein-overexpression cell model, a genome-wide siRNA modifier screen and two compound screens have been conducted to identify molecular targets and drug-like compounds for their ability to reduce synuclein-induced toxicity. Objective: In the proposed SynOD project, we will assemble the unique large OMICS datasets described above and explore them with powerful computational methods to generate an integrated map of molecular pathways involved in synucleinopathies, with a particular focus on drug-target identification.

Aims: We will collate the existing datasets to generate a multi-dimensional map of molecular alterations occurring in synucleinopathies. Secondly, by analysing the interventional datasets in conjunction with the aforementioned map, we aim to identify molecularly defined targets for therapeutic interventions aimed at preventing neuronal dysfunction and death. After the project completion the assembled dataset will be made publicly available as resource.

Methods: The large set of existing data generated previously in human brains and neuronal cell models by the applicants with both observational methods (DNA methylation, miR-NA, mRNA, proteome) and interventional methods (siRNA screen, FDA drug-screen, compound screen) and further enrichment with genetic, transcriptomic and epigenetic datasets from major inter-national consortia allows linking observational markers to therapeutic approaches. These unique multi-omics datasets will be explored by powerful and efficient computational methods. The analytical power will be increased by conducting hypothesis-free analyses and taking analyses on existing in-formation into account. Thereby, we will generate an integrated map of molecular pathways involved in synucleinopathies. The therapeutic relevance of the identified drug targets will be examined in vitro by qualified researchers to facilitate the international research activities into synucleinopathies.

Expected outcome: The proposed project will ultimately lead to a more profound and comprehensive understanding of the genomic, epigenomic, transcriptomic and proteomic mechanisms and their interplay implicated in synucleinopathies. The SynOD project will pave the way to the identification of new molecular targets to cure the disease, which imposes a growing socio-economic burden to the ageing European society.

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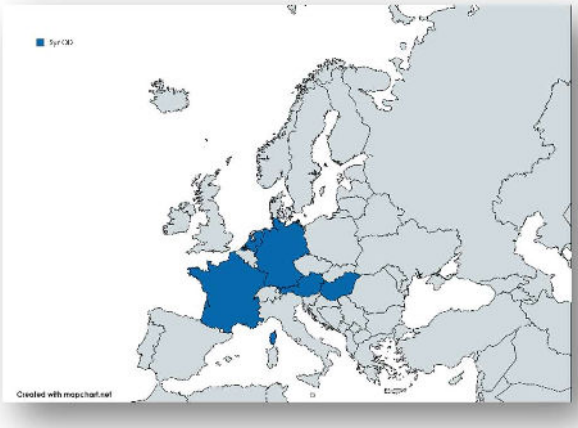

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