

DEVELOPMENT OF A PANCREATITIS-INDUCED LUNG INJURY MODEL



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Introduction

Acute Pancreatitis and Lung Injury

- Acute pancreatitis (AP) is the #1 cause of GI-related hospitalizations in the U.S.
- Severe inflammation leads to vascular disruption and systemic enzyme release, ending in multi-organ injury
- ~1/3 of AP deaths are due to acute lung injury (ALI) with progression to ARDS
- There are NO effective therapies to prevent AP-induced ALI

Endothelial Dysfunction in AP

- Microvascular endothelial cells (ECs) are crucial for maintaining vascular barrier function and controlling inflammation.
- Dysregulation of ECs is linked to the severity of AP and ALI.

Role of 3-OS HS

- 3-O-sulfated heparan sulfate (3-OS HS), regulated by the HS3ST1 gene, reduces clotting and inflammation
- AP reduces HS3ST1 expression in pancreas
- HS3ST1 KO mice have worse AP and remote lung injury in inflammatory models
- Synthetic 3-OS HS reduces multi organ injury in mouse models
- Notably, alcohol exposure, which is a major risk factor for AP, reduces HS3ST1 expression

Methods

Acute Pancreatitis Model:

Caerulein-induced acute pancreatitis in male and female mice (C57BL/6(WT) and HS3ST1 knockout).

*Mice monitored daily for weight loss, lethargy, and dehydration.

Groups (n=10 per group):

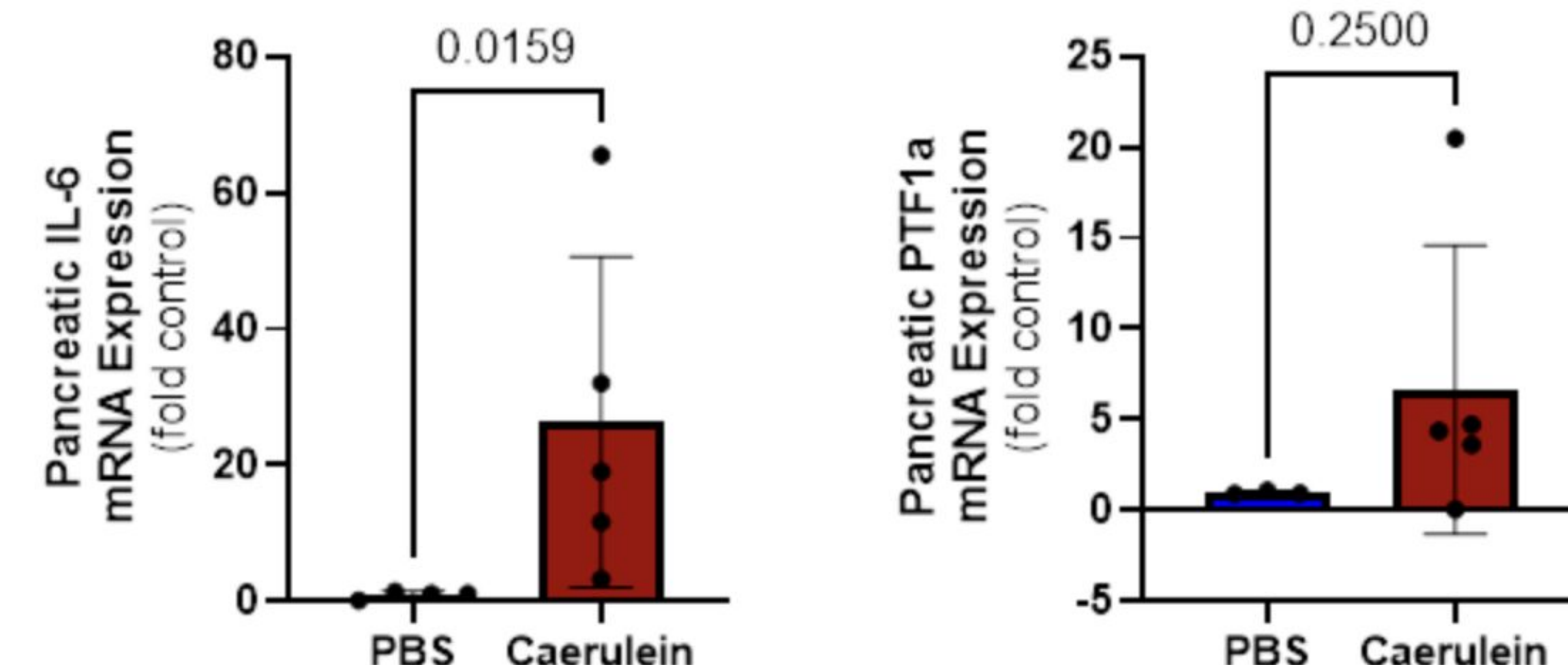
WT PBS || WT caerulein || HS3ST1 +/+ PBS || HS3ST1 +/+ caerulein || HS3ST1 -/- PBS || HS3ST1 -/- caerulein

Timeline



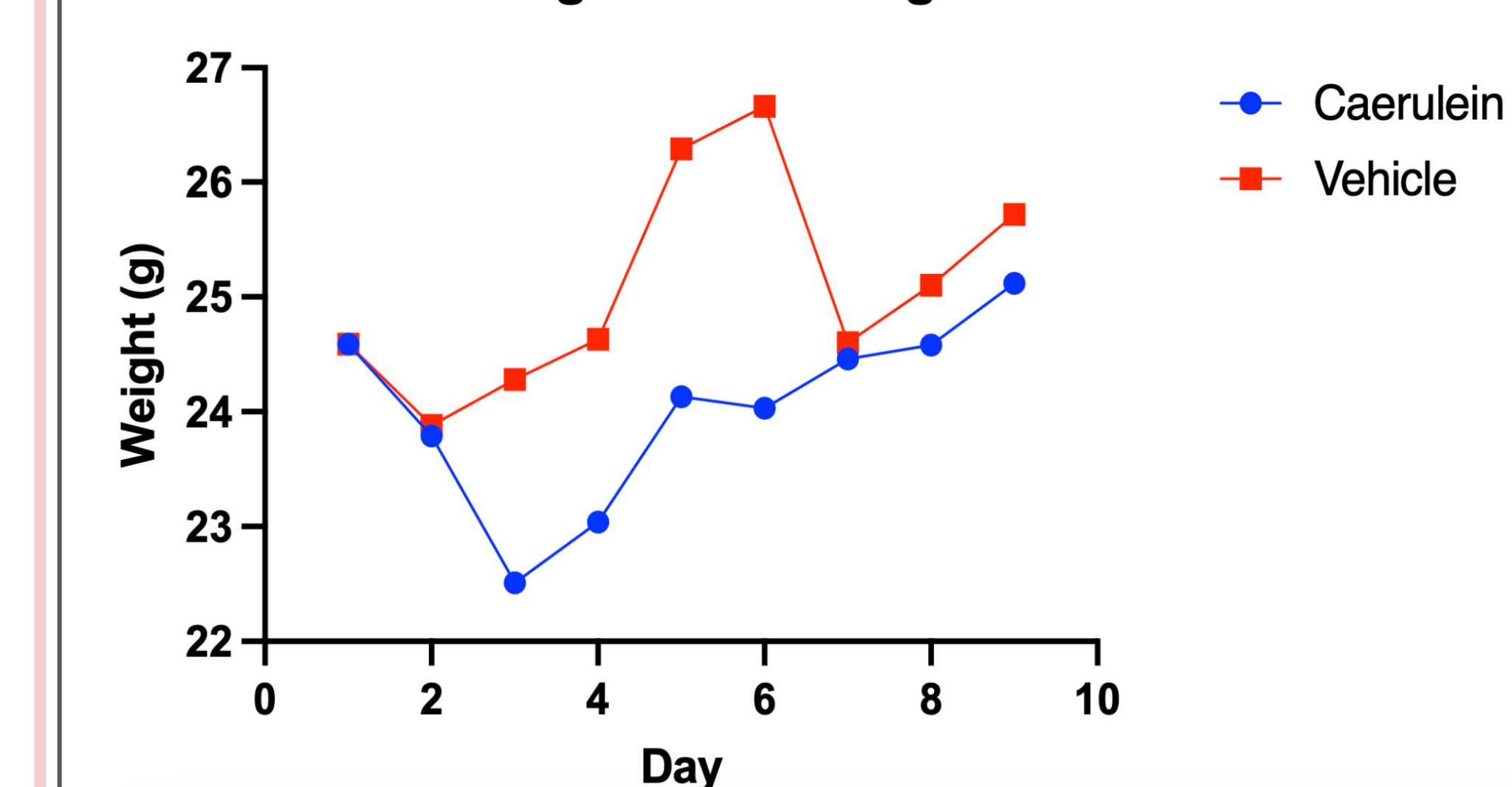
- Primary Outcome: HS3ST1 expression, pancreas edema.
- Secondary Outcomes: Pancreas inflammation, severity scores, lung injury, RNA sequencing.
- Data Analysis: Compare HS3ST1 KO vs. WT, ethanol-exposed vs. non-exposed, with dekaparin treatment

Results

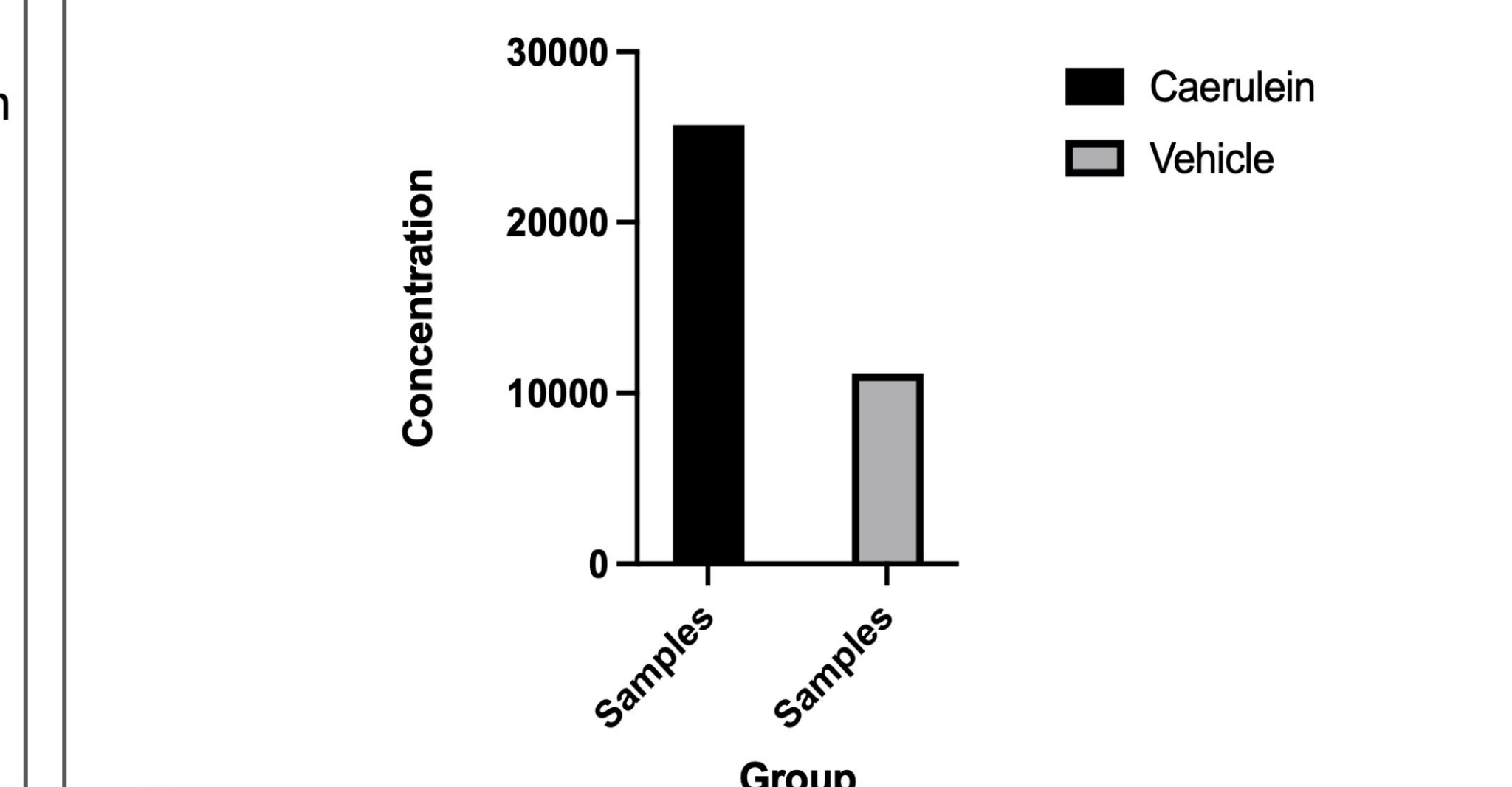


Results

WT C57BL/6 Average Mouse Weights Over Time



WT C57BL/6 Average Adjusted Concentration of Pancreatic Lipase



Conclusion + Next Steps

- The established model provides a reproducible platform to investigate endothelial contributions to systemic inflammation and identify novel therapeutic targets for AP and eventually ALI.
- Ongoing studies will test whether synthetic 3-OS HS(dekaparin) mitigates AP and ALI severity in alcoholic and non-alcoholic murine models.
- Translational studies will assess whether loss-of-function HS3ST1 variants correlate with worse clinical outcomes
 - Retrospective analysis of AP patient samples from UCD and UNMC biorepositories
 - Integrate clinical outcomes, histopathology, and ELISA data to validate mechanistic findings in humans.

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