SIG-005: Novel Encapsulated Non-Viral Cell-Based Therapy for MPS I

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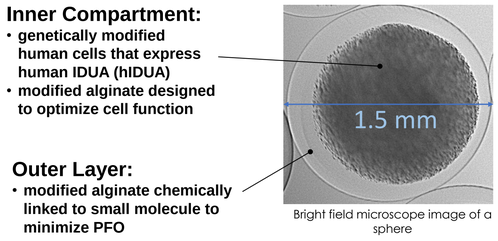
Introduction

- **Mucopolysaccharidosis I (MPS I)** is a rare genetic disease with incidence of ~1/100,000 live births
- Deficiency of lysosomal enzyme α-L-iduronidase (IDUA) leads to the accumulation of GAGs within cells
- Standard therapy includes enzyme replacement therapy (ERT) for Hurler-Scheie and Scheie and bone marrow transplantation (BMT) for Hurler
- **Key challenges include suboptimal long-term efficacy and treatment burden**

Hypothesis

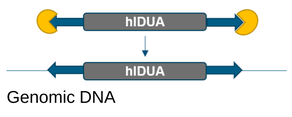
Better outcomes could be achieved with **sustained, long-lasting hIDUA levels** via administration of **hIDUA-secreting allogeneic human cells shielded within spheres** designed to avoid immune rejection and pericapsular fibrotic overgrowth (PFO) in the patient.



Bright field microscope image of a sphere

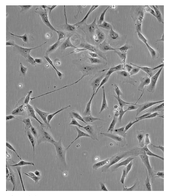
Methods

1. Engineer cells to express hIDUA



Genomic DNA

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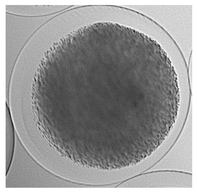
3. *In vitro* evaluation of encapsulated cells



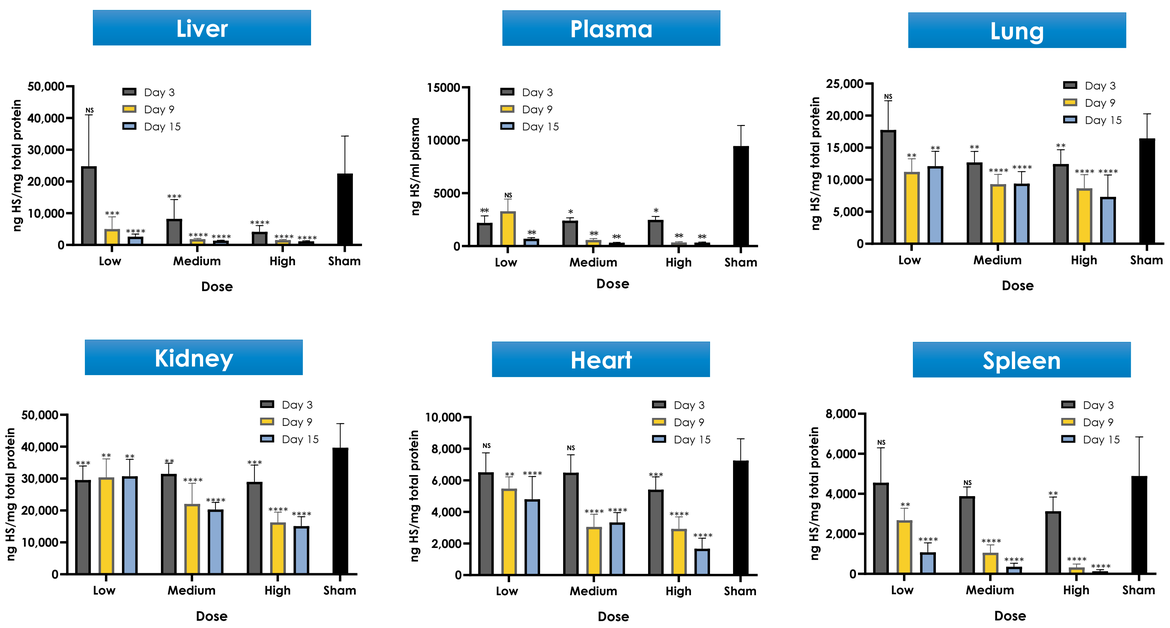
4. *In vivo* evaluation of the final product


Clarke Hum Mol Genet 1997
JAX stock #004068

Results

- hIDUA produced by engineered cells has comparable biochemical characteristics as the commercial enzyme
- Fibroblasts obtained from MPS I patients can uptake hIDUA produced by engineered cells as demonstrated with reduction of heparan sulfate in the fibroblasts

In Vivo Heparan Sulfate Reduction in MPS I Mice 2 Weeks After SIG-005



Error bars indicate SEM for plasma, SD for other tissues; HS heparan sulfate**;** each time point, n=10; each dose level, n=10; sham, n=30; unpaired t-test vs sham: ******** p<0.001; ******* p<0.001; ****** p<0.01; ***** p<0.05; **NS** p>0.05

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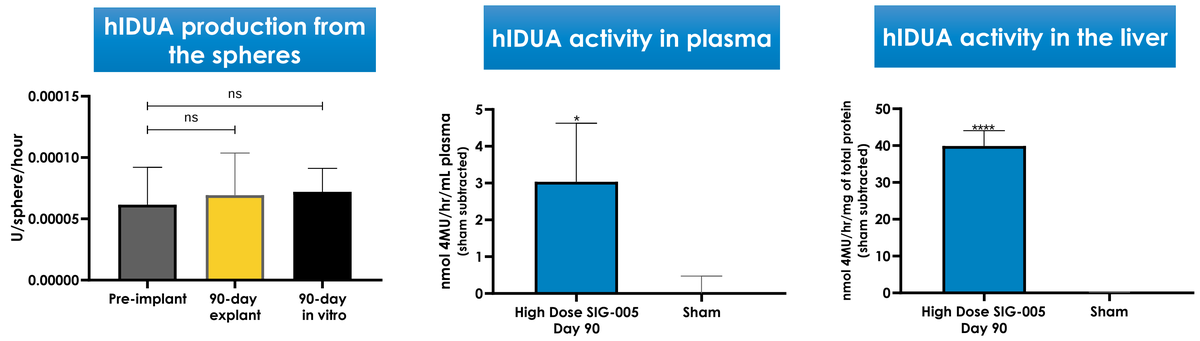
Conclusions

- **SIG-005** produces active **hIDUA** with biochemical properties **comparable to commercial enzyme**
- Single administration of **SIG-005 in MPS I mice** led to:
  - Significant **reduction of heparan sulfate across tissues**
  - Long-term study resulted in:
    - **Reduced thickness of bone diameter** due to **reduced GAG** levels on surface of the bones
    - **Reduction of substrate** in tissues with clear improvement in hard-to-target tissues such as kidney and lung
- **hIDUA activity** was maintained *in vitro* and in **NSG mice** for **at least 3 months** after single administration of SIG-005
- SIG-005 program is **on track to move into the next stage** of non-clinical development, in preparation for the clinic

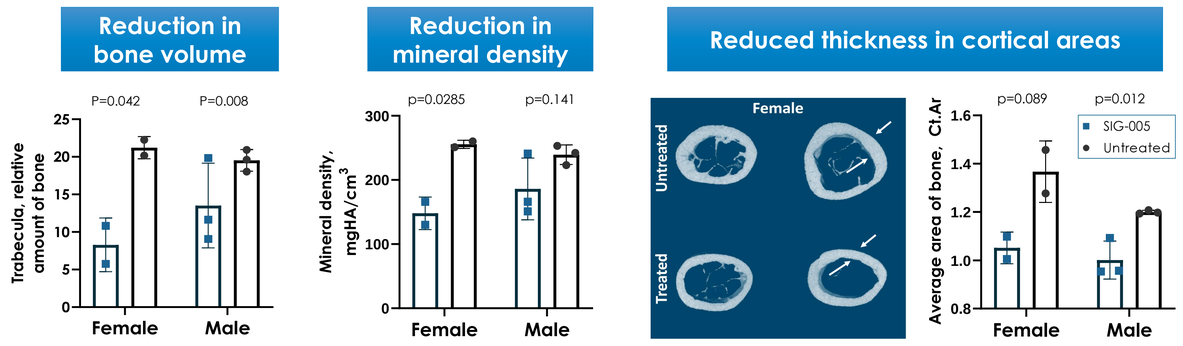
Results (cont'd)

In Vivo SIG-005 Activity in NSG Mice 3 Months After Administration

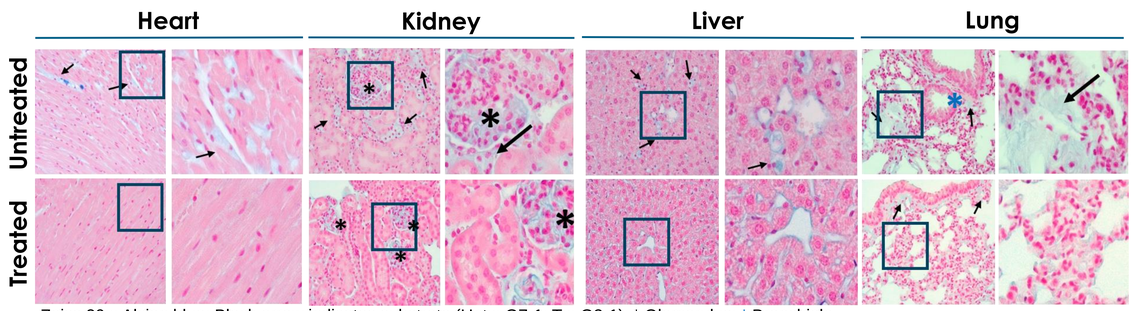


******** p<0.001; ******* p<0.001; ****** p<0.01; ***** p<0.05; **NS** p>0.05

Phenotypic Correction in Bone of MPS I Mice 5 Months After SIG-005



Reduction of Substrate in Tissues of MPS I Mice 5 Months After SIG-005



Zeiss 20x; Alcian blue; Black arrow indicates substrate (Untx: G7-1; Tx: G3-1); * Glomerulus; * Bronchiole

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