IL-15 superagonist at ART initiation expands SIV-specific CD8+ T cells in blood and lymphoid tissues

Benjamin Varco-Merth[1,2], Alejandra Marenco[1,2], Hiroshi Takata[1,2], Omo Fadeyi[1,2], Julian Pacheco[1,2], William Goodwin[1,2], Leo Ratzan[3], Thomas A. Premeaux[3], Scott Bowler[3], Jian Yu[4], Yaoxing Huang[4], David Ho[4], Lishomwa C. Ndhlovu[3], Lydie Trautmann[5,6] and Afam Okoye[1].

[1]Vaccine and Gene Therapy Institute, Oregon Health & Science University, Beaverton, OR, USA. [2]Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR, USA. . [3]Division of Infectious Diseases, Department of Medicine, Weill Cornell Medicine, New York, NY, USA. [4]Aaron Diamond AIDS Research Center, Columbia University, New York, NY, USA. [5]U.S. Military HIV Research Program, CIDR, Walter Reed Army Institute of Research, Silver Spring, MD, USA. [6]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA.

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Background

Interleukin-15 (IL-15) is a pleiotropic cytokine that plays an essential role in both innate and adaptive immune function. IL-15 superagonists (IL-15SA) incorporate modifications that enhance potency and prolong half-life relative to wild-type IL-15. When administered therapeutically, IL-15SA has been shown to augment CD8$^+$ T-cell and NK-cell activity.

The RV550 clinical trial conducted in Bangkok, Thailand, evaluated the effects of the IL-15 superagonist Anktiva administered alongside ART during acute HIV infection on NK cells, HIV-specific T-cell responses in blood and lymph nodes, and cell-associated viral loads.

Here, we model the RV550 trial in SIVmac239-infected, ART-treated rhesus macaques to explore the effects of IL-15SA administered during acute SIV infection alongside ART on immune and viral dynamics in blood, lymphoid tissues, and the central nervous system.

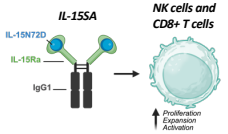


Figure 1: *IL-15SA is composed of 2 IL-15N72D proteins noncovalently bound to a bivalent IL-15 receptor alpha (IL-15Rα)-IgG1 Fc fusion construct. These modifications increase the half-life and potency relative to wild-type IL-15. IL-15SA increases proliferation, expansion and activation of cytotoxic T lymphocytes (CTLs).*

IL-15SA potently stimulates NK cell and CD8+ memory T cell proliferation

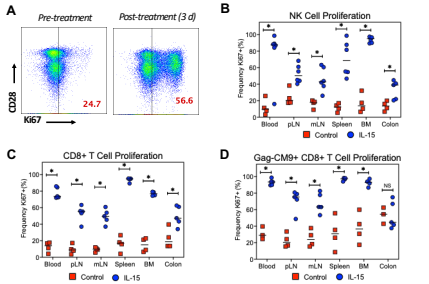
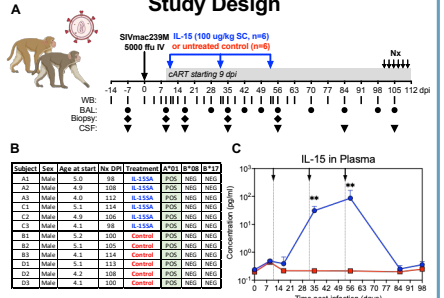


Figure 2. *(A) Representative flow cytometry plot showing Ki-67 expression in CD8$^+$ memory T cells following IL-15SA treatment in ART-naive SIV-infected rhesus macaques (RM). Proliferation (Ki-67$^+$) in* ***(B)*** *NK cells,* ***(C)*** *total CD8$^+$ T cells, and* ***(D)*** *SIV-specific Gag-CM9 MHC class I tetramer$^+$ CD8$^+$ T cells in blood, peripheral lymph nodes (pLN), mesenteric lymph nodes (mLN), spleen, bone marrow (BM), and colon.*

Study Design



Subject	Sex	Age at start	Nx DPI	Treatment	A*01	B*08	B*17
A1	Male	5.0	98	IL-15SA	POS	NEG	NEG
A2	Male	4.9	108	IL-15SA	POS	NEG	NEG
A3	Male	4.0	112	IL-15SA	POS	NEG	NEG
C1	Male	5.1	114	IL-15SA	POS	NEG	NEG
C2	Male	4.9	106	IL-15SA	POS	NEG	NEG
C3	Male	4.1	98	IL-15SA	POS	NEG	NEG
B1	Male	5.2	100	Control	POS	NEG	NEG
B2	Male	5.1	105	Control	POS	NEG	NEG
B3	Male	4.1	114	Control	POS	NEG	NEG
D1	Male	5.1	113	Control	POS	NEG	NEG
D2	Male	4.2	108	Control	POS	NEG	NEG
D3	Male	4.1	100	Control	POS	NEG	NEG

Figure 3. *(A) Experimental schematic. Twelve Mamu-A*01$^+$ RM were divided into two balanced groups (n = 6 per group) and inoculated intravenously with SIVmac239M (5,000 IU), followed by initiation of daily ART (TDF, FTC, DTG) at 9 days post-infection (dpi). Six RM received subcutaneous IL-15SA (100 μg/kg) at 11, 32, and 53 dpi. Blood, cerebrospinal fluid (CSF), lymph nodes, bone marrow, and spleen were collected longitudinally prior to necropsy at the study endpoint (15 ± 1 weeks).* ***(B)*** *Demographics of study animals.* ***(C)*** *Mean plasma IL-15 concentrations over time relative to SIV infection.*

IL-15SA transiently increases inflammatory cytokines in plasma

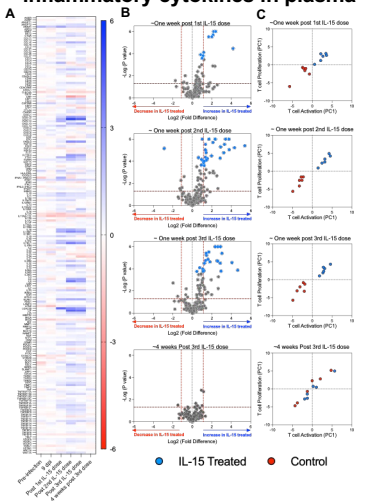


Figure 4. *(A) Heat map depicting differential cytokine expression in plasma.* ***(B)*** *Volcano plot highlighting cytokines significantly upregulated following IL-15 treatment.* ***(C)*** *Principal component analysis (PCA) plot identifying cytokines associated with T-cell proliferation and activation in relation to IL-15 treatment.*

IL-15SA transiently increases NK and memory T cell counts in blood

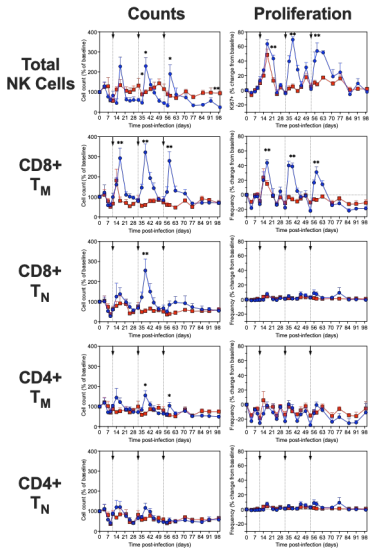


Figure 5: *Absolute counts (Left) and frequencies of proliferating (Ki67+; Right) total NK cells, CD8+ memory T cells (CD8+ TM), CD8+ naive T cells (CD8+ TN), CD4+ memory T cells (CD4+ TM) and CD4+ naive T cells (CD4+ TN) in blood.*

IL-15SA at time of ART enhanced the expansion of SIV-specific CD8+ T cells in blood and lymphoid tissues but did not substantially impact plasma or cell-associated viral loads

IL-15SA increases proliferation and expansion of CD8+ memory T cells in tissues

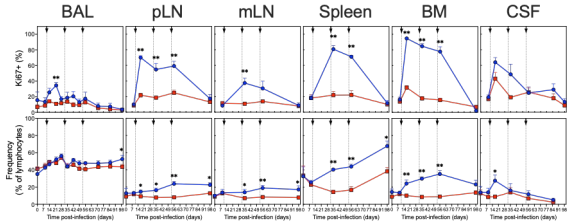


Figure 6. *Frequencies of proliferating (Ki-67$^+$; top) and total CD8$^+$ memory T cells (% of total small lymphocytes; bottom) in bronchoalveolar lavage (BAL), peripheral lymph nodes (pLN), mesenteric lymph nodes (mLN), spleen, bone marrow (BM), and cerebrospinal fluid (CSF).*

IL-15SA transiently expands SIV-specific CD8+ T cells

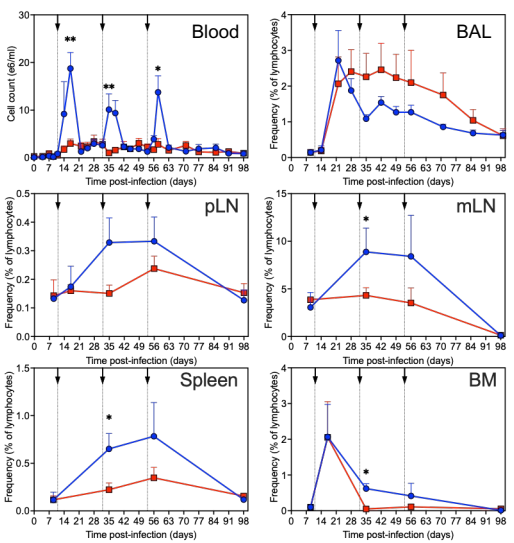


Figure 7: *Frequency of SIV-specific Gag-CM9 MHC class I tetramer$^+$ CD8$^+$ T cells in blood, bronchoalveolar lavage (BAL), peripheral lymph nodes (pLN), mesenteric lymph nodes (mLN), spleen and bone marrow (BM).*

IL-15SA did not substantially impact SIVmac239 viral loads

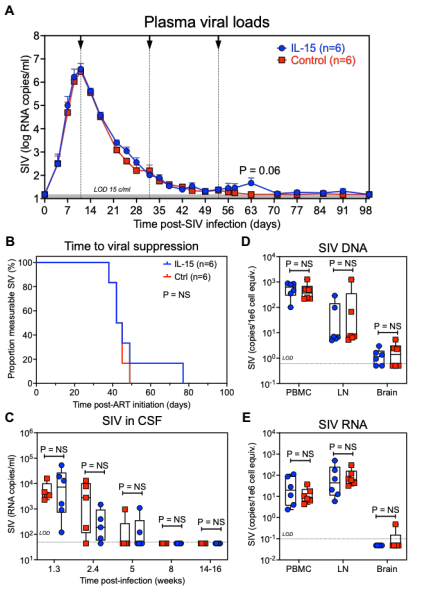


Figure 8. *(A) Longitudinal plasma SIVmac239 viral loads. (B) Time to SIVmac239 suppression following ART initiation. (C) SIV RNA levels in cerebrospinal fluid (CSF). (D) Cell-associated SIV DNA and (E) RNA in peripheral blood mononuclear cells (PBMC), lymph nodes (LN), and brain at the study endpoint (14–16 weeks post-infection).*

Summary and conclusions

- IL-15SA potently stimulated proliferation of CD8+ T cells and NK cells in blood and tissues.
- IL-15SA transiently increased expression of cytokines associated with T cell activation and proliferation one week after infusion.
- IL-15SA enhanced proliferation and expansion of both total CD8+ T cells and SIV-specific CD8+ T cells in blood and tissues.
- When administered alongside ART during acute SIV infection, IL-15SA did not significantly impact SIV replication or measures of viral persistence in blood or tissues.

Plain language summary:
IL-15SA treatment during early infection boosted immune responses during ART, but did not reduce viral persistence.

Acknowledgements

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