5-Fluorotroxacitabine displays potent anti-leukemic effects and circumvents resistance to Ara-C

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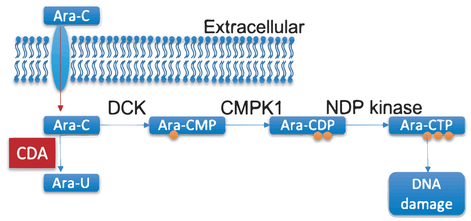
INTRODUCTION

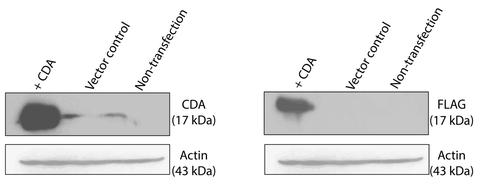
Cytarabine has been a major backbone of Acute Myeloid Leukemia (AML) treatment. But eventually, 60-70%% patients relapse. Several mechanisms of drug resistance for Ara-C have been described one of which is increased Cytidine deaminase (CDA) deaminating Ara-C; thereby preventing generation of the triphosphorylated active metabolite.

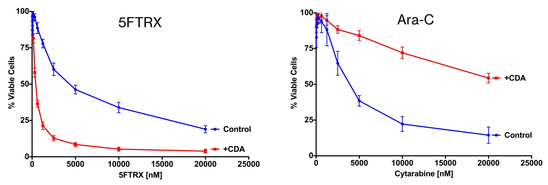


We evaluated a novel nucleoside analogue, 5FTRX, for its efficacy in Acute Myeloid Leukemia and ability overcome resistance due to increased CDA.

RESULTS

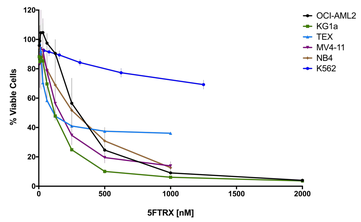
5FTRX overcomes resistance due to increased CDA





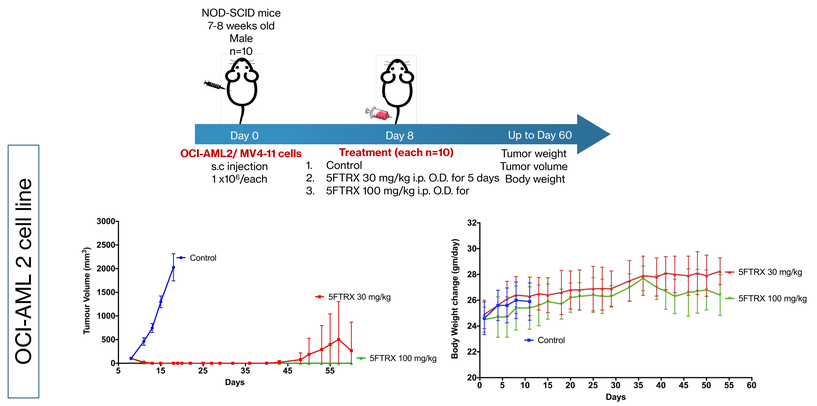
	HEK293 Cell line	IC50 (nM)	95% CI (nM)
5FTRX	Control	4446	4162-4749
	CDA+	446.6	428.2-465.9
Ara-C	Control	3990	3646-4366
	CDA+	25799	22924-29034

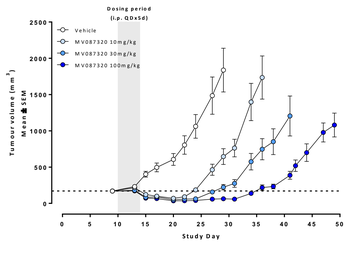
5FTRX shows efficacy in AML cell lines



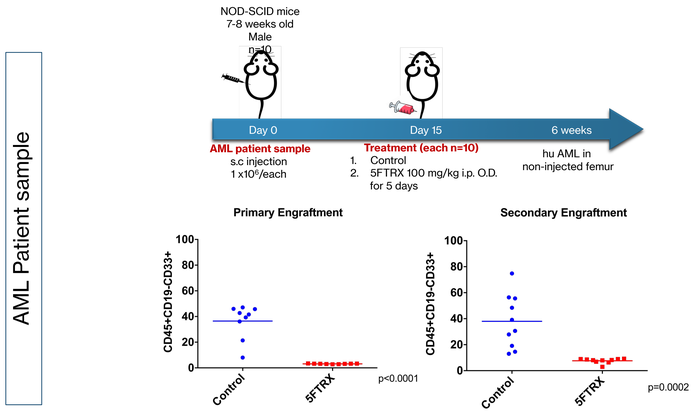
AML cell line	IC50 (nM)	95% CI (nM)
OCI-AML2	297.5	279.1-317.1
TEX	179.2	135.1-237.7
MV4-11	160.8	114.7-225.5
KG1A	109.2	96.2-123.9
NB4	237.3	180.5-312.1
K562	6236	5234-7289

5FTRX reduces engraftment in mouse xenograft models



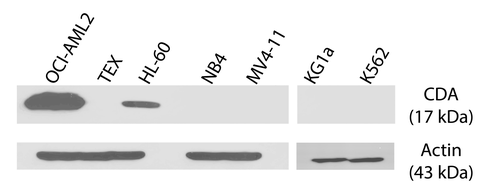


5FTRX displayed robust and dose-dependent inhibition of OCI-AML2 and MV4-11 tumors in mouse xenograft models, with complete tumor regressions and long-lasting tumor growth delays with no changes in body weight.



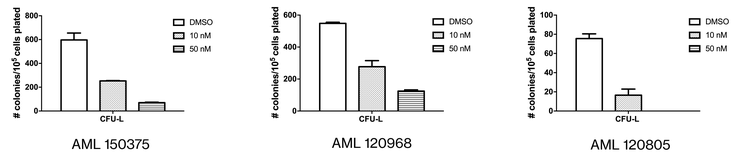
5FTRX (100 mg/kg i.p, x 5 days) reduced primary and secondary AML engraftment >95% compared to controls without toxicity

Basal levels of CDA do not correlate with 5FTRX efficacy in AML cell lines

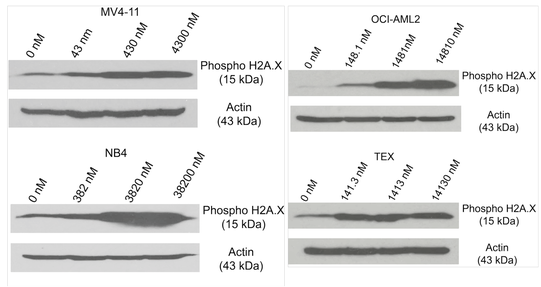


Immunoblot showing basal CDA levels

5FTRX reduced colony formation in primary AML samples



5FTRX induced DNA damage and increased Phospho H2A.X levels



CONCLUSION

- CDA-overexpressing cells were more sensitive to 5FTRX, and less sensitive to Ara-C.
- 5FTRX reduced viability in AML cell lines.
- 5FTRX decreased colony formation of AML patient samples.
- 5FTRX reduced AML engraftment in mice.