Glucocerebrosidase deficiency, alpha-synuclein and Parkinson’s: A zebrafish study

https://neurodegenerationresearch.eu/survey/glucocerebrosidase-deficiency-alpha-synuclein-and-parkinsons-a-zebrafish-study/

Principal Investigators

Professor Oliver Bandmann

Institution

University of Sheffield

Contact information of lead PI
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United Kingdom

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Glucocerebrosidase deficiency, alpha-synuclein and Parkinson's: A zebrafish study

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Parkinson's UK

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2

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Research Abstract

Background: Heterozygote mutations in the glucocerebrosidase 1 gene (GBA1+/-) are the most common genetic susceptibility factor for Parkinson’s disease (PD). Enzymatic glucocerebrosidase activity is also decreased in PD brains in the absence of a GBA1+/- mutation.
However, only some GBA1+/-carriers develop PD and the precise mechanisms how partial glucocerebrosidase deficiency (PGD) leads to neuronal cell loss are only partially understood.
Pilot data: We have established a stable mutant zebrafish (Danio rerio) line, carrying a 23 bp deletion in gba1, the zebrafish orthologue of human GBA1. Juvenile gba-/- zebrafish develop

marked behavioural, morphological and biochemical abnormalities, all consistent with glucocerebrosidase deficiency. We have also generated stable alpha-synuclein transgenic zebrafish lines, overexpressing either wild-type (Tg(SNCAwt)) or E46K-mutant alpha-synuclein (Tg(SNCAE46K)).
Objectives and methods: 1. To determine the effect of PGD on alpha-synuclein-related neurotoxicityin vivo (by crossing gba+/- with Tg(SNCAwt) or Tg(SNCAE46K); 2. To undertake an in vivo compound screen to identify drugs which upregulate enzymatic glucocerebrosidase activity in brain tissue (initial readout: effect of compounds on gba1 expression with subsequent validation experiments).
Expected outcome: Better understanding of PGD-related mechanisms and identification of compounds enhancing glucocerebrosidase activity in brain tissue will hopefully lead to improved therapy for PD.

Further information available at:

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Investments < €500k

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