Investigating the Role of the Immune Checkpoint Receptor TIGIT in T cells During HIV Disease Progression and as a Target for Immune Restoration

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HIV Curative Strategies

“Shock and Kill” as a viable HIV Cure Strategy

**Shock:**
HDACi, PKC Activators, BET Bromodomain Inhibitors, Disulfiram, TLR7 Agonist. etc.

**Kill:**
CD8\(^+\) T cells, NK cells, B cells (bNAbs), Therapeutic Vaccines etc.
Modulation of CD8$^+$ T cell Effector Function by Negative Checkpoint Receptors (NCR)

- Tim-3 Mark Dysfunctional CD8$^+$ T cell in HIV and SIV Infection
  - (Jones, Ndlovu et al. JEM 2008; Fujita, Chew, Sacha, Ndlovu, et al. JI 2014)

- Tim-3 appears to be co-expressed with several NCR

(Adapted from Freeman et al. Nature Immunology 2012)
TIGIT (T cell Ig and ITIM domain)

- An extracellular Ig like V type domain, 2 immunoreceptor tyrosine inhibitory motif (ITIM) in its cytoplasmic tail
- Expressed on CD4+ T cells (Tfh, Tregs), CD8+ T cells and NK cells
- TIGIT interactions indirectly inhibit T cell responses by driving DCs to produce immunosuppressive cytokine, IL-10 (Yu et al. Nat Immunology 2009)
- TIGIT exerts intrinsic inhibitory effects by recruitment of SHP phosphatases to ITIM (Joller et al. JI 2011)
- TIGIT interacts with CD226 in cis and disrupts homodimerization abrogates activating signals (Johnston et al. JCI 2014)
Objectives

• To investigate the role of TIGIT expression and function on CD8\(^+\) T cell during treated HIV disease
• Determine whether targeting the TIGIT pathway can elicit HIV specific CD8\(^+\) T cell responses relevant to “Shock and Kill” strategies
Expression of TIGIT\(^+\) CD8\(^+\) T cells During HIV Infection

HD: HIV uninfected
AI: Acute HIV infection
NC: Non-Controllers
AS: cART suppressed
EC: Elite Controllers
Expression of TIGIT$^+$ CD8$^+$ T cells During HIV Infection

TIGIT remains elevated on CD8$^+$ T cells despite viral suppression
Expression of TIGIT and PD-1 on CD8 T cells in HIV infection

TIGIT is co-expressed with PD-1 on CD8+ T cells, and remains elevated despite viral suppression

HD: HIV uninfected
AI: Acute HIV infection
NC: Non-Controllers
AS: cART suppressed
EC: Elite Controllers
Regulation of TIGIT Expression

Dashed: IgG
Solid: cytokine
Shaded: No Stim

*\(p=0.0313\)
Regulation of TIGIT Expression

Dysregulated cytokine profile driven by the γ–chain cytokines may drive elevated TIGIT expression on CD8⁺ T cells
TIGIT Expression on HIV-Specific CD8$^+$ T cells
TIGIT Expression on HIV-Specific CD8⁺ T cells

TIGIT and PD-1 may negatively regulate anti-HIV CD8⁺ T cells
Function of TIGIT+ CD8+ T cells
**Function of TIGIT⁺ CD8⁺ T cells**

*TIGIT⁺ CD8⁺ T cells have poor cytokine production and despite high levels of Perforin/Granzyme B, do not have enhanced degranulation capacity.*
Effects of TIGIT Blockade on HIV CD8⁺ T cell Responses

anti-TIGIT mAb / PD-L1 mAb
Single TIGIT blockade Increases HIV specific IFN-γ CD8+ T cell Responses
Effects of TIGIT Blockade on HIV Specific CD8⁺ T cell Proliferation

anti-TIGIT mAb / PD-L1 mAb
Effects of TIGIT Blockade on HIV Specific CD8+ T cell Proliferation

Combinational blockade increases the expansion of HIV specific CD8+ T cells greater than single blockade alone.
Summary I

• TIGIT\(^+\) and TIGIT\(^+\) PD-1\(^+\) CD8\(^+\) T cells are expanded during HIV infection, despite viral suppression.

• TIGIT and PD-1 are co-expressed on HIV specific CD8\(^+\) T cells

• TIGIT expression can be regulated by γ–chain cytokines

• TIGIT CD8\(^+\) T cells retain high levels of CTL activity but have poor cytokine responses to HIV Gag peptides

• Exposure to blockade of TIGIT enhances HIV specific CD8\(^+\) T cell IFN-γ responses

• Whereas combinational blockade of TIGIT and PD-1 increased HIV specific CD8\(^+\) T cell proliferation
TIGIT Expression on CD4+ T cells

- 19 Chronic HIV infected “ART Initiators” with persistent virologic suppression from SCOPE meeting strict inclusion criteria, who have been on cART for at least 3 years with a CD4 T cell count >350 cells/mm3
Summary II

• Given the strong association between TIGIT\(^+\) cells and the cell associated viral reservoir in CD4\(^+\) T cells, TIGIT may directly or indirectly participate in the establishment or maintenance of the HIV viral reservoir.

- The TIGIT and PD-1 NCR pathways may be targeted with mAbs to enhance broad anti-viral CD8\(^+\) T cell activity required for an effective “Shock and Kill” approach targeting the latently reactivated virus \textit{in vivo}.

- Furthermore, the effects of TIGIT blockade may serve a dual role facilitating the decline of the latently HIV infected CD4\(^+\) T cell population.
Rhesus Macaque TIGIT and SIV infection

• Collaboration Sacha lab (OHSU) – Cloned rhTIGIT
• 87% protein homology between Human and Rhesus

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