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## 604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

### mRNA Translation Inhibition Targets Bioenergetic Homeostasis in AML Cells *in Vitro* and *In Vivo* and Synergizes with Cytarabine and Venetoclax

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Acute myeloid leukemia (AML) is an aggressive hematological cancer resulting from uncontrolled proliferation of differentiation-blocked myeloid cells. Seventy percent of AML patients are currently not cured with available treatments, highlighting the need of novel therapeutic strategies. Recently, inhibition of BCL-2 with venetoclax in combination with hypomethylating agents has emerged as an attractive strategy for high-risk AML cases. Another promising target in AML is the mammalian target of rapamycin complex 1 (mTORC1) (Oki et al, Nature Comm, 2021). However, clinical inhibition of mTORC1 is limited by its reactivation through compensatory and regulatory feedback loops. To curtail these drawbacks, we adopted a strategy of inhibiting an important effector of the mTORC1 signaling pathway controlling mRNA translation - the eukaryotic initiation factor 4A (eIF4A), subunit of the translation initiation complex eIF4F.

Recent evidence suggests that translational programs mediated by the mTORC1/4E-BP/eIF4F axis can support resistance to therapy in various cancer models driven by oncogenic kinases, in part by allowing cellular metabolic plasticity (Hulea L et al, Cell Metab. 2018). In fact, metabolism, and specifically mitochondrial oxidative phosphorylation, has emerged as a central dependency of AML cells, sustaining resistance to therapy and recurrence.

Using the MOLM-14 human AML cell line to model therapy-resistant disease, we previously demonstrated the anti-leukemic effect of a potent and specific eIF4A inhibitor (eIF4Ai), CR-1-31-B, both *in vitro* and *in vivo* (Fooks et al, J Exp Clin Cancer Res 2022). eIF4Ai affected cellular metabolism, by reducing mitochondrial membrane potential (MMP) and the rate of ATP synthesis from mitochondrial respiration and glycolysis. Concomitantly, eIF4Ai decreased intracellular levels of specific metabolic intermediates of the tricarboxylic acid cycle (TCA cycle) and glucose metabolism, while enhancing mitochondrial ROS. Furthermore, eIF4i enhanced apoptotic priming while reducing the expression levels of the antiapoptotic factors BCL2, BCL-XL and MCL1. Importantly, CR-1-31-B acted synergistically *in vitro* in combination with cytarabine or venetoclax.

Recently, we have expanded our characterization of the eIF4Ai/venetoclax combination in MOML-14 cells, and showed that venetoclax potentiates the CR-1-31-B-induced inhibition of cellular respiration, glycolysis and ATP production (Seahorse). The combination provokes a robust apoptotic response with different temporal dynamics to single treatment, as measured using the Incucyte platform. *In vivo*, we have validated the strong anti-leukemic response induced by CR-1-31-B in a MOLM-14 transplantation model, after only 7 days of treatment, and showed that venetoclax slightly potentiates this effect. In addition, eIF4A inhibition reduces the levels of several metabolic proteins (GLS1, IDH1), which supports our previous observations of decreased levels of TCA cycle metabolites.

We have confirmed the metabolic and pro-apoptotic effect of eIF4Ai in a second cellular model of AML, U937. Consistent with previous results, in U937 cells CR-1-31-B induces apoptosis at low nM concentrations, reduces cellular bioenergetics, ATP production, as well as levels of pro-proliferative (cyclin D3, CDK4) and anti-apoptotic (BCL-2, MCL-1) proteins.

Our collective studies highlight (i) the importance of the crosstalk between mRNA translation and metabolic regulation and (ii) that direct inhibition of translation represents an appealing therapeutic strategy for clinical cases of therapy resistance that

are dependent on the mTORC1/eIF4F axis. This is of interest as several translation inhibitors are currently tested in phase 1/2 clinical trials in solid malignancies.
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