Sequential immunization to induce Silent Face bNAbs in IgKI mice

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A major goal for HIV vaccine research is the induction of broadly neutralizing antibodies (bnAbs) capable of neutralizing diverse viral strains. The conserved silent face (SF) epitope of the HIV-1 Envelope protein (Env) is a promising target for vaccine design because potent bNAbs with relatively limited somatic hypermutations have been isolated from different human donors.

To investigate strategies for eliciting SF-directed bNAbs, we generated immunoglobulin knock-in (Ig KI) mice expressing an inferred precursor of the human SF10 bNAb. We have used this new Ig KI mouse to design and evaluate sequential immunization regimens to induce SF10-like bNAbs.

Here we present a novel sequential immunization protocol that induces SF10-like bNAbs in SF10 Ig KI mice. This immunization strategy successfully activated SF10 precursors in vivo and subsequently matured these precursors to acquire neutralization potency and breadth through the acquisition of key improbable mutations. Sera and monoclonal antibodies (mAbs) isolated from the immunized mice specifically recognized the silent face epitope on both autologous and heterologous Env proteins from clades AE, B, and C. Neutralization assays using the sera and mAbs demonstrated acquisition of SF10-like neutralization activity, with one monoclonal antibody exhibiting improved neutralization potency and breadth compared to the parental SF10 bNAb.

Collectively, we present the first sequential immunization protocol rationally designed to elicit SF bNAbs and establish the SF epitope as a promising target for HIV vaccine development.