

ORAL ABSTRACT SESSION 07: T CELL RESPONSES TO VACCINE

OA07-01

HIV-Specific CD8⁺ T-cells of vaccinees exhibit proliferative and cytotoxic capacities comparable to those of progressors

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Background: HIV-specific CD8⁺ T-cells of long-term nonprogressors (LTNP) exhibit extraordinary per-cell cytotoxic capacity. To adapt cytotoxicity assays for vaccine trials, we compared HIV-specific CD8⁺ T-cell cytotoxic capacity with proliferation and perforin expression using cells from LTNP, viremic progressors, antiretroviral recipients with <50 HIV RNA copies/ml plasma (R_x<50) and seronegative individuals who had or had not received the Merck Ad5 trivalent vaccine.

Methods: HIV-specific CD8⁺ T-cell cytotoxic responses to HIV_{SF162}-infected CD4⁺ T-cell targets were measured at 1 hour by flow cytometric detection of granzyme (Gr) B delivery to live targets or infected CD4 elimination (ICE). Cytotoxicity, IFN- γ production, perforin expression, and proliferation of HIV-specific CD8⁺ T-cells were examined following a 6-day stimulation with HIV_{SF162}-infected CD4⁺ T-cell targets.

Results: The HIV-specific CD8⁺ T-cell cytotoxic responses of vaccinees (medians 16.8% GrB activity, 37.2% ICE) were clearly distinguishable from those of seronegative controls (1.7% GrB activity, p<0.001; 0.3% ICE, p<0.001), but were comparable to those of progressors (16.6% GrB activity, p>0.5; 37.4% ICE, p>0.5). Among vaccinees, those with the protective alleles HLA B*27, B*57, or B*58 tended to have higher responses. Vaccinee responses were significantly less than those of LTNP (50.7% GrB activity, p<0.001; 82.5% ICE, p<0.001). GrB activity and ICE were strongly correlated with HIV-specific CD8⁺ T-cell proliferation (R=0.85, p<0.001 and R=0.87, p<0.001, respectively) and perforin expression (R=0.86, p<0.001 and R=0.9, p<0.001, respectively). When measured on a per-cell basis, cytotoxicity of most vaccinees remained at the level of progressors, even with higher effector:target ratios.

Conclusion: GrB activity and ICE correlate strongly with CD8⁺ T-cell proliferation and perforin expression in expanded cells suggesting these parameters are reasonable surrogate measurements of CD8⁺ T-cell-mediated killing requiring fewer cells. GrB activity and ICE of vaccinees were similar to those of progressors, suggesting these low responses might contribute to suboptimal control in cases of HIV infection following vaccination.

OA07-02

Adenovirus vectors induce expansion of memory CD4 T cells with a mucosal homing phenotype that are readily susceptible to HIV-1 infection

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Background: In the recently halted human immunodeficiency virus type 1 (HIV-1) vaccine STEP trial individuals that were seropositive for adenovirus serotype 5 (Ad5) showed increased rates of HIV-1 infection on vaccination with an Ad5 vaccine. We undertook a series of ex vivo strategies to address the hypothesis that immunisation of Ad5 seropositive individuals with adenoviral vectors may result in activation, expansion, and trafficking of Ad5-specific memory CD4 T cells to mucosal tissues thereby increasing the number of HIV-1 susceptible targets at the initial sites of infection.

Methods: Ad5 and Ad11 antibody titers were measured in 20 healthy volunteers. Dendritic cells (DC) were generated from these individuals, pulsed with replication defective Ad5 or Ad11 and co-cultured with autologous lymphocytes. Cytokine profiles, proliferative capacity and the migration potential of the adenovirus-stimulated memory T cells were measured. The susceptibility of re-stimulated memory Ad-specific T cells to infection with a CCR5-utilising HIV-1 was also assessed by multi-colour flow cytometric analysis and p24 ELISA assays.

Results: Stimulation of T cells from Ad5 seropositive but Ad11 seronegative individuals with Ad5, or serologically distinct Ad11 vectors induced expansion of adenovirus memory CD4 T cells expressing alpha 4 beta 7 and CCR9, indicating a mucosal-homing phenotype. CD4 T cell proliferation and IFN-gamma production in response to Ad stimulation correlated with Ad5 antibody titers. In contrast, Ad5 serostatus did not correlate with total cytokine production upon re-challenge with Ad5 or Ad11. Expanded Ad5 and Ad11 memory CD4 T cells showed an increase in CCR5 expression and higher susceptibility to infection by R5 tropic HIV-1.

Conclusion: Adenoviral-based vaccination against HIV-1 in individuals with pre-existing immunity against Ad5 may result in preferential expansion of HIV-susceptible activated CD4 T cells that home to mucosal tissues, increase the number of virus targets and lead to a higher susceptibility to HIV infection.

OA07-03

Influence of preexisting vaccinia immunity on a DNA/MVA SIV vaccine, decreased cellular immunity but enhanced control of a pathogenic SIV challenge

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Background: The influence of preexisting immunity to viral vectors is a major issue for the development of viral vectored vaccines. Here we report that for a DNA/MVA vaccine, preexisting immunity to vaccinia virus (Dryvax) decreases cellular immune responses but enhances control of an intrarectal SIV challenge.

Methods: Three groups of rhesus macaques, eight per group, were studied. The Dryvax-naive and Dryvax-immune groups received the DNA/MVA SIV vaccine (DNA at weeks 0 and 8, and rMVA at weeks 16 and 24). In addition, the Dryvax-immune group received the Dryvax vaccine 1.5 years prior to the DNA prime. The control group did not receive any vaccine. All macaques were challenged intrarectally with SIV251 at 9 months after the final MVA.

Results: Following vaccination, the frequency of SIV Gag-specific CD4 and CD8 T cells were 5-10 fold lower in the Dryvax-immune group than the Dryvax-naive group. Despite their low SIV-specific T cell responses, the Dryvax-immune macaques exhibited the best control of SIV challenge with viremia 480-fold lower at peak and 40-fold lower at set point than in the unvaccinated control animals ($p=0.01$). The enhanced control in the Dryvax-immune animals was not restricted to Mamu A*01+ animals and was strongly associated with reduced colorectal virus at 2 weeks post challenge. Factors that correlated with early colorectal viral control included the magnitude of vaccine-elicited CD4 T cells displaying the CCR5 viral co-receptor, which was dampened in the Dryvax-immune animals; the presence of anti-viral mucosal IgA, which was more frequent in the Dryvax-immune animals, and the avidity of the anti-Env Ab response. The frequency of anti-viral CD8 T cells did not correlate with early colorectal viral control.

Conclusion: These results highlight important roles for vaccine-elicited CCR5+ CD4 T cells in augmenting, and mucosal IgA and high avidity anti-Env IgG in restricting the early replication of a colorectal immunodeficiency virus challenge.