

## Oral Abstract Session 09: HIV Antibodies: The Good, the Bad and the Ugly

## OA09.05

### Structure of a CH58-like V2 Antibody from Natural Infection Reveals Convergent Heavy Chain Maturation and a Novel K169 Binding Light Chain Motif

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**Background:** K169-dependent V2 binding antibodies were a correlate of reduced infection risk in RV144. CH58, a V2-specific antibody isolated from one vaccinee competed with  $\alpha 4\beta 7$ , and used a key light chain encoded CDRL2 ED-motif to bind K168/K169. Here we determine the structure of a V2/K169 reactive antibody isolated from CAPRISA donor CAP228 (CAP228-16H) bound to a V2 peptide, and compare this to CH58.

**Methods:** Complexes were screened for crystal growth across 396 conditions. The structure was solved using Phenix/Coot, and interactions were weighted by mutagenesis and ELISA. Longitudinal deep sequencing of CAP228-16H immunoglobulin variable regions was used to trace specific maturation pathways.

**Results:** Optimised crystals diffracted to 2.4Å in P2<sub>1</sub>2<sub>1</sub>1. The V2 conformation in both CH58 and CAP228-16H bound structures was strikingly similar, with residues 166-176 adopting an  $\alpha$  helix and residues 177-182 an extended coil. CAP228-16H was derived from the same VH5-51 gene as CH58, and shared germline encoded contacts between its anionic CDRH2 and K/R178 in V2. Deep sequencing of CAP228-16H identified similar pathways of affinity maturation in the CDRH1 of both antibodies that formed a key salt bridge with residue D180 in the  $\alpha 4\beta 7$  binding motif. Only CDRH3 interactions between the two antibodies differed, in that CAP228-16H preferred Y173 over H173, and made contacts with Y177 that allowed for tyrosine sulfation, likely to occur in natural infection. CAP228-16H used a VL3-21 gene that does not encode the signature ED-motif, but still forms key V2 interactions with K168 and K169 via an anionic pocket formed by the germline CDRL2 DDSD-motif.

**Conclusions:** By solving the CAP228-16H crystal structure we identify V2-interacting signatures in the VH5-51 CDRH2, as well as two identical maturation pathways used by CAP228-16H and CH58 to contact the  $\alpha 4\beta 7$  binding motif. The use of VL3-21 identifies a new CDRL2 motif able to recognise K168/K169, broadening the light chain germline repertoire used by RV144-like V2 antibodies.

## OA09.06LB

### Structure of a Natively-glycosylated HIV-1 Env Reveals a New Mode for VH1-2 Antibody Recognition of the CD4 Binding Site Relevant to Vaccine Design

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**Background:** Structural studies of broadly neutralizing antibodies (bNAbs) bound to Env trimers have revealed mechanisms by which bNAbs targeting various epitopes penetrate the glycan shield to either accommodate or include N-glycans in their epitopes. Although accessibility to the conserved host receptor (CD4) binding site (CD4bs) is restricted by surrounding glycans, 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 (V<sub>H</sub>) 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. However, we recently isolated a VH1-2\*02-derived CD4bs bNAb, named IOMA, that includes a normal-length (8 residues) CDRL3.

**Methods:** We used X-ray crystallography to solve the first structure of a fully- and natively-glycosylated Env trimer in complex with IOMA, and the V3-loop-directed bNAb 10-1074.

**Results:** Our structure revealed antibody-vulnerable glycan holes and roles of complex-type N-glycans on Env that are relevant to vaccine design, while also demonstrating that IOMA is a new class of CD4-mimetic bNAb that contains features of both VH1-2/VRC01-class and VH1-46/8ANC131-class bNAbs.

**Conclusions:** Analysis of the native glycan shield on HIV-1 Env allows the first full description of the interplay between heterogeneous untrimmed high-mannose and complex-type N-glycans within the CD4bs, V3-loop, and other epitopes on Env. In addition, the structural characterization of IOMA revealed an alternative pathway from VRC01-class bNAbs relevant to vaccine design, which could more readily lead to an effective vaccine response due to higher frequencies of normal-length CDRL3s compared with the rare 5-residue CDRL3s required for VRC01-class bNAbs, and a lower need for SHMs.