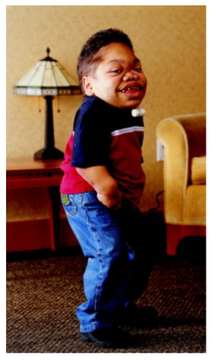
Development of a Novel Encapsulated Non-Viral Cell-Based Therapy for MPS VI

Erika Pearson[1], Susan Yu[1], Drew Tietz[1], Marissa Donovan[1], Lauren Sohn[1], Kathleen Barrett[1], Greg Hussack[2], Danica Stanimirovic[2], Elina Makino[1], Philip G. Ashton-Rickardt[1]

[1]Sigilon Therapeutics, Cambridge, MA, United States; [2]Human Health Therapeutics Research Centre, National Research Council Canada, Ottawa, ON, Canada

Introduction

- **Mucopolysaccharidosis type VI** (MPS VI, Maroteaux-Lamy syndrome) is caused by a deficiency of the lysosomal enzyme **arylsulfatase B (ARSB)**
- **ARSB deficiency** results in incomplete or blocked degradation of **glucosaminoglycans (GAGs)**, which **accumulate** in the lysosome and disrupt normal cell function
- **Disruption of cell function** manifests in **symptoms of MPS VI:**
  - Short stature, coarse facial features, stiff joints, breathing problems, difficulty walking, hip pain
  - Photo on the right shows rapidly progressing 16yr old male patient



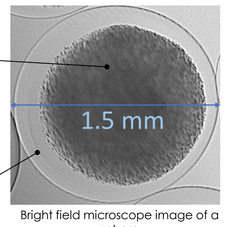
Valayannopoulos Mucopolysaccharidosis VI Orphanet J Rare Dis. 2010; 5: 5. Published online 2010 Apr 12. doi: 10.1186/1750-1172-5-5 (Creative Commons Attribution License)

Hypothesis

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

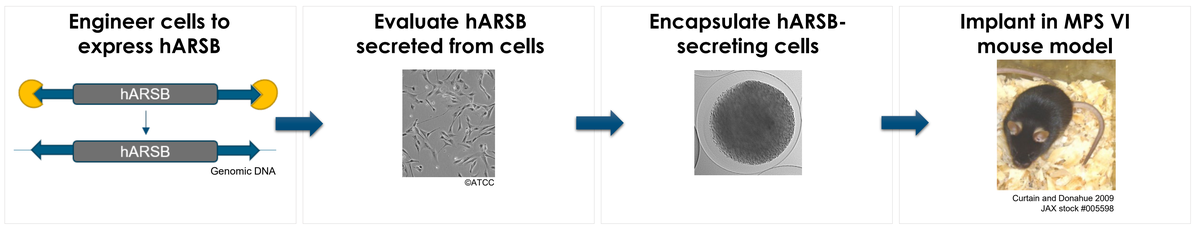
Inner Compartment:
- genetically modified human cells that express hARSB
- modified alginate designed to optimize cell function

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



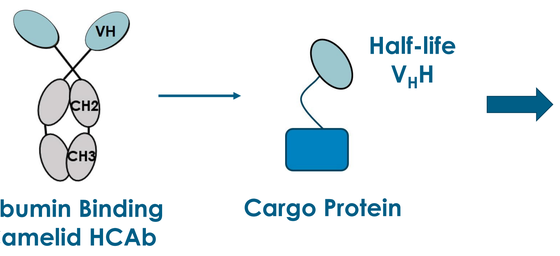
Bright field microscope image of a sphere

Methods



Generation of HL-hARSB Fusion Enzyme

- **National Research Council Canada** (NRC) has isolated a class **of high affinity sdAbs (V_HHs)** that **extends the half-life** of a cargo protein in plasma



Goal: To fuse Half-Life extending V_HH to hARSB to increase plasma half-life and circulation of hARSB in vivo

HL-hARSB = Fusion of hARSB to Half-Life extending V_HH

Conclusions

- **Native and Half-Life extending V_HH-fused Arylsulfatase B** produced by engineered cells show **equivalent CS/DS lowering in MPS VI fibroblasts relative to recombinant enzyme** treatment
- **MPS VI mice** treated for 1 week with an encapsulated cell line secreting hARSB fused to **Half-Life extending V_HH showed higher tissue activity** when compared to treatment with Native hARSB
- Treatment of **MPS VI mice** with an encapsulated cell line secreting active hARSB fused to Half-Life extending V_HH results in **significant substrate reduction within 14-28 days of administration**

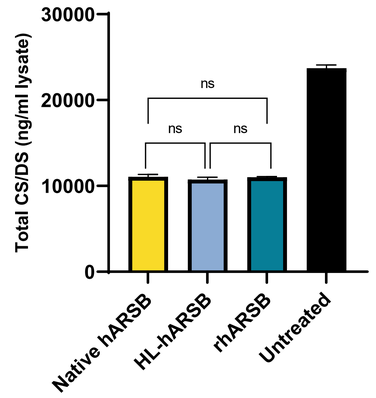
ACKNOWLEDGEMENTS: The authors would like to acknowledge the team at Sigilon Therapeutics for guidance, laboratory work and helpful discussions.
The work presented in this poster was fully funded by Sigilon Therapeutics, Inc.

Presented at the 18th annual WORLD*Symposium*™ held February 7th – 11th 2022.

Results

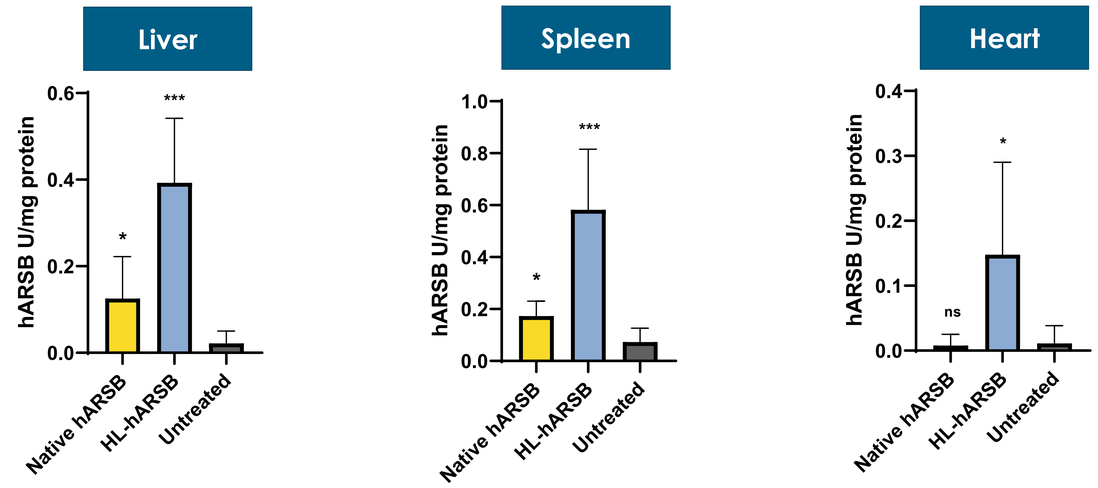
Comparison of Native and HL-hARSB Fusion Enzymes Produced from Allogeneic Cells vs Recombinant hARSB

Total Chondroitin/Dermatan Sulfate in MPS VI patient fibroblasts



Equivalent CS/DS lowering in MPS VI fibroblasts by Native hARSB and hARSB fused to Half-Life extending V_HH (HL-hARSB) in cell media vs recombinant enzyme (rhARSB)

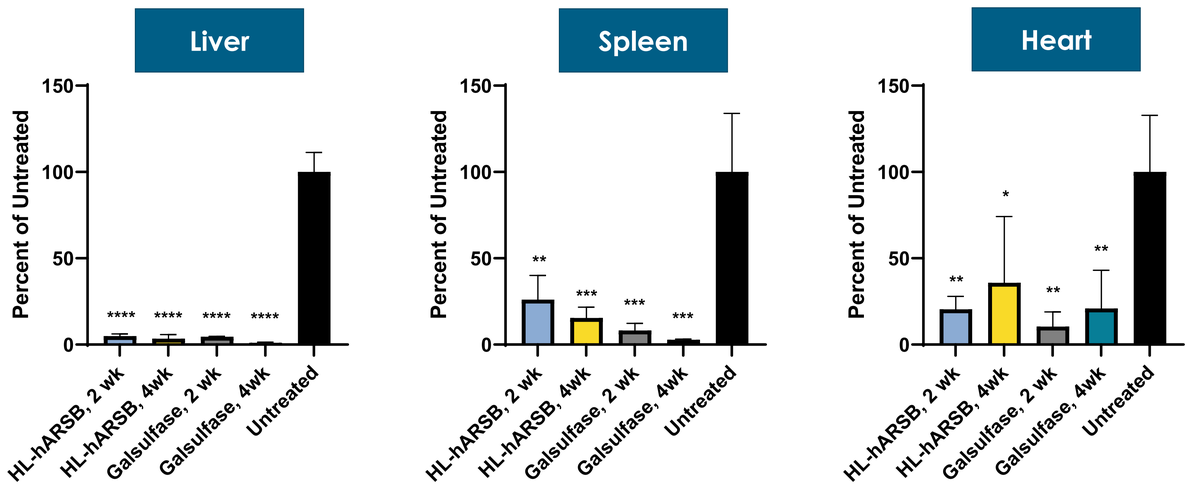
Native hARSB vs HL-hARSB fusion activity in MPS VI mouse tissues



HL-hARSB Half-Life extending V_HH fusion to hARSB; **U** nanomole per hour; Timepoint = 1 wk; Each condition, n=5; **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; ns p>0.5

Fusion of Half-Life extending V_HH to hARSB results on average in 2-10x higher hARSB activity relative to Native hARSB in MPS VI mouse tissues

Chondroitin Sulfate (CS) and Dermatan Sulfate (DS) Substrate Reduction in MPS VI Mouse Tissues



HL-hARSB Half-Life extending V_HH fusion to hARSB; **CS** chondroitin sulfate; **DS** dermatan sulfate; Each condition/time point, n=5; **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; ns p>0.5

Fusion of Half-Life extending V_HH to hARSB results in a statistically significant reduction in CS/DS substrate in MPS VI mouse tissues