Retrovirology

Poster presentation

P12-15. Replication enhancement of an alphaviral-lentiviral replicating chimeric particle (RCP) vaccine

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Background

We have developed a novel, acutely replicating VEE-SHIV chimeric particle (RCP) as a vaccine against HIV that combines the superior and long-lived immunity of a live-attenuated virus with the safety of non-replicating particulate antigens. These chimeric particles contain a replicating VEE-SHIV genome and are capable of infecting susceptible cells bearing hCD4/hCCR5, undergoing cytoplasmic replication, genomic RNA encapsidation, assembly and particle release. Due to the replicative nature of the RCPs, lentiviral proteins will be expressed for an extended period of time in vaccinated individuals thus inducing a more comprehensive immune response compared to nonreplicating antigens but without the safety issues associated with integrating, live-attenuated lentiviruses.

Methods

VEE-SHIV RCP vaccines contain the VEE UTRs along with nonstructural genes required for RNA replication. Structural genes of VEE, which are under the control of the VEE subgenomic 26S promoter, were replaced with SIV gag +/- an attenuated protease (PR, A28S). The VEE capsid fragment (aa75-132), predicted to bind VEE genomic RNA, was incorporated by replacing the NC region of gag while maintaining the proteolytic cleavage sites. HIV Env was added downstream from a second VEE subgenomic promoter.

Results

VEE-SHIV RCP vaccines were evaluated for particle formation, encapsidation of genomic RNA and infectivity in both primate and rodent. Inclusion of the VEE C fragment and attenuated protease in the VEE-SHIV RCP increased the specific infectivity by two logs. In addition, these chimeric particles replicated for more than 35 passages in both rodent and primate cell lines. At the conclusion of the viral passage experiment, the total viral titer increased 1-2 logs compared with the non-passaged virus.

Conclusion

The novel replicative nature of these chimeric particles should lead to enhanced immunogenicity and will be investigated in hCD4/hCCR5 transgenic mice as well as non-human primates.