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

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Marissa Donovan Disclosures

• Employed by Sigilon Therapeutics, Inc.
• Has stock ownership in Sigilon Therapeutics, Inc.
MPS II (Hunter Syndrome)

• 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.
Allogeneic Cell-Based Therapy: Challenges

- Biomaterials can physically protect the cells but they themselves activate foreign body response resulting in pericapsular fibrotic overgrowth (PFO)

![Blood glucose graph](image)

- Normal Range
- 10X fibrous tissue formation
- 40X immune cell adhesion

Adapted from Lim Science 1980
Sigilon data on file
Non-Viral Cell-Based Engineered Platform

• This **non-viral, cell-based, modular platform** was designed to address both challenges:

  - Cell-to-cell interaction and rejection
  - Pericapsular fibrotic overgrowth (PFO)

  - Physical shield (2-compartment, modified alginate sphere)
  - Small-molecule conjugated alginate in outer layer

No PFO observed after 180 days

Empty spheres were administered to the non-human primates intraperitoneally via laparoscopic procedure.
SIG-018: Encapsulated Non-Viral Cell-Based Platform

**Inner Compartment:**
- genetically modified human cells that express hIDS
- 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 typical sphere

- The shielded spheres are placed in the peritoneal space where they can absorb nutrients while the released therapeutic protein can enter the blood compartment
SIG-018: Development Path

1. Engineer cells to express hIDS

2. Evaluate secreted hIDS biochemical characteristics & in vitro functionality

3. Encapsulate engineered cells

4. Evaluate hIDS production from spheres

5. Implant in Ids⁻/⁻ mice

Muenzer Acta Paediatrica 2002
JAX stock #024744
©ATCC
Comparison of hIDS Produced From Engineered Allogeneic Cells to Commercial Idursulfase

**K_m: hIDS from cell media vs idursulfase**

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<th>RFU</th>
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<th>1000</th>
<th>1500</th>
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<tr>
<td>4-Methylumbelliferon-α-L-Iduronide, [mM]</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Idursulfase</td>
<td>[•••]</td>
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<tr>
<td>hIDS</td>
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| Equivalent GAG lowering in MPS II fibroblasts by hIDS from cell media vs commercial idursulfase |
|-----|-----|-----|-----|
| Total HS, ng/mg protein | hIDS cell media | untreated | ns |
|   | 400 | 600 | 800 |
| Equivalent uptake by MPS II fibroblasts of hIDS from cell media vs commercial idursulfase |
| % uptake by MPSII fibroblast | ns | ns |
|   | 10 | 20 |

<table>
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<tr>
<th>Secreted hIDS</th>
<th>Idursulfase</th>
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<tr>
<td>K_m (mM)</td>
<td>1.89 ± 0.20</td>
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hIDS Levels and Heparan Sulfate (HS) Reduction in MPS II Mice Plasma

hIDS is detectable in MPS II KO mouse plasma resulting in significant HS reduction at all timepoints.
Heparan Sulfate (HS) Reduction With Low Dose of SIG-018 Across Tissues in MPS II Mice

4-week treatment with SIG-018 demonstrated reduction of HS across MPS II KO mouse tissues
Dose Response PD Study in MPS II Mice

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

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
Conclusions

This **modular platform** can be applied across a range of chronic diseases.

- SIG-001, product that utilizes the same technology platform, is currently being studied in the first-in-human clinical trial in patients with severe or moderately severe hemophilia A (NCT04541628).

- 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.**
SIG-018 Team: Drew Tietz, Marissa Donovan, Erika Pearson, Brian Fluharty, Devyn Smith, Elina Makino

Thank you for your attention!

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