

MPS 2021

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

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16th International
Symposium
on MPS and
Related Diseases

Virtual Conference
Jul 23-25, 2021
Barcelona

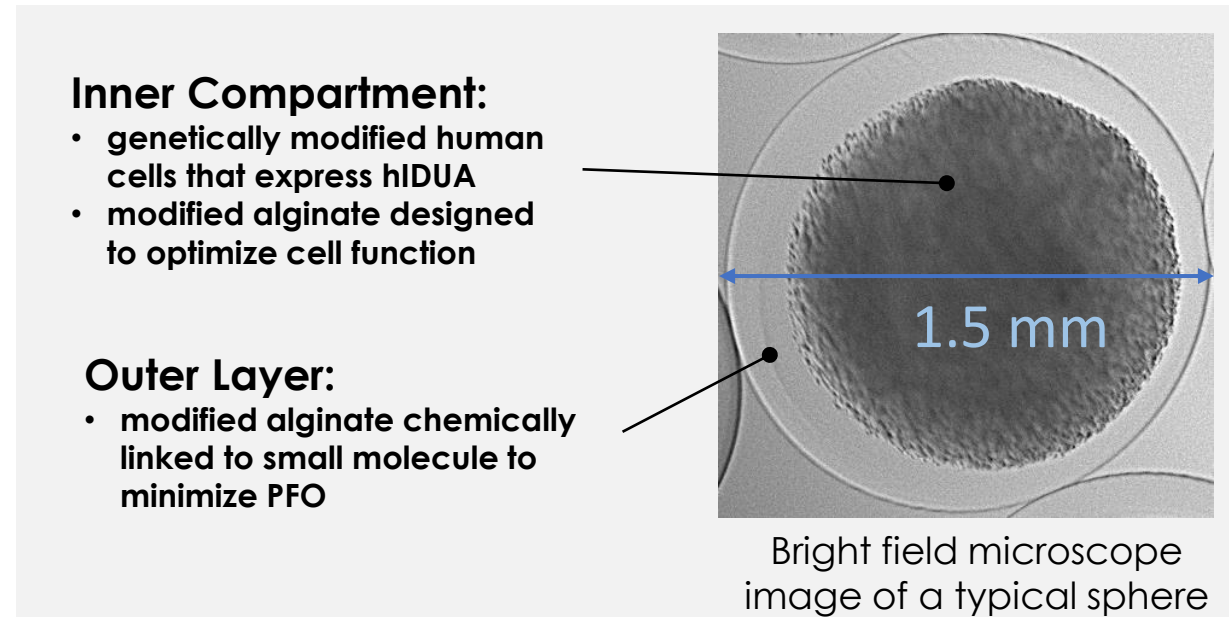
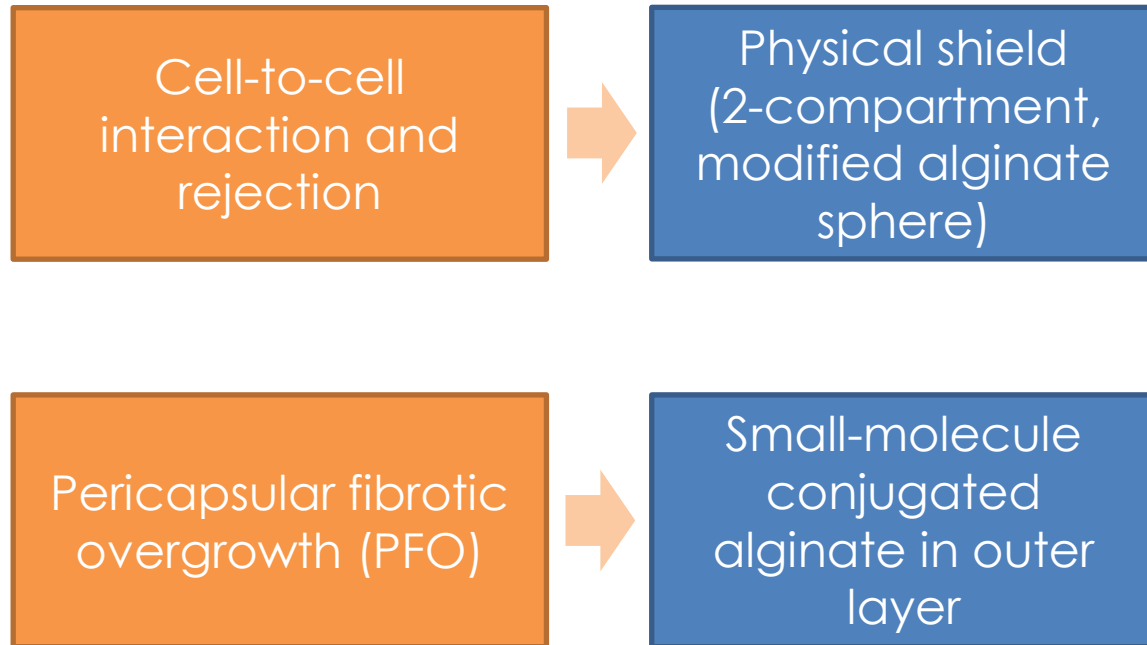


Author Disclosures

Research Support/P.I.	No relevant conflicts of interest to declare
Employee	Sigilon Therapeutics
Consultant	No relevant conflicts of interest to declare
Stockholder	Sigilon Therapeutics
Speakers Bureau	No relevant conflicts of interest to declare
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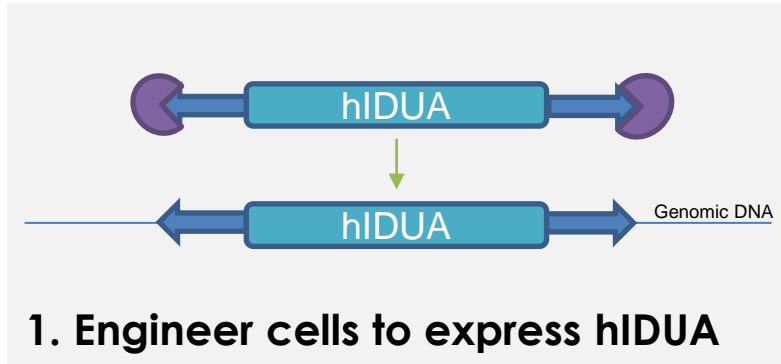
Shielded Living Therapeutics™ Platform

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

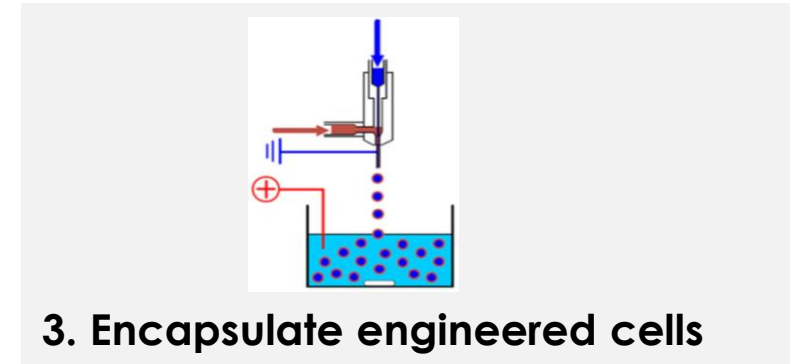
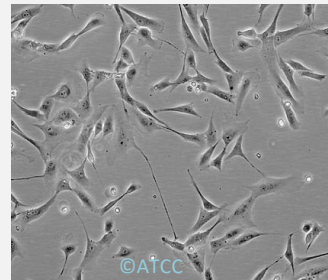


HYPOTHESIS: sustained therapeutic effect could be achieved by **administration of IDUA-secreting allogeneic human cells** shielded within **spheres designed to avoid immune rejection** and pericapsular fibrotic overgrowth (PFO)

SIG-005: Development Path



2. Evaluate secreted hIDUA biochemical characteristics & *in vitro* functionality

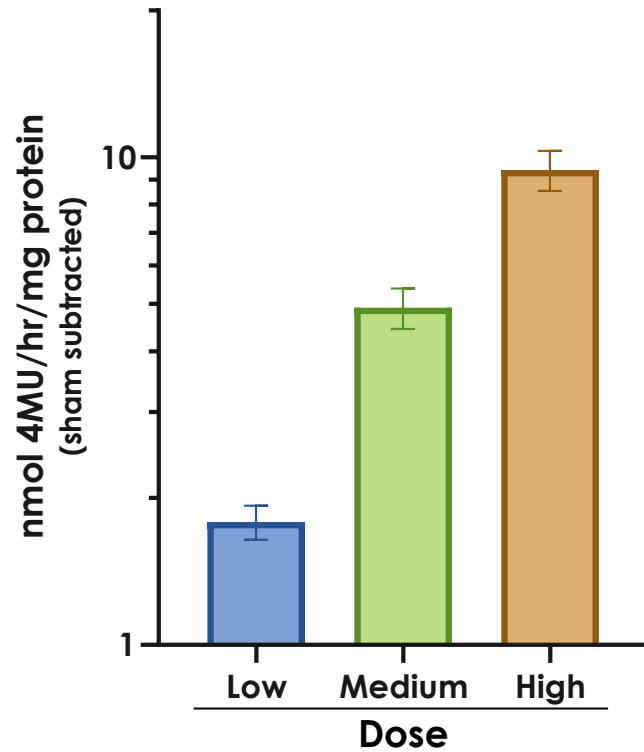


4. Implant in MPS-1H mice

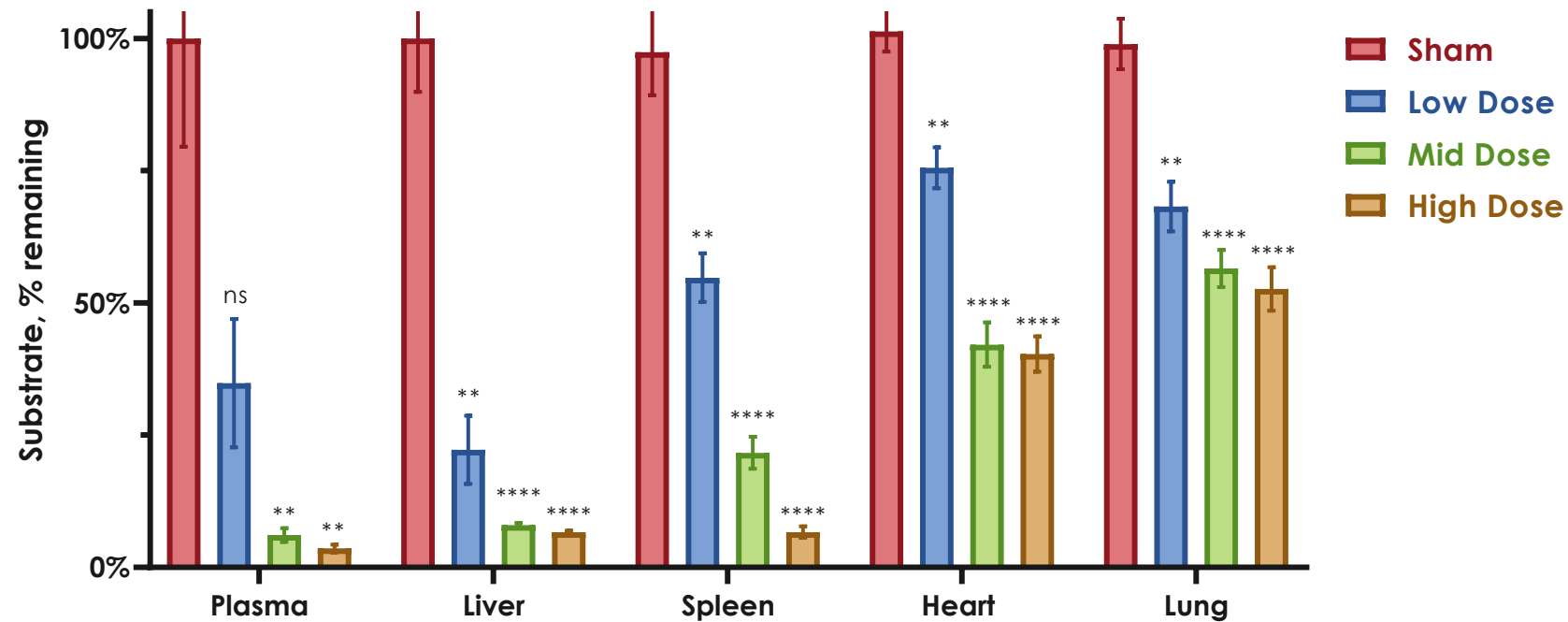


Short-Term Pharmacodynamic Study in MPS-1H Mice

Liver hIDUA activity



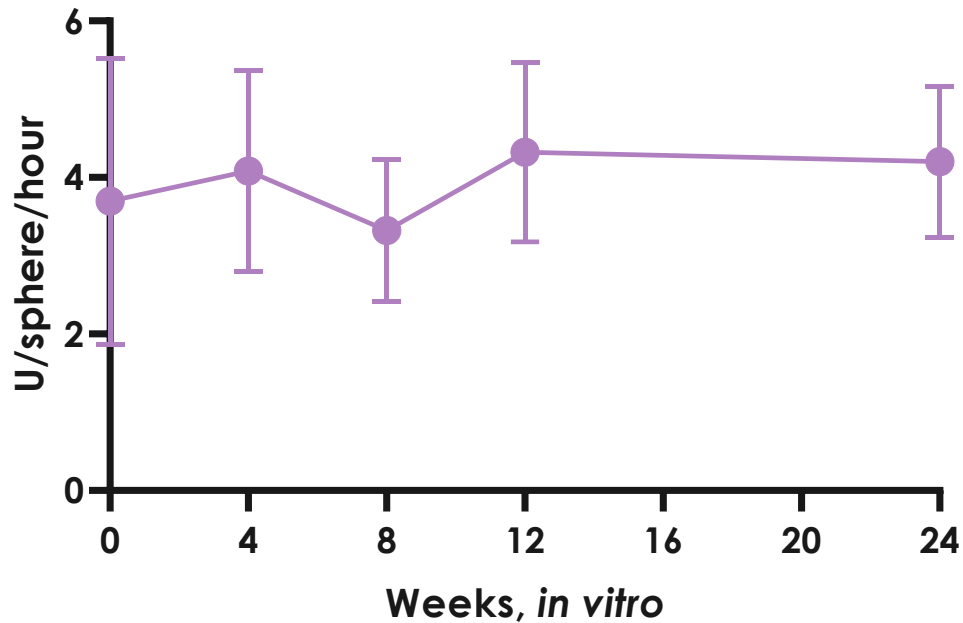
Tissue total heparan sulfate (HS)



SIG-005 reduces HS build-up in MPS-1H mouse tissues at all tested doses

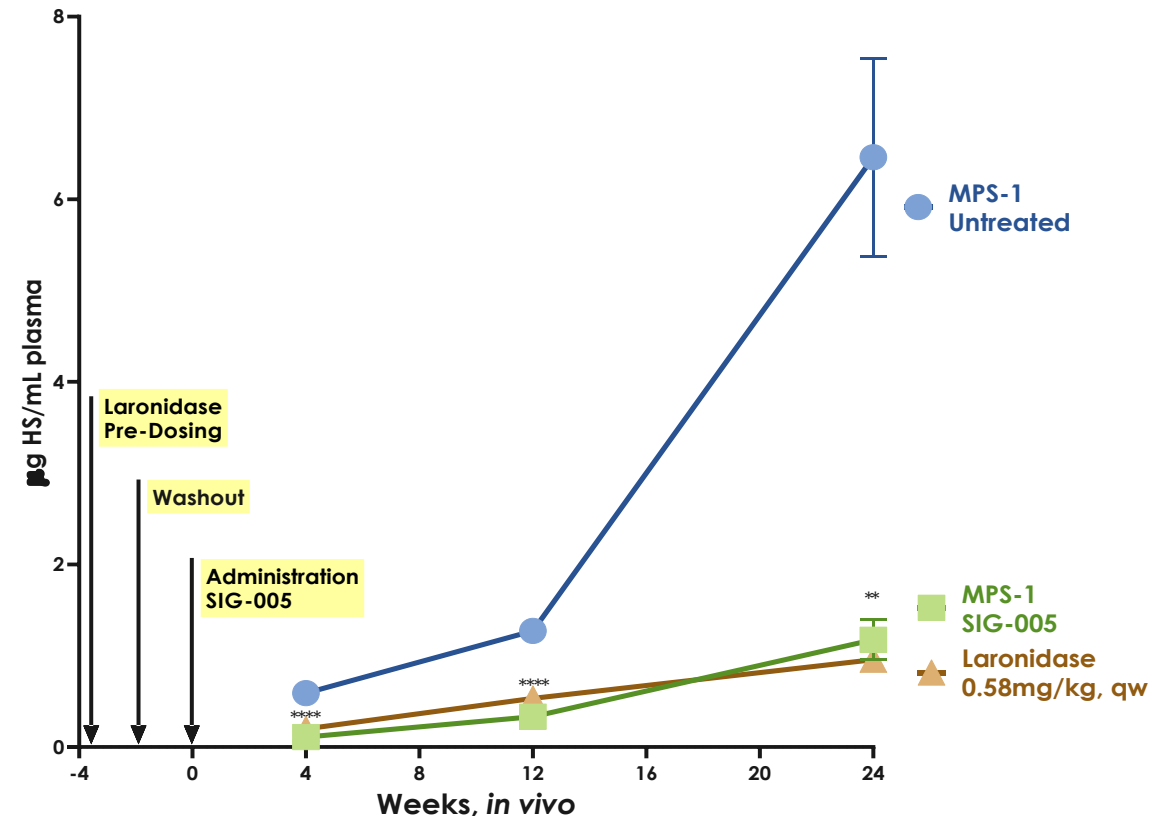
SIG-005 Produces Active hIDUA Both *In Vitro* and *In Vivo* For At Least 6 Months

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



*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.

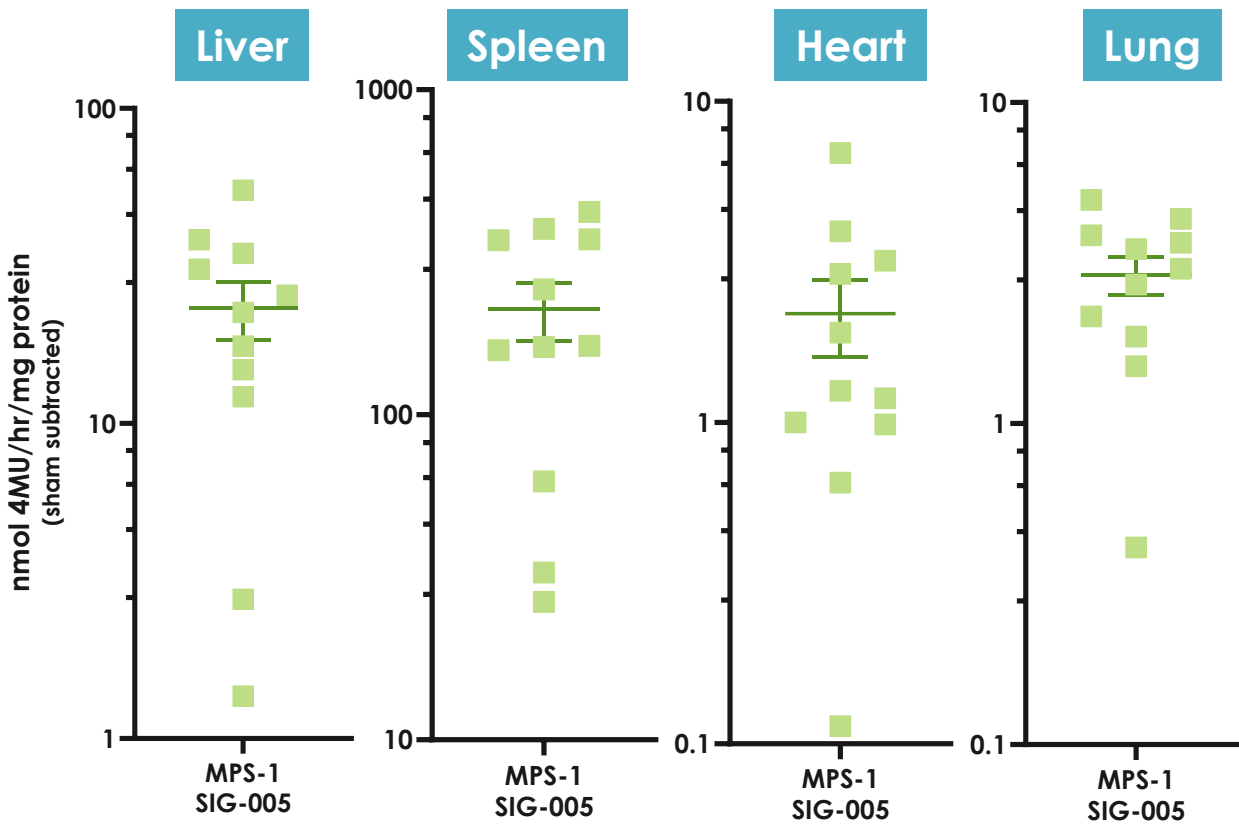
SIG-005: Low levels of HS in plasma 6-months post-administration in MPS-1H mice*



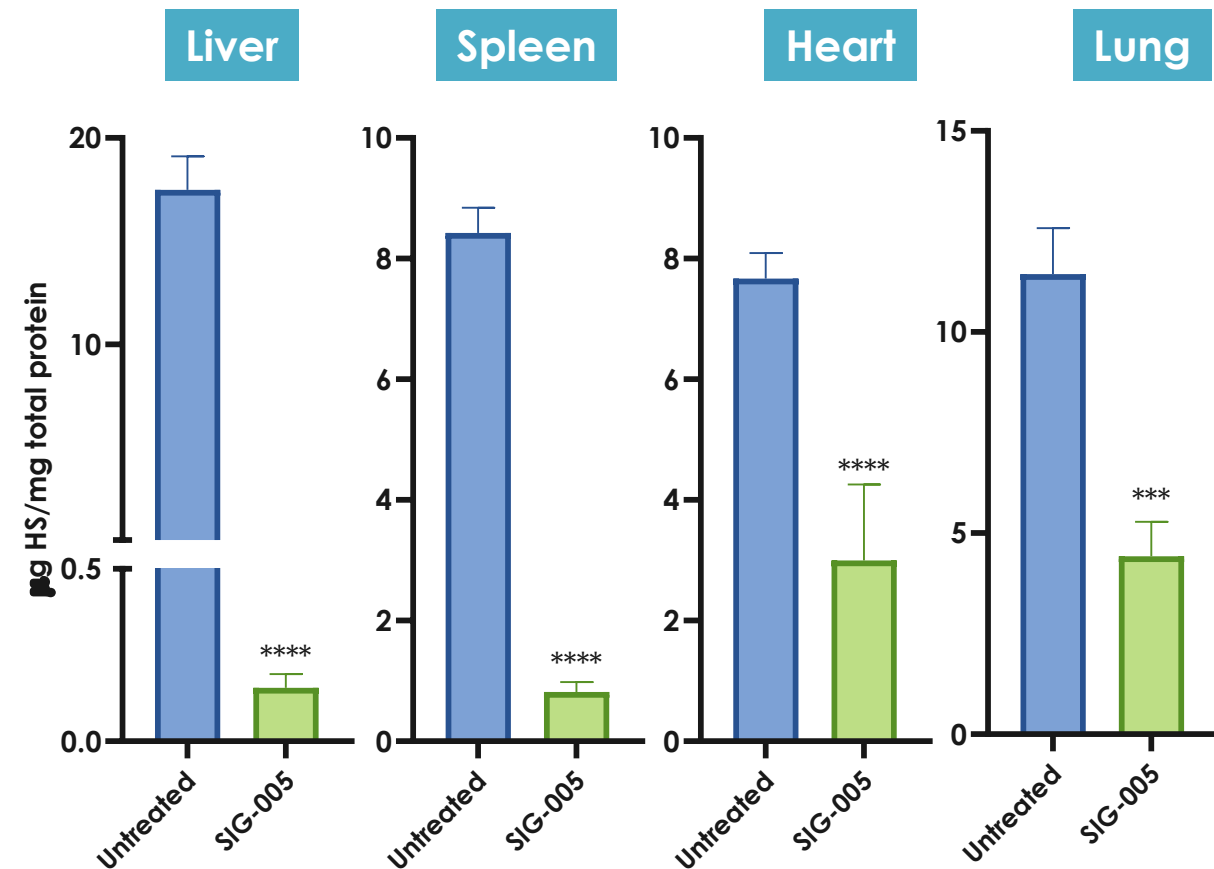
MPS-1: mucopolysaccharidosis type I; HS: heparan sulfate; U: nmol 4MU per hour
Error bars indicate SEM; Untreated, n=25; SIG-005, n=9; Laronidase, n=17;
unpaired t-test vs untreated **** p<0.001; *** p<0.001; ** p<0.01; * p<0.05; n.s. p>0.05

Enzyme Activity, Substrate Reduction 6 Months After SIG-005 Administration in MPS-1H Mice

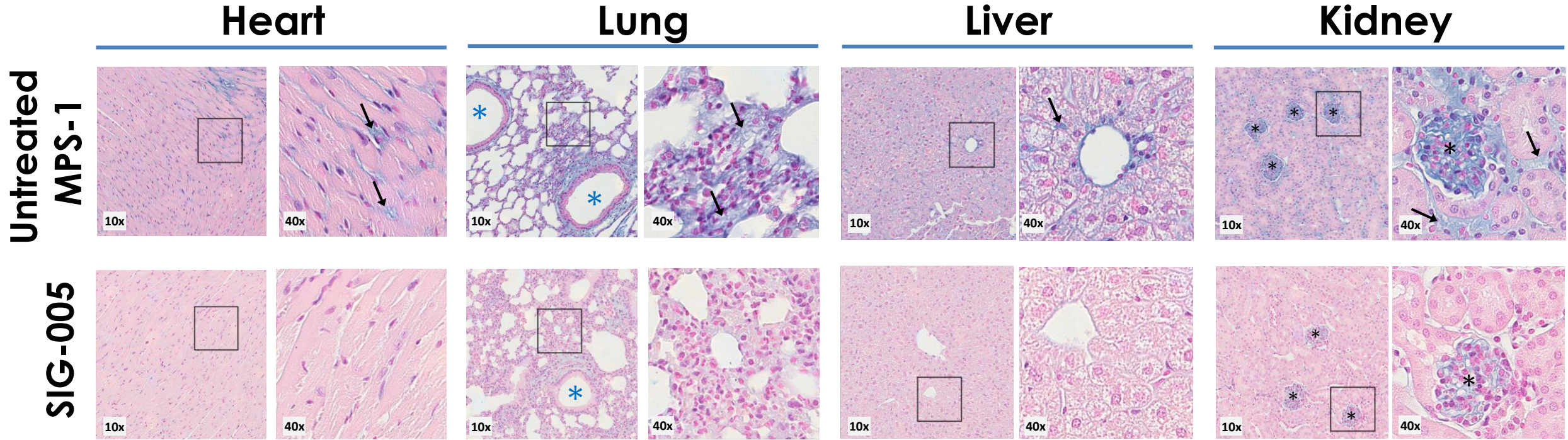
High to normal levels of hDUA activity
6 months post administration



Significant reduction in total HS
6 months post administration



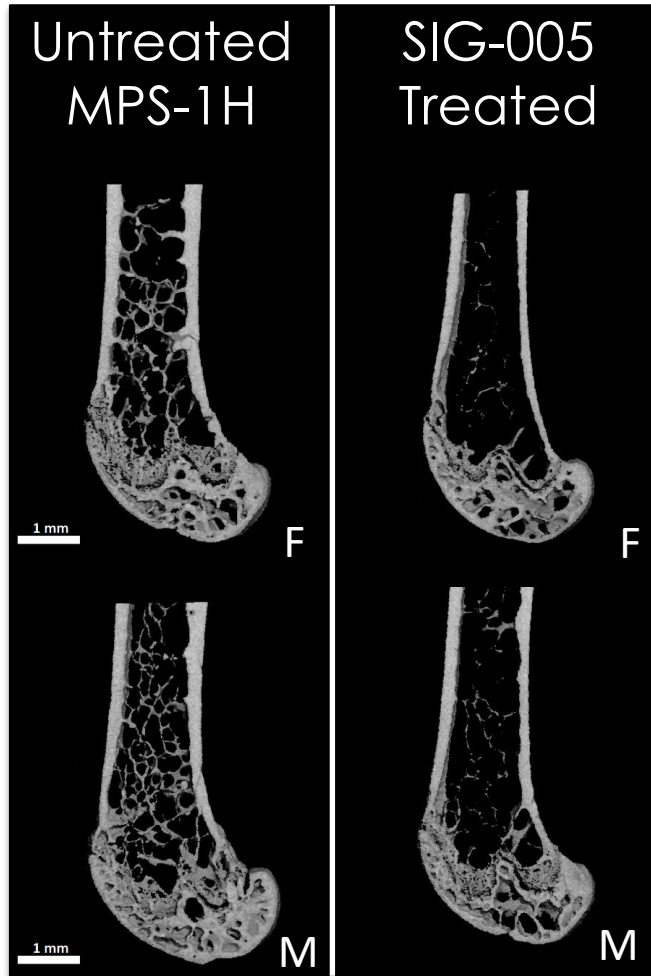
Reduction of Substrate in Tissues of MPS-1H Mice 6 Months After SIG-005



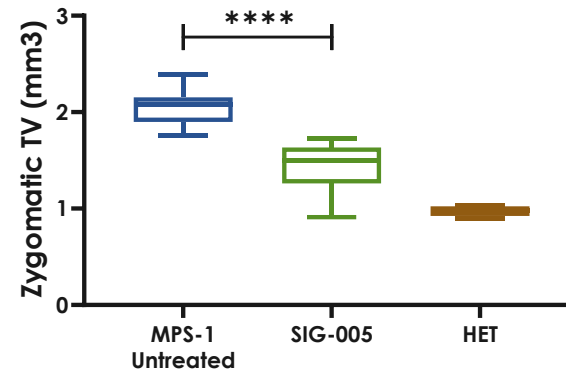
Alcian blue; Black arrow indicates substrate; * Bronchiole; * Glomerulus

SIG-005 Corrects Bone Phenotype in MPS-1H Mice

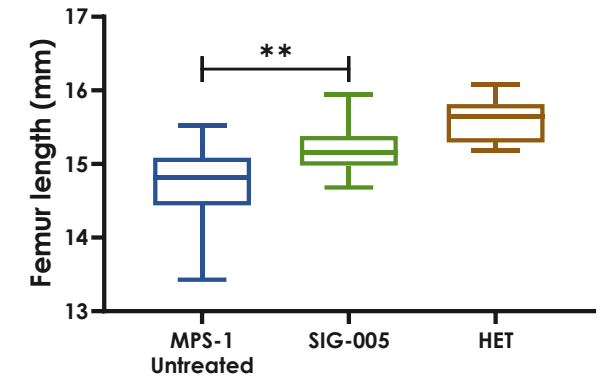
6 Months After Administration



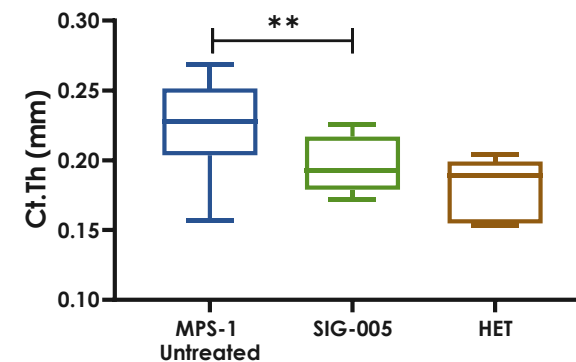
Total Bone Volume (Zygomatic Arch)



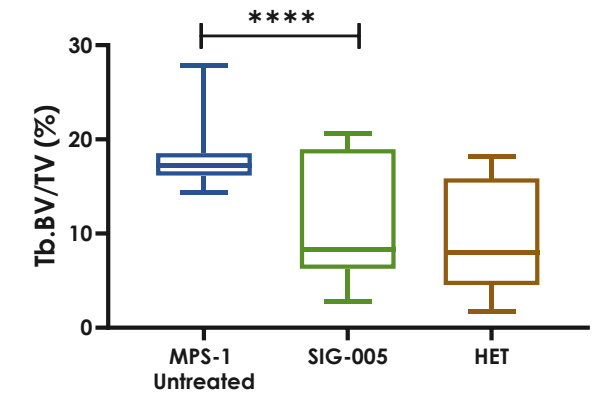
Bone Length (Femur)



Cortical Thickness (Femur Midshaft)



Trabecular Bone Volume (Distal Femur)



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