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HIV-1 Conserved Mosaics Delivered by Regimens with Integration-deficient, DC-targeting Lentivirus Induce Robust T Cells

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Background: To be effective against HIV-1, vaccine-induced T cells must selectively target functionally conserved and, at the same time, protective epitopes present on the majority of currently circulating and reactivated HIV-1 strains, and rapidly reach protective frequencies upon exposure to the virus. Heterologous prime-boost regimens using virally vectored vaccines are currently the most promising strategy towards achieving this goal, nevertheless, induction of robust long-term memory remains challenging. To this end, lentiviral vectors induce high frequencies of memory cells due to their low-inflammatory nature, while typically inducing only low anti-vector immune responses.
Methods: We describe construction of novel candidate vaccines ZVex.tHIVconsv1 and ZVex.tHIVconsv2, which are based on an integration-deficient lentiviral vector platform with preferential transduction of human dendritic cells and express bivalent mosaic of conserved-region T-cell immunogens with a high global HIV-1 match.
Results: Each of the two mosaics was individually immunogenic and together in heterologous prime-boost regimens with non-replicating simian (chimpanzee) adenovirus or non-replicating poxvirus MVA vaccines induced very high frequencies of plurifunctional and broadly cross-reactive T cells in BALB/c and outbred CD1-SWISS mice.
Conclusions: These data support further development of this vaccine concept.

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Mucosal Vaccination with a Live Recombinant Rhinovirus Followed by Intradermal DNA Administration Elicits Protective HIV-specific Immune Responses

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Background: Most HIV-1 transmissions occur via genitorectal mucosa, highlighting the need for vaccines that elicit mucosal immunity. HIV Gag-specific cell mediated immunity (CMI) and anti-Tat neutralizing antibodies are considered essential for long-term control of HIV. Thus, Gag and Tat are desirable components of a HIV vaccine. We developed a candidate mucosal vaccine by engineering a replication-competent human rhinovirus serotype A1 (HRV-A1) to encode Gag and Tat (rHRV-Gag/Tat). Intranasal administration of this novel vaccine may generate robust pan-mucosal and systemic HIV-specific immunity.
Methods: Balb/c mice (n=7 per group) were vaccinated intranasally with 2 doses ($5x10^6$ $TCID_{50}$/dose) of rHRV-Gag/Tat (referred to hereafter as rHRV-DNA vaccination) or WT-HRV then boosted intradermally with a 50 µg of a DNA vaccine encoding Gag and a novel oligomerised Tat (pVAXGag/Tat). Another group of mice received 3 intradermal doses (50 µg/dose) of pVAXGag/Tat (referred to hereafter as pVAXGag/Tat vaccination). Splenocytes and lymphocytes from mesenteric lymph nodes were analysed for Gag-specific systemic and mucosal CMI by ELIspot and ICS. We also analysed blood and cervical vaginal lavage (CVL) samples for Tat-specific systemic (IgG) and mucosal (IgA), respectively.
Results: rHRV-DNA vaccination elicited superior multi-functional $CD8^+$T cell responses in lymphocytes harvested from mesenteric lymph nodes and spleens, and higher titres of Tat-specific antibodies in blood and vaginal lavages, and reduced the viral load more effectively after challenge with EcoHIV, a murine HIV challenge model, in peritoneal macrophages, splenocytes and blood compared compared with wt-HRV-A1/pVAX vaccination or administration of 3 ID doses of pVAX-Gag-Tat (3X pVAX-Gag-Tat vaccination).
Conclusions: Data shows that rHRV-DNA vaccination can induce HIV-specific immune responses in the gut, vaginal mucosa and systemically, and supports further testing of this regimen in the development of an effective mucosally-targeted HIV-1 vaccine.