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Myeloid Driven Stem Cell Gene Therapy Corrects the Neuropathology of Lysosomal Disease

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Mucopolysaccharidosis IIIA (MPS IIIA) is an inherited lysosomal storage disorder resulting from a mutation in the gene coding for N-sulfoglucosamine sulfohydrolase (SGSH), an enzyme involved in the degradation of heparan sulphate (HS). The disease is characterised by progressive loss of cognitive and motor functions which present during early childhood. Enzyme replacement therapy is feasible in this disease but fails due to the presence of the blood brain barrier. Haematopoetic Stem Cell Transplant (HSCT) circumvents this by trafficking of donor derived monocytes to the brain and engraftment as microglia, however cells produce insufficient enzyme for cross-correction. We have previously used a lentiviral vector to overexpress SGSH in WT HSCT, demonstrating neuropathological correction, however, lentiviral SGSH expression in autologous MPSIIIA HSCs is not sufficient, therefore reducing the clinical relevance of these findings.

To improve expression and specificity, codon-optimised SGSH lentiviral vector constructs under the myeloid specific CD11b (LV-CD11b-SGSH) or ubiquitous PGK promoter (LV-PGK-SGSH) were developed and used to transduce MPS IIIA HSCs. The transduced HSCs were then transplanted into MPS IIIA mice.

At 8 months, LV-PGK-SGSH provided some improvement in neuropathology, achieving correction of GM2 ganglioside storage and pre-synaptic vesicles within the cortex. However, on analysis of brain enzyme activity, LV-CD11b-SGSH increased SGSH to 11% of WT activity manifesting significantly higher levels than the 7% achieved by LV-PGK-SGSH. LV-CD11b-SGSH fully corrected neuroinflamation, lysosomal swelling and HS accumulation within the cortex and amygdala.

Therefore we would suggest that the LV-CD11b-SGSH vector should be the vector of choice when pursuing the treatment of MPS IIIA through transplant of transduced MPS IIIA HSCs.