

POSTER PRESENTATION

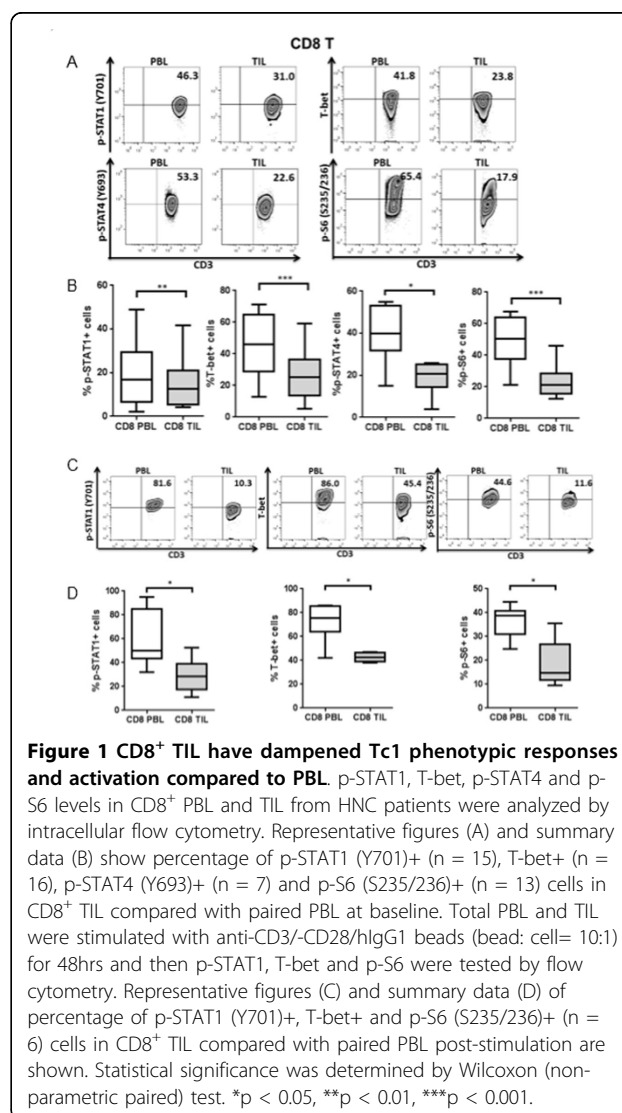
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PD-1/SHP-2 negatively regulate Tc1/Th1 phenotypic responses and activation of T cells in the tumor microenvironment

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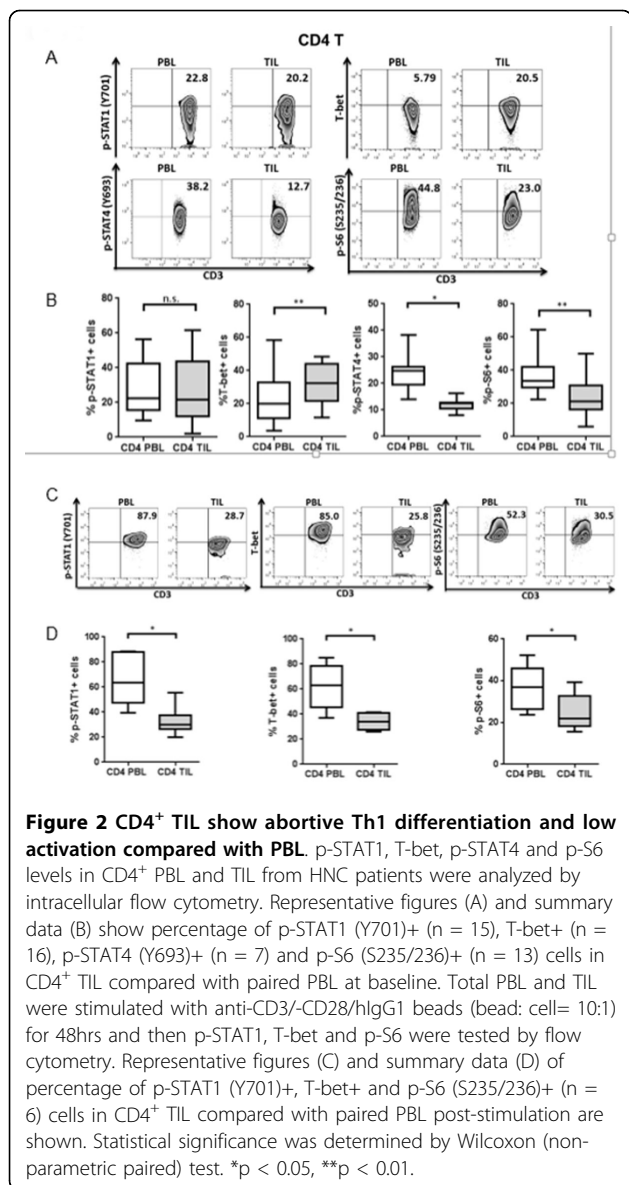
From Society for Immunotherapy of Cancer 29th Annual Meeting
National Harbor, MD, USA. 6-9 November 2014

Rejection of tumor cells by a robust cellular immune response relies on production of type 1 cytokines (such as IFN- γ) and cytolytic activity of T cells. Programmed Death 1 (PD-1), a co-inhibitory receptor proposed to represent T cell dysfunction, is highly expressed on tumor infiltrating lymphocytes (TIL) [1], and may reflect T cell exhaustion marked by decreased proliferation, production of type 1 cytokines and poor cytolytic activity [2]. T-bet, a T-box transcription factor which can be activated by phosphorylated signal transducers and activators of transcription 1 (p-STAT1), plays an important role in Tc1/Th1 skewing. Although anti-PD-1 antibodies enhance IFN- γ secretion after TCR stimulation [3], the mechanistic link between PD-1 and Tc1/Th1 skewing remains unclear. In prospectively collected cancer tissues, TIL manifested dampened Tc1/Th1 skewing and activation compared to PBL (Figure 1 and 2). In addition, PD-1 triggering using PD-L1 coated beads further suppressed TCR-stimulated upregulation of p-STAT1, T-bet and p-S6 as well as Th1 cytokines, while PD-1 blockade reversed suppressive effects of PD-1: PD-L1 ligation (Figure 3). We also found that Src homology-2 domain-containing phosphatase (SHP-2) is higher in TIL than in PBL, tightly correlates with PD-1 expression (Figure 4), and negatively regulates STAT1 and T-bet activation (Figure 5). Thus, the PD-1/SHP-2/p-STAT1/T-bet axis provides an important mechanism for PD-1 suppression of type 1 immunity at tumor sites. PD-1 blocking Abs, which are clinically effective in several solid cancers, should improve T cell-based cancer immunotherapy by restoring robust type 1 immunity and T cell activation to reverse immunosuppression in the tumor



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microenvironment. SHP-2 inhibitory strategies may also be useful to improve type 1-biased TIL.

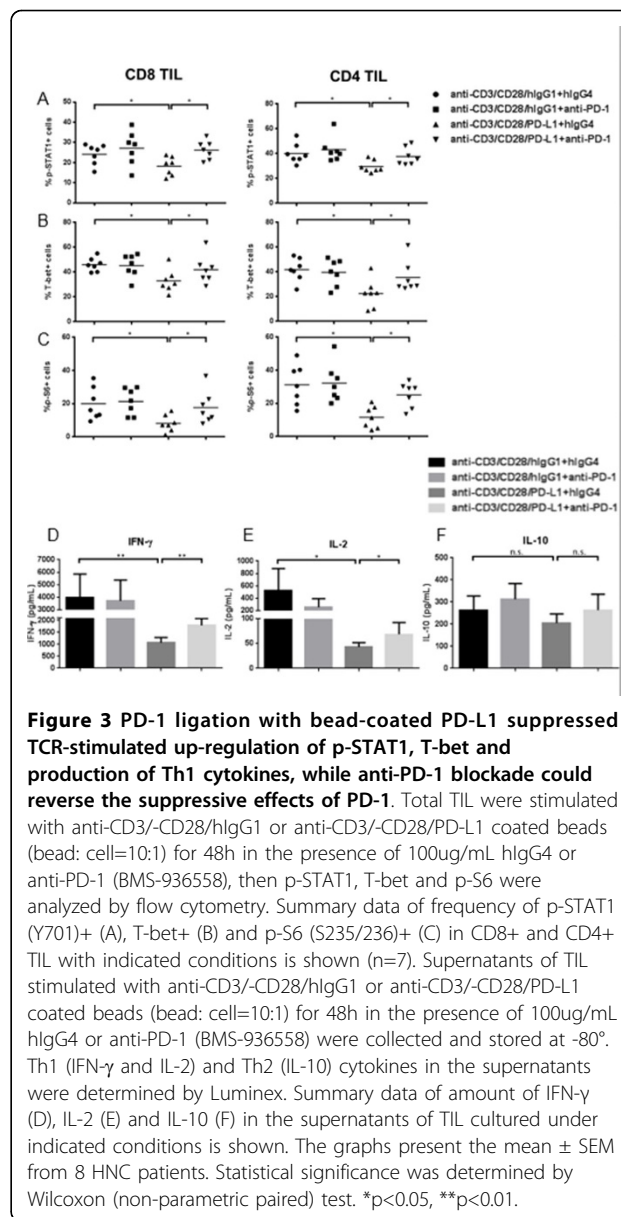
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Published: 6 November 2014

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doi:10.1186/2051-1426-2-S3-P221

Cite this article as: Li and Ferris: PD-1/SHP-2 negatively regulate Tc1/Th1 phenotypic responses and activation of T cells in the tumor microenvironment. *Journal for ImmunoTherapy of Cancer* 2014 **2**(Suppl 3): P221.

