RARγ Agonist Compound IRX5010 Inhibits Tumor Growth, Promotes Effector Memory Tumor Infiltrating T-cells, and Inhibits Tumor Infiltrating Myeloid Derived Suppressor Cells in Multiple Cancer Models

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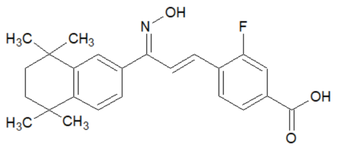
Background

RARγ agonism plays an essential role in CD8 T-cell-mediated immunity to infectious pathogens (1). However, before we initiated our drug discovery program for novel RARγ agonists, we found no previous reports on effects of RARγ agonists on promotion of anti-tumor immunity *in vivo*. We undertook a drug discovery program to evaluate whether RARγ agonists could promote T-cell-mediated immunity in cancers.

Methods

We screened RARγ agonist compounds *in vitro* by measuring their effects on production of interferonγ (a marker of memory T-cell activation) by CMV immune human PBMCs treated with CMV. We performed *in vivo* evaluation of a second generation lead compound IRX5010, in syngeneic murine models of triple negative breast (EMT6), colorectal (MC38), and prostate cancer (MyC-CaP). We also evaluated IRX5010 in a beta-2 microglobulin deficient mouse model given human PBMCs to establish a humanized immune system, xenografted with the human Her2+ breast cancer JIMT-1. Tumor growth was assessed by serial measurement of tumor size. Flow cytometry was performed to quantitate tumor infiltrating lymphocytes (TILs) and myeloid derived suppressor cells (MDSCs).

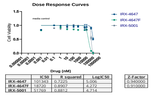


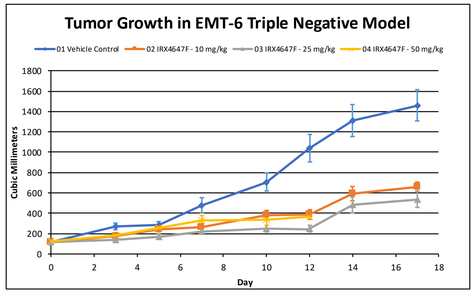
Structure of IRX5010

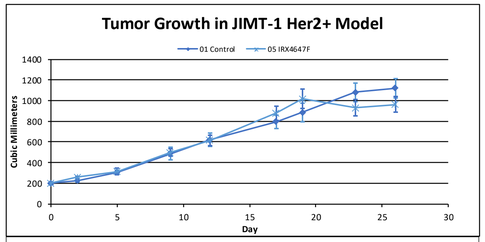
EC50 of IRX5010 in RARγ transactivation assay is less than 0.1 nM
EC50 in RARα transactivation assay is greater than 100 nM

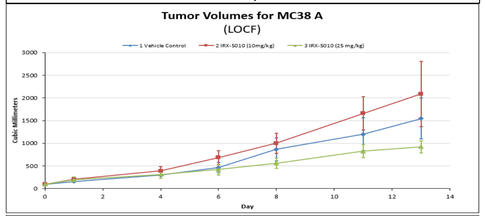
RARγ agonist compound IRX5010 is not active at pharmacologic concentrations on proliferation of EMT-6 in vitro

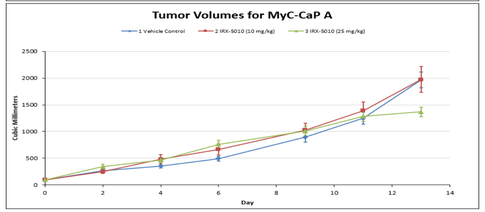
Triple Negative Breast Cancer EMT-6











Effects of IRX5010 on Tumor Growth
IRX5010 demonstrated substantial tumor growth inhibition at 10 and 25 mg/kd/day in the EMT-6 model. IRX5010 inhibited growth in MC38, and Myc-CAP A models at 25 mg/kg/day. It inhibited growth moderately at 25 mg/day in the JIMT-1 human Her2+ breast cancer xenograft model.

Flow Cytometric Quantitation of Tumor Infiltrating T-cells (TIL) and Myeloid Derived Suppressor Cells (MDSC) Example data of tumor infiltrating effector memory phenotype T-cells in the EMT-6 and JIMT-1 models are shown above right. Similar results for flow cytometric quantitation of effector memory phenotype infiltrating T-cells were observed in the MC38, and Myc-Cap A models (above left). Tumor infiltrating M-MDSC and G-MDSC numbers were inhibited by IRX5010 in colon and prostate tumors. TILs are quantified as cells per mg of harvested tumor tissue. MDSC are quantitated as percent of cells detected in the parent flow cytometry gate for CD11b that are either Ly-6C high vs Ly-6G- for myeloid MDSC, or Ly-6C low vs Ly6-G+ for granulocytic MDSC.

TIL in Colon, Prostate Tumors (mean cells/mg)

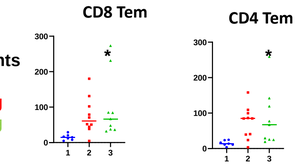
	Treatment	CD3 T	CD4 Tem	CD8 Tem
MC38	Vehicle	639	295	122
	10 mg/kg	385	211	37
	25 mg/kg	1163	630	226
MyC-CaP A	Vehicle	175	38	9
	10 mg/kg	609	290	35
	25 mg/kg	1041	206	153

MDSC in Colon and Prostate Tumors % Gate

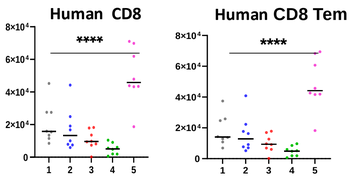
		M-MDSC	G-MDSC
MC38	Vehicle	37.9	9.0
	10 mg/kg	26.2	8.4
	25 mg/kg	24.2	3.9
MyC-CaP	Vehicle	8.3	48.8
	10 mg/kg	5.4	41.5
	25 mg/kg	2.3	38.3

T-cells in Breast Cancer Tumors (cells/mg)

EMT-6 Triple Negative Syngeneic Model



JIMT-1 Human Her2+ Xenograft Model



Treatments
Vehicle
IRX4204 (RXR)
Anti-PD1
IRX4204 + Anti-PD1
IRX5010

- P< 0.05 **** P< 0.0001
- one-way ANOVA with Dunnett's test compared to vehicle control group

Results

IRX5010 demonstrated substantial tumor growth inhibition at 10 and 25 mg/kd/day in the EMT-6 model. IRX5010 inhibited growth in MC38, and MyC-CAP A models at 25 mg/kg/day. It inhibited growth moderately in the JIMT-1 human Her2+ breast cancer xenograft model (but substantially promoted tumor infiltrating human effector memory phenotype T-cells in this model).The second generation RARγ agonist IRX5010 demonstrated *in vivo* inhibition of tumor growth in models of multiple types of the most prevalent human cancers, associated with increased numbers of effector memory phenotype TILs and decreased tumor infiltrating MDSCs. These data support that RARγ agonism is a potential new approach for immunotherapy of cancers.

Conclusions

RARγ agonists demonstrated *in vivo* inhibition of tumor growth in models of multiple types of cancers, associated with increased numbers of effector memory phenotype TILs and decreased tumor infiltrating MDSCs. These data support that RARγ agonism is a potential new approach for immunotherapy of cancers. They expand studies recently published by our collaborators at the Frederick National Laboratory for Cancer Research with ourselves, which demonstrated effects of our first generation RARγ agonist IRX4647 on tumor growth and microenvironment in a murine model of NSCLC, with increased TILs, and combination treatment effects on lung tumor growth with anti-PD-L1 checkpoint inhibitor (2).

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Acknowledgement

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COI Disclosures

Martin Sanders and Vidyasagar Vuligonda are directors, officers, shareholders, and patent inventors of Io Therapeutics, Inc.

References

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2. Wei CH, et al., A novel retinoic acid receptor-γ agonist antagonizes immune checkpoint resistance in lung cancers by altering the tumor immune microenvironment. Sci Rep. 2023 Sep 9;13(1):14907.

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