The potential role of PD-1/PD-L1 blockade in HIV Remission and Cure Strategies

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Definitions and Quantifications of HIV cure

- **Viral Eradication**: Extremely difficult to achieve
- **Virologic Remission**: More feasible?

**Elimination of all virus from the body**

- Host control of viral replication without continued treatment
- Immune function restored and stabilized
- Reduction of HIV-induced inflammation
- Reduced risk of transmission to others

**Ultimate goal**

Life-long or completely drug-free remission

... how do we get there?


HIV remission likely will require combination of agents targeting different barriers to eradication
Which combinations … ?

Immunomodulators
Enhance innate and adaptive immunity

Therapeutic Vaccine
Enhance antigen recognition

Latency Activator
Activate & reduce the latent reservoir

Broadly Neutralizing Antibodies
Recognize and reduce the latent reservoir

HIV Remission
Which combinations … ?

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**HIV Remission**
**PD-1/PD-L1 pathway in T cell exhaustion**

- **Virus-specific T-cells are critical to control of chronic viral infections**\(^1,2,3,4,5\)
- **PD-1 is a key inhibitory receptor affecting T-cell response**\(^6\)
  - Elevated on virus-specific T-cells in chronic HIV\(^3,7\), HBV\(^8\) and HCV\(^9\) infection
    - Both CD4+ and CD8+ subsets
    - Cells display exhausted phenotype *ex vivo / in vitro*
    - Decreases with epitope escape mutation\(^7,10\) or control of infection\(^3,4,7\)
- **PD-1/PD-L1 blockade restores function to exhausted T cells**
  - Significant effects on T-cell function and viral load observed upon PD-1/PD-L1 blockade both *in vitro*\(^3,4,11,12\) and *in vivo*\(^5,6,13\)

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PD-1 blockade in unsuppressed SIV-infected macaques

Treatment with $\alpha_{\text{PD-1}}$:
- Transiently affected viremia
- Restored T and B cell numbers & functions
- Prolonged survival

PD-1 pathway blockade during suppressive cART?
- Most relevant situation for HIV-infected patients
PD-L1 blockade in ARV suppressed SIVmac251-infected Rhesus Macaques

Hypothesis:
- Treatment of ARV-suppressed SIV infected macaques with αPD-L1 should:
  - restore SIV-specific T cell function. Subsequently, this may:
    - reduce the latent SIV reservoir
    - lead to host control of virus following interruption of ARV

Study design:
- SIV Infection
- Start ARV
- PD-L1 blockade
- ARV TI
- 2 weeks
- 6 weeks
- Viral load rebound off ARV

BMS-936559 (8)
Isotype control (5)
5 X 10mg/kg

Objectives:
- Determine whether multiple doses of BMS-936559 affect:
  1. Cell-associated viral DNA (latent reservoir) in tissues and periphery,
  2. Virus recrudescence after cessation of ARV treatment.

In collaboration with James Whitney (BIDMC, Boston)
Individual post-TI VL rebound kinetics:

Comparison of BMS-936559- and Isotype-treatment groups

- All animals experienced rebound in viral load post-TI
- Most viral loads stabilized at an apparent a new set-point
BMS-936559 treatment group could be separated into two distinct groups: BMS-936559-responders and -non-responders.
Individual post-TI VL rebound kinetics:  
*BMS-936559 Treatment-response group*

- BMS-936559-responders: 4 out of 8 BMS-936559-treated animals had lower viral loads
- 3 had episodic periods of undetectable VL
Individual data on kinetics of post-TI VL rebound: *BMS-936559 Treatment-response group (2)*

- 2 of 4 treatment responders had undetectable VL for 3-4 weeks.
- These treatment responders remained below 1000 RNA cp/mL until the end of the study (day 170 post-TI).
• Most animals in the BMS-936559-treatment group had significantly lower post-TI VL compared to pre-ART VL set point

†M817 died due to AIDS-related thrombus on day 46 post-ARV

* Mamu*A01
Comparison of pre-ART and post-TI VL

- Most animals in the BMS-936559-treatment group had significantly lower post-TI VL compared to pre-ART VL set point

†M817 died due to AIDS-related thrombus on day 46 post-ARV
* Mamu*A01
• SIV DNA in isotype group increased post-TI, but not in the BMS-936559 treatment responders
Effect of Anti-PD-L1 in SIV-infected Monkeys

SIV Infection → Start ARV → PD-L1 blockade → ARV TI

5 x 10 mg/kg → BMS-936559 (8) Isotype control (5)

Viral load rebound off ARV

How can anti-PD-L1 post-ATI responses be expanded and sustained?
Combinations of modalities likely will be required to Achieve Remission...

- **Immunomodulators**
  - Enhance innate and adaptive immunity
  - ? Anti-PD-L1

- **Latency Activator**
  - Activate & reduce the latent reservoir

- **Therapeutic Vaccine**
  - Enhance antigen recognition

- **Broadly Neutralizing Antibodies**
  - Recognize and reduce the latent reservoir

...which ones?
Fully Addressing T Cell Exhaustion

T cell Exhaustion:
- Progressive loss of function
- Accompanied by expression of multiple inhibitory receptors

Are multiple Checkpoint blockades required to fully restore T cell function?

Wherry Nat Imm 2011
Evidence that combination of αPD-L1 & Therapeutic Vaccination can clear chronic viral infections

LCMV mouse model of chronic viral infection

Combination therapy provided:
- Better virologic control both in periphery and tissues
- Correlated with improved LCMV-specific T cell number/function
- Produced a response in a greater number of animals
Can additional agents add to the arsenal?

BnAb therapeutic effect in viremic SHIV-infected monkeys

- Particularly effective in those animals with low baseline VL

Combination of BnAb with latency activators produced sustained effect in HIV/Hu Mouse model

Stromberg et. Al., Cell 2014

Barouch et al., Nature 2013
Effect of a strong Latency Re-activating Agent on VL

→ Screening and characterizing new compounds as LRAs

Sogaard et al Melbourne, July 20. 2014
Model for effect of anti-PD-L1 in SIV study

Treatment with αPD-L1

Exhausted T-cell

Restore SIV-antigen specific T cell activity

Functional SIV-specific T cell

CTL function

Latently infected cells

Low level spontaneous viremia from latent SIV

Control or Partial reduction of infected cells

Incomplete response
BMS Strategy for HIV-1 Functional Cure: Dual Approach

Treatment with αPD-L1

Exhausted T-cell

Restore HIV-antigen specific T cell activity

Functional HIV-specific T cell

Latently infected cells

Higher level expression of HIV antigens

CTL function

Reduction of latently infected cells

Potentially broader responses

Induced re-activation of latent HIV-1

HIV-1 Remission?
Complete HIV remission must surpass EC-state:
- better virologic suppression
- lower inflammatory state

Can these states be approximated therapeutically as intermediate steps toward complete remission?
- Is there medical benefit to “Controller-like states” to make such intermediate goals worthwhile?
If Complete HIV remission is our goal...

...it likely will require:

- Combinations of modalities
- Intermediate goals to find the right combinations along the way to complete remission

Is there an intermediate state that would provide value to patients?

- What could that intermediate state look like?
  - Low level yet detectable viremic state?
  - Shorter periods of drug-free suppression?
  - Requiring re-dosing of agents?
  - How to reduce inflammation?
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