Novel Oxidative phosphorylation inhibitor IACS-010759 inhibits p38MAPK-NFkB signaling pathways

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The higher basal metabolic energetic capacity and kinase activation affects sensitivity to OxPhos Inhibition in AML cells.

1. IACS-010759 resistant cells show
   - High baseline expression of mitochondrial metabolism related genes.
   - High baseline level of OxPhos which is further increased by co-culture with MSCs.
2. Hypoxia reduces oxidative metabolism and causes resistance to IACS.
3. IACS-010759 inhibits p38MAPK-NFkB and mTOR signaling in sensitive cells but not in resistant cells.

BACKGROUND

- Acute myeloid leukemia (AML) cells frequently adjust to increased energy/substrate demands under stress conditions in the bone marrow microenvironment.
- MAML cells are highly dependent on oxidative phosphorylation (OxPhos) for survival.
- IACS-010759 is a novel oral nanomolar complex I inhibitor that blocks cellular respiration through inhibition of complex I of the electron transport (Marszałek et al. Nature Medicine, 2018). It is currently in Phase 1 clinical trial in AML (NCT#02882321).

PURPOSE OF THE STUDY

To assess the biomarkers of anti-AML activity of IACS-010759.

MATERIALS

Primary samples:
- 14 primary AML samples.
- 11 sensitive / 3 resistant to IACS-010759

Human AML cell lines:
- OCI-AML3 (sensitive to IACS-010759)
- MOLM13 (resistant to IACS-010759)

Reagents:
- OxPhos (complex I) inhibitor IACS-010759

METHODS

- Cell viability assay
- Western blotting
- Seahorse Extracellular Flux Analysis
- Cap Analysis of Gene Expression (CAGE) sequencing

FUTURE PLAN

- Investigate the promoter-enhancer network associated with IAC-010759 sensitivity.
- Investigate the resistant mechanisms against OxPhos inhibition in the BM microenvironment, focusing on the interactions between AML cells and stromal cells.

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