

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

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## 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

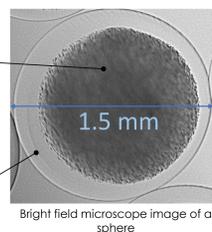


Vanempenopoulos Mucopolysaccharidosis VI. Opened J. Rare Dis. 2014; 1(1):1-10. doi: 10.1186/1750-1977-5-1 (Creative Commons Attribution License)

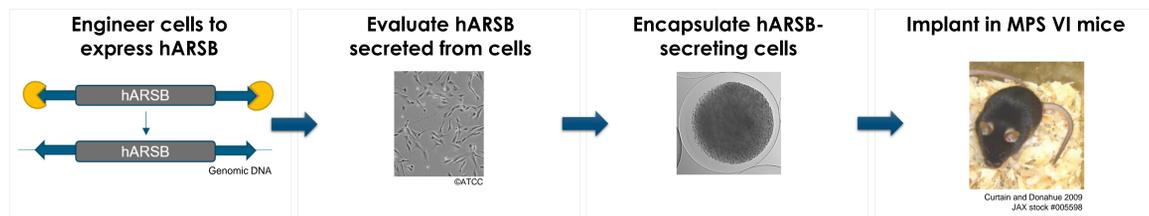
## Hypothesis

Better outcomes could be achieved with **sustained, long-lasting 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 human ARSB (hARSB)
  - modified alginate designed to optimize cell function
- Outer Layer:**
- modified alginate chemically linked to small molecule to minimize PFO

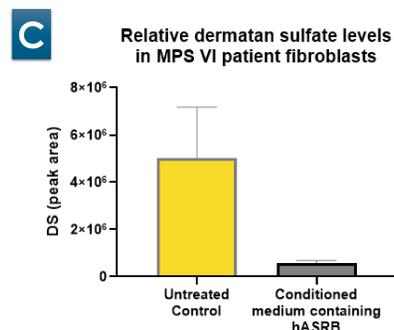
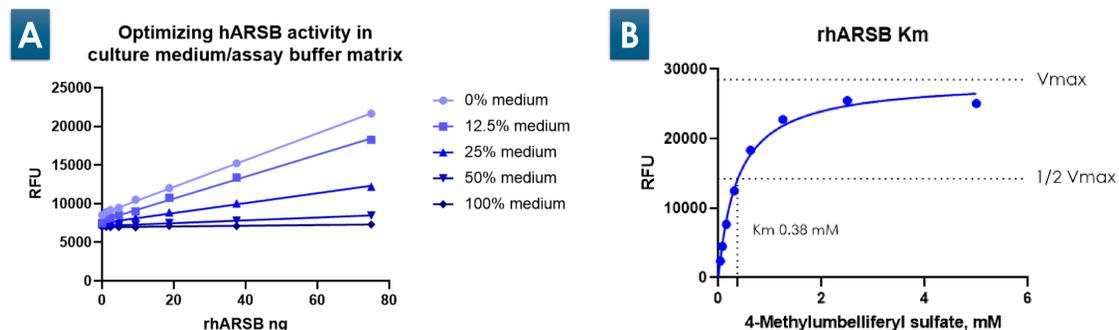


## Methods



## Results

### Establishing *In Vitro* Assays to Assess hARSB Function



### Panels A&B: Biochemical Analysis of hARSB

- Optimization of enzymatic assay helped to establish Km for hARSB – 0.38 mM of substrate

### Panel C: hARSB uptake into MPS VI patient fibroblasts

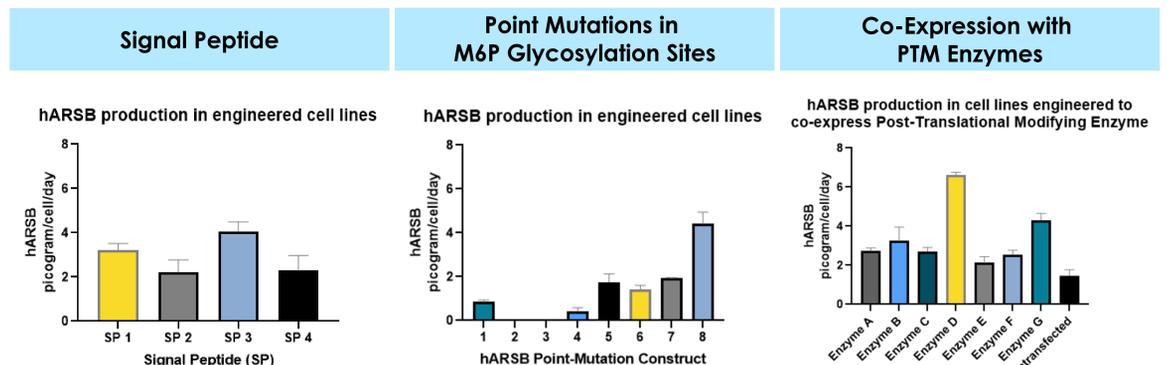
- Dermatan sulfate (DS) levels are reduced after exposure to culture medium containing hARSB produced by engineered cells

## Conclusions

- Dermatan sulfate levels are reduced** in **MPS VI patient fibroblasts** upon exposure to culture medium containing hARSB from engineered cells
- Co-expression with post-translation modifying enzymes** yielded engineered cell lines with **highest secretion levels of hARSB**
- Encapsulated engineered cell line secretes active hARSB
- Treatment of **MPS VI mice** with an encapsulated cell line secreting active hARSB results in **substrate reduction within 7 days of administration**

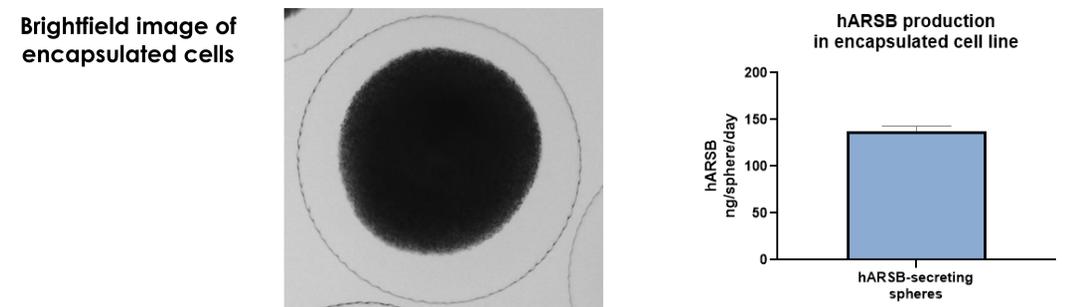
## Results (cont'd)

### Strategies to Enhance Secretion of hARSB

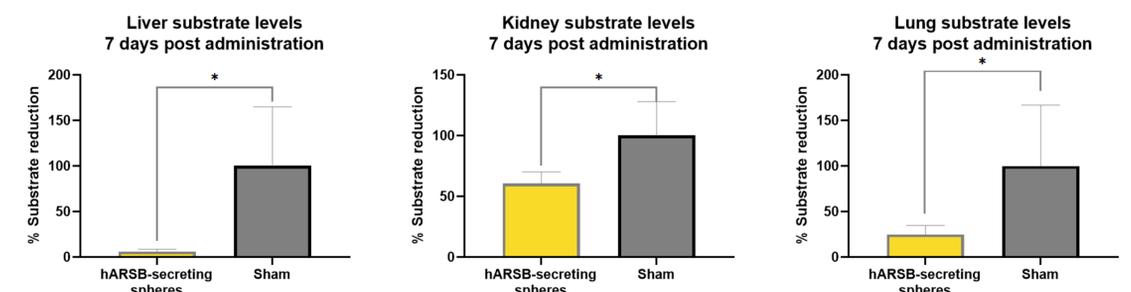


- The secretion was assessed by Western blotting and found to be consistent with the production results above (data not shown)
- Removing M6P glycosylation sites did not result in improved hARSB production and secretion
- Co-expression of hARSB with enzymes affecting post-translation modifications (PTM, right panel), yielded cell lines with highest production and secretion levels of hARSB**

### Encapsulated Cell Line Secretes Active hARSB



### Substrate Reduction in MPS VI Mouse Tissues



- Treatment of MPS VI mice with an encapsulated cell line secreting active hARSB results in substrate reduction 7 days after administration

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