Patient-Derived Xenograft Models: An Emerging Platform for Translational Cancer Research

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ABSTRACT

Recently, there has been an increasing interest in the development and characterization of patient-derived tumor xenograft (PDX) models for cancer research. PDX models mostly retain the principal histologic and genetic characteristics of their donor tumor and remain stable across passages. These models have been shown to be predictive of clinical outcomes and are being used for preclinical drug evaluation, biomarker identification, biologic studies, and personalized medicine strategies. This article summarizes the current state of the art in this field, including methodologic issues, available collections, practical applications, challenges and shortcomings, and future directions, and introduces a European consortium of PDX models.

Significance: PDX models are increasingly used in translational cancer research. These models are useful for drug screening, biomarker development, and the preclinical evaluation of personalized medicine strategies. This review provides a timely overview of the key characteristics of PDX models and a detailed discussion of future directions in the field. Cancer Discov; 4(9); 998–1013. © 2014 AACR.

INTRODUCTION

The use of preclinical models is a core component in every aspect of translational cancer research, ranging from the biologic understanding of the disease to the development of new treatments (1, 2). With regard to drug development, the use of human cancer models for drug screening began at the NCI in the 1970s following a nearly three-decade period in which screening of new drugs was performed in rapidly growing murine models. Over the past 40 years, a number of studies have established basic methodology and a systematic approach for preclinical testing of anticancer agents both in vitro and in vivo (1, 2). Currently, the NCI-60 cancer cell line panel represents the best-characterized and most frequently used collection of human cancer models used for in vitro drug screening and development (3). These cells were derived from patients with cancer and have been adapted to grow indefinitely in artificial culture conditions. Xenografts developed by growing these cell lines subcutaneously in immunodeficient mice are the most commonly used in vivo platform in preclinical drug development.

These so-called conventional cell lines, although convenient and easy to use, have important limitations in preclinical drug development. The most relevant is their lack of predictive value with regard to activity in specific cancer types in clinical trials. Although, in general, agents active in at least one third of the preclinical models explored to date showed activity in phase II clinical trials, there has been poor prediction for activity in specific disease entities, except in lung cancer (4). Although the underlying cause of this limited predictive value is not fully understood, evidence suggests that the process of generating cancer cell lines results in major and irreversible alterations in biologic properties, including...
gain and loss of genetic information, alteration in growth and invasion properties, and loss of specific cell populations (5, 6). In addition, cell lines are usually established only from the more aggressive tumors and hence are not representative of complex tumor heterogeneity evident in the clinic. For all these reasons, the establishment of cell lines is not an appropriate strategy for personalized medicine applications. Novel approaches, such as short-term primary cultures or organoids, are being developed, although important validation studies are still required before broad application in conventional preclinical screening projects.

In an attempt to circumvent these issues, there has been increasing interest in the application of more advanced preclinical cancer models, including patient-derived tumor xenograft (PDX) as well as genetically engineered mouse models (GEMM). PDX models are not new, and studies conducted in the 1980s have already shown a high degree of correlation between clinical response to cytotoxic agents in adult patients with lung cancer and response to the same agent in PDX models generated from these patients (7). Similar observations were made in studies of childhood rhabdomyosarcomas (8). In addition, PDX models have been used to conduct preclinical phase II studies with classic chemotherapeutics (9). In recent years, there has been a renewed interest in the development of PDX models from different tumor types. Indeed, these models are becoming the preferred preclinical tool in both the industry and academic groups in an attempt to improve the drug development process (10–12). Currently, there are several collections of extensively characterized PDX models in use for different translational research applications. These collections broadly represent the complex clinical tumor heterogeneity and molecular diversity of human cancers. In this article, we review current methodology for the generation of PDX models, provide a summary of currently available collections of these models, list current applications and major contributions of PDX models to cancer therapeutics and personalized medicine, and highlight important issues for the future development of this approach. Finally, we introduce a European initiative aimed at establishing an academic consortium of laboratories having established collections of PDX models with the goal of triggering scientific collaboration, conducting multicenter preclinical trials, and developing new models. As studies demonstrate the significant heterogeneity of human cancer, large collections of PDX models, not affordable by individual groups but through the setup of collaborative networks, are key to tackling the challenge of precision medicine.

METHODOLOGIC ASPECTS

The process of generating PDX models in mice from fresh primary or metastatic human cancer is extensively described in the literature (10, 13). Although individual groups have developed specific methodologic approaches, the fundamentals are common. Table 1 provides a summary of approaches used to generate the most comprehensive PDX collections currently available. Briefly, pieces of primary or metastatic solid tumors maintained as tissue structures are collected by surgery or biopsy procedures. Some studies have also used fluid drained from malignant ascites or pleural effusions. Tumors are implanted as pieces or single-cell suspensions, either alone or in some studies coated with Matrigel or mixed with human fibroblasts or mesenchymal stem cells. The most common site of implantation is on the dorsal region of mice (subcutaneous implantation), although implantation in the same organ as the original tumor may be an option (orthotopic implantation, i.e., pancreas, oral cavity, ovary, mammary fat pad, brain, etc.). In addition, independent of the tumor origin, several approaches have implanted primary tumors in the renal capsule in an effort to increase engraftment success rates. A variety of mouse strains having different degrees of immunosuppression have been used in these studies. Supplementary Table S1 lists the principal characteristics of the most commonly used mouse strains, including their level of immune suppression as well as advantages or disadvantages. For hormone-sensitive tumors, some studies have used hormone supplementation with the intent of increasing engraftment rates.

Some approaches may have theoretical advantages with regard to higher and faster engraftment rates and generation of models that better recapitulate human tumors and are, therefore, more predictive. However, it is important to mention that very few studies have properly addressed comparative implantation methods for these endpoints. Studies in which PDX models have been generated simultaneously from primary tumors and metastatic lesions suggest that metastases have a higher engraftment rate (14, 15). Defining the most appropriate host mouse strains to generate PDX models is an important consideration. It is assumed that more severely immunosuppressed models, such as NOD/SCID or NOD/SCID/IL2 receptor null (NSG) models, are better suited for PDX generation due to higher engraftment rates. Indeed, these are the preferred rodent strains for many groups. However, in human breast cancer, where this question has been robustly interrogated, implantation in NOD/SCID versus NSG mice yielded similar take rates (16). In addition, host supplementation with estradiol pellets increased engraftment rates from 2.6% to 21.4%, whereas, for reasons that are unclear, coimplantation with immortalized human fibroblasts decreased engraftment rate (16). In contrast, in another study, a mixture of irradiated and nonirradiated human fibroblasts provided improved results (17). Likewise, orthotopic tumor implantation (“orthoxenografts”; ref. 18) may also confer a translational advantage, as the tumor develops in the same anatomic microenvironment. The generation of orthoxenografts is more labor-intensive, requires complex surgery, is more expensive, and often requires imaging methods to monitor tumor growth. However, for several tumor types (e.g., ovarian cancer or lung cancer), this approach substantially increases tumor take rates (19). In this vein, orthotopic implantation in the testis is essential for the growth of testicular germ cell tumors. As for tumor implantation in the renal capsule, it yielded an impressive 90% engraftment rate in non–small cell lung cancer (NSCLC) as compared with 25% following subcutaneous implantation, although these results were not obtained from a single comparative study (20, 21). Furthermore, renal cell capsule implantation shortens time to engraftment, which is one of the most important variables for studies seeking to implement real-time PDX data for personalized cancer treatment (20).
Table 1. Key methodologic aspects of selected PDX collections

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tumor type</th>
<th>Available models</th>
<th>Origin</th>
<th>Procurement</th>
<th>Processing</th>
<th>Mice strain</th>
<th>Implantation site</th>
<th>Engraftment rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(28)</td>
<td>CRC</td>
<td>130</td>
<td>Metastasis</td>
<td>Surgery</td>
<td>Fresh tumor pieces in Matrigel</td>
<td>NOD/SCID</td>
<td>s.c.</td>
<td>87%</td>
</tr>
<tr>
<td>(29)</td>
<td>CRC</td>
<td>54</td>
<td>Primary (35) Metastasis (19)</td>
<td>Surgery</td>
<td>Fresh tumor pieces</td>
<td>Nude</td>
<td>s.c.</td>
<td>64%</td>
</tr>
<tr>
<td>(76)</td>
<td>CRC</td>
<td>41</td>
<td>Primary</td>
<td>Surgery</td>
<td>Fresh tumor pieces</td>
<td>Nude</td>
<td>Orthotopic</td>
<td>89.1%</td>
</tr>
<tr>
<td>(34)</td>
<td>HBC</td>
<td>25</td>
<td>Primary</td>
<td>Surgery</td>
<td>Fresh tumor pieces</td>
<td>Nude</td>
<td>s.c.</td>
<td>13%</td>
</tr>
<tr>
<td>(30)</td>
<td>HBC</td>
<td>12</td>
<td>Primary (4) Metastasis (8)</td>
<td>Surgery/fluid drainage</td>
<td>Fresh tumor pieces in Matrigel</td>
<td>NOD/SCID with estrogen supplementation for ER+ tumors</td>
<td>Mammary fat pad</td>
<td>27%</td>
</tr>
<tr>
<td>(16)</td>
<td>HBC</td>
<td>24</td>
<td>Primary</td>
<td>Biopsies/surgery/fluid drainage</td>
<td>Fresh tumor pieces</td>
<td>SCID/Beige and NSG w/wo estrogen and immortalized human fibroblasts</td>
<td>Mammary fat pad</td>
<td>3%-21%</td>
</tr>
<tr>
<td>(21)</td>
<td>NSCLC</td>
<td>25</td>
<td>Primary</td>
<td>Surgery</td>
<td>Fresh tumor pieces</td>
<td>NOD/SCID</td>
<td>s.c.</td>
<td>25%</td>
</tr>
<tr>
<td>(20, 22)</td>
<td>NSCLC</td>
<td>32</td>
<td>Primary</td>
<td>Surgery</td>
<td>Fresh tumor pieces</td>
<td>NOD/SCID</td>
<td>Renal capsule</td>
<td>90%</td>
</tr>
<tr>
<td>(33)</td>
<td>PDAC</td>
<td>42</td>
<td>Primary</td>
<td>Surgery</td>
<td>Fresh tumor pieces in Matrigel</td>
<td>Nude</td>
<td>s.c.</td>
<td>61%</td>
</tr>
<tr>
<td>(26)</td>
<td>PDAC</td>
<td>14</td>
<td>Primary</td>
<td>Surgery</td>
<td>Fresh tumor pieces in Matrigel</td>
<td>Nude</td>
<td>s.c.</td>
<td>NR</td>
</tr>
<tr>
<td>(77)</td>
<td>PDAC</td>
<td>16</td>
<td>Primary (11) Metastasis (5)</td>
<td>Surgery</td>
<td>Fresh tumor pieces</td>
<td>Nude</td>
<td>Orthotopic</td>
<td>62%</td>
</tr>
<tr>
<td>(78)</td>
<td>SCCHN</td>
<td>22</td>
<td>Primary</td>
<td>Biopsy/surgery</td>
<td>Fresh tumor pieces in Matrigel</td>
<td>NSG</td>
<td>s.c.</td>
<td>85%</td>
</tr>
<tr>
<td>(25)</td>
<td>SCCHN/SCC</td>
<td>21</td>
<td>Primary</td>
<td>Surgery</td>
<td>Fresh tumor pieces in Matrigel</td>
<td>Nude</td>
<td>s.c. FOM/FOT</td>
<td>54%</td>
</tr>
<tr>
<td>(14)</td>
<td>Uveal Melanoma</td>
<td>25</td>
<td>Primary (73) Metastasis (17)</td>
<td>Surgery</td>
<td>Fresh tumor pieces</td>
<td>NOD/SCID</td>
<td>s.c.</td>
<td>28%</td>
</tr>
</tbody>
</table>

NOTE: This table provides a summary of the methodologic approaches used to generate the most comprehensive PDX collections currently available. Abbreviations: CRC, colorectal cancer; FOM, floor of the mouth; FOT, floor of the tongue; HBC, human breast cancer; NR, not reported; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell cancer; s.c., subcutaneous implantation; SCC, squamous cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.
SALIENT FEATURES OF PDX MODELS

As mentioned, the principal limitation of conventional preclinical models (“in vitro” cell line studies as well as “in vivo” xenograft models generated by implanting these cells in immunodeficient mice) is their poor predictive value with regard to clinical outcome (4). The reasons why conventional cancer models have such poor predictive power are not completely understood. However, variations in the basic biology of the models as they evolve are likely a key factor. The process of adaptation to in vitro growth conditions leads to changes in the biologic circuits of the cancer cells that differ from the host-derived entity. These include modifications in key properties such as genetic content, invasive capabilities, maintenance of a heterogeneous cell population, and the reliance on specific growth and survival pathways (6).

The rationale for developing PDX models is based on the expectation that these models will represent enhanced preclinical tools and will be more predictive of human cancer biology and patient response to treatments. In addition, PDX models offer the potential for personalizing patient cancer treatment. Proving the value of PDX models may be approached from different perspectives: one such approach is to compare the histopathologic, biologic, and genetic features of a PDX model with its donor tumor (also called “validation”). The underlying hypothesis is that PDX models will retain key characteristics of the donor tumor and that these characteristics will be maintained through successive mouse-to-mouse passages in vivo. Table 2 summarizes the data from different studies in which PDX models have been compared with donor tumors using a variety of methods. In general, these studies show that PDX models retain the principal characteristics of donor tumors, including fine tissue structure and subtle microscopic details such as gland architecture, mucin production, or cyst development. At the biologic level, most studies also show good concordance between tumors and the models derived from them. An analysis of gene expression profiles shows that there are no substantial changes between donor tumors and their corresponding PDX, with only genes involved in the stromal compartment and immune function being less represented in models, due to the replacement of the human stroma by murine elements. Indeed, using unsupervised clustering analysis, paired donor tumor and PDX models cluster together in most of the studies. Analyses of copy-number alterations (CNA) and exome sequencing data also show extraordinary concordance between paired samples, with a trend toward higher frequency of genomic alterations in the PDX model likely as a result of increased human tumor DNA purity in the PDX model. Indeed, in PDX, the cross-contamination by normal DNA from the human stromal tissue is avoided. A recent study reports whole-genome sequencing of several trios (primary tumors, lymphocytes, and PDX) in breast cancer, showing that PDX have relatively stable genomes without a significant accumulation of DNA structural rearrangements but with some enrichment for PDX-unique single-nucleotide variants (22). These PDX-unique mutations could be the result of adaptation to transplantation into the new microenvironment, but could also be present in the original tumor below detectable limits. A study showed that many CNA changes found in sarcoma PDX are frequently observed in patients with sarcoma, suggesting that xenografts may in some way represent the genomic rearrangement intrinsic to tumor progression (23). This was also suggested in another study describing that many of the mutations detected in the breast PDX were also observed in brain metastases derived from the same patient (24). Furthermore, mouse-to-mouse propagation does not substantially change the functional characteristics of the grafted tumor. Studies that have compared the response to drug treatments of PDX models from different passages (up to 10) show stable response rates across generations, further supporting the phenotypic stability of these models (25, 26). In contrast, an interesting study compared the gene expression profiles of a donor tumor with those of PDX models and cell lines developed from that tumor, both in vitro and in vivo in conventional xenograft models. The data show that although the gene expression profile of PDX models is similar to the original tumor, cell lines developed from the same specimen display a different expression profile that is not restored by in vivo subcutaneous propagation in mice (27).

An additional way to examine model fidelity as compared with the original tumor is to focus on well-known disease-based genomic alterations rather than directly comparing an individual donor with PDX characteristics. In PDX models of squamous cell carcinoma of the head and neck (SCCHN), for example, the prevalence of TP53 and NOTCH mutations is similar to those reported in human tumors (25). Similar results have been observed in colorectal cancer and pancreatic ductal adenocarcinoma (PDAC) models in which the frequency of mutations in genes such as TP53 or RAS closely mirrors the frequency of these mutations in human samples (26, 28, 29).

In human breast cancer PDX models, several studies using gene expression profiles have shown that intrinsic breast cancer phenotypes are well represented and in concordance with the original tumors (16, 30, 31). Nevertheless, estrogen receptor–positive (ER+) subtypes are underrepresented, in particular, the recently described ER subtypes with good prognosis. Furthermore, when examining metabolism, the metabolic profiles as detected by high-resolution magic angle spinning magnetic resonance (MR) spectroscopy are remarkably similar when comparing patient material and tissue from orthotopically growing basal-like and luminal-like breast cancer (32).

A complementary approach to determine the value of PDX models in cancer research (discussed and illustrated below) is by analyzing the predictive value of the data obtained from PDX studies with regard to drug efficacy, biomarker analysis, and patient outcome. In this sense, a similar level of activity as observed in the clinic has consistently been shown in studies in which clinically applied drugs or regimens have been tested in PDX models. Table 3 provides a summary of studies in which PDX models from different cancer types have been treated with agents used in the clinical care of these patients. Although the analysis of data is complicated by different response criteria used, in general, there is a remarkable similarity between the activity of agents, such as cetuximab in colorectal cancer models and gemcitabine in PDAC models, and respective clinical trial data (28, 29, 33).
Table 2. Fidelity and stability of PDX models

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tumor type</th>
<th>Original tumor-first passage</th>
<th>Subsequent passages</th>
</tr>
</thead>
<tbody>
<tr>
<td>(28)</td>
<td>CRC</td>
<td>Conserved histopathology characteristics between donor and PDX models. Similarities in CNA between donor and PDX models. Consistent KRAS, NRAS, BRAF, and PI3K mutation status.</td>
<td>Stable CNA across passages.</td>
</tr>
<tr>
<td>(29)</td>
<td>CRC</td>
<td>Unsupervised clustering analysis using aCGH and GE shows that the donor tumors and PDX clustered together. 203 differentially expressed annotated genes correspond to stroma-related genes and pathways.</td>
<td>Stable aCGH and GE profile across passages.</td>
</tr>
<tr>
<td>(31, 34)</td>
<td>HBC</td>
<td>Conserved IHC expression of ER, PR, and HER2. Analysis of CNA showed 14/18 paired tumors-PDX shared more than 56% CNA. 16/18 paired tumors-PDX clustered together in unsupervised hierarchical analysis. PDX showed losses in 176 and gains in 202 chromosome regions compared with primary tumors. Stable GE profile with less than 5% variations.</td>
<td>Stable CNA and GE profile across passages. Variations in stromal related genes.</td>
</tr>
<tr>
<td>(30)</td>
<td>HBC</td>
<td>Conserved histopathology characteristics between donor and PDX models. Conserved IHC expression for CK, E-cadherin, β-catenin, vimentin, ER, PR, and HER2. Unsupervised clustering analysis using GE shows that donor tumors and PDX clustered together. Maintenance in the pattern of CNA. Intrinsic breast cancer subtypes concordant between the donor tumors and PDX.</td>
<td>Stable IHC profile over time.</td>
</tr>
<tr>
<td>(16)</td>
<td>HBC</td>
<td>Conserved histopathology characteristics between donor and PDX models. Conserved IHC expression for CK, p53, Ki67, ER, PR, HER2, and EGFR. Intrinsic breast cancer subtypes represented in PDX models.</td>
<td>Stable histopathologic and IHC expression.</td>
</tr>
<tr>
<td>(21)</td>
<td>NSCLC</td>
<td>Conserved histopathologic characteristics between donor and PDX models. Conserved IHC expression of Ki67 and EpCAM. Unsupervised clustering analysis using GE shows the donor tumors and PDX clustered together with correlation coefficient ranging from 0.78 to 0.94. 134 differentially expressed genes correspond to cell adhesion and immune response genes and pathways.</td>
<td>Stable GE, RPPA, and SNP across passages.</td>
</tr>
<tr>
<td>(25)</td>
<td>SCC/SCCHN</td>
<td>Conserved histopathologic characteristics between donor and PDX models. High correlation ($R^2 = 0.91$) in EGFR expression. High correlation ($R^2 = 0.8$) in GE. Variation in immune-related pathways.</td>
<td>High correlation ($R^2 = 0.94$) in GE from F2-F4. Concordance in cetuximab response between F2 and F4.</td>
</tr>
</tbody>
</table>

NOTE: This table summarizes the data from different studies in which PDX models have been compared with donor tumors using a variety of methods. Abbreviations: aCGH, comparative genomic hybridization array; CRC, colorectal cancer; GE, gene expression; HBC, human breast cancer; IHC, immunohistochemistry; NGS, next-generation sequencing; PR, progesterone receptor; RCC, renal cell cancer; RPPA, reverse phase protein array; SNP, single-nucleotide polymorphism; SCC, squamous cell carcinoma.
Of greater relevance is the remarkable one-to-one concordance in studies that compare the individual donor patient response to conventional anticancer agents with that of the PDX (16, 21, 33, 34). Furthermore, the analysis of clinically validated biomarkers, such as KRAS mutations, and resistance to EGFR inhibitors in PDX studies reached the same conclusions as clinical trials, as discussed in more detail below (28). Finally, emerging studies in which patients have been treated with drugs selected for their activity against their PDX counterparts show a high predictive power, further supporting the notion that response in PDX models correlates with clinical outcome (35).

### Applications of PDX Models in Cancer Research

#### Drug Screening and Biomarker Development

It is well known that one of the major issues in oncology drug development is the low success rate of new agents (36). Many compounds are advanced to large phase III studies, which consume considerable resources, to end up failing because of a lack of efficacy. Part of the reason for these poor results is that conventional preclinical models used to screen new agents for clinical development have poor predictive value (4). In addition, new drugs are, in general,
tested without appropriate biomarkers for patient selection and response monitoring. Thus, strategies to diminish this high attrition rate are needed. In this regard, the availability of preclinical models with high predictive value is of major interest, as it will permit the conducting of preclinical phase II studies to select potential indications for subsequent clinical trials.

The rationale for implementing PDX models to achieve this objective relies on the fact that these models are predictive of clinical outcome. This has been shown in several retrospective studies and more recently in prospective clinical trials. As listed in Table 3, a number of reports in colorectal cancer, NSCLC, SCCHN, human breast cancer, and renal cell cancer (RCC) have tested the response rate of drugs used as standard of care in medical oncology in PDX models. These experiments show that the response rates in PDX models correlate with those observed in the clinic, both for targeted agents and for classic cytotoxics. For example, an extensive analysis of the EGFR inhibitor cetuximab in 47 unselected colorectal cancer PDX models showed a 10.6% response rate, which is identical to the response rate observed with this agent in patients with this disease (28). Similar data have also been published for SCCHN, the other indication in which cetuximab is commonly used (25). The MEK and PI3K/mTOR inhibitors proved to be poorly effective in a panel of 40 KRAS-mutant colorectal cancer PDX models, again in accordance with clinical data from phase I trials (37). In RCC, PDX models showed response to the mTOR inhibitor sirolimus and the angiogenesis inhibitors sunitinib and dovitinib, but not to erlotinib as was also observed in clinical trials (15). With regard to conventional chemotherapy, studies in NSCLC, human breast cancer, colorectal cancer, and PDAC demonstrated that response rates to clinically used agents, such as paclitaxel, carboplatin, gemcitabine, 5-Fluorouracil, irinotecan, and adriamycin, among others, are comparable between PDX models and clinical data (Table 3).

More recently, the role of PDX models as potential screening platforms for clinical trials has also been shown in a prospective study in PDAC. This work showed that the combination of nab-paclitaxel and gemcitabine is effective in PDX models of PDAC, a finding that correlated with the clinical efficacy of this combination. In fact, this regimen has recently been demonstrated to provide a survival benefit for patients with advanced PDAC in a randomized phase III study, and is likely to become a standard of care in this setting (38). Likewise, failure to exert antitumor efficacy in PDX models correlates with negative clinical results. This is illustrated in PDAC for agents such as the SRC inhibitor saracatinib and the mTOR inhibitor sirolimus, for which lack of efficacy in unselected PDX preclinical studies predicted failure of the same strategy in the clinic (39, 40). Based on these data, PDX models have now become an integral part of the preclinical screening of new anticancer agents.

One critical aspect of large preclinical studies in PDX models is that they not only help to prioritize potential clinical indications, but may also facilitate the identification of potential drug efficacy biomarkers. The concordance between PDX models and human trials with regard to biomarkers of drug susceptibility and drug resistance is indeed notable. In colorectal cancer, for example, it has been clearly shown in a number of studies that KRAS-mutant PDX models do not respond to cetuximab. KRAS wild-type status is now a well-documented clinical biomarker for this targeted therapy (28, 29). Similar data were observed in NSCLC (21). In fact, it could be argued that if these preclinical studies had been conducted before or in parallel to the clinical development of cetuximab, the discovery, validation, and approval of KRAS mutation as a marker of resistance would have been expedited. In PDAC, PDX studies with gemcitabine identified expression of the gemcitabine-activating enzyme deoxycytidine kinase as a predictor of drug efficacy. A subsequent analysis of this marker in clinical samples confirmed these results (26, 41). Likewise, PDX models have been used to identify metabolic as well as imaging biomarkers (42, 43).

Equally important is the discovery of resistance biomarkers that may help to design combination clinical trials. In colorectal cancer, it has been shown that tumors resistant to EGFR inhibition harbor amplifications of other genes such as HER2 and MET (28, 44). Preclinical combination studies with agents targeting these genes showed promising preclinical efficacy resulting in clinical translation. Likewise, in SCCHN, activating mutations in the PI3KCA gene confer resistance to EGFR inhibitors that can be modulated by agents that inhibit the PI3K pathway (25). PDX models are also versatile tools for simulating resistance when exposed to treatment strategies used in the clinical setting. This has been shown for example in ovarian cancer, in which prolonged exposure to cisplatin results in the induction of resistance to this agent in a platinum-sensitive model, similar to what is observed in the clinical setting. This model has been used to explore new agents, with a goal to select drugs to be tested in platinum-resistant patients such as the DNA minor groove binder lurbinectedin (18). Interestingly, cisplatin-sensitive and cisplatin-resistant ovarian orthoxenografts recapitulate characteristic features of primary human tumor response, such as the histopathologic tumor regression criteria associated with patient treatment response (36). Resistance to targeted drugs, such as vemurafenib, has been induced in melanoma PDX models. Not only was a mechanism of resistance was identified, but also a novel drug administration strategy applicable to the clinic was proposed to overcome resistance (45). Until now, no published work compared PDX models established from primary and recurrent tumor samples from the same patient.

Preclinical testing in PDX models can also facilitate optimization of clinical trial design. This is perhaps best illustrated in studies with cancer stem cell (CSC) therapeutics such as inhibitors of the Sonic Hedgehog, Nodal/Activin, TGFβ, and Notch pathways (46–49). In PDX studies, these agents failed to induce synergistic tumor regression responses when combined with chemotherapy but resulted in tumor growth delay and, importantly, in a decrease in tumor initiation and relapse. In addition, in reimplantation studies, it was shown that administration of an agent directed at CSCs prevented reengraftment of treated tumors when excised and re.injected in host mice (49). The use of
PDX models in this context is crucial to assess and understand the effect of pharmacologic compounds on CSCs. These findings may have further implications for clinical trial design, as it would suggest that treatment of minimal residual disease (such as during the postoperative period or after debulking chemotherapy) and using a time-to-event endpoint may be an appropriate setting in which to apply this approach.

On the basis of these data, PDX models may play an important role in drug–response studies to help select populations of patients most likely to be sensitive to a new agent, as well as to prioritize the development of new biomarkers. Figure 1 depicts a proposed path for the integration of PDX models in new drug development. For agents that are selected for clinical studies, we propose to perform PDX testing in parallel to phase I safety and pharmacologic studies. PDX preclinical testing should be done in tumor types of interest selected by prior preclinical data both with regard to disease type but also in molecularly defined groups as in basket-type trials. Indeed, one of the advantages of the existing PDX model collections is that they have been extensively characterized at the histologic, molecular, and genomic level.

On the basis of the type of agent, studies can be adapted to test single agents or clinically meaningful combinations, using appropriate endpoints such as response rate (short-response assay) or tumor growth delay (long-term response). Agents showing activity in initial screens can be further studied in a larger group of models using statistical methodologies similar to two-stage clinical trial design. Once again, the availability of a larger collection of models through the collaboration of academic and nonprofit organizations would enable these larger screens. Biologic and genetic comparisons between sensitive and resistant models can be explored for the prioritization of biomarkers for inclusion in clinical studies.

Co-Clinical Trials

Once a drug enters clinical trials, there are limited opportunities to, on a real-time basis, analyze and integrate information that may be useful for the development of that agent (50). Even in studies that select patients based on molecular abnormalities and that incorporate tumor tissue, normal tissue, and imaging-based pharmacodynamic endpoints, there are few options for real-time integration
and exploitation of the observed information in the trial. This is in part due to the intrinsic nature of clinical trials in which patients are treated with one drug or regimen at a time and followed under very specific criteria, but also due to the lack of sufficient and easily accessible biological materials for more in-depth studies of clinical observations. Thus, patients may develop extreme responses or rapid resistance, but it is in general difficult to study the underlying mechanisms in detail.

To solve some of these issues, the concept of co-clinical trials has been proposed. In their original format, these studies refer to the use of GEMMs of cancer to determine patient selection strategies as well as to discover mechanisms of resistance to treatment approaches (51, 52). PDX models have been used in this context in parallel studies in rodent models and patients, and have indeed been useful in identifying potential biomarkers (39, 53). Moreover, PDX models may also be used in another application of the co-clinical trial concept, as depicted in Fig. 2. In this approach, a personalized PDX model, a so-called “Avatar” model, is developed from a patient enrolled in a clinical trial and treated with the same experimental agents to emulate clinical response. This strategy permits the assessment of drug response simultaneously in the patient and mouse model, providing an interesting platform to investigate biomarkers of susceptibility and resistance, as well as interrogation of novel combination strategies to overcome emergent resistance pathways.

**Personalized Medicine**

The field of oncology is rapidly evolving from an “all comers” approach to cancer therapy to an era in which patients’ tumors are profiled in greater detail to select the most appropriate treatment (54). Colorectal cancer, NSCLC, and human breast cancer tumors, to name a few, are now routinely profiled to aid in the treatment decision-making process (55). Furthermore, cell free circulating tumor DNA is now also analyzed to direct patients to appropriate clinical trials with molecularly targeted agents (56). Although this tailored strategy represents a significant advancement in translational cancer research, further advancements are required. One such outstanding advancement requires consideration of patients for whom, despite extensive testing, no biomarkers of drug efficacy are detected. These patients cannot have their treatment personalized. The opposite situation is also true: as cancer profiling evolves and becomes more comprehensive,
multiple potential targets are identified in some patients, confounding the selection of the most appropriate one.

Avatar mouse models have been used to personalize cancer treatment (57). Interest in using these models emerges from studies such as those listed in Table 3 that have demonstrated a remarkable correlation between drug response in PDX models and clinical response. In NSCLC, for example, PDX models have been used to test the efficacy of three of the most commonly used first-line chemotherapy regimens in this setting. The results of this study show that approximately two thirds of the patients with NSCLC are sensitive to first-line chemotherapy, whereas one third are resistant. Interestingly, patients are not sensitive to all regimens equally and some patients are sensitive to one but resistant to another, suggesting that there is potential to personalize regimen selection (20). In another study, investigators used Avatar models from patients with advanced cancer to screen a large battery of anticancer agents and select the most effective agent to treat the donor patient. The results of this trial show that when all factors involved are correctly aligned, the response in Avatars and patients is highly correlated. However, in most patients, the approach is not feasible for reasons such as failure of the tumor to engraft, lack of effective agents, and length of time required for a complete study (33, 35). Thus, strategies to optimize these issues, as discussed below, are needed.

It is likely that the contribution of PDX models to personalized cancer treatment will increase by their integration in more global personalized medicine approaches like the one represented in Fig. 3, rather than as a stand-alone platform. The significant revolution in cancer genetics is permitting, for the first time, the gathering of enormous amounts of genomic information, including the assessment of a complete cancer genome, to aid in clinical decision-making (55, 58). In many oncology clinics, it is now becoming common practice to analyze a set of 50 to 100 relevant cancer genes for hundreds of mutations. From this approach, numerous potential targets have emerged for individual patients that may potentially be linked to clinical response. In addition to bioinformatics and in silico prediction data from cancer cell line data, personalized PDX models may now be useful in this setting, as they facilitate testing of candidate regimens in the patient’s own tumor to select for the most efficacious treatment approach (3, 59). Furthermore, the integration of observed responses in mice with the tumor genetic information would eventually
lead to the discovery of new biomarkers of drug efficacy. For patients whose tumors do not take in mice or those who require a long time to be established and characterized, an alternative to the Avatar strategy could be to orient treatment choice based on drug response of a similar PDX. Biopsies of primary tumors or metastases would be molecularly characterized and compared with available PDX collections from the same pathology, for which responses to chemotherapies and targeted agents have been previously determined (Supplementary Fig. S1).

**LIMITATIONS OF PDX MODELS**

Although the incorporation of PDX models in cancer research brings some improvements as detailed above, it is clear that they still have important limitations that need to be addressed to improve their use in translational cancer research. Some of these limitations are technical in nature and include several issues, such as (i) consideration of the most appropriate tissue from which to generate a PDX model and the processing of this tissue. Most of the published studies have relied on surgical specimens that naturally provide large quantities of tissues. Although this approach is useful to generate PDX collections, smaller samples, such as tumor biopsies or fine-needle aspirations, are better suited for personalized medicine applications. (ii) It is important to define the best strategy of engraftment in mice (subcutaneous vs. orthotopic implantation) for different tumor types. (iii) Delay between engraftment time in mice and treatment schedules for patients is also a limiting factor for real-time personalized medicine applications. It normally takes 4 to 8 months to develop a PDX model ready for a preclinical study, a time frame that many patients do not have. (iv) Another problem is engraftment failure that is still high for some tumor types with particular phenotypes, such as hormone receptor–positive human breast cancer. For personalized medicine strategies, it is mandatory to improve tumor take rates to an acceptable 60% to 70%, this being one of the main aspects requiring improvement. This is not only a problem in personalized medicine, as most patients do not have a linked PDX model, but also in drug-screening studies, as current PDX collections are skewed toward certain cancer subtypes and do not broadly represent the disease heterogeneity.

One key aspect in PDX research is the need to use immunodeficient host strains for tumor engraftment and propagation. These mice lack functional elements of the immune system (Supplementary Table S1) to avoid rejection of foreign tissues and permit engraftment of the tumor. For this reason, PDX models are of limited use in screening immune-mediating agents, such as vaccines and immune modulators (e.g., anti-PD1), or agents that function by activating immune elements, such as anti-CD40 antibodies.

Another critical aspect is the substitution of human tumor by murine stroma throughout tumor growth in mice. In different studies in which this aspect has been addressed, it has been consistently shown that the human cancer stroma included in the implanted tumor pieces is rapidly replaced by murine stroma, so that after three to five passages when the models can be used for drug testing, stroma is in essence murine. This includes the extracellular matrix, cancer-associated fibroblasts, blood vessels, and inflammatory and immune-mediating cells such as leukocytes and macrophages. This new murine stroma probably results in changes in paracrine regulation of the tumor as well as in physical properties such as interstitial pressure, that may limit the study of agents directed against this tumor compartment (50, 60).

An important use of preclinical models in cancer research is for drug screening. Traditionally, this has been done using established cell lines that, as mentioned above, have very poor predictive value and are overly permissive. Using PDX models for this application would be ideal, although at the present time, cost and resources required make this approach unfeasible. As an alternative, some groups are using short-term single-cell suspensions and short-term culture in organoid bioreactors.

The process of generating a PDX model clearly results in the selection of tumors that engraft and propagate in mice. This has been shown across multiple studies with the general impression that more aggressive tumors have a higher take rate. In human breast cancer, for example, hormone receptor–negative tumors have a higher take rate than hormone-sensitive tumors and are overrepresented in the existing PDX collections (16, 30, 34). Patients with human breast cancer, RCC, PDAC, and uveal melanoma whose tumors successfully engraft show the worst prognosis, indicating that there is a selection toward more aggressive higher metastatic tumors (14, 15, 22, 30, 33, 61). In addition, although this is still poorly understood, it is possible that tumors that engraft do so by propagation of selected clones that divide actively to form a new tumor in the host mice that is not necessarily identical to the parental tumor. Thus, although in general there are close similarities in global genetic surveys such as unsupervised clustering analyses between a PDX model and the original patient tumor, there are still likely changes in more specific genes and drug targets. In that sense, some studies have shown that there are discrepancies in the expression of selected drug targets and subtle variations in the expression of gene signatures reflecting stromal, immune infiltrate, or angiogenesis components. Indeed, several studies have reported that the gene expression profile and genetic characteristics of PDX models are reminiscent of the cancer metastasis and relapse environment (15, 24, 33).

**FUTURE DIRECTIONS**

Over the last few years, there has been a growing interest in developing PDX collections and using them for different cancer research applications (11, 12). Although there has been important progress in the field, there are several crucial areas that will benefit from additional research. These include such diverse issues as implantation procedures, consideration of mouse host strain, post-engraftment manipulations, robust application of translational imaging modalities in the assessment of PDX models toward the elucidation of imaging response biomarkers, and nomenclature and harmonization in study design and reporting. Furthermore, because of significant expansion in the field, organized and collaborative efforts will also be needed to optimize the use of existing collections and the generation of new ones.
As mentioned above, the process of generating PDX models is, in general, well established and implemented in a consistent fashion by most research groups (10, 13). However, each research group has developed its own approach and few comparative methodologic studies are available. Issues such as the minimum sample size needed, best preservation media, the need to add other components, such as Matrigel or mesenchymal cells, site of implantation (subcutaneous, orthotopic, or renal cell capsule), and time spent on processing the specimen for better results are currently unknown. Of major importance, particularly for personalized medicine applications, is the development of methods to increase engraftment rates and to generate models from difficult-to-engraft cancer types such as prostate cancer or hormone-dependent human breast cancer. Of great interest in this sense are newer three-dimensional models of glioblastoma, colorectal cancer, and human breast cancer, for example. These tissue-originated spheroids are generated by digesting and growing primary tumor cells under controlled culture conditions (62). Spheroids can survive for several days under in vitro conditions, can be subjected to ex vivo manipulation, and can generate full tumors, of even well-differentiated histology, when implanted in mice (63). Likewise, flow cytometry strategies to purify tumor-initiating cells before implantation in mice can improve engraftment rates (64).

Once a PDX model has been developed, there is also interest in generating cell lines to facilitate high-throughput drug-screening and functional studies (65). However, as discussed above, any ex vivo manipulation may preclude significant modifications in fundamental biologic properties of the tumor, thus compromising the translational value of the models (27).

It is now well established that cancer is genetically heterogeneous in an inter- and intra-individual manner and that there is a genetic evolution in cancer as the tumor progresses (66–68). Thus, a PDX model generated from one individual lesion at a single time point is indeed a snapshot view of a tremendously dynamic process and may not be representative of the full diversity of the disease. Furthermore, the process of PDX generation, as discussed in detail above, selects for more aggressive tumors and likely for more aggressive clones, with metastatic features, within the tumor. At present, there are no solutions to this issue. However, recent studies attempting to generate PDX models from circulating tumor cells have shown promising early results (69). One approach to at least partially overcome this problem is the generation of models from rapid autopsy programs that permit sampling of multiple lesions from the same cancer (70). In addition to their role in studies of cancer evolution, these models are also a better representation of end-stage disease, which is where new drugs are ultimately tested. Furthermore, it is to be expected that the more rigorous grafting of tumors before, during, and after treatments, as it is being performed nowadays, will also result in novel PDX models from paired clinically drug-sensitive and drug-resistant tumors.

One key aspect in PDX research is the host mouse model used. With the premise that immunodeficient hosts are required to allow engraftment, investigators have used different mouse strains to generate PDX collections. These strains differ with regard to their immune system deficiencies and provide different permissive environments (Supplementary Table S1). The prevailing notion that a more severely immunodeficient mouse is a better host has not been properly assessed. Although this question may not be relevant for small-scale experiments, large preclinical studies, which use hundreds of mice, would benefit from the use of cheaper and less delicate strains. Of major interest, however, is the development of mouse models with reconstituted immune systems from the individual donor, or models able to replicate human, rather than murine, stroma (71). A “personalized immune” mouse, with a robust immune reconstitution with hematopoietic stem cells aspirated from the bone marrow of an individual patient with cancer, may provide a new model to observe the role of the autologous immune response in the PDX setting of the same patient with cancer. These models would permit the testing of agents directed against the immune system or the stromal component.

Another critical requirement is the ability to noninvasively and longitudinally monitor PDX tumor growth kinetics and response to therapies. Small animal imaging techniques, such as computed tomography, magnetic resonance imaging, and positron-emission tomography, allow for detailed appraisal of tumor anatomy, vascularization, and metabolic activity (72). Nevertheless, these approaches are limited with respect to high-throughput implementation and require costly equipment and infrastructure and a high level of technical expertise. Conversely, bioluminescence imaging (BLI) requires ectopic transduction of a light-emitting enzyme (usually luciferase) in tumor cells, but represents a cost-effective and relatively high-throughput and facile preclinical imaging modality (73). Recent studies have reported efficient expression of exogenous proteins, including luciferase, by infecting patient-derived tumor-cell suspensions and spheroid cultures with lentiviral particles (74). Although these advancements attest to the feasibility of genetic modification of PDX tumor preparations for imaging purposes, their utility in the routine implementation of BLI to follow PDX tumors in vivo remains to be seen.

Efforts to harmonize and standardize study design and data analysis are also needed. For PDX preclinical studies to be fully integrated in clinical development pipelines, there first needs to be a consensus in the design of preclinical studies. This includes areas such as the number of models representing the tumor heterogeneity of the majority of tumor types, and the number of mice per model required for robust statistical interrogation, as per a clinical trial. Another important question is the homogeneity of the batch of mice in which a drug will be assayed, important when a large number of mice are needed. A key question is the efficacy endpoint selected and the degree of efficacy required for a positive result. For example, when testing conventional cytotoxic agents, tumor regression may be the preferred endpoint, whereas if testing agents against the CSC compartment, endpoints such as growth delay and latency to growth after retransplantation may be favored. Regardless of the selected endpoint, a consensus is needed in reference to the level of activity considered sufficient to advance an agent to clinical development.

As the number of groups, both in industry and in academia, working on developing PDX collections increases, efforts to develop collaborative networks are ongoing. These networks
will likely house thousands of models with well-annotated biologic, clinical, and drug-response data. With proper confidentiality and data protection systems, this information can be shared to permit the rapid assessment of model availability, which will be particularly important for rare molecularly defined tumor types. Furthermore, these networks will allow the conducting of multicenter preclinical trials as done for patients under a single protocol with rapid accrual and data generation.

In that sense, within Europe, a consortium of centers having interest and significant expertise in PDX models has now emerged: EurOPDX is an initiative of translational and clinical researchers across Europe having the common goal to create a network of clinically relevant and annotated models of human cancer, and in particular PDX models. The primary goal of our initiative is to share PDX models in diverse cancer pathologies, to constitute a unique collection reproducing the heterogeneity of human cancer. Supplementary Table S2 provides a summary of the models and the level of characterization of those models currently available across the EurOPDX Consortium.

A shared database with harmonized annotation of models will be established and integrative systems-based analyses developed to elucidate novel therapeutic strategies and to uncover predictive biomarkers for personalized cancer treatment. Annotation of the models will include anatomopathologic data, clinicopathologic data from the patients the PDX models were derived from, deep molecular profiling in particular with gene expression, CNAs, and proteomics platforms, as well as pharmacogenomic data corresponding to current anticancer therapies. Additional technologies such as imaging are increasingly being used, and the ideal database will also include such data as well as scanned images of pathology slides (75). In this way, the consortium will be able to quickly include any newly developed multimodal prognostic and predictive tool in the analysis pipeline. Making the data available for the analysis is not a trivial task as it implies standardization of platforms used for molecular characterization, data acquisition, data curation, normalization, and quality control. Moreover, and as discussed above, harmonization and standardization of working practices for the implementation and use of PDX models and, in particular, for the performance of more reproducible and predictive multicenter preclinical trials will be a key objective of the network.

Hypotheses will then be validated in proof-of-concept collaborative multicenter PDX trials within molecularly defined tumor subsets and on a population scale, as a prelude for prospective clinical trials in humans. The consortium will be in absolute compliance with European rules for the use of experimental animals. A coordinated and rational design of the experiments, troubleshooting, and sharing of positive and negative results across the various centers will enable a reduction in the overall number of experimental animals used and optimize the use of each precious patient sample, avoiding unnecessary replicas of experiments, while maximizing the statistical significance and robustness of the data.

Finally, the performance of research programs among this academic consortium will allow us to address the current limitations of the PDX models described above and advance their use as clinically relevant cancer models.

Through the building of this network and its collaboration with pharmaceutical and biotech companies, the EurOPDX initiative will accelerate the emergence of novel therapeutic strategies with a real impact on quality of life and overall survival of patients with cancer through more predictive preclinical or “co-clinical” data, ultimately reducing attrition rates in oncology clinical trials in Europe.

CONCLUSIONS

Over the last decade, there has been an interest in developing and characterizing collections of PDX models from different cancer types, which are now available at academic and nonprofit organizations. These models are becoming an integral part of the drug development arena, including drug screening and biomarker development. In addition, PDX models bear the promise of assisting clinical trial designs as well as being integrated into personalized medicine strategies. It is envisioned that PDX models will eventually play a broader role in the drug development process and become a must-have element in that process. At present, however, there are still some critical issues that must be addressed to make this platform more useful and informative. This includes increasing the take rate and time to model generation, recapitulation of the human stroma and immune-related elements, as well as strategies to develop models more representative of different cancer entities, tumor heterogeneity, and chemorefractory patients. Finally, initiatives to harmonize nomenclature, study designs, and procedures are needed. We propose that the new European EurOPDX initiative, which represents a PDX collaborative consortium, will offer a unique opportunity to address translational challenges in oncology research.

Disclosure of Potential Conflicts of Interest

M. Hidalgo is a founder and shareholder of Champions Oncology, Inc. No potential conflicts of interest were disclosed by the other authors.

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