Dual approach to HIV-1 cure: Activation of latency and restoration of exhausted virus-specific T cell function

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Sterilizing or Functional Cure for HIV-1?

Sterilizing cure: complete elimination of all latent HIV-1

- Extremely high bar to attain

Functional cure: control of viremia in the absence of cART

- Ideally obtained through finite therapy

Is a broadly applicable functional cure for HIV-1 a realistic goal? If so, how do we get there?
Achieving Functional Cure:
Need to address two primary barriers

Current cART
Latently infected cell → Re-activation from latency

Reduce latent HIV reservoir

Exhausted T cell → Reinvigorated T cell

Restore immune function

Functional CURE?
Addressing the first barrier to functional cure: *HIV-1 latency*

**BMS approach:**

- Obtain novel small molecule activators of latent virus
  \[\Rightarrow\] Develop assays appropriate for HTS screening

- **Characteristics of optimal compounds:**
  
  - Able to activate in all/multiple HIV latency models
    » from a high proportion of latently infected cells
  
  - Alone or in combination with other agents (e.g. HDACi's)
  
  - Do not cause global T cell activation
  
  - Active latent virus from HIV-infected patients
    » from multiple patient isolates
Development of HIV Latency Assays

1. Transfect reporter virus and packaging plasmids
2. Produce pseudoviral particles
3. Transduce target cells
4. Establish latency (GFP\(^{-}\) resting CD4\(^{+}\))
5. Dual LTR-reporter construct
6. GFP and Luciferase reporters
7. Read-out to establish latency & monitor reactivation
8. Both T cell lines & 1\(^{0}\) CD4\(^{+}\) T cells
9. HTS

B. Rose, C. Mazzucco, A. Walsh, D. Tenney
Activity of Benchmark Compounds

Latent Jurkat Cells

Latent Primary Cells

HIV-infected Patient Cells

♦ PKC agonist/HDACi synergy seen in all three HIV latency models
♦ Recapitulates observations from the literature (Reuse 2009 PLoS One)
♦ Synergy arm added to BMS sub-deck screen

B. Rose, C. Mazzucco, A. Walsh, H. Qi, M. Lee, A. Sheaffer, D. Tenney
BMS approach to latency:
*Screening for activation of latent HIV*

**Multiple Assays for HTS: maximizing chance of success**

- **Compound sub-deck**
  - **Latent reporter assays**
    - Jurkat cell line
    - HDACi synergy in primary CD4+ T cells
    - Primary CD4+ T cells

*Parallel screening approach will enable detection of multiple modes of latent HIV activators*
Achieving Functional Cure:
Need to address two primary barriers

Current cART

Reduce latent HIV reservoir

Restore immune function

Functional CURE?
Addressing the second barrier to functional cure

*T cell exhaustion*

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

*Wherry Nat Imm 2011*

**PD-1 pathway is a key target**
**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\(^3,4,7\)

- Significant effects on T-cell function and viral load observed upon PD-1/PD-L1 blockade both *in vitro*\(^3,4,11,12\) or *in vivo*\(^5,6,13\)

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Blockade of either PD-1 or PD-L1 in treatment of cancers

PD-1 pathway blockade improved response rates in various oncologic indications
Proof of Concept for Anti-PD-1 (BMS-936558) in Chronic HCV

- Blinded, single ascending dose, randomized placebo controlled trial
  - 3 out of total 54 subjects had $>4 \log_{10}$ HCV RNA decline
  - All 3 were in 10 mg/kg cohort (20 subjects)
  - 1 subject remains undetectable > 1 year post treatment (B)
- Sporadic responses, but provides POC for PD-1 pathway blockade in chronic viral infection

Gardiner et al PLoS One 2013
PD-1 blockade in unsuppressed SIV-infected macaques

Treatment with αPD-1:
- Transiently affected viremia
- Restored T and B cell numbers & functions
- Prolonged survival

What would be the outcome of PD-1 pathway blockade if the SIV-infected macaques were on suppressive ARV?

Velu et al, Nature 2009
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:

Objectives:
– Determine whether multiple doses of BMS-936559 affect:
  1. Virus-specific T cell functionality,
  2. Cell-associated viral DNA (latent reservoir) in tissues and periphery,
Kinetics of viral load rebound post-treatment interruption

- Half of BMS-936559-treated animals had rebound similar to isotype-treated animals
- BMS-936559-responder group remained below 1000 cp/mL for >8 weeks
- Two had undetectable VL for 3-4 weeks
Comparison of treatment groups
Pre-ARV and Post-rebound viral loads

- A significant difference was observed in post-rebound VL between BMS-936559- and isotype-treated groups

S. Sanisetty, J. Whitney
S. Balsitis
Quantification of BMS-936559 occupancy on PD-L1 on expressing cell *ex vivo*

- PD-L1 occupancy maintained at 100% throughout dosing period
- 2 animals with sustained occupancy were not among the responders
- PK and immunogenicity of antibody is pending
SIV study: Summary & Future Plans

• **Efficacy:**
  – 4 of 8 animals in BMS-936559 group had a delay in VL rebound (compared to control group) and sustained lower VL
  – 2 of 8 in BMS-936559 group had undetectable VL for 3-4 weeks after an initial rebound (none in control group) post-TI

• **Safety:**
  – Multiple doses of BMS-936559 in ARV-suppressed SIV-infected Rhesus macques appeared to be generally well tolerated

• **Future plans:**
  – Continue monitoring VL; determine effects on T cell function and latent reservoir
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

Latently infected cells

Low level spontaneous viremia from latent SIV

Need to understand how to

- Expand response
- Translate finding to HIV-1 infected subjects
  - Find biomarkers in SIV study → HIV-1 patients
Toward Functional Cure in HIV: 
**ACTG-5326**

Safety, Pharmacokinetics and Immunotherapeutic Activity of an Anti-PD-L1 Antibody (BMS-936559) in HIV-1 Infected Subjects on Suppressive cART: *a Pilot, Double-Blind, Placebo-Controlled, Single Ascending Dose Study*

**Hypotheses:**

Single doses of anti-PD-L1 HuMAb (BMS-936559) will:

- Be safe and well tolerated in HIV-1 infected patients with plasma HIV-1 RNA suppressed on cART.
- Enhance HIV-1 specific immune responses that promote the clearance of HIV-1 expressing cells and
- Reduce persistent viremia.

**Response to IND: Safe to proceed**

**Enrollment to begin in 1Q2014**
Translation from NHP to humans

Cautions:

- Although the SIV-infected macaque is a well characterized model that has implications for HIV infection,
- No animal model can predict with absolute certainty the outcomes for human disease.
- Therefore, caution must be exercised when translating the effects observed in this SIV study to HIV disease.
BMS Strategy for HIV-1 Functional Cure: Dual Approach

**Treatment with αPD-L1**

**Exhausted T-cell**

- **Restore HIV-antigen specific T cell activity**
- **Higher level expression of HIV antigens**

**Latently infected cells**

- **Induced re-activation of latent HIV-1**

**Functional HIV-specific T cell**

**Reduction of latently infected cells**

**Potentially broader responses**

**HIV-1 Functional Cure?**
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