Novel combined gene/cell therapy strategies to provide full rescue of the Sandhoff pathological phenotype

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LAY SUMMARY

The goal of this study was to evaluate gene and cell therapy approaches in the mouse model of Sandhoff disease (SD). In particular, we tested the therapeutic advantage of combining direct intracerebral lentiviral gene therapy and bone marrow transplantation (BMT) performed from the early postnatal days in affected mice. The combinatorial approach has already demonstrated a synergistic effect in a mouse model of a similar disease, thus providing the rationale to assess these therapies in the Sandhoff model.

- Neonatal intracerebral injection of LV.HEXA+LV.HEXB resulted in local clearance of GM2 storage but no advantage in lifespan
- BMT (performed in neonates or in 2 month-old mice) significantly increases the average lifespan of SD mice (20-22w vs. 16w of untreated mice) and decreases neuroinflammation but is not impacting on GM2 storage in the brain.
- When we combined neonatal intracerebral LV injection and BMT, we were able to see an increase of HexA activity in brain and spinal cord regions (up to 50-70% of normal), normalization of HexA activity in peripheral nerves and peripheral organs (liver, spleen), and global reduction of lysosomal expansion, GM2 storage and inflammation.
- Combined treated mice have currently reached 8 months of age and show normal body weight and good motor coordination.

These results show that LV-mediated gene delivery in the brain coupled to BMT provide a timely and long-lasting therapeutic source of therapeutic HexA enzyme and trophic support to CNS tissues, PNS and periphery. We are testing a novel LV encoding both HEXA and HEXB genes that might provide an additional advantage in this combined setting. Also, it will pave the way to the development of gene therapy approaches using autologous hematopoietic stem cells engineered to overexpress HexA, which may overcome the current limitation of allogeneic hematopoietic stem cell transplant in TSD and SD patients.