Technical Summary

Computational Study of Vaccination Strategies to Change B cell Immunodominance

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Vaccination offers a remarkably simple yet effective solution to one of humanity's most daunting health challenges: infectious diseases. Upon exposure to a pathogenic protein through vaccination, the adaptive immune system undergoes a learning phase. During this phase, antibodies and memory cells that specifically recognize this antigen with high affinities are generated and expanded. If the body encounters the actual pathogen later, the immune system can rapidly respond to neutralize the threat.

However, developing effective vaccines can be difficult. Many viruses, such as Influenza and HIV, employ various strategies to evade our immune defense. These viruses are highly mutable, allowing them to quickly evade pre-existing immune responses formed by vaccination. They also adeptly protect their most vulnerable epitopes from being targeted by the immune response. An epitope is a specific portion of an antigen that is bound by a given antibody. A typical antigen, such as a viral spike protein, contains numerous conformational epitopes on its surface. While many of them can easily mutate, some that are critical for viral functions are conserved across diverse strains.

B cell Immunodominance is a phenomenon where B cells targeting certain epitopes of a pathogen are preferentially selected over others that target diverse epitopes. This presents a challenge in developing potent and long-lasting vaccines against mutable viruses like HIV, influenza, and SARS-CoV-2. Since the immune system preferentially targets immunodominant epitopes, functionally important and conserved epitopes are less often targeted, posing a barrier to generating broadly neutralizing antibodies.

Computational modeling is a valuable tool for understanding the stochastic and dynamic processes of immune response, including how immunodominance arises. By simulating the systemic interactions between B cells, helper T cells, antibodies, and antigens, we can gain insights into the underlying mechanisms of immunodominance and inform more effective design strategies for immunogens and dosing schemes. In this thesis, we present three projects where we developed computational models to investigate strategies for modulating B cell immunodominance in vaccines. We used experimental data from collaboration to validate model findings.

In the first project, we investigated how a third dose of the SARS-CoV-2 vaccine (i.e. a booster shot) drastically enhanced protection against the Omicron variant, even though it still contained the original Wuhan strain. The Omicron variant is not effectively neutralized by most antibodies elicited by two doses of mRNA vaccines. However, a third dose

significantly increases anti-Omicron neutralizing antibodies. We uncovered the mechanisms behind this phenomenon by integrating computational modeling with data from vaccinated humans. After the first dose, limited availability of antigen in germinal centers (GCs) results in a response primarily from B cells targeting highly mutable immunodominant epitopes. Following the second dose, these memory cells proliferate and differentiate into plasma cells, producing antibodies ineffective against the Omicron variant. However, antigen availability significantly increases in the secondary GCs compared to the primary counterparts, since pre-existing antigen-specific antibodies transport antigen efficiently. The antibodies also partially mask immunodominant epitopes. These two effects, the enhanced antigen availability and epitope masking, result in generation of memory B cells targeting subdominant, less mutated epitopes in Omicron from secondary GCs. The third dose expands these cells, boosting anti-Omicron neutralizing antibodies.

In the second project, we investigated the mechanisms through which rationally designed influenza immunogens elicit cross-reactive B cells targeting the receptor-binding site (RBS). We developed a computational model to study antibody evolution by affinity maturation after immunization with two types of immunogens: a heterotrimeric ‘chimera’ hemagglutinin enriched for the RBS epitope, and a cocktail of three non-epitope-enriched homotrimers. The model elucidates the differential mechanisms by which these two immunogen designs influence B cell immunodominance. It demonstrates how the interplay between B cells engagement with antigens and interactions with helper T cells drive immunogen effectiveness. Experiments in mice by collaborators revealed that the chimera was more effective than the cocktail in inducing RBS-directed antibodies. Our findings indicate that this outcome requires stringent T cell-mediated selection of GC B cells, shedding light on antibody evolution and underscoring the role of immunogen design and T cells in shaping vaccination outcomes.

In the third project, our goal was to devise practical 'slow delivery' immunization strategies. A dose-escalation scheme involving seven shots over 12 days has been shown to elicit superior immune response compared to conventional bolus immunization, generating both a more robust overall GC response and a higher proportion of antigen-binding B cells within the GC B cells. However, the seven-injection regimen is not clinically viable. Collaborating with experimentalists, we investigated how just two optimally timed injections can retain the benefits of slow delivery, albeit not to the same extent as the seven-dose scheme. We developed mathematical models to analyze the influence of dosing scheme on helper T cell priming dynamics, which governs the magnitudes of GC response. We used the model to also explore the antigen presentation dynamics affecting the balance between native antigen-binding and non-binding responses. These models elucidated the mechanisms behind experimental observations and iteratively informed further experimental design for improved performance and mechanistic understanding.

In conclusion, this thesis provides valuable insights into the mechanisms of B cell immunodominance and strategies for modulating it, with implications for developing more effective vaccines against mutable viruses. The findings from these three projects enhance our understanding of immune response dynamics and offer practical guidance for vaccine development.