

Change in Anti- gp120 Human Monoclonal Antibody Isotype Significantly Improves HIV-1 Neutralization

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HIV vaccine efforts tend to focus on the induction of IgG neutralizing antibodies. In part, this may stem from the observations that most HIV infected individuals fail to produce significant mucosal IgA. However, this is unlike most other infections and in turn it can be argued that mucosal IgA with appropriate function and specificity may contribute significantly to the prevention of HIV transmission. To explore this, we previously isotype switched F425A1g8, an anti-HIV CD4i human monoclonal antibody that binds to epitopes exposed upon CD4 binding (CD4i). The VH and VL chains were amplified from the IgG hybridoma and inserted into IgA1 or IgA2 and IgKappa vectors respectively. Stable cell lines were produced and antibody was collected and purified. Initial results showed that the IgA1 variant neutralized a number of HIV-1 isolates better than its parental form IgG1. We believe the increased neutralization of HIV is mainly due to the structural differences between IgG1 and IgA1. We hypothesize that the extended hinge of IgA1 may increase segmental flexibility and change the interaction of antibody with CD4i epitopes of the HIV, resulting in greater avidity. To look at this further, we have generated monomeric and dimeric IgA1 and IgA2 variants of three different CD4i antibodies: F425A1g8, 17b and E51. All antibody variants will be tested for immunoreactivity, HIV neutralization, prevention of transmission and ADCVI activity. Consistent with our previous results, there are significant differences in functional activity of the other CD4i antibodies with IgA1 more effective than the IgA2 variants. Additional activities will contribute to the hypothesis that the extended hinge region of the IgA1 antibody increases the antibodies ability to access the CD4i epitopes upon HIV-1 binding to CD4. These studies should impact on the design of active and passive immunotherapy and the prevention of HIV transmission.

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