SIG-018: Novel Encapsulated Non-Viral Cell-Based Therapy for MPS II

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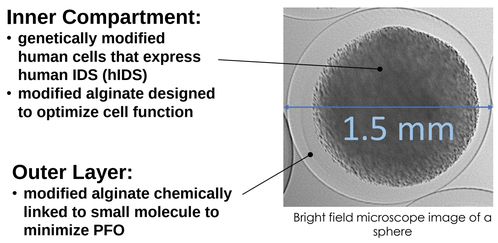
Introduction

- **MPS II (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

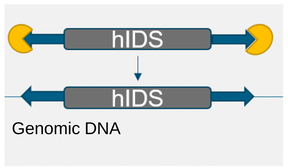
Sustained therapeutic effect can be achieved by administration of **hIDS-secreting allogeneic human cells** shielded **within spheres designed to avoid immune rejection** and pericapsular fibrotic overgrowth (PFO) in the patient



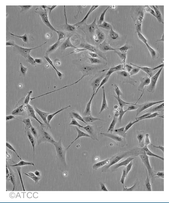
Bright field microscope image of a sphere

Methods

1. Engineer cells to express hIDS



2. *In vitro* evaluation of engineered cells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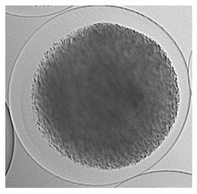
3. *In vitro* evaluation of encapsulated cells



4. *In vivo* evaluation of the final product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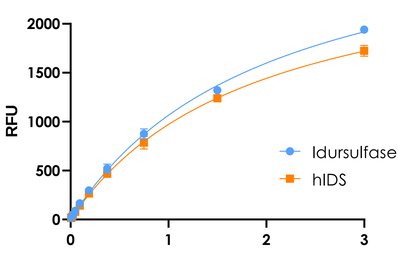
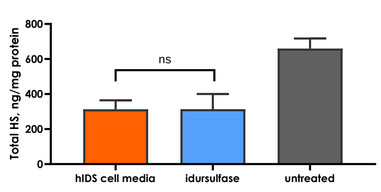
Results

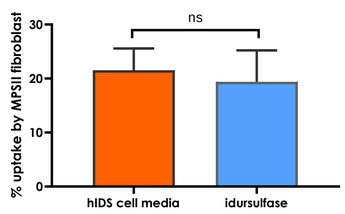
Comparison of hIDS Produced From Engineered Allogeneic Cells to Commercial Idursulfase

K_m: hIDS from cell media vs idursulfase



	Secreted hIDS	Idursulfase
K_m (mM)	1.89 ± 0.20	2.01 ± 0.26

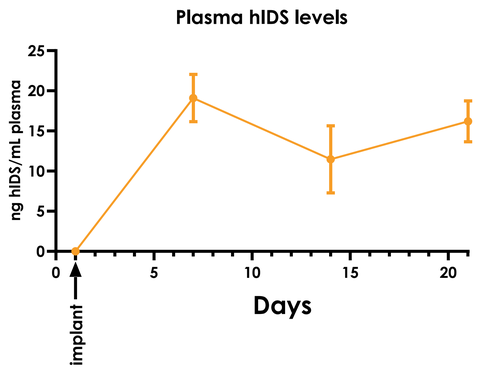




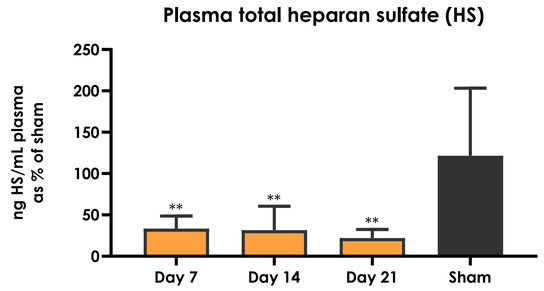
- **Equivalent GAG lowering** in MPS II fibroblasts by hIDS from cell media vs commercial idursulfase
- **Equivalent uptake** by MPS II fibroblasts of hIDS from cell media vs commercial idursulfase

hIDS Levels and Heparan Sulfate (HS) Reduction in MPS II Mice Plasma

Plasma hIDS levels



Plasma total heparan sulfate (HS)



- hIDS is detectable in MPS II KO mouse plasma resulting in **significant HS reduction at all timepoints**

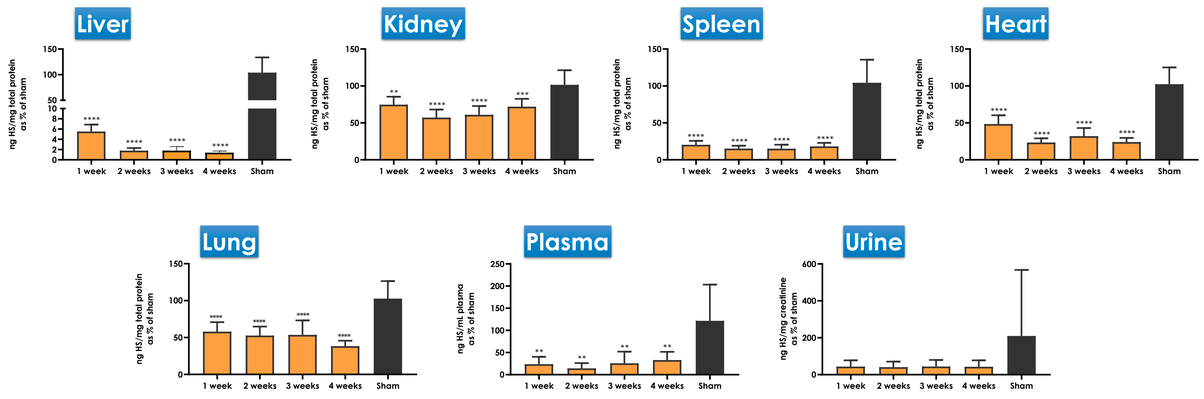
HS heparan sulfate; Each time point, n=4; Each dose level, n=4; Sham, n=16; **** p<0.001; *** p<0.001; ** p<0.01; * p<0.05; **n.s.** p>0.05

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 II 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)

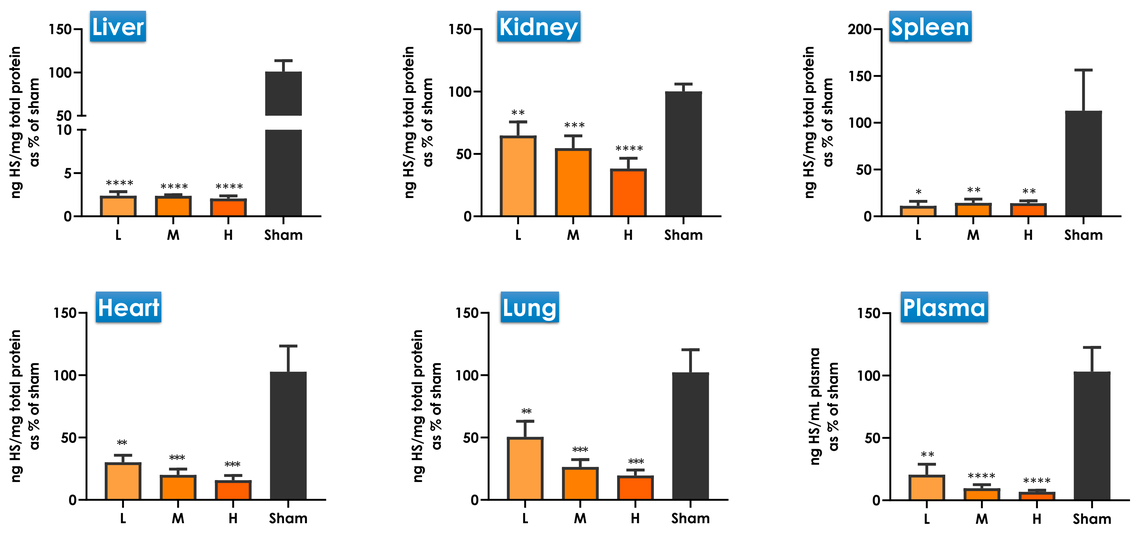
Heparan Sulfate (HS) Reduction With Low Dose of SIG-018 Across Tissues in MPS II Mice



HS heparan sulfate; Each time point, n=4; Sham, n=16; **** p<0.001; *** p<0.001; ** p<0.01; * p<0.05; **n.s.** p>0.05

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

Dose Response PD Study in MPS II Mice



HS heparan sulfate; **L** Low Dose; **M** Medium Dose; **H** High Dose; Each dose level, n=4; Sham, n=4; **** p<0.001; *** p<0.001; ** p<0.01; * p<0.05; **n.s.** p>0.05

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

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Platform Presentation: 9:54am, Contemporary Forum, Thursday February 11th
Poster Presentation #254 - live Q&A Thursday, February 11th