

# NEWSLETTER

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## SC2i Mission:

The Surgical Critical Care Initiative (SC2i) is a Uniformed Services University of the Health Sciences Center, funded by the Department of Defense, Defense Health Program.

SC2i was established in 2013 to develop biomarker-driven clinical decision support tools (CDSTs) for the critically ill, with the goal of improving clinical outcomes while reducing costs.

### For questions, please contact:

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## HARNESSING GENE EXPRESSION PROFILES OF COMBAT WOUNDS TO UNDERSTAND WOUND PROGRESSION

**Purpose:** Biomarkers associated with the progression of wound healing or dehiscence after a traumatic event are largely unknown. The mechanisms of wound healing can be categorized into two phases, the inflammatory phase and the proliferative phase. When these processes are disrupted wound dehiscence can occur. (Figure 1) The goal of this study is to examine gene expression profiles to understand wound progression (i.e. healed vs dehisced).

**Methods & Results:** Previously, 21 wounds from traumatic, extremity wound patients were investigated using RNA Sequencing. The differentially expressed genes (DEGs) between 10 healed and 11 dehisced wounds revealed little difference. However, when comparing critically colonized to non-colonized wounds, the gene expression profiles revealed significantly more DEGs. Colonized wounds had 657 significant genes while non-colonized wounds had 84 significant genes. A collaboration with Lawrence Livermore National Laboratory has enabled exploration into the host-microbe interactions through machine learning models to classify predictors of wound progression. Applying a generalized linear model with elastic net regularization revealed that prescriptions for aminoglycoside and antimicrobial resistance genes for aminoglycoside are potential predictors for wound progression. (Figure 2)

**Future Steps:** This study will be expanded to include more patients, both military and civilian, for RNA Sequencing to increase statistical power. Further development of machine learning models to understand the impact of microbes on wound progression is ongoing. The results from these analyses will aid in the determination of therapeutic targets for interrogation in animal models. Additionally, these results will guide a DARPA-funded, collaboration project, which aims to create a wound healing bandage that senses and modulates the microenvironment to promote wound healing.

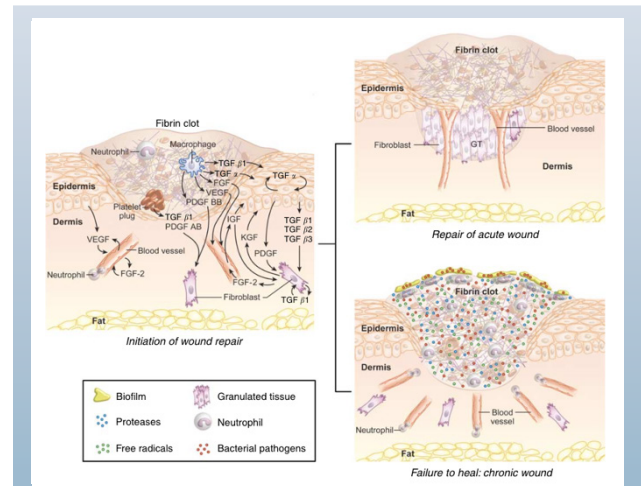


Figure 1. Wound healing progression, adapted from Clark *et al.* (2007) 127, 1018 – 1029. doi: 1.1038/sj.jid.5700715

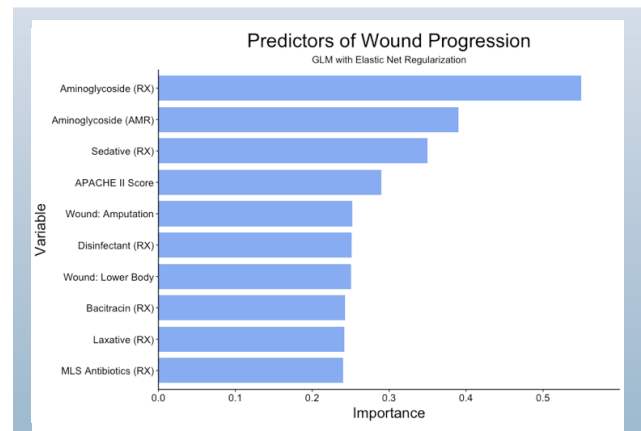
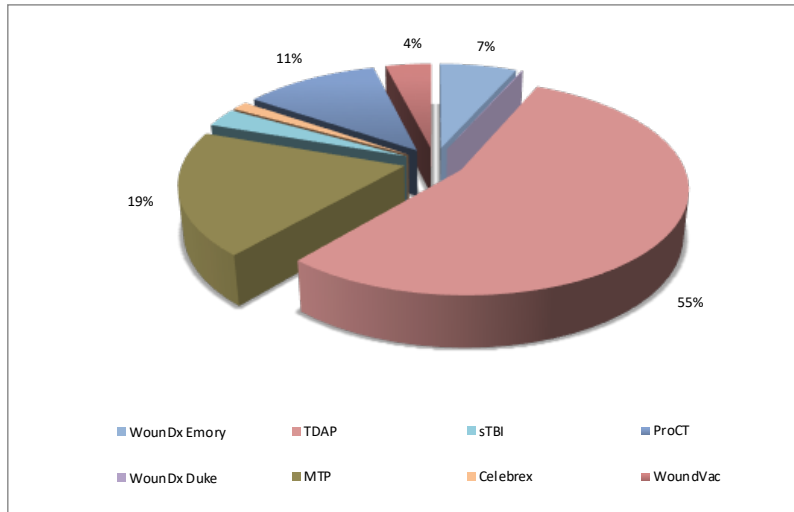


Figure 2. Predictors of wound progression. RX indicates prescription and AMR indicates Antimicrobial Resistance genes

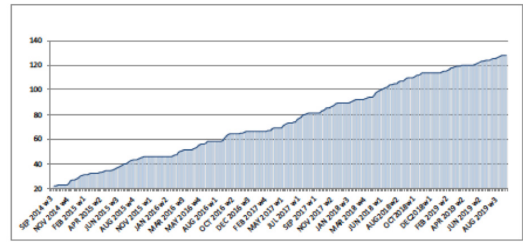
# STUDY ENROLLMENTS

The center has enrolled ~1,900 patients to date, contributing to a growing biobank (67,000 specimens) and databank (46,000,000 elements) to power the development of 'precision' clinical decision support tools.

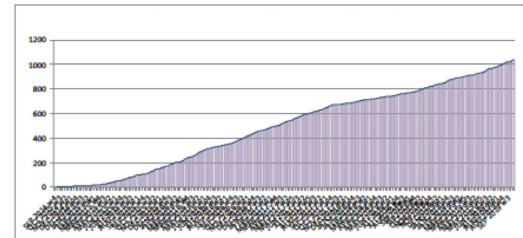
**Enrollment by Study**



**WoundDX (Extremity Injuries)**



**Tissue Data Acquisition Protocol (TDAP)**



# RESEARCH HIGHLIGHTS

## POST-TRAUMATIC ACUTE KIDNEY INJURY (PTAKI)

This study aims to investigate combat related post-traumatic acute kidney injury (PTAKI) in recent military conflicts, using machine learning to identify predictors of the development of PTAKI. A retrospective cohort review of 73 critically injured US military service members who sustained major extremity wounds and had injury characteristics, serum and tissue biopsy samples collected. Bivariate analyses and random forest (RF) algorithms were used to identify associated injury characteristics and biomarker variables. The incidence of PTAKI was 20.5%, 86% recovered baseline renal function and only two of the AKI group required RRT. RF algorithms were able to estimate PTAKI with AUC of 0.93, sensitivity of 0.91, and specificity of 0.91. PTAKI was associated with ISS, serum EGF, and tissue ACVR1, MMP10, and XCL1 expression. The occurrence of PAKI in combat casualties can be estimated using injury characteristics and serum and tissue biomarkers. External validation is needed to generalize these results.

**Table: Comparison of random forest recursive feature elimination (RF-RFE) models to identify PTAKI.**

	RF-RFE Model		
	M1: Clinical only	M2: Clinical & cytokines	M3: Clinical, cytokines & mRNA
<b>Variables remaining as indicators of PTAKI</b>	<ul style="list-style-type: none"> <li>Injury severity score</li> <li>Presence of vascular injury</li> <li>Wound count</li> </ul>	<ul style="list-style-type: none"> <li>Injury severity score</li> <li>Abbreviated injury score for head region</li> <li>Presence of vascular injury</li> <li>Serum interleukin-3</li> </ul>	<ul style="list-style-type: none"> <li>Injury severity score</li> <li>Serum epidermal growth factor</li> <li>Activin A type receptor 1</li> <li>Matrix metalloproteinase 10</li> <li>X-C motif chemokine ligand 1</li> </ul>
<b>Sensitivity</b>	0.84	0.98	0.91
<b>Specificity</b>	0.80	0.79	0.91
<b>Area Under Curve (95% Conf. Interval)</b>	0.83 (0.81-0.86)	0.91 (0.89-0.93)	0.93 (0.91-0.94)
<b>Calibration: Bias, Fitting</b>	0.50, 1.45	1.11, 1.20	1.53, 1.67
<b>Scaled Brier Score</b>	0.28	0.36	0.34

## DEMONSTRATION OF 2 DEPLOYED CLINICAL DECISION SUPPORT TOOLS AT MHSRS

The SC2i held a demonstration of two Clinical Decision Support Tools (CDSTs) at this year's Military Health System Research Symposium (19-22 August 2019, Orlando, FL). Loaded onto a deployable 'Toughbook', the Invasive Fungal Infection (IFI) and Massive Transfusion Protocol (MTP) CDSTs were both developed to enhance surgical decision making for critically injured warfighters. These two tools can function throughout all echelons of care (Roles 1 through 4), as either standalone applications (embedded on a smartphone, tablet, or computer) or applications linked to Electronic Medical Records such as Cerner or Epic. The IFI CDST is currently in-use at the Walter Reed National Military Medical Center, being run systematically on every trauma enrolled under the Center's Tissue Data Acquisition Protocol (TDAP); the MTP CDST is currently in-use at Emory University / Grady Memorial Hospital and Duke University. Both efforts demonstrate how a Federal and non-Federal partnerships like the SC2i can rapidly respond to critical care gaps by developing, validating, and deploying multi-platform CDSTs within a three-year window.

# RECENT PUBLICATIONS AND PRESENTATIONS

## MANUSCRIPTS:

Utilizing Precision Medicine to Estimate Timing for Surgical Closure of Traumatic Extremity Wounds. Lisboa FA, Dente C, Schobel SA, Khatri V, Potter BK, Kirk AD, Elster EA (Published - Annals Of Surgery)

PRECISION MEDICINE APPLICATIONS TO MANAGE MULTIPLY INJURED PATIENTS WITH ORTHOPAEDIC TRAUMA. McKinley T, Lisboa F, Horan A, Gaski G, Mehta S (Published - Journal Of Orthopaedic Trauma)

Random Forest Modeling Can Predict Infectious Complications Following Trauma Laparotomy Rondi Gelbard, Hannah Hensman, Seth Schobel, Vivek Khatri, Carl Rosene, Cameron Patterson, Christopher Dente, Timothy Buchman, Allan Kirk, Eric Elster (Published - Journal of Trauma and Acute Care Surgery)

Damaged- And Pathogen-Associated Molecular Patterns Play Differential Roles in Late Mortality After Critical Illness John Eppensteiner, Jean Kwun, Uwe Scheurmann, Andrew Barbas, Alexander Limkakeng, Eric Elster, Allan Kirk, Jaewoo Lee (Published - JCI Insight)

An Integrative Approach to Predictive Modeling for Post-Traumatic Acute Kidney Injury. Gelbard R, Hensman H, Seth Schobel S, Khatri V, Rosene C, Bachman K, Allison A, Tracy B, Paterson C, Dente C, Buchman T, Kirk A, Elster E (Submitted - Journal of Trauma and Acute Care Surgery)

A Random Forest Model To Predict Pneumonia In Combat Trauma Patients Matthew Bradley, Christopher Dente, Vivek Khatri, Seth Schobel, Felipe Lisboa, Audrey Shi, Hannah Hensman, Allan Kirk, Timothy G. Buchman, Eric Elster (Submitted - World Journal of Surgery)

A Random Forest Model To Predict Pneumonia In Combat Trauma Patients Matthew Bradley, Christopher Dente, Vivek Khatri, Seth Schobel, Felipe Lisboa, Audrey Shi, Hannah Hensman, Allan Kirk, Timothy G. Buchman, Eric Elster (Submitted - World Journal of Surgery)

Driving Biology: The effect of standardized wound management on wound biomarker profiles. Dente, Styrnisdottir, Schobel, Khatri, Potter, Forsberg, Buchman, Kirk, Elster. (Submitted - Journal of Trauma and Acute Care Surgery)

Prediction of Venous Thromboembolism using Clinical and Serum Biomarker Data from Trauma Patients. Bradley M, Shi A, Khatri V, Schobel S, Silvius S, Kirk A, Buchman T, Oh J, Elster E. (Submitted - Journal of Trauma and Acute Care Surgery)

RAPID DEVELOPMENT AND DEPLOYMENT OF A CLINICAL DECISION SUPPORT TOOL Arnaud Belard, Allan Kirk, Timothy Buchman, Bryan Morse, Christopher Dente, Eric Elster (Resubmission – Pending Internal Review)

Clinical Risk Factors And Inflammatory Biomarkers Of Post-traumatic Acute Kidney Injury In Combat Patients Beau J. Muñoz, MD, Seth A. Schobel, Felipe A. Lisboa, Vivek Khatri, Christopher J. Dente Timothy G. Buchman, Allan D. Kirk, and Eric A. Elster (Resubmission – Pending Internal Review)

Predicting the need for operative management of non-emergent small bowel obstruction with machine learning. Bozzay J, Walkrer P, Khatri V, Zielinski M, Wydo S, Cullinane D, Dunn J, Duane T, Inaba K, Rosenthal M, Watras J, Pakula A, Widom K, Cull J, Toschlog E, Hayward T, Schobel S, Elster E, Rodriguez C, Bradley M. (Resubmission – Pending Internal Review)

Immune Response Profiling in Patients with Traumatic Injuries Associated with Alcohol Ingestion Alexander Limkakeng, Adam Breslin, Catherine Staton, Chandi Quigley, Linda Stempora, Jennifer Cheeseman, Joseph Borawski, Bria Johnston, Thomas Irons, Allan Kirk, CAPT Eric Elster (Under Development)

## POSTERS/PRESENTATIONS:

- ASA 2019:** Utilizing Precision Medicine to Estimate Timing for Surgical Closure of Traumatic Extremity Wounds Lisboa F/Elster E
- AAST 2019:** Random Forest Model Predicts Acute Kidney Injury After Trauma Laparotomy Gelbard R
- Venom Week VII 2020:** Snake envenoming as a novel model of acute, non-infectious, sterile inflammation compared to polytrauma Gerardo C (Under Development)
- MHSRS 2019:** A Random Forest Model To Predict Bacteremia In Combat Trauma Patients Bradley M (Poster)
- MHSRS 2019:** Continuing Towards Early Prediction Of Vasospasm And Mortality Following Severe Traumatic Brain Injury (Stbi) Khatri V (Poster)
- MHSRS 2019:** Predicting Severe Sepsis In Surgical Icu Patients Schobel S (Poster)
- MHSRS 2019:** Predicting Acute Respiratory Distress Syndrome In Surgical Icu Patients Schobel S (Poster)
- MHSRS 2019:** Trauma Patients Wound Infection And The Relations With Injury And Clinical Progress Song M (Poster)
- MHSRS 2019:** A Possible Role For Vascular Endothelial Growth Factor In Predicting Duration Of Mechanical Ventilation After Cardiac Surgery Lisboa F (Oral Presentation)
- MHSRS 2019:** Estimating The Development Of Heterotopic Ossification In Combat-related Extremity Trauma Lisboa F (Poster)
- MHSRS 2019:** Multi-Site Harmonization and Standardization of Biorepository Terminology Joshi M (Poster)
- MHSRS 2019:** Surgical Critical Care Initiative: Maintenance Of Good Clinical Laboratory Practices Through Proficiency Testing Of Peripheral Blood Mononuclear Cells Osborne R (Poster)
- MHSRS 2019:** Woundx-SC2i Program For Tissue And Data Acquisition: Supporting Advances In Precision Medicine For Wound Closure In The Military And Civilian Sectors Iwakoshi N (Poster)
- MHSRS 2019:** Characterization Of Cellular Microrna In Polytrauma Patients Vicente D (Oral Presentation)
- MHSRS 2019:** Clinical Risk Factors And Inflammatory Biomarkers Of Post-traumatic Acute Kidney Injury In Combat Patients Muñoz B (Oral Presentation)
- MHSRS 2019:** Composition, Function, And Relevance Of The Microbial Microenvironment In Wounds From Combat Injuries Be N (Poster)
- MHSRS 2019:** A Random Forest Model To Predict Pneumonia In Combat Trauma Patients Bradley M (Oral Presentation)

## ON THE HORIZON

- 2020 Academic Surgical Congress (ASC)  
2020 February, Orlando Florida
- 2020 Venom Week VII 2020 March,  
Gainesville, FL
- 2020 Military Health System Research  
Symposium (MHSRS), 2020 August,  
TBD: Location and Dates
- 2020 American Association for the Surgery  
of Trauma (AAST), 2020 September,  
Waikoloa, HI