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## BIOGRAPHICAL SKETCH

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NAME: **Neal, Matthew David**

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

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POSITION TITLE: Roberta G. Simmons Associate Professor of Surgery, Associate Professor of Clinical and Translational Science and Critical Care Medicine, Director, Pittsburgh Trauma Research Center

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### EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Georgetown University, Washington, DC	B.S.	05/02	Biology
University of Pittsburgh School of Medicine, Pittsburgh, PA	MD	05/06	Medicine
University of Pittsburgh Medical Center, Pittsburgh, PA		06/06-06/14	General Surgery Residency
University of Pittsburgh School of Medicine, Pittsburgh, PA	Postdoctoral	07/09-06/12	Inflammation and Innate Immunity
University of Pittsburgh Medical Center, Pittsburgh, PA		07/14-06/15	Surgical Critical Care Fellowship

### A. Personal Statement

I am a surgeon-scientist with a clinical practice consisting of trauma, emergency general surgery, and surgical critical care as well as a translational research focus on hemostasis and thrombosis as well as surgical outcomes. My laboratory focuses on understanding the mechanisms of hemostasis and coagulation following trauma and hemorrhagic shock with a specific interest in the impact of inflammation and innate immune activation on platelet function. Over 25% of severely injured patients will present with impaired coagulation; a merciless problem called trauma-induced coagulopathy, which increases morbidity and mortality. Our lab has recently discovered a link between sterile inflammation and impaired coagulation, and our focused translational efforts seek to define mechanism that guides novel resuscitation and care strategies at the bedside. My lab is funded by the NIH, DoD, and private industry, and in addition, I am the principal investigator or co-investigator on a number of ongoing clinical trials in trauma and surgical care. I serve as the Director of the Pittsburgh Trauma Research Center, which is a coordinating center to leverage collaboration and resource in trauma care. I also serve as one of the three directors of the Coordinating Center and the co-chair of the in-patient clinical trial committee for the NIH and Operation Warp Speed funded Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 (ACTIV-4) pandemic response. Key recent contributions include:

a. Vogel S, Bodenstern R, Chen Q, Feil S, Feil R, Rheinlaender J, Schäffer TE, Bohn E, Frick JS, Borst O, Münzer P, Walker B, Markel J, Csanyi G, Pagano PJ, Loughran P, Jessup ME, Watkins SC, Bullock GC, Sperry JL, Zuckerbraun BS, Billiar TR, Lotze MT, Gawaz M, **Neal MD**. Platelet derived HMGB1 is a critical mediator of thrombosis. *Journal of Clinical Investigation*. 2015 Dec 1;125(12):4638-54. PMC4665785.

b. Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, Adams PW, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Witham WR, Putnam AT, Duane LM, Alarcon LH, Callaway CW, Zuckerbraun BS, **Neal MD**, Rosengart MR, Forsythe RM, Billiar TR, Yealy DM, Peitzman AB, Zenati MS, for the PAMPer study group. Prehospital Air Medical Plasma Following Trauma and Hemorrhagic Shock: Results of the PAMPer Cluster Randomized Trial. *New England Journal of Medicine*. 2018 Jul 26;379(4):315-326

## **B. Positions and Honors**

### **Positions and Employment**

2006-2009 Resident, General Surgery, UPMC, Pittsburgh, PA  
2009-2012 Postdoctoral Research Fellow, Laboratory of David J. Hackam MD, PhD, Pittsburgh, PA  
2012-2013 Senior Resident, General Surgery, UPMC, Pittsburgh, PA  
2013-2014 Administrative Chief Resident, General Surgery, UPMC, Pittsburgh, PA  
2014-2015 Fellow, Surgical Critical Care, UPMC, Pittsburgh, PA  
2015-present Assistant Professor of Surgery and Critical Care Medicine, Department of Surgery, University of Pittsburgh School of Medicine  
2015-present Member, Vascular Medicine Institute, University of Pittsburgh  
2018-present Assistant Professor of Clinical and Translational Science, Clinical and Translational Science Institute (CTSI), University of Pittsburgh  
2018-present Roberta G. Simmons Endowed Assistant Professor of Surgery, University of Pittsburgh  
2019-present Director, Pittsburgh Trauma Research Center and Director, UPMC Trauma Quality Improvement  
2020-present Roberta G. Simmons Associate Professor of Surgery (with tenure)

### **Other Experience and Professional Memberships**

2006- Alpha Omega Alpha  
2015- Shock Society  
2015- Association for Academic Surgery  
2016- International Society of Thrombosis and Hemostasis  
2017- Fellow, American College of Surgeons  
2018- Society of University Surgeons

### **Honors**

1. Jacobson Promising Investigator Award, American College of Surgeons (2017)
2. Young Physician Scientist Early Career Investigator Award, American Society for Clinical Investigation (2017)
3. Philip Troen, MD Excellence in Medical Student Research Mentoring Award, University of Pittsburgh School of Medicine, Pittsburgh, PA (2015 and 2016)
4. Fellow of the Year Award, University of Pittsburgh Medical Center, Department of Critical Care Medicine, Pittsburgh, PA (2015)
5. American Heart Association Fellow's Research Day First Prize, Pittsburgh, PA (2015)
6. Dorothy Maxwell Research Award, UPMC Department of Surgery (2014)
7. Simmons Research Symposium Award for Most Outstanding Presentation, Richard L. Simmons Annual Research Day, Department of Surgery, UPMC (2012, 2010)
8. American College of Surgeons Committee on Trauma, Runner-up, National COT Research Competition, Washington DC (2011)
9. Raymond H. Alexander Award, Most Outstanding Presentation, Eastern Association of the Surgery for Trauma (EAST) (2011)
10. Susman Award, Most Significant Manuscript in Surgical Infection, 30<sup>th</sup> Annual Surgical Infection Society Meeting, Las Vegas, Nevada (2010)
11. Wyeth Scholarship of the American College of Surgeons for the Study of Inflammation (2009-2011)
12. Alpha Omega Alpha (AOA) (2006)
13. Graduated *cum laude*, top 10%, University of Pittsburgh School of Medicine (2006)

## **C. Contributions to Science and Selected Publications (from 113 total):**

1. Investigating the role of innate immune signaling in platelet dysfunction and coagulopathy following trauma and hemorrhagic shock. My laboratory focuses on the merciless problem of the acute coagulopathy of trauma, which I face regularly in my clinical practice. My lab seeks to define the molecular mechanisms that govern this coagulopathy. As a result of my training in innate immunity and inflammation, the lab is now focused on

understanding the role of inflammatory signaling on platelets as a bridge between hemostasis and inflammation. My lab has recently discovered that platelets become excessively activated following sterile injury and contribute to the pathogenesis of acute lung injury and liver injury following hemorrhagic shock. We further have defined the molecular signaling pathways, including HMGB1, TLR4, and critical downstream signaling molecules as well as the release of extracellular vesicles. This work provides the potential for identification of novel therapeutic targets to attenuate platelet dysfunction and regulate coagulopathy following injury. Our lab collaborates extensively with a group of international platelet experts, and well as local authorities in platelet biology and advanced biological imaging techniques.

- a. Dyer MR, Alexander W, Hassoune A, Chen Q, Alvikas J, Liu Y, Haldeman S, Plautz W, Loughran P, Li H, Boone B, Sadovsky Y, Sundd P, Zuckerbraun BS, **Neal MD**. Platelet-derived extracellular vesicles released after trauma promote hemostasis and contribute to DVT in mice. *J Thromb Haemost*. 2019 Oct;17(10):1733-1745
- b. Dyer M, Chen Q, Haldeman S, Loughran P, Tsung A, Hawaz H, Zuckerbraun BS, Simmons RL, **Neal MD**. Deep vein thrombosis in mice is regulated by platelet HMGB1 through release of neutrophil-extracellular traps and DNA. *Sci Reports*. 2018 Feb 1;8(1):2068
- c. Vogel S, Bodenstern R, Chen Q, Feil S, Feil R, Rheinlaender J, Schäffer TE, Bohn E, Frick JS, Borst O, Münzer P, Walker B, Markel J, Csanyi G, Pagano PJ, Loughran P, Jessup ME, Watkins SC, Bullock GC, Sperry JL, Zuckerbraun BS, Billiar TR, Lotze MT, Gawaz M, **Neal MD**. Platelet derived HMGB1 is a critical mediator of thrombosis. *Journal of Clinical Investigation*. 2015 Dec 1;125(12):4638-54. PMC4665785.
- d. Ding N, Chen G, Hoffman R, Loughran PA, Sodhi CP, Hackam DJ, Billiar TR, **Neal MD**. Toll-like receptor 4 Regulates Platelet Activation and Contributes to Coagulation Abnormality and Organ Injury in Hemorrhagic Shock and Resuscitation. *Circulation: Cardiovasc Gen*. 2014 Oct;7(5):615-24. PMC4270899.

## 2. Clinical outcomes in coagulopathy, massive transfusion, trauma resuscitation, and surgical prehabilitation.

As part of a clinical and translational focus to my research interest, I have collaborated with multiple investigators locally and nationally to investigate outcomes in coagulopathy and patients undergoing massive transfusion and trauma resuscitations. I serve as PI for an adaptive platform clinical trial, Strategies to Promote Resiliency (SPRY), focused on surgical prehabilitation. I also serve as a Co-Investigator on the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial, which is a multicenter randomized controlled trial studying the pre-hospital administration of tranexamic acid in trauma patients and is funded by the Department of Defense (DoD). I am also a Co-Investigator for the Linking Investigations in Trauma and Emergency Services (LITES) research network, which is a research consortium of US trauma centers with the capability to conduct prospective, multicenter, injury care and outcomes research of relevance to the DoD. I chair the Coagulopathy Committee for LITES.

- a. Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, Adams PW, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Witham WR, Putnam AT, Duane LM, Alarcon LH, Callaway CW, Zuckerbraun BS, **Neal MD**, Rosengart MR, Forsythe RM, Billiar TR, Yealy DM, Peitzman AB, Zenati MS, for the PAMPer study group. Prehospital Air Medical Plasma Following Trauma and Hemorrhagic Shock: Results of the PAMPer Cluster Randomized Trial. *New England Journal of Medicine*. 2018 Jul 26;379(4):315-326
- b. Reitz KM, Marroquin OC, Zenati MS, Kennedy J, Korytkowski M, Tzeng E, Koscum S, Newhouse D, Garcia RM, Vates J, Billiar TR, Zuckerbraun BS, Simmons RL, Shapiro S, Seymour CW, Angus DC, Rosengart MR, **Neal MD**. Association between preoperative metformin exposure and postoperative outcomes in adults with type 2 diabetes. *JAMA Surg*. 2020 Jun 1;155(6)e200416 Epub 2020 Jun 17. PMID: 32267474
- c. Alvikas J, Myers SP, Wessel CB, Okonkwo DO, Joseph B, Pelaez C, Doberstein C, Guillotte AR, Rosengart MR, **Neal MD**. A systematic review and meta-analysis of traumatic intracranial hemorrhage in patients taking prehospital antiplatelet therapy: Is there a role for platelet transfusions? *J Trauma Acute Care Surg*. 2020 Jun;88(6):847-854. PMID: 32118818
- d. Etchill EW, Myers SP, McDaniel LM, Rosengart MR, Raval JS, Triulzi DJ, Peitzman AB, Sperry JL, **Neal MD**. Should All Massively Transfused Patients Be Treated Equally? An Analysis of Massive

Transfusion Ratios in the Nontrauma Setting. *Crit Care Med.* 2017 Aug;45(8): 1311-1316. PMID: 28537938

3. Understanding the mechanisms of immunothrombosis and endothelial injury after trauma and diseases of sterile inflammation. Through a series of collaborative studies where I have served as co-Investigator or co-PI, we have extended our observations about platelet innate immune signaling, endothelial injury, and immunothrombosis into a cross-disciplinary approach with recent publications in sickle cell disease, pulmonary thrombosis, and hepatic ischemia/reperfusion.

- a. Brzoska T, Vats R, Bennewitz MF, Tutuncuoglu E, Watkins SC, Ragni MV, **Neal MD**, Gladwin MT, Sundd P. Intravascular hemolysis triggers ADP-mediated generation of platelet-rich thrombi in pre-capillary pulmonary arterioles. *JCI Insight.* 2020 Jun 16:139437. Online ahead of print.
- b. Dyer MR, Plautz WE, Ragni MV, Alexander W, Haldeman S, Sperry JL, Guyette FX, Zuckerbraun BS, Rollins-Raval MA, Raval JS, **Neal MD**; A TACTIC Publication. Traumatic injury results in prolonged circulation of ultralarge von Willebrand factor and a reduction in ADAMTS13 activity. *Transfusion.* 2020 Jun;60(6):1308-1318
- c. Vats R, Brzoska T, Bennewitz MF, Jimenez MA, Pradhan-Sundd T, Tutuncuoglu E, Jonassaint J, Gutierrez E, Watkins SC, Shiva S, Scott M, Morelli AE, **Neal MD**, Kato GJ, Gladwin MT, Sundd P. Platelet extracellular vesicles drive inflammasome-IL1 $\beta$ -dependent lung injury in Sickle Cell Disease. *American Journal of Respiratory and Critical Care Medicine.* 2020 Jan 1;201(1):33-46.
- d. Zhang H, Goswami J, Varley P, van der Windt DJ, Ren J, Loughran P, Yazdani H, **Neal MD**, Simmons RL, Zhang J, Tsung A, Huang H. Hepatic Surgical Stress Promotes Systemic Immunothrombosis That Results in Distant Organ Injury. *Front Immunol.* 2020 May 22;11:987.

4. Design and implementation of synthetic platelet and platelet-based drug delivery platforms. Our lab works closely with bioengineering collaborators on the design and implementation of synthetic platelet substitutes for resuscitation. This is a critical question in trauma resuscitation, as platelet transfusion has been shown to be life-saving, but storage requirements make platelets largely unavailable in many military and civilian settings.

- a. Dyer MR, Hickman D, Luc N, Haldeman S, Loughran P, Pawlwoski C, Gupta AS, **Neal MD**. Intravenous administration of synthetic platelets (SynthoPlate) in a mouse liver injury model of uncontrolled hemorrhage improves hemostasis. *J Trauma Acute Care Surg.* 2018 Jun;84(6):917-923.
- b. Hickman DA, Pawlowski CL, Shevitz A, Luc NF, Kim A, Girish A, Marks J, Ganjoo S, Huang S, Niedoba E, Sekhon UDS, Sun M, Dyer M, **Neal MD**, Kashyap V, Sen Gupta A. Intravenous synthetic platelet (SynthoPlate) nanoconstructs reduce bleeding and improve 'golden hour' survival in a porcine model of traumatic arterial hemorrhage. *Sci Reports.* 2018 Feb 15;8(1):3118
- c. Shukla M, Sekhon U, Betapudi V, Li W, Hickman DA, Pawlowski CL, Dyer MR, **Neal MD**, McCrae KR, SenGupta A. In vitro characterization and in vivo evaluation of SynthoPlate (synthetic platelet) technology in severely thrombocytopenic mice. *J Thromb Haem.* 2017 Feb;15(2):375-387.

Complete list of published works in MyBibliography: <http://www.ncbi.nlm.nih.gov/sites/myncbi/1-GV-cQyNuCQE/bibliography/42360347/public/?sort=date&direction=ascending>

#### D. Ongoing Research Support

**Grant information:** 1R35GM119526-01 NIH

**Title:** Mechanistic Elucidation and Targeted Therapy of Platelet Dysfunction After Trauma

**Role in project:** Principal Investigator (51% effort)

**Project Goals/Aims:** Elucidate the mechanisms of platelet dysfunction following trauma and identified targeted therapies to attenuate organ injury and coagulopathy related to microvascular thrombosis

**Years inclusive:** 2016-2021

**Grant information:** R01HL141080-01A1 NIH

**Title:** Mechanisms of platelet exosome-mediated acute chest syndrome in sickle cell disease

**Role in project:** co-Principal Investigator (5% effort)

**Project Goals/Aims:** Acute chest syndrome (ACS) is the leading cause of mortality in Sickle Cell Disease (SCD). We hypothesize that ACS involves NLRP3-inflammasome mediated release of IL-1 $\beta$ -containing platelet exosomes in SCD, which promote platelet-neutrophil aggregation leading to arrest of blood flow in lung.  
**Years inclusive:** 2019-2023

**Grant information:** DM160354 Department of Defense JPC-6 Combat Casualty Care Research Program  
**Title:** SynthoPlate Nanotechnology For Intravenous Hemostasis and Wound Healing in Prolonged Field Care  
**Role in project:** Co-Principal Investigator (with Anirban Sen Gupta) (5% effort)  
**Project Goals/Aims:** Develop and refine a novel synthetic platelet substitute (SynthoPlate) for resuscitation of hemorrhage and promotion of wound healing.  
**Years inclusive:** 2017-2020

**Grant information:** Department of Defense CDMRP JPC-6 Combat Casualty Care Research Program  
**Title:** Field-Deployable Dried Platelet Surrogate Nanotechnology for Hemorrhage Control in RDCR  
**Role in project:** Co-Principal Investigator (with Anirban Sen Gupta) (5% effort)  
**Project Goals/Aims:** To analyze the in vitro and in vivo bioactivity of lyophilized SynthoPlates and assess safety, time of delivery, hemostatic outcomes and survival in models of intraperitoneal hemorrhage  
**Years inclusive:** 2020-2023

**Grant Information:** UPMC Immune Transplant and Therapy Center  
**Title:** Strategies to Promote Resiliency (SPRY-1)  
**Role in project:** Principal Investigator (15% effort)  
**Project Goals/Aims:** The major goals of this project are to study the effects of metformin on pre-habilitation of non-diabetic elderly and frail patients prior to major surgery.  
**Years inclusive:** 2018-2020

**Grant information:** W81XWH-16-D-0024  
**Title:** Linking Investigations in Trauma and Emergency Services (LITES)  
**Role in project:** Co-Investigator (5% effort)  
**Project Goals/Aims:** Creation of research consortium of US trauma centers with the capability to conduct prospective, multicenter, injury care and outcomes research of relevance to the Department of Defense.  
**Years inclusive:** 2017- (Indefinite Delivery, Indefinite Quantity Contract)

**Grant information:** Accriva Diagnostics Investigator Initiated Study (Industry sponsored)  
**Title:** Testing for Platelet Inhibition in Traumatic Brain Injury (TPI-TBI)  
**Role in project:** Principal-Investigator (5% effort)  
**Project Goals/Aims:** Assess whether point of care platelet function testing correlates with whole blood aggregometry in patients with traumatic brain injuries taking anti-platelet agents  
**Years inclusive:** 2016-2020

**Grant information:** UM1HL120877-01 (Mann, Esmon, Wisniewski (PIs))  
**Title:** Analysis and Characterization of Trauma-Induced Coagulopathy  
**Role in project:** Site Principal Investigator (2% effort)  
**Project Goals/Aims:** To elucidate the mechanisms that drive coagulopathy following sterile injury. The site co-I role is to investigate the response of platelets to sterile inflammatory ligands as a sub-project of the aims.  
**Years inclusive:** 2013-2020

**Grant information:** R34 HL135224-01A1  
**Title:** Pragmatic, Prehospital Group O Whole Blood Early Resuscitation Pilot Trial (pPOWER)  
**Role in project:** Co-Investigator (2% effort)  
**Project Goals/Aims:** Determine the feasibility, most appropriate study population and outcomes of a study protocol that will lead to a large multicenter clinical trial designed to evaluate the effectiveness of prehospital thru in-hospital LTLR-WB as compared to standard care practice in patients at risk of hemorrhagic shock.