Host-directed, injury agnostic microvascular repair to prevent and treat secondary acute lung injury

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Disclaimers

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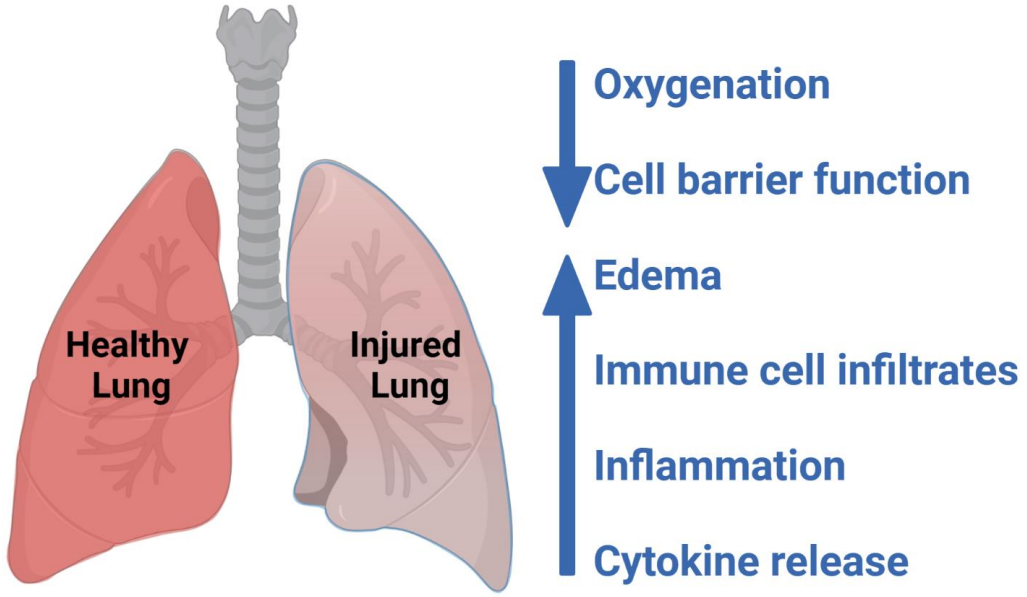
Acute lung injury (ALI) & acute respiratory distress syndrome present unique challenges in the military



Combat Trauma & Battlefield Injuries

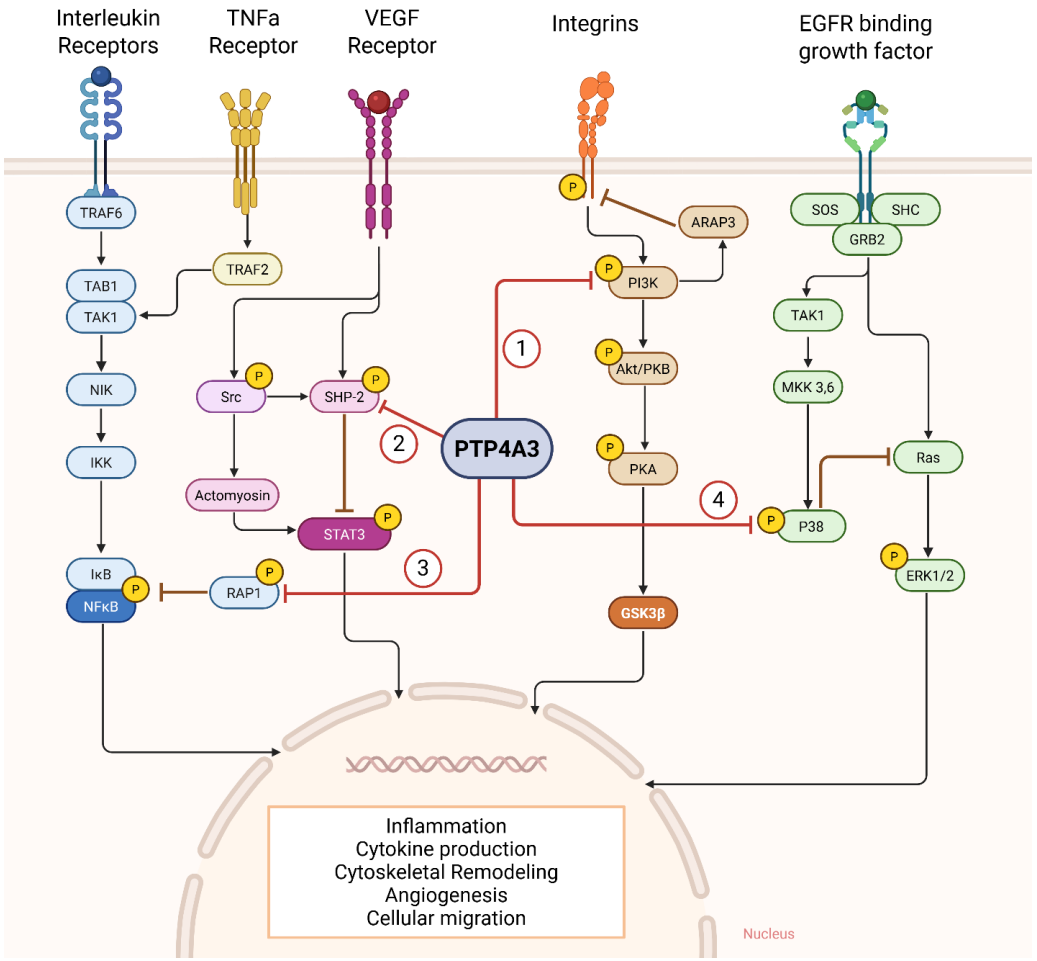
- Blast injuries, blunt/penetrating chest trauma, hemorrhagic shock
- Multi-trigger & convergent (i.e., complex)
- Central node of multi-organ failure
- Environmental exposures
- Austere environments
- Direct impact: readiness, survivability, return-to-duty

Problems with Current Treatments

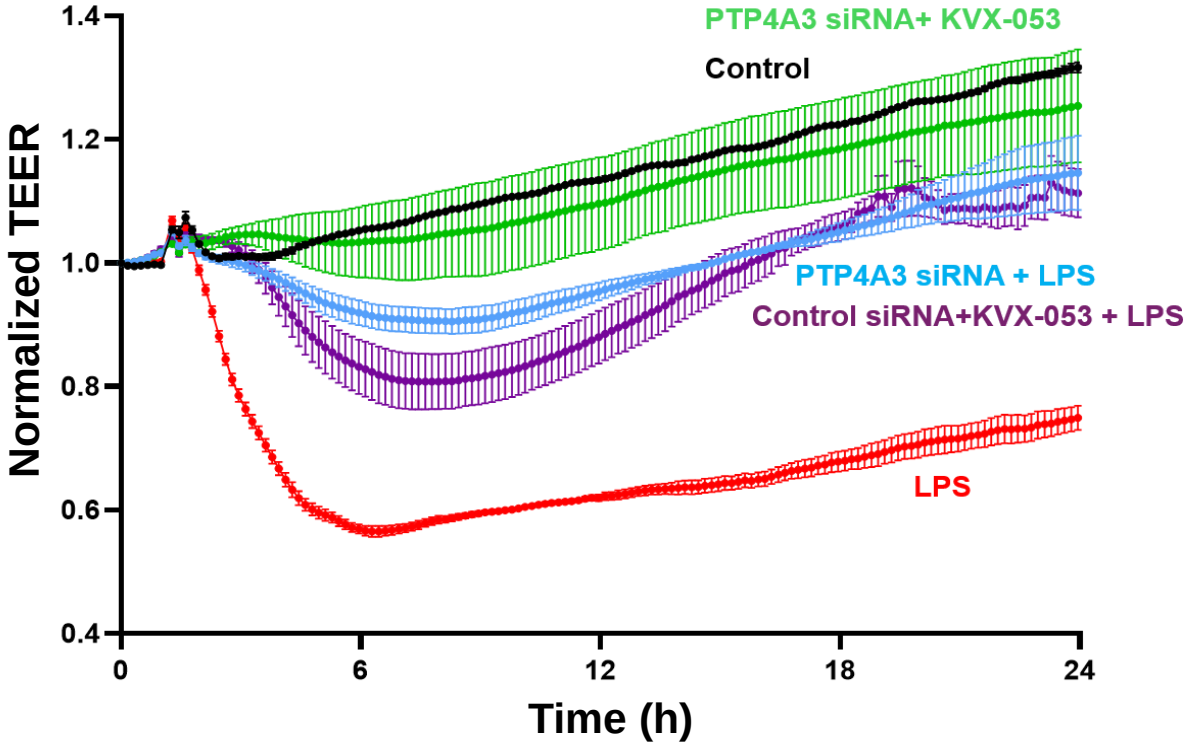
- Steroids are often ineffective
- Mechanical ventilation is damaging

No FDA-approved interventional drugs

KVX-053 restores endothelial barrier function by blocking injury-induced PTP4A3 signaling



KVX-053 & PTP4A3-targeted siRNA reverse LPS-induced endothelial barrier dysfunction

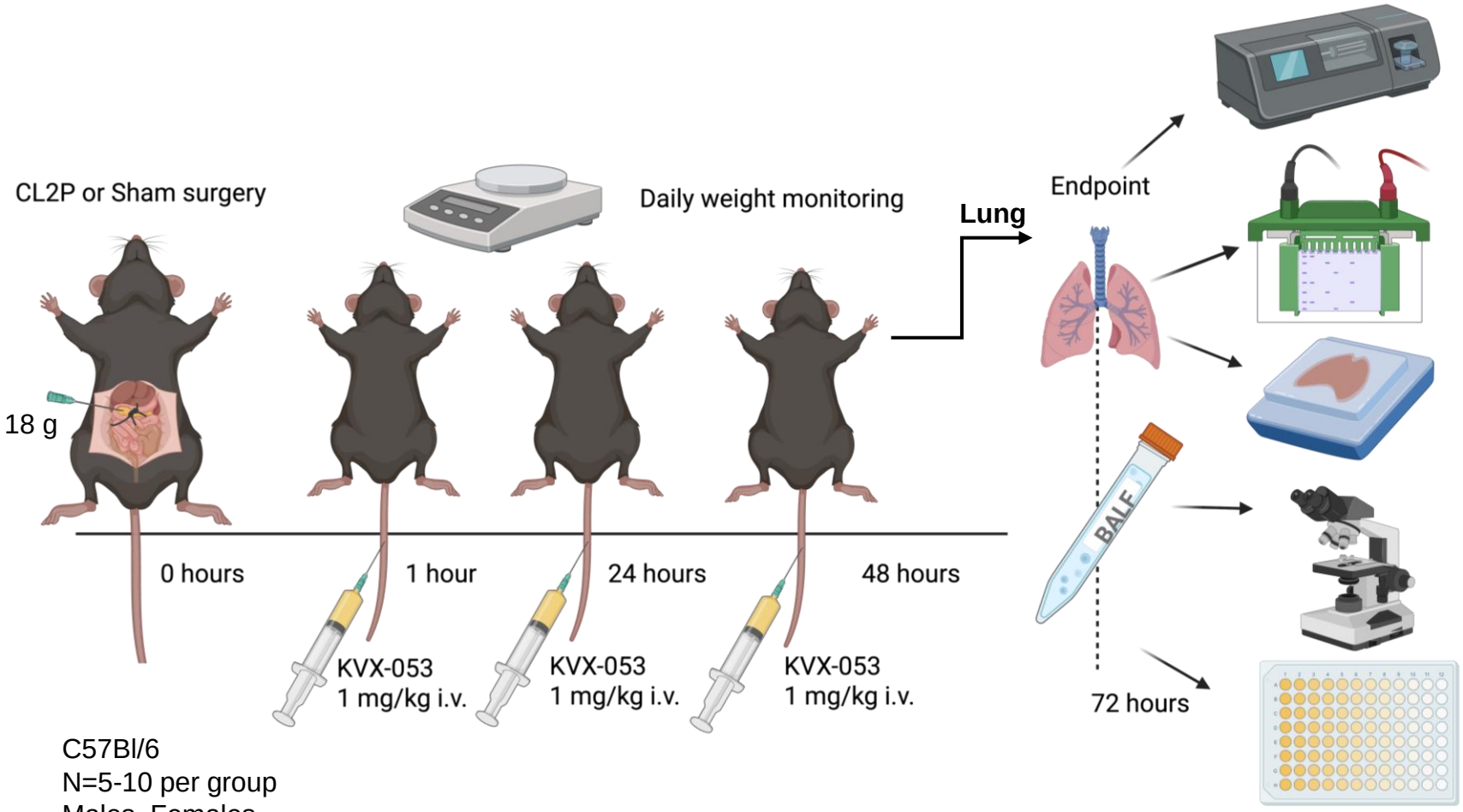


HLMVEC
KVX-053, 500 nM
siRNA, 10 nM, 72 h pretreatment
LPS concentration, 500 ng/mL
TEER, transendothelial electrical resistance

KVX-053 effects are host-directed & agnostic to ALI triggers in preclinical studies

Lung injury model	Injury classification	Administration route	Key KVX-053 effects
Sepsis-CL2P	**Secondary**	**Intravenous**	▲**Lung function** ▼**Lung injury indicators** ▼**Biomarkers of lung injury in bronchial alveolar lavage fluid** ▼**Inflammatory signaling & inflammation**
Sepsis-LPS	Secondary	Intraperitoneal	
Aspiration	Primary	Intravenous	
Chemical (CEES)	Primary	Intravenous	
Live virus	Primary	Intraperitoneal	
Viral protein	Primary	Intraperitoneal	
Ventilator	Primary	Intravenous	

Murine cecal ligation two puncture study design and methods



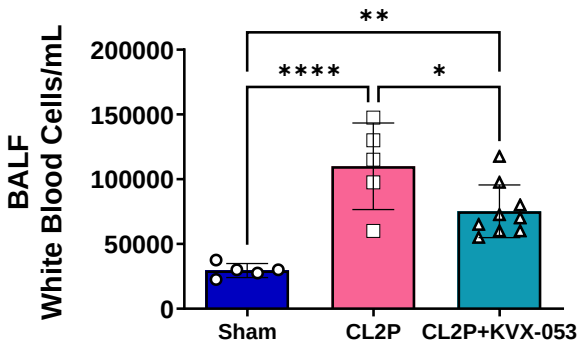
C57Bl/6
N=5-10 per group
Males, Females

Endpoints

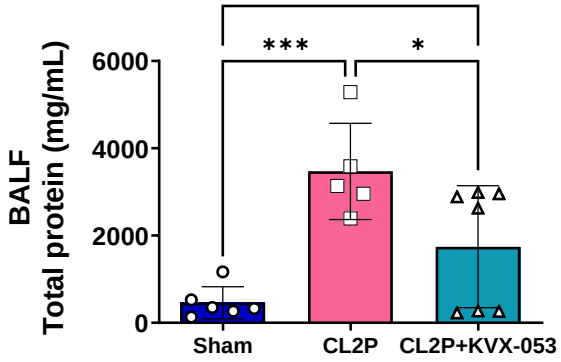
- Lung function
  PV loops, elastance, resistance, compliance
- Inflammatory markers
  STAT3
- Lung injury scores
- Inflammatory cytokine/chemokine expression
- Immune cell infiltration into the lung
- Protein (i.e., capillary leak, edema)

KVX-053 treatment reduces inflammation, vascular leak, and lung injury

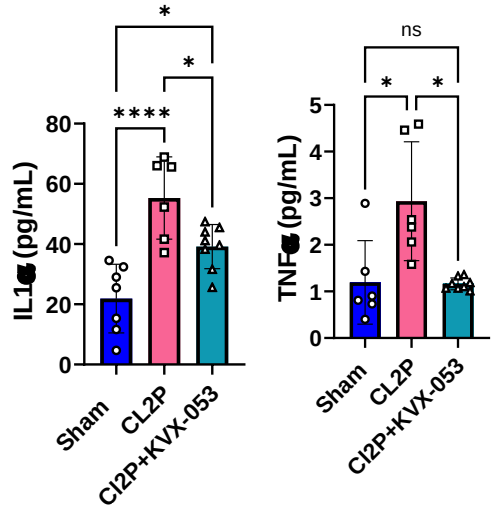
White blood cell infiltration
(inflammatory injury, immune cell trafficking)

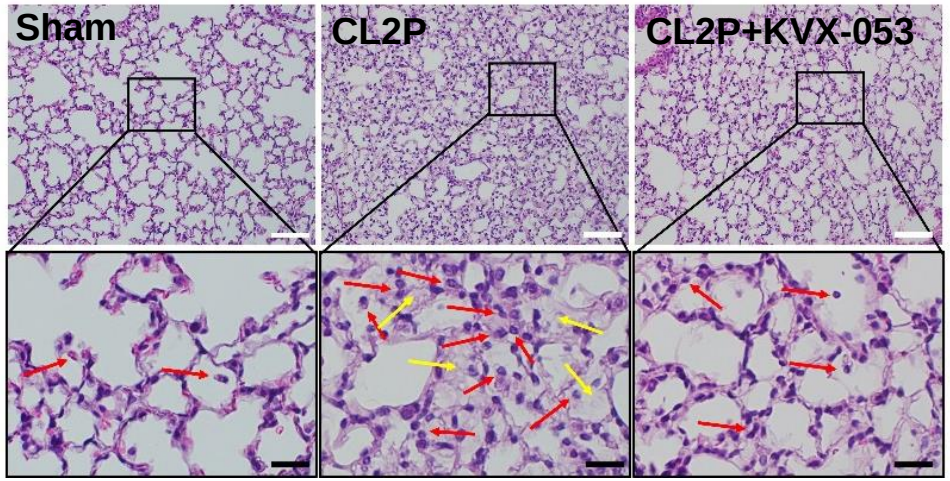


Total protein
(microvascular leak)



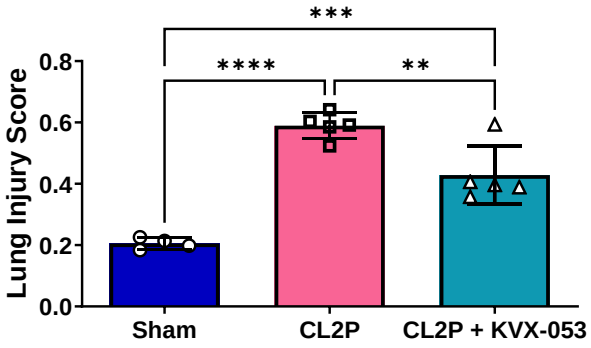
Proinflammatory cytokines
(endothelial damage)



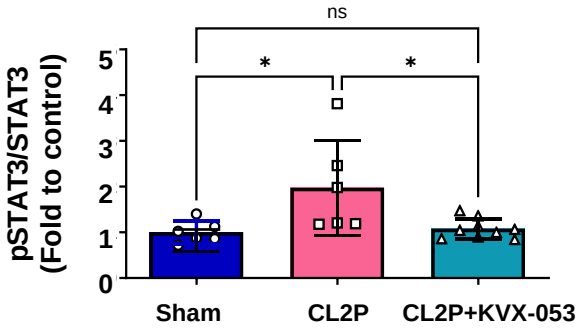


red arrow, neutrophil; yellow arrow, edema

Lung injury score

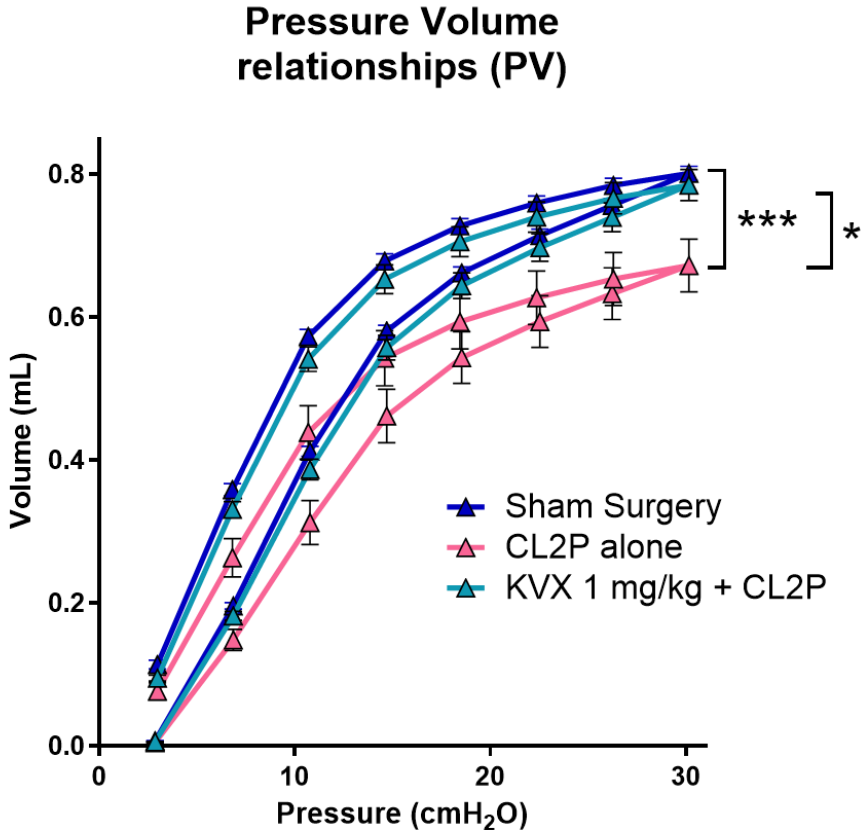


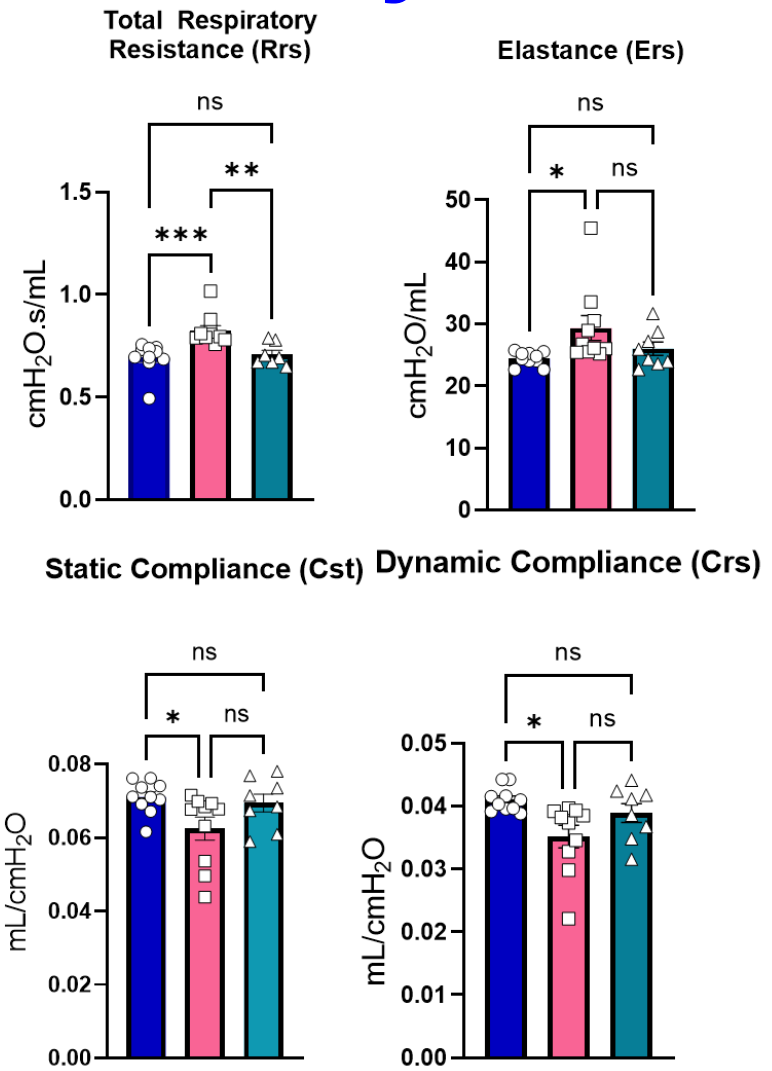
Cytokine-mediated injury biomarker



Male mice

KVX-053 treatment improves lung function in the CL2P sepsis-induced secondary ALI model

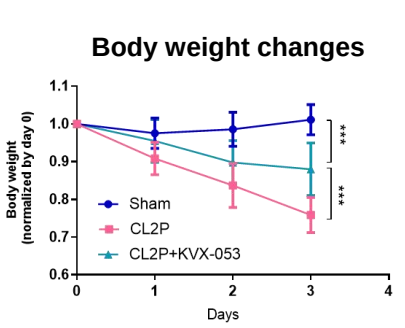


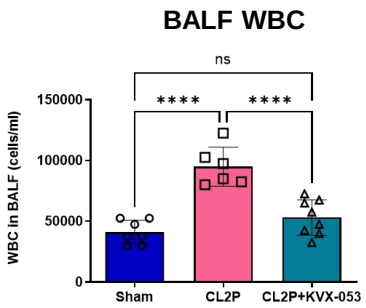


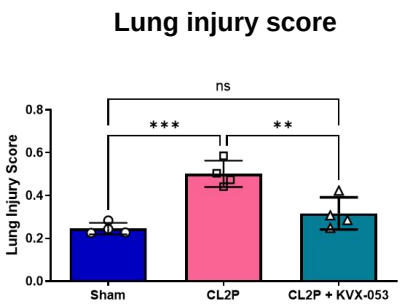
Male mice

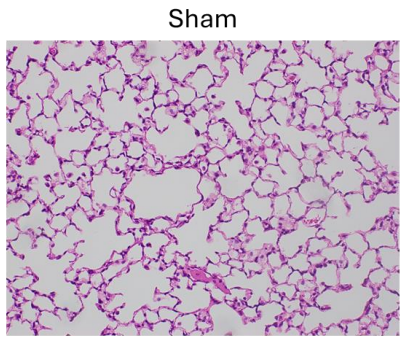
Sham **CL2P** **CL2P+KVX-053**

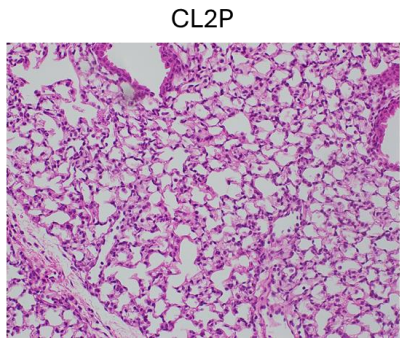
Female cohort supports KVX-053 efficacy in CL2P-induced secondary ALI

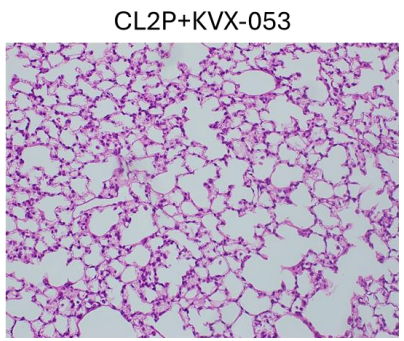


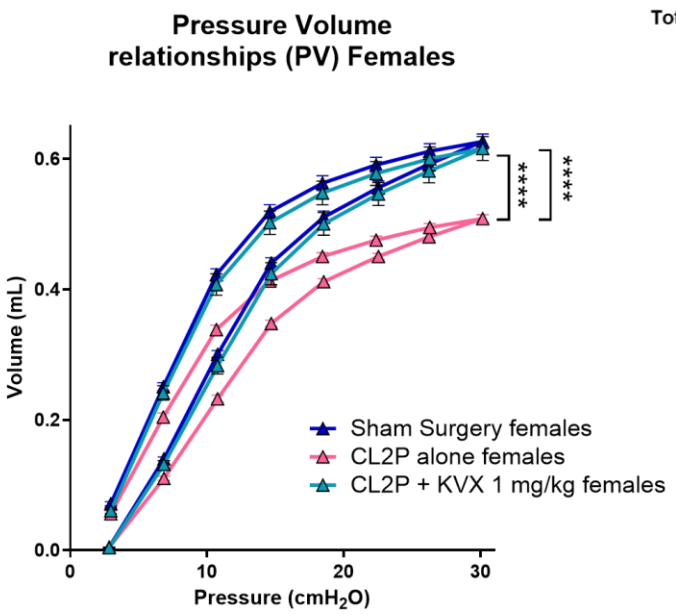


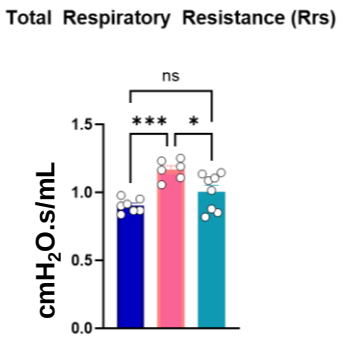


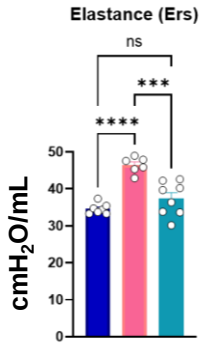


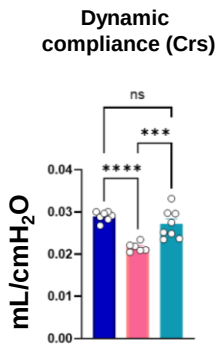


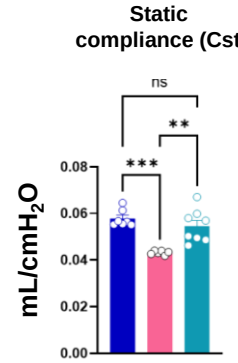








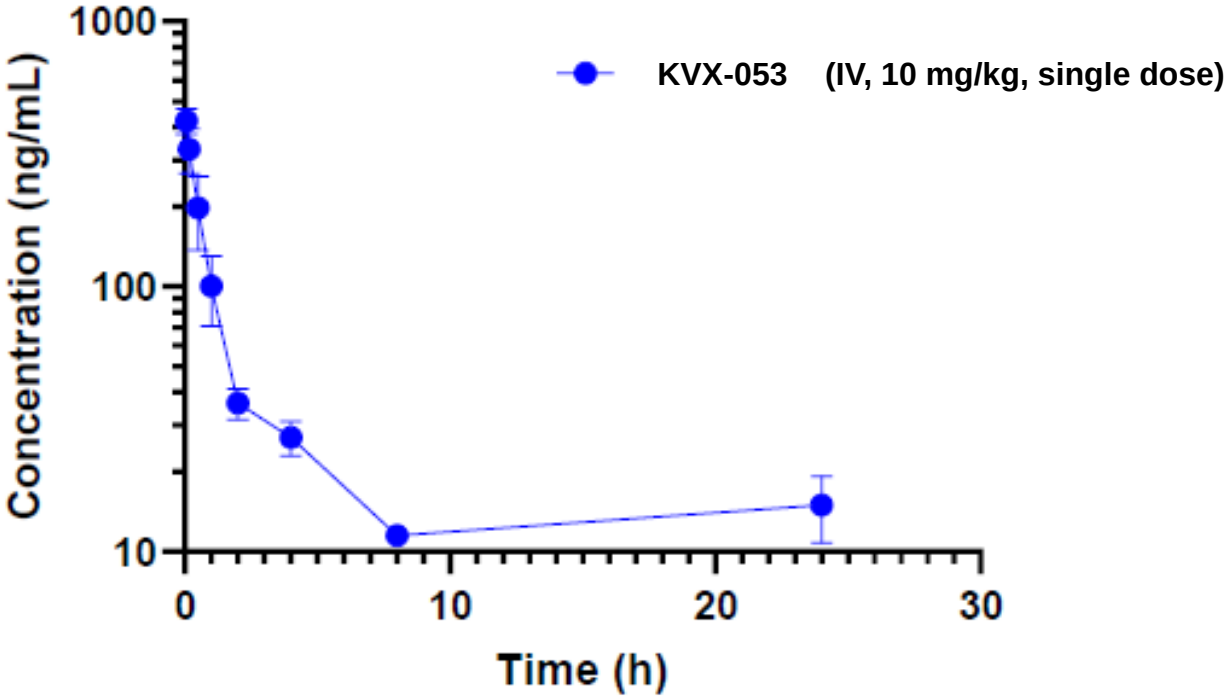




Female mice

Sham **CL2P** **CL2P+KVX-053**

Robust mouse PK & absence of toxicity in early rat studies



Exposure
AUC_{last}=735±235 h*ng/mL
C_{max}=447±70 ng/mL

Disposition
$T_{1/2}$=4.8±1.16 h
C_L=201.57±48.83 mL/min/kg
V_{ss}=83.24±35.21 L/kg

Early rat toxicology studies:

- Well tolerated at clinically relevant exposures with some irritation at injection site.
- No target-organ toxicity identified.
- Supports progression to GLP repeat-dose studies.

Key takeaways

(1) KVX-053 is a host-directed, ALI-agnostic therapeutic candidate.

(2) In the CLP2 sepsis model, a low-complexity model of secondary lung injury, KVX-053:

- Reduced lung injury, including immune cell infiltration and lower BALF protein.
- Reduced proinflammatory cytokine release
- Reduced expression of cytokines involved in immune-cell chemotaxis
- Improved lung function

(3) Early toxicology data supports good tolerability of KVX-053.

(4) Assessment in more complex lung injury models is planned.

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