Rapid elicitation of neutralizing Asn332-glycan-independent antibodies to the V3-glycan epitope of HIV-1 Env in nonhuman primates

Relano-Rodriguez I, Du J, Lin Z.J, Kerwin M, Tarquis-Medina M, Urbano E, Cui J, Watkins M, Lavine C.L, Zhao P, Habib R, Agostino C, Ghosh S, Park J, Boroughs C, Walsh A.A, Melo M.B, Shukla N, Shaw G.M, Hahn B.H, Irvine D.J, Wells L, Weiner D.B, Seaman M.S, Kulp D.W, Veazey R.S, Pallesen J, Escolano A

The Wistar Institute, Indiana University, University of Pennsylvania, Tulane National Primate Research Center, Beth Israel Deaconess Medical Center, University of Georgia, Scripps Research Institute, Howard Hughes Medical Institute

Sequential immunization is a promising strategy to activate broadly neutralizing antibody (bNAb) precursors and drive their maturation into bNAbs. The conserved V3-glycan epitope of the HIV-1 envelope protein (Env) is an important target for vaccine design. V3-glycan bNAbs recognize a conserved GDIR motif and several surrounding glycans, including the key glycan at position N332. The N332 glycan is thought to be indispensable for initiating the activation of V3-glycan bNAb precursors and for driving their further development into potent bNAbs. However, we have recently shown that the N332-glycan is not required for the binding and activation of V3-glycan lineages and that N332-glycan-deficient immunogens are efficient at activating broad V3-glycan responses. Here we present the results of immunization experiments using WIN332, the first rationally designed immunogen to elicit N332-glycan independent antibodies. Remarkably, WIN332 binds to precursors of multiple N332-glycan-dependent and independent bNAbs. Prime immunization with WIN332 in nonhuman primates (NHPs) activates robust and broad V3-glycan responses that resemble N332-glycan dependent bNAbs like PGT121 and BG18 and N332-glycan independent bNAbs like EPTC112 and 007. Serum antibodies and a monoclonal antibody isolated from the immunized NHPs neutralize the autologous wild-type HIV pseudovirus. This neutralization is further boosted by a heterologous immunization, increasing potency against BG505 and breadth against seven wild-type pseudoviruses. Altogether, WIN332 induces multiple classes of V3-glycan-bNAb-like antibodies and early neutralization activity in non-human primates. These results together with the recent identification of N332-glycan independent bNAbs support the advancement of WIN332 to clinical testing.