

Introduction

Acute pancreatitis (AP) is a devastating human disease that is responsible for ~300,000 hospitalizations in the United States annually. The mortality rate for acute pancreatitis is 5%, and 20% of patients develop severe disease. Currently, there is no pharmacologic therapy available to treat acute pancreatitis or prevent and mitigate the progression to chronic pancreatitis. AP is largely driven by pro-inflammatory cytokines, including IL-6, IL-1 β , and TNF α . Blocking IL-6 has been shown in preclinical studies to reduce pancreatic inflammation and limit tissue injury, highlighting its potential as a therapeutic target.

Here, we aim to establish a cerulein-induced pancreatitis model and measure a broad cytokine panel in each animal, which will allow us to identify novel cytokine targets and better understand the impact of IL-6 inhibition on pancreatic injury. Despite the availability of four FDA-approved IL-6 antagonists for other conditions, none have yet been investigated in acute pancreatitis. Generating detailed preclinical data will provide critical evidence to inform future therapeutic strategies and clinical trial design in this disease.

Study Aims

- Aim 1. Establish murine model of acute pancreatitis (AP).
- Aim 2. Determine cytokine levels from Aim 1 to select cytokine targets.
- Aim 3. Test the role of immunomodulation (such as aIL-6) in the AP model.

Methods

Aim 1: Acute Pancreatitis (AP) Model

C57BL/6J mice were induced with AP via IP cerulein injections, 1x/hour for 6 hours. Mock isotype IP injections were given twice: 30 minutes after the 3rd cerulein injection and 30 minutes after the 6th and final cerulein injection. Mice were sacrificed 72 hour post-final cerulein injection.

Aim 3: Acute Pancreatitis with treatment

C57BL/6J mice with cerulein-induced AP received cytokine therapy IP at same schedule as mock injections. Mice were sacrificed 72 hour post-final cerulein injection to evaluate the effect of cytokine blockade on pancreatic injury.

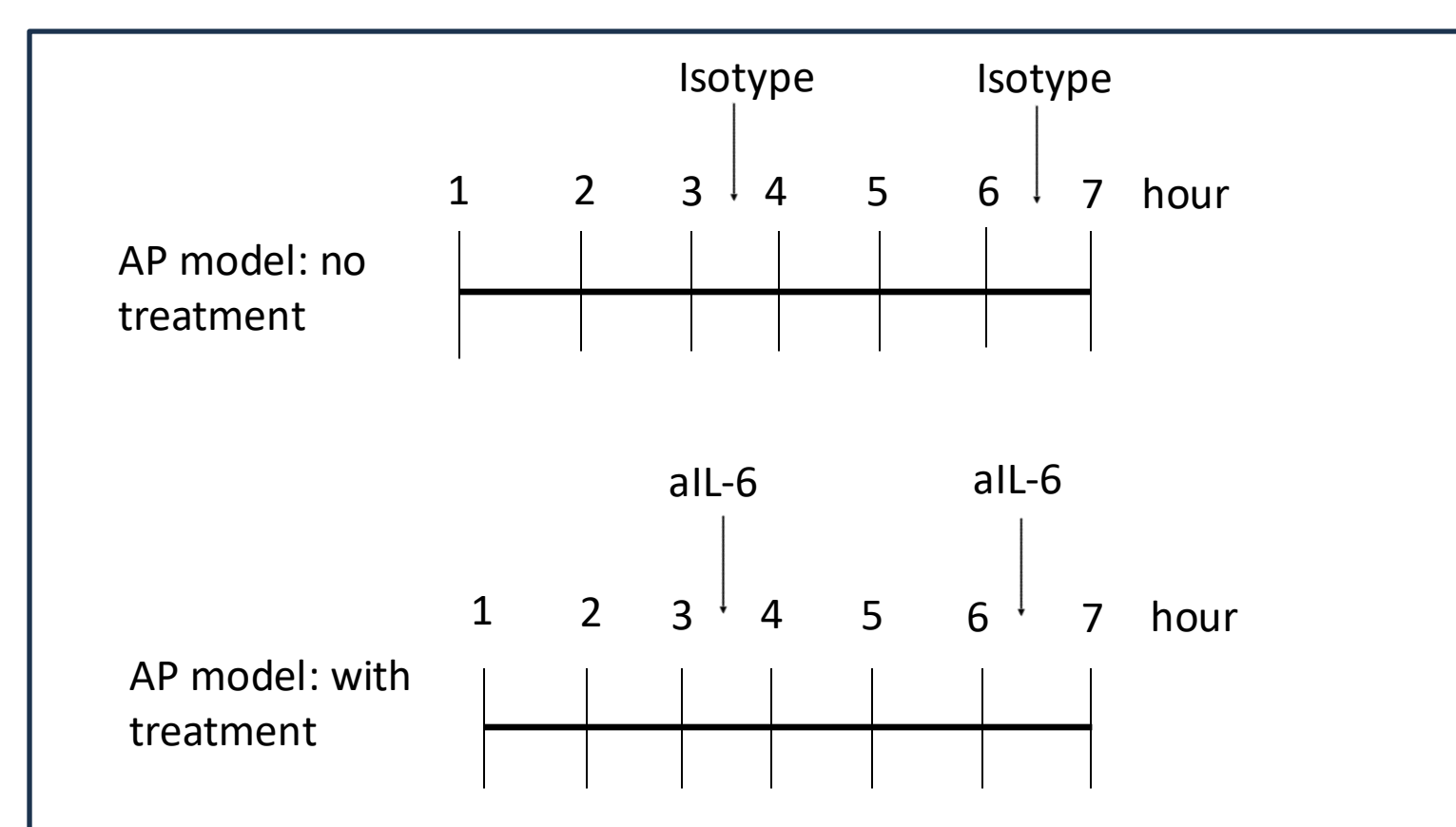


Figure 1. Procedure of AP induction

Cerulein-Injected Mice Developed Pancreatic Injury

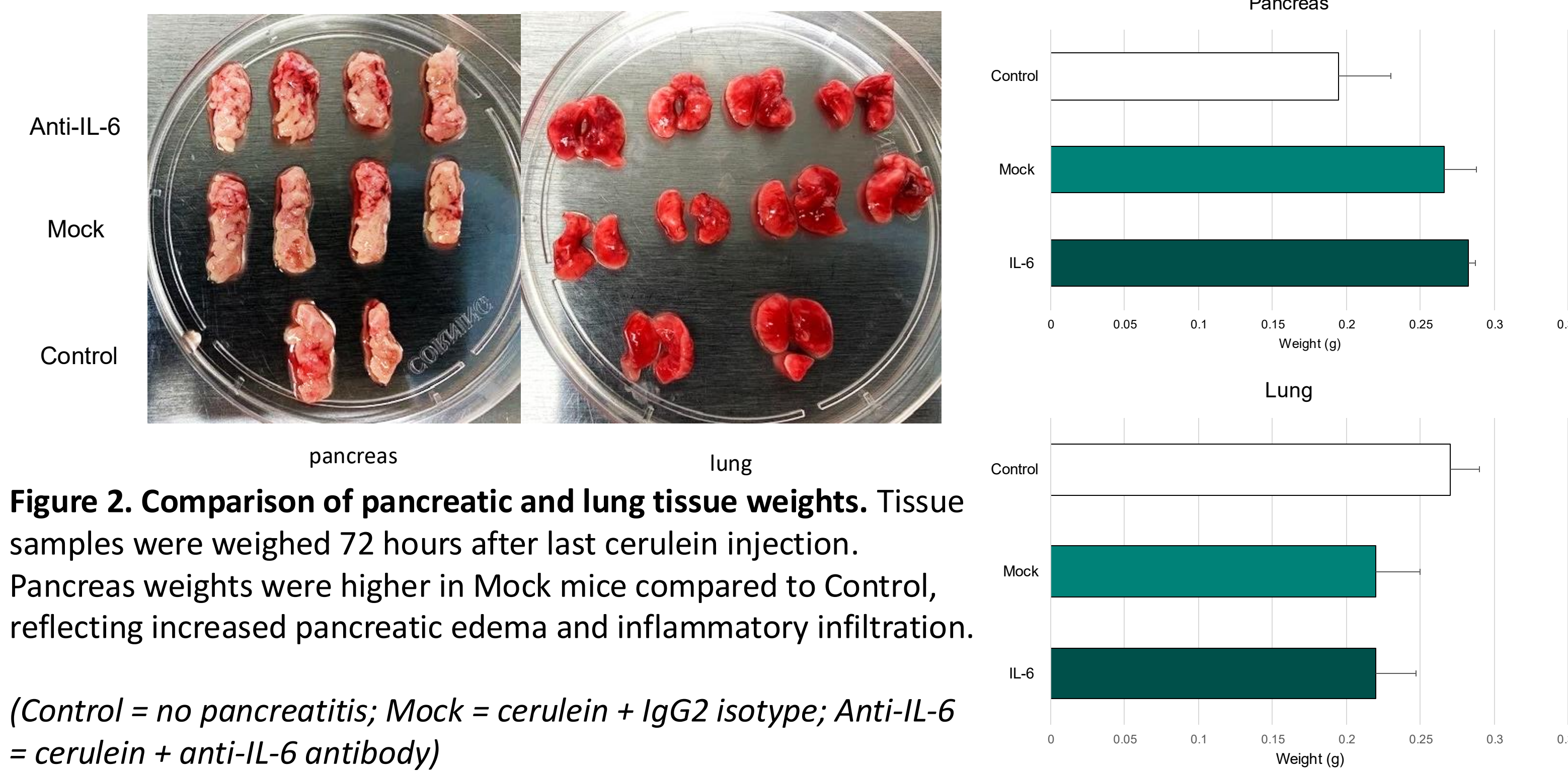


Figure 2. Comparison of pancreatic and lung tissue weights. Tissue samples were weighed 72 hours after last cerulein injection. Pancreas weights were higher in Mock mice compared to Control, reflecting increased pancreatic edema and inflammatory infiltration.

(Control = no pancreatitis; Mock = cerulein + IgG2 isotype; Anti-IL-6 = cerulein + anti-IL-6 antibody)

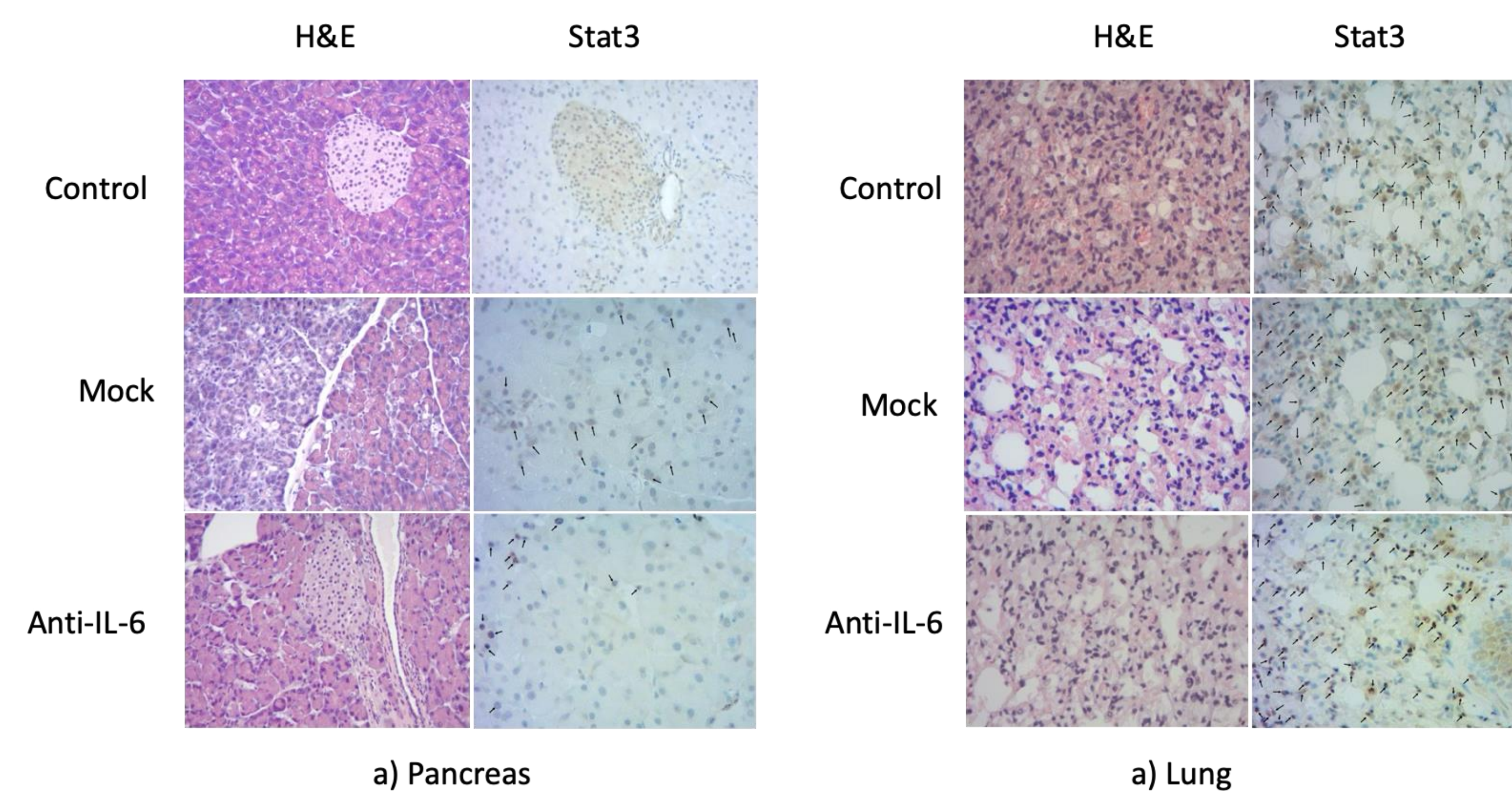
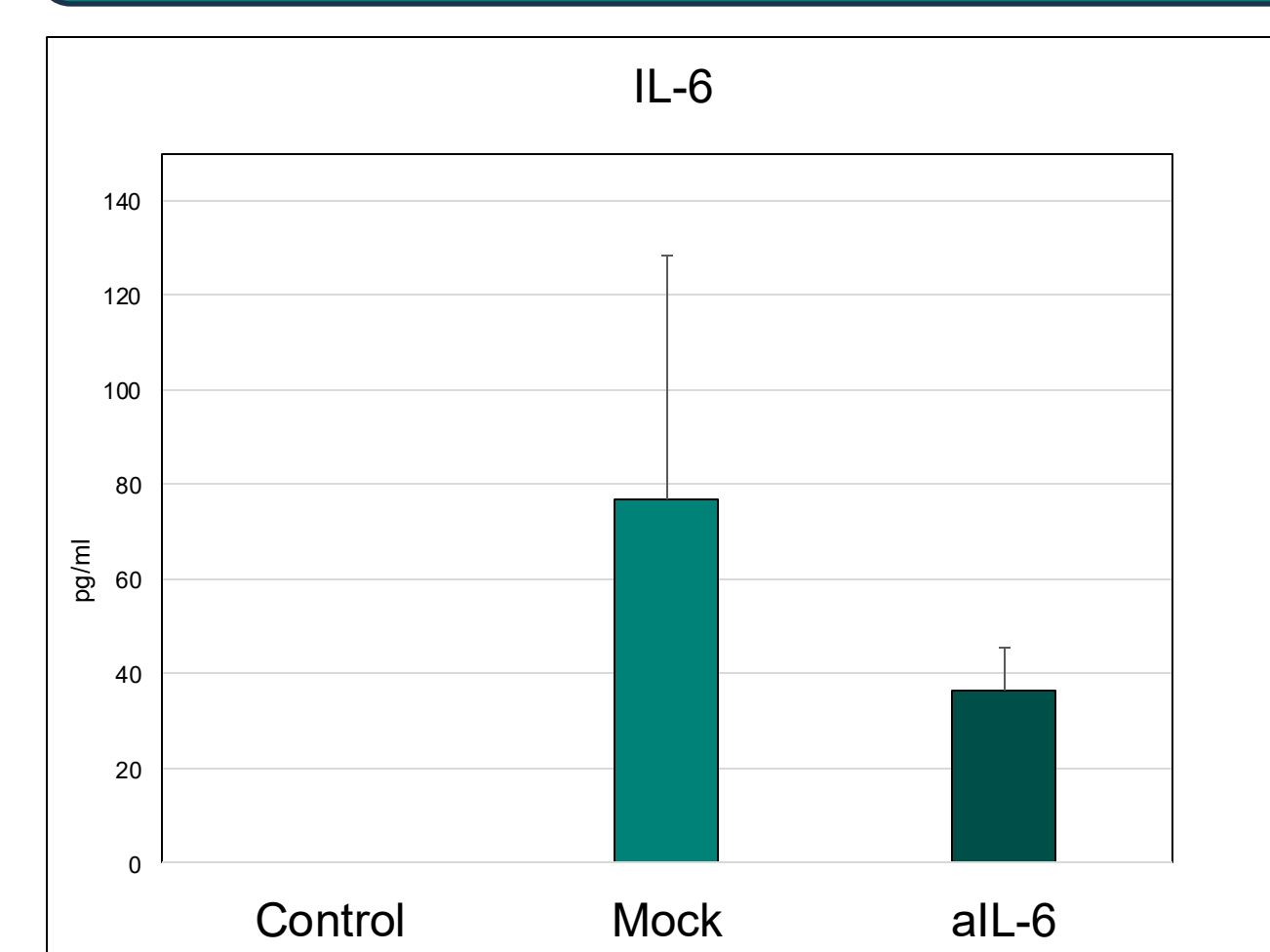


Figure 3. Histopathological examination of pancreas and lung tissue in mice with cerulein-induced pancreatitis. Pancreatic and lung tissue were obtained after 72 hours of last cerulein injection. Slides were stained with H&E and Stat3, a downstream mediator of the IL-6 pathway. Mice with pancreatitis showed histomorphological features of acute pancreatitis, including inflammation and interlobular edema compared to control mice. Stat3 expression in acinar cells was also increased in the Mock and Anti-IL6 groups relative to controls.

Serum IL-6 Levels Differ Across Control, Mock, and Anti-IL-6 Treated Mice



➤ Figure 4. Serum IL-6 concentrations. Serum IL-6 concentrations differed significantly across groups (one-way ANOVA, $F(2,23) = 10.84$, $p = 0.00044$). IL-6 was highest in Mock mice, reduced in Anti-IL-6 mice, and lowest in Control mice. All pairwise comparisons were significant ($p < 0.05$). (80.99 ± 12.9 pg/mL for Mock vs 36.64 ± 2.61 pg/mL for aIL-6 vs 1.195 pg/mL for Control)

Results

Cerulein Induces an Inflammatory Cytokine Profile in Mice

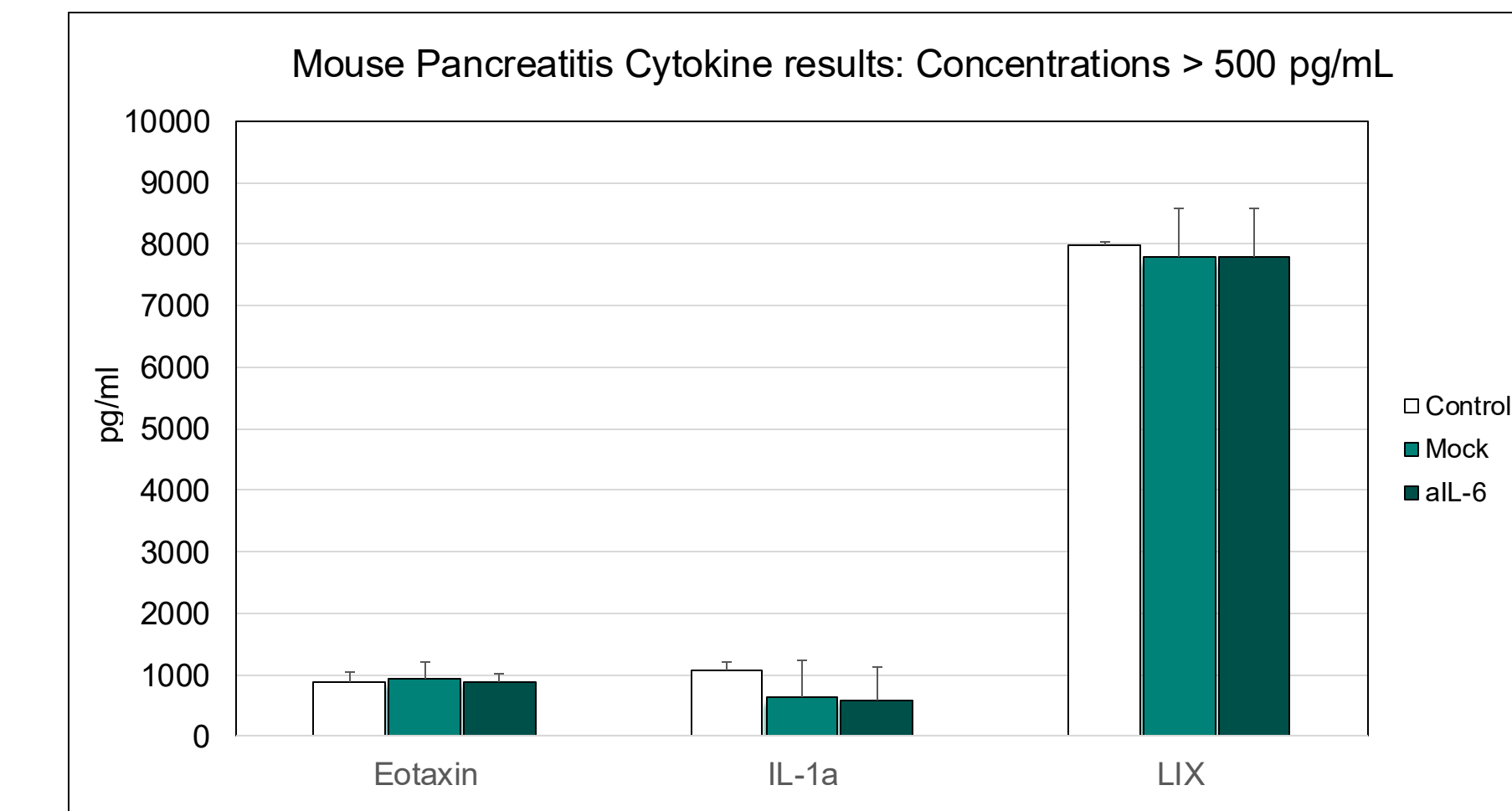
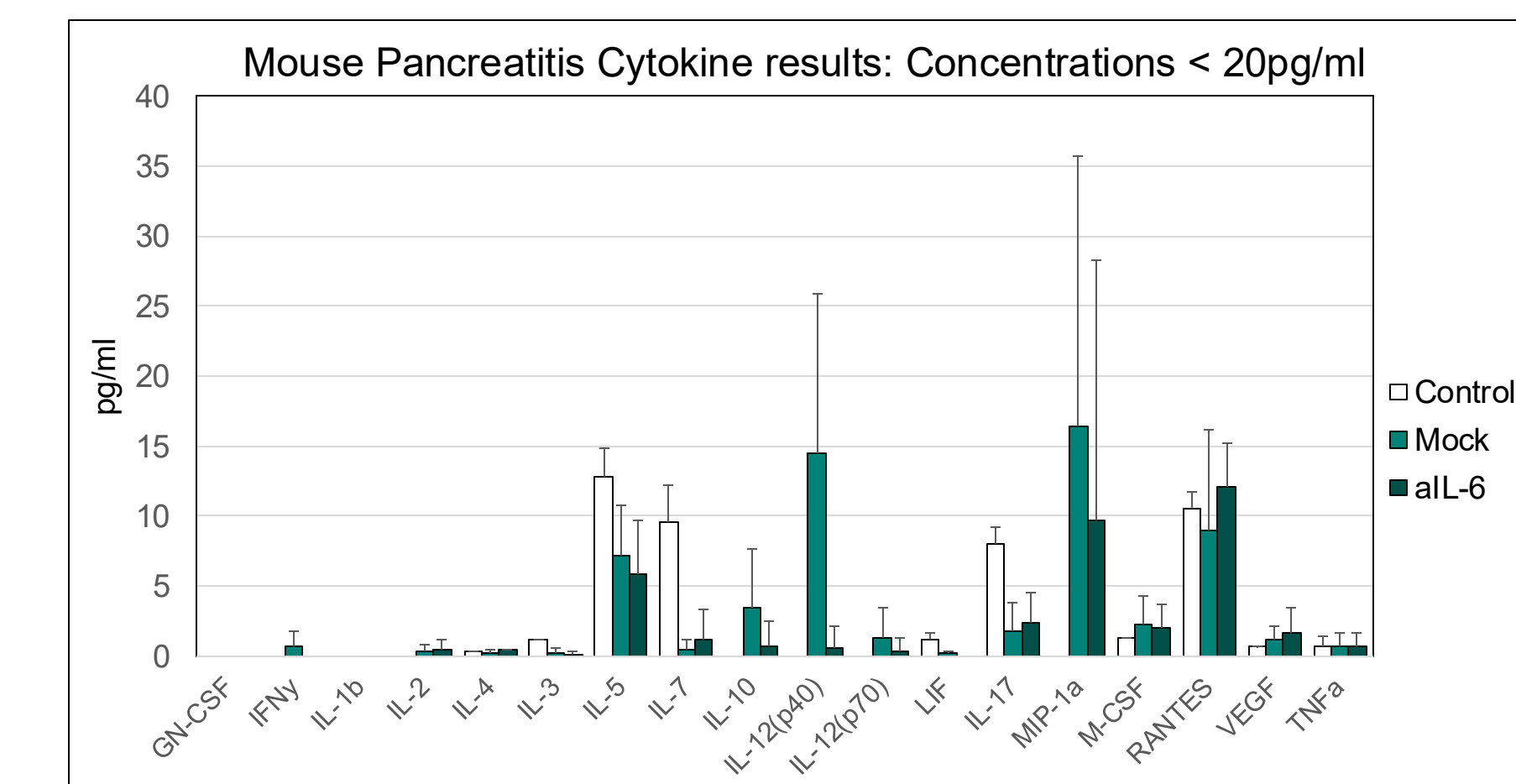
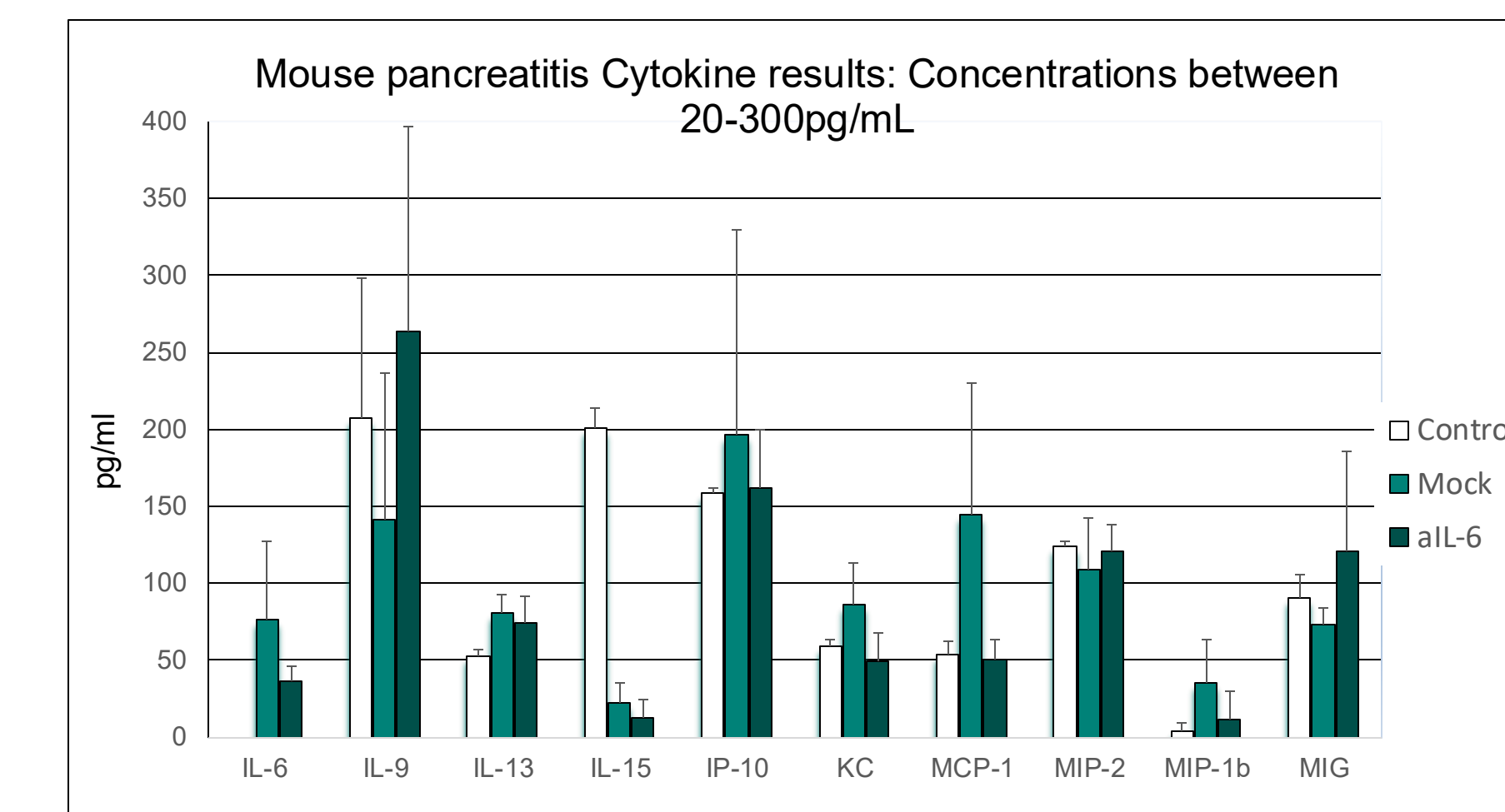


Figure 5. Serum cytokine levels measured by Luminex assay 72 hours after the final cerulein injection.

➤ Mock mice showed higher levels of inflammatory mediators including IL-6, IL-10, KC, MCP-1, MIP-1b, M-CSF, and IL-12 compared to controls.

➤ IL-6 inhibition effectively reduced IL-6 in addition to other inflammatory mediators including IL-10, IL-12, KC, MIP-1b, MCP-1 compared to Mock group.

Conclusion

- We generated a cerulein-induced mouse model of acute pancreatitis.
- Cerulein-injected mice showed pancreatic injury and cytokine changes consistent with prior AP studies.
- IL-6 inhibition in mice effectively reduced serum IL-6 compared to control and mock mice.

Next Steps

- Future work involves repeating the experiment with additional necropsy timepoints (e.g., 6, 24, 48, and 72 hours) and expand cytokine profiling (Luminex) across timepoints.
- Detailed pathology review of IHC to better quantify edema and inflammatory infiltration caused by AP between Control, Mock, and IL-6 groups.
- Quantify histology injury and correlate with cytokine profiles across timepoints.