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Targeting HIV using Structure-Based Rational Design of Antibodies

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Isolating and studying broadly anti HIV neutralizing antibodies from infected individuals is a major effort in the combat against HIV. We hope to gain better understanding for vaccine design by elucidating the exact epitope of such antibodies. Furthermore, by providing evermore potent and broadly neutralizing antibodies new strategies like passive immunization or using antibodies as topical microbicides for HIV prevention become feasible. One class of promising antibodies is anti CD4 binding site antibodies. Such antibodies can show exceptional potency and breadth. We used X-ray crystallography to study the structure of NIH45-46, one of the most potent anti CD4 binding site antibodies ever described in complex with gp120, the HIV receptor binding domain. Our structural analysis identified a region in the inner domain of gp120 that is important for the binding and neutralization of NIH45-46 (Diskin et al., 2011). This region is contacted by a four-residue insertion in CDRH3 that does not exist in VRC01, a less potent clonal member of NIH45-46. We further used structure-based rational design to improve NIH45-46. By replacing Gly54 in the CDRH2 with a tryptophan we allowed NIH45-46G54W to bind a unique hydrophobic pocket on the surface of gp120 that is normally accommodating Phe43 of CD4. Remarkably, NIH45-46G54W shows increase both in breadth and potency compared with NIH45-46 (Diskin et al., 2011). We took this approach further and engineered NIH45-46G54W to bind a conserved glycan on gp120. This effort resulted with the most potent and broadly neutralizing anti HIV antibody ever described (Diskin et al., 2013). I will present this work and additional efforts to modify NIH45-46 to accommodate potential escape mutations of HIV.

[1] *Diskin, R., Klein, F., Horwitz, J. A., Halper-Stromberg, A., Sather, D. N., Marcovecchio, P. M., Lee, T., West, A. P., Gao, H., Seaman, M. S., Stamatatos, L., Nussenzweig, M. C. & Bjorkman, P. J. (2013). J Exp Med 210, 1235-1249.,* ***[2]*** *Diskin, R., Scheid, J. F., Marcovecchio, P. M., West, A. P., Jr., Klein, F., Gao, H., Gnanapragasam, P. N., Abadir, A., Seaman, M. S., Nussenzweig, M. C. & Bjorkman, P. J. (2011). Science 334, 1289-1293.*

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