GBA-PARK
GBA1 MUTATIONS IN PARKINSON DISEASE: CLINICAL AND BIOCHEMICAL PRODROME, RISK PROFILE AND PATHOGENETIC MODELLING FOR THERAPEUTIC INTERVENTION (GBA-PARK)

Anthony H.V. Schapira[1]
Fabio Blandini[2], Paolo Ciana[3], Donato A. Di Monte[4], David Park[5]
[1]University College London, UK; [2]IRCCS Mondino Foundation, Pavia, Italy; [3]University of Milan, Italy; [4]DZNE, Bonn, Germany; [5]CIHR-University of Ottawa, Canada

Background
Heterozygous mutations of the GBA1 gene, encoding lysosomal enzyme glucocerebrosidase (GCase), represent the most important risk factor for Parkinson disease (PD), increasing PD risk by 20-30x. In Europe, 5-10% of all PD patients carry GBA1 mutations.

Expected outcomes
The primary objective of this project was the standardization of clinical and experimental practices for studying GBA1-linked PD, as a critical step toward the definition of diagnostic biomarkers, pathogenetic pathways and therapeutic strategies.

Collaboration within the consortium and main results
An active collaboration within the consortium was achieved thanks to a fruitful exchange of researchers, biological samples and procedures primarily between Bonn, London and Pavia. This maximized the results of the GBA-PARK project, reported below.

Clinical findings: a longitudinal study conducted in Gaucher Disease type 1 patients, GBA heterozygous carriers and mutation negative controls confirmed that **GBA mutation positive subjects show a worsening in both motor and non-motor prodromal PD features over time, potentially predicting a conversion to PD**. A biochemical study, including also PD patients, showed that reduced GCase activity in blood lympho-monocytes of PD-GBA patients is associated with higher alpha-synuclein levels. A lipidomic analysis of fibroblasts from healthy controls and PD patients with or without GBA1 mutations showed not only a specific lipid profile in mutation-carrying samples, but also significant **changes in lipid chain lengths associated with GBA inhibition that can enhance alpha-synuclein propensity to aggregate**.
Experimental findings: we found significantly greater formation and spread of α-synuclein inclusions in GBA1 L444P mutant mice, indicating that the **GBA1 mutation accelerates α-synuclein pathology and spreading**. GCase chaperone ambroxol induced a number of modifications, at lysosomal and mitochondrial levels, including an increase in the protein levels and activity of GCase and levels of its transporter LIMP2. Transcription factor EB (TFEB), the master regulator of the CLEAR pathway involved in lysosomal biogenesis, was increased upon ambroxol treatment. Mitochondria content also increased upon ambroxol treatment via the PGC1-α receptor.

Using a co-culture system of neuronal/astrocytic/microglial cells we identified morphodynamic changes suggesting that **GCase inhibition may drive specific microglia phenotypes** influencing neuronal pathways involved in neurodegeneration. These results were in keeping with other GBA-PARK results showing that, ***in vivo*, GCase inhibition activates microglia in the nigrostriatal pathway**. We also found that mutation-induced **GCase inhibition promotes oxidative modifications of alpha-synuclein and protein aggregation** into oligomeric species, enhancing the ability to "jump" from neuron to neuron and to spread throughout the brain.

Conclusions
GBA1 mutations represent the most important risk factor for PD identified to date and influence the emergence of prodromal features that may help predict conversion to PD in asymptomatic carriers. These clinical features may have a biological substrate - combining reduced lysosomal and mitochondrial efficiency with increased oxidative stress and neuroinflammation – that, once clarified, may provide new therapeutic targets for PD.