mRNA-based dendritic cell vaccination induces potent antiviral T-cell responses in HIV-1 infected patients

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Setting
Phased therapeutic vaccination, based on autologous monocyte-derived dendritic cell (Mo-DC), electroporated with mRNA encoding H2b Gag, Tat, Rev and Nef in HIV-1 infected subjects under stable HAART.

Research question
Safety, feasibility and induced T cell responses: ELISPOT, proliferation, polyfunctionality and virus-suppressive activity.

Subjects and methods
Subjects (Table 1): Six chronic HIV-1 patients with baseline CD4 T cell counts above 500 cells/µl, nadir CD4 T cell counts not below 300 cells/µl and plasma viral loads < 50 copies/ml for at least 3 months.

Vaccination scheme (Fig 1A and B): Clinical grade DC vaccines were prepared from Mo after activation/stimulation by anti-CD3/CD28 Ab plus IL-2 in vitro. Mo-DC were electroporated (EP) with codon optimized HIV-1 Gag, 2 Tat, 5 Nef pools in the x-axis. The number of IFN-γ spot forming cells (SFC) per million PBMC is shown; the color of the graphs corresponds to the time points indicated on the time axis on top. Increased breadth of IFN-γ responses was indicated by a star; w, number of weeks in relation to the first DC vaccination (T1). Overall % of T cells with > 2 functions increased after vaccination in all patients (p < 0.001).

Results
SAFETY AND FEASIBILITY (Table 1): Only local side effects. No feasibility problems. Stable clinical, viral and other parameters.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>UPN</th>
<th>Demographic data</th>
<th>CD4+ T cell count/µL</th>
<th>Plasma viral load (copies/mL)</th>
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<td>1251</td>
<td>&lt;50</td>
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<tr>
<td>H025</td>
<td>48</td>
<td>1102</td>
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</tbody>
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Discussion
1. Gag and TatRevNef mRNA loaded autologous DC vaccination is safe, feasible and immunogenic in HIV-infected subjects under stable HAART.
2. CD4 T cell mediated virus suppression activity against a vaccine-related strain can be induced and correlates with Gag specific T cell responses.
3. Breadth and polyfunctionality of the responses should be improved by including more universal sequences (e.g. conserved or mosaic) and more powerful immune enhancers (e.g. IL-21 or PD1 blocking).

InterRELATION BETWEEN VARIOUS RESPONSES:
- Virus suppressive activity at T4 correlated with Gag ELISPOT magnitude (R = 0.57 p < 0.05) and breadth (R = 0.56 p < 0.05).
- No correlation with TatRev-Net.
- Polyfunctionality also correlated with ELISPOT and proliferative responses.

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