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Title: Resolving productive and pathogenic T cell responses with single-cell transcriptomics

Abstract: As central orchestrators of immune responses, CD4+ T cells have remarkable functional plasticity. Understanding the full extent of this heterogeneity and the mechanisms by which it is generated, has been challenging especially *in vivo*. Single-cell RNA-sequencing (scRNA-seq) provides a powerful method for unbiased interrogation of cell identities and functional states. We are leveraging this technology to understand CD4+ T cell fate decisions during infection and autoimmunity.

Many infections result in simultaneous differentiation of inteferon-gamma-producing Th1 cells and follicular T helper (Tfh) cells. We have used scRNA-seq and a murine model of *Plasmodium* infection to study such T cell fate bifurcation. By studying activated antigen-specific T cells in five consequtive time points, we were able to construct a computational model of Th1 and Tfh differentiation trajectories, revealing potential regulatory genes associated with each fate.

The studies of immune cell populations in human clinical samples have been compromised by their typically very high degree of heterogeneity. However, the recent introduction of high-through droplet-based scRNA-seq has greatly facilitated such endeavors. We are currently using droplet-based scRNA-seq in combination with single-cell T cell receptor sequencing to better understand the T cell responses activated during Rheumatoid arthritis. Our preliminary results reveal CD4+ T cell populations specific to inflamed synovial tissue and provide clues about their relationships with other T cell subsets.

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