BIOGRAPHICAL SKETCH

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NAME: Lee, Ji Young

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

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
Pusan National University, Pusan, South Korea	M.D.	02/2004	Medicine
Daedong Hospital, Pusan, South Korea	Internship	02/2007	Medicine
Lincoln Medical and Mental Health Center, Bronx, NY	Residency	06/2010	Internal Medicine
Elmezzi Graduate School of Molecular Medicine, Manhasset, NY	Ph.D.	07/2016	Molecular Medicine
University of South Alabama, Mobile, AL	Fellowship	06/2016	Pulmonary/Critical Care Medicine
University of South Alabama, Mobile, AL	Postdoctoral	03/2018	Lung Biology

A. Personal Statement

The goal of my research is to investigate the pathophysiology of sepsis. My interest in sepsis research started during the ICU rotations as a resident in internal medicine. Encountering complex and oftentimes relentlessly progressing vascular failure in sepsis strongly motivated me to seek a path that I can participate in the process of better understanding the disease. I was formally introduced to clinical research during residency training and was trained in working with endothelial cells and sepsis animal models during Ph.D. training. I then moved into a pulmonary and critical care fellowship that highly values matching clinical and research interests. During research rotations and following additional full-time research fellowship training in lung biology, I studied fundamental mechanisms of pulmonary endothelial cell heterogeneity and developed comprehensive cardiopulmonary ultrasound exam protocol. Using techniques and results from this work, my current research as an independent investigator is focused on elucidating acid handling mechanisms of pulmonary endothelial cells.

a. **Lee JY**, Linge HM, Ochani K, Lin K, Miller EJ. N-ethylmaleimide sensitive factor (NSF) inhibition prevents vascular instability following gram-positive pulmonary challenge. *PLoS One* 2016 Jun 29;11(6):e0157837. PMID: 27355324
b. **Lee JY,** McMurtry S, Stevens T. Single cell cloning generates lung endothelial colonies with conserved growth, angiogenic and bioenergetic characteristics. *Pulm Circ* 2017 Oct-Dec;7(4):777-792. PMID: 28841087
c. **Lee JY**, Alexeyev M, Kozhukhar N, Pastukh V, White R, Stevens T. Carbonic anhydrase IX is a critical determinant of pulmonary microvascular endothelial cell pH regulation and angiogenesis during acidosis. *Am J Physiol Lung Cell Mol Physiol*. 2018 Jul 1;315(1):L41-L51. PMID: 29631360

B. Positions and Honors

Positions and Employment

2006-2007 Intern, Daedong Hospital, Pusan, South Korea
2007-2010 Resident, Lincoln Medical and Mental Health Center, Bronx, NY
2010-2013 Scholar, Elmezzi Graduate School of Molecular Medicine, Manhasset, NY

2013-2016 Clinical Fellow, Pulmonary and Critical Care Medicine, University of South Alabama, Mobile, AL
2016-2018 Research Fellow, Physiology and Cell Biology, University of South Alabama, Mobile, AL
2018- Assistant Professor, Physiology/Cell Biology and Pulmonary/Critical Care Medicine, University of South Alabama, Mobile, AL

Other Experiences and Professional Memberships

2015- Member, American Thoracic Society
2017- Early Career Reviewer, American Journal of Respiratory and Critical Care Medicine
2019 Ad-hoc Reviewer, Pulmonary Circulation
2020 Ad-hoc Reviewer, PLOS ONE

Academic and Professional Honors

2009 Winner of Research Category, Annual Hippocrates Awards Resident Research Competition
2015 Jureta Horton Presidential Travel Award, Annual Conference on Shock
2015 Oral presentation, Annual Conference on Shock
2015 Oral presentation, Annual College of Medicine Research Forum
2017 Abstract Scholarship, American Thoracic Society International Conference
2017 Oral presentation, American Thoracic Society International Conference

Certifications

2004 Korean Medical License
2010 American Board of Internal Medicine
2015 American Board of Pulmonary Medicine
2016 American Board of Critical Care Medicine
2016 Certification in Critical Care Ultrasound by American College of Chest Physicians

C. Contributions to Science

1. My graduate research in Dr. Edmund Miller's lab focused on understanding the pathophysiology of vascular dysfunction in sepsis. Angiopoietin-2 (Ang-2) is a sepsis biomarker that correlates with disease severity and mortality. Using a mouse pneumonia sepsis model, we demonstrated that the inhibition of N-Ethylmaleimide Sensitive Factor, a trafficking molecule mediating endothelial cell exocytosis, attenuates pulmonary release of Ang-2 and improves oxygen saturation and hemodynamic status. Taking it further, I investigated the in vitro mechanisms of Ang-2 secretion in pulmonary microvascular endothelial cells (PMVECs). We found that Ang-2 secretion is mediated by two distinctive mechanisms: constitutive and regulated pathways. Constitutive secretion of Ang-2 is mediated by cAMP-PKA and nitric oxide-cGMP-PKG pathways, and lipoteichoic acid/ peptidoglycan mediated regulated Ang-2 secretion is mediated by N-ethyl-maleimide-sensitive factor and Ca^{2+} signaling. The findings offer insights into a potential therapeutic approach of targeting global endothelial exocytosis to stabilize vascular tone during sepsis.

a. **Lee JY**, Miller EJ. Angiopoietin-2: a key to understanding sepsis and its pulmonary sequelae? *J Pulm Respir Med* 2014 4:172. Doi:10.4172/2161-105X.1000172
b. **Lee JY**, Linge HM, Ochani K, Lin K, Miller EJ. N-ethylmaleimide sensitive factor (NSF) inhibition prevents vascular instability following gram-positive pulmonary challenge. *PLoS One* 2016 Jun 29;11(6):e0157837. PMID: 27355324
c. **Lee JY**, Linge HM, Ochani K, Lin K, Miller EJ. Regulation of angiopoietin-2 secretion from human pulmonary microvascular endothelial cells. *Exp Lung Res* 2016 Sep;42(7):335-345. Epub 2016 Sep 1. PMID: 27585839

2. As a pulmonary fellow in Dr. Stevens' lab, I was fascinated by the mechanisms of pulmonary endothelial cell heterogeneity. His laboratory previously identified intrinsic phenotypic differences of pulmonary endothelial cells, depending on their origin. Those phenotypic differences include lectin binding, growth rate, proliferative and angiogenic potentials, epigenetic factor expression and bioenergetics pathway utilization patterns. I contributed to this project by carrying on and expanding it to study cells from different individual and strains of rats, and by studying cells that are grown out of single cell sorted environments. In addition, I identified a phenotypic difference in acid handling among pulmonary endothelial cells, which served as the basis of this

application and my independent research career. During these studies, I adapted and modified techniques, such as the Seahorse extracellular flux analysis, carbonic anhydrase (CA) functional assay and CRISPR-Cas9 gene editing. Results support a novel finding that pulmonary endothelial cells develop intrinsic hierarchy of phenotypic characteristics in population growth, even when the environmental factors have been identical. Further investigating molecular and genetic characteristics of these cells will potentially explain how heterogeneous populations of cells and vascular segments are selectively involved in vascular complications of sepsis, such as in ARDS.

a. **Lee JY**, McMurtry S, Stevens T. Single cell cloning generates lung endothelial colonies with conserved growth, angiogenic and bioenergetic characteristics. *Pulm Circ* 2017 Oct-Dec;7(4):777-792. PMID: 28841087
b. **Lee JY**, Alexeyev M, Kozhukhar N, Pastukh V, White R, Stevens T. Carbonic anhydrase IX is a critical determinant of pulmonary microvascular endothelial cell pH regulation and angiogenesis during acidosis. *Am J Physiol Lung Cell Mol Physiol*. 2018 Jul 1;315(1):L41-L51. PMID: 29631360

3. My current work as an independent investigator aims to identify fundamental mechanisms of acid handling in pulmonary endothelial cells. PMVECs are major constituents of the alveolar capillary membrane where pH constantly fluctuates due to gas exchange occurring in the setting of, rhythmical but asynchronous, vascular perfusion and alveolar ventilation. Despite this unique environment, little is known regarding how PMVECs maintain their acid base homeostasis. My lab has described two distinctive mechanisms of extracellular acidosis; extrinsic and intrinsic acidosis, depending on the primary source of the proton. Extrinsic acidosis is a passive cellular exposure to protons that other cells have generated through intrinsic acidosis, which is fundamentally linked to metabolism as a primary source of proton. This compartmentalized analysis of acidosis led to the identification of multiple non-pH regulatory roles of CA IX on PMVECs including metabolism, migration and angiogenesis, which are critical parameters to determine repair potential of endothelium in injured lungs. Further studying the complex interplay between cellular movements and acid balance, we discovered previously unknown metabolism and permeability modifying effect of KD025, a rho kinase isoform 2 inhibitor, on PMVECs. Currently my lab is focusing on elucidating secretory mechanisms of CA IX as proposed in this application. From this work, a first and corresponding author manuscript describing metalloproteinase-mediated CA IX ectodomain shedding is in revision with *Am J Respir Cell Mol Biol* (2021). In future studies, I plan to expand the work to understand implications of systemic and tissue-level acidosis in the context of lung infection, potentially develop noninvasive diagnostic modality to probe microenvironmental acidosis using ultrasound and FRET technology, and ultimately discover more efficient but minimally complicating strategies to treat acidosis by identifying domain or cell type specific CA functions.

a. **Lee JY** (corresponding author), Onanyan M, Garrison I, White R, Crook M, Alexeyev M, Kozhukhar N, Pastukh V, Swenson ER, Supuran CT, Stevens T. Extrinsic acidosis suppresses glycolysis and migration while increasing network formation in pulmonary microvascular endothelial cells. *Am J Physiol Lung Cell Mol Physiol* 2019 Aug 1; 317(2):L188-L201. PMID: 31042076
b. **Lee JY** (corresponding author), Stevens RP, Kash M, Zhou C, Koloteva A, Renema P, Paudel SS, Stevens T. KD025 shifts pulmonary endothelial cell bioenergetics and decreases baseline lung permeability. *Am J Respir Cell Mol Biol* 2020 Oct;63(4):519-530. PMID: 32628869
c. **Lee JY**, Fagan KA, Zhou C, Batten L, Cohen MV, Stevens T. Biventricular diastolic dysfunction, thrombocytopenia and red blood cell macrocytosis in experimental pulmonary arterial hypertension. *Pulm Circ* 2020 Apr-Jun;10(2):2045894020908787. PMID: 32518619
d. **Lee JY**, Stevens RP, Migaud M, Stevens T. Salvaging the endothelium in acute respiratory distress syndrome: A druggable intersection between TLR4 and NAD+ signaling. *Eur Respir J* 2021 (*In press*).

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1HSEewzo6jcQA/bibliography/50533598/public/?sort=date&direction=descending

D. Research Support

18CDA34080151 (Lee) 07/01/2018-06/30/2021
American Heart Association Career Development Award
“Carbonic anhydrase IX and pulmonary endothelial cell acidosis during infection”
This grant tests the hypothesis that Pseudomonas aeruginosa infection induces cytotoxic amyloid production that causes loss of CA IX in pulmonary microvascular endothelial cells, increasing acidosis and lung injury.
Role: Principal Investigator

1R01HL148069-01A1 (Stevens) 07/01/2020-06/30/2024
NIH/NHLBI
“Lung Endothelial Aß in infectious proteinopathy”
This project tests the hypothesis that the P. aeruginosa type 3 secretion system effector, exoenzyme Y, promotes the production of cytotoxic Aß dependent upon γ secretase activating protein.
Role: Faculty