

Quantitative systems pharmacology model of B cell immune response

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Introduction

- B cell immunity plays a crucial role in adaptive immune response. Dysregulation of autoreactive B cell selection, excessive activation, and B lymphocyte proliferation can lead to the development of autoimmune diseases [1].
- Despite recent advances in understanding autoimmunity, clinical studies indicate that up to 50% of patients do not exhibit significant improvement with existing therapies [2,3], highlighting the urgent need to identify novel therapeutic targets for autoimmune disease treatment.

Aim

- To develop a quantitative systems pharmacology (QSP) model of B cell immune response in mice to characterize the dynamics of antibody-secreting cell (ASC) and provide a mechanistic framework for understanding heterogeneity in B cell immunity.

Methods

- The overall workflow consisted of a systematic literature review, model development, evaluation and validation, sensitivity analysis, and forward simulations [4] (Figure 1A).
- The developed QSP model consists of 20 ordinary differential equations with 31 parameters, 12 of which were fixed based on physiological values (Figure 1B).

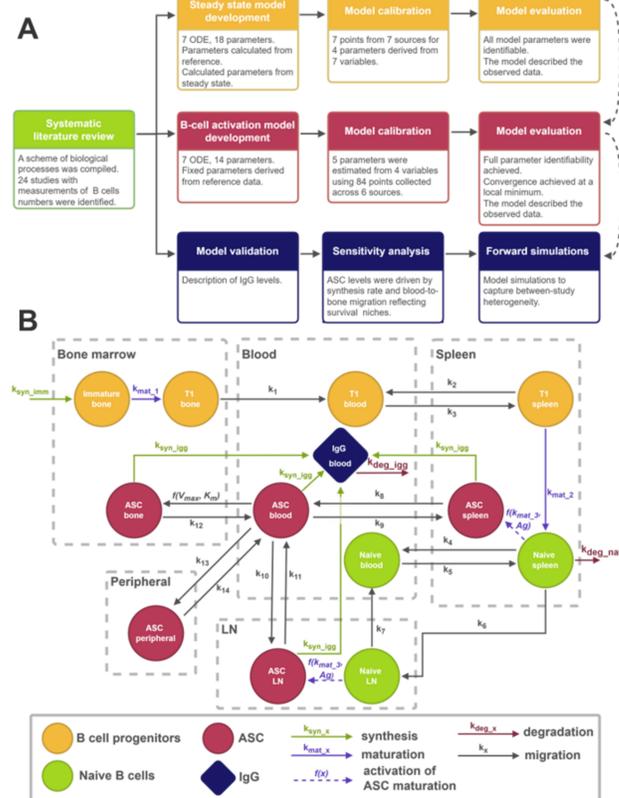


Figure 1: Model development workflow. (A) Workflow diagram. (B) QSP model scheme.

- Model calibration was performed using maximum likelihood approach and Nelder-Mead algorithm.
- The model was validated using the data on IgG response to immunization from 5 experimental studies. Local sensitivity analyses was performed by family of curves and via one-at-a-time.
- Data processing, model development and evaluation were performed in R statistics (version 4.2.2).

Results

The model reflects B cell subpopulations across organs before and after immunization

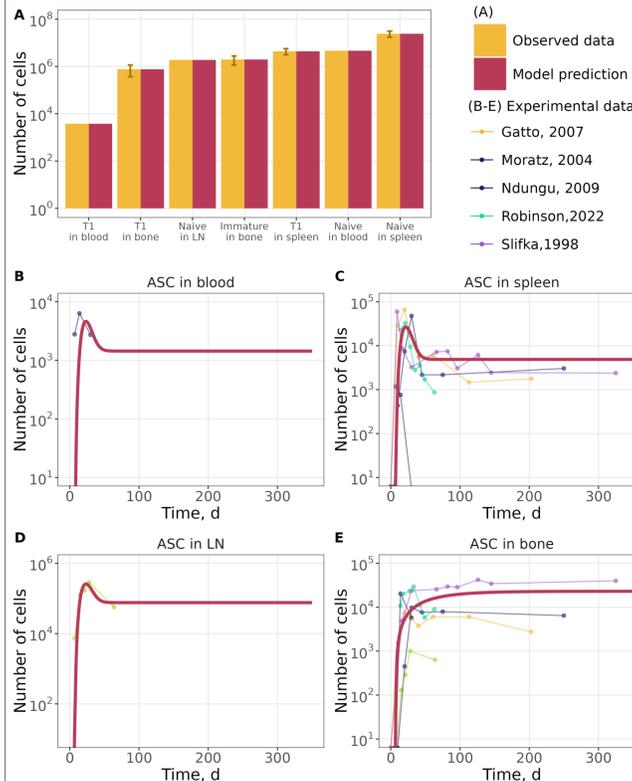


Figure 2: Description of B-cell data. (A-E). Model calibration against data on stationary states of non activated B-cells (A). Red bars - model predictions, yellow bars - experimental data, mean with SD or individual data. Model calibration against data on the dynamics of ASC cells in the blood (B), the lymphatic node (D) and the bone marrow (E). Red lines - model predictions, color lines with points - experimental data.

- The model accurately captures the steady-state concentrations of various B cell subpopulations across different tissues, including the blood, spleen, lymph nodes, and bone marrow (Figure 2A).
- The model successfully reproduces experimental ASC time-course data from multiple sources in blood, spleen, lymph nodes, and bone marrow (Figures 2B-E).
- The model captures both the peak of ASC generation in secondary lymphoid organs and the subsequent redistribution and accumulation of these cells in the bone marrow via circulation.

The model was successfully validated based on IgG concentrations

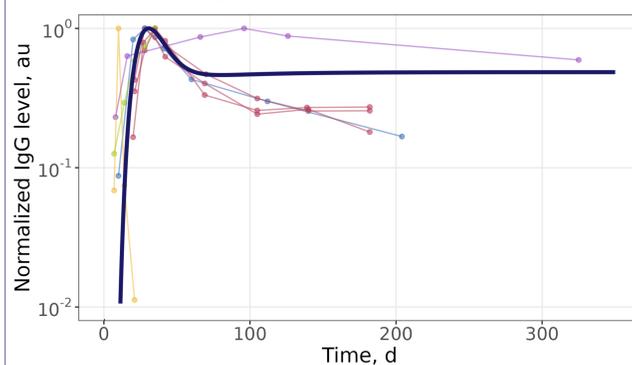


Figure 3: The time-course of IgG levels predicted by the model in comparison with experimental observations. Blue lines - model predictions, color lines with points - experimental data.

- The model captures key features of the IgG response: the peak concentration, the upward trend toward the peak, the subsequent decline, and a brief period of apparent steady-state levels.

Key factors driving the ASC counts by sensitivity analysis

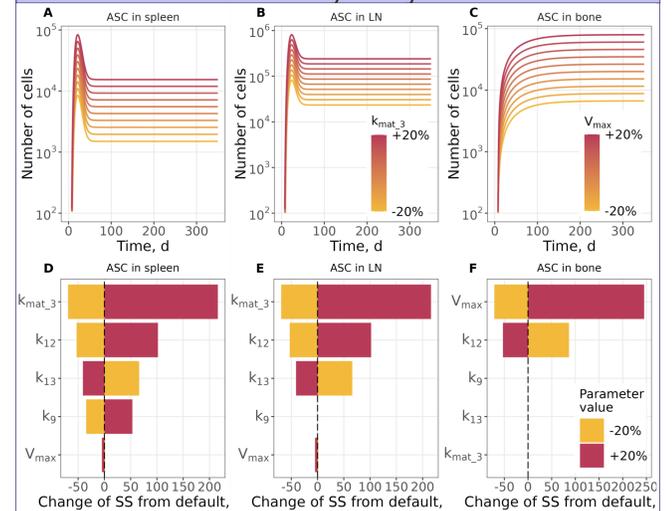


Figure 4: Local sensitivity analysis for ASC dynamics. Local sensitivity analysis for ASC dynamics in spleen (A,D), lymphatic node (B,E) and bone (C,F). (A-C) Family of curves for the k_{mat_3} (A,C) and for the V_{max} (B) parameters. (D-F) OAT for ASC steady-state numbers.

- The peak and steady-state concentrations of ASC in secondary lymphoid organs were sensitive to ASC synthesis rate (k_{mat_3}) (Figures 4A,B,D,E).
- ASC concentration in bone marrow primarily dependent on the transition rate from blood to bone marrow which reflects the availability of survival niches for ASC (V_{max}) (Figures 4C, F).

Simulation for describe the between-study heterogeneity

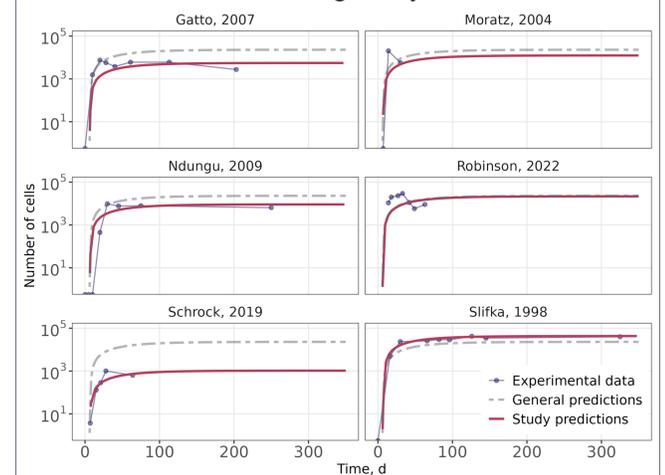


Figure 5: Model simulations to capture heterogeneity

- Between-study heterogeneity of ASC concentration in bone can be described by varying the parameter representing the hypothetical size of the survival niche for ASC from ~2-fold, we were able to capture between-study heterogeneity for the majority of the observed data.

Conclusions

- We have developed and validated a QSP model of B cell immune response following the administration of an exogenous antigen in mice.
- Model evaluation revealed ASC synthesis rate and the availability of survival niches as key parameters potentially explaining heterogeneity across the studies.
- The proposed model can be used as a generalized submodel for the development more complex QSP modeling platforms studying the mechanisms of long-lived plasma cell maintenance autoreactive ASC cells caused effects in autoimmune diseases.

