A Novel Immunotherapeutic Platform for Amplifying HIV, CMV or SARS-CoV-2-Specific T Cell Responses

Marta Santos Bravo, E. Cole, A. Mueller, C.Hiner, A. Sydenstricker, A. Voss, J.H. Zheng, S.J. Garforth, S. Almo, H. Goldstein.
Albert Einstein College of Medicine, Bronx, New York.

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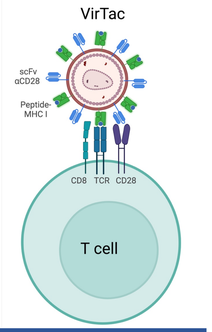
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BACKGROUND

While adoptive cell transfer of HIV-specific T cells is a promising immunotherapy to provide a functional cure for HIV, its development and broader application is limited by the cost, logistical complexity, and variability of current methods for ex vivo expansion of HIV-specific T cells *(Derdak et al, PNAS, 2006; Kueng et al, Int Arch Allergy Immunol 2011).*

To address these needs, we hypothesized that we could develop a novel modular and highly scalable lentiviral-based immunotherapeutic platform, **VirTac** (Viral particle-based T cell Activator), that can mimic Antigen Presenting Cells (APC) for the ex vivo and in vivo expansion of viral-specific T cells recognizing highly conserved virus-derived antigens.



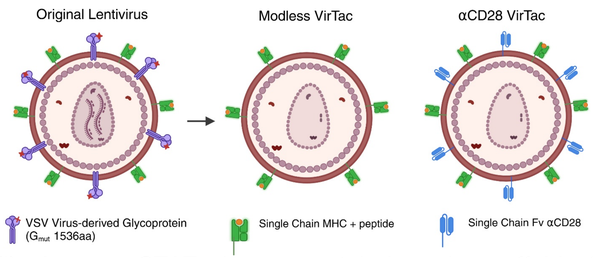
METHODS

- **VirTac construction:**

HEK293T cells were transfected with the plasmid encoding for single chain HLA-A*0201 MHC molecules tethered to viral-derived peptides (CMV: NLVPMVATV; HIV: SLYNTVATL; CoV2: YLQPRTFLL) +/- the plasmid encoding for single chain scFv agonist αCD28.

- **Generation of safe non-infectious VirTac:**

VirTacs only express immunomodulatory proteins on their surface, therefore, we excluded genomic payload and lentiviral fusion proteins to generate safe non-infectious particles. Vesicular Stomatitis Virus-Glycoprotein (VSV-G) is neither expressed on the VirTac surface to avoid human serum inactivation, as we previously tested.

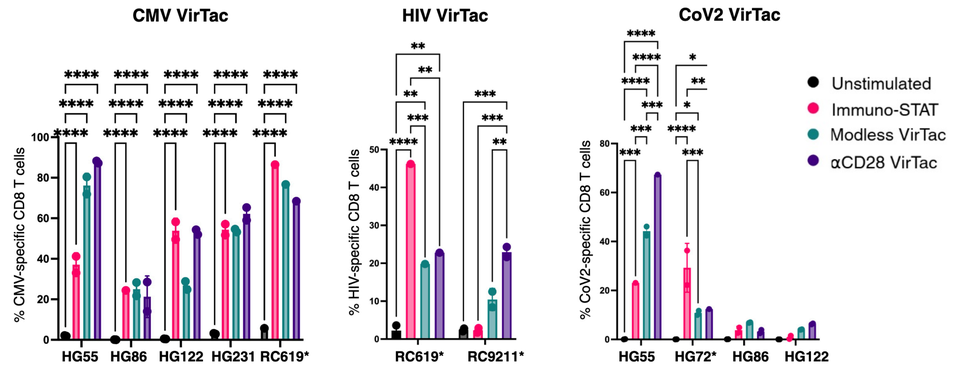


(*) Immuno-STAT is a protein-based scaffold for presentation of MHC-peptide used as positive control for antigen-specific T cell expansion *(Li et al, J Clinical Inves, 2021).*

Statistical analysis were conducted using 2-way ANOVA.

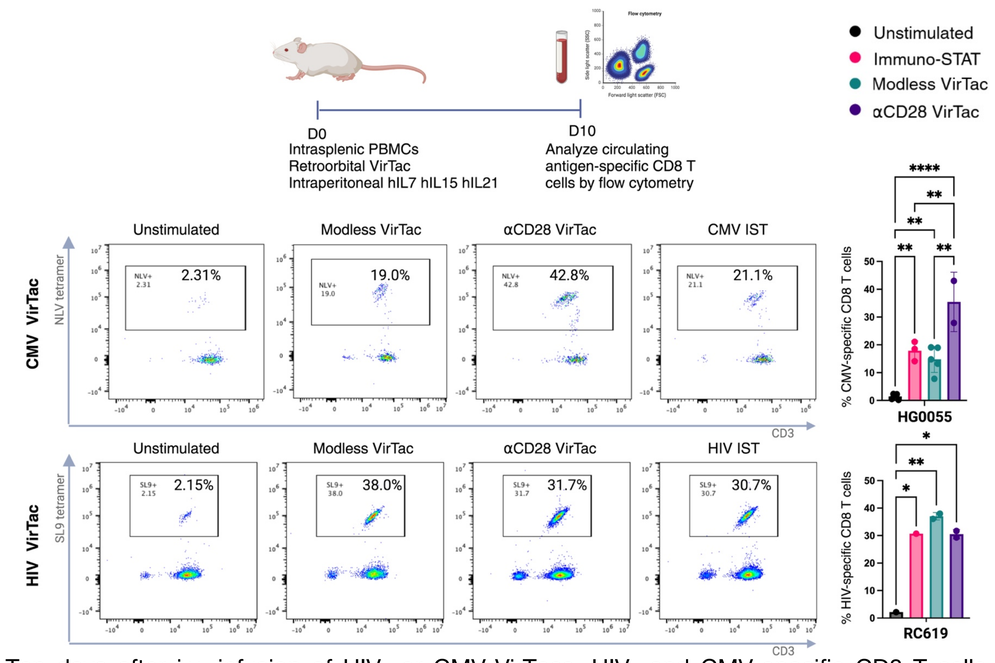
RESULTS

VirTac selectively expand in vitro HIV- CMV- and CoV2-specific CD8 T cells from people without HIV (PWoH) and people with HIV (PWH)*.



In vitro treatment of PBMCs (n=2-5 donors) with VirTac presenting HIV (SL9), CMV (NLV) or CoV-2 (YLQ) peptide MHC constructs markedly expanded the fraction of CD8 T cells that were CMV-specific (up to 87%), HIV-specific (up to 23%) or CoV2-specific (up to 67%). Antigen-specific T cell expansion was quantified by tetramer staining.

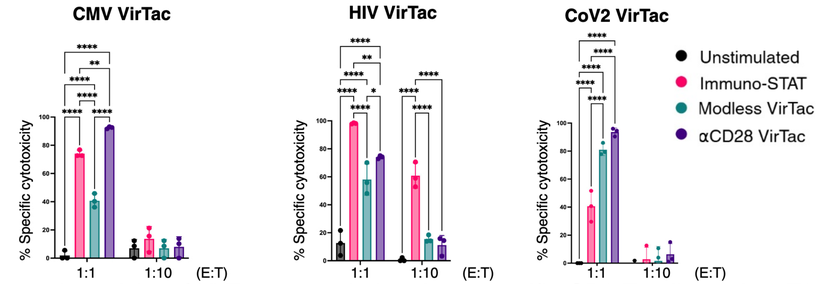
Selective in vivo VirTac expansion of HIV (SL9) and CMV (NLV) CD8 T cells.



Ten days after i.v. infusion of HIV- or CMV-VirTacs, HIV- and CMV-specific CD8 T cells, respectively, were expanded by ~30-fold in NSG mice i.s. engrafted with donor PBMCs.

RESULTS

VirTac-expanded antigen-specific CD8 T cells present a potent selective cytotoxic activity.



Cytotoxic activity of VirTac-expanded antigen-specific CD8 T cells against T2 cells loaded with NLV, SL9 or YLQ antigen compared to T2 cells alone was measured by flow cytometry after staining with antibodies and viability dye.

VirTac-expanded antigen-specific CD8 T cells selectively produce proinflammatory cytokines after peptide presentation by T2 cells.

IFNγ and TNFα production by VirTac-expanded antigen-specific T cells after viral-peptide presentation by T2 cells was measured by flow cytometry.

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  Study volunteers

CONCLUSIONS

VirTac represents a flexible and robust platform for the **ex vivo expansion** of CD8 T cells targeting HIV and other viral-derived epitopes **for adoptive cell transfer**. This strategy may also support **in vivo T cell activation and expansion** to provide sustained anti-HIV activity and enable personalized antigen-specific strategies to achieve a functional cure for HIV, as well as other viral diseases.