Editorial

Patient-derived xenografts, a multi-faceted *in vivo* model enlightening research on rare liver cancer biology

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Modeling human cancer in pre-clinical models is of fundamental importance to gain a better understanding of the biological and molecular basis of the disease and to evaluate novel therapeutic strategies. To this end both *in vitro* and *in vivo* models are being developed with a clear emphasis on the effort to preserve the characteristics of the original human tumors both in terms of tissue architecture and clinically relevant drug responses. Recent major improvements in 3D culture conditions now allow growth of organoids from several human cancers allowing unprecedented potential for disease modeling and high-throughput screening (1). The complexity of the interactions taking place between cancer cells and their environment can however be fully recapitulated only *in vivo*. In this context patient-derived xenografts (PDXs) which are obtained by direct implant of primary human tumor tissue fragments in immunocompromised mice and subsequent expansion as tumor explants ('never *in vitro*') are emerging as extremely valuable tools to evaluate novel therapeutic strategies and biomarkers in oncology due to their ability to closely mirror the original patient's tumor (2,3).

In general there are two major clinical settings in which the value of developing PDXs as pre-clinical models has been evaluated: (I) the possibility to recapitulate in mice the disease heterogeneity observed in human tumors (e.g., using PDX models as 'xenopatients') to investigate mechanisms of response/resistance to targeted treatments (3); and (II) building avatar models of a patient's tumor to streamline treatments and implement personalized medicine (4,5). Both possibilities have been shown to have the potential to provide relevant clinical information although the second scenario is hampered by the time required to establish and characterize the models and may not be generally applicable to the benefit of individual patients.

To fully take advantage of all opportunities offered by this *in vivo* model, the size of the PDXs platform has to be large enough to encompass the whole heterogeneity of the tumors investigated. However, the number of available models strongly relies on the availability of fresh tissue from patients as well as on the take rate of the collected samples. This implies, especially for rare tumors, that it is difficult, time consuming and often considered impractical to develop a useful PDXs platform.

The recent article from the group of Stefano Cairo (6) clearly highlights a specific setting in which PDXs might represent a distinctive and irreplaceable resource: modeling rare cancers and in particular pediatric liver carcinomas, allowing a unique opportunity to cross the gap between basic and clinical research.

Pediatric liver tumors are very rare and the most common form is hepatoblastoma with an estimated incidence of 2.6 per million among children aged 0–14 years and a usually relative good prognosis (over 80% 5-year survival rate) (7,8). For these reasons a very small number of patients

with pediatric liver tumors are enrolled in clinical trials with innovative drugs. A recent study from the Innovative Therapies for Children with Cancer (ITCC) consortium reported that out of 248 pediatric patients participating in dose-finding trials in Europe, only 2% were affected by hepatoblastoma (9). Nevertheless there are aggressive pediatric liver cancers that unfortunately result in a fatal outcome. These tumors are those which more easily engraft in preclinical models and for which the need for innovative therapies remains an issue.

Development of PDXs models from pediatric cancers in general has been a recent priority as testified by the Pediatric Preclinical Testing Program (PPTP) developed by the NCI (http://pptp.nchresearch.org). To date however very little information was available on models of pediatric liver cancer. In their study Nicolle *et al.* (6) report establishment and characterization of a preclinical platform consisting of 24 pediatric liver cancer PDXs (PLC-PDXs) from 20 hepatoblastomas (HB), 1 transitional liver cell tumor (TLCT), 1 hepatocellular carcinoma (HCC) and 2 malignant rhabdoid tumors (RT). The success rate for PDX generation was high from recurrent or metastatic tumors (75%) but models could also be established successfully from one third of primary tumors (33.3%). Growth in mouse was correlated with poor prognosis also in primary tumors. As commonly observed the PDXs faithfully recapitulated original tumors for histology and molecular features. More importantly also key physiopathological properties were preserved including growth properties and secretion of alpha-fetoprotein (AFP): interestingly one PDX model generated from an aggressive AFP-negative HB maintained low levels of secretion when implanted in mice. The maintenance of key biological and metabolic properties in PDXs is in line with the recent observation of preservation of glucose metabolism as measured by FDG-PET measurements in lung cancer-derived PDXs (10). Finally the different PDXs showed variable response to standard treatment (cisplatin) demonstrating representation in this platform of the heterogeneity observed in the clinic. In a proof of concept study the combination between irinotecan and temozolomide showed efficacy in one model established from an aggressive HB, highlighting again the potential clinical relevance of PDXs for identification of novel therapeutic options.

In their paper Cairo and co-workers confirmed that the successful implant of samples is related to tumor aggressiveness. This is an interesting feature that seems to be shared also by PDXs derived from other tumor types for which take rate is far from 100% (11). Of note the authors described the successful implant of tumor samples in interscapular region of immunodeficient mice as potentially representing the growth in a "metastatic site". This is probably the best-fitting description for these models, at least for those not implanted orthotopically. The implications of this point of view are particularly interesting, since cancer mortality for the majority of cancer types is mainly due to metastasis rather than to primary tumor and few models are available to investigate this setting. In any case, both primary tumor and metastasis strongly rely on tumor-microenvironment crosstalk for their development. An intriguing idea is that PDXs engraftment in mouse may also rely on tumor-microenvironment interactions, although these models loose human stromal cells that are progressively substituted by murine counterparts albeit at lower levels compared to xenografts from long-term established cancer cell lines (12). Thus PDXs may also be exploited as an operational method to study interactions between cancer cells and stromal cells including residual cells from the innate immune system present in immunodeficient mouse models.

PDXs represent therefore a multi-faceted model that may bring some new lights to develop novel research strategies in the field of rare tumor biology. Indeed, PDXs offer a never ending reservoir of biological material closely resembling the parental tumor. This reservoir enables a plethora of different approaches in the fields of tumor biology and preclinical evaluation of anticancer drugs, offering the opportunity to bring into the clinic only the most promising strategies. Interestingly the potentially useful combination of irinotecan and temozolomide described in this study has never been evaluated in pediatric liver cancer patients. Thus the initial investment, in terms of time and money, to develop a PDXs platform from rare tumors is fully paid back by the opportunities given by these *in vivo* models reducing the risk of exposing patients to ineffective treatments. Moreover, the organization of multi-centered collections of samples such as the ones empowered by recent efforts both in the U.S. and Europe (2,3) may greatly help in overcoming the rarity issue of tumors such as hepatoblastoma or even more rare tumors such as pediatric HCC, TLCTs or hepatic sarcomas.

In conclusion the potential clinical implications of this study are wide ranging and we may hope that it could represent a crucial step towards finally reaching the main goal of the International Society of Paediatric Oncology (SIOP): "No child should die of cancer".

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Footnote

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

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