

Poster presentation

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P13-01. Crystal structure and function of a monoclonal antibody against primate CD4 that blocks HIV/SIV infection

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Background

The HIV cellular receptor, CD4, is not subject to the high rate of mutation found in viral gene products. Therefore antibodies that target the gp120 binding domain of CD4 that do not interfere with its physiological role might provide an effective means to prevent HIV infection. Here, we report on the development and characterization of a CD4 antibody that blocks HIV/SIV infection by binding to the gp120 binding domain of CD4.

Methods

A mouse monoclonal antibody against primate CD4 (mAb2D5) was generated and screened for blocking of HIV/SIV envelope mediated entry into target cells using a pseudotyped lentiviral entry assay. The mAb2D5 was characterized for its ability to block T cell immune responses *in vitro*. The crystal structure of the mAb2D5 Fab complexed with the two N-terminal domains of CD4 was determined to 3.6 Å using molecular replacement. Finally, the Ab was passively administered to rhesus macaques and monitored for toxicity, mAb2D5 serum levels and CD4 receptor occupancy.

Results

The CD4 antibody, mAb2D5, inhibited HIV/SIV envelope mediated entry into target cells at concentrations of 1–10 µg/ml and was not associated with the inhibition of immune functions associated with CD4. The crystal structure of the complex between the mAb2D5 Fab and CD4 reveals an epitope on domain 1 of CD4 that partially overlaps with the binding site for gp120 and is therefore able to directly inhibit interaction between CD4 and HIV

envelop. Passive transfer of mAb2D5 to rhesus macaques did not deplete CD4+ T cells from the peripheral blood and showed high receptor occupancy. Challenge studies are planned, and the available results regarding its ability to inhibit SHIV162P3 infection will be described.

Conclusion

The mAb2D5 potently inhibits HIV and SIV replication *in vitro* and is safely tolerated by monkeys. The crystal structure provides insight into its mechanism of viral entry inhibition.