BIOGRAPHICAL SKETCH

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NAME: Rosengart, Matthew R., MD MPH

eRA COMMONS USER NAME (credential, e.g., agency login): ROSENGARTMR

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
The Johns Hopkins University, Baltimore, MD	B.A.	05/1991	Biology
University of Alabama at Birmingham, Birmingham, AL	M.D.	06/1995	Medicine
University of Alabama at Birmingham, Birmingham, AL	Residency	06/1998	General Surgery
University of Washington, Seattle, WA	Fellowship	06/2000	Molecular Biology
University of Washington, Seattle, WA	Residency	06/2002	General Surgery
University of Washington, Seattle, WA	MPH	06/2003	Epidemiology
University of Washington, Seattle, WA	Fellowship	06/2004	Trauma/Critical Care

A. Personal Statement

My lab has a long-standing record of examining the role of immunity in the systemic response to injury and infection, with particular expertise in phagocyte biology, calcium homeostasis and signaling, mitochondrial dynamics and function, and circadian biology, using clinically relevant models of sepsis and trauma. My collective training in the clinical, biological, and epidemiological sciences has provided me particular expertise in the conduct of translational studies, particularly those of a T1 nature. By combining diverse strategies of molecular and cellular biology, clinical analytics and bioinformatics, network analysis and mathematical modeling we have contributed substantially to understanding the biology of the inflammatory states of sepsis, ischemia and shock. Our novel use of implantable biotelemetry generates a murine 'ICU' that enables the monitoring of physiology in real-time. Furthermore, it has enabled the creation of a physiology-based platform of testing interventions that more closely resembles the conduct of human clinical trial design. Although my expertise is in innate immune activation signals, I also have published experience in the response of parenchymal cells, such as the kidney and liver, to septic and ischemic insults. The strong translational perspective of our investigations, which capitalize upon analyses of human cohort data and clinical correlates of our animal-based studies, has enabled us to provide mechanistic insight into the clinically relevant outcomes of organ dysfunction and survival. I am particularly interested in novel mechanisms, strategies and therapeutics to improve the morbidity and mortality outcomes of sepsis and shock, and the publications listed below directly relate to the overarching goal and focus of investigation of our laboratory.

A1 Yuan D, Collage RD, Huang H, Zhang X, Kautza BC, Lewis AJ, Zuckerbraun BS, Tsung A, Angus DC, **Rosengart MR**. Blue light reduces organ injury from ischemia and reperfusion. *Proc Natl Acad Sci U S A*. 2016 May 10;113(19):5239-44. PMID: 27114521. PMCID: 4868436.

A2 Lewis AJ, Zhang X, Griepentrog JE, Yuan D, Collage RD, Waltz PIk Angus DC, Zuckerbraun BS, **Rosengart MR**. Blue light enhances bacterial clearance and reduces organ injury during sepsis. *Crit Care Med*. 2018 Aug;46(8):e779-787. PMID: 29727369.

A3 Zhang X, Yuan D, Sun Q, Su L, Lee E, Lewis AJ, Zuckerbraun BS, **Rosengart MR**. Calcium/calmodulin-dependent protein kinase regulates the PINK1/Parkin and DJ-1 pathways of mitophagy during sepsis. *FASEB J*. 2017 Oct;31(10):4382-4395. PMID: 28615325.

A4 Lewis A, Griepentrong JE, Zhang X, Angus DC, Seymour CW, **Rosengart MR**. Prompt administration of antibiotics and fluids in the treatment of sepsis: a murine trial. *Crit Care Med* 2018 Jan 23. PMID: 29369056.

B. Positions and Honors

Positions and Employment

2004-11 Assistant Professor, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
2005-11 Assistant Professor, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA
2008-11 Assistant Professor, Clinical and Translational Science Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA
2011-17 Associate Professor with tenure, Departments of Surgery and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA
2013-17 Associate Professor with tenure, Clinical Translational Science Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA
2012 Co-Director, Trauma/Acute Care Surgery ICU, University of Pittsburgh, Pittsburgh, PA
2013 Program Director, Fellowship in Surgical Critical Care, Departments of Surgery and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA
2013 Director, Pittsburgh Surgical Outcomes Research Center (PittSORCe), University of Pittsburgh
2017 Professor with tenure, Departments of Surgery and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA
2017 Professor with tenure, Clinical Translational Science Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA
2018 Vice Chair of Academic Training, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
2019 Watson Family Endowed Professor in Surgery, Department of Surgery, University of Pittsburgh, Pittsburgh, PA

Other Experience and Professional Memberships

2004 Shock Society; Program Committee (2013-present)
2005 Association for Academic Surgery; Program Committee (2010-11)
2006 American College of Surgeons, Fellow
2007 Eastern Association for the Surgery of Trauma (EAST); Program Committee (2010-12)
2007 Surgical Infection Society; Chair, ACS (2010-13); Chair, Therapeutics and Guidelines Committee(2013-present); Program Committee (2007-10).
2010 Society of University Surgeons
2010 University of Pittsburgh; General Surgery Residency Committee
2012-15 University of Pittsburgh; Tenured Faculty and Promotions Appointment Committee
2013 American Association of Immunologists
2004 Ad hoc reviewer: *Journal of Immunology, Journal of Leukocyte Biology, PLoS One, Critical Care Medicine, Journal of Critical Care, Journal of Trauma and Acute Care Surgery (Editorial Board), Molecular Medicine, Surgical Infections, Journal of the American College of Surgeons, JAMA Surgery, Journal of Cellular and Molecular Medicine, Surgery, Journal of the Canadian Medical Association, Journal of Cellular and Molecular Medicine, American Journal of Nephrology, American Journal of Respiratory Critical Care Medicine, Annals of Surgery, Journal of the American Medical Association (JAMA), Scientific Reports Nature.*
2012 Canadian Institutes of Health Research (CIHR); Haematology, Digestive Diseases & Kidney (HDK) Peer Review Committee; Standing Member
2017 American Society of Clinical Investigators (ASCI)

Honors

1991 Graduated *cum laude*, The Johns Hopkins University
1994 Alpha Omega Alpha Society, University of Alabama at Birmingham, School of Medicine
1998-2000 NIH/NRSA Research Fellowship Award, National Institutes of Health
1999 Young Investigators Award in Shock Research, Shock Society
2004 Resident Research Award, First Place, Clinical Investigation, American College of Surgeons Committee on Trauma National Meeting

2005 Samuel & Emma Winters Foundation Award, University of Pittsburgh
2009 AAST/Novo Nordisk Research Scholarship Award in Hemostasis and Resuscitation
2011 Surgical Infection Society/Foundation Award for Resident Research
2012 Surgical Infection Society/Foundation Award for Resident Research
2014 Surgical Infection Society/Foundation Award for Resident Research
2014 Beckwith Award, University of Pittsburgh
2015 Bahnson Teaching Award (runner-up), University of Pittsburgh
2016 Bahnson Teaching Award, University of Pittsburgh
2017 Bahnson Teaching Award, University of Pittsburgh
2018 Bahnson Teaching Award (runner-up), University of Pittsburgh
2019 Distinguished Alumnus, Clinical and Translational Science Institute, University of Pittsburgh
2019 Richard L. Simmons Mentorship Award, University of Pittsburgh

C. Contributions to Science

1. Role of calcium/calmodulin-dependent protein kinases (CaMK) signaling in sepsis. Our lab has spent the last decade characterizing the regulatory role of Ca^{2+} signaling through a family of multifunctional CaMK in the adaptive and phenotypic responses of immune and non-immune cells responding to the stress of sepsis. This work highlights a cooperative relationship between CaMKI and CaMKIV in such functions as HMGB1 secretion and the induction of autophagy in the liver, kidney and immune tissues. Operant *in vivo*, they underlie systemic inflammation and the risk of subsequent organ failure (**1a**). A perceived discordance between attenuated inflammation, yet heightened organ injury, prompted our investigation of CaMK-dependent adaptive mechanisms of mitophagy. We showed that mice deficient in CaMKIV had less mitophagy and accumulated injured mitochondria in both immune cells, as well as, the kidney, which correlated with heightened inflammation and worse kidney injury (**1b**). We further delineated that CaMKIV inhibited the ubiquitin-dependent degradation of mTOR, the expression of which was vital for autophagy/mitophagy. As CaMKI deletion is embryologic lethal, we developed a novel technique of *in vivo* RNAi to design an animal deficient in CaMKI expression (**1a, 1c, 1d**). Thus, we were able to characterize a CaMKI-AMPK-dependent, mTOR-independent mechanism of autophagy that mediated neutrophil recruitment and subsequent organ injury during LPS-induced, neutrophilic lung inflammation (**1d**). We further characterized the mechanisms by which CaMKI regulates mitophagy, showing that loss of mitochondrial membrane potential induces a Ca^{2+} signal that recruits CaMKI to the mitochondrion where it regulates DJ-1 and PINK/Parkin-dependent mitophagy (**1d**).

1a. Zhang X, Guo L, Collage RD, Stripay JL, Tsung A, Lee JS, **Rosengart MR**. Calcium/calmodulin-dependent protein kinase (CaMK) Ialpha mediates the macrophage inflammatory response to sepsis. *J Leukoc Biol*. 2011 Mar 3. PMID: 21372190. PMCID: 3133437.

1b. Zhang X, Howell GM, Guo L, Collage RD, Loughran PA, Zuckerbraun BS, **Rosengart MR**. CaMKIV-dependent preservation of mTOR expression is required for autophagy during lipopolysaccharide-induced inflammation and acute kidney injury. *J Immunol*. 2014 Sep 1;193(5):2405-15. PMID: 25070845. PMCID: 4215705.

1c. Guo L, Stripay JL, Zhang X, Collage RD, Hulver M, Carchman EH, Howell GM, Zuckerbraun BS, Lee JS, **Rosengart MR**. CaMKIα regulates AMP kinase-dependent, TORC-1-independent autophagy during lipopolysaccharide-induced acute lung neutrophilic inflammation. *J Immunol.* 2013 Apr 1;190(7):3620-8. PMID: 23447692. PMCID: 3608723.

1d. Zhang X, Yuan D, Sun Q, Su L, Lee E, Lewis AJ, Zuckerbraun BS, **Rosengart MR**. Calcium/calmodulin-dependent protein kinase regulates the PINK1/Parkin and DJ-1 pathways of mitophagy during sepsis. *FASEB J*. 2017 Oct;31(10):4382-4395. PMID: 28615325.

2. Calcium regulation and CaMK signaling during sepsis. The relevance of these mechanisms to human biology and care of the septic patient was determined through a series of translational studies. Nearly 100% of severely septic ICU patients experience hypocalcemia, and the standard of practice is to administer Ca^{2+}. We conducted a registered systemic review with the Cochrane Collaboration and concluded that there are no data to support the routine administration of Ca^{2+} in the management of hypocalcemia of critical illness (**2a**). Applying our observations to a murine model of sepsis, we showed that derangements in Ca^{2+} handling occur frequently and render Ca^{2+} administration harmful. Indeed, giving clinically relevant doses of Ca^{2+} to septic mice heightened systemic inflammation and vascular leak, exacerbated shock, and worsened organ failure and survival (**2b**). This too involved the CaMK cascade. Translating these observations back into the clinical arena, we conducted a risk-adjusted analysis of septic ICU patients, which yielded identical

results: Ca^{2+} administration worsened pulmonary, renal, and hepatic dysfunction and survival (**2b**). These data have contributed to a more comprehensive understanding of the complex biology of sepsis as it relates to the development of organ dysfunction and influenced patient care (**2b**).

2a. Forsythe RM, Wessel CB, Billiar TR, Angus DC, **Rosengart MR**. Parenteral calcium for intensive care unit patients. *Cochrane Database Syst Rev*. 2008 Oct 8;(4):CD006163. PMID: 18843706.

2b. Collage RD, Howell GM, Xhang X, Stripay JL, Lee JS, Angus DC, **Rosengart MR**. Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase kinase signaling. *Crit Care Med*. 2013 Nov;41(11):e352-60. PMID: 23887235. PMCID: 3812408.

3. CaMK and mitochondrial biology in sterile inflammation. We have established a network of fruitful collaboration to extend these investigations into sterile inflammatory states, such as I/R, and into other organs. Early on we showed that in the ischemic liver, CaMKIV regulates TLR4-dependent release of HMGB1, a key mediator of tissue injury (**3a**). However, despite attenuating HMGB1 release, loss of CaMKIV exacerbated organ injury, which we showed, similar to what was observed in sepsis, was due to a loss of CaMKIV-dependent adaptive autophagy (**3b**). We have subsequently explored causal relationships between dynamic changes in mitophagy and mitochondrial biology that manifest as protective alterations in cellular bioenergetics that permit cell survival during sepsis (**3c**). We recently widened our collaborative group and now show the relevance of CaMK biology to the pathogenesis of inflammatory bowel disease (**3d**).

3a. Tsung A, Klune JR, Zhang X, Heyabalan G, Cao Z, Peng X, Stolz DB, Geller DA, **Rosengart MR***, Billiar TR*. HMGB1 release induced by liver ischemia involves Toll-like receptor 4 dependent reactive oxygen species production and calcium-mediated signaling. *J Exp Med*. 2007 Nov 26;204(12):2913-23. PMID: 17984303. PMCID: 21185528. *(co-senior authorship)

3b. Evankovich J, Zhang R, Cardinal JS, Zhang L, Chen J, Huang H, Beer-Stolz D, Billiar TR, **Rosengart MR**, Tsung A. Calcium/calmodulin-dependent protein kinase IV limits organ damage in hepatic ischemia-reperfusion injury through induction of autophagy. *Am J Physiol Gastrointest Liver Physiol*. 2012 Jul 15;303(2):G189-98. PMID: 22575222. PMCID: 3404570.

3c. Carchman EH, Whelan S, Loughran PA, Mollen K, Stratamirovic S, Shiva S, **Rosengart MR**, Zuckerbraun BS. Experimental sepsis-induced mitochondrial biogenesis is dependent on autophagy, TLR4, and TLR9 signaling in liver. *FASEB J.* 2013 Aug 27. PMID: 23982147. PMCID: 3834775.

3d. Cunningham KE, Novak EA, Vincent G, Siow VS, Griffith BD, Ranganathan S, **Rosengart MR**, Piganelli JD, Mollen KP. Calcium/calmodulin-dependent protein kinase IV (CaMKIV) activation contributes to the pathogenesis of experimental colitis via inhibition of intestinal epithelial cell proliferation. *FASEB J.* 2018 Aug 16:fj201800535R. PMID:30113881.

4. Blue light therapy during critical illness. A reproducible observation that the results of our models varied with the circadian time cultivated an interest in light and circadian biology. We showed for the first time that humans, like animals, exhibit photoperiodism, the ability to 'interpret' day length and physiologically adapt to environmental conditions. Similar to what occurs in animals, a shortening of the photoperiod (i.e., the approaching winter) preceding ICU admission was associated with improved survival from critical illness (**4a**). More recently, we directed our attention to light spectrum as a critical determinant of the biological response to ischemic and septic stress (**4b-d**). In several models of sepsis, we showed that blue light functions through an optic pathway to shift autonomic tone towards parasympathetic predominance to enhance immune competence, augment bacterial clearance, and reduce neutrophil inflammation and organ injury; this increases survival (**4d**). Several translational trials are underway (NCT03482245, 02928887).

4a. Castro RA, Angus DC, Hong SY, Lee C, Weissfeld LA, Clermont G, **Rosengart MR**. Light and the outcome of the critically ill: an observational cohort study. *Critical Car*e. 2012 Jul 24;16(4):R132. PMID: 22827924. PMCID: 3580717.

4b. Yuan D, Collage RD, Huang H, Zhang X, Kautza BC, Lewis AJ, Zuckerbraun BS, Tsung A, Angus DC, **Rosengart MR**. Blue light reduces organ injury from ischemia and reperfusion. *Proc Natl Acad Sci U S A*. 2016 May 10;113(19):5239-44. PMID: 27114521. PMCID: 4868436.

4c. Lewis AJ, Zhang X, Griepentrog JE, Yuan D, Collage RD, Waltz PIk Angus DC, Zuckerbraun BS, **Rosengart MR**. Blue light enhances bacterial clearance and reduces organ injury during sepsis. *Crit Care Med*. 2018 Aug;46(8):e779-787. PMID: 29727369.

4d. Griepentrog JE, Zhang X, Lewis AJ, Gianfrate G, Labiner HE, Zou B, Xiong Z, Lee JS, **Rosengart MR**. Rev-Erba links blue light with enhanced bacterial clearance and improved survival in muring Klebsiella pneumoniae pneumonia. *J Leukoc Biol*. 2020 Jan;107(1):11-25. PMID: 31379019.

5. Novel therapeutics. I am particularly interested in advancing the care of the septic patient (**5a**) particularly by addressing the translational impediments that exist at the mouse model-human sepsis interface. We first developed an innovative biotelemetric platform that enables us to measure physiology in real-time and recreate an ICU setting within the lab (**5b**). Using this technology, we defined physiologic 'signatures' derived from high-throughput data and its derivative 'domains' that validly represent discrete biologic states. This enabled us to test time-sensitive therapies at validated human correlates of sepsis thresholds, accurately excluding mice that did not meet 'inclusion' criteria (**5c**). These are fundamental characteristics of clinical trial design. Our collaborative group has continued to test other novel therapeutics to modulate mitochondrial biology and improve the outcome of shock states (**5d**).

5a. Seymour CW, **Rosengart MR**. Septic Shock: Advances in Diagnosis and Treatment. *JAMA*. 2015 Aug 18;314(7):708-17. PMID: 26284722. PMCID: 4646706.

5b. Lewis AJ, Yuan D, Zhang X, Angus DC, **Rosengart MR***, Seymour CW*. Use of biotelemetry to define physiology-based deterioration thresholds in murine cecal ligation and puncture model of sepsis. *Crit Care Med*. 2016 Jun;44(6):e420-31. PMID: 26862708.

5c. Lewis A, Griepentrong JE, Zhang X, Angus DC, Seymour CW, **Rosengart MR**. Prompt administration of antibiotics and fluids in the treatment of sepsis: a murine trial. *Crit Care Med* 2018 Jan 23. PMID: 29369056.

5d. Howell GM, Gomez H, Collage RD, Loughran PA, Zhang X, Escobar DA, Billiar TR, Zuckerbraun BS, **Rosengart MR**. Augmenting autophagy to treat acute kidney injury during endotoxemia in mice. *PLoS One.* 2013 Jul 30;8(7):e69520. PMID: 23936035. PMCID: 3728340.

Complete list of published work:
https://www.ncbi.nlm.nih.gov/sites/myncbi/matthew.rosengart.1/bibliography/40858837/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1UG3DK114861-01 Rosengart (Co-PI) 7/01/2017 – 6/30/2022
NIH/NIDDK
Total Direct: pending
Phenytypic Renal Cases in Sepsis and surgery for Early Acute Kidney Injury (PReCISE AKI).
The major goal of this research program is to characterize the biological phenotype of renal tissue in subjects with sepsis.

1R01-GM-116929 Rosengart (PI) 9/20/2016 – 6/30/2020
NIH/NIGMS
Blue light protects against ischemia-induced organ injury.
Annual Direct: $192,000
The major goals are to 1) determine the neurophysiologic and cellular mechanisms through which blue light attenuates organ injury in murine models of hepatic and renal ischemia/reperfusion (I/R); and 2) to conduct a pilot clinical trial to determine that blue light reduces organ injury in patients undergoing liver resection and cardiopulmonary bypass surgery, operation characterized by a period of tissue I/R.

NIH/NLM DP2 LM12339-01 Mohan (PI) 10/01/2015 – 9/30/2020
Developing a novel intervention to make physician heuristics a source of power.
The major goal of this research program is to evaluate the effect of improved physician heuristic on outcomes for time-sensitive conditions.
Role: Co-Investigator

Completed Research Support

NIH/NIGMS 2R01-GM-082852 Rosengart (PI) 8/03/2009 – 7/31/2020
CAMK: Central Regulators of the response to surgical sepsis.
The major goals of this project are to 1) define the mechanisms by which the calcium/calmodulin-dependent protein kinases regulate mitophagy and cellular bioenergetics in the macrophage and the parenchymal cells of peripheral organs during sepsis; 2) correlate these mechanisms with loss of cell-specific phenotype (i.e., organ dysfunction); and 3) determine whether these mechanisms are operant in human subjects with sepsis.