Minocycline Hydrogel for Burn Wound Stabilization and Infection Control in Austere Settings

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RESEARCH & DEVELOPMENT

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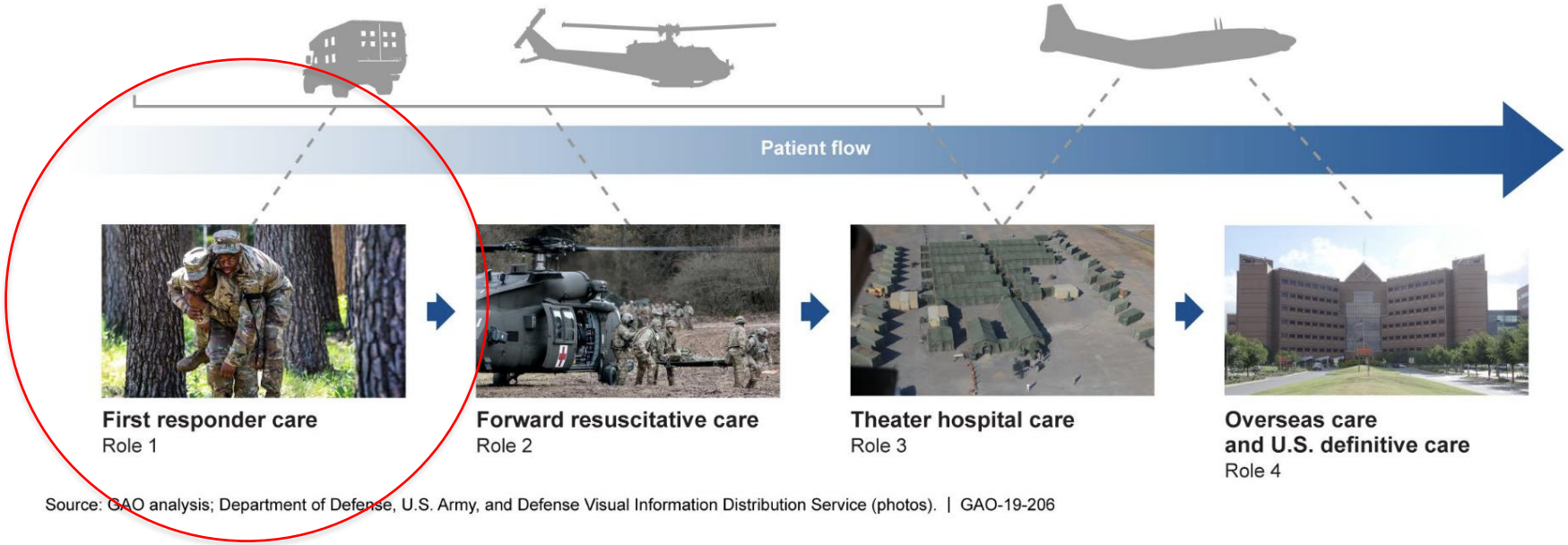
Research was conducted in compliance with Animal Welfare Act, the implementing Animal Welfare regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this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

All the animals used in the studies were anesthetized during the procedures and analgesia was provided prior to all surgical procedures.

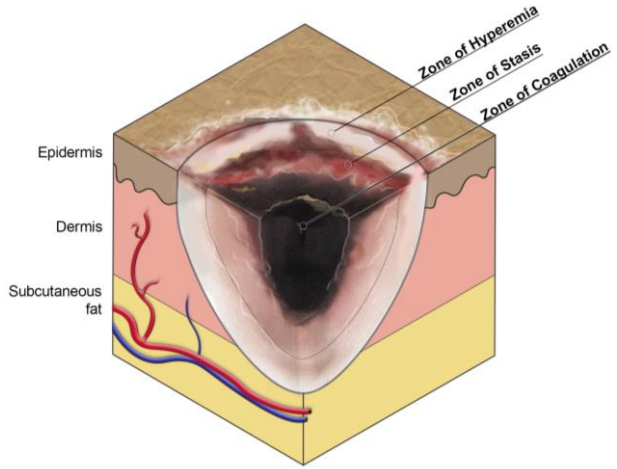
Kristo Nuutila, MSc, PhD has no conflicts to report.

Combat Burn Care

- Burns are common in military conflicts.
- Surgical debridement is not contemplated in austere settings.
- Open wounds awaiting definitive treatment are at risk of infection and delayed healing.



Source: GAO analysis; Department of Defense, U.S. Army, and Defense Visual Information Distribution Service (photos). | GAO-19-206



Objective and Aims

Objective

- Develop and test novel and innovate strategies utilizing biomaterials, delivery platforms, and active compounds to treat battlefield burns.

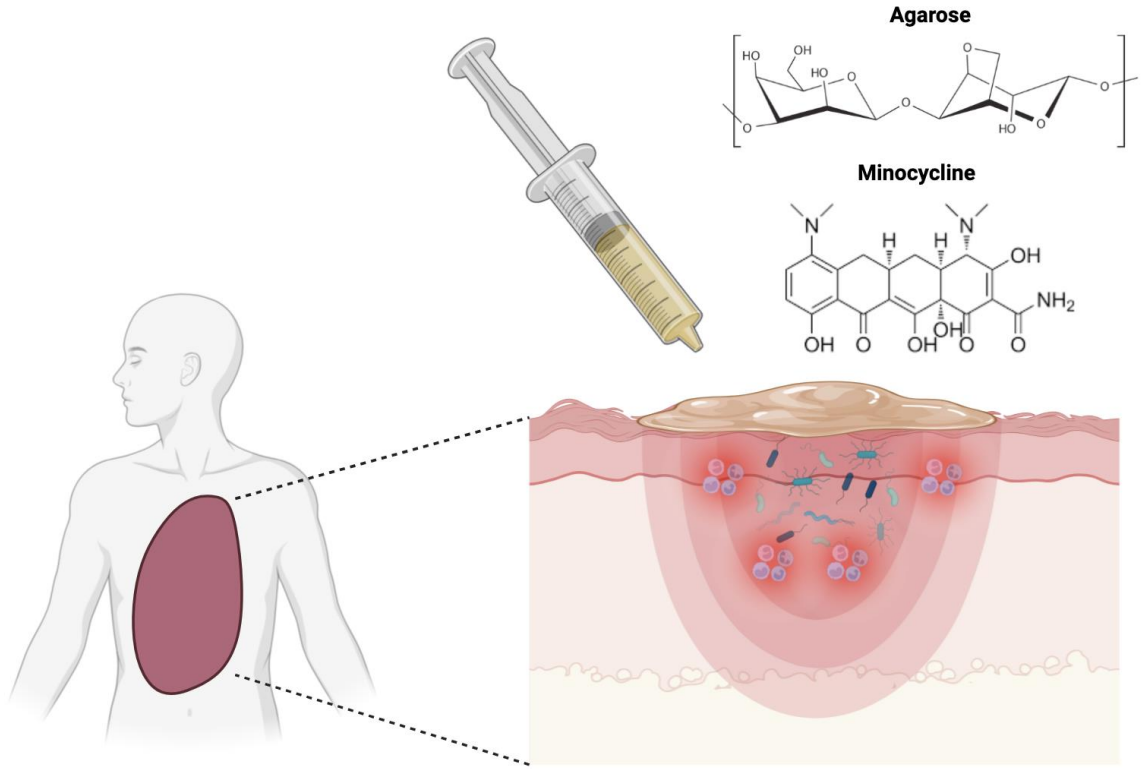
Aims

- Formulate and optimize a minocycline-containing agarose hydrogel in vitro
- Evaluate the efficacy of the treatment in porcine burn models

Agarose and Minocycline

Agarose

- Excellent biocompatibility
- High water content
- Minimal immunogenicity
- Tunable mechanical and diffusion properties
- Provides a stable, inert matrix

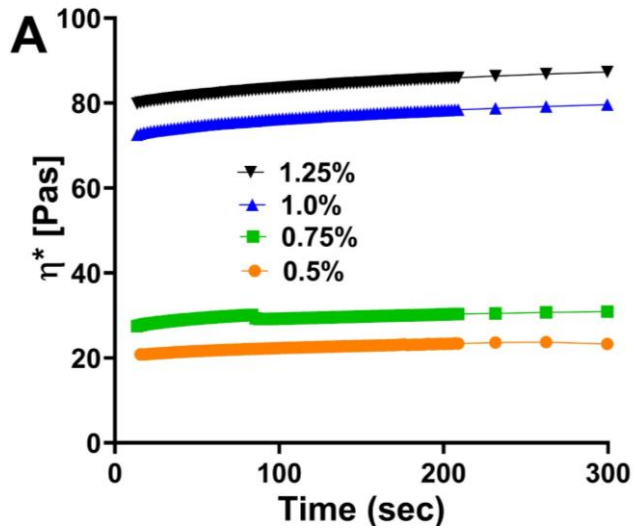


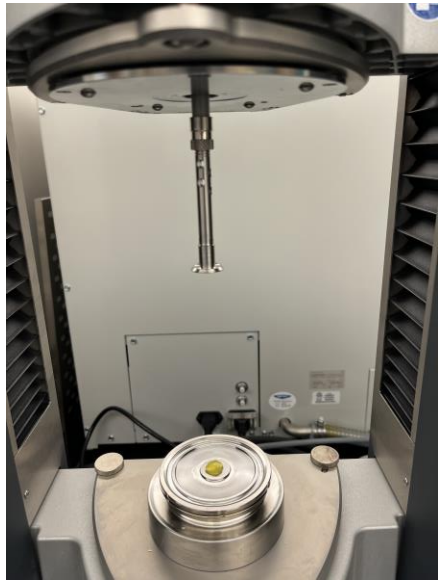
Minocycline

- Tetracycline-class antibiotic
- Broad-spectrum activity against Gram-positive and Gram-negative bacteria
- Intrinsic anti-inflammatory effects via downregulation of pro-inflammatory cytokines

Material Characterization - Viscosity

- To assess the influence of agarose concentration on the physical properties of minocycline hydrogels (8 mg/mL minocycline), hydrogels containing 0.5, 0.75, 1.0 and 1.25% agarose were prepared.
- Complex viscosity (η*) of each hydrogel were measured using a rotational rheometer.
- Viscosity increased substantially between hydrogels containing 0.5% agarose (20 Pa·s) and 1.25% agarose (80 Pa·s), indicating increased agarose chain entanglement.

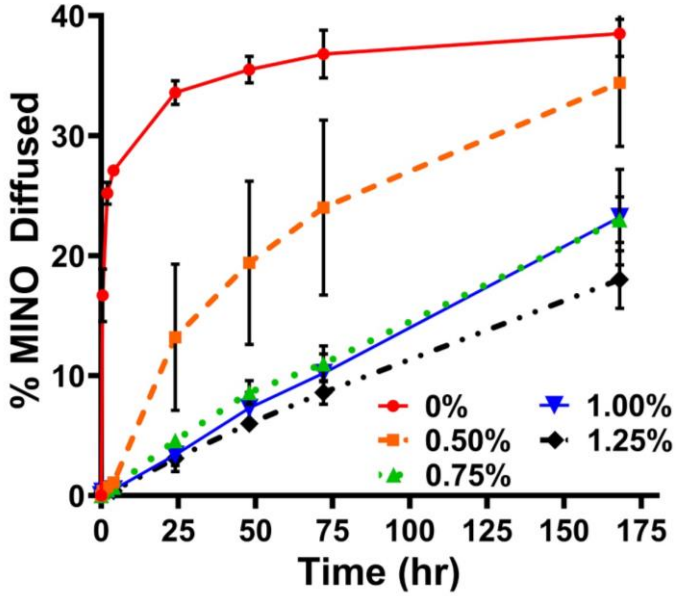




Material Characterization – Minocycline Release

- The effects of agarose concentration on minocycline diffusion across semipermeable membranes (0.4 µm pore size) were evaluated over 7 days at 22 °C using LC-MS/MS.

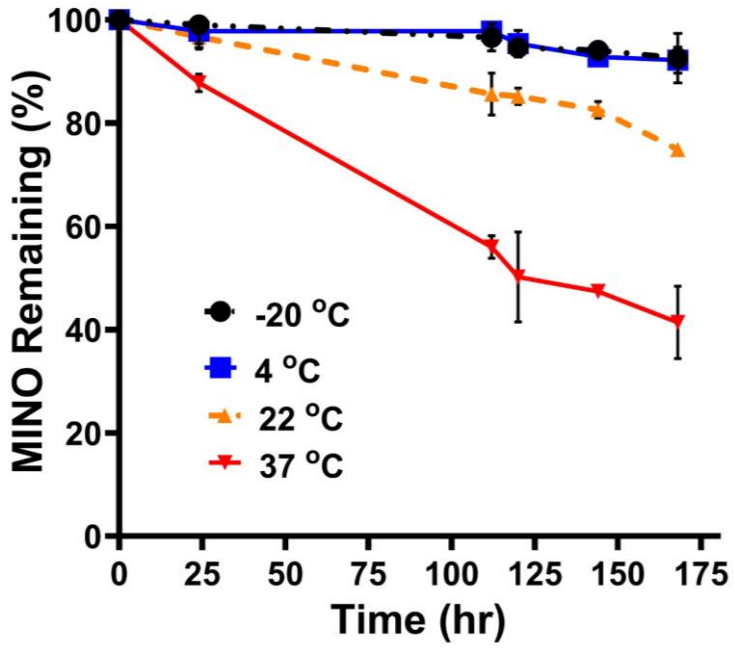
- After 7 days, 34%, 23%, 23%, and 18% diffused from hydrogels containing 0.5, 0.75, 1.0, and 1.25% agarose, respectively.



Material Characterization – Minocycline Stability

- Stability of minocycline in the hydrogel over time at at –20, 4, 22, and 37 °C were studied.

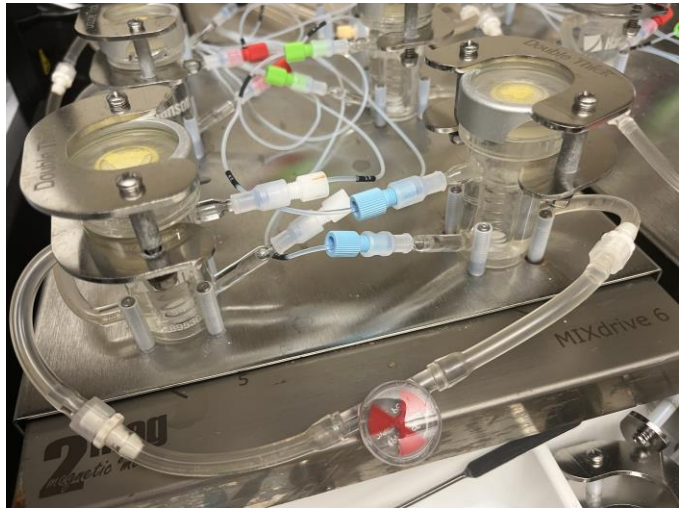
- Minocycline retained stable (<10% degradation) for 1 day at 37 °C, 3 days at 22 °C, and for more than a week at 4 °C and -20 °C.

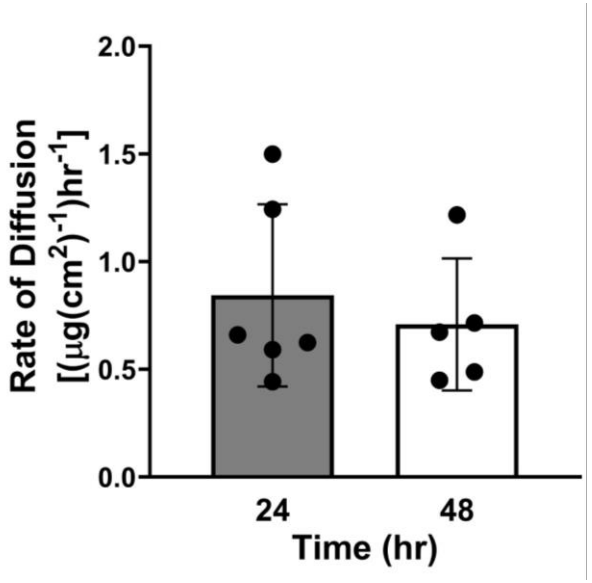


Material Characterization – Permeation Testing

- *Ex vivo* diffusion of minocycline was assessed using Franz cells with burnt porcine skin and 1% agarose hydrogels containing 8 mg/mL minocycline at 37 °C

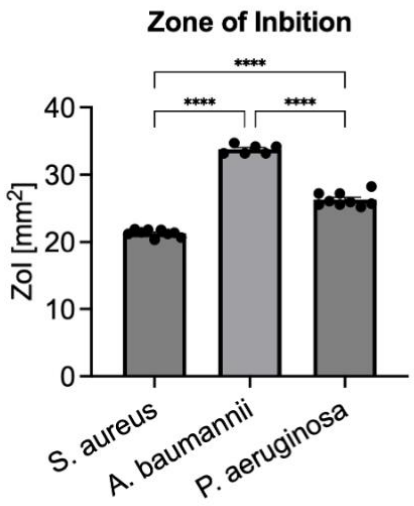
- The diffusion rates during the 0–24 and 24–48-hour intervals were 1.5 and 1.3 μg $(cm^2)^{-1}$ hr^{-1}, respectively.

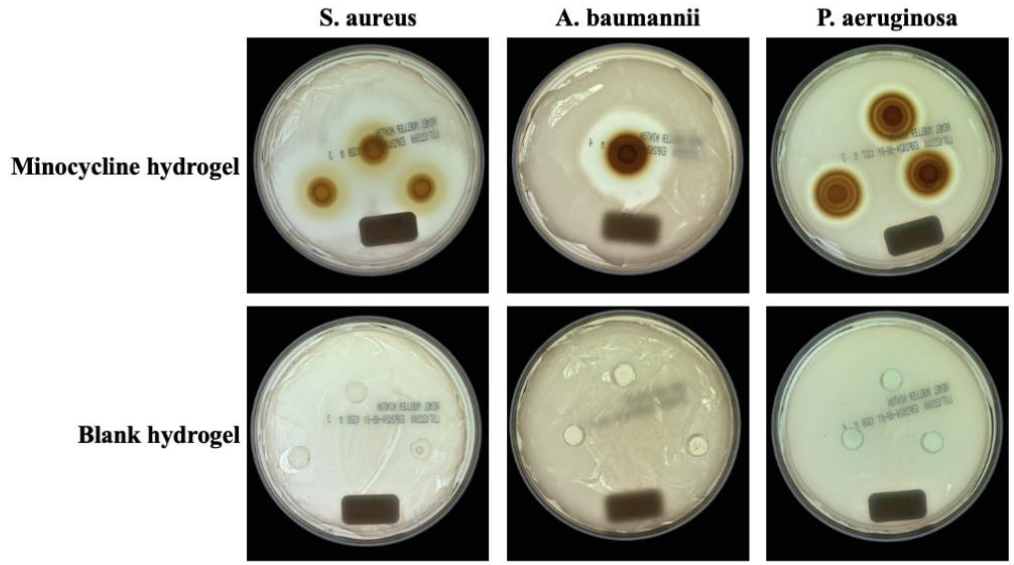




Material Characterization – Antimicrobial Activity

- ZoI assay confirmed antibacterial activity of the minocycline–agarose hydrogel against *S. aureus*, *P. aeruginosa*, and *A. baumannii* .
- Clear inhibition zones observed for all three organisms.
- Significantly greater inhibition of *A. baumannii* compared to others ($p < 0.0001$).





Preclinical Evaluation

Uninfected burn study (3 Yorkshire pigs)

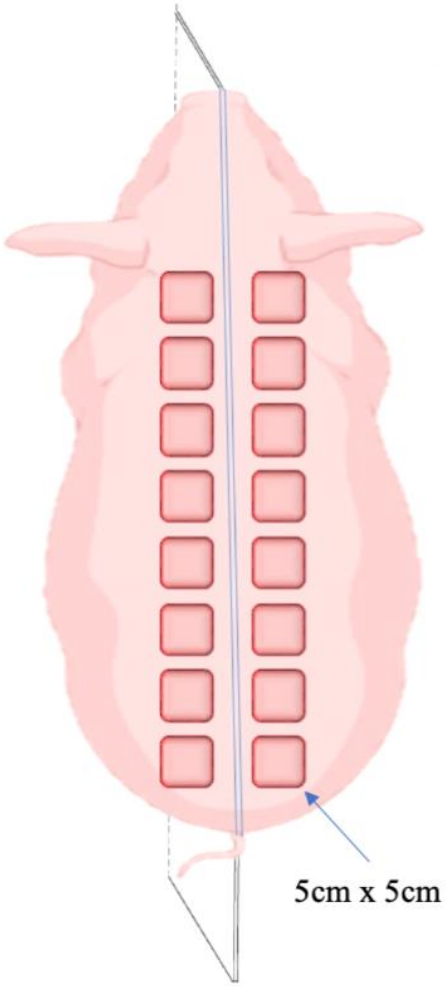
- Evaluated the effects of the minocycline–agarose hydrogel on inflammation, burn wound progression, and overall healing in uninfected deep partial-thickness burns.

Infected burn study (3 Yorkshire pigs)

- Assessed the therapeutic efficacy of the minocycline–agarose hydrogel in porcine burns infected with a polymicrobial cocktail of ***A. baumannii***, **P. *aeruginosa***, and ***S. aureus***.

Treatment groups (n=4/animal, total n=12)

- Minocycline (8 mg/ml)–agarose (1%) hydrogel
- Blank agarose (1%) hydrogel (vehicle control)
- Silvadene cream (SoC control)
- Gauze



Day 0
- Blood draw
- Burn creation
- (infection*)
- Treatment
- Biopsy
- Assessment/Imaging
- Treatment

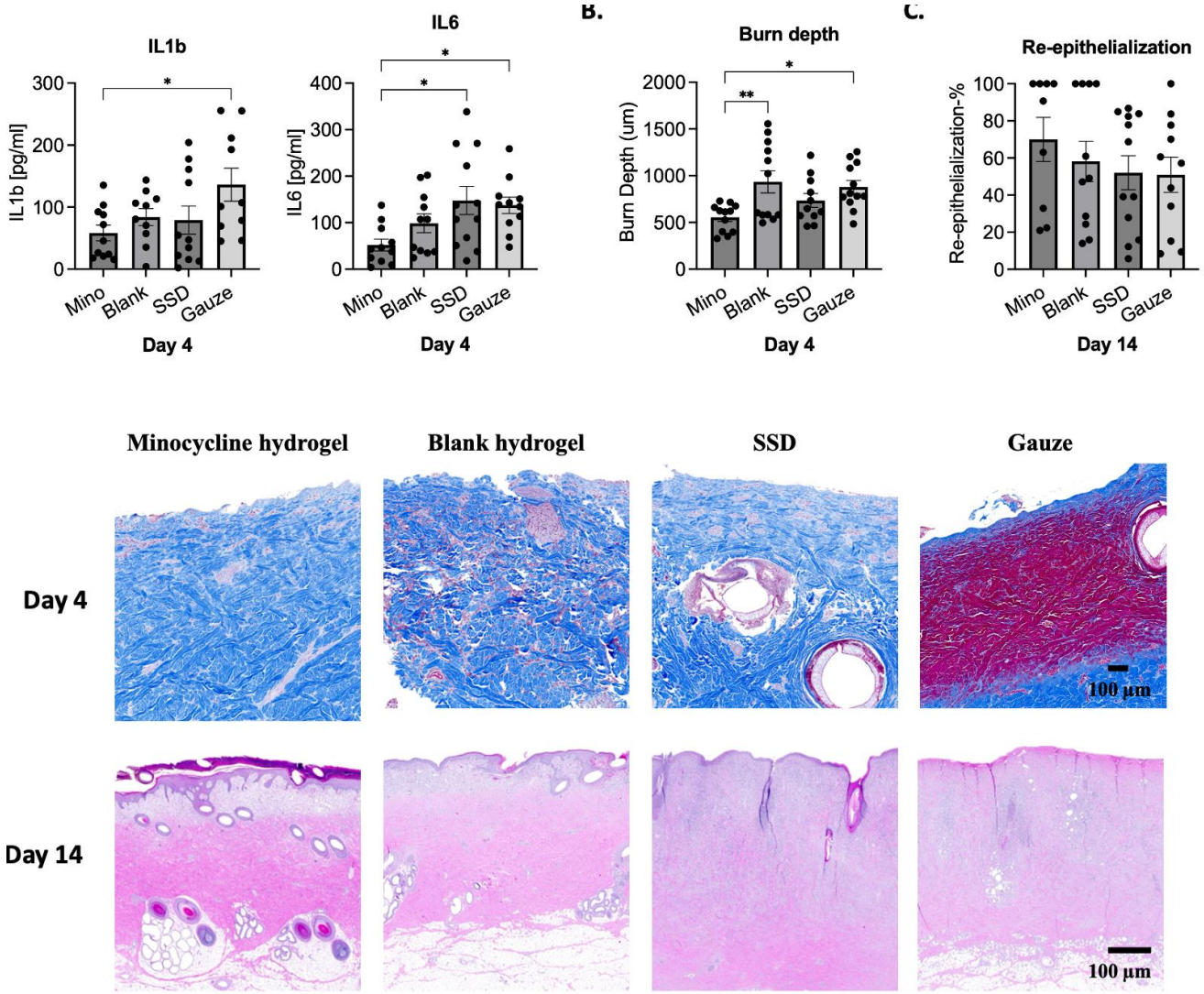
Days 1, 4, and 7
- Blood draw
- Biopsy
- Assessment/Imaging
- Treatment

Day 14
- Blood draw
- Assessment/Imaging
- Euthanasia
- Biopsy

Uninfected Burn Study

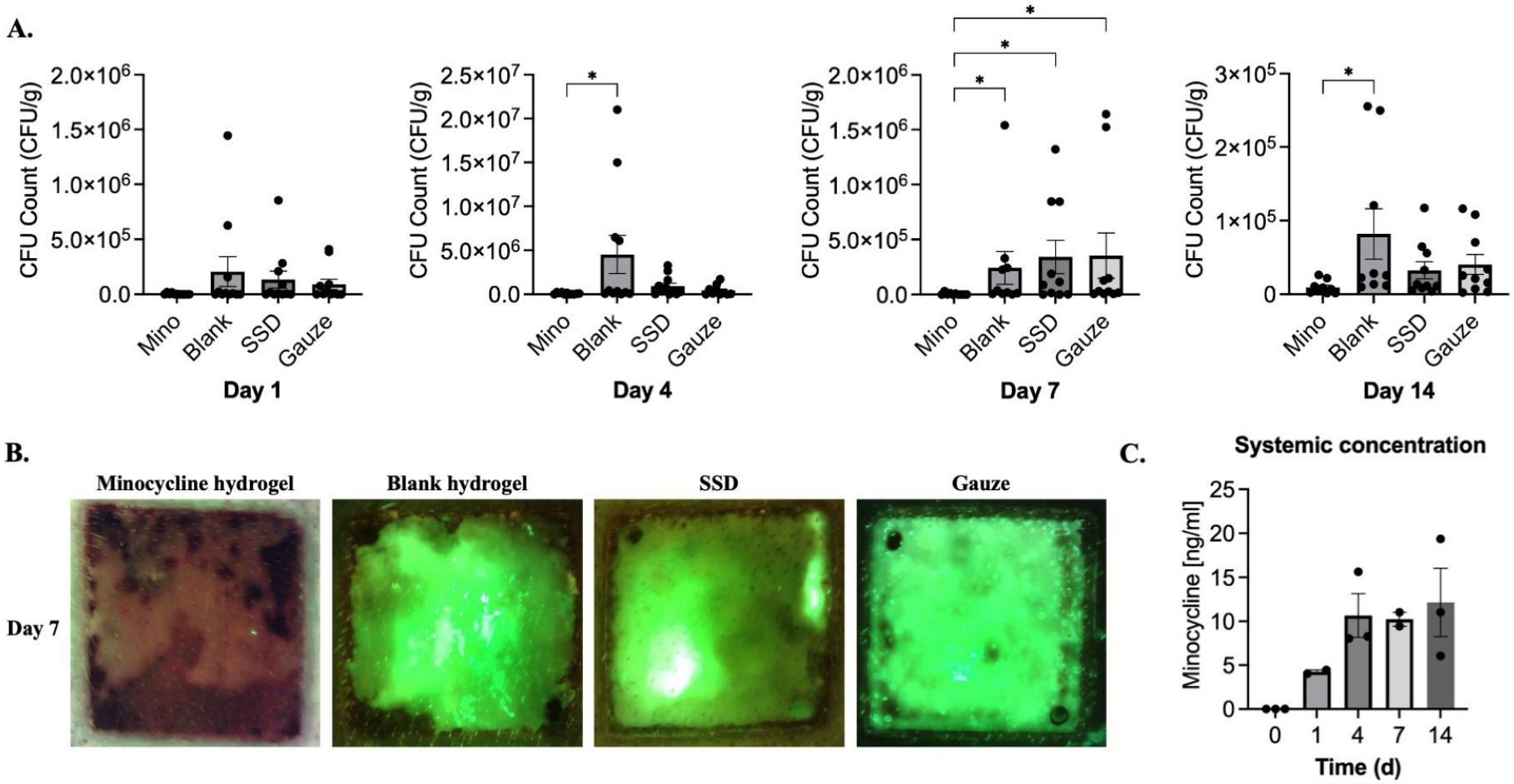
The minocycline–agarose hydrogel:

- Reduced inflammation (↓ IL-1b, IL-6)
- Mitigated burn progression → significantly shallower burn-induced damage by day 4 vs. controls ($p < 0.05$)
- Accelerated healing → 70% re-epithelialization by day 14 vs. 51–58% (controls)



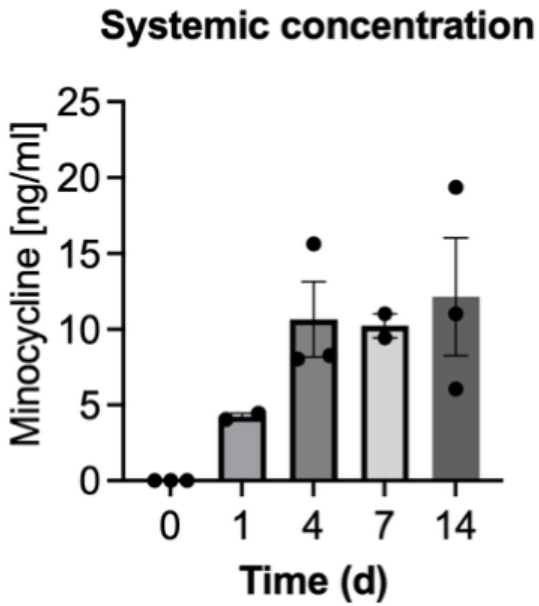
Infected Burn Study

- Reduced bacterial load in infected burns (days 4–14) vs. controls



Systemic Toxicity

- Assessed systemic toxicity due to high minocycline concentration in the hydrogel (8 mg/ml)
- Plasma minocycline levels: 4–31 ng/ml
- ~100× lower than peak levels from systemic administration → minimal systemic exposure



Conclusions

- Topical application of minocycline in high concentrations is safe.

- The agarose–minocycline hydrogel represents a promising approach for combat burn management, providing:
  - sustained drug release
  - effective infection control (against *S. aureus*, *P. aeruginosa*, and *A. baumannii)*
  - mitigation of burn wound progression
  - enhanced healing

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Questions

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