Introduction

- Hepatoblastoma (HB) is the most frequent liver malignancy of childhood with an annual incidence of 1.5 per million.
- Treatment options are surgery, chemotherapy, trans-arterial chemembolization (TACE) and radioembolization.
- However, the survival rate is less than 50% for high-risk, relapse, and treatment refractory patients.
- As the standard chemotherapy for HB has significant side effects and is usually ineffective for relapse refractory disease, treatment options are now shifting focus towards using targeted therapies as they work differently from standard chemotherapy drugs and often have less side effects.

Objective

To assess the therapeutic efficacy and anti-cancer mechanism of novel drug with HB through a drug sensitivity testing pipeline utilizing multiple novel, clinically relevant pre-clinical patient-derived cell lines (PDCL) and patient-derived xenograft (PDX) models.

Methods

- With the intrahepatic implantation of tumor thrombus from a non-metastatic stage 3 patient who recurred after transplantation, a patient derived xenograft (PDX) mouse model and a stable patient derived cell line (PDCD) HB17 was generated.
- Dinaciclib (cyclin-dependent kinase (CDK) inhibitor), was tested in HB17 along with other PDCL’s from different PDX models using CellTiter-Glo Luminescent Viability assays.
- Anti-proliferative effects of dinaciclib were assayed in vitro in HB cell lines with phenotypic assays for cell toxicity (MTT assay) and proliferation (CCK-8 assay).
- Immunoblotting assays were used to assess the induction of apoptosis (PARP cleavage) as well as to see the endogenous expression levels of pRNAP II and pRB in different cell lines.
- Differential expression of CDKs was checked by microarray analysis between normal liver and HB patients. Results were confirmed by immunoblotting. Immunoblot was also used to see the effect of dinaciclib on CDK 1/2/5/9 in vitro.
- Dinaciclib was also tested in vivo in our orthotopic PDX models of high-risk HB. Magnetic resonance imaging (MRI) and alpha-fetoprotein (AFP) ELISA were done to evaluate tumor growth.
- Tumor weights were also used to assess effects of drug in vivo.

Results

- Figure 1A is created with BioRender.com
- Table 1. Cell lines from PDX model

<table>
<thead>
<tr>
<th>Cell lines from PDX model</th>
<th>IC50 (µM)</th>
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<tr>
<td>HB17</td>
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</tr>
<tr>
<td>HB32(+1)</td>
<td>0.28</td>
</tr>
<tr>
<td>HB32(-)</td>
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<tr>
<td>HB39</td>
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</tr>
<tr>
<td>HB52</td>
<td>0.07</td>
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</table>

Conclusions

- Drug screening of a novel HB PDCL identified an agent, dinaciclib, that shows pre-clinical efficacy with refractory disease.
- Further, in vitro and in vivo validation confirmed that dinaciclib is a promising therapeutic agent for the treatment of HB.

Acknowledgements

- CPRIT MIRA-180674
- Macy Easom Cancer Research Foundation
- Owls for Avery Foundation
- Pamela Parsons (Digestive Disease Centre, TCH)
- Baylor College of Medicine Dept of Surgery, Houston, TX
- Texas Children’s Hospital Dept of Surgery, Houston, TX

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