SIG-007: Novel Encapsulated Non-Viral Cell-Based Therapy for Fabry

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Introduction

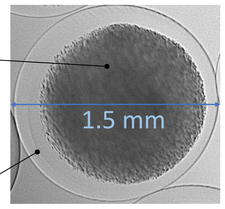
- Fabry disease is a progressive, X linked disorder of glycosphingolipid metabolism due to deficient or absent lysosomal αGal A (GLA) activity.
- It results in progressive accumulation of Gb3 and related glycosphingolipids within lysosomes, in a variety of cell types.
- Comprehensive therapy includes enzyme replacement therapy, conventional medical treatment and adjunctive therapies.
- **Current standard of care is not curative, long term complications still occur, and the patient burden is high.** Therapeutic access to the brain tissue remains a significant challenge.

Hypothesis

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

Inner Compartment:
- genetically modified human cells that express human GLA (hGLA)
- modified alginate designed to optimize cell function

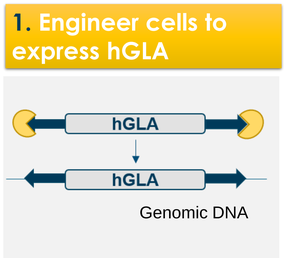
Outer Layer:
- modified alginate chemically linked to small molecule to minimize PFO



Bright field microscope image of a sphere

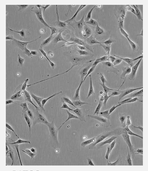
Methods

1. Engineer cells to express hGLA



Genomic DNA

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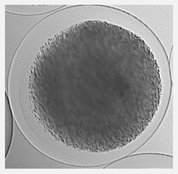
3. *In vitro* evaluation of encapsulated cells*



4. *In vivo* evaluation of the final product


Ohshima PNAS 1997
JAX stock #003535

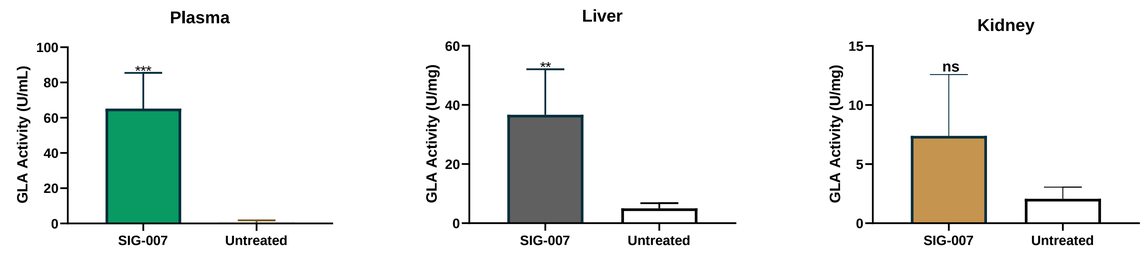
*Fluharty WORLD 2020

Conclusions

- SIG-007 produces **sustained** and **active hGLA** *in vivo*
- Intraperitoneal administration of a **single dose of SIG-007** results in **consistent reduction of Gb3 and Lyso-Gb3** across tissues of **GLA KO mice** long-term
  - **Significant reduction of Lyso-Gb3** in **hard-to-target tissues** such as kidney and heart
- SIG-007 program is **on track to move into the next stage** of non-clinical development, in preparation for human trials

Results

hGLA activity in NSG mice 1 month after SIG-007 administration

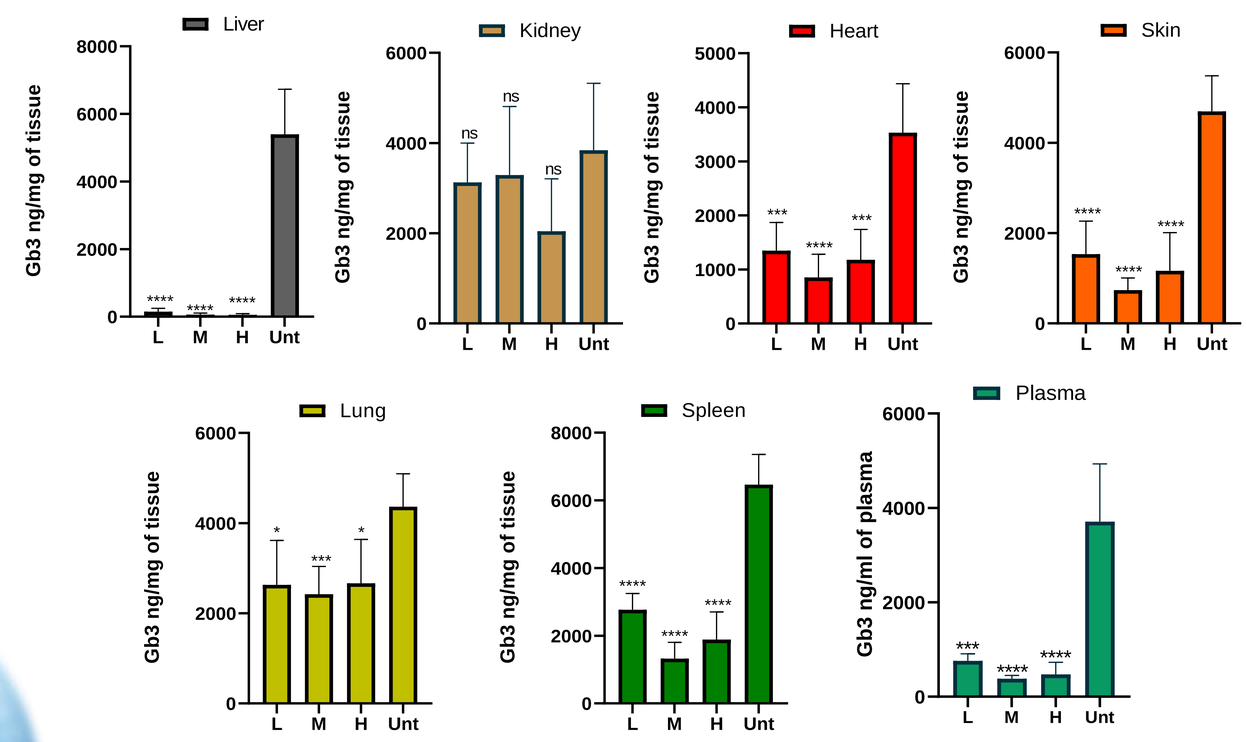


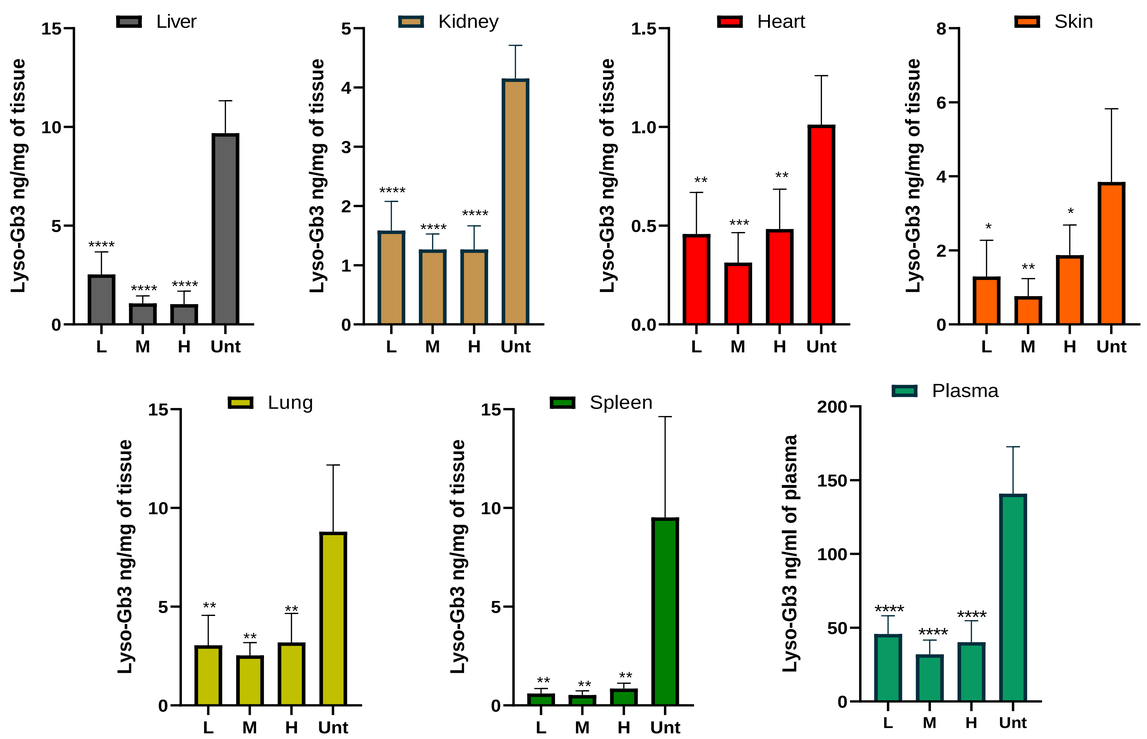
- N=5 per group
- SIG-007 was administered to NSG mice intraperitoneally
- GLA activity was measured using the fluorescent substrate 4-MU a-D-galactopyranoside

unpaired t-test vs untreated: ******** p<0.001; ******* p<0.001; ****** p<0.01; ***** p<0.05; **ns** p>0.05

Results

Consistent Reduction of Gb3 and Lyso-Gb3 Across Tissues in GLA KO Mice 1 Month After SIG-007 Administration





N=6/group; **L** low dose; **M** medium dose; **H** high dose; **Unt** untreated;
unpaired t-test vs untreated: ******** p<0.001; ******* p<0.001; ****** p<0.01; ***** p<0.05; **ns** p>0.05

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