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Using the iron chelator deferasirox to overcome venetoclax resistance in mantle cell lymphoma

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Background

- Venetoclax resistance is a major clinical obstacle in mantle cell lymphoma (MCL) due to primary- and *de novo*- resistance.
- Deferasirox (DFX) is a clinically approved iron chelator with minor side effects.
- We have previously shown DFX to exert an anti-tumoral effect in MCL cell lines and patient-derived cells.
- We have previously shown DFX to induce ROS levels leading to oxidative stress and DNA damage and to trigger CD1 proteolysis by modulating the PI3K/AKT/GSK3β pathway.
- Studies show that rationally combined therapies act synergistically and continuously improve median survival of MCL patients.

Results

- Venetoclax significantly reduced REC-1 cell viability in a dose-dependent manner, while Z138 and Jeko-1 cells were relatively resistant to this treatment (Fig. 1A).
- DFX increased Jeko-1 cell sensitivity to venetoclax (CI=0.46) (Fig. 1B).
- DFX restored Z138 cell sensitivity to venetoclax, (CI=0.38) (Fig. 1C).
- Venetoclax treatment did not reduce CD1 levels in Jeko-1 & Z138 cells (Fig. 1D, E).
- DFX-venetoclax combination substantially reduced CD1 level to 22.3±4.3% and 28.2±3.3% in REC-1 and in resistant Z138 cells, respectively (Fig. 1D, E).
- DFX induced apoptosis in venetoclax-resistant generated MCL cell-line (Jeko-1VR) (Fig. 1F, G).

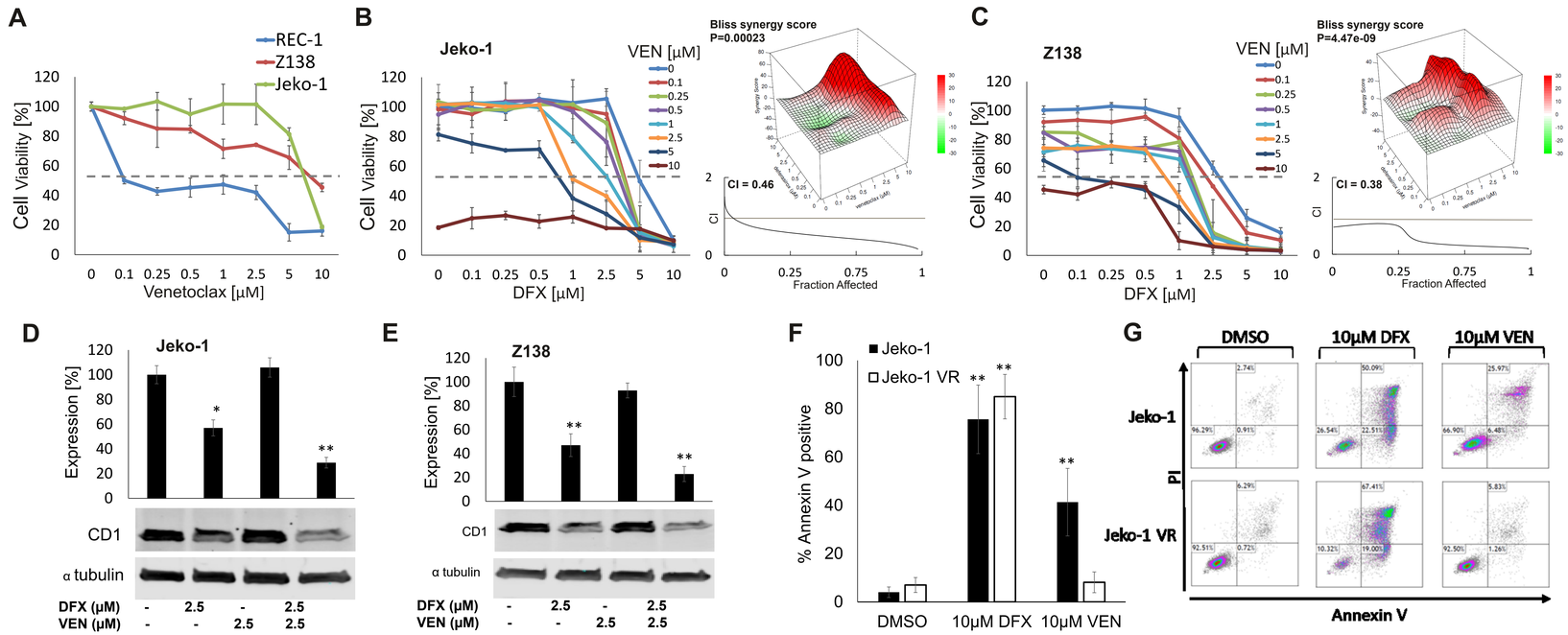


Fig. 1 | DFX synergizes with venetoclax in MCL cells. (A) Jeko-1, REC-1 and Z138 cells were exposed to increasing concentrations of venetoclax for 72h. **(B, C)** Jeko-1 and Z138 cells were exposed to different concentrations of DFX and ibrutinib for 72h. Shown Bliss synergy score 3D plot and combination index plot. **(D, E)** Representative Western blot and quantitative analysis of CD1 levels in REC-1 and Z138 cells treated with or without 2.5μM DFX and 2.5μM venetoclax for 24h. **(F, G)** Jeko-1/Jeko-1 venetoclax resistant (VR) cells were treated with 10μM venetoclax or DFX for 48h. Apoptosis was analyzed by annexin-V/PI. Values represent a mean of 3 experiments ± SEM. *P<0.05, **P<0.01.

Conclusion

- Our findings support the relevance of the DFX-venetoclax combination treatment in MCL.
- This combination enhances the efficacy of both drugs and restores the anti-proliferative activity of the drugs in resistant MCL cells.
- The efficiency of the drugs correlates with their ability to mediate CD1 degradation.
- An effective synergistic effect of DFX and venetoclax provides potential, clinically feasible therapeutic options for MCL patients and hopefully, a novel approach to overcome drug-resistance in the more aggressive relapsed/refractory MCL.