



**Karolinska  
Institutet**

**Institutionen för mikrobiologi, tumör- och cellbiologi**

# **B cell responses against the HIV-1 envelope glycoproteins**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorexamen vid Karolinska  
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## ABSTRACT

The fine specificities of vaccine-elicited B cell responses against complex proteins are not well understood, including those directed against the HIV-1 envelope glycoproteins (Env). Env is the only surface-exposed viral protein and hence a major vaccine target, in particular the conserved determinants of Env. It is now well appreciated that HIV-1 has evolved mechanisms to occlude conserved determinants of Env to limit antibody recognition of these sites. Such structural constraints are thought to contribute to the limited capacity of current Env immunogens to stimulate broadly neutralizing antibodies. Numerous strategies have been undertaken to improve the capacity of Env immunogens to stimulate effective antibody responses, but so far this has met with limited success. An improved understanding of basic B cell biology and how it relates to Env immunogenicity is therefore needed.

The primary goal of this thesis was to ask a number of basic questions regarding vaccine-induced B cell responses using an antigen that is highly relevant to human health, HIV-1 Env. To accomplish this, we developed an optimized B cell ELISpot assay, which can be used to enumerate total Env-specific B cells, as well as B cells directed against different sub-determinants of Env. In **paper I**, we immunized mice with recombinant, soluble Env trimers and we demonstrate that the relative proportion of Env sub-specificities changes significantly in response to boosting, with a robust expansion of B cells recognizing the gp41 moiety of Env after the first boost and of those recognizing variable region 3 after the second boost. In **paper II**, we designed a system to investigate how B cell responses to different elements of the same antigen affect one another. Using this system we show that different specificities develop independently of each other, suggesting that there is no or limited competition between B cell populations recognizing distal epitopes of the same antigen during the development of the immune response.

In **paper III**, we used computationally designed scaffold immunogens displaying a specific broad neutralization epitope of Env. We show that heterologous scaffold proteins could be used sequentially to boost B cell responses that were reactive with the target epitope, but that this regimen did not provide an advantage over the use of a single scaffold. In **paper IV**, we exploited recombinant B Lymphocyte Stimulating factor (BLyS) to modulate the naïve B cell repertoire prior to Env immunization. We show that a transient treatment with BLyS increased the peripheral naïve B cell pools and interestingly, qualitatively enhanced Env-specific responses as evidenced by improved neutralization of HIV-1. Our data suggests that BLyS-regulated processes can be targeted to favorably affect the quality of Env vaccine-elicited neutralizing antibody responses against HIV-1.

Collectively, the findings presented in this thesis provide new insights into the development of B cell responses to protein-based vaccines, specifically to recombinant HIV-1 Env immunogens. This information may accelerate the design of improved Env-based immunization regimens and may also be of more general use for the development of vaccines against highly variable, neutralization-resistant pathogens.

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