**Abstract**

Strategically positioned as the gatekeepers between the circulation and the immune system, splenic marginal zone (MZ) B cells form a frontline of defense against blood-borne pathogens. They mediate early protective responses against diverse T-dependent and T-independent antigens, by employing strategies that blur the boundary between innate and adaptive immunity. In humans, MZ B cell deficiency is linked to reduced IgM titers and heightened susceptibility to sepsis and mortality related to encapsulated bacterial infections. In addition, impairment in their function and localization is associated with several autoimmune pathologies. Despite their importance, many aspects of the ontogeny and homeostasis of MZ B cells remain obscure.

The establishment and maintenance of MZ B cells in their splenic niche are determined by a complex set of rules that regulate cell division, the influx of new bone marrow (BM) derived cells, death, and onward differentiation. We hypothesize that the rules governing MZ B cell dynamics evolve as we age, and are modulated significantly during immunogenic encounters, resulting in a profound variation in their niche size and clonal composition. Here, we propose a unique integrative approach that synthesizes mathematical and experimental strategies **to quantitatively map the developmental trajectories of MZ B cells and dissect the mechanisms that maintain their numbers and clonal diversity, across the lifespan.**

Specifically, we will develop probabilistic models and linear PDE systems to identify the rules governing the establishment of MZ B cell niche in early life to quantify the dynamic transitions in cells’ ability to persist, as a function of time since their compartmental entry. Further, we will develop mechanistic mathematical models to describe the data derived from a well-established experimental system in which one can track the constitutive replacement within the MZ B cell compartment, over long timescales in healthy mice. This approach will allow us to measure turnover, reveal any heterogeneity within the MZ B cell pool, and define their developmental trajectories. Next, we will develop a dynamical modeling strategy to map B cell differentiation pathways during immune responses, using novel mouse strains expressing an antigen-inducible reporter gene and B cell-specific mutations in Notch2. We will use data from B cell receptor (BCR) transgenic strains to study the influence of BCR affinity on cell-fate decision during immune responses. Lastly, we will employ a computational pipeline to study the single-cell immune repertoire and transcriptomic profiles of activated B cells and to generate phylogenetic trees of antigen-specific clones as they diversify during immune responses.