Elucidating the clonal and microenvironmental determinants of B cell lymphomagenesis

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Abstract**:** The cells of origin and step-wise transformation pathways of many solid tumors and leukemias are known, providing successful classification systems, screening and early intervention strategies. However, the evolutionary trajectories and identities of clonal precursor B cells (CPCs) that give rise to common B cell lymphomas such as follicular lymphoma (FL) and diffuse large B cell lymphoma (DLBCL) are unknown. Hence there is a critical need to systematically identify and characterize lymphoma CPCs and their trajectories to overt lymphomas to solve this unmet need. Without this knowledge, the promise of precision medicine and early detection and intervention in lymphoma will likely remain unrealized. The plasticity and complexity of the immune system requires novel methods, physiologically relevant models, and access to the right human specimens to solve this challenge. Here we bring together national leaders in immunology, lymphomagenesis, advanced spatial genomics technologies and computational modeling to address this challenge. Our central hypothesis is that divergent lymphoma subtypes arise through distinct immunological trajectories by distinct CPCs, which are associated with specific therapeutic vulnerabilities. We contend that this is best determined through comparing and contrasting distinct FL and DLBCL entities. Therefore, we will: 1) define the step-wise evolution of CPCs that lead to high-risk DLBCL and FL and 2) elucidate the interactions between CPCs and the microenvironment that are required for transformation to high-risk DLBCL and FL. This approach is paradigm-shifting for the field, as it will lay the groundwork for early diagnosis and intervention using precision CPC-targeted therapies, potentially eradicating currently incurable lymphomas.