Targeting Immune Suppressive Myeloid Cell Pathways for the Treatment of Cancer

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Introduction

The tumor microenvironment is populated by a variety of myeloid cell subsets (Figure 1, left) that contribute to maintaining an immunosuppressive tumor microenvironment.

Increased myeloid cell infiltration in tumors is associated with reduced survival and reduced responses to immunotherapy in several types of cancers.

Myeloid cells mediate their immunosuppressive effects via multiple mechanisms, including the downregulation of proinflammatory cytokines, signal transduction activation of the PD-1 pathway, and release of arginase 1 (ARG1) (Figure 1, right).

The significant role of myeloid cells in dampening tumor immunity makes them an attractive target. To that end, we have shown that ARG1 expression is upregulated in T cell responses:

- A0305137, a phagomimetic-derived kinase predominantly involved in suppressing pro-inflammatory responses from myeloid cells.

Results

**ARG1 is Expressed in Suppressive Immune Cells**

Figure 2. A) ARG1 expression was measured in human whole blood MDCSC subsets by flow cytometry. B) Mice ARG1 expression measured by flow cytometry in M2A253 tumors. Red: isotype control, blue: stain.

**AB474 Rescues ARG1-mediated Inhibition of CD8⁺ T Cell Activation**

Figure 3. CD8⁺ T cells were isolated from the peritoneum of resuscitated ARG1⁻/⁻ AB474⁻/⁻ mice and transferred into wild-type mice and ARG1⁻/⁻ AB474⁻/⁻ recipients, respectively. The recipients were treated with AB474 or vehicle for the indicated days. CD8⁺ T cell proliferation is shown. *p<0.05.

**PI3Kγ is Expressed in Myeloid Cell Subsets**

Figure 4. PI3Kγ is expressed in CD14⁺ monocytes, CD155⁺ moDCs, and CD66b⁺ MDSCs. Cytokine expression in M2A253 tumors.

**PI3Kγ Inhibition Increases IL-12 Production from Monocytes**

Figure 5. A) PI3Kγ expression derived from (left) human peripheral immune cells from healthy donors and (right) M2A253 cells (Banuelos et al. Cell Reports 2019). B) PI3Kγ expression in monocytes and in in vitro differentiated moDCs and macrophages and polarized macrophages.

**PI3Kγ Inhibition Increases M1 Macrophage T Cell Activation Capacity**

Figure 6. A) A0305137 treated M1 macrophages have an increased capacity to stimulate CD T cells in an MLR. B) A0305137 stimulated M1 macrophages (B) and M0 macrophages (A) acquires arginase I expression.

**PI3Kγ Inhibition Acts in Combination with PD-1 Blockade to Increase T Cell Activation**

Figure 7. A3005137 increases IL-12 production from CD14⁺ monocytes stimulated with LPS+IFNγ - p<0.05.

**Conclusions**

- Targeting ARG1 (PD-1) or abrogate mechanisms of immunosuppressive myeloid cell mediated immune suppression, resulting in effective immune response.