Vaccines that target dendritic cells: Lessons learned

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Dendritic cell in dermal sheet (collagen fibers; skin explant); courtesy of Patti Stoitzner, Kristian Pfaller, Nikolaus Romani
Zanvil A. Cohn and Ralph M. Steinman
As a academic/scientific group we were used to paying attention to ideas, concepts and scientific data. In human clinical vaccine development we began from this starting point but, learned several life lessons.
Randomized, double-blinded, placebo-controlled phase I study to evaluate the safety and immunogenicity of anti-DEC205-HIV gag p24 (clade B) fusion monoclonal antibody protein vaccine plus poly ICLC in healthy volunteers

• HIV-1 gag p24 (clade B – BH10)
Differences Between Most Conventional Vaccines and Directly Targeted vaccines

1. Our 1st Target is DEC-205/CD205, one of many “pattern recognition receptors” on DCs
2. DEC-205/CD205, expressed by most DCs in human lymphoid tissues
3. Anti-DEC-205 s.c. quickly (minutes) targets to most DCs in lymph node
Decisions in Planning the Clinical Trial

• DEC-205 Targeting Monoclonal = 3G9
• HIV-1 Antigen = gag p24 BH10 clade B
  • Adjuvant = poly ICLC Hiltonol®
• Dose Escalation = 0.3 mg, 1.0 mg, 3.0 mg
  • Dose of Adjuvant = 1.6 mg
  • Route = subcutaneous
• Schedule = 0, 4 and 12 weeks
Clinical Development of DC-Vax

- 1995: Identification of DEC-205 receptor
- 1999: Anti-mDEC-205 fusion mAb
- 2001: Anti-human DEC-205 mAb (MG38)
- 2003: Anti-hu DEC-205-p24 mab construction
- 2005: Pre-clinical Testing
  - Funding from Gates- GCGH

- 2008: IND filed with US FDA
- Q1/2009: IRB Approval
- Q2/2009: GMP product
- Q4/2009: Phase-I proof of concept begins

Key Steps:
- Choice of mAb clone
- Choice of adjuvant
- Pre-IND meeting with FDA – discussion of trial design and safety animal studies
Challenges:
The Devil is in the details

• Manufacturing
• Adjuvant Selection
• Regulatory Issues
• Operational Issues (Processing, Archiving, Shipping)
• Funding/Path Forward
Human α-human DEC205 (clone 3G9) HIV gag Antibodies: Analysis by FPLC

Blue: 3G9
Red: 3G9 gag p24
Green: 3G9 gag p41

Buffer Peak for 3G9 gag p41

3G9 gag p41 forms multimers
3G9 gag p41 is degraded
Which human α-human DEC205 HIV gag antibody should we use in our human trial?

- 3G9 gag p41:
  Antibody produces in low yield, is partially degraded and forms multimers

- 3G9 gag p24:
  Antibody produces in higher yield, is not degraded and doesn’t multimerize

3G9 gag p24 BH10 (clade B) is the selected vaccine for human trial
Poly IC and Poly ICLC* are Superior Adjuvants for CD4+ T Cell Immunity to DEC-Targeted HIV gag p24

% CD4+ IFNγ+ T cells

Poly IC and Poly ICLC* are Superior Adjuvants for CD4+ T Cell Immunity to DEC-Targeted HIV gag p24

Poly IC and Poly ICLC* are Superior Adjuvants for CD4+ T Cell Immunity to DEC-Targeted HIV gag p24

Which synthetic double stranded RNAs should we use as the adjuvant in our human trial?

- Poly IC from ‘Invivogen’
  not available for clinical use

- Poly ICLC ‘2001’ from Oncovir
  not available for clinical use

- Poly ICLC ‘2004’ from Oncovir
  available for clinical use

- poly ICLC ‘2004’ is selected adjuvant for human trial
The Rockefeller University Hospital,
Clinical Scholars Program for Research in Patients,
Support from a CTSA, the Gates Foundation, and NIAID
Timeline

• April 2009 – Pre-IND meeting
• September 2009 – DC-Vax-001 manufactured and vialled
• December 2009 – Main toxicology NHP study completed
• January 2010 – First submission to the Rockefeller University’s IRB
• April 2010 - Submission of IND to FDA and RU IRB approval
• May 2010 - FDA agreement to proceed with clinical trial
• June 2010 – Screening / Enrollment of low dose cohort
• July 12th 2010 - Vaccination of first subject
## Study Design

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Regimen</th>
<th>Route</th>
<th>Dose DEC mAb</th>
<th>Dose pICLC</th>
<th>Subjects</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>DEC-gag p24 + pICLC</td>
<td>sc</td>
<td>300 µg</td>
<td>1.6 mg</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>pICLC</td>
<td>sc</td>
<td>-</td>
<td>1.6 mg</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sterile saline</td>
<td>sc</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>DEC-gag p24 + pICLC</td>
<td>sc</td>
<td>1 mg</td>
<td>1.6 mg</td>
<td>9</td>
</tr>
<tr>
<td></td>
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<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>DEC-gag 24 + pICLC</td>
<td>sc</td>
<td>3 mg</td>
<td>1.6 mg</td>
<td>9</td>
</tr>
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<td>3</td>
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</tbody>
</table>

### Boosting Vaccination
- Week 64

### Priming Vaccination
- Week 0

### Study Conclusion
- Week 64
DEC-205 trial - Immunomonitoring

Week 0
Priming Vaccination

Week 4
Boosting Vaccination

Week 12
Boosting Vaccination

12 month Follow up

Week 64
Study Conclusion

Baseline Immunomonitoring

Day 1
Day 2
Day 7

4 weeks

Day 1
Day 2
Day 7

4 weeks

late timepoints 24, 36, 48, 60 weeks
What about immunization of rhesus macaques with the proof of concept clinical product, 3G9-gag p24 plus Hiltonol/poly ICLC?

Collaboration with Barbara Flynn and Bob Seder at the VRC
### NHP Immunogenicity Study: DEC Targeted vs. Non-Targeted HIV gag p24 + poly ICLC

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccines</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>$\alpha$-Dec Gag p24 + Poly ICLC</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Gag p24 + Poly ICLC</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Gag p24 Protein alone</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>$\alpha$-Dec Gag p24 alone</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Empty $\alpha$-Dec + Poly ICLC</td>
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</table>

200 $\mu$g DEC-Gag and 60 $\mu$g Gag were given s.c +/- 1 mg poly ICLC.
Magnitude: Both Protein Vaccines Plus Poly ICLC Generate Strong CD4⁺ T Cell Responses But DEC Gag Plus Poly ICLC Is More Effective in Generating CD8⁺ T Cell Immunity

CD4⁺ T cell cytokine response %

CD8⁺ T cell cytokine response %

8 wks after priming
2 weeks post first boost
12 weeks post first boost
2 weeks post second boost
6 weeks post second boost
Anti-Gag Antibody Responses Are Strong to Both DEC Gag and GAG Vaccine but Require Adjuvant
### NHP Immunogenicity Study: NYVAC-Gag Boost of DEC Targeted vs. Non-Targeted HIV gag p24 + poly ICLC

<table>
<thead>
<tr>
<th>Group</th>
<th>Protein Immunization</th>
<th>Boost</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\alpha$-Dec Gag p24 + Poly ICLC</td>
<td>NYVAC</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Gag p24 + Poly ICLC</td>
<td>NYVAC</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Gag p24 Protein alone</td>
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<td>3</td>
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<tr>
<td>4</td>
<td>$\alpha$-Dec Gag p24 alone</td>
<td>NYVAC</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Empty $\alpha$-Dec + Poly ICLC</td>
<td>NYVAC</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>PBS</td>
<td>NYVAC</td>
<td>4</td>
</tr>
</tbody>
</table>

Protein #1 Protein #2 Protein #3 Boost NYVAC-Gag

Week 0 8 27 58

5 X 10^8 particles of NYVAC-Gag were given once s.c per animal
A Single Dose of NYVAC-gag Resulted in a Large Boost of CD8⁺ T Cell Immunity in NHP Primed to Either DEC-targeted Gag or Non-targeted Gag Protein + Poly ICLC
Pox Vector Boost – Study Design

**Ongoing DEC-p24 plus poly ICLC trial**

- **Protein vaccine prime**
  - wk 0: DCVax-001 (0.3 mg) Poly ICLC
  - wk 4: DCVax-001 (0.3 mg) Poly ICLC
  - wk 12: DCVax-001 (0.3 mg) Poly ICLC
  - n=9

- **Viral vector boost**
  - wk 0: Poxvirus Vector-based HIV vaccine
  - wk 4: Poxvirus Vector-based HIV vaccine
  - 36 – 48 wks
  - n=3

- **Sterile Saline**
  - wk 0: Poxvirus Vector-based HIV vaccine
  - wk 4: Poxvirus Vector-based HIV vaccine
  - 36 – 48 wks
  - n=3

- **Study conclusion**
  - Wk 28 after vector boost

Follow up 24 weeks
Lessons Learned

The Devil is in the details: Pay close attention at the start

Pick very good partners: We ended with very good partners with Complimentary Expertise (Celldex, Oncovir) but, we were very fortunate

We have to do the experiment
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