THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER
ANNOUNCES THE FINAL EXAMINATION OF

Vineet I. Patel

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GRADUATE COLLEGE
DEPARTMENT OF MICROBIOLOGY & IMMUNOLOGY
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Macrophage and Dendritic Cell Clades with Unique Functional and Gene Signatures Exist in Human Airways

COMMITTEE IN CHARGE: Jordan Metcalf, M.D., Chair; Darrin Akins, Ph.D.; Jimmy Ballard, Ph.D.; Mark Coggeshall, Ph.D.; William Hildebrand, Ph.D.; Susan Kovats, Ph.D.

ABSTRACT: The respiratory system is a complex network of many cell types, including subsets of macrophages and dendritic cells that work together to maintain steady-state respiration. Due to limitations in acquiring cells from healthy human lungs, these subsets remain poorly characterized transcriptionally and phenotypically. We set out to systematically identify these subsets in human airways by developing a schema of isolating large numbers of cells by whole lung bronchoalveolar lavage. Six subsets of phagocytic antigen presenting cells were consistently observed from airway lavage. These cell subsets were confirmed as airway-resident by comparison to lavage and blood cell types from healthy volunteers. Aside from alveolar macrophages, subsets of Langerin^{+}, BDCA1^{-} CD14^{+}, BDCA1^{+} CD14^{+}, BDCA1^{+} CD14^{-}, and BDCA1^{-} CD14^{-} cells were identified. These subsets varied in their ability to internalize *Escherichia coli*,

Staphylococcus aureus, and *Bacillus anthracis* particles. All subsets were more efficient at internalizing *S. aureus* and *B. anthracis* compared to *E. coli*. Alveolar macrophages and $CD14^+$ cells were overall more efficient at particle internalization compared to the four other populations. Subsets could be further separated into two groups based on their inherent capacities to upregulate surface CD83, CD86, and CCR7 expression levels. Whole genome transcriptional profiling revealed a clade of "true dendritic cells" consisting of $Langerin^+$, $BDCA1^+$ $CD14^+$, and $BDCA1^+$ $CD14^-$ cells. The dendritic cell clade was distinct from a macrophage/monocyte clade, as supported by higher mRNA expression levels of several dendritic cell-associated genes, including *CD1*, *FLT3*, *CX3CR1*, and *CCR6*. Monocyte-derived dendritic cells and macrophages were poor models for their respective clades based on both whole transcriptome and select-transcript comparisons. Each clade, and each member of both clades, were discernable by specific upregulated genes, which can serve as markers for future studies in healthy and diseased states. Overall, studies in this dissertation provide a functional and transcriptomic reference of six steady-state macrophage and dendritic cell subsets found in human airways. This work builds a schema for future investigations into lower respiratory tract infections, chronic lung diseases, and targeted-cell vaccines.