A novel aryl hydrocarbon receptor antagonist (PX-A24590) with anti-tumor activity in a syngeneic mouse pancreatic cancer model

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Abstract

The aryl hydrocarbon receptor (AhR) is a ligand-controlled transcription factor that is widely known for mediating toxicity and tumor-promoting activities of halogenated hydrocarbons (like Dioxin, TCDD) and polycyclic aromatic hydrocarbons (e.g. Benzo[a]pyrene and 3-Methylcholanthrene). Other ligands include metabolites produced by commensal microorganisms on the skin and in the gut and are known to modulate the transcriptional activity of AhR in different immune cells (e.g. ILC type 3 in the gut) and epithelial cells, thereby balancing the immune system’s response towards these microorganisms. In recent years, endogenous L-Tryptophan metabolites, such as L-Kynurenine and Kynureninic acid, that are produced under control of the indole-3,3-Dioxygenases IDO1 and TDO2 pathways, were shown to activate AhR.

Constitutive activation of the IDO1/TDO2/AhR pathway and nuclear AhR protein accumulation is frequently observed in different tumor types, which is thought to be linked to the observed diminished anti-tumor immune response. It is believed that secreted AhR activating ligands aid in reducing the pressure exerted on tumors by the immune system through increasing the numbers and function of regulatory T cells and reducing the numbers and function of cytotoxic CD8+ T-cells. Inhibition of IDO1 by Epacadostat improved anti-tumor efficacy of the anti-PD-1 checkpoint inhibitor Keytruda in a Phase II study in melanoma but unfortunately not in the recently terminated Phase III ECHO-301 study in melanoma.

In order to relieve AhR-mediated immune-suppression, Phenex Pharmaceuticals initiated a program to identify small molecule AhR antagonists to block downstream signaling of AhR due to activating endogenous ligands. To this end, we have identified a novel AhR antagonist, PX-A24590, which showed strong antagonistic activity against human AhR in a cell based CYP1A1 promoter-driven luciferase reporter assay in HepG2 cells. PX-A24590 displays good oral bioavailability and low clearance in mice. In C57BL/6 mice transplanted with syngeneic Panc02 pancreatic tumor cells, we were able to demonstrate anti-tumor efficacy with three different oral doses of PX-A24590 compared to an effective dose of the IDO1 inhibitor Epacadostat.

Study design

Subcutaneous pancreatic cancer model with Panc02-HA cells in syngeneic C57BL/6 mice

Tumors were isolated on day 35 post tumor cell implantation and COH+ and COH- cell numbers determined by flow cytometry. * = P<0.01; ** P<0.001; *** P<0.0001

Comounds

IDO1/TDO-Kynurenin-AhR immunosuppression pathway

AhR antagonist

- increased CD8+ T cells
- increased M1 macrophages

Fig. 1

Screening hits from „in-house“ library & published AhR antagonists

PX-A24590

Cellular IC50 huAhR~60m mAhR~1µM t1/2 = 3.3 h F89% (µM/pM)

Patents for 3 structurally related AhR modulator series have been filed

Fig. 2

Epacadostat

PX-A24590 antagonizes natural and synthetic AhR agonists in HepG2-CYP1A1-Luciferase cells

Fig. 3

PX-A24590 antagonizes mouse Pan02-4A4 cells in vitro

Fig. 4

Summary

- AhR antagonist PX-A24590 shows anti-tumor activity in syngeneic PDAC model (Pan02-HA)
- AhR antagonist increases intra-tumoral CD8+ T cells and M1 macrophages
- AhR antagonism increases CD8+ T cell numbers in aCD3/CD28 stimulated human PBMC in vitro
- AhR antagonist PX-A24590 enhances anti-PD-L1 efficacy in a subcutaneous CT26 colon tumor model
- AhR antagonists may show anti-tumor efficacy in ID01, ID01/TDO2 and TDO2 expressing tumors