377 IL-15 TREATMENT ENHANCES THE IN VIVO ANTI-TUMOR EFFICACY OF SIPULEUCEL-T BY ACTIVATING CD8+ T AND NKT EFFECTOR CELLS, AUGMENTING TUMOR INFILTRATION, AND REVERSING IMMUNORESISTANCE PATHWAYS

[1]Russell Pachynski*, [1]Muhammad A Saeed, [1]Bo Peng, [1]Kevin Kim, [1]Ariel Borkowski, [1]Brian Van Tine, [2]Nadeem Sheikh, [2]Tuyen Vu, [1]Daniel Thorek, [1]Todd Fehniger. *[1]Washington University School of Medicine, St Louis, MO, USA; [2]Dendreon Pharmaceuticals, Seattle, WA, USA*

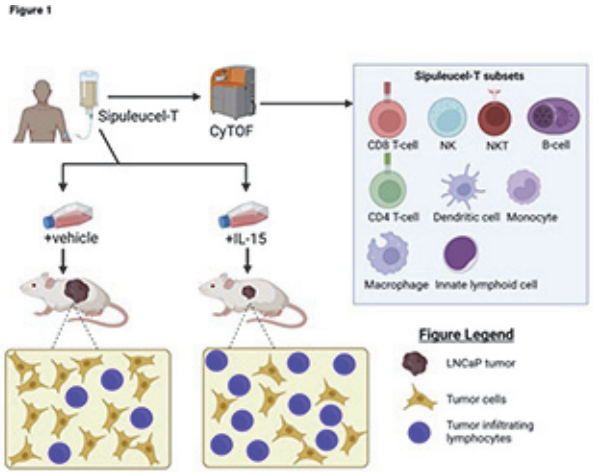
Background Metastatic castration-resistant prostate cancer (mCRPC) represents the most lethal form of prostate cancer. Sipuleucel-T (sip-T) is an autologous therapeutic produced using a tumor antigen-cytokine fusion protein, and the only FDA approved cellular immunotherapy for mCRPC patients. Sip-T significantly improves overall survival (OS), but has limited impact on PSA and radiographic responses. Here, we present the first high dimensional analysis of sip-T in detail using a mass cytometric approach, and highlight immune subsets and inhibitory/stimulatory receptors expression. Furthermore, we show the effects of IL-15 on the anti-tumor efficacy of sip-T using in vitro and in vivo and studies.

Methods We performed a comprehensive assessment of the sip-T product (n=13 samples) collected from prostate cancer patients using mass cytometry (CyTOF). Control and IL-15 stimulated sip-T were evaluated, and changes in leukocyte subsets as well as markers of activation and exhaustion were identified. Finally, we examined the effects of IL-15 on cytotoxicity of sip-T against human prostate cancer lines using in vitro cytotoxicity assays and in vivo studies in NSG mice. (figure 1)

Results CyTOF analysis revealed that CD3+ T cells constituted the highest proportion of sip-T, followed by B-cells, natural killer (NK) cells, NKT, and monocytes, with only a small percentage of dendritic cells. Following sip-T stimulation with IL-15, a significant expansion and activation of CD8+ T-cell and NK cell populations was seen. Co-culture of sip-T with IL-15 and control or prostate-relevant antigens showed significant activation and expansion of CD8 T and NKT cells in an antigen-specific manner. Furthermore, IL-15 stimulated sip-T showed significantly higher in vitro tumor cytotoxicity compared to control or other cytokines tested. Adoptive transfer of IL-15 treated sip-T into NSG mice resulted in potent prostate tumor growth inhibition compared to control. Evaluation of tumor-infiltrating lymphocytes revealed a 2 to 14-fold higher influx of sip-T and a significant increase in interferon (IFN)-γ producing CD8+ T and NKT cells within the tumor microenvironment in the IL-15 group. Tumor transcriptomic analyses revealed IL-15 treatment was able to reverse immunoresistance induced by sip-T alone.

Conclusions This is the first comprehensive study to evaluate sip-T from prostate cancer patients using high dimensional CyTOF analysis, and reveals potential targets for improvement of sip-T efficacy. Furthermore, this is the first pre-clinical in vivo prostate tumor model of sip-T adoptive transfer, showing that IL-15 treatment can significantly enhance anti-tumor efficacy, effector immune cell activation and tumor infiltration, and reverse mediators of immune suppression.

Ethics Approval Sip-T samples from patients were collected after their verbal and written consent under an Washington University IRB approved banking protocol (#201411135). All animal studies were performed in accordance with approved Washington University (St. Louis, MO) and NIH Institutional Animal Care and Use Committee guidelines under an approved protocol (No. 20–0383).



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