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A Novel Sphingosine 1-Phosphate Analog Provides Protection from Lung Ischemia-Reperfusion Injury

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Current State of Lung Transplantation

- Lung transplantation remains only treatment for end-stage pulmonary disease.

- Limitations to advancement and success of lung transplantation remain.
  - Ischemia-reperfusion (IR) injury
  - Acute and chronic graft dysfunction

- Early mechanisms of IR injury are defined.
  - Pneumocyte apoptosis
  - Alveolar macrophage recruitment
  - T-cell activation
  - Neutrophil infiltration

Sphingosine-targeted therapy

Sphingosine → *Sphingosine Kinase* → **Sphingosine 1-Phosphate (S1P)**

Sphingosine ↓ **Apoptosis**

Sphingosine 1-Phosphate (S1P) ↓ **S1P Receptors (S1PR 1-5)** ↓ **Cell Growth and Survival *and* Inhibition of Lymphocyte Egress**

Sphingosine and IR Injury

- S1P administration increases oxygenation capacity and decreases pro-inflammatory cytokine production, endothelial cell apoptosis, and neutrophil numbers following lung transplantation.

  Okazaki et al. *Am J Transplant* 2007; 7.

- Early administration of FTY 720 (S1PR 1,3-5 agonist) decreases vascular sclerosis and bronchiolitis obliterans in a rat transplantation model.

  Hirt et al. *Transplant Proc* 2013; 45(2).

Central to both treatment strategies is S1PR 3 agonism.

S1P Receptor Subtypes

✔

S1PR 1

- Endothelial barrier stabilization
- Upregulation of ICAM-1
- Target for inhibition of lymphocyte egress

✖

S1PR 3

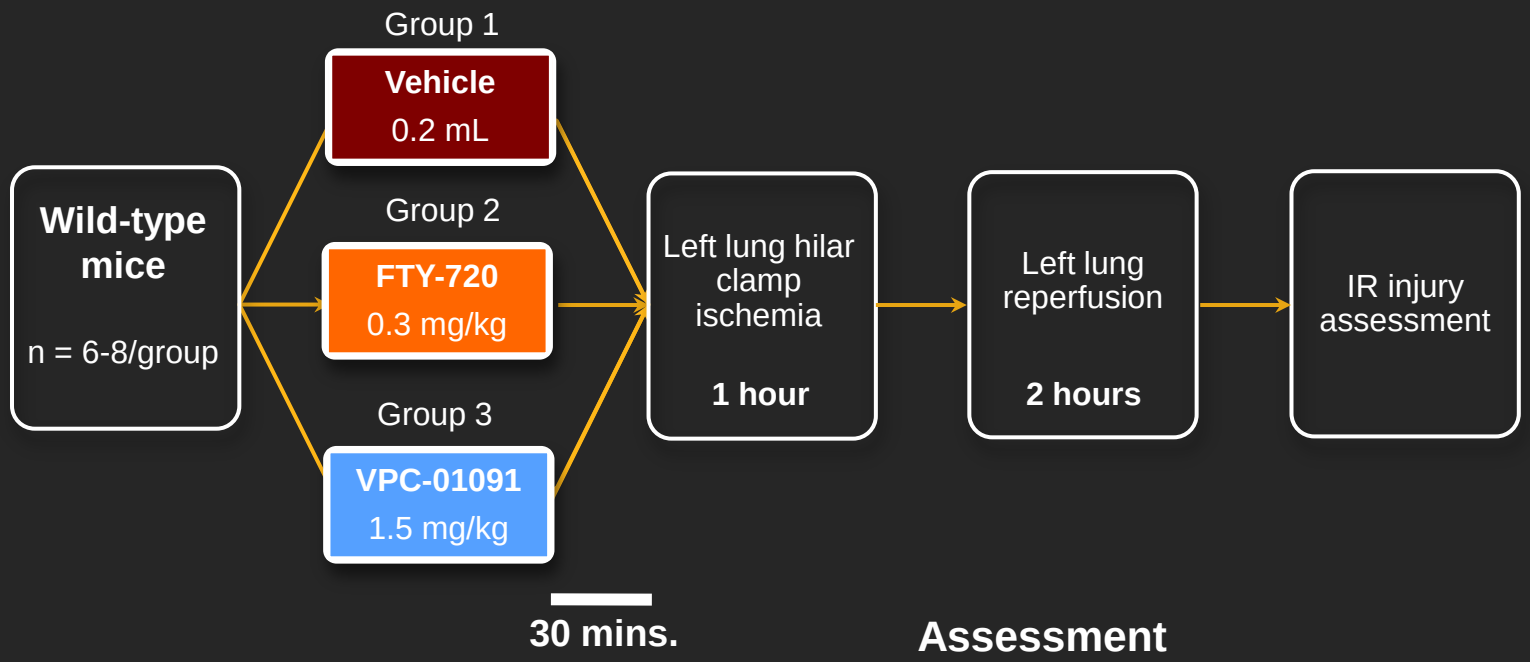
- Decreased endothelial integrity
- Airway hyper-reactivity
- Pulmonary fibrosis
- Coronary artery vasoconstriction

Purpose

- To test a pharmacologic agent (VPC-01091) that acts as an agonist at S1PR 1 and antagonist at S1PR 3.
    - Promote S1PR 1 and inhibit S1PR 3 activity prior to IR injury.

- Evaluate the hypothesis that VPC-01091 provides protection from acute lung IR injury.

Methods



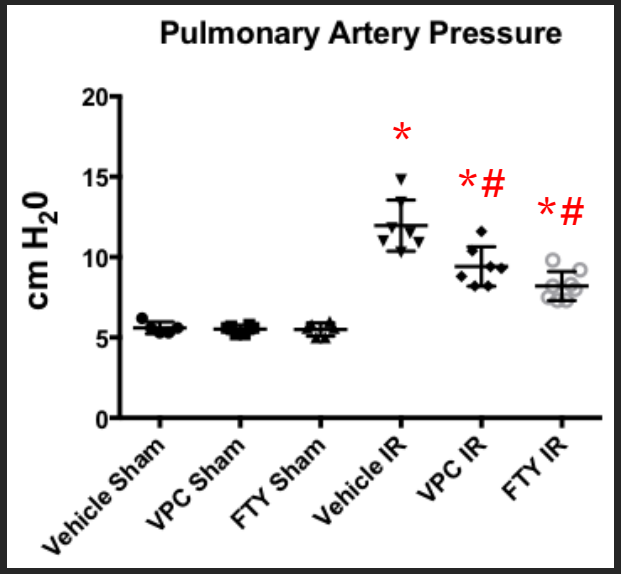
Vehicle: 3% fatty-acid free BSA/PBS

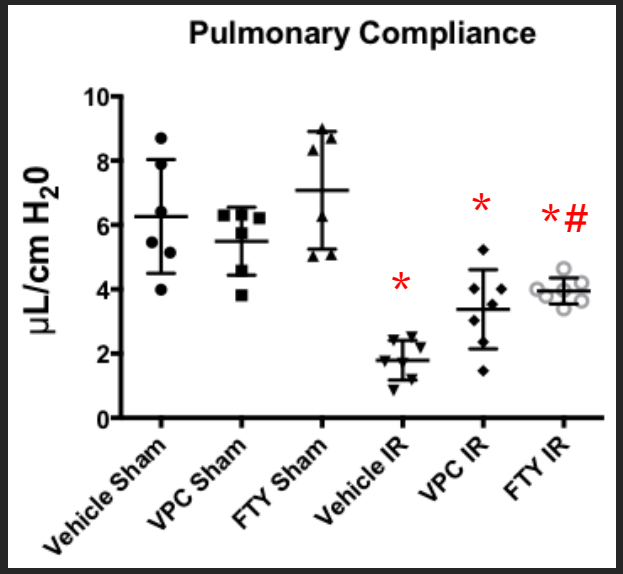
Assessment

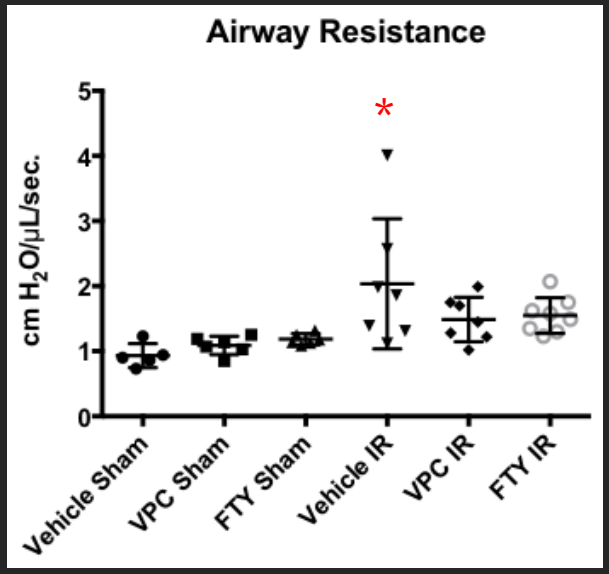
- PULMODYN™ function analysis
- Bronchoalveolar lavage
- Whole lung tissue preservation

- Statistical analyses performed by one-way ANOVA with post-hoc Tukey's multiple comparison correction.

VPC-01091 and FTY-720 afford functional protection from lung IR injury.

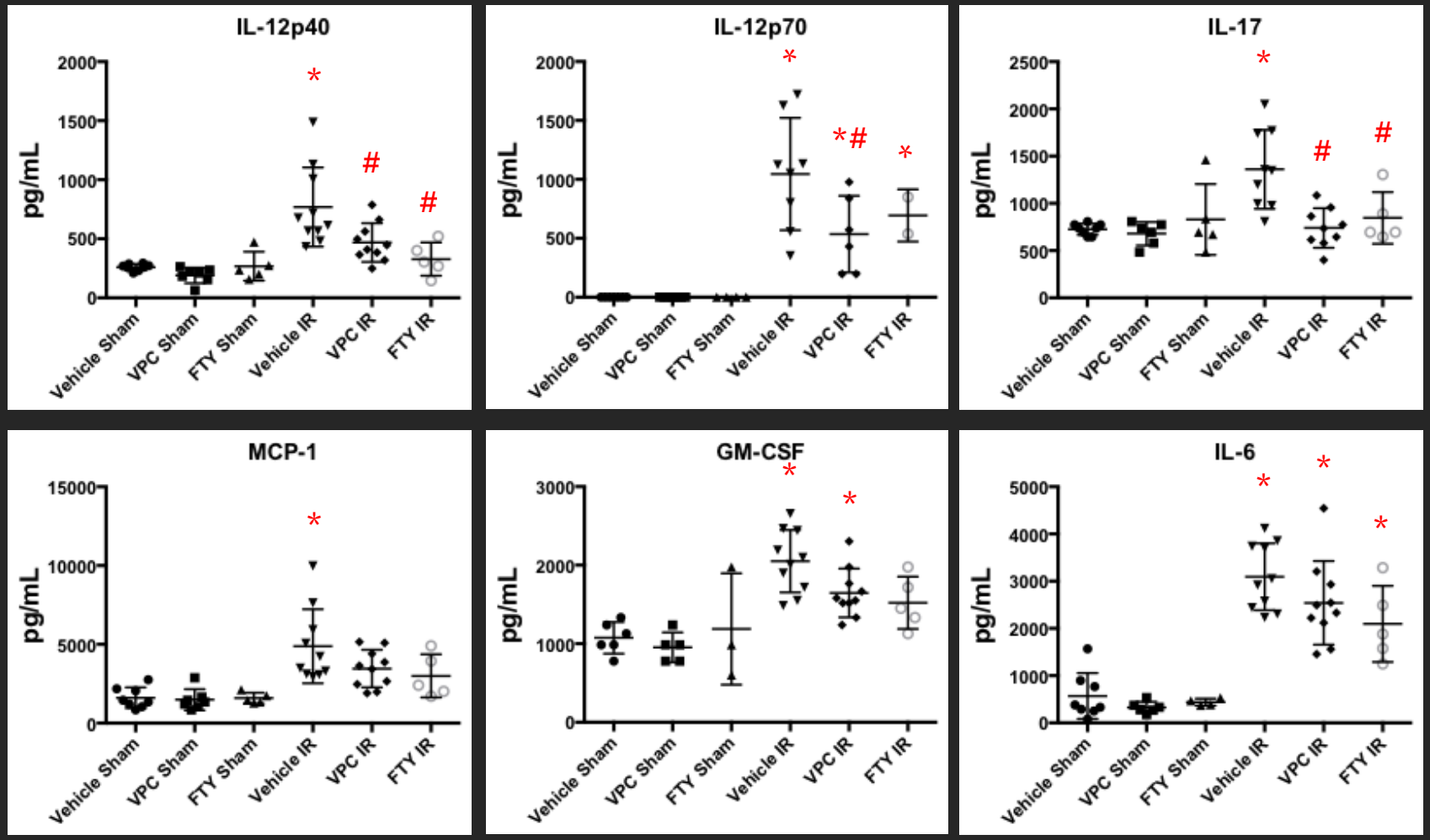






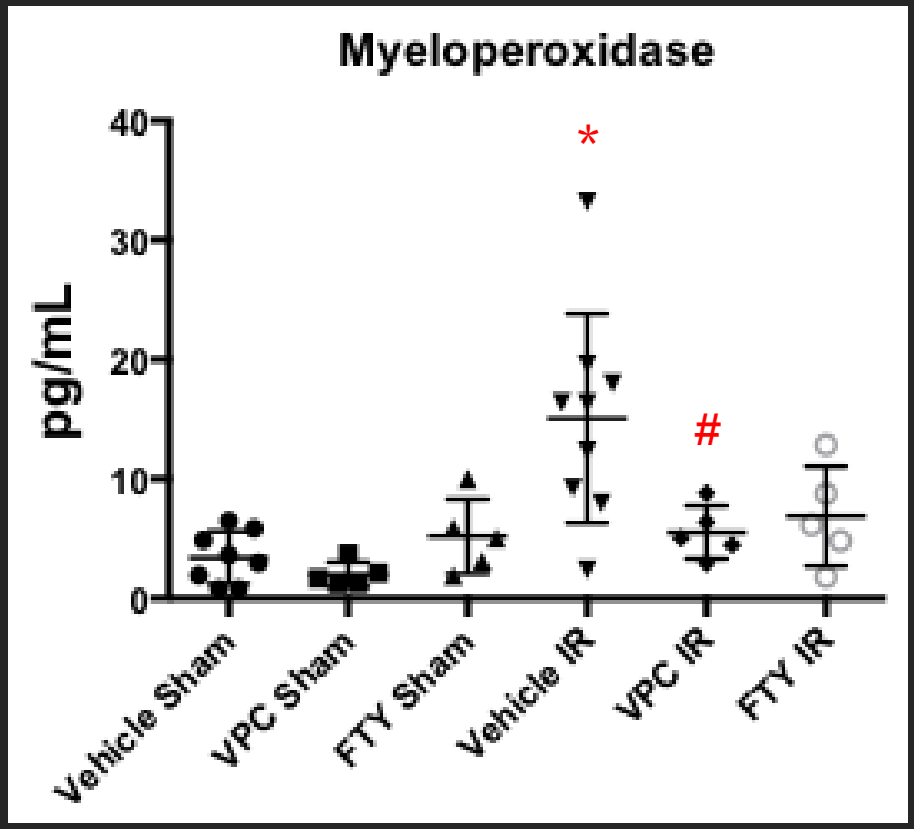
*: $p<0.05$ vs. Vehicle Sham; #: $p<0.05$ vs. Vehicle IR.

VPC-01091 and FTY-720 decrease pro-inflammatory cytokine production following lung IR injury.



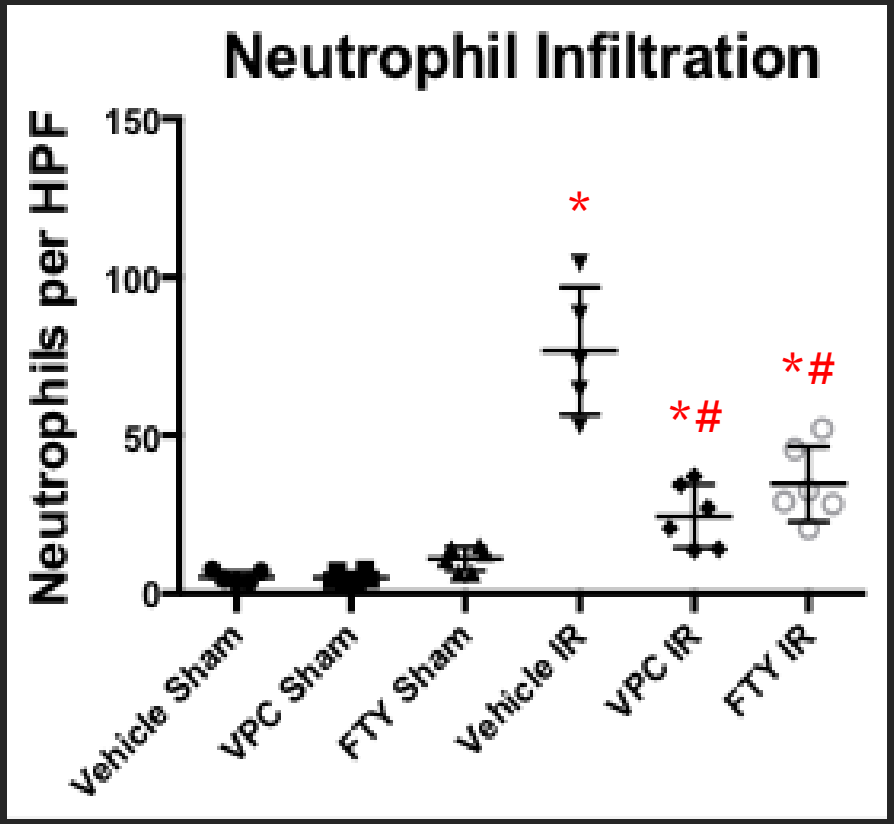
*: $p<0.05$ vs. Vehicle Sham; #: $p<0.05$ vs. Vehicle IR.

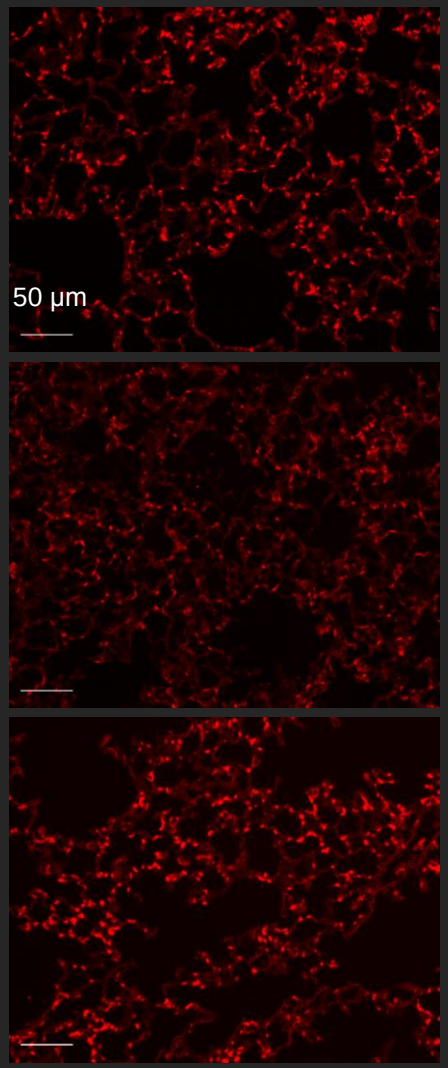
VPC-01091 results in significantly decreased myeloperoxidase concentration following lung IR injury.



*: $p<0.05$ vs. Vehicle Sham; #: $p<0.05$ vs. Vehicle IR.

Neutrophil infiltration is significantly decreased following lung IR injury with VPC-01091 and FTY-720.





Vehicle IR

VPC IR

FTY IR

*: $p<0.05$ vs. Vehicle Sham; #: $p<0.05$ vs. Vehicle IR.

Conclusions

- Pharmacologic S1P analogs provide a promising strategy for lung IR injury prevention.

- VPC-01091 provides comparable protection to FTY-720 in a murine IR model offering S1PR 3 antagonism.

- This strategy demonstrates that S1P-mediated protection is independent of S1PR 3 receptor.

- S1PR 3 antagonism may provide a more effective approach to S1P-directed therapy to avoid established S1PR 3-mediated lung injury.

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