GBA-paCTS

Personalised medicine for Parkinson disease: clinical and therapeutic stratification

Parkinson disease (PD) has a lifetime risk of 3-4%, and there are approximately 60,000 new cases annually in the EU. All PD-related costs in the EU are estimated at 13 billion euros per annum.

Recent advances in PD have identified that glucocerebrosidase 1 (GBA1) mutations are numerically the most important risk factor for PD. They are found in 10-15% of PD (25% in Ashkenazi Jews), and increase the risk for PD by 20-30x.

This grant will investigate the evolution of clinical features prior to and during the development of PD in those that carry GBA1 mutations, and the downstream molecular, biochemical and cellular consequences of the mutations in patient material, patient-derived cell and animal models. This will be translated into a personalised clinical and biochemical biomarker risk profile for GBA-PD. We will further test a small molecule GBA1 chaperone to slow or reverse the pathology of PD in cell and animal models as a means to develop personalised medical therapy for GBA1-PD.

We will develop clinic and web-based recruitment of GBA1 mutant carriers (currently >700) to provide integrated and harmonised clinical and biochemical biomarker assessment tools across 4 European countries. This will provide the largest cohort of GBA1 carriers in the world and sufficient power to develop clear understanding of the clinical and biochemical evolution to PD in this group. The cohort will also provide the applicants with additional patient material for investigation and a large cohort for clinical trial of GBA1 personalised therapies.

We will investigate the molecular basis for the link between GBA1 mutations and PD pathology, specifically their relationship to the levels of alpha-synuclein (A-SYN) and its aggregation and spread. This will use patient-derived neuronal stem cells and 3-D mid-brain organoids, and animal models of GBA1 mutations with adeno-associated viral vector (AAV)-induced or endogenous overexpression of A-SYN or direct intrastriatal injection of A-SYN fibrils. We will also determine the mitochondrial and lysosomal functional consequences of GBA1 mutations, and their effects on glia and inflammatory activation.

We will further investigate the ability of ambroxol, a GBA1 chaperone to reverse the abnormalities seen in our cell and animal GBA1 models, to confirm this therapeutic approach as a rational intervention to slow or prevent PD development or progression.
The applicants are all active in the field of GBA1 research, have all the necessary tools, and expertise and have an excellent track record of existing scientific collaborations and high impact publications together. This application brings members into a new formal arrangement to support clinical and basic science research for the personalised medicine for GBA1-related PD.

Total Funding : 1.6 M€

Duration : 3 years

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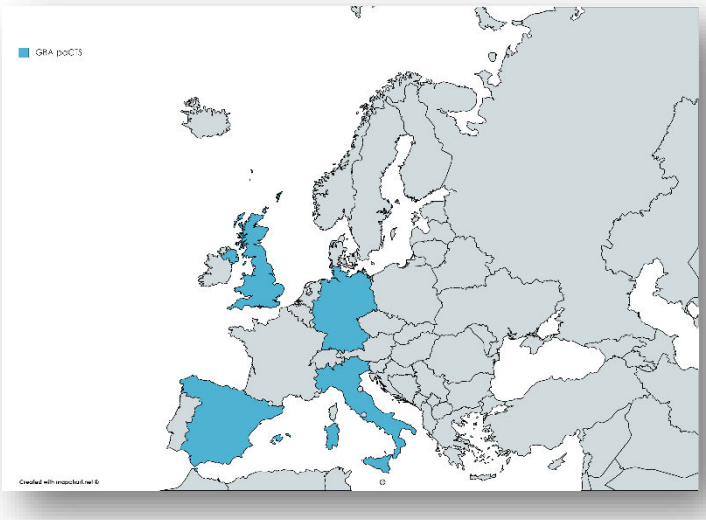

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