BIOGRAPHICAL SKETCH

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NAME: Jamie E. Meegan, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): JMEEGAN1

POSITION TITLE: Assistant 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
Trine University, Angola, IN	B.S.	05/2013	Chemistry (Honors)
University of South Florida, Tampa, FL	Ph.D.	12/2018	Medical Sciences, Cardiovascular Biology
Vanderbilt University Medical Center, Nashville, TN	Postdoctoral	08/2024	Microvascular dysfunction in sepsis and acute lung injury

A. Personal Statement

My long-term research interest is to identify novel signaling mechanisms regulating microvascular endothelial hyperpermeability during sepsis that have potential to be targeted therapeutically for the resolution of sepsis-induced organ dysfunction. My training thus far has provided a great foundation for building technical expertise and scientific knowledge in this area. After receiving my Bachelor of Science in Chemistry from Trine University, I joined the lab of Dr. Sarah Yuan at the University of South Florida to complete my Ph.D. in Medical Sciences. During my Ph.D., I was able to gain a foundational knowledge base in cardiovascular biology, physiology, and pharmacology and developed several techniques to investigate microvascular endothelial regulation. The goal of my project was to identify novel mechanisms of endothelial dysfunction in response to neutrophil extracellular traps (NETs) during sepsis. I discovered that citrullinated histone 3, a modification unique to NETs, potently disrupted the microvascular endothelial barrier. My work in Dr. Yuan's lab resulted in two first author and seven co-author publications in highly respected journals, including *Nature Communications*, *Microcirculation*, and *Cardiovascular Research*.

After completing my PhD studies, I immediately joined Vanderbilt University Medical Center as a Postdoctoral Research Fellow under the mentorship of Drs. Julie Bastarache and Lorraine Ware, prominent researchers and physician-scientists in acute lung injury and critical illness. The goal of my research was to elucidate novel mechanisms of cell-free hemoglobin (Hb)-mediated microvascular endothelial hyperpermeability during sepsis, for which I was awarded a position on the Interdisciplinary Training Program in Lung Research T32 (HL094296, PI: Blackwell). I identified that elevated circulating Hb during sepsis exacerbates vascular permeability in the lung and increases mortality during murine sepsis, but the direct cause of Hb-mediated endothelial barrier dysfunction is not due to cell death. During my postdoctoral fellowship, I published six first author, two senior author, and two co-author articles and received funding from the prestigious and highly competitive Parker B. Francis Fellowship and a NIH NHLBI K99/R00 Pathway to Independence Award to elucidate novel mechanisms of the Hb-oxLDL-LOX-1 axis contributing to microvascular hyperpermeability during sepsis that may reveal novel therapeutic targets for the resolution of sepsis-mediated lung injury.

Currently a tenure-track Assistant Professor in the Department of Physiology & Cell Biology at the University of South Alabama, I am continuing my work on understanding the contributions of the endothelial LOX-1 receptor to microvascular dysfunction and organ injury during sepsis and expanding my research program to achieve my research and career goals of becoming a leader in mechanistic and translational studies of microvascular dysfunction in sepsis.

B. Positions, Scientific Appointments, and Honors

Positions

2024-Present	Assistant Professor, Department of Physiology & Cell Biology, University of South Alabama, Mobile, AL
2018-2024	Postdoctoral Research Fellow, Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN
2013-2018	Graduate Research Assistant, Department of Molecular Pharmacology and Physiology, University of South Florida, Tampa, FL

Honors

2023-2027	NIH NHLBI K99/R00 Pathway to Independence Award (K99HL166865, PI: Meegan)
2024-2025	Program Committee Apprentice, American Thoracic Society, Pulmonary Circulation Assembly
2024	Outstanding Trainee Award, American Physiological Society, Respiration Section
2023	Investigator-Initiated (Type A-V) VICTR Resource Request VR68441, Vanderbilt Institute for Clinical and Translational Research
2023	Research Recognition Award, American Physiological Society, Respiration Section
2022-2025	Parker B. Francis Fellowship, Francis Family Foundation
2022	Microcirculatory Society Emerging Leader Award, Microcirculatory Society Annual Meeting at Experimental Biology, Philadelphia, PA
2021-2022	*AJP-Lung* Editorial Board Fellowship Program
2019-2022	Interdisciplinary Training Program in Lung Research T32 (HL094296, PI: Blackwell), Vanderbilt University Medical Center, Nashville, TN
2020	Pappenheimer Postdoctoral Travel Award, Microcirculatory Society Annual Meeting at Experimental Biology [meeting not held]
2016, 2017, 2018	Association for Medical Science Graduate Students Travel Award, University of South Florida, Tampa, FL
2009-2013	Bateman Kolb Full-Tuition Scholarship, Trine University, Angola, IN

Service

2024	NIH NHLBI R13 Review
2020-Present	Ad Hoc Reviewer, *AJP-Lung, Microcirculation, Physiological Reports, Critical Care*
2024-Present	PhD and Basic and Translational Science Working Group, American Thoracic Society
2023-Present	Steering Committee, Newsletter, American Physiological Society, Respiration Section
2023-Present	Communications Committee, Microcirculatory Society
2022-Present	Trainee Committee, Microcirculatory Society
2022	Course Facilitator, Effective Scientific Communication (CBIO-8310), Vanderbilt University, Nashville, TN
2021	Judge, Vanderbilt Summer Science Academy Research Symposium, Nashville, TN
2019	Judge, Vanderbilt Center for Science Outreach Research Symposium, Nashville, TN
2015	Secretary, Association for Medical Science Graduate Students, Tampa, FL
2014	Student Rep, Association for Medical Science Graduate Students, Tampa, FL
2013	Judge, Ohio State Science Day, The Ohio Academy of Science, Columbus, OH

Professional Membership

2015-Present	American Physiological Society
2016-Present	Microcirculatory Society
2016-Present	American Heart Association
2020-Present	North American Vascular Biology Organization
2022-Present	American Thoracic Society
2013-2018	Association for Medical Science Graduate Students
2011-2015	American Chemical Society

C. Contributions to Science

1. Elucidated novel roles of cell-free hemoglobin (CFH) in mediating microvascular hyperpermeability and inflammation. My postdoctoral research has focused on injurious effects of CFH on endothelial dysfunction and inflammation during inflammatory pathologies like sepsis and pulmonary arterial hypertension (PAH). Our group has discovered that elevated levels of CFH during these disease states, released from red blood cells due to increased fragility, not only has potential as a biomarker, but is also a driver of endothelial dysfunction, increased inflammation, and pulmonary dysfunction. Specifically, I demonstrated that increased circulating CFH during a murine model of polymicrobial sepsis increased lung inflammation, hyperpermeability, and mortality. Furthermore, direct stimulation of CFH on primary human lung microvascular endothelial cells increases barrier dysfunction; the hemoglobin scavenger haptoglobin could prevent the barrier disrupting effects of CFH, but several inhibitors of common cell death pathways had no effect. In a separate collaborative project, we discovered that elevated levels of CFH arose from the pulmonary circulation during PAH and that dysregulated clearance of CFH may contribute to PAH pathology. Additionally, I played an integral role in projects from our laboratory demonstrating the ability of CFH to increase endothelial activation and leukocyte adhesion, as well as the therapeutic potential of ascorbate in reducing CFH-mediated lung hyperpermeability.

Conger AK, Tomasek T, Riedmann KJ, Douglas JS, Berkey LE, Ware LB, Bastarache JA, **Meegan JE**. Hemoglobin increases leukocyte adhesion and initiates lung microvascular endothelial activation via toll-like receptor 4 signaling. *Am J Physiol Cell Physiol.* 2023 Jan 30. doi: 10.1152/ajpcell.00211.2022. Epub ahead of print. PMID: 36717098.

Meegan JE, Kerchberger VE, Fortune NL, McNeil JB, Bastarache JA, Austin ED, Ware LB, Hemnes AR, Brittain EL. Transpulmonary generation of cell-free hemoglobin contributes to vascular dysfunction in pulmonary arterial hypertension via dysregulated clearance mechanisms. *Pulm Circ.* 2023 Jan 16;13(1):e12185. doi: 10.1002/pul2.12185. PMID: 36743426; PMCID: PMC9841468.

Tomasek T, Ware LB, Bastarache JA, **Meegan JE**. Cell-free hemoglobin-mediated human lung microvascular endothelial barrier dysfunction is not mediated by cell death. *Biochem Biophys Res Commun.* 2021 Jun 4;556:199-206. doi: 10.1016/j.bbrc.2021.03.161. Epub 2021 Apr 10. PMID: 33848934; PMCID: PMC8483287.

Meegan JE, Shaver CM, Putz ND, Jesse JJ, Landstreet SR, Lee HNR, Sidorova TN, McNeil JB, Wynn JL, Cheung-Flynn J, Komalavilas P, Brophy CM, Ware LB, Bastarache JA. Cell-free hemoglobin increases inflammation, lung apoptosis, and microvascular permeability in murine polymicrobial sepsis. *PLoS One*. 2020 Feb 3;15(2):e0228727. doi: 10.1371/journal.pone.0228727. PMID: 32012200; PMCID: PMC6996826.

2. Identified novel signaling mechanisms mediating microvascular hyperpermeability during sepsis. In addition to my main projects during my graduate and postdoctoral studies, I have played an integral role in several projects aiming to identify novel signaling mechanisms mediating microvascular endothelial hyperpermeability during sepsis. This work has led to several high impact publications delineating mechanisms such as purinergic signaling, palmitoylation, proteases and glycocalyx shedding, and release of microvesicles in the context of systemic inflammation.

Meegan JE, Komalavilas P, Cheung-Flynn J, Yim TW, Putz ND, Jesse JJ, Smith KD, Sidorova TN, Lee HNR, Tomasek T, Shaver CM, Ware LB, Brophy CM, Bastarache JA. Blocking P2X7 receptor with AZ 10606120 exacerbates vascular hyperpermeability and inflammation in murine polymicrobial sepsis. *Physiol Rep*. 2022 Jun;10(11):e15290. doi: 10.14814/phy2.15290. PMID: 35668576; PMCID: PMC9170948.

Chatterjee V, Yang X, Ma Y, Cha B, **Meegan JE**, Wu M, Yuan SY. Endothelial microvesicles carrying Src-rich cargo impair adherens junction integrity and cytoskeleton homeostasis. *Cardiovasc Res*. 2020 Jul 1;116(8):1525-1538. doi: 10.1093/cvr/cvz238. PMID: 31504252; PMCID: PMC7314637

Yang X, **Meegan JE**, Jannaway M, Coleman DC, Yuan SY. A disintegrin and metalloproteinase 15-mediated glycocalyx shedding contributes to vascular leakage during inflammation. *Cardiovasc Res*. 2018 Nov 1;114(13):1752-1763. doi: 10.1093/cvr/cvy167. PMID: 29939250; PMCID: PMC6198742.

Beard RS Jr*, Yang X*, **Meegan JE**, Overstreet JW, Yang CG, Elliott JA, Reynolds JJ, Cha BJ, Pivetti CD, Mitchell DA, Wu MH, Deschenes RJ, Yuan SY. Palmitoyl acyltransferase DHHC21 mediates endothelial dysfunction in systemic inflammatory response syndrome. *Nat Commun*. 2016 Sep 22;7:12823. doi: 10.1038/ncomms12823. PMID: 27653213; PMCID: PMC5036164.

3. Identified mechanisms by which neutrophil extracellular traps (NETs) increase microvascular hyperpermeability. My Ph.D. thesis project was focused on identifying novel mechanisms involved in microvascular endothelial barrier dysfunction in response to the release of neutrophil extracellular traps (NETs) during sepsis. NETs are a unique killing mechanism released by neutrophils during infections characterized by long strands of DNA with attached histones and proteolytic enzymes. The purpose for release of NETs is to trap and prevent the dissemination of infectious agents, but overstimulation can lead to disruption of the microvascular endothelium. I discovered that citrullinated histone 3, a modification unique to NETs, had a potent effect on microvascular endothelial barrier dysfunction.

Meegan JE, Bastarache JA. NET Gain for Sepsis Research: A New Approach to Assess Neutrophil Function in Patients. *Am J Respir Crit Care Med*. 2019 Oct 1;200(7):798-799. doi: 10.1164/rccm.201905-1074ED. PMID: 31185179; PMCID: PMC6812453.

Ma Y, Yang X, Chatterjee V, **Meegan JE**, Beard RS Jr, Yuan SY. Role of Neutrophil Extracellular Traps and Vesicles in Regulating Vascular Endothelial Permeability. *Front Immunol*. 2019 May 9;10:1037. doi: 10.3389/fimmu.2019.01037. PMID: 31143182; PMCID: PMC6520655.

Meegan JE, Yang X, Beard RS Jr, Jannaway M, Chatterjee V, Taylor-Clark TE, Yuan SY. Citrullinated histone 3 causes endothelial barrier dysfunction. *Biochem Biophys Res Commun*. 2018 Sep 10;503(3):1498-1502. doi: 10.1016/j.bbrc.2018.07.069. Epub 2018 Jul 17. PMID: 30029877; PMCID: PMC6119499.

Meegan JE, Yang X, Coleman DC, Jannaway M, Yuan SY. Neutrophil-mediated vascular barrier injury: Role of neutrophil extracellular traps. *Microcirculation*. 2017 Apr;24(3):10.1111/micc.12352. doi: 10.1111/micc.12352. PMID: 28120468; PMCID: PMC5404986.

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