**Brief summary of work:**

Although effective molecular targeted therapies exist for chronic myeloid leukemia and acute promyelocytic leukemia but 3+7 cytotoxic chemotherapy and stem cell transplantation continue to be essential means in the treatment of AML. However, current chemotherapy regimens remain inadequate and fail to induce or sustain long-term remissions in AML, due to the emergence of leukemic blasts, which remain resistant to apoptosis following chemotherapy. This resistant leads to relapse and eventually patients die of leukemia. It is well established that apoptotic block and proliferation of undifferentiated cells of myeloid progeny is responsible for the development of AML.

The discovery and development of small molecule cancer drugs has been revolutionized over the last decade. Defects in apoptotic machinery are one of the main mechanisms that cells use to escape cell death. Small molecule inhibitors aiming at restoring apoptosis in leukemic cells have shown encouraging activity in early clinical trials and some of these drugs including Venetoclax are currently being evaluated in randomised controlled trials. The majority of AMLs are genetically diverse. Cell-to-cell variability in apoptosis signaling contributes to heterogenic responses to cytotoxic/targeted stress in AML. Within a clonal cell population, some cells rapidly induce apoptosis, while other cells appear more resistant and continue to proliferate. Thus, improved therapeutic strategies to overcome apoptotic resistance and enhanced proliferation are needed.

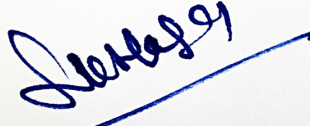
Targeting the apoptotic defects by direct inhibition of BCL-2 family proteins and uncontrolled proliferation by CDK inhibitors can restore cell sensitivity to cell death. Therefore, there is a critical need to develop robust in vitro and animal models to study signaling between BCL-2 proteins and cyclin dependent kinases and combining their targeted actions for the improved therapeutic strategies to overcome apoptotic resistance in AML.

In the present study, we describe orally bioavailable non-covalent inhibitor of CDK7 that inhibits leukemic growth in vitro as well as in mouse model. CRI-256 showed antiproliferative activity in different leukemic cell lines as well as patient derived blast cells. As the IC50 of the compound was in a narrow range in comparison to Venetoclax and cytarabine, it suggests that CDK7 inhibition can work effectively in patients of different risk groups. Also, a higher IC50 value of compound in comparison to AML blast in healthy PBMC demonstrated low toxicity in normal cells.

Further transcriptomic data suggested that mechanism of action underlying the efficacy of CRI-256 in leukemic cells might relate to the preferential modulation of gene involved in cell cycle and apoptosis. Several studies have reported c-Myc as a candidate oncogenic driver in different cancer models. Here, we further discovered that a selective CDK7 inhibitor, CRI-256 exerted antineoplastic activity by disrupting c-myc-dependent transcriptional machinery leading to cell-cycle arrest in leukemic cells.

The inhibitor showed antileukemic effect in subcutaneous AML model as a single agent. It was also found to be synergistic in combination with Venetoclax in leukemic cell lines as well as in patient samples. Furthermore, it decreases the expression of MCL-1, which was reported to be the emerging cause of Venetoclax resistance.

In conclusion, we have shown extensive preclinical evidence that novel transcriptional suppressor CRI-256 serves as a promising therapeutic option for the acute myeloid leukemia. Although AML blast display tremendous heterogeneity however it remains exquisitely addicted to oncogenes which are responsible for high transcriptional rates such as c-MYC & MCL-1. The development in molecular characterization of AML, identification of mutations playing role in pathogenesis of disease as well as frustrating clinical outcomes of conventional 7+3 chemotherapy, strongly encouraged the idea of more efficacious targeted therapies, which can be more specific and less toxic. Our study highlights CDK7 inhibition by novel inhibitor, CRI-256 as a new molecular target in combination with Venetoclax as an alternative to conventional chemotherapy.



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