Targeting PD-1 Co-Inhibitory Pathway for Functional Cure of HIV/AIDS

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COI Statement

I am a co-inventor of PD-1 technology that has been licensed to Genentech by the Emory University
High Levels of PD-1 Expression on Anti-viral CD8 T cells During Chronic Infections Regulates T Cell Exhaustion

Chronic LCMV infection
Barber et al (Nature 2006)

High PD-1 on T cells
In vivo PD-1 Blockade
↑ T cell proliferation & function
↓ Viral replication

Chronic HIV infection
Day et al (Nature 2006)
Trautman et al (Nat Med 2006)

High PD-1 on T cells
In vitro PD-1 Blockade
↑ T cell proliferation & function

Chronic SIV infection
Velu et al (Nature 2009)

High PD-1 on T cells
In vivo PD-1 Blockade
↑ T cell proliferation & function
↓ Viral replication
PD-1+ CD4 T Cells Contribute to The Pool of Viral Reservoirs in HIV+ ART Treated Patients

HIV-infected humans

SIV-infected macaques

More recently in LNs by Banga, Perreau, Nat Med 2016
Targeting PD-1 Pathway for Functional Cure

(Current Model)

- Exhausted CD8 T cells
  - PD-1 blockade
  - Functional CD8 T cells

- Latent/Viral reservoirs
  - PD-1 blockade
  - Reactivation of Latent virus
  - Killing
  - Productively infected cells

- Activated B cells
  - PD-1 blockade
  - Enhanced Antibody Production

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Study Design
PD-1 Blockade Combined with ART

**Phase I**

- SIVmac251
- Time-point blockade Initiated:
  - αPD-1 Ab, 3mg/kg
  - 0 3 7 10 14 Days Post Blockade

- 24-30 weeks
- ART Suppression
- Saline

**Phase II**

- αPD-1 Ab, 10mg/kg

- Double αPD-1 Treated
  - N = 10

- 4 wks 4 wks 2 wks

- Single αPD-1 Treated
  - N = 5

- Saline

- Saline

- Saline

- Treatment Interruption (24 Weeks)

*Anti-PD-1 antibody, IgG4, intravenous administration*
Effects on CD4 and CD8 T cells
PD-1 Blockade induces Proliferation of $T_{CM}$ CD4 T cells and CD8 T cells

**Ki-67+ CD4 $T_{CM}$**

**Ki-67+ CD8**

* Shows mean values

Days Post Anti-retroviral Treatment

Days Post Anti-retroviral Treatment

PD-1 Treated PI and PII
PD-1 Treated PII
Saline Treated
Increase in Proliferation and Function of GagCM9+ CD8 T cells during Phase I

**No difference in the magnitude of GagCM9+ CD8 T cells**
Increased polyfunctionality of SIV specific CD8 T cells in PD-1 Treated Macaques during Phase I

Stimulated with 1ug/mL of Gag, Env1, and Env2
Cumulative SIV specific response

Increase observed in IFN-γ+ SIV specific CD8 T cells as well

** p < 0.01
Enhanced Th17 Frequencies in the Gut of PD-1 Treated ART suppressed RM

Stimulated with PMA/ ionomycin (40ng/1ug; per mL)

Observed Increased Th17 Frequencies in the Blood for both Treatment Groups at Wk24 Post ART
Lower Density of Neutrophils in the Rectum of Double PD-1 Group

34 weeks post ART
Day of interruption

Jake Estes
Effects on Viremia
Enhanced Kinetics of Viral Suppression with PD-1 blockade and ART (Phase I)

αPD-1 Treated Phase I

Saline Treated Phase I

Plasma SIV RNA (Log_{10} copies/mL)

Days Post ART

Days Post ART
Enhanced Kinetics of Viral Suppression with PD-1 blockade and ART (Phase I)

**Graphs:**
- **Left Graph:**
  - X-axis: Days Post ART
  - Y-axis: Log_{10} copies/mL of Plasma SIV RNA
  - Anti-retroviral Treatment shaded
  - Data points indicate a decline in viral load over time, with * indicating statistical significance from a Mann-Whitney Test.

- **Right Graph:**
  - X-axis: Days to Viral Suppression
  - Y-axis: Percent Viremic
  - Two curves: αPD-1 and Control
  - Log Rank Mantel Cox Test, P = 0.01
Transient Increases in Plasma Viremia Following PD-1 Blockade Under ART

**αPD-1 Treated Phase I and II**

- Anti-retroviral treatment
- 10 mg/kg αPD-1

**Saline Treated Phase I and II**

- Anti-retroviral treatment
- Saline

<table>
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<tr>
<th>RM</th>
<th>Transient and Detectable Plasma Viremia during PD-1 Blockade under ART</th>
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<tr>
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<td>Weeks Post αPD-1 Blockade</td>
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<tr>
<td>RFF14</td>
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- Limit of Detection 60 copies/mL of plasma
Live Imaging for SIV Env at 2 weeks after the 3rd PD-1 infusion under ART

- Single PD-1 <60
- Single PD-1 <60
- Double PD-1 585 copies
- ART Only <60

Francois Villinger
Phil Santangelo
GSEA of PD-1 treated group under ART D7 vs D0 of First PD-1 Ab Infusion

ISG Enrichment

NFAT_3PATHWAY Enrichment
Viral Set-points Post Treatment Interruption (Wk 8)

Pre ART vs Post ART Interruption

Fold Change in Set-point Post Blockade

Unpaired t-test
With Welch’s correction
Conclusions

• PD-1 blockade with the Initiation of ART (Phase I)
  – Induced proliferation of central memory CD4 T cells and total and SIV specific CD8 T cells
  – Enhanced the polyfunctionality of SIV specific CD8 T cells
  – Synergized with ART resulting in more rapid viral suppression
  – Enhanced Th17 frequencies in the rectal mucosa during ART

• PD-1 blockade administered during suppressive ART (Phase II)
  – Induced proliferation of CD4 and CD8 T cells
  – Induced transient increases in plasma viremia
  – lower set-point VL in anti-PD-1 treated RM

• PD-1 blockade in tandem with other therapeutic interventions and latency reversing drugs may provide additional benefit
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