Dr. Donna Farber

Overall Program Summary

Immune responses occur in diverse anatomical sites, including protective responses to pathogens and dysregulated immune responses in autoimmune and inflammatory diseases. Human immune responses have largely been defined based on characterization of immune cells in peripheral blood or extrapolated based on results in mouse models. In this research program, we have moved the study of human immunology substantially beyond peripheral blood, through use of a unique human tissue resource where we obtain multiple primary and secondary lymphoid (thymus, bone marrow, spleen, lymph nodes) and mucosal (lungs, intestines) sites from individual organ donors. Through coordinated study of these unique samples on the cellular and molecular level, we have newly defined how lymphocyte subsets are organized and distributed throughout diverse sites, identified new subsets of human tissue resident lymphocytes and revealed new mechanisms and insights for anatomic control of human immune responses. In this renewal application consisting of three projects and three scientific cores, we will build substantially on our novel findings and identify mechanisms for how human lymphocyte subsets in diverse tissue sites are generated, function and maintained. *Our central hypothesis is that lymphocyte compartmentalization in specific tissues or circulation determines their differentiation pathway, functional capacities, and clonal maintenance.* There are three main aims of the overall program that link the projects and cores. In the first aim, we will define mechanisms for the generation, maintenance and functional heterogeneity of human tissue-resident versus circulating lymphocyte populations, with a focus on tissue-resident T and B lymphocytes as identified in the previous funding period. We will dissect molecular control of tissue targeting in organ donor tissues and intestinal transplant biopsies through transcriptome, epigenetic and functional profiling on the population and single-cell level. Second, we will identify networks for lymphocyte migration, maintenance and homeostasis by analysis of clonal organization and diversity in tissues and circulation, by state-of-the art deep sequencing of TCR and BCR from organ donor tissues and tissue biopsies. We will define lymphocyte migratory networks, clonal evolution, and the effect of antigen, tissue, differentiation and age in driving lymphocyte compartmentalization and distribution in the body. Finally, our studies aim to define a new baseline of immunological health in tissues to understand tissue pathology in diseases. A deeper understanding of how resident lymphocytes are generated and maintained in health and how this is perturbed in tissue transplantation can set the stage for further studies to build upon this unique resource and gain new insights into mechanisms of systemic and tissue-based autoimmune, inflammatory and neoplastic diseases.