

Shock 2023

View Abstract

CONTROL ID: 3908525
TITLE: ENDOTYPING SEPTIC AND CRITICALLY ILL PATIENTS USING ELISPOT: THE 'SPIES' EXPERIENCE
PRESENTATION TYPE: Oral or Poster
PREFERRED TOPIC: Novel Technologies and Approaches to Study Shock Pathophysiology, Outcomes and Treatments
AUTHORS (FIRST NAME, LAST NAME): Lyle L. Moldawer ¹ , Monty Mazer ⁷ , Michael D. Goodman ² , Patrick McGonagill ⁵ , robert gould ³ , Philip A. Efron ¹ , Letitia Bible ¹ , Ivanna Rocha ¹ , Muxuan Liang ⁴ , Isaiah R. Turnbull ⁹ , Scott Brakenridge ⁶ , Kenneth Remy ⁷ , vladimir badovinac ⁵ , Thomas S. Griffith ³ , Richard Hotchkiss ⁸ , Charles Caldwell ⁶
INSTITUTIONS (ALL): 1. Surgery, University of Florida College of Medicine, Gainesville, FL, United States. 2. Surgery, University of Cincinnati, Cincinnati, OH, United States. 3. Surgery, University of Minnesota Twin Cities School of Medicine, Minneapolis, MN, United States. 4. Biostatistics, University of Florida College of Medicine, Gainesville, FL, United States. 5. Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA, United States. 6. Surgery, University of Washington School of Medicine, Seattle, WA, United States. 7. Pediatrics, University Hospitals, Cleveland, OH, United States. 8. Anesthesiology, Washington University in St Louis, St Louis, MO, United States. 9. Surgery, Washington University in St Louis, St Louis, MO, United States.
ABSTRACT BODY: Introduction: Sepsis is a heterogenous immune response to infection and organ injury. Recent efforts to endotype the host response to sepsis have attempted to identify patients who may benefit from targeted biological therapies. In general, endotypes have relied on static protein and transcriptomic measures to characterize patients. We posit that a functional bioassay will identify critically ill, immunosuppressed patients with increased risk of adverse clinical outcomes who may benefit from therapies targeting immunosuppression. Methods: This is a planned interim analysis of a prospective, multicenter clinical trial conducted at seven U.S. sites to determine the ability of ELISpot to identify the immunosuppressed endotype and predict clinical outcomes in sepsis and critically ill non-sepsis (CINS) patients as part of an NIGMS funded clinical study (R01 GM139046). Blood samples were collected at 1-3, 4-7, and 14 days after ICU admission. Validated ELISpot assays were conducted using 5 ml whole blood stimulated <i>ex vivo</i> with 1 mg/ml of anti-CD3/CD28 mAb, and IFN γ production (spot number, spot size, total production) determined 18-22 hours later. ELISpot performance in predicting in-hospital and 90-day mortality was summarized as area under the receiver operating characteristic curves (AUROC). Results: 179 sepsis, 93 CINS, and 47 healthy control subjects have been enrolled to date, with 107 sepsis, 68 CINS patients, and 46 healthy control subjects being analyzed here. 90-day mortality in sepsis patients was 16.8%, and 1.5% in CINS patients. Cox regression analysis on time to death in the

sepsis patients was <0.01 at both 1-3 and 4-7 days for total IFN γ production (spot number times spot size). AUROCs for in-hospital and follow-up mortality were 0.69 (0.56-0.82) and 0.70 (0.55-0.84), and 0.74 (0.62-0.87) and 0.71 (0.58-0.84) for days 1-3 and 4-7, respectively (all $p<0.02$; **Figure 1**). ELISpot values had weak associations with secondary infections and development of chronic critical illness. In sepsis patients with an ELISpot $< 2028 \text{ cm}^2/\text{m}^2$ (sensitivity 90.9%, specificity 54.3% for in-hospital mortality) at days 4-7, absolute lymphocyte counts were reduced while SOFA score was significantly increased at both 1-3 and 4-7 days, and sPD-L1 was significantly higher at days 1-3 (all $p<0.05$).

Conclusions: Interim analyses suggest IFN γ production measured by whole blood ELISpot can identify critically ill patients who are likely to die. Both sepsis and CINS patients with reduced *ex vivo* IFN γ production have an immunosuppressed endotype based on absolute lymphocyte counts, and plasma sPD-L1. ELISpot may prove helpful in identifying sepsis patients at risk of dying who would benefit from targeted immune stimulant interventions.

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TABLE TITLE: (No Tables)

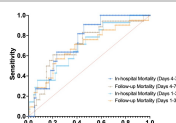


Figure 1, AUROC Scores for Mortality using ELISpot Collected at Days 1-3 and 4-7 Post ICU Admission

AWARDS:

Disclosure: YES, there are relationships to disclose.

Extra Info: Several of authors and their universities have sought intellectual property protection by filing patent applications. Other authors are the chief administrative officers of a start up intended to develop these technologies.

Submission Rules Confirmation: I confirm that I have read and complied with the submission guidelines.

ARE YOU A MEMBER?:

Lyle Moldawer : Yes

Monty Mazer : Yes

Michael Goodman : Yes

Patrick McGonagill : Yes

robert gould : No

Philip Efron : Yes

Letitia Bible : Yes

Ivanna Rocha : No

Muxuan Liang : No

Isaiah Turnbull : Yes

Scott Brakenridge : Yes

Kenneth Remy : Yes

vladimir badovinac : Yes





Thomas Griffith : Yes

Richard Hotchkiss : Yes

Charles Caldwell : Yes

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Product version number 4.17.4 (Build 172). Build date Wed Mar 8 10:04:16 EST 2023. Server ip-10-236-26-7