

Avatars to personalized medicine: of mice and men

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Hepatoblastoma is a paradox. Although it is the most common liver tumor in children, its incidence of only 1 in 1–1.5 million makes it an exceptionally rare tumor even within the rare group of pediatric solid organ cancers. For example, while there are roughly 700 new cases of neuroblastoma and about 600 new cases of Wilms tumor in the United States each year, there are only about 50 cases of hepatoblastoma in the same time period. Despite its rarity—and this is the seemingly paradox aspect of hepatoblastoma—this tumor has attracted a steep increase in scientific attention both within the field of pediatric oncology and surgery, but more importantly, way past their borders and into the field of cancer research in general. The general attention to this rare tumor stems from a successful implementation of three essential components for the development of innovative anticancer strategies over the last two decades: (I) international collaboration; (II) interdisciplinary cooperation; and (III) translational research.

While the first two have already shown a significant positive impact on the outcomes of children with hepatoblastoma and will improve its numbers in the short and middle term, translational research in the field holds great promise to further effect the prognosis of these children in the long haul. Notably, the concepts in these three areas of innovation that have been applied successfully to children with hepatoblastoma have served, and continue to serve, as general paradigms in modern anticancer

strategies. This may translate into improved cancer care for all patients with malignant disease.

The examples that clarify this insight are powerful and multiple. Foremost to mention in this context is the global effort of hepatoblastoma researchers to engage in international cooperation. Traditionally, knowledge for hepatoblastoma had been extracted from the four major cooperative trial groups (the International Childhood Liver Tumours Strategy Group, Children's Oncology Group, the German Society for Paediatric Oncology and Haematology, and the Japanese Study Group for Paediatric Liver Tumours). Hindered by small patient numbers and the use of multiple contrasting staging systems by these four groups individually, a global coalition was formed and is now known as the Children's Hepatic tumors International Collaboration (CHIC). The idea behind this global collaborative effort was to identify a common approach to staging and medical decision-making in hepatoblastoma. As a result of this effort, a new system has been acknowledged based on over 1,600 children with hepatoblastoma treated over the last 25 years in all four major collaborative trial groups. This risk stratification will serve as new ground in the forthcoming Pediatric Hepatic International Tumor Trial (PHITT), in which children with hepatoblastoma (and hepatocellular carcinoma) will universally be included throughout the world. The new stratification created by the CHIC as well as the global PHIT trial will now become the new international standard for biological interrogation,

therapy intensification, and therapy reduction. The implications of this global effort become immediately apparent and serve as guidance for other pediatric solid organ cancers.

Apart from the clinical implications that the PHIT trial will bring forth, most importantly it will help to optimize the collection of biologic specimens and establish the world's largest repository of blood and tissue samples from pediatric patients with hepatic cancers. Undoubtedly, such an effort will have significant impact on future translational research in the field. Many recent successes in this line of investigation have already proven themselves both important and clinically applicable. Mentionable examples in this concept are the subgrouping of hepatoblastoma according to a newly described 16-gene signature, which was highly prognostic of clinical behavior (1). Another one is the discovery that overactivity of canonical Wnt signaling due to mutations in this pathway appears to play a pivotal role in the development and maintenance of hepatoblastoma (2-4). Understandingly, targeting the canonical Wnt signaling pathway is one of the most promising anticancer strategies not only in hepatoblastoma, but also in many adult and childhood cancers. Other similar cancer pathways, such as the Hedgehog pathway, appear to hold great therapeutic promise in hepatoblastoma (5). Also, Wagner *et al.* showed that rapamycin can limit hepatoblastoma growth by inhibiting the mTOR/AKT pathway (6). Additionally, the neurokinin-1 receptor (NK1R) has been identified as a potent new target for hepatoblastoma and can be inhibited with small molecules (7). Of note, a considerable extent of cross-talk between these pathways was recently discovered (8). However, in terms of its genetic makeup hepatoblastoma represents the most simple cancer ever described with only three mutations per tumor genome and therefore awaits further exploration (9).

Unfortunately, despite these efforts, the problem of being an exceptionally rare tumor remains a significant problem, especially when trying to address treatment options for rare subgroups of liver tumors. Hepatoblastoma falls well below the threshold of dedicated drug developing programs due to its exceptional rarity and this effect is only intensified for subgroups of this tumor. Hence, treatment options for hepatoblastoma and its relapse in particular are poorly investigated and yet to be fully understood.

Recognizing this limitation, Nicolle *et al.* opted to create pediatric liver cancer patient-derived xenografts (PLC-PDXs). These distinct tumor models represent an unprecedented clinical platform both for the individual

child affected by hepatoblastoma as well as the research community interested in drug effects and interaction in hepatoblastoma in general. Overall, her group and collaborators established 24 such tumor models out of 58 implanted specimens from 51 patients, out of which 20 were hepatoblastomas, 1 was a transitional liver cell tumor, 1 was a hepatocellular carcinoma, and 2 were malignant rhabdoid tumors. Intriguingly, 75% of recurrent or metastatic tumor specimens grafted successfully, whereas only 33.3% of primary tumors succeeded. Further strong predictors of PDX engraftment were the clinical parameters of insufficient tumor necrosis/fibrosis as well as high residual alpha fetoprotein (AFP) levels after chemotherapy.

The PLC-PDXs showed conservation of all molecular features with high reproducibility when compared to their corresponding parental tumor including the tumors' histology, cytogenetic and mutational patterns as well as the tumor's production of AFP. Moreover, these characteristics remained stable even after serial transplantation suggestive of a robust surrogate model of this rare disease. When the corresponding mice were treated *in vivo*, the PLC-PDXs responded to standards of care or therapeutic options already in use for other pediatric malignancies the way one would expect from previous clinical experience. For example, the combination of irinotecan and temozolomide led to a robust inhibition of tumor growth in a model derived from an aggressive AFP-negative and relapsing HB, matching the clinical situation and promising hope for cases with little therapeutic options.

Overall, the evidence provided by this exceptional study suggests that PLC-PDXs could serve as avatars to personalize and tailor treatments as a preclinical platform. It could help to accelerate the identification and modification of anti-cancer strategies for pediatric liver cancers for standard and aggressive subtypes, but especially for the rarest and relapsed forms with little established forms of treatment. The future will show whether predictive markers could also be established using this source of PLC-PDX models. Last, ease of engraftment seemed to act as a surrogate predictor for poor prognosis of hepatoblastoma patients.

Therefore, this study may have great implications for the future development and design of targeted therapy in pediatric liver cancer. Creating PLC-PDX with the aim to validate specific therapeutic options for individual patients or patient populations without engaging in lengthy phase II clinical trials, for which patient numbers—despite international collaborative efforts—are often too small to

provide adequate insight, could bundle and appropriately direct limited resources and optimize therapeutic options.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Cairo S, Armengol C, De Reyniès A, et al. Hepatic stem-like phenotype and interplay of Wnt/beta-catenin and Myc signaling in aggressive childhood liver cancer. *Cancer Cell* 2008;14:471-84.
2. Koch A, Denkhaus D, Albrecht S, et al. Childhood hepatoblastomas frequently carry a mutated degradation targeting box of the beta-catenin gene. *Cancer Res* 1999;59:269-73.
3. Oda H, Imai Y, Nakatsuru Y, et al. Somatic mutations of the APC gene in sporadic hepatoblastomas. *Cancer Res* 1996;56:3320-3.
4. Taniguchi K, Roberts LR, Aderca IN, et al. Mutational spectrum of beta-catenin, AXIN1, and AXIN2 in hepatocellular carcinomas and hepatoblastomas. *Oncogene* 2002;21:4863-71.
5. Eichenmüller M, Gruner I, Hagl B, et al. Blocking the hedgehog pathway inhibits hepatoblastoma growth. *Hepatology* 2009;49:482-90.
6. Wagner F, Henningsen B, Lederer C, et al. Rapamycin blocks hepatoblastoma growth in vitro and in vivo implicating new treatment options in high-risk patients. *Eur J Cancer* 2012;48:2442-50.
7. Berger M, Neth O, Ilmer M, et al. Hepatoblastoma cells express truncated neurokinin-1 receptor and can be growth inhibited by aprepitant in vitro and in vivo. *J Hepatol* 2014;60:985-94.
8. Ilmer M, Garnier A, Vykoukal J, et al. Targeting the Neurokinin-1 Receptor Compromises Canonical Wnt Signaling in Hepatoblastoma. *Mol Cancer Ther* 2015;14:2712-21.
9. Eichenmüller M, Trippel F, Kreuder M, et al. The genomic landscape of hepatoblastoma and their progenies with HCC-like features. *J Hepatol* 2014;61:1312-20.

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