TARGETING CLEVER-1 TO OVERCOME TREATMENT RESISTANCE IN ACUTE MYELOID LEUKEMIA

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CELL BIOLOGY

Background and Aim

Current frontline treatments for acute myeloid leukaemia (AML) effectively achieve remission, yet relapse is common. Relapse is caused by therapy-resistant leukemic stem cells, and the expression of stemness markers indicates a poor prognosis. Expression of Clever-1 is also a poor prognostic factor, and its suppression inhibits AML cell line proliferation. Clever-1 blockade suppresses oxidative phosphorylation in AML cell lines and may overcome therapy resistance. Bexmarilimab, an anti-Clever-1 antibody, is currently under clinical investigation. This work focused on elucidating the role of Clever-1-blockade in overcoming therapy resistance.

Conclusions

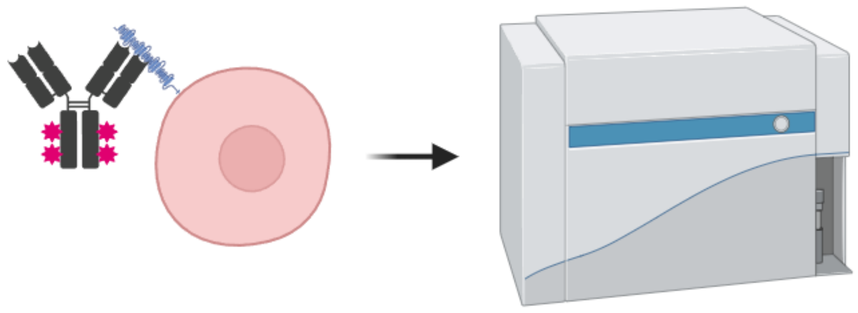
Although Clever-1 blockade inhibits oxidative phosphorylation, it did not affect the concentrations of key metabolites. This may suggest that inhibition is mediated by differential compartmentalization of the metabolites rather than their total amounts. Further work is needed to discover the mechanism of action and significance in therapy resistance.

Methods

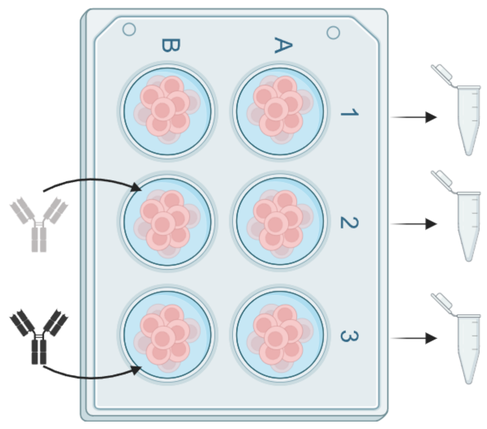
Bexmarilimab-responsive cell lines:
- HL-60
- MOLM-13
- KG-1

Bexmarilimab-resistant cell lines:
- Kasumi-1
- MV4-11

Flow cytometry analysis of Clever-1 and stemness markers on parental and resistant cell lines

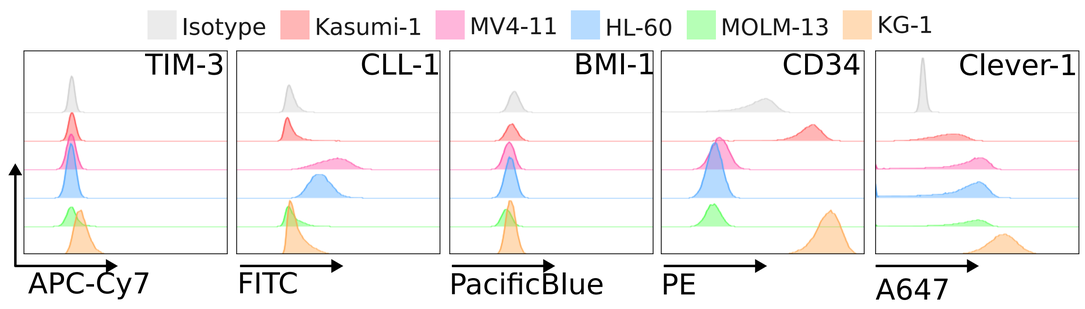


Metabolite analysis after 48 h Clever-1 blockade

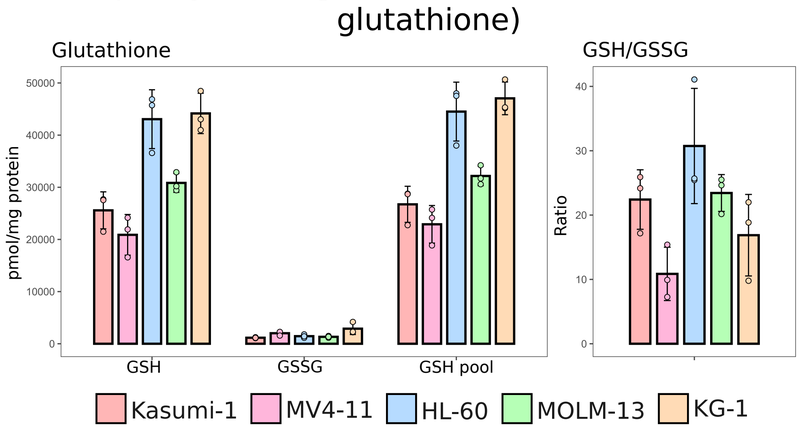


Results

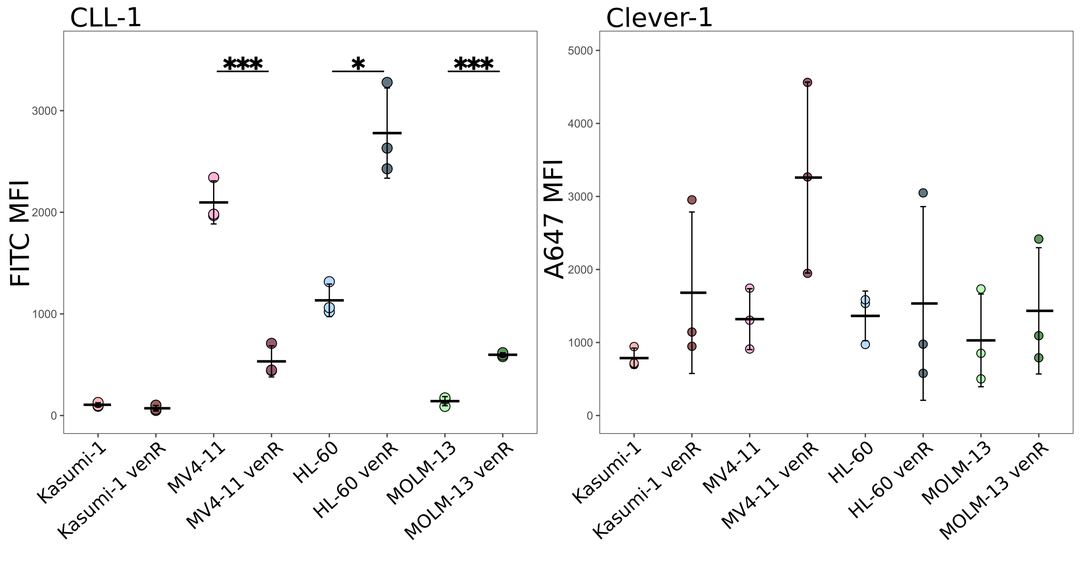
AML cell lines expressed little stemness markers at baseline



Bexmarilimab-resistant cell lines had reduced capacity to mitigate oxidative stress (baseline glutathione)



Bexmarilimab-responsive and venetoclax-resistant cell lines upregulated CLL-1. Venetoclax-resistant cells showed a trend toward higher surface Clever-1 expression.



Bexmarilimab treatment did not directly affect metabolite concentrations