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Targeted treatment options for childhood hepatoblastoma using high-throughput drug screening

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INTRODUCTION

Hepatoblastoma (HB) is a pediatric liver malignancy with median age at diagnosis being one year. Current treatment entails chemotherapy (platinum-based alone or combined with doxorubicin) followed by surgery (tumor resection or liver transplantation). Survival rate of HB patients has improved; however, high-risk tumors are still difficult to treat with 20-30% of HB patients responding poorly to current treatment options. Furthermore, side effects of the chemotherapeutics can have a significant effect on the life quality of HB survivors.

In this study a drug sensitivity and resistance testing (DSRT) was conducted with five high-risk patient derived HB cell models. Pediatric primary hepatocytes (PH) were used as a control. Testing was done using 3D spheroids.

FIGURE 1

Drug screen included 528 treatment modalities. (A). 527 of the drugs were approved or emerging oncological compounds with various mechanisms of action and one was a drug combination. (B). Z-scores demonstrate the robustness of the screens.

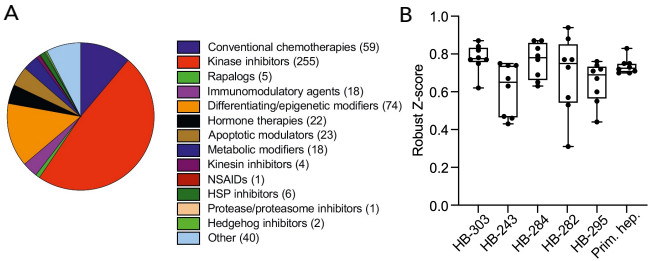
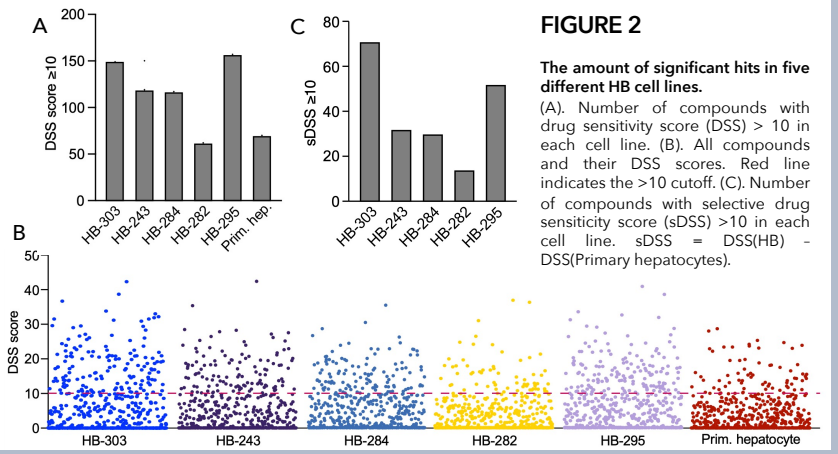


FIGURE 2



The amount of significant hits in five different HB cell lines.

(A). Number of compounds with drug sensitivity score (DSS) > 10 in each cell line. (B). All compounds and their DSS scores. Red line indicates the >10 cutoff. (C). Number of compounds with selective drug sensiticity score (sDSS) >10 in each cell line. sDSS = DSS(HB) – DSS(Primary hepatocytes).

FIGURE 3

Heatmap of top 10 compounds in each cell line with the highest overall DSS scores. Intensity of the colour describes the scale of the sDSS score. PH = primary hepatocytes.

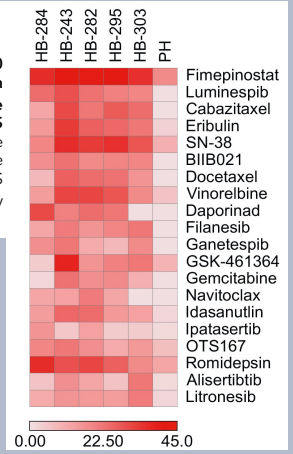
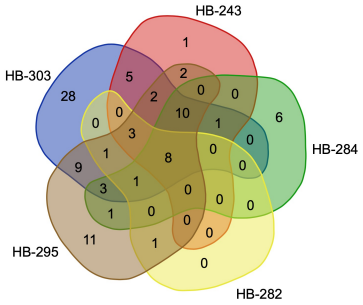


FIGURE 4

Venn diagram showing the number of shared hits with sDSS > 10 among the five HB cell models. Eight compounds in common in all models were onalespib, fimepinostat, idasanutlin, cabazitaxel, filanesib, BIIB021, eribulin and luminespib.



CONCLUSIONS

The screen revealed many new promising compounds for treatment of hepatoblastoma. Interestingly, standard treatments of HB only demonstrated a minor effect.

CONTACT INFORMATION

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