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Neutralizing antibodies elicited in rabbits by patient-derived Env trimer immunization

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Background

Eliciting broad cross neutralizing antibodies (bNAb) remains the primary and most challenging goal in HIV-1 vaccine development. So far no vaccine candidate has induced such bNAb. Selecting Env vaccine candidates will require both antigenic and immunogenic optimization and testing in relevant animal models.

Methods

Based on in-vitro neutralizing activity in serum, patients (n=6, subtype A and B infected) were selected and Env sequences of early HIV-1 variants, still sensitive to autologous neutralization, were used to generate soluble Env as immunogens. Gp140 trimeric proteins were expressed (293T cells) and purified. Rabbits (4/group) were immunized s.c. at weeks 0, 2, 4, 8 with 100μg trimer adjuvanted with cationic CAF01. Control groups received 20μg and 100μg trimer plus/minus CAF01 respectively. Sera collected at weeks 0, 2, 4, 8, 12 and 14 were screened in gp120-IIIB ELISA and IgG was analyzed in the TZMbl neutralization assay.

Results

All rabbits generated a gp120-IIIB specific IgG response 2 weeks after the first immunization and titers were boosted after each subsequent immunization. IgG titers measured 4 weeks after the last immunization clearly differed between groups (n=5) receiving 100μg/immunization (Geometric mean titer (GMT) : 152.601) and the group receiving 20μg/immunization (GMT : 13.262) or the group omitting CAF01 (GMT : 27.262). Only IgG from rabbits receiving the highest dose and in the presence of CAF01 were able to neutralize Tier 1 pseudoviruses of different subtypes.

Neutralizing activity was detected after the 2nd immunization and was boosted after each immunization. No significant differences were observed between the different trimers.

Conclusion

Gp140 trimers based on HIV-1 variants of patients with bNAb in serum elicited gp120-IIIB specific IgG and NAb given that enough immunogen was administrated in the presence of CAF01. These results indicate that the development of HIV-1 Env specific NAb is dose dependent and strengthen the rabbit model for HIV vaccine studies.

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