Introduction

Acute myeloid leukemia (AML) is an aggressive malignancy. Outcomes in relapsed disease are dismal especially in older patients and those with poor risk cytogenetics. New therapies are desperately needed. Metabolism in AML cells is dysregulated. Shown is the average OCR from 3 independent experiments each developed by Cornerstone.

Metabolism in AML Cells

assessed. Shown is the average OCR from 3 independent experiments each treated with Ara (KGDH) and associated with cytogenetics. Outcomes in relapsed disease are dismal.

613 is a novel lipote derivative developed by Cornerstone. Lipote is a simplified derivative that inhibits the PDH (KGDH) and mitochondrial metabolism. OCI-AML3 is 0.0387 and for K562 is <0.0001. 613 targets AML and is a simplified derivative of 613. 613 is a Novel Lipote Derivative that inhibits the PDH complex (PDH) and associated with cytogenetics.

Chemotherapy Induces Mitochondrial Metabolism in AML Cells

CPI-613 is a novel lipote derivative that inhibits the TYK2 cycle. The structure of lipote and CPI-613 are shown on the right. On the left is a simplified schematic of core metabolism with the CPI-613 target shown.

CPI-613 is Synergistic with Chemotherapy In Vivo

CPI-613 is synergistic with chemotherapy in vivo as well. CPI-613 is synergistic with chemotherapy in vivo as well.

Phase I Clinical Trial Schema

TCA Cycle Inhibition by CPI-613 Increases Sensitivity to Chemotherapy in Older and Poor Risk Acute Myeloid Leukemia (AML)

Tutwiler Fund. TSP is supported by NCI 1K08CA169809 The MacKay Foundation for Cancer Research, and the Frances P

AMPK Contributes to Resistance to CPI-613

AMPK promotes resistance to CPI-613. Left: Competition assay. Cas9 expressing MFL2 cells with AMPK tagged with GFP. Cells were incubated with the indicated drug for 72 hours and the %GFP+ determined in the viable population. Both

Conclusions

1. Chemotherapy induces mitochondrial oxygen consumption via the TCA cycle.
2. TCA cycle inhibition with the novel agent CPI-613 sensitizes leukemia to chemotherapy.
3. CPI-613 is a novel lipote derivative that inhibits the PDH complex (PDH) and mitochondrial metabolism.
4. Chemotherapy reduces mitochondrial oxygen consumption and does not promote resistance to CPI-613.
5. The presence of an immune cell signature may be predictive of those patients most likely to respond to the approach.
6. Loss of p53 impairs mitochondrial oxygen consumption, WFL2 cells expressing Cas9 were infected with sgRNAs against P53 or P53 and oxygen consumption measured 24h later. The same cells were treated with chemotherapy at the same time. Following treatment viability was assessed (Right Panel). Overexpressed in Responders Differential gene expression analysis of baseline samples revealing several significant biological categories related to immune infiltration. Heat map on the right shows the top 20 differentially expressed genes between responders (R) and non-responders (NR).