Selective T cell Redirection Proteins (STR) Enhance the Anti-Tumor Activity of Checkpoint Inhibitors (CPIs) and can Lead to Long-Lasting Immunity Against the Tumor

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Abstract

Background
Tumor-targeted superantigens (TTS) such as Naptumomab Estafenatox (Nap) are fusion proteins that consist of genetically engineered Superantigens (Sag) linked to Fragment antigen binding (Fab) moieties directed to tumor-associated antigens. Unlike CD3-based T cell redirection approaches (e.g. BiTES) which bind and activate all T cells, TTS only bind and activate subsets of T cells that contain certain TCR β variable (TRBV) regions, e.g. TRBV 7-9 [1] and are thus defined as STR. We previously reported the synergistic anti-tumor effect of combining CPI with our lead STR compound, Nap (ST4 targeted Sag) or its murine surrogate protein [2]. Here, we present new pre-clinical data showing that STR not only enhances the anti-tumor effect of CPIs, but also stimulates the overall immune response that could lead to long term immunity against the tumor.

Methods
The combination of Nap with PD-L1 inhibitor (durvalumab) was tested in vitro against high (MDA-MB-231) and low (RKO) ST4-expressing cancer cell lines in the presence of human PBMCs. For the in vivo studies, mice bearing H2Kb transduced MC38 tumors were treated with TTS (consisting of a Fab against H2Kb), an anti-PD-1 antibody, or the combination. Tumor growth and survival were assessed and tumor recurrence following re-challenge was evaluated.

Results
Combination of Nap with durvalumab had synergistic anti-tumor effect against both high and low ST4-expressing cancer cell lines. Concomitant treatment of MC38-H2Kb+CM tumor bearing mice with TTS and anti-PD-1 achieved complete tumor rejection in 4 of 10 and significantly prolonged survival and delayed outgrowth of tumors compared to the monotherapies. All cured mice rejected re-challenge with MC38-H2Kb+CM and parental MC38 tumors, indicating long-term memory responses.

Conclusion
Our studies show that combination of CPI with STR overcomes the limited effect of CPI monotherapy regardless of tumor antigen expression level. In addition, our in vivo studies demonstrate that the combination of STR with CPI may lead to long term durable responses not possible in most patients receiving single agent CPI therapy. Moreover, the ability of these "cured mice" to reject tumor re-challenge suggests that STRs can cause release of secondary antigens that prime subsequent immune responses. Taken together, our data suggests that combining anti-PD-L1/STR with CPI may be a promising therapeutic strategy for patients with solid tumors.

References