364.

Neurological Correction of Mucopolysaccharidosis IIIB Mice by Haematopoietic Stem Cell Gene Therapy

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Mucopolysaccharidosis Type IIIB (MPSIIIB) is a paediatric, autosomal recessive Lysosomal Storage Disease (LSD) caused by deficiency of α-N-acetylglucosaminidase (NAGLU), an enzyme in the heparan sulfate (HS) degradation pathway. Absence of NAGLU leads to the accumulation of partially degraded HS glycosaminoglycan in cell lysosomes, giving rise to cellular dysfunction with devastating clinical consequences. Individuals affected by this fatal disease exhibit severe central nervous system degeneration with progressive cognitive impairment and behavioural problems, alongside more attenuated somatic symptoms. There are currently no effective treatments available. Enzyme replacement therapy with recombinant NAGLU enzyme is ineffective for MPSIIIB since enzyme cannot cross the blood brain barrier (BBB) to where it is needed. Modified recombinant NAGLU enzymes that utilise the insulin growth factor II (IGFII) peptide to facilitate improved uptake across the BBB are currently in development. Haematopoietic stem cell gene therapy (HSCGT) is a promising therapeutic strategy that can circumvent the BBB via monocyte trafficking and engraftment in the brain, allowing delivery of enzyme by cross correction. We have developed a novel stem cell gene therapy approach to investigate the therapeutic potential of HSCGT for MPSIIIB. We designed two lentiviral vectors expressing therapeutic enzyme; the first vector expressing codon optimised NAGLU, and the second expressing a NAGLU.IGFII fusion to aid cellular uptake, both driven by the myeloid specific promoter CD11b and compared these in autologous MPSIIIB transplants against a normal WT bone marrow transplant. Here we present for the first time neurological correction of MPSIIIB mice by HSCGT. We observed correction of the MPSIIIB behavioural phenotype in treated mice to wild-type levels with normalisation of path length, average speed, frequency entering the centre and duration of speed >100mm/s in open field tests. In addition, we observed a significant correction of astrogliosis and lysosomal compartment size in the brains of CD11b. NAGLU LV treated mice with an accompanied normalisation of inflammatory cytokines TNFα, IL1B and IL1RN. Furthermore, NAGLU enzyme activity was substantially increased in the brain. Interestingly, WT transplant alone was able to mediate a partial brain correction, although levels of inflammation and lysosomal storage remain high.