Chapter 9

Summary of applications (Addendum II)

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The various developed lipid analyses (section I) were put into practice in studies dealing with diagnosis and monitoring of disease progression and correction by therapeutic intervention. The individual studies were published in peer-reviewed journals and are presented in the addendum II.

Studied was the value of lysoGb3 as disease marker for Fabry disease [1]. It is shown that the formation of antibodies against therapeutic enzyme (recombinant α-galactosidase A) in male Fabry disease patients results in relapses in plasma and urinary (lyso)Gb3 reduction. This finding illustrates that the efficacy of the therapy is hampered by the formation of antibodies that indeed are found to be neutralizing in enzymatic assays.

Investigated was the impact of interruption of enzyme therapy in Fabry disease patients with respect to plasma lysoGb3 levels [2]. A viral contamination of Genzyme's production facility resulted in a worldwide shortage of agalsidase beta leading to involuntary dose reductions (1 mg/kg/eow → 0.5 mg/kg/month), or switch to agalsidase alpha (0.2 mg/kg/eow). Plasma lysoGb3 was found to be increased in both patients switching to agalsidase alpha and on a reduced agalsidase beta dose.

The efficacy of enzyme therapy (ERT) and substrate reduction therapies (SRTs) with *Miglustat* and *Eliglustat* for type 1 Gaucher disease was compared by clinical evaluation and measurement of plasma biomarkers, including glucosylsphingosine [3]. The study revealed that reductions in plasma glucosylsphingosine mimic those in chitotriosidase, an established Gaucher cell marker. ERT and *Eliglustat*-SRT were found to result in marked reductions of biomarkers as compared to *Miglustat*-SRT.

Finally, the value of lipid analysis was demonstrated in an investigation on the effects of gene therapy in a mouse model of Gaucher disease [4]. Gene transfer with self-inactivating lentiviral vectors (SIN LVs) with the GBA gene under the control of human phosphoglycerate kinase (PGK) and CD68 promoter, was found to prevent, as well as reverse, symptoms such as splenomegaly, bone marrow infiltration by Gaucher cells and hematological abnormalities. These changes were accompanied by corrections in tissue glucosylceramide and glucosylsphingosine levels.

References:

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3 Smid BE, Ferraz MJ, Verhoek M, Mirzaian M, Wisse P, Overkleeft HS, Hollak CE, Aerts JM. Biochemical response to substrate reduction therapy versus enzyme replacement therapy in Gaucher disease type 1 patients. Orphanet J Rare Dis. 2016 Mar 24;11:28.

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