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Poster presentation



# P03-07. Autologous neutralizing antibodies that select viral escape variants emerge late after SIV infection of rhesus monkeys

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## Background

Autologous neutralizing antibody responses against HIV-1 have been shown to emerge a number of months after primary infection. It is not known why neutralizing antibodies against HIV-1 are relatively slow to appear. We use the SIV/rhesus macaque model to characterize the kinetics of autologous neutralizing antibody responses and envelope sequence evolution in 4 rhesus monkeys infected intrarectally with SIVmac251.

## Methods

We assessed the presence of autologous neutralizing antibodies at 3, 5, 8, 16, and 22 months post-infection using pseudovirion-based, luciferase-reporter gene neutralizing antibody assays. We then analyzed full-length SIV env sequences at selected time points. The capacity of sera to neutralize variant viruses was also determined.

## Results

Sera from 4 SIVmac251-infected monkeys neutralized the inoculating virus at 8 months, but not at 5 months after infection. These sera did not neutralize autologous or heterologous SIV variants that were cloned at later time points, indicating that variant viruses had mutated to escape neutralization. After escape, these circulating viral variants became the predominant viral quasispecies in all animals. The majority of genotypic changes clustered in variable loops 1/2 (V1/2) and 4 (V4) of env. These changes resulted in the deletion of neutralizing epitopes and shifts in potential N-linked glycosylation sites.

## Conclusion

We show that SIVmac251, a strain of SIV that is relatively resistant to antibody-mediated neutralization, induces potent autologous neutralizing antibodies by 8 months post-infection. The late emergence of neutralizing antibodies appears to be related to the inherent properties of primate lentiviruses, since the kinetics of SIVmac251 neutralization mirrors what has been reported with HIV-1. The evolution of SIV env implicates V1/2 and V4 region as the determinants of antibody neutralization. The development of these antibodies resulted in complete replacement of neutralization-sensitive virus by resistant viruses, providing evidence that humoral immune responses exert potent selection pressure on SIV despite their late emergence.