Dr. Donna Farber

Program Summary

Studies of human immune responses to viruses and other pathogens have focused, by necessity, on sampling of peripheral blood; however, innate and adaptive immune responses are initiated, function and maintained in diverse tissue sites. Innate cells, including tissue macrophages and dendritic cells (DC) that encounter pathogens at key entry points (e.g., lungs, intestines) do not appear in circulation. Similarly T cells infiltrate infection sites and can persist as non-circulating tissue-resident memory T cells, which provide protective responses *in situ*. At present, our understanding of tissue-localized innate and adaptive immune responses is based on mouse models, and we lack fundamental knowledge on how innate and adaptive cells are organizedand function in human tissues. The overall goal of this research program in human immunity is to obtain in depth profiles of how human innate and adaptive immune cells in tissues respond to viral infection, with a focus on the globally pervasive herpesvirus, Cytomegalovirus (CMV). CMV establishes lifelong persistence in multiple sites, has broad effects on aging and immunity, and can be reactivated during immunosuppression in transplantation and cancer, causing serious disease and mortality. The proposed research program, consisting of three projects, and five cores, will obtain in-depth profiles of human immune cells involved in controlling CMV in human tissue sites using our unique tissue resource where lymphoid, mucosal and peripheral tissue are obtained from individual organ donors, compared to blood responses from living cohorts with active infection. Project 1 (PL: Farber) will study T cell responses to CMV in tissues and circulation from organ donors and transplant patients; Project 2 (PI: B. Reizis) will study how DC subsets in different sites functionally respond to CMV and CMV-infected cells from both tissues and cohorts of transplant patients; and Project 3 (PI: M. Merad) will profile macrophages in tissues and their responses to innate stimuli through TLR agonists and CMV, and effect of CMV infection on macrophage function. The administrative core will coordinate organization and financial aspects of the program, the Clinical Core will provide all samples including tissues from organ donors and blood samples from transplant cohorts to the three projects. The Transcriptomics (RNAseq) and single cell core (Core A) will provide high throughput RNA sequencing on the population and single cell level, and multidimensional proteome profiling using cytometry by time-of-flight (CyTOF). The Viral assays core (Core B) will measure CMV persistence in different tissue sites to dissect how virus persistence impacts tissues immune responses. The data management and analysis core (DMAC) will store, curate and analyze all data outputs from the projects and cores, apply bioinformatics for analysis of transcriptomic and proteomic data, generate models to integrate the datasets, and submit raw data to public databases such as ImmPort and NCBI. The results from this program will identify signatures for tissue-specific control of human immune responses for promoting *in situ* protective immunity in vaccines and immunotherapies.