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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.

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## PREDICTING ABDOMINAL WOUND HEALING OUTCOMES USING A MACHINE LEARNING ALGORITHM

Clinical examination of abdominal wounds after trauma laparotomy inconsistently predicts which will heal when initial or delayed primary fascial closure is planned. Relying on the judgement and experience of the surgeon may result in either the premature closure of an abdomen destined for clinical failure, or alternatively, performing additional unnecessary washouts on abdomens that may never close.

There appears to be a statistical difference in the distribution of biomarkers among patients who fail fascial closure compared to those who close successfully (Figure 1). We set out to discover if multiclass modeling could be used to predict wound outcomes of abdominal wall closure after abdominal trauma.

Our method focused on selecting the variables most strongly associated with outcome and then optimizing a predictive model based on those variables. After evaluating many different cytokines in the serum and wound effluent of 75 trauma patients undergoing trauma laparotomy, we found the strongest relationship and predictive power in the following molecular biomarkers: Peritoneal Lavage Procalcitonin (ProCT), Serum ProCT, Peritoneal Lavage Interleukin (IL) 17 and Serum IL4.

These variables were used to train a random forest classification model. We found that our multi-class model best predicts which patients will heal after primary fascial closure. Next steps include validating this predictive model across a broader patient cohort. Our hope is that this model can be used to develop clinical decision support tools to direct appropriate therapy pertaining to the timing of wound closure based on each patient's biomarker expression in response to injury.

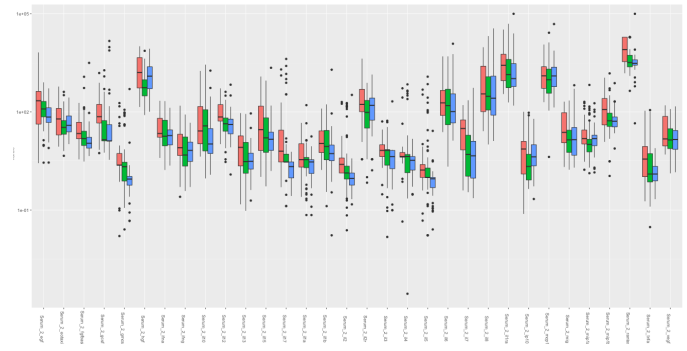


Figure 1. Distribution of biomarkers among 3 groups of patients: 1) "Healed" - those who underwent successful primary fascial closure; 2) "Failed" - those who dehiscid after primary fascial closure; 3) "Open" - those managed with damage control laparotomy without ever achieving fascial closure.

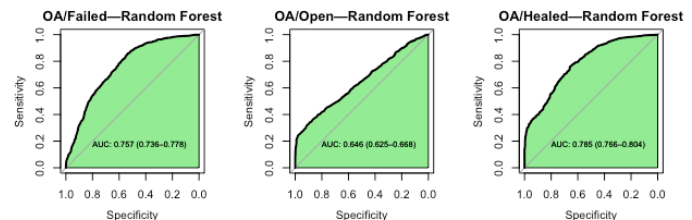


Figure 2. A reduced variable set was used to train a random forest classification model that performed well (Kappa 0.41). The model accuracy rate of 0.64 outperformed the no information rate of 0.48. The sensitivity, specificity, and AUC for the 3 groups are shown here. Predicting successful fascial closure had the highest sensitivity (73%). Comparing the AUC between groups revealed that predicting successful fascial closure performs the best compared to the other groups.

# STUDY ENROLLMENT

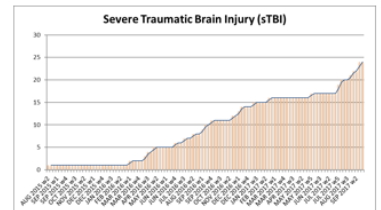
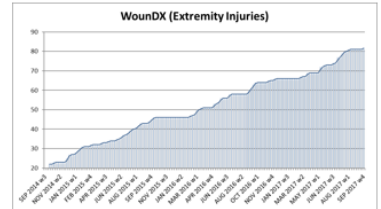
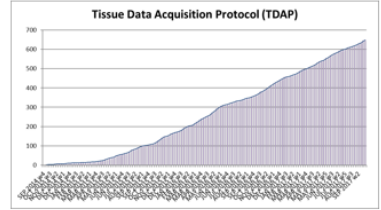
The Surgical Critical Care Initiative (SC2i) has enrolled 1,415 patients across its various studies, adding 300 patients alone this past year.

**Enrollment**

**1,415 Patients**

**+6~8 per week**

Study	Focus	Cohort	Patients	Status	Location
WoundVac	Military Trauma (extremity injuries)	Military	75	Closed enrollment	WRNMMC
ProCT	Military Trauma (procalcitonin/wound healing)	Military	220	Closed enrollment	WRNMMC
TDAP	Critically ill or injured	Mixed	651	Open enrollment	WRNMMC Emory-Grady Duke
WoundX	Civilian Trauma (extremity injuries)	Civilian	82	Open enrollment	Emory-Grady Duke
MTP	Civilian Trauma (requiring massive transfusion)	Civilian	363	Open enrollment	Emory-Grady
sTBI	Civilian Trauma (severe Traumatic Brain Injury)	Civilian	24	Open enrollment	Emory-Grady



# RESEARCH HIGHLIGHTS

## STBI UPDATE

Purpose: To examine the inflammatory profile of patients who have undergone severe traumatic brain injuries and determine if it is possible to predict complications and other outcomes with these data. It is also our goal to determine if data generated from procedures and diagnostics of a less invasive nature (i.e. blood or csf tests) can be used in lieu of more invasive and costly measures.

Project Status: We currently have 24 patients enrolled in the sTBI study with 15 of those having complete initial datasets. Long-term follow-ups are still pending. The examination of inflammatory profiles in the sTBI cohort has begun and early results indicate a correlation between serum biomarkers and various outcomes including vasospasm, the need for ventricular shunts, and mortality.

Future Steps: Our next steps for the sTBI study are to continue to enroll patients and stratify our analysis of biomarker profiles in patients with sTBI alone versus sTBI with polytrauma injury patterns. Additionally, we aim to examine the correlation of BIS/INVOS monitoring on patients with various complications such as vasospasm.

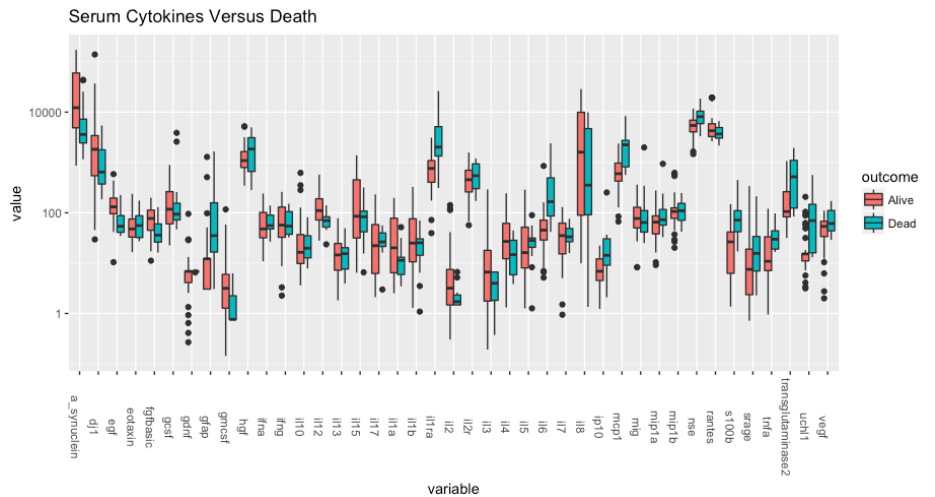


Figure 1. Boxplot depiction of protein distributions in sTBI patients that survived versus those that died. Several protein levels were determined to be statistically different at the 0.05 level in patients in these two outcome groups.

# RESEARCH HIGHLIGHTS

## TRANSLATIONAL RESEARCH UPDATE - RNASEQ

**Purpose:** As part of our efforts to move findings from the bench back to the bed, the SC2i has produced a RNASeq dataset from our WoundVAC study. The aim of our current RNASeq analysis has been to examine the transcriptional profile of patients with healed versus dehisced wounds in the presence and absence colonizing microbes. We also aim to identify novel biomarkers with the potential to add predictive power to our clinical decision support models of wound-healing and infectious processes.

**Project Status:** Our RNASeq work in the WoundVAC study has progressed through the completion of two phases of transcriptomic analysis in dehisced versus healed wounds. We have sequenced transcriptomes from 21 wounds across 3 to 4 timepoints, including patients with and without microbial colonization, for a total of 60+ transcriptomic datasets. Our initial bioinformatics analysis has identified hundreds of putative differentially expressed genes across the various conditions and timepoints being examined. We have identified several putative targets for use as predictive biomarkers.

**Future steps:** Our goal with the RNASeq project is to continue to identify putative biomarkers for use in predictive algorithms. This work will include confirmation of biomarker suitability through QRT-PCR and Western Blot analyses. Confirmed biomarkers may be used in later work as either additional analytes for SC2i studies or as potential therapeutic targets in later studies. In addition to this work, we aim to examine the microbial transcriptomic content from our RNASeq data to examine the Host-Pathogen interactions at play in colonized wounds.

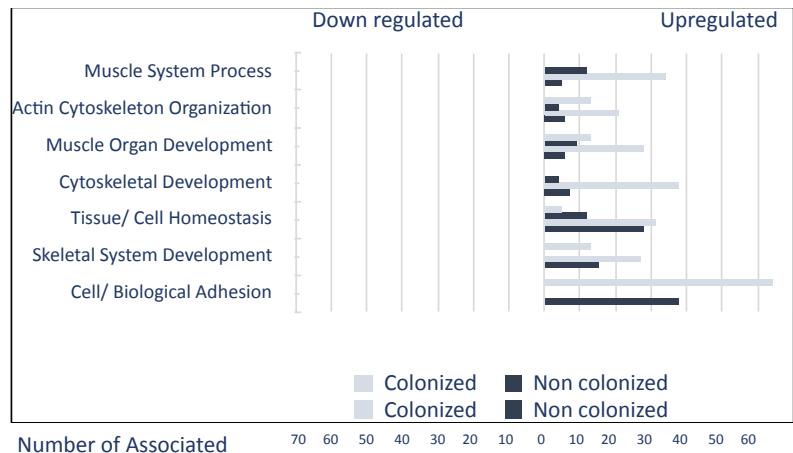


Figure 2. Number of gene transcript targets determined to be up and down regulated in patients with impaired healing with microbial colonization broken down by biological function analysis. Genes associated with Cell/Biological Adhesion appears to be impaired in wounds with microbial colonization.

## RECENT PUBLICATIONS AND PRESENTATIONS

### MANUSCRIPTS:

**Dismounted Complex Blast Injury Patterns: A Review of Current Management and Outcome Literature International Review of the Armed Forces Medical Services**

(Published - Journal of the American College of Surgeons)

**The Impact of a Big Data Decision Support Tool on Military Logistics: Medical Analytics Meets the Mission**

(Published - Defense Acquisition and Research Journal)

**Towards Precision Medicine: Accurate Predictive Modeling of Infectious Complications in Combat Casualties**

(Published - Journal of Trauma and Acute Care Surgery)

**Transforming Medicine with Data A white paper capturing the cost avoidance associated with the deployment of SC2i clinical decision support tools** (Released via [www.sc2i.org](http://www.sc2i.org))

**Nucleic acid scavenging microfiber mesh inhibits trauma-induced inflammation and thrombosis** (Accepted - Biomaterials)

**The Uniformed Services University's Surgical Critical Care Initiative (SC2i): Brining Precision Medicine to the Critically Ill** (Accepted - Journal of Military Medicine)

**Optimizing Surgical Outcomes with Biomarker-Based Decision Making Out of the Crucible** (Accepted - Chapter 38)

**Early Sepsis Detection in Critical Care Patients Using Multiscale Blood Pressure and Heart Rate Dynamics** (Accepted - Journal of Electrocardiology)

**Machine Learning Algorithm Predicts Successful Fascial Closure After Trauma Laparotomy.** (Submitted - Journal of Trauma and Acute Care Surgery)

**Battlefield to Bedside: Bringing Precision Medicine to Surgical Care.** (Submitted - Journal of the American College of Surgeons)

**Predicting the Need for massive Transfusion Protocol Activation: Prospective Validation of a Smartphone-Based Clinical Decision Making Application.** (Submitted - Journal of Trauma and Acute Care Surgery)

## PRESENTATIONS:

MHSRS 2017: **Surgical Critical Care Initiative (SC2i) Tissue and Data Acquisition Protocol: Integrated Research Support Driving Precision Medicine for Wounded Warriors** (Cheeseman et al)

MHSRS 2017: **Surgical Critical Care Initiative Tissue and Data Acquisition Protocol: Clinical Data Standardization across Multi-Site Consortiums** (Davis et al)

MHSRS 2017: **Development of Predictive Models for Acute Respiratory Distress Syndrome using Serial Inflammatory Biomarkers: A Preliminary Analysis** (Gutierrez et al)

MHSRS 2017: **Clinical Risk Factors and Inflammatory Biomarkers of Post-Traumatic Acute Kidney Injury in Combat Patients** (Munoz et al)

MHSRS 2017: **Predicting Sepsis in the ICU using a Proportional Hazards Model** (Stanley et al)

MHSRS 2017: **Standardization of Biological Sample Processing and Clinical Data Capture to Support the Delivery of Precision Medicine** (Seth et al)

MHSRS 2017: **Advanced Modeling to Predict Pneumonia in Combat Trauma Patients** (Bradley et al)

MHSRS 2017: **Timing of Delayed Wound Closure May Be Estimated By The Cytokine Response In Combat-Related Extremity Wounds** (Lisboa et al)

MHSRS 2017: **Tranexamic Acid (TXA) Independently Predicts Thromboembolic Complications** (Johnston et al)

MHSRS 2017: **Transcriptomic profile of combat wounds at the various stages of wound healing progression** (Upadhyay et al)

MHSRS 2017: **Neurodegenerative Biomarker Analysis in Traumatic Brain Injury Patients** (Iwakoshi et al)

MHSRS 2017: **Cost Savings Associated with the Forecast and Prevention of Sepsis in the Intensive Care Unit** (Chang et al)

MHSRS 2017: **A predictive model of venous thromboembolism in combat casualties using a supervised machine learning algorithm** (Oh et al)

MHSRS 2017: **Assessing Risk and Related Complications Following Reversal of Combat Associated Ostomies** (Johnston et al)

ACEP 2017: **Evaluation of Phenylalanine and Tyrosine Concentrations in Traumatically Injured Patients** (Johnston et al)

ASM 2017: **Application of Genomics-based Microbial Detection for Prediction of Combat Wound Outcome** (Be et al)

CBD S&T 2017: **Association of genomics-based microbial detection with wound outcome in combat injuries** (Be et al)

ISBER 2017: **Surgical Critical Care Initiative (SC2i) Tissue and Data Acquisition Protocol: Supporting Innovations in Precision Medicine for Wounded Warriors** (Cheeseman et al)

ISBER 2017: **Surgical Critical Care Initiative: Evidence to Inform Practices of Clinical Data Standardization across Multi-Site Consortiums** (Davis et al)

AAI 2017: **Local Host Level of Cytokines and Gene Expression are Associated With Successful Healing of Combat-related Extremity Wounds With Persistent Critical Colonization** (Lisboa et al)

EAST 2017: **Towards precision medicine: Accurate predictive modeling of infectious complications in combat casualties** (Dente; Oral)

AAST 2017: **Predicting the Need for Massive Transfusion Protocol Activation: Prospective Validation of a Smartphone-Based Clinical Decision Making application** (Morse; Oral)

AAST 2017: **Machine Learning Algorithm Predicts Successful Fascial Closure After Trauma Laparotomy** (Gelbard; Oral)

SOMOS 2017: **Tranexamic Acid Administration And Venous Thromboembolism In Combat Casualties With Orthopedic Injury** (Baird; Oral)

AAST 2017: **The Role of Procalcitonin in the Decision to Close Open Abdomens after Damage Control Laparotomy** (Gelbard et al; Poster).

EAST 2017: **Towards precision medicine: Accurate predictive modeling of infectious complications in combat casualties** (Dente et al; Oral).

ASC 2017: **Toll-like Receptor Signaling as a Prognostic Tool in Trauma Patients** (Darabie et al; Oral).

## ON THE HORIZON

- 5th Bi-annual Investigators/Oversight Committee Meeting (IM/OCM), 20-21 October 2016, Bethesda, MD
- American College of Surgeons (ACS) Clinical Congress 2016, 16-20 October 2016, Washington, DC
- Association of Academic Health Centers (AAHC) Precision Medicine Research Meeting, 8-9 December 2016, Washington, DC
- 30th EAST Annual Scientific Assembly, 10-14 January 2017, Hollywood, FL
- 12th Annual Academic Surgical Congress(ASC), 7-9 February 2017, Las Vegas, NV
- 76th Annual AAST Meeting, Research Symposium 13-16 September 2017, Baltimore, MD