Broadly Neutralizing Antibody Sites

We are currently developing a panel of immunogens which mimic the multiple bnAb sites, rather than focusing on just a single site, for two major reasons. First, comprehensive neutralization coverage is more likely to be achieved by vaccine targeting of more than one site, so the chances of vaccine failure are reduced. Second, the basis for these vaccine regimens is worked out in animal models before going in to the clinic; given the uncertainties involved in translation into humans, we consider it wise not to restrict study to a single site. We therefore propose to focus on the induction of bnAbs to several sites (Fig 1) with the ultimate goal of combining the corresponding immunogens to achieve the requisite breadth and potency.

Fig 1. Electron microscopy representations of bNAbs binding to the Env trimer. Prototype bNAbs are represented. Ann Rev Immun 2016.
BnAbs can be grouped according to the sites they recognize: those specific for the V2-apex, V3-glycan (N332 and adjacent glycans), CD4 binding site (CD4bs), gp120-gp41 interface (including the fusion peptide [FP]), and membrane proximal external region (MPER). Four of the five sites were first defined by bnAbs isolated by Scripps CHAVI-ID investigators. We have subsequently isolated numerous potent bnAbs against these sites that have been instrumental in understanding the defining characteristics of bnAbs and in guiding vaccine design. We have distinct vaccine programs against each of the five bnAb sites of vulnerability on Env described above.

All of the potential vaccine products described above are highly innovative. As each have progressed through early laboratory design, preclinical testing, iterative design, GMP manufacturing, and (pending) human Phase I trials, it has been important that the Scripps CHAVI-ID continuously re-evaluate prioritization of the vaccine candidates. Prioritization is based on preclinical animal model results, manufacturability, and human preclinical and clinical trial results compared to the current best-in-class vaccine product candidate for a given bnAb site, Env trimer design, or nnAb concept. We have a rich vaccine product concept pipeline, from diverse PIs and in most cases we actively have three distinct immunogen designs for each HIV target of interest. Many designs have been discarded because of failures at critical preclinical junctures, whereas the candidates named below have exciting characteristics that have succeeded in testing to date.

![Diagram of HIV Env with labeled sites](image)

**Fig 2.** Immunogens (grey text) entering the clinic (eOD-GT8 and BG505 SOSIP) and initiating GMP manufacturing (N332-GT5 and MT145K) in 2018 and their targets (black text) on HIV Env.