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Inactivated retroviral virions with functional envelope glycoproteins

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Abstract

We have exploited the intrinsic chemistry of retroviruses to develop a novel method for chemical inactivation of their infectivity, while preserving the conformational and functional integrity of the viral envelope glycoproteins. The approach is based on the fact that the cysteines of key internal proteins of retroviruses, such as the nucleocapsid protein, have free sulfhydryls, while the cysteines of the viral envelope glycoproteins present on the virion surface are involved in disulfide linkages. Treatment of virions with mild oxidizing agents can thus mediate preferential covalent modification of the internal proteins, altering their structure, and abrogating their critical functions in viral replication, resulting in the inactivation of infectivity, without affecting the disulfide-linked cysteines of proteins on the virion surface.

We have demonstrated the ability of a variety of different oxidizing agents to inactivate retroviral infectivity via this mechanism. Among the agents evaluated, we have focused on 2,2'-dithiodipyridine (aldriethiol-2, AT-2) as the inactivating agent of choice, for reasons of activity, solubility, availability and cost. AT-2 inactivated virions are non-infectious but interact authentically with target cells. On CD4+ co-receptor+ T cells, the envelope glycoproteins on AT-2 inactivated HIV and SIV virions bind, undergo post-binding induced conformational changes, and mediate membrane fusion. However, no reverse transcription ensues, and the virions are not infectious, *in vitro*. AT-2 inactivated virions also interact with antigen presenting cells such as dendritic cells (DCs) in the same manner as native (infectious) virions, being taken up by an env-dependent process. After uptake, AT-2 inactivated virions are processed via the proteasome pathway, transported via a TAP dependent mechanism, and the derived viral antigens can be presented via both MHC II and MHC I to stimulate responses by CD4+ and CD8+ T cells.

We are evaluating AT-2 inactivated virions as a candidate vaccine immunogen in both prophylactic and therapeutic models in non-human primates. AT-2 inactivated SIV virions are not infectious *in vivo*, even after direct i.v. inoculation of large amounts of inactivated virus. AT-2 inactivated SIV is immunogenic, inducing both binding and neutralizing antibody responses, along with T-cell responses, including responses by CD8+ T cells, demonstrated by IFN-gamma ELISPOT analysis. Preliminary evidence of partial protective efficacy has been obtained in initial prophylactic immunization to challenge studies. We are also evaluating AT-2 inactivated SIV virions as a candidate immunogen in therapeutic vaccination studies, in which rhesus macaques are infected with highly pathogenic SIV, and antiretroviral drug treatment (ART) is initiated in early chronic infection. Current studies are comparing matched animals that simply received continuous ART and animals that received continuous ART along with vaccination. For these studies, AT-2 inactivated SIV was administered with synthetic oligonucleotides containing immunostimulatory CpG motifs and via autologous monocyte-derived dendritic cells pulsed *ex vivo* with AT-2 SIV. Strong boosting of SIV-specific immune responses has been seen following

immunization. Both viral replication profiles and immune responses will be compared between ART treated and ART treated/vaccinated animals, following discontinuation of ART.

Overall, inactivated retroviral virions with functional envelope glycoproteins appear to be a safe and immunogenic vaccine approach warranting further evaluation in both prophylactic and therapeutic vaccination settings for the prevention of HIV/SIV infection and AIDS.

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