Dendritic Cell Vaccine for Treatment of HIV

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No conflicts of interest to declare
Aims

• To overview different vaccines for HIV/AIDS treatment
• Review the rational and results of current protocols for therapeutic immunization with dendritic cells
• Present the ongoing Brazilian phase II study of dendritic cell therapeutic vaccine for HIV
• Discuss the role of apheresis to obtain therapeutic vaccines for HIV
Global statistics HIV/AIDS

35 MILLION PEOPLE WORLDWIDE ARE CURRENTLY LIVING WITH HIV/AIDS.

THE VAST MAJORITY OF PEOPLE LIVING WITH HIV ARE IN LOW- AND MIDDLE-INCOME COUNTRIES, PARTICULARLY IN SUB-SAHARAN AFRICA.

3.2 MILLION CHILDREN WORLDWIDE ARE LIVING WITH HIV. MOST OF THESE CHILDREN WERE INFECTED BY THEIR HIV-POSTIVE MOTHERS DURING PREGNANCY, CHILDBIRTH OR BREASTFEEDING.

www.aids.gov
Global statistics HIV/AIDS

Adults and children estimated to be living with HIV | 2013

North America and Western and Central Europe
2.3 million
[2.0 million – 3.0 million]

Caribbean
250,000
[230,000 – 280,000]

Latin America
1.6 million
[1.4 million – 2.1 million]

Middle East & North Africa
230,000
[160,000 – 330,000]

Sub-Saharan Africa
24.7 million
[23.5 million – 26.1 million]

Eastern Europe & Central Asia
1.1 million
[980,000 – 1.3 million]

Asia and the Pacific
4.8 million
[4.1 million – 5.5 million]

Total: 35.0 million
[33.2 million – 37.2 million]

Source: UNAIDS
HIV vaccines

• **Prophylactic vaccines**
  – best strategy for controlling the HIV pandemic.
  – the lack of immunogens capable of inducing broadly neutralizing antibodies responses to prevent infection is the major limiting

• **Therapeutic vaccines**
  – elicit cellular immune responses to control viral load and delay progression to disease are possible to be obtained

*Klein M. Vaccine 2003;21:616-619*
Development of therapeutic vaccines

• HIV target cell
  – CD4+ lymphocyte

• Loss of function and numbers of CD4+ lymphocytes reduces the hosts immune capacity

• Central roles of antigen-specific CD4+ T-helper and CD8+ cytotoxic T lymphocytes (CTL) in the control of HIV viremia

Wahren B et al. NEJM 1986;315:393-394
Ogg GS et al. Science 1998;279:2103-2106
What is the role of dendritic cells in HIV infection?
Development of therapeutic vaccines

• Most prototypes of therapeutic vaccines were developed to treat certain types of cancer

• In the HIV/AIDS context
  – In adjunction to ART may reduce adverse side-effects
  – Allow structured treatment interruptions of ART
  – Limit the emergence of viral mutations
  – Promote the clearance of the virus and eliminate latent reservoirs (functional HIV cure)
Types of therapeutic vaccines

• whole inactivated vaccines
• recombinant proteins
• synthetic peptides or lipopeptides
• virus-like particles
• DNA vaccines
• live recombinant viral or bacterial-vectored vaccines
• dendritic cells loaded with inactivated virus or viral antigens
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In Vitro Human Immunodeficiency Virus Eradication by Autologous CD8+ T Cells Expanded with Inactivated-virus-pulsed Dendritic Cells

WEI LU AND JEAN-MARIE ANDRIEU
J Virol 2001;75:8949-56
Therapeutic dendritic-cell vaccine for chronic HIV-1 infection

Wei Lu, Luiz Claudio Arraes, Wylla Tatiana Ferreira, Jean-Marie Andrieu

HIV whole blood cultured
Therapeutic dendritic-cell vaccine for chronic HIV-1 infection

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Therapeutic Immunization with Dendritic Cells loaded with Heat-Inactivated Autologous HIV-1 in Patients with Chronic HIV-1 Infection

Felipe Garcia et al

- therapeutic vaccine with autologous monocyte-derived DCs loaded with heat-inactivated autologous HIV
- 12 patients with chronic HIV infection who were receiving ART
- 3 plasmapheresis were performed to obtain autologous virus to pulse DCs (PVL peak)
- Whole blood plasma monocytes were collected and culture
- Tolerance of vaccine was good
- There was a decrease in set-point PVL of $\geq 0.5 \log_{10}$ in 4 of 12 immunized patients (24 weeks)
- Responses were weak and transient
Fig. 3 Drop of pVL setpoint at weeks 12, 24, 36, and 48.

Felipe García et al., Sci Transl Med 2013;5:166ra2
Dendritic cell-based therapeutic vaccine elicits polyfunctional HIV-specific T-cell immunity associated with control of viral load

Yves Lévy\textsuperscript{1,2,3,4}, Rodolphe Thiébaut\textsuperscript{4,5,6,7}, Monica Montes\textsuperscript{4,8,9}, Christine Lacabaratz\textsuperscript{1,2,4}, Louis Sloan\textsuperscript{8,10}, Bryan King\textsuperscript{10}, Sophie Pérusse\textsuperscript{5,6}, Carson Harrod\textsuperscript{4,8,9}, Amanda Cobb\textsuperscript{8,9}, Lee K. Roberts\textsuperscript{8}, Mathieu Surenaud\textsuperscript{1,2,4}, Céline Boucherie\textsuperscript{5}, Sandra Zurawski\textsuperscript{4,8,9}, Constance Delaugerre\textsuperscript{11}, Laura Richert\textsuperscript{4,5,6,7}, Geneviève Chêne\textsuperscript{4,5,6}, Jacques Banchereau\textsuperscript{1,2,4,8,9,12} and Karolina Palucka\textsuperscript{4,8,9}

Efforts aimed at restoring robust immune responses limiting human immunodeficiency virus (HIV)-1 replication therapeutically are warranted. We report that vaccination with dendritic cells generated ex vivo and loaded with HIV lipopeptides in patients ($n = 19$) on antiretroviral therapy was well tolerated and immunogenic. Vaccination increased: (i) the breadth of the immune response from 1 (1–3) to 4 (2–5) peptide-pool responses/patient ($p = 0.009$); (ii) the frequency of functional T cells (producing at least two cytokines among IFN-\(\gamma\), TNF-\(\alpha\), and IL-2) from 0.026 to 0.32\% ($p = 0.002$) and from 0.26 to 0.35\% ($p = 0.005$) for CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells, respectively; and (iii) the breadth of cytokines secreted by PBMCs upon antigen exposure, including IL-2, IFN-\(\gamma\), IL-21, IL-17, and IL-13. Fifty percent of patients experienced a maximum of viral load (VL) $1 \log_{10}$ lower than the other half following antiretroviral treatment interruption. An inverse correlation was found between the maximum of VL and the frequency of polyfunctional CD4\textsuperscript{+} T cells ($p = 0.007$), production of IL-2 ($p = 0.006$), IFN-\(\gamma\) ($p = 0.01$), IL-21 ($p = 0.006$), and IL-13 ($p = 0.001$). These results suggest an association between vaccine responses and a better control of viral replication. These findings will help in the development of strategies for a functional cure for HIV infection.
Phase II study of a therapeutic autologous dendritic cell vaccine pulsed with inactivated HIV in patients with HIV-1 infection
Recruitment & Endpoints

• Recruitment
  • 25 chronic infected HIV-1 patients
    – Group 1: $3 \times 10^7$ DCs (n=5)
    – Group 2: $3 \times 10^6$ DCs+HIV (n=10)
    – Group 3: $3 \times 10^7$ DCs+HIV (n=10)
  • ≥18 years-old
  • Untreated HIV+
  • CD4+ ≥350 cels/µl
  • PVL ≥ 5,000 copies/mL

• Endpoints
  – Tolerance and safety
  – PVL & CD4+ 12 months after vaccination
Therapeutic vaccine

3 doses (0, 15, 30 days)
Morphological profile of monocytes, differentiated into immature and mature DCs (100x)

1. Monocyte
2. Immature DCs
3. Mature DCs (vaccinal product)
Vaccine production
Biosafety level 3 lab
Leukapheresis: demographics and hematologic parameters

• 45 volunteers
• 27 included
• 34 collections
• Gender
  – 22 men (81.5%)
  – 5 women (18.5%)
• Age (mean=32y)
  – Range 22-48y
• TBV (mean=4785mL)
  – Range 3743-5767mL

• Hemoglobin (median)
  – Before: 14.2 g/dL
  – After: 12.8 g/dl (9.8%)

• WBC (median)
  – Before: 5531/mm³
  – After: 4576/mm³ (17.2%)

• Platelets (median)
  – Before: 195X10³/mm³
  – After: 139X10³/mm³ (28.7%)
Leukapheresis: run & collection

- Terumo® Spectra - MNC
- Processed volume (median) = 7.638 mL
- Processed TBV (median) = 1.61
  - Range 1.06-2.75
- Time (median)=129 minutes
- Flow = 50-70 mL/min
- Collection volume (median)=126mL
  - Range 23-222mL
- MNC collected (median)=1.1x10^{10} cells
  - Range: 1-1.6X10^{10} MNC cells
- Adverse events
  - 8 (23.5%) perioral paresthesia
  - 1 (2.9%) nausea & vomiting
  - 2 (5.9%) lost access
Monocytes viability after collection

<table>
<thead>
<tr>
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<th>% viable monocytes (CD14+Dioc6+)</th>
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<tbody>
<tr>
<td>Whole blood</td>
<td>90</td>
</tr>
<tr>
<td>≥2 TBV</td>
<td>50</td>
</tr>
<tr>
<td>1.5 TBV</td>
<td>80</td>
</tr>
</tbody>
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T lymphocytes activation (CD3+ and CD38+)

- Whole blood
- ≥2 TBV
- 1.5 TBV
P57/26

CD14 | HLADR | CD1a | CD80 | CD86 | CD83 | CD40
--- | --- | --- | --- | --- | --- | ---
[10] | [90] | [10] | [20] | [30] | [5] | [2]

P40/12

CD14 | HLADR | CD1a | CD80 | CD86 | CD83 | CD40
--- | --- | --- | --- | --- | --- | ---
[10] | [80] | [10] | [40] | [60] | [5] | [20]
### Vaccinal product

<table>
<thead>
<tr>
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<th>Participant 40/12</th>
<th>Participant 57/26</th>
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<tbody>
<tr>
<td>Mature DCs in the final product*</td>
<td>5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Viability**</td>
<td>&gt;70%</td>
<td>40%</td>
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</tbody>
</table>

% of Mature DCs from the total of PBMNC collected
** Minimum viability >70%
Results - DC $3 \times 10^7$

Overall good tolerance and minor adverse events related to vaccine application
Results - DC $3 \times 10^6$+HIV
Results – DC 3X10⁷+HIV
Conclusions

• Dendritic cell vaccines pulsed with autologous HIV were safe and well tolerated.
• No immunological response
• Virological responses were modest with better results when a higher number of DCs were inoculated.
• Leukapheresis was essential:
  – to collect the amount of viable PBMC to produce the vaccine
  – to culture autologous HIV
  – to reduce participants visits
  – to save time (collections, cultures)
• Knowledge acquired can be used to research the role of therapeutic vaccines in other infections, as HCV or HBV, for instance.
• Elucidation of basics aspects of production and applications of this vaccine are needed before a Phase III clinical trial.
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doe sangue
E Passe a bola para um amigo

PRO SANGUE
HEMOCENTRO DE SÃO PAULO