DIRECT, POTENT AND TP53-INDEPENDENT ACTIVITY OF STING AGONISTS AGAINST ACUTE MYELOID LEUKEMIA ENHANCES VENETOCLAX EFFICACY *IN VIVO*

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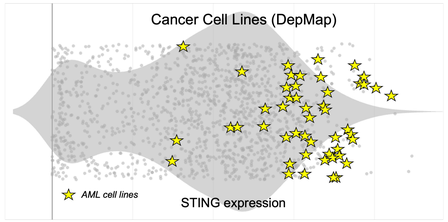
WEHI brighter together

INTRODUCTION

- Outcomes for acute myeloid leukaemia (AML) remain poor, especially for patients with adverse risk profiles, highlighting the ongoing need for new therapies
- A particular area of high unmet need is AML with *TP53* aberrations[1,2]
- The canonical role of the stimulator of interferon genes (STING) pathway is to sense cytosolic double-stranded DNA and elicit a type 1 interferon response[3]
- STING activation can also induce cell death in contexts of high STING protein expression[4,5]
- We report that STING agonists have novel, direct and potent cell-intrinsic activity via induction of apoptosis in AML, where there is high-level expression of STING
- Importantly, STING-induced apoptosis is active in TP53-defective AML and activity is enhanced by combination with BH3-mimetics, including venetoclax



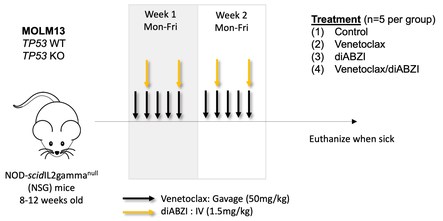
HYPOTHESIS AND AIM

Hypothesis: STING agonists activate apoptosis in malignant cells expressing high levels of STING and that activity will be STING dependent

Aim: To explore the preclinical efficacy of STING agonists in models of AML *in vitro* and *in vivo*

METHODS

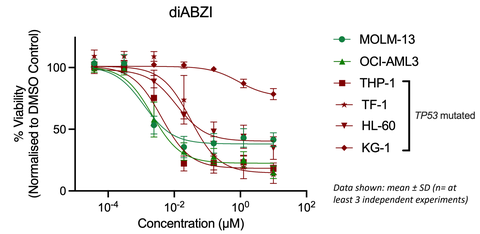
- We tested the small molecule STING agonist diABZI (GSK3745417), which is currently in early phase clinical trials (NCT03843359, NCT05424380)
- Drug sensitivity assays were performed using human AML derived cell lines and primary bone marrow or peripheral blood mononuclear cells from patients with AML or myelodysplastic syndrome with increased blasts. Cells were cultured for 48 hours and cell death assessed by flow cytometry
- Bliss scores for combination assays were computed using the web application Synergy Finder
- *In vivo* testing was conducted using a cell line-derived xenograft as per the displayed schema
- Statistical analysis was performed using log-rank test with Bonferroni correction



RESULTS

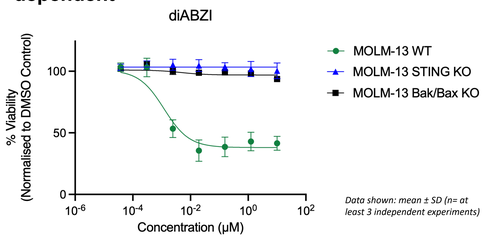
In vitro

1. The STING agonist diABZI is active in multiple human AML-derived cell lines, including lines with *TP53* mutations (maroon)



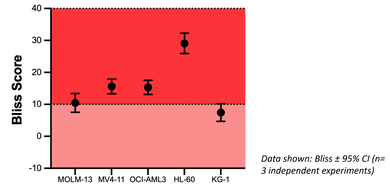
Data shown: mean ± SD (n= at least 3 independent experiments)

2. diABZI activity is STING and BAX/BAK dependent



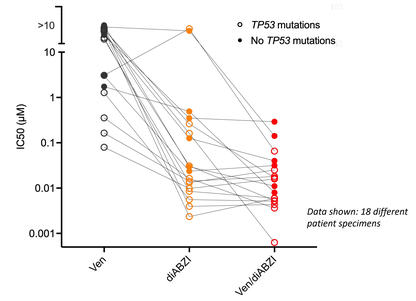
Data shown: mean ± SD (n= at least 3 independent experiments)

3. The STING agonist diABZI combined with venetoclax has synergistic activity in AML



Data shown: Bliss ± 95% CI (n= 3 independent experiments)

4. diABZI mono- and combination therapy with venetoclax is efficacious against primary AML *ex vivo*

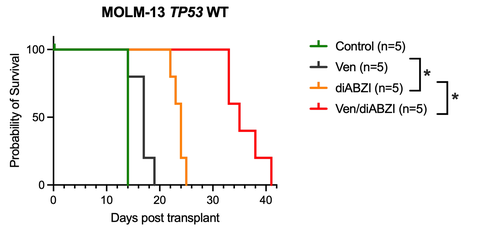


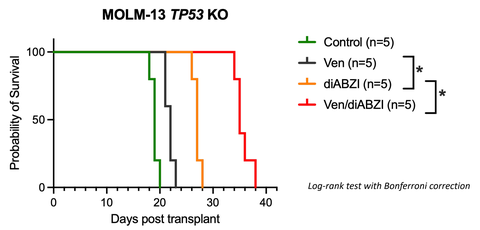
Data shown: 18 different patient specimens

In vivo

5. STING agonist and venetoclax therapy prolongs AML survival independent of TP53

Survival of mice engrafted with *TP53* KO MOLM-13 cells was significantly prolonged by the STING agonist diABZI in combination with venetoclax





Log-rank test with Bonferroni correction

CONCLUSIONS

- STING agonists exert potent cell-intrinsic anti-leukemic activity against human AML
- Drug activity is STING and BAX/BAK dependent
- The activity of the STING agonist diABZI enhances the effect of venetoclax and prolongs survival in a model of AML independent of TP53
- STING agonist monotherapy and combination therapy with venetoclax represent a promising and novel therapeutic approach for AML, including for *TP53* mutant AML, strongly supporting further clinical trial development

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