Development of a novel encapsulated non-viral cell-based therapy for MPS-6

Erika Pearson, Susan Yu, Drew Tietz, Anya Hsu, Katie Jordan, Lauren Sohn, Tiffany Vo, MaryLouise Ross, Kyle Reusch, Elina Makino

Sigilon Therapeutics, Inc., Cambridge, MA, United States

Introduction

- Mucopolysaccharidosis type VI (MPS-6, Maroteaux-Lamy syndrome) is caused by a deficiency of the lysosomal enzyme arylsulfatase B (ARSB)
- ARSB deficiency results in incomplete or blocked degradation of glycosaminoglycans (GAGs), which accumulate in the lysosome and disrupt normal cell function
- Disruption of cell function manifests in symptoms of MPS-6:
  - Short stature, coarse facial features, stiff joints, breathing problems, difficulty walking, hip pain
  - Photo on the right shows rapidly progressing 16yr old male patient

Results (cont’d)

MPS-6 Patient Fibroblasts Uptake Engineered hARSB Fusion Proteins

- Shown are examples of hARSB attachment to fusion proteins; Fusion of the proteins to hARSB:
  - does not change the biochemical properties of the enzyme
  - does not change uptake into cells nor the enzyme’s functionality within patient fibroblasts

Methods

- In a standard reaction, recombinant human ARSB (rhARSB, R&D Systems) was serially diluted in the established Assay Matrix. The diluted enzyme was combined with an equal volume of 5 mM 4-Methylumbelliferyl Sulfate (4-MUS, Sigma Aldrich) substrate and incubated at ambient temperature in the dark for 1 hour. The reaction was monitored with a spectrometer at 460 nm and 360 nm.
- To perform a Km analysis, 8 ng of rhARSB was incubated with serially diluted 4-MUS solution (top concentration at 5 mM) at ambient temperature in the dark for 1 hour and is processed as described above.

Conclusions

- Dermatan sulfate levels are reduced in MPS-6 patient fibroblasts upon exposure to culture medium containing hARSB from engineered cells
- Fusion of proteins to hARSB did not change its biochemical properties nor uptake by MPS-6 patient fibroblasts
- Encapsulated engineered cell line secretes active hARSB
- Treatment of MPS-6 mice with an encapsulated cell line secreting active hARSB results in substrate reduction within 7 days of administration

Results

- Treatment of MPS-6 mice with an encapsulated cell line secreting active hARSB results in substrate reduction 7 days after administration *p<0.05

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