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Response to Letter to the Editor: Secondary ganglioside G_{M2} accumulation in mucopolysaccharidoses

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We write to respond to the issues raised in Professor Sandhoff's letter and to thank Professor Sandoff for his interest in our paper and for taking the time to express his concerns.

In his letter to the editor, Professor Sandhoff notes potential concerns with assay of the specific artificial soluble substrate 4MU-β-GlcNAc. He states that we do not correlate their G_{M2}- relevant observations with the ganglioside G_{M2} splitting activity of the samples, but with the 4MU-β-GlcNAc hydrolyzing activity, which is not relevant to G_{M2} cleavage activity.

It was not the author's intention to correlate the MUGS-β-hexosaminidase (combined activities of A, B and S) total activity to G_{M2} cleaving ability and we appreciate that different isoforms of the β -hexosaminidase enzymes can be measured in different assays to correlate to this.

Our intent was to use the total β-hexosaminidase enzyme levels as an example of more global changes in lysosomal enzymes in MPS. This was detected using the soluble substrate 4MU-β-GlcNAc and is both elevated in disease and decreases with therapy in a number of murine MPS model systems [1–5].

The manuscript's aim was to show the timing of primary and secondary substrates in different MPS mouse models and that storage of these substrates precedes the detection of functional behaviour deficits which has not been assessed before. There is still much debate amongst researchers on the timing of the biochemical changes and how the cascade of pathological changes in neurodegeneration and cognitive decline arise in these models.

The authors accept the validity of the comments in the last paragraph of Prof Sandhoff's critique regarding comments on genotype, residual enzyme activity, severity of disease, and there being an implied window of therapeutic opportunity and thank him for this astute correction. The authors agree to modify the final sentence of the last paragraph of the abstract as follows to address these concerns and will issue a corrigendum to the journal.

"This suggests that in models with low levels of residual enzyme activity the prediction of phenotype is challenging. Technologies that define the biochemical and clinical consequence of mutations and biomarkers that accurately predict the threshold of irreversible neurological onset remain an important and unmet need."

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