Development of a Novel Encapsulated Non-Viral Cell-Based, BBB-Penetrant Therapy for MPS I

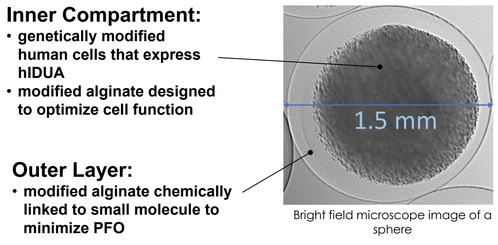
Erika Pearson[1], Anya Hsu[1], Drew Tietz[1], Marissa Donovan[1], Lauren Sohn[1], Greg Hussack[2], Danica Stanimirovic[2], Elina Makino[1], Philip G. Ashton-Rickardt[1]
[1]Sigilon Therapeutics, Cambridge, MA, United States; [2]Human Health Therapeutics Research Centre, National Research Council Canada, Ottawa, ON, Canada

Introduction

- **MPS I** is caused by a **deficiency o**f the lysosomal enzyme **α-L-iduronidase (IDUA)** leading to GAG accumulation in multiple tissues and organs
- This **accumulation results** in a complex array of progressive, multi-systemic pathologies, including **CNS manifestations**
- Approved therapies include enzyme replacement therapy (ERT), with chaperone and gene therapies under investigation
- Treatment with approved **ERT does not** adequately **address CNS manifestations**

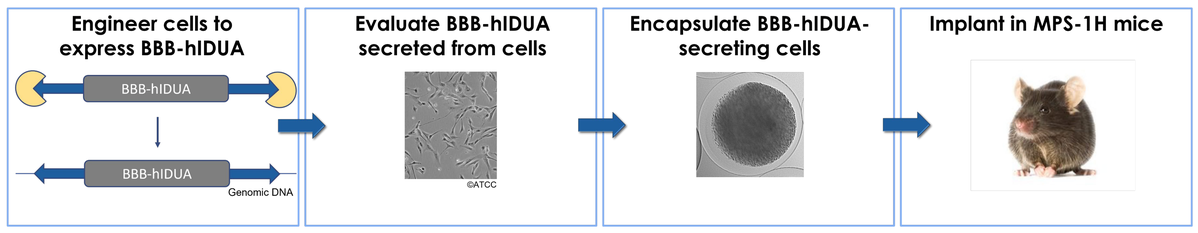
Hypothesis

Better outcomes could be achieved with **sustained, long-lasting levels** of a human IDUA **(hIDUA) fusion enzyme capable of penetrating the BBB** via administration of **hIDUA-secreting allogeneic human cells shielded within spheres** designed to avoid immune rejection and pericapsular fibrotic overgrowth (PFO) in the patient.



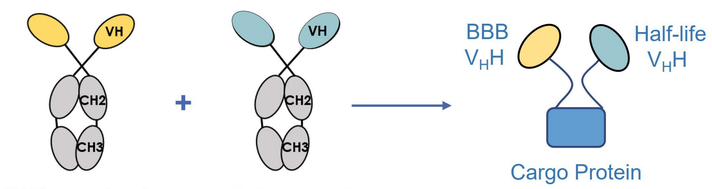
Bright field microscope image of a sphere

Methods



Generation of BBB-hIDUA Fusion Enzyme

- **National Research Council Canada** (NRC) has isolated several classes of **high affinity sdAbs (V_HHs)** that:
  1) Target a **Receptor on the BBB**
  2) Extend **Half-life in plasma**
- V_HHs can **function as transporter molecules** able to **ferry cargo proteins across the BBB**



BBB-penetrant Camelid HCAb — Half-life extending Camelid HCAb

- **Goal:** To fuse hIDUA to **two functional V_HHs** isolated at the NRC to generate **BBB-hIDUA fusion enzyme:**

1) BBB-penetrating V_HH
- Target receptor on BBB
- Mediate shuttling of hIDUA across BBB

2) Half-life extending V_HH
- Extend hIDUA half-life in plasma
- Increased plasma half-life to drive BBB shuttling

Conclusions

- **Dual V_HH fusion** to hIDUA results in **3x higher Plasma hIDUA activity** levels in MPS-1H mice relative to historical native hIDUA levels
- **Tissue activity** levels of the dual fusion enzyme are on average **2-10x higher** compared to historical native hIDUA levels
- **BBB-penetrant and half-life extending V_HH** fusions results in **32% decrease in Brain heparan sulfate** levels relative to untreated MPS-1H mice
- **Dual fusion hIDUA** enzyme exhibits **good systemic tissue penetration and substrate reduction** in MPS-1H mice

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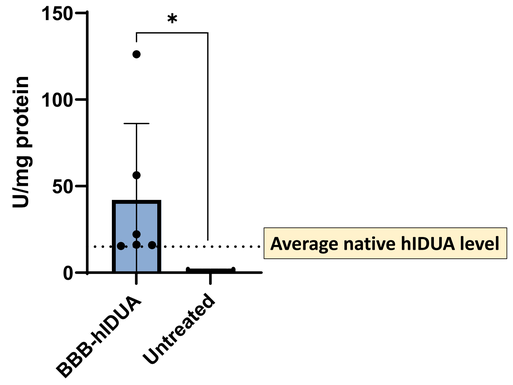
Results

Plasma hIDUA activity in MPS-1H mice

Plasma activity



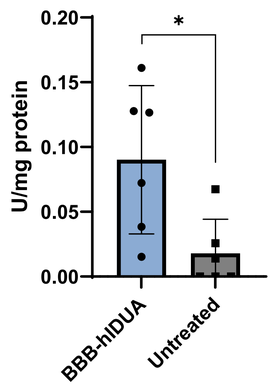
Fusion to BBB-penetrant and half-life extending V_HHs results on average in 3x higher plasma hIDUA activity levels in MPS-1H mice relative to historical native hIDUA levels*

*Historical native hIDUA levels = Sigilon's historical data in MPS-1H mice treated with encapsulated cells that secrete wild-type hIDUA

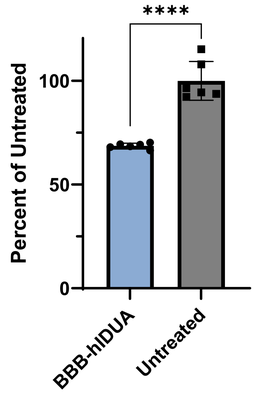
U nanomole per hour; Timepoint = 3 wks; Each condition, n=6; **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; ns p>0.5

Brain hIDUA activity and substrate reduction in MPS-1H mice

Brain hIDUA activity



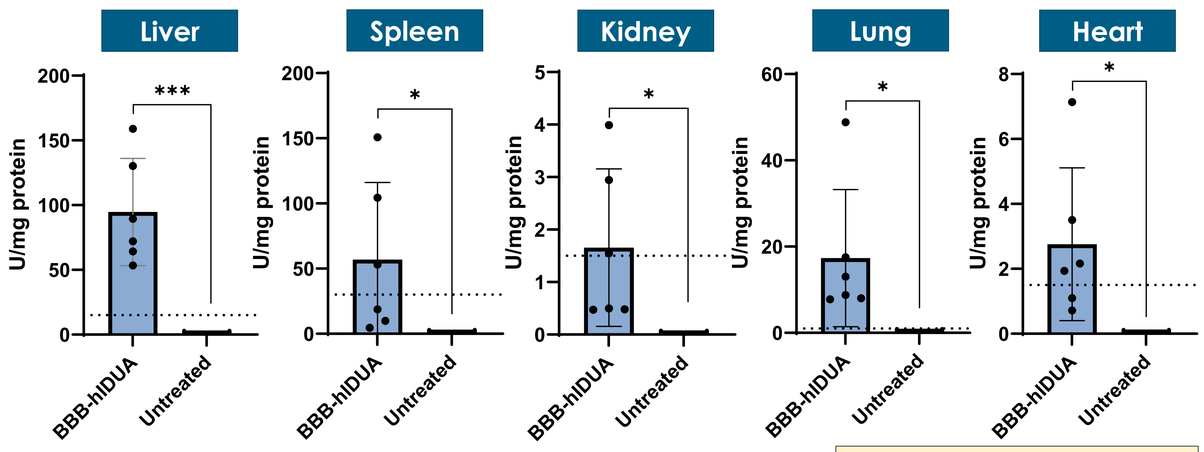
Brain heparan sulfate reduction



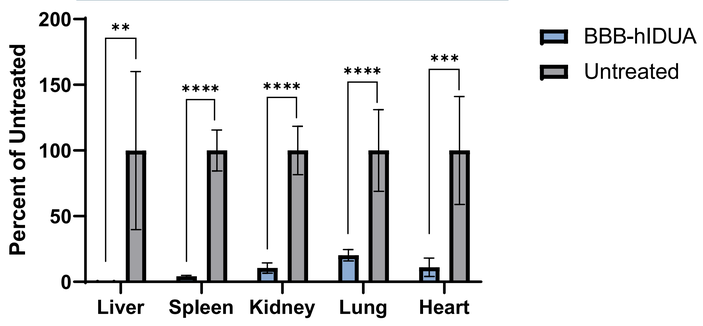
Fusion to BBB-penetrant and half-life extending V_HHs results in successful BBB penetration of hIDUA in MPS-1H mice as judged by activity levels and substrate reduction in the brain

U nanomole per hour; Timepoint = 3 wks; Each condition, n=6; **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; ns p>0.5

Systemic tissue hIDUA activity and substrate reduction in MPS-1H mice



Total heparan sulfate reduction in systemic tissues



Dual V_HH fusion hIDUA demonstrates good systemic tissue penetration and functional activity towards target substrate

U nanomole per hour; Timepoint = 3 wks; Each condition, n=6; **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; ns p>0.5