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BROADLY NEUTRALIZING ANTIBODY KNOCK-IN MODELS AS LEAD DISCOVERY PLATFORMS FOR IDENTIFYING NEW HIV VACCINE APPROACHES

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A truly effective HIV vaccine will likely require rapid and robust elicitation of broadly neutralizing antibodies (bNAbs), but the pathways to achieve this remain elusive. A critical roadblock has been the lack of practical animal models for reliably tracking development of bNAb responses to HIV vaccination. This talk will overview the various humanized immunoglobulin mouse strains we and others have collectively developed and/or are using for HIV vaccine research over the last decade, in order to highlight how they are helping to rank candidate regions in the HIV-1 envelope (Env), for which it may be most feasible for vaccination to induce bnAbs against. First, the pre- and post-immunization repertoires of various bNAb knock-in (KI) models we have engineered to produce unmutated precursor B-cells of various prototype bNAbs will be presented, to illustrate how such models can be effective tools in pinpointing mechanisms limiting bNAb development. Then, bNAb responses elicited in two of our recent knock-in models will be described, which are specifically directed to the V2 apex (a region in Env to which bNAb responses in infected donors arise more rapidly and frequently, and require less somatic mutation to develop), to further support the notion that the V2 apex may be a relatively more tractable HIV vaccine target. Our KI's V2 apex-specific responses will also be presented to demonstrate how such models can serve as practical lead testing platforms to iteratively down-select HIV immunogens or vaccine regimens re-designed to more selectively trigger bNAb responses and/or overcome any remaining impediments to their induction.

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