Development of a Novel Encapsulated Non-Viral Cell-Based, BBB-Penetrant Therapy for MPS I

Introduction

• MPS I is caused by a deficiency of the lysosomal enzyme α-L-iduronidase (IDUA) leading to GAG accumulation in multiple tissues and organs
• This accumulation results in a complex array of progressive, multi-systemic pathologies, including CNS manifestations
• Approved therapies include enzyme replacement therapy (ERT), with chaperone and gene therapies under investigation
• Treatment with approved ERT does not adequately address CNS manifestations

Hypothesis

Better outcomes could be achieved with sustained, long-lasting levels of a human IDUA (hIDUA) fusion enzyme capable of penetrating the BBB via administration of hIDUA-secreting allogeneic human cells shielded within spheres designed to avoid immune rejection and pericapsular fibrotic overgrowth (PFO) in the patient.

Methods

Engineer cells to express BBB-hIDUA Evaluate BBB-hIDUA secreted from cells Encapsulate BBB-hIDUA-secreting cells Implant in MPS-1H mice

Generation of BBB-hIDUA Fusion Enzyme

• National Research Council Canada (NRC) has isolated several classes of high affinity sdAbs (VHHs) that:
  1. Target a Receptor on the BBB
  2. Extend Half-life in plasma
• VHHs can function as transporter molecules able to ferry cargo proteins across the BBB

Conclusions

• Dual VHH fusion to hIDUA results in 3x higher Plasma hIDUA activity levels in MPS-1H mice relative to historical native hIDUA levels
• Tissue activity levels of the dual fusion enzyme are on average 2-10x higher compared to historical native hIDUA levels
• BBB-penetrant and half-life extending VHH fusions results in 32% decrease in Brain heparan sulfate levels relative to untreated MPS-1H mice
• Dual fusion hIDUA enzyme exhibits good systemic tissue penetration and substrate reduction in MPS-1H mice

Results

Plasma hIDUA activity in MPS-1H mice

Fusion to BBB-penetrant and half-life extending VHHs results on average in 3x higher plasma hIDUA activity levels in MPS-1H mice relative to historical native hIDUA levels

Brain hIDUA activity and substrate reduction in MPS-1H mice

Fusion to BBB-penetrant and half-life extending VHHs results in successful BBB penetration of hIDUA in MPS-1H mice as judged by activity levels and substrate reduction in the brain

Systemic tissue hIDUA activity and substrate reduction in MPS-1H mice

Dual VHH fusion hIDUA demonstrates good systemic tissue penetration and functional activity towards target substrate