Joint MD/PhD Fellowships Groningen-Oldenburg

Outline PhD Project

Working title of project	Mechanisms and determination of disease progression in the early phase of NPC1 disease
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Short Summary of PhD project (mx. 500 words), incl. research question(s), methods, approx. schedule (incl. times in Groningen/Oldenburg)

Niemann-Pick disease type C (NPC) is a rare neurodegenerative disease with no curative therapy available. NPC belongs to the class of lipid storage diseases and it is mainly caused by mutations in *NPC1* gene (95% of clinical cases), which encodes for the Niemann-Pick type C1 (NPC1) protein. Patients suffering from this devastating disease show a multisystemic spectrum of symptoms, for instance extensive loss of Purkinje cells in the cerebellum, a variety of progressive neurological and visceral symptoms, such as ataxia, dystonia, dysphagia, psychiatric problems and hepatosplenomegaly as one of the first symptoms occurring. NPC1 is responsible for the clearance of cholesterol from the lysosome. The functional absence of NPC1 leads to the accumulation of unesterified cholesterol and phospholipids in the lysosomal compartment. In this context, we already demonstrated that the metabolism of the phospholipid sphingosine-1-phosphate is disrupted in the brain of *Npc1*$^{-/-}$ mice.

1) **Use NPC1KO mouse model for OMIC study in an early phase without phenotype (lipidomic and proteomic).**

The breeding and expansion of the existing biobank of NPC1 KO mice takes place in Oldenburg. An animal experiment application has been approved for the next five years. The OMIC analyses are carried out in cooperation with Oldenburg, Groningen and external partners. The biometric analyses of the OMIC data will be done in cooperation with partners in Groningen.

2) **Comparison of identified factors from 1) with human samples and datasets available in public repositories and biobanks, like the Lifelines Biobank in Groningen (https://www.lifelines.nl/)**

The majority of this analysis can be performed remotely; however some coordination meetings will take place in Groningen.

3) **Functionally analyse factor regulations (possibly mutations) from 1) and 2) in cell cultures and mouse models.**

Initial functional biochemical and cell biological experiments will be carried out in Groningen in established cell culture models. Live cell experiments and cell culture experiments with primary cells will take place in Oldenburg.

PhD Candidate Profile/desired qualifications

The PhD candidate should have a strong interest in basic research, cell biology, molecular biology, and statistical analyses. The acquisition of an animal experimentation licence at the University of Oldenburg will be required. The handling and killing of mice is expected afterwards. The familiarisation with the clinical symptoms of lysosomal storage diseases with a focus on NPC1 is required. Thus, a great interest in paediatrics and medical genetics should be present.