Sivelestat Improves Survival and Reduces Organ Dysfunction Following Polytrauma in a Rat Model

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06 August 2026

Defense Health Agency
RESEARCH & DEVELOPMENT ®

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- Research was conducted in compliance with Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by the AAALAC International

Background

- **Trauma is the leading cause of death for individuals ages 1-44 (*CDC, Key Injury and Violence data, 2022*).**

- **Polytrauma is known to trigger a systemic inflammatory response that drives acute kidney injury (AKI), Acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and high mortality (Sauaia et al., Crit Care Clin. 2017; Pfeifer et al., J Trauma 2017).**

- **In the military setting, organ failure is also frequently encountered in combat casualties. 12.5% of combat casualties suffered from AKI. (Stewart et al., *Am J Kidney Dis.* 2016).**

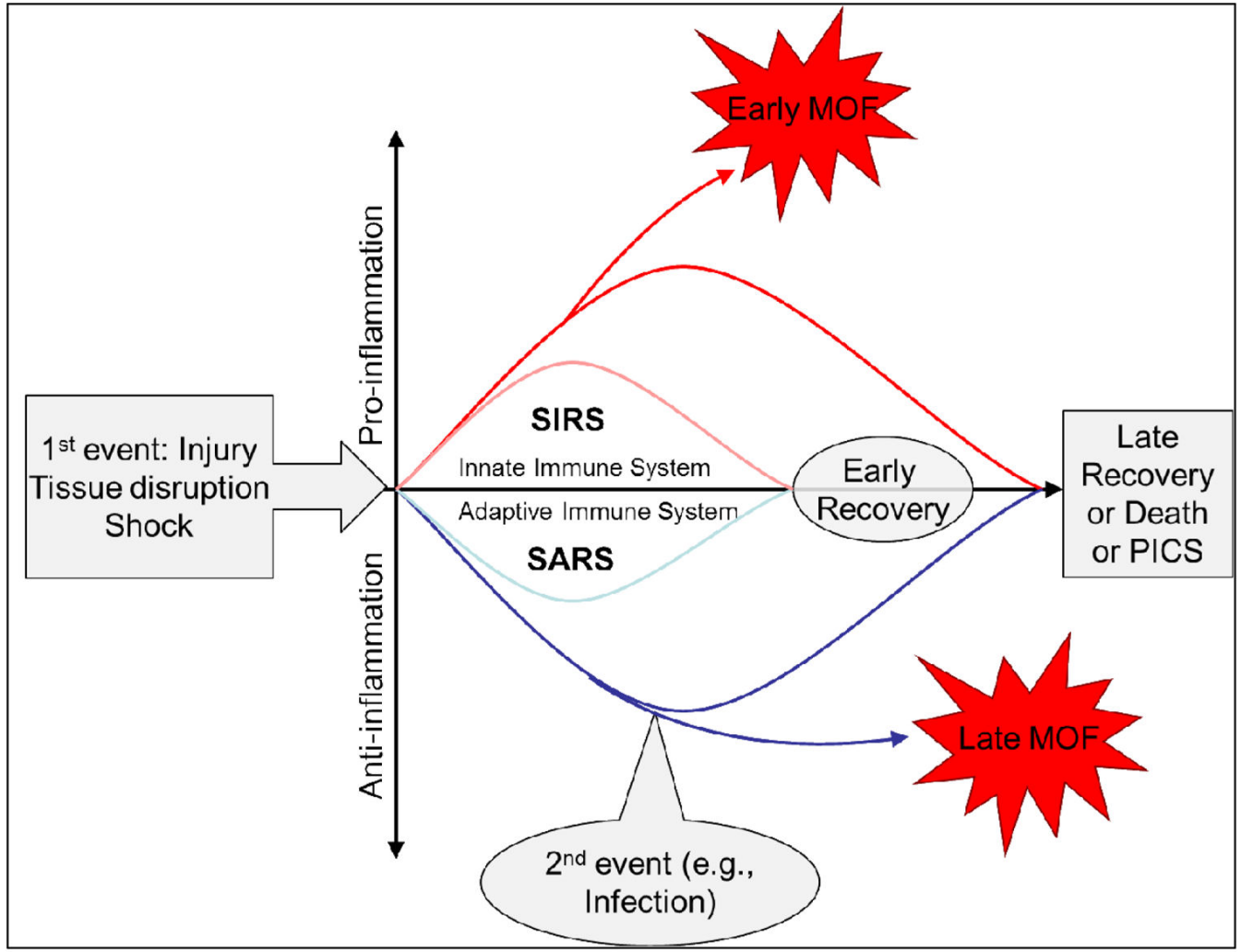
- **In severe injured warfighters (with a median ISS=22), the AKI incidence can be up to 21%. (Elterman et al., *J Trauma Acute Care Surg.* 2015).**

- **However, effective pharmacological treatments for trauma-induced AKI and organ failure are lacking, representing a serious unmet clinical need.**

Trauma-Induced Immune Dysfunction

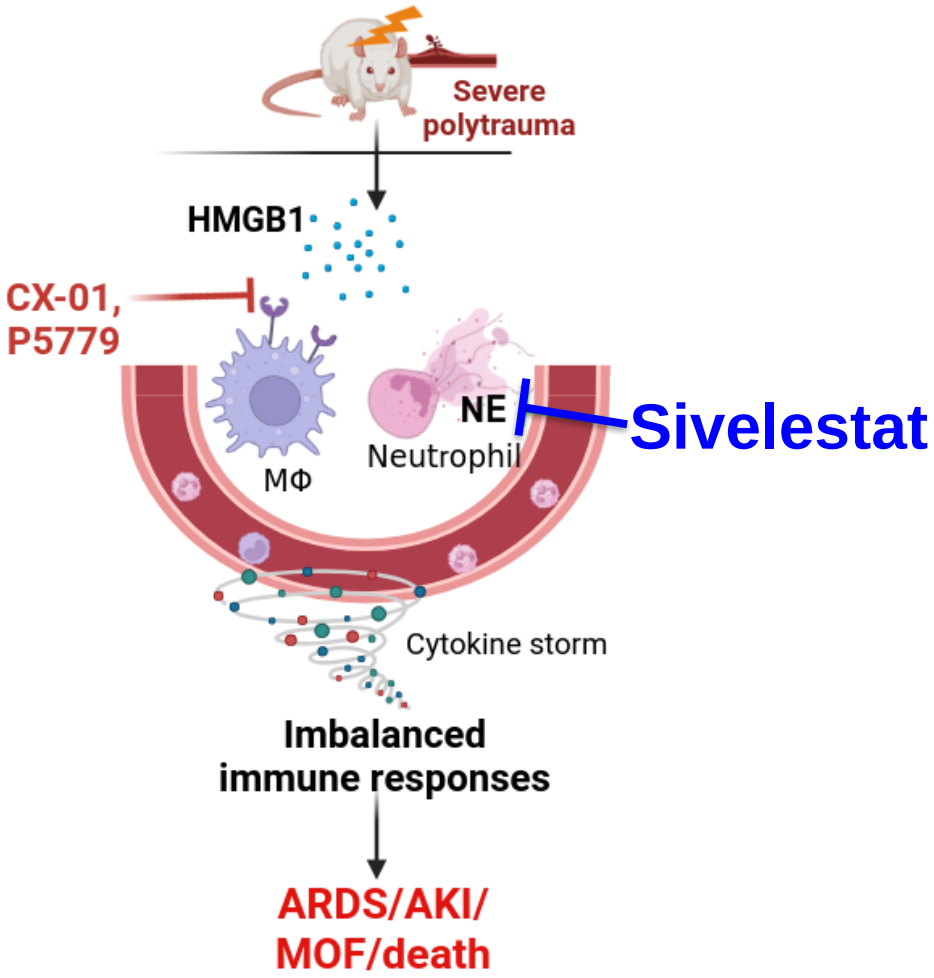
SARS: systemic anti-inflammatory response syndrome, also called

CARS: compensatory anti-inflammatory response syndrome



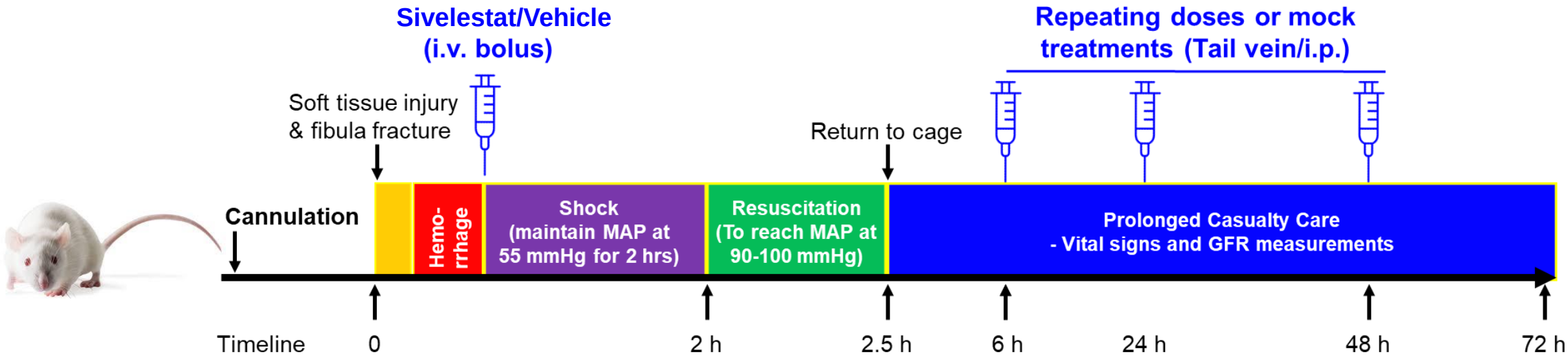
Sauaia, et al. Crit Care Clin. 2017

Hypothesis



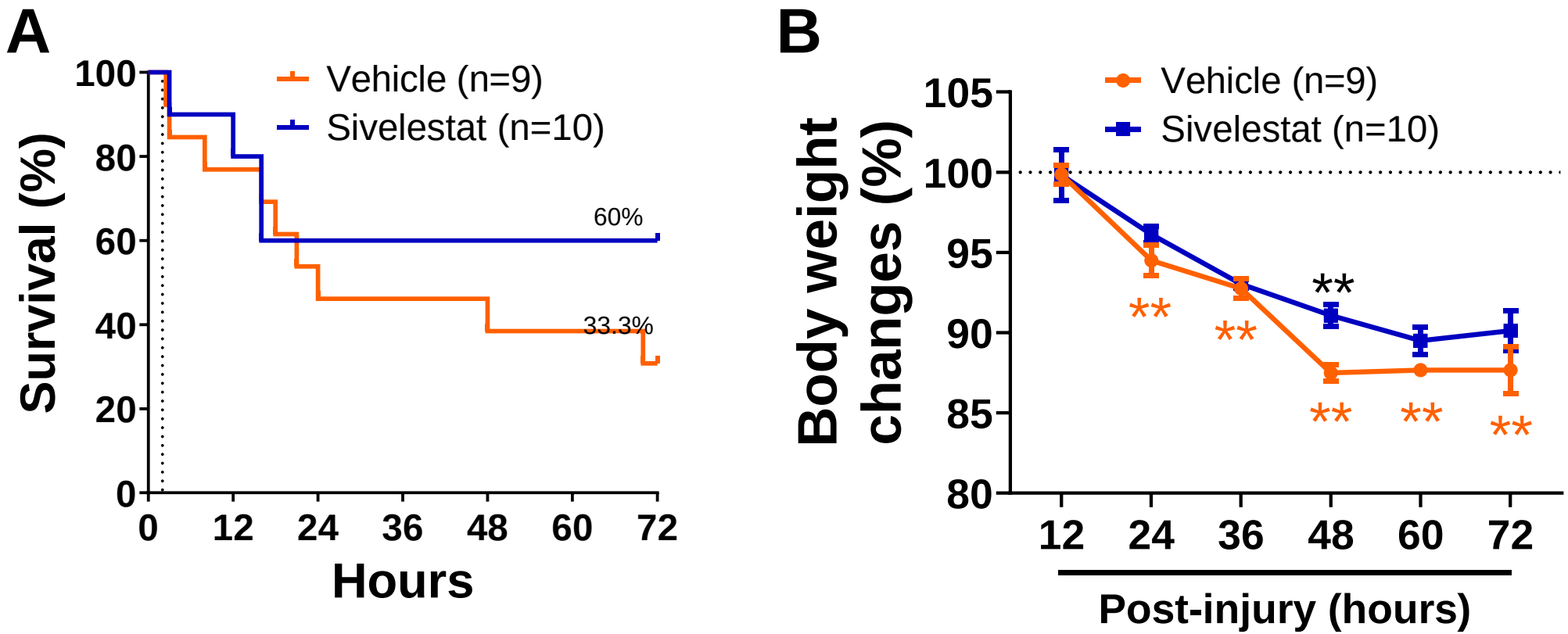
Therapeutic targeting of the trauma-induced immune response will improve survival and reduce trauma-induced organ failure?

Study Design

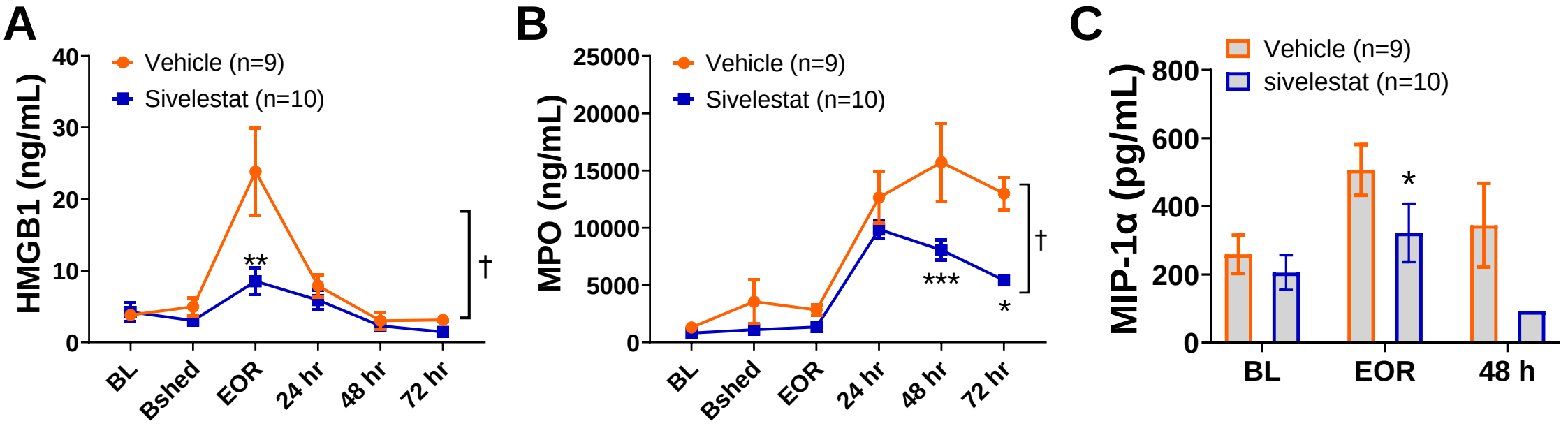


Note: All animals received adequate anesthesia and analgesia during the experimental procedures.

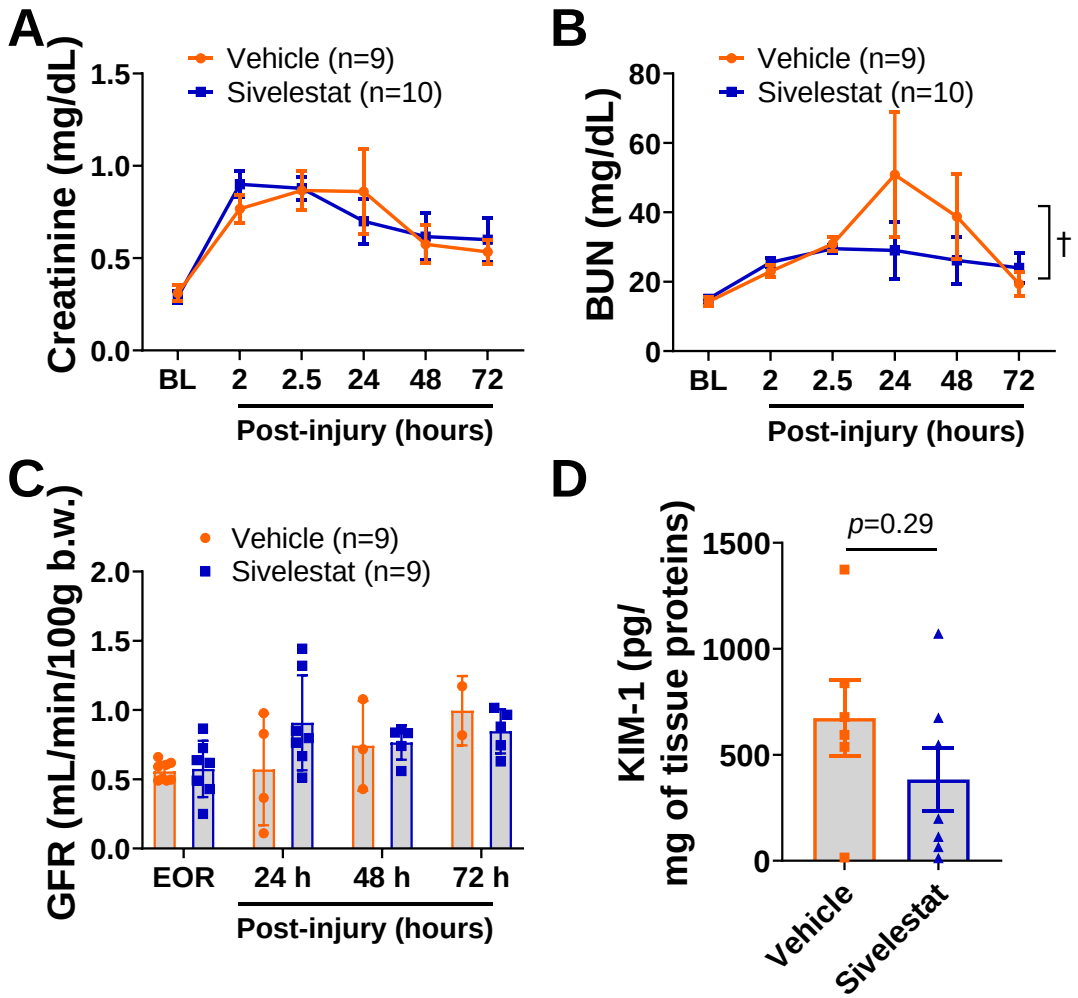
Sivelestat Treatment Improves Clinical Outcomes



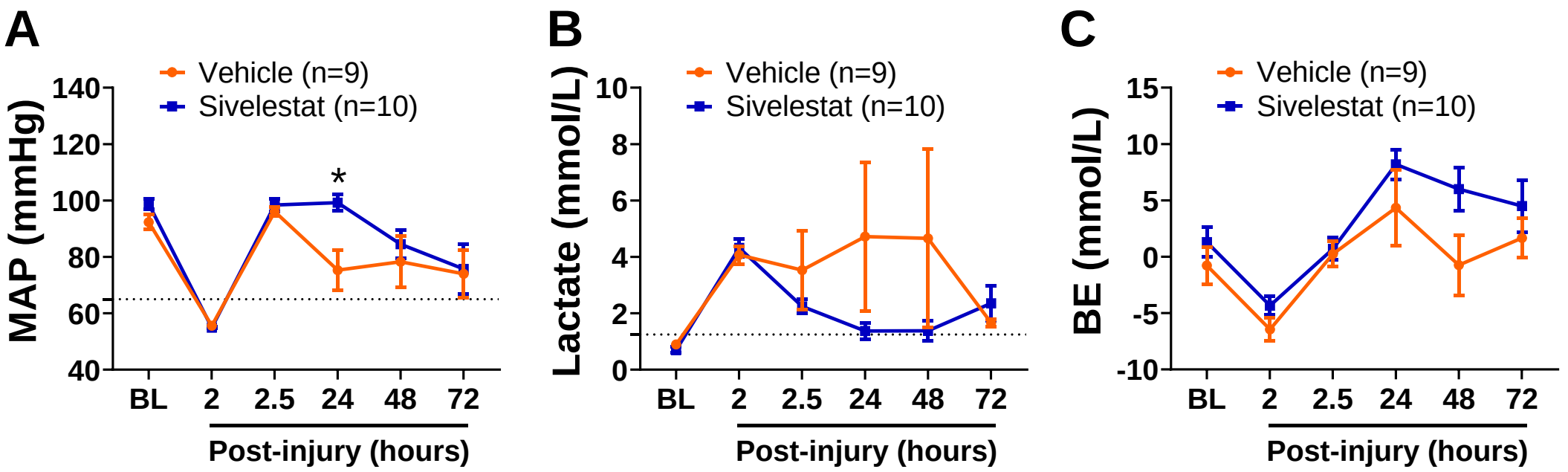
Sivelestat Treatment Reduces HMGB1 and Cytokines



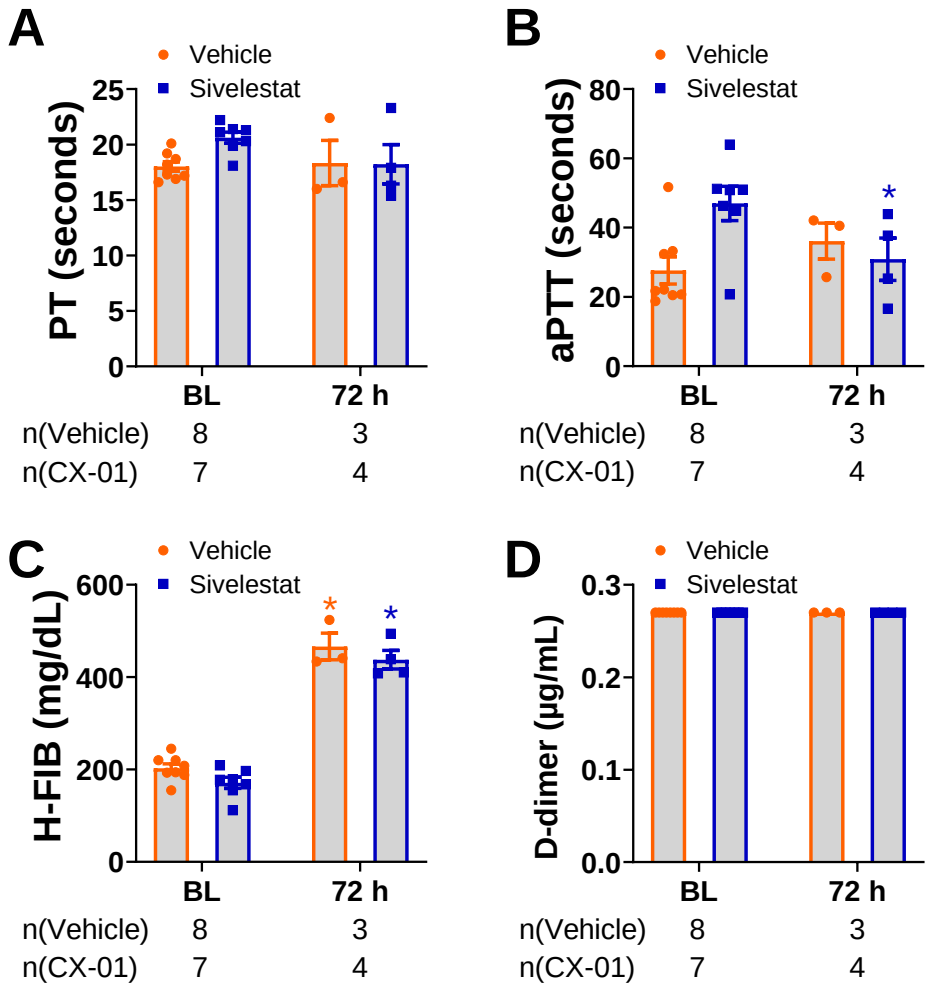
Sivelestat Treatment Impacts on AKI Parameters



Sivelestat Impacts on MAP and Systemic Acidosis



Sivelestat Does Not Alter the Coagulation Profile

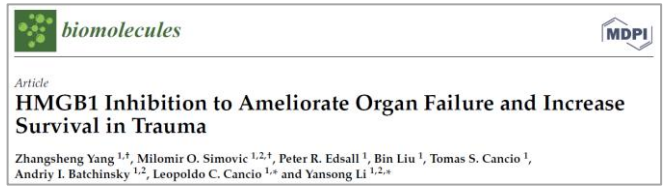


Conclusions

- **Sivelestat treatment increased survival and attenuated body weight loss in a rat polytrauma model.**
- **Sivelestat treatment reduced neutrophil activity and decreased inflammatory responses.**
- **Sivelestat treatment reduced trauma-induced acute kidney injury (AKI), improved mean arterial pressure (MAP) and attenuated trauma-induced lactate elevation.**
- **Sivelestat treatment did not significantly alter the coagulation profile triggered by polytrauma.**
- **Sivelestat may be a potential therapeutic agent to mitigate trauma-induced organ failure in prolonged care scenarios.**

Pipelines & Platform

» **Lab Pipeline 1: CX-01 improves survival and reduces AKI in rats (Poster #1004).**

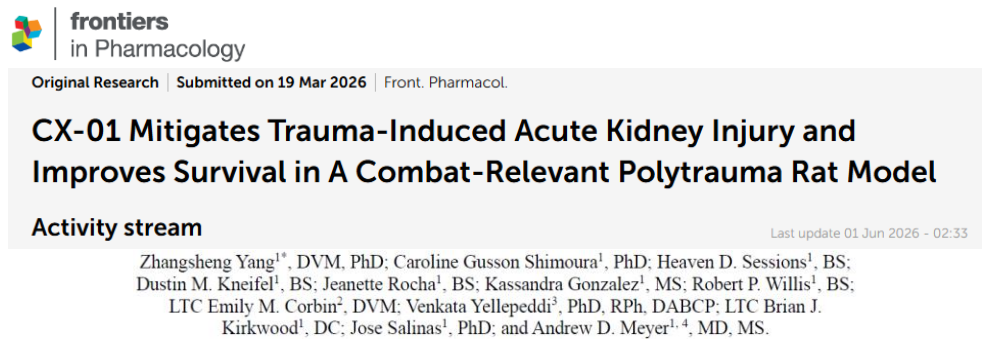


biomolecules MDPI

Article

HMGB1 Inhibition to Ameliorate Organ Failure and Increase Survival in Trauma

Zhangsheng Yang [1,†], Milomir O. Simovic [1,2,†], Peter R. Edsall [1], Bin Liu [1], Tomas S. Cancio [1], Andriy I. Batchinsky [1,2], Leopoldo C. Cancio [1,*] and Yansong Li [1,2,*]



frontiers in Pharmacology

Original Research | Submitted on 19 Mar 2026 | Front. Pharmacol.

CX-01 Mitigates Trauma-Induced Acute Kidney Injury and Improves Survival in A Combat-Relevant Polytrauma Rat Model

Activity stream

Last update 01 Jun 2026 - 02:33

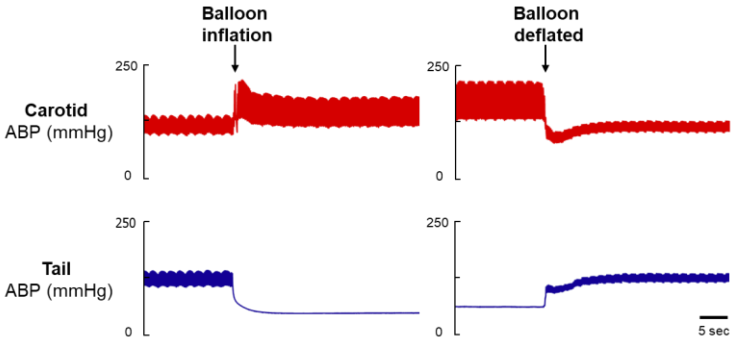
Zhangsheng Yang[1*], DVM, PhD; Caroline Gusson Shimoura[1], PhD; Heaven D. Sessions[1], BS; Dustin M. Kneifel[1], BS; Jeanette Rocha[1], BS; Kassandra Gonzalez[1], MS; Robert P. Willis[1], BS; LTC Emily M. Corbin[2], DVM; Venkata Yellepeddi[3], PhD, RPh, DABCP; LTC Brian J. Kirkwood[1], DC; Jose Salinas[1], PhD; and Andrew D. Meyer[1, 4], MD, MS.

» **Lab Pipeline 2: Roflumilast improves survival and reduces AKI in rats .**

Manuscript under review

- **Developed a rat model of REBOA-induced IRI to evaluate novel therapeutics (Poster #608).**

Manuscript in preparation



Acknowledgements

Personnel Supports:

- Jose Salinas, PhD
- LTC Brian J. Kirkwood, DC
- Andrew D. Meyer, MD, MS
- Caroline Gusson Shimoura, PhD
- Heaven D. Sessions, BS
- Dustin M. Kneifel, BS
- Jeanette Rocha, BS
- Kassandra Gonzalez, MS
- Venkata Yellepeddi, PhD
- Patrick P. Willis, BS
- Michael L. Lucas, BS
- LTC Emily M. Corbin, DVM & VSG support

Funding Supports:

- **US Army Medical Research & Development Command**
- DM230026
- CO240046
- CO250068

Questions

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"Military medicine is not just about treating injuries; it's about ensuring the health and readiness of those who serve, so they can accomplish their mission and return home safely."

- MG Paula C. Lodi, Commanding General, USAMRDC