An Aerosolized Connexin43 Mimetic Peptide (aCT1) Improves Clinical Metrics in Animal Models of Acute Lung Injury

Meghan A. Bowler, PhD, Carissa C. James, PhD, Lauren A. Jeffers, PhD, Yasmin K. Ibrahim, PhD, Michael Koval, PhD, and Christina L. Grek, PhD

July 18th, 2022 – Morning Plenary Session of IGJC

Disclosures

- ***Employment***
  - Dr. Meghan Bowler is currently a full-time employee of Xequel Bio
- ***Intellectual Property***
  - Xequel Bio holds >50 granted US and international patents that protect aCT1 technology's use
- ***Funding***
  - Work was partially funded by the National Institutes of Health
  - Work was partially funded by the Department of Defense
  - Work was partially funded by Xequel Bio

Overview

Company Snapshot

Introduction to aCT1 Technology

Efficacy in Acute Lung Injury Models

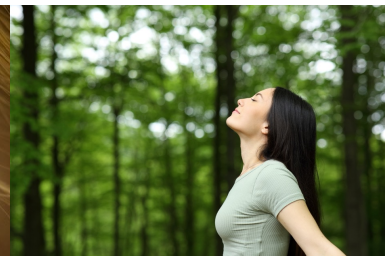
Translational Relevance and Feasibility

Company Snapshot

Etiology Agnostic Therapeutic

- Platform technology in **Dermatology**, **Ophthalmology**, and **Pulmonology**
- aCT1 peptide (**New Chemical Entity**) has been rigorously tested for safety and efficacy in preclinical and clinical studies
- Developed as a molecular tool to probe **gap junctions**





Jerry St. Peter, CEO

Wes Brazell, CFO

David Leffell, MD, CMA

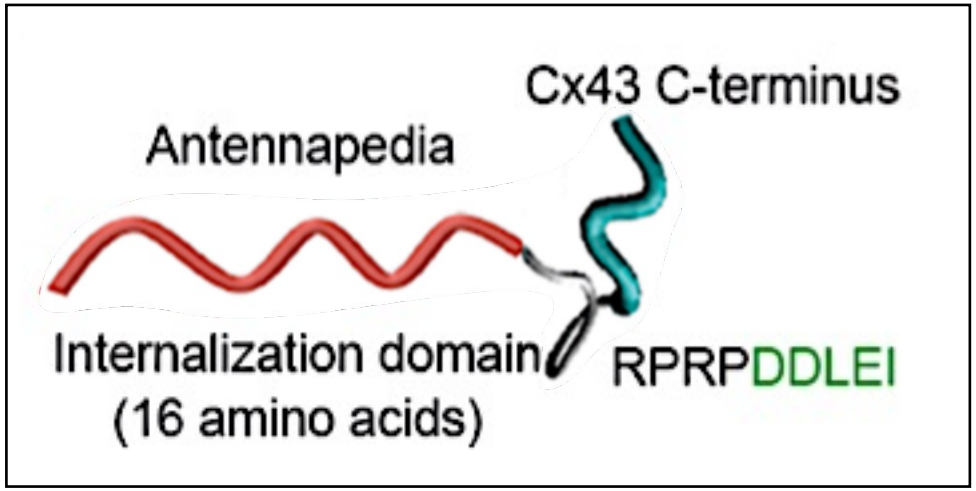
Christina Grek, PhD
Sr. Director of R&D

Carissa James, PhD
Director of R&D

Meghan Bowler, PhD
Translational Scientist

aCT1: Connexin43 Mimetic Peptide

aCT1 peptide



Rhett et al. 2008 Trends Biotech
Rhett et al. 2011 MBoC
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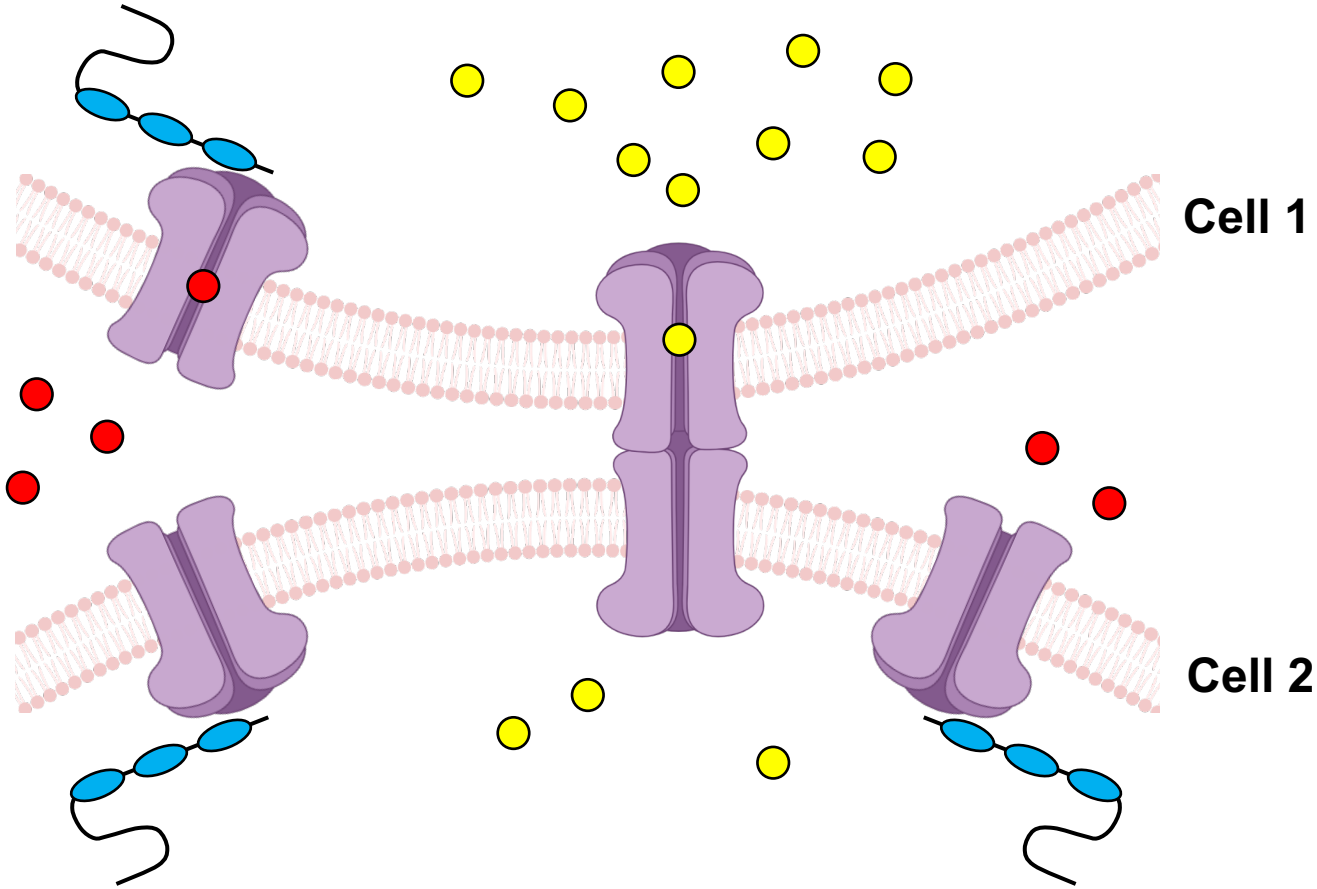
Montgomery et al. 2021 FASEB
Jiang et al. 2019 JAHA



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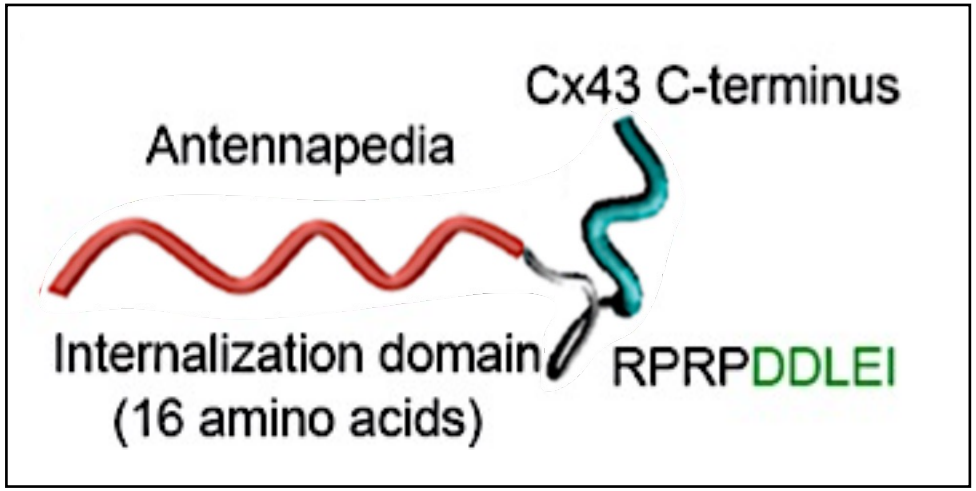
aCT1: Connexin43 Mimetic Peptide

aCT1 peptide



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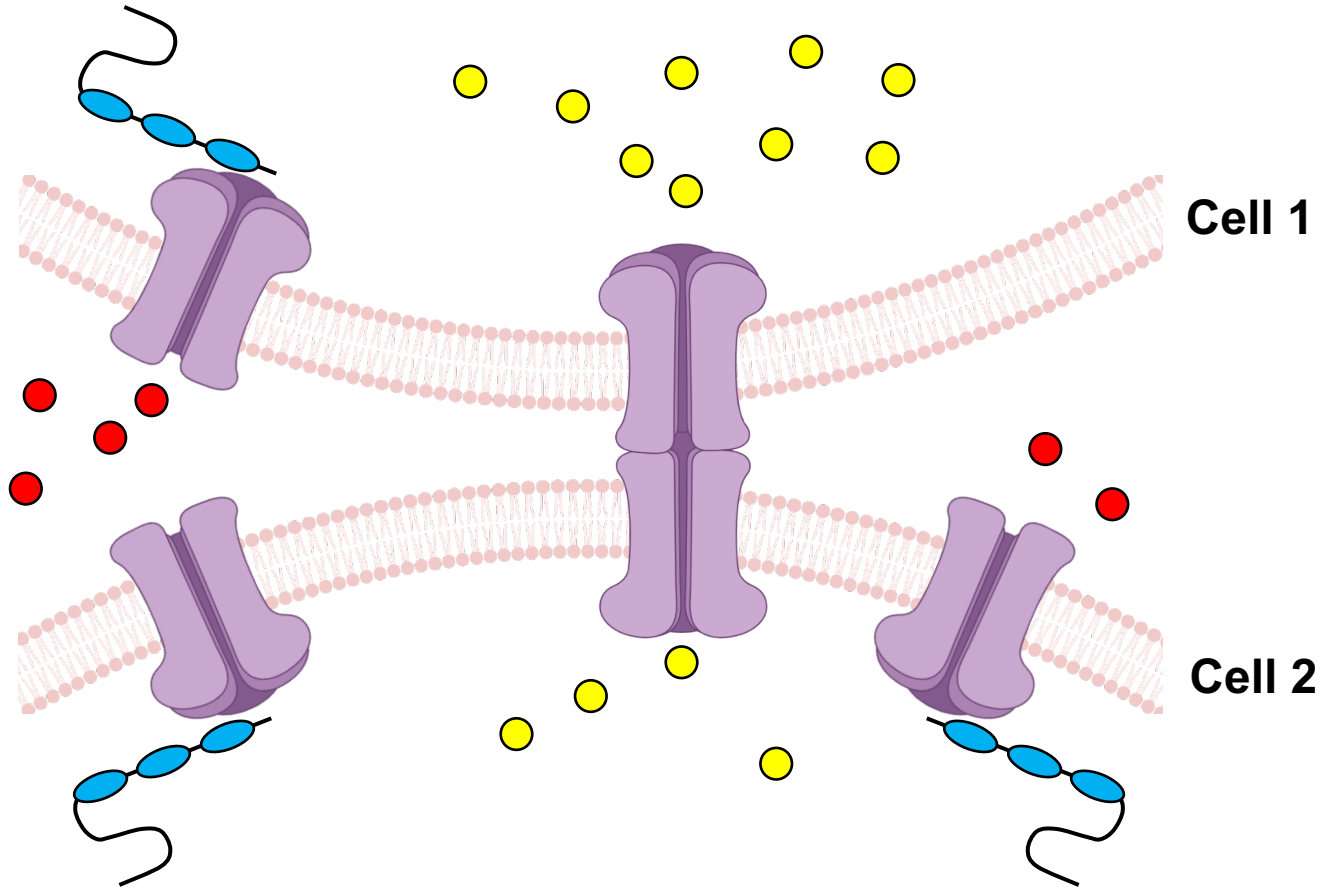

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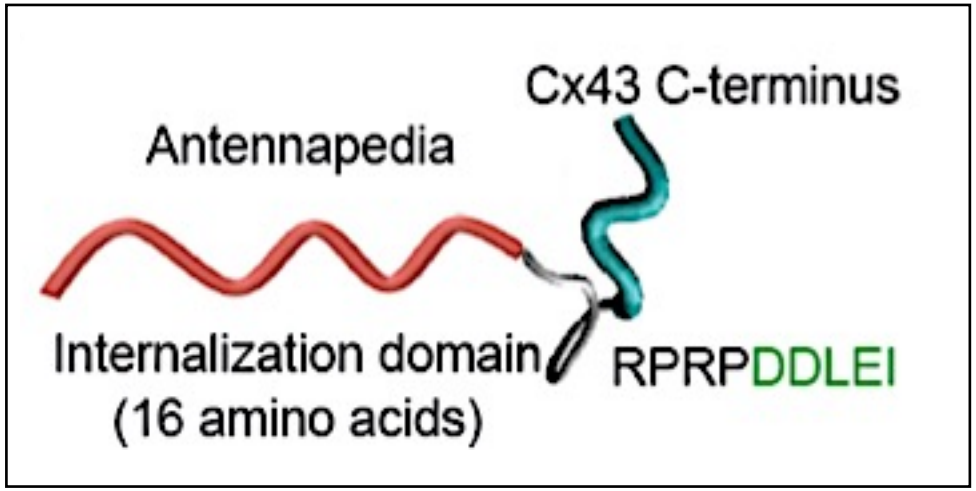
aCT1 peptide



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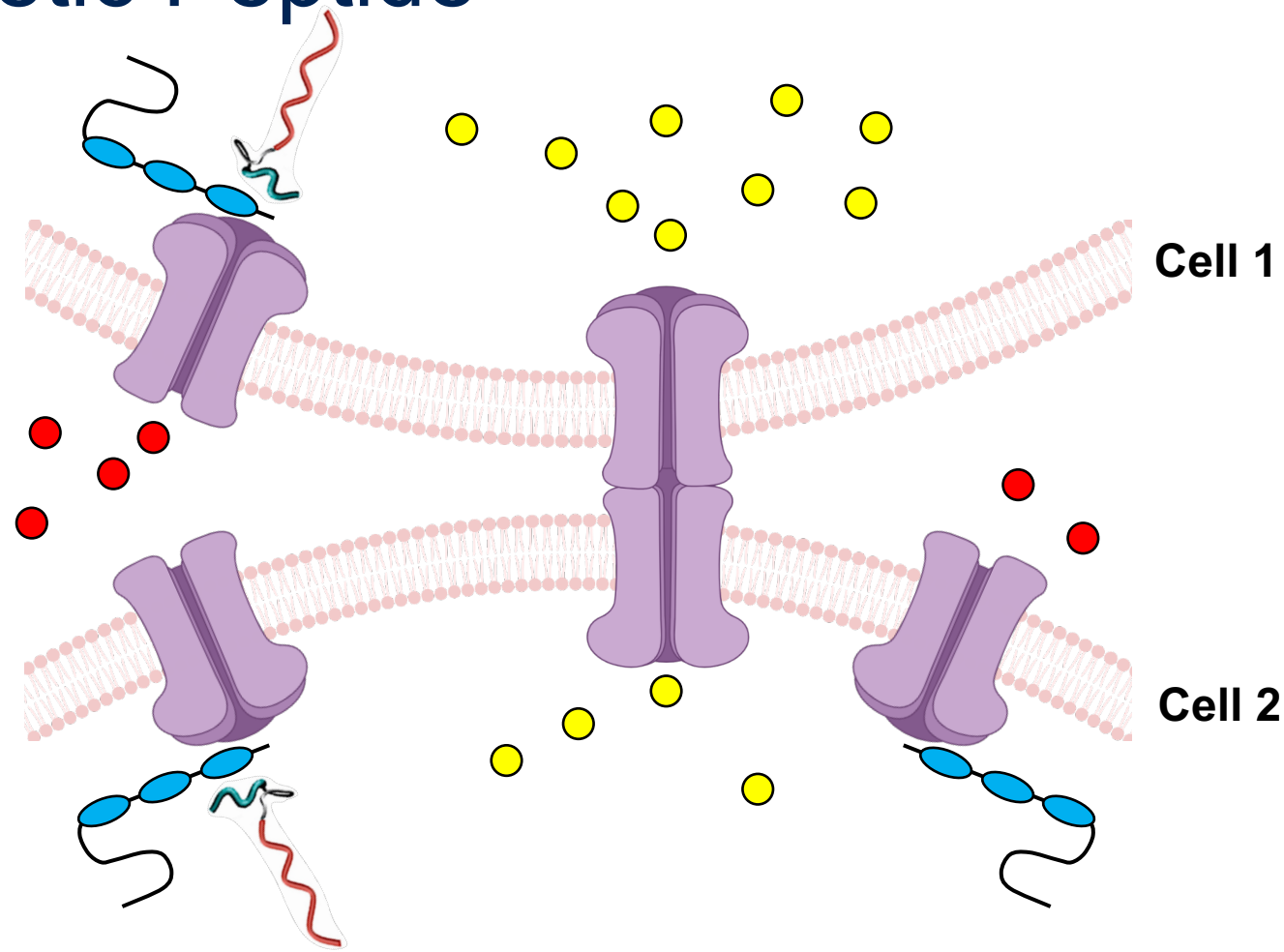

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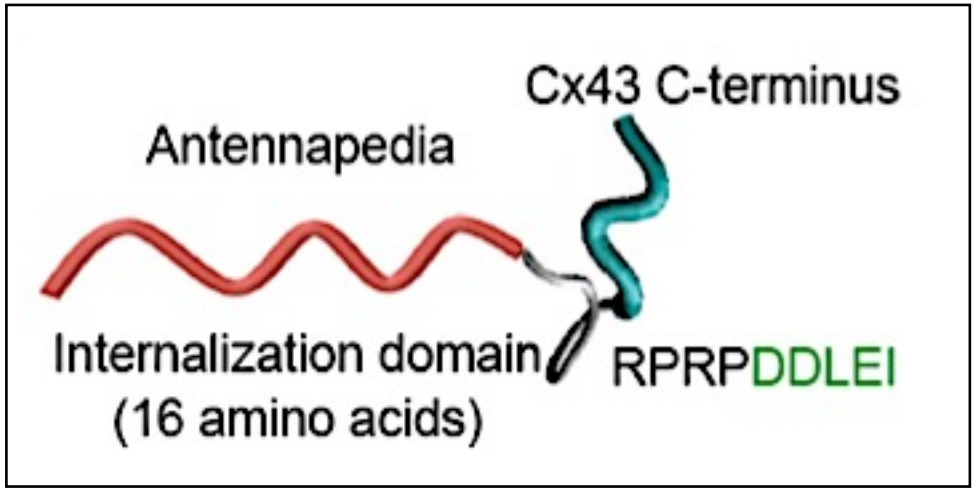
aCT1: Connexin43 Mimetic Peptide

aCT1 peptide



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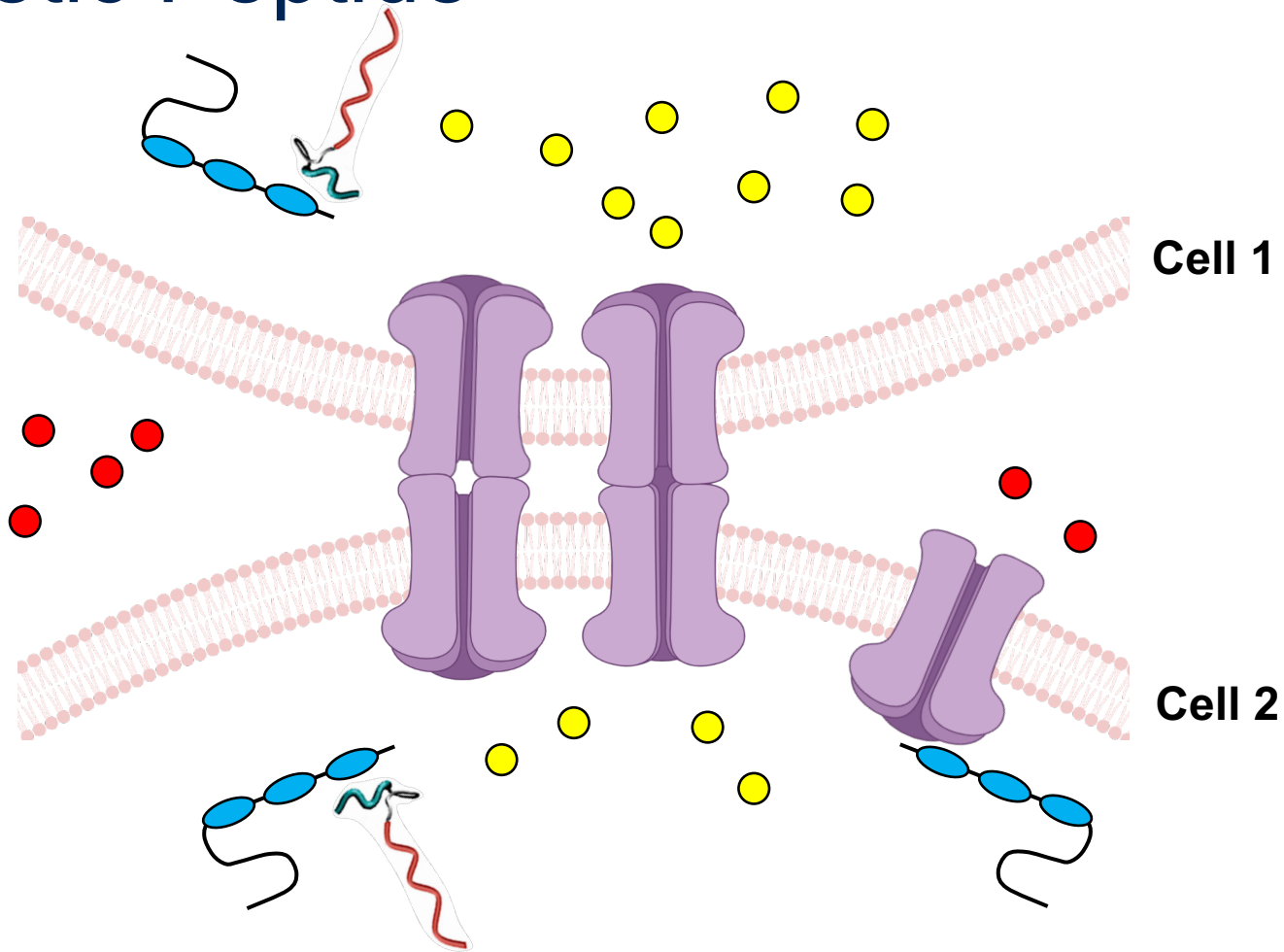

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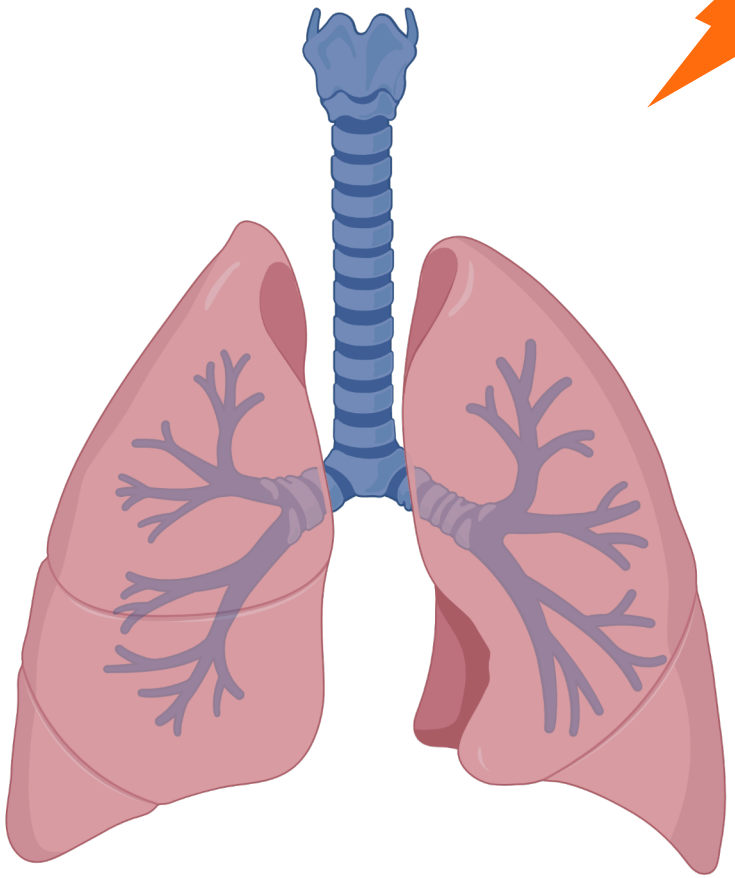
Unmet Respiratory Needs

ARDS

Acute Lung Injury

VILI

Smoke Inhalation



Toxic Gas Inhalation

Infection

Alcoholic Lung Syndrome

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Unmet Respiratory Needs

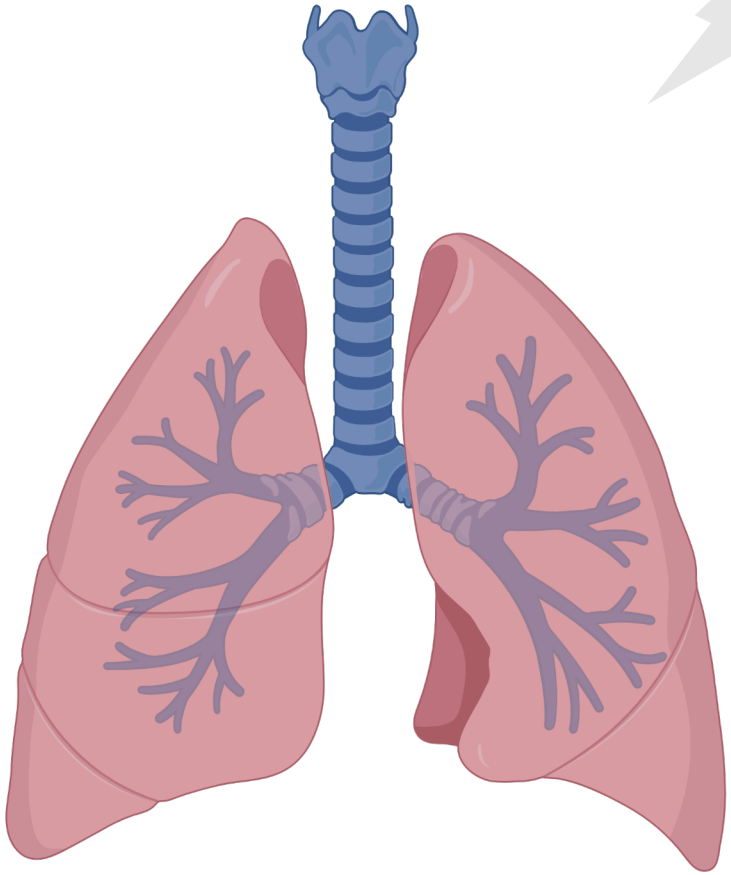
Acute Lung Injury

ARDS

VILI

Smoke Inhalation

Toxic Gas Inhalation



Infection

Alcoholic Lung Syndrome

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aCT1 to Treat SARS-CoV-2 Induced Lung Injury

Syrian Hamster
SARS-CoV-2 susceptible

Treatment Period
Aerosolized aCT1 [10 ug/kg, 20 ug/kg]
Remdesivir [15 mg/kg IP]

Day 0 | Day 1 | Day 4 | Day 5 | Day 7

Inoculation
SARS-CoV-2

Necropsy
- Lung Histopathology
- Viral Titers

Necropsy
- Lung Histopathology
- Viral Titers

Yuan et al. 2020 Nat Microbiol

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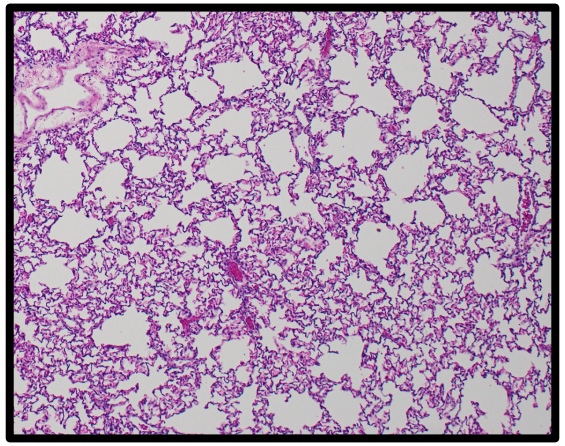
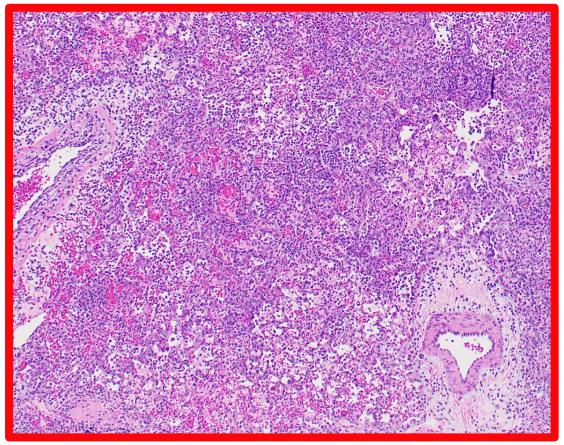
aCT1 Reduces Inflammation and Edema in Acute Lung Injuries

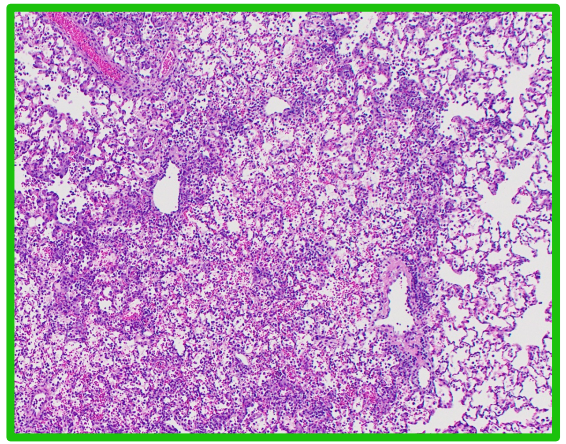
Uninfected + aCT1



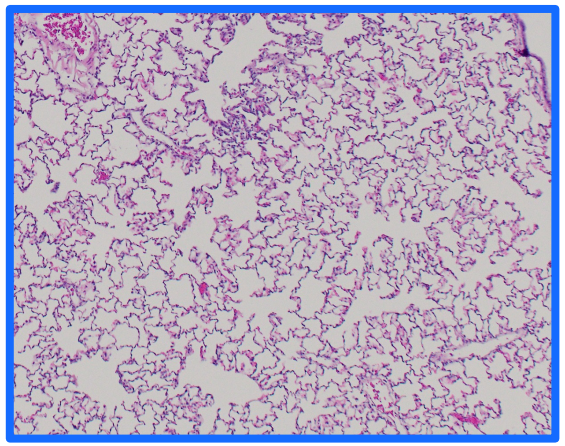
SARS-CoV-2 Infected



SARS-CoV-2 Infected + Remdesivir

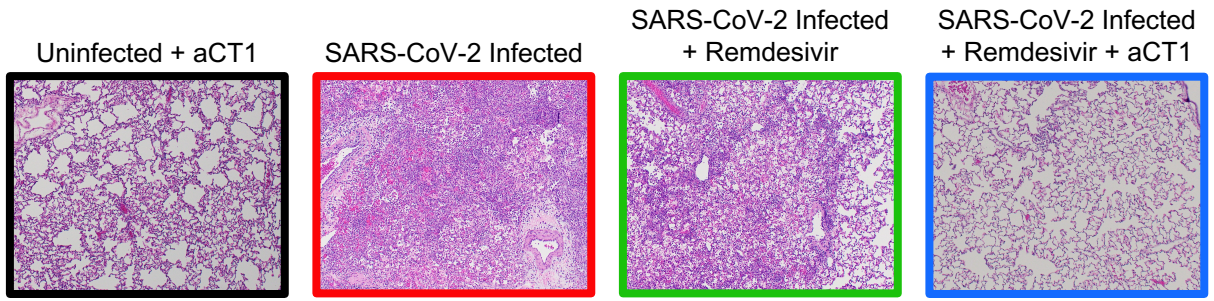


SARS-CoV-2 Infected + Remdesivir + aCT1



Representative 4X images of lung tissue 7 days after SARS-CoV-2 infection

aCT1 Reduces Inflammation and Edema in Acute Lung Injuries



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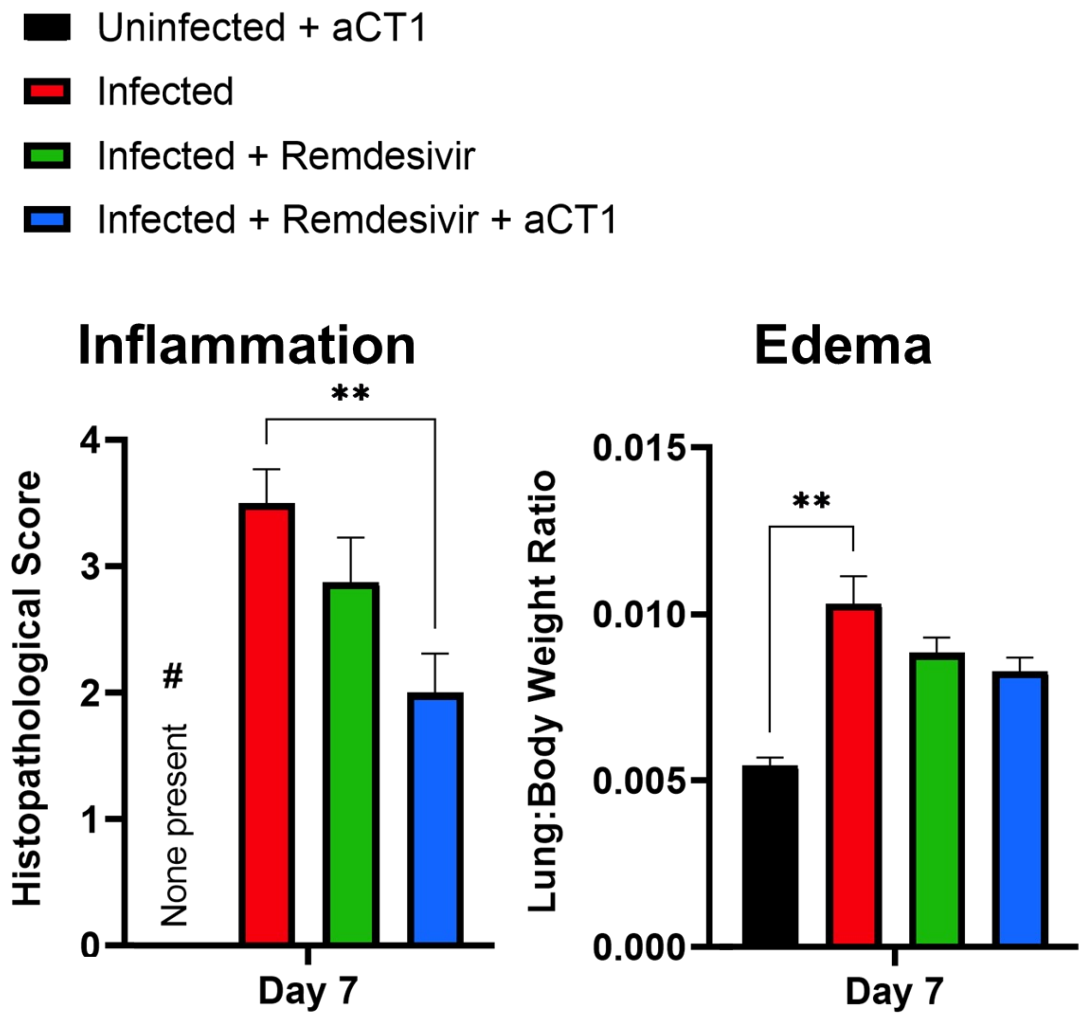
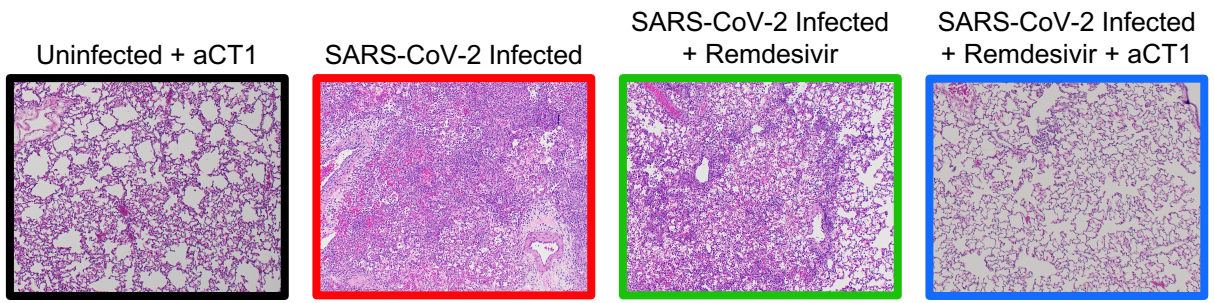


aCT1 Reduces Inflammation and Edema in Acute Lung Injuries

Aerosolized aCT1 prevents COVID-19 induced pulmonary edema and reduces infiltration of inflammatory cells.



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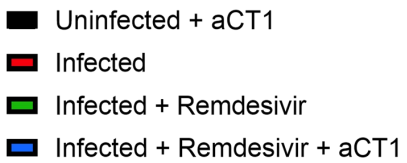
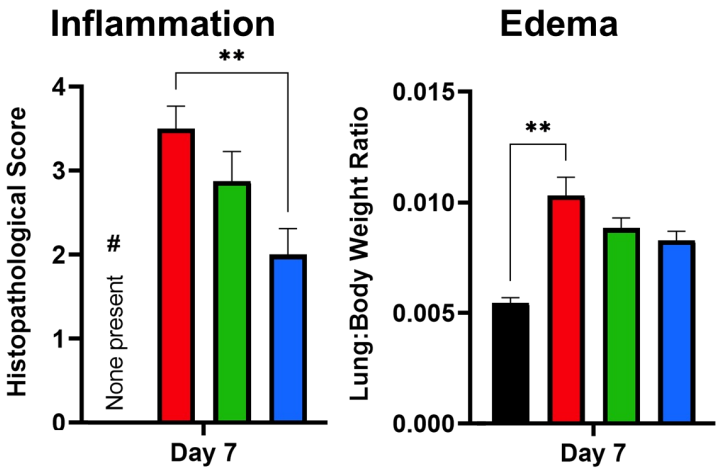


*n=4-8/group; *p<0.05; **p<0.01; #p<0.05 compared to all other groups at same day*



aCT1 to Treat Alcoholic Lung Syndrome

C57/BL6 Mouse
Established Model

Alcohol Maintenance
20% EtOH ad libitum

Treatment Period
Aerosolized aCT1 [5 mg/kg]

LPS
[5 mg/kg IT]

Day 0 | Week 2 | Week 12 | Day 85 | Day 86

Alcohol Induction

Necropsy
- Evans Blue Assay

Smith et al. 2019 Alcohol

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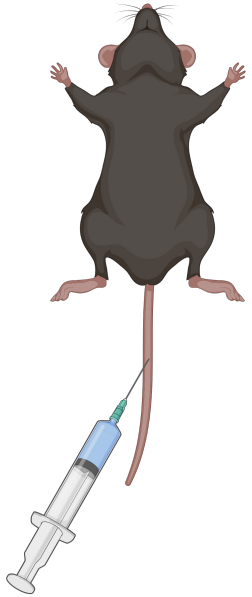
aCT1 Reduces Barrier Permeability in Acute Lung Injuries

1. Inject Evans Blue dye



Smith et al. 2021 Methods Mol Biol

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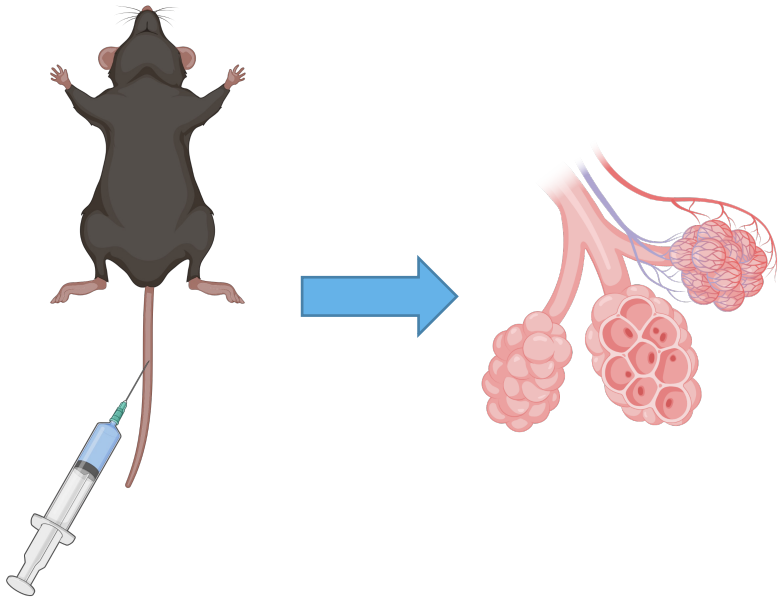
aCT1 Reduces Barrier Permeability in Acute Lung Injuries

1. Inject Evans Blue dye **2. Allow dye to circulate**



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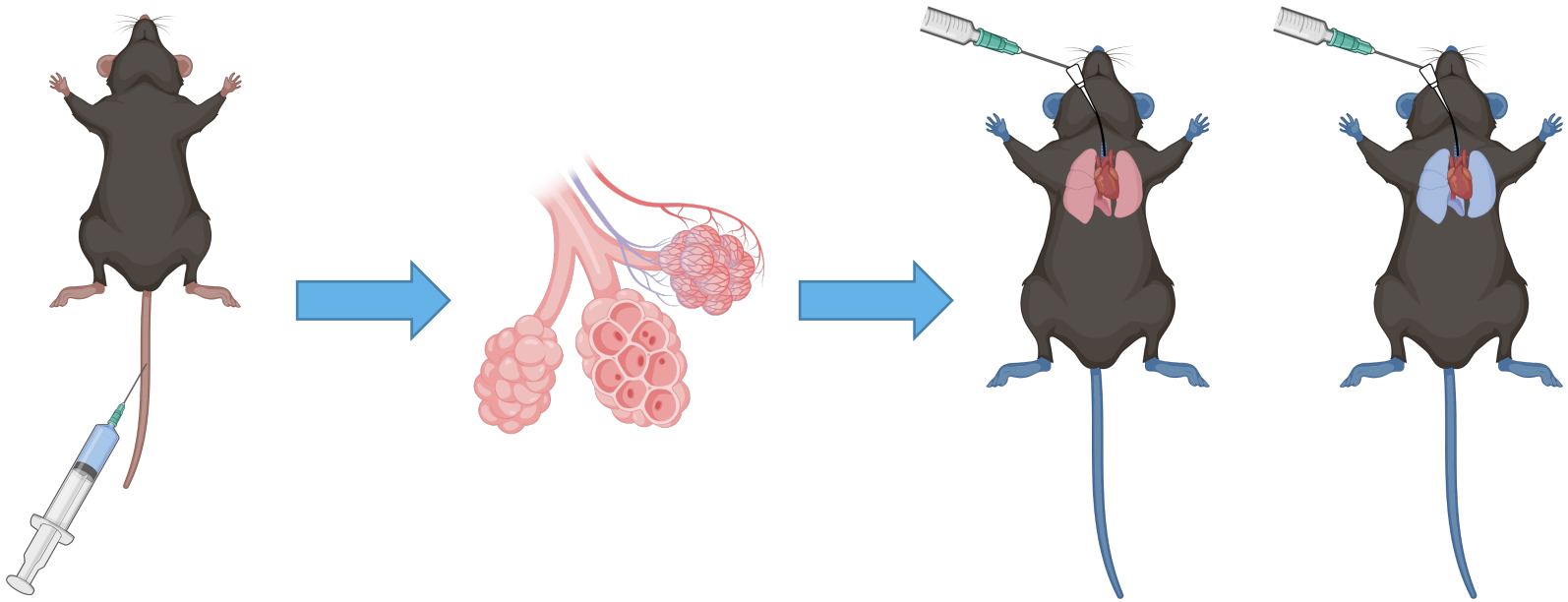
aCT1 Reduces Barrier Permeability in Acute Lung Injuries

1. Inject Evans Blue dye **2. Allow dye to circulate** **3. Perform bronchoalveolar lavage (BAL)**



Healthy Lungs Injured Lungs

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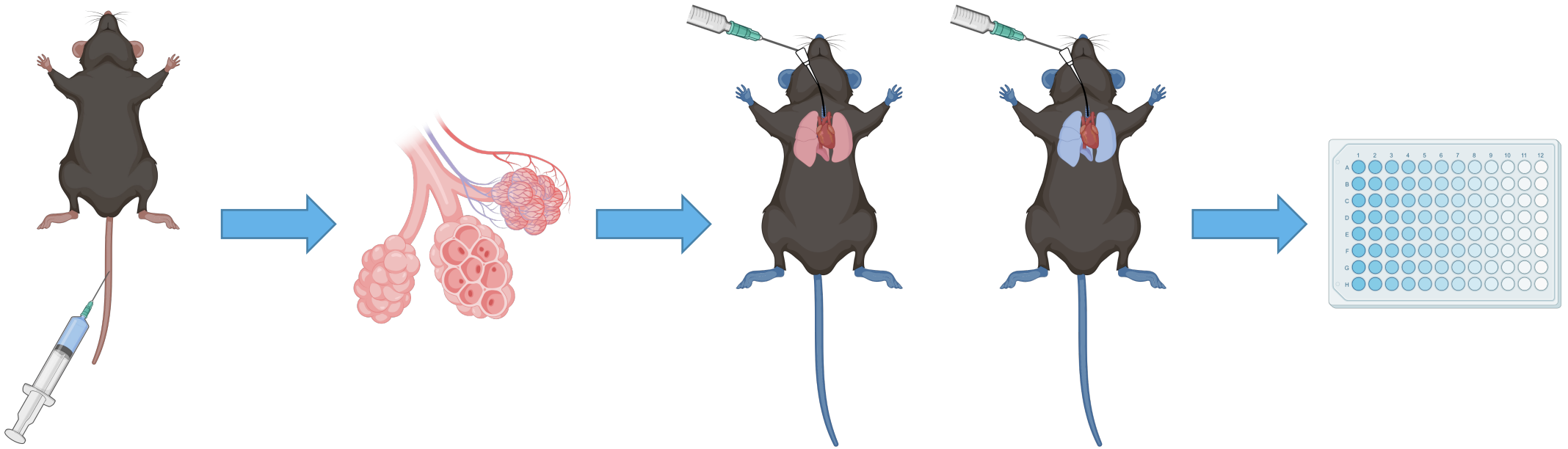
aCT1 Reduces Barrier Permeability in Acute Lung Injuries

1. Inject Evans Blue dye **2. Allow dye to circulate** **3. Perform bronchoalveolar lavage (BAL)** **4. Measure absorbance of BAL**



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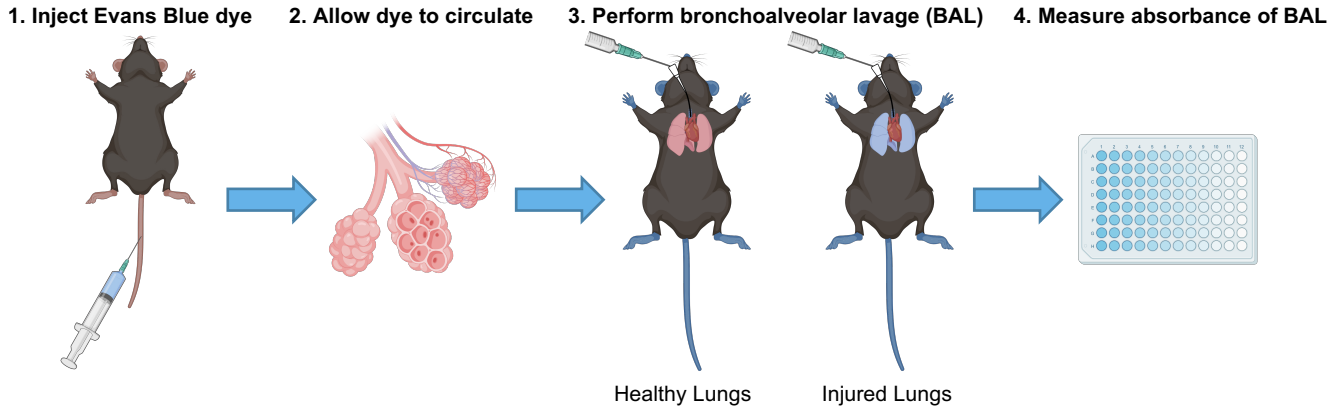
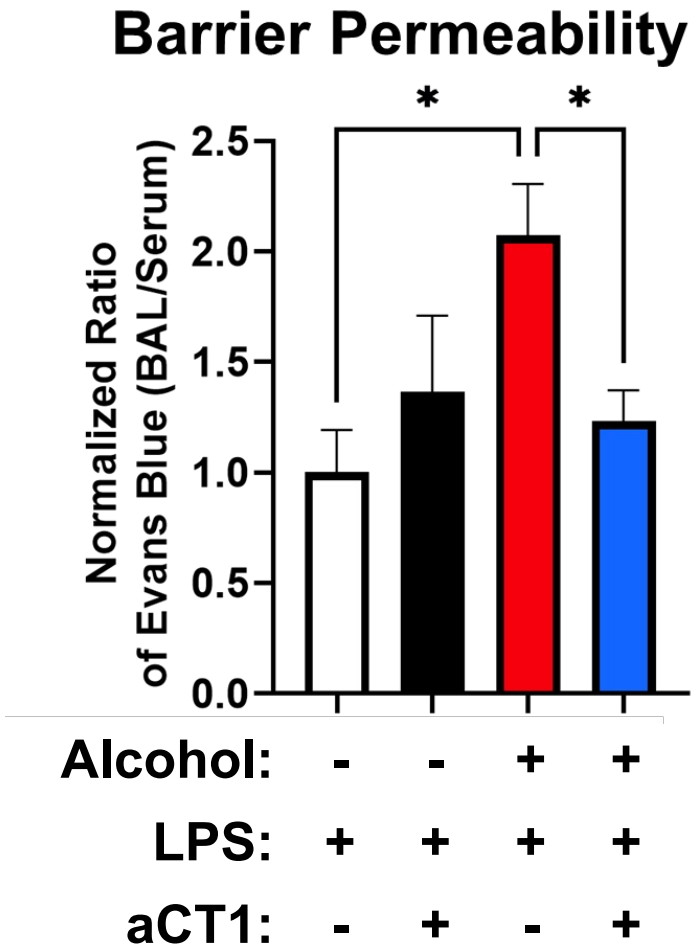


Smith et al. 2021 Methods Mol Biol



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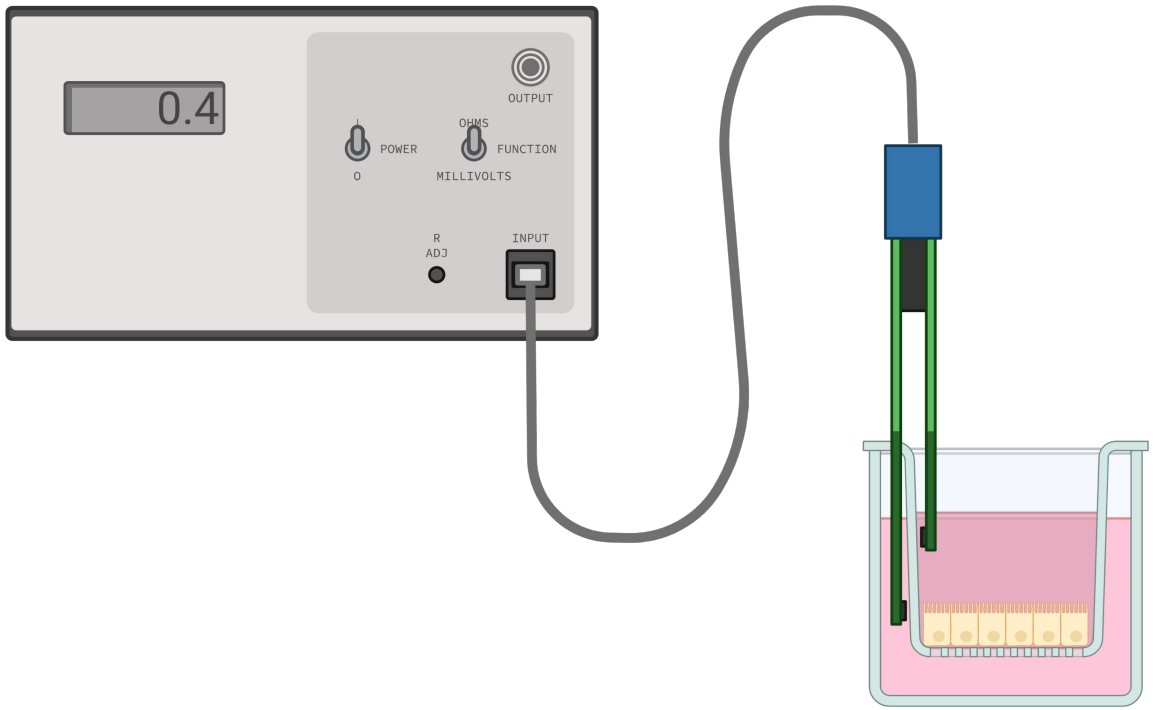
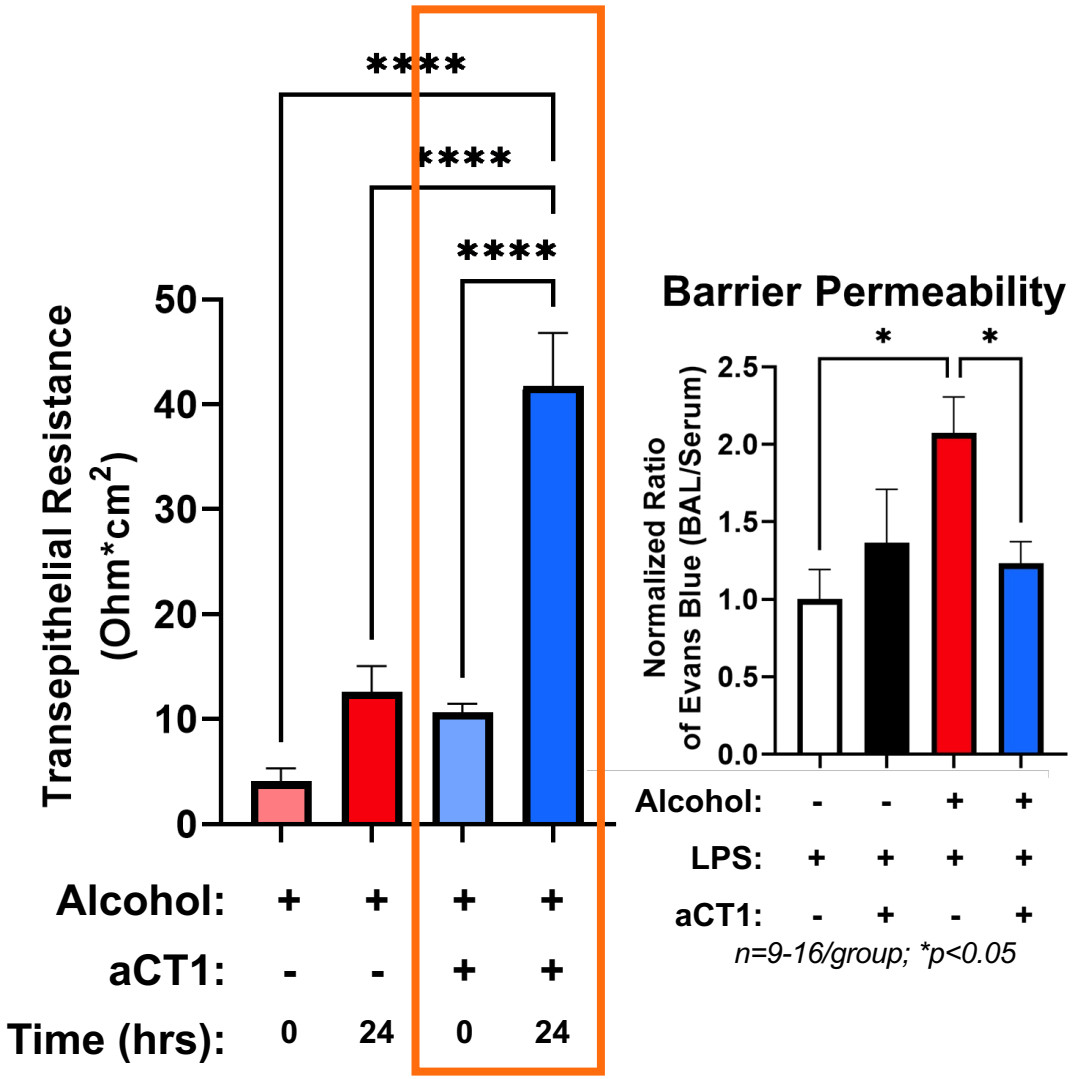
aCT1 Reduces Barrier Permeability in Acute Lung Injuries

TEER Assay





*n=9-16/group; *p<0.05*

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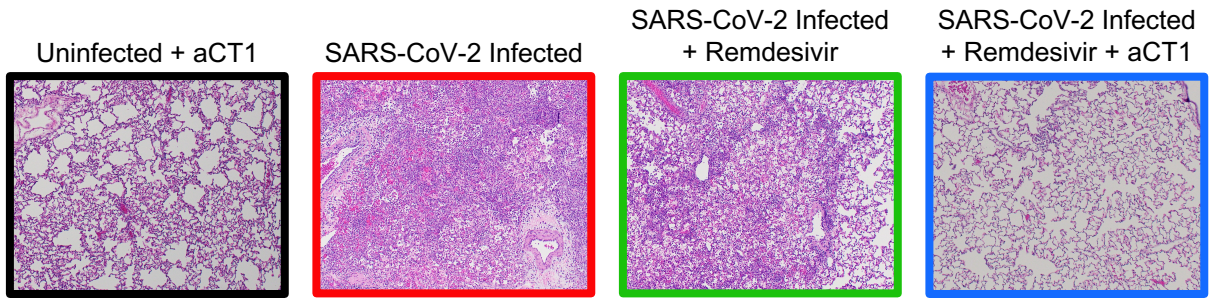
Aerosolized aCT1 to Treat Acute Lung Injury

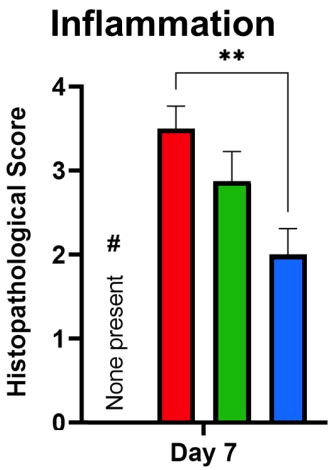
Aerosolized aCT1 prevents COVID-19 induced pulmonary edema and reduces infiltration of inflammatory cells.

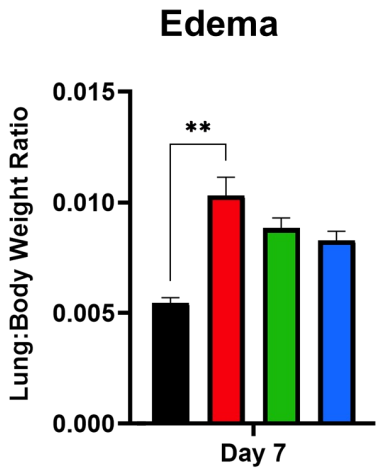


Representative 4X images of lung tissue 7 days after SARS-CoV-2 infection

- Uninfected + aCT1
- Infected
- Infected + Remdesivir
- Infected + Remdesivir + aCT1

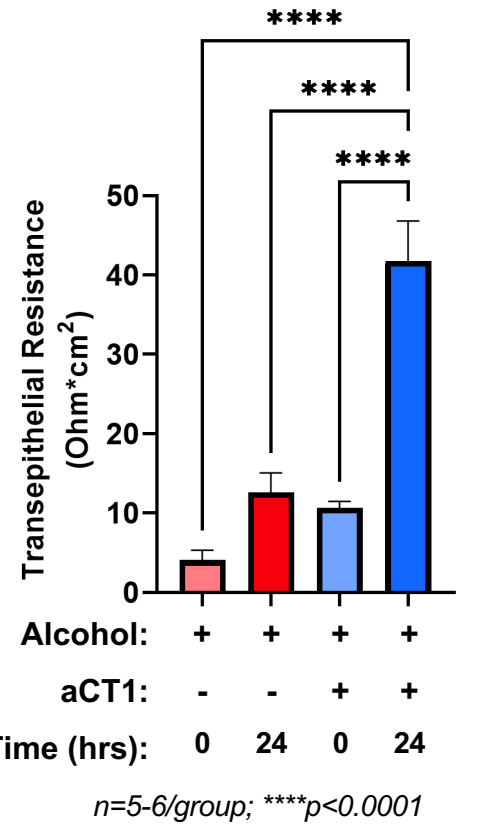
*n=4-8/group; *p<0.05; **p<0.01; #p<0.05 compared to all other groups at same day*



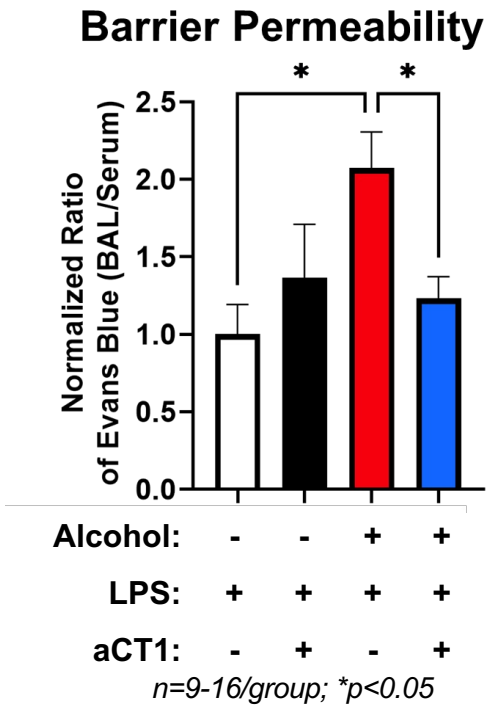


Collaborators
Lovelace Biomedical Research Institute
Melanie Doyle-Eisele, PhD

Aerosolized aCT1 improves pulmonary barrier function in models of alcoholic lung syndrome after acute lung injury.



*n=5-6/group; ****p<0.0001*



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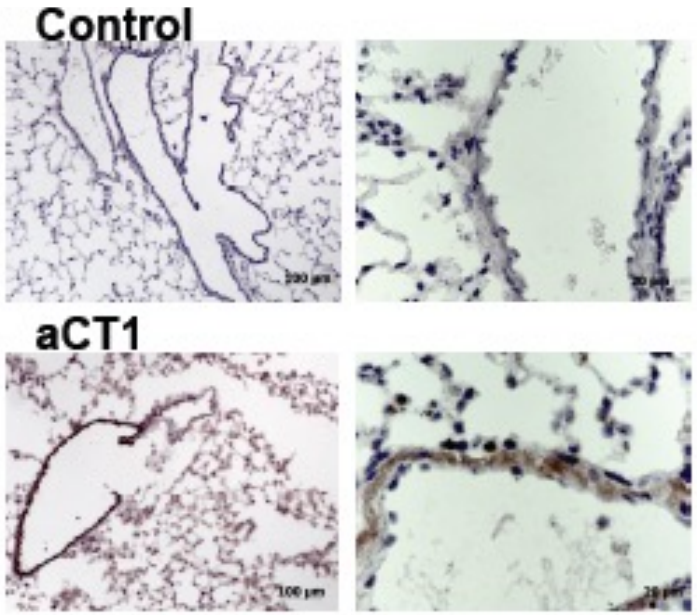
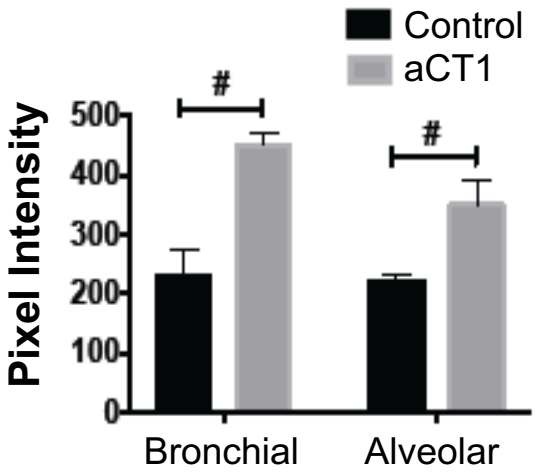
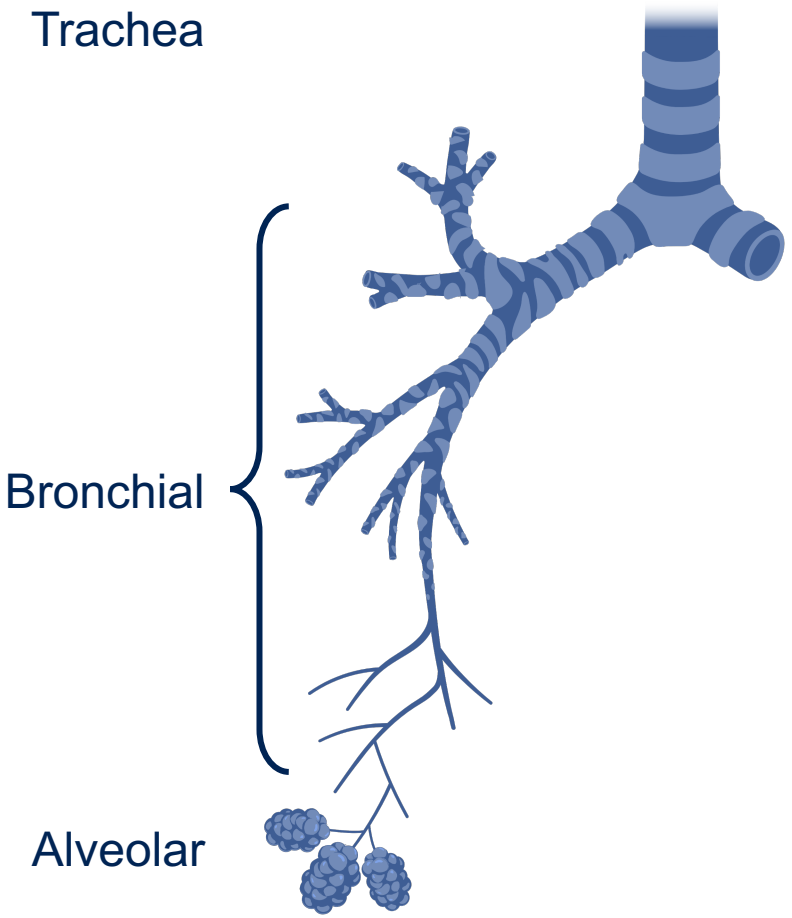
Yasmin K. Ibrahim

Aerosolized aCT1 Delivery







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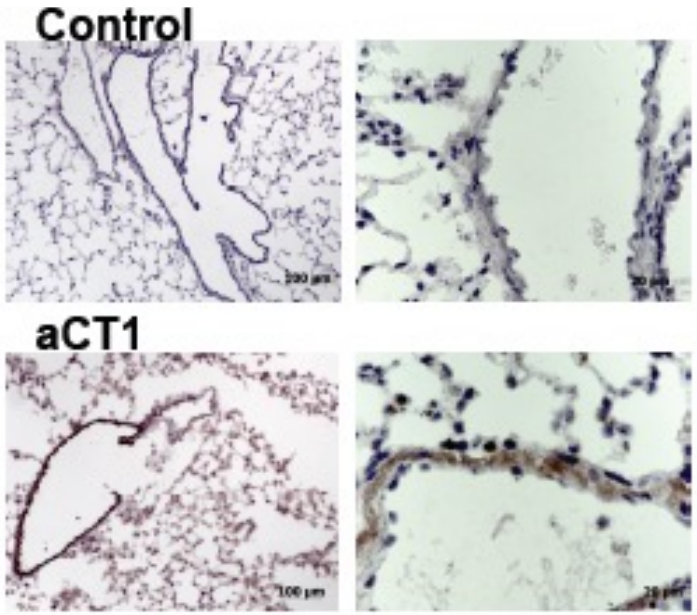
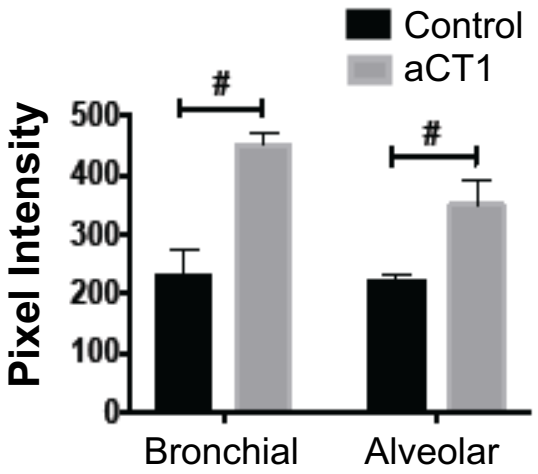
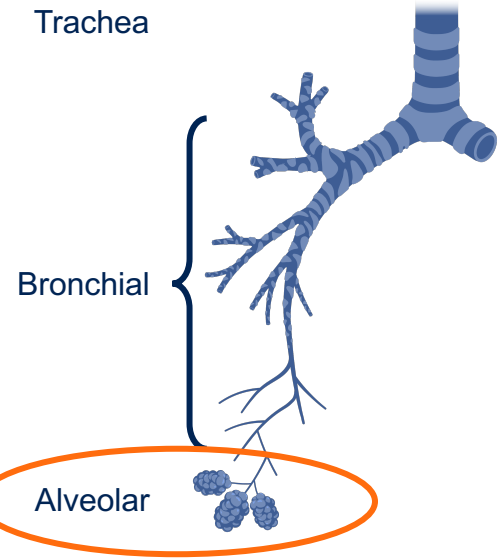
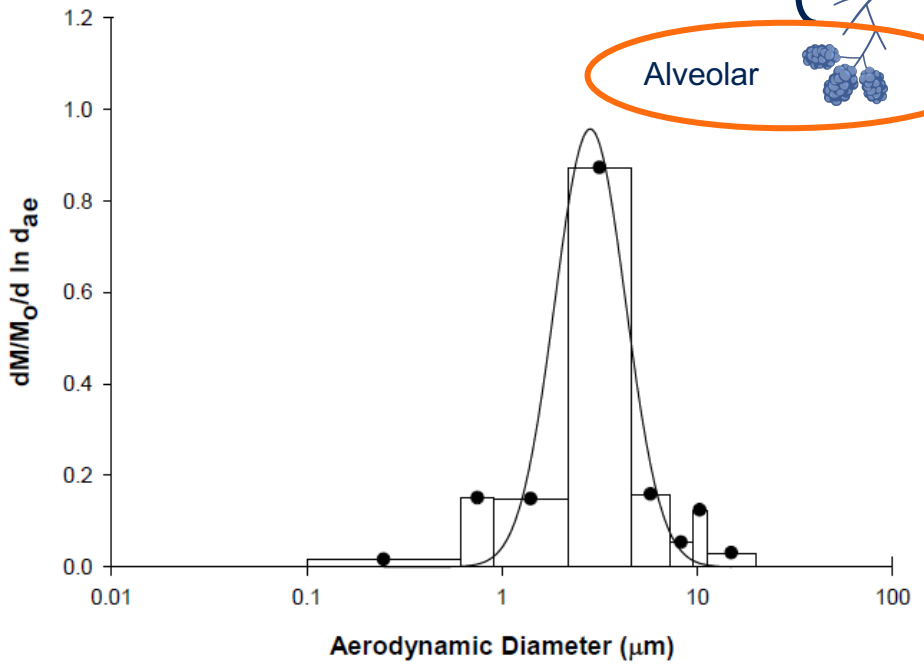
Aerosolized aCT1 Delivery









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Take-Aways

Aerosolized aCT1 peptide:

- Has demonstrated efficacy in translationally relevant models of several acute lung injuries
  - SARS-CoV-2 induced lung injury
  - Alcoholic lung syndrome + acute lung injury
  - Human lung cells
- Reaches distal airspaces
- Has an attractive particle distribution profile
- Has demonstrated no adverse effect on pulmonary function

Aerosolized aCT1 peptide is an etiology agnostic respiratory therapeutic that holds immense potential for treatment of acute lung injury and many other conditions with unmet clinical needs.

Acknowledgements

Koval Lab

- Michael Koval, PhD
- Lauren A. Jeffers, PhD
- Yasmin K. Ibrahim

Lovelace Biomedical Research Institute

- Melanie Doyle-Eisele, PhD
- Hammad Irshad, MS
- David Revelli, PhD

Atkinson Lab

- Carl Atkinson, PhD

Xequel Bio

- Christina L. Grek, PhD
- Carissa C. James, PhD

Funding

- Department of Defense
  - Enhancement Award
- National Institutes of Health
  - Phase I SBIR Award

Visit Us at Our Booth!

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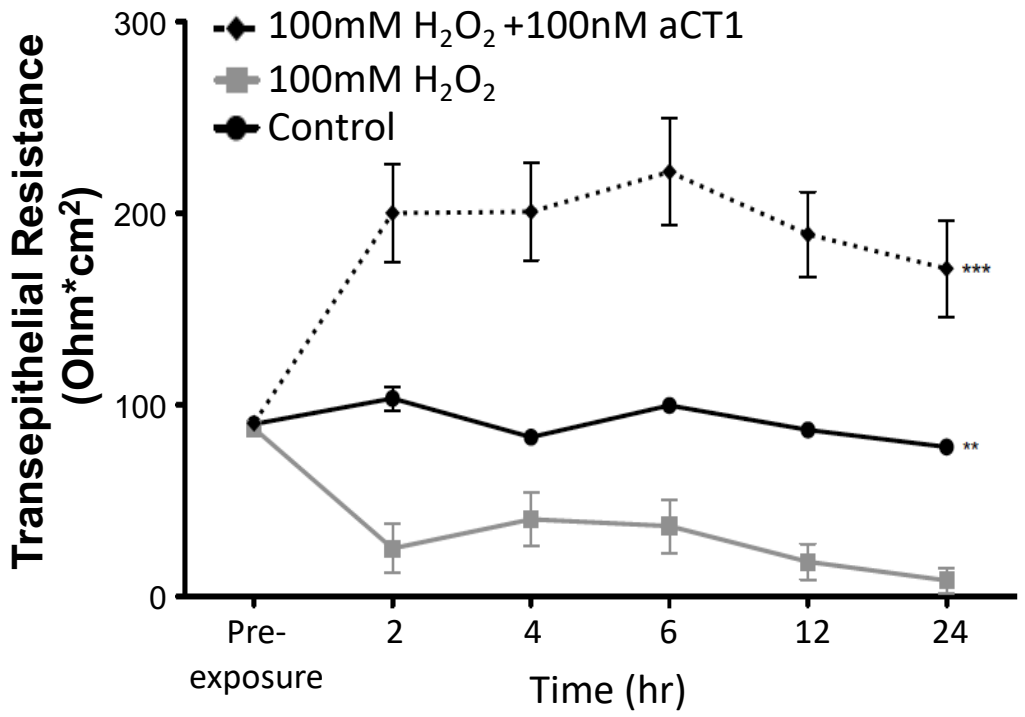
cjames@xequel.com

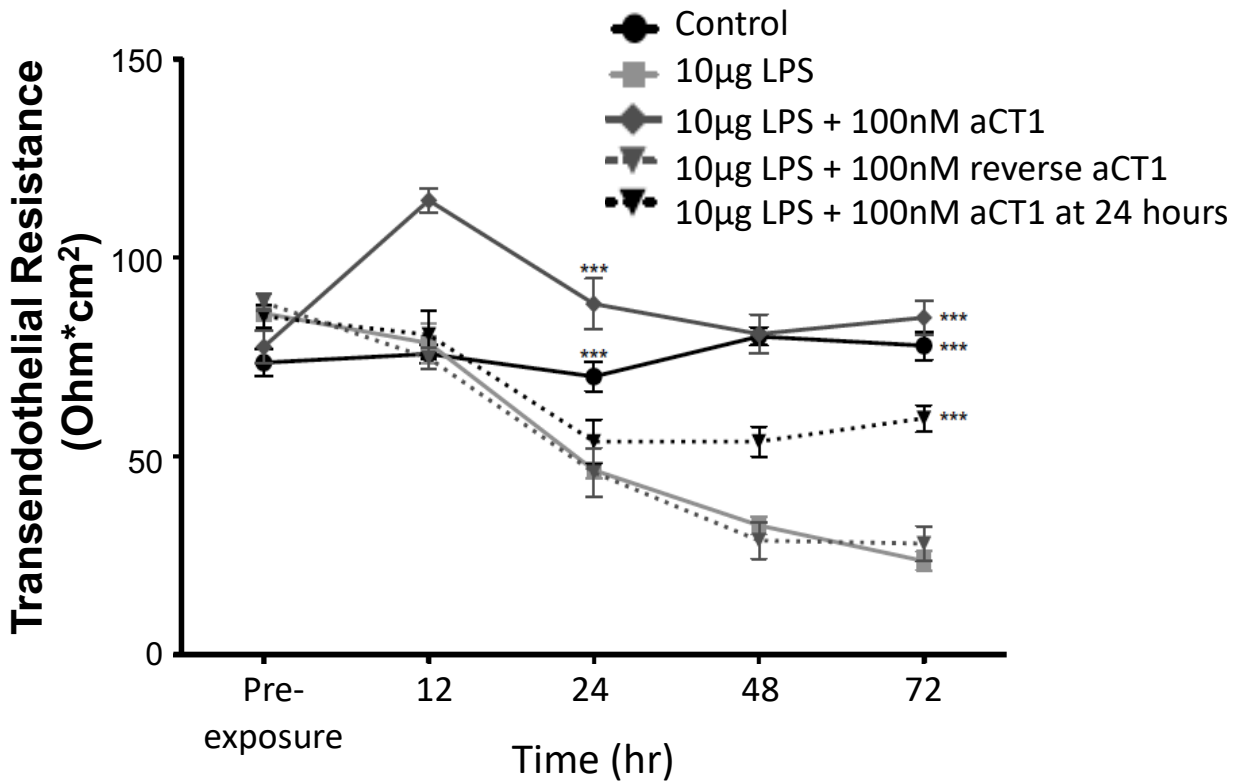
aCT1 Reduces Barrier Permeability in Human Cells

aCT1 pretreatment improves transepithelial electrical resistance in NHBEs subjected to oxidative stress.



*Mean ± SEM; n=3; Compared to H_2O_2 **p<0.01, ***p<0.0001*

aCT1 improves transendothelial electrical resistance in HMLECs subjected to LPS insult.



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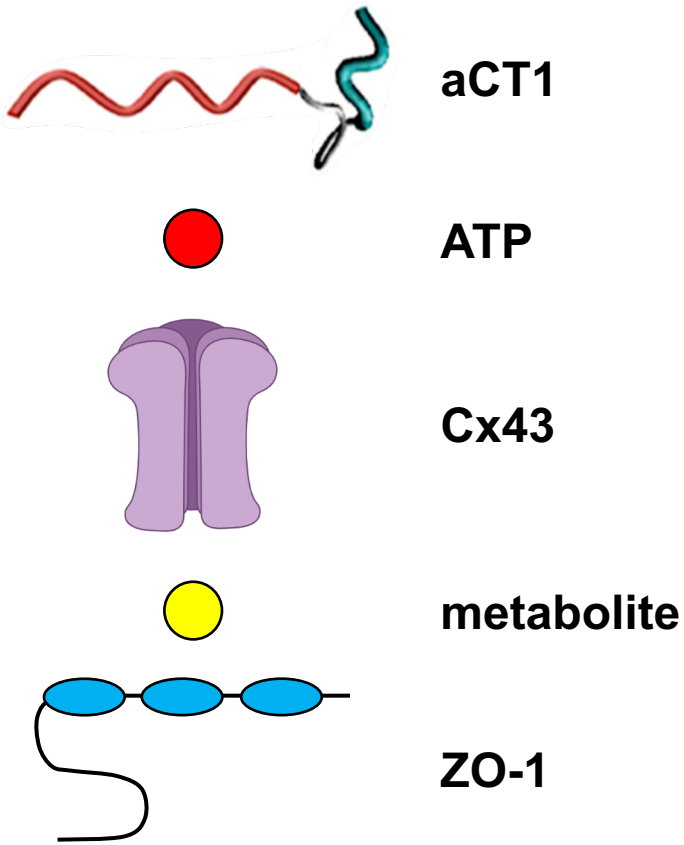

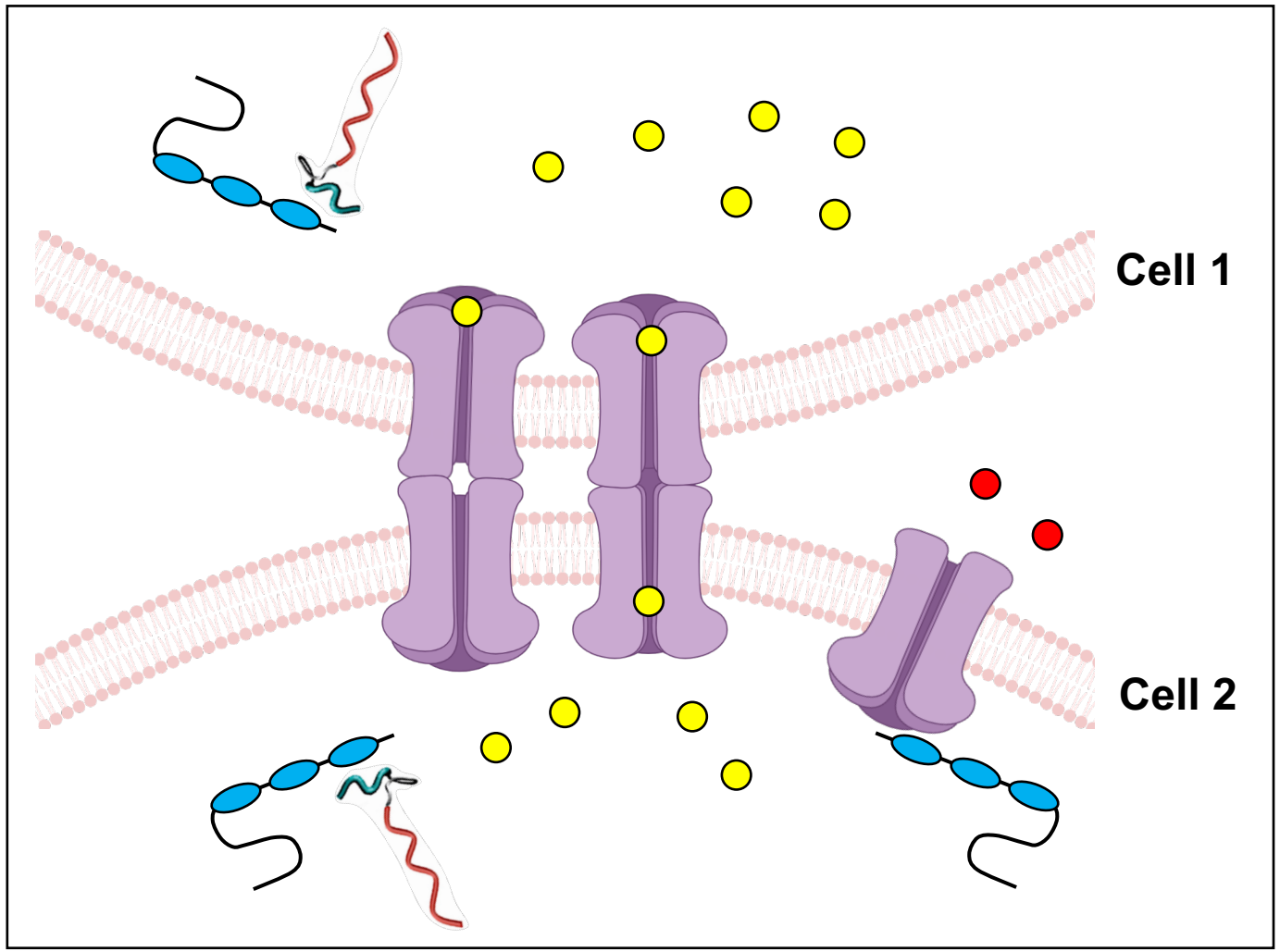

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Aerosolized aCT1 Delivery