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Complexity of antibody maturation as a bottleneck for elicitation of bnAbs by structure-based designed immunogens

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Abstract

I have proposed an antibody germline/maturation hypothesis which is summarized below (Chen W et al Extensive Maturation of Cross-reactive HIV-1 Neutralizing Antibodies. AIDS Vaccine 2007, Seattle; Chen W et al All known cross reactive HIV-1 neutralizing antibodies are highly divergent from germline. AIDS Res Hum Retroviruses 2008, Cape Town; Xiao X et al BBRC 2009; Xiao et al Viruses 2009; Dimitrov DS mAbs 2010)

Initial observation and hypothesis: All known cross-reactive potent HIV-1-neutralizing antibodies (bnAbs) are highly divergent from germline antibodies in contrast to bnAbs against henipaviruses and SARS CoV – germline antibodies may not bind the epitopes of the mature antibodies because they are very different.

Initial experiment and calculations: absent or very weak binding of putative germline predecessors of bnAbs to frequently occurring native Envs; enormous number of possible maturation pathways

Hypothesis – the immunogenicity of the highly conserved epitopes on the HIV-1 native Envs is reduced or eliminated by their very weak or absent interactions with germline antibodies which could not initiate and/or sustain immune responses leading to elicitation of bnAbs; even if immune responses are initiated and sustained the maturation pathways are so complex that help and long times may be needed for elicitation of bnAbs.

A number of groups including Bart Haynes, Peter Kwong's and Leo Stamatatos' have obtained large amount of data supporting and further expanding this hypothesis. There are successes with the design of vaccine immunogens that could bind germline antibodies that are putative predecessors of known bnAbs. However, a major challenge remains how to guide the immune system through the exceptionally complex antibody maturation pathways in order to elicit those bnAbs with specific sequences.