SIG-005: Novel Encapsulated Non-Viral Cell-Based Therapy for MPS-1

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## Author Disclosures

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Shielded Living Therapeutics™ Platform

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

  **Cell-to-cell interaction and rejection**

  **Physical shield (2-compartment, modified alginate sphere)**

  **Pericapsular fibrotic overgrowth (PFO)**

  **Small-molecule conjugated alginate in outer layer**

  **Inner Compartment:**
  - genetically modified human cells that express hIDUA
  - modified alginate designed to optimize cell function

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

**HYPOTHESIS:** sustained therapeutic effect could be achieved by administration of **IDUA-secreting allogeneic human cells** shielded within **spheres designed to avoid immune rejection** and pericapsular fibrotic overgrowth (PFO)
SIG-005: Development Path

1. Engineer cells to express hIDUA

2. Evaluate secreted hIDUA biochemical characteristics & in vitro functionality

3. Encapsulate engineered cells

4. Implant in MPS-1H mice
Short-Term Pharmacodynamic Study in MPS-1H Mice

**Liver hIDUA activity**

**Tissue total heparan sulfate (HS)**

SIG-005 reduces HS build-up in MPS-1H mouse tissues at all tested doses.
SIG-005 Produces Active hIDUA Both *In Vitro* and *In Vivo* For At Least 6 Months

**SIG-005: Consistent levels of hIDUA produced from spheres for 6-months *in vitro***

![Graph showing consistent levels of hIDUA produced from spheres for 6-months *in vitro*.](image)

**SIG-005: Low levels of HS in plasma 6-months post-administration in MPS-1H mice***

![Graph showing low levels of HS in plasma 6-months post-administration in MPS-1H mice.](image)

*MPS-1H animals were treated with anti-mouse monoclonal antibody which modulates CD4 antigen (Qin et al., 1990; Waldmann, 1989) in order to prevent the xenogeneic response to human cells in SIG-005.*

MPS-1: mucopolysaccharidosis type I; HS: heparan sulfate; U: nmol 4MU per hour

Error bars indicate SEM; Untreated, n=25; SIG-005, n=9; Laronidase, n=17; unpaired t-test vs untreated ***p<0.001; **p<0.01; *p<0.05; n.s. p>0.05.*
Enzyme Activity, Substrate Reduction 6 Months After SIG-005 Administration in MPS-1H Mice

High to normal levels of hIDUA activity 6 months post administration

Significant reduction in total HS 6 months post administration

Liver | Spleen | Heart | Lung

MPS-1 SIG-005

nmol 4MU/hr/mg protein (sham subtracted)

Error bars indicate SEM; Untreated, n=25; SIG-005, n=9; unpaired t-test vs untreated **** p<0.001; *** p<0.001; ** p<0.01; * p<0.05; n.s. p>0.05

MPS-1: mucopolysaccharidosis type I; HS: heparan sulfate

16th International Symposium on MPS and Related Diseases
Virtual Conference | Jul 23-25, 2021 | Barcelona
Reduction of Substrate in Tissues of MPS-1H Mice 6 Months After SIG-005

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<th>Heart</th>
<th>Lung</th>
<th>Liver</th>
<th>Kidney</th>
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Alcian blue; Black arrow indicates substrate; * Bronchiole; * Glomerulus
SIG-005 Corrects Bone Phenotype in MPS-1H Mice 6 Months After Administration

**Untreated MPS-1H**

**SIG-005 Treated**

**Total Bone Volume (Zygomatic Arch)**

![Graph showing total bone volume](image)

**Bone Length (Femur)**

![Graph showing bone length](image)

**Cortical Thickness (Femur Midshaft)**

![Graph showing cortical thickness](image)

**Trabecular Bone Volume (Distal Femur)**

![Graph showing trabecular bone volume](image)

MPS-1: mucopolysaccharidosis type I; HET: heterozygous

Error bars indicate min to max; Untreated, n=23; SIG-005, n=9; HET: n=10

unpaired t-test vs untreated: **** p<0.001; *** p<0.001; ** p<0.01; * p<0.05; n.s. p>0.05

- MPS2021: 16th International Symposium on MPS and Related Diseases
- Virtual Conference | Jul 23-25, 2021 | Barcelona
Conclusions

- Encapsulated engineered cells (SIG-005) produced **active human α-L-Iduronidase**
- SIG-005 produced **active hIDUA** for up to 6 months **in vitro**
- SIG-005 demonstrated **dose-dependent IDUA activity** in tissues of MPS-1H mice
- SIG-005 **demonstrated dose-dependent substrate reduction** in MPS-1H mice
- MPS-1H mice treated with SIG-005 had IDUA activity in all tested tissues and **sustained reduction of accumulated substrate** 6 months after administration
- **Phenotypic corrections** were observed in **bones and other tissues** 6 months after SIG-005 administration