Forward: Launch of the SC2i Newsletter

We are pleased to announce the launch of the Surgical Critical Care Initiative (SC2i) newsletter. Issues will take the form of biannual research updates targeting audiences concerned with the delivery of precision medicine in the ‘acute care’ space.

Established in 2013 to develop biomarker-driven clinical decision support tools (CDSTs) for the critically ill, 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). A consortium formed of both Federal (Uniformed Services University, Walter Reed National Military Medical Center, Naval Medical Research Center) and non-Federal (Duke, Emory, DecisionQ, Henry M. Jackson Foundation) entities, SC2i facilitates tissue acquisition and data analysis to develop clinical decision-making algorithms. The methods developed by the Center are expected to help maximize outcomes across any discipline requiring complex medical decision making, including surgery, critical care, emergency medicine, orthopedics, transplant and oncology.

Building on a legacy of 320 service members injured during OEF/OIF, 800 additional critically ill civilian and military patients have been prospectively enrolled under four SC2i trials since the Fall of 2014. A ‘Precision Medicine’ initiative at heart, the USU Center is well on its way to achieving Good Clinical Laboratory Practices (GCLP) across its molecular core laboratories and is establishing a consortium-wide databank on GovCloud to aggregate de-identified clinical and instrument data in a standardized fashion. In its short existence, the SC2i has already deployed two CDSTs (predicting the incidence of invasive fungal infection or the need to activate a massive transfusion protocol) and is leveraging its growing databank to develop predictive algorithms for venous thromboembolism (VTE), acute kidney injury (AKI), and bacteremia/pneumonia.

As a USU Center, SC2i positions itself at the crossroads of research (developing clinical decision support tools for the critically wounded warfighter) and education (embedding students and residents into its translational studies), and is thus uniquely positioned to support the next conflicts by maintaining critical-care currency for the battlefield surgeons of tomorrow. The Center’s predictive models will also assist military readiness by either accelerating return to duty (abridged length-of-stay across the ICU, general ward, and rehabilitation continuum of care) or curbing logistical burdens (e.g. reduced need for blood products and airlifts) during conflicts.

CAPT Eric Elster, Professor and Chairman of the USU Walter Reed Department of Surgery, is the Director of the Center. LTC Benjamin Kyle Potter, Vice-Chair of Research for the USU Walter Reed Department of Surgery, and Dr. Allan Kirk, Chairman of the Department of Surgery at Duke University, are both Deputy Directors.

Our goal with this newsletter is to not only inform but also encourage collaboration. If interested in joining our mailing list or meeting with Center representatives, please contact Ms. Myra Yusuf, SC2i Program Coordinator, at myra.yusuf.ctr@usuhs.edu.

Contributor: Arnaud Belard, MBA
Toll-like Receptor (TLR) Activity May Help Identify Patients with Increased Risk of Complication

Despite vast improvements in injury prevention and emergency response systems, hospitalized combat or civilian patients who survive pre-hospital transport are at risk for sepsis and multi-organ dysfunction. Upon injury, these patients produce large quantities of damage molecules (DAMPs) which bind endogenous immune receptors called Toll-like Receptors (TLR). Our Tissue Data Acquisition Protocol (TDAP analysis seeks to address this problem by determining TLR signaling after traumatic injury and correlating TLR activity with clinical course in traumatically injured patients. We can evaluate longitudinal human TLR signaling patterns utilizing downstream TLR signaling activity in the context of our TDAP patient cohort. Our initial studies demonstrate a marked biological response in traumatically injured patients or patients with abdominal sepsis compared to healthy controls (Figure 1). Additionally, we can model temporal patterns in TLR activity along clinical course of both survivors and non-survivors as well as patients with abnormalities in clinical trajectory suggestive of complications (Figure 2). These studies suggest that there are detectable differences in TLR activity in traumatically injured patients and that severely injured patients demonstrate increase TLR activity. Furthermore, temporal increases in TLR activity occur with deteriorating clinical status. Conversely, TLR signaling decreases in patients that are clinically improving. These initial studies lay the ground work for future mechanistic studies as well as therapeutic agents that may modulate TLR activity both in our non-human primate and human TDAP patients. 

Contributor: Marcus Darrabie, MD

Supporting Medical Education and Surgical Residents

The SC2i, in-line with the educational mission of its Sponsor (the Uniformed Services University of the Health Sciences), supports both medical students and residents across its Federal and non-Federal sites.

Activities range from analytics & modelling mentorship to CDST development. Each year, three surgical residents (SC2i Fellows) and approximately six medical students support key projects.

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<thead>
<tr>
<th>Current SC2i Fellows</th>
<th>Affiliation</th>
<th>Area of Research</th>
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<tr>
<td>LCDR Beau Munoz, MD</td>
<td>USU Walter Reed Surgery</td>
<td>Predicting Acute Kidney Injury (AKI)</td>
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<tr>
<td>LT Luke Johnston, MD</td>
<td>USU Walter Reed Surgery</td>
<td>Exploring the Role of Procalcitonin in Wound Healing</td>
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<tr>
<td>Matthew Stanley, MD</td>
<td>Emory University</td>
<td>Predicting Decompensation and Sepsis</td>
</tr>
<tr>
<td>Muath Bishawi, MD</td>
<td>Duke University</td>
<td>Role of Caspase/Apoptosis in Total Body Injury</td>
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Research Highlights

Bacteremia/Pneumonia

**Purpose:** The purpose of the bacteremia and pneumonia study is to develop predictive models for the onset of these infections in extremity wound patients. It is also a goal to establish the usefulness of these models in a broader surgical care context. Once modeling is complete, CDSTs will be developed to aid in the identification of patients at risk for both infectious complications.

**Project Status:** Random Forest models were developed using Bayesian variable selection techniques using data from first washout. Currently developing clinical only models for comparison to biomarker models.

**Future Steps:** The way forward for this project will include incorporating data from other study cohorts to establish the universal usefulness of these models in treating any critically ill surgical patients. This will be executed by collecting clinical end point data for WoundDX patients with respect to the development and timing of onset of bacteremia and pneumonia infections. Once clinical endpoints have been delivered, we will refine these models with WoundDX data to include performing external validations. Validation with TDAP patients is also planned.

Open Abdomen

**Purpose:** The purpose of the open abdomen study is to first evaluate if a clear biomarker signature can be derived using TDAP instrumentation data that can be associated with healing outcomes and development of surgical complications. Once this has been established predictive modeling will be performed in support of the development of a CDST.

**Project Status:** Current project status includes a descriptive analysis with repeated measures analysis of ProCalcitonin (ProCT) only. Serum and effluent ProCT levels vary by outcome. Age also varies by outcome, repeated measures show different profiles of serum ProCT levels based on outcome.

**Future Steps:** The way forward is to work on developing clinical and instrumentation based models using Bayesian variable selection and Random Forest modeling. This will include examining clinical end points of:

- Fistula
- Failed closure

Massive Transfusion Protocol (MTP) App

**Purpose:** The purpose of the MTP App analysis is to evaluate the use statistics collected during the trial phase of MTP app at Emory. This includes an examination of the correlation between app use and physician decision-making with respect to the implementation of a Massive Transfusion Protocol during the resuscitation of critically injured trauma patients.

**Project Status:** Data on the usage of the MTP app has been collected and delivered, as well as project priorities have been outlined and an analysis plan is under development. The MTP app usage analysis began the week of 9/19/2016.

**Future Steps:** Analysis deliverables will include an examination of both the users willingness to follow the apps advise, as well as the development of various measures of predictive accuracy.

*Contributor: Seth Schobel, PhD*
Ongoing Analyses

**Bacteremia / Pneumonia: Christopher Dente, MD (Emory Surgery) & LCDR Matthew Bradley, MD (USU Walter Reed Surgery)**
- Analyze effluent and serum biomarkers to predict incidences of bacteremia & pneumonia in civilian and military trauma patients.

**Venous Thromboembolism: COL John Oh, MD (USU Walter Reed Surgery)**
- Analyze clinical and biomarker variables to identify incidences of VTE.

**Wound Healing for Extremity Injuries: Christopher Dente, MD (Emory Surgery)**
- Refine model to accurately time the closure of traumatic wounds, thereby reducing resources to low probability outcomes and accelerating healing pathway.
- Toll-like Receptors (TLRs) - Allan Kirk, MD, PhD (Duke Surgery)

**Correlate TLR activity to tissue injury, with the goal of developing scavenger assays to mitigate response.**

**Massive Transfusion Protocol: Bryan Morse, MD (Emory Surgery)**
- Collect data on use of MTP app (two-year clinical trial) to better evaluate utility of tool in expediting MTP activations and reducing unnecessary activations and transfusions.

**Open Abdomen: Rondi Gelbard, MD (Emory Surgery)**
- Evaluate whether serum procalcitonin is associated with delayed fascial closure post laparotomy.

**Physiologic Monitoring: Timothy Buchman, PhD, MD (Emory Surgery)**
- Collect streams data from intensive care units and develop models to proactively detect and act upon episodes of decompensation (current focus on sepsis).

**Severe Traumatic Brain Injury: Nicholas Boulis, MD (Emory Neurosurgery)**
- Develop biomarker informed models to decrease ventriculostomy time, unindicated angiography, infections, and hemicraniotomies.

**RNA Sequencing: CAPT Eric Elster, MD (USU Walter Reed Surgery)**
- Identify genes associated with wound healing and integrate into existing models.

**Delayed Primary Closure: Felipe Lisboa, MD (USU Walter Surgery)**
- Pursue work on an interactive model that predicts the number of wound débridements needed until closure can occur.

**Acute Kidney Injury: LCDR Beau Munoz, MD (USU Walter Reed Surgery)**
- Develop joint clinical-biomarker model to reduce nephrotoxicity and need for renal replacement therapy.

**Appendectomy: LCDR Beau Munoz, MD (USU Walter Reed Surgery)**
- Retrospectively validate model internally developed on an Android app.
Study Enrollment

1,100 patients enrolled (including legacy military studies)

Recent Publications and Presentations

Manuscripts:


Elster EA, Belard A. Optimizing Surgical Outcomes with Biomarker-based Decision Making. The Crucible. (ACCEPTED)


Radowsky JS, Neely R, Forsberg JA, Lisboa FA, Dente CJ, Elster, EA, Crane NJ. Preclosure Spectroscopic Differences Between Healed and Dehisced Traumatic Wounds (SUBMITTED - Trauma and Accurate Care Surgery).
Presentations:

White House Conference. ‘AI for Social Good’. Surgical Critical Care Initiative (SC2i): Bringing Precision Medicine to the Critically-III (Elster; Oral).

MHSRS 2016: Utilization of Toll-like Receptor Signaling as a Prognostic Aid in Traumatically Injured Patients (Darrabie et al; Oral).

MHSRS 2016: Differences Between Military and Civilian Wound Characteristics and Implications for Civilian Application of a Military Clinical Decision Support Tool (Dente et al; Oral).

MHSRS 2016: An Integrated Central Data Repository Connecting Translational Research Methods with Personalized Tools for Patient Care (McCourt et al; Oral).

MHSRS 2016: Gene Expression and Cytokine Response in Combat-related Extremity Wounds with Persistent Critical Colonization may be Associated with Different Healing Outcomes (Lisboa et al; Oral).

MHSRS 2016: The Surgical Critical Care Initiative (SC2i): Precision Medicine for Critical Care (Belard et al; Poster).

MHSRS 2016: Spectroscopic Differences Between Health and Dehisced Traumatic Wounds (Radowsky et al; Poster).

MHSRS 2016: Surgical Critical Care Initiative (SC2i) Tissue and Data Acquisition Protocol: Bio-banking to Enhance Precision Medicine for Wounded Warriors (Cheesenman et al; Poster).

MHSRS 2016: Evaluation of Acute Responses to Tissue Injury in a Nonhuman Primate Model of Severe Polytrauma (Darrabie et al; Poster).


MHSRS 2016: Prospective Evaluation of a Web-based Clinical Decision Making Tool to Assist in Determining the Need for a Massive Transfusion: a Preliminary Analysis (Dente et al; Poster).

MHSRS 2016: Bacterial Surface Determinants Modulate Host Inflammatory Responses in Impaired Wound (Updhyay et al; Poster).

MHSRS 2016: Applications of the Trauma Embolic Scoring System (TESS) to Military Trauma: Need for a Refined Model in Combat Casualties (Walker et al; Oral).

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


ASC 2017: Toll-like Receptor Signaling as a Prognostic Tool in Trauma Patients (Darrabie 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

Leadership and Senior Investigators

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<tr>
<th>Site</th>
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