Scientific Abstract:

Lysosomal storage diseases represent a large group (>40 distinct diseases) of inherited metabolic disorders usually caused by a deficiency in a single lysosomal enzyme. The lack of one of these enzymes leads to the progressive intralysosomal accumulation of undegraded material in many cells of the body. Consequently, these diseases affect many organ systems and have a broad spectrum of clinical signs, including hepatosplenomegally, auditory defects, visual deficits, cardiac anomalies, skeletal dysplasia and cognitive impairment, to mention just a few. For the vast majority of these diseases no conventional therapy currently exists. However, the principle of "cross-correction" provides the basis for the development of effective therapies for this class of disease. "Cross-correction" refers to the ability of lysosomal enzymes to be secreted from one cell and subsequently endocytosed by cells at a distance. It has been shown *in vitro* and *in vivo* that small amounts of endocytosed enzyme can reduce or eliminate lysosomal storage material in affected cells. This phenomenon has been exploited clinically to treat these diseases using bone marrow transplantation (BMT). Bone marrow-derived cells from a normal donor are able to reconstitute the hematopoietic system of an affected patient and supply the deficient enzyme to many tissues. Partial correction of the disease has been demonstrated clinically in several lysosmal storage diseases. However, BMT has limitations, including the lack of suitable donors and the harsh conditioning regimens required for engraftment. Another severe consequence of allogeneic BMT is graft vs. host disease which can have a mortality rate as high as 50%. Pre-clinical experiments performed with syngeneic BMT, where graft vs. host is eliminated, have demonstrated increased efficacy compared to allogeneic BMT. A hematopoietic-directed gene therapy approach using autologous hematopoietic progenitor cells (HPCs) would eliminate the need to identify a suitable donor and eliminate graft vs. host disease. In addition, we now have the ability to over-express the therapeutic protein in the hematopoietic compartment thereby potentially increasing the efficacy compared to normal donor bone marrow cells. Pre-clinical data in animal models of lysosomal storage disease support this conclusion. We are proposing to perform a lentiviral-mediated, HPC-directed gene therapy clinical trial in patients with the lysosomal storage disease mucopolysaccharidosis type VII. MPS VII is a lysosomal storage disease caused by a deficiency in β-glucuronidase activity. β-Glucuronidase deficiency results in the progressive accumulation of glycosaminoglycans in many cell types and leads to severe skeletal dysplasia, cognitive deficits, auditory defects, visual impairment and hepatosplenomegally. There currently is no conventional therapy for this inherited metabolic disorder. However, there is a plethora of pre-clinical data demonstrating the efficacy of syngeneic BMT and HPC-directed gene therapy in the mouse model of MPS VII. In addition, a recent study has shown that human MPS VII HPCs can engraft a xenotransplantation model of MPS VII and express therapeutic levels of enzyme following ex vivo transduction with a lentiviral vector.