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

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MPS I

- **MPS I** is caused by **deficiency of** 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: **therapeutic effect** can be achieved with **sustained levels** of an **hIDUA fusion enzyme capable of penetrating the BBB** via administration of **hIDUA fusion-secreting allogeneic human cells** shielded within spheres designed to avoid immune rejection and pericapsular fibrotic overgrowth (PFO) in the patient

Encapsulated Non-Viral Cell-Based Platform

Cell-to-cell interaction and rejection → Physical shield (2-compartment, modified alginate sphere)

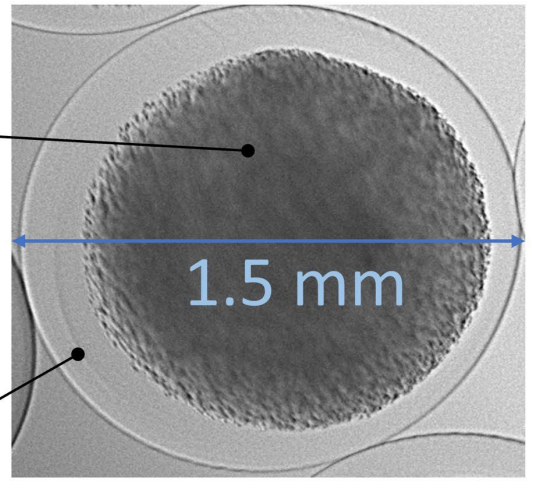
Pericapsular fibrotic overgrowth (PFO) → Small-molecule conjugated alginate in outer layer

Inner Compartment:

- **genetically modified human cells that express human IDUA (hIDUA)**
- **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

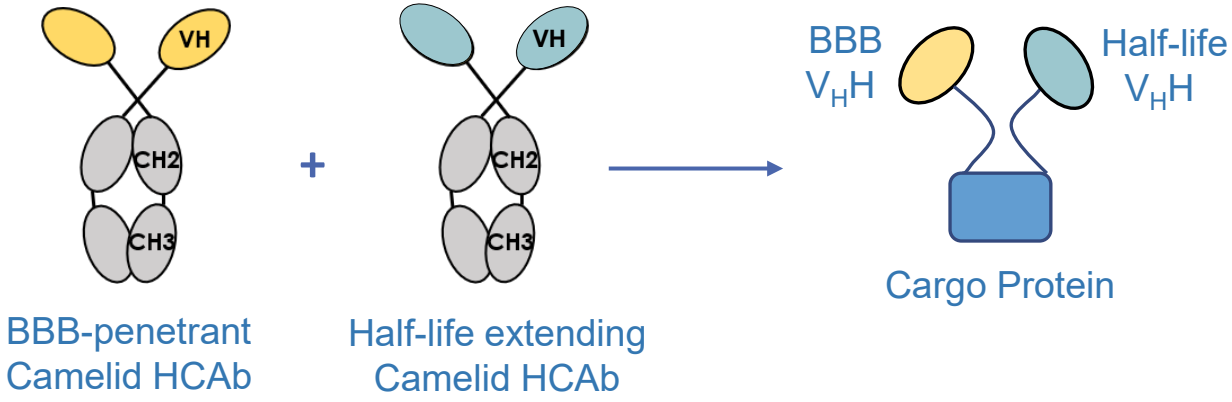
- The shielded spheres are placed in the peritoneal space where they can absorb nutrients while the released therapeutic protein can enter the blood compartment

Generating BBB-hIDUA Fusion Enzyme

Technology Details

- **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**



Dual V_HH fusion to hIDUA

- **Fuse hIDUA** to **two functional V_HHs** isolated at the **NRC** :

1) BBB-penetrating V_HH

- Target receptor on BBB
- Mediate shuttling of hIDUA across BBB

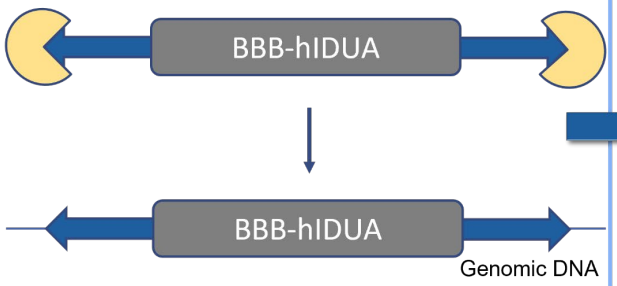
2) Half-life extending V_HH

- Extend hIDUA half-life in plasma
- Increased plasma half-life to drive BBB shuttling

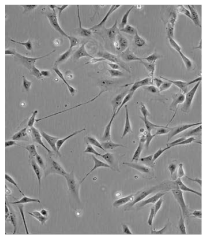
BBB-hIDUA = Fusion of hIDUA to BBB-penetrant V_HH + Half-life extending V_HH

Development Path of BBB-hIDUA

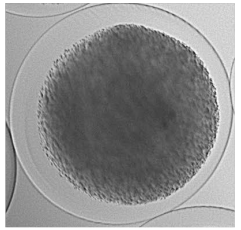
Engineer cells to express BBB-hIDUA



Evaluate BBB-hIDUA secreted from cells



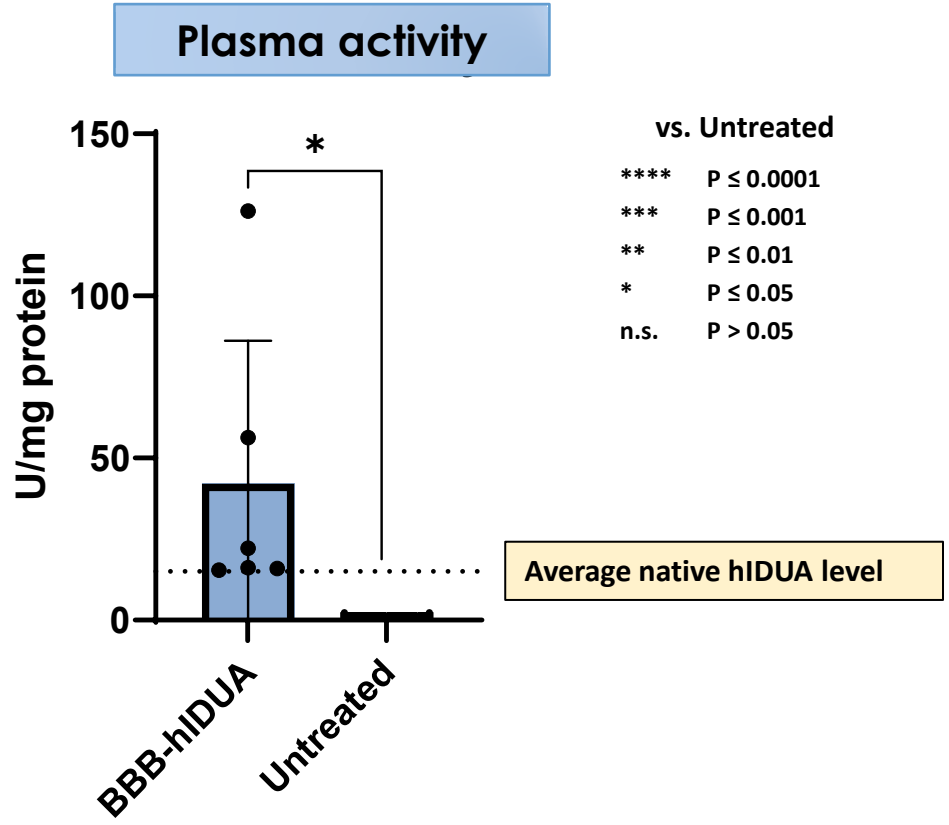
Encapsulate BBB-hIDUA-secreting cells



Implant in MPS-1H mice

Plasma hIDUA activity in MPS-1H mice

Day 21 post sphere administration



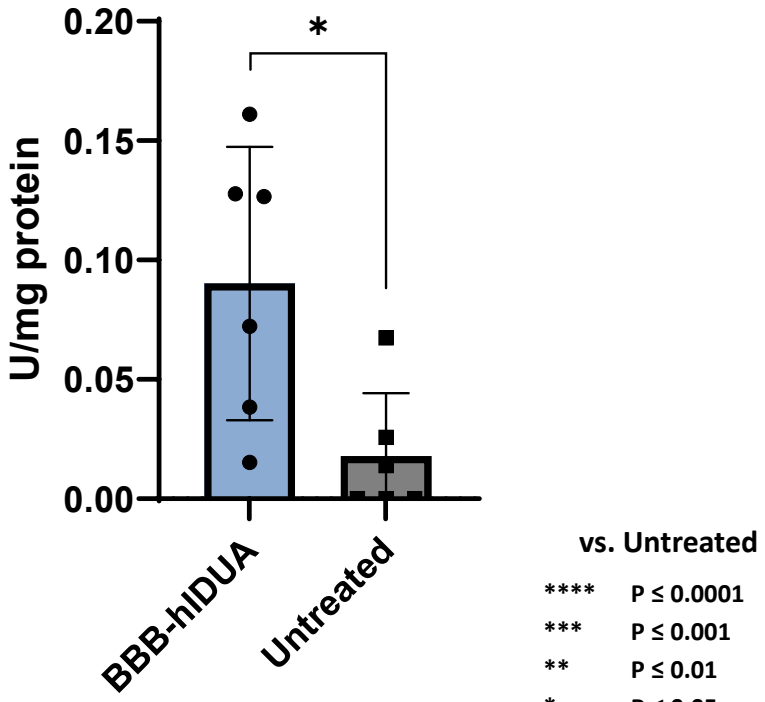
- Fusion to **BBB-penetrant** and **half-life extending V_HHs** results on average in **3x higher plasma hIDUA activity** levels in MPS-1H mice relative to historical native hIDUA levels*

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

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

Day 21 post sphere administration

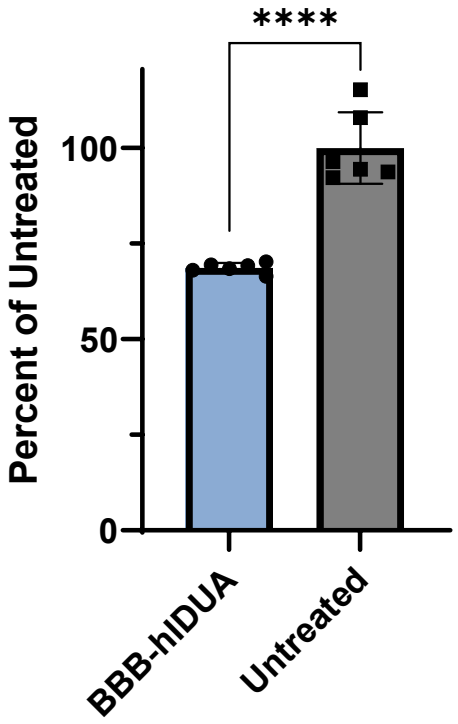
Brain hIDUA activity



vs. Untreated

****	P ≤ 0.0001
***	P ≤ 0.001
**	P ≤ 0.01
*	P ≤ 0.05
n.s.	P > 0.05

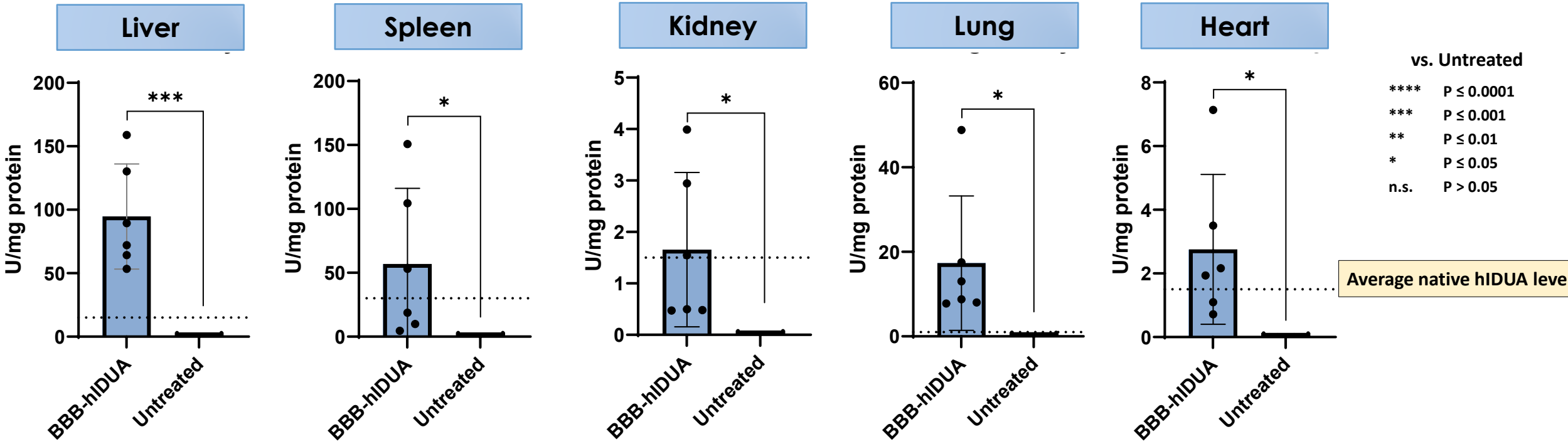
Brain heparan sulfate reduction



- **Fusion to BBB-penetrant and half-life extending V_HHs** results in **successful BBB penetration of hIDUA** in MPS-1H mice
  1) hIDUA **activity detected** in brain
  2) 32% **decrease in brain Heparan sulfate** levels

Systemic tissue hIDUA activity in MPS 1H mice

Day 21 post sphere administration

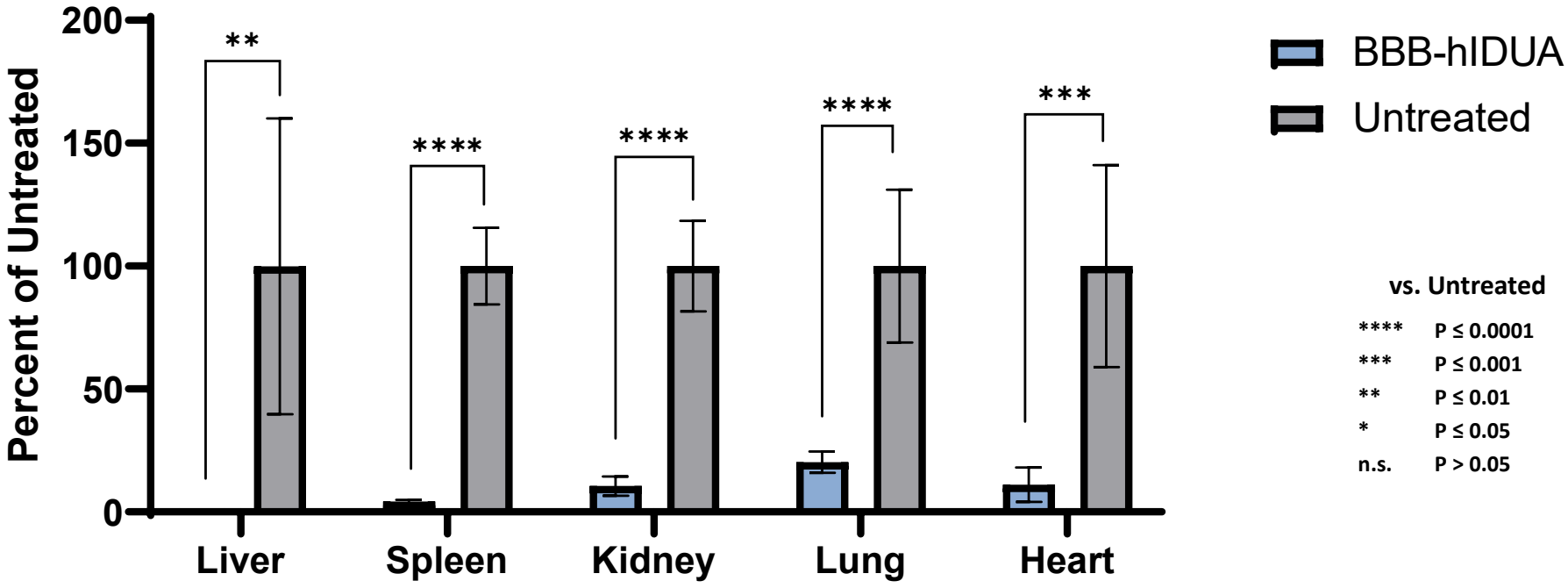


- **Dual V_HH fusion hIDUA** results in **2-10x higher hIDUA activity** levels relative to historical native hIDUA levels **in most systemic organs surveyed** in MPS 1H mice

Systemic tissue substrate reduction in MPS-1H mice

Day 21 post sphere administration

Total heparan sulfate reduction in systemic tissues



- hIDUA **dual fusion enzyme** demonstrated **good systemic tissue penetration and functional activity** towards target substrate

Conclusions

- **Dual V_HH fusion** to hIDUA resulted 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 were on average **2-10x higher** compared to historical native hIDUA levels
- **BBB-penetrant and half-life extending V_HH** fusions resulted in **32% decrease in Brain Heparan Sulfate** levels relative to untreated MPS-1H mice
- **Dual fusion hIDUA** enzyme exhibited **good systemic tissue penetration** and **substrate reduction** in MPS-1H mice

Acknowledgements

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Thank you for your attention!