Harnessing novel immune escape mechanisms for cancer therapeutics: 
OXAB1 target validation, proof of concept and preclinical development

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Introduction
The evasion of the host's immune system by tumor cells is a well-established mechanism of tumor establishment and progression. Identification of the PD-1/PDL-1 axis immune escape mechanism has led to numerous therapeutic strategies; nevertheless, there remains a significant majority of patients who are unable to benefit from current therapies. Here we present our findings of (i) an active novel immune escape mechanism mediated via T cell modulation OX001/OX001L, receptor-ligand axis, and (ii) an antibody targeting this axis with potential therapeutic benefits. The receptor (OX001R) is expressed on activated CD8+ T cells and functions as a co-stimulatory molecule. The ligand (OX001L) is expressed on various cancer cells. According to our analysis of the overall survival in multiple cancers, the downregulation of OX001L correlated with poorer prognosis. Our analysis of NSCLC samples showed the degree of tumor cell infiltration to be significantly correlated with OX001L downregulation and PD-1L upregulation (see poster No. 2772). We also demonstrated that (i) stably transduced with OX001L+ cells activate T-cells with concomitant IFNγ and IL-2 release, (ii) tumor cells downregulate OX001L and upregulate PD-1 upon T cell engagement and (iii) OX001L downregulation results in direct cell-cell contact in contrast to soluble-factor-mediated PD-1L upregulation. Further, anti-OX001R-specific agonistic antibodies promote T cell activation resulting in enhanced IL-2 and IFNγ production, and activate patient TILs in ex vivo tumor explants. In a humanized animal model of lung cancer, agonistic anti-OX001R antibody demonstrated tumor growth inhibition comparable to that of pembrolizumab (anti-PD-1). Additivity was observed when the combination of anti-OX001R and anti-PD-1 was tested. Finally, we have developed OXAB1, an agonistic humanized anti-OX001R antibody, which demonstrates enhanced T cell activation in both in vitro and ex vivo modes relative to other agonistic antibodies. Collectively, our results validate OX001R/001L axis as important tumor immune escape axis. Further support development and the clinical translation of an agonistic OXAB1 antibody for cancer therapy, either as monotherapy or in combination with other non-immune escape mechanisms.

i. Signaling via OX001L/OX001R axis is associated with a better prognosis

ii. OX001L/OX001R interaction activates T cell

iii. OX001L/OX001R and PD-L1/PD-1 axes represent non-redundant pathways

iv. OBT Immune Escape Hypothesis

v. OX001R activates T cells and enhances cytokine release

vi. Anti-OX001R induces immune cell mediated cytotoxicity

vii. Anti-OX001R promotes tumor growth inhibition in vivo

viii. OXAB1 activates T cells and enhances cytokine release

ix. OXAB1 enhances the cytotoxic potential of CD8 T cells

x. OXAB1 induction cell mediated cytotoxicity

Conclusions
- OX001R activates CD8 T cells and NK cells.
- Anti-OX001R agonist promotes anti-tumor response.
- Anti-OX001R clinical development lead demonstrates superior activity.
- Patient selection strategy identified.