

The Impact of Burn Injury on Inflammatory and Immunologic Functions: Clinical and Experimental Perspectives

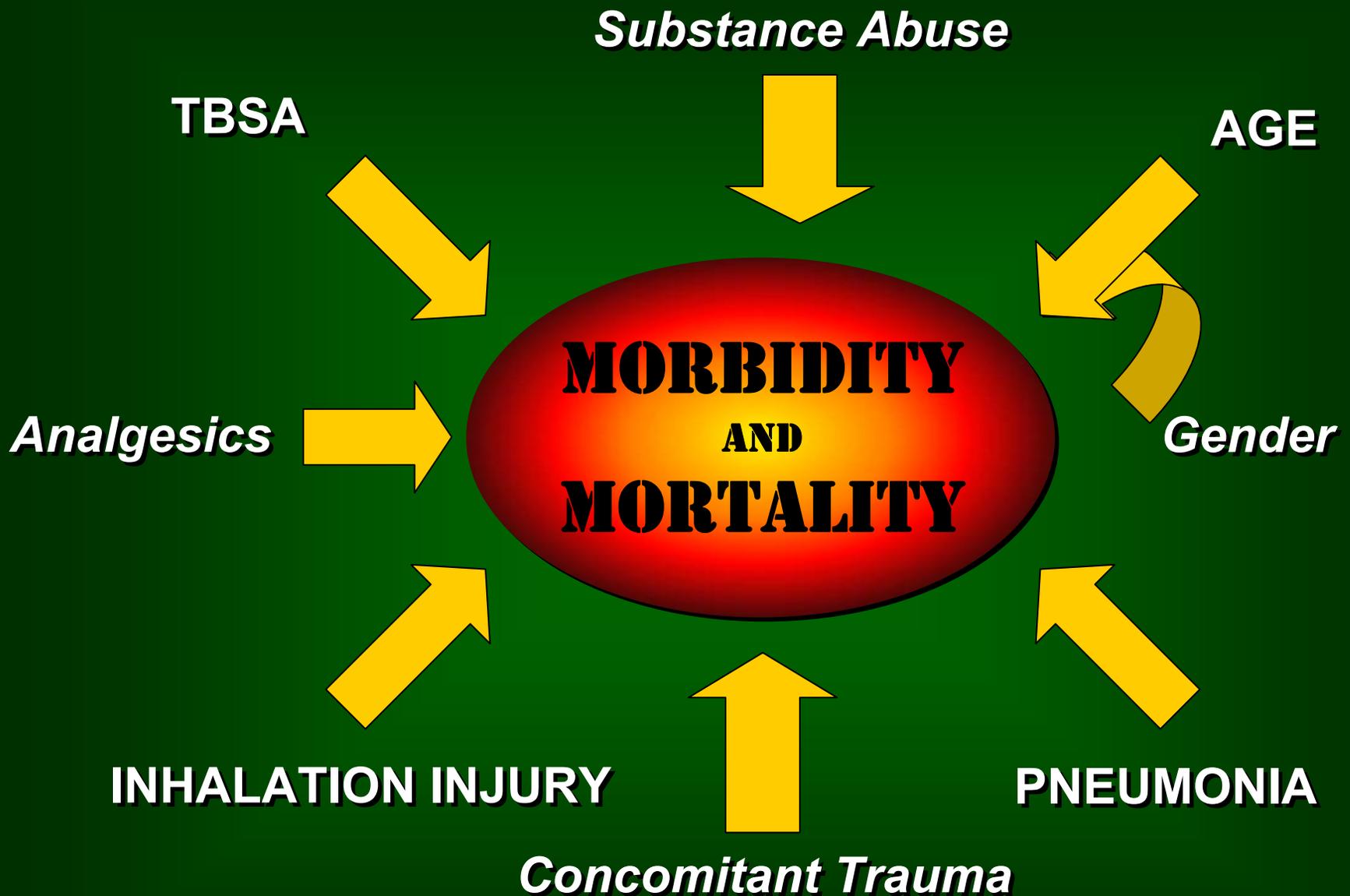
Martin G. Schwacha, PhD

*Associate Professor of Surgery, Center for Surgical Research and
Department of Surgery, University of Alabama at Birmingham,
Birmingham, Alabama*



Introduction

-  The WHO predicts injury will surpass infectious diseases as the leading cause of death worldwide by 2020.
-  The American Burn Association estimates 1.1 million burn injuries require medical attention in the US per year; 50% in specialized burn facilities.
-  Up to 10,000 people in the US die every year of burn-related infections.



Clark WR, Fromm BS. Acta Chir Scand 537(Suppl):1-126, 1987.

Shirani KZ, Pruitt BA, Mason Ann Surg 205:82-87, 1987.

Tenets of Burn Management



ATLS/ABLS (Advanced Trauma (Burn) Life Support)



Appropriate Facilities and Resources



Resuscitation: *early & appropriate*

- *Reduced incidence of organ dysfunction*



Wound Management

- *Escharotomy*
- *Early Excision and Grafting*
- *Topical Applications*

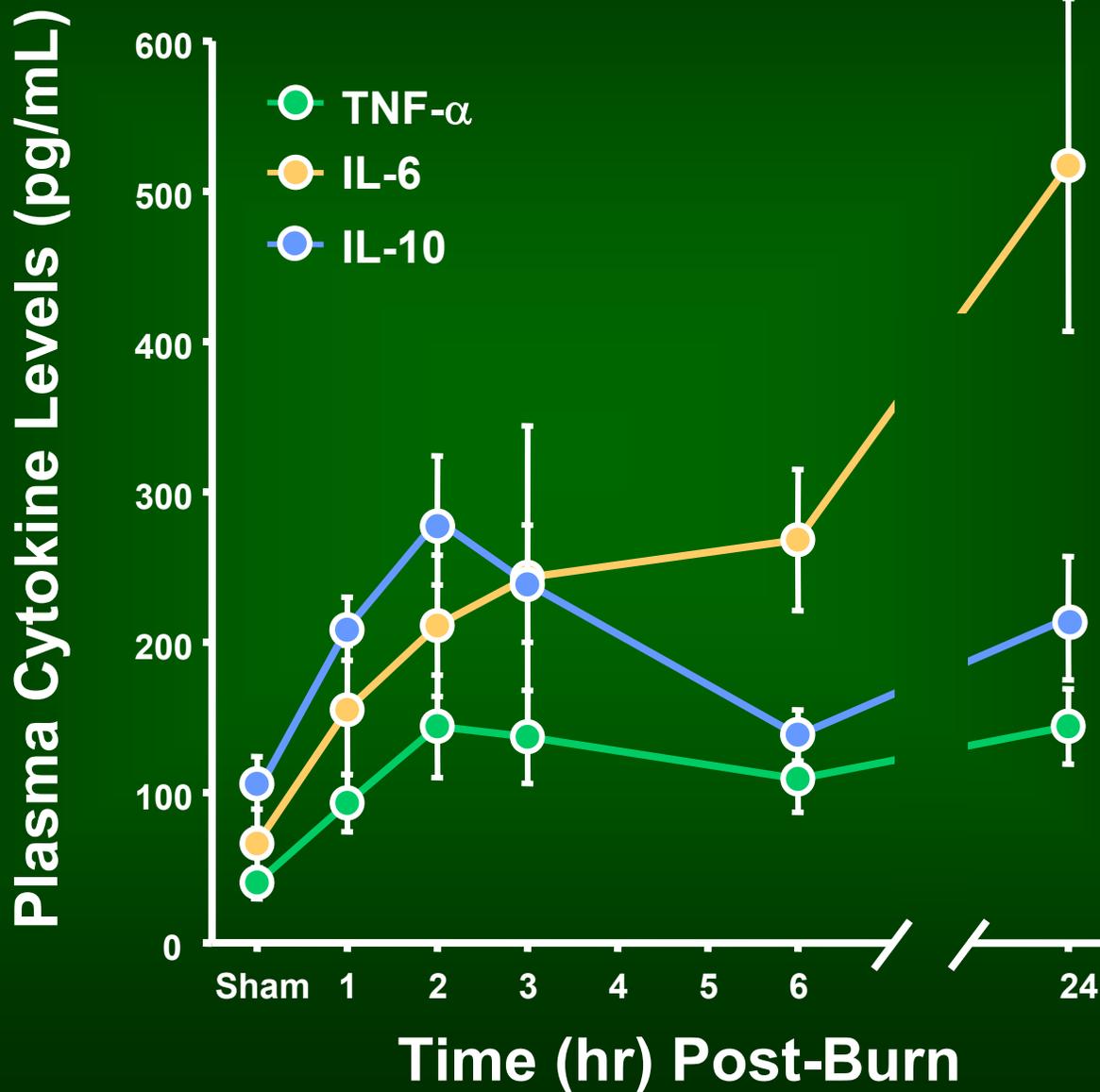


Nutritional Support



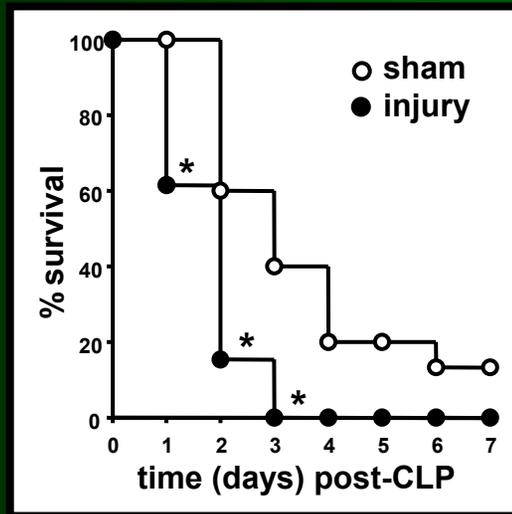
Early Diagnosis of Inhalation Injury

Early Systemic Inflammatory Responses

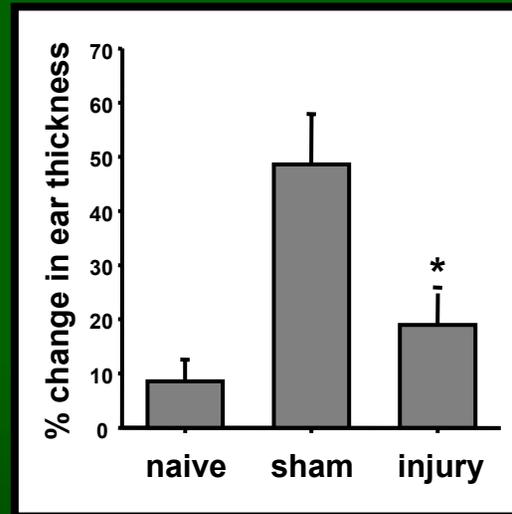


Post-Burn Immunosuppression

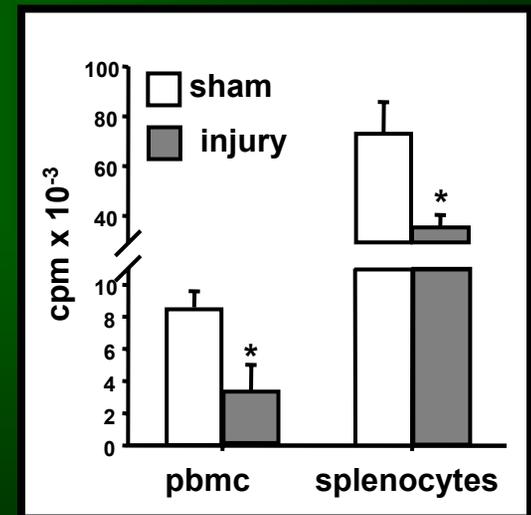
Numerous studies have demonstrated that thermal injury induces an immunosuppressed state that predisposes patients to subsequent sepsis and multiple organ failure.



Sepsis

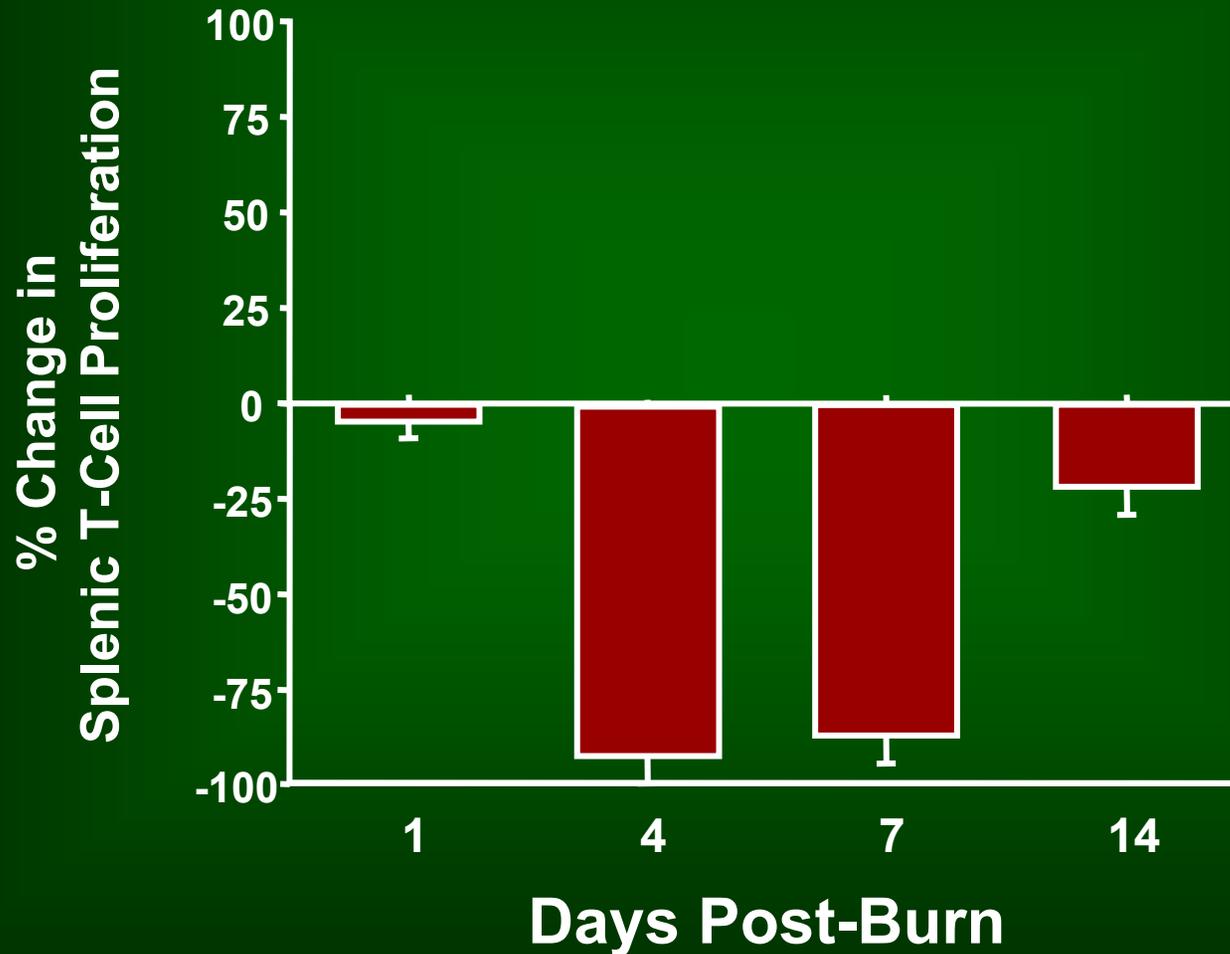


DTH



In Vitro T-Cell Function

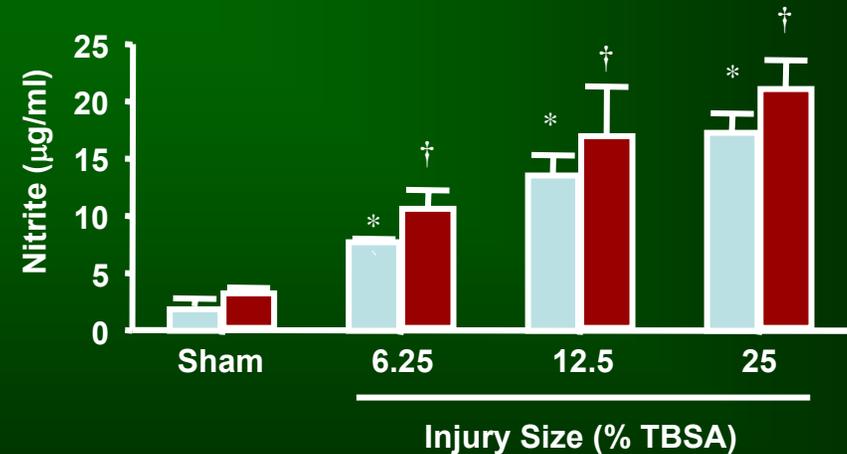
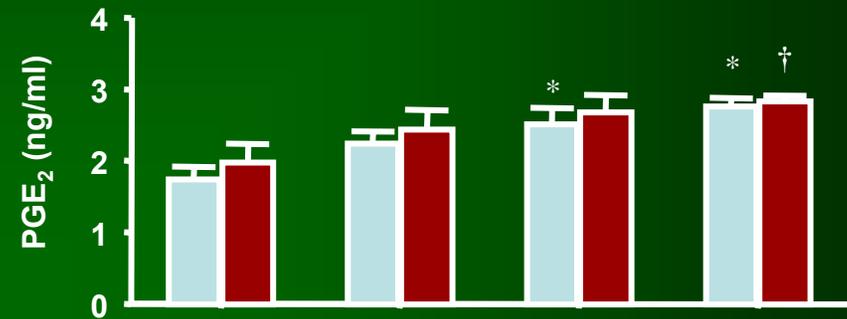
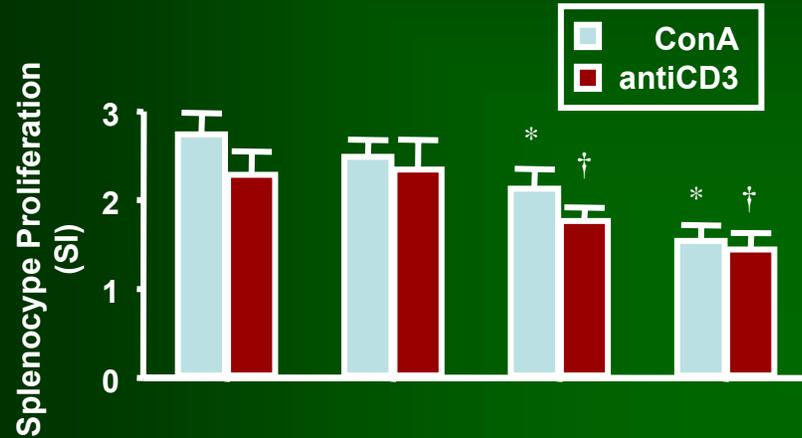
Time Course of Post-Burn Immunosuppression



The Effect of Burn Size of Post-Burn Immunosuppression

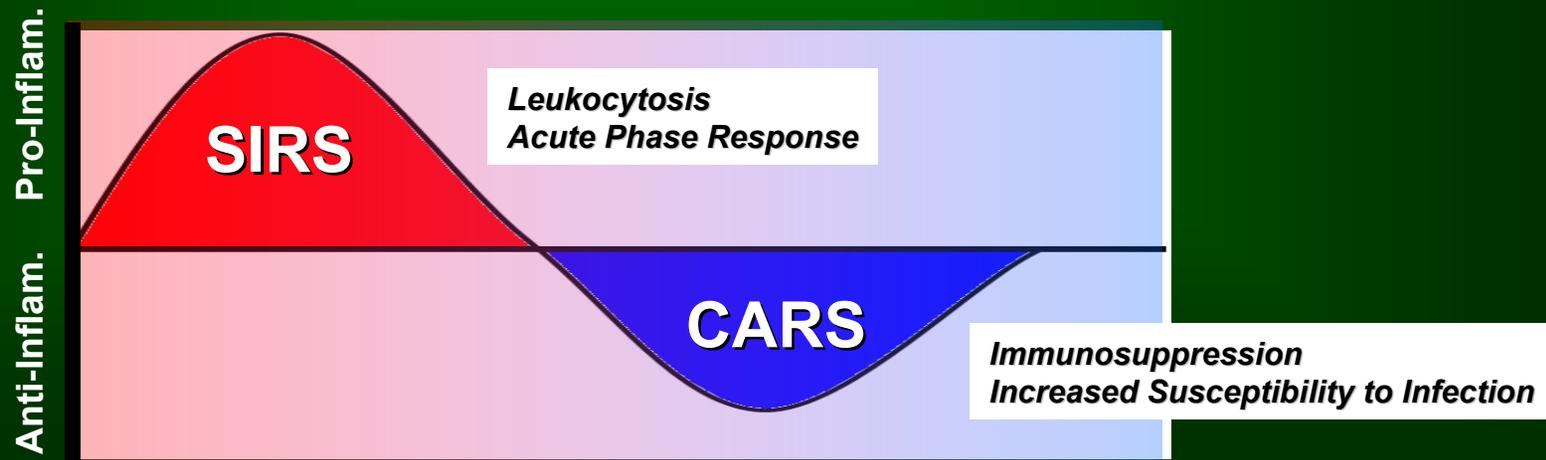
T-Cell Proliferation

Immunosuppressive Mediators



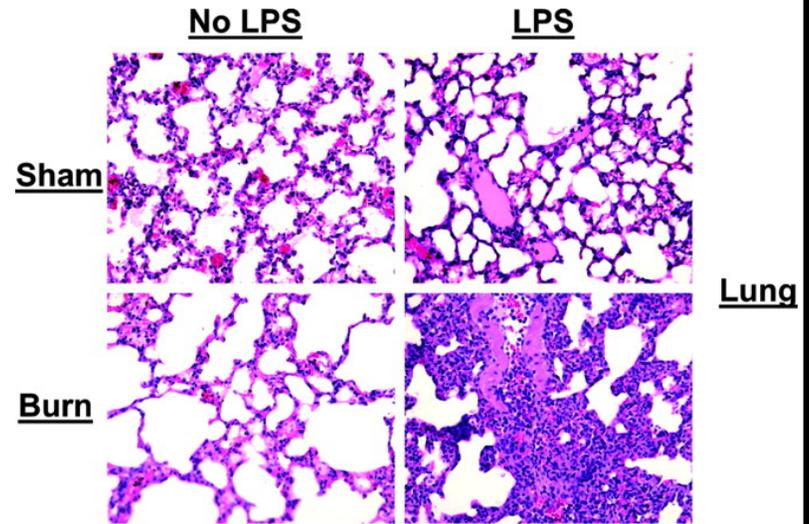
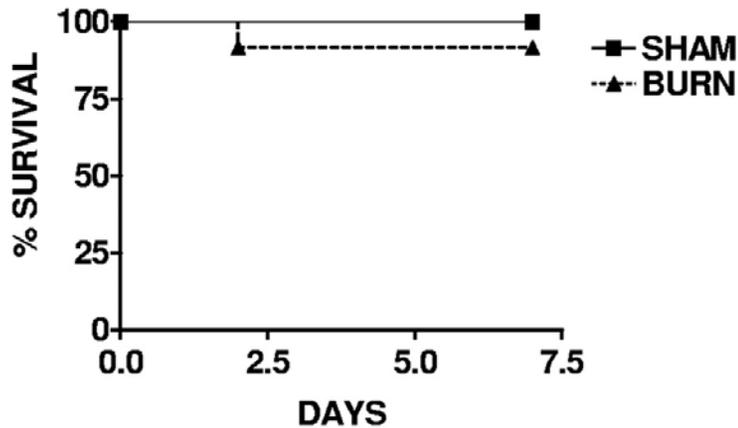
The SIRS/CARS Paradigm

- 🔥 Studies have shown that the initial immune response to injury is inflammatory, (**the systemic inflammatory response; SIRS**).
- 🔥 In most injured patients, SIRS remits after several days and is followed by **the compensatory anti-inflammatory response syndrome (CARS)**.
- 🔥 CARS is characterized by the production of counter-inflammatory cytokines which can suppress immune responsiveness.

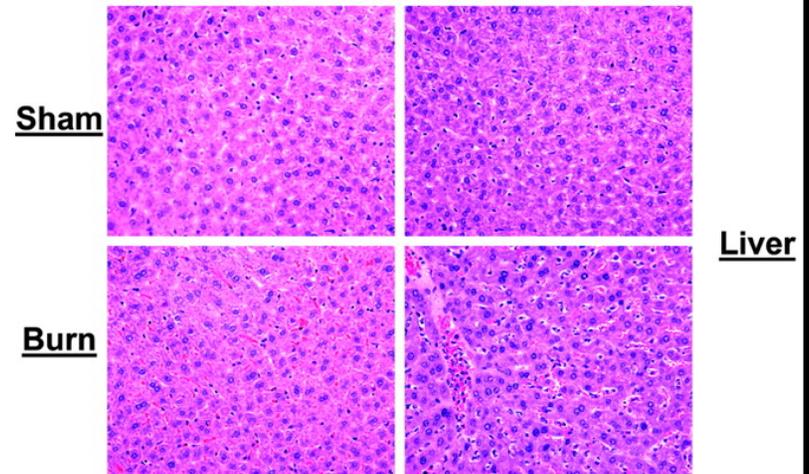
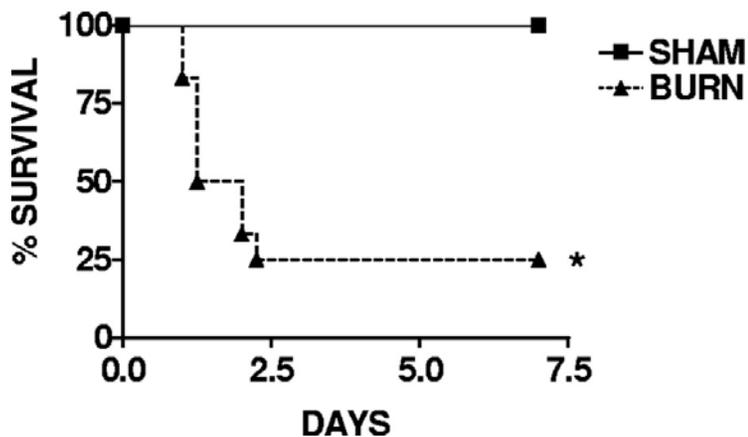


Burn Injury Predisposes Mice for a Lethal LPS Response

A. LPS Challenge at 1 Day After Injury



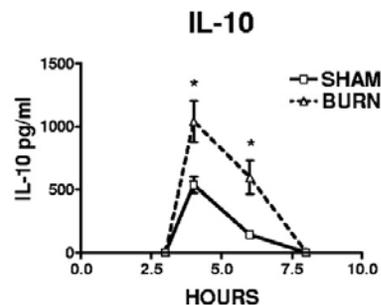
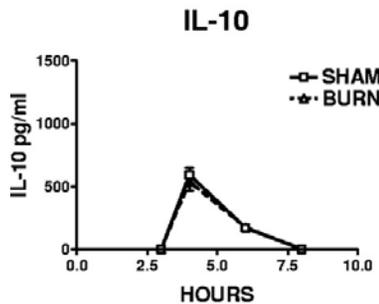
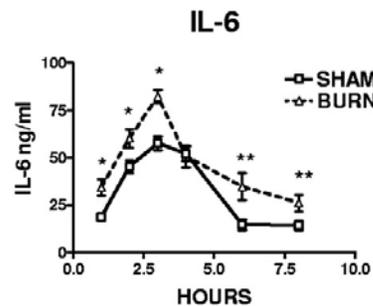
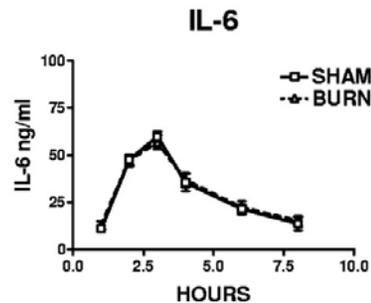
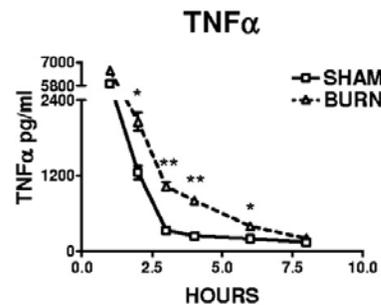
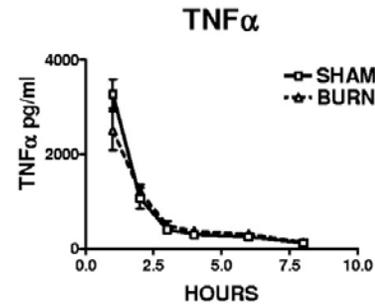
B. LPS Challenge at 7 Days After Injury



Impact of Burn Injury on Systemic Inflammatory Response to LPS

A. LPS at 1 Day Post-Injury

B. LPS at 7 Days Post Injury

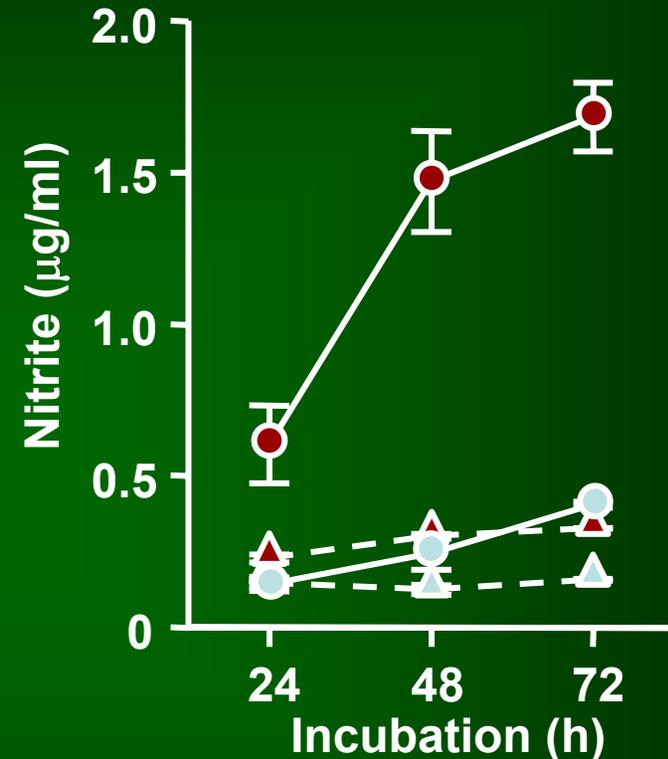
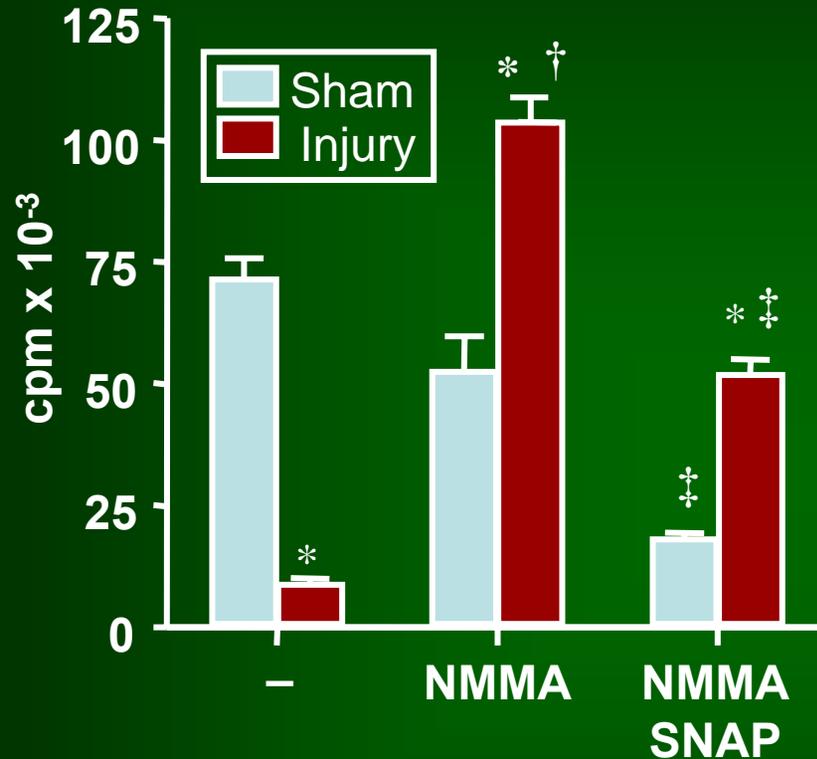


Sequential analysis of plasma TNF, IL-6, and IL-10 levels of LPS-challenged mice. sham- or burn-injured mice given 10 mg/kg LPS at 1 (A) or 7 (B) days after injury.

* $P < 0.05$

** $P < 0.01$ burn vs. sham

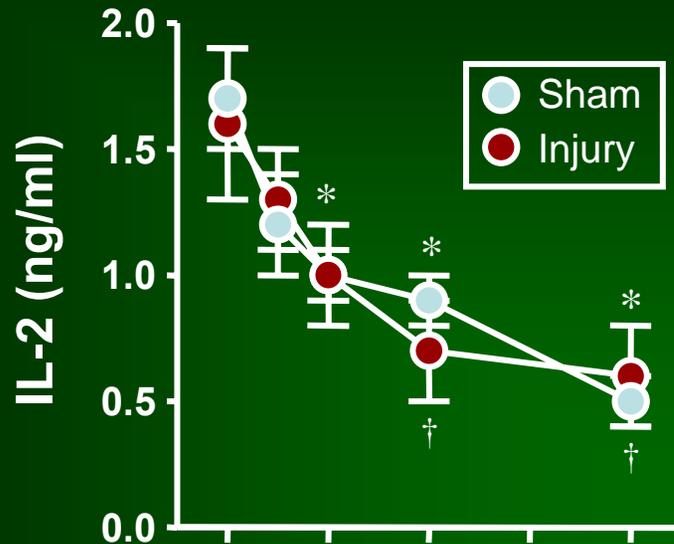
The Effect of Burn Injury on T-Cell Proliferation and Nitric Oxide Production



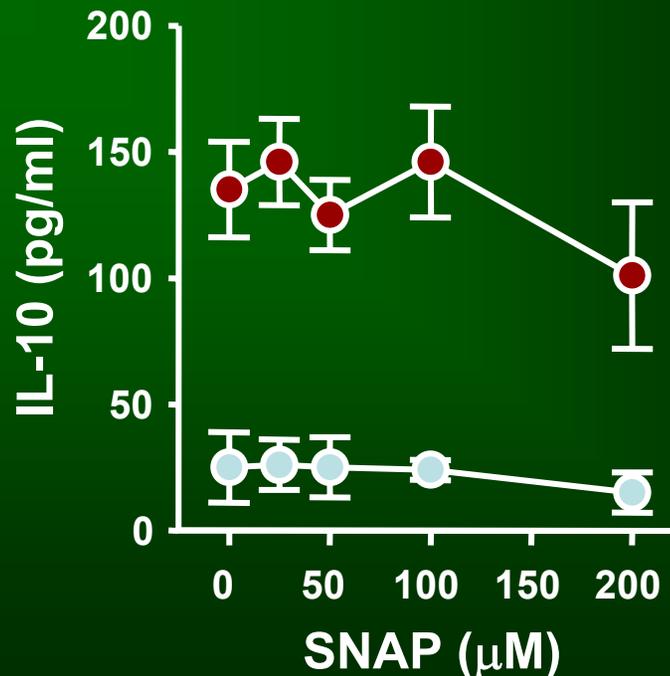
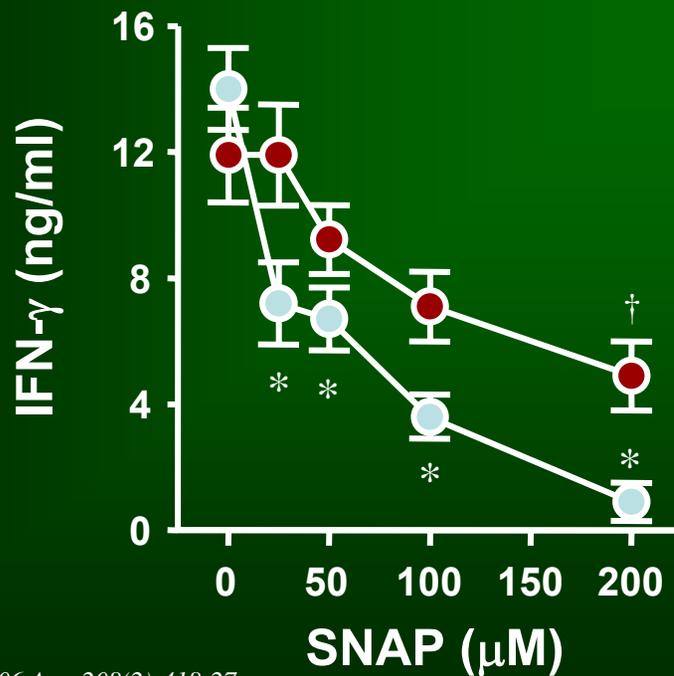
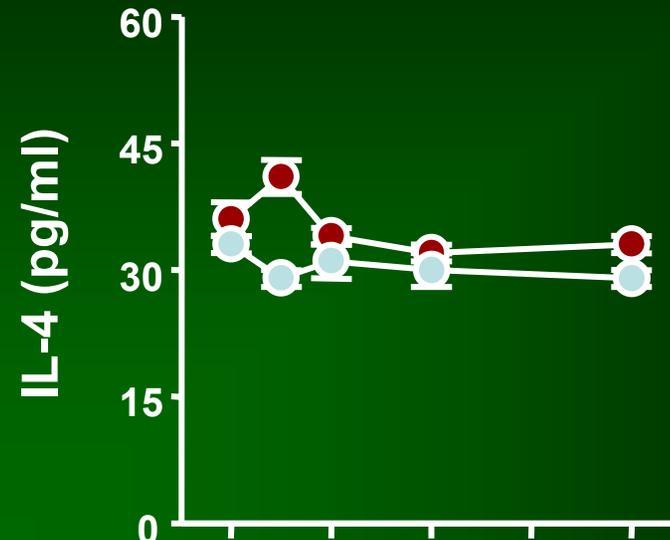
Splenocytes were stimulated with antiCD3 and proliferative responses were assessed in the presence of media (-), NMMA, and NMMA with the NO donor SNAP * $P < 0.05$ vs. sham group. † $P < 0.05$ as vs. media only; ‡ $P < 0.05$ vs. NMMA.

Δ represent values with NMMA.

Th-1



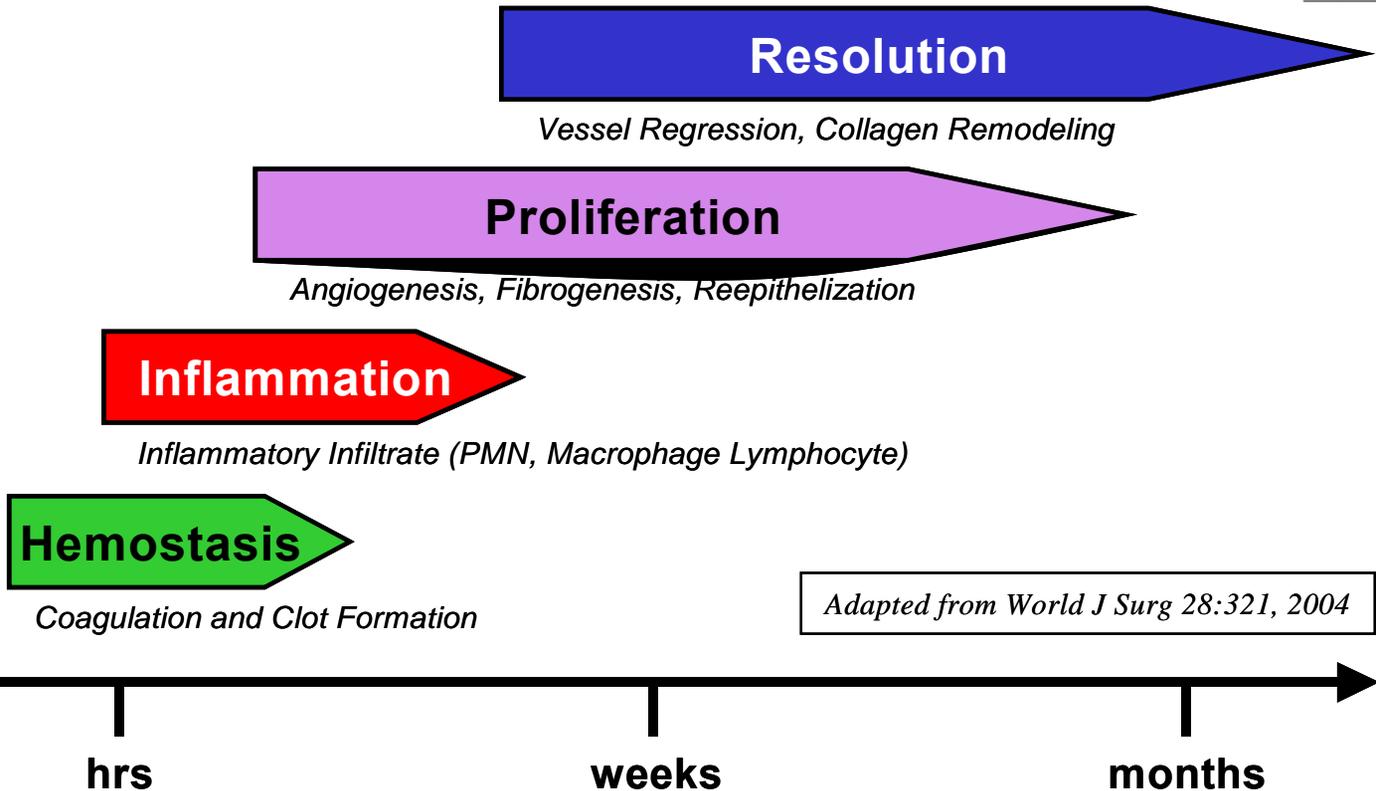
Th-2



Wound Healing

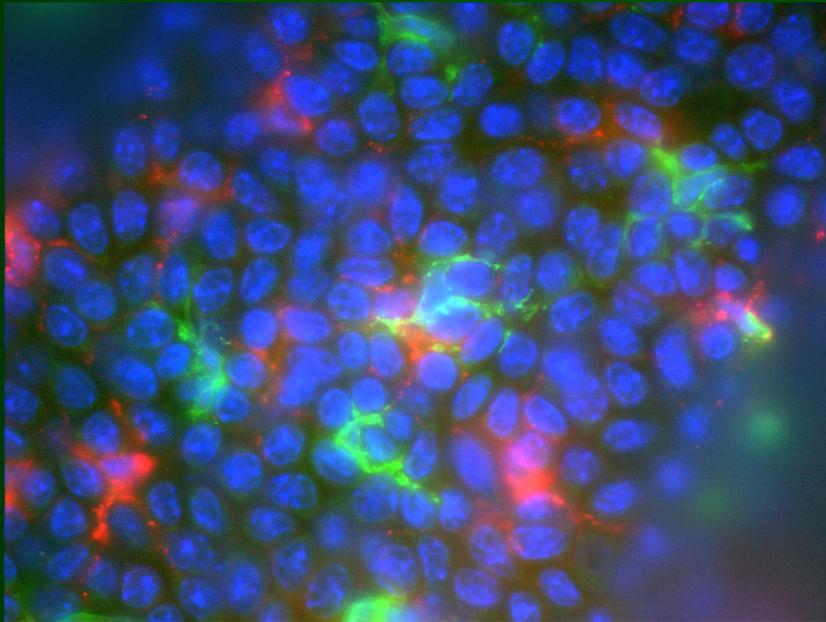


INJURY

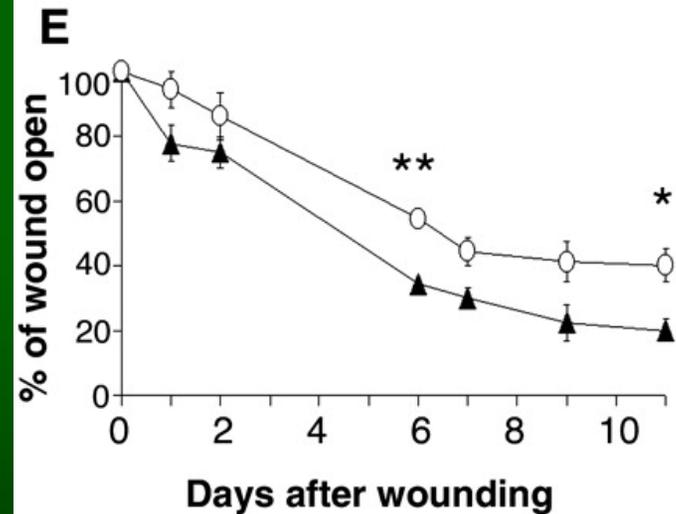
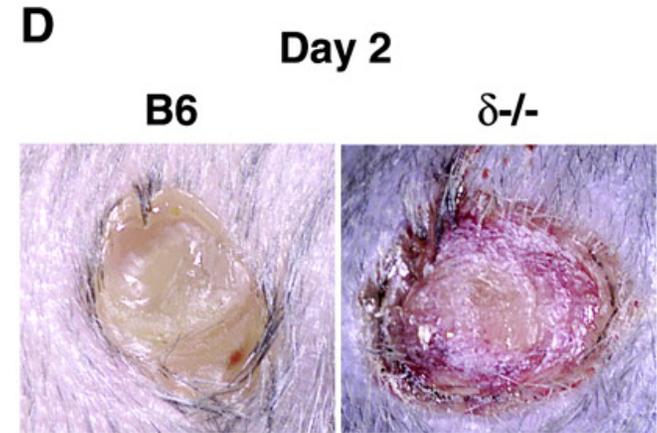


Adapted from World J Surg 28:321, 2004

$\gamma\delta$ T-Cells and Wound Healing

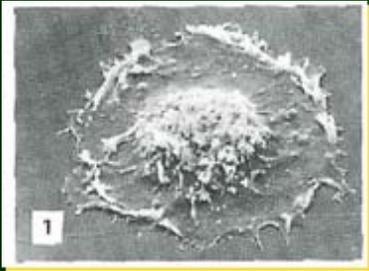


Epidermal sheet showing the interactions of $\gamma\delta$ T cells, Langerhans Cells, and keratinocytes.



Photographic images of excision wounds from B6 and δ TCR $^{-/-}$ mice 2 days after wounding.

$\gamma\delta$ T-Cells



Large granular lymphocyte cell morphology.



Common in mucosal epithelial, but minor circulation population (5%).



Specific TCR repertoire for bacterial or viral antigens and autoantigens (HSPs).



More a component of the innate immune system (host defense).



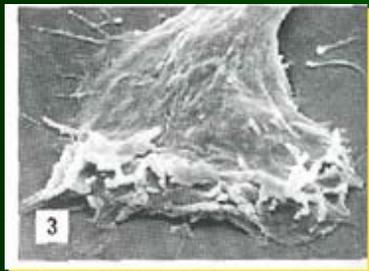
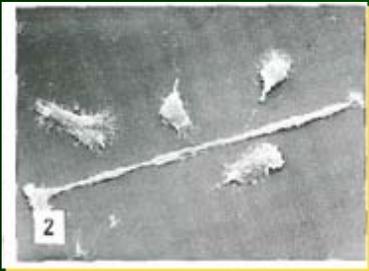
Recognize antigens on stressed or damaged keratinocytes.



Produce chemokines for recruitment of immune cells to injured tissue.



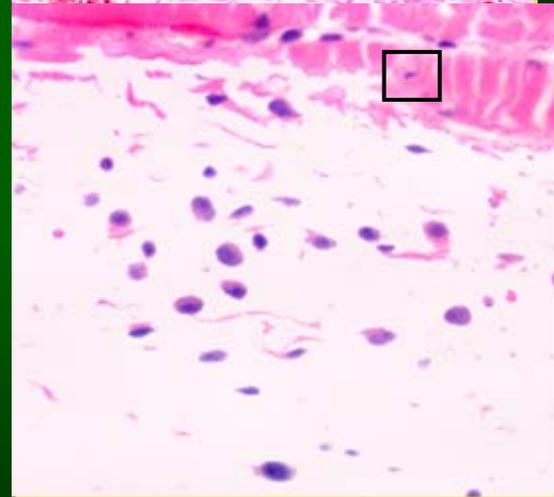
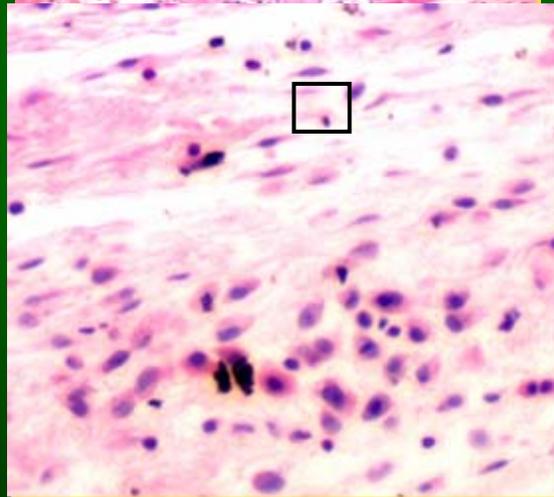
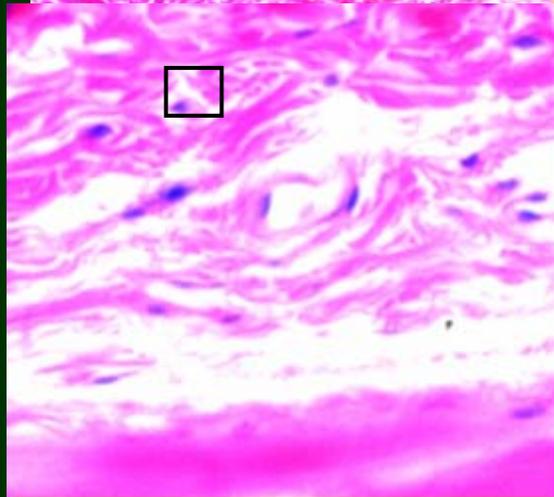
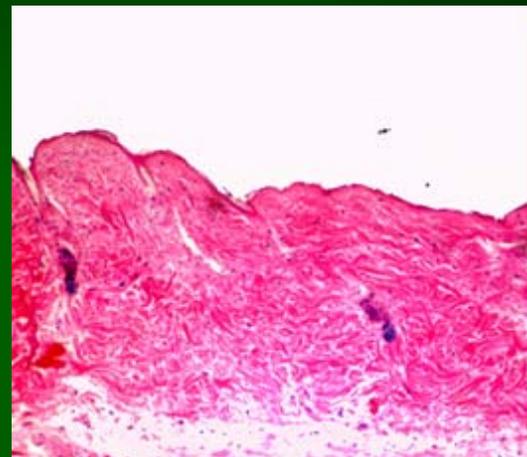
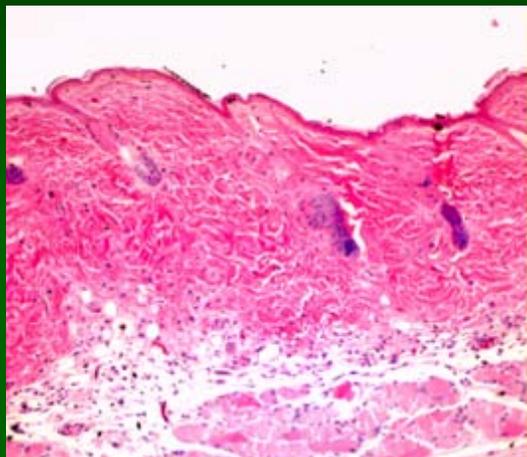
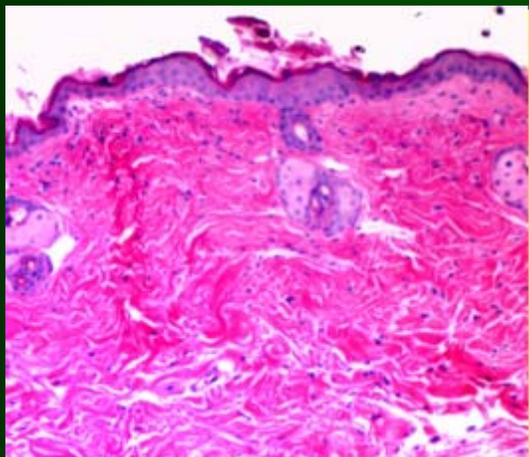
Important in wound healing.



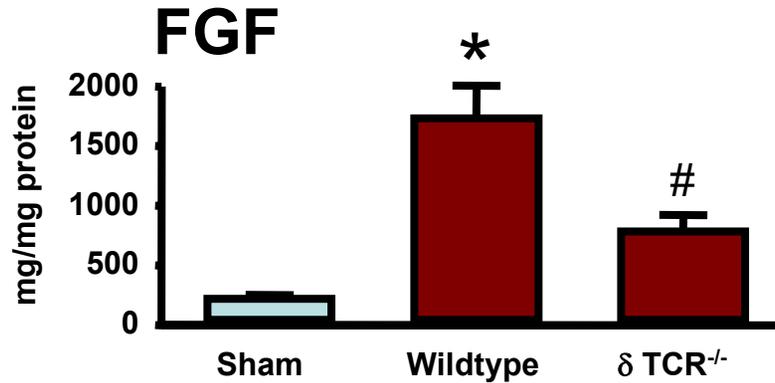
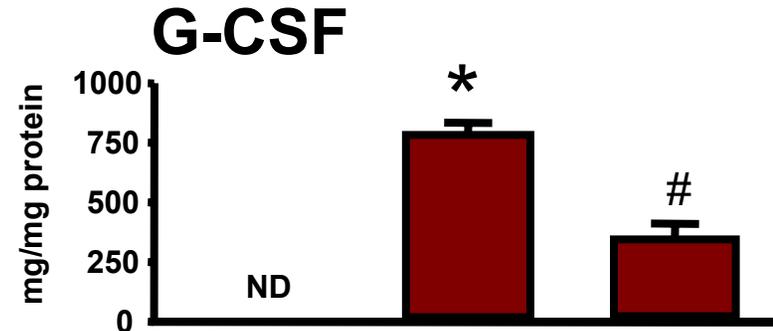
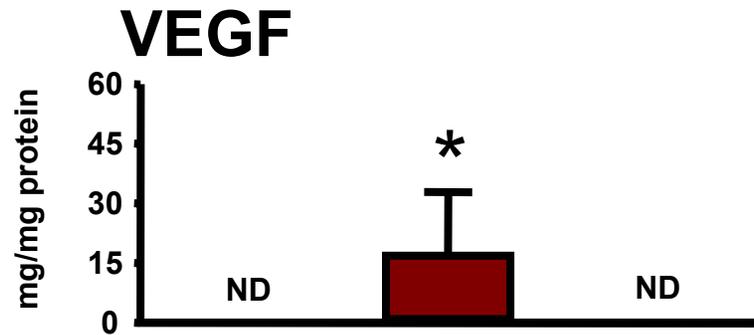
Wildtype Sham

Wildtype Burn

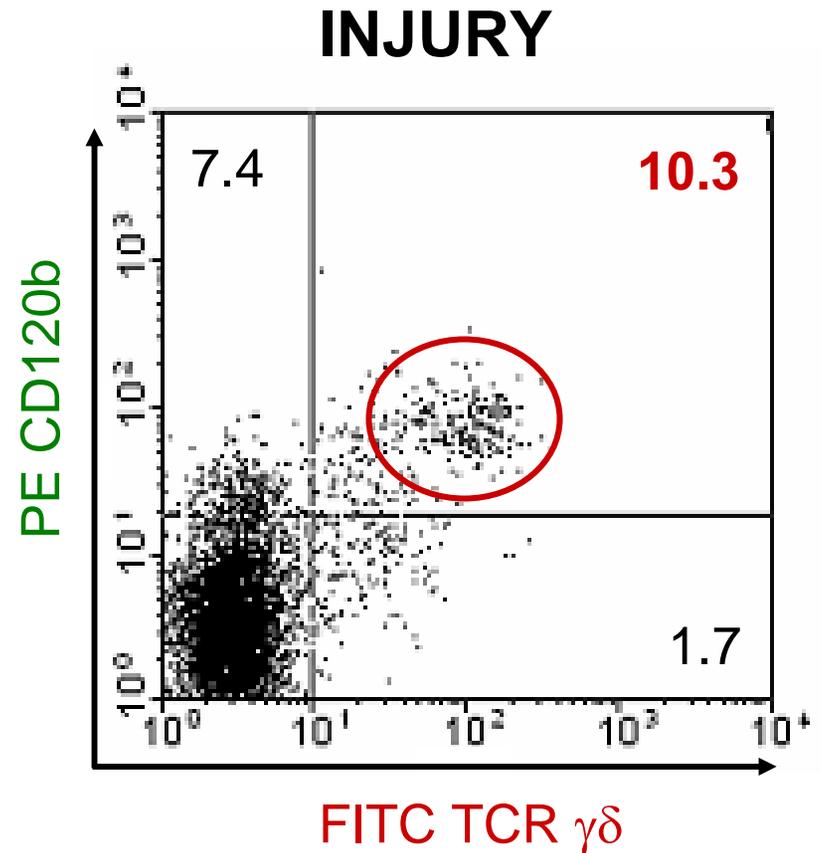
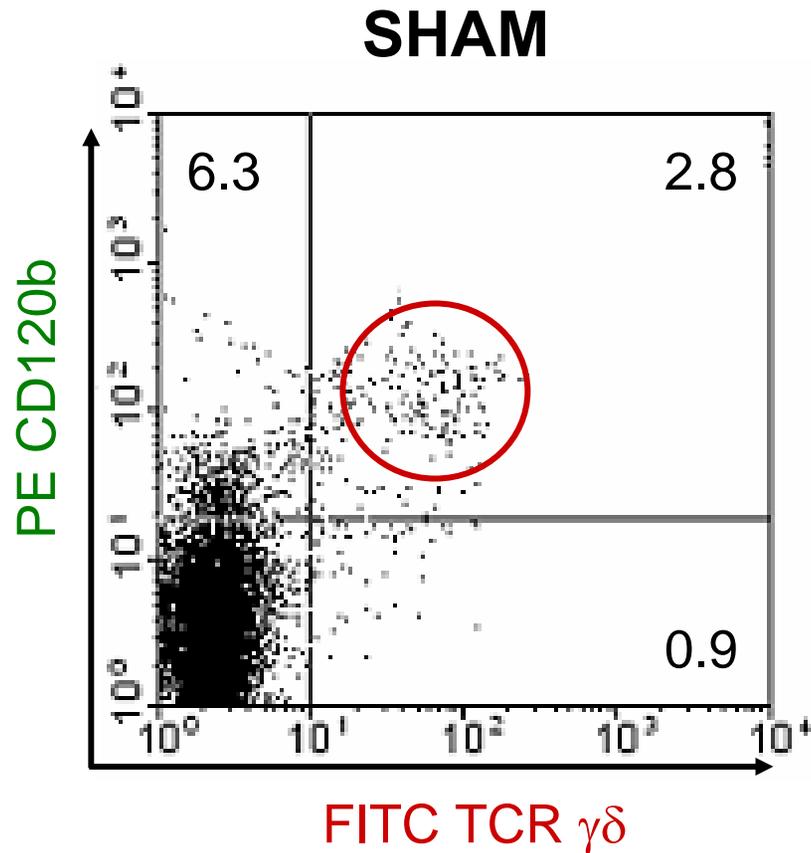
$\gamma\delta$ KO Burn



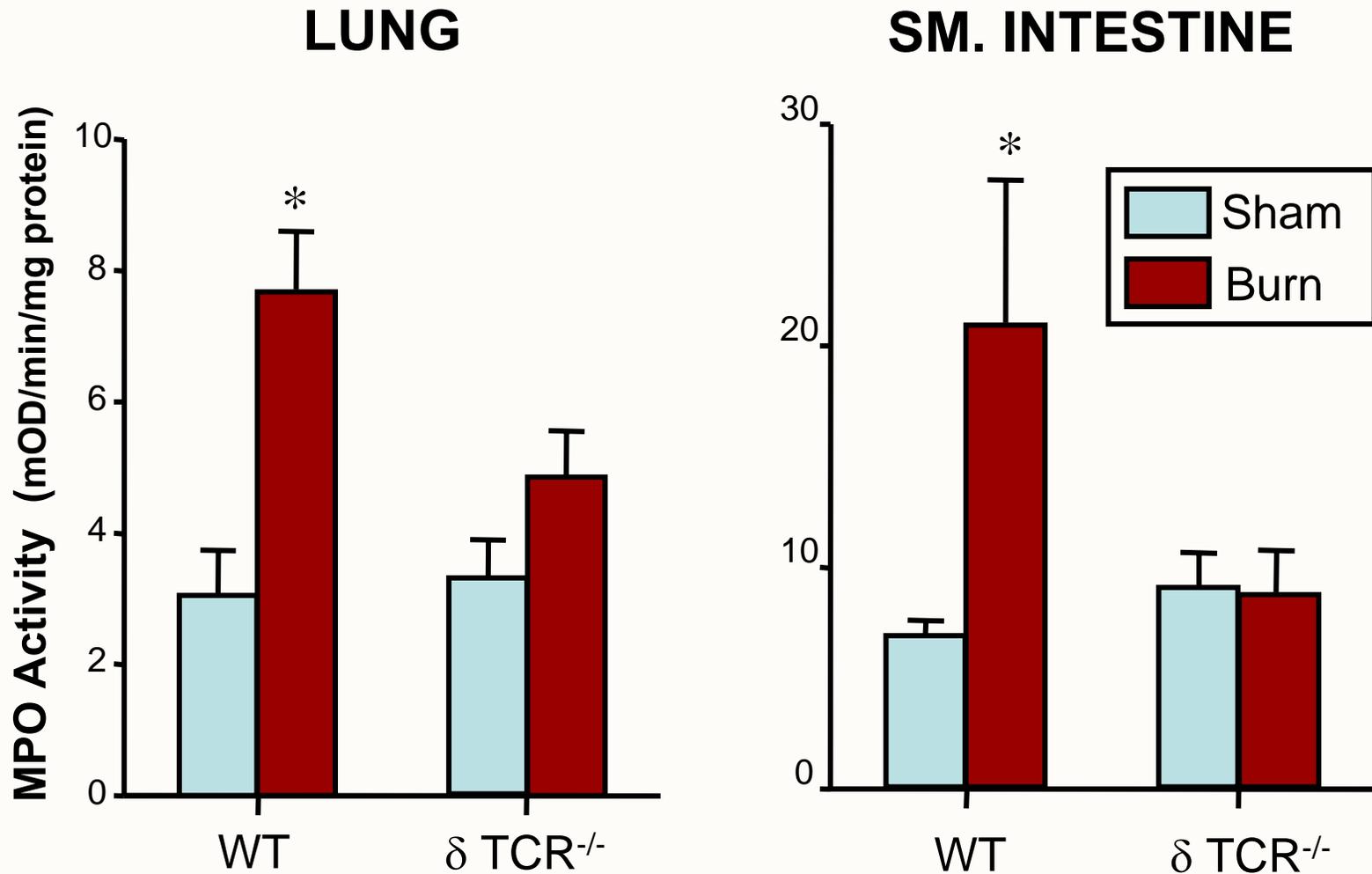
Growth Factor Content of Burn Skin



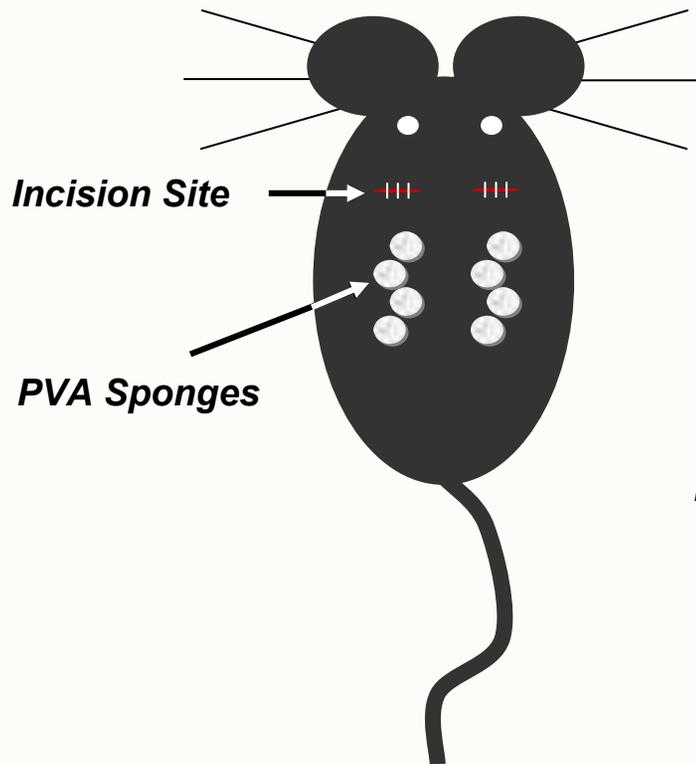
$\gamma\delta$ T-Cell Activation



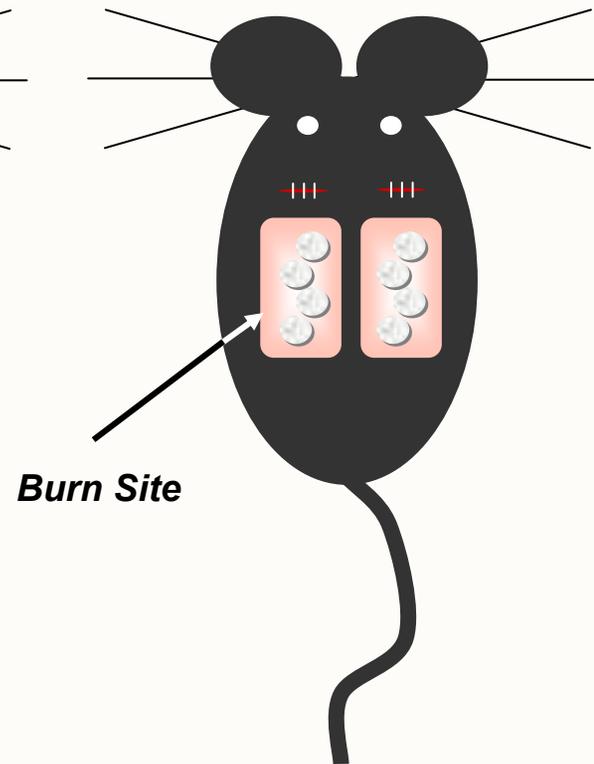
Neutrophil Infiltration



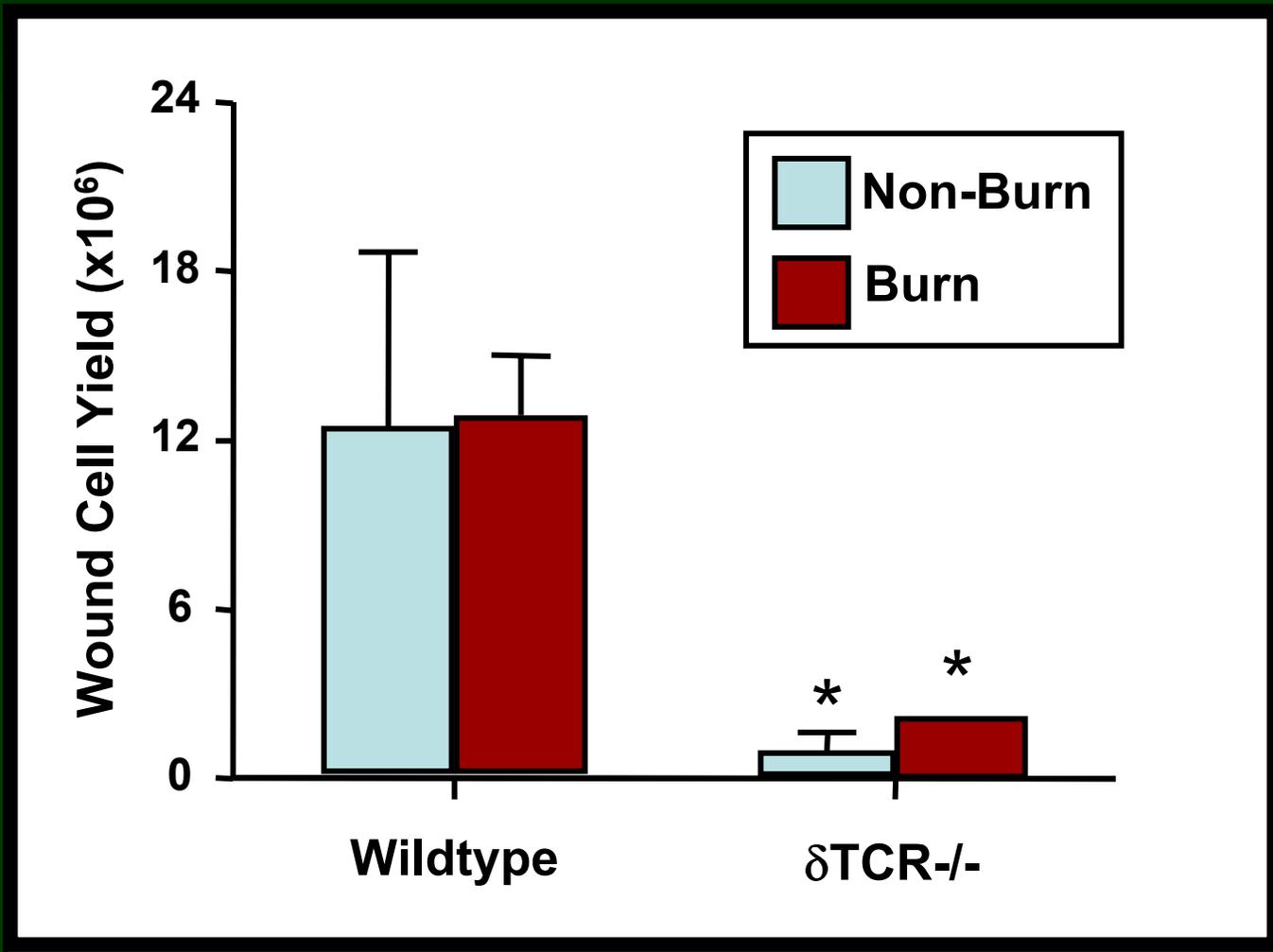
Non-Burn Wound



Burn Wound

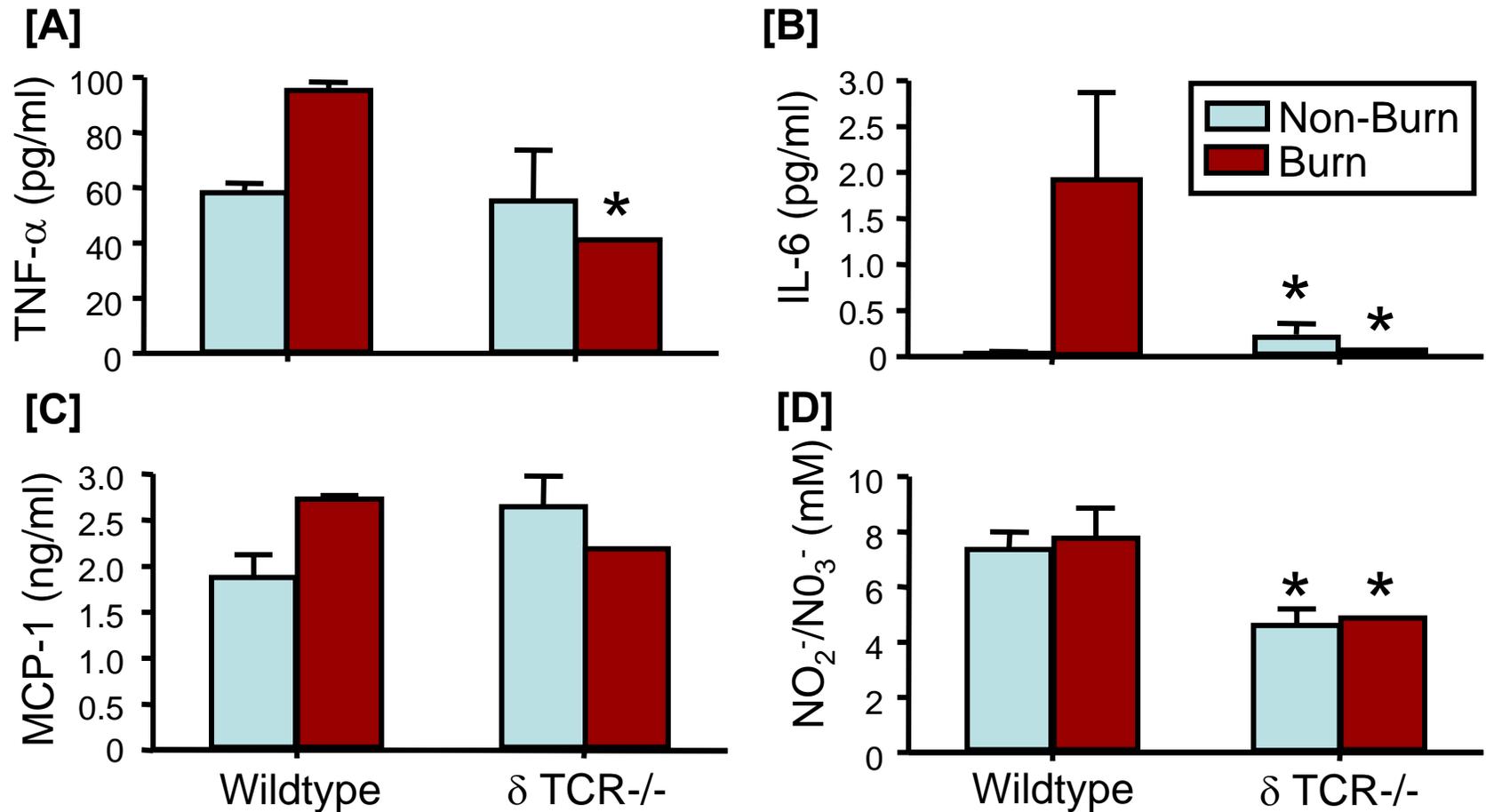


Implantation of PVA Sponges



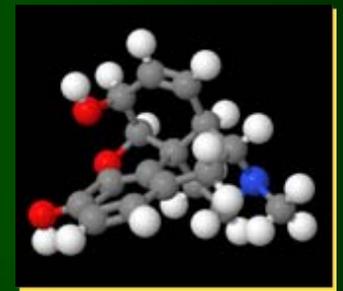
Effect of $\gamma\delta$ TCR deficiency on wound site infiltration.

PVA sponges were implanted s.c. beneath normal skin in sham and the injury site in burned wildtype and $\gamma\delta$ KO mice. Cells were collected 3 days later.

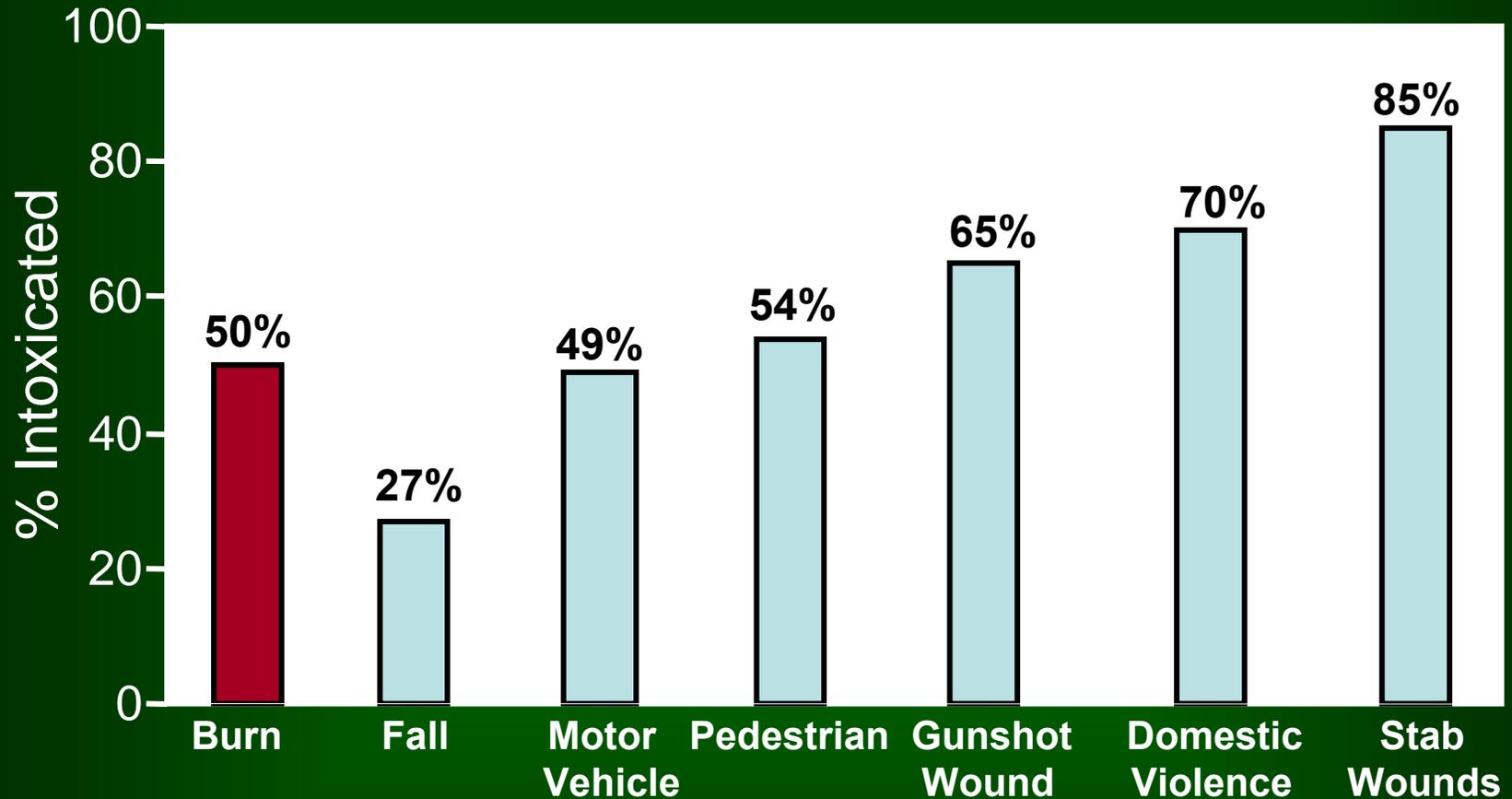


Effect of $\gamma\delta$ TCR deficiency on wound fluid inflammatory mediators. PVA sponges were implanted s.c. beneath normal skin in sham and the injury site in burned wildtype and $\gamma\delta$ T-cell KO mice. Wound fluid was collected 3 days later .

Impact of Preexisting Conditions and Therapeutic Interventions on Outcome



Alcohol and Injury



Maier (2001) Surgical infections 2: 133-144

Kovacs and Messingham (2002) Alcohol Res Health 26:257-63

Choudhry et al, (2004) Alcohol 33:199-208

Alcohol Intoxication and Burn Injury

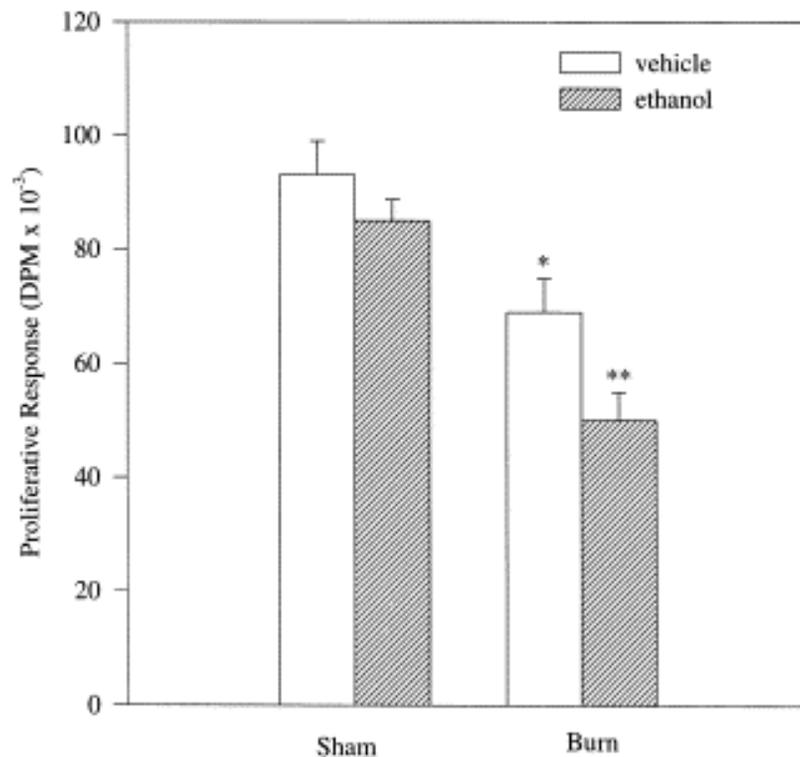
Burn/trauma patients who consumed alcohol prior to injuries have:

- *longer hospital stays*
- *higher incidence of infection*
- *higher morbidity*
- *increased mortality*



Jones et al. J Burn Care Rehabil 1991;12:148-152;
Powers et al. J Burn Care Rehabil 1994; 15:386-391;
McGill et al. J Trauma 1995; 38:931-934;
Haum et al. Burns. 1995; 21:194-199.

Ethanol Intoxication Exacerbates T-Cell Dysfunction Post-Burn

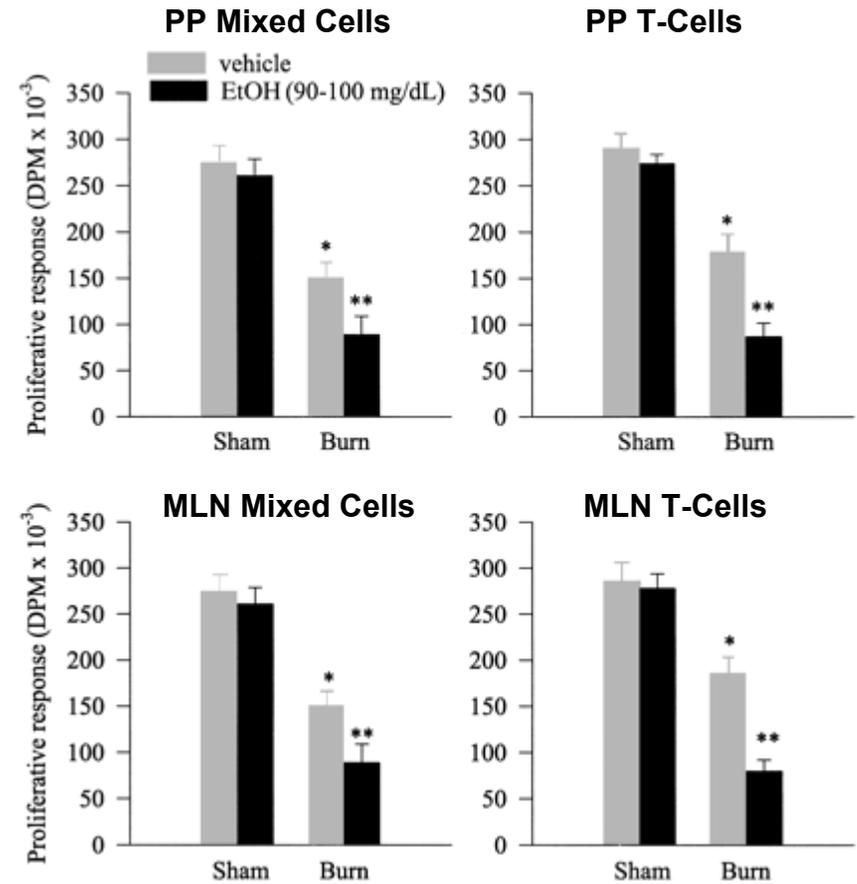
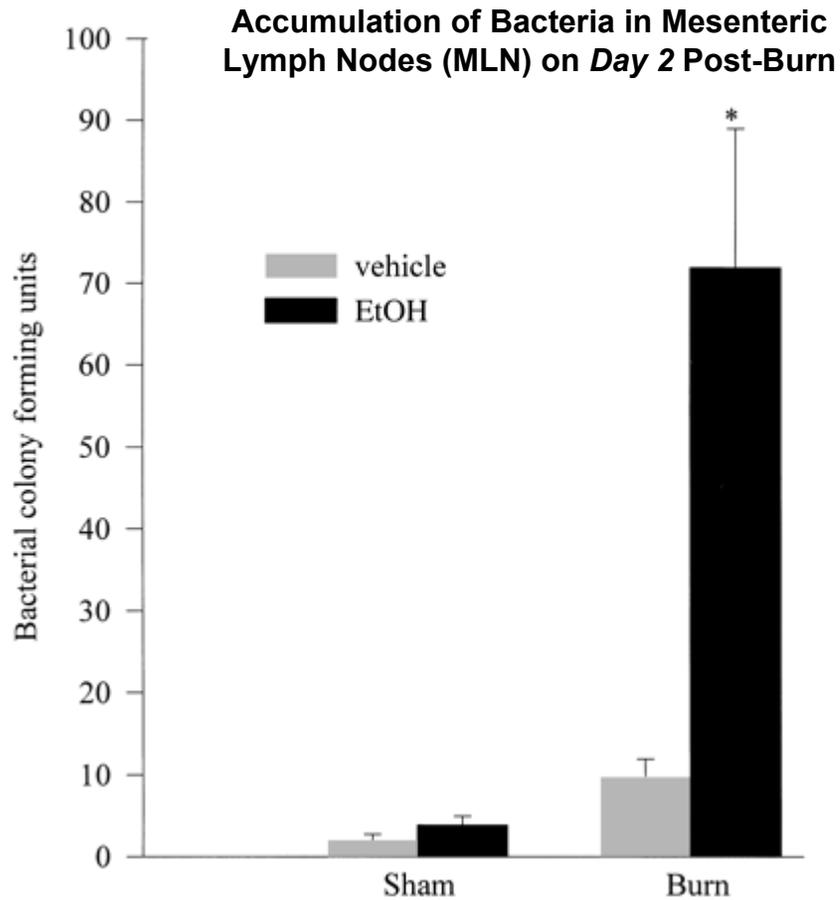


Splenocyte proliferation after acute alcohol exposure prior to burn injury. Spleens were obtained 48 h after injury and cultured for 72 hr in the presence of ConA.

* $p \leq 0.01$ vs. sham vehicle

** $p \leq 0.01$ vs. all other groups.

Gut-Associated T-Cell Dysfunction Enhances Bacterial Translocation in Alcohol and Burn Injury



Methamphetamines & Burn Patients



The use of methamphetamine (MA) as a recreational drug has markedly increased in recent years.



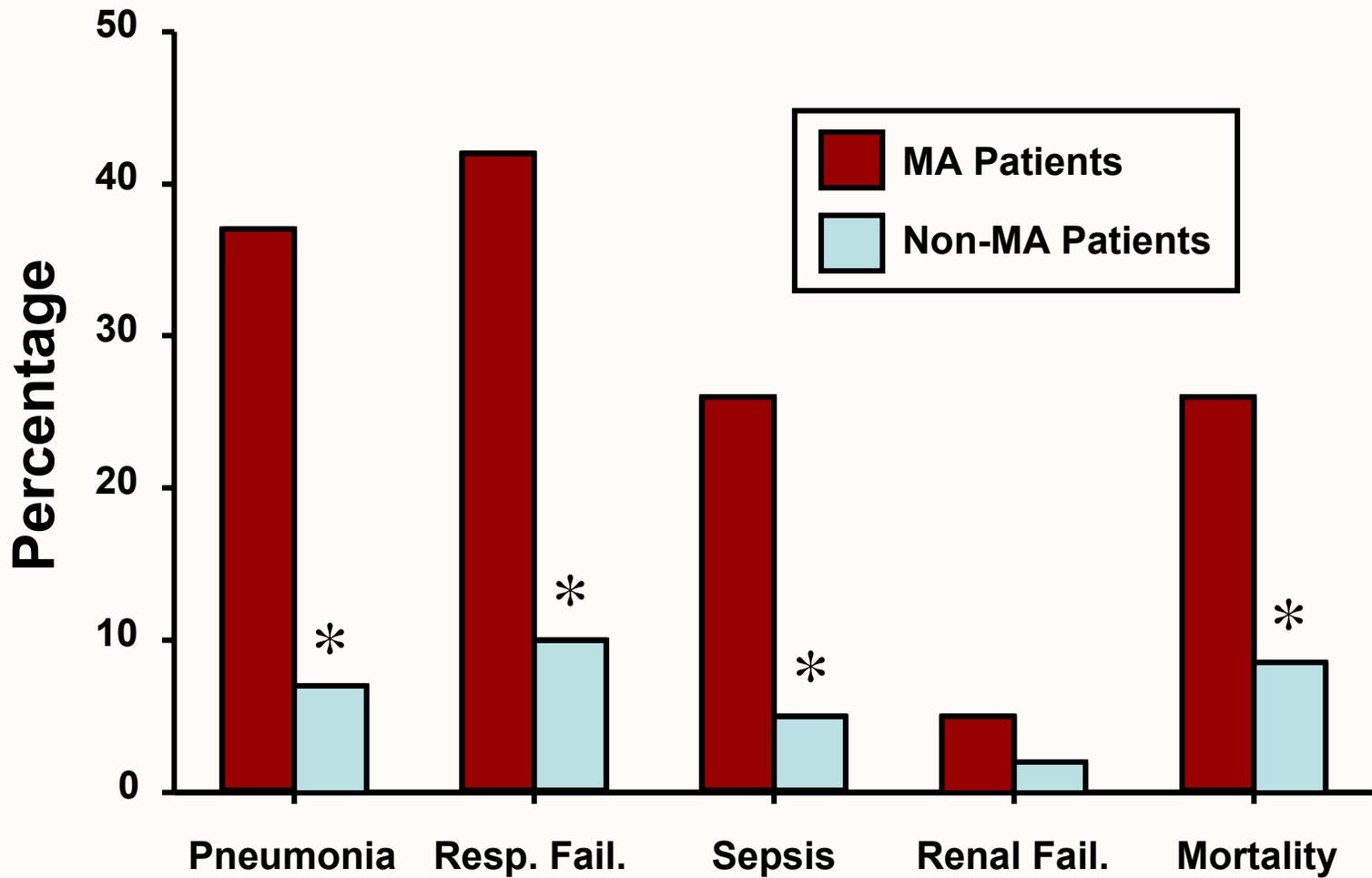
Burn centers are admitting burn patients due to the consequences of the volatile manufacturing process of MA.



Managing burn patients from MA lab explosions can be more difficult due to accompanying drug use.



It is well documented that substance abuse is associated with increased infections and other forms of complications.



Opiates Analgesics and Burn Patients



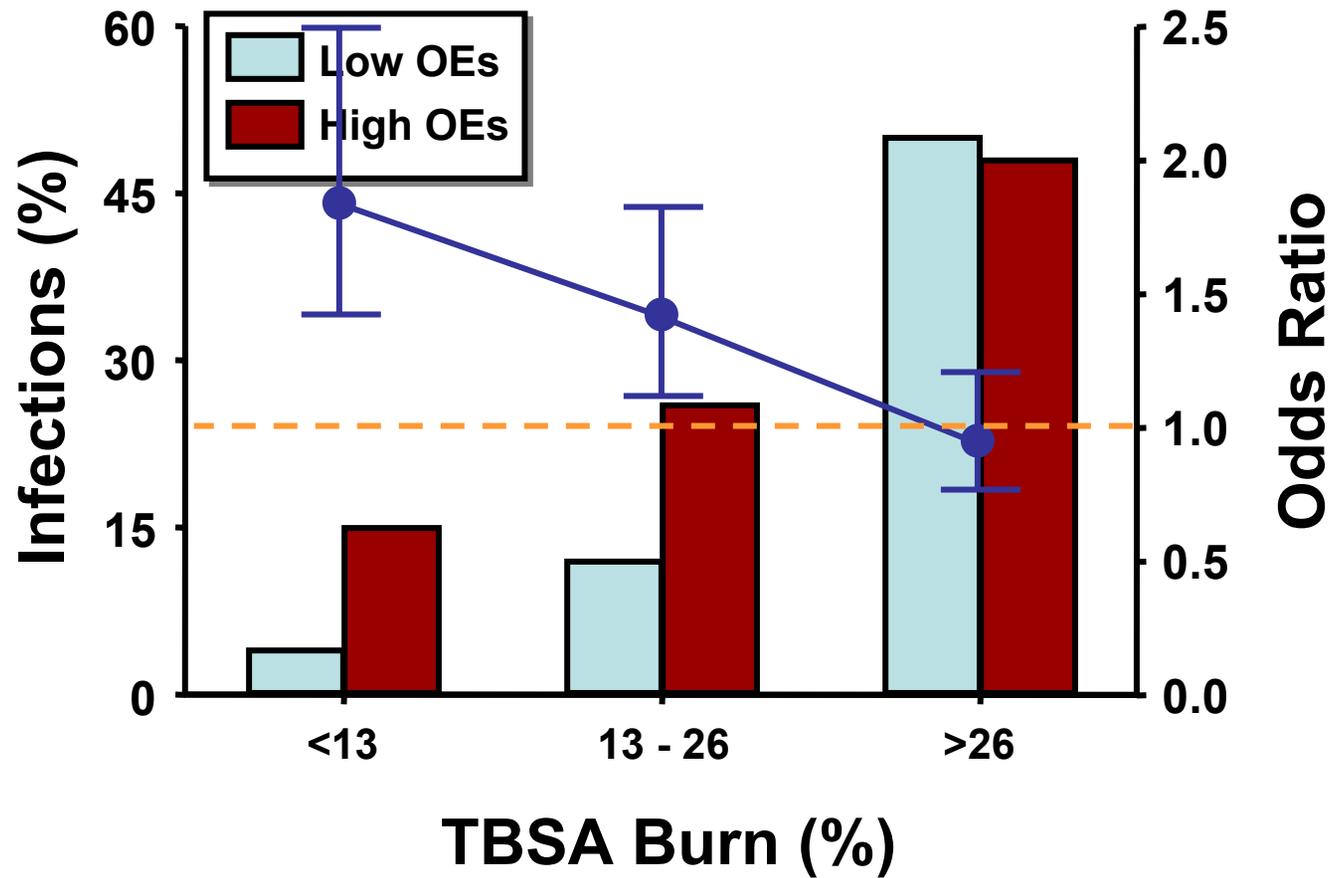
Despite advances, immunosuppression and increased susceptibility to sepsis and MOF remain a major cause of burn morbidity and mortality.



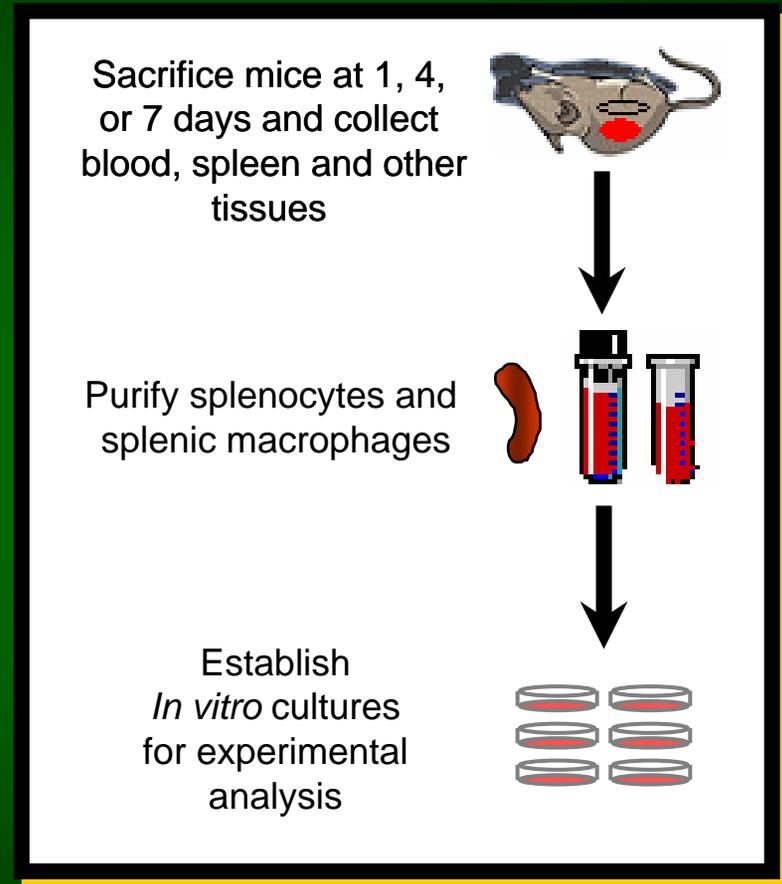
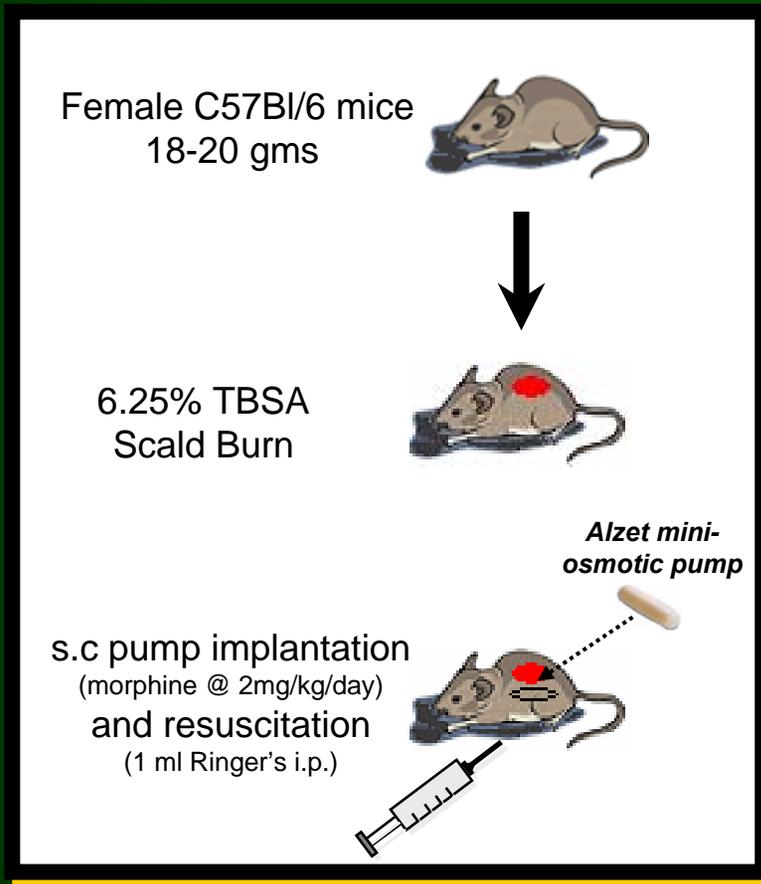
Due to the severity of pain associated with burn injury and subsequent interventions opiate administration is the standardized analgesic used.



Opiate use compromises a wide range of immune functional parameters and increases susceptibility to infection in experimental animal models.

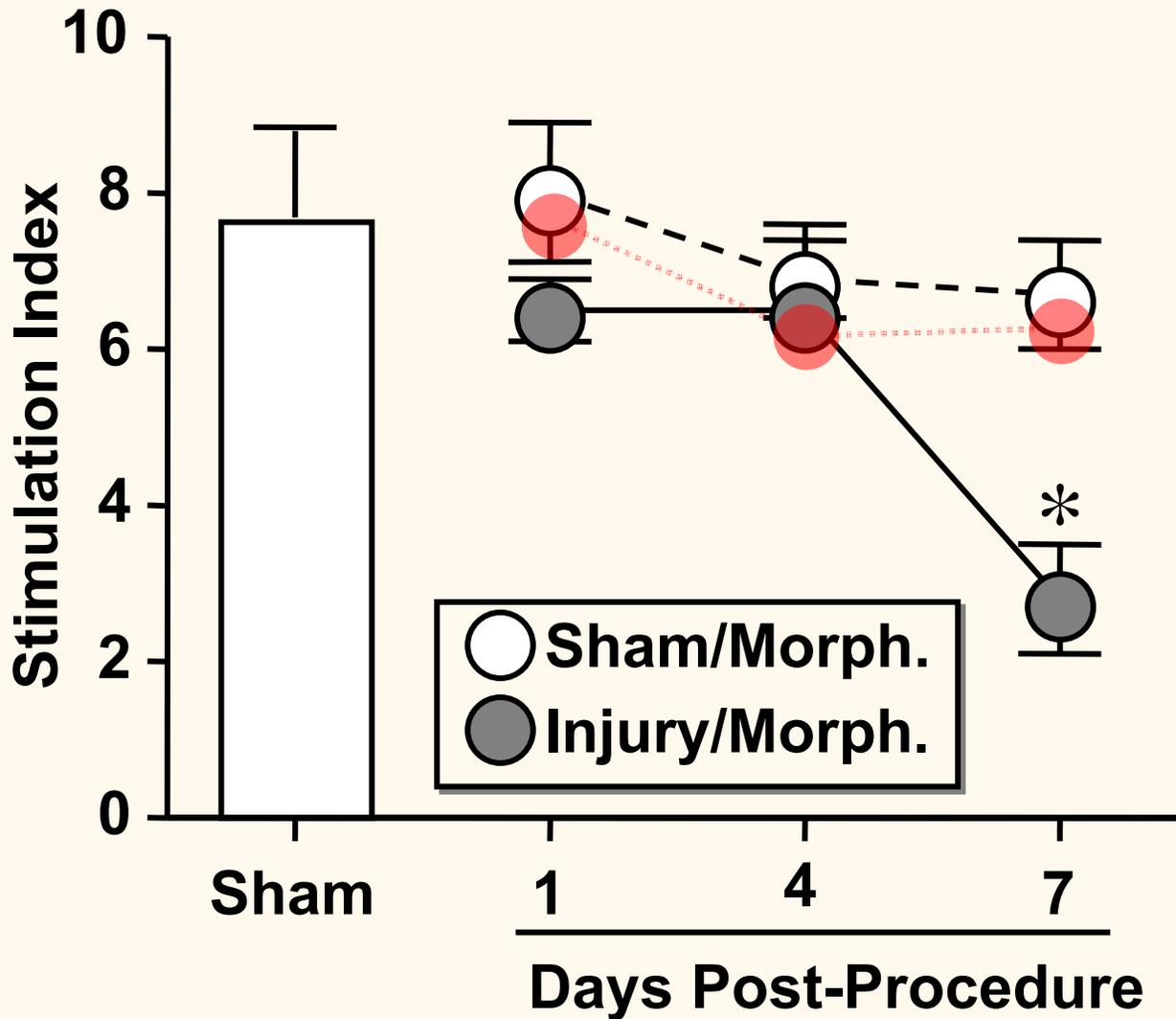


Opiates and Post-Burn Immune Function



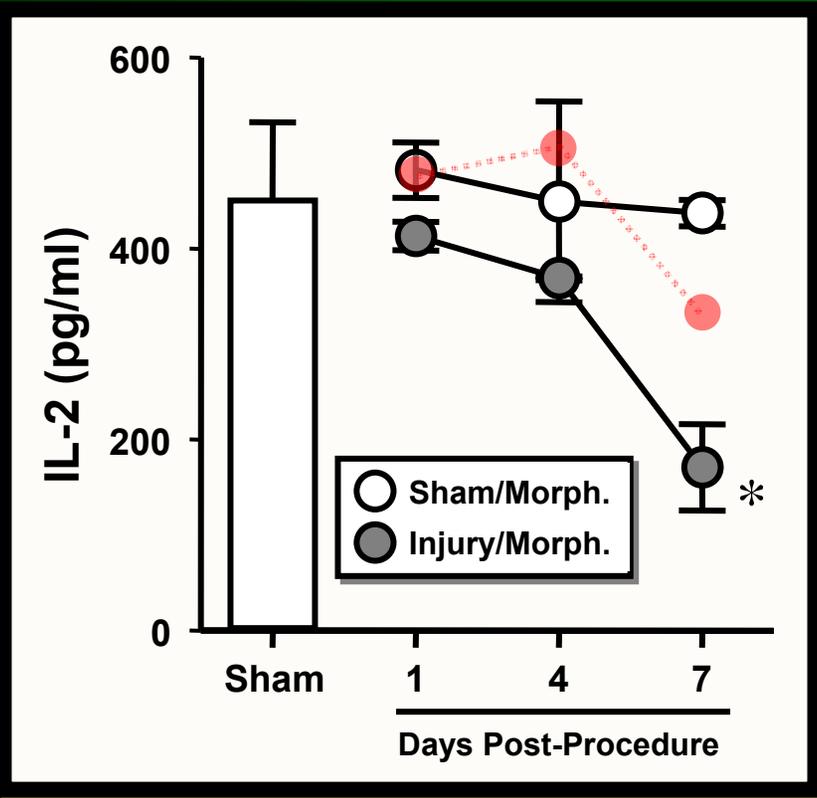
The recommended dose of morphine sulfate, clinically is 12-120 mg/day.
(~0.4-4.0 mg/kg bwt/day)

T-Cell Proliferation

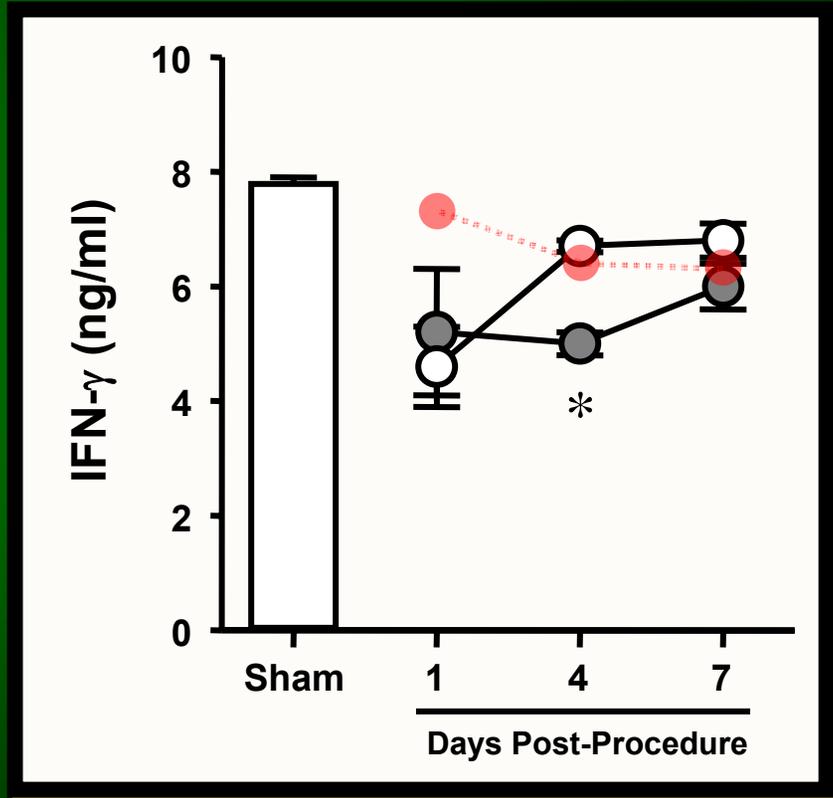


Th-1 T-Cell Response

IL-2

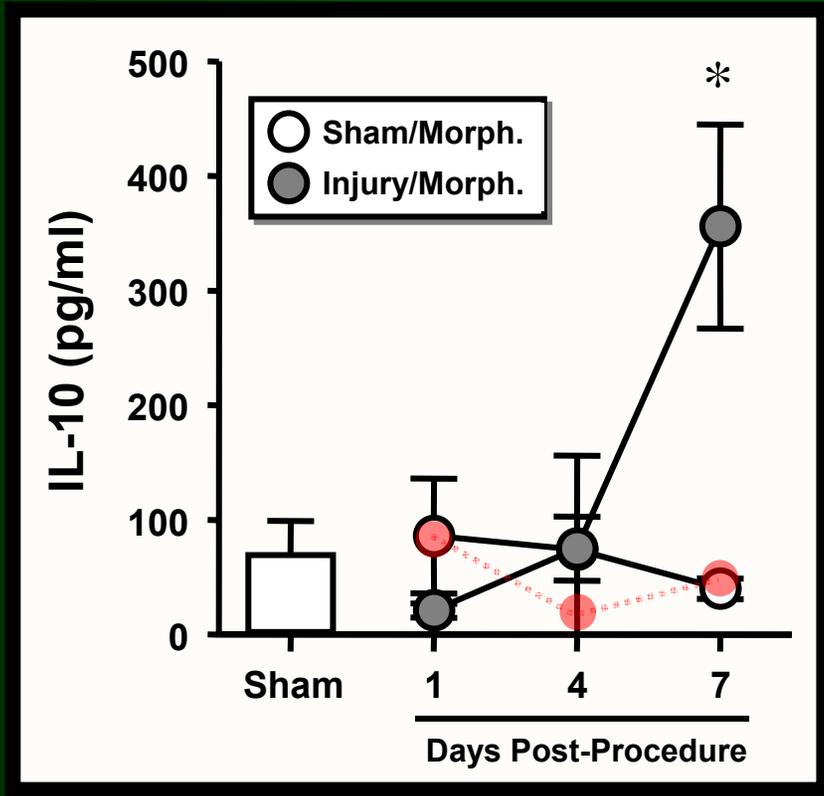


IFN- γ

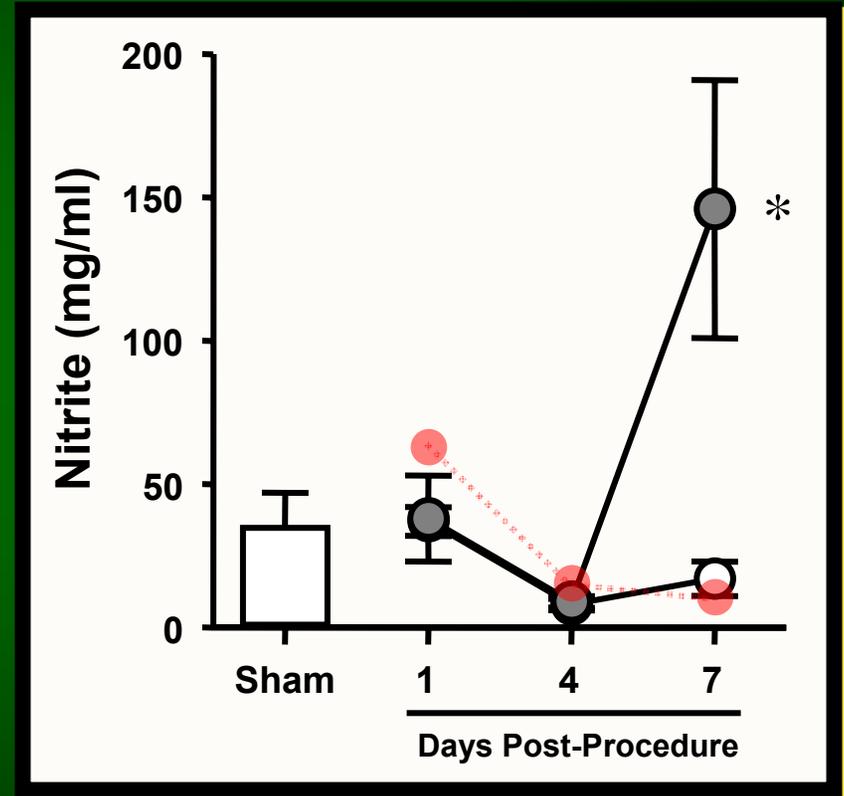


Th-2 and CARS Mediators

IL-10



Nitric Oxide



Gender and Burn Patients



A substantial literature exists on the impact of sex hormones on immune and physiological functions in experimental animal models.

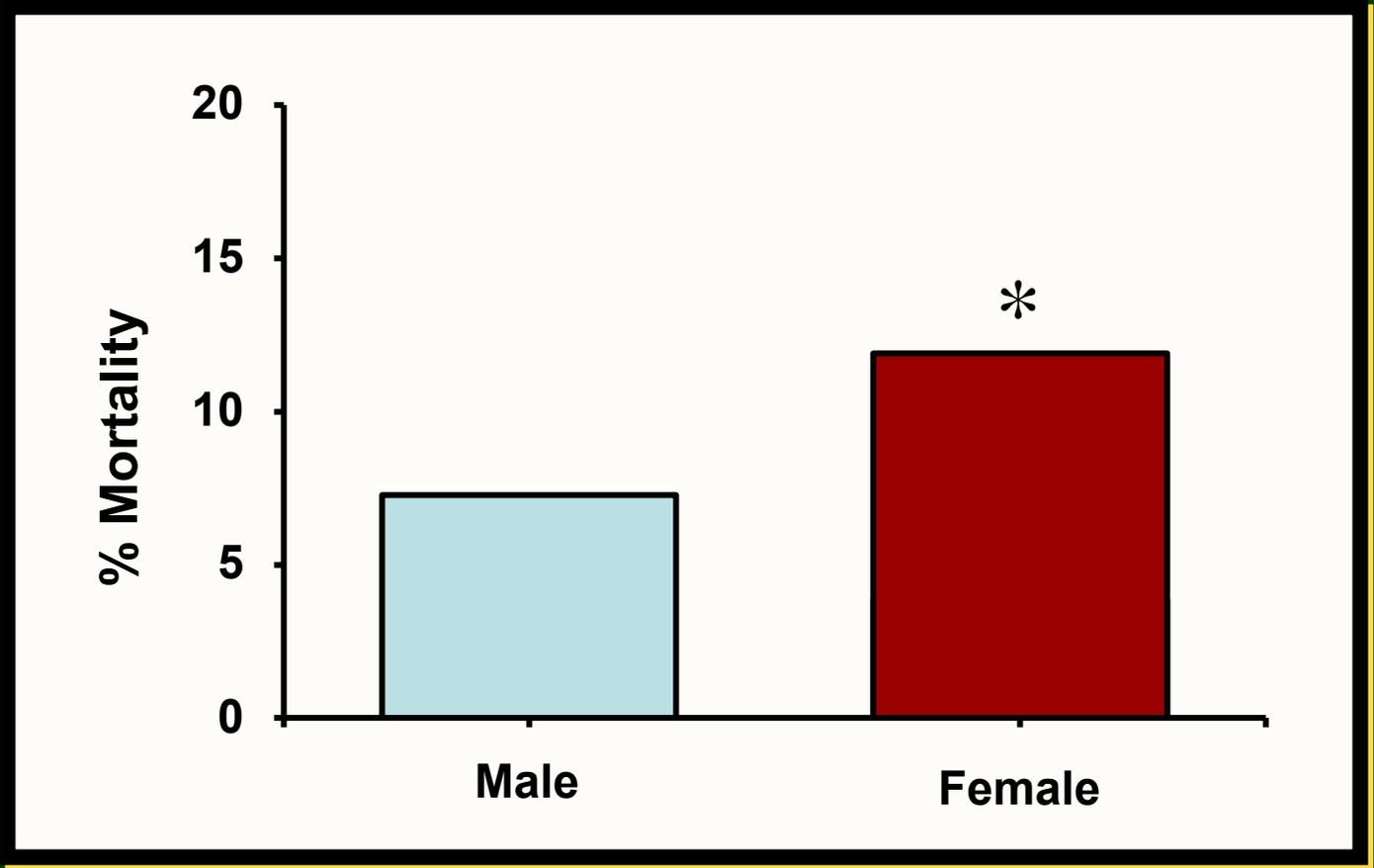
- *Estrogens improve immune and organ function after hemorrhagic shock.*
- *Female sex hormones contribute to post-burn immune complications.*

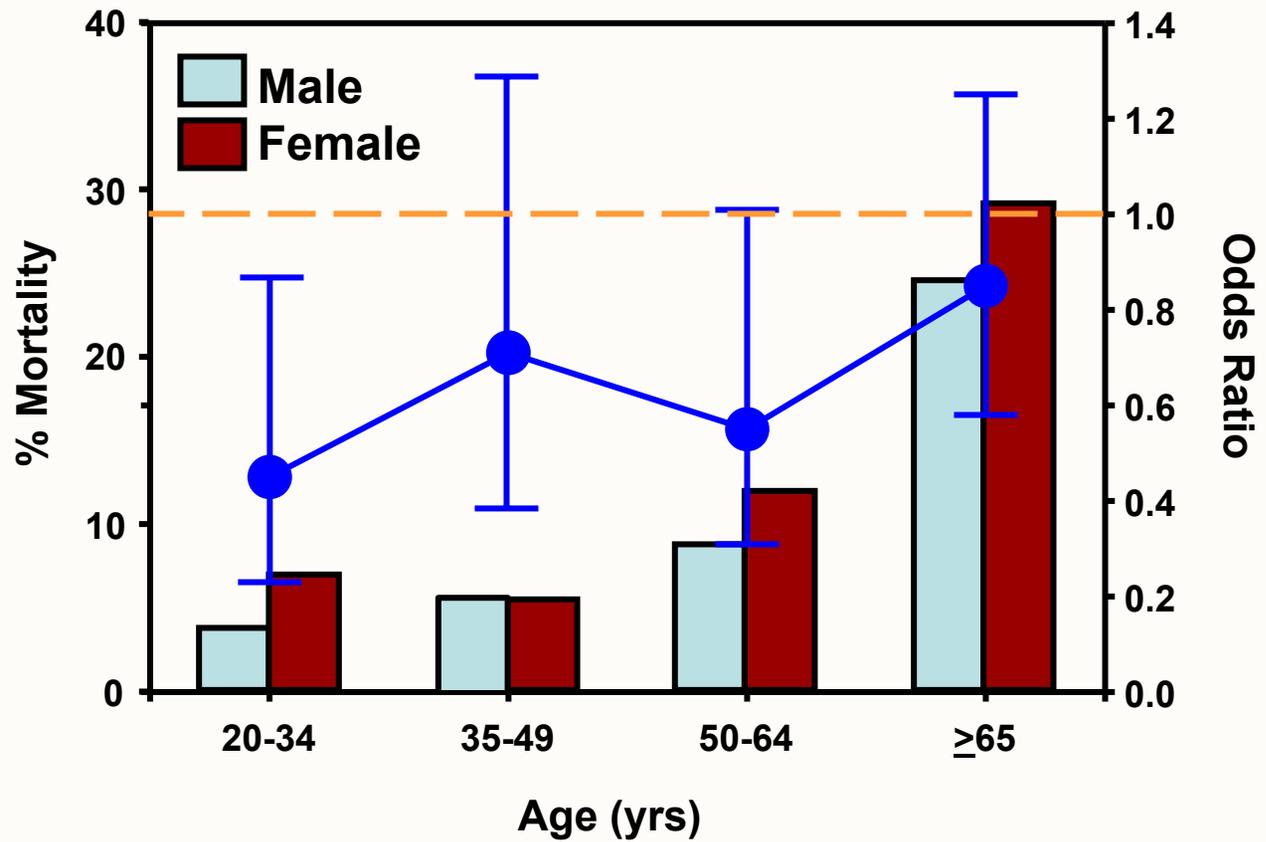


Clinical data supports the concept of improved outcome in female patients sustaining trauma.



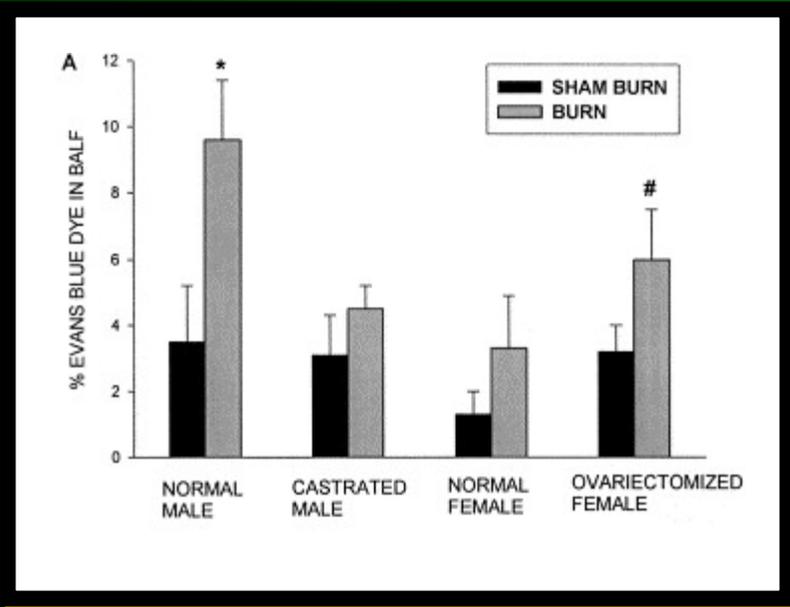
Clinical data on burn patients is less conclusive.





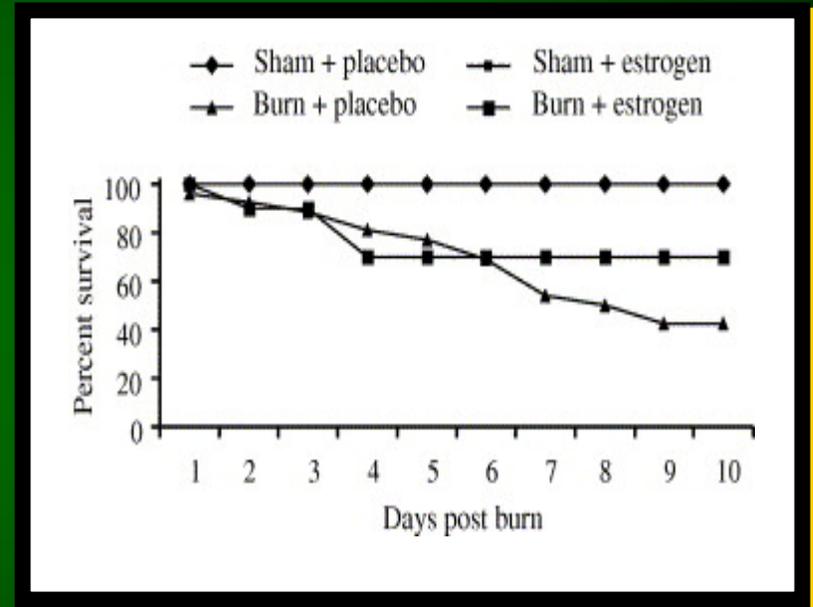
Experimental Studies are Less Clear

Estrogen....good?



Ananthkrishnan et al. Sex hormones modulate distant organ injury in both a trauma-hemorrhagic shock model and a burn model. Surgery. 2005

Estrogen....bad?



Gomez et al. Aging and estrogen: Modulation of inflammatory responses after injury. Exp Gerontol. 2007

Summary



Major burn injury induces a significant immunopathologic response that contributes to numerous complications.



As opposed with other forms of traumatic injury, the development of post-burn immune dysfunction is delayed.



Post-burn immunosuppression is related to the development of a CARS (Th-2) response.



Wound healing is a central component of the recovery from burn injury and $\gamma\delta$ T-cells appear to be critical to this response.



Preexisting conditions, such as substance abuse (alcohol and drugs) can profoundly impact the post-burn immune and inflammatory response.



Analgesic regimes (opiates) can influence the post-burn immune response.



Gender and sex hormones may or *may not* influence the immune and inflammatory response to burn injury.

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Wendy Havran

UAB et al.

*Richard Lopez
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