Dr. Donna Farber

Immune responses in the lung are essential for protecting against respiratory pathogens which constitute the most prevalent cause of illness and infant/child mortality worldwide. The majority of T cells in the lung comprise the memory subset, which is generated during a previous antigen exposure, and is functionally enhanced compared to naive T cells which reside in lymphoid tissues. Memory T cells resident in lung tissue can potentially mediate rapid *in situ* immunity for clearing respiratory pathogens; however, there are no strategies to specifically promote lung-resident immune responses. My laboratory has identified a novel population of influenza-specific memory CD4 T cells that are retained and remain resident in lung tissue, and can promote rapid, optimal protection to influenza virus infection compared to circulating memory T cells found in spleen and lymphoid tissue. These "tissue-resident" memory CD4 T cells (designated CD4 T_{RM}) are distinct from circulating effector-memory T cells (T_{EM}), and constitute a new memory subset analogous to tissue-resident memory CD8 T cell subsets (CD8 T_{RM}) identified in skin, intestines and other mucosal sites. We have used innovative *in vivo* antibody labeling and imaging approaches to study lung CD4 T_{RM} *in situ*, as well as RNA next-gen sequencing to compare lung T_{RM} to spleen T_{EM} to identify key pathways involved in lung CD4 T_{RM} generation and retention. We have uncovered a novel role for the integrin CD11d, specifically expressed in mouse and human lung CD4 T_{RM}, in sustaining T cell activation and differentiation, and a role for inflammatory signals via type I IFN in lung T_{RM} maintenance. *Our central hypothesis is that generation and tissue targeting of lung CD4 T_{RM} involves antigenic and inflammatory signals in the lung coupled with T cell intrinsic expression of CD11d, while maintenance of lung T_{RM} relies on low-level inflammation.* In the proposed research, we will use murine targeted deletion models, imaging, and bioinformatics to investigate the roles of inflammation, antigen stimulation, and CD11d expression in the generation and maintenance of lung T_{RM}. Results from these studies will provide crucial insights for targeting lung resident populations to enhance protective immunity, and for understanding maintenance of immune homeostasis in the respiratory tract.