MHSRS 2026

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Mitsugumin 53 (MG53) Protects Against Smoke Inhalation Induced Acute Lung Injury

via Suppression of the Proinflammatory Response in a Rat Model

Chuanxi Cai, PhD
Associate Professor
Department of Surgery
University of Virginia

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University of Virginia
School of Medicine

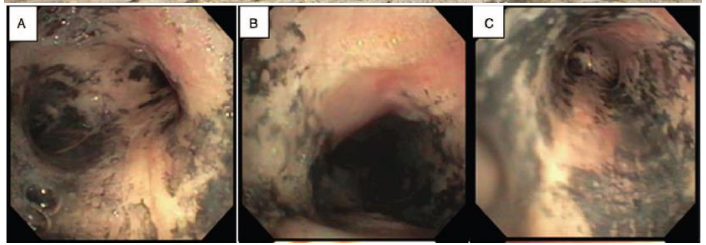
MHSRS 2026

Non- Disclosure

Chuanxi Cai, PhD, has no conflicts to report.

Background

- **Inhalation injury is present in 30% of all burn cases**
- **Accounts for up to 90% of all burn-related mortality**
- **20% incidence of acute respiratory distress syndrome (ARDS)**
- **Current treatments are largely supportive**



Military Relevance & Clinical Problem

Military Risk Factors

Combat & Training Exposure
Explosive & incendiary devices create intense smoke exposure during combat operations

4× Increased Mortality Risk
SI-ALI increases odds of mortality four-fold in burn patients

Progression to ARDS
Without targeted therapy, SI-ALI can progress to acute respiratory distress syndrome

No Approved Targeted Therapy
Current treatment remains purely supportive — a critical unmet need

Expanding Public Health Burden

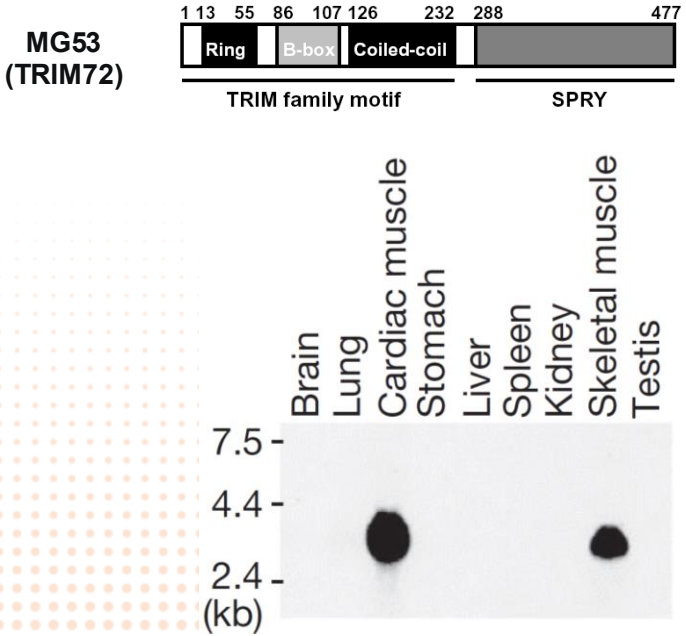
~100 Million

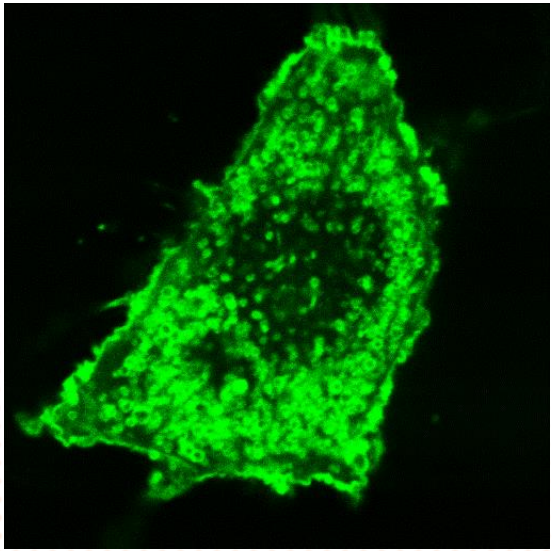
individuals exposed to wildfire smoke globally in 2024

Climate-Driven Increase
Rising wildfire frequency & intensity is contributing to residential fires worldwide

Mechanistic Targets Available
Widespread immune activation and inflammasome signaling are attractive therapeutic candidates for SI-ALI

MG53, a member of the tripartite motif family protein (TRIM72), as an important component of tissue repair

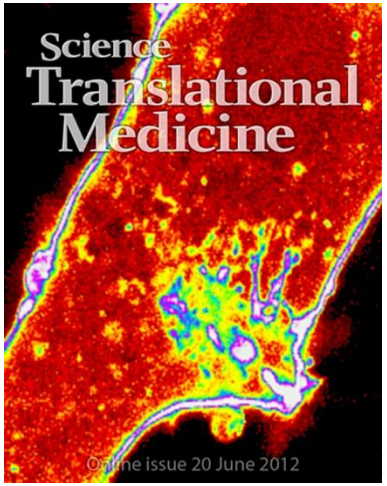




UVA Health
SCHOOL OF MEDICINE

Cai et al. (2009) J. Biol. Chem. 284: 3314-3322

Tissue repair function of MG53 protein



2012, *Weisleder* et al.
Muscular dystrophy and injury

nature COMMUNICATIONS

ARTICLE

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Treatment of acute lung injury by targeting MG53-mediated cell membrane repair

Yanlin Jia[1,*], Ken Chen[2,*], Peihui Lin[3,4,*], Gissela Lieber[1], Miyuki Nishi[5], Rosalie Yan[6], Zhen Wang[2], Yonggang Yao[2], Yu Li[2], Bryan A. Whitson[3], Pu Duann[3], Haichang Li[3], Xinyu Zhou[3], Hua Zhu[3,4], Hiroshi Takeshima[5], John C. Hunter[1], Robbie L. McLeod[1], Noah Weisleder[4,6,7], Chunyu Zeng[2] & Jianjie Ma[3,4,6]

2014, *Jia* et al.
Acute Lung Injury

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

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ELSEVIER

2015, *Liu* et al.
Acute Cardiac Injury

Original article

Cardioprotection of recombinant human MG53 protein in a porcine model of ischemia and reperfusion injury

Jianxun Liu [a,*,1], Hua Zhu [b,1], Yongqiu Zheng [a,1], Zhaobin Xu [c], Lei Li [a], Tao Tan [d], Ki Ho Park [b], Jincai Hou [a], Cuixiang Zhang [a], Dan Li [a], Ran Li [a], Zhenguo Liu [e], Noah Weisleder [c,d], Desheng Zhu [f], Peihui Lin [b], Jianjie Ma [b,d,**]

RESEARCH ARTICLE

Science Transl Med

KIDNEY DISEASE

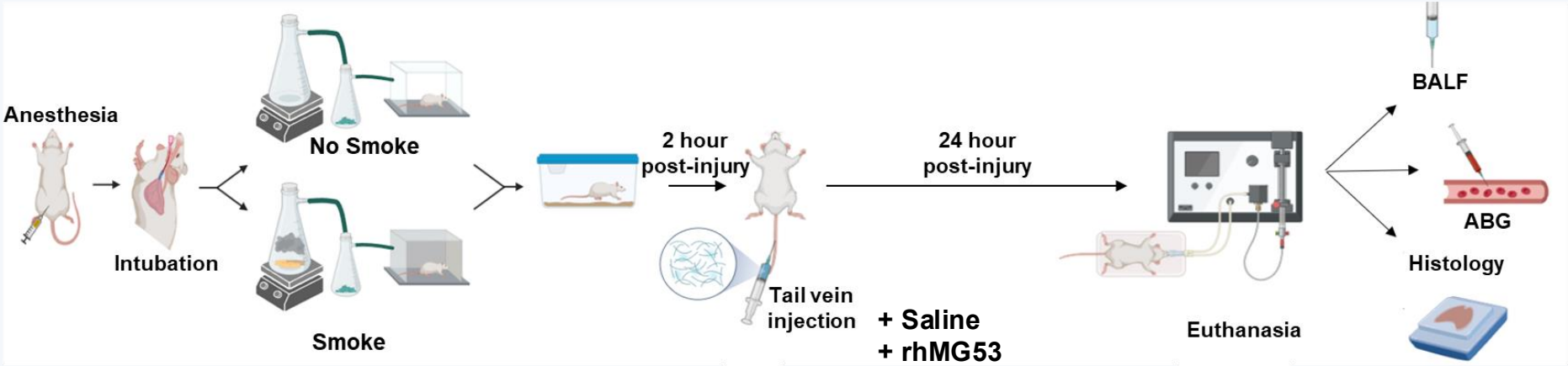
MG53-mediated cell membrane repair protects against acute kidney injury

Pu Duann,[1]* Haichang Li,[1]* Peihui Lin,[1] Tao Tan,[1] Zhen Wang,[2] Ken Chen,[2] Xinyu Zhou,[1] Kristyn Gumpper,[1] Hua Zhu,[1] Thomas Ludwig,[3] Peter J. Mohler,[4,5] Brad Rovin,[5] William T. Abraham,[5] Chunyu Zeng,[2] Jianjie Ma[1,3†]

2015, *Duann* et al.
Acute Kidney Injury

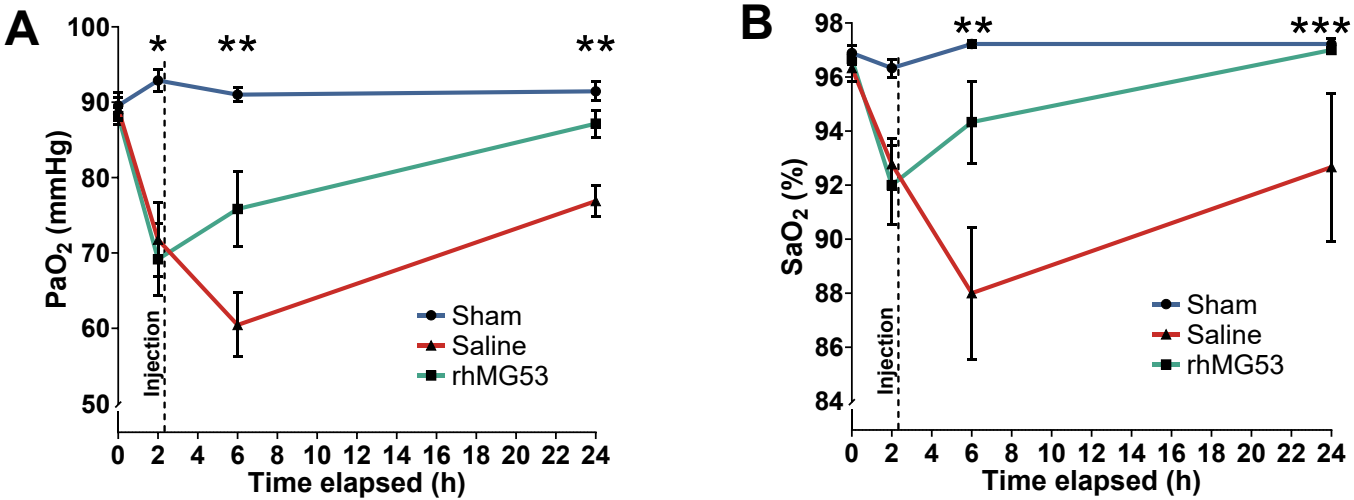
Study Design & Methods

Sprague Dawley Rats	Smoke Inhalation or Sham	IV Injection @ 2h	Serial ABGs	Sacrifice @ 24h
300-400g n=6-9/group	8 min, 60% density (Ringelmann)	rhMG53 (10mg/kg) or Saline	Baseline, 2h, 6h, 24h	Tissue Harvest



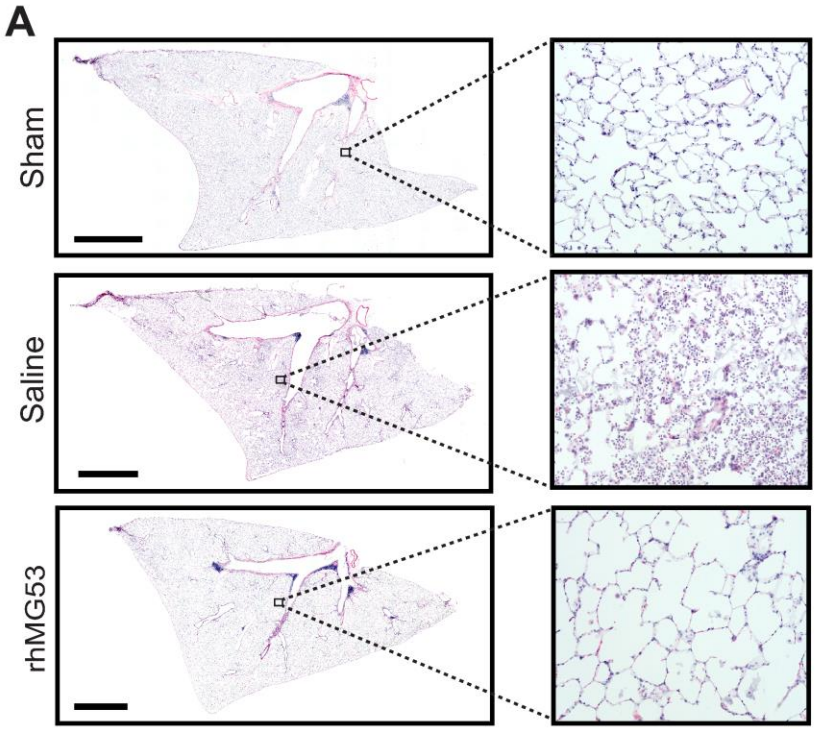
Hypothesis: A single systemic dose of rhMG53 will improve pulmonary function, reduce inflammatory injury, and suppress inflammasome activation following smoke inhalation injury.

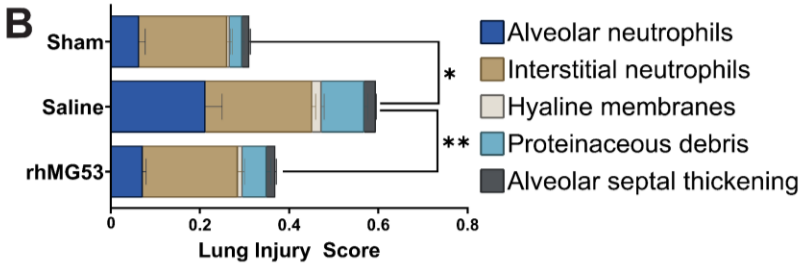
rhMG53 Improves Oxygenation After Smoke Inhalation



Aziz, …, Cai & Kibbe, Free Radic Biol Med. 2026

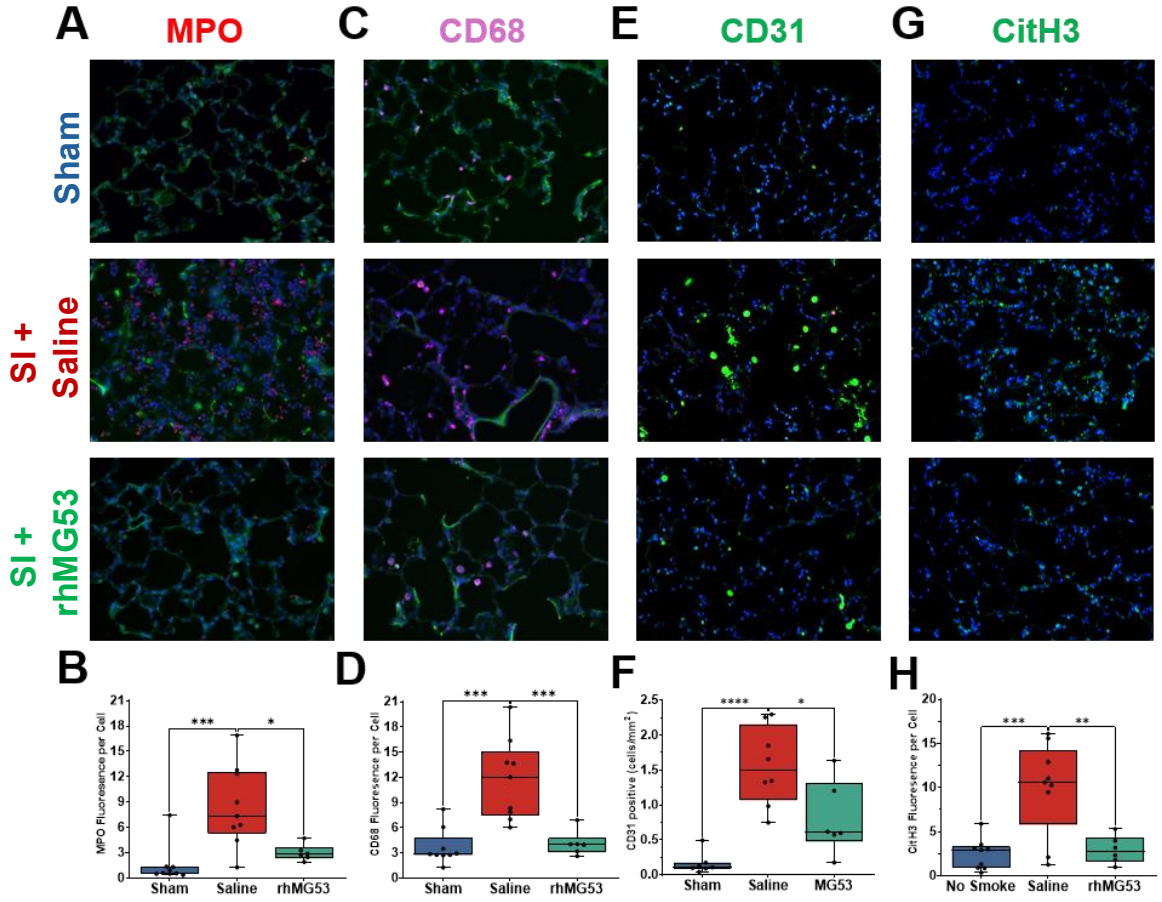
rhMG53 Reduces Histopathological Lung Injury





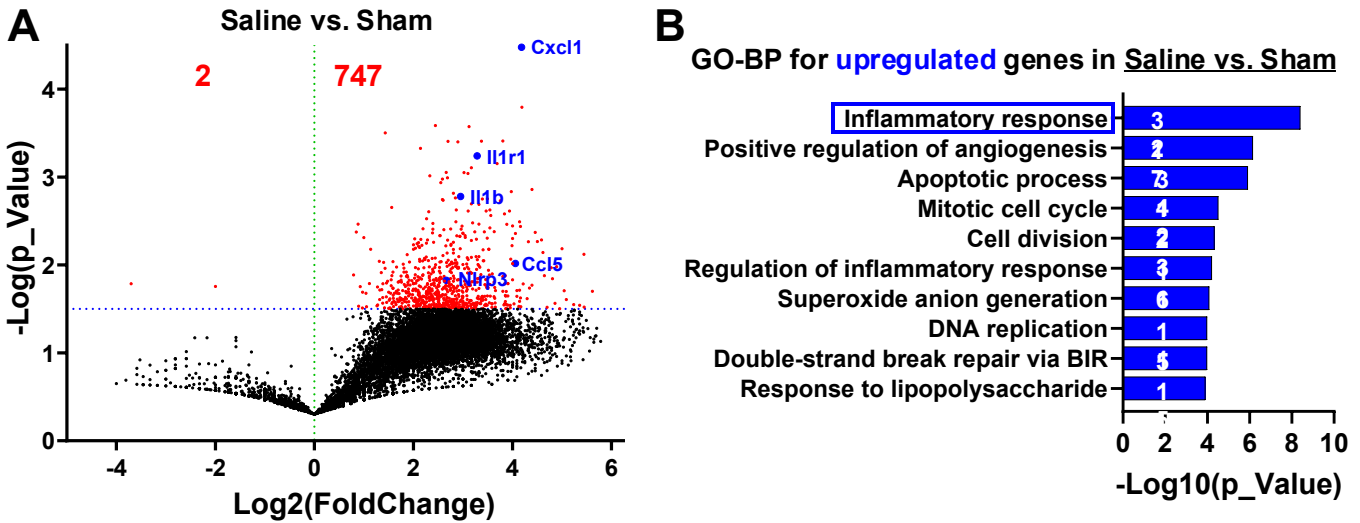
Aziz, …, Cai & Kibbe, Free Radic Biol Med. 2026

rhMG53 Suppresses Immune Cell Infiltration



Aziz, …, Cai & Kibbe, Free Radic Biol Med. 2026

RNA Sequencing: rhMG53 Broadly Suppresses Inflammation



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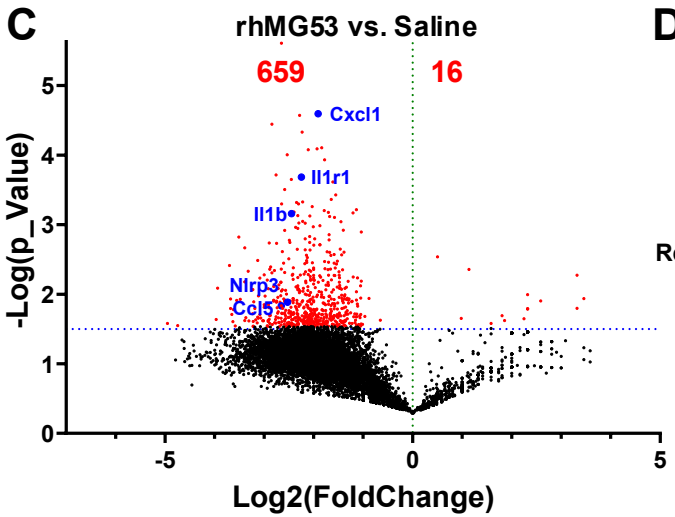
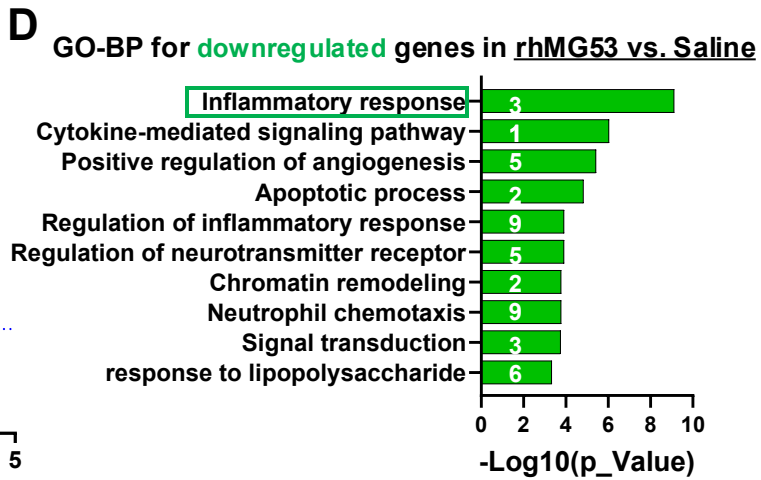
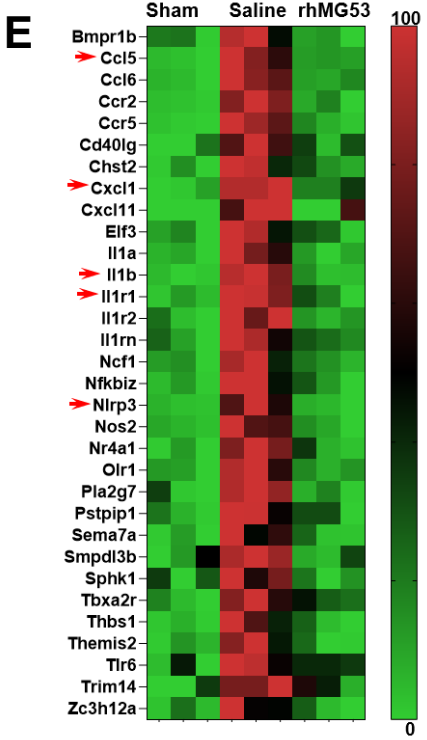
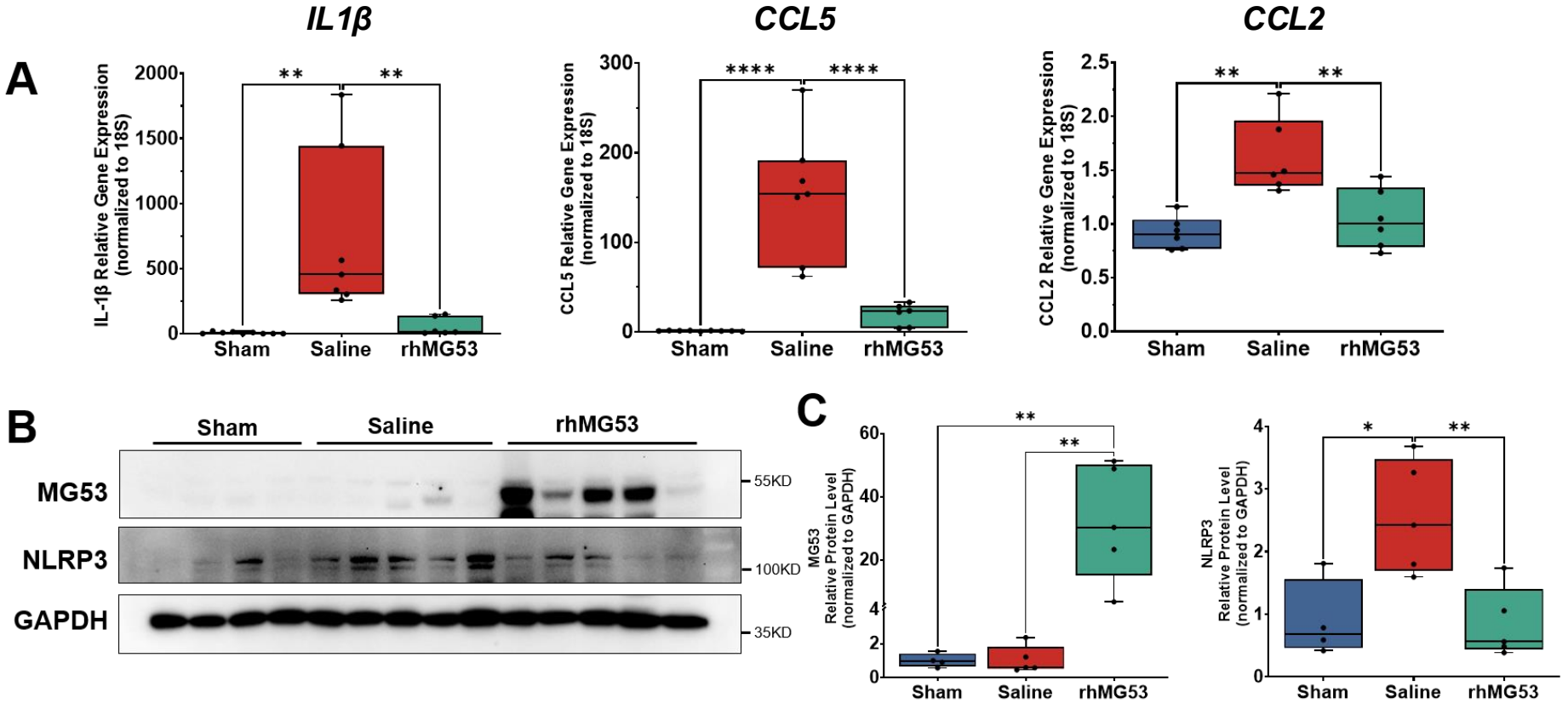






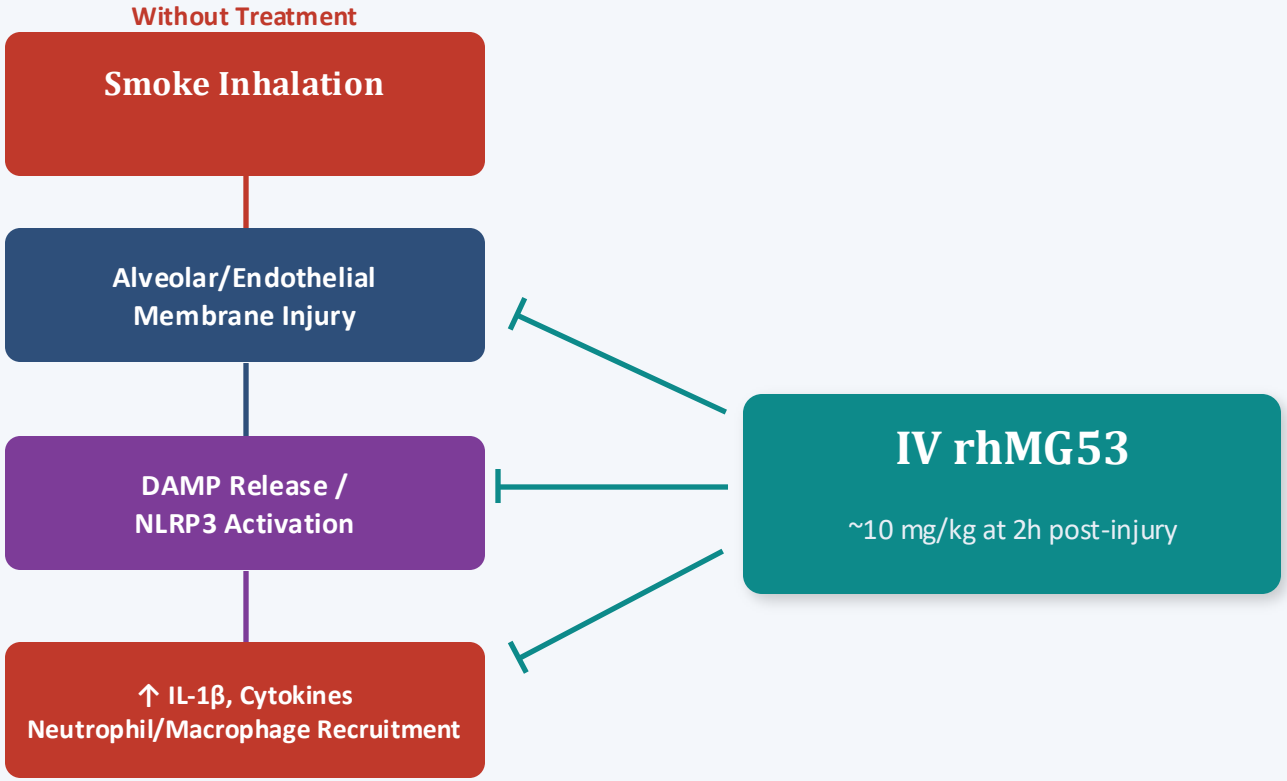
Aziz, …, Cai & Kibbe, Free Radic Biol Med. 2026

Suppression of Proinflammatory Genes & NLRP3 Inflammasome



Aziz, …, Cai & Kibbe, Free Radic Biol Med. 2026

Proposed Mechanism of rhMG53 Protection in SI-ALI



Outcomes with rhMG53

- ✓ ↑ Oxygenation (PaO_2/SaO_2)
- ✓ ↓ Histopathology Score
- ✓ ↓ Neutrophil/Macrophage Infiltration
- ✓ ↓ 659 Inflammatory Genes (RNA-seq)

Limitations & Future Directions

Single Dose / Timing

Treatment given at 2h post-injury; full pharmacokinetics and optimal dosing frequency for this model remain to be defined

24-hour Window Only

Study assessed the acute inflammatory phase; long-term survival and chronic sequelae (e.g., fibrosis) not evaluated

No Serum Collection

ABG blood volume restrictions precluded serum cytokine profiling; future studies should include serum biomarker analysis

Mechanism Specificity

Precise molecular target of NLRP3 suppression by rhMG53 is not yet defined; cell-type specific labeling and uptake studies are warranted

Next Steps: Large animal model · Sex-stratified efficacy study · Dose-response optimization · Combination therapy · Downstream mechanistic studies

Conclusions

1. rhMG53 significantly improved oxygenation following smoke inhalation injury, with full PaO_2 recovery to baseline at 24h
2. rhMG53 reduced histopathological lung injury and significantly decreased neutrophil, macrophage, and NET infiltration
3. RNA sequencing revealed 659 inflammatory genes downregulated by rhMG53, with 'inflammatory response' as the dominant suppressed pathway
4. rhMG53 suppressed NLRP3 inflammasome mRNA and protein to sham-control levels — a novel mechanistic finding in SI-ALI
5. rhMG53 represents a promising, mechanism-based therapeutic candidate for SI-ALI — a critical unmet military and civilian medical need

Thank You

Questions & Discussion

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