Targeting autotaxin to suppress stromal signaling in the tumor microenvironment to improve outcome to therapy in fibrotic tumor types

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Background
Recent findings indicate that in cancer, host immune suppression and resistance to therapy is orchestrated by the presence and activity of stromal cells in the tumor microenvironment. Therefore novel approaches to overcome stromal mediated resistance to therapy represent a potential strategy to improve the outcome to chemotherapy and immune checkpoint blockade, particularly in tumors that have a fibrotic microenvironment. Autotaxin is an enzyme that converts lysophosphatidylcholine (LPC) to lysophosphatic acid (LPA), a key pathway that is aberrantly activated in fibrosis. LPA has also been described to act directly on tumor cells, promoting their growth and proliferation via G protein-coupled LPA Receptors (LPAr). IOA-289 is a novel, potent, selective and orally bioavailable inhibitor of autotaxin, a target with known clinical application in fibrotic diseases and with a strong rationale for exploration in cancer.

Methods
• Analysis of ATX (gene name ENPP2) expression in various cancers and sample types using TCGA and GTEx data.
• CA19-9 and ATX levels measured in patients’ plasma using a commercial ELISA kit. Growth and proliferation of MIA PaCa-2 cells were assessed upon treatment using time-lapse imaging (Incucyte). Nuclight rapid red dye was used for live-cell nuclear labelling. For condition media generation, 0082T cells were treated with 12 µM IOA-289 or 0.1% DMSO
• Plasma concentrations of IOA-289 and LPA were measured following a single oral dose of IOA-289 10 mg/kg p.o. showed dose-dependent reduction of circulating LPA C18:2 with an ED50 value at 1 h post-dose of around 3 mg/kg (Fig. 4A-B). Plasma exposure was measured up to 24 h post dose in HV subjects (Fig. 4C). LPA C18:2 in plasma was measured at baseline and up to 24 h post dose (Fig. 4D). Using the PK and PD data, the IC50 of IOA-289 was calculated as 15 ng/mL in human plasma (Fig. 4E).

Conclusion
• ATX is elevated in PDAC and directly impacts cancer cell line growth in vitro
• Cancer associated fibroblasts stimulate PDAC cell growth in vitro and ATX is a key mediator driving the tumor supporting action of CAFs.
• ATX is a novel solid tumor target that orchestrates the interplay between stromal cells, immune cells and tumor cells.
• IOA-289 is the first ATX inhibitor to be investigated in solid tumors and here we demonstrate that IOA-289 reduced tumor burden in a mouse model of PDAC.
• IOA-289 is a potent, orally bioavailable ATX inhibitor with a PK/PD relationship directly translatable from mouse to human with a plasma IC50 of 15 ng/mL.
• IOA-289 is in clinical development for the treatment of solid tumors burdened with a high degree of fibrosis.

Conflict of Interest Statement:
2J, MD, KNS, LV & ML are employees and shareholders of iOnctura

Figure 1: ATX expression in PDAC. Pancreatic adenocarcinoma (PDAC) samples have high ENPP2 expression compared to normal tissue (Fig. 1A). ATX levels in PDAC patient plasma correlate with CA19-9 levels (Fig. 1B).

Figure 2: IOA-289 inhibits the growth and proliferation of PDAC cell lines in vitro (Fig. 2A, B). CAFs but not PDAC cells are the main source of LPC (Fig. 2C). Conditioned media (CM) from CAFs stimulate the growth of PDAC cells (Fig. 2D). IOA-289 inhibits the growth stimulating effect of CAFs (Fig. 2E). IOA-289 also inhibits key mediators secreted by activated fibroblasts that play a role in tumor-stroma-immune cross-talk (Fig. 2F-H).

Figure 3: Effect of IOA-289 on PDAC growth in vivo: IOA-289 has single agent activity on orthotopic pancreatic cancer growth in vivo (Fig. 3A-B). IOA-289 increased the infiltration of CD3+ cells into the tumors (Fig. 3C), with a simultaneous reduction in Treg cells (Fig. 3D).

Figure 4: Mice dosed with IOA-289 p.o. showed dose-dependent reduction of circulating LPA C18:2 with an ED50 value at 1 h post-dose of around 3 mg/kg (4A-B). Plasma exposure was measured up to 24 h post dose in HV subjects (4C). LPA C18:2 in plasma was measured at baseline and up to 24 h post dose (4D). Using the PK and PD data, the IC50 of IOA-289 was calculated as 15 ng/mL in human plasma (4E).