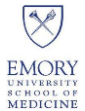
From Inflammation to Remodeling: Molecular Patterns Linked to Combat Wound Outcomes

2LT Moriamo Adedeji, BSN, U.S. Army

Surgical Critical Care Initiative (SC2i)
Uniformed Services University of the Health Sciences (USUHS)



Coauthors

Moriamo A. Adedeji, BS[1]; Sreya Mukherjee, PhD[1,3]; Felipe A. Lisboa, MD[1-3]; Cameron D. Leonard, BS[1]; Katherine Nagel, BA[1]; Katherine A. Weathersby, BA[1]; Mitchel Haddad, BS[1]; Daniel Thompson, MBBS[1,4]; Fausto A. Bustos Carrillo, PhD[1,3]; Matthew J. Bradley, MD[1,2]; Christopher J. Dente, MD[1,5]; Allan D. Kirk, MD[1,6]; Eric A. Elster, MD[1,2]; Seth A. Schobel, PhD[1]

1. Uniformed Services University of the Health Sciences, Bethesda, MD
2. Walter Reed National Military Medical Center, Bethesda, MD
3. The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD
4. Royal Centre for Defence Medicine, Birmingham
5. Emory University, Atlanta, GA
6. Duke University, Durham, NC

Uniformed Services University | SC2i Surgical Critical Care Initiative

Disclaimer and Conflict of Interest Statements

The contents of this presentation are the sole responsibility of the author(s) and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences (USUHS); Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.; Department of War (DoW); or Departments of the Army, Navy, or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

No conflicts of interest to declare.

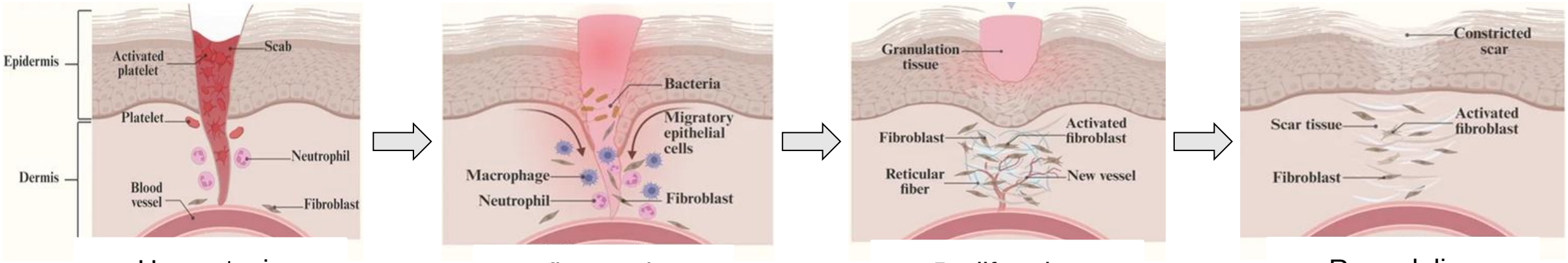
Funding

This study was supported by the Surgical Critical Care Initiative, funded through the Department of War's Health Program—Joint Program Committee 6/Combat Casualty: HT 9404-13-1-0032, HU 0001-15-2-0001, HU 0001-20-2-0018, HU 0001-21-2-0029, HU 0001-22-2-0018, HU 0001-23-2-0037.

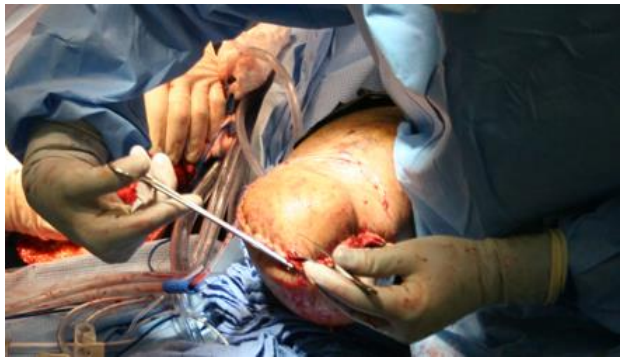
Uniformed Services University | SC2i Surgical Critical Care Initiative

Integrating Biological Phases of Healing with Clinical Trajectories

- Successful wound healing requires the coordinated processes of inflammation, proliferation, and remodeling
- Healed wounds differ from failed wounds by obvious physical outcomes
- However, the molecular patterns distinguishing healed from failed wounds are incompletely understood



Hemostasis | Inflammation | Proliferation | Remodeling

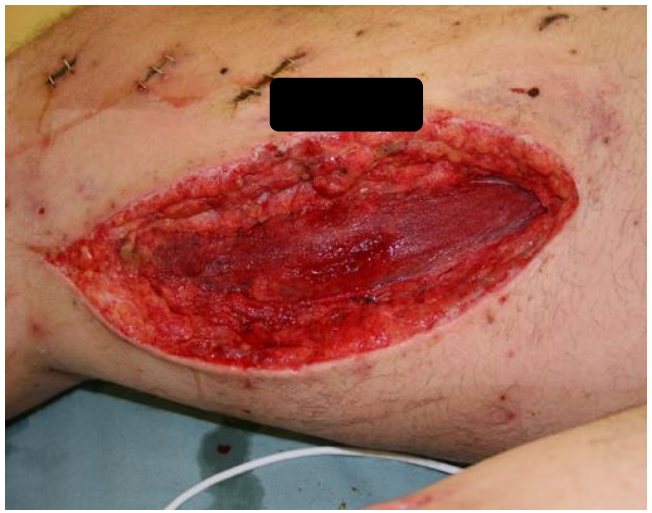


Delayed wound closure (shown left) is optimally performed during the **late proliferative phase**, when granulation tissue is well established and inflammation has subsided

Delayed Wound Closure Challenge: Understanding Why Wounds Fail

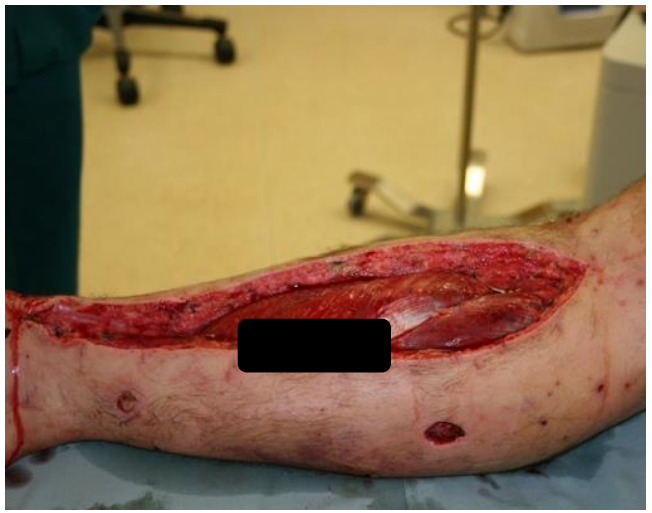
- Delayed wound closure (DWC) failure persists despite antibiotic use, repeated debridement, and negative pressure wound therapy
- Clinical problem: Inconsistent healing outcomes (~20% fail)
- Goal: Identify molecular patterns (local and systemic) that differentiate healed vs. failed wounds

Delayed closure attempt ➡ Healed



Preoperative image before DWC attempt

Delayed closure attempt ➡ Failed



Preoperative image before DWC attempt

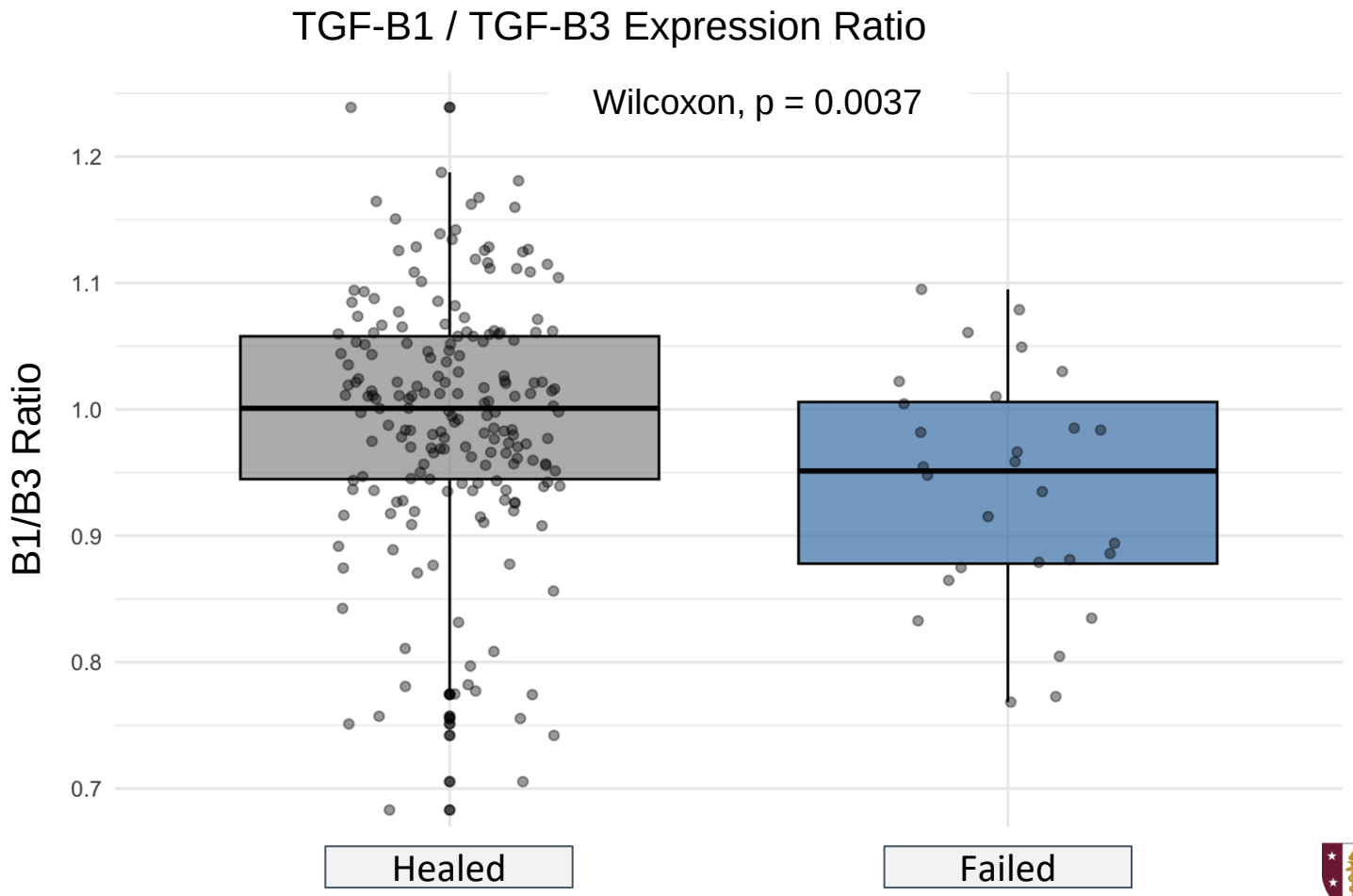
Materials and Methods

- **Study sample:**
  - 41 patients with 64 combat-related wounds (Operations Iraqi/Enduring Freedom) treated at Walter Reed and legacy institutions
  - All patients were treated with negative pressure wound therapy and wound debridements, typically every 2-3 days, until delayed closure was achieved
  - Wound outcomes 30 days post wound closure: 52 (81%) healed, 12 (19%) failed

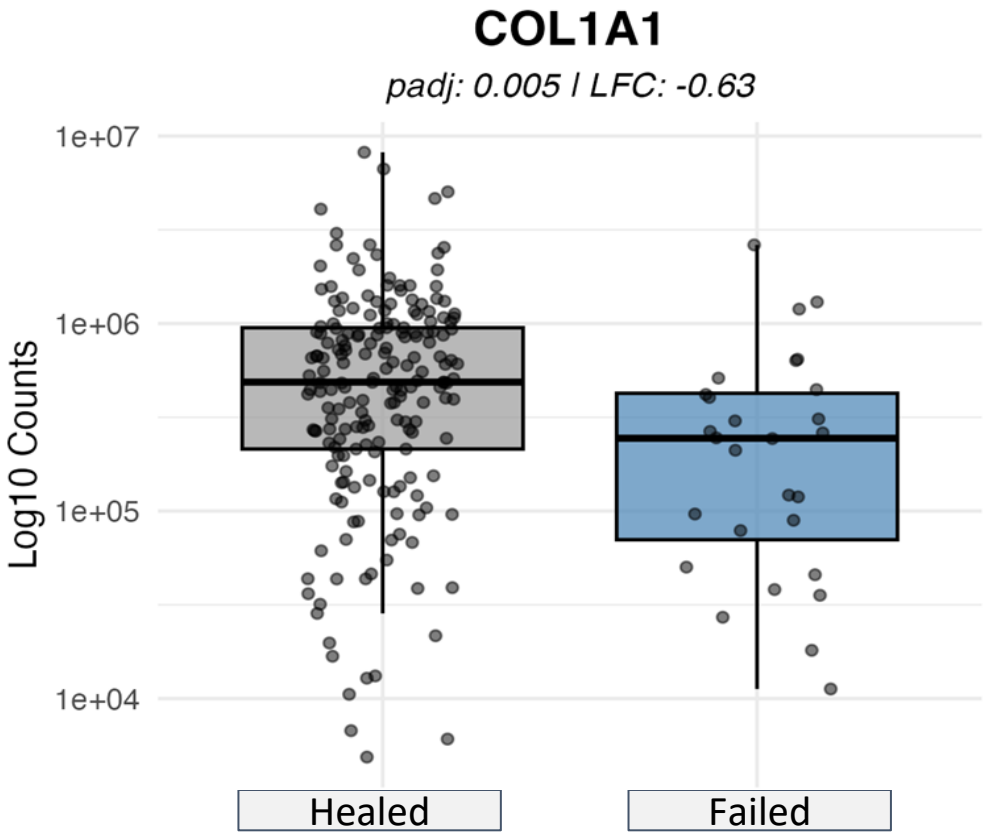
- **Methods:**
  - Samples of muscle tissue and serum were collected at each debridement until closure
  - RNA sequencing
  - Differential expression analysis
  - Luminex multiplex assays quantified 32 cytokines related to systemic inflammatory responses
  - Biostatistical approaches:
    - Kendall correlation
    - Wilcoxon rank-sum tests
    - False discovery rate correction accounted for multiple testing

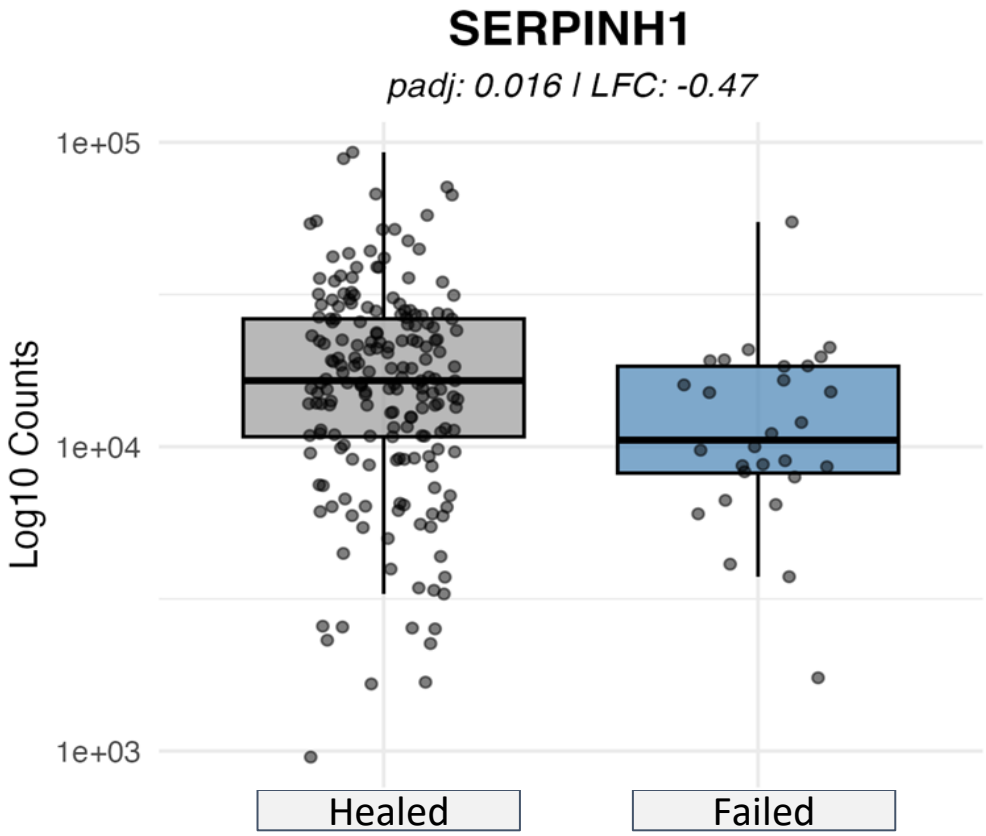
Healed Wounds Exhibited a Higher TGF-β1 / TGF-β3 Ratio

- Elevated TGF-β1 / TGF-β3 ratio suggests the biologic environment is conducive to granulation tissue formation, extracellular matrix (ECM) deposition, and wound contraction
  - These processes are necessary for successful delayed wound closure



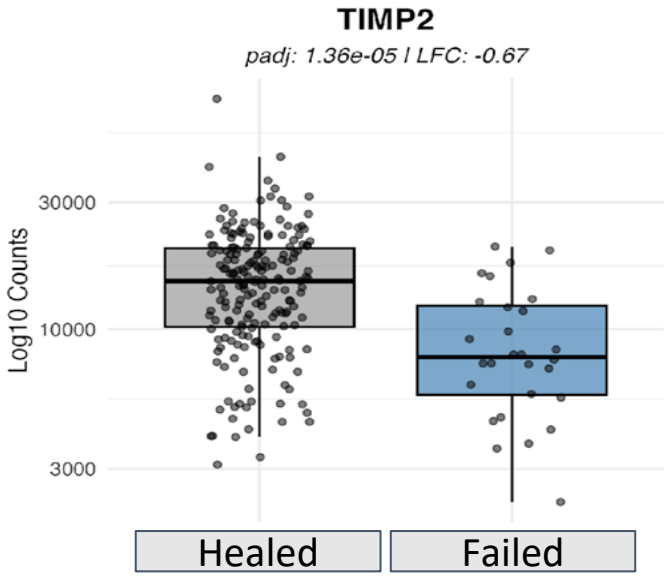
Collagen-Related Genes Are Downregulated in Failed Wounds

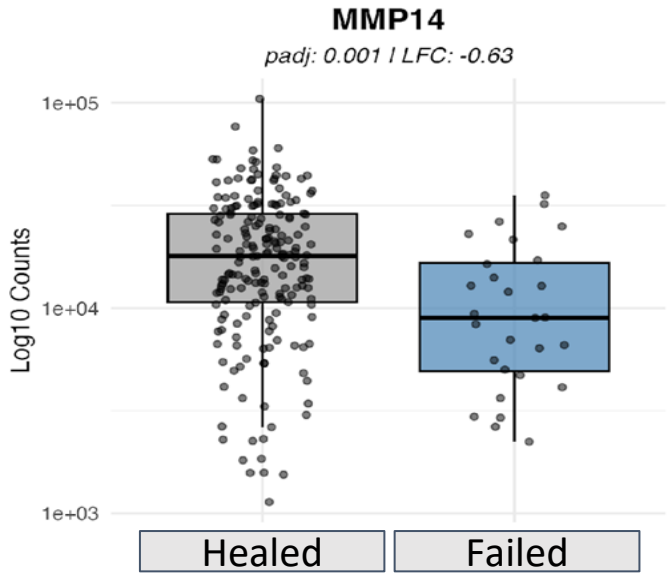


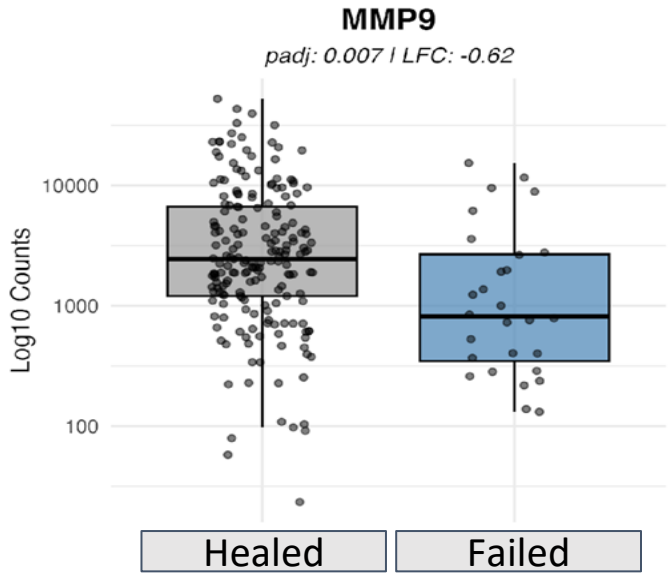


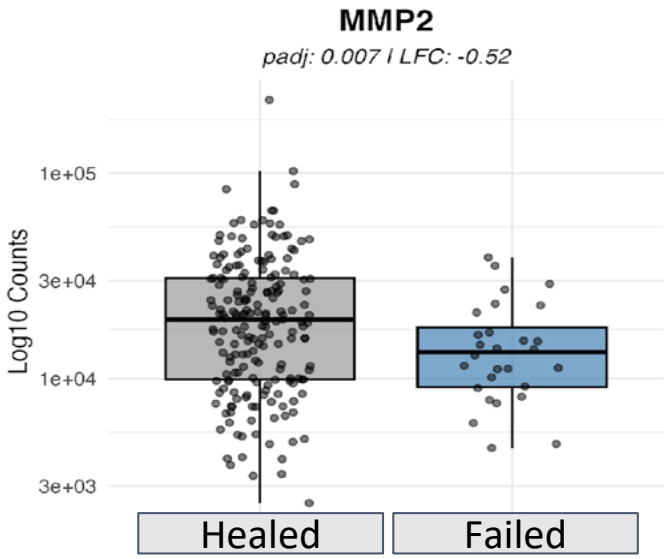
*padj: p-value adjusted for the false discovery rate
*LFC: Log_{10} fold change

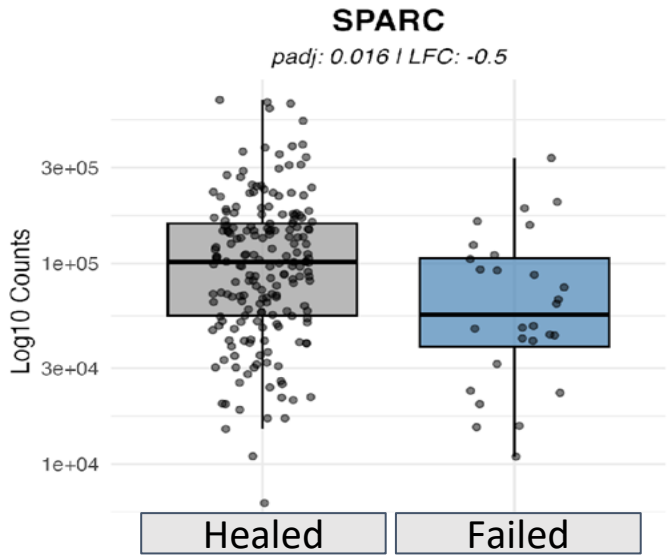
Matrix Tissue Remodeling Genes Were also Downregulated in Failed Wounds











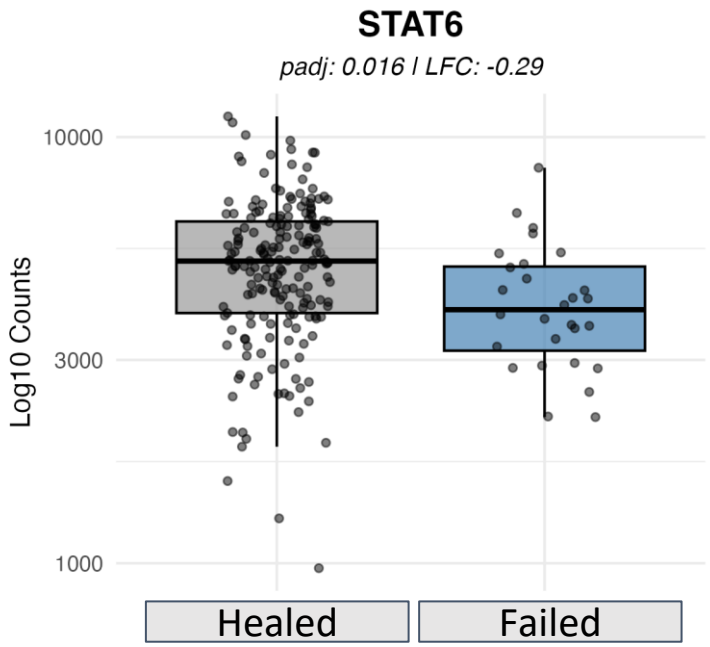
*padj: p-value adjusted for the false discovery rate
*LFC: Log_{10} fold change

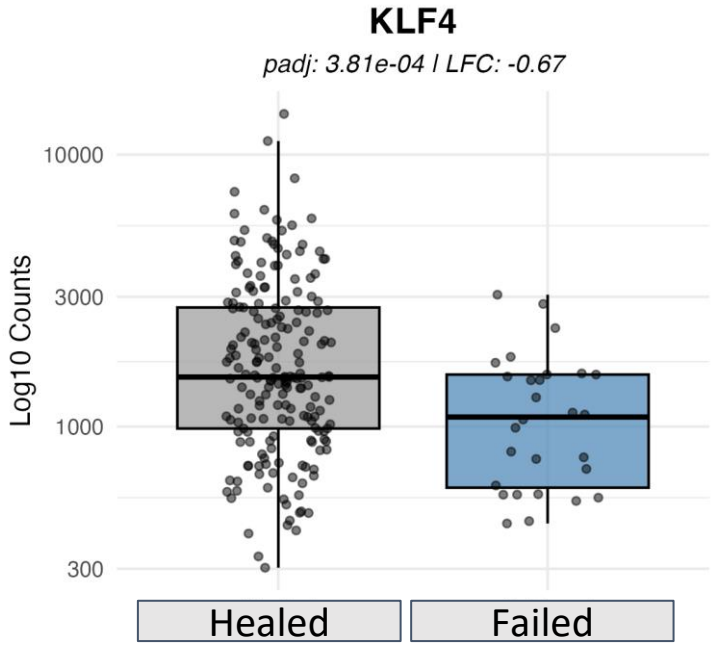
Reference:
Utz ER, Elster EA, Tadaki DK, et al. Metalloproteinase expression is associated with traumatic wound failure. *Journal of Surgical Research*. 2010;159(2):633–639.

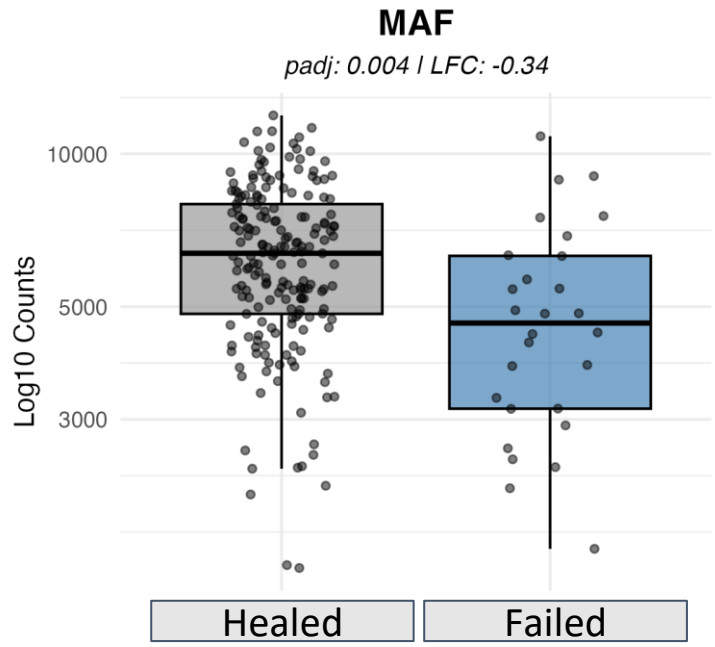
Uniformed Services University | SC2i Surgical Critical Care Initiative

STAT6, KLF4, and MAF Are Upregulated in Healed Wounds

- STAT6, KLF4, and MAF are transcriptional regulators associated with reparative (M2-like) macrophage polarization
- These genes coordinate pathways involved in inflammation resolution, tissue remodeling, angiogenesis, and wound repair
- Higher expression of STAT6, KLF4, and MAF in healed wounds is consistent with published reparative macrophage-associated transcriptional signatures







*padj: p-value adjusted for the false discovery rate
*LFC: Log_{10} fold change

Summary and Way Forward

- **Key Findings**
  - Healed wounds: Exhibit coordinated TGF-β signaling, collagen biosynthesis, and ECM remodeling
  - Failed wounds: Characterized by inflammatory signaling and suppressed structural repair genes (*SERPINH1*, *ACTA2*)
- **Next Steps**
  - Longitudinal analysis of key gene and cytokines associated with healed and failed outcomes
  - Continue exploring biological pathways associated with wound healing, including macrophage activity, extracellular matrix remodeling, collagen deposition, tissue regeneration, and their relationships with clinical wound characteristics