BIOGRAPHICAL SKETCH

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NAME: McCubbrey, Alexandra L

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

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
Kalamazoo College, Kalamazoo, MI	B.A.	06/2008	Biology
University of Michigan, Ann Arbor, MI	Ph.D.	05/2014	Immunology
National Jewish Health / University of Colorado - Denver, Denver, CO	Postdoctoral	07/2018	Pulmonary Immunology

A. Personal Statement

My long-term research goals focus on understanding the intersection between apoptosis and tissue repair. Strong evidence supports that apoptotic cells promote tissue repair. However, we still have much to learn about the cells and signals involved. Dogma and the focus of prior research, including my own, has been on how macrophage engulfment of apoptotic cells drives resolution and repair. My early work focused understanding how apoptotic cell engulfment, a phagocytic process termed efferocytosis, is regulated in alveolar macrophages. I have also worked to define macrophage subsets in the lung including their different phagocytic functions and roles during repair and fibrosis. Our recent work has involved studying macrophage metabolism after efferocytosis as a mechanism of macrophage reprogramming. We found that polyamine metabolites accumulate in macrophages after efferocytosis and cause immunomodulation, leading to suppression of IL-1β and IL-6 transcription. We are also very interested in how non-professional phagocytes change following interactions with apoptotic cells and are currently studying how fibroblast-AC interactions impact fibroblast metabolism and collagen production.

Our lab has expertise in the study of cell death, phagocytosis, lung injury, and cell metabolism. Our focus centers around apoptotic cell interactions with phagocytes during lung repair. We have developed strategies to measure cell death, quantify and manipulate phagocytosis, induce and evaluate lung injury, and trace cell metabolite use and fate.

My current funding related to this research focus is shown below.

R00 HL141658
McCubbrey (PI)
08/01/2020 – 07/31/2023
Macrophage metabolism after target cell ingestion regulates anti-inflammatory reprogramming

R01 HL149741-01A1
Henson (PI), Role: Co-Investigator
07/01/2020 – 06/30/2024
Roles for interstitial and airspace macrophages in resolution of inflammation

B. Positions and Honors

Positions and Employment

2020- Assistant Professor, Pulmonary and Critical Care Medicine, National Jewish Health, Denver, CO
2020- Assistant Professor, Pulmonary and Critical Care Medicine, University of Colorado, Aurora, CO
2018-20 Instructor, Pulmonary and Critical Care Medicine, National Jewish Health, Denver, CO
2014-18 Postdoctoral Research Fellow, Pulmonary and Critical Care Medicine, National Jewish Health and University of Colorado – Denver, Denver, CO
2008-14 Graduate Student Research Associate, Pulmonary and Critical Care Medicine, University of Michigan Medical Center, Ann Arbor, MI
2005-07 Undergraduate Summer Research Assistant, Pulmonary and Critical Care Medicine, University of Michigan Medical Center, Ann Arbor, MI

Academic and Professional Honors

2019 Gordon Research Conference: Polyamines Selected Oral Presenter and Travel Award
2019 National Jewish Health MOOR Clinical and Translational Travel Award
2019 American Thoracic Society AJRCMB Award for outstanding paper by a junior investigator
2018 ATS AII Assembly Travel Award
2018 National Jewish Health Viola Vestal Coulter Foundation Fellowship for Exceptional Pulmonary Researcher
2017 National Jewish Health Natalie V. Zucker Award for Promising Junior Female Investigators
2016 ATS AII Assembly Travel Award
2016 National Jewish Health Department of Medicine Poster Award
2015 ATS RSF Assembly Travel Award
2014 University of Michigan Department of Medicine Poster Award
2013 University of Michigan Rackham Pre-doctoral Fellowship
2013 Gordon Research Seminar: Apoptotic Cell Recognition and Clearance Selected Oral Presenter and Travel Award
2011 University of Michigan Immunology Program Monte V. Hobbs Abstract Award
2008 Kalamazoo College Diebold Scholar Award for Senior Thesis in Biology
2008 Kalamazoo College Honors on Senior Thesis in Biology
2008 Kalamazoo College Senior Leadership Recognition Award
2004- 08 National Merit Scholar

C. Contributions to Science

1. Discovery of a unique polyamine response to engulfment of apoptotic cells in macrophages.

Apoptotic cells are engulfed by phagocytes through a phagocytic process termed efferocytosis. An engulfed apoptotic cell presents a rich meal for a phagocyte, yet little has been known about the fate of those metabolites and how they impact cell function. I investigated macrophage metabolite responses to engulfing live, apoptotic, and necrotic cells. I used stable isotope tracing to show that amino acids from engulfed target cells are retained by engulfing macrophages. Only in response to apoptotic cells, macrophages increased intracellular polyamines, spermidine and spermine. I went on to show that these were not apoptotic cell-derived or newly synthesized, but rather imported from the extracellular environment dependent on Rac-1. Both polyamines and apoptotic cells have separately been shown to suppress macrophage cytokine production. We asked whether polyamines were required for efferocytosis-driven immunomodulation. Rac-1 dependent import of polyamines was required to suppress IL-1β and IL-6 in response to LPS. This significantly advanced our understanding of macrophage metabolism in response to apoptotic cells.

1. **McCubbrey AL**, McManus SA, McClendon JD, Thomas SM, Chatwin HB, Reisz JA, D'Alessandro A, Mould KJ, Bratton DL, Henson PM, Janssen WJ. 2022. Polyamine import and accumulation causes immunomodulation in macrophages engulfing apoptotic cells. *Cell Rep*. Jan 11;38(2):110222.

2. Study of the unique functions of lung Mϕ subsets, particularly the pathogenic function of recruited Mϕ during lung injury and fibrosis.

Recent work has identified Mϕ subpopulations in every organ that can be distinguished both by origin and phenotype. We have sought to better describe these subpopulations in the lung and to understand their functional roles during lung injury and repair. In order to study lung Mϕ subpopulations, we developed a novel mouse model to inducibly delete floxed genes in Mϕ that arise from circulating monocytes and are recruited to the lung during inflammation (recMϕ) without affecting embryonic-derived resident alveolar Mϕ. I am first-author on a paper describing this work, which constitutes the first transgenic mouse model identified for discrete targeting of recMϕ and lung interstitial Mϕ without targeting resident alveolar Mϕ. I expanded upon this work in a second first-author paper and detailed the specificity and penetrance of four transgenic lines in lung myeloid cells, including the data that two pulse-wait inducible systems can be used to refine targeting of lung interstitial Mϕ. In a third first-author paper I showed that recMϕ drive an increase in total lung Mϕ numbers during fibrotic lung injury and (using the transgenic system described in my earlier paper) demonstrated that these recMϕ promote the development of fibrosis. This publication was featured with an editorial in AJRCMB and a mention in their "Red Alert" section, which highlights work by junior investigators. I have also contributed to work using bulk and single cell-RNA sequencing to identify and describe lung macrophage subpopulations in mouse and human. This collective body of work significantly increased our understanding of Mϕ in the lung.

1. **McCubbrey AL**, Barthel L, Mould KJ, Mohning MP, Redente EF, Janssen WJ. 2016. Selective and inducible targeting of CD11b+ mononuclear phagocytes in the murine lung with hCD68-rtTA transgenic systems. Am J Physiol Lung Cell Mol Physiol. Jul 1;311(1): L87-L100. PMCID: PMC4967193
2. Mould KJ, Barthel L, Mohning MP, Thomas SM, **McCubbrey AL**, Danhorn T, Leach SM, Fingerlin TE, O'Connor BP, Reisz JA, D'Alessandro A, Bratton DL, Jakubzick CV, Janssen WJ. 2017. Cell origin dictates programming of resident versus recruited macrophages during acute lung injury. Am J Respir Cell Mol Biol. Sep;57(3): 294-306. PMCID: PMC5625228
3. **McCubbrey, AL**, Barthel, L, Mohning, MP, Redente, EF, Mould, KJ, Thomas, SM, Leach, SM, Danhorn, T, Gibbings, SL, Jakubzick, CL, Henson, PM, Janssen, WJ. 2018. Deletion of c-FLIP from CD11b^{hi} macrophages prevents development of bleomycin-induced lung fibrosis. Am J Respir Cell Mol Biol. Jan;58(1): 66-78. PMCID: PMC5941310
   *Highlighted article with Editorial and "Red Alert" in AJRCMB, January, 2018.
4. Mould KJ, Moore CM, McManus SA, **McCubbrey AL**, McClendon JD, Griesmer CL, Henson PM, Janssen WJ. 2021. Airspace Macrophages and Monocytes Exist in Transcriptionally Distinct Subsets in Healthy Adults. Am J Respir Crit Care Med. Apr 15;203(8):946-956. PMCID: PMC8048748

3. Discovery of regulatory pathways controlling efferocytosis and how these are affected by common respiratory pharmaceuticals.

Apoptotic cell clearance, termed efferocytosis, is essential for maintenance of tissue homeostasis and resolution of inflammation. I have focused on studying efferocytosis by resident tissue Mϕ during homeostasis. Results from my research identified a mechanism by which glucocorticoids act to enhance efferocytosis in alveolar Mϕ. I further examined this mechanism in statins and macrolides and studied the synergistic effects of these three compounds on efferocytosis. This work was featured "In This Issue" in the Journal of Immunology, which highlights work identified by the reviewers and editors as the top 10% in a given field. In a subsequent publication, I connected the ability of glucocorticoids to enhance efferocytosis with increased susceptibility to bacterial pneumonia. We speculate that this may relate to the increased rates of pneumonia observed in COPD patients treated with inhaled corticosteroids. During my studies of alveolar Mϕ, I identified miR-34a as a novel negative regulator of efferocytosis that is highly expressed in the lung. Moreover, I identified two mechanisms of miR-34a action, including a connection with the metabolic sensor SIRT1, which piqued my interest in the connection between efferocytosis and cellular metabolism. This collective body of work significantly increased our understanding of efferocytosis in the lung.

1. **McCubbrey AL**, Sonstein J, Ames TM, Freeman CM, Curtis JL. 2012. Glucocorticoids relieve collectin-driven suppression of apoptotic cell uptake in murine alveolar macrophages through downregulation of SIRPalpha. J Immunol. Jul 1; 189(1): 112-9. PMCID: PMC3381851
   *Highlighted article "In This Issue" in the Journal of Immunology, July, 2012.
2. **McCubbrey AL**, Curtis JL. 2013. Efferocytosis and lung disease. Chest. Jun 1:143(6): 1750-7. PMCID:

PMC3673667
3. Stolberg VR*, **McCubbrey AL***, Freeman CM*, Brown JP, Crudgington SW, Taitano SH, Saxton BL, Mancuso P, Curtis JL. 2015. Glucocorticoid-augmented efferocytosis inhibits pulmonary pneumococcal clearance in mice by reducing alveolar macrophage bactericidal function. J Immunol. Jul 1;195(1): 174-84. PMCID: PMC4475455
4. **McCubbrey AL**, Nelson JD, Stolberg VR, Blakely PK, McCloskey L, Janssen WJ, Freeman CM, Curtis JL. 2016. MicroRNA-34a negatively regulates efferocytosis by tissue macrophages in part via SIRT1. J Immunol. Feb 1;196(3): 1366-75. PMCID: PMC4724467

Complete list of published works in my bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/14K3hyoEwgdkB/bibliography/public/