

## POSTER PRESENTATION

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# Differential expression of PD-1 and Tim-3 marks activation versus exhaustion status of T cells in the tumor microenvironment

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Programmed Death 1 (PD-1) and T cell Ig and mucin domain-3 protein (Tim-3) are two immune checkpoint receptors (ICR) highly co-expressed on tumor infiltrating T lymphocytes (TIL). PD-1 has been shown to inhibit T cell activation and type 1 T cell responses, while Tim-3 has been proposed as a further marker of exhaustion on TIL [1,2], leading us to investigate the phenotypic and functional characteristics of TIL with differential PD-1 and Tim-3 expression from head and neck cancer (HNC) patients. Our data showed that PD-1<sup>+</sup>Tim-3<sup>+</sup> CD8<sup>+</sup> and Foxp3<sup>-</sup> CD4<sup>+</sup> TILs manifested high phosphorylated signal transducers and activators of transcription 1 (p-STAT1) and the associated Th1 transcription factor T-bet, which might correlate with T cell exhaustion, both at baseline and upon TCR stimulation. Moreover, the sorted PD-1<sup>+</sup>Tim-3<sup>+</sup> CD8<sup>+</sup> TILs expressed the lowest IFN- $\gamma$  and TNF- $\alpha$  transcripts and the least amount of secreted IFN- $\gamma$  upon TCR stimulation, indicating they are the most dysfunctional T cells in the tumor microenvironment (TME). Among CD4<sup>+</sup>CD25<sup>lo/-</sup> TIL subsets, PD-1<sup>hi</sup>Tim-3<sup>-</sup> cells are more defective in terms of IFN- $\gamma$  expression. Sorted PD-1<sup>int</sup>Tim-3<sup>-</sup> CD8<sup>+</sup> and CD4<sup>+</sup>CD25<sup>lo/-</sup> TILs showed higher TCR-stimulated expression of IFN- $\gamma$  and TNF- $\alpha$  transcripts and secretion of IFN- $\gamma$ , suggesting they are the most activated subsets. In addition, sorted PD-1<sup>+</sup>Tim-3<sup>+</sup> and PD-1<sup>hi</sup>Tim-3<sup>-</sup> TIL were less proliferative than other subsets, concomitant with lower expression of phosphorylated S6 (p-S6), while PD-1<sup>int</sup>Tim-3<sup>-</sup>, PD-1<sup>-</sup>Tim-3<sup>+</sup> and PD-1<sup>-</sup>Tim-3<sup>-</sup> TIL retained p-S6 activation or proliferation, suggesting that high expression of PD-1 on T cells interferes with TCR or Tim-3 signaling and associated cellular activation status. Taken together,

PD-1<sup>+</sup>Tim-3<sup>+</sup> and PD-1<sup>hi</sup>Tim-3<sup>-</sup> TIL are most dysfunctional, while PD-1<sup>int</sup>Tim-3<sup>-</sup> TIL are more activated in terms of both Th1 cytokine production and proliferation. These results provide a better understanding of the functional status of TIL subsets and roles of PD-1 and Tim-3 in regulating anti-tumor T cell response, as targets for cancer immunotherapy.

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