GT-GM1: Ex vivo gene therapy for GM1-gangliosidosis

GM-gangliosidosis (OMIM #230500) is a rare, autosomal recessive, neurodegenerative Lysosomal Storage Disorder. It is caused by mutations in the GLB1 gene, encoding the lysosomal hydrolase β-galactosidase. Infantile GM1-gangliosidosis is characterized by neurodevelopmental delay, hypotonia, dysphagia, seizures and death by 3 years of life. Due to the rapid progression and severe nature of this disease, which involves storage of undegraded metabolites and secondary mechanisms of cell damage, correction requires a rapid and robust enzyme delivery to the whole central nervous system (CNS), possibly associated to reduction of local inflammation. Here we propose an ex vivo gene therapy (GT) strategy aimed at preventing or ameliorating the symptoms of the disease in the murine model. Multiple copies of GLB1, alone or in association with a neuroprotective factor, will be delivered ex vivo to hematopoietic stem/progenitor cells by lentiviral gene transfer to determine a sustained and robust expression of the therapeutic enzyme in the CNS of transplanted mice.
Genetically modified HSPCs will be administered by a novel approach combining the conventional intravenous route with direct administration into the brain lateral ventricles, to anticipate the myeloid reconstitution in the brain and possibly the therapeutic effect. Our working hypothesis is that this optimized GT strategy could successfully control disease manifestations in the animal model. Moreover, a deep genome-wide genomics analysis will be performed on individual brain cells to elucidate the molecular mechanisms at the basis of the disease and mediating the therapeutic effect. The study will generate a proof of concept for a future clinical development of an efficacious ex vivo GT for infantile GM1-gangliosidosis and will inspire the development of therapies for other LSDs.

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