DISCOVERY AND CHARACTERIZATION OF PM-4321, A SELECTIVE INHIBITOR OF THE ARYL HYDROCARBON RECEPTOR (AHR) WITH ANTI-TUMOR IMMUNOMODULATORY EFFECTS

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Background The aryl hydrocarbon receptor (AHR) is a transcription factor activated by several endogenous and exogenous ligands which regulate the activity of immune cells. Endogenous AHR ligand concentrations are elevated in the tumor microenvironment (TME). Cells expressing IDO1, TDO2, and IL4I1, produce kynurenine and kynurenic acid, leading to AHR pathway activation and suppression of anti-tumor immunity. Efforts to target production of AHR ligands using IDO1 and TDO2 inhibitors have failed in the clinic. We hypothesize that inhibiting AHR, the terminal mediator in this pathway, provides an attractive target for cancer immunotherapy.

Methods We report the discovery of a small molecule AHR inhibitor, PM-4321, as a therapeutic for the treatment of cancer. The pharmacological activity of PM-4321 was characterized in multiple cell lines and primary immune cell assays. In vivo studies were performed to evaluate anti-tumor effects in syngeneic mouse models where mice were treated with PM-4321 as monotherapy or in combination with immune checkpoint inhibitors. Tumor volume and growth inhibition were characterized, and effects on immune cell infiltration and activity were analyzed with flow cytometry and transcriptomic profiling.

Results PM-4321 reversed the effects of the synthetic AHR ligand, 2,3,7,8-tetrachlordibenzodioxin (TCDD) on target gene expression in cell lines and human primary immune cell assays. PM-4321 enhanced activation of human CD8 T cell effector function via restoring IFNg, perforin and Granzyme B expression in a dose dependent manner. PM-4321 exhibited immunomodulatory phenotypes including inhibition of IL-22, and rescue of IL-2 production in T cells. In vivo, oral administration of PM-4321 as a monotherapy and in combination with anti-PD1 was efficacious in inhibiting tumor growth in syngeneic mouse models. Immunophenotyping of the TME showed that PM-4321 treated mice had increased infiltration of activated immune cells such as CD8 T cells and NK cells and reduced infiltration of MDSCs and M2 macrophages correlating with the observed anti-tumor effect.

Conclusions Our data demonstrate the potential of PM-4321 as a promising therapeutic candidate, for inhibition of AHR signaling in cancer immunotherapy.

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