In Vivo Electroporation Induces Broad HIV-1 Envelope-Specific T-cell Responses to ADVAX HIV-1 DNA Vaccine in Humans

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Introduction

DNA-based vaccines have been found safe, stable, easily manufactured and are unencumbered by pre-existing vector-specific immune responses, although previous studies have shown them to be poorly immunogenic. Administration of the DNA-based candidate HIV-1 vaccine ADVAX, through electroporation has been shown safe and to result in increased and more durable cellular immunogenicity over intramuscular administration. The majority of responses induced were of a polyfunctional phenotype in CD4+ T-cell populations. Here, we sought to resolve the breadth of T-cell responses towards the ADVAX clade B/C envelope (ENV) insert along with the identities of regions recognized through epitope mapping.

Methods

Study Vaccinations

Forty healthy volunteers aged 18-60 were enrolled in a double blind randomized Phase-I trial (Vasan et al. 2011). Eight volunteers each received either low dose (LD, 0.2mg); mid dose (MD, 1.0mg); or high dose (HD, 4.0mg) ADVAX DNA vaccine (Gag-Pol, Nef-Tat and Env) or saline placebo via EP. Another eight volunteers received 4.0mg ADVAX intramuscularly (IM). Vaccinations were given at weeks 0 and 8. The protocol was subsequently amended to administer a third dose of HD EP/placebo at week 36 to volunteers receiving either HD ADVAX via EP (n=8) or placebo via EP (n=3).

IFNγ ELISpot

Following initial screening ELISpot, PBMCs isolated from 16 individuals vaccinated through electroporation, were selected based on ELISpot responses of >100 SFU/million and subjected Following initial screening ELISpot, PBMCs isolated from 16 individuals vaccinated through electroporation, were selected based on ELISpot responses of >100 SFU/million and subjected to peptide mapping using a matrix containing sequences corresponding to the ADVAX ENV insert along with the identities of regions recognized through epitope mapping.

Results

Of the 16 individuals mapped 11 had responses successfully identified at the peptide level (1 Low Dose, 3 Mid Dose, 7 High Dose), with a median of 3 responses/volunteer (Figure 1). Overall a trend towards higher response breadth coincided with increased vaccine dose. The most common regions targeted were C1, V2 and V3/C3 regions of ENV (Table 1 and Fig 2). With all vaccinees responding to at least one of these regions. Interestingly, 5/11 individuals recognized the FYRLDIVPLNK region containing the +1/7 integrin binding motif.

Table 1. Regions recognized by vaccinees.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Region</th>
<th>No. Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>GYRP/HV/HV/DV/PL/KN</td>
<td>C1</td>
<td>1/11</td>
</tr>
<tr>
<td>FYL/PS/EV/LE/PL/KN</td>
<td>V2</td>
<td>5/11</td>
</tr>
<tr>
<td>GYP/TV/AA/PL/KN</td>
<td>V3</td>
<td>1/11</td>
</tr>
<tr>
<td>WNETLQRVGKKLAEHF</td>
<td>C3</td>
<td>2/11</td>
</tr>
<tr>
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<td>C3</td>
<td>1/11</td>
</tr>
<tr>
<td>CRD/PS/EV/LE/PL/KN</td>
<td>C4</td>
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<tr>
<td>FYL/PS/EV/LE/PL/KN</td>
<td>C4</td>
<td>1/11</td>
</tr>
</tbody>
</table>

Discussion

DNA-based vaccines have been shown to be safe and immunogenic and do not have the disadvantage of vector specific immunity. In addition to boosting immunogenicity it was shown that using electroporation as a means of delivery was also capable of inducing broad insert-specific T-cell responses comparable to those induced by other vaccine delivery systems Hansen et al. 2008, Koop et al. 2010. Response breadth had a tendency of increasing along with vaccine dose. Furthermore, 5/11 individuals recognize the tripalpida +6/7 integrin binding motif within the V2 loop, a potentially important region during initial virus infection. The ability of HIV-1 vaccines to target immune responses towards such a region could play a role in limiting acute viral burst.

References


Table 1. Regions recognized by vaccinees.

Breadth of ENV-specific Responses

Fig 1. Breadth of ADVAX ENV-specific T-cell responses by volunteer. Light blue low dose, blue medium dose, dark blue high dose

Fig 2. Locations of targeted regions superimposed on a schematic gp120 backbone (adapted from Sanders et al. 2008)

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