Novel Single-Agent Immunotherapies

1313 CHARACTERIZATION OF THE ANTI-TUMOR IMMUNE ACTIVATION POTENTIAL OF AUR107, A NOVEL SMALL MOLECULE P300/CBP BROMODOMAIN INHIBITOR

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Background Ubiquitously expressed histone acetyl transferases (HAT), E1A binding protein (p300) and its paralog CREB binding protein (CBP or CREBBP) are critical regulators of gene expression in both tumor and immune cells. Conditional deletion of either p300 or CBP in mouse Tregs or inhibition of their HAT activity resulted in impairment of Treg suppressive function, reduced peripheral Treg generation, and Treg apoptosis. These effects led to allograft rejection and decreased murine tumor growth. We have identified a novel small molecule p300/CBP bromodomain inhibitor, AUR107, as therapeutic agent for solid and hematological cancers. AUR107 has significant activity in a broad range of cancer cell lines with good selectivity. Here, we demonstrate the relevance of CBP/p300 bromodomain inhibition by AUR107 on function of Tregs cells and modulation of T helper cells in addition to its potent activity against various haematological and solid tumour models.

Methods AUR107 was profiled in human Treg differentiation assay, human Th17 assay and MDSC proliferation assay. AUR107 combination efficacy studies with anti-PD-1/anti-CTLA-4 antibodies are in progress in syngeneic models

Results Inhibition of CBP/p300 bromodomains by AUR107 resulted in decrease in differentiation of human Tregs in an *ex vivo* assay. AUR107 caused dose-dependent increase in the $CD127^{+}CD25^{-}FoxP3^{-}$ effector cells with corresponding decrease in the $CD127^{+}CD25^{+}$ cells in the differentiated $CD4^{+}$ cells population. In the human PBMC assay, AUR107 caused increase in Th1 cell population with decrease in Th2 cell population. These observations indicate that inhibition of CBP/p300 bromodomains affects the function of regulatory T cells. Recruitment of regulatory T cells to tumors is known to be one of the major mechanisms of immune evasion by cancer cells, and hence AUR107 is expected to produce antitumour immunity. These results demonstrate that CBP/p300 bromodomain inhibition could be a novel approach for cancer immunotherapy in addition to their development as direct anti-cancer agents

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