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Vaccine Induction of VRC01-class Neutralizing Antibodies in a Knock-in Mouse Model

Xuejun Chen[1], Stephen D. Schmidt[1], Hongying Duan[1], Cheng Cheng[1], Nicole Doria-Rose[1], Ming Tian[2], Frederick W. Alt[2], John R. Mascola[1]

[1]National Institute of Allergy and Infectious Diseases, United States, [2]Boston Children's Hospital, United States

Background: Elicitation of VRC01-class neutralizing antibodies (Abs) is a major goal of HIV-1 vaccine design. Despite recent progress made using transgenic mouse models in initial activation of VRC01-class B cell precursors and elicitation of neutralizing VRC01-class, few of the elicited Abs can neutralize viruses with the N276 glycan that is present in over 95% of the circulating HIV strains.
Methods: To assess immunogens and immunization regimens, we used a unique double knock-in mouse model that expresses the human V_H1-2 gene segment in combination with diverse mouse $D_H$and $J_H$segments via V(D)J recombination and a human V_K3-20 gene segment attached to the VRC01 mature CDRL3. We tested two sequential immunization strategies: 1) homologous boosts with differentially deglycosylated gp120 cores and 2) heterologous boosts with gp120 cores from different strains. Immune sera were tested for neutralization. Monoclonal Abs were isolated at different time points and tested for neutralization.
Results: Both immunization strategies elicited detectable serum neutralizing titers against seven selected virus strains including those with an intact N276 glycan. Single B cell sorting with an engineered outer domain (eOD-GT8) probe and its CD4bs knock out variant led to isolation of various VRC01-class lineages that neutralized mostly N276-glycan deficient viruses. By adding a third probe, BG505. SOSIP, we isolated a VRC01-class monoclonal antibody lineage with 26 somatic mutations in the $V_H$region, and it neutralized five wild type viral strains with an intact N276 glycan, with the IC50 in the range of 0.8-28 μg/ml.
Conclusions: We elicited neutralizing VRC01-class Ab that can neutralize N276 glycan-containing viruses by sequential immunization in a knock-in mouse model expressing a repertoire of VRC01-class precursors with diverse CDRH3s. This work provides proof of concept that even highly somatic mutated broadly-neutralizing Abs like the VRC01-class Abs can be elicited through rationally designed sequential immunization.

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Engineering HIV Immunogens to Elicit IOMA-like Antibodies Targeting the CD4 Binding Site

Harry Gristick[1], Jelle van Schooten[1], Harald Hartweger[2], Morgan Abernathy[1], Jimena Pavlovitch-Bedzyk[1], Amelia Escolano[2], Anthony West Jr.[1], Michel Nussenzweig[2], Pamela Bjorkman[1]

[1]Caltech, United States, [2]Rockefeller University, United States

Background: The most effective way to control the AIDS epidemic would be through active vaccination. The current focus of HIV vaccine design is induction of broadly neutralizing antibodies (bNAbs) against the HIV Envelope protein (Env) that neutralize the majority of circulating viral strains. Due to their breadth and potency, the most desirable bNAbs to elicit through immunization are the VRC01-class bNAbs that target the conserved host receptor (CD4) binding site (CD4bs). VRC01-class bNAbs mimic CD4 binding to share a common mode of gp120 binding and glycan accommodation using a VH1-2*02-derived variable heavy (VH) domain. While attractive candidates for immunogen design, features of VRC01-class bNAbs such as a high degree of somatic hypermutation (SHM) and a short (5-residue) light chain (LC) complementarity determining region 3 (CDRL3) (found in only 1% of human LCs) suggest they might be difficult to elicit through vaccination. We recently published a structural characterization of a novel VH1-2*02-derived CD4bs bNAb, named IOMA, that is an attractive target for immunogen design due to its relatively low levels of SHMs and normal-length CDRL3 (8 residues). Here we describe our work to design an immunogen that elicits IOMA-like antibodies by engineering a gp120 from the 426c Env.
Methods: We used a yeast display approach coupled with multiple rounds of enrichment by fluorescent-activated cell sorting (FACS) to select gp120 variants that bind to the inferred germline of IOMA (IOMA iGL).
Results: Binding studies using enzyme-linked immunosorbent assays (ELISAs) and surface plasmon resonance (SPR) demonstrated that our novel gp120 immunogens bind to IOMA iGL with micromolar affinity.
Conclusions: We will present the results of immunization experiments using these novel immunogens in mouse models.