

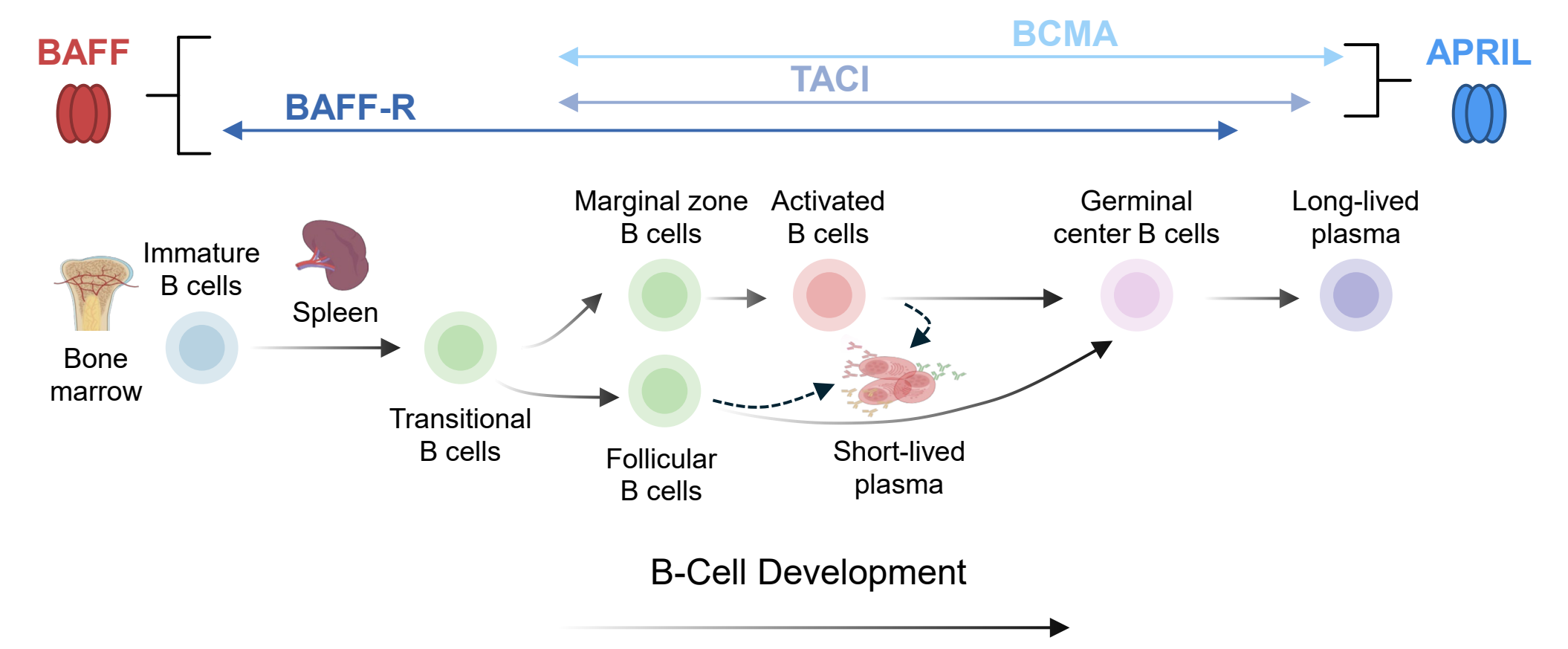
Targeting APRIL and BAFF pathways: Divergent effects on immune populations and protective immunity, with implications for IgAN management

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INTRODUCTION

- APRIL and BAFF are related cytokines (~30% homology) both implicated in humoral immunity and kidney diseases, but with distinct roles, receptor specificities, and activity at different stages of the B-cell lifecycle^{1,2}
- Several dual anti-APRIL/BAFF inhibitors are in clinical development for IgAN; however, prior clinical trials evaluating anti-BAFF or dual anti-APRIL/BAFF inhibitors have resulted in increased frequency of infection and lower vaccine response rates³⁻⁶
- Sibeprenlimab is an investigational selective anti-APRIL monoclonal antibody that has demonstrated a 51.2% reduction in 24-hour uPCR in a Phase 3 interim analysis of patients with IgAN⁷
- By targeting different stages of B-cell development, these investigational therapies may lead to varying effects on B-cell subsets and subsequent immune function and competence⁸
- To further explore the immunologic consequences of selective versus dual inhibition, an anti-APRIL antibody (4540) that has shown efficacy in preclinical IgAN models⁹ was used as a surrogate comparator to explore impacts on the immune system relative to dual APRIL/BAFF inhibition

APRIL and BAFF Regulate B-Cell Maturation and Plasma Cell Survival

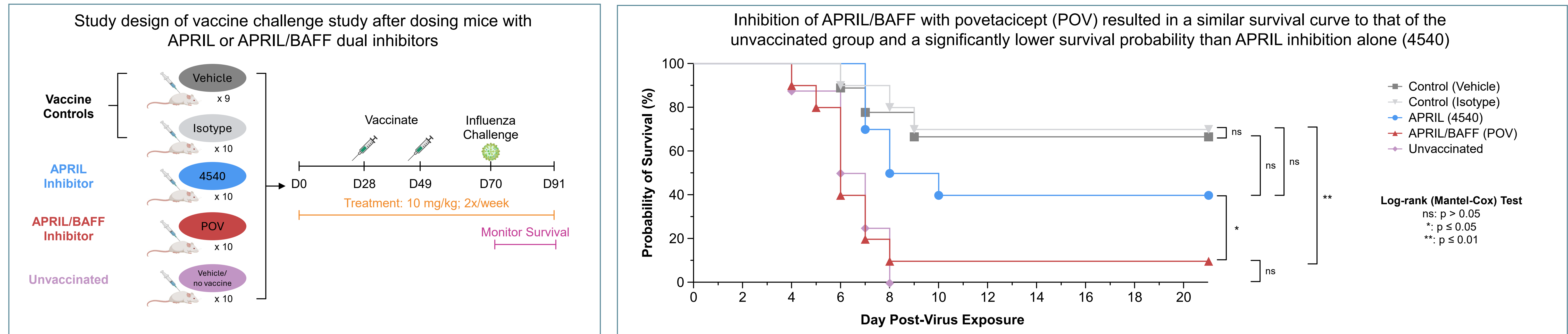


OBJECTIVE AND METHODS

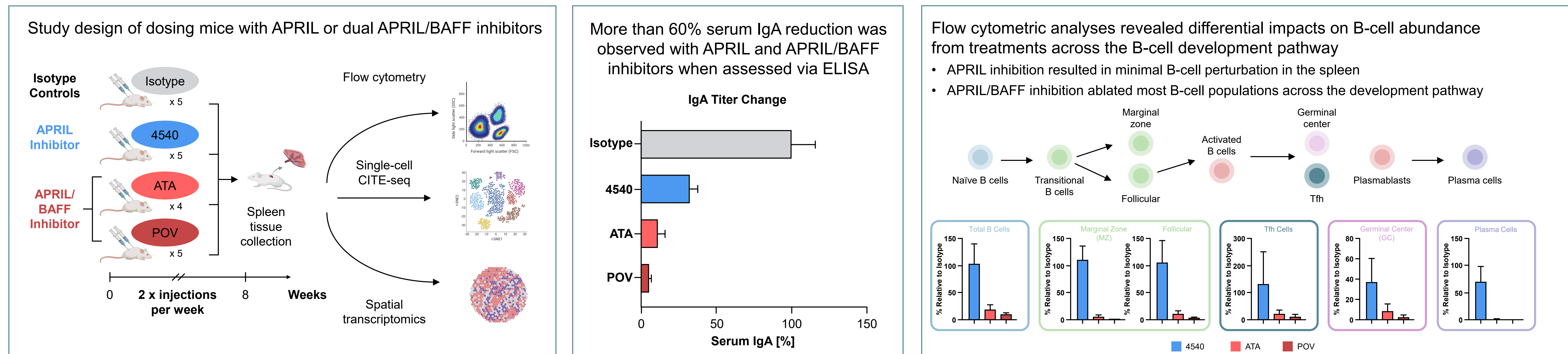
This study evaluated the distinct immunological and functional impacts of selective APRIL versus APRIL/BAFF blockade in mice. We studied the differential effects of these inhibitors on protective immunity using a murine influenza model. Furthermore, we employed a multi-modal approach combining serologic assays, flow cytometry, and single-cell Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITE-seq) to resolve immune system changes at the molecular, protein, and cellular levels.

RESULTS

Differential Effects of APRIL vs APRIL/BAFF Inhibition on Protective Immunity

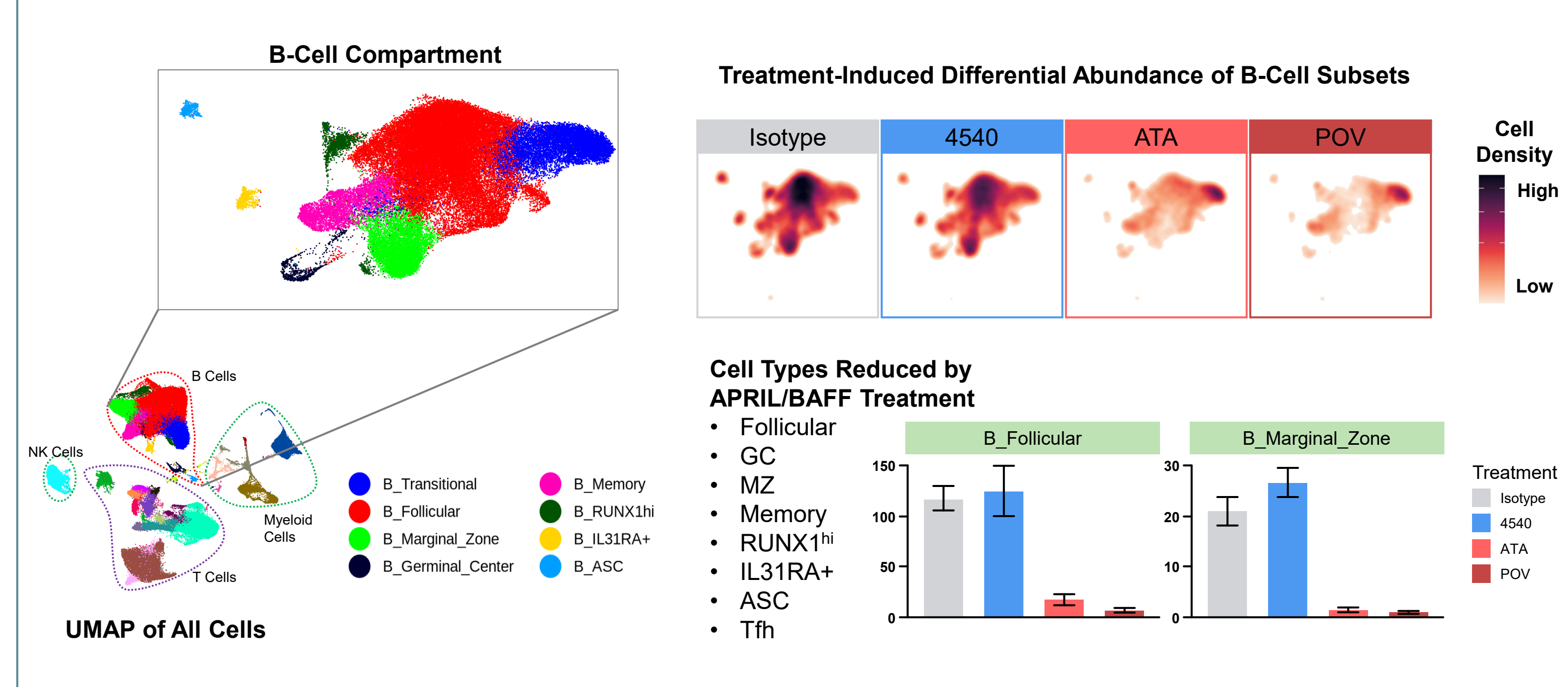


Differential Effects of APRIL vs APRIL/BAFF Inhibition on B-Cell Subsets and Their Development Trajectories



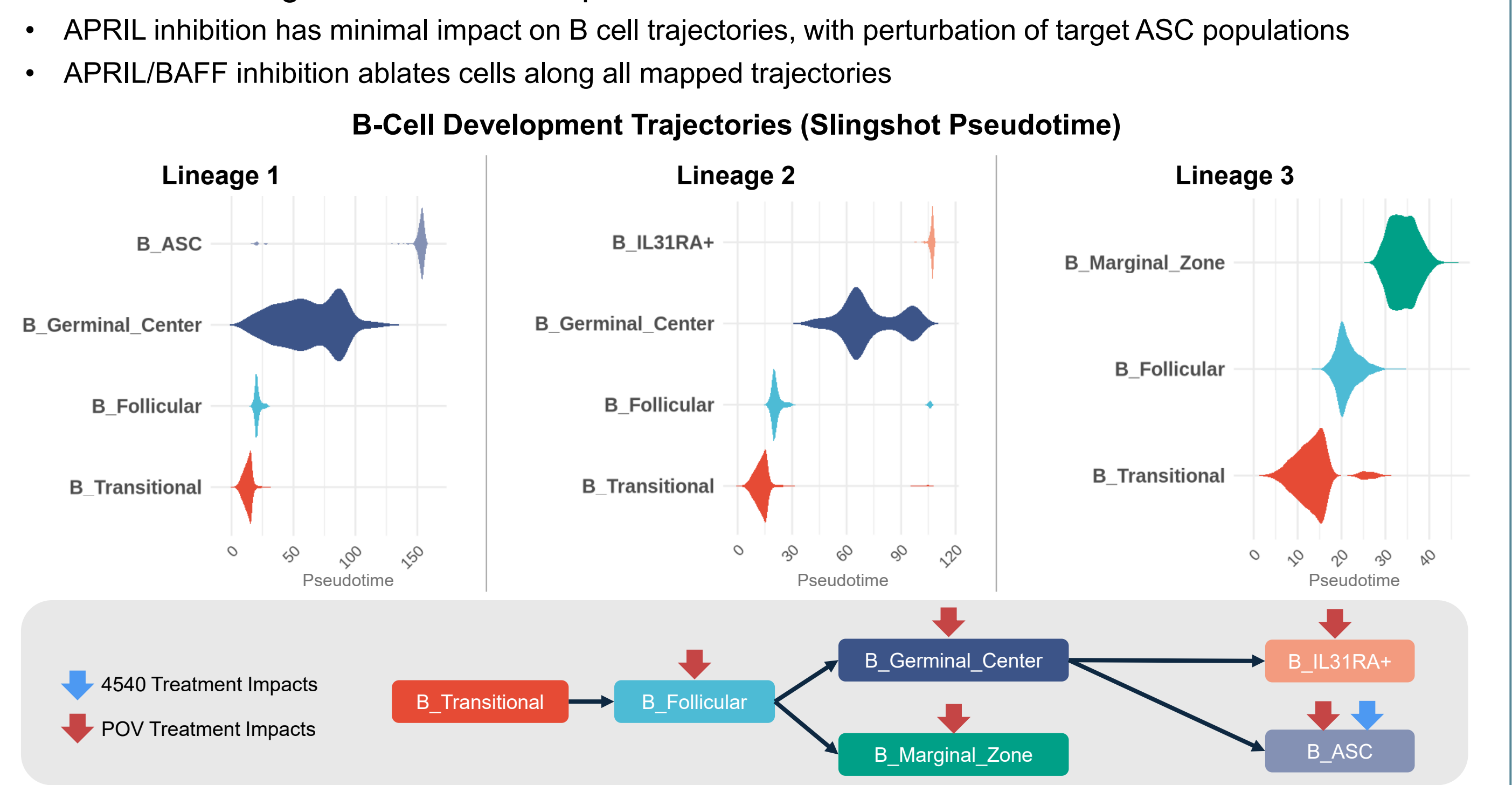
Single-cell CITE-seq (transcriptomics and surface proteins) maps drug impacts on B-cell and T-cell subsets

- APRIL inhibition resulted in minimal B-cell perturbation in spleen
- APRIL/BAFF inhibition ablated most B-cell populations and reduced additional B-cell subsets identified



scRNA-seq of B-cell trajectories reveals that APRIL and APRIL/BAFF treatments differentially affect distinct stages of B-cell development

- APRIL inhibition has minimal impact on B cell trajectories, with perturbation of target ASC populations
- APRIL/BAFF inhibition ablates cells along all mapped trajectories



CONCLUSIONS

- This study demonstrates distinct immunomodulatory profiles, where dual APRIL/BAFF inhibition broadly depletes B-cell subsets and disrupts B-cell development, whereas selective APRIL inhibition has minimal impact on B-cell populations and development
- Additionally, functional differences in immune competence are observed in an influenza challenge model where dual APRIL/BAFF inhibition significantly impairs vaccine-mediated protection, while selective APRIL inhibition better preserves protective immunity
- Both anti-APRIL and dual anti-APRIL/BAFF inhibitors reduce serum IgA levels, a desired effect in treating IgA nephropathy

