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

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Disclosure: Paid employee of BMS

6th HIV Persistence Workshop

Miami, December 5, 2013

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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

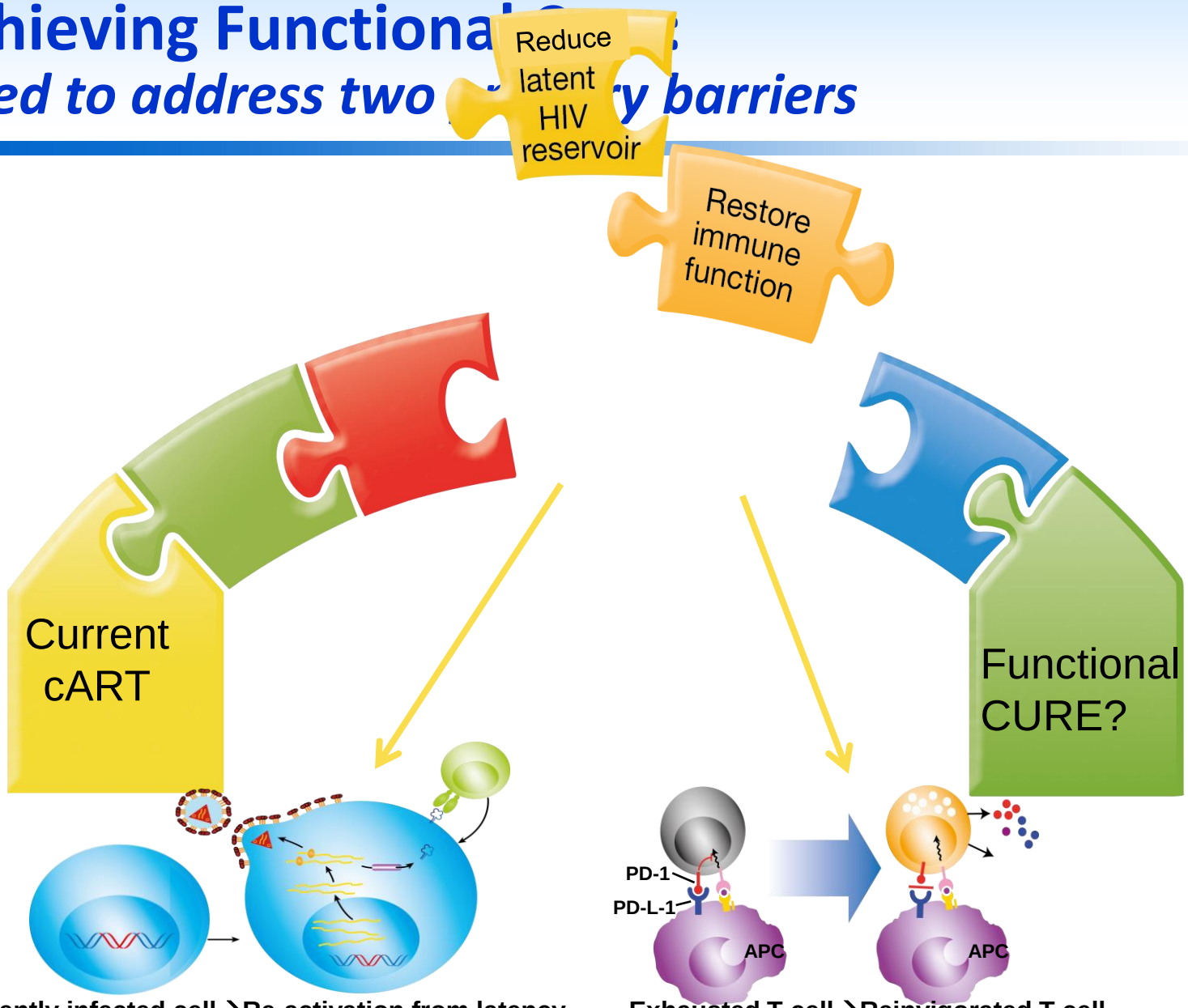
- Ideally obtained through finite therapy

Is a broadly applicable functional cure for HIV-1 a realistic goal?

If so, how do we get there?

Achieving Functional [illegible]

Need to address two [illegible]y barriers



Latently infected cell→Re-activation from latency

Exhausted T cell→Reinvigorated T cell

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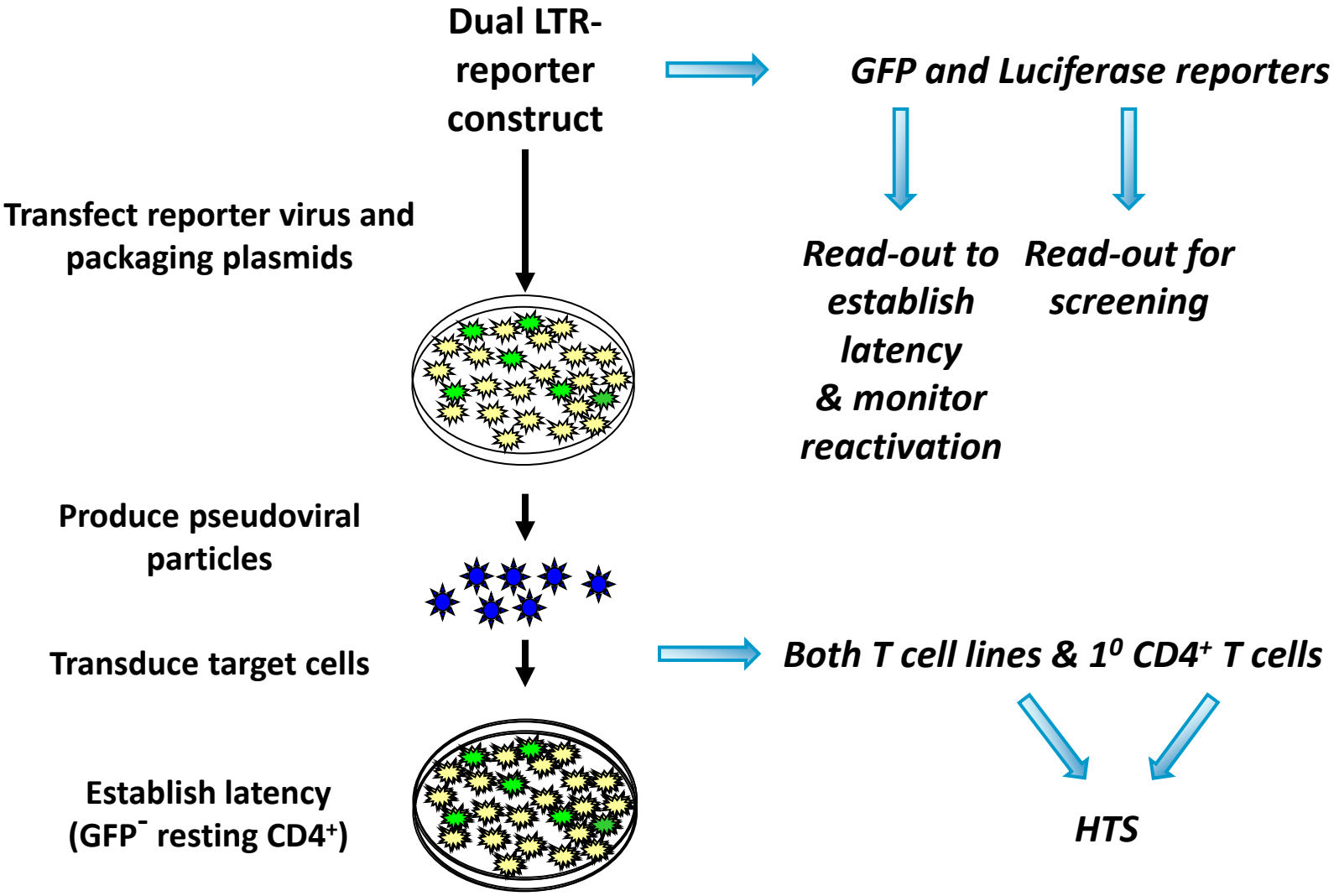
Addressing the first barrier to functional cure: *HIV-1 latency*

BMS approach:

- **Obtain novel small molecule activators of latent virus**
  → 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



B. Rose, C. Mazzucco, A. Walsh, D. Tenney

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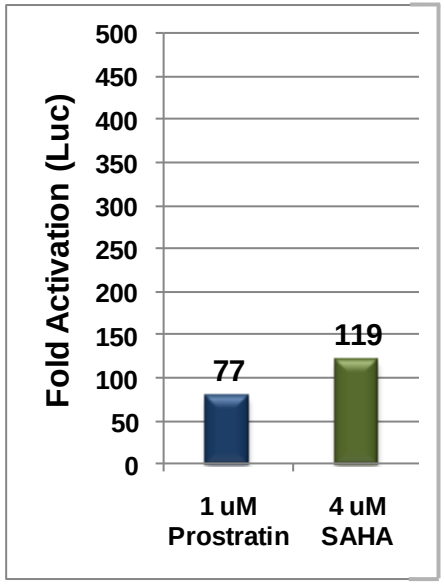
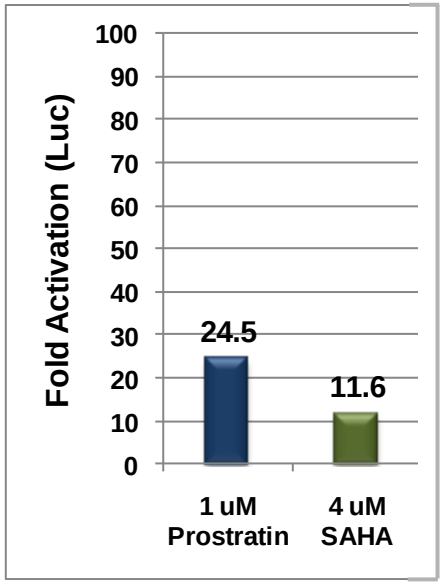
Activity of Benchmark Compounds

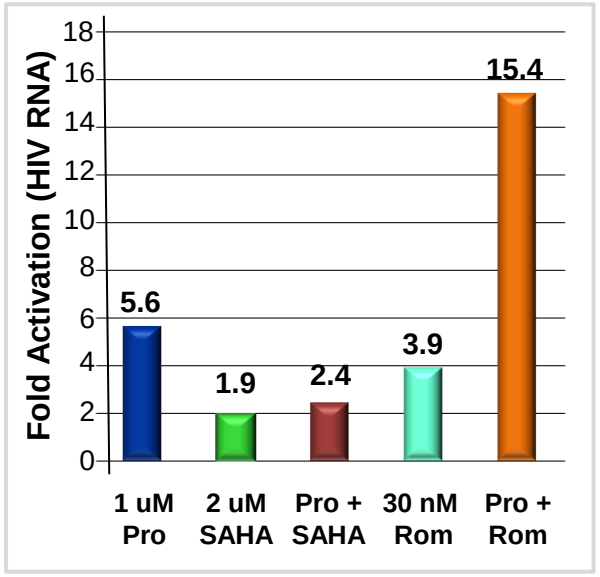
Latent Jurkat Cells



Latent Primary Cells



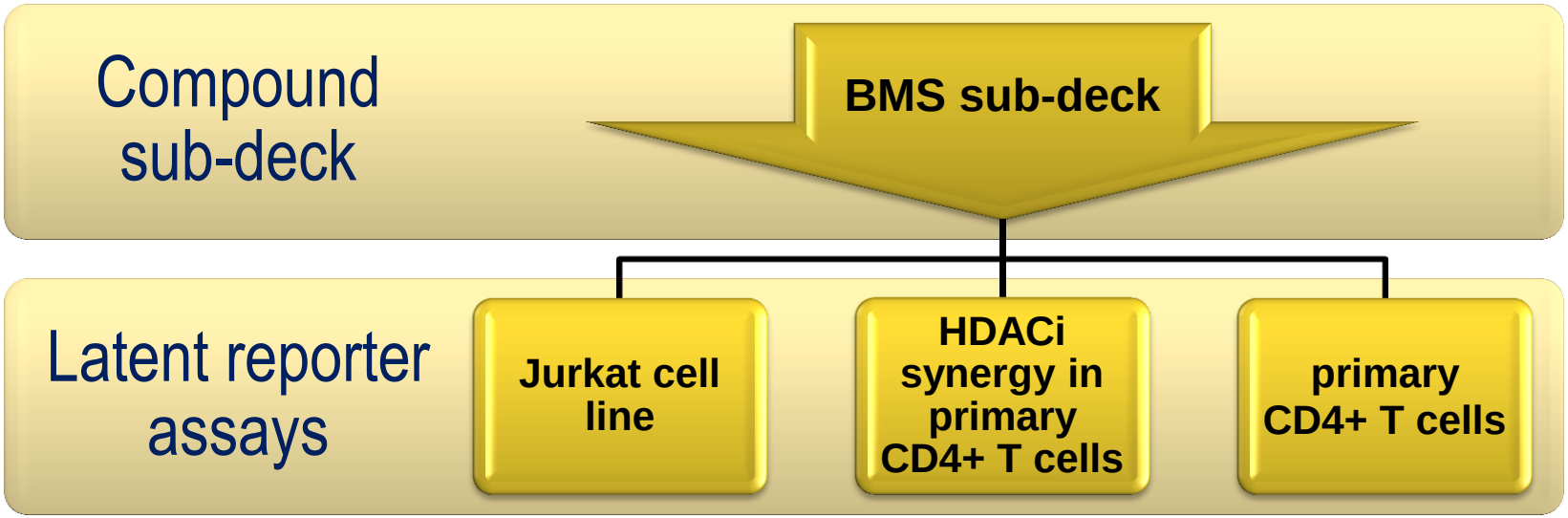
HIV-infected Patient Cells



- **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**

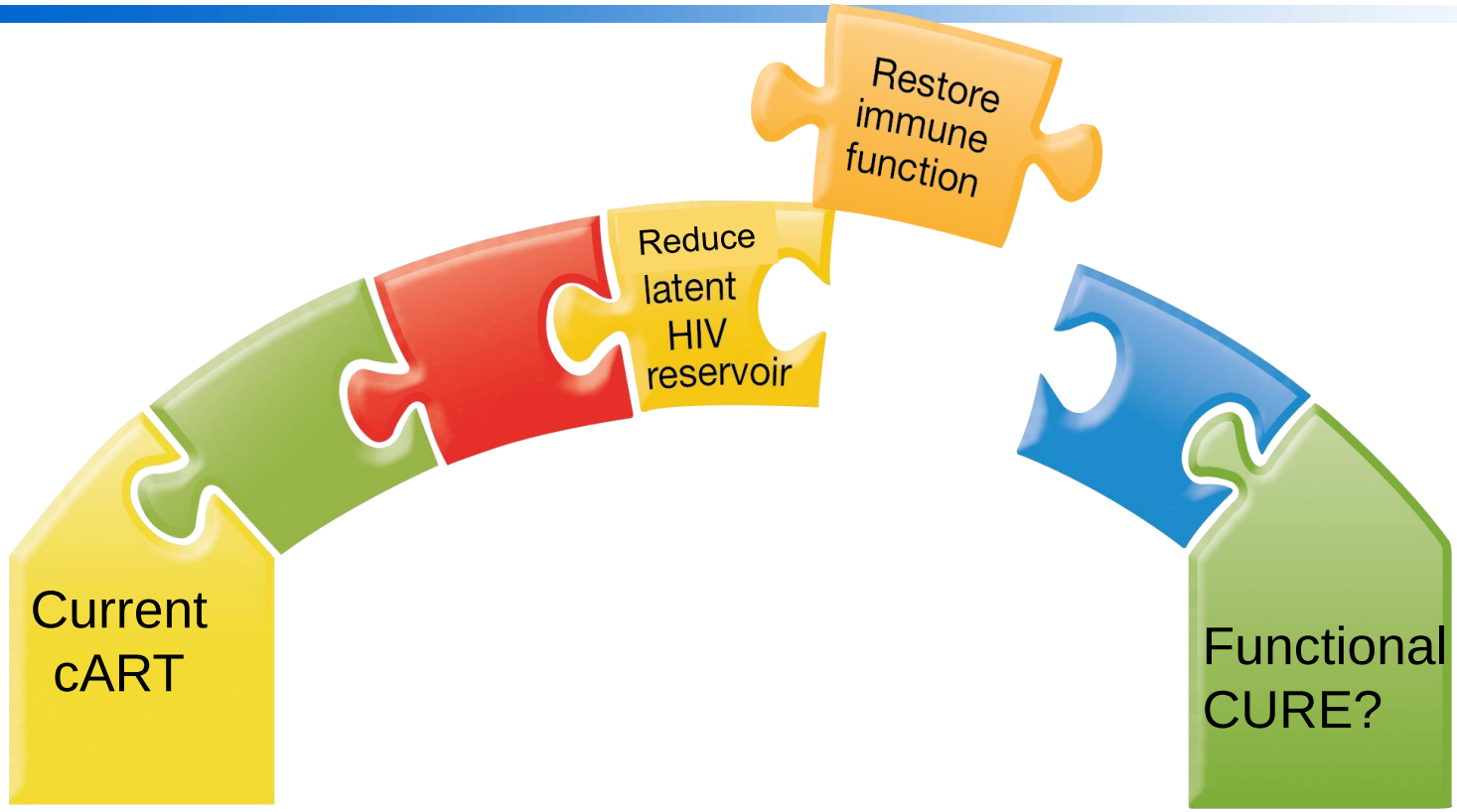
BMS approach to latency:
Screening for activation of latent HIV

Multiple Assays for HTS: maximizing chance of success

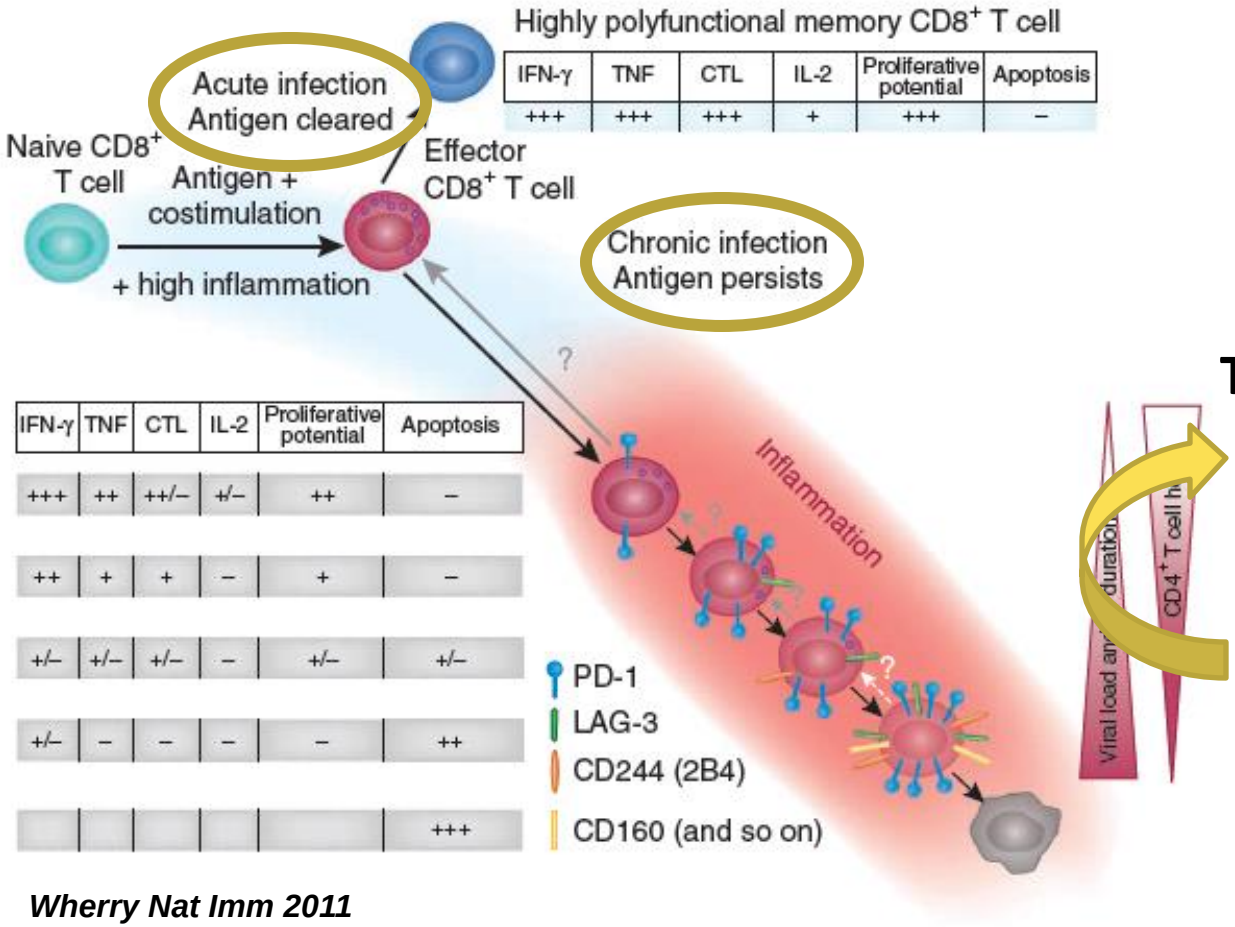


Parallel screening approach will enable detection of multiple modes of latent HIV activators

Achieving Functional Cure:
Need to address two primary barriers



Addressing the second barrier to functional cure
T cell exhaustion



Wherry Nat Imm 2011

T cell Exhaustion:

- Progressive loss of function
- Accompanied by expression of multiple inhibitory receptors

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]

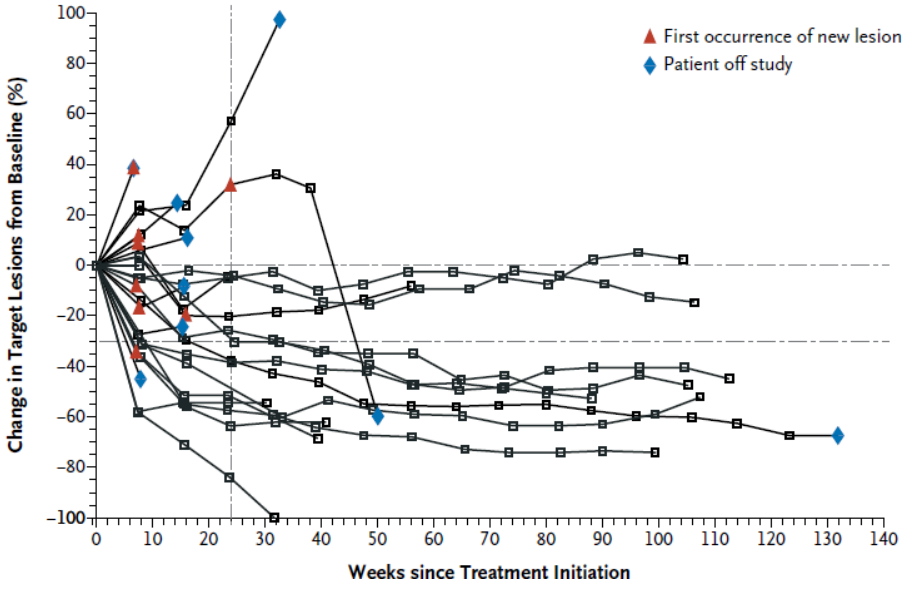
1. Day CL. et.al. J Virol. 2002; 2. Thimme R. et.al. J Virol. 2003;
3. Trautmann L. et al Nat.Med. 2006; Day CL. et.al. Nature. 2006; Petrovas C. et al., JEM 2006;
4. Evans A. et.al. Hepatol. 2008; 5. Velu V. et al. Nature. 2009; 6. Barber D.L. et al. Nature. 2006;
7. Streeck H. PLOS Med. 2008; 8. Boni C. et.al. J Virol. 2007; 9. Golden-Mason L. et.al. J Virol. 2007;
10. Rutebemberwa A. et.al. J Immunol. 2008; 11. Urbani S. et.al. J Hepatol. 2008;
12. Fisicaro J. et al. Gastro. 2010; 13. Palmer B. et al J. Imm. 2012.

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

The NEW ENGLAND JOURNAL of MEDICINE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

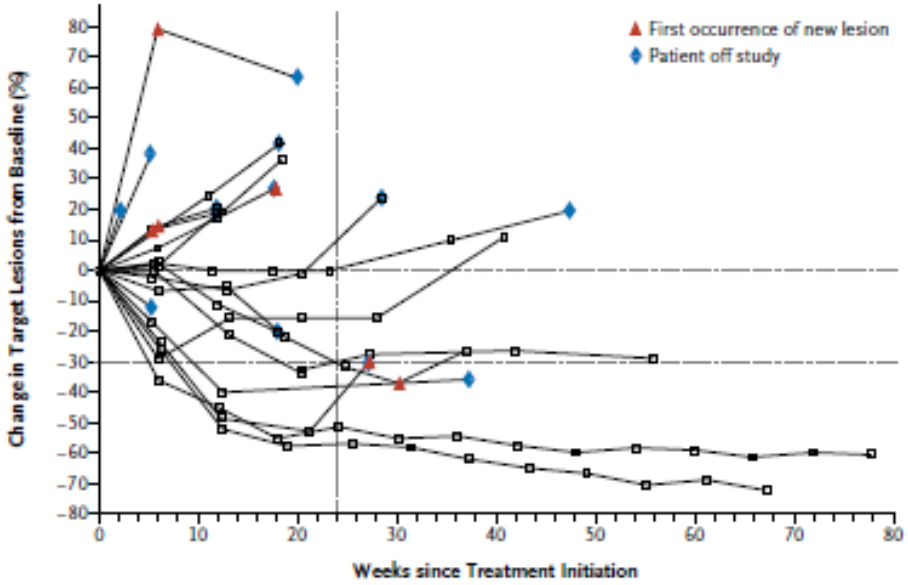
Suzanne L. Topalian, M.D. , F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., et al



The NEW ENGLAND JOURNAL of MEDICINE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., et al



PD-1 pathway blockade improved response rates in various oncologic indications

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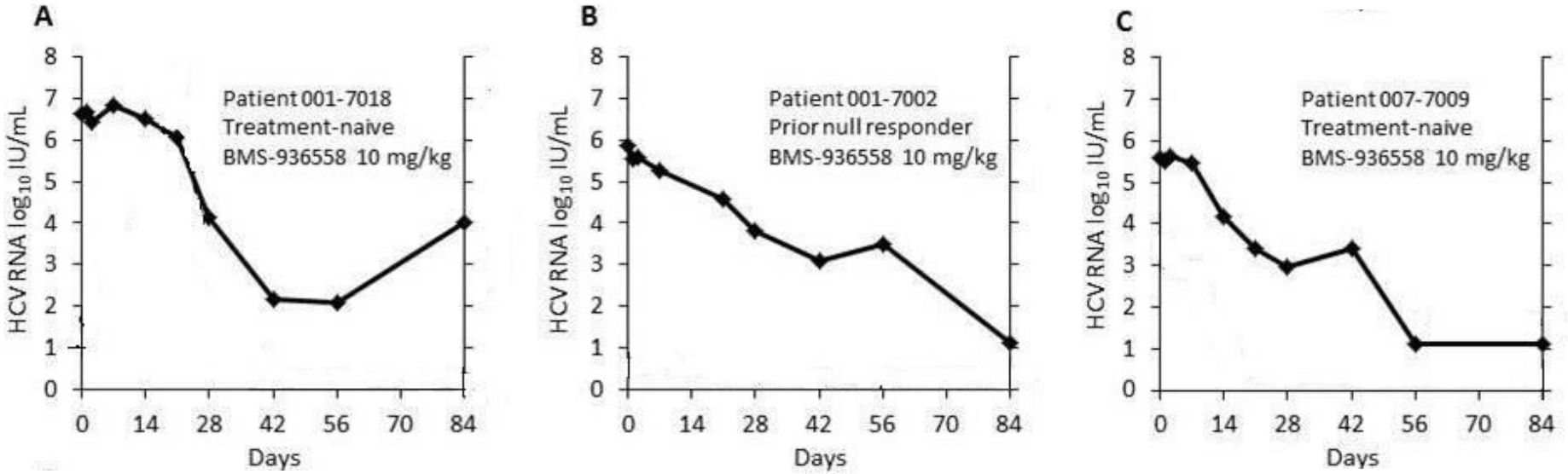
Proof of Concept for Anti-PD-1 (BMS-936558) in Chronic HCV

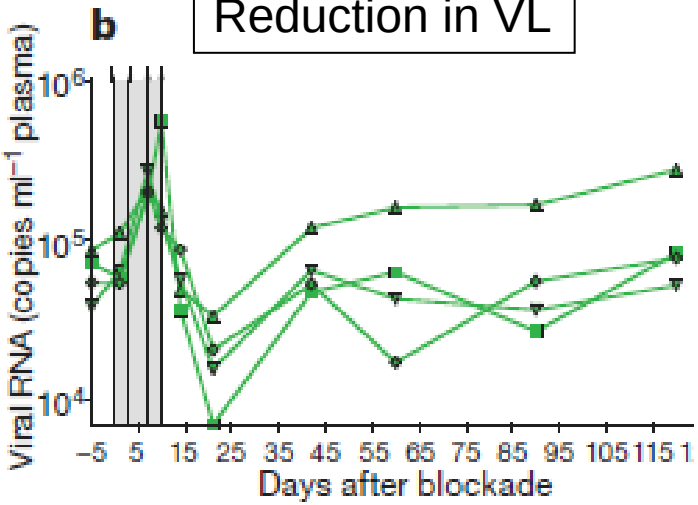
Gardiner et al PLoS One 2013



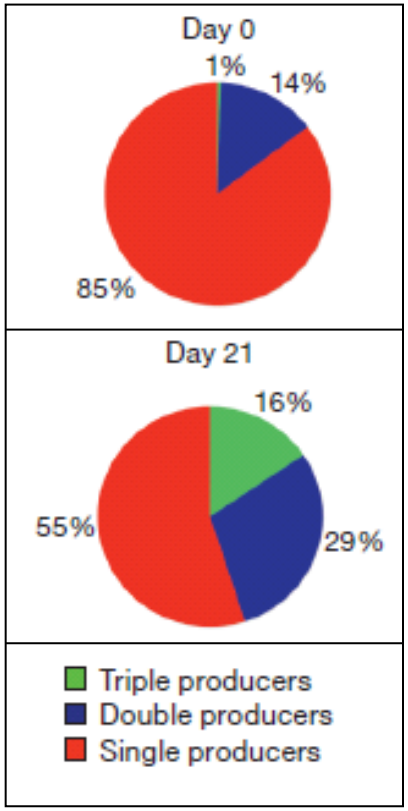
- **Blinded, single ascending dose, randomized placebo controlled trial**
  - 3 out of total 54 subjects had >4 $\log_{10}$ HCV RNA decline
  - All 3 were in 10 mg/kg cohort (20 subjects)
  - 1 subject remains undetectable > 1 year post treatment (B)
- **Sporadic responses, but provides POC for PD-1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

PD-1 blockade in unsuppressed SIV-infected macaques

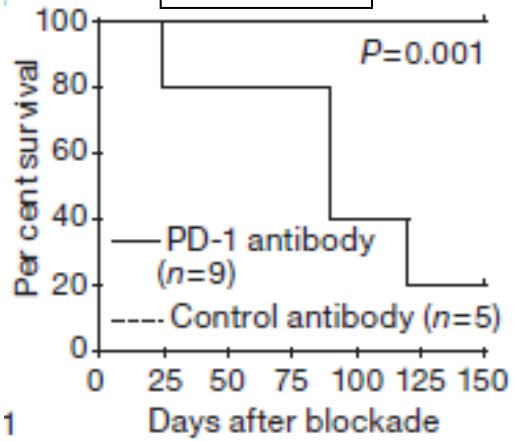
Reduction in VL



Function



Survival



Velu et al, Nature 2009

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?

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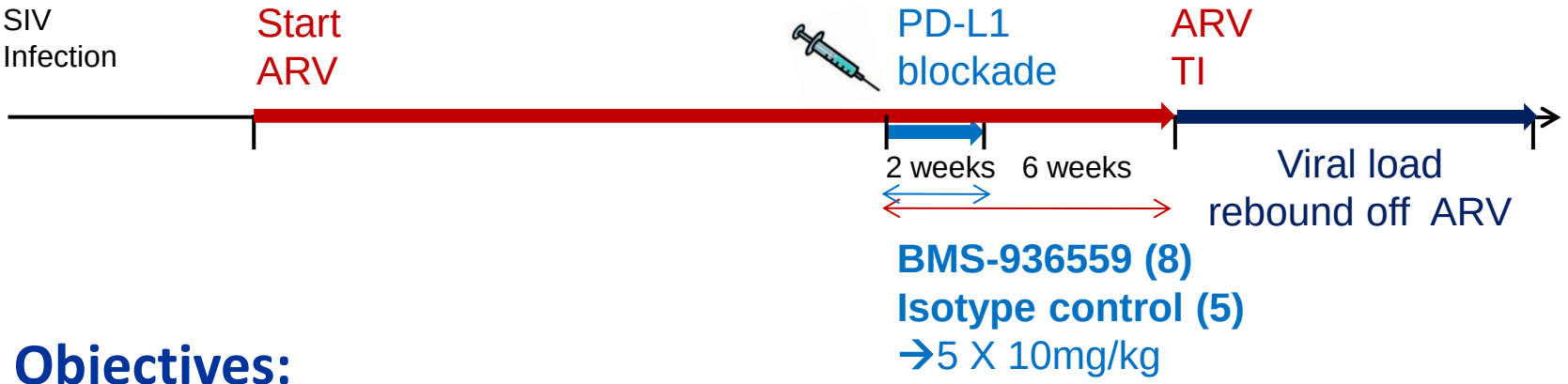
PD-L1 blockade in ARV suppressed SIVmac251-infected Rhesus Macaques

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,

3. Virus recrudescence after cessation of ARV treatment.

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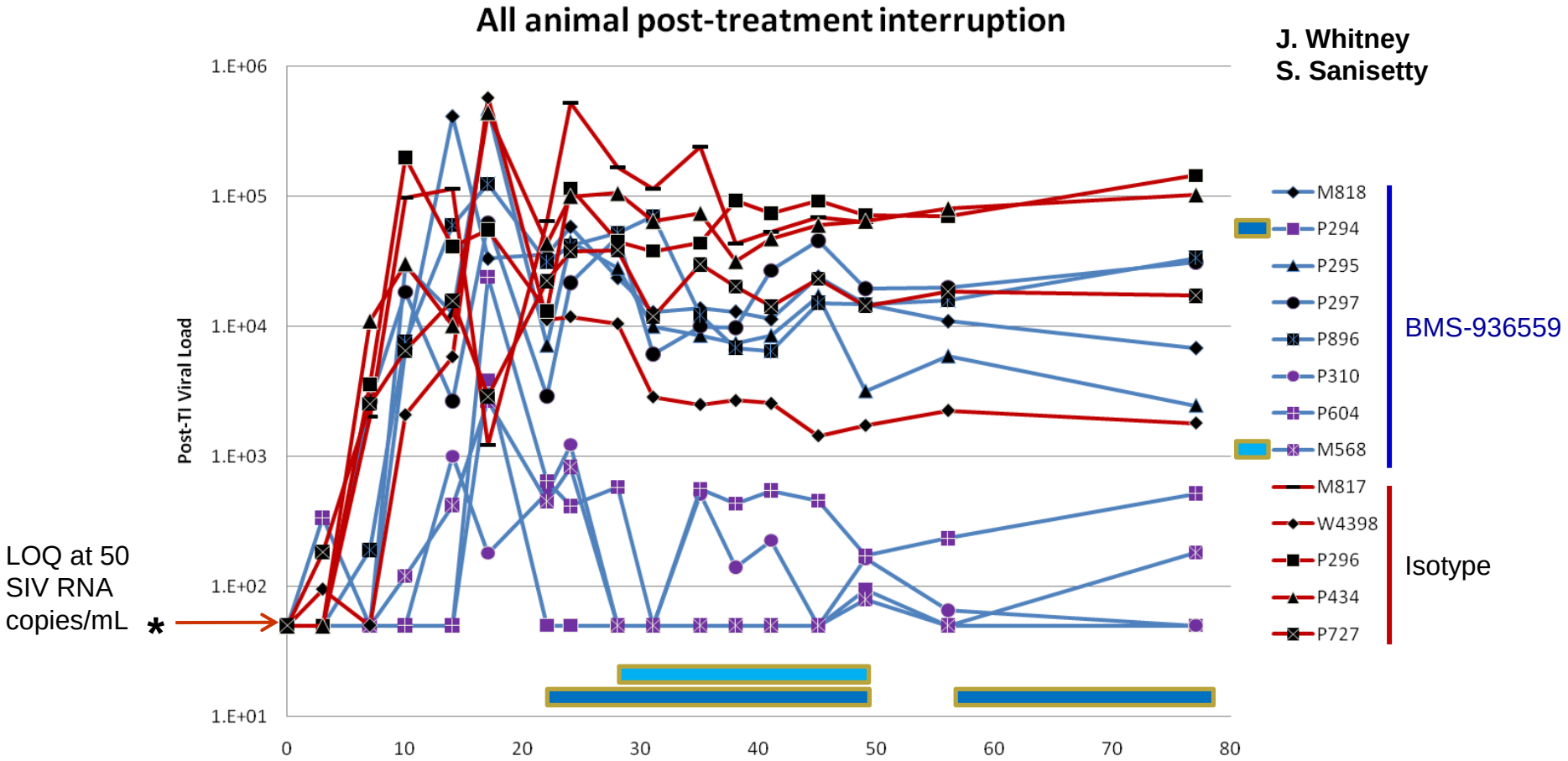
Kinetics of viral load rebound post-treatment interruption



- 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

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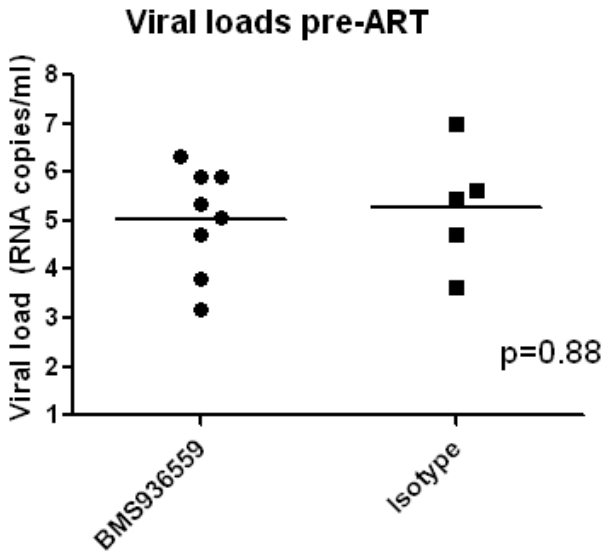
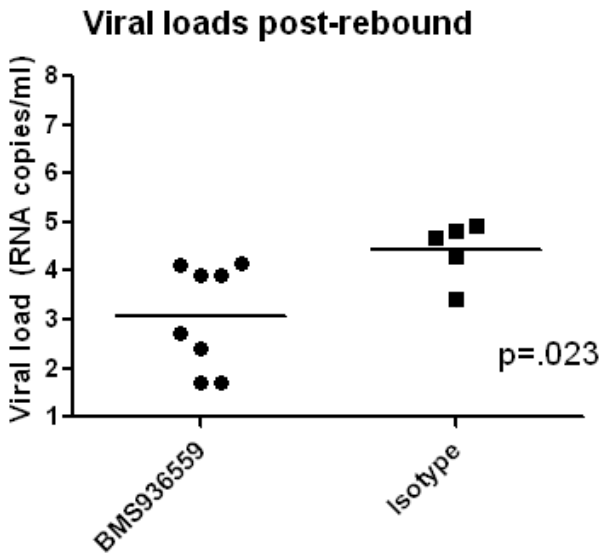
Comparison of treatment groups Pre-ARV and Post-rebound viral loads



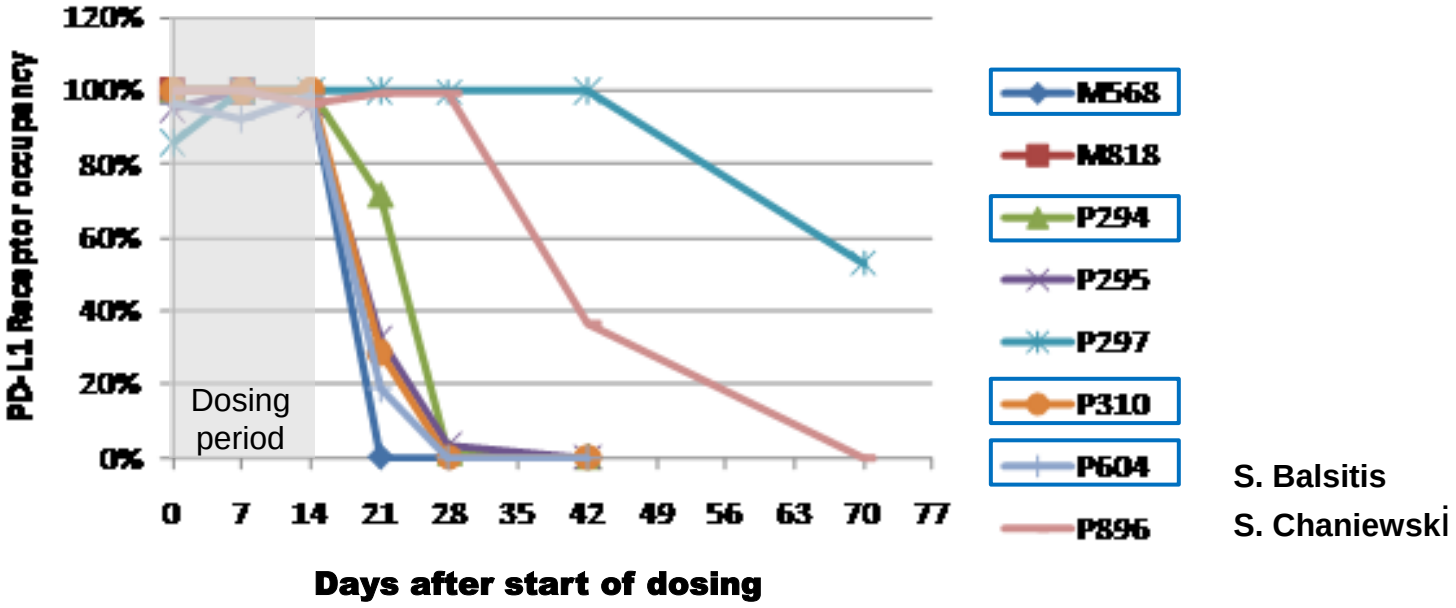


P-values from Mann-Whitney U-test

- 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

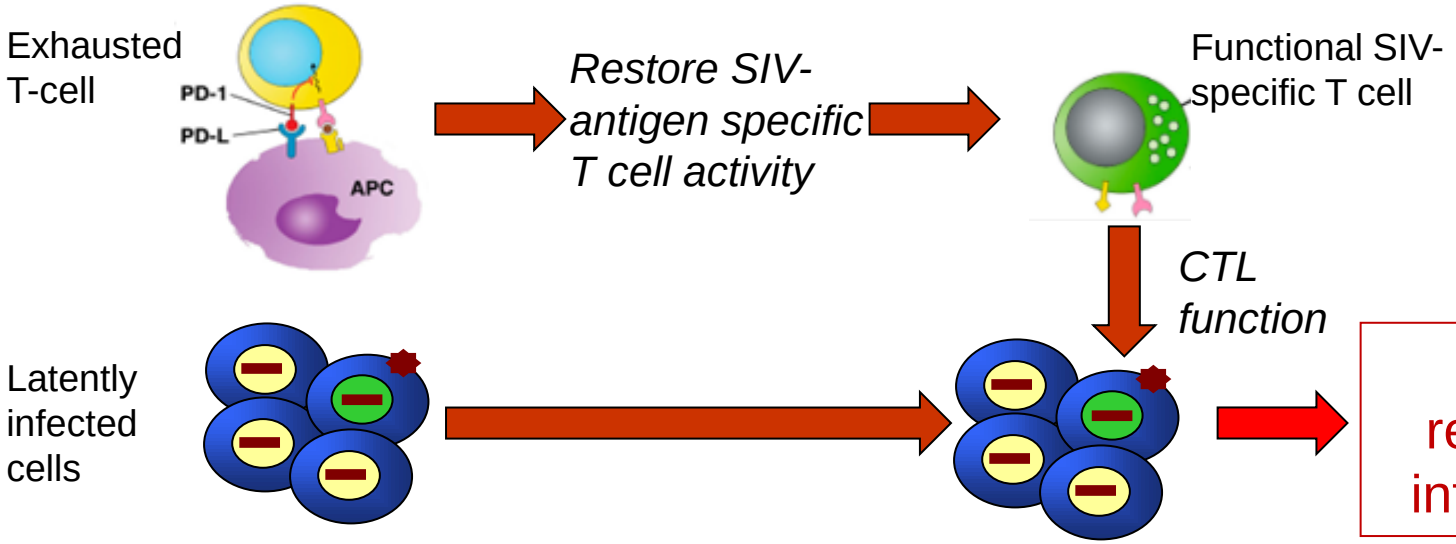
- **Efficacy:**
  - 4 of 8 animals in BMS-936559 group had a delay in VL rebound (compared to control group) and sustained lower VL
  - 2 of 8 in BMS-936559 group had undetectable VL for 3-4 weeks after an initial rebound (none in control group) post-TI

- **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



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

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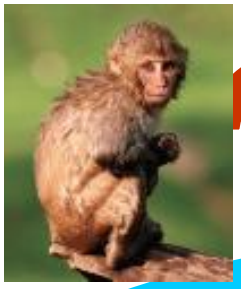
Translation from NHP to humans



PD-L1 blockade in SIV infected macaques

BMS-936559 in HIV-1 infected subjects

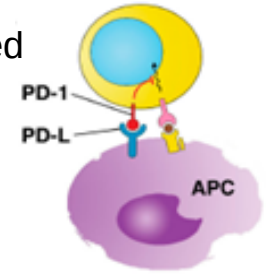
Cautions:

- 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

Functional HIV-specific T cell

CTL function

Latently infected cells

Higher level expression of HIV antigens

Induced re-activation of latent HIV-1

Reduction of latently infected cells

Potentially broader responses

HIV-1 Functional Cure?

Acknowledgements

BIDMC Boston

- James Whitney
- Srisowmya Sanisetty
- Christa Osuna-Gutierrez
- So-Yon Lim

Bioqual

- Mark Lewis

A5326 Core team:

- Joe Eron, UNC
- Cynthia Gay, UNC
- Ronald Bosch Harvard
- John Coffin, Tufts
- Richard Koup, NIH
- John Mellors, UPitt

Gilead

- Romas Geleziunas

BMS

Discovery Virology

- Dan Tenney
- Scott Balsitis
- Burt Rose
- Shalyn Campellone
- Michael Wichroski
- Charlie Mazzucco
- Ann Walsh
- Amy Sheaffer
- Bo Ding
- Huilin Qi
- Min Lee
- Sue Chaniewski
- Volodymyr Gali
- Mark Cockett

Immuno-Oncology

- Alan Korman
- Mark Selby
- Nils Lonberg

Discovery Medicine-Virology

- Carey Hwang
- David Gardiner
- Dennis Grasela

Global Clinical Research Virology

- George Hanna

Clinical Pharmacology

- Matt Hruska

Clinical Biomarkers

- Neela Ray

Applied Genomics

- Namjin Chung

Drug Safety Evaluation

- Matt Holdren

Preclinical Candidate Optimization

- Narendra Kishnani

Contracts

- Fred Asare

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