Critical Care Medicine

Division Details

RESEARCH AND TRAINING DETAILS

<table>
<thead>
<tr>
<th>Faculty</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Annual Grant Award Dollars</td>
<td>$2,669,743</td>
</tr>
<tr>
<td>Total Annual Industry Award Dollars</td>
<td>$85,000</td>
</tr>
<tr>
<td>Total Publications</td>
<td>49</td>
</tr>
</tbody>
</table>

CLINICAL ACTIVITIES AND TRAINING

| Clinical Fellows | 12 |
| Inpatient Encounters | 10,177 |

Significant Publications


OBJECTIVE: Inhibition of matrix metalloproteinase-8 improves survival following cecal ligation and puncture in mice, making it a potential therapeutic target. In the current study, we expand our understanding of the role of matrix metalloproteinase-8 in sepsis by using an adoptive transfer approach and alternative sepsis models.

DESIGN: We used three different sepsis models: cecal ligation and puncture, cecal slurry, and intestinal implantation. In our first model, we followed adoptive transfer experiments by cecal ligation and puncture to test the hypothesis that matrix metalloproteinase-8-containing myeloid cells are a critical factor in sepsis following cecal ligation and puncture. Our second model, cecal slurry, used intraperitoneal injections of cecal contents to induce polymicrobial peritonitis without tissue compromise in the recipient. Our third model, intestinal implantation, involved ligating and puncturing a cecum from a donor, and then removing the cecum and placing it into the recipient's peritoneal cavity. Clinically, blood samples drawn from pediatric patients were within 24 hours of meeting criteria for septic shock.

MEASUREMENTS AND MAIN RESULTS: In our adoptive transfer experiments, matrix metalloproteinase-8 null mice receiving wild-type marrow had a survival advantage when compared with wild-type mice receiving matrix metalloproteinase-8 null marrow,
suggesting that matrix metalloproteinase-8-containing myeloid cells are not a critical factor in sepsis following cecal ligation and puncture. In our cecal slurry model, we did not see survival advantage among matrix metalloproteinase-8 null mice. Our third model, intestinal implantation, found that mice receiving matrix metalloproteinase-8 null intestine had a survival advantage when compared with mice receiving wild-type intestine, regardless of recipient genotype. Clinically, median matrix metalloproteinase-8 serum concentrations were higher in patients with sepsis and primary intestinal pathology than in septic patients without primary intestinal pathology.

CONCLUSIONS: Intestine-derived matrix metalloproteinase-8 is a critical component of septic peritonitis secondary to intestinal compromise.


Lung stretch is critical for normal lung development and for compensatory lung growth after pneumonectomy (PNX), but the mechanisms by which strain induces matrix remodeling are unclear. Our prior work demonstrated an association of chymotrypsin-like elastase 1 (Cela1) with lung elastin remodeling, and that strain triggered a near-instantaneous elastin-remodeling response. We sought to determine whether stretch regulates Cela1 expression and Cela1 binding to lung elastin. In C57BL/6J mice, Cela1 protein increased 176-fold during lung morphogenesis. Cela1 was covalently bound to serpin peptidase inhibitor, clade A, member 1, resulting in a higher molecular mass in lung homogenate compared to pancreas homogenate. Post-PNX, Cela1 mRNA increased 6-fold, protein 3-fold, and Cela1-positive cells 2-fold. Cela1 expressed predominantly in alveolar type II cells in the embryonic lung and predominantly in CD90-positive lung fibroblasts postnataally. During compensatory lung growth, researchers induced Cela1 expression in nonproliferative mesenchymal cells. In ex vivo mouse lung sections, stretch increased Cela1 binding to lung tissue by 46%. Competitive inhibition with soluble elastin completely abrogated this increase. Areas of stretch-induced elastase activity and Cela1 binding colocalized. The stretch-dependent expression and binding kinetics of Cela1 indicate an important role in stretch-dependent remodeling of the peripheral lung during development and regeneration.


OBJECTIVE: This review provides an overview of what we know about violent injury requiring critical care, including child physical abuse, homicide, youth violence, intimate partner violence, self-directed injury, firearm-related injury, and elder physical abuse.

DATA SOURCES: We searched PubMed, Scopus, Ovid Evidence-Based Medicine Reviews, and the National Guideline Clearinghouse. We also included surveillance data from the Centers for Disease Control and Prevention and National Trauma Data Bank.

STUDY SELECTION: Search criteria limited articles to English and reports of humans utilizing the following search terms: intentional violence, intentional harm, violence, crime victims, domestic violence, child abuse, elder abuse, geriatric abuse, nonaccidental injury, nonaccidental trauma, and intentional injury in combination with trauma centers, critical care, or emergency medicine. Additionally, we included relevant articles discovered during review of the articles identified through this search.

DATA EXTRACTION: Researchers reviewed two hundred one abstracts for relevance, selected 168 abstracts, and divided into eight categories (child physical abuse, homicide, youth violence, intimate partner violence, self-directed injury, firearm-related injury, and elder physical abuse) for complete review by pairs of authors. In our final review, we included 155 articles (139 articles selected from our search strategy, 16 additional highly relevant articles, many published after we conducted our formal search).

DATA SYNTHESIS: A minority of articles (7%) provided information specific to violent injury requiring critical care. Given what we know about violent injury in general, the burden of critical violent injury is likely substantial, yet we know little about violent injury requiring critical care.

CONCLUSIONS: Significant gaps in knowledge exist and need addressed by meaningful, sustained tracking and study of the epidemiology, clinical care, outcomes, and costs of critical violent injury. Research must aim for not only information but also action, including effective interventions to prevent and mitigate the consequences of critical violent injury.

Mesenchymal stem cells (MSCs) have shown to elicit cardio-protective effects in sepsis. However, the underlying mechanism remains obscure. While recent studies have indicated that miR-223 is highly enriched in MSC-derived exosomes, whether exosomal miR-223 contributes to MSC-mediated cardio-protection in sepsis is unknown. In this study, researchers utilized loss-of-function approach, and induced sepsis cecal ligation and puncture (CLP). We observed that injection of miR-223-KO MSCs at 1 h post-CLP did not confer protection against CLP-triggered cardiac dysfunction, apoptosis and inflammatory response. However, WT-MSCs were able to provide protection associated with exosome release. Next, treatment of CLP mice with exosomes released from miR-223-KO MSCs significantly exaggerated sepsis-induced injury. Conversely, WT-MSC-derived-exosomes displayed protective effects. Mechanistically, we identified that miR-223-KO exosomes contained higher levels of Sema3A and Stat3, two known targets of miR-223 (5p &3p), than WT-exosomes. Accordingly, these exosomal proteins transferred to cardiomyocytes, leading to increased inflammation and cell death. By contrast, WT-exosomes encased higher levels of miR-223, delivered to cardiomyocytes, resulting in down-regulation of Sema3A and Stat3. These data for the first time indicate that exosomal miR-223 plays an essential role for MSC-induced cardio-protection in sepsis.


OBJECTIVES: Prognostic and predictive enrichment strategies are fundamental tools of precision medicine. Identifying children with septic shock who may benefit from corticosteroids remains a challenge. We combined prognostic and predictive strategies to identify a pediatric septic shock subgroup responsive to corticosteroids.

DESIGN: We conducted a secondary analysis of 288 previously published pediatric subjects with septic shock. For prognostic enrichment, we assigned each study subject a baseline mortality probability using the pediatric sepsis biomarker risk model. For predictive enrichment, we allocated each study subject to one of two septic shock endotypes, based on a 100-gene signature reflecting adaptive immunity and glucocorticoid receptor signaling. The primary study endpoint was a complicated course, defined as the persistence of two or more organ failures at day 7 of septic shock or 28-day mortality. We used logistic regression to test for an association between corticosteroids and complicated course within endotype.

MEASUREMENTS AND MAIN RESULTS: Among endotype B subjects at intermediate to high pediatric sepsis biomarker risk model-based risk of mortality, corticosteroids were independently associated with more than a 10-fold reduction in the risk of a complicated course (relative risk, 0.09; 95% CI, 0.01-0.54; p = 0.007).

CONCLUSIONS: A combination of prognostic and predictive strategies based on serum protein and messenger RNA biomarkers can identify a subgroup of children with septic shock who may be more likely to benefit from corticosteroids. Prospective validation of these strategies and the existence of this subgroup is warranted.

Division Publications


---

### Grants, Contracts, and Industry Agreements

#### Annual Grant Award Dollars

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Title</th>
<th>Sponsor</th>
<th>ID</th>
<th>Dates</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranjit Chima, MD</td>
<td>Life After Pediatric Sepsis Evaluation</td>
<td>National Institutes of Health (Children's Hosp &amp; Reg Med Ctr-Seattle)</td>
<td>R01 HD073362</td>
<td>4/1/2015 - 6/30/2016</td>
<td>$39,000</td>
</tr>
<tr>
<td>Ranjit Chima, MD</td>
<td>Heart and Lung Failure? Pediatric Insulin Titration Trial</td>
<td>National Institutes of Health (Children's Hospital Boston)</td>
<td>U01 HL107681</td>
<td>7/1/2011 - 6/30/2016</td>
<td>$48,000</td>
</tr>
<tr>
<td>Ranjit Chima, MD</td>
<td>Approaches and Decisions for Acute Pediatric TBI (ADAPT)</td>
<td>National Institutes of Health (University of Pittsburgh)</td>
<td>U01 NS081041</td>
<td>7/1/2013 - 6/30/2018</td>
<td>$27,750</td>
</tr>
<tr>
<td>Lesley Doughty, MD</td>
<td>Early Rehabilitation Protocol in the Pediatric ICU for Children with Acute Brain Injury</td>
<td>Patient-Centered Outcome Research Inst. (Children's Hospital of Pittsburgh)</td>
<td>CER-1310-08343</td>
<td>9/1/2015 - 8/31/2017</td>
<td>$77,000</td>
</tr>
<tr>
<td>Investigator</td>
<td>Project Title</td>
<td>Funding Agency</td>
<td>Grant Number</td>
<td>Start Date</td>
<td>End Date</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>--------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Sue Poynter, MD</td>
<td>Multi-Center Trial of Limiting PGY 2&amp;3 Resident Work Hours In ICU</td>
<td>National Institutes of Health</td>
<td>U01</td>
<td>9/15/2012</td>
<td>1/31/2018</td>
</tr>
<tr>
<td>Erika L Stalets, MD</td>
<td>Age of Blood in Children in Pediatric Intensive Care Units</td>
<td>National Institutes of Health</td>
<td>U01</td>
<td>7/15/2013</td>
<td>5/31/2016</td>
</tr>
<tr>
<td>Brian Varisco, MD</td>
<td>Cela1 Mediates Stretch-regulated Elastin Remodeling During Alveolar Septation</td>
<td>National Institutes of Health</td>
<td>K08</td>
<td>1/7/2016</td>
<td>12/31/2019</td>
</tr>
<tr>
<td>Hector R Wong, MD</td>
<td>Stratification of Pediatric Septic Shock</td>
<td>National Institutes of Health</td>
<td>R01</td>
<td>8/7/2012</td>
<td>6/30/2017</td>
</tr>
<tr>
<td>Basilia Zingarelli, MD-PHd</td>
<td>PPARgamma and PPARgamma Agonists in Septic Shock</td>
<td>National Institutes of Health</td>
<td>R01</td>
<td>9/14/2012</td>
<td>6/30/2017</td>
</tr>
<tr>
<td>Basilia Zingarelli, MD-PHd</td>
<td>Role of Eicosanoids in Shock</td>
<td>National Institutes of Health</td>
<td>R01</td>
<td>7/1/2012</td>
<td>3/31/2016</td>
</tr>
<tr>
<td>Basilia Zingarelli, MD-PHd</td>
<td>Duplex miR-223 and Exosomes in Sepsis</td>
<td>National Institutes of Health</td>
<td>R01</td>
<td>1/1/2015</td>
<td>12/31/2018</td>
</tr>
<tr>
<td>Basilia Zingarelli, MD-PHd</td>
<td>Age-dependent Mechanisms of Metabolic Recovery in Hemorrhagic Shock</td>
<td>National Institutes of Health</td>
<td>R01</td>
<td>9/1/2015</td>
<td>8/31/2019</td>
</tr>
</tbody>
</table>

**Total Annual Grant Award Dollars**: $2,669,743

**Annual Industry Award Dollars**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Industry Sponsor</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajit K Basu, MD</td>
<td>La Jolla Pharmaceuticals</td>
<td>$85,000</td>
</tr>
</tbody>
</table>

**Total Annual Industry Award Dollars**: $85,000