

## TARGETING VIRUS-RECEPTOR INTERACTIONS BY CROSS-REACTIVE HUMAN MONOCLONAL ANTIBODIES AND ENGINEERED ANTIBODY DOMAINS

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Heterogeneity of virus envelope glycoproteins (Envs) is a fundamental problem leading to low efficacy and development of resistance to drugs targeting virus-receptor interactions. Possible solution to this problem is to identify conserved targets, improve potency and hit multiple targets. Our research has been therefore focused on the identification and characterization of highly potent antibody-based candidate therapeutics against multiple conserved targets on Envs. Receptor-binding sites (RBS) on Envs are appropriate targets because they are functionally important and relatively easy to access. We have developed a number of human monoclonal antibodies (hmAbs) and engineered antibody domains, including VH-based (domain antibodies, dAbs) and CH2-based (nanoantibodies, nAbs), against HIV-1 and biodefense-related viruses (SARS CoV, Hendra and Nipah viruses). Most of them target receptor or coreceptor BSs, and exhibit potent and broad neutralizing activity in tissue cultures and animal models of infections. Crystal structures of several Fabs from these antibodies in complex with Envs (gp120 core, SARS CoV RB domain, Hendra G) were solved. They suggest possible mechanisms of cross-reactivity and indicate relatively low probability of development of resistance. In initial *in vitro* experiments treatment with one of these antibodies, scFv m9, did not lead to emergence of antibody-resistant HIV-1 isolates. The dAbs and nAbs are very small but highly specific and could access highly conserved restricted regions of proteins and tissues not accessible or partly-accessible by full-size antibodies. We have identified and characterized several dAbs and nAbs against HIV-1. One of these dAbs, m36, was isolated from a very large ( $2.5 \times 10^{10}$ ) dAb library with novel design (Chen et al JMB 2008); it potently neutralized a range of HIV-1 primary isolates from different clades (Chen et al PNAS 2008). This antibody and several others are currently under evaluation as potential therapeutics against HIV-1, Nipah and Hendra viruses.

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