PLK4 as a Novel Therapeutic Target in TP53-mutant Acute Myeloid Leukemia

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Introduction
Resistance to current therapies is one of the major challenges for the cure of TP53-mutant (mut) acute myeloid leukemia (AML). Polo-like kinases (PLK1-PLK5) are serine/threonine kinases that have vital regulatory functions in the cell cycle.1 Previous studies reported that TP53-mut cancer cells, including lung cancer and AML overexpress PLK4.1,2 PLK4 overexpression could potentially contribute to drug resistance in these cells. Therefore, PLK4 could be a promising therapeutic target for TP53-mut AML and potentially improve the efficacy of current AML therapeutic agents.

Hypothesis
Inhibition of PLK4 may exhibit antileukemia activity in TP53-mut AML, and potentially improve the efficacy of current AML therapeutic agents.

Methods
➢ Human MOLM-13 AML cells with TP53 wild-type (WT), TP53 knockout (KO), or TP53-mut were treated with PLK4 inhibitor CFI-400945 and/or venetoclax at various doses for 24 and 48 hours.
➢ Cell cycle and polyploidy were measured using an Edu Click-it Kit and FXCycle.
➢ Apoptosis was measured using FACs-flow cytometry after cells were stained with Clv-PARP antibody or AnnexinV/7AAD.
➢ Intracellular protein levels were measured by western blot.

Results
Increased PLK4 RNA levels in TP53-KO or mut compared to TP53-WT AML cells

![Graph showing increased PLK4 RNA levels](image)

Fig. 1. RNA sequencing analysis of PLK4 transcript level in MOLM-13 TP53-WT, TP53-KO, and TP53-mut cells.2

CFI-400945 and venetoclax combination induces more polyploidy and apoptosis in MOLM-13 TP53-mut compared to TP53-WT isogenic cells

![Graph showing CFI-400945 and venetoclax combination](image)

Fig. 2. TP53 isogenic MOLM-13 cells were treated with 25 nM PLK4 inhibitor (CFI-400945) for 48 hr. A) FACs-flow cytometry analysis of cell cycle and total DNA content in MOLM-13 TP53 isogenic cells, also showing Clv-PARP. B) Polyploidy percentage in MOLM-13 TP53 isogenic cells using the live cell population. C) Normalized percentage of Clv-PARP+ population within each subpopulation.

CFI-400945 decreases viability in cells from a patient TP53-mut AML

![Graph showing CFI-400945 decreases viability](image)

Fig. 3. TP53-mut AML patient sample was treated with CFI-400945 (n=1) for 48 hr. Blasts 85%.

Conclusions
➢ TP53-mut or TP53-KO AML cells express higher PLK4 than the isogenic TP53-WT cells.
➢ Inhibition of PLK4 induces polyploidy and cell death in TP53-mut cells.
➢ PLK4 inhibition-mediated cell death induction is further enhanced by combination with venetoclax.
➢ PLK4 inhibition enhances the therapeutic efficacy of venetoclax in TP53-mut AML cells.

References

Acknowledgments
Thanks to Marites Melanson, Chandra Bartholomeusz, and Nancy Strange for their incredible hard work curating this summer experience.