**Introduction**

- MPS-2 (Hunter Syndrome) is caused by deficiency of the lysosomal enzyme iduronate 2-sulfatase (IDS) leading to GAG accumulation in multiple tissues and organs.
- The accumulation results in a complex array of progressive, multi-organ, clinical manifestations with 2/3 of the patients presenting with CNS involvement.
- Approved treatments include enzyme replacement therapy, with gene therapies under investigation.

**Hypothesis**

- **Sustained therapeutic effect** can be achieved by administration of hIDS-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 hIDS**
- **In vitro evaluation of engineered cells**
- **In vitro evaluation of encapsulated cells**
- **In vivo evaluation of the final product**

**Results**

**Comparison of hIDS Produced From Engineered Allogeneic Cells to Commercial Idursulfase**

- $K_m$, hIDS from cell media vs idursulfase
- **4-Methylumbelliferyl-$\alpha$-L-iduronide ($\mu$M)**
- Secreted hIDS
- Ion Exchange (Sephadex G100) Concentration

**hIDS Levels and Heparan Sulfate (HS) Reduction in MPS-2 Mice Plasma**

- Heparan sulfate
- Sustained therapeutic effect can be achieved
- good correlation with substrate reduction
- Ongoing work is addressing CNS access

**Conclusions**

- **Iduronate 2-sulfatase** produced by the engineered cells has similar biochemical characteristics as recombinant protein
- Encapsulated engineered cells (SIG-018) produced active human iduronate 2-sulfatase
- MPS-2 KO mice treated with SIG-018 showed continuous levels of active hIDS in plasma resulting in sustained reduction of accumulated substrate in multiple tissues
- Administration of various doses of SIG-018 demonstrated good correlation with substrate reduction
- Ongoing work is addressing CNS access
- Data supports transition of SIG-018 into the next phase of preclinical development

**Results (cont’d)**

**Heparan Sulfate (HS) Reduction With Low Dose of SIG-018 Across Tissues in MPS-2 Mice**

**Liver**

**Kidney**

**Spleen**

**Heart**

**Lung**

**Plasma**

**Urine**

4-week treatment with SIG-018 demonstrated reduction of HS across MPS-2 KO mouse tissues

**Dose Response PD Study in MPS-2 Mice**

**Liver**

**Kidney**

**Spleen**

**Heart**

**Lung**

**Plasma**

After one week SIG-018 reduces HS build-up across MPS-2 mouse tissues at the lowest dose level

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