1/2 pediatric trials are ongoing. We present a quantitative systems pharmacology (QSP) model to support the development of olipudase alfa. The model utilizes a mechanistic, multi-scale approach to link the enzymatic activity deficiency driving ASMD with consequent lipid accumulation, cellular abnormalities, and organ-level clinical manifestations. The QSP model was developed by integrating knowledge from ASMD natural history, preclinical, and clinical data, and takes as input patient-specific PK profiles and indicators of disease severity. The model successfully reproduces both transient and long-term patient-specific responses to olipudase alfa. At the molecular level, it describes plasma ceramide and dried blood spot lyso-sphingomyelin profiles; at the organ level, it describes spleen volume and pulmonary function. Overall, the QSP model enables quantitative representation of systemic treatment responses to olipudase alfa. Due to the clinical heterogeneity of ASMD, this provides insight into treatment effects on different aspects of the overall disease burden, as a function of patient variability. The QSP model provides a platform for addressing clinical questions of interest such as alternative dosing regimens, patient stratification, and pediatric extrapolation.

[1] McGovern et al. (2013) Genet Med. 15(8):618-623.
[2] Wasserstein et al. (2015) Mol Genet Metab. 116(1-2):88-97.
[3] Thurberg et al. (2016) Am J Surg Pathol. 40(9):1232-1242.

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163
The effects of sub-maximal aerobic exercise in adults with late-onset Pompe disease (LOPD)

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Effectiveness of enzyme replacement therapy (ERT) is well documented in patients with LOPD. Positive effects of sub-maximal (≤70%HRmax) exercise in LOPD are also emerging. This pilot study explored whether an individualised, sub-maximal exercise program alongside ERT improved walking (6-minute walking test (6MWT)), respiratory function (Forced Vital Capacity (FVC)) and overall functional ability (Quick Motor Function Test (QMFT)) over 6 months. Adults (n = 11) with LOPD, on ERT for at least 12 months, able to walk > 50m, and able to safely transfer were randomized to either cycling-between or cycling-during ERT infusions with an individualised cycling prescription. Outcome measures were assessed at baseline, 3 and 6 months. Significant changes were observed in mean walking distance in the cycling-during ERT group (n = 4) (mean baseline = 397m, end-point = 497m, change = +101m). These patients improved their walking distance by +26%, +179%, +18%, and +6% respectively (Minimal Clinically Important Difference (MCID) = 6%). In the cycling-between ERT group (n = 7) mean walking distance remained stable (baseline = 428m, end-point = 429m). In the cycling-during ERT group two patients significantly improved FVC by 6% and 16% (MCID = 6%). In the cycling-between ERT group two patients significantly improved their FVC by 8% and 10% (MCID = 6%). Changes in mean FVC were not significant in either group. Overall functional ability (QMFT) improved in both groups. In LOPD, sub-maximal exercise during ERT significantly affects walking distance. Exercise, either during or between infusions, in addition to ERT, demonstrates stabilization of disease over 6 months with modest functional improvements. This pilot study supports previous findings regarding the positive effects of ERT and exercise on pulmonary function and functional activities. (This study was funded by Sanofi Genzyme.)

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164
AAAV5-mediated gene therapy with choroid plexus-directed α-n-acetyl-glucosaminidase expression in Sanfilippo syndrome type B mice

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Mucopolysaccharidosis type IIIB (MPS IIIB; Sanfilippo syndrome type B) is an inherited neurodegenerative disorder for which has no effective treatment currently. The cause of Sanfilippo syndrome type B is the deficiency of a lysosomal enzyme, α-*N*-acetyl-glucosaminidase (NAGLU) and resultant the storage of heparan sulfate. Current studies have shown that intracerebroventricular (ICV) enzyme replacement therapy (ERT) with IGF-2 fusion protein is a feasible treatment mouse model. It overcomes two impediments to ERT: the absence of mannose 6-phosphate (M6P) on recombinant human NAGLU (rhNAGLU) and the blood brain barrier. In this study, we administered a recombinant adeno-associated virus, serotype 5 (AAV5) vector expressing hNAGLU or hNAGLU-IGF2 that targets the choroid plexus epithelia to produce the missing enzyme into the cerebrospinal fluid (CSF) which will distribute hNAGLU throughout the brain in the mouse model. $2.5x10^{10}$ vector genomes (v.g.) of rAAV5 was administered into ventricles bilaterally in MPS IIIB mice at postnatal day 1 or 2. NAGLU activity reached 2-8 fold of control level in the brain section around the injection site after 6 weeks and 0.25 folds after 10 months post-treatment with rAAV5-hNAGLU. Hexosaminidase activity, which is elevated in MPS IIIB mice, was stably reduced to carrier levels in most of the brain areas except in cerebrum and brainstem 10 months after treatment. Immunohistochemistry demonstrated the expression of hNAGLU in the choroid plexus epithelia and significant reduction of Lamp1 expression in the treated mice. Partial hexosaminidase activity reduction was observed in animals treated with rAAV5-hNAGLU-IGF2. Although no detectable NAGLU activity in liver in either treated group was measured, hexosaminidase activity was partially reduced in rAAV5-hNAGLU treated mice. Choroid plexus-targeted viral gene therapy with rAAV5-hNAGLU has the potential to provide long-term, efficient treatment of the brain for Sanfilippo syndrome type B.

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165
PQ-interval and QRS duration increased in Fabry patients treated by enzyme replacement therapy for 12 years

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