Reinvigorating Exhausted T Cells with PD-1 Blockade
CD8 T Cell Differentiation during Acute vs. Chronic Viral Infection

Zajac et al. JEM 1998
CD8 T Cell Dysfunction during Chronic Viral Infection

Zajac et al., JEM 1998
Wherry et al., J. Virol. 2003
Role of PD-1 in CD8 T cell exhaustion

The PD-1 Pathway

Antigen-presenting cell

MHC

TCR/CD3

B7

CD28

PD-L

PD-1

Inhibition of antigen receptor signaling

PI3K → Akt

CD28 → Bcl-xL, IL-2, IFN-γ


PD-1 in Human Chronic Viral Infections

- HIV
- HCV
- HBV
PD-1 in Non-Human Primate Models for HIV and HCV

• **SIV/Monkey** - Rama Amara (Emory)
  
  

• **HCV/Chimpanzee** - Chris Walker (Ohio)
## Chimpanzees used for anti-PD-1 therapy

<table>
<thead>
<tr>
<th>Chimp</th>
<th>Duration of HCV infection</th>
<th>Viral Titer</th>
<th>T cell responses Blood</th>
<th>T cell responses Liver</th>
<th>Breadth of T cell responses</th>
<th>Efficacy of PD-1 blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ch1535</td>
<td>12 years</td>
<td>~10^6</td>
<td>–</td>
<td>–/+</td>
<td>Narrow</td>
<td>NO</td>
</tr>
<tr>
<td>Ch5276</td>
<td>2 years</td>
<td>~5 x 10^4</td>
<td>–/+</td>
<td>–/+</td>
<td>Narrow</td>
<td>NO</td>
</tr>
<tr>
<td>Ch5300</td>
<td>2 years</td>
<td>~2 x 10^4</td>
<td>++</td>
<td>++</td>
<td>Broad</td>
<td>YES</td>
</tr>
</tbody>
</table>
PD-1 Inhibitory Pathway: A General Mechanism for Regulating T Cell Function during Chronic Virus Infection (Mouse, Monkey, Man)
Tumor Immunotherapy Directed at PD-1
Antoni Ribas, M.D., Ph.D.

Combination Therapy with PD-1 Blockade:

- Therapeutic vaccination
- Antiviral / Cancer drugs
- Blockade of other inhibitory receptors and molecules
  - CTLA-4, LAG-3, Tim-3, 2B4
- Cytokines
Can PD-1 Blockade Synergize with Therapeutic Vaccination to Treat Chronic Infection?
Therapeutic Vaccination of Chronically Infected Mice Combined with PD-L1 Blockade

Infection with LCMV CL-13

28 days

Therapeutic Vaccination

Gr1: VV/WT
Gr2: VV/GP33
Gr3: VV/WT + αPD-L1 Ab
Gr4: VV/GP33 + αPD-L1 Ab

CD8 T cell response
Virus titer in serum
T Cell Response

- **D\textsubscript{b}GP33-41**
  - VV/WT
  - VV/GP33
  - VV/WT + αPD-L1
  - VV/GP33 + αPD-L1

- **D\textsubscript{b}GP276-286**
  - VV/WT
  - VV/GP33
  - VV/WT + αPD-L1
  - VV/GP33 + αPD-L1

Antigen-specific CD8\textsuperscript{+} T cells \(/10^6\) PBMC

Days post-infection

- VV/WT
- VV/GP33
- VV/WT + αPD-L1
- VV/GP33 + αPD-L1
Improved Antigen Presentation after Therapeutic Vaccination of Chronically Infected Mice

Infection with LCMV CL-13 → Vaccination with VV/WT or VV/GP33 → Isolation of splenic DCs → Culture of DCs with CFSE-labeled P14 CD8+ T cells

CD11c+ source

<table>
<thead>
<tr>
<th></th>
<th>VV/WT</th>
<th>VV/GP33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counts</td>
<td>31.5</td>
<td>52.3</td>
</tr>
</tbody>
</table>

CFSE
### Synergistic Effect of Therapeutic Vaccination Combined with PD-1/PD-L1 Blockade during Chronic Infection

<table>
<thead>
<tr>
<th></th>
<th>T cells</th>
<th>Antigen Presentation</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>Exhausted</td>
<td>Suboptimal</td>
<td>±</td>
</tr>
<tr>
<td>Therapeutic vaccines</td>
<td>Exhausted</td>
<td>Improved</td>
<td>+ ±</td>
</tr>
<tr>
<td>PD-1/PD-L1 blockade</td>
<td>More functional</td>
<td>Suboptimal</td>
<td>+++</td>
</tr>
<tr>
<td>Therapeutic vaccines + PD-1/PD-L1 blockade</td>
<td>More functional</td>
<td>Improved</td>
<td>++++++</td>
</tr>
</tbody>
</table>

PD-L1 Blockade + Therapeutic Vaccination

Potential for Synergistic Effects

- Chronic Infections
- Tumors
Combination Therapy with PD-1 Blockade:

- Therapeutic vaccination
- Antiviral / Cancer drugs
- Blockade of other inhibitory receptors and molecules
  - CTLA-4, LAG-3, **Tim-3**, **2B4**
- Cytokines
Cooperation of Tim-3 and PD-1 in CD8 T-cell exhaustion during chronic viral infection

Jin et al. Proc Natl Acad Sci USA. 2010;107(33)
Tight Regulation of Memory CD8⁺ T Cells Limits Their Effectiveness during Sustained High Viral Load

West et al. Immunity. 2011;35(2)
Combination Therapy with PD-1 Blockade:

- Therapeutic vaccination
- Antiviral / Cancer drugs
- Blockade of other inhibitory receptors and molecules
  - CTLA-4, LAG-3, Tim-3, 2B4
- Cytokines
  - IL-7, IL-15, IL-2
IL-2 therapy synergizes with PD-1 blockade to rescue exhausted CD8 T cells during chronic infection

**Pre-treatment**

<table>
<thead>
<tr>
<th>PBMC</th>
<th>PBS</th>
<th>IL-2</th>
<th>αPD-L1</th>
<th>IL-2 + αPD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**Day 8**

| D^bGP276-286 | 0.2 | 0.8 | 2.8 | 11.8 |

**Day 14**

| 0.1 | 1.3 | 3.9 | 30.3 |

αPDL1: 200μg every 3 days for 5 total treatments

IL-2: 15,000 IU twice daily

Gated on CD8^+ cells
<table>
<thead>
<tr>
<th>Tissues</th>
<th>PBS</th>
<th>IL-2</th>
<th>αPD-L1</th>
<th>IL-2 + αPD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>1.1</td>
<td>4.0</td>
<td>5.7</td>
<td>23.6</td>
</tr>
<tr>
<td>Lung</td>
<td>0.8</td>
<td>6.3</td>
<td>15.0</td>
<td>25.8</td>
</tr>
<tr>
<td>D(^b) GP33-41</td>
<td>4.1</td>
<td>6.8</td>
<td>10.8</td>
<td>28.2</td>
</tr>
<tr>
<td>Liver</td>
<td>1.5</td>
<td>3.4</td>
<td>7.4</td>
<td>16.8</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gated on CD8\(^+\) cells
Selective expression of the interleukin 7 receptor identifies effector CD8 T cells that give rise to long-lived memory cells

Susan M Kaech¹, Joyce T Tan², E John Wherry¹, Bogumila T Konieczny¹, Charles D Surh² & Rafi Ahmed¹

Antigen-independent memory CD8 T cells do not develop during chronic viral infection

E. John Wherry*, Daniel L. Barber, Susan M. Kaech¹, Joseph N. Blattman‡, and Rafi Ahmed*

Emory Vaccine Center and Department of Microbiology and Immunology, Emory University School of Medicine, 1510 Clifton Road, Room G211, Atlanta, GA 30322
Increased expression of CD127 (IL-7Rα) on exhausted CD8 T cells after IL-2 treatment or combination therapy.
Decreased viral load following treatment

West et al. JCI, in press (2013)
CD8 T Cell Differentiation during Acute vs. Chronic Viral Infection

- **Viral Infection (Acute Phase):**
  - Naive CD8 T Cell
  - Rapid Proliferation/Differentiation

- **Acute Infection (Antigen Cleared):**
  - Effector CD8 T Cell

- **Chronic Infection (Antigen Persists):**
  - Exhaustion

- **Functional Memory:**

- **Immune Strategies**
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